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 µ in diameter) or in more subtle diffuse cerebral dysfunction such as neuropsychological disorders (microemboli ; < 40 µ)

- 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
Bullet Embolus to the Thoracic Aorta with Successful Endovascular Snare Retrieval
Keele et al, JVIN, 2010

• A 44-year-old man was seen at an outside institution following a gunshot wound to his right chest. A single bullet entered the Rt upper arm and continued into the thorax. There was no exit wound, a persistent loculated Rt pleural effusion.

• 2nd admission. Object consistent with a .22 caliber bullet at the base of the heart. This was believed to be located in the region of the transverse sinus abutting the aortic root, but not definitively intraluminal. Position of bullet (arrow) immediately after completion of the angiogram. This appeared to remain in a relatively stable position in the mid-descending thoracic aorta.

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 from 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
• Takayasus'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
  - Paradoxic 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
**EMBOLI CHARACTERISTICS**

**Cerebral Arterial Emboli**  
**Basic Identification Criteria**

- A Doppler microembolic signal is transient, usually lasting less than 30 milliseconds.
- 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 Monitoring
CPB stage, emboli asymmetrical

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

PFO
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.

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

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....

PFO

Ariel Sharon, 85-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-a-hole-in-my-heart-too-4-a-192332

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PFO

- 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.

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WHAT IS KNOWN ABOUT PFO AND STROKE

- PFO occurs up to 26% of all adults, number may actually higher
- 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%-5% 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 headaches, atrial septal aneurysm (seen by echo), and large PFO shunting (seen by TCD).
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
**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.

**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 or PFO.

**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 four fold (even on blood thinning medications). The presence of an ASA in a PFO stroke patient means that the YEARLY 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

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<tr>
<th>Study</th>
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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 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

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.

PFO Diagnosis: Contrast TCD or Contrast TTE/TEE?
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.

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.
- Contrast-TCD or 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 out-patient settings
**HOW ARE PFO DIAGNOSED?**

**CONTRAST-TRANSCRANIAL DOPPLER (c-TCD)**

- C-TCD is a 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+TEE 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.

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**TEE or TCD?**

**Initial Diagnosis of PFO**

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.
Diagnosis and Quantification of Patent Foramen Ovale. Which Is the Reference Technique? Simultaneous Study With Transcranial Doppler, Transthoracic and Transesophageal Echocardiography
González-Alujas et al, Rev Esp Cardiol. 2011

- 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 patent 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 (26%-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 manomter compared with Valsalva maneuver before closure 28.7 ± 6.6 mm Hg vs. 21.8 ± 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

<table>
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<th>Reference</th>
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<th>TTE Sens/Spec %</th>
<th>TCD Sens/Spec %</th>
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<td>saline-air-blood</td>
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<td>Di Tullio et al 1993</td>
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TCD vs. TTE

- Bubble-TEE
  - Sedation
  - Not possible to perform in patients with swallowing difficulties
  - Involves many specialists, expensive equipment
- Global Fee $1,400.00

- Bubble-TCD
  - Direct demonstration of embolism through a PFO to the cerebral circulation has been demonstrated

TCD and TEE

- Bubble-TCD is the cost-effective and minimally invasive compared to bubble-TEE
- Global Fee $219.00

Global Fee $1,400.00
**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
- Washington, DC Transesophageal Echocardiography Cost Average: $4,500
- Philadelphia, PA Transesophageal Echocardiography Cost Average: $3,900
- Houston, TX Transesophageal Echocardiography Cost Average: $3,600
- Miami, FL Transesophageal Echocardiography Cost Average: $3,200
- Dallas, TX Transesophageal Echocardiography Cost Average: $3,000
- Chicago, IL Transesophageal Echocardiography Cost Average: $3,000
- Los Angeles, CA Transesophageal Echocardiography Cost Average: $4,400
- New York, NY Transesophageal Echocardiography Cost Average: $4,000
- Atlanta, GA Transesophageal Echocardiography Cost Average: $3,600

