Advanced Emboli Monitoring: PFO and Stroke & PFO and Migraine

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Emboli

- Brain emboli consisting in white cells and platelet aggregates, fat or air, may be implicated in large focal neurological deficits such as stroke (macroemboli; > 200 μm in diameter) or in more subtle diffuse cerebral dysfunction such as neuropsychological disorders (microemboli; < 40 μm).

- Gaseous emboli are believed to be infrequently associated with cerebral ischemia, although little substantial evidence exists to support this contention, whereas solid emboli are considered responsible for neurological and neuropsychological deficits in stroke patients, as well as in both cardiac and carotid surgery.

EMBOLI

Transcranial Doppler of a Paradoxical Brain Embolism Associated with a Pulmonary Arteriovenous Fistula
Kimura et al, AJNR, 1999
Types of Embolism

- **Thromboembolism:** This is when a part of a blood clot (thrombus) blocks blood flow to a major organ such as the heart or lungs. It's the most common type of embolism.
- **Arterial embolism:** This is when one or more blockages form in major arteries, often as a complication of heart disease or atrial fibrillation (a heart rhythm disorder).
- **Venous embolism:** This type of blockage is caused by a particle of fat or piece of bone marrow, which is sometimes released from a fractured bone. It's much less common than an arterial embolism.
- **Cerebral embolism:** This is when an embolism, usually a blood clot, gets trapped in an artery in the brain. It's one of the most common causes of a stroke.
- **Pulmonary embolism:** This is when a blood clot in a vein in the leg (deep vein thrombosis) breaks away and travels up to the heart in the blood stream. It can eventually get stuck in one of the main arteries to the lungs, which can cause sudden and unexpected death.
- **Air embolism:** This is a rare type of embolism that happens when a bubble of air gets trapped in the blood and causes a blockage.
- **Cholesterol embolism:** This type of embolism can form by itself, or following treatment to widen the arteries if they've become blocked up with fatty deposits (plaques). Tiny crystals of cholesterol are sometimes released from the fatty deposits and can cause blockages in small arteries.

Causes of Embolism

- Fat embolism
- Amniotic fluid embolism
- Hughes-Stovin syndrome
- Marantic endocarditis
- Paradoxical embolism
- Atherosclerosis
- Femoral artery aneurysm
- Air embolism
- Takayasu's arteritis
- Deep vein thrombosis
- Mitral valve prolapse
- Polyarteritis nodosa
- Myocardial infarction
- Pelvic vein thrombosis
- IV catheter infection
- Renal vein thrombosis
- Dilated cardiomyopathy
- Aortic aneurysm, abdominal
### Causes of Embolism (cont)

- Endocarditis
- Atrial myxoma
- Ventricular aneurysm
- Surgery complication
- Cholesterol embolism
- Atrial fibrillation
- Valve prosthesis (cardiac)
- Idiopathic dilated cardiomyopathy
- Renal vein thrombosis
- Dilated cardiomyopathy
- Aortic aneurysm, abdominal
- Idiopathic dilated cardiomyopathy

### Emboli Monitoring: Clinical Implications

- Asymptomatic/ Symptomatic carotid stenosis
- Acute Stroke
- Dissection
- Intracranial arterial stenosis
- PFO, Right-to-Left shunt
- CEA
- CABG
- Angioplasty/Stenting
- Neurosurgery: Aneurysm, SAH
- Invasive procedures (cerebral & coronary angiography, hemodyalisis)

### Detection of Cerebral Arterial Emboli

- **Clinical conditions associated with emboli:**
  - Carotid artery ulcerations and thrombus
  - Artery-to-artery embolization
  - Carotid/VA dissection
  - Aortic arch atheroma
  - Stroke and TIA
  - Paradoxical cerebral embolism
  - Artificial heart valves
  - DVT
- **The emboli can be detected during:**
  - Hyperbaric decompression with and w/o symptoms
  - CPB and cardiotomy procedures
  - CEA
  - Contrast injections, angiography (cerebral, coronary)
  - Angioplasty/Stent placement
  - Orthopedic surgery

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**EMBOLI CHARACTERISTICS**
Cerebral Arterial Emboli
Basic Identification Criteria

- A Doppler microembolic signal is transient, usually lasting less than 30 millisecond
- The amplitude of a Doppler microembolic signal is usually at least 3 dB higher than that of the background blood flow signal
- Short-duration (lasting 0.01-0.1 sec)
- Unidirectional
- High-intensity signal visible in Doppler spectrum
- Occurring randomly
- Characteristic “chirping” or “clicking” sound

Additional Features of Doppler Embolic Signals

- Change in frequency if changing velocity or changes direction
- Detected sequentially if recording at tandem site or multiple gates
- May occur anywhere within the Doppler spectrum
- Cease upon elimination of the source (artery, thrombus, etc.)

Additional Features of Doppler Embolic Signals

- Embolus size:
  - Proportional signal
- Blood volume in sample gate
  - Weaker in large sample volume
- Ultrasound carrier frequency
  - Embolus display dependent on ultrasonic frequency

Emboli

- Microembolic signals – MES
- High Intensity Transient Signals - HITS
Emboli


CPB stage, emboli asymmetrical

Emboli Monitoring
TCD Emboli Monitoring: Clinical Applications

1. Localization of the embolic source responsible of stroke
2. Identification of high-risk patients for stroke recurrence
3. Monitoring of the therapy effectiveness
4. Monitoring of cardiovascular surgery
5. Monitoring different type of invasive procedures

Stroke and PFO

• Stroke is the third leading cause of death in the United States. One million people suffer from stroke each year.
• Stroke is the major cause of disability in the United States. There are 5 million survivors of stroke in this country.
• Stroke is not rare in young people under 50 years of age accounting for 5% of all strokes.
• Until recently, 40% of all strokes were of unknown cause or cryptogenic. We now know that most of these unexplained strokes are caused by a PFO

PFO

• PFO occurs up to 26% of all adults
• PFO is diagnosed in 50-70% of patients with stroke of unknown cause.
• After a first stroke due to PFO, ½ of patients still have moderate to severe disability after 1 year.
• After a first stroke due to PFO, second strokes occur at a rate of 2%-9% each year (depending on risk)
• After several strokes from PFO, repeat strokes occur at a rate of 6%-20% each year.
• The risk of repeat stroke due to PFO is increased in patients with leg clots, migraine headache, atrial septal aneurysm (seen by echo), and large PFO shunting (seen by TCD).

