Transcatheter Closure of ASD and PFO

Transcatheter Closure of Atrial Septal Defect

Relative Frequency Occurrence of Cardiac Malformations at Birth

Ventricular Septal Defect	30.5%
Atrial Septal Defect	9.8%
Persistent Ductus Arteriosus	9.7%
Pulmonary Stenosis	6.9%
Aortic Coarctation	6.9%
Tetralogy of Fallot	5.8%
Transposition of Great Vessels	4.2%
Persistent Truncus Arteriosus	2.2%
Tricuspid Atresia	1.3%
All others	16.5%

Hurst's The Heart 11th ed.

Benefits from ASD Closure

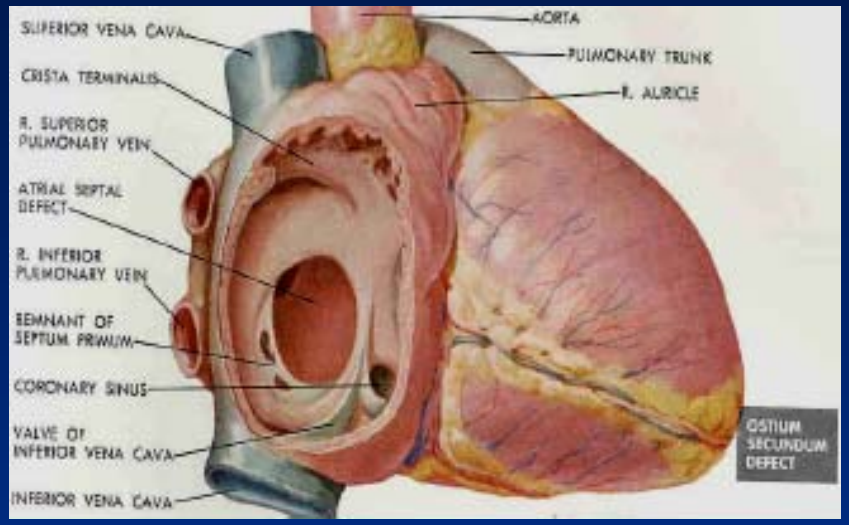
- Improved functional class, exercise capacity[1]
- Improved survival after youthful repair[2]
- Resolution of right heart enlargement[3]
- Reduced risk of atrial fibrillation, esp. <55 yo[4]
- Decrease of pulmonary arterial pressure[5]

1. Brochu M-C et al. Circulation 2002;106:1821-6
2. Murphy JG et al. N Engl J Med 1990;323:1645-50
3. Kort HW et al. J Am Coll Cardiol 2001;38:1528-32
4. Silversides CK et al. Heart 2004;90:1194-8
5. De Lezo JS et al. presented at AHA 2006

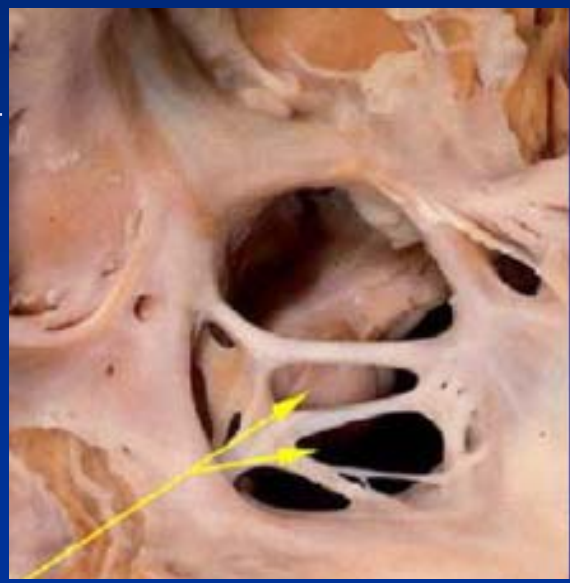
Consideration of ASD Closure

- Evidence of RV volume overload
- Type of ASD
- Size of ASD
- Multiplicity of ASD
- Atrial septal anatomy
- Reversibility of pulmonary hypertension
- Atrial arrhythmia

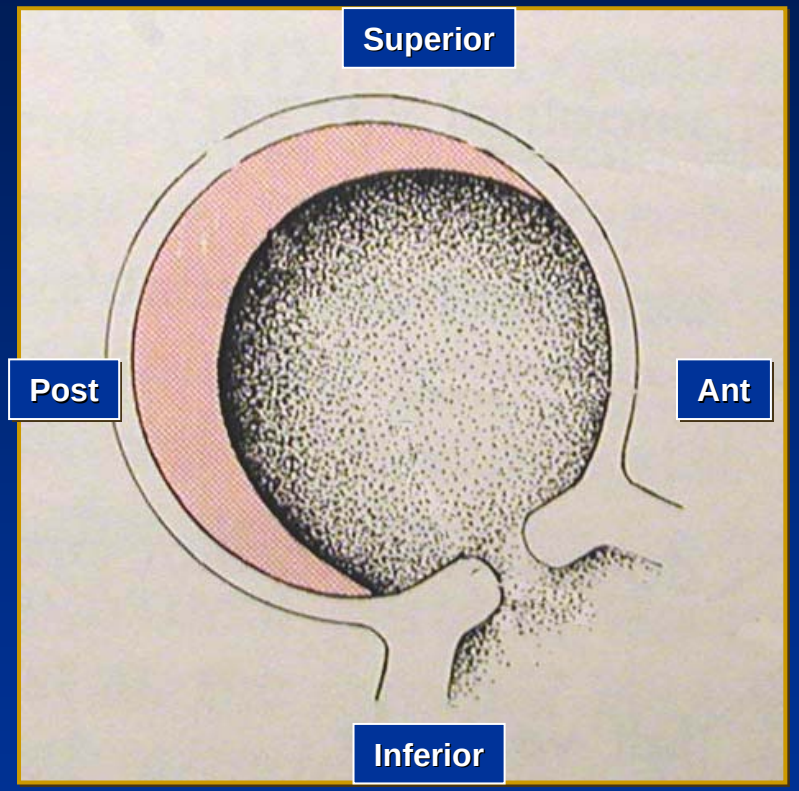
Anatomy of Secundum ASD



Central part of fossa ovalis	66%
Upper part of fossa ovalis	4%
Inferior part of fossa ovalis	8%
Absent posterior rim	2%
Multifenestrated	15%



Embryology
Formation of Atrial Septum - 1



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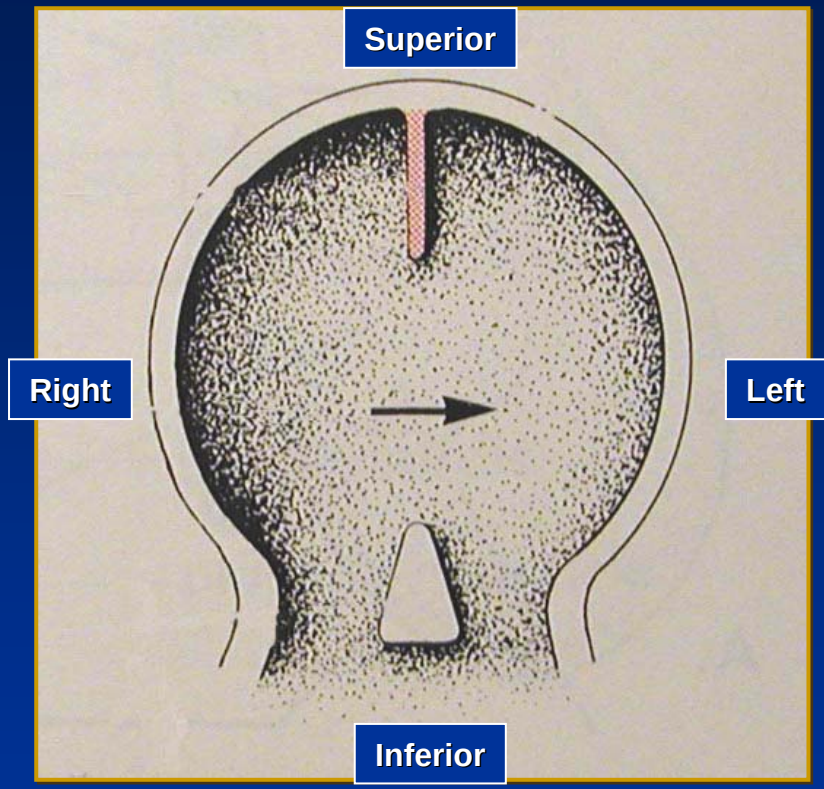
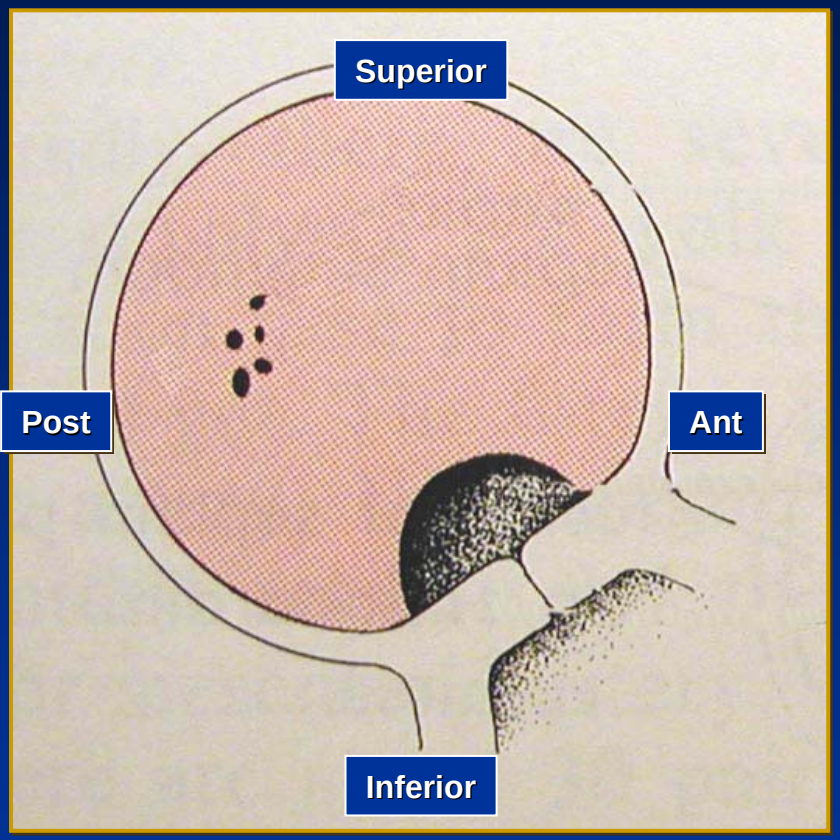