**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

**Contrast**

- The use of "contrast" in echocardiography has been known for almost 40 years. Various contrast agents such as saline mixed with air, dextrose and water, the patient's own blood, carbon dioxide gas, hydrogen peroxide, sonicated iodinated contrast, and other commercially available agents have been used to opacify cardiac structures using echocardiography.
### Summary of c-TCD procedure

- Supine position, insert 18G (22G) needle into (right) cubital vein, insonate MCA
- Syringe I: 9 ml saline, Syringe 2: 1 ml air
- Connect both syringes with 3-way stopcock connected with a short flexible line to an iv 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

Merrill P. Spencer, M.D.
Merrill P. Spencer, M.D. 1922-2006

Power M-Mode Transcranial Doppler for Diagnosis of Patent Foramen Ovale and Assessing Transcatheter Closure
Spencer et al., 2004

- 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
(personal experience, more than 140 bubble-TCD tests)

- 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”!

Cerebral Ischemic Events Associated With ‘Bubble Study’ for Identification of Right to Left Shunts
{Romero et al. Stroke, 2009}

- Since January 2008, an average of 113 posts per month have been registered in the AAN list serve. Five neurologists with expertise in vascular neurology from 4 different institutions certified as stroke centers answered the question posted by one member and 5 (0.15%) cases were identified.
- In 2008, there were 3314 BS performed in the 4 institutions where cases were reported, including BS done during TTE, TEE, and TCD studies

- Based on a survey of 363 physicians, the American Society of Echocardiography acknowledged that there is a risk for transient side effects (0.062%), including TIAs, but implied that the diagnostic benefits of the procedure still outweighed the risks as long as precautions were undertaken.
- Specifically, one should prevent the injection of visible amounts of air (i.e., air that is no longer in microbubble form induced by the agitation and has collected as a large bubble at the top of the syringe), especially in patients with right to left shunt or arterial catheters.
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 image 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 *

Case Report

This is a 33-year-old-female that had an episode of slurred speech and a moderate headache lasting two minutes in March 2002. He complains of occasional dizziness and had a history of migraine with visual aura since his teenage years. We are asked to evaluate for the presence of a right to left cardiac/pulmonary shunt.

RESTING BUBBLE STUDY

Courtesy of Spencer Technologies

STRAINING BUBBLE STUDY

Courtesy of Spencer Technologies
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.
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

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

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

- 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 TEE of 13,092 patients without prior diagnosis of PFO or atrial septal defect undergoing surgery at the Cleveland Clinic, from 1995 through 2006. 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 639 PFO patients (28%), and surgeons were more likely to close defects in patients who were younger, were undergoing mitral or tricuspid valve surgery, or had history of TIA or stroke. 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 = .10).

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.

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

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

BioSTAR (NMT)
**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 18 mm, 25 mm, 30 mm

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.

STROKE PFO CLOSURE
CLINICAL TRIALS
Stroke PFO Closure Trials Design

<table>
<thead>
<tr>
<th>PFO</th>
<th>Cryptogenic Stroke</th>
<th>Medical Treatment (Life-long anticoagulation or aspirin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Percutaneous closure of PFO</td>
</tr>
</tbody>
</table>

Stroke PFO Closure Clinical Trials

- CLOSE (France)      ongoing
- CLOSURE I (USA)     Closed
- CLOSEUP             Closed
- RESPECT             Closed
- PC                  Closed
- REDUCE              ongoing (2015?)

Gore REDUCE (Started 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 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.
**Gore REDUCE**

- 664 patients
- Cryptogenic ischemic stroke or imaging confirmed TIA
- Presence of PFO confirmed by TEE
- No evidence of an alternative etiology for stroke
- Primary Endpoint: Freedom from recurrent ischemic stroke or TIA through at least 24 months post-randomization
- As of January 2013 total enrollment 316

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

*Buschbeck 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 thrombo-embolic events such as stroke.

