Cardiogenic Stroke

How might these cardiac defects be affecting your patients and what can be done?

14th Annual CV and Medicine Symposium

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Disclosures

• none
Case #1

- 50 year old medical school professor
- No Past Medical History or vascular risk factors
- Event:
  During 7 hour air travel, reads book, does not get up. After flight, enters terminal walking to customs. Has vigorous sneezing. Within minutes becomes confused and staggers to floor, but recovers in minutes. Hospitalized.
Case #1

• Work-up:
  • normal CTA head and neck
  • routine ECHO
  • Carotid duplex
  • CBC, coagulation labs
  • Lower extremity dopplers
  • 12 Lead EKG / telemetry
Case#1

MRI: acute right MCA territory infarcts
Cardiogenic Causes of Stroke

- Classification of CVA
- Sources of Cardiogenic Emboli
- Diagnosis / Treatment
Cardiogenic Causes of Stroke

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CAUSES OF STROKE
Understanding the many different causes of stroke

USA STROKE
1 million strokes per year
30% are recurrent
Mortality 10%
Disability 25-50%
Institution 20%

ESTIMATED 4-10 MILLION SILENT STROKES

15% HEMORRHAGIC
85% ISCHEMIC

25% THROMBOTIC
75% EMBOLIC

SOURCE: NINDS DATABASE
AAN GUIDELINES 2006
Types of Stroke

85% Ischemic

15% hemorrhagic
Classification & Etiology of Strokes

Ischemic 85%
- Thrombotic
- Embolic
- Cryptogenic (30-40%)

Hemorrhagic 15%
- Subarachnoid
- Parenchymal
Stroke Mimics

- Hypoglycemia
- Hyperglycemia
- Seizure
- Subdural Hematoma
- Medications / Drugs
- Altered Hemodynamics
Cardiogenic Causes of Stroke

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Cardiogenic Causes of Stroke

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Many Causes of Stroke

- Intracranial Atherosclerosis
- Penetrating Artery Disease
- Carotid Plaque with Arteriogenic Emboli
- Flow Reducing Carotid Stenosis
- Aortic Arch Plaque
- Atrial Fibrillation
- Valve Disease
- Cardiogenic Emboli
- Left Ventricular Thrombi
Sources of Cardiogenic Emboli

**Mitral Valve**
- Infective endocarditis
- Non-bacterial endocarditis
- Myxomatous valvulopathy
- Prosthetic valves
- Vegetations due to prothrombotic states

**Left Atrium**
- Atrial fibrillation
- Myxoma
- Atrial septal aneurysm

**Paradoxical Emboli**
- Patent foramen ovale
- Atrial septal defect

**Aortic Valve**
- Calcific stenosis
- Infective endocarditis
- Prosthetic valve

**Left Ventricle**
- Ischemic dyskinesis
- Cardiomyopathy
- Thrombi due to prothrombotic states
Cardiogenic Causes of Stroke

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Cardiogenic Causes of Stroke

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Physical findings

• Findings suggestive of cardiogenic embolism include the following:
  – Evidence of cardiac atrial dysrhythmias (eg, atrial fibrillation, *sinus node dysfunction*)
  – Presence of cardiac murmurs (eg, *mitral stenosis*, calcific aortic stenosis)
  – Signs of congestive *heart failure* (eg, after acute myocardial infarction, nonischemic cardiomyopathies)
  – Concomitant diseases (eg, *systemic lupus erythematosus* and *Libman-Sacks endocarditis*, neoplasia, non-bacterial endocarditis)
  – Evidence of embolic phenomenon
Atrial Fibrillation
LA and Appendage Thrombus
Atrial Fibrillation Management

• Treatment
  – Anti-coagulation Strategies
  – Rhythm vs. rate control
  – Medicines vs Ablation Strategies

ESC Guidelines

European Society of Cardiology (ESC) 2012 Atrial Fibrillation Guidelines recommend that interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation as a Class IIb recommendation with a level of Evidence B.
Left Ventricular CM
Treatment of LV Thrombus

• Coumadin for at least three months with goal INR=2-3
Aortic Arch Atheromas

- Aortic Atheromas > 4 mm in diameter
  - Plan: addition of Coumadin Tx
Cardiac Tumors

Atrial Myxoma

LA myxoma - MRI
Echo – Myxoma
Angiosarcoma “Tumor Blush”
Background on Cardiac Tumors