From Anterior

From: Moore KL, *The Developing Human*, 2nd Edition, 1977

Embryology
Formation of Atrial Septum - 2



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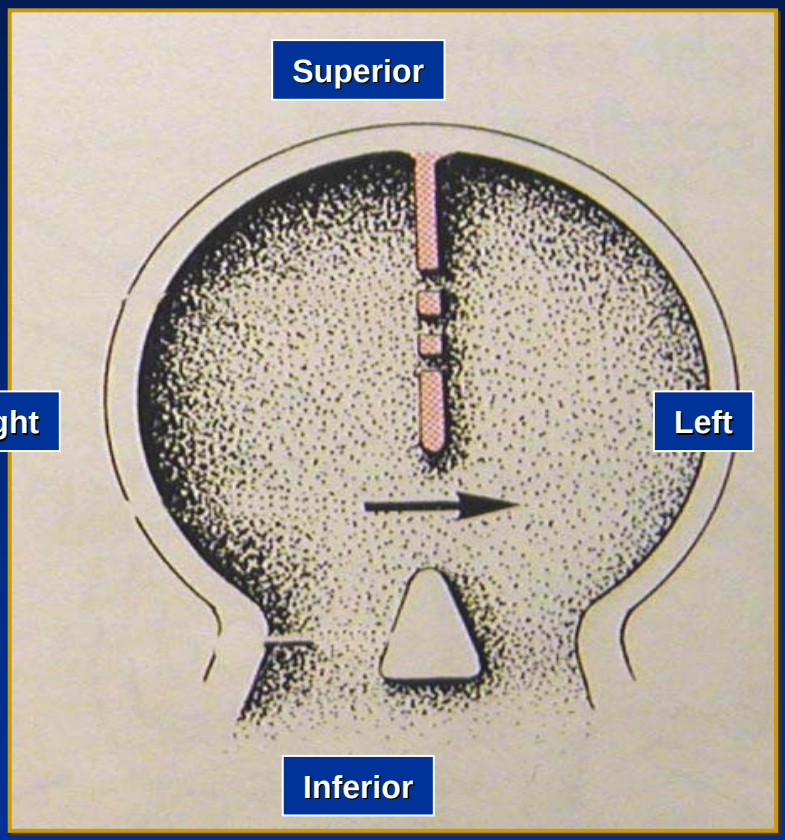
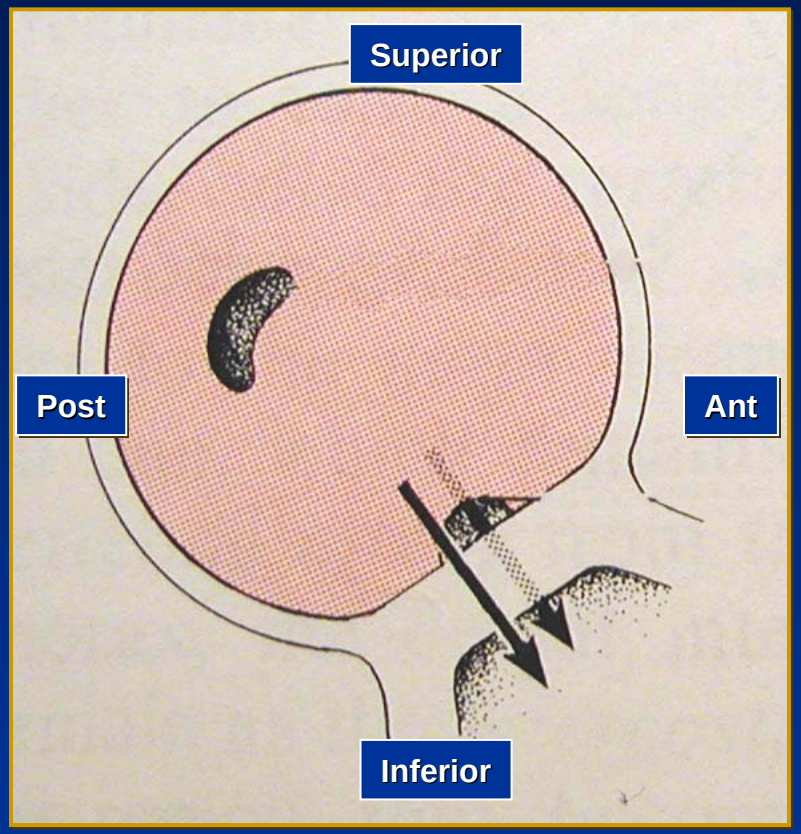


From Anterior

Embryology

Formation of Atrial Septum - 3



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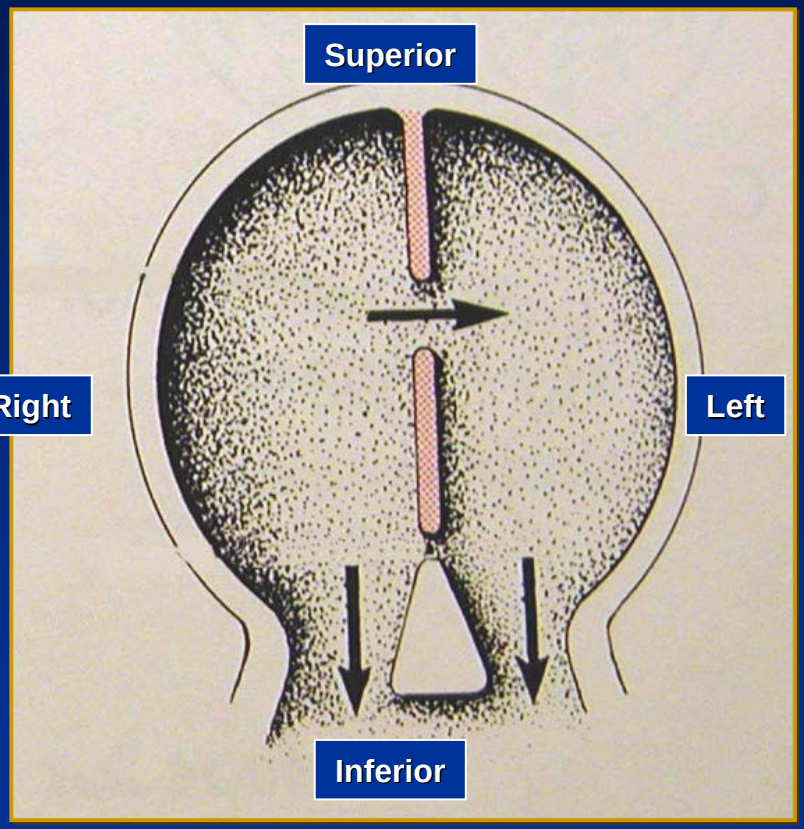
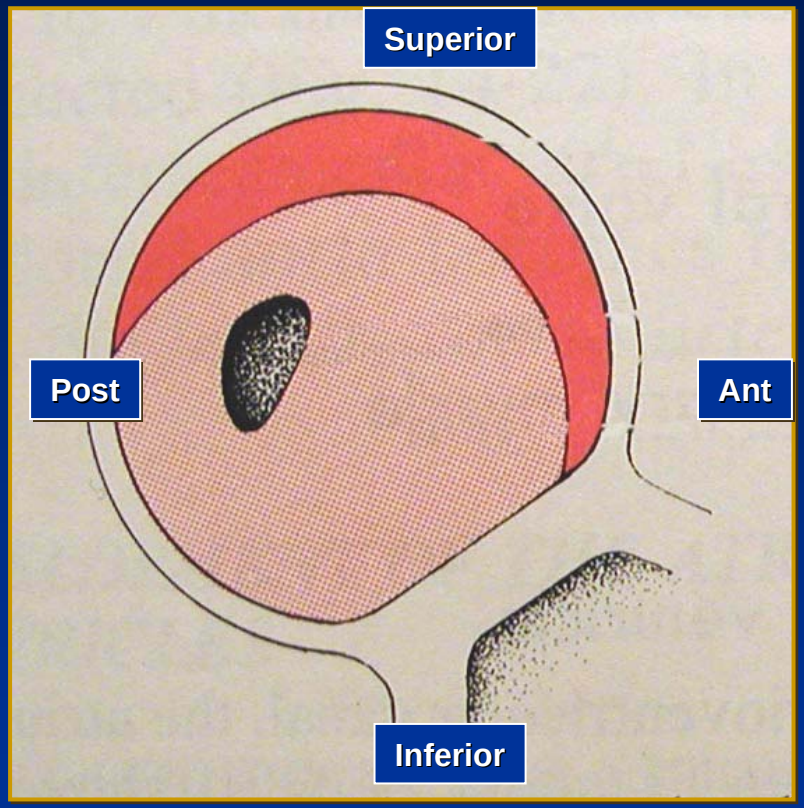


From Anterior

Embryology

Formation of Atrial Septum - 4



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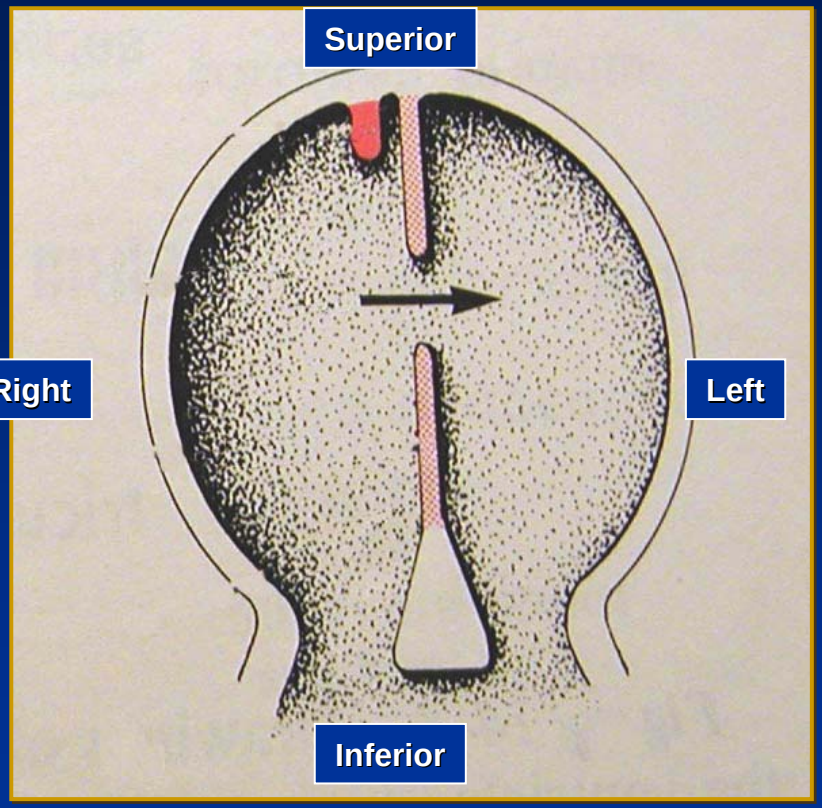
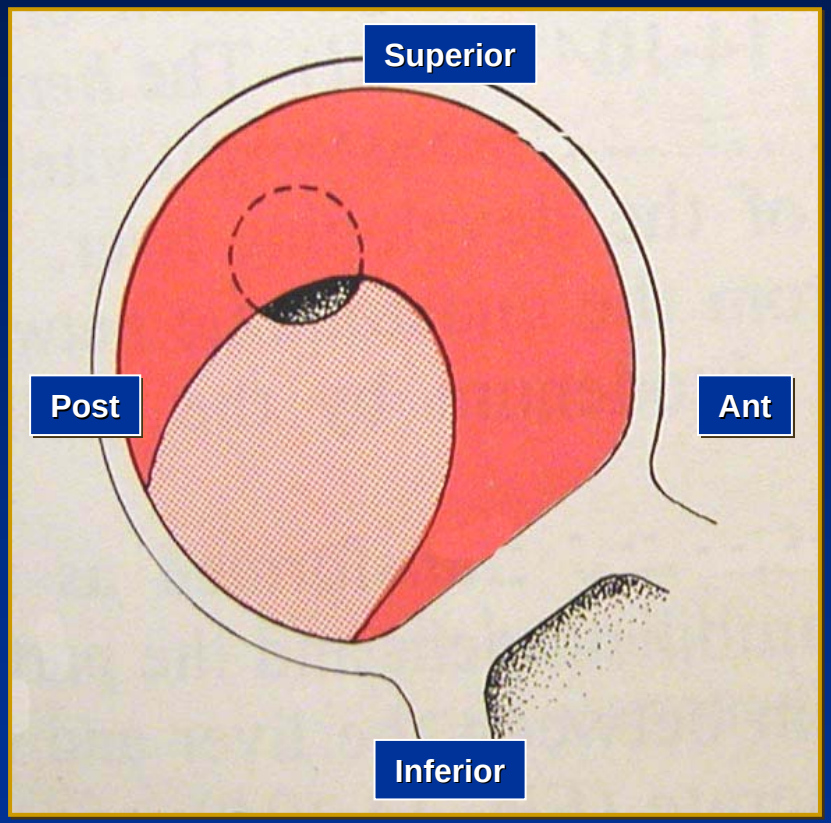