**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
### 2 Year Primary Endpoint ITT

<table>
<thead>
<tr>
<th>STARFlex (n=447)</th>
<th>Medical (n=462)</th>
<th>Adjusted P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.9% (n=25)</td>
<td>7.7% (n=30)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1% (n=12)</td>
<td>3.4% (n=13)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3% (n=13)</td>
<td>4.6% (n=17)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Adjusting performed using Cox Proportional Hazard Regression and adjusting for related patient characteristics including age, atrial septal aneurysm, prior TIA/CV A, smoking, hypertension, hypercholesterolemia.

### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>STARFlex N=402</th>
<th>Medical N=458</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major vascular complications</strong></td>
<td>3.2% (n=13)</td>
<td>0.0% (n=0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>5.7% (n=4/23 periprocedural)</td>
<td>0.7% (n=3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>2.0% (n=13)</td>
<td>1.1% (n=1)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Death (all causes)</strong></td>
<td>0.5% (n=1)</td>
<td>0.7% (n=1)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>3.3% (n=12)</td>
<td>5.3% (n=20)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Any SAE</strong></td>
<td>16.9% (n=68)</td>
<td>16.6% (n=76)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Perforation LA (1); hematoma >5cm at access site (4); vascular surgical repair (1); peripheral nerve injury (1); procedural related transfusion (1); periprocedural bleed (1)

### CONCLUSIONS

- 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%) vs 0.7%.
- 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

The PC Trial

- 414 patients, of whom 204 were randomized to percutaneous PFO closure and 210 to medical therapy.
- The primary endpoint was a composite of all-cause mortality, non-fatal stroke, TIA, and peripheral embolism. After five years of follow-up, there was a non-significant 37% relative risk reduction in the incidence of the primary composite endpoint favoring PFO closure.
- A multicenter trial in 29 centers in Europe, Canada, Brazil, and Australia in which the assessors of endpoints were unaware of the study-group assignments.
- The mean duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical-therapy group.

- At a mean follow-up of 4 years, the rate of the primary endpoint — a composite of death, nonfatal stroke or TIA, and peripheral embolism — was 3.5% in the closure group and 5.2% in the medical-therapy group (hazard ratio, 0.63; 95% confidence interval, 0.24–1.62; P=0.34).
- Closure of a PFO for secondary prevention of cryptogenic embolism was not significant in a reduction in the risk of recurrent embolic events or death as compared with medical therapy.
- There were no significant differences in the incidence of secondary endpoints or bleeding complications between treatments.
- The PC Trial: PFO Closure Not Statistically Superior to Medical Therapy for Stroke Prevention.
- The study did find an 80% relative risk reduction in the incidence of stroke favoring PFO closure. According to the study investigators, this finding may be clinically relevant if confirmed by future trials.
PFO and medical treatment for secondary stroke prevention
Kitsos et al. Stroke, 2012

- 52 single-arm studies, 7 comparative non-randomized studies and the CLOSURE I were reviewed
- Further randomized trial data are needed to precisely determine effects of closure on stroke recurrence, the results of CLOSURE I trial challenge the credibility of a substantial body of observational evidence strongly favoring mechanical closure over medical therapy

Respect data
AHA Stroke meeting
February 5-8, 2013

- Data indicates that the risk of a stroke was reduced by 46.6% to 72.7% when patients were treated with the Amplatzer PFO Occluder over conventional medical management
- Despite missing its primary endpoints, St. Jude plans to submit the product for FDA clearance by mid-2013

RESPECT data
AHA Stroke meeting
February 5-8, 2013

- All 25 primary endpoint events were recurrent ischemic strokes: 16 in the medical management group and nine in the device group. In the device group, three ischemic strokes occurred without a device in place and three occurred in a deep penetrator artery distribution, according to the study abstract.
According to time-to-event analyses, there was a trend for benefit associated with device therapy in the intention-to-treat population (HR=0.5; 95% CI, 0.22-1.13). There was significant benefit in the per-protocol (HR=0.37; 95% CI, 0.14-0.97) and as-treated (HR=0.28; 95% CI, 0.1-0.76) populations.