• **75%** of all primary cardiac tumors – **BENIGN**
  
  • **Myxoma** – most common

• **25%** of all primary cardiac tumors – **MALIGNANT**
  
  • **Angiosarcoma** – most common
Papillary Fibroelastomas

- **Background:**
  - Most common tumors of cardiac valves
  - Usually affect already damaged valves
  - CMV has been recovered in these tumors
  - Benign papilloma of endocardium
  - Average age at dx – 60 y.o.
  - Men & women affected equally
  - >90% are single
  - **Aortic & Mitral valves** – most commonly
  - Located on arterial side of semi-lunar valves & atrial surface of atrioventricular valves
Papillary Fibroelastoma
Papillary Fibroelastomas

- **Clinical Manifestations:**
  - Potential to embolize
  - Mimic infective endocarditis
  - Valvular dysfunction – uncommon
  - TTE – 62% sensitivity
  - TEE – 77% sensitivity
  - Shimmer or vibration seen at tumor-blood interface
  - Too small to be seen well on CT or MRI
Papillary Fibroelastomas

- **Pathology:**
  - Frond-like appearance – like *sea anemone*
  - Covered by endothelium that covers avascular core of loose connective tissue rich in glycosaminoglycans, collagen, elastin
  - Not usually found at valvular contact areas [unlike Lambl’s excrescences]
Pathology
Papillary Fibroelastomas

• **Treatment:**
  • Complete resection of tumor – especially if left-sided
  • 6-25% risk of embolic event over 3 years
  • Risk of emboli *not* lowered with anti-coagulation
  • >90% of tumors can be resected utilizing conservative, valve-sparing approach
  • Recurrences have *not* been reported
Valvular Disease - Stenotic
Aortic Stenosis
Prosthetic Heart Valves
Mechanical Valve Thrombosis
Summary – Management of Thrombosis

Large Thrombus > 0.8cm²
Most Class III-IV

Class III-IV
High Surgical Risk
Contraindication for Surgery

Class I-II
& Failed IV UFH

TEE

Size > 0.8 cm²
Surgery

Size < 0.8 cm²
Thrombolysis
Valvular Disease – Anticoagulation / Antiplatelet Pearls

• What is the goal INR for a mechanical Mitral and Aortic Valve?
  – MV=2.5-3.5, AV=2-3

• Do tissue valves require anticoagulation?
  – First 1-3 months following implantation

• Do tissue valves require any longer term antiplatelet therapy?
  – Yes, at least ASA 81mg po qday
Valvular Disease - Endocarditis
Valvular Disease - Infective Endocarditis
Valvular Disease – Non-infective Endocarditis
Mycotic Aneurysm
Roth Spots
Endocarditis

• **Treatment**
  – IV antibiotics for at least 4-6 weeks
  – Follow-up TEE following Antibiotics

• **Are there urgent / emergent surgical indications for endocarditis?**
  – Persistent embolization and/or failure to clear bacteremia
  – Heart failure
  – AV block = abscess
Case #1

- Work-up: normal CTA head and neck, routine ECHO, coagulation labs, extremity dopplers
- ECHO with **bubbles** reveals large PFO with shunting at valsalva
- **Diagnosis**: presumed extremity/pelvic vein clot related to stasis (prolonged sit during air travel) with paradoxical embolus after mobilizing clot (walking) and powerful valsalva (sneeze)
Case #1

• He gets referred for an opinion regarding Percutaneous PFO Closure.

• Did my PFO cause stroke? And if it did why don’t you close it?

• Do I have to survive another stroke before I qualify for PFO closure?

• Do I have to be randomized into a clinical trial with either medical therapy or PFO closure?
700,000 strokes/yr in US
80-85% ischemic
30-40% of strokes remain defined as cryptogenic

40-60% frequency of PFO among cryptogenic strokes
itures ~100,000 strokes/yr with PFO as only identified potential etiology

Implicating the PFO in Cryptogenic Stroke

Prevalence of PFO in “Normal” Population: 10-25%
  Lechat, et al - NEJM 5/88
  Webster, et al - Lancet 1988
  Mayo Autopsy Study

Prevalence in Stroke Population <60 y.o.: 40-50%
  Ranous, Mas, et al - STROKE 1/93
  Webster, et al - Lancet 1988
  Lausanne Study - Neurology 5/96
  Lechat, et al - NEJM 5/88
INTRA-CARDIAC RIGHT-TO-LEFT SHUNTING

