Diagnosis and Management of PFO
Sarah A. Johnson, M.D.

What is a Patent Foramen Ovale (PFO)?
• A patent foramen ovale (PFO) is a persistent, usually flap-like opening between the atrial septum primum and secundum at the location of the fossa ovalis.
• In utero, the foramen ovale serves as a physiologic conduit for right-to-left shunting.
• After birth, with the establishment of pulmonary circulation, the increased left atrial blood flow and pressure results in functional closure of the foramen ovale.
• A PFO is fairly common—it is found in approximately 1 in 5 people, or 20% of the population.
Cryptogenic Stroke

- 600,000 ischemic strokes per year in the United States
- Up to 40% of all strokes are presumed cryptogenic
- Prevalence of PFO -50% to 60% in patients with cryptogenic stroke
- 30,000 -100,000 strokes per year attributable to PFO

PFO

ASYMPTOMATIC

SYMPTOMATIC CRYPTOGENIC

MIGRAINE

PFO

DIAGNOSIS

ASYMPTOMATIC   TTE + BUBBLE

SYMPTOMATIC   TEE + MRI

? CTA/MRI
PFO

SMALL

MEDIUM – LARGE

PFO + ATRIAL SEPTAL ANEURYSM

Assessment of Shunting

Resting State

- Grading: Number of microbubbles in left atrium within 3 beats
  - Grade 1: 1-9
  - Grade 2: 10-20
  - Grade 3: >20

Assessment of Shunting

Valsalva

- Grading: Number of microbubbles in left atrium within 3 beats
  - Grade 1: 1-9
  - Grade 2: 10-20
  - Grade 3: >20
Stroke

- Do PFO's and Atrial Septal Aneurysm's (ASA) increase the risk of stroke?
- What clinical factors increase this risk?

Atrial Septal Aneurysm

Data not core lab adjudicated

<table>
<thead>
<tr>
<th>ASA Frequency in All Patients</th>
<th>ASA Size % of All ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Septal Aneurysm: 34.6%</td>
<td>&lt;10mm: 24%</td>
</tr>
<tr>
<td>No Atrial Septal Aneurysm: 65.2%</td>
<td>10-15mm: 26%</td>
</tr>
<tr>
<td>ASA Excursion Direction</td>
<td>&gt;15mm: 50%</td>
</tr>
<tr>
<td>RA 8%</td>
<td>RA 8%</td>
</tr>
<tr>
<td>LA 32%</td>
<td>LA 32%</td>
</tr>
<tr>
<td>Both 60%</td>
<td>Both 60%</td>
</tr>
</tbody>
</table>

Atrial Septal Aneurysm

[Diagram of atrial septum with RA and LA indicated]
Baseline Characteristics of Patients with Cryptogenic Stroke or with Stroke of Known Cause

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cryptogenic Stroke (n=25)</th>
<th>Stroke of Known Cause (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65 (35-79)</td>
<td>64 (31-88)</td>
<td>0.98</td>
</tr>
<tr>
<td>Female sex—no. (%)</td>
<td>9 (36.0)</td>
<td>9 (37.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Previous stroke—no. (%)</td>
<td>11 (44.0)</td>
<td>13 (54.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>History of smoking—no. (%)</td>
<td>13 (52.0)</td>
<td>9 (37.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension—no. (%)</td>
<td>15 (60.0)</td>
<td>15 (62.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diabetes—no. (%)</td>
<td>4 (16.0)</td>
<td>4 (16.7)</td>
<td>0.93</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>32 (23-40)</td>
<td>30 (20-40)</td>
<td>0.10</td>
</tr>
<tr>
<td>Left ventricular systolic sys.</td>
<td>84 (79-92)</td>
<td>85 (73-97)</td>
<td>0.65</td>
</tr>
<tr>
<td>Echocardiography—no. (%)</td>
<td>17 (68.0)</td>
<td>20 (83.3)</td>
<td>0.16</td>
</tr>
</tbody>
</table>