WHAT IS KNOWN ABOUT PFO AND STROKE
PATENT FORAMEN OVALE

- Cryptogenic strokes and TIA’s are those in which no obvious cause is found by patient history, carotid Doppler studies, or cardiac conditions such as atrial fibrillation, myocardial infarction, or valve diseases.
- The cause of ischemic stroke remains cryptogenic in 35-40% of all cases.
- PFO, has been associated with Cryptogenic stroke allowing paradoxical embolism from the veins to the brain through a right-to-left shunt.

PFO Epidemiology

- Because stroke occurs more frequently in older population, with only 3% of cerebral infarctions occurring in patients 40 years of age, the number of stroke patients with PFO 40 years of age is much larger than in the younger patients.
- Several studies reported the association of PFO with cryptogenic stroke in older patient populations. However, this has not been seen in other studies. Therefore, although the association between cryptogenic stroke and PFO is established among the younger population, it is not clearly established in the older population.

Ariel Sharon, 78-years old, Prime-Minister of Israel

Bret Michaels news: Rumor true, Celebrity Apprentice hospitalized again after second stroke

Bret Michaels (born Bret Michael Sychak, March 15, 1963) is an American singer, actor, director, screenwriter, producer and reality television personality. He first gained fame as the lead vocalist of the glam metal band Poison.
- On May 20, 2010, it was reported that Bret Michaels has been "readmitted to the hospital this week after suffering numbness on the left side of his body". While conducting diagnostic tests it was found that Michaels has a PFO. It was further reported that his condition is "operable and treatable" and his doctors believe they "have diagnosed the problem that caused the TIA or warning stroke".
I have a hole in my heart, too
http://www.ivillage.com/i-have-hole-my-heart-too/4-a-192332

- "I have something in common with Bret Michaels—we both have a patent foramen ovale, or PFO, which is a flap-covered hole between the left and right sides of the heart. After a string of health problems—an appendectomy, a brain hemorrhage, and a small stroke (transient ischemic attack) which often precedes a more serious stroke, Michaels' doctors found the PFO. In the fall he'll undergo a procedure to repair the defect in order to lessen his chances of having a full-blown stroke."

- A couple of years ago I found out during some tests that I have a PFO, so I'm pretty curious about Michaels' treatment. Should I do something about mine? I'm in my 30s and healthy and I've never had a stroke. David Coven, M.D., an interventional cardiologist at St. Luke's Hospital in New York, NY, and my doctor says the vast majority of people who have PFOs don't have strokes…"

PFO

WHAT IS A PFO?
PATENT FORAMEN OVALE

- During formation of the heart in the fetus, two pieces of the wall grow to overlap each other to divide the upper chambers (atria) of the heart into right and left chambers.

- Before birth, the lower divider acts as a flap or tunnel which allows blood to flow from the right side of the heart to the left side. This blood flow contains oxygen from the mother's placenta.

- In 1877, Cohnheim initially described the term paradoxical embolism (PDE) and the association of PFO with stroke in a young woman with cerebral arterial embolism. However, it has been difficult to diagnose PFO in vivo until the development of echocardiography and its ability to image the interatrial shunting with an injection of saline contrast. With the use of contrast echocardiography, a strong association of cryptogenic stroke with PFO has become evident in patients <55 years of age.

Julius Friedrich Cohnheim, July 20, 1839–August 15, 1884.
From the collection of W. Bruce Fye, M.D., M.A.
**What is PFO?**

- After birth, right to left blood flow is no longer needed. The two dividers of the right and left atria fuse to form a solid wall (septum). The septum is supposed to be fused by 18 months of age.
- However, the dividers which form the septum do not fuse in 10% to 30% of people leaving a flap or tunnel which may open and close as right heart pressure changes.
- This opening (flap or tunnel) is the Patent Foramen Ovale (PFO).

**WHY PFO CAUSE STROKE**

- In the normal adult heart, the right and left sides are completely separated.
- Blood from the body enters the right atrium and flows to the lungs.
- Filtered blood from the lungs carries oxygen and is pumped to the brain and organs of the body.

- With a PFO present, blood from the body can bypass the lungs and travel to the left side of the heart.
- In the normal heart (no PFO), a blood clot from the body would be stopped in the lungs.
- But if a clot crosses the PFO, it can go to the brain causing a stroke.

- Where do blood clots come from to cause stroke in patients with a PFO?
  - Blood clots may form in the veins in the legs, break loose, and travel with blood flow to the heart. These clots may pass through the PFO causing a stroke.
WHY PFO CAUSE STROKE

- Or, blood trapped within the PFO flap or tunnel for a period of time may clot.
- When increased pressure in the right heart opens the flap of the PFO, the clot may dislodge and travel to the left side of the heart and then to the brain.

NOT ALL PFO ARE THE SAME
RISK AND AMOUNT OF PFO FLOW

- While blood flow from the right atrium to the left atrium is the hallmark of a PFO, it is the amount of flow (or shunt) that is associated with the risk of recurrent stroke: the greater the flow, the greater the risk.
- Bubbles injected by an IV appear in the right atrium and are detected by echo when they appear in the left atrium. A small number of bubbles may pass through the lungs.
- Tiny PFO communications are low risk for stroke and do not need treatment.
- Large PFO are much more likely to result in stroke, migraine, decompression illness in divers, and low oxygen levels in the blood.
- Mistakenly thinking that all PFO are the same is one of the reasons doctors may disagree on PFO treatment.