### Device Closure vs. Medical Therapy

**Khairy: Heart 2004**

<table>
<thead>
<tr>
<th>Event Endpoints</th>
<th>Medical</th>
<th>Device Closure</th>
<th>HR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0.42%</td>
<td>0.2%</td>
<td>2.09</td>
<td>1.04-4.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Death</td>
<td>1.42%</td>
<td>0.6%</td>
<td>2.31</td>
<td>1.15-4.62</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke or death</td>
<td>1.86%</td>
<td>0.7%</td>
<td>2.45</td>
<td>1.27-4.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke or death at 1 year</td>
<td>2.71%</td>
<td>0.61%</td>
<td>4.53</td>
<td>1.82-11.13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adjusted stroke or death at 1 year</td>
<td>2.71%</td>
<td>0.77%</td>
<td>4.36</td>
<td>1.89-9.94</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Adjusted by Cox survival analysis for diabetes, hypertension, and smoking.*

**NAC:** number needed to treat; **HR:** hazard ratio; **CI:** confidence interval; **TAB:** transeptal ablation study.
What we have today

- The superiority of percutaneous PFO closure to medical treatment among patients with stroke of unknown origin remains controversial for a number of reasons
- Observational studies suggested a lower risk of recurrence with PFO closure compared with medical treatment
- The CLOSURE I trial failed to show superiority of PFO closure over medical treatment
- The PC Trial did find an 80% relative risk reduction in the incidence of stroke favoring PFO closure.
- The RESPECT trial showed a trend for benefit associated with device therapy in the intention-to-treat population

What we have today

- Those in favor of PFO closure have emphasized that these findings, together with the secondary endpoint analyses, reaffirm that carefully selected patients with a history of cryptogenic stroke and PFO may, indeed benefit in stroke risk reduction from device closure vs. medical management alone
- Others, have, are quick to point out that this evidence is inconclusive given the lack of statistically significant primary endpoint resulting demonstrating superiority of one therapy over intervention
- The need for further investigation of device closure as a superior treatment to medical therapy alone in patients with PFO and cryptogenic stroke is warranted

More Inconclusive Results from PFO-Closure Trials

- The RESPECT trial provides something for everyone. For skeptics of PFO closure, the primary intention-to-treat analysis is negative (although there is some suggestion of effect). For enthusiasts, the per-protocol analysis suggests benefit.
- The PC Trial offers similar uncertainty: The hazard ratio indicates a 37% reduction in risk for the primary endpoint with PFO closure, with a number needed to treat of about 1 in 50; however, the finding is non-significant and could have occurred by chance.
- Is the therapy ineffective, or are these studies underpowered for a meaningful effect?
What we have today

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)

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
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 hyperintensities 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 ½ 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.

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

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®.
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.

**MIST I Clinical Trial**

- Screened 432 Migraine with aura patients for a PFO and enrolled 147 patients into the study. A significant finding is that over 80% 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 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.
### Premium Migraine Trial
This study is currently recruiting participants.

