Charles E. Schmidt College of Medicine

Presenters do not have a financial interest/arrangement with one or more organization that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Case

- 54 YO M with no PMH or Hospitalizations
- Went to bed at 6:00 in normal state and woke up at 14:00 with facial drooping, dysphagia, dysarthria and generalized weakness
- Denied CP, SOB, HA, and changes in vision. The patient reports no recent infection and no prior stroke.
- Does not see a doctor regularly. Denies ever having routine screening or blood work
- No recent or past history of seizure, trauma, or syncope.

Additional History

- Umbilical Hernia repair 4 years prior
- No allergies or current medications
- Family history significant for:
  - Father (87) - DMII; atrial fibrillation; MI at age 75
  - Mother (83) - Atrial fibrillation; otherwise healthy
- Single, never married, no children, not sexually active
- Lives with his parents. Able to all perform ADL's
- Previously in Army/Air Force
- Denies current or past use of cigarettes, alcohol or recreational drugs

Physical Examination:

- VITALS: 130/73mmHg, HR 70, RR 18, temp 98.1F-oral, 97% O2 sat on room air
- GENERAL: Well-developed, well-nourished male, AAOx3
- HEENT: NC/AT, Moist mucosa, no LA or JVD
- HEART: RRR, No MGR
- LUNGS: CTA BL
- ABDOMEN: ND/NT, +BS
- MUSCULOSKELETAL: no muscle atrophy, no joint redness or swelling

Physical Examination:

- VASCULAR: 2+ DP pulses bilaterally, no edema
- NEUROLOGIC: good visual acuity, PERRL, EOMI, sensation intact throughout all 3 divisions of the face, muscles of mastication in tact, facial drooping on the left side which spares the forehead; uvula midline, no deviation of tongue, strength 5/5 throughout; Speech fluent and appropriate

Differential Diagnosis

- TIA
- Stroke
- Seizure
- Infection
- Malignancy
- Psychiatric
- Bell's Palsy

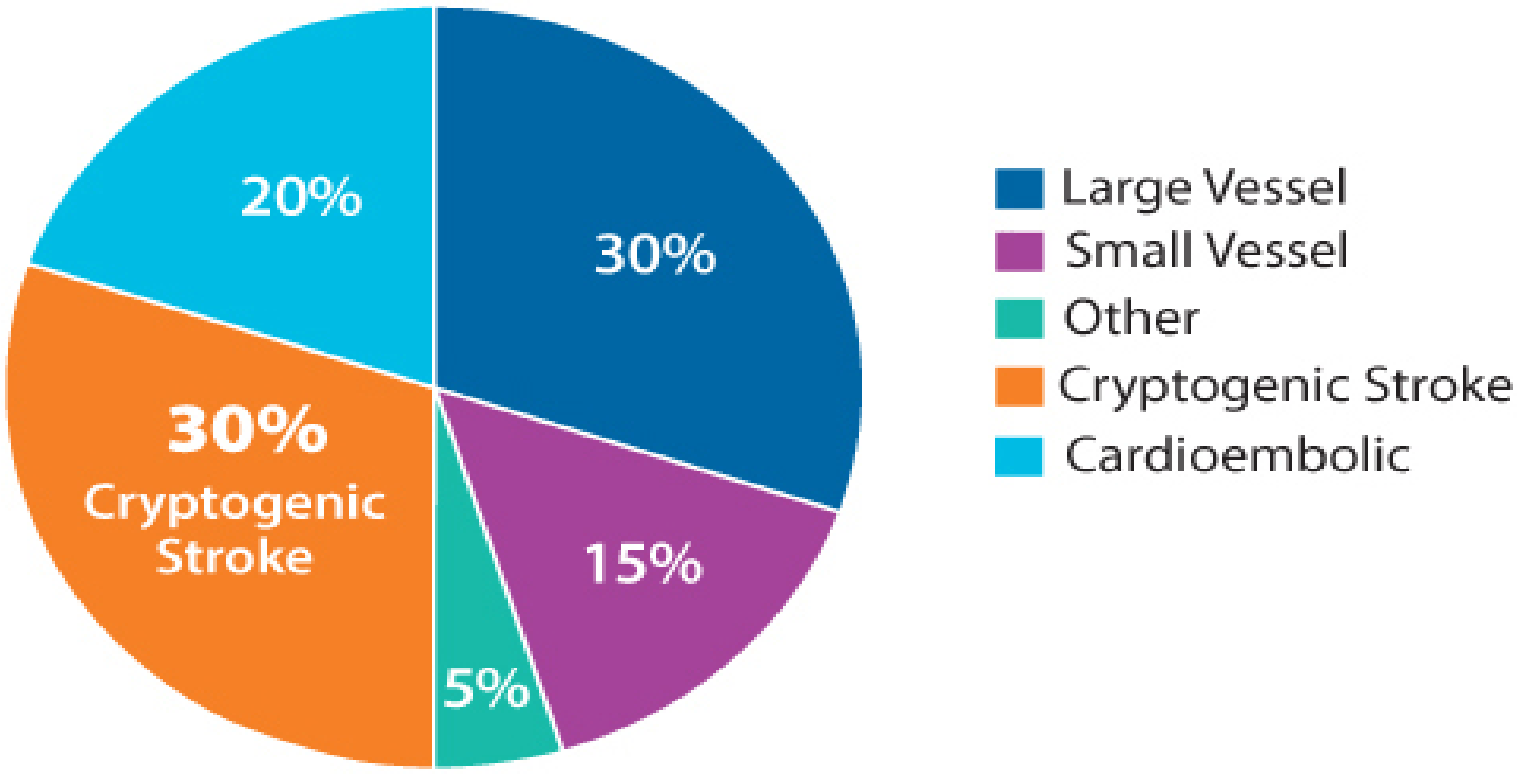
Work Up

- CBC
- CMP
- CXR
- EKG
- UA
- Drug Screen
- TSH
- HbA1c
- Coagulation Profile
- ESR
- Lipid Panel
- CT Brain
- Perfusion Scan
- TTE/TEE
- Carotid Doppler
- CT Neck Angio

Types of Strokes

- Ischemic Stroke 83%
  - Cryptogenic 30%
  - Lacunar 25%
  - Atheroembolic 20%
  - Embolic 20%
- Hemorrhagic Stroke 17%
  - Intracerebral Hemorrhage 59%
  - Subarachnoid Hemorrhage 41%

Ischemic Stroke

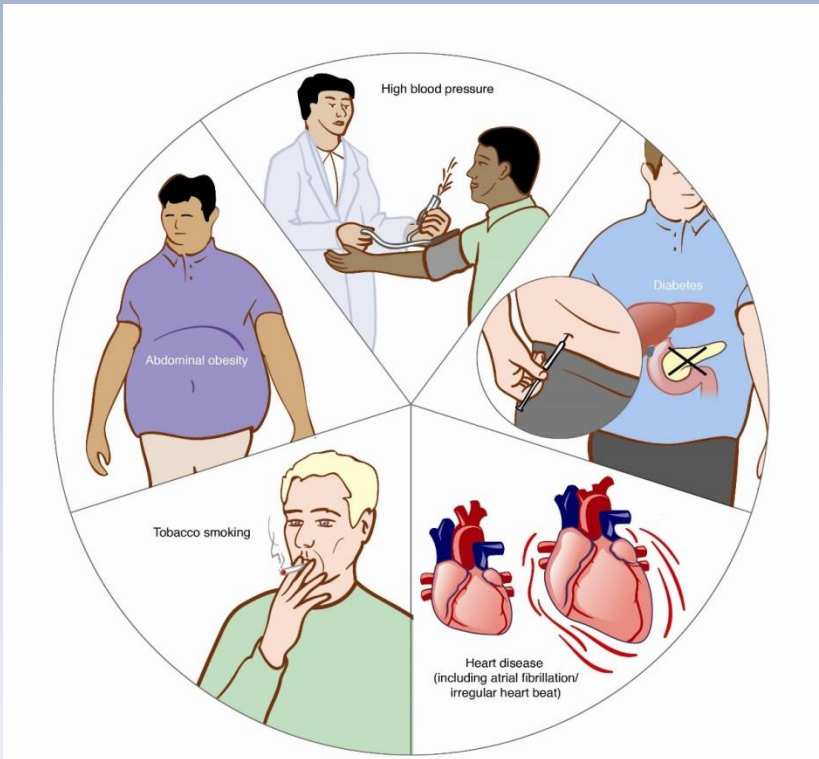


Cryptogenic Stroke

- 30 to 40 percent of ischemic strokes
- ~800,000 new or recurrent strokes yearly
- 690,000 ischemic strokes every year in the US
- Approximately 200,000 cryptogenic strokes (CS) annually

Epidemiology And Risk Factors

- Age
- Gender
- Race and ethnicity
- Atrial septal abnormalities
- Cardiac disease
- Diabetes
- Family history
- Hypertension
- Homocysteine
- Inflammatory and infectious causes
- Lipids
- Prior TIA
- Pulmonary shunts
- Smoking



Cardinal Stroke Risk Factors

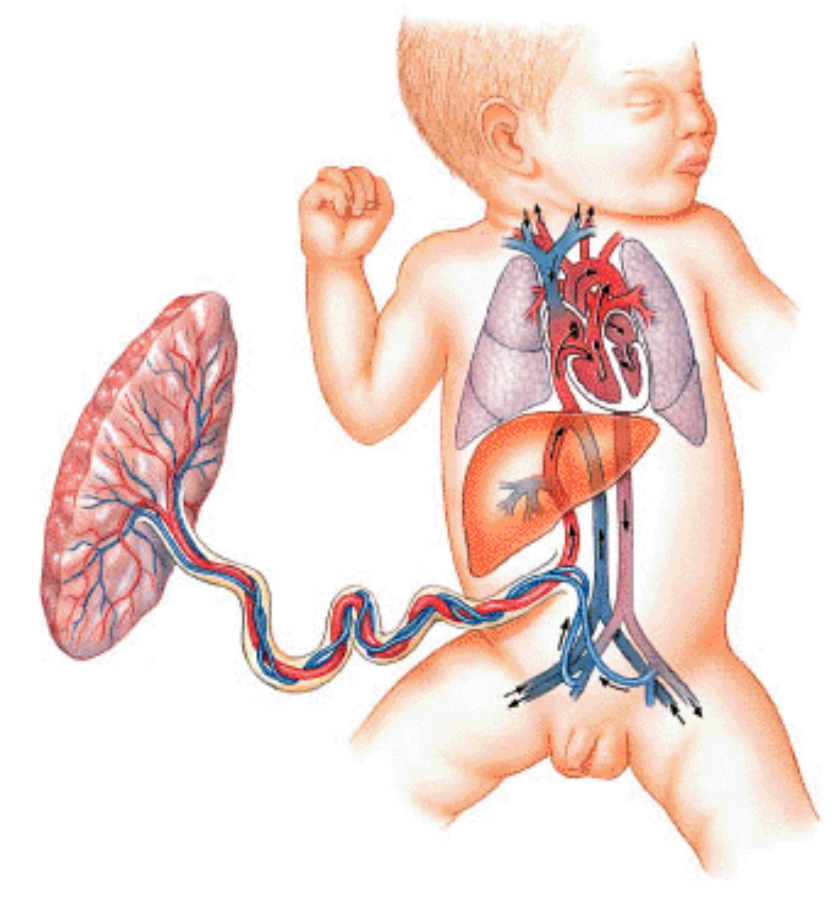
Pathogenesis

- Occult cardiac embolism secondary to paroxysmal atrial fibrillation, aortic atheromatous disease, or other cardiac sources
- Paradoxical embolism secondary to patent foramen ovale (PFO) or other atrial septal abnormalities
- Thrombophilia (hypercoagulable states including those related to antiphospholipid antibodies or to occult cancer with hypercoagulability of malignancy)
- Preclinical or subclinical cerebrovascular disease (ie, intracranial and extracranial vascular changes)
- Potentially inflammatory processes (e.g, elevated C-reactive protein or chronic infections)

Treatment of Strokes

- Ischemic Strokes:
  - tPA within 3 hours(and up to 4.5 hours in certain eligible patients) for ischemic strokes
  - Mechanical thrombectomy, within six hours of acute stroke symptoms, and only after a patient receives tPA.
  - Acute management of cryptogenic stroke should not differ from other ischemic stroke subtypes.
- Hemorrhagic Strokes:
  - Anticonvulsants - To prevent seizure recurrence
  - Antihypertensive agents - To reduce BP and other risk factors of heart disease
  - Osmotic diuretics - To decrease intracranial pressure in the subarachnoid space

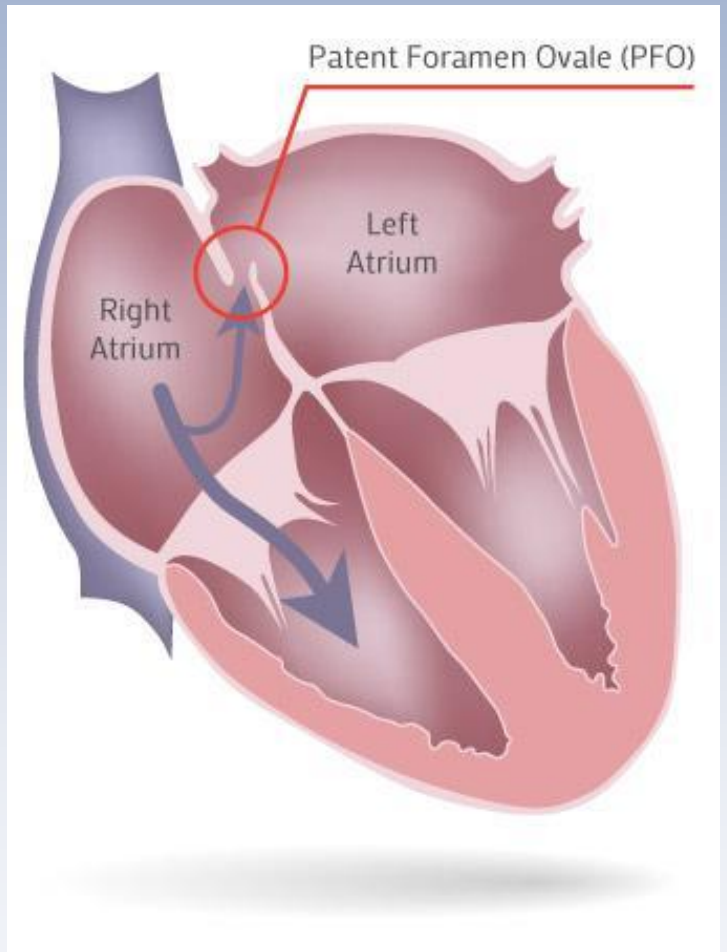
Patent Foramen Ovalis



- Required during fetal development to allow oxygenated blood to flow from the RA to the LA

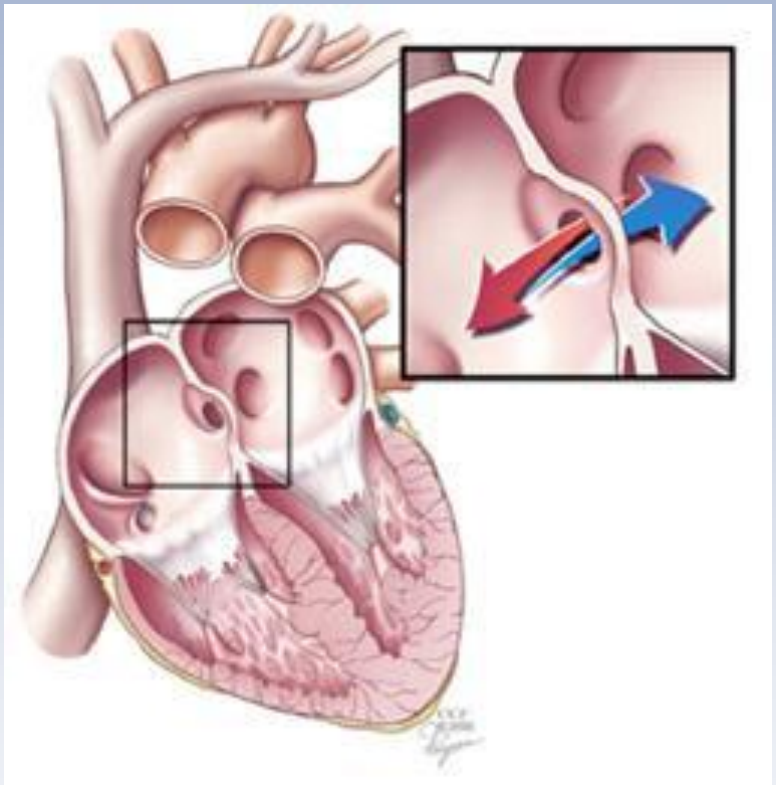
Patent Foramen Ovale

- Fusion usually occurs by age 2
- Complete closure occurs in 75%
- Remaining 25% having a PFO



Atrial Septal Aneurysm

- Defined as a redundant and mobile tissue in the area of the fossa ovalis.
- Rare. Prevalence is <2%.
- Usually an incidental finding on routine TTE
- Commonly asymptomatic.
- Most likely to be congenital rather than acquired.



Classification of ASA

- 1R protrudes to the right atrium throughout the cardiorespiratory cycle
- 2L protrudes to the left atrium throughout the cardiorespiratory cycle
- 3RL Protrudes to right atrium with a lesser excursion towards the left atrium throughout the cardiorespiratory cycle
- 4LR Protrudes left atrium with a lesser excursion towards the right atrium throughout the cardiorespiratory cycle
- 5 The aneurysm excursion is bidirectional and equidistant to the right and the left atrium throughout the cardiorespiratory cycle

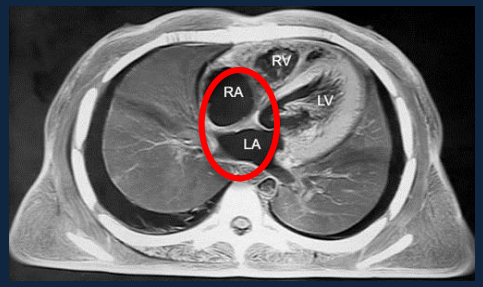
Atrial Septal Aneurysm

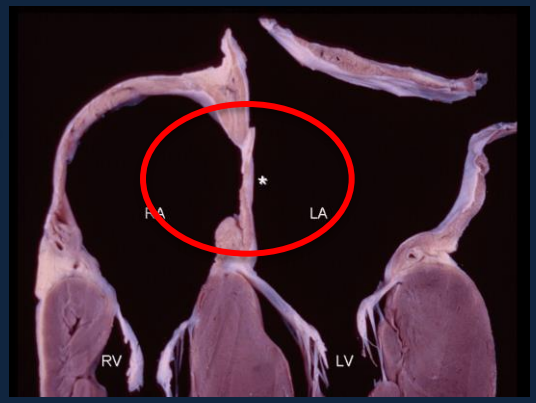
- Cryptogenic stroke is among the most concerning manifestations of ASA.
- Patients with ASA and no ASD are unique because they lack an intracardiac shunt.
- Almost all patients with ASA have at least one additional source/cause for the patient's cryptogenic emboli.

Atrial Septal Aneurysm

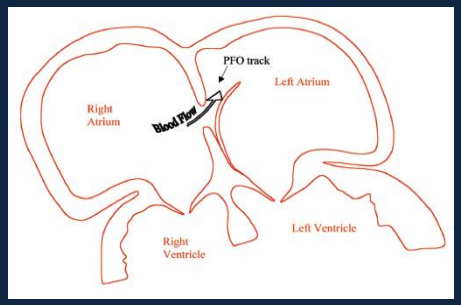
- An ASD with a diameter greater than 4mm correlates with an increased risk of multiple strokes in different time periods and TIA.
- Leads to the question: How should these defects be managed?