NOT ALL PFO ARE THE SAME
ATRIAL SEPTAL ANEURYSM AND INCREASED STROKE RISK

- In ½ of patients with high flow PFO, the septum primum (lower divider) is redundant and floppy due to excessive tissue. This floppy divider is called an atrial septal “aneurysm” (ASA). It is not at all like a true arterial aneurysm and cannot burst.
- In patients with both ASA + PFO, the chance of repeat stroke is increased fourfold (even on blood thinning medications). The presence of an ASA in a PFO stroke patient means that the 1-year stroke risk is 4%. (Risk > 1.5% / year is considered very high)
- Evidence for PFO
  - PFO Prevalence in “normal” population
  - 20-30% PFO patency at surgery/autopsy
    - Hagen et al, Mayo Clinic Proc, 1984
    - Others dating back nearly 20 yrs
  - 10-15% “Functional” patency by TEE:
    - Lechat et al, NEJM, 1988
    - Webster et al, Lancet, 1988
### Autopsy Prevalence of PFO
*Homma et al., Circulation, 2005*

<table>
<thead>
<tr>
<th>Study</th>
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<td>Fawcett and Blanchford</td>
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<td>Scammon et al</td>
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<td>Wright et al</td>
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<td>Total</td>
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### Varisolve BTG trial
*Wright et al, 2010, JVS*

- 221 subjects were tested for the presence of R-L S
- The total number of patients positive for R-L shunts either at rest or of after Valsalva was 130 (59.8%)
- R>L shunt prevalence was 59%, twice as high in C3 varicose vein patients than in the general population

### Is it a cryptogenic stroke?

- **GOLD STANDARD:**
  - Clinical and brain imaging consistent
  - Absence of risk factors of atherosclerosis
  - Normal vessels on ultrasound
  - Normal vessels on CTA/MRA
  - Normal vessels on selective angiograms
  - Lacking specific risk factors

### We need to combine all the circumstantial information we can get

- **Theoretically required:**
  - « Cardiac source »
  - Clinical and neuroimaging features
  - No other cause
  - Complete evaluation

- **Real world:**
  - Sources uncertain
  - Nonspecific syndrome, imaging sometimes normal (TIAs)
  - 15-25% with coexisting causes
  - Often incomplete
Clinical information: summary
Stockholm ESC/ESC Joint Meeting, 2005
MG Hennerici, Germany

- Clinical information is highly valuable and sometimes the only available
- However, specificity of clinical features alone is insufficient and agreement is poor
- Reconsideration of technical findings is mandatory….

DEFINING PFO STROKE RISK

- Four risk factors are established in medical research which indicate a higher risk for stroke due to PFO.
- Brain injury on MRI(1) and migraine headache(2) increase the risk of stroke several fold in addition to high flow(3) and septal “aneurysm”(4)
- Other conditions may also increase risk: leg clots, sleep apnea, and diving.

HOW ARE PFO DIAGNOSED?
TRANSTHORACIC ECHO

- Heart disorders are the most common cause of stroke.
- TransThoracic Echocardiography (or TTE) is a noninvasive, ultrasound test which evaluates heart structures. Microscopic bubbles injected into a vein show a PFO when they cross to the left side.
- TTE is about 60% reliable in finding a PFO.

PFO DIAGNOSIS: CONTRAST TCD OR CONTRAST TTE/TEE?
HOW ARE PFO DIAGNOSED?
TRANSESOPHAGEAL ECHO

- Although surface echo (or TTE) can define most heart structures, the atrial septum (the site of the PFO) is hard to see.
- Transesophageal Echo (or TEE) uses a special ultrasound probe which is placed in the esophagus after giving sedation. The atrial septum and PFO can be clearly seen by this technique.

Right-to-Left Shunt Testing

- Currently, TEE is the gold standard for identifying Right-to-Left shunt/PFO
- TCD "bubble-test" is a new, simple, accurate, reliable, cost effective, and safe method for testing for Right-to-Left shunt/PFO
  - excellent non-invasive test
  - excellent sensitivity (especially with Valsalva)
  - excellent specificity
  - can be done in neurologists’ office

HOW ARE PFO DIAGNOSED?
CONTRAST-TRANSCRANIAL DOPPLER (c-TCD)

- C-TCD is a new, non-invasive test for diagnosing the presence of a PFO or Rt-to-Lt cardiac shunting. TCD is more sensitive than TTE or TEE for finding a PFO, but does not show heart anatomy. TCD+TTE may render TEE unnecessary.
- When microscopic bubbles are injected by IV into a vein in a normal heart, the lungs reduce their passage to the left side of the heart.
- When a PFO/Rt-to-Lt shunt is present, TCD detects bubbles which pass through the PFO/Rt-to-Lt shunt and travel to the arteries in the brain. TCD, unlike TTE/TEE, is quantitative.
- The abnormal flow of blood through the PFO/Rt-to-Lt shunt (detected by TCD) is called “shunting”. Shunting is one of the hallmarks of the PFO/Rt-to-Lt shunt.

TEE or TCD?
Initial Diagnosis of PFO

- C-TCD may be useful as an initial test or to follow up a positive TEE or TCD test.
A MULTICENTER TRIAL ON PATENT FORAMEN OVALE (PFO) DETECTION: TRANSCRANIAL DOPPLER (TCD) VS TRANSESOPHAGEAL ECHO (TEE). TCD BETTER THAN TEE? Vavlitou et al, 2010

- One hundred ICU patients
- The prevalence of PFO detected with TEE was 28% and with TCD 48%. There was no PFO detected with TEE and missed by TCD. TCD was more sensitive than TEE in detecting PFO of grade I (7 with TEE, 17 with TCD) and II (6 with TEE, 16 with TCD), while for grade III the two techniques had equal sensitivity (15 with TEE, 15 with TCD)
- The prevalence of PFO detected by TCD is very high in mechanically ventilated ICU patients and this may have important clinical implications. TCD is more sensitive than TEE in detecting a small PFO.