From Anterior

Embryology

Formation of Atrial Septum - 5



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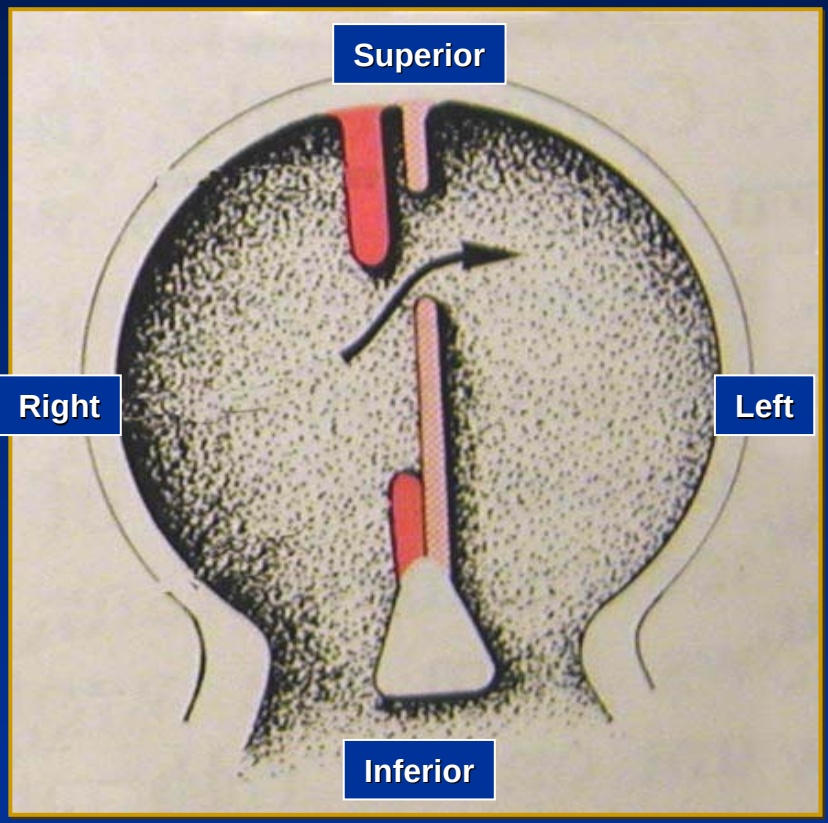
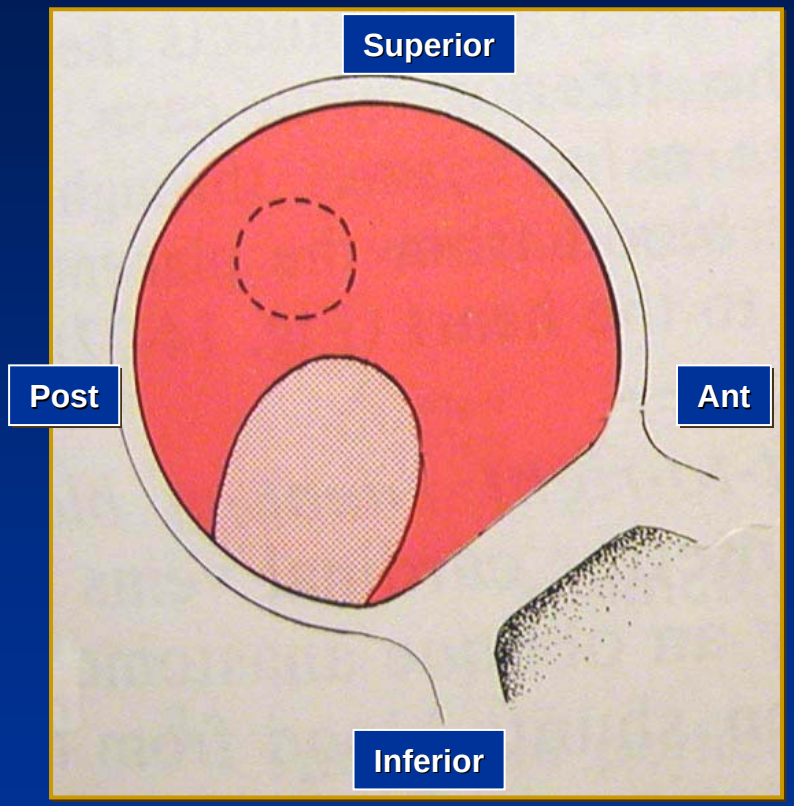


From Anterior

Embryology

Formation of Atrial Septum - 6



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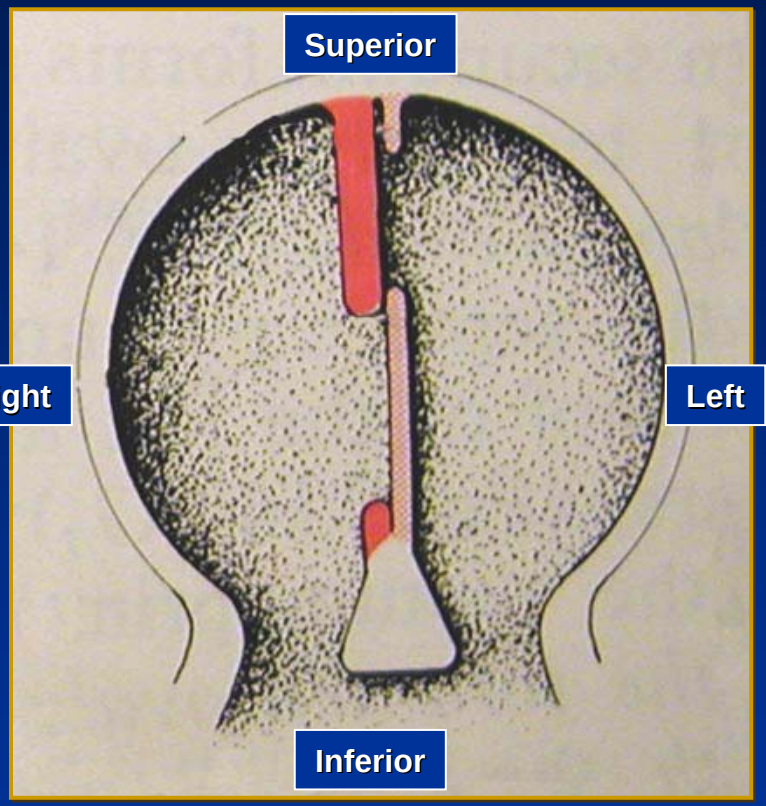
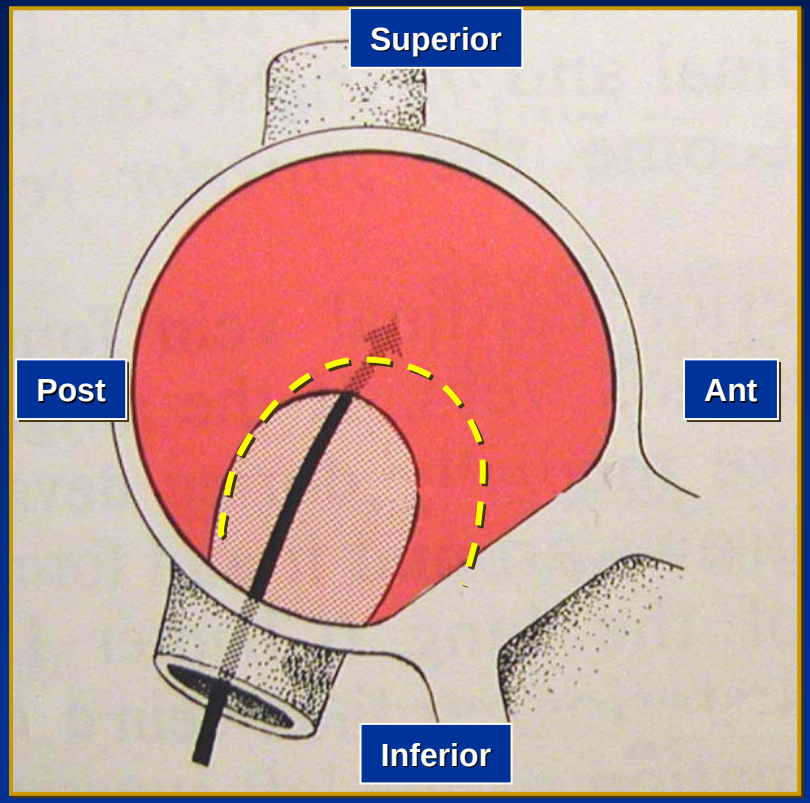


From Anterior

Embryology

Formation of Atrial Septum - 7



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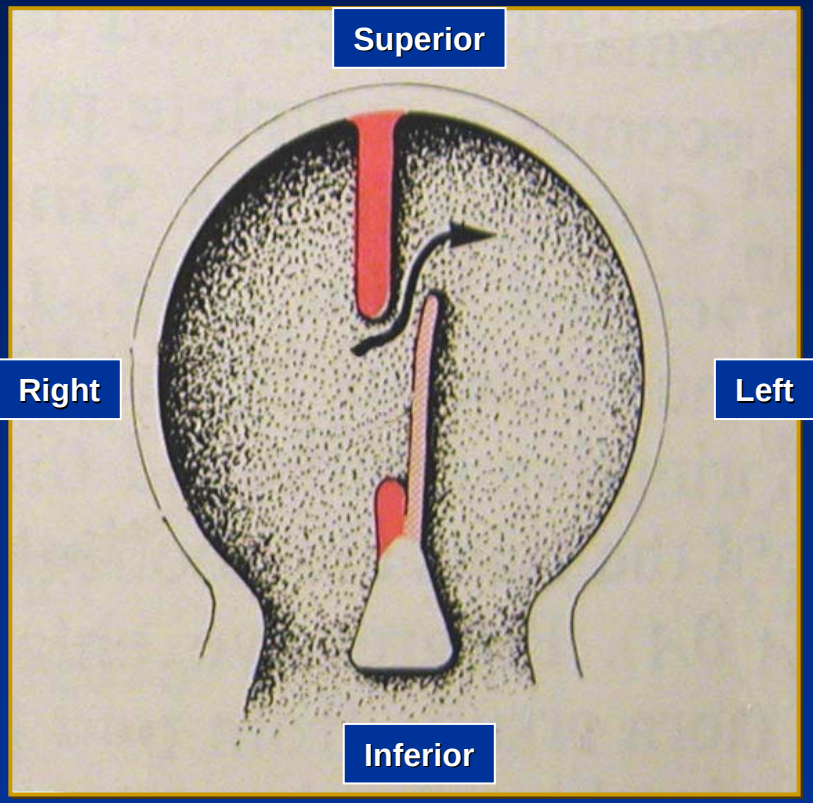


From Anterior

Indications for ASD Closure

- Right atrial and right ventricular dilatation by echo, MRI, or CT (without advanced pulmonary arterial hypertension) manifested with one or more of the following:

  - ASD minimum diameter >10 mm on echo
  - Qp/Qs >1.5 by echo or MRI flow assessment or cath data when performed for other reason

Webb G. Circulation 2006;114:1645-53

Contraindications of Device Closure of ASD

High pulmonary vascular resistance
($\geq$10 units/m^2, >7 units/m^2 with vasodilators)*

Eisenmenger syndrome

Associated congenital cardiac anomalies which require cardiac surgery

Unfavorable atrial septal anatomy

? Nickel hypersensitivity

*from Pediatric Cardiology for Practitioners, 4th ed., Park

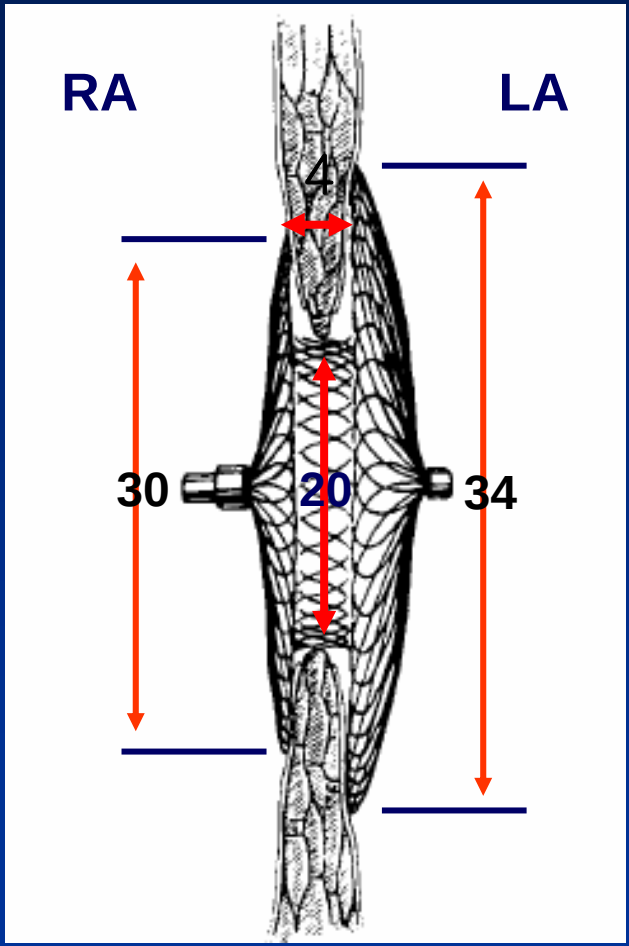
Technical Aspects for Device Closure of ASD

