The ABCs of PFOs and ASDs

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Disclosure

- Consultant, Proctor AGA / St. Jude Medical
Hippocrates

- Described “stroke”
  - “Sudden onset of paralysis”
  - Apoplexy
  - Cause - “black bile”

The PFO / Stroke Story

>2,400 yrs-ago
The PFO / Stroke Story

Leonardo da Vinci

Heart Drawings

“I have found a perforating channel from the left auricle to right auricle.”

Windsor Folios, part of the Royal Collection, held at Windsor
The PFO / Stroke Story

1877

Julius Friedrich Cohnheim

- German Pathologist
- Protégé of Virchow
- Patent Foramen Ovale

"I recently had a case of a deadly embolus in the \textit{frontal lobe} of a 35-year old woman with \textit{apoplexy}. In the lower extremity a long thrombus was found and ... \textbf{what I found next I never thought of, to put these two together, until I had a close look at the heart.}"

"I found a very large foramen ovale through which I could pass three fingers with ease. Now I could no longer ignore the fact that a torn-off piece of thrombus arising from the lower extremity, while traveling through the heart, passed out of the RA into the LA and to the \textit{frontal lobe}."
Paradoxical Emboli via a PFO
Patent Foramen Ovale

- In utero, the foramen ovale allows blood to flow from the right atrium to the left, bypassing the lung.
- Usually it closes after birth.
- But in 25% of people it stays open.
IV Saline Contrast Study
Thrombus in Transit Caught in Long Tunnel PFO
The PFO / Stroke Story

1975

King and Mills

♥ Ochsner Clinic, New Orleans
♥ ASD transcatheter closure in 17 year old girl
♥ 25mm ASD / 2:1 shunt

We know that a PFO can cause stroke

- We do not know:
  - how frequent is this?
  - why don’t all patients with a PFO eventually get a stroke
  - who needs stroke prevention
What’s the risk of recurrent events?
PFO with and without Atrial septal aneurysm treated with Aspirin: Risk for future events?

• Mas et al. 581 pts with cryptogenic CVA < 55y.o. Pts followed for 4 years and assessed for recurrent STROKE/TIA; all pts were treated with aspirin 300mg qd

• PFO and ASA

• No PFO or ASA

• PFO alone

• ASA alone
Causes of Stroke

750,000 recognized strokes annually in US
The leading cause of disability
Third leading cause of death (200,000/yr)

15% Hemorrhagic

85% Ischemic

15% Hemorrhagic

>95% Lacunar
<5% Large vessel

25% Thrombotic

~30% Arch, Large vessel

75% Embolic

~40% Cryptogenic

~30% Arch, Large vessel

75% Embolic

~40% Cryptogenic

~30% Arch, Large vessel

Atrial fibrillation

Akinetic segment

Cardiomyopathy

Mitral Stenosis

Other

~30% Cardiac Source

~40% Cryptogenic

~30% Cardiac Source
The Final Results with Primary End Point Analyses

RESPECT
CLINICAL TRIAL

RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

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FOR THE RESPECT INVESTIGATORS
AMPLATZER PFO Occluder

- Percutaneous, transcatheter device
- Self-expanding, double-disc design
- Nitinol wire mesh with polyester fabric/thread
- Radiopaque marker bands
- Sizes: 18, 25, 35 mm
- Recapturable and repositionable

*CAUTION: Investigational device in the United States. Limited by Federal (or U.S.) law to investigational use. Not available for sale in the U.S.*
Primary Endpoint Analysis – ITT Cohort
50.8% risk reduction of stroke in favor of device

- 3/9 device group patients did not have a device at time of endpoint stroke

HR: 0.492
Log-rank P-value: 0.0825
(95% Confidence interval = 0.217 - 1.114)
Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device

- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment.

HR: 0.273
Log-rank P-value: 0.0067
(95% Confidence interval = 0.100 - 0.747)
Atrial Septal Aneurysm
Problem: differences in shunts
How real is the association with cryptogenic stroke and PFO?