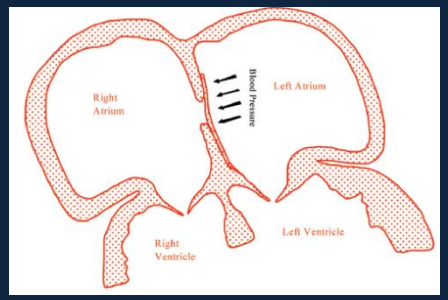
DEFINITIONS

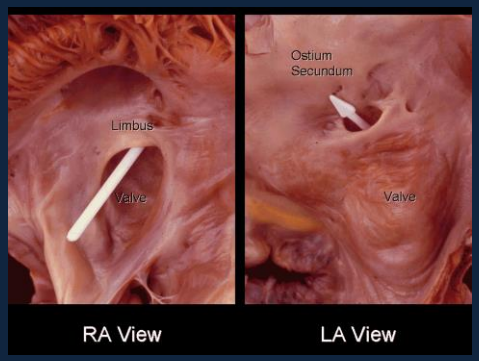




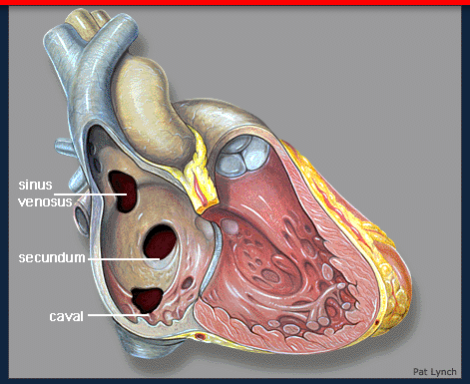
P.F.O

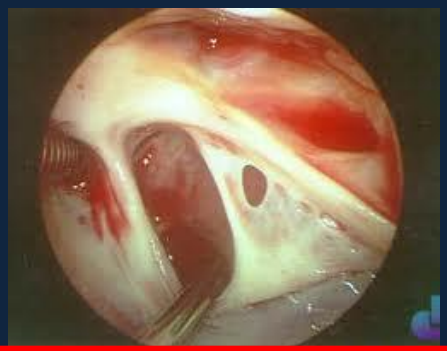




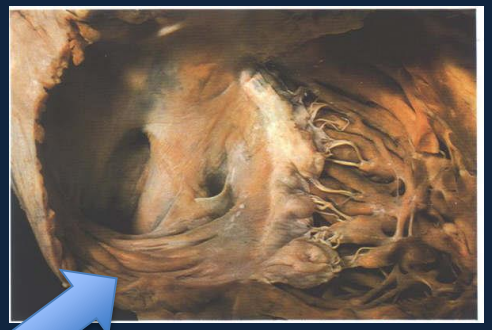


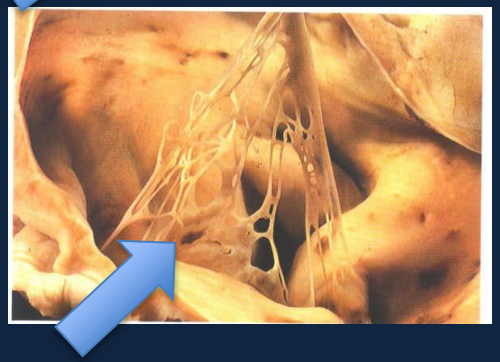
A.S.D

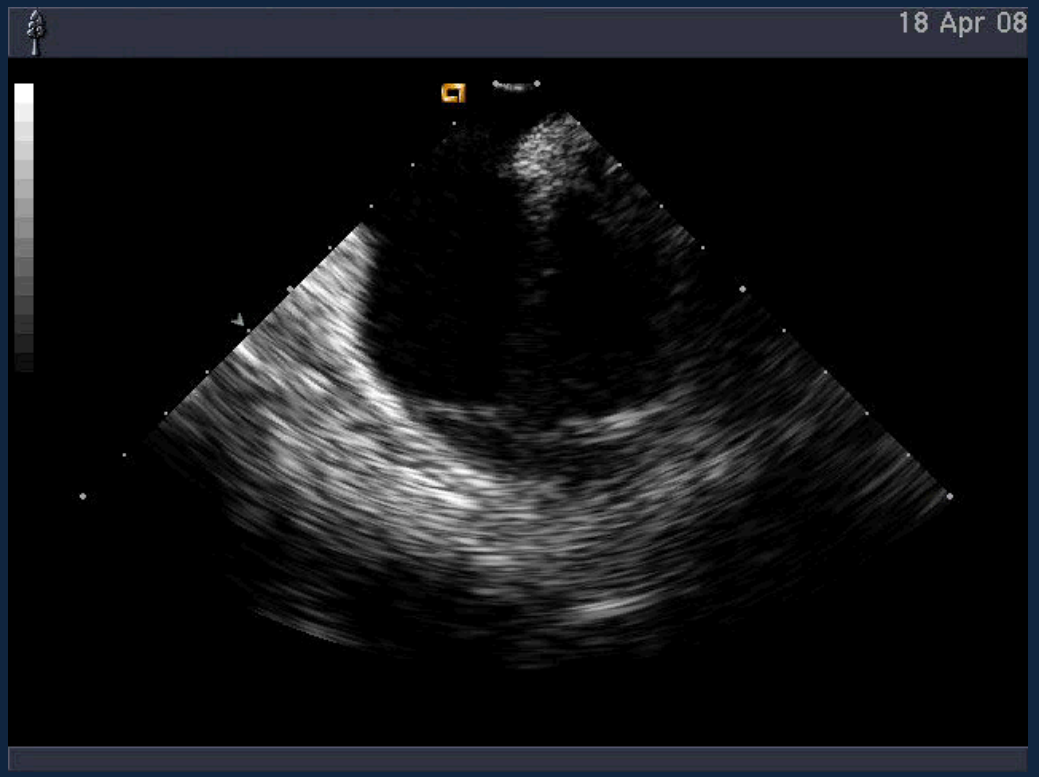


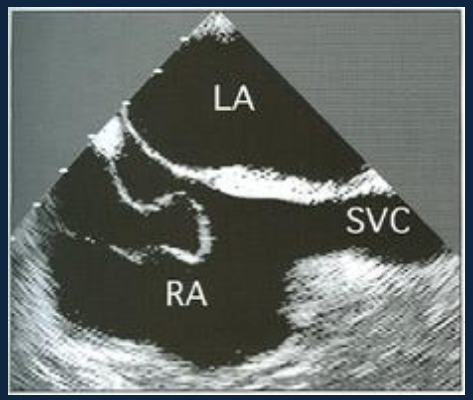


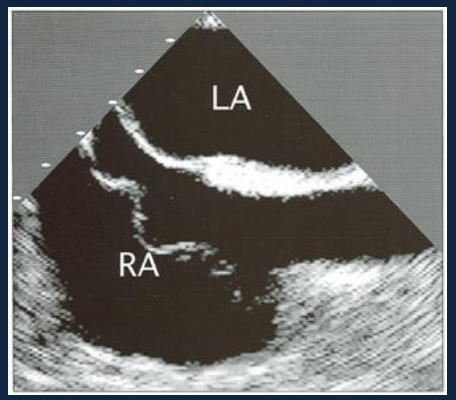
Chiari's Network / Eustachian Valve





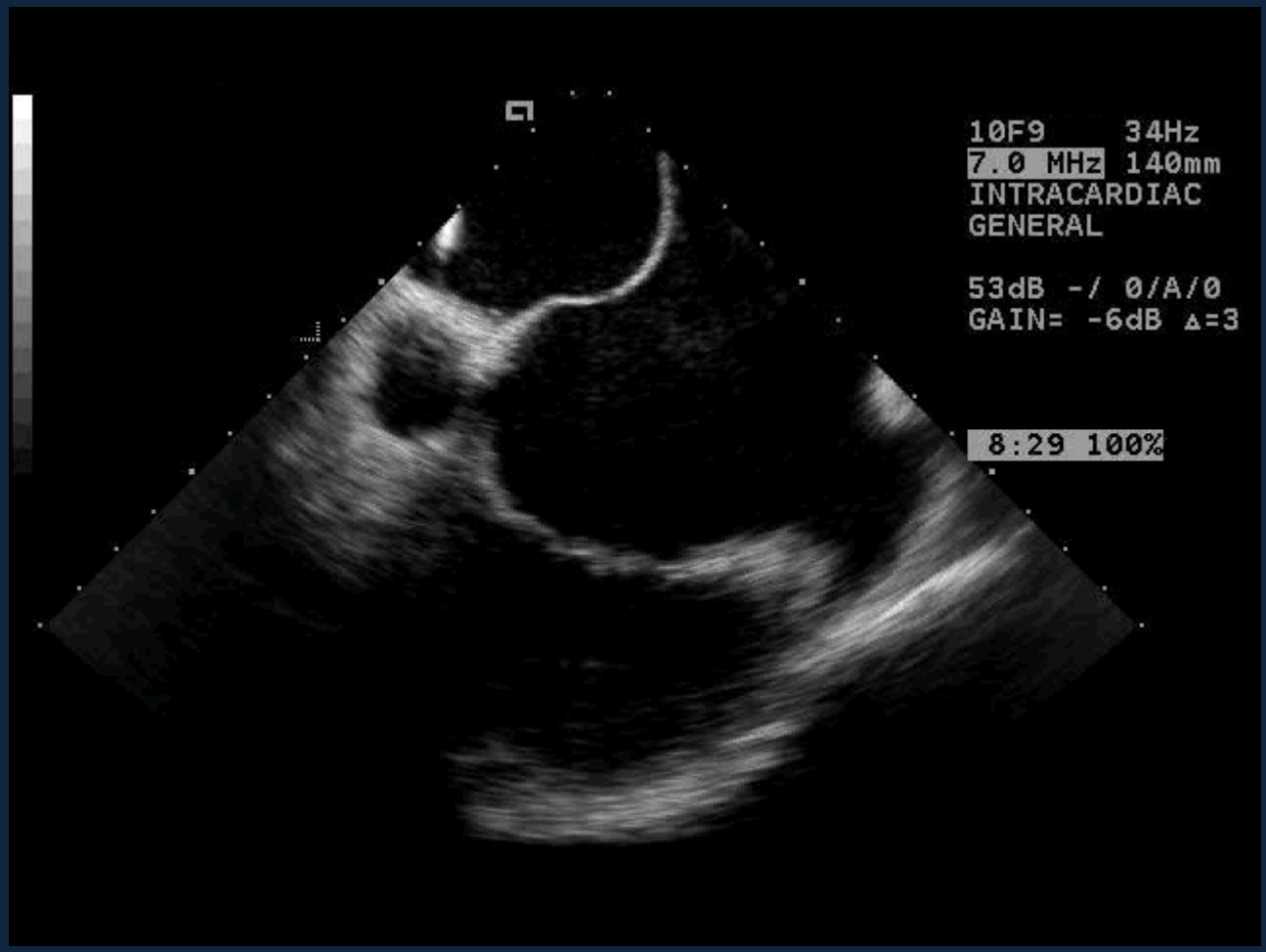






Atrial Septum Features

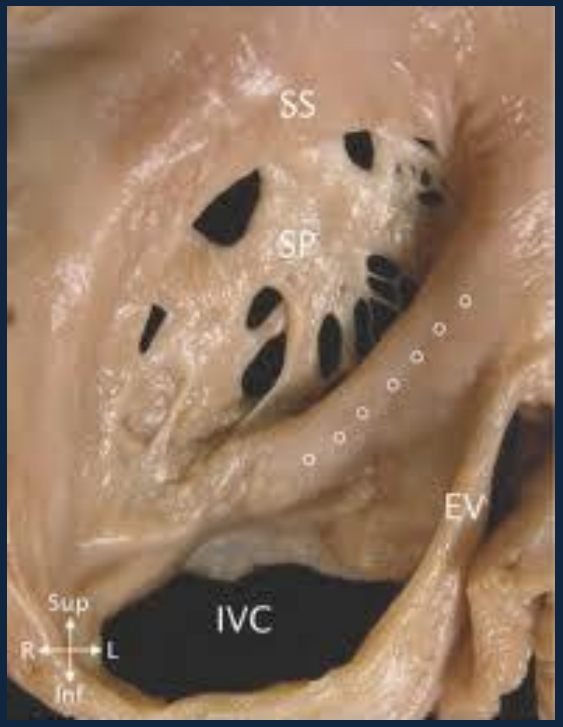
Aneurysmal Atrial Septum

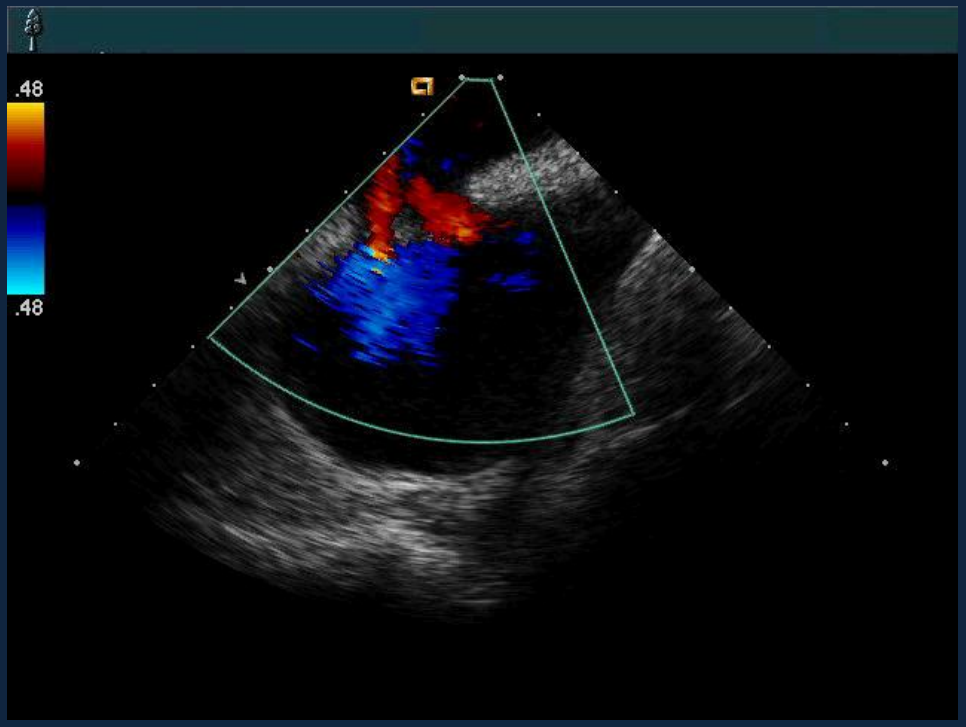


Overell JR, et al. Neurology 2000;55(8):1172-9

Atrial Septum Features

Multifenestrated / Swiss-cheese

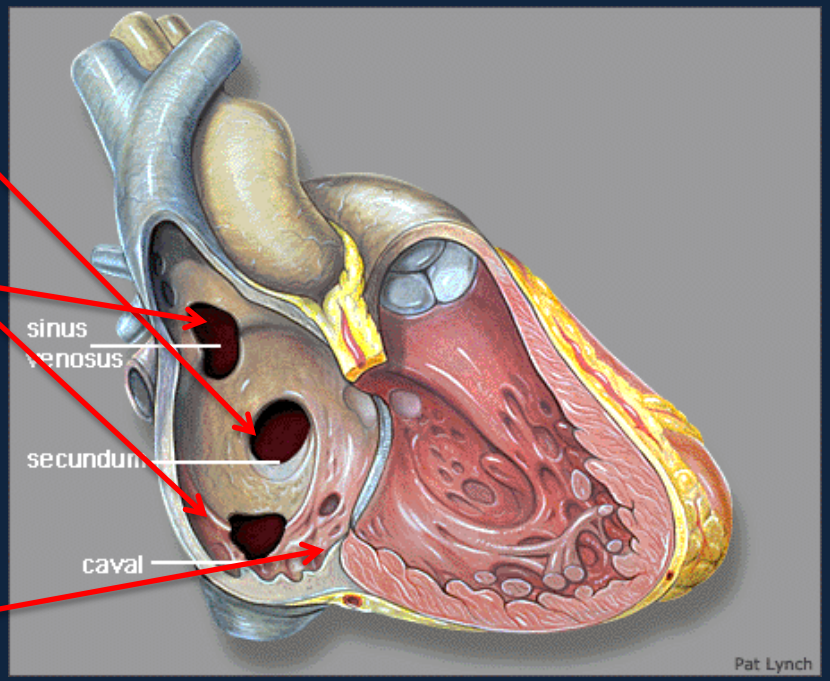




Atrial Septal Defects

Real embriologic opening/defect between atria (excludes PFO!)

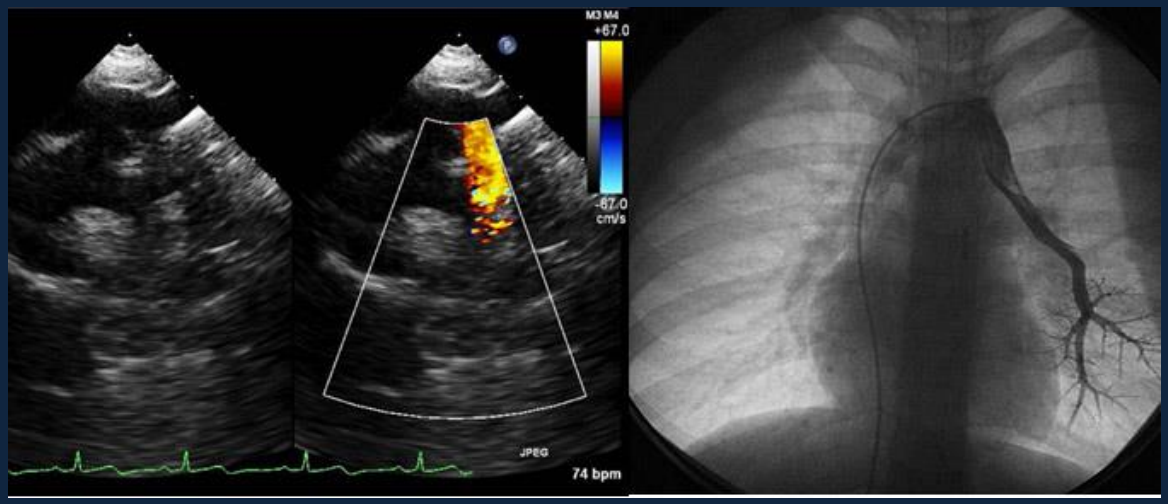
- Secundum defects, 75%
- Primum defects, 15-20%
  - Down Sd
- Sinus venosus, 5-10%
  - SVC type
    - Anomalous PVs
  - IVC type
- Coronary sinus defects, <1%