- TEE has been accepted as the reference diagnostic technique. The purpose of this study was to compare the accuracy of TTE, TEE and TCD in the diagnosis and quantification of patient foramen PFO.
- 134 patients prospectively. Simultaneous TTE with TCD and TEE with TCD were performed, using agitated saline solution to detect right to left shunt.

In 93 patients diagnosed with PFO, the shunt was visualized at baseline by TCD in 69% of cases, by TTE in 74% and by TEE in 58%. The Valsalva maneuver produced a similar improvement in shunt diagnosis with all 3 techniques (28%-28%). TTE and TCD showed higher sensitivity (100% vs 97%; non significant difference) than TEE in the diagnosis of PFO (86%; P<.001). TCD performed during TEE did not diagnose 12 (13%) shunts previously diagnosed during TTE. Similarly, TEE underestimated shunt severity.

TTE enables adequate diagnosis and quantification of PFO. TEE is less sensitive and tends to underestimate the severity of the shunt.

Sensitivity of Transcranial Doppler Versus Intracardiac Echocardiography in the Detection of Right-to-Left Shunt HoHai Van et al, J Am Coll Cardiol Img, 2010

- 38 consecutive patients who were undergoing PFO closure had simultaneous TCD and ICE performed. Agitated saline injections were performed at rest, with Valsalva maneuver, and with forced expiration into a manometer to 40 mm Hg before and after closure, as well as 3 or more months after closure. Right atrial pressures were measured in the periprocedural period, and RLS were graded according to standard methods during these maneuvers.
  - Right atrial pressures were significantly higher with Valsalva maneuver compared with rest (before closure 21.6 ± 11.9 mm Hg vs. 6.6 ± 2.6 mm Hg, p < 0.001; after closure 28.4 ± 13.9 mm Hg vs. 6.8 ± 2.6 mm Hg, p < 0.001) and with manometer compared with Valsalva maneuver (before closure 38.7 ± 6.6 mm Hg vs. 21.6 ± 11.9 mm Hg, p < 0.001; after closure 44.0 ± 9.5 mm Hg vs. 28.4 ± 13.9 mm Hg, p < 0.001).
  - ICE underestimated shunting in 34% of patients with Valsalva maneuver or manometer after closure compared with TCD.
  - TCD with immediate feedback provided by forced expiration against a manometer to 40 mm Hg is more sensitive than echocardiographic imaging for the detection of RLS. These observations have significant implications for determining the incidence of RLS in patients with stroke or migraine.
PFO Screening Accuracy

- **TTE (63% accuracy)**
  - 30% false negative
  - Poor sensitivity
- **TEE (88% accuracy)**
  - Invasive
  - 15-20% false neg.
  - Inability to perform calibrated Valsalva
  - Patient sedated
- **TCD (94% accuracy)**
  - Minimally invasive
  - Highly sensitive
  - Calibrated Valsalva to standardize strain

### TCD vs. TTE

<table>
<thead>
<tr>
<th>Reference</th>
<th>C.M. (l.w.)</th>
<th>TTE Sens/Spec %</th>
<th>TCD Sens/Spec %</th>
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<tr>
<td>Nemec et al 1991</td>
<td>saline-air-blood</td>
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<td>Di Tullio et al 1993</td>
<td>aerated saline</td>
<td>47/130</td>
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<td>Lam et al 1994</td>
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<td>39/75</td>
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<td>Droste et al 2000</td>
<td>aerated saline</td>
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<td>100/100</td>
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### TCD and TEE

- **Bubble-TEE**
  - Sedation
  - Not possible to perform in patients with swallowing difficulties
  - Involves many specialists, expensive equipment
  - Global Fee $1,400.00
- **Bubble-TCD**
  - The cost-effective and minimally invasive compared to bubble-TEE
  - Direct demonstration of embolism through a PFO to the cerebral circulation has been demonstrated
  - Global Fee $219.00

### TEE Cost

- National Transesophageal Echocardiography Procedure Pricing Summary
  - National Minimum Price $875 (Harriman, TN)
  - National Average Price $3,700
  - National Maximum Price $10,100 (Lock Haven, PA)
- Transesophageal Echocardiography Cost Averages Around the Country
  - Phoenix, AZ Transesophageal Echocardiography Cost Average $3,200
  - Philadelphia, PA Transesophageal Echocardiography Cost Average $3,100
  - Houston, TX Transesophageal Echocardiography Cost Average $3,200
  - Miami, FL Transesophageal Echocardiography Cost Average $3,400
  - Dallas, TX Transesophageal Echocardiography Cost Average $3,600
  - Los Angeles, CA Transesophageal Echocardiography Cost Average $3,100
  - New York, NY Transesophageal Echocardiography Cost Average $3,700
  - Atlanta, GA Transesophageal Echocardiography Cost Average $2,700
Contrast-TCD (c-TCD)

- TCD with saline contrast (c-TCD) is a simple bedside procedure and involves minimal discomfort for the patient compared with TEE
- C-TCD provides evidence of direct potential involvement of the cerebral arterial circulation

Summary of c-TCD procedure

- Supine position, insert 18G (22G) needle into (right) cubital vein, insonate MCA
- Syringe 1: 9 ml saline, Syringe 2: 1 ml air
- Connect both syringes with 3-way stopcock connected with a short flexible line to an i/v gauge with the patient
- Exchange air/saline mixture energetically at least 10 times
- Inject immediately as bolus
- Repeat examination with Valsalva
- Valsalva should start on examiner’s command 5 sec injection

The positions of the patients in the diagnosis of PFO by TCD.
Telman et al, J Neuroimaging, 2003

- 34 patients with TEE-proved PFO were examined by contrast TCD. Examinations were done in both the sitting and supine positions in random order.
- Patients’ positions and the sequence of testing did not affect the number of microemboli detected. Yet for each individual, 1 of the 2 positions was more sensitive.
- To improve the sensitivity of TCD in the detection of PFO, it is recommended, in the case of a first negative test, to change the patient’s position for a repeated TCD examination.