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

- **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

### Effect of PFO Closure on Migraine
**Observational studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>% Improved</th>
<th>% Improved or Cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilmshurst 2000</td>
<td>37</td>
<td>57%</td>
<td>86%</td>
</tr>
<tr>
<td>Morandi 2003</td>
<td>62</td>
<td>37%</td>
<td>88%</td>
</tr>
<tr>
<td>Schwarzmann 2004</td>
<td>215</td>
<td>22%</td>
<td>81%</td>
</tr>
<tr>
<td>Post 2004</td>
<td>66</td>
<td>39%</td>
<td>65% cured</td>
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<tr>
<td>Reisman 2004</td>
<td>120</td>
<td>42%</td>
<td>90%</td>
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<tr>
<td>Azarbal, 2005</td>
<td>89</td>
<td>42%</td>
<td>74%</td>
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<tr>
<td>Reisman 2005</td>
<td>162</td>
<td>35%</td>
<td>70%</td>
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<tr>
<td>Giardini 2006</td>
<td>131</td>
<td>27%</td>
<td>91%</td>
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<tr>
<td>Kimmelstein 2007</td>
<td>41</td>
<td>34%</td>
<td>80%</td>
</tr>
<tr>
<td>Loermans 2008</td>
<td>92</td>
<td>27%</td>
<td>70%</td>
</tr>
<tr>
<td>Dubiel 2008</td>
<td>191</td>
<td>24%</td>
<td>87%</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
Case History
Dr. Michael Mullen, Royal Brompton Hospital, London

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
Advanced Emboli Monitoring: PFO and Stroke & PFO and Migraine

- Questions?
- arazumovsky@sentientmedical.com

Alex, may I be excused? My brain is FULL...

POSTTRAUMATIC VASOSPASM
TBI

**Civilian**
- Every 21 seconds, one person in the US sustains traumatic brain injury (TBI)
- An estimated 5.3 million Americans – little more than 2% of the US population – currently live with disabilities resulting from brain injury
- Each year, 80,000 Americans experience the onset of long-term disability following TBI

**Battlefield**
- Okie, NEJM, 2005: Among surviving soldiers wounded in combat in Iraq and Afghanistan, TBI appears to account for a larger proportion of casualties than it has in other recent U.S. wars.
  According to the Joint Theater Trauma Registry, 22% had injuries to the head, face, or neck.

Blast TBI

- Peacetime terrorism over the last decade has reminded us otherwise.

**Why we need talk about blast TBI?**

- **Mortality:**
  - Oklahoma City: 167
  - US Embassy: 223
  - World Trade Center: 2,801
  - Madrid train bombings: 191
  - London: 56
  - Domodedovo: 37
  - Minsk metro: 12

  Large number of injured...
TBI PATHOPHYSIOLOGY

Balancing Multisystem Interactions

TBI: Pathophysiology

Primary Injury:
- Contusions/Hemorrhages
- Diffuse Axonal Injury (DAI)

Secondary Injury (Intracranial) occurs hours to weeks after injury:
- Blood Flow and Metabolic Changes
- Traumatic Hematomas
- Cerebral Edema
- Hydrocephalus
- Increased Intracranial Pressure
Decrease in CBF
BRAIN EDEMA

More Brain Edema
Ischemic brain cells
Cell Injury

Increased ICP
Blood Vessels Dilate

TBI and VSP
• Cerebral posttraumatic VSP (PTV) was first described by Lorn in 1936
• The incidence of CT documented traumatic SAH has been identified in 4% to 63% of pts after TBI
• Study from the University of Mississippi Medical Center indicated that traumatic SAH complicate course of TBI in 69% of the patients due to the presence of PTV

Clinical Significance
• 41% of patients who died from TBI had PTV (MacPherson et al., 1973)
• 24% with massive tSAH developed ischemic symptoms in contrast to 3% of patients with mild tSAH (Taneda et al., 1996)
• Ischemic symptoms accompanying arterial VSP following tSAH are comparable to those found following aneurysmal SAH
Post-Traumatic VSP

- Ischemic symptoms caused by cerebral arterial spasm following traumatic SAH are comparable to those found following aneurysmal SAH:
  - appearance of symptoms between Days 4 and 16 after injury, with the peak incidence on Days 9 and 10
  - close correlation between the main site of the subarachnoid blood and the location of severe vasospasm responsible for the symptoms; and a higher incidence of symptoms in patients with massive SAH than those with slight SAH
- Subarachnoid blood plays an important role in the later development of vasospasm, not only following aneurysm rupture but also after head injury. Nevertheless, there is no general agreement that subarachnoid blood in head injury is an important risk factor in the development of vasospasm and ischemic brain damage.