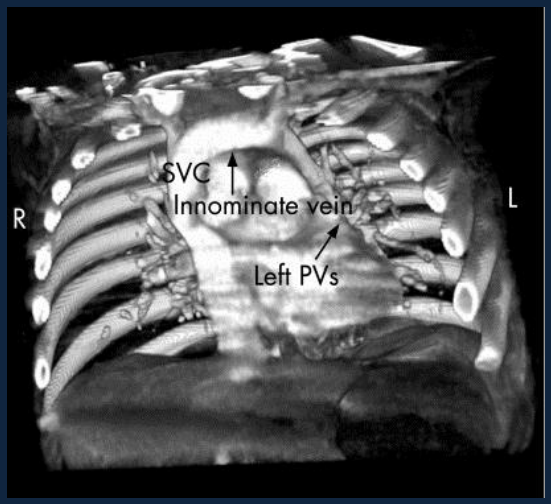


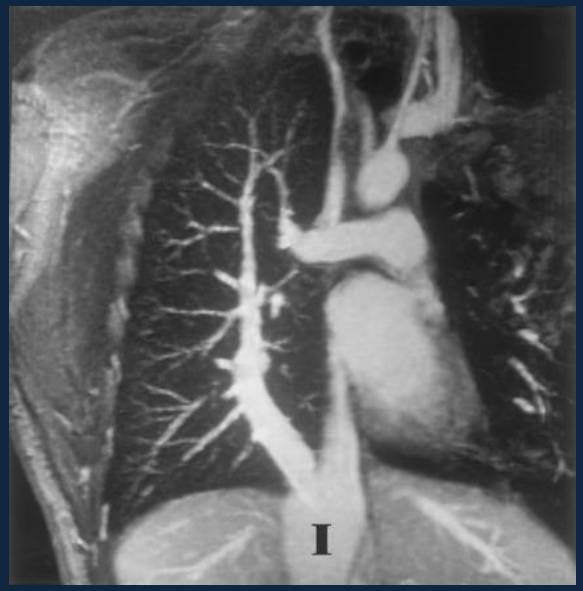
Type of ASD and Associated Anomalies

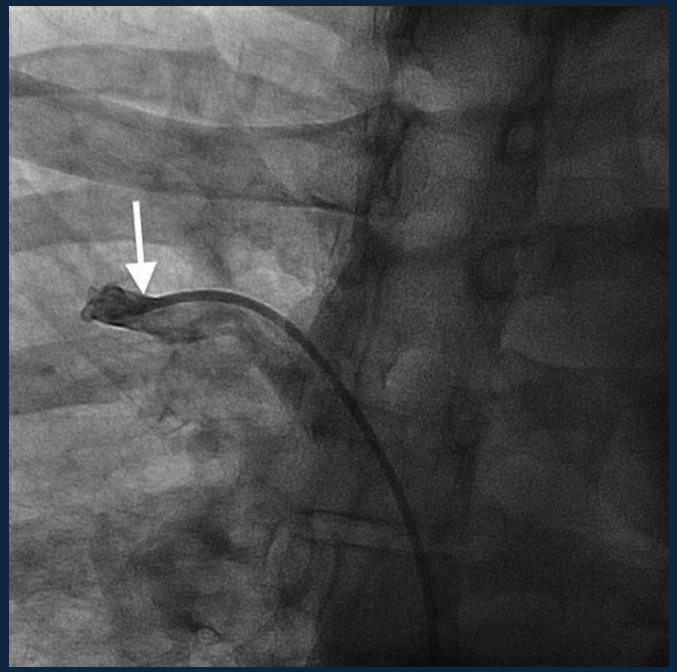
- Other associated malformations in 30%
- Primum ASD – cleft anterior MV leaflet
- Sinus venosus – anomalous drainage right PV
- Secundum ASD – LUPV to LtSVC to innominate
- Secundum ASD – pulmonic valve stenosis
- Coronary sinus ASD – anomal pulm ven, Lt SVC

Type of ASD and Associated Anomalies









Pathophysiology of ASD

- **The important physiologic determinants are:**
  - Differences in Rt and Lt atrial pressures
  - Ventricular compliance (determines atrial ones), also determined by PVR and SVR
- **In small defects LA pressure>RA pressure, in large ones they equalize and shunt depends more on SVR/PVR (effects of BP, etc)**
- **LA to RA shunt leads to right-sided overflow and eventually to pulmonary HTN**

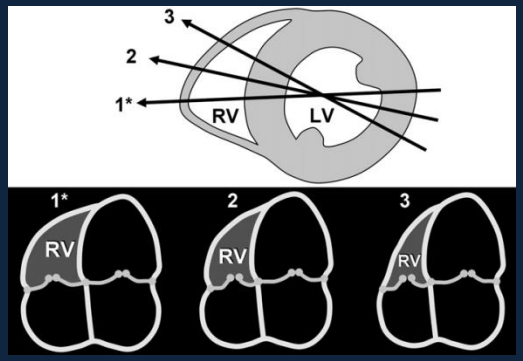
Clinical Presentation

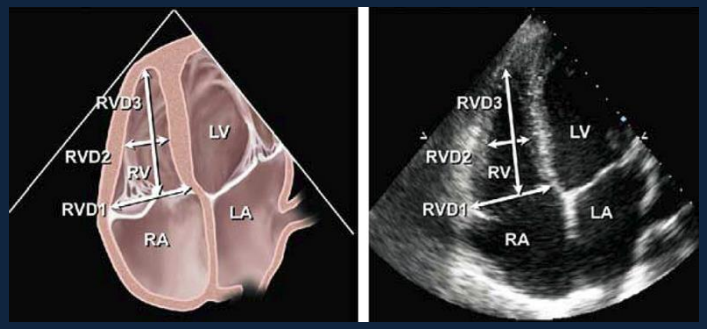
- Small defects (<5mm) usually asymptomatic? (some close spontaneously)
- Majority of mod to large ASDs become symptomatic during second decade of life
  - Progressive increase in exercise intolerance
  - Occasional CHF (>40's yrs age)
  - Atrial arrhythmias (Flutter, Fibrill) (>50% in 60's)
- During 4th to 5th decade, 5-10% develop PHT

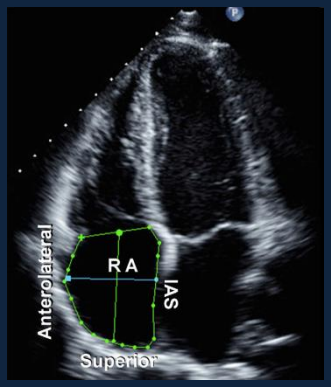
Murphy JG, et al. NEJM 1990; 323

TRANSTHORACIC ECHO IN ASD

- Helpful in delineating L-R shunt
- Flow acceleration across TV and PV (indirect sign)
- Increased pulmonary artery pressure
- May visualize appropriate pulm venous return
- Dilated RA and RV (+/- paradox ventricular septal motion)

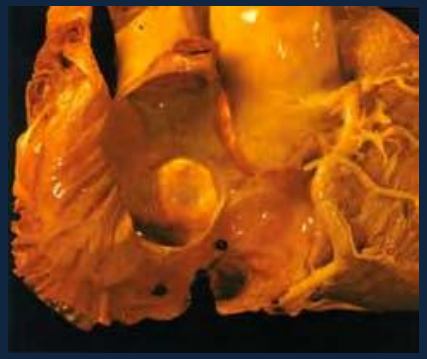


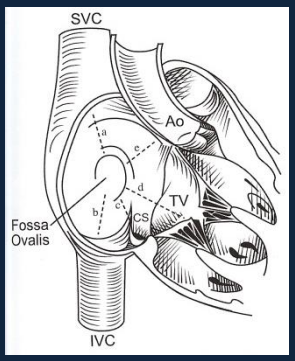


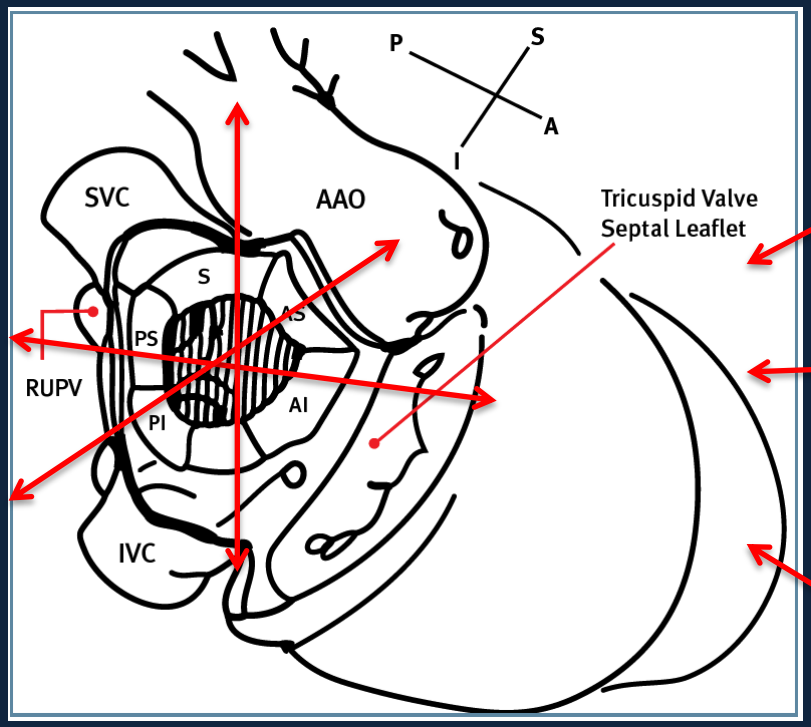


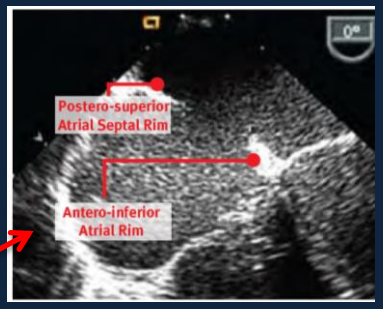
Anatomy of RIMS

(Important Rims By TEE)

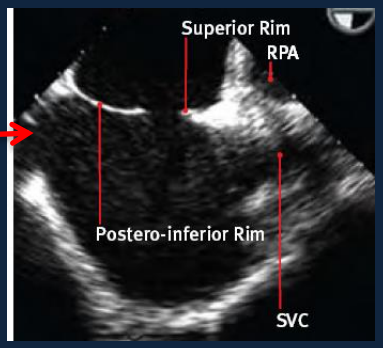




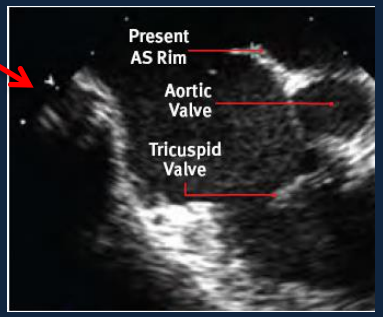




Post-Sup + Ant-Inf (4-chamber)



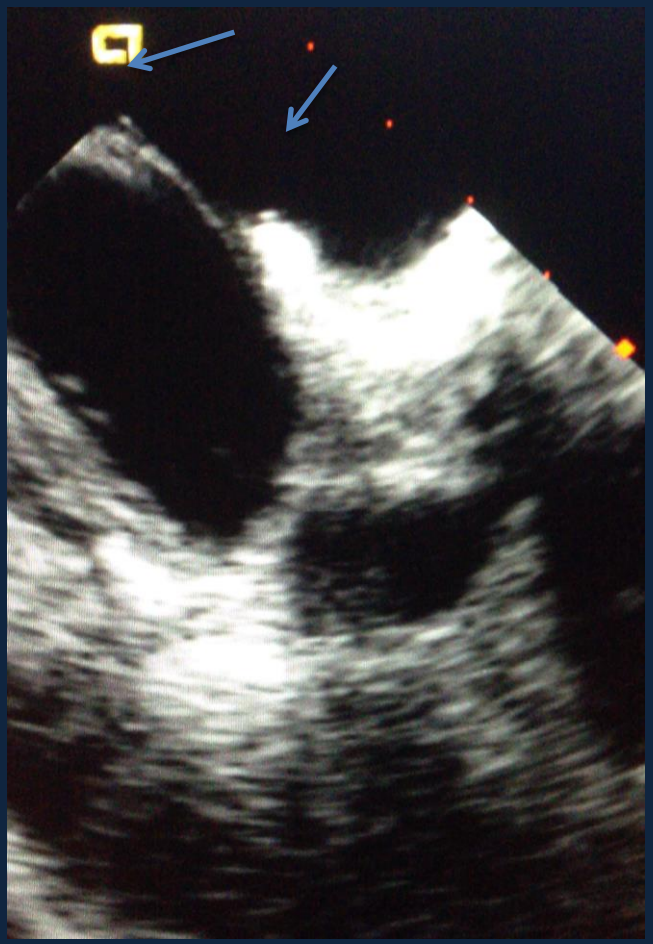
Sup + Post-Inf (bicaval)

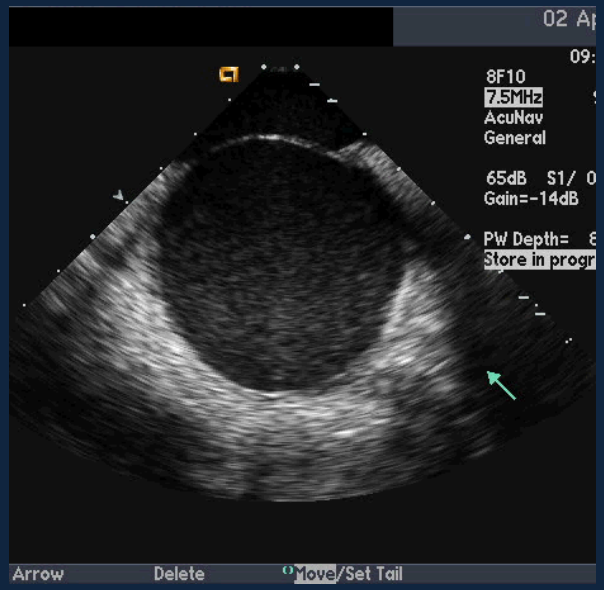


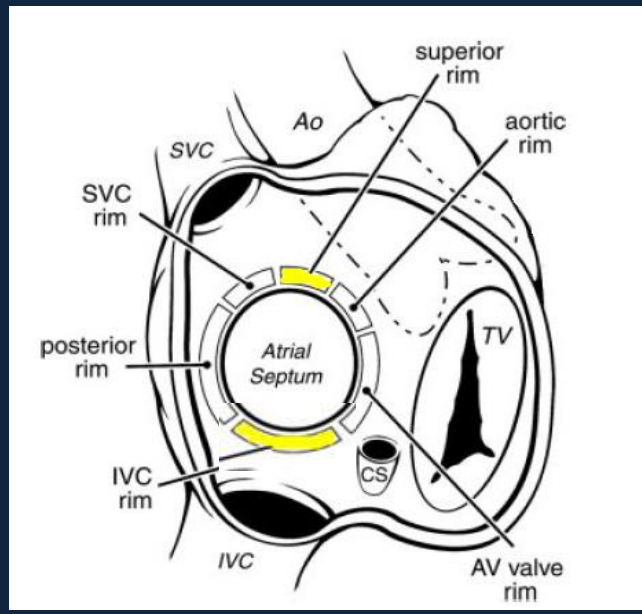
Ant-Superior (short-axis)

Atrial Septal Defect

IVC and SUPERIOR Rims (ICE)





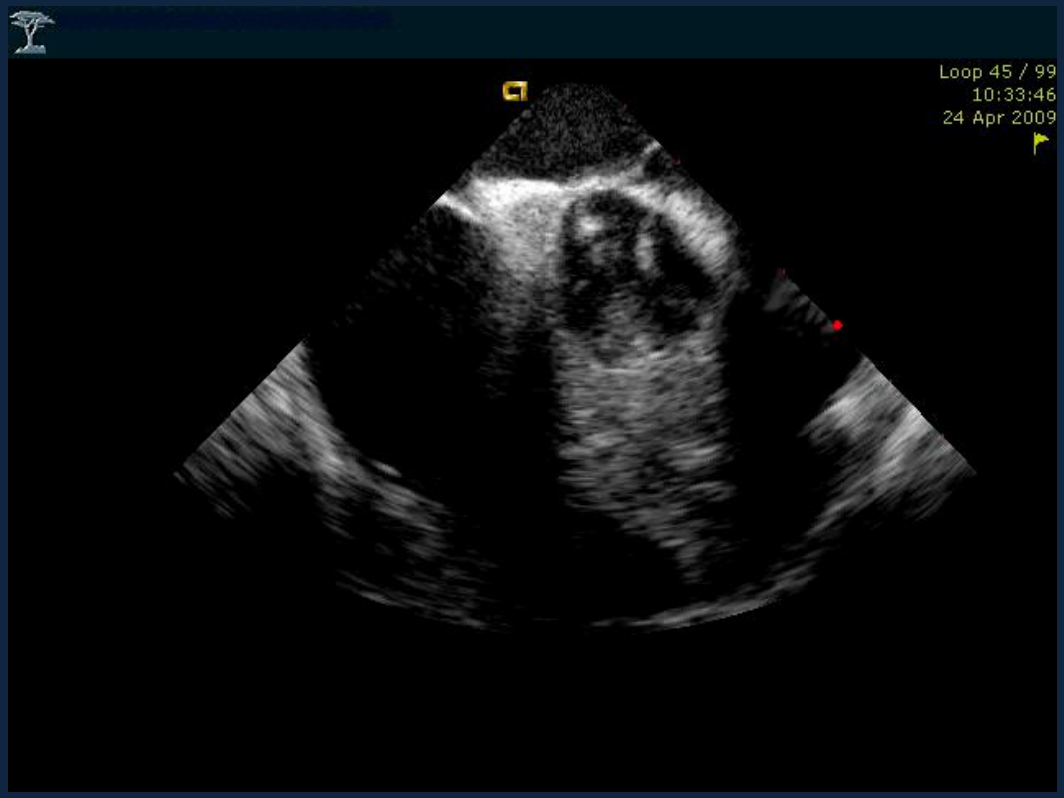


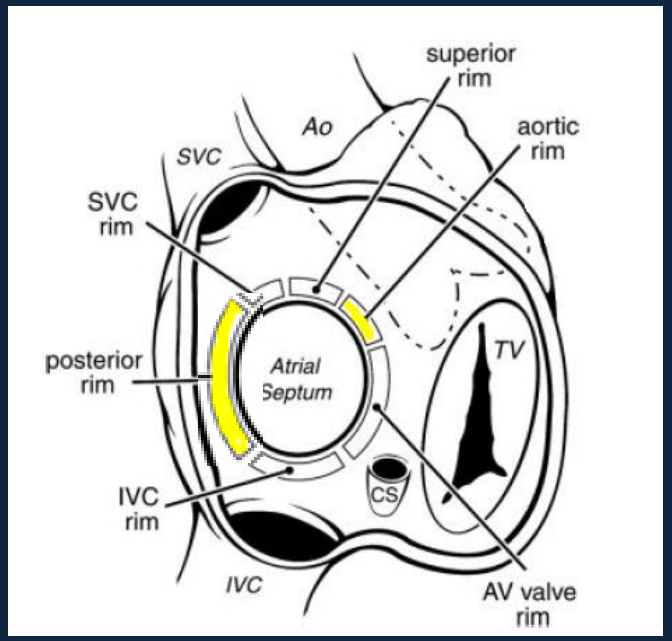
DISTANCE FROM THE IVC!!

Atrial Septal Defect

Aortic Rim (ICE)

(Antero-Superior Rim)





DISTANCE FROM THE AORTA!!