- Minimum of **4~5 mm** sufficient rim around the defect
- Amplatzer may not require anterior (aortic) rim and device may wrap around aortic root.
- Deficient superior rim, close to RUPV, close to AV valve or coronary sinus, surgery is the treatment of choice.
- Amplatzer waist **2~4 mm** larger than diameter
- Defect size upto **30 mm** or more? (Amplatzer upto 38mm)

Du Z-D et al. Am J Cardiol 2002;90:865-9

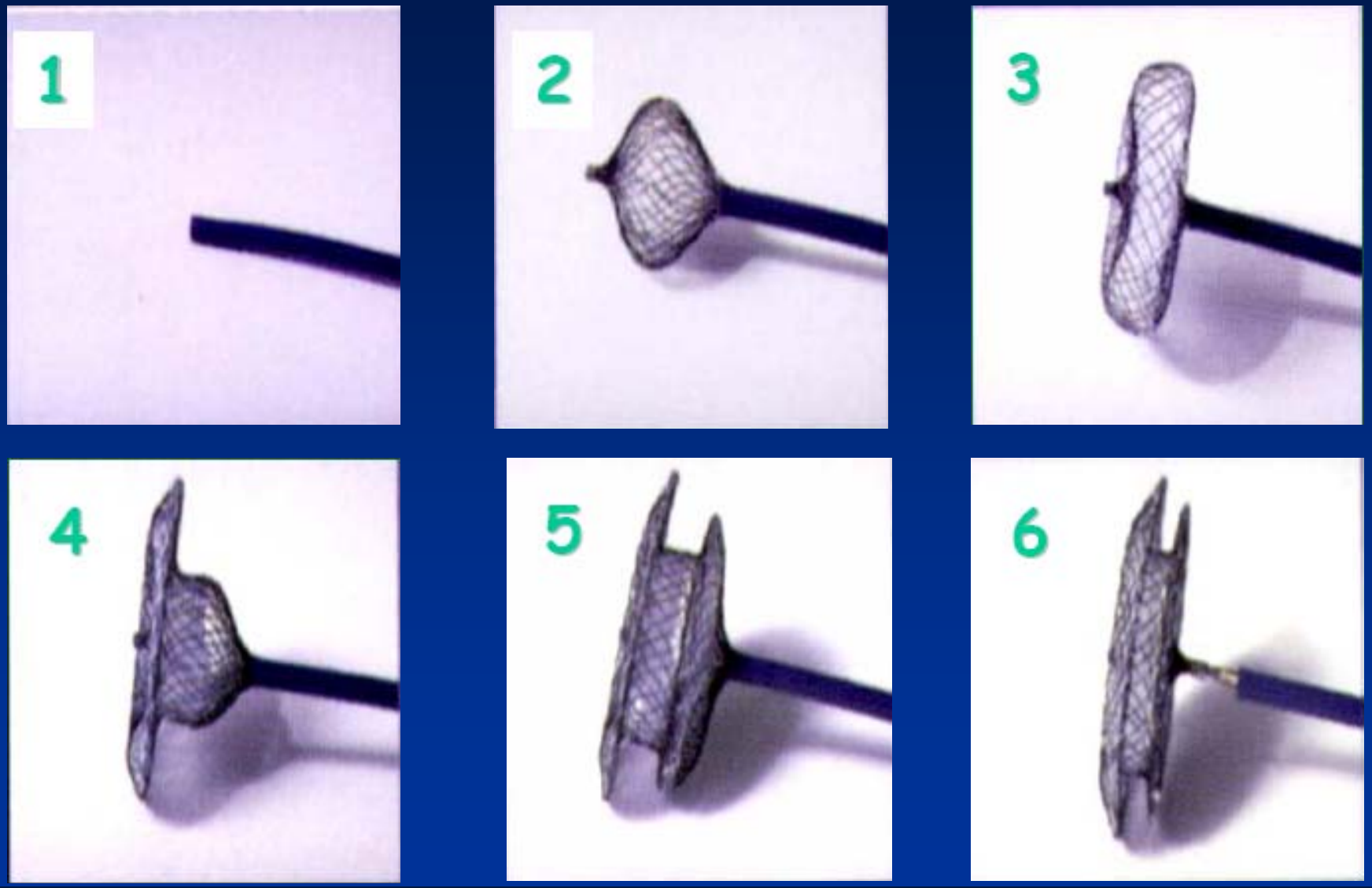
Amplatzer Septal Occluder (ASO)

only one FDA approved for ASD closure

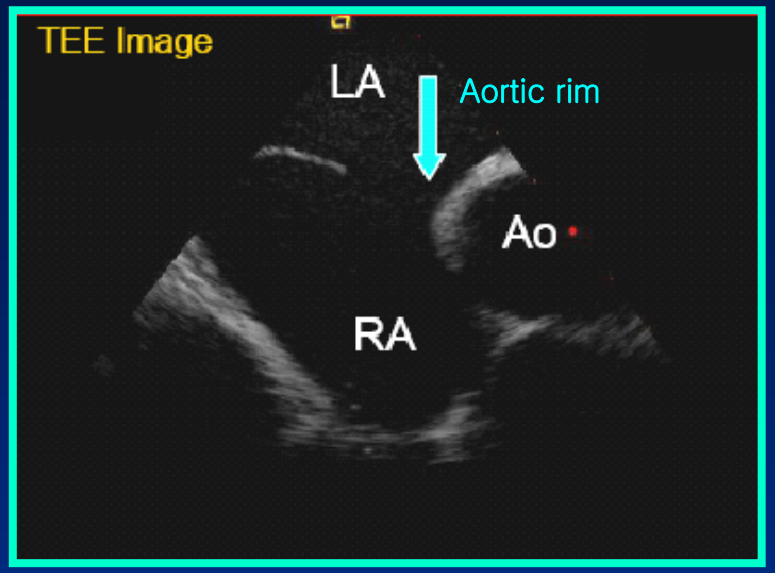


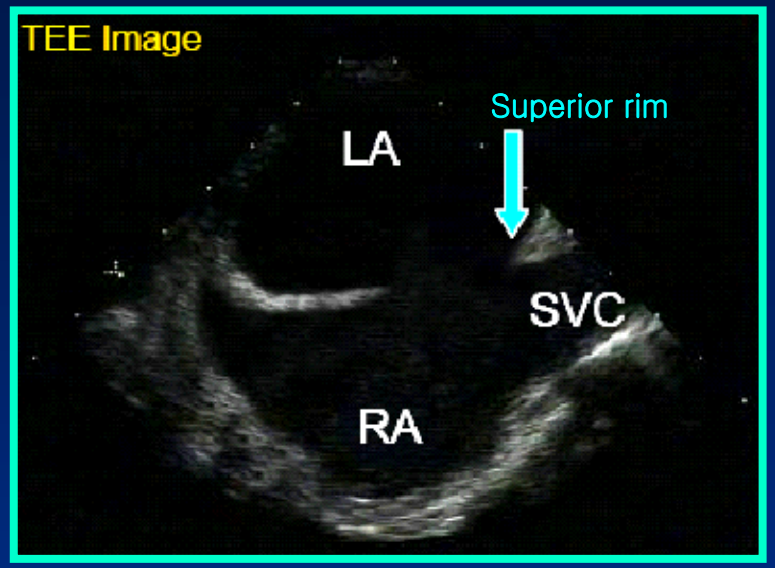
- Double disk (self expandable) connected by waist (4~38 x 3~4 mm)
- LA disk > RA disk
- Nitinol wire mesh (shape-memory) + biocompatible polyester fabric (thrombogenecity and tissue ingrowth)
- Delivery cable 7~12F

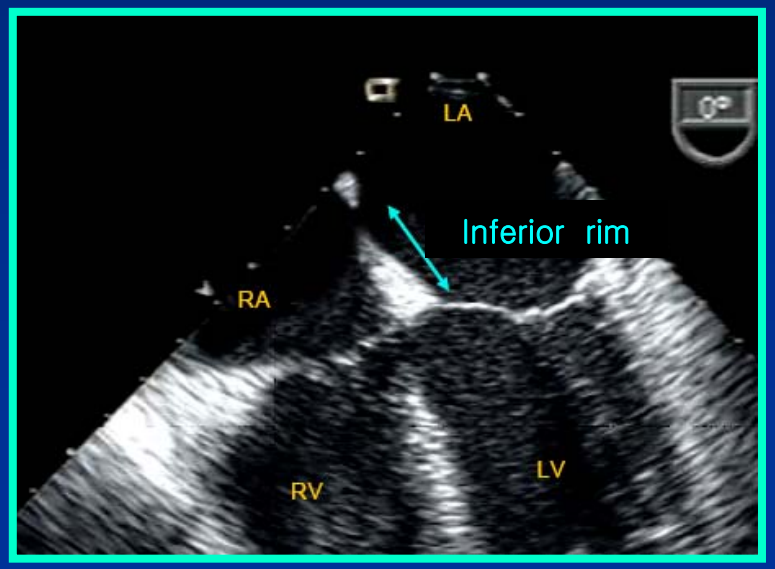
Implantation of ASO

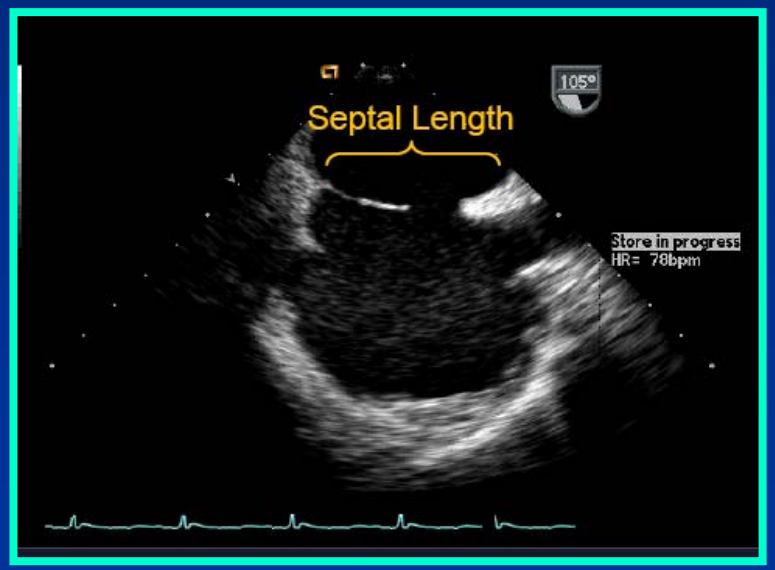


Check Points on TEE

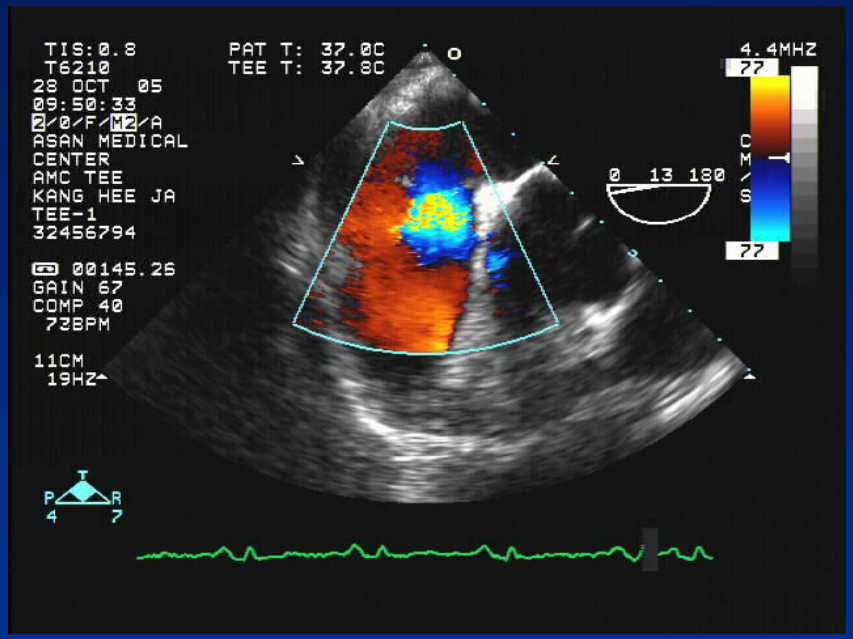








Case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CENTER
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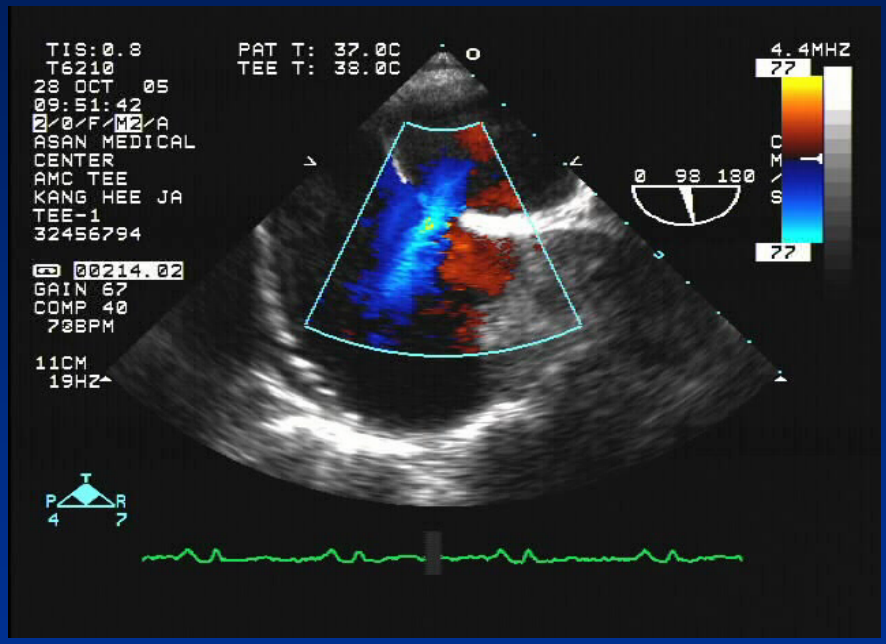
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COMP 40
70BPM
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PAT T: 37.0C
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0 98 180
77

Implantation of ASO

Efficacy
Comparable with Surgery?