Are we really swimming in shark infested waters?
There are no FDA-approved devices for PFO but off-label use abounds

- Amplatzer Septal Occluder
  - AGA Medical Corporation
- Gore Helex Septal Occluder
  - W.L. Gore & Associates
Two rectangular discs
each consisting of four wire spring arms
Covered with a polyester patch
Microspring system (CardioSEAL-STARflex)

CardioSEAL and CardioSEAL-STARFlex

23, 28, 33, 40 mm
Occlutech PFO Occluder

Single layer PFO

Double layer PFO

Similar to Amplatzer but no left atrial hub

Not FDA approved
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
Nit-Occlud PFO

- Double umbrella occluder with single-layer left atrial disc
- 3 sizes: 20, 26, 30 mm
- made from a single Nitinol wire
  - Low profile
  - No protruding clamps
- Pre-mounted
- Very flexible delivery system
  - No tension between delivery cable and device before release
Spider™ PFO Occluder

- Self-expandable, double disc device
  - right atrial disc made of ceramic coated Nitinol wire mesh
  - left atrial disc is made of an ePTFE patch and ceramic coated braided Nitinol anchors

- available in sizes 18mm, 25mm, 30mm
Premere PFO Closure Device

- Right Atrial Anchor
- Left Atrial Anchor
- Tether
- Lock
- Delivery System
- Delivery System Release Mechanism

- Fabric only on the right side
- A flexible tether holds the two anchors together
- The tether allows a variable distance between the anchors

Not FDA approved
Variable Distance

Long Tunnel

Short Tunnel
BioSTAR (NMT)

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

Not FDA approved
In-Tunnel Devices

SeptRX
In clinical trials

Coherex FlatStent EF
CE mark

Not FDA approved
Coherex FlatStent EF

Nitinol
Polyurethan
Conditions Associated with PFO (Patent Foramen Ovale)

1. Cryptogenic Stroke < 60yo, or older
2. Migraine Headache with or w/o aura
3. Orthodeoxia Platypnea (O₂ Sat < 92%)
4. Acute MI with normal coronaries
5. Decompression Illness
6. High Altitude Pulmonary Edema
7. Obstructive Sleep Apnea Exacerbation
8. Raynaud’s Phenomena
9. Dementia?

Unifying Hypothesis: some venous particulate clot or platelets, or chemical, bypasses the lung and enters the arterial circulation.
PFO, migraine with aura and cryptogenic stroke

Large atrial shunts (PFO & ASD) are present in:

- 7.3% - population controls
- 38.1% - migraine with aura but no stroke
- 55.6% - stroke but no migraine
- 84% - stroke and migraine with aura

2006
The PFO / Stroke Story

2015

- PFO
- Recurrent Cryptogenic Stroke
- DCI
- Migraine Headache
The PFO / Stroke Story

2005

Tedy Bruschi
- New England Patriot Linebacker
- Stroke
- PFO Device Closure
The PFO / Stroke Story

Bret Michaels, the 47-year-old singer of rock group Poison, undergoes closure of a PFO after a TIA.
PFOs? A Tiger waiting to be released
ATRIAL SEPTAL DEFECT

GENERAL PHYSIOLOGY

- RA and RV volume overload
- Excess volume may result in pulmonary hypertension may develop
  - More often in women
  - Generally not severe
- May result in paradoxical emboli

Brickner et al  *NEJM* 2000
Hemodynamic Consequences of ASD

• Magnitude of and direction of flow depends on
  – Size of the defect
  – Relative diastolic filling properties of the left and right ventricles.
    • Increased left-to-right shunting results from reduced LV compliance (eg, LVH) and mitral stenosis.
    • Reduced left-to-right shunt and/or reversal of shunt (right-to-left shunt) results from reduced RV compliance (eg, pulmonary hypertension or pulmonary stenosis) and tricuspid stenosis

Webb G and Gatzoulis MA. *Circulation* 2006;114;1645-1653
Hemodynamic Consequences of ASD

• Size and Shunt
  – As a rule, an ASD must be at least 10 mm in diameter to carry a significant left-to-right shunt
  • CAVEAT: symptoms may develop with increasing age even with small defects owing to an increase in shunting caused by a decrease in LV compliance secondary to coronary artery disease, acquired valvular disease, or hypertension.
  – A left-to-right atrial shunt is considered significant when the Qp/Qs ratio is greater than 1.5/1.0, or if it causes dilation of the right heart chambers.