Indications for Closure

- **Any hemodynamically significant** (to prevent arrhythmias, PHT, RV failure)**:**
  - Qp/Qs > 1.5 (depends on RV, LV compliance)
  - Echocardiographic signs:
    - RA+RV overload
    - PHT
- **Moderate sized ASD without symptoms or PHT or echo findings of Right-heart overload(??)**
- **Assure no hemodynamic contraindications**

Indications for ASD Closure

ACC/AHA GUIDELINES ADULTS WITH CONGEN. HEART DZ (2008)

CLASS I

1. Closure of an ASD either percutaneously or surgically is indicated for right atrial and RV enlargement with or without symptoms. (*Level of Evidence: B*)

CLASS IIa

2. Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of:
   a. Paradoxical embolism. (*Level of Evidence: C*)
   b. Documented orthodeoxia-platypnea. (*Level of Evidence: B*)

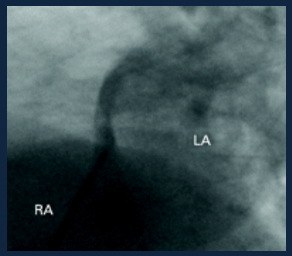
CLASS IIb

1. Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, PVR less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (patients should be treated in conjunction with providers who have expertise in the management of pulmonary hypertensive syndromes). (*Level of Evidence: C*)

Diagnosis of PFO

a. **Demonstrating spontaneous or induced (at end of prolonged valsalva) *Right to Left interatrial shunt* at Fossa Ovalis:**
   - Color-flow doppler (TEE > TTE)
   - Bubble study (TEE > TTE)
   - Transcranial doppler
   - Angiogram (contrast injection in RA at FO)

} Contrast Echo Techniques

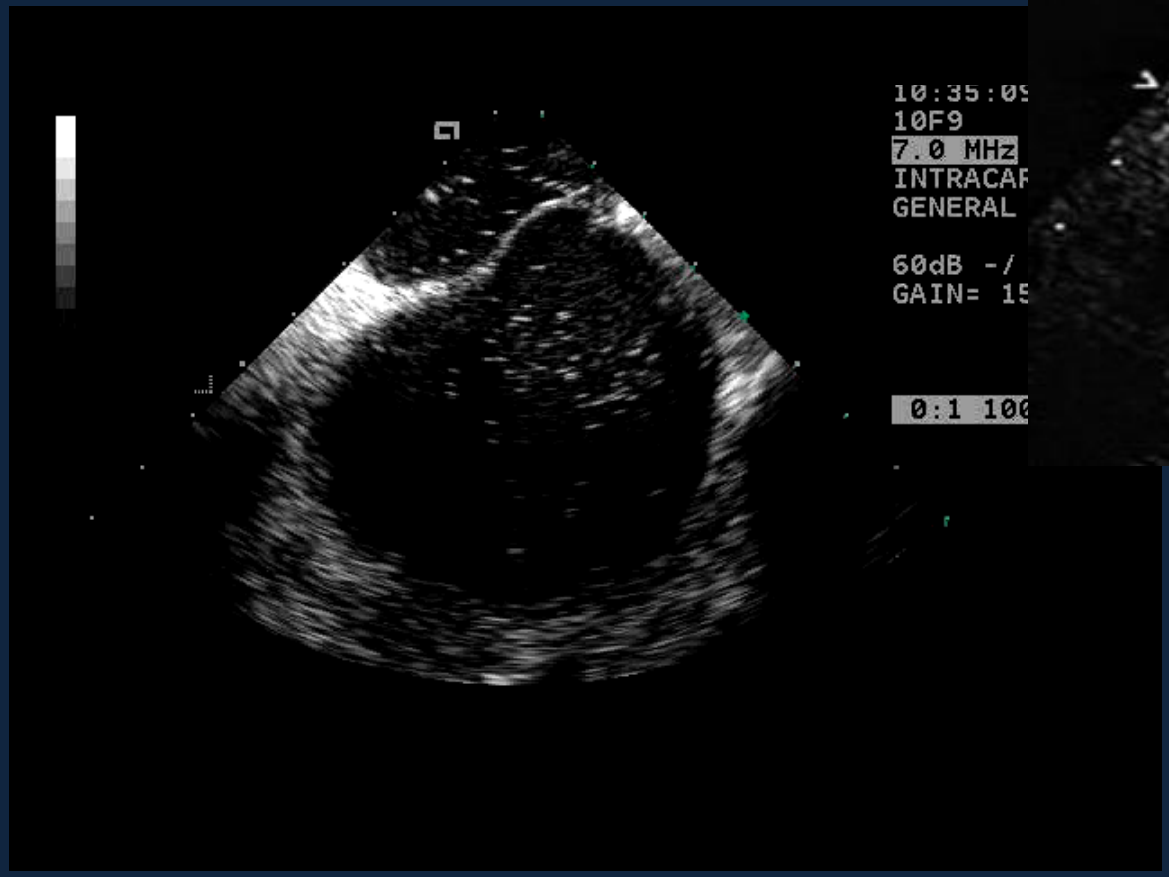


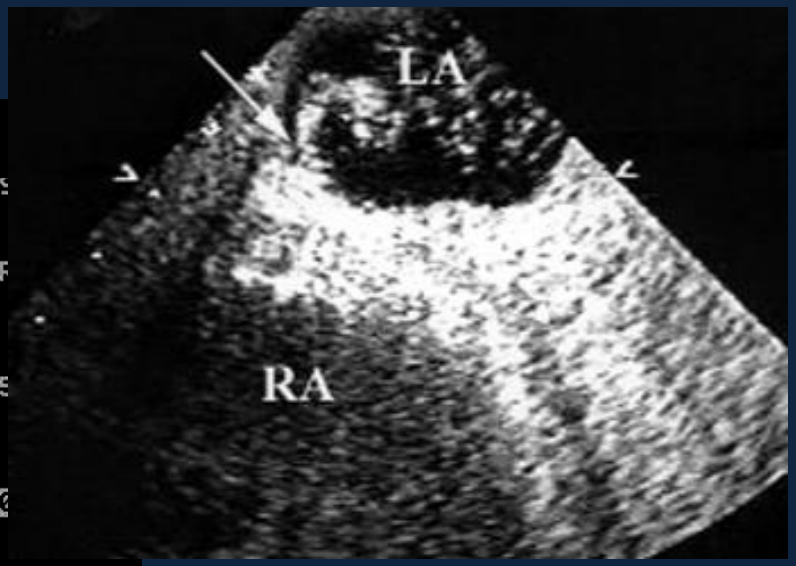
b. **Demonstrating *separation septum prim. - secund.***

a. **Probing (catheter and guidewire)**

Patent Foramen Ovale

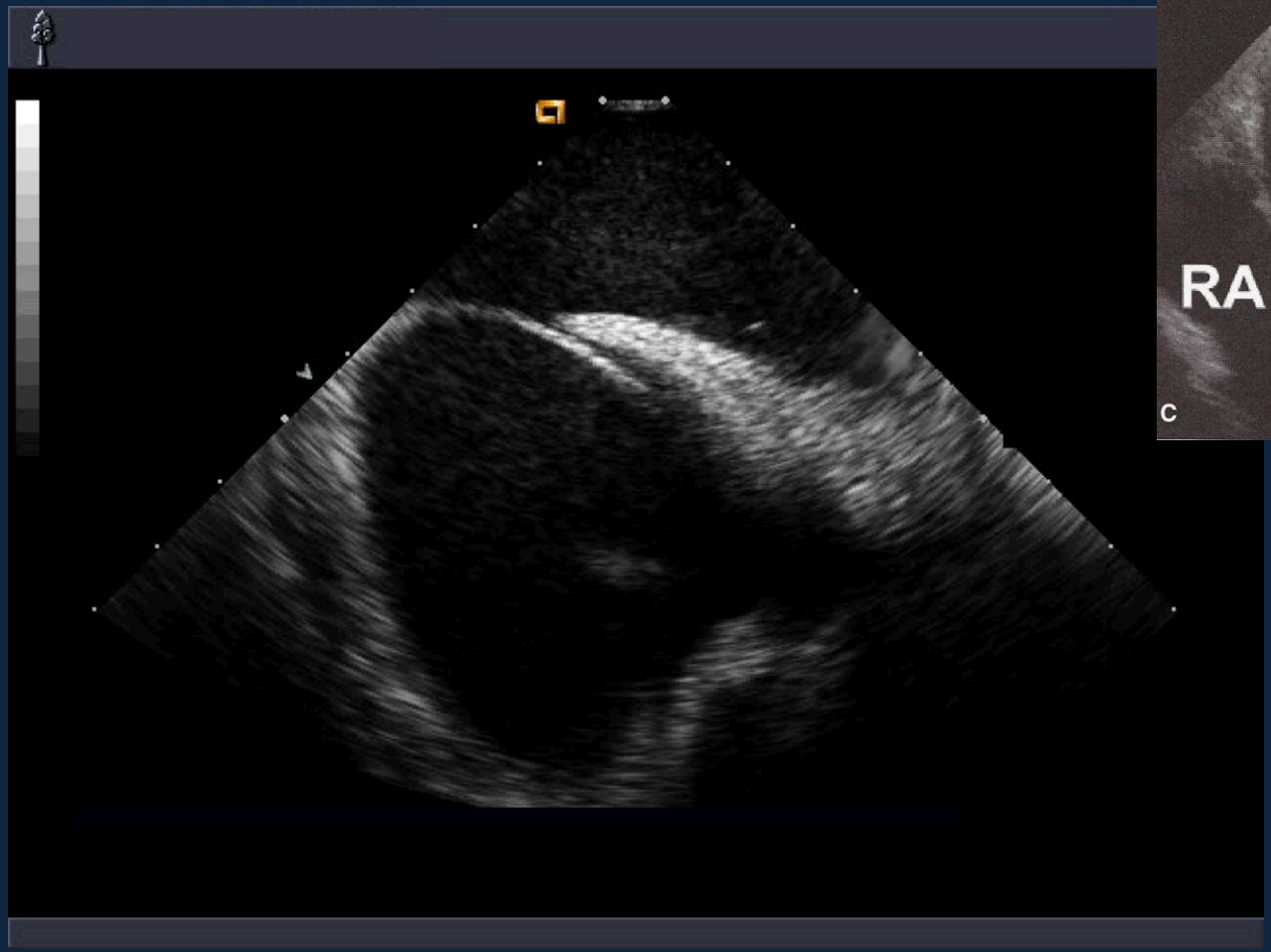
With Positive *Bubble Study* by TEE

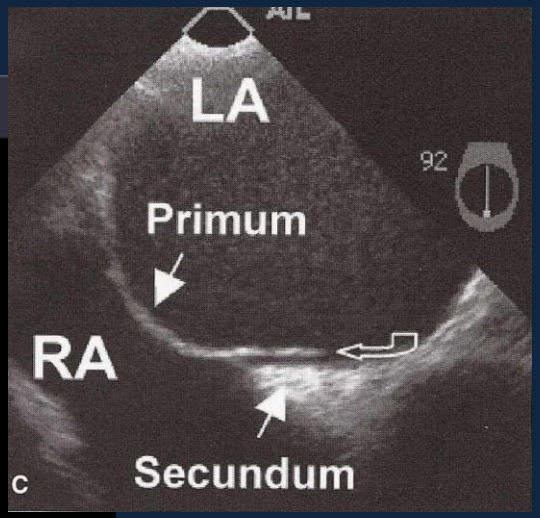




Patent Foramen Ovale

Tunnel-Type by *B-Mode*

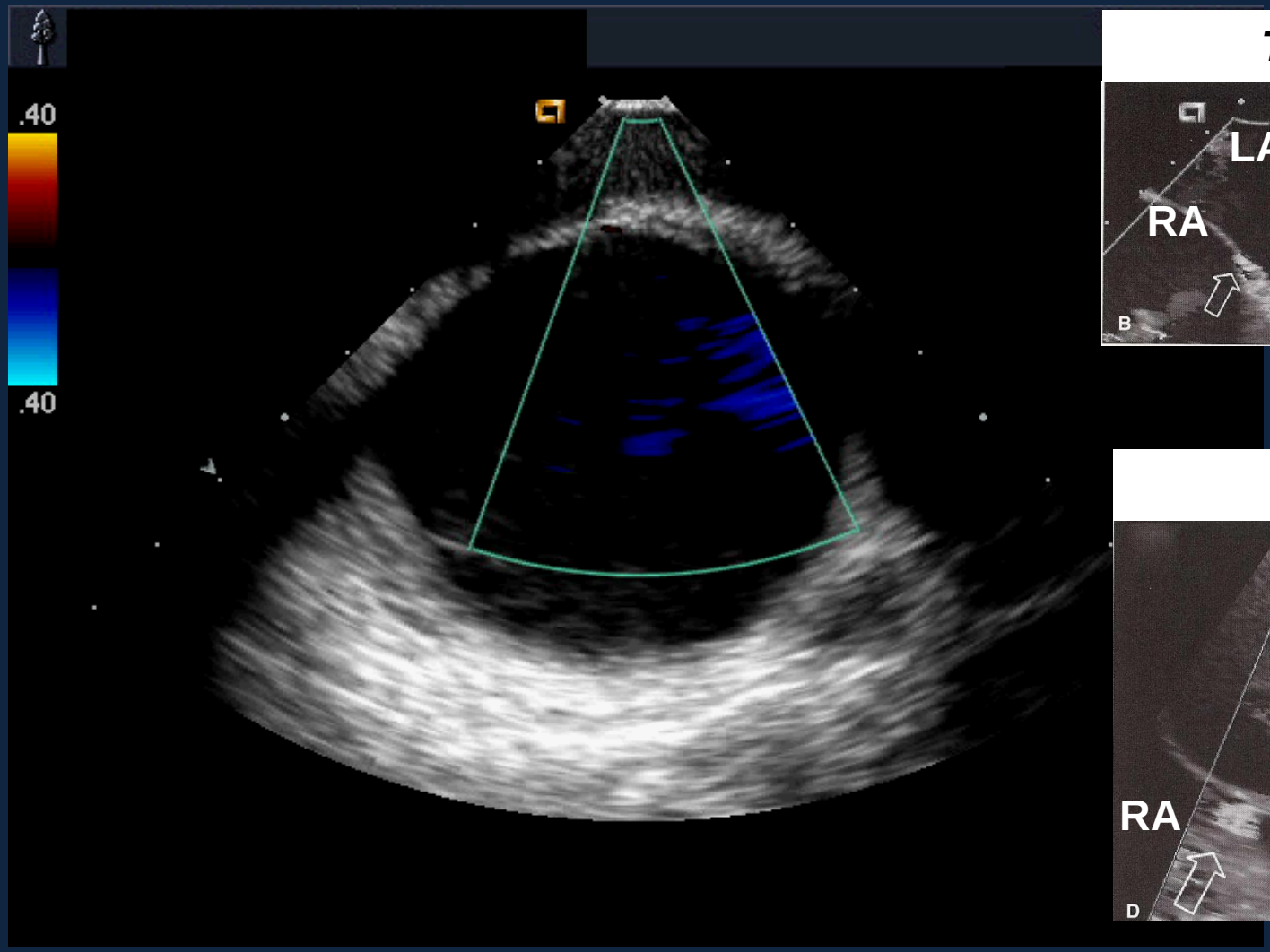




Patent Foramen Ovale

Color Doppler: Small Left-to-Right Shunt

Fossa-type ASD



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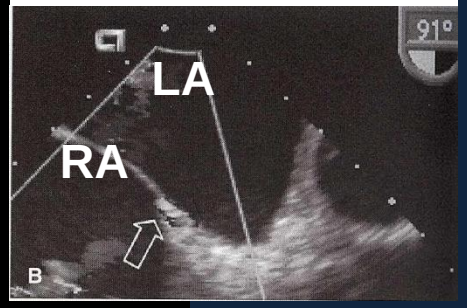

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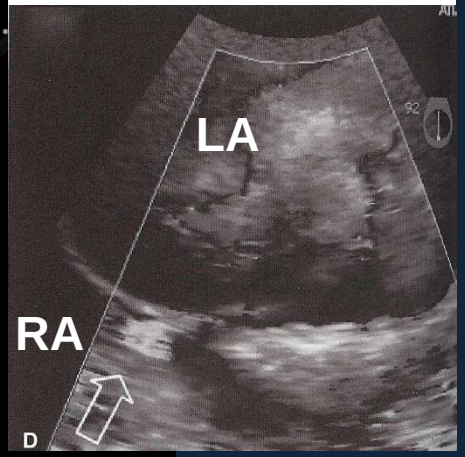
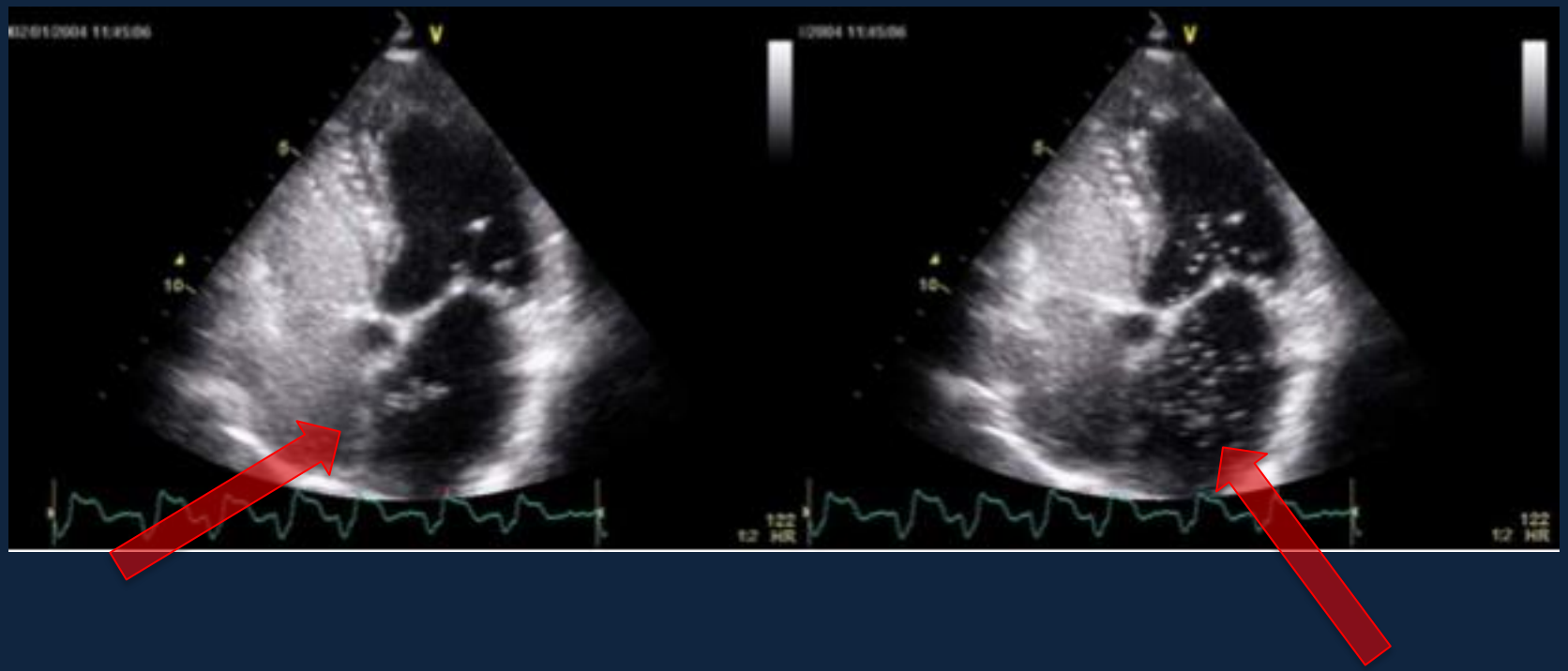


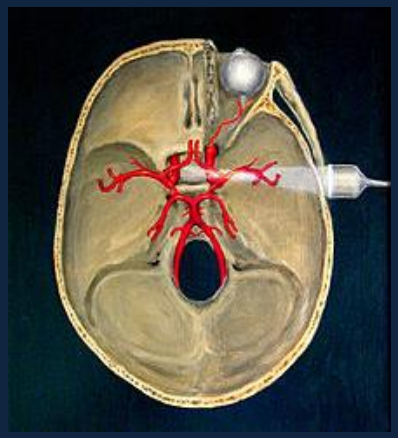
Patent Foramen Ovale

With Positive *Bubble Study* by TTE



Transcranial Doppler

High Intensity Signals (HITS)?