Comparison between Transcatheter and Surgical Closure of ASD

Nonrandomized Multicenter Trial

	Device (n=442)	Surgery (n=154)	p value
Age	18.1 ± 19.3	5.9 ± 6.2	<.001
ASD size (mm)	13.3 ± 5.4	14.2 ± 6.3	NS
Number of multiple ASDs	47 (10.6%)	30 (19.4%)	NS
Procedure attempt success	423/442 (95.7%)	154/154 (100%)	NS
Immediate procedural success	413/423 (97.6%)	154/154 (100%)	NS
Procedure success at 6 months	376/387 (97.2%)	154/154 (100%)	NS

Du Z-D et al. J Am Coll Cardiol 2002;39:1836-44

Comparison between Transcatheter and Surgical Closure of ASD

Nonrandomized Multicenter Trial

	Device (n=442)	Surgery (n=154)	p value
Primary efficacy success	326/331 (98.5%)	149/149 (100%)	NS
moderate+large residual shunt	5/331 (1.5%)	0	
Secondary efficacy success	405/442 (91.6%)	137/154 (89%)	NS
major complication	1/442 (0.2%)	8/154 (5.2%)	
cardiac arrhythmia treated	12/442 (2.7%)	9/154 (5.8%)	
surgical reintervention	5/442 (1.1%)	0	
Length of hospital stay (day)	1.0 ± 0.3	3.4 ± 1.2	<.001

Du Z-D et al. J Am Coll Cardiol 2002;39:1836-44

Long-Term Outcome

Long-Term Outcome of ASD Closure using Amplatzer Septal Occluder

Observational Study

Median follow-up period	78 months
Number of patients	151
Mean age	11.9 ± 11.6 yrs
Mean maximal defect diameter (TEE)	12.9 ± 4.4 mm
Mean stretched defect diameter	15.9 ± 4.8 mm
Number of septal occluder implanted	152
Mean size of septal occluder	16.1 ± 5.3 mm

Masura J et al. J Am Coll Cardiol 2005;45:505-7

Long-Term Outcome of ASD Closure using Amplatzer Septal Occluder

Observational Study

Follow-up	Residual shunt : moderate + small (%)
Immediate	31 : 6+25 (20.5)
1 day	13 : 4+9 (8.6)
1 month	7 : 3+4 (4.6)
3 months	2 : 2+0 (1.3)
1 year	1 : 0+1 (0.6)
3 years	1 : 0+1 (0.6)

Masura J et al. J Am Coll Cardiol 2005;45:505-7

Outcomes in Adults

Outcome of ASD Closure in Adults ≥ 40 years of age

Observational Study

Number of patients	113
Median follow-up	3 years
Mean age	57.9 ± 11.9 yrs
Mean 2D maximal defect diameter	17.2 ± 7.3 mm
Mean stretched defect diameter	21.6 ± 7.3 mm
Single/Two/Three devices	104/7/1
Mean size of septal occluder	24.0 ± 7.5 mm

Patel A et al, J Interv Cardiol 2007;20:82-8

Outcome of ASD Closure in Adults ≥ 40 years of age

Observational Study

Procedural success	112/113 (99.1%)
Successful closure	
immediate	110/113 (97.3%)
24 hours	110/112 (98.2%)
6 months	111/112 (99.1%)
Complications*	4/113 (3.5%)

* 1 device migration, 2 atrial arrhythmia, 1 large hematoma

Patel A et al, J Interv Cardiol 2007;20:82-8

Safety

Potential Complications of Device Closure of ASD

Malpositioning or migration of device	2-15%
Air embolism	1-3%
Atrial arrhythmia	1-3%
Thromboembolism formed on the device	1-2%
Interference with AV valve function	1-2%
Perforation of atrial wall or aorta	0.1-4%
Systemic or pulmonary vein obstruction	1%

Presented at TCT 2006

Complication Rates of Percutaneous ASD/PFO Closure in US Adult Population

		N	Complications % (95% CI)	p value	Multivariate OR(95% CI)
Overall		5973	7.2 (5.5-9.0)		
Sex	female	3428	7.4 (5.5-9.4)	0.83	0.94
	male	2480	7.1 (4.9-9.3)		(0.60-1.48)
Hospital volume*	<50	2985	10.1 (7.7-12.4)	<.001	2.34
	≥50	2988	4.4 (2.8-6.0)		(1.46-3.75)
Comorbidities	≥2	235	21.1 (10.7-31.3)	<.001	2.03
	1	1260	9.8 (5.7-13.8)		(1.41-2.92)
	0	4478	5.8 (4.1-7.4)		
Year	2003	3230	6.1 (4.2-7.9)	0.02	0.77
	2002	1923	7.3 (5.5-9.1)		(0.58-1.02)
	~2001	820	11.6 (4.8-18.5)		

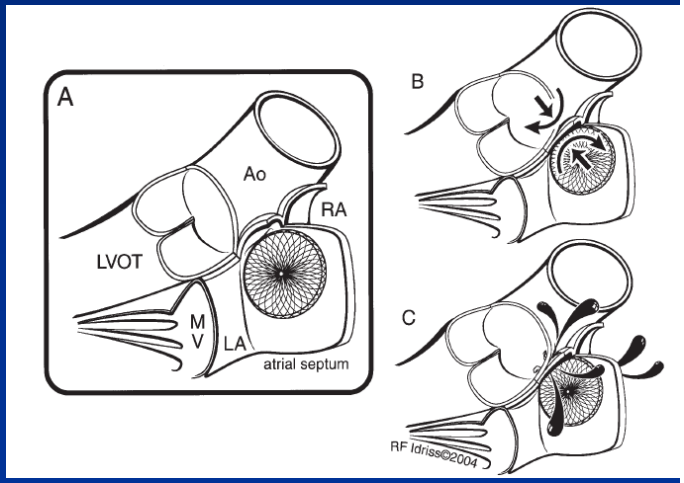
* hospital procedure number

Presented at AHA 2006

Cardiac Perforation

Registry data with Amplatzer Septal Occluder

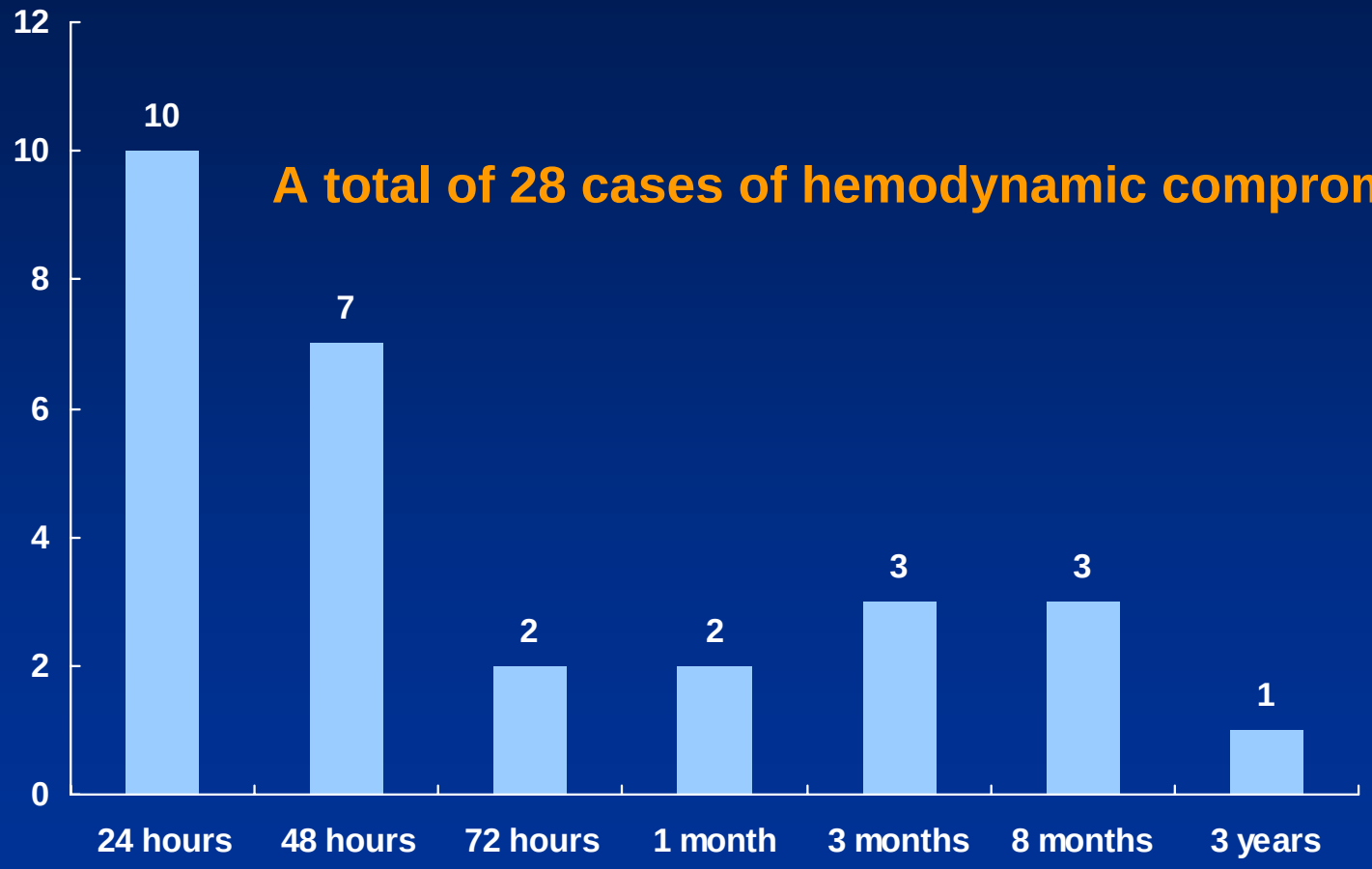
- Between 1998 and March 2004, a total of 28 cases (14 US) of adverse events reported to AGA Medical
- All erosions occurred at the dome of atria, near the aortic root.
- Deficient aortic rim in 89% &/or deficient superior rim
- Incidence 0.1% (28 /~30,000 devices implated worldwide)
- Predictor of erosion or perforation
  - Oversized Amplatzer Septal Occluder
  - Deficient aortic rim and/or superior rim



Amin Z et al. Catheter Cardiovasc Interv 2004;63:496-502

Time to Adverse Event (ASD only)