Bubble Study
Sizing a PFO

- Amount of ‘bubbles’ crossing the septum
- Measurement of opening

SEPTAL LENGTH
**Device Selection**

<table>
<thead>
<tr>
<th>Shortest Defect to Aortic Root or Defect to Superior Vena Cava Orifice Distance (mm)</th>
<th>Suggested AMPLATZER PFO Occluder Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 - 12.4</td>
<td>18</td>
</tr>
<tr>
<td>12.5 - 17.4</td>
<td>25</td>
</tr>
<tr>
<td>&gt; 17.5</td>
<td>30</td>
</tr>
</tbody>
</table>

**Hematological**

RESPECT Trial coagulation parameters:

* Antithrombin activity assay
* Prothrombin G20210A mutation
* Factor V Leiden mutation and/or activated protein C resistance
* Fasting plasma homocysteine
* Lupus anticoagulant
* Anticardiolipin Ab of the IgG and IgM subtypes
* Anti-β2-glycoprotein I antibodies
* Factor VIII activity assay
* Protein C activity assay
* Free Protein S antigen assay

**PFO MEDICAL TREATMENT**

**ASYMPTOMATIC**

- **SMALL**
  - ASA
- **LARGE**
  - ASA
- **ATRIAL SEPTAL ANEURYSM**
  - ASA + PLAVIX

**SYMPTOMATIC**

- **SMALL**
  - ASA + PLAVIX + ? COUMADIN
- **LARGE**
  - ASA + COUMADIN
- **MIGRAINE**
  - ASA + PLAVIX
PFO
TREATMENT WITH CLOSURE DEVICE

PFO ACCESS REGISTRY
2 CRYPTOGENIC STROKE ON ASA, PLAVIX, COUMADIN

CLOSURE WITH APPROVED ASD DEVICE

MIGRAINE – PREMIUM STUDY

PFO Closure for Strokes?
- No consensus
- No occluder device approved in US
- Two currently ongoing clinical trials
  - CLOSURE I
  - RESPECT

What are the next steps....
- Stroke Randomized trial status-
  Closure one –COMPLETED
  RESPECT-nearing completion

MIGRAINE
  lots need to be sorted out
Current Clinical Trials - problems

- Randomized clinical studies:
  - Medical vs. PFO-closure
- Subjects present with treatment preference:
  - Randomized Controlled Studies
  - Unwilling to participate
- Patients / physicians willing to just close the PFO
  - outside clinical studies
  - devices readily available for off-label closure

Clinical Trial Design

- The RESPECT PFO Clinical Trial is a randomized evaluation comparing PFO device closure versus medical therapy.
  - Maximum 900 patients (450 per arm)
    - Recent cryptogenic stroke (270 days)
    - 18-60 years of age
  - Maximum 75 participating institutions across the U.S. and Canada (60 approved sites)

Gore REDUCE Study Design

- Advantages
  - 2:1 randomization scheme - allows two device arm subjects for every control arm subject
  - MR imaging of every subject prior to enrollment and at an endpoint event or two years post-randomization
  - Standardized antiplatelet medical therapy across treatment arms
  - Multinational study including sites in the US and the Nordic countries
  - Utilization of the GORE HELEX Septal Occluder
## Stroke Prevention: Medical Therapy vs. Transcatheter PFO Closure

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Medical Therapy</th>
<th>PFO Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-Analysis</td>
<td>3.8-12/year</td>
<td>0-4.9/year</td>
</tr>
<tr>
<td>Retrospective</td>
<td>24.3/4-year</td>
<td>8.5/4-year (p=0.05)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>13/1-year ASA</td>
<td>0.6/year (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>5.6/year warfarin</td>
<td></td>
</tr>
</tbody>
</table>