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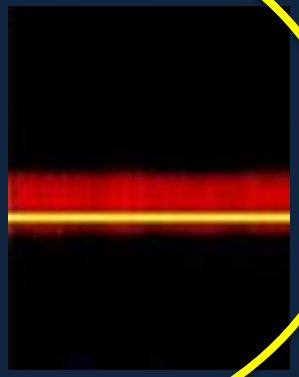


Associated Condition

- **Paradoxical embolism**
  - Cryptogenic stroke *(young patients) (PFO+parad em—3.4-3.8% yearly risk recurrent event)*
  - Neurologic complicat. deep see divers *(4.5x more if PFO)*
- **Hypoxia secondary to right-to-left shunting**
  - Platypnea-Orthodeoxia
  - Refractory hypoxia (Post RV MI, acute PE)
- **Migraine (with aura)** ***(PFO in 50%)***
- **Most pts with PFO will remain asymptomatic**
  - Therefore not systematically closed

B. Determining likelihood / high risk features for paradoxical embolism:

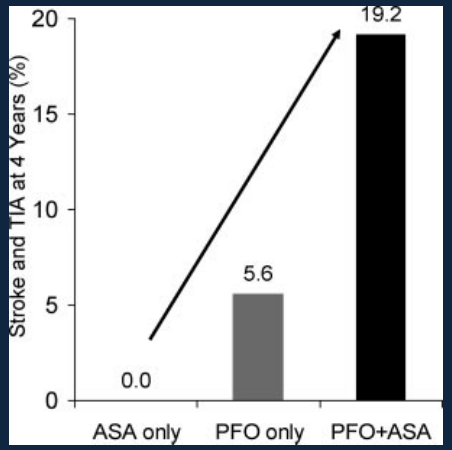
- **RULE OUT OTHER CAUSE OF STROKE 1ST**
  - Imaging findings (+ and – findings)
  - Laboratory (hypercoagulable, rheumatologic)
- **CLINICAL CLUES**
  - To rule out other causes
  - To convince high chance of paradoxical embolism
- **PFO ANATOMY (echo)**

Anatomic Conditions Increasing Risk of Paradoxical Embolism

Atrial septal aneurysm:

- Part or all the septum protrudes into either septum with the cardio-respiratory cycle
- Diagnostic criteria: phasic septal excursion of ≥10-15mm during cardio-respiratory cycle (into either LA/RA or the sum) + base of >15mm
- Incidence CVA higher in patients with ASA + PFO (4x higher risk)

  (PFO and CVA → 5x higher incidence of ASA)

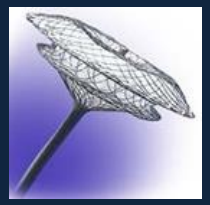


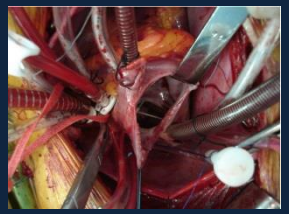
Mas JL, et al. (French Study) *N Engl J Med. 2001;345:1740–1746..*

Treatment Options Patients with PFO + Paradoxical Embolism

- **Optimal treatment to prevent recurrent stroke or TIA in patients with cryptogenic stroke and PFO has not been defined**

- **Treatment choices include:**
  - medical therapy (antiplatelets or coumadin)
  - percutaneous device closure
  - open surgical repair





Established indications for Closure in patients with Paradoxical Embolism

1. Recurrent events while on antiplatelet or anticoagulant therapy
2. Intolerant to antiplatelet or anticoagulant Rx
3. Strong patient's preference (educated about data and other options)
4. Very high risk for recurrent events based on PFO anatomy, physiology, other patient's data

What The Guidelines Say

Table 1. Guidelines From Professional Societies[1,2]

	American Academy of Neurology	American College of Chest Physicians
PFO	Insufficient evidence to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death (level U), but risks of minor bleeding are possibly greater with warfarin (level C); there is insufficient evidence regarding the effectiveness of surgical or percutaneous PFO closure (level U)	. . .
PFO alone	. . .	Antiplatelet therapy recommended over no therapy (grade 1C+), and antiplatelet therapy recommended over warfarin (grade 2A)
PFO and ASA	. . .	Inadequate data available to allow recommendation of optimal therapy
PFO with DVT or PE	At least 3 months of anticoagulation	Anticoagulation recommended

ASA indicates atrial septal aneurysm; DVT, deep vein thrombosis; and PE, pulmonary embolism. Data derived from Albers et al[1] and Messé et al.[2]

AHA/ASA Guideline

Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke

Co-Sponsored by the Council on Cardiovascular Radiology and Intervention

For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event.	Class IIa, Level B
Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis.	Class IIa, Level C
Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy.	Class IIb, Level C

Recurrent Events By Treatment

	TIA	Stroke	TIA+Stroke
Catheter Closure (F/U 12 months)	0.83	0.47	1.30
Medical Managem (F/U 12 months)	2.72	3.12	4.82
Catheter Closure (F/U 24 months)	0.54	0.26	0.80
Medical Managem (F/U 24 months)	2.68	2.62	5.28

Dahlöf CGH, et al. CLDigest 2009, Vol 17

ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

ABSTRACT

BACKGROUND

The prevalence of patent foramen ovale among patients with cryptogenic stroke is higher than that in the general population. Closure with a percutaneous device is often recommended in such patients, but it is not known whether this intervention reduces the risk of recurrent stroke.

METHODS

We conducted a multicenter, randomized, open-label trial of closure with a percutaneous device, as compared with medical therapy alone, in patients between 18 and 60 years of age who presented with a cryptogenic stroke or transient ischemic attack (TIA) and had a patent foramen ovale. The primary end point was a composite of stroke or transient ischemic attack during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years.

RESULTS

A total of 909 patients were enrolled in the trial. The cumulative incidence (Kaplan–Meier estimate) of the primary end point was 5.5% in the closure group (447 patients) as compared with 6.8% in the medical-therapy group (462 patients) (adjusted hazard ratio, 0.78; 95% confidence interval, 0.45 to 1.35; P=0.37). The respective rates were 2.9% and 3.1% for stroke (P=0.79) and 3.1% and 4.1% for TIA (P=0.44). No deaths occurred by 30 days in either group, and there were no deaths from neurologic causes during the 2-year follow-up period. A cause other than paradoxical embolism was usually apparent in patients with recurrent neurologic events.

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)

From University Hospitals Case Medical Center, Cleveland (A.J.F.); Swedish Medical Center, Seattle (M.R.); Harvard Clinical Research Institute (J.M., L.M.) and Brigham and Women's Hospital (M.L.) — both in Boston; University of Iowa, Iowa City (H.A.); Stanford University Medical Center, Palo Alto, CA (G.W.A.); Geisinger Medical Center, Danville, PA (R.F.); University of Pennsylvania, Philadelphia (H.H.); Cedars–Sinai Medical Center, Los Angeles (S.K.); Methodist Hospital, Houston (A.R.); and University of Pittsburgh, Pittsburgh (L.W.). Address reprint requests to Dr. Furlan at the Department of Neurology, University Hospitals Case Medical Center, 11100 Euclid Ave., Mail Stop HAN 5040, Cleveland, Ohio 44106, or at anthony.furlan@uhhospitals.org.

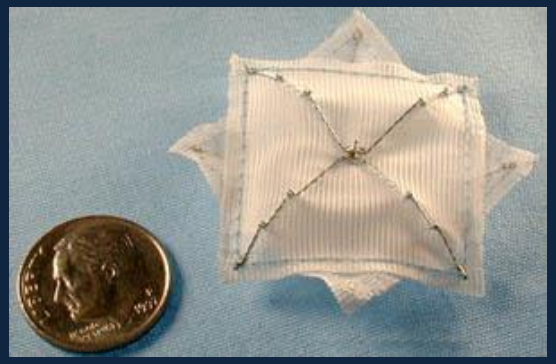
*Investigators in the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (CLOSURE I) study are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2012;366:991-9.

INTERPRETING CLOSURE I RESULTS

- **Closure no different to warfarin/ASA/both**
  - No difference in primary endpoint *(stroke or TIA at 2-yrs, mortality at 30-days, neurol mortality between 31-days and 2-yrs)*
- **In up to 80% other cause identified for recur. stroke**
- **Disadvantages of the trial:**
  - Medical arm has warfarin (+/-ASA) in up to 50% of cases
  - TIA diagnosed by clinical criteria only (no imaging needed)
  - Stroke incidence ≈ +/-3% (both arms) when TIA removed, but in device arm 25% in first 30-days (procedure? Device clot?)
  - NMT device known to be less effective: more residual shunts
  - The more severe/at risk patients are being treated outside trials

STARFLEX Device Failure!



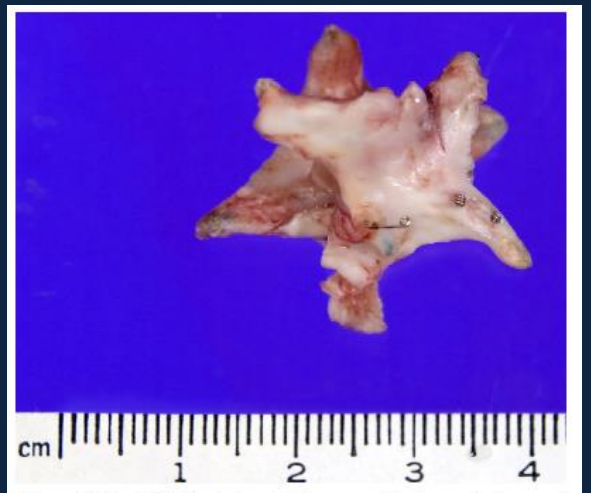


Figure 5. *CardioSEAL device with the arrow pointing to the fractured left superior arm with a part of the arm missing.*

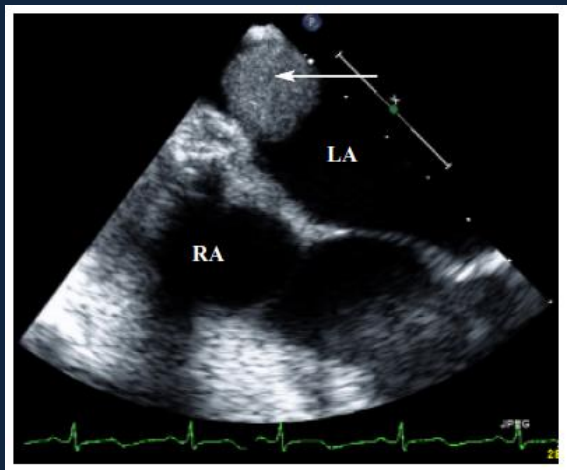


Figure 2. *Transesophageal echocardiographic image with the arrow pointing to the left atrial thrombus measuring 1.7 x 1.8 cm, attached to the patent foramen ovale closure device.*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

From the University of Colorado Denver/University of Colorado Hospital, Aurora (J.D.C.); University of California Los Angeles, Los Angeles (J.L.S.); Tufts University/Tufts Medical Center, Boston (D.E.T.); University of Texas/Memorial Hermann Heart and Vascular Institute, Houston (R.W.S.); Berry Consultants, Austin, TX (S.B.), South Denver Cardiology/Swedish Medical Center, Littleton, CO (L.A.M.); Medical College of Wisconsin Milwaukee, Milwaukee (D.S.M.); and the University of Washington, Seattle (D.L.T.). Address reprint requests to Dr. Carroll at the University of Colorado Denver, Anschutz Medical Campus, Leprino Bldg., 12401 East 17th Ave., Mail Stop B132, Aurora, CO 80045, or at john.carroll@ucdenver.edu.

*The investigators, institutions, and other organizations participating in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;368:1092-100.
DOI: 10.1056/NEJMoa1301440

ABSTRACT

BACKGROUND

Whether closure of a patent foramen ovale is effective in the prevention of recurrent ischemic stroke in patients who have had a cryptogenic stroke is unknown. We conducted a trial to evaluate whether closure is superior to medical therapy alone in preventing recurrent ischemic stroke or early death in patients 18 to 60 years of age.

METHODS

In this prospective, multicenter, randomized, event-driven trial, we randomly assigned patients, in a 1:1 ratio, to medical therapy alone or closure of the patent foramen ovale. The primary results of the trial were analyzed when the target of 25 primary end-point events had been observed and adjudicated.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. The medical-therapy group received one or more antiplatelet medications (74.8%) or warfarin (25.2%). Treatment exposure between the two groups was unequal (1375 patient-years in the closure group vs. 1184 patient-years in the medical-therapy group, P=0.009) owing to a higher dropout rate in the medical-therapy group. In the intention-to-treat cohort, 9 patients in the closure group and 16 in the medical-therapy group had a recurrence of stroke (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22 to 1.11; P=0.08). The between-group difference in the rate of recurrent stroke was significant in the prespecified per-protocol cohort (6 events in the closure group vs. 14 events in the medical-therapy group; hazard ratio, 0.37; 95% CI, 0.14 to 0.96; P=0.03) and in the as-treated cohort (5 events vs. 16 events; hazard ratio, 0.27; 95% CI, 0.10 to 0.75; P=0.007). Serious adverse events occurred in 23.0% of the patients in the closure group and in 21.6% in the medical-therapy group (P=0.65). Procedure-related or device-related serious adverse events occurred in 21 of 499 patients in the closure group (4.2%), but the rate of atrial fibrillation or device thrombus was

CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks.

Primary End Point Analysis – Intent to Treat (ITT) Raw Count Cohort

RESPECT CLINICAL TRIAL

Subjects N total (nD / nM)	Events N total (nD / nM)	Relative Risk (RR) [D vs M][1] RR (95% CI)	Risk Reduction (1 – RR)	P value[2]
980 (499 / 481)	25 (9 / 16)	0.534 (0.234, 1.220)	46.6%	0.157

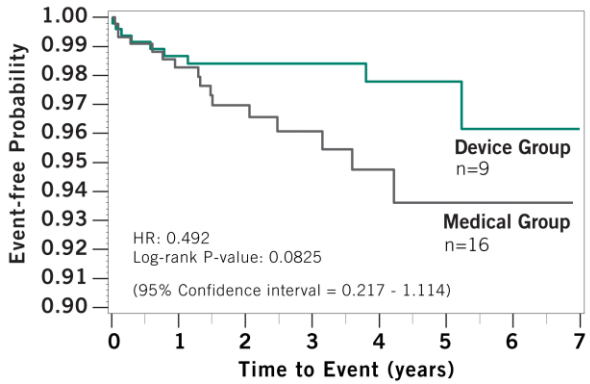
Abbreviations: D = Device group; M= Medical group

The event-rate point estimates for recurrent ischemic stroke in the intention-to-treat cohort were 1.3% in the closure group as compared with 1.7% in the medical-therapy group at 1 year, 1.6% as compared with 3.0% at 2 years, and 2.2% as compared with 6.4% at 5 years. Analyses to

gested that closure may have provided a greater benefit in patients with a substantial (grade 3) right-to-left shunt and in those with an atrial septal aneurysm (Fig. 2). The size of recurrent ischemic strokes differed between the treatment

Primary Endpoint Analysis – ITT Cohort

50.8% risk reduction of stroke in favor of device



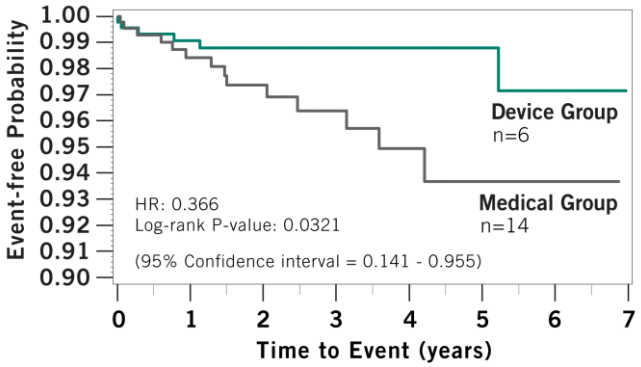
- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

Rate: 0.66 vs 1.38 events per 100 pt-yrs (HR with closure 0.49; 95% CI, 0.22 to 1.11; P=0.08

Primary Endpoint Analysis – Per Protocol Cohort

63.4% risk reduction of stroke in favor of device



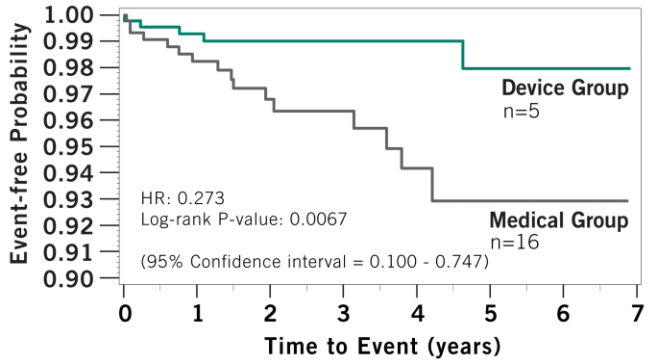
- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

1. Cox model used for analysis

Rate: 0.46 vs 1.30 events per 100 pt-yrs (HR with closure 0.37; 95% CI, 0.14 to 0.96; P=0.03

Primary Endpoint Analysis – As Treated Cohort

72.7% risk reduction of stroke in favor of device



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

1. Cox model used for analysis

Rate: 0.39 vs 1.45 events per 100 pt-yrs (HR with closure 0.27; 95% CI, 0.10 to 0.75; P=0.007

Subpopulation Differential Treatment Effect

RESPECT CLINICAL TRIAL

Subgroup	Device Group	Medical Group	Hazard Ratio and 95% CI		Pvalue (Log Rank)	Interaction Pvalue
	no. of patients/total number (%)					
Overall	9/499 (1.8%)	16/481 (3.3%)		0.492 (0.217, 1.114)	0.0825	
Age						0.5156
- 18-45	4/230 (1.7%)	5/210 (2.4%)		0.698 (0.187, 2.601)	0.5901	
- 46-60	5/262 (1.9%)	11/266 (4.1%)		0.405 (0.140, 1.165)	0.0828	
Sex						0.7312
- Male	5/268 (1.9%)	10/268 (3.7%)		0.448 (0.153, 1.311)	0.1321	
- Female	4/231 (1.7%)	6/213 (2.8%)		0.571 (0.161, 2.024)	0.3789	
Shunt Size						0.0667
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)		1.034 (0.347, 3.081)	0.9527	
- Substantial	2/247 (0.8%)	10/231 (4.3%)		0.178 (0.039, 0.813)	0.0119	
Atrial septal aneurysm						0.1016
- Present	2/180 (1.1%)	9/169 (5.3%)		0.187 (0.040, 0.867)	0.0163	
- Absent	7/319 (2.2%)	7/312 (2.2%)		0.889 (0.312, 2.535)	0.8259	
Index infarct topography						0.3916
- Superficial	5/280 (1.8%)	12/269 (4.5%)		0.366 (0.129, 1.038)	0.0487	
- Small Deep	2/57 (3.5%)	1/70 (1.4%)		1.762 (0.156, 19.93)	0.6429	
- Other	2/157 (1.3%)	3/139 (2.2%)		0.558 (0.093, 3.340)	0.5167	
Planned medical regimen						0.1966
- Anticoagulant	4/132 (3.0%)	3/121 (2.5%)		1.141 (0.255, 5.098)	0.8628	
- Antiplatelet	5/367 (1.4%)	13/359 (3.6%)		0.336 (0.120, 0.944)	0.0299	

Recurrent Cerebral Infarct Size[1]

Methods pre-specified; analysis post-hoc

RESPECT CLINICAL TRIAL

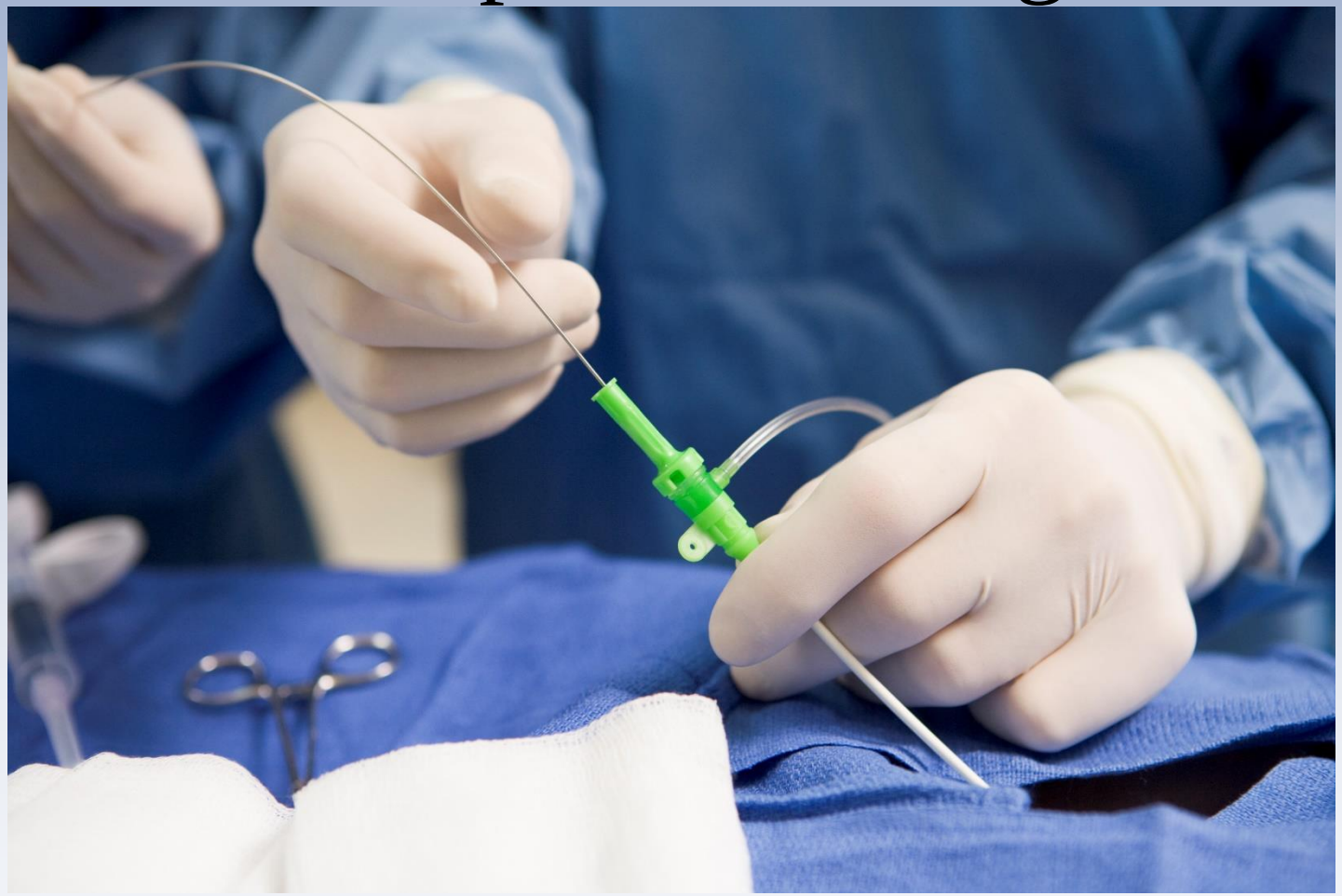
Event	Device Group n/N (%)	Medical Group n/N (%)	P-value[2]
Larger infarct >1.5cm	1/7 (14%)	9/13 (69%)	P=0.0573
Smaller infarct ≤ 1.5cm	6/7 (86%)	4/13 (31%)	

- This exploratory analysis of site-reported recurrent cerebral infarct size is provocative in suggesting that recurrent ischemic strokes in the medical versus device group are not only more frequent but also larger

Conclusion

- Treatment is not well established.
- Medical management is currently preferred over surgical intervention. Specifically, antiplatelet and anticoagulation treatments are most frequently used.
- Anticoagulation is only indicated in those who simultaneously are found to have a DVT or hypercoagulable state. If anticoagulation is contraindicated an inferior vena cava filter should be considered
- In cases where antiplatelet therapy or anticoagulation therapy fails to prevent recurrence of stroke/TIA surgical correction is a plausible option.