Registry, between 1998 and March, 2004

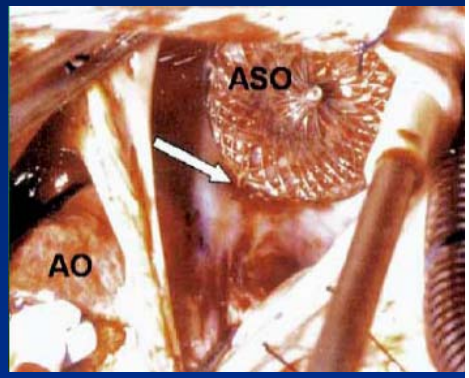


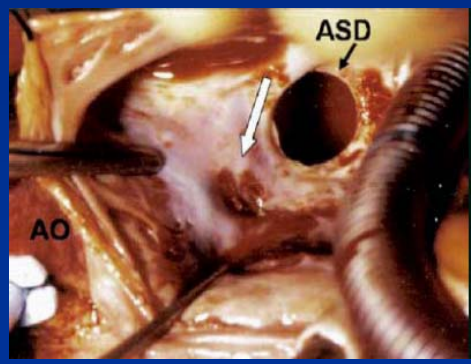
Amin Z et al. Catheter Cardiovasc Interv 2004;63:496-502

Recommendation to Minimize Risk

Using Amplatzer Septal Occluder (ASO)

- Avoid overstretching balloon when balloon-sizing the defect
- Use stop-flow technique for maximum inflation of sizing balloon
- Be gentle with to and fro of the device while the device is attached to the delivery cable
- Identify patients at higher risk requiring closer follow-up
  - significantly larger ASO (>1.5 times) than ASD diameter
  - small pericardial effusion at 24 hr follow-up
  - deformation of ASO at aortic root
  - high defect (minimal aortic and superior rims)
- Mandatory 24 hr follow-up in all patients
- Educate the patients about the risk and need for echo with symptoms

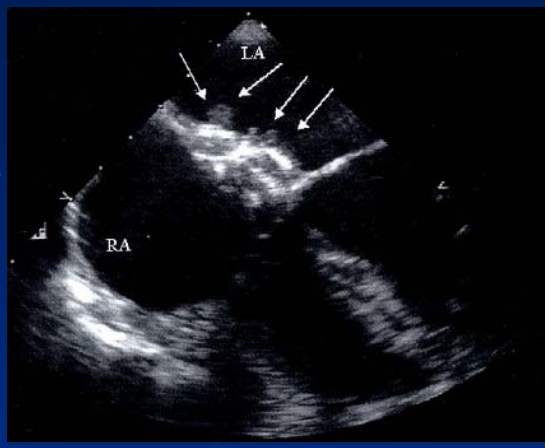




Amin Z et al. Catheter Cardiovasc Interv 2004;63:496-502

Device Thrombosis

Single Center Experience



- From 1992 to 2003, 1000 patients with device closure
- Incidence evaluated using TEE at 4 weeks and 6 months
- 15/593 (2.5%) in PFO, 5/407 (1.2%) in ASD
- 14/20 found after 4 weeks, 6/20 later on
- In LA (n=11), RA (n=6), or both atria (n=3)
- Amplazter and Helex seem less thrombogenic than others
- 17/20 resolves with anticoagulation, 3/20 removed surgically
- Clopidogrel was added to only 264 patients since 2001
- Nine different devices were used.

Krumsdorf et al. J Am Coll Cardiol 2004;43:302-9

After Device Closure

- Subsequent anticoagulation regimen : controversial
  - aspirin + clopidogrel for 6 months in AMC
  - endothelializtion should be complete by that time
- Endocarditis prophylaxis for the same duration and possibly for life?
- Manatory 24 hour and regular follow-up afterwards
- Patient education

Conclusion

- Presently evolving as an established mode for closure of secundum ASD
- The same indication as surgical closure but patient selection is important
- Generally safe and effective, but potential complications should not be ignored

Transcatheter Closure of Patent Foramen Ovale

Prevalence of PFO

- PFO in the “Normal” Population
  - 20-30% “probe” patency at surgery/autopsy
    - dating back to nearly 200 years ago
    - Hagen et al. Mayo Clin Proc 1984;59:17
  - 10-15% “functional” patency by TEE
    - Lechat et al. N Engl J Med 1988;318:1148
    - Webster et al. Lancet 1988;2:11

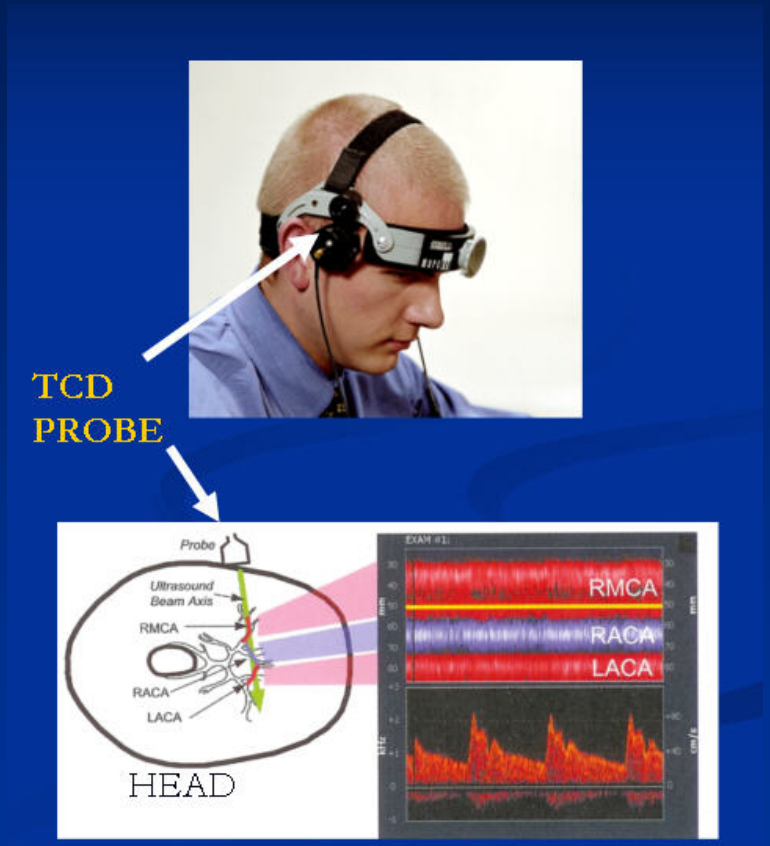
PFO has been linked to increased risk of

- Stroke[1]
- Migraine[2]
- Decompression illness in divers[3]
- Obstructive sleep apnea[4]
- Platypnea-orthodeoxia[5]
- “Economy-class” stroke syndrome[6]
- Multiple infact dementia[7]
- Cerebral microemboli following total knee arthroplasty[8]

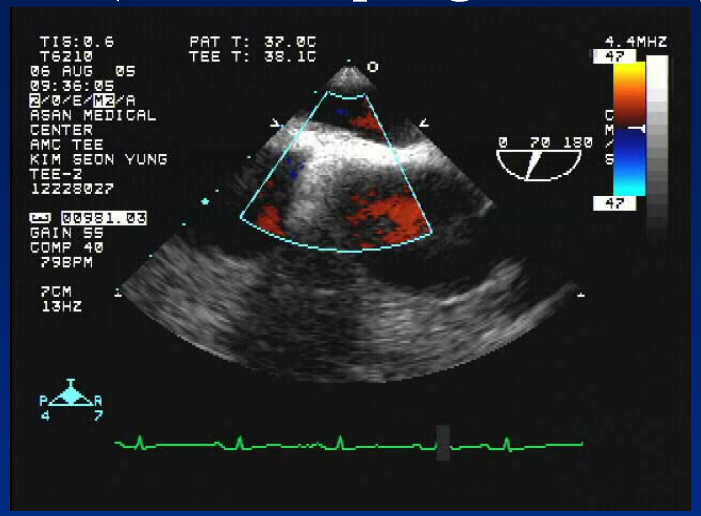
1. Lamy C et al. Stroke 2002;33:706-11
2. Del Sette M et al. Cerebrovasc Dis 1998;8:327-30
3. Wilmshurst P et al. Spums J 1997;27:82-3
4. Agnoletti G et al. J Inverven Cardiol 2005;18:393-5
5. Kerut EK et al. J Am Coll Cardiol 2001;38:613-23
6. Isayev Y et al. Neurology 2002;58:960-1
7. Angeli S et al. Eur Neurol 2001;46:198-201
8. Sulek CA et al. Anesthesiology 1999;91:672-6

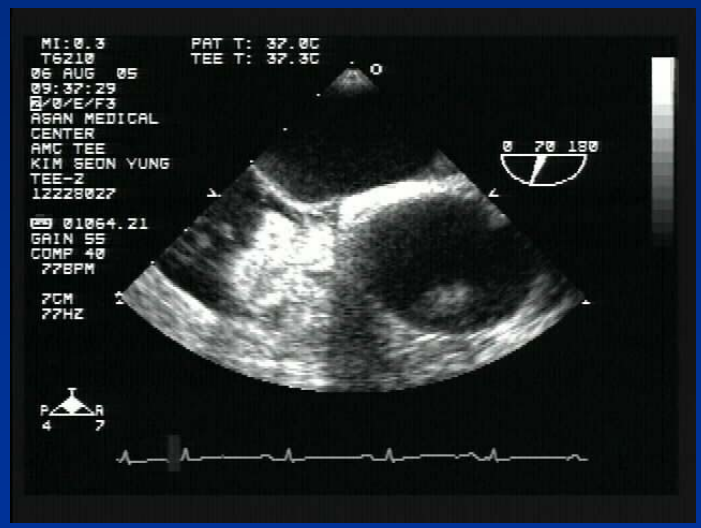
Diagnosis of PFO

- TCD (Transcranial Doppler)
- TEE (Transesophageal Echo)



TCD brain blood flow display





Diagnosis of PFO

- TCD (Transcranial Doppler)
  - Non-invasive
  - Bubble quantification
  - Less specificity
- TEE (Transesophageal Echo)
  - More invasive
  - Inability to do good Valsalva
  - Specificity

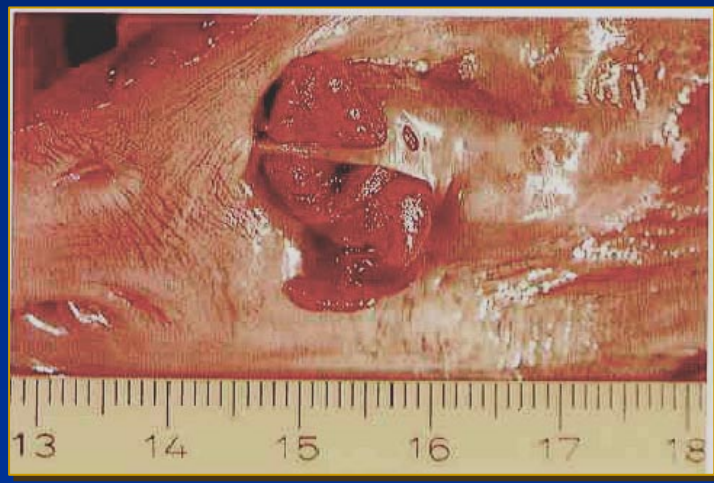
- Screening - TCD
- Anatomy - TEE

PFO and Stroke

PFO and Stroke

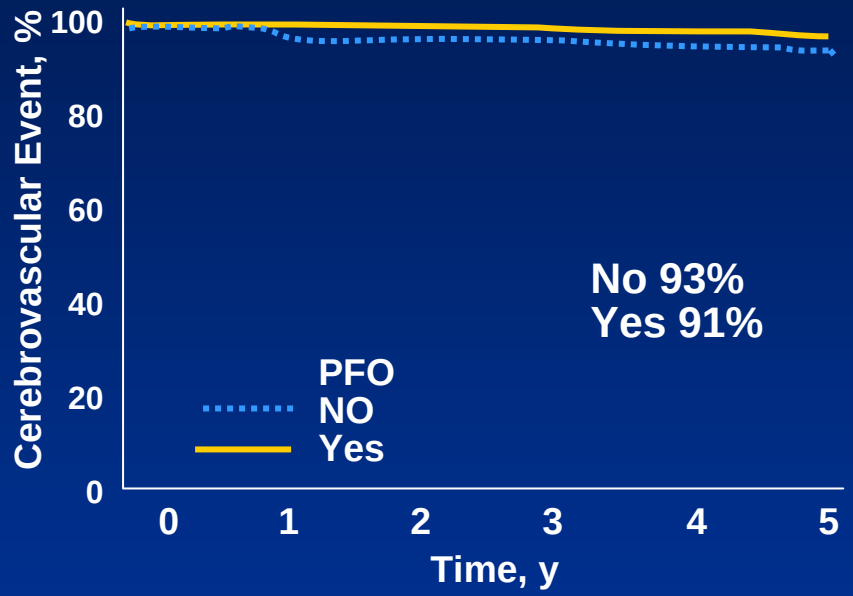
- 41-60% prevalence of PFO in Cryptogenic Stroke[1]
- 2.3-15%/**year** of stroke recurrence without PFO closure[2]
- Larger PFO size associated with higher recurrence rate[3]

