PFO detection in young stroke patients

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Summary

• What is PFO
• How to diagnose it
• Why to diagnose it
• When to diagnose it
What is PFO: neither foramen, nor patent
Prevalence of PFO

- Ischemic stroke: 40% (range: 32%-50%)
- Cryptogenic ischemic stroke: 50% (49%-62%)
- Normal controls: 20% (17%-35%)

- Controls: 20.8%
- Heart disease: 8.4%
- Non-cryptogenic stroke: 10.8%
- Cryptogenic stroke: 16.5%
Relationship PFO- Age

- Prevalence falls with age: over 80 years = 20%
- Dimension increases with age:
  - 1-10 years = 3.4 mm
  - over 90 years = 5.8 mm
sensitivity: 95%
specificity: 75%

Droste et al., ‘99
Comparison of VBC and MCA Recording at Rest
(Del Sette et al., Stroke 2007)

<table>
<thead>
<tr>
<th></th>
<th>MCA +</th>
<th>MCA -</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VBC+</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>VBC−</td>
<td>12</td>
<td>155</td>
<td>167</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>155</td>
<td>183</td>
</tr>
</tbody>
</table>

Sensitivity 57.14%; specificity 100%; positive predictive value 100%; negative predictive value 92.81%.
## Comparison of VBC and MCA Recording After the Valsalva Maneuver

(Del Sette et al., Stroke 2007)

<table>
<thead>
<tr>
<th></th>
<th>MCA+</th>
<th>MCA-</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>VBC+</td>
<td>36</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>VBC−</td>
<td>7</td>
<td>140</td>
<td>147</td>
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<tr>
<td>Total</td>
<td>43</td>
<td>140</td>
<td>183</td>
</tr>
</tbody>
</table>

Sensitivity 83.72%; specificity 100%; positive predictive value 100%; negative predictive value 95.24%.
Comparison of VBC and MCA Recording for Medium and Large Shunts (>10 Mb)

( Del Sette et al., Stroke 2007)

<table>
<thead>
<tr>
<th></th>
<th>MCA+</th>
<th>MCA -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VBC+</td>
<td>22</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>VBC−</td>
<td>0</td>
<td>161</td>
<td>161</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>161</td>
<td>183</td>
</tr>
</tbody>
</table>

Sensitivity 100%; specificity 100%; positive predictive value 100%; negative predictive value 100%.
Other techniques

- Cardiac MR: inferior to TEE for PFO and ASA \( (Nusser \ et \ al., \ JACC \ 2006) \)

- 3D echo: useful for large atrial septal defects \( (Mehmood \ et \ al, \ Ecocard. \ 2004) \)

- Intra Cardiac Echography: Useful during procedure \( (Ponnuthuray \ Int \ J \ Cardiol \ 2007) \)
In which conditions?

- Ischemic stroke
- Migraine with aura
- CADASIL
- Transient global amnesia
- Pneumopathies and obstructive sleep apnoea syndrome (OSAS)
### Methanalysis (Overell et al, Neurology 2000;55:1172-1179)