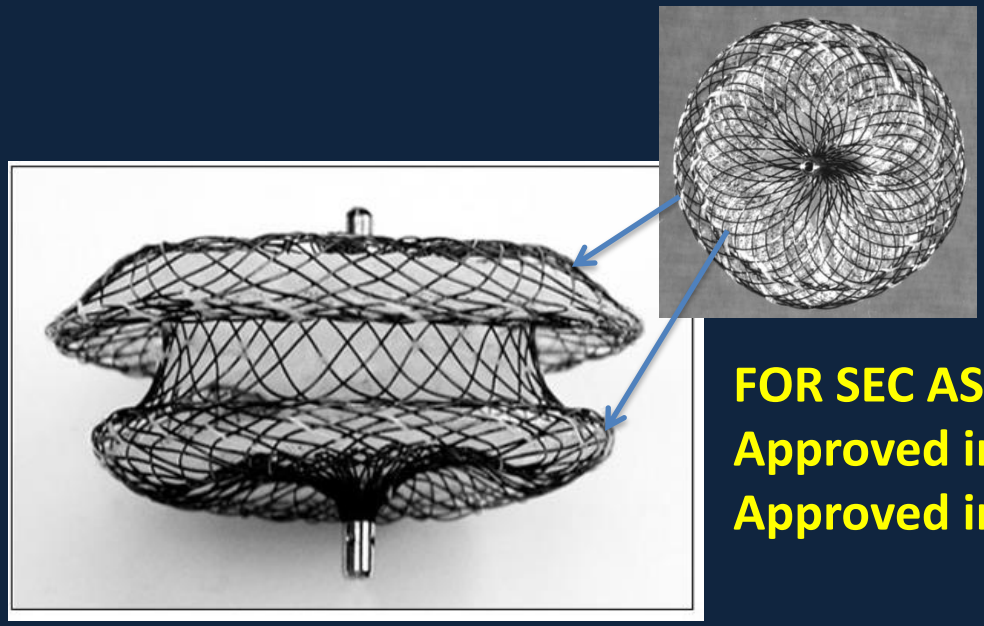
How was this patient managed?



The Procedure

Amplatzer Septal Occluders

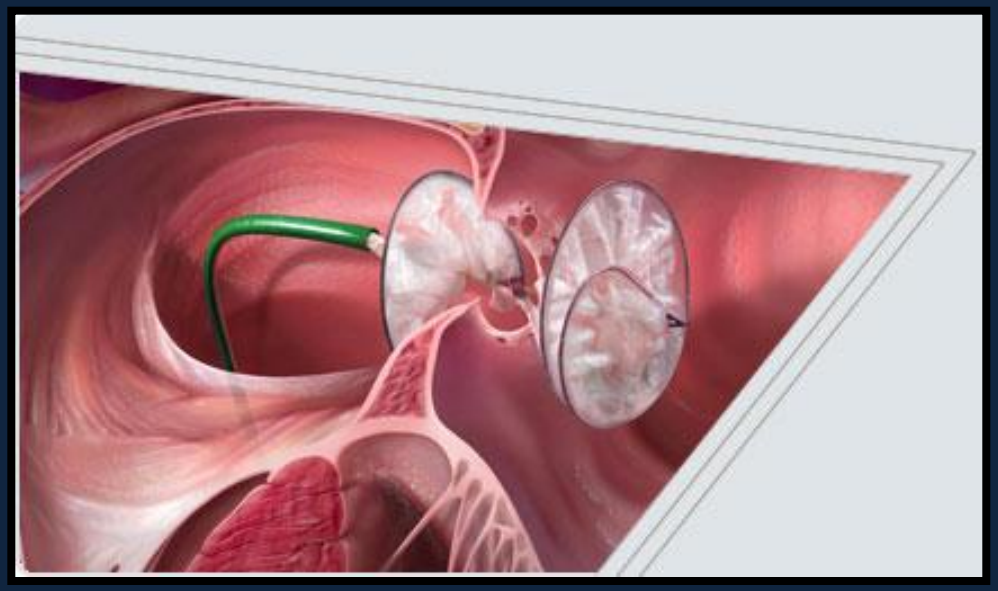
AMPLATZER® Atrial Septal Occluder

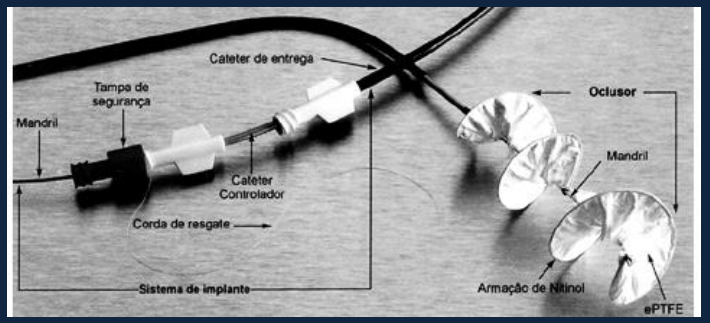


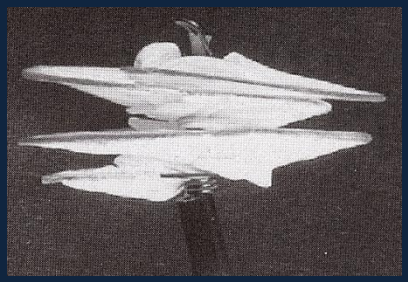
FOR SEC ASD CLOSURE:
Approved in US
Approved in EU

AMPLATZER® Multi-Fenestrated Septal Occluder – "Cribriform"

GORE HELEX Septal Occluder



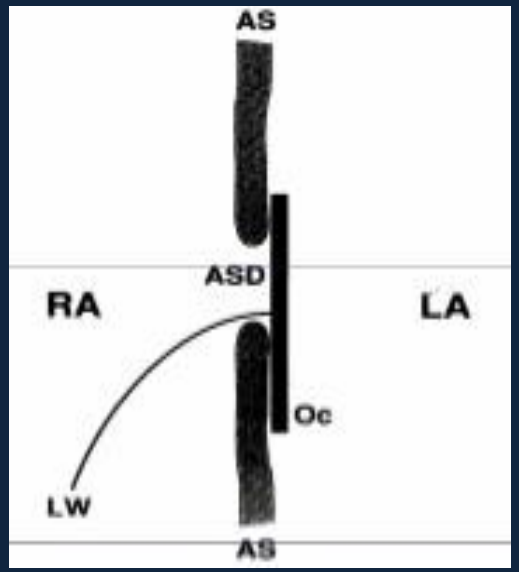


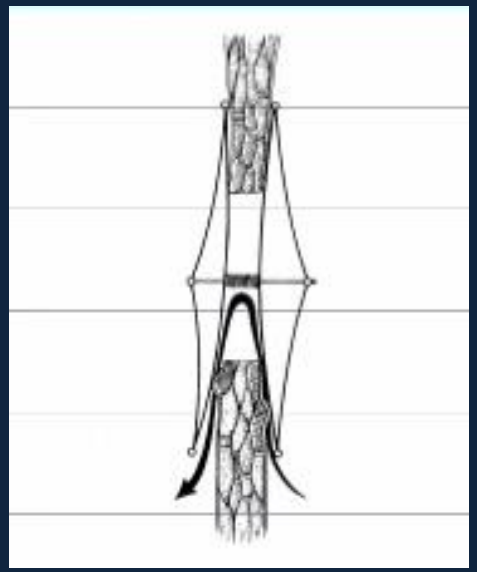


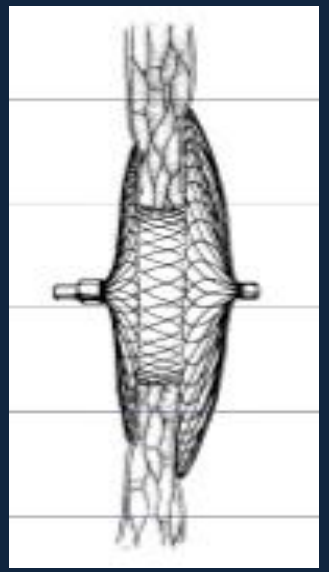
Approved in US for ASD closure
Approved in EU for ASD closure

Self-centering vs Non Self-centering

- Non self-centering devices require larger device, depend on disc size to cover entire defect → Therefore, require 2X larger left disc than self-centering
- Need to consider that waist can land at one end of the defect
- Non self-centering devices have higher risk persistent/residual shunt in larger ASD's

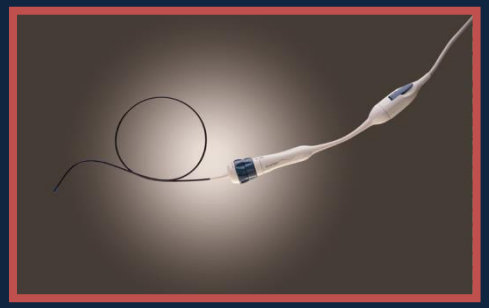






Intracardiac Echo (ICE)

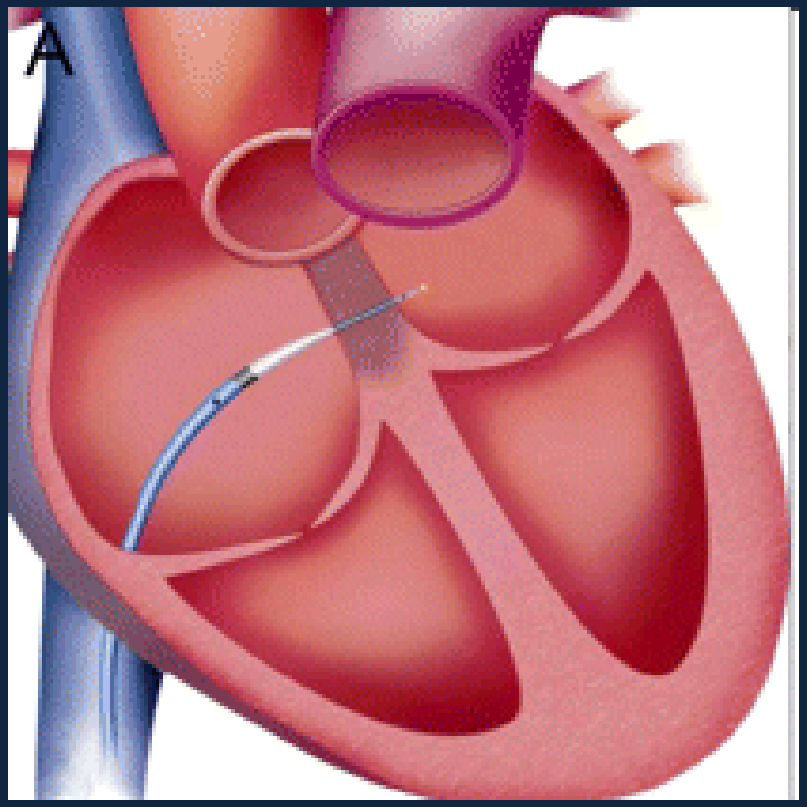
Four way steering

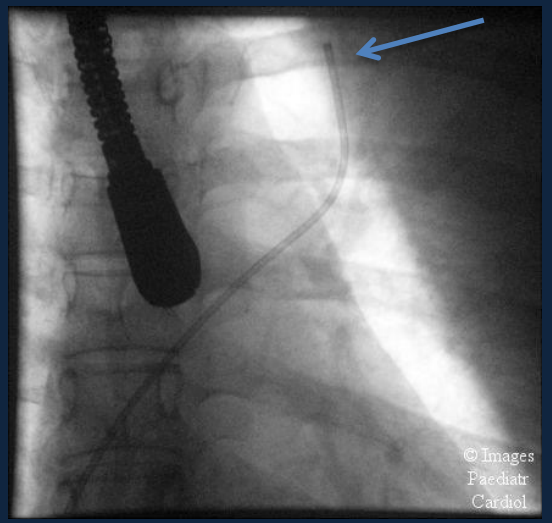


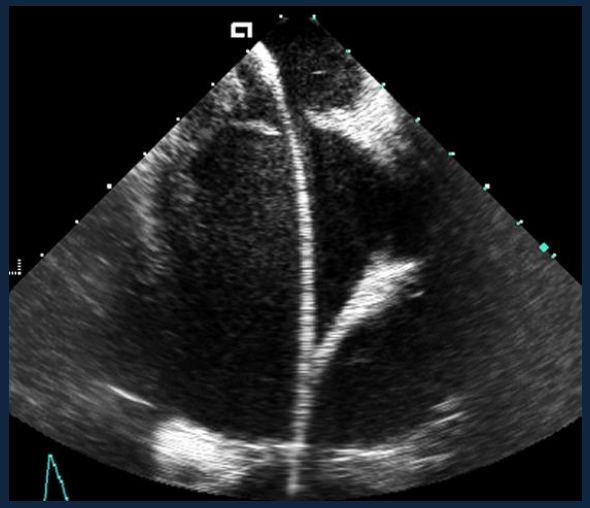
- More patient comfort
- No need for general anesthesia
- Allows procedure performance by only one operator
- Unlimited scan planes
- 160° in four directions
- Anterior-Posterior and Right-Left controls

Cross The ASD / PFO

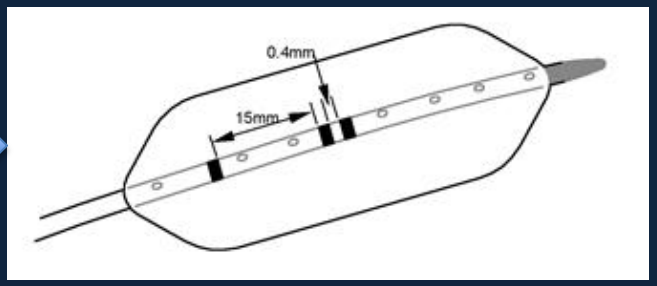
(from RA into LA)