Postural Dependency of Right-to-Left Shunt
Caputi et al, Stroke, 2008

- Current recommendations indicate testing in the recumbent position
- Testing in a standing position may represent a better way to detect RLS occurring during normal daily activity because it reproduces the natural body position usually held for the most of the day
- 109 pts, both positions at rest and with Valsalva
- The amount of permanent RLS was posture dependent in 40% of pts
- Testing in the standing position may thus be warranted in doubtful or inconclusive results
Effects of Posture on Rt-to-Lt Shunt (RLS) Detection by c-TCD

Agustin et al. 2011, Stroke

• 240 pts, at rest/Valsalva, supine, right lateral decubitus, right lateral leaning and upright sitting

• RLS is best detected in the upright sitting position with Valsalva

Bubble-TCD

Step 1

Step 2

Step 3

Connection & Injection

Consensus Statement

Cerebrovasc Dis, 2000

• A 4-level categorization was accepted according microemboli appearance using unilateral MCA monitoring:
  1. No occurrence of microemboli
  2. 1-10 microemboli
  3. >10 microemboli but no curtain
  4. curtain or shower where a single microemboli cannot be discriminated within the TCD spectrum
To grade RLS, a 6-level logarithmic scale was used for both resting and Valsalva injections as follows:

- Grade 0 = 0 ETs,
- Grade I = 1–10 ETs,
- Grade II = 11–30 ETs,
- Grade III = 31–100 ETs,
- Grade IV = 101–300 ETs,
- Grade V > 300 ETs.

Factors influencing number of HITS

- The numbers of HITS represented tracers of the conductance of RLS flow to the anterior circulation of the brain. The conductance takes into account many factors including:
  - The RLS flow distribution to the anterior circulation of the brain,
  - The size of the foramen while open
  - The right-to-left pressure gradient when the foramen is open
  - All HITS must be counted visually.

Differentiation of shunts?

- So far, no attempt made to differentiate pulmonary shunts from cardiac shunts with pmTCD
- Assumption is that HITS from a pulmonary capillary shunt would fall within grade I and that grades I and II may not be of sufficient conductance to justify closure
- If a pulmonary arteriovenous malformation (AVM) present, then it could be identified and located at catheterization
- Based on Spencer et al. (2004) data initially, patients with any positive grade of conductance were selected for closure. Later, it was realized that crossing the septum with the guide-wire in patients with grade I or II conductance was technically difficult. Thereafter, only patients who had grades higher than grade II were selected for catheterization
Complications

- Injection of agitated saline mixed with air bubbles appeared to be well tolerated
- No patients reported symptoms during or immediately after the c-TCD, except two patients who reported hearing of passage of bubbles like "sounds from a water stream"?!

Case Report

- This is a 35-year-old-female that is status-post PFO closure on July 11, 2001. Prior to closure she experienced a stroke on 5/6/2001, with symptoms of right side weakness and aphasia. She reports no current problems other than moderate headaches (without aura) 4 days per month.

The ideal approach for PFO evaluation

- For diagnosis
  - TCD for screening
  - TTE (PFO or ASD?)
- In the Cath Lab
  - TEE or ICE to confirm the diagnosis
    - To exclude intrapulmonary shunts
    - To assess anatomical characteristics
    - To guide PFO closure

TCD for PFO Diagnosis?!

- You can exclude a PFO by TCD
  …… but you can not diagnose it!
Why no diagnosis of PFO by TCD?

- TCD is unable to locate the source of the right-to-left shunt PFO or ASD or intrapulmonary shunt?
- However, TCD and TTE in combination can detect a PFO accurate and reliable in comparison to TEE *

**Option for patients with PFO/Stroke**

- No treatment
- Life-long anticoagulation therapy
- Surgical closure of PFO
  - traditional open-heart surgery
  - new, minimally invasive open-heart
  - robotic surgery
- Transcatheter Closure of PFO

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**To Do or Not To Do?**

- A research letter appearing in the February 7, 2008 issue of the *Journal of the American Medical Association* reports that the number of adults undergoing PFO/atrial septal defect (ASD) closure between 1998 and 2004 increased more than 50-fold, despite a lack of randomized clinical-trial evidence proving that PFO closure prevents stroke or TIA.

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**Prevalence and repair of intraoperatively diagnosed patent foramen ovale and association with perioperative outcomes and long-term survival**

Krasuski et al., *JAMA*. 2009

- A recent survey suggested that cardiothoracic surgeons may alter planned procedures to repair incidentally discovered PFO. How frequently this occurs and the impact on outcomes remain unknown.
- The authors reviewed the intraoperative transesophageal echocardiograms of 13,000 patients without prior diagnosis of PFO or atrial septal defect undergoing surgery at the Cleveland Clinic, from 1995 through 2005. Postoperative outcomes were prospectively collected until discharge.
- All-cause hospital mortality and stroke were predetermined primary outcomes; length of hospital stay, length of ICU stay, and time on CPB were secondary outcomes.
- Intraoperative PFO was diagnosed in 2277 patients in the study population (17%), and risk factors for stroke were similar in patients with and without PFO. After propensity matching was performed with the comparator groups, patients with PFO demonstrated similar rates of in-hospital death (3.4% vs. 2.6%, \( P = .11 \)) and postoperative stroke (2.3% vs. 2.3%, \( P = .84 \)). Surgical closure was performed in 839 PFO patients (28%), and surgeons were more likely to close defects in patients who were younger (mean [SD] age, 61.1 [14] vs. 64.4 [13] years; \( P < .001 \)) and undergoing mitral or tricuspid valve surgery (51% vs. 32%, \( P < .001 \)) or had history of TIA or stroke (16% vs. 10%, \( P < .001 \)). Patients with repaired PFO demonstrated a 2.47-times greater odds of having a postoperative stroke compared with those with unrepaired PFO (2.8% vs. 1.2%, \( P = .04 \)). Long-term analysis demonstrated that PFO repair was associated with no survival difference (\( P = .12 \)).
- Incidental PFO is common in patients undergoing cardiothoracic surgery but is not associated with increased perioperative morbidity or mortality. Surgical closure appears unrelated to long-term survival and may increase postoperative stroke risk.
Patent Foramen Ovale Is Indicted, but the Case Hasn’t Gone to Trial