WARTIME TRAUMATIC CEREBRAL VASOSPASM: RECENT REVIEW OF COMBAT CASUALTIES
Armonda et al., Neurosurgery, 2006

- The first study to analyze the effects of blast-related injury on the cerebral vasculature.
- This study showed that TCV occurred in a substantial number of patients (47.7%) with severe neurotrauma, and clinical outcomes were worse for those with this condition.

Patient after blunt TBI, no blood was detected by CT and MRI
Case 35. 25 yo, blunt TBI, no SAH
(Courtesy of Dr. Armonda)

CBFV 120 cm/s  CBFV 57 cm/s

CBFV 112 cm/s  CBFV 89 cm/s

25 yo, blunt TBI
no SAH (Courtesy of Dr. Armonda)
Methods

- Prospective TCD database maintained in the Sentient NeuroCare Services
- TCD recordings of mean cerebral blood flow velocities (CBFV, in cm/s) and Pulsatility Indices (PI) were recorded using a 2-MHz transducer (Doppler Box, DWL/Compumedics, USA).
- A comprehensive TCD protocol was applied in all cases
- Study and analysis of the data were done according to the IRBNet protocol 363439-4.

Clinical Material

- 122 consecutive patients with TBI, admitted to the Walter Read National Military Medical Center (WRNMMC) from Oct. 1, 2008 to Nov. 30, 2012
- Mean age 26.1 ± 5.4 years
- The mean time between day of injury and admission to the WRNMMC was 6.7 ± 3.8 days
Results

- TCD signs of mild, moderate and severe VSP involving anterior circulation vessels were observed in 71%, 42% and 16% of patients, respectively.
- TCD signs of mild, moderate and severe VSP involving posterior circulation vessels were observed in 57%, 32% and 14% of patients, respectively.
- TCD signs of intracranial hypertension were recorded in 43%.
- Eight patients (7%) underwent transluminal angioplasty for post-traumatic symptomatic vasospasm treatment.

Results

- There were 88 patients with PHI, among them 45 (51%) had secondary diagnosis of blast injury.
- There were 34 patients with CHI, among them 15 (44%) had had secondary diagnosis of blast injury.

Results

<table>
<thead>
<tr>
<th>TCD signs of vasospasm</th>
<th>Anterior circulation CBFV (cm/s) Mean ± SD</th>
<th>Posterior circulation CBFV (cm/s) Mean ± SD</th>
<th>Initial GCS Mean ± SD</th>
<th>Discharge GOS Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild vasospasm</td>
<td>122.5 ± 9.4</td>
<td>61.0 ± 15.7</td>
<td>8.0 ± 4.3</td>
<td>6.1 ± 1.9</td>
</tr>
<tr>
<td>Moderate vasospasm</td>
<td>156.6 ± 15.2</td>
<td>77.5 ± 17.9</td>
<td>5.9 ± 3.7</td>
<td>5.3 ± 2.2</td>
</tr>
<tr>
<td>Severe vasospasm</td>
<td>241.9 ± 31.6</td>
<td>101.8 ± 32.8</td>
<td>4.8 ± 2.8</td>
<td>4.8 ± 2.6</td>
</tr>
</tbody>
</table>
Limitations

- We were not able to correlate clinical vasospasm with angiographic vasospasm and combine TCD data with other neuroimaging methods that help to identify impaired cerebral perfusion in patients with TBI
- The lack of established TCD criteria for vasospasm in young patients presents interpretative issues
- Work in progress
- Current data should be validated prospectively

Conclusions

- Our data suggest that abnormal TCD findings are frequent in patients with wartime TBI and showed post-traumatic vasospasm and intracranial hypertension in a significant number of patients
- Delayed cerebral arterial spasm is a frequent complication of combat TBI, and severity of cerebral vasospasm is comparable to that seen in aneurysmal SAH
- Our results confirm earlier data that traumatic SAH is associated with a high incidence of cerebral vasospasm with a higher probability in patients with severe TBI