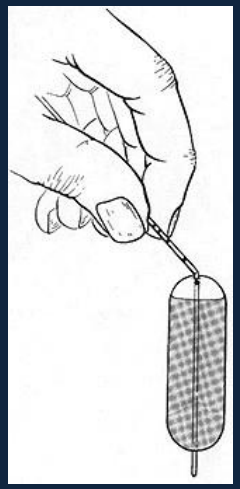


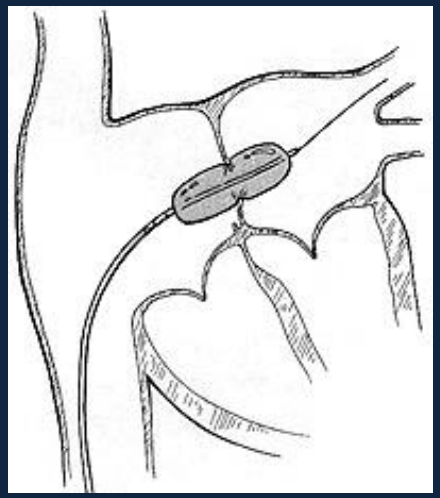


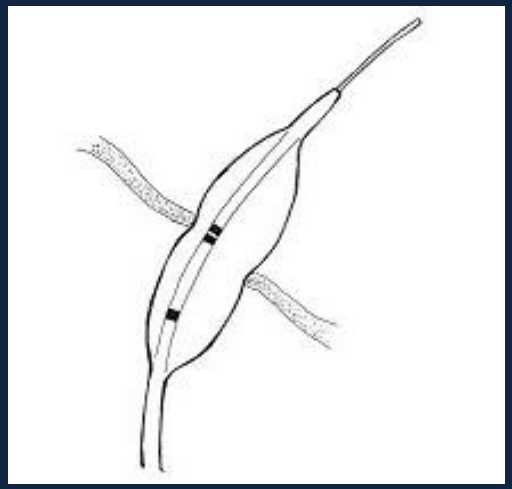


Balloon Sizing (Stop Flow) In ASD

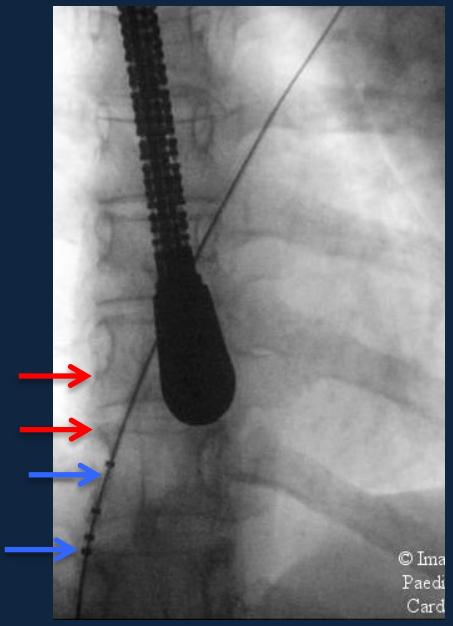


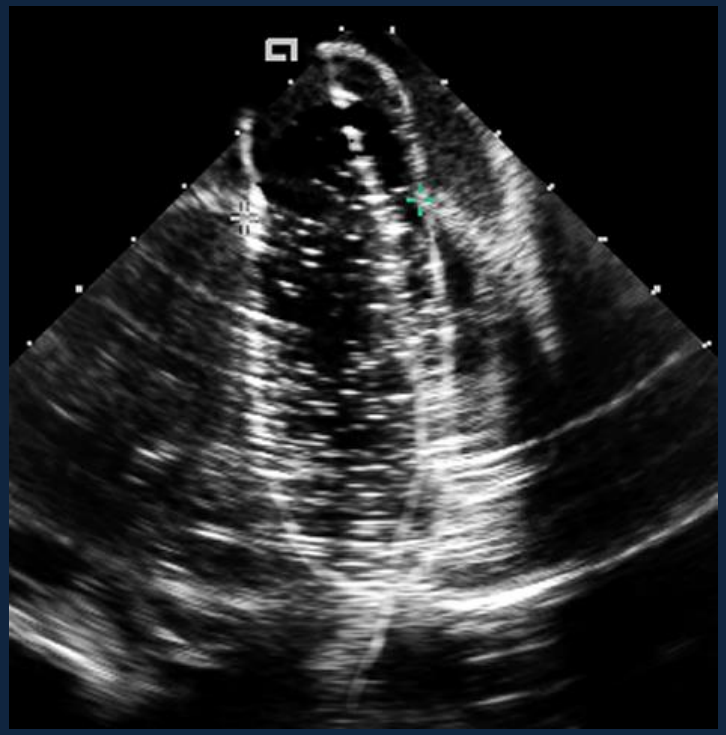


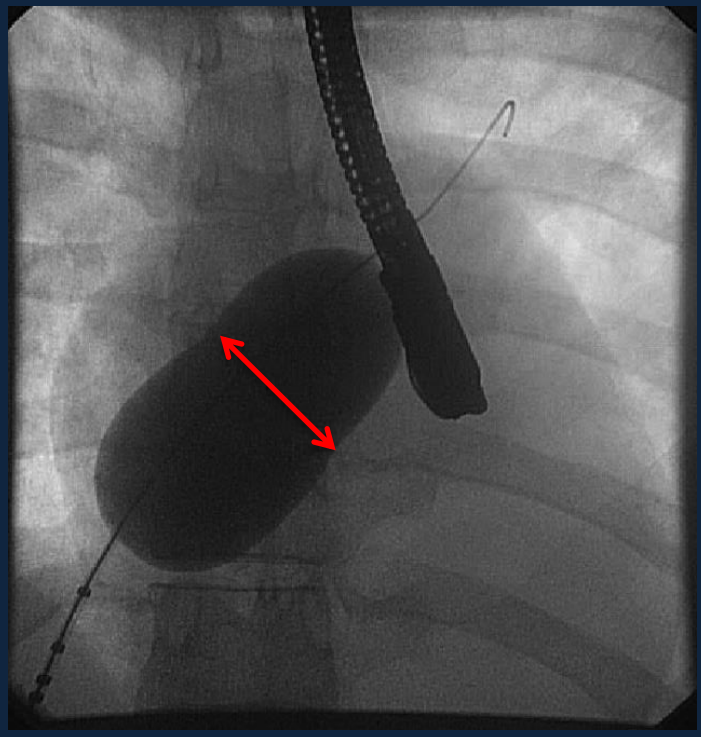




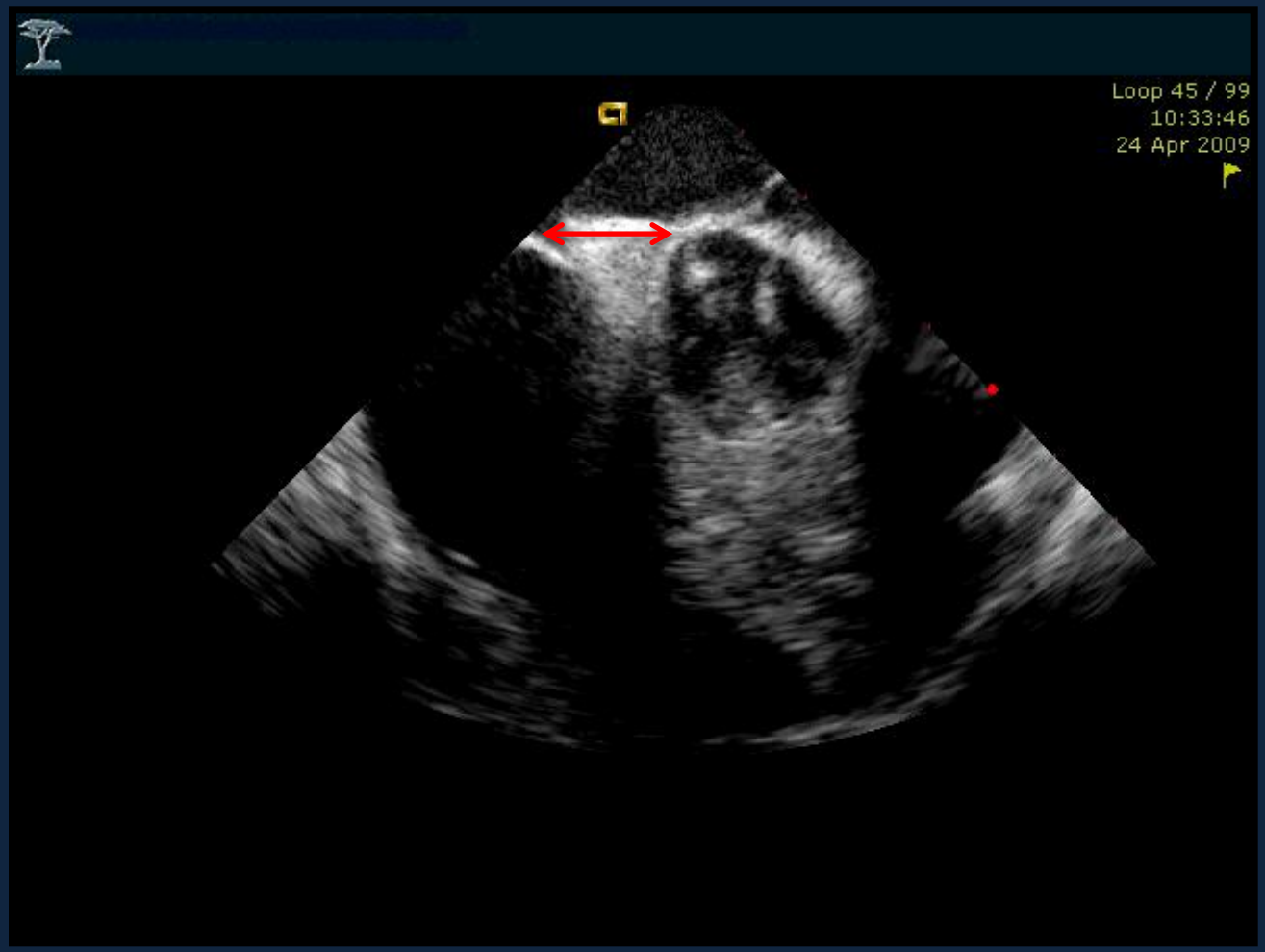
Balloon Sizing (Stop Flow) In ASD





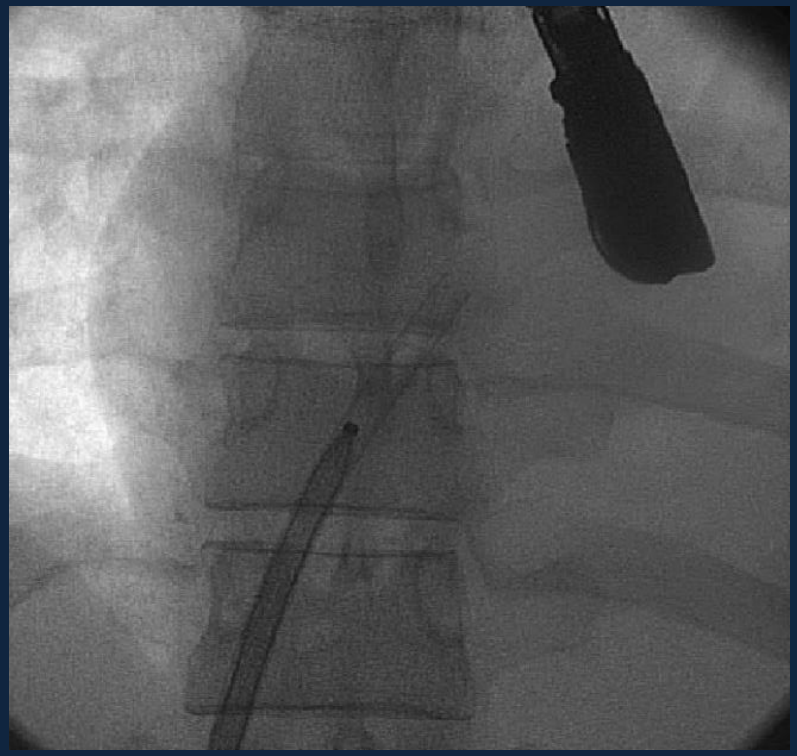


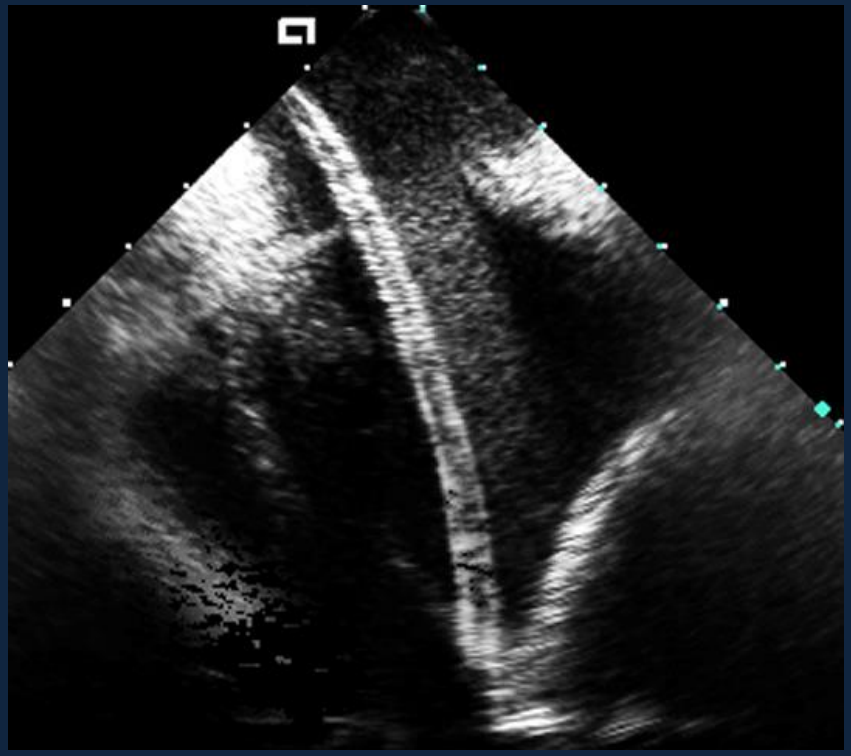
Patent Foramen Ovale-”Sizing by ICE”



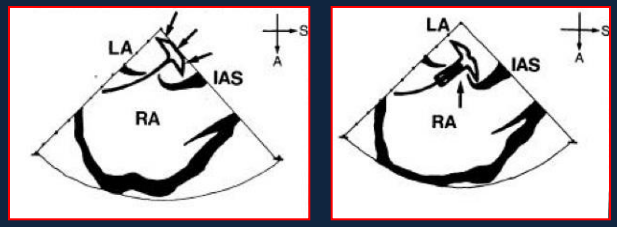
Advance Delivery Sheath

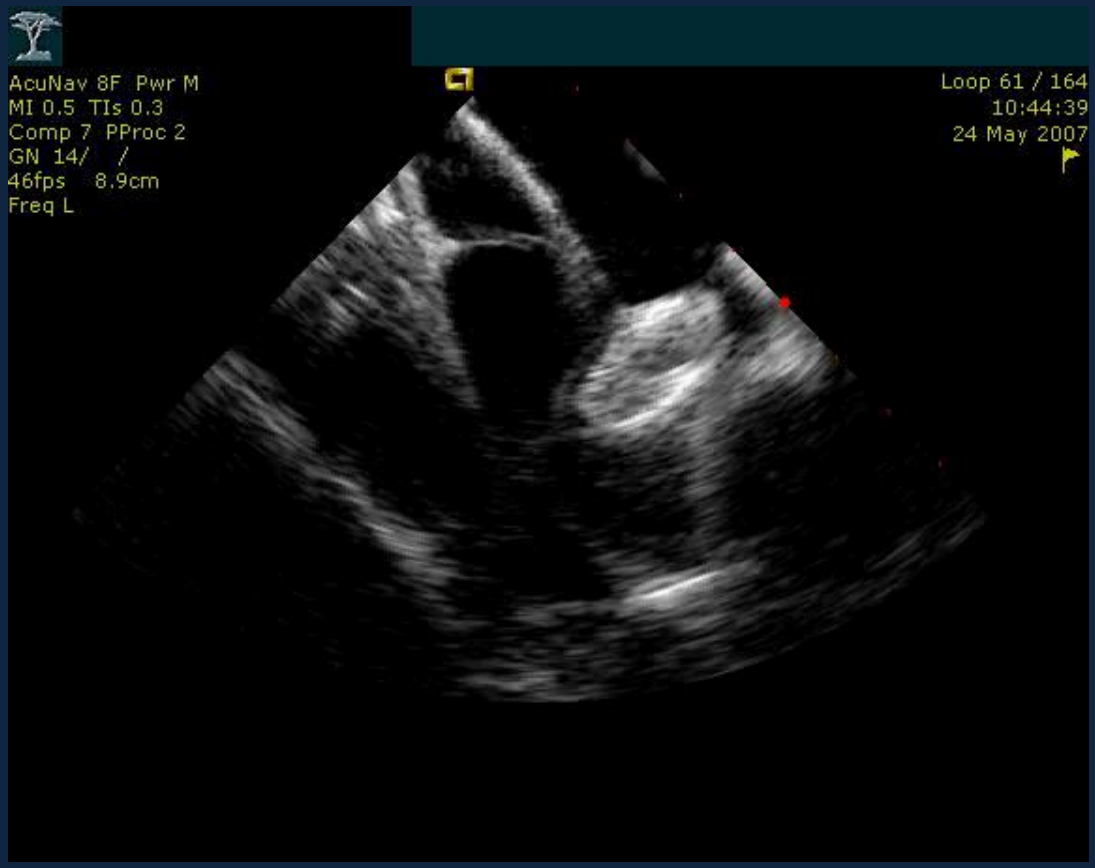
(Across ASD / PFO)