• Chronic volume overload of the pulmonary vasculature may result in pulmonary arterial hypertension

Webb G and Gatzoulis MA. Circulation 2006;114;1645-1653
Secundum ASD

- Atrial septal defects
  - Three-dimensional size
  - Assessment of rim
    - Percutaneous closure
  - Assessment of anomalous pulmonary veins
By conventional definition
1. Margin ≥ 5 mm is considered adequate
2. Margin ≤ 3 mm is considered absent

Conventionally, the 5 rims of a secundum ASD are labeled as:

- **Aortic (anterosuperior)**
- **Atrioventricular (AV) valve (mitral or anteroinferior)**
- **Superior venacaval (SVC or posterosuperior)**
- **Inferior venacaval (IVC or posteroinferior)**
- **Posterior (from the posterior free wall of the atria).**
Secundum ASD Rims
Currently available devices within the United States for percutaneous closure of atrial-level defects within randomized controlled trials.

- CardioSEAL™ (NMT Medical; Massachusetts, USA)
- STARFlex™ (NMT Medical; Massachusetts, USA)
- Amplatzer PFO Occluder™ (AGA Medical, Minnesota, USA)
- Helex™ Septal Occluder (W.L. Gore and Associates; Delaware, USA)
- Cardia PFO Occluder (Intracept™) (Cardia; Minnesota, USA)
- Premere PFO Closure™ (St. Jude Medical, Minnesota, USA)

Currently available FDA approved devices in the United States

**AMPLATZER ASO**
Polyester material sewn into 0.004”-0.008” braided nitinol wires

**GORE® HELEX® Septal Occluder**
ePTFE patch material supported by a single nitinol wire frame
Fenestrated Secundum ASD


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Failure to Close a Fenestrated ASD
SECUNDUM ASD VARIANTS:
MULTI-FENESTRATED TYPES

...they are not all the same!
Fenestrated ASD (multiple holes)

Courtesy Y. Joe Woo, MD
HUP Cardiac Surgery
## ACC/AHA Guidelines

### Class 2.5.2. Recommendations for Interventional and Surgical Therapy

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>I 1. Closure of an ASD either percutaneously or surgically is indicated for right atrial and RV enlargement with or without symptoms.</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. A sinus venosus, coronary sinus, or primum ASD should be repaired surgically rather than by percutaneous closure.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>3. Surgeons with training and expertise in CHD should perform operations for various ASD closures.</td>
<td>C</td>
</tr>
<tr>
<td>IIa</td>
<td>1. Surgical closure of secundum ASD is reasonable when concomitant surgical repair/replacement of a tricuspid valve is considered or when the anatomy of the defect precludes the use of a percutaneous device.</td>
<td>C</td>
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<tr>
<td></td>
<td>2. Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of:</td>
<td>C</td>
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<tr>
<td></td>
<td>a. Paradoxical embolism.</td>
<td>B</td>
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<td></td>
<td>b. Documented orthodeoxia-platypnea.</td>
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<tr>
<td>IIb</td>
<td>1. Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, PVR less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (patients should be treated in conjunction with providers who have expertise in the management of pulmonary hypertensive syndromes).</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>2. Concomitant Maze procedure may be considered for intermittent or chronic atrial tachyarrhythmias in adults with ASDs.</td>
<td>C</td>
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<tr>
<td>III</td>
<td>Patients with severe irreversible PAH and no evidence of a left-to-right shunt should not undergo ASD closure.</td>
<td>B</td>
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Summary

- PFOs have been conduits for trouble as recognized for centuries.
- The most recent trials regarding cryptogenic stroke suggest the high risk groups (ASA/ large PFO) benefit from closure.
- The CVA type reduced by the device is the type seen from embolic events.
- Certain indications exist for closure already - DCI, MI/peripheral embolizations.
- Certain anatomies can be closed up front (fenestrated septum or small ASDs) or have been reclassified to allow closure (acquired ASD).
- Migraines with aura are still in play – if the patient has a history of a TIA/CVA
- Does a trial really need to show superiority or isn’t getting off coumadin with equivalent results good enough for the patient?
What a Stroke Looks (and Sounds) Like