#### Table A

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke n/N</th>
<th>Control n/N</th>
<th>OR (95%CI Fixed)</th>
<th>Weight %</th>
<th>OR (95%CI Fixed)</th>
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</thead>
<tbody>
<tr>
<td>Cabanes, 1993 (P)</td>
<td>43 / 100</td>
<td>9 / 50</td>
<td>13.8</td>
<td></td>
<td>3.44[1.51,7.83]</td>
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<tr>
<td>Chen, 1991 (P)</td>
<td>15 / 34</td>
<td>7 / 40</td>
<td>7.2</td>
<td></td>
<td>3.72[1.29,10.74]</td>
</tr>
<tr>
<td>Del Sette, 1998 (P)</td>
<td>26 / 73</td>
<td>8 / 50</td>
<td>12.3</td>
<td></td>
<td>2.90[1.19,7.11]</td>
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<tr>
<td>Job, 1994 (P)</td>
<td>38 / 74</td>
<td>27 / 63</td>
<td>28.6</td>
<td></td>
<td>1.41[0.72,2.77]</td>
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<tr>
<td>Jones, 1994 (P)</td>
<td>7 / 26</td>
<td>2 / 19</td>
<td>3.4</td>
<td></td>
<td>3.13[0.57,17.18]</td>
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<tr>
<td>Lechat, 1988 (P)</td>
<td>24 / 60</td>
<td>10 / 100</td>
<td>9.1</td>
<td></td>
<td>6.00[2.61,13.80]</td>
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<tr>
<td>Webster, 1988 (P)</td>
<td>20 / 40</td>
<td>6 / 40</td>
<td>6.0</td>
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<td>5.67[1.95,16.46]</td>
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<tr>
<td>Zahn, 1995 (P)</td>
<td>50 / 120</td>
<td>11 / 55</td>
<td>17.7</td>
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<td>2.86[1.34,6.07]</td>
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<tr>
<td>de Belder, 1992 (P)</td>
<td>5 / 39</td>
<td>1 / 39</td>
<td>1.8</td>
<td></td>
<td>5.59[0.62,50.25]</td>
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<tr>
<td><strong>Total (95%CI)</strong></td>
<td>228 / 566</td>
<td>81 / 456</td>
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<td>100.0</td>
<td>3.10[2.29,4.21]</td>
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</table>

Chi-square 9.40 (df=8) P: 0.31

#### Table B

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke n/N</th>
<th>Control n/N</th>
<th>OR (95%CI Random)</th>
<th>Weight %</th>
<th>OR (95%CI Random)</th>
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<tr>
<td>Jones, 1994 (P)</td>
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<td>29 / 183</td>
<td>45.4</td>
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<td>0.90[0.51,1.57]</td>
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<td>Zahn, 1995 (P)</td>
<td>15 / 68</td>
<td>4 / 26</td>
<td>28.4</td>
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<td>1.56[0.46,5.22]</td>
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<tr>
<td>de Belder, 1992 (P)</td>
<td>13 / 64</td>
<td>3 / 58</td>
<td>26.2</td>
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<td>4.50[1.21,16.74]</td>
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<tr>
<td><strong>Total (95%CI)</strong></td>
<td>56 / 326</td>
<td>36 / 265</td>
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<td>100.0</td>
<td>1.60[0.63,4.06]</td>
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</table>

Chi-square 5.15 (df=2) P: 0.08
Methanalysis (Overell et al, Neurology 2000;55:1172-1179)

### Table A

<table>
<thead>
<tr>
<th>Study</th>
<th>Cryptogenic n/N</th>
<th>Known cause n/N</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
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<tr>
<td>Cabanes, 1993 (P)</td>
<td>36 / 64</td>
<td>7 / 36</td>
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<td>Di Tullio, 1992 (P)</td>
<td>10 / 21</td>
<td>1 / 24</td>
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<td>Jeannraud 1990 (P)</td>
<td>8 / 11</td>
<td>0 / 5</td>
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<td>Job, 1994 (P)</td>
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<td>11 / 33</td>
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<td>Jones, 1994 (P)</td>
<td>4 / 14</td>
<td>3 / 12</td>
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<td>Lechat, 1988 (P)</td>
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<td>4 / 19</td>
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<td>Ranoux, 1993 (P)</td>
<td>31 / 54</td>
<td>1 / 14</td>
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<td>Webster, 1988 (P)</td>
<td>19 / 34</td>
<td>1 / 6</td>
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<td>Yeung, 1996 (P)</td>
<td>16 / 27</td>
<td>0 / 15</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>171 / 307</strong></td>
<td><strong>28 / 164</strong></td>
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<tr>
<td>Chi-square 9.70 (df=8) P: 0.29</td>
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### Table B

<table>
<thead>
<tr>
<th>Study</th>
<th>Cryptogenic n/N</th>
<th>Known cause n/N</th>
<th>OR (95% CI Random)</th>
<th>Weight %</th>
<th>OR (95% CI Random)</th>
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<tbody>
<tr>
<td>Di Tullio, 1992 (P)</td>
<td>9 / 24</td>
<td>6 / 77</td>
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<tr>
<td>Jones, 1994 (P)</td>
<td>10 / 57</td>
<td>18 / 137</td>
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<tr>
<td>Yeung, 1996 (P)</td>
<td>27 / 89</td>
<td>17 / 79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>46 / 170</strong></td>
<td><strong>41 / 293</strong></td>
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</tr>
<tr>
<td>Chi-square 5.56 (df=2) P: 0.06</td>
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</tr>
</tbody>
</table>

A: Negative association to Positive association
B: Negative association to Positive association
Which variables for stratification of risk?