Conclusions

- The high sensitivity of TCD to identify abnormally high CBFVs and PIs due to the onset of vasospasm and intracranial hypertension, respectively, demonstrates that TCD is an excellent first-line examination to determine those patients who may need urgent aggressive treatment and continuous invasive ICP monitoring
- TCD screening may allow for invasive/endovascular treatment of vasospasm, as was done in a minority subset of our study population
- Because vasospasm and intracranial hypertension represent significant events in a high proportion of patients after wartime TBI, daily TCD monitoring is recommended for the management of such patients
TCD & INTRACRANIAL HYPERTENSION

Intracranial Pressure

- Normal <15 mm Hg
- ICP >20-25 mm Hg
  - Increases morbidity and mortality
- ICP monitoring rarely available in the ED or in military field hospital or during medevac
- Must use physical findings
  - Neurologic deterioration
  - Unilaterally dilated pupil

ICP Monitoring Methods

- IV catheter “Gold Standard”
  - Most invasive method
  - High infection rate
  - May be difficult to insert
  - Simultaneous CSF drainage and ICP monitoring not possible
- I/P Probe
  - Measures local pressure
  - Drift of zero over time
- ED Probe
  - Limited accuracy
  - Relatively delicate
- SA Probe
  - Limited accuracy
  - High failure rate
  - Periodic flushing necessary
Typical morphology of TCD wave-form

- MCA (M1 and M2 segm)
- ICA (C1, C3 and C4 segm)
- ACA (A1 segm)
- PCA (P1, P2 segm)

- Low peripheral resistance/Low PI
- OA
- High peripheral resistance/High PI

TCD wave-form progression from intact CBFV to circulatory arrest

Hassler et al., 1988

TCD wave-form changes with development of intracranial hypertension

Moreno et al., 2000; Beliner et al., 2004; et al., 2005; Splavski et al., 2007; Melo et al., 2011; de Riva et al., 2012 and many others

Normal ICP

PI > 1.25 (Bouat et al., 2013)
ICP 20 mm Hg and higher
Patient with GSW
Trend shows almost direct inverse relationship between CBFV and PI

Epidural ICP monitor

TCD and ICP

- Numerous data shows a highly significant correlation between TCD PI and ICP independent of intracranial pathology.
- Accordingly, in patients with suspected increase in ICP or where an increased ICP has to be excluded, PI may be of guidance and repeated PI measurements might prove a useful tool in neurointensive care or out patient.

TCD in the management of TBI

- This non-invasive and simple procedure must be engaged in the daily management of TBI patients
- Pulsatility Index (PI) measurements permit the early identification of patients with low CPP/high ICP and high risk of cerebral ischemia. In emergency situations it can be used alone when ICP monitoring is contraindicated or not readily available
Non-Invasive ICP monitoring would enable

- Triage at the point of contact
  Battlefield, football field, ambulance, ER…
- In-time and evidence-based application of therapy
  Titrate therapy to ICP targets
- Long-term monitoring
  Without the risk of infection or damage to vital brain structures
- Expansion of patient pool for which monitoring might be beneficial
  Mild and moderate TBI, migraines, pediatric patients,…
Role of TCD: Intracranial hypertension evaluation

- TCD wave-form changes indicates abnormally high ICP, especially after 20 to 30 mm Hg
- TCD changes may alarm Neuro-ICU personnel and may indicate malfunctioning of ICP probe
- Abnormally globally decreased pattern of the CBFV's in parallel with increased PI's indicate onset of diffuse intracranial hypertension
- Sudden onset of asymmetrical CBFV's and PI's changes may indicate potential mid-line shift
- TCD quantitative and qualitative analysis must be taken into account for evaluation of intracranial hypertension, however, MAP, PaCO2 and cardiac output must be within the normal limits