James E. Lock, Circulation 2000

- The PFO stands accused. The evidence is strong and getting stronger. Acquittal or conviction will only occur after a randomized trial in patients who have a PFO and a first event, comparing closure (either by catheter or surgery) with anticoagulation. Until such a trial is completed, neurologists and cardiologists have real patients with real strokes to manage. A review of the available data would seem to support the following recommendation: those embolic stroke patients who are younger, who have largish PFOs and no other stroke source, and who fail anticoagulant therapy or should not take anticoagulants may be considered candidates for anatomic closure of their PFO

Implantation technique today is straight forward

- Local anesthesia
- Transvenous 8-11 F sheath
- 10,000 E Heparin
- Multipurpose catheter left upper pulmonary vein
- Balloon sizing
- Device implantation
- < 30 min door to door
- < 24 hours hospital stay

PFO Closure Devices: Contenders

CardioSEAL

Helex

Amplatzer

HOW CLOSURE DEVICES WORK

Amplatzer® PFO

Amplatzer® SO

©2011 Alexander Razumovsky

©2011 Alexander Razumovsky
BioSTAR (NMT)

- CardioSEAL® framework
- STARFlex® self-centering mechanism
- Bioresorbable collagen matrix derived from the submucosal layer of the porcine small intestine (ICL)
- Heparin coating

Solysafe® (Carag)

- Self-centering
- Two foldable Polyester patches, attached to eight Phynox wires
- Stretched device fits into 10 F introducer
- In the defect, wire-holders are moved towards each other
- Clicking mechanism keeps the wire-holders together

Premere PFO Closure Device
St. Jude

- No fabric on the left side
- Flexible tether holds anchors together
- Variable distance between the anchors
- CE-Mark; US: Clinical trials

New Developments

- New double-disc devices
- In-tunnel devices
- Suture based techniques
**Nit-Occlud® PFO**

- Double umbrella occluder with single-layer left atrial disc
- Occluder is knitted from a single Nitinol wire
  - Low profile
  - No protruding clamps
- CE Mark since July 2010
- 3 sizes: 20 mm, 26 mm, 30 mm

**The SpiderTMPFO Occluder**

- Self-expandable, double disc device
- Right atrial disc: ceramic coated Nitinol wire mesh.
- Left atrial disc: ePTFE patch and ceramic coated braided nitinol anchors
- Joint between the left atrial disc allows free rotation for adaption to PFO morphology
- Sizes 18mm, 25mm, 30mm.

**SeptRx PFO Closure Device**

- Closes the PFO tunnel from within
- Nitinol frame and Nitinol wire mesh
- Small left and right atrial anchors
- Minimal material in left and right atrium

**Coherex - Designed to "Stent" the PFO tunnel**
The Suture Closure of PFO

- The suture closure of a PFO is intuitively attractive:
  - No device left behind
  - No risk for device erosion
  - No risk of embolisation
  - Minimal risk of thrombosis
  - No need for aggressive antiplatelet regimen
  - No obstruction of atrial septum

The Sutura SuperStitch®EL Arms and Needles

- Profile: 12 Fr
- Working length: 90 cm
- Suture type: Polypropylene 4-0
- Knot type: Polypropylene
- CE marked

Take Home Message

- PFO Screening → TTE and TCD
- Confirming of the diagnosis and intraprocedural Guidance → TEE or ICE
- Follow-up → TTE, TCD and TEE
- PFO closure is a straightforward procedure
- New devices are available or under development and may have some advantages

Device-less PFO closure by radiofrequency thermal energy

Nazan et al, SWISS MED WKLY 2008

- The PFx™-PFO closure system (CIERRA Inc. Redwood City, CA, USA) produces monopolar RF energy, which denatures the tissue to the end of fusing the tunnel between the atrial septum secundum and septum primum at the level of the fossa ovalis, thereby closing the PFO.
- The procedure is carried out from the groin through the inferior vena cava and the right atrium. The metal electrode, which is connected to the RF generator, has a diameter of 15 or 19 mm.
- An external generator produces the ablation energy. It monitors impedances and has an automatic shut down feature, germane to standard electrophysiology ablation equipment. As the energy is monopolar, a defibrillator pad is used as the return electrode.
Stoke PFO Closure Clinical Trials

- **CLOSE (France)**  ongoing
  PFO Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence
- **CLOSURE I (USA)**  Closed
- **CLOSEUP**  Closed
  In the Closure Using Premere (CLOSE UP) trial a total of 29 patients underwent the procedure with the PFX Closure System under local anesthesia. The PFX catheter was guided into the right upper atrium of the heart, a vacuum was used to pull the ends of the septum together, and radiofrequency energy was applied to fuse them.
- **REDUCE**  ongoing (2015?)
- **RESPECT**  ongoing
  AMPLATZER® PFO Occluder vs. the current standard of care

**Gore REDUCE (Start May 2008)**

- W. L. Gore & Associates (Gore) announced that it has received approval from the US Food & Drug Administration (FDA) to proceed with the Gore REDUCE® Clinical Study.
- The Gore REDUCE Clinical Study is a prospective, randomized, multi-center, multinational trial designed to demonstrate safety and effectiveness of the GORE HELEX Septal Occluder for Patent Foramen Ovale (PFO) closure in patients with a PFO and history of cryptogenic stroke or imaging confirmed Transient Ischemic Attack (TIA).
- Patients will be randomized to one of two treatment arms, either antiplatelet medical management alone or device closure of the PFO in conjunction with antiplatelet medical management. The primary endpoint is freedom from recurrent ischemic stroke, imaging confirmed TIA, or death due to stroke through 24 months post-randomization. The study sponsor is currently recruiting up to fifty investigational sites in the US and Nordic countries.