- Atrial Septal Aneurysm (ASA)
- Magnitude of shunt
PFO -ASA
(Meissner et al., JACC 2006)

• 585 subjects (population-based)
• Prevalence:
  – PFO: 24.3%
  – ASA: 1.9%
• Risk of having stroke (HR)
  – PFO: 1.46 (0.74 - 2.88) p=0.28
  – ASA: 3.72 (0.88 - 15.71) p=0.074
Functional characteristics of PFO and risk of stroke

• 101 patients
• Symptomatic PFO vs. asymptomatic
• Symptomatic PFO:
  – More frequent shunt at rest
  – Higher septal mobility (>6.5 mm)
• Risk at 3 years:
  – 4.3% for low-risk group
  – 12.3% for high-risk group

(De Castro et al., ’00)
ASA, PFO, stroke risk

- 100 pat. (<55 years): strong association with stroke if PFO + ASA (O.R. 33.3 – 95% C.I. 4.1-270)
  
  (Cabanes et al., ’93)

- 581 pat.: recurrence risk at 4 years
  - FOP: 5.6%
  - FOP + ASA: 19.2%

  (Mas et al., 2001)
Magnitude of shunt and stroke risk

- Large PFO (cTEE >5 mm) have higher risk (45% vs. 23%  p=.02)
  (Steiner et al., '98)

- Large shunt ampio (“shower” or “curtain” pattern on cTCD) associated to higher risk
  (O.R. 3.5; C.I.: 1.29-9.87)
  (Serena et al., ‘98)
Why is PFO an independent cause of stroke?

- Paradoxical embolism
- “In situ” thrombus formation
- Arrithmya (“atrial vulnerability”)
- Comorbidities:
  - Coagulopathies
  - Migraine
  - Pneumopathies and OSAS
Embolic lesions due to patent foramen ovale in young subjects are frequently distributed in vertebrobasilar circulation
(Del Sette et al., submitted)

<table>
<thead>
<tr>
<th>Vascular territory of lesions</th>
<th>Patients with PFO-related stroke (n=40)</th>
<th>Patients with PFO-unrelated stroke (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Circulation Only</td>
<td>26 (65.00 %)</td>
<td>51 (75.00 %)</td>
</tr>
<tr>
<td>Anterior and Posterior Circulation</td>
<td>0 (0.00 %)</td>
<td>6 (8.82 %)</td>
</tr>
<tr>
<td>Posterior Circulation Only</td>
<td>14 (35.00 %)</td>
<td>11 (16.18 %)</td>
</tr>
</tbody>
</table>
Pneumopathies and PFO

- Platypnea-orthodeoxia syndrome (POS): desaturation in ortostatic position due to PFO (Legras et al., ’99; Kubler et al., ‘00)

- COPD: PFO in 70%. In half of them desaturation during Valsalva (Soliman et al., ‘99)
OSAS and PFO

- PFO in 33/48 OSAS (69%) vs. 4/24 (17%) (p<0.0001)
  (Shanoudy et al., ‘98)

- SHUNT: 21/78 OSAS (27%) vs. 13/89 controlli (15%) (p<0.05)
  (Beelke et al., ‘02)
SHUNT during apnoea

- 10 subjects OSAS + FOP:
  - 9/10: shunt during apnoea, if duration > 17 seconds

(Beelke et al., '02)
Magnitude of shunt in apnoea is proportional to Valsalva

- Number of Mb apnoea-Valsalva significantly correlated (p<0.0001)

(Beelke et al., '02)
OSAS

Hypertension

Increased cardiac output

High fibinogen; increased PTL aggregation

Cardiac arrhythmia

Hyperviscosity

I.C.P. ↓ C.B.F.