The mechanism of paradoxical embolism

In healthy adults, right to left shunt is unique to ASD. PFO

ASD (Secundum)

Aorta (Ao)

Pulmonary Artery (PA)

Left Atrium (LA)

Right Atrium (RA)

Right Ventricle (RV)

Left Ventricle (LV)

Right atrium

Septum

Increased pressure

Left atrium
Mechanism of Stroke

PRA > PLA

- Early systole
- Valsalva
- Coughing
- Pulmonary hypertension
- COPD
- Pregnancy
- Asthmatics
- Wind instruments
- Decompression sickness (diving)
- High altitude flying
- Obstructive sleep patterns
Diagnosis of PFO

- TEE
- Transcranial Doppler
- TTE

- All can detect associated right to left shunt, usually after injection of contrast such as agitated saline, augmented by cough or valsalva maneuver.

- Highly recommended to do TEE
Caught in Transit!
Role of PFO in Clinical Disease

- Cardio-embolic stroke
- Cryptogenic stroke
- Platypnea-orthodeoxia
- Decompression illness
- High altitude space-walking
- Brain abscess
- Migraine with aura
Treatment Options Include

1. Medical therapy with anti-platelet alone
2. Medical therapy with coumadin alone
3. Medical therapy with both aspirin and coumadin
4. Percutaneous PFO closure
5. Surgical PFO closure
• There is insufficient evidence of superiority of aspirin or warfarin
• Risks of minor bleeding appear greater with warfarin
• There is insufficient evidence to evaluate efficacy of surgical or endovascular closure
• Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO.
Systematic review: stroke and TIA following transcatheter PFO closure compared to medically treated patients.

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<th>Effect name</th>
<th>Event</th>
<th>Event-free</th>
<th>Effect</th>
<th>Lower</th>
<th>Upper</th>
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<td>5/1107</td>
<td>28/895</td>
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<td>Annualised rate of TIA</td>
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<td>23/895</td>
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<td>1.058</td>
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<td>Annualised rate of stroke or TIA</td>
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Landzberg M J , Khairy P Heart 2004;90:219-224
Available Percutaneous Devices

- CardioSEAL STARFlex
- CardioSEAL
- Amplatzer PFO Occluder
- Helex Occluder
- Intratect
- Guardian Angel
- Sideris Buttoned Device
Device Description

• Self Expandable
• Nitinol wire .005”-.006”
• Polyester Patch
• Short connecting waist
• Sizes 18 mm, 25 mm, 35 mm
CLOSURE I

Trial design: Patients with cryptogenic stroke/TIA presumably due to a PFO were randomized to PFO closure with the STARFlex device (n = 447) vs. medical therapy (n = 462).

Results

- Recurrent stroke/TIA by 2 years, all-cause death by 30 days, or neurological death between 31 days and 2 years: 5.9% with PFO closure vs. 7.7% with medical therapy (p = 0.30)
- Strokes (n): 12 vs. 13 (p = 0.77)
- TIAs (n): 13 vs. 17 (p = 0.39)
- Atrial fibrillation: 5.7% vs. 0.7% (p < 0.001)

Conclusions

- Among patients with cryptogenic stroke/TIA, percutaneous PFO closure with the STARFlex device did not reduce the incidence of the primary outcome at 2 years, nor did it reduce the number of strokes or TIAs
- Atrial fibrillation was higher in the device group

Presented by Dr. Anthony Furlan at AHA 2010
• CLOSURE I is the first completed, prospective, randomized, independently adjudicated PFO device closure study

• Superiority of PFO closure with STARFlex® plus medical therapy over medical therapy alone was not demonstrated
  – no significant benefit related to degree of initial shunt
  – no significant benefit with atrial septal aneurysm
  – insignificant trend (1.8%) favoring device driven by TIA
  – 2 year stroke rate essentially identical in both arms (3%)

• Major vascular (procedural) complications in 3% of device arm

• Significantly higher rate of atrial fibrillation in device arm (5.7%)
  – 60% periprocedural
CONCLUSIONS

• **Alternative explanation unrelated to paradoxical embolism present in 80% of patients with recurrent stroke or TIA**
  – cryptogenic stroke and TIA include multiple etiologies
  – in many patients with cryptogenic stroke or TIA a PFO may be coincidental
  – diagnostic criteria for paradoxical embolism are imprecise
  – potential efficacy of PFO device closure in better defined patient subgroups requires further study

• **Percutaneous closure with STARFlex® plus medical therapy does not offer any significant benefit over medical therapy alone for the prevention of recurrent stroke or TIA in patients < age 60 presenting with cryptogenic stroke or TIA and a PFO**
**Trial design:** Patients with a cryptogenic stroke and evidence of a patent foramen ovale (PFO) were randomized to PFO closure with the Amplatzer PFO Occluder or medical management. Patients were followed for 5 years.