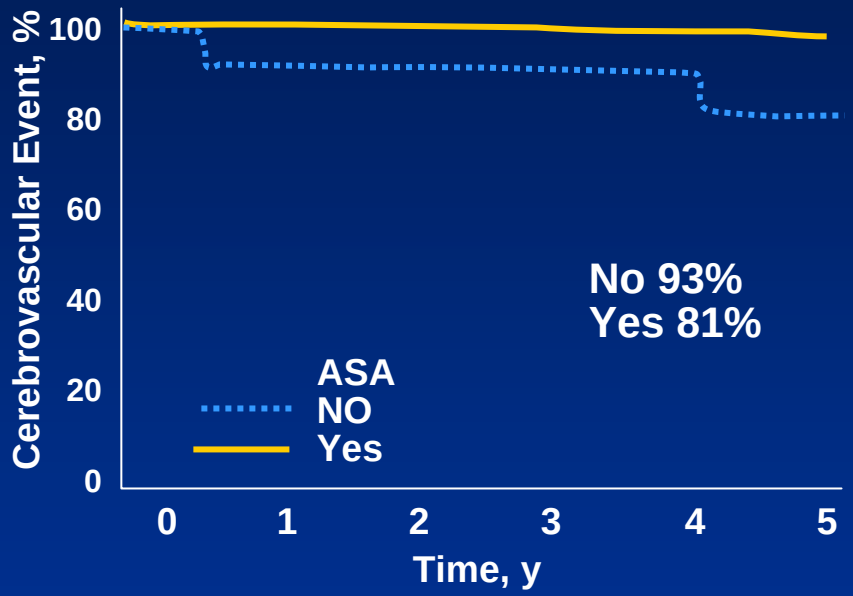
1. Webster et al. Lancet 1988;2:11
   Lechat et al. N Engl J Med 1988;318:1148
   Ranous et al. Stroke 1993;1:31
2. Bogousslavsky et al. Neurology 1996;46:1301
   Cujec et al. Can J Cardiol 1999;15:57
   Wahl et al. Neurology 2001;57:1330
   Mas et al. N Engl J Med 2001;345:1740
   Homma S et al. Circulation 2002;105:2625
3. Homma S et al. Stroke 1994;25:582-6
   Hausmann D et al. J Am Coll Cardiol 1995;26:1030-8
   Schuchlenz HW et al. Am J Med 2000;109:456-62



Conflicting Data About the Risk of Stroke in Patients with PFO

The Presence of PFO or ASA Does not Increase Risk of Cerebrovascular Events* in Prospective Population-based Study





* Stroke, TIA, or death due to cerebrovascular disease
Kaplan-Meier estimate

Meissner I et al. J Am Coll Cardiol 2006;47:440-5

Size of PFO Does not Increase Risk of Recurrent Stroke or Death (PICSS Cohort)

Two-Year rates of Recurrent Stroke or Death

	No PFO (N=398)	Small PFO* (N=119)	Large PFO* (N=84)
Event rate, %	15.4	18.5	9.5
Hazard ratio (95% CI)	1.0	1.23 (0.76-2.00)	0.59 (0.28-1.24)
p value		0.41	0.16

* Large PFO: ≥2 mm separation of septum secundum and primum or ≥10 microbubbles appearing in left atrium on TEE; all other PFOs classified as small

Homma S, Sacco RL et al. Circulation 2002;105:2625-31

Four Choices to Prevent Recurrent Stroke in Patients with PFO

- Surgical closure (open heart)
- Percutaneous transcatheter closure

closure

- Medical Therapy with anticoagulant
- Medical Therapy with antiplatelet agent

medical

To Close or Not to Close ?

No Prospective Randomized Controlled Trials

comparing medical treatment with defect closure

Recurrent Stroke Prevention in Patients with Cryptogenic Stroke:

Medical vs. Transcatheter PFO Closure

Study	Design	Medical therapy	PFO Closure	p value
Khairy et al[1]	Meta-analysis	3.8-12/year	0-4.9/year	
Windecker et al[2]	Retrospective	24.3/4-year*	8.5/4-year*	*0.05*
Schuchlenz et al[3]	Retrospective	13/year aspirin 5.6/year warfarin	0.6/year	*<0.001*

* risk reduction of death, stroke, or TIA combined

1. Ann Intern Med 2003;139:753-60
2. J Am Coll Cardiol 2004;44:750-8
3. Int J Cardiol 2005;101:77-82

Safety

Transcatheter PFO Closure Procedureal Complications

	Windecker[1]	Braun[2]
No. of procedures	78	276
Device migration	3 (3.9%)	2 (0.8%)
Cardiac Tamponade	1 (1.3%)	0
Retroperitoneal hemorrhage	2 (2.6%)	4 (1.6%)
Transient AV block	0	1 (0.4%)

1. Circulation 2000;101:893-898
2. J Am Coll Cardiol 2002;2019-2025

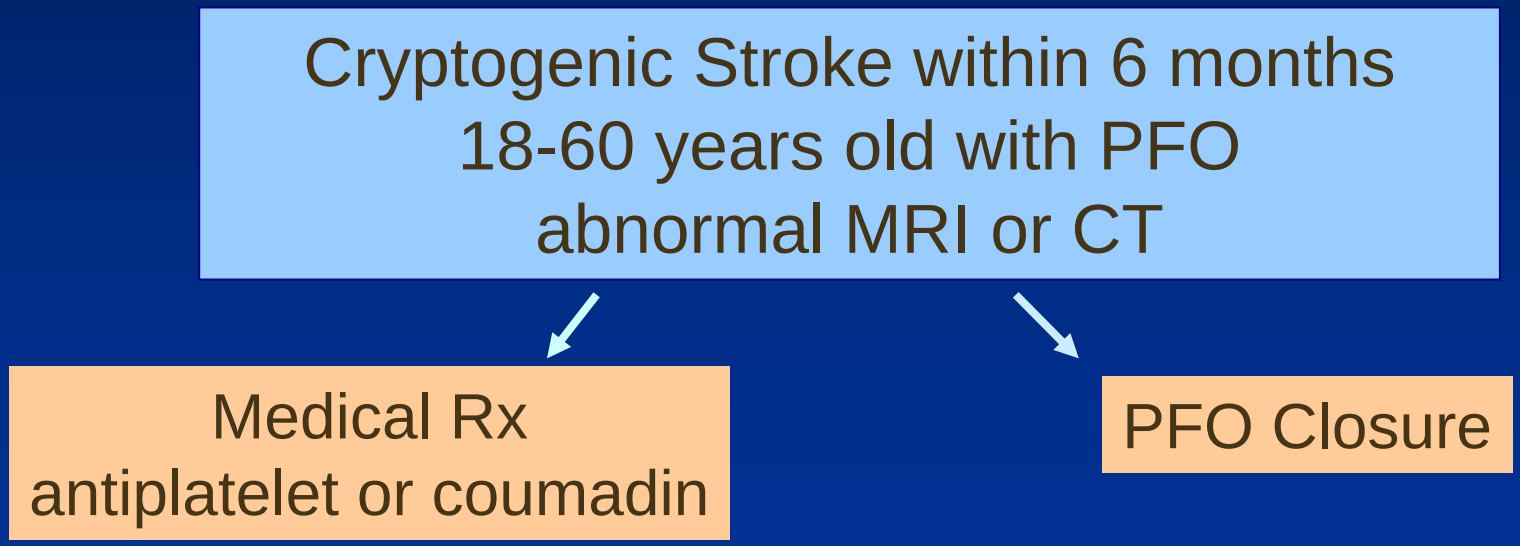
AHA/ASA 2006 Guidelines for Transcatheter Closure of PFO

- Insufficient data exist to make a recommendation about PFO closure in patients with first stroke and a PFO.
- PFO closure may be considered for patients with recurrent stroke despite medical therapy (Class IIb, Level C)

Sacco RL et al. Stroke 2006;37:577-617
Sacco RL et al. Circulation 2006;113:e409-49

Ongoing Randomized Trials on PFO and Stroke

The CLOSURE I Trial (US and Canada, NMT)
The RESPECT Trial (US, AGA)



Endpoints: recurrent stroke, death, or adverse events

PFO and Migraine

Prevalence of PFO in Migraineurs

Study	Method	Migraine with aura	Migraine without aura	Controls
Del Sette[1]	TCD	18/44 (41%)	NA	8/50 (16%)
Anzola[2]	TCD	54/113 (48%)	12/53 (23%)	5/25 (20%)
Schwerzmann[3]	TEE	44/93 (47%)	NA	16/93 (17%)
Dowson[4]	TEE	220/370 (59%)	NA	NA
Total		336/620 (54%)	12/53 (23%)	29/168 (17%)

1.Cerebrovasc Dis 1998;8:327-30

2.Neurology 1999;52:1622-1625

3.Neurology 2005;65:1415-18

4.On behalf of MIST trial. Presented at American Headache Society 2005

Prevalence of Migraine in Patients with PFO

Study	Year	Method	Migraine with aura	Migraine without aura
Wilmshurst	2001	TTE	42/190 (35%)	11/120 (9%)
Wilmshusrt	2005	TTE	59/119 (50%)	4/119 (3%)
Schwerzmann	2004	postclosure	37/215 (17%)	11/215 (5%)
Reisman	2005	postclosure	39/162 (24%)	18/162 (11%)
Morandi	2003	postclosure	8/62 (13%)	9/62 (15%)
Post	2004	postclosure	12/66 (18%)	14/66 (21%)
Azarbal	2005	postclosure	20/66 (30%)	10/66 (15%)
Total			217/810 (27%)	77/810 (10%)

Schwedt TJ et al. Headache 2006;46:663-671

Mechanism of PFO Causing Migraine

- Some chemical or circulating substance (eg. serotonin) normally filtered by the lungs, passes through PFO, enters cerebral circulation causing headache and focal neurologic symptoms (in neurologically vulnerable patients)
  - Platelet aggregation and serotonin release
  - Neurohormonal factor
  - Unoxygenated blood

Effects of PFO Closure on Migraine Observational Studies

Study	Year	Incidence of Migraine	%improved or cured	follow-up (months)
Wilmshurt	2000	21/37 (57%)	86%	upto 30
Morandil	2003	17/62 (27%)	88%	all 6
Schwerzmann	2004	48/215 (22%)	81%	all 12
Post	2004	26/66 (39%)	65% cured	all 6
Reisman	2005	57/162 (35%)	70%	all 12
Azarbal	2005	37/89 (42%)	76%	mean 18
Total		206/631 (33%)	78%	

Schwedt TJ et al. Headache 2006;46:663-671

MIST I Trial

: *M*igraine *I*ntervention with *S*tarflex *T*echonology

- First prospective randomized double-blind, placebo controlled study to assess PFO closure on migraine
- 147 patients randomized to PFO closure (n=74) vs. sham procedure (n=73)
- 13 centers in United Kingdom, Jan to Jul, 2005