Endoteliel damage

Patent Foramen Ovale

Yaggi and Mohsenin, Lancet Neurology '04
Case report

- 2 subjects with stroke on awakening
- Both had OSAS + PFO
Treatment

- Medical

(second event within 1 year despite medical treatment: 4.22%, 95% CI 3.43-5.01)

- Transcatheter closure

(event rate after closure at 1 year: 1.62%, 95% CI 1.13-2.24)
<table>
<thead>
<tr>
<th>Type of study</th>
<th>Cohort</th>
<th>Case-control</th>
<th>Cohort</th>
<th>RCT</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>36 (10-91)</td>
<td>31 (4-58)</td>
<td>37.8 ± 9.7</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>N</td>
<td>340</td>
<td>160</td>
<td>581</td>
<td>265</td>
<td>630</td>
</tr>
<tr>
<td>Annual risk (no pfo)</td>
<td>-</td>
<td>4.5</td>
<td>1.8</td>
<td>6.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Annual risk (pfo)</td>
<td>3.1</td>
<td>3.7</td>
<td>1.5</td>
<td>7.2</td>
<td>7.4</td>
</tr>
</tbody>
</table>
5 retrospective studies (1966 to 1999)

- Warfarin better than ASA (OR 0.37; 95% CI, 0.23 - 0.60).

- Similar efficacy warfarin-surgery (OR 1.19; 95% CI, 0.62 - 2.27).

(METHANALYSIS (Orgera et al., South Med J 2001;94:699-703))
• 216 patients (18 – 55 anni)
• Cryptogenic stroke + PFO
• vs. 304 no PFO
• All treated with ASA 300 mg

• FOP (only): risk at 2 years (2.3% PFO[+] vs 4.2% PFO[-]).
• FOP + ASA: (15.2%; OR 4.17; 1.47 - 11.84)
PICSS

- Substudy of Warfarin Aspirin Recurrent Stroke Study (WARSS)
- 630 non-young stroke (age 30-85, mean 59): cryptogenic (42%) or lacunar (39%) stroke.
- Randomized
- ASA (325 mg) vs. warfarin (INR 1.7 to 2.2).
- No difference
- Large PFO: low recurrence (9.5% vs. 18.5%)
- PFO + ASA: not increased risk

PICSS Two-Year Stroke or Death Rate*

• 308 subjects
  – 158: antiplatelets
  – 150: closure

• Follow-up (4 years):
• Global trend to less deaths, stroke and TIA (8.5% vs. 24.3%; p=n.s.)
• Significant difference:
  – Multiple events (7.3% vs. 33.2%; p=0.01)
  – Complete closure (6.5% vs. 22.%; p=0.04)

Windecker et al., Journal of the American College of Cardiology 2004 Aug;44:750-758
Windecker et al., JACC 2004;44:750-758
Closure: synthesis

• Success rate: 86% - 100%
• Recurrent stroke: 0% - 3.8%
• Complications:
  – Major: < 1.5%
  – Minor: 7.9%
• Closure complete at 6 months in 95% of patients
• No sufficient comparison between devices to indicate preference

(Wilson et al, Circulation 2007)
Closure of patent foramen ovale in cryptogenic stroke. Ready or not, here come the trials

ONGOING TRIALS

- PC trial (Amplatzer)
- Respect PFO Trial (Amplatzer - AGA Medical, Golden Valley, Minnesota)
- Closure I Trial (CardioSeal - NMT Medical, Boston, Massachusetts)
- CARDIA (PFO- STAR)
AHA/American Stroke Association guidelines

• First choice: antiplatelets

• Warfarin: only in presence of DVT or hypercoagulability

• Closure: after second event or high-risk

New percutaneous options

• Radio-frequency
  – Complete closure in 43% after 6 months (Sievert et al, Circulation 2007)
• HeartStich PFO I (automatic suture)
• BioTREK (bioabsorbable)
Conclusions - I

• Diagnosis of PFO possible with cTCD

• PFO is risk factor when:
  – Stroke is cryptogenic (and juvenile)
  – Large (>2 mm)
  – With large shunt (>25 Mb)
  – Associated to Atrial Septal Aneurysm
Conclusions - II

• Subgroup with high prevalence:
  – Migraine
  – OSAS

• There is still uncertainty for PFO closure