**Results**
- Primary endpoint (all-cause mortality, nonfatal stroke, TIA, and peripheral embolism) for PFO closure vs. medical therapy: 3.4% vs. 5.4%; HR 0.63; 95% CI 0.24-1.62; p = 0.34
- Stroke: 0.5% vs. 2.4%, p = 0.14; PFO related hospitalizations: 6.4% vs. 6.2%, p = 0.95
- Bleeding: 3.4% vs. 5.7%, p = 0.25; atrial fibrillation: 2.5% vs. 1%, p > 0.05

**Conclusions**
- PFO closure with the Amplatzer PFO Occluder was not superior to medical management in reducing recurrent embolic episodes including strokes in patients with cryptogenic stroke and evidence of a PFO
- Data do not support routine PFO closure in these patients; further data are awaited

Presented by Dr. Stephan Windecker at TCT 2012
RESPECT

**Trial design:** Patients with a cryptogenic stroke and evidence of a patent foramen ovale (PFO) were randomized to PFO closure with the Amplatzer PFO Occluder or medical management. Patients were followed for a median of 2.1 years.

**Results**
- Primary endpoint (recurrent strokes) for PFO closure vs. medical therapy: 1.8% vs. 3.3%, RR 0.53, 95% CI 0.23-1.22, p = 0.16; similar results on time-to-event analysis
- Possible benefit on per-protocol analysis (p = 0.03)
- Procedural complications infrequent: major bleeding (1.6%), major vascular complications (0.8%), and cardiac thrombus formation (0.4%)

**Conclusions**
- PFO closure with the Amplatzer PFO Occluder was not superior to medical management in reducing recurrent strokes in patients with cryptogenic stroke and evidence of a PFO, although suggestion of benefit on per-protocol analysis
- Data do not support routine PFO closure in these patients; further data are awaited

Presented by Dr. John Carroll at TCT 2012
A Intention-to-Treat Cohort

- Closure group (N=9)
- Medical-therapy group (N=16)

Hazard ratio, 0.49 (95% CI, 0.22–1.11)
P=0.08 by log-rank test
B As-Treated Cohort

Event-free Probability

Hazard ratio, 0.27 (95% CI, 0.10–0.75)
P = 0.007 by log-rank test

Years to Event

Closure group (N=5)
Medical-therapy group (N=16)
Conclusion Regarding PFO Management

• More information is still likely required

• “No Closure on Closure”
  – Many challenges
    • Enrollment bias
    • Properly powered study
    • Making the proper diagnosis of TIA/CVA
    • Stronger evidence / definitive evidence PFO was the cause
Percutaneous PFO Closure Off-Label Considerations

- **1\textsuperscript{st} Time CVA, PFO only finding**
  - Anti-platelet tx (unless a secondary indication for anti-coagulation, i.e. dvt)
- **2\textsuperscript{nd} CVA, PFO only finding**
  - Anticoagulation
- **3\textsuperscript{rd} CVA, PFO only finding**
  - Was on anti-coagulation for a minimum of three months, then proceed to percutaneous closure
  - * percutaenous closure when anti-coagulation in contra-indicated
Conclusions Regarding Cardiogenic Causes of Stroke

• No quantitatively valid clinical criterion standards exist for the diagnosis of cardioembolic stroke.

• The diagnosis is based on the triad of

• (1) identification of a potential cardiac source of embolism,

• (2) absence/exclusion of other potential sources of cerebral ischemia, and

• (3) consideration of clinical neurologic features
Conclusions (summary)

• Most patients with a first time cerebral vascular event deserves a comprehensive evaluation
  – 2D Echo with / without bubble study
  – TEE with bubble study
  – Blood Dyscrasias and Appropriate Serology Evaluation
  – Holter / Event Monitor / EKG
  – Comprehensive Imaging of neck and head
Questions?

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