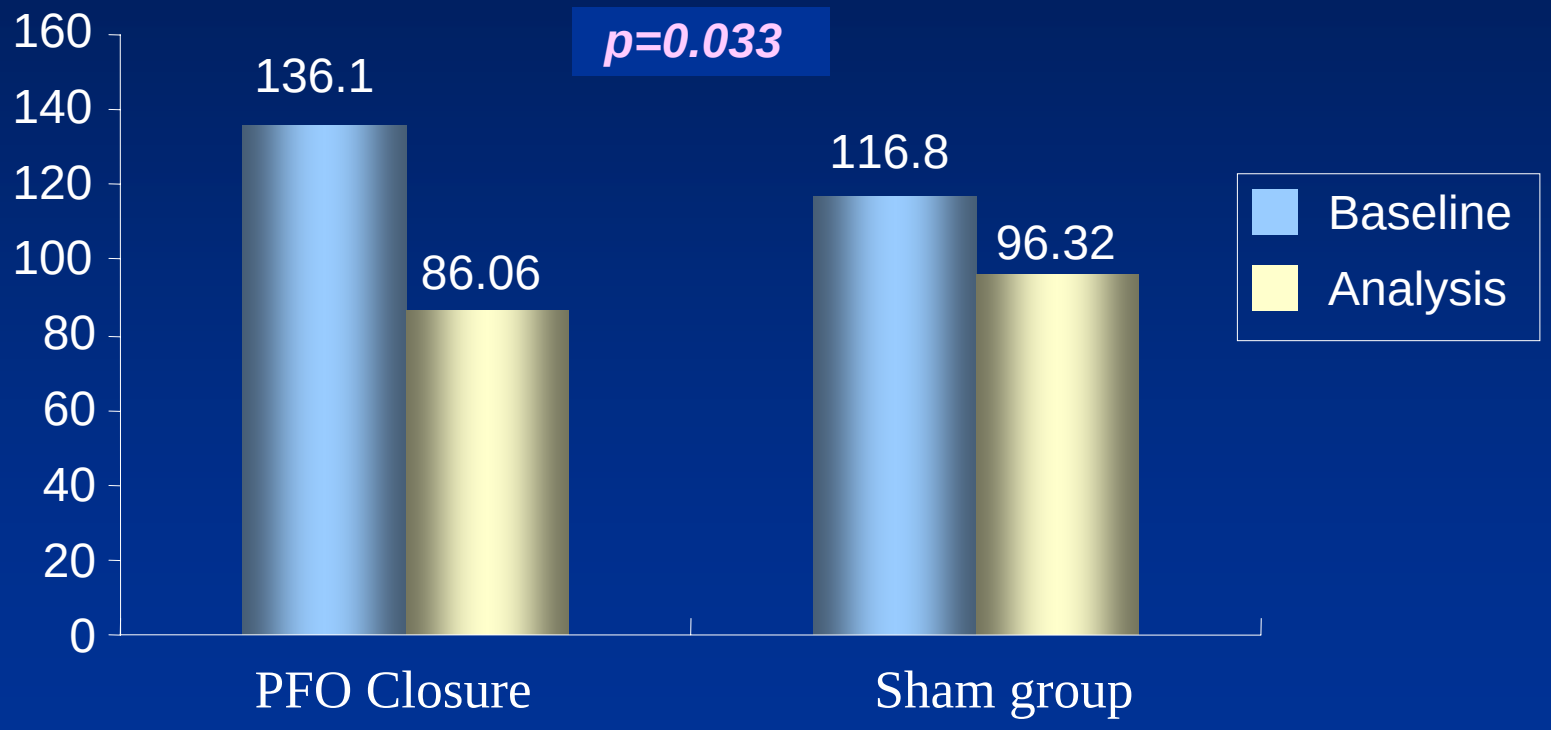
Presented at ACC 2006

MIST I : PFO Overrepresented

Results	total number	%
Total studied	432	
Small shunts (atrial and pulmonary)	72	16.7
Large pulmonary shunts	22	5.1
ASD	3	0.7
Large PFO	163	**37.7**
Large shunts (all types)	188	43.5
Total shunts	260	**60.2**

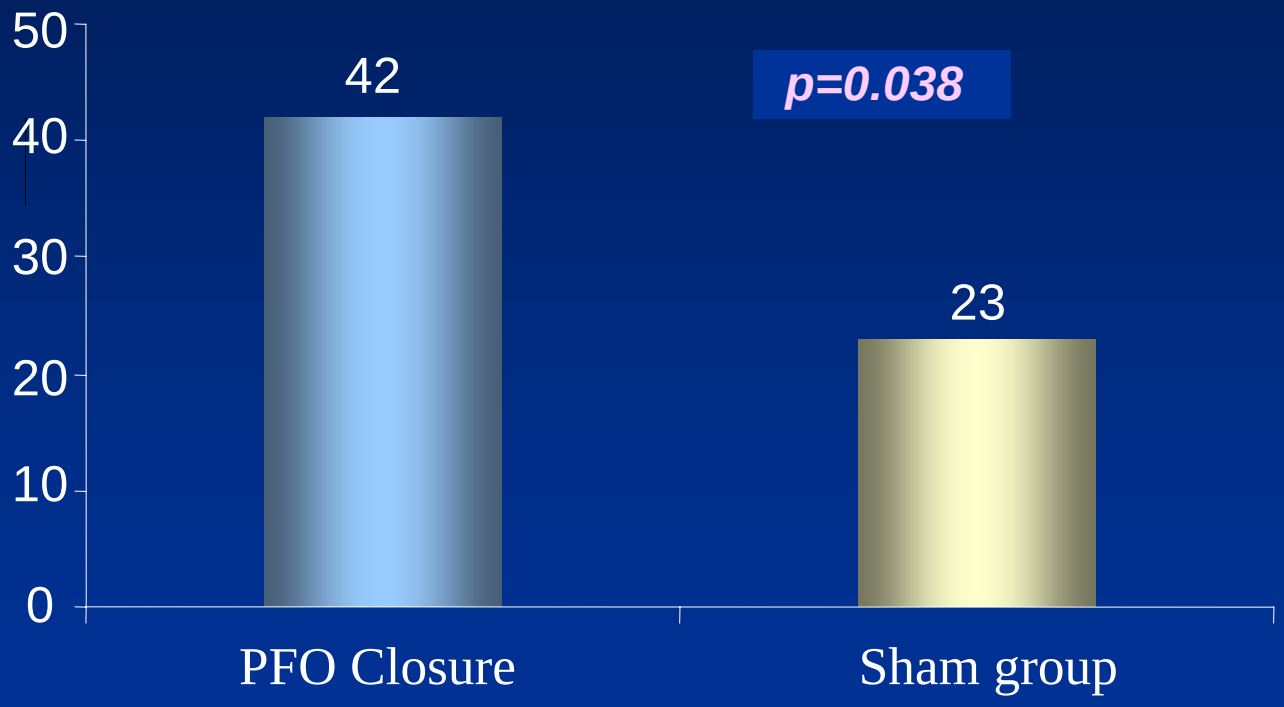
Presented at ACC 2006

MIST I : Reduction in Headache Burden (frequency x duration)



Presented at ACC 2006

MIST I : ≥50% reduction in headache days at 6mo



Presented at ACC 2006

Ongoing Randomized Trials on PFO and Migraine

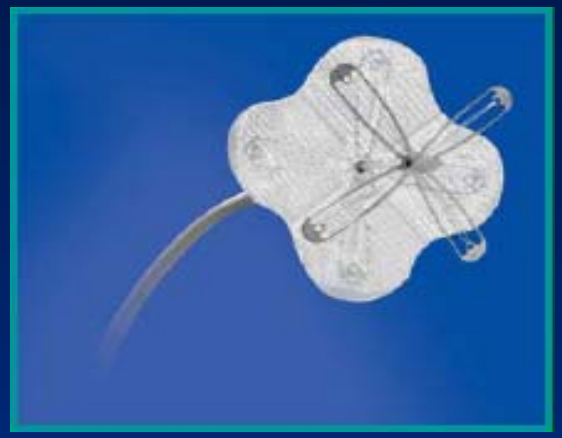
The MIST II Trial (UK, NMT)

The PREMIUM Trial (US, AGA)

The ESCAPE Trial (US, SJ Medical)

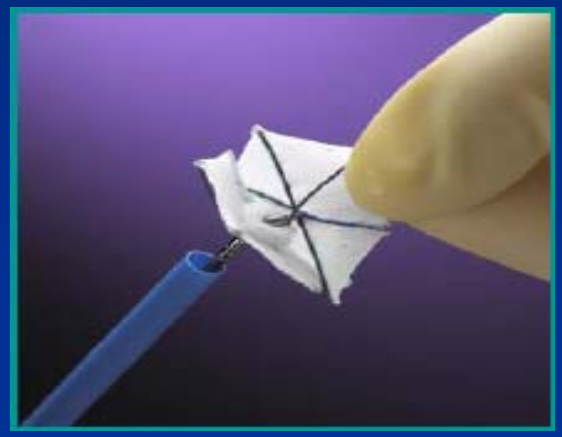
Current Devices for PFO Closure

Amplatzer PFO Occluder



Premere PFO Occluder

STARFlex Septal Occluder



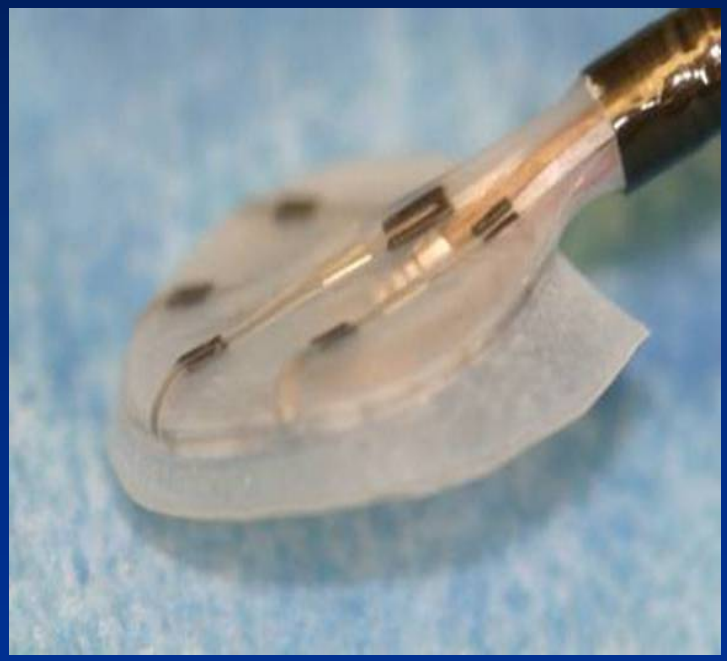
Intrasept PFO Occluder

New PFO Closure Devices

BioSTAR™: NMT

Bioabsorbable Drug Eluting Implant

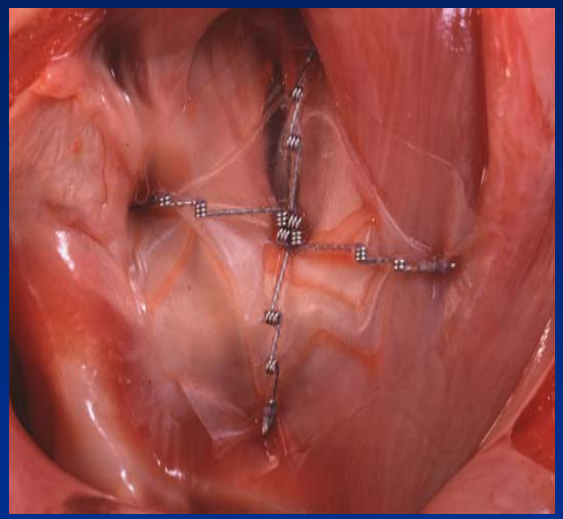
PFX™ : Cierra



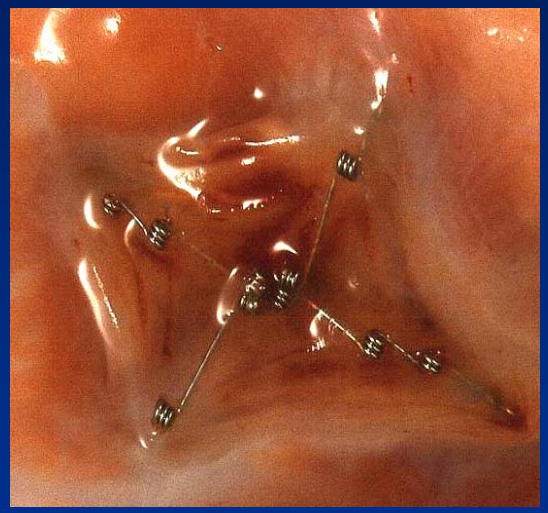
Radiofrequency Closure

BioSTAR™: NMT Medical

After implant



After 30 days



After 90 days

Photos provided by: Dr. Christian Jux, University of Goettingen/Germany and Dr. Peter Wohlsein, Institute of Pathology, School of Veterinary Medicine Hannover, Hannover/Germany

Presented at CRT 2006

Conclusion

- The role PFO in a variety of conditions suggestive but not definite cause and effect relationship
- Benefits of PFO device closure vs. medical therapy requires randomized trials
- PFO closure associated with reduction in migraine frequency in uncontrolled series – trials in progress