**Witness REDUCE (France)**

**CLOSURE I**

- The multicenter study included more than 900 patients, randomized 1 to 1 in each arm of either device closure or best medical therapy. Study patients, who averaged 46 years of age, ranging from 18 to 65, had experienced cryptogenic stroke or TIA and had a PFO documented by TEE. More than half of the enrolled patients had a large or moderate shunt as a result of PFO, with nearly 40% having an Atrial Septal Aneurysm -- considered to be a higher risk patient profile.
- The primary endpoint was the two-year incidence of stroke or TIA, all cause mortality for the first 30 days, and neurological mortality 31 days to 2 years.
- The final trial results did not demonstrate superiority of PFO closure with STARFlex® plus medical therapy over medical therapy alone. The rate of recurrent stroke was approximately 3% in both arms.
- The effective closure rate of the procedure was 86.7%, based on review by a core laboratory, and is in line with other transcatheter closure devices. The results also demonstrated that recurrent stroke and TIA had multiple possible causes, often unrelated to paradoxical embolism.

**Patent foramen ovale using the Premere device: the results of the CLOSEUP trial**

Buscheck F, et al. 2006

- The CLOSEUP trial was conducted to determine the safety and effectiveness of the Premere closure device in closure of patent foramen ovale (PFO).
- Patients between 18 and 65 years of age who had a cryptogenic ischemic stroke or a transient ischemic attack and a PFO underwent percutaneous PFO closure using the Premere device.
- Of the 73 enrolled patients, six patients had atrial anatomy not appropriate for the Premere; 27 patients received the 15 mm and 40 patients received the 20 mm device. Implantation was successful in all patients. At 6 months of follow-up, 86% of patients had no shunt that could be provoked with Valsalva as assessed during contrast echocardiography. Closure rates were better with the 20 mm versus the 15 mm device, and three patients with residual shunt had atrial septal aneurysms at baseline. One patient had transient atrial fibrillation which resolved by 3 months. There were no instances of thrombus, death, or stroke.
- These data demonstrate that the Premere device can safely and effectively close PFO. Additional studies should be undertaken to demonstrate the effectiveness of PFO closure in reducing thromboembolic events such as stroke.
PFO and Stroke Trials

- PICSS: Presence of a PFO did not influence lower rate of stroke recurrence on warfarin, which was 9.5% in patients with PFO and 8.3% in patients without PFO.
- CODICIA (Spain): Neither massive RLS nor massive RLS with concurrent ASA is an independent risk factor for recurrent stroke, in either the general or younger stroke populations.

Device Closure vs. Medical Therapy

Khairy; Heart 2004

<table>
<thead>
<tr>
<th>Recurrent events</th>
<th>PFO closure</th>
<th>Medical treatment</th>
<th>RR</th>
<th>RR 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke rate</td>
<td>6.42%</td>
<td>6.43%</td>
<td>1.00</td>
<td>0.79 to 1.25</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>1.40%</td>
<td>1.41%</td>
<td>1.00</td>
<td>0.81 to 1.24</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Stroke or death</td>
<td>1.62%</td>
<td>1.83%</td>
<td>1.00</td>
<td>0.79 to 1.25</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>1.64%</td>
<td>1.66%</td>
<td>1.00</td>
<td>0.79 to 1.25</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Adjusted stroke</td>
<td>2.77%</td>
<td>2.17%</td>
<td>1.28</td>
<td>1.02 to 1.60</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adjusted death</td>
<td>1.59%</td>
<td>1.99%</td>
<td>1.00</td>
<td>0.79 to 1.25</td>
<td>&gt;0.90</td>
</tr>
</tbody>
</table>

Role of TCD: Stroke & R-to-L shunt

- The efficient use of c-TCD among patients with acute ischemic stroke will decrease the number of cases labeled as cryptogenic and will lead to more informed choices among current long-term therapeutic options or endovascular/surgical interventions.

PFO AND MIGRAINE
### Migraine and PFO

- 50% of migraine patients have a PFO and most of these have large shunts.
- The theory is that substances in the blood bypass the lungs and trigger migraine. Alternatively, small clots may pass through the PFO and trigger migraines without causing stroke.
- Scuba divers often have migraines after diving and the chance is much higher in divers with large PFO performing deep dives where bubbles come out of the blood and travel to the brain through the PFO (rather than stopping in the lungs). Our first understanding of migraine improvement with PFO closure came from divers with migraine & decompression illness.

### Migraine and Stroke

- Migraine is a significant risk for stroke. Migraine medicines used properly do not cause stroke or heart attack.
- Patients having a stroke due to a PFO are much more likely to have a second stroke if they also have migraine.
- MRI in migraine patients shows that the risk of stroke is increased 15 times for women with migraine with aura and 1 attack per month.
- Smaller brain lesions (WMH= white matter hyper-intensities or so-called “spots”) are 3 fold increased in migraine patients and are related to neurologic disability in the future.

### Relief of Migraine After PFO Closure

- Wilmshurst in England first reported the improvement of migraine headache (84%) and the complete relief of migraine (45%) in divers who had PFO closure to prevent decompression illness.
- The graph shows the results of migraine relief with PFO closure in patients treated because of stroke caused by the PFO.
- There are now over 15 studies of catheter PFO closure for stroke prevention where the secondary benefit of migraine relief occurred in very similar numbers. Usually 80% said they were better and 1/3 of those said they had complete resolution of migraine symptoms.

### Migraine PFO Closure Trials

- ESCAPE  ongoing
- MIST I  37% reduction in migraine burden
- MIST II  halted
- PREMIUM  ongoing
ESCAPE Trial, St. Jude Medical

• ESCAPE (Effect of Septal Closure of Atrial PFO on Events of Migraine with Premere™) is an approved clinical trial that studies the link between PFO and the incidence of migraines. Several clinical experiences have shown a strong association between the presence of PFO and migraines, and several physicians have shown that closure of PFO in patients with migraine and a previous stroke has been associated with a reduction in intensity and frequency of migraine attacks.