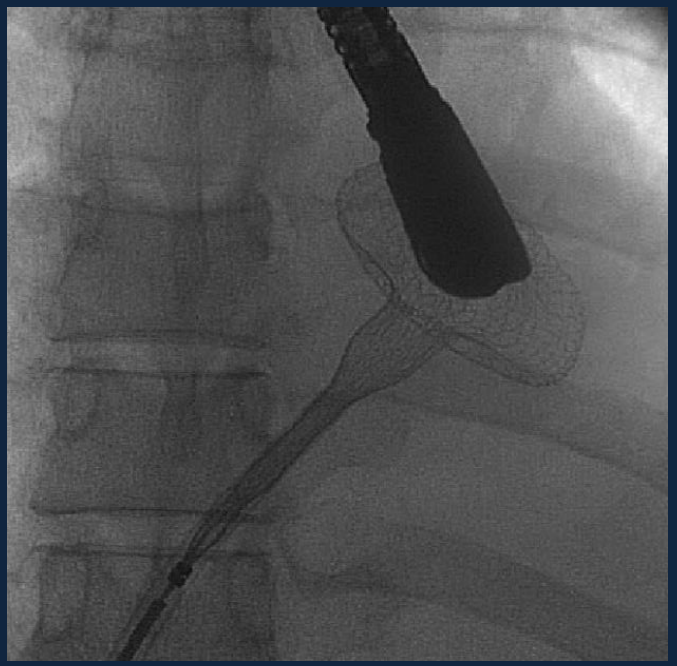




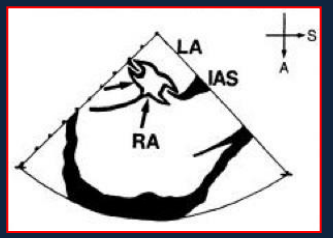
Deployment of LA Disc

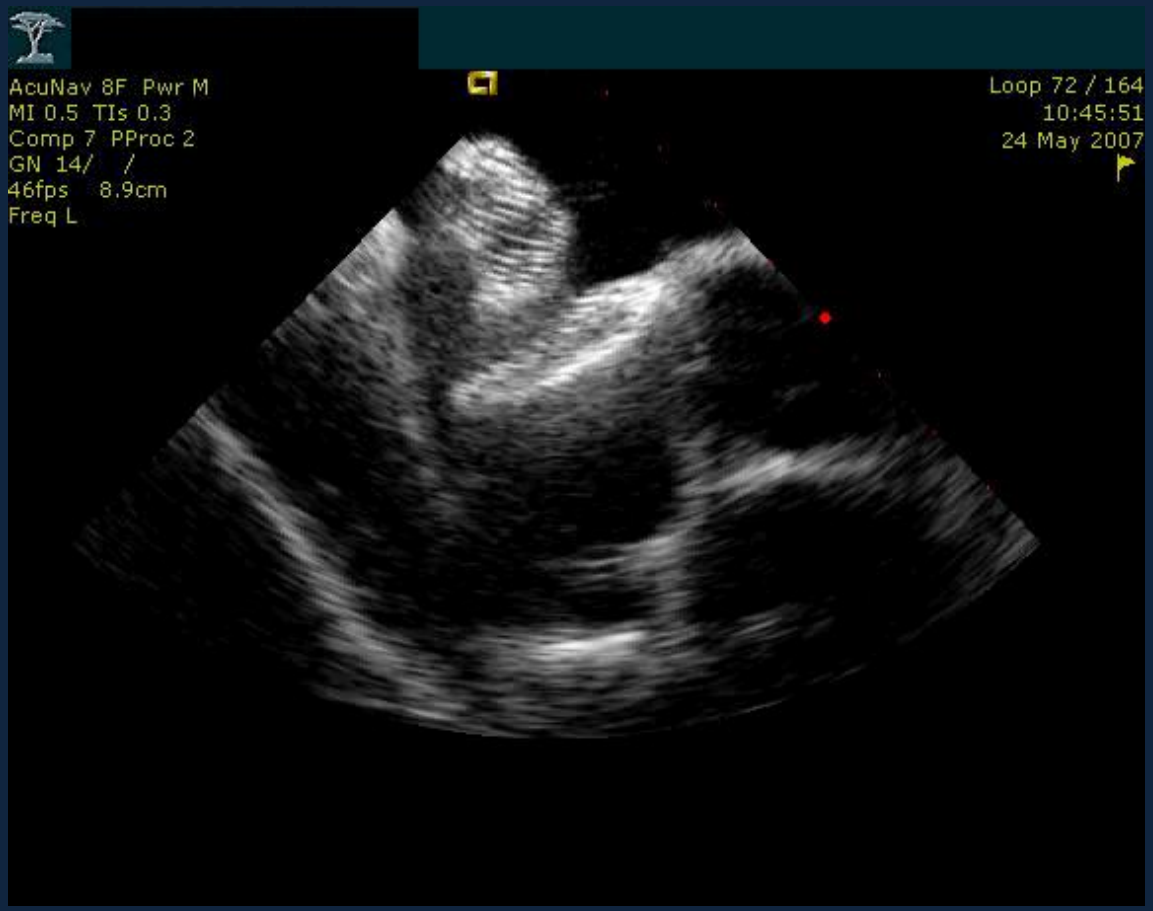


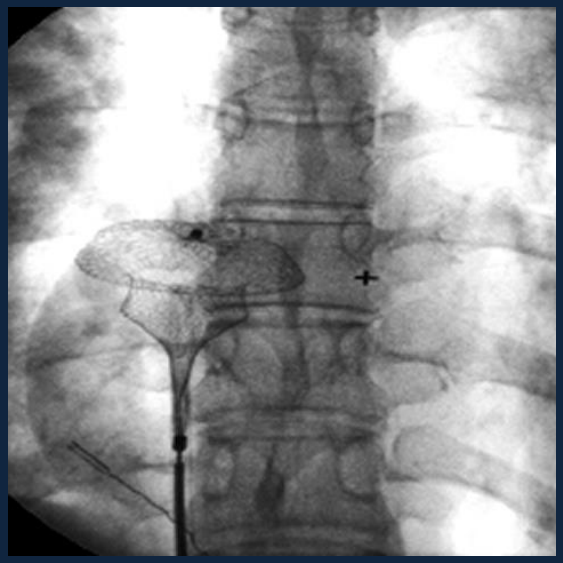


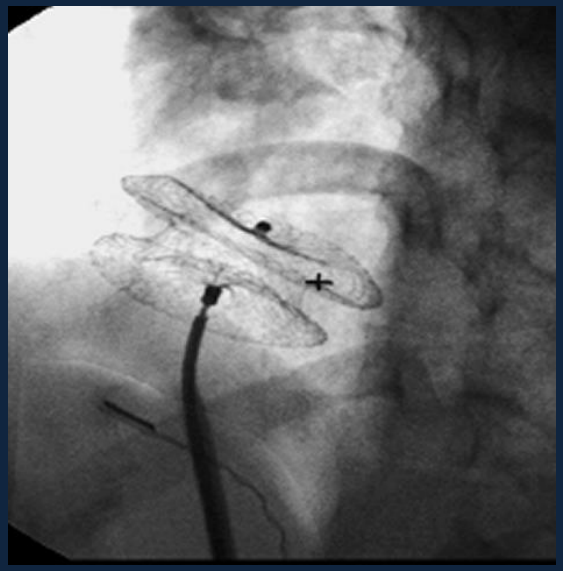


Deployment of Waist and RA Disc

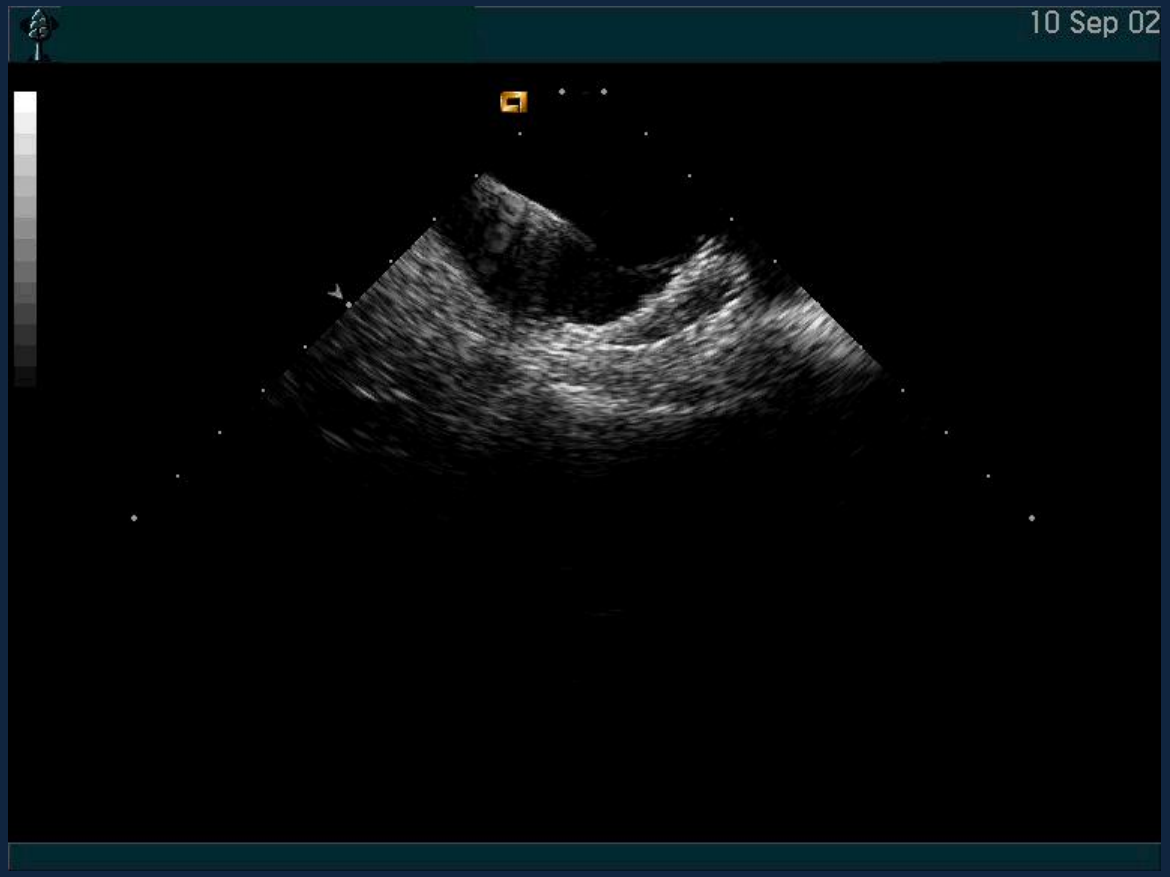


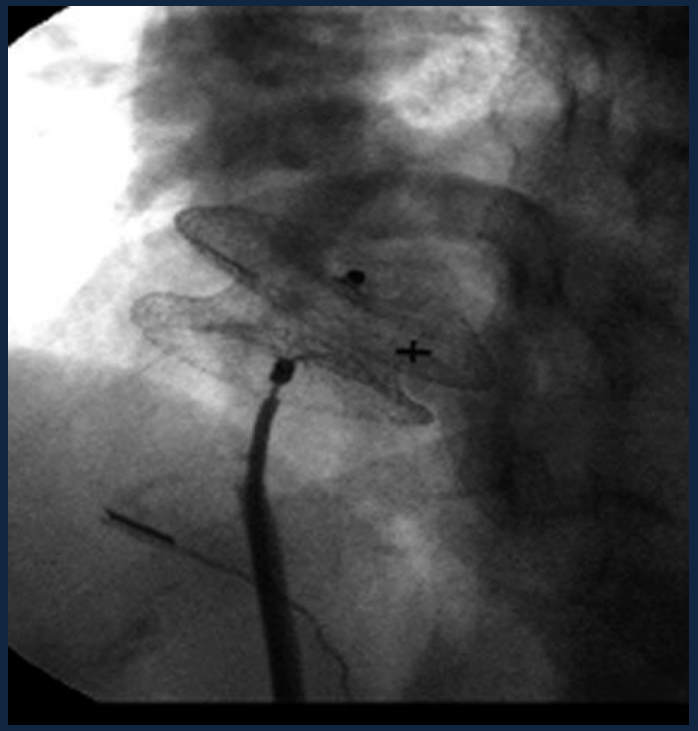






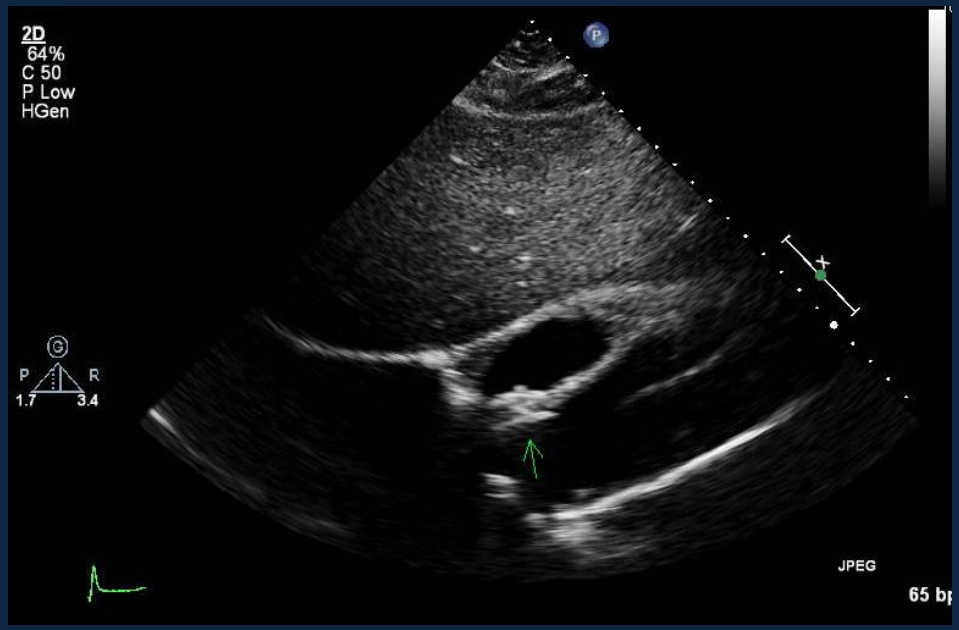
Assessing Stability



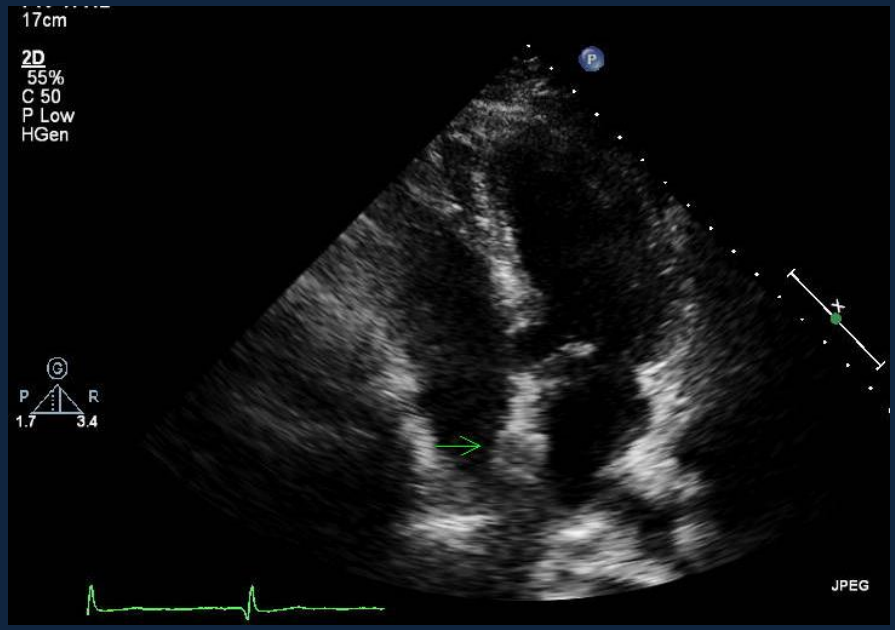


Follow-Up TTE
Best views

Subcostal View



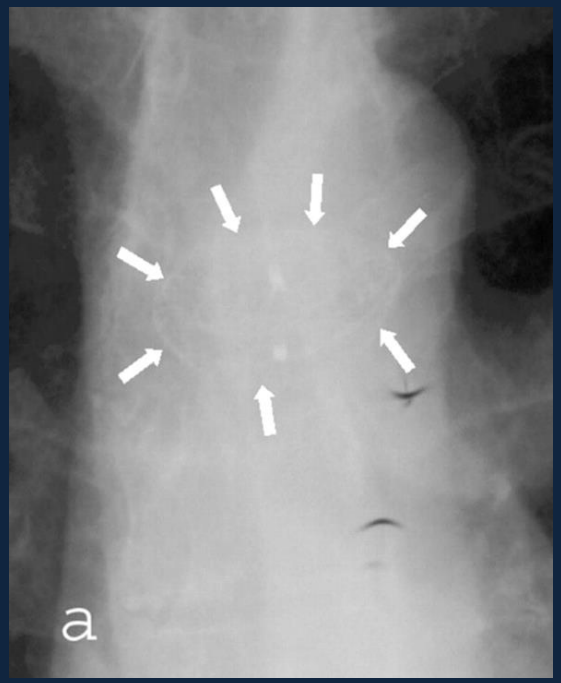
Apical 4-Chamber View



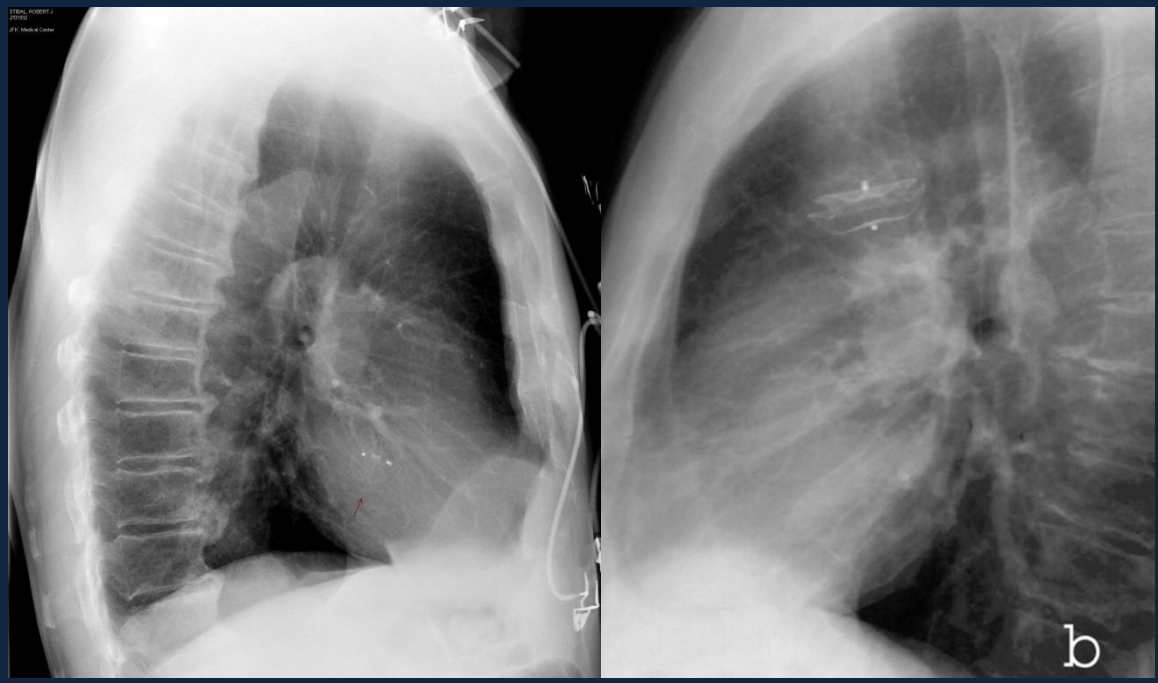
Veldtman GR, et al. JACC 2001; 37:2108-113

FOLLOW-UP CXR

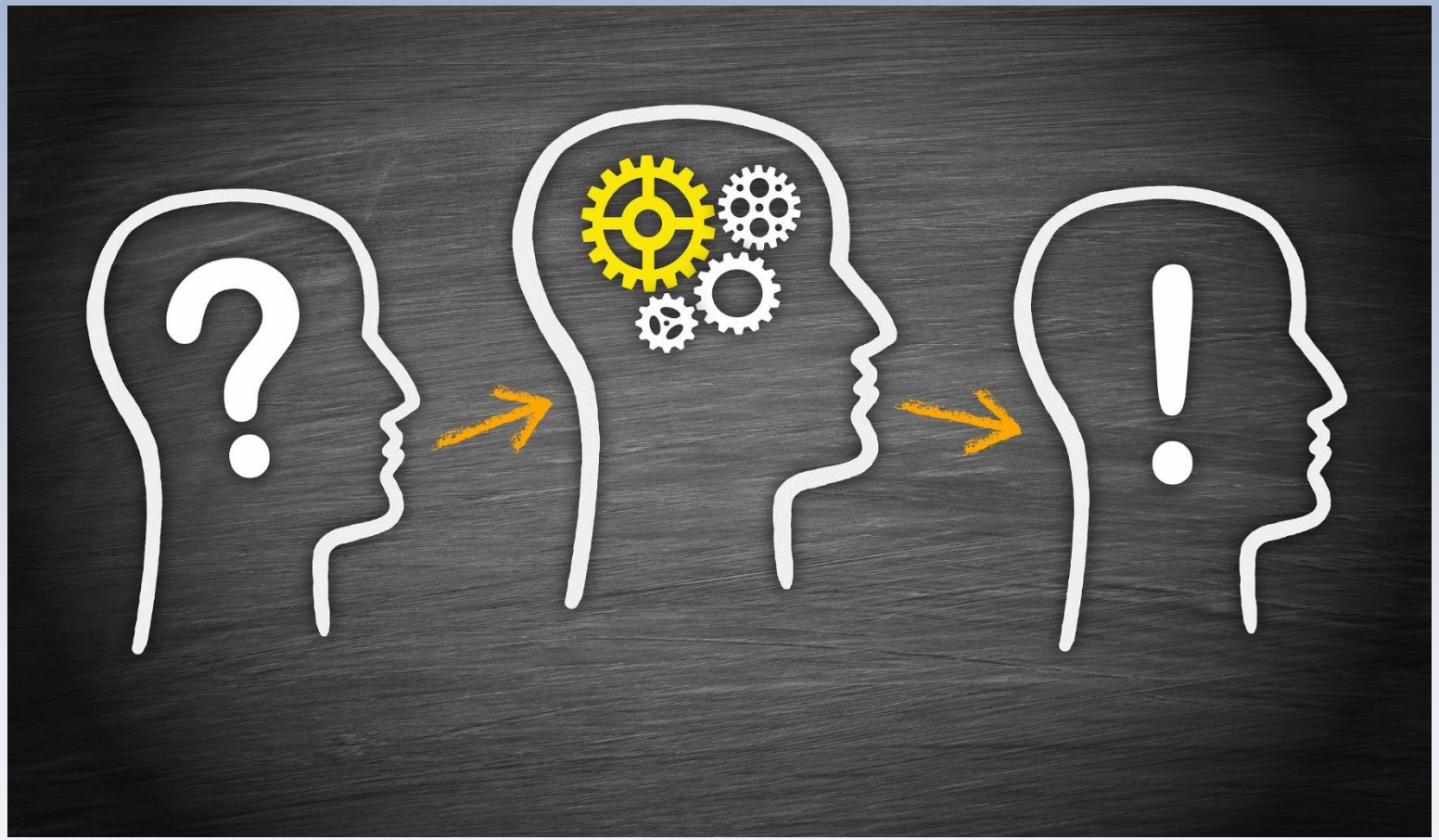
PA



Lateral



Questions



Thank you!

- Presenters
  - Gustavo Cardenas, MD
  - Habibollah Ghanavati, MD
  - Jonathan Wiener, MD
  - Touqir Zahra, MD
  - Jonathan P. Nieves, MD PGY-2
  - Jose Rodriguez, MD PGY-1
  - Jordan Smith MS-3

References

- Pearson AC, Nagelhout D, Castello R, et al. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. J Am Coll Cardiol 1991; 18:1223.
- Hanley PC, Tajik AJ, Hynes JK, Edwards WD, Reeder GS, Hagler DJ, Seward JB. Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. J Am Coll Cardiol. 1985;6:1370-1382
- Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993; 24:1865.
- Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology. 2000;55(8):1172-9.
- Rigatelli G, Rigatelli A. Closing patent foramen ovale in cryptogenic stroke: The underscored importance of other interatrial shunt variants. World J Cardiol. 2015;7(6):326-30.
- RESPECT Trial
- Schuchlenz HW, Weihs W, Horner S, Quehenberger F. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. Am J Med. 2000;109(6):456-62.
- Mattioli AV, Aquilina M, Oldani A, et al. Atrial septal aneurysm as a cardioembolic source in adult patients with stroke and normal carotid arteries. A multicentre study. Eur Heart J 2001; 22:261.
- Ilercil A, Meisner JS, Vijayaraman P, et al. Clinical significance of fossa ovalis membrane aneurysm in adults with cardioembolic cerebral ischemia. Am J Cardiol 1997; 80:96.
- Mügge A, Daniel WG, Angermann C, et al. Atrial septal aneurysm in adult patients. A multicenter study using transthoracic and transesophageal echocardiography. Circulation 1995; 91:2785.
- Agmon Y, Khandheria BK, Meissner I, et al. Frequency of atrial septal aneurysms in patients with cerebral ischemic events. Circulation 1999; 99:1942.
- Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001; 345:17
- Meier B, Lock JE. Contemporary management of patent foramen ovale. Circulation 2003; 107:5.
- Homma S, Sacco RL, Di Tullio MR, et al. Atrial anatomy in non-cardioembolic stroke patients: effect of medical therapy. J Am Coll Cardiol 2003; 42:1066.
- Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013; 368:1083.