### Amplatzer Occluder: Complications

*Khositseth, Mayo 2004*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Type of complication</th>
<th>ADO</th>
<th>APO</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus Malformation</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Confirmative to patient</td>
</tr>
<tr>
<td>Brain infarction</td>
<td>1</td>
<td></td>
<td></td>
<td>Tentative to patient</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td></td>
<td></td>
<td>Death: families' decision</td>
</tr>
<tr>
<td>Penetrating complication</td>
<td>1</td>
<td></td>
<td></td>
<td>Device retrieval</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ADO = Amplatzer PFO Amplatzer occluder, APO = Amplatzer occluder model*

### Amplatzer Occluder: Residual Shunt

*Khositseth, Mayo 2004*
PFO Closure Devices

- Umbrella devices
- Suture based techniques
- Non device closure
- Bioresorbable devices
- In-tunnel devices

Amplatzer

Nitinol wire frame mesh
Dacron patches inside
Two discs, short connecting waist
The left atrial disc is smaller (exception: 18mm device)

Not FDA approved

CardioSEAL and CardioSEAL-STARflex

Two rectangular discs
each consisting of four wire spring arms
Covered with a polyester patch
Microspring system (CardioSEAL-STARflex)
Helex
- One single Nitinol wire formed into a spiral
- Two discs
- ePTFE
- Monorail delivery catheter

Occlutech PFO Occluder

AtriaSept PFO
- PFO-Star 6th Generation
- Two discs (Ivalon)
- Stranded wires to prevent fractures
- Right side is retrievable and repositionable
- Articulated connection to achieve better adaption to the septum
- 20-35 mm

Not FDA approved
**Premere PFO Closure Device**

- Fabric only on the right side
- A flexible tether holds the two anchors together
- Variable distance between the anchors

**BioSTAR (NMT)**

- CardioSEAL® framework
- STARFlex® self-centering mechanism
- Biodegradable collagen matrix, heparin coating
- Only the metallic framework remains

**The Sutura SuperStitch® EL**

- Based on a puncture site closure technique
- Profile: 12 Fr
- Working length: 90 cm
- Suture type: Polypropylene 4-0

In clinical trials
PFO Closure by Radiofrequency

Clinical trial 2010

Not FDA approved

Coherex EF

Designed to "Stent" the PFO tunnel
Nitinol and Polyurethan

Recent Non-Randomized Studies of PFO Closure in Migraine

<table>
<thead>
<tr>
<th>Patients</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisman et al. JACC 2005;45:493-5</td>
<td>50, ± aura</td>
<td>37±23 weeks</td>
</tr>
<tr>
<td>Ázarbal et al. JACC 2005;45:489-92</td>
<td>30, ± aura</td>
<td>3 months</td>
</tr>
<tr>
<td>Giardini et al. Am Heart J 2006; 151:922-6</td>
<td>35, all ± aura</td>
<td>1.7±1.3 yr</td>
</tr>
</tbody>
</table>
MIST – BOTH PRIMARY AND SECONDARY ENDPOINTS WERE NEGATIVE

And two major US Migraine trials were terminated MIST II and ESCAPE...

Some facts

- Migraine affects roughly 17% of the population
- Migraine is associated with stroke
- Migraine is now considered a progressive neurological disorder
- Migraine patients have both white and gray matter changes ((cognitive, exec. Function, no longer just “motor track neurology”)
- Migraine is not just a headache it is a functional disorder
- Migraine medications treat symptoms not pathology, especially in the episodic type.
- There is no “pathologic disease signature” or biomarker,

Some facts II

- 4% of migraines *transform from episodic to chronic headache.
- There are genetic factors, predominantly in the rare types NOT the common sporadic types
- Migraines have thrombophilia and platelet dysfunction
- Aura appears to be a major component of the PFO headache
- Migraine – “PFO” – stroke complex….. predicting the patient to most benefit from closure
- The Placebo conundrum, nocebo conundrum.
The optimal therapy for prevention of recurrent stroke or transient ischemic attack in patients with cryptogenic stroke and patent foramen ovale has not been defined. Completion and peer review of ongoing trials are critical steps to establish an evidence base from which clinicians can make informed decisions regarding the best therapy for individual patients.

Circulation. 2009.