Premium Migraine Trial

This study is currently recruiting participants.

• Primary Outcome Measures:
  - Whether subjects with percutaneous PFO closure experience a reduction in migraine attacks

NMT Medical, Boston, MA

• The STARFlex Septal Repair Implant has been proven to be safe and effective in stroke patients. It is approved for PFO closure in the UK and throughout Europe, and to date over 18,000 patients worldwide have been successfully treated with a STARFlex device or its predecessor CardioSEAL®.

ESCAPE Trial, St. Jude Medical

This study is ongoing, but not recruiting participants.

• Primary Outcome Measures:
  - Primary Endpoint 1: Effectiveness; the primary effectiveness measure is the decrease in the frequency of migraine headaches;
  - The primary safety endpoint is the rate of major complications

• Secondary Outcome Measures:
  - Secondary Endpoint 1: Effect of Aura
  - Secondary Endpoint 2: Assessment of Procedural Success and Long-Term Device Performance

• Secondary Outcome Measures:
  - Change in the average number of migraine days; change in MIDAS score; reduction in the number of acute and/or rescue migraine medications; complete closure of the defect; improvement of Quality of Life; Improvement in the BECK Depression Inventory
The studies investigating patients with PFO have strongly indicated that there is a link between PFO and migraine, and that in some patients, particularly those suffering from migraine with aura, closure of their PFO leads to cessation or a significant improvement in the frequency and severity of migraines. Until now all the studies have had limitations in that they investigated stroke patients or divers, and were retrospective. Therefore, PFO closure is not currently a proven treatment for migraine alone. The MIST Trial has been specifically designed to investigate migraine sufferers with a PFO and demonstrate if PFO closure can offer an effective treatment for this type of migraine sufferer.

The MIST results indicated an approximate 37% reduction in Migraine burden (number of headaches multiplied by the length, in hours of headache) in those patients who received a STARFlex® implant and a 17% reduction in those who received the sham procedure and no implant (essentially, a placebo). This represents a statistically significant treatment effect. It also was reported that this variance appears to increase over time. If you’ve seen some of the recent news stories, you may have noticed that some of the headlines termed the MIST study a “failure.” That’s an unfortunate choice of words and leaves readers with the wrong impression. MIST did not meet the exact endpoint projection of 40% decrease in Migraine, the study is hardly a failure. It was an important first step toward evaluating the impact of PFO closure on Migraine; a step that must be taken if we’re to discover how significant the PFO/Migraine connection is and if PFO closure is a viable treatment.

Screened 432 Migraine with aura patients for a PFO and enrolled 147 patients into the study. A significant finding is that over 60% of those screened had a right to left shunt. Of those patients, almost 40% had a moderate or large PFO, six times greater than the general population.

The CODICIA Study Results from the Prospective Spanish Multicenter Study, Stroke, 2008

- 486 pts with cryptogenic stroke, c-TCD, c-TTE and/or c-TEE, MRI and/or CT
- Mean follow up 1.9 years, the independent relationship between RLS magnitude and stroke recurrence analyzed
- Massive RLS was detected in 200 pts (41.2%)
- Stroke recurrence was low (5.8%) and similar in pts with m-RLS, with non-massive RLS and with no RLS
Regulations for PFO closure

- country specific

- limited for specific purposes such as
  “...for the closure of a patent foramen ovale in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through the PFO and who have failed conventional drug therapy...” (FDA)

Effect of PFO Closure on Migraine
Observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No (%) migraine</th>
<th>% improved or cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilmshurst 2008</td>
<td>37 57%</td>
<td>66%</td>
</tr>
<tr>
<td>Morandi 2003</td>
<td>62 23%</td>
<td>86%</td>
</tr>
<tr>
<td>Schwannmann 2004</td>
<td>215 22%</td>
<td>81%</td>
</tr>
<tr>
<td>Post 2004</td>
<td>66 39%</td>
<td>65% cured</td>
</tr>
<tr>
<td>Reisman 2005</td>
<td>120 42%</td>
<td>90%</td>
</tr>
<tr>
<td>Azarbal, 2005</td>
<td>89 42%</td>
<td>76%</td>
</tr>
<tr>
<td>Reisman 2005</td>
<td>162 35%</td>
<td>70%</td>
</tr>
<tr>
<td>Giardini 2006</td>
<td>131 37%</td>
<td>94%</td>
</tr>
<tr>
<td>Kimmelstein 2007</td>
<td>41 24%</td>
<td>80%</td>
</tr>
<tr>
<td>Luermans 2008</td>
<td>92 27%</td>
<td>70%</td>
</tr>
<tr>
<td>Dubiel 2008</td>
<td>191 24%</td>
<td>82%</td>
</tr>
</tbody>
</table>

PFO and migraine
Case History
Dr. Michael Mullen, Royal Brompton Hospital, London

13 yr old girl
Frequent incapacitating vertigo
Headache
Occ visual aura

Well between attacks
Normal neurological examination
Normal MRI and EEG

Missing significant amount of school
Large resting shunt on echo

Neurological opinion
Met with parents and patient on 2 occasions
Explained potential for benefit (~50%) and potential for complication (death <1:1000, embolization 1:200, tamponade 1:500, stroke 1:500, transient AF 1:10)

Catheterisation under GA July 2007
Large PFO - closed with 28 mm BioSTAR
No complications
FU Jan 08:
Almost complete resolution of symptoms:
No loss of school
Should PFO be closed for migraine

• So far, the results of clinical trials do not support routine PFO closure for migraine alone – however observational data still highly suggestive of link and in selected cases it is justified

Role of TCD: Right-to-Left shunt

• The efficient use of c-TCD among patients with migraine for future endovascular treatment not yet established
• Successful conclusion of the current trials will lead to more proactive utilization of TCD for PFO screening