



# ΔΙΑΔΕΡΜΙΚΗ ΣΥΓΚΛΕΙΣΗ ΑΝΟΙΚΤΟΥ ΩΘΕΙΔΟΥΣ ΤΡΗΜΑΤΟΣ ΚΑΙ ΜΕΣΟΚΟΛΠΙΚΟΥ ΕΛΛΕΙΜΜΑΤΟΣ

ΔΗΜΗΤΡΗΣ Δ ΤΣΙΚΑΔΕΡΗΣ

MD MRCP

ΚΛΙΝΙΚΗ ΑΓΙΟΣ ΛΟΥΚΑΣ

IICE

11/2011



# ΕΝΔΟΚΑΡΔΙΑΚΑ ΕΛΛΕΙΜΜΑΤΑ

- Μεσοκοιλιακή επικοινωνία δευτερογενούς (ASD)
- Ανοιχτό ωοειδές τρήμα (PFO)

PHILIPS PASXOU XARA 09/11/2007 13:17:20 TIS0.6 MI 0.7  
 46091320071109 X7-2t/Adult

FR 20Hz  
5.2cm

Live 3D  
3D 47%  
3D 40dB  
HGen

0 90 180



M4

JPEG

PAT T: 37.0C  
TEE T: 40.6C

62 bpm

# ASD

The most common congenital anomaly after bicuspid aortic valve



PHILIPS ZAVALINOS PANAGIOTIS 19/11/2007 10:18:43 TIS0.2 MI 0.5  
 24021020071119 X7-2t/Adult

FR 17Hz  
8.0cm

Live 3D  
3D 10%  
3D 40dB  
Gen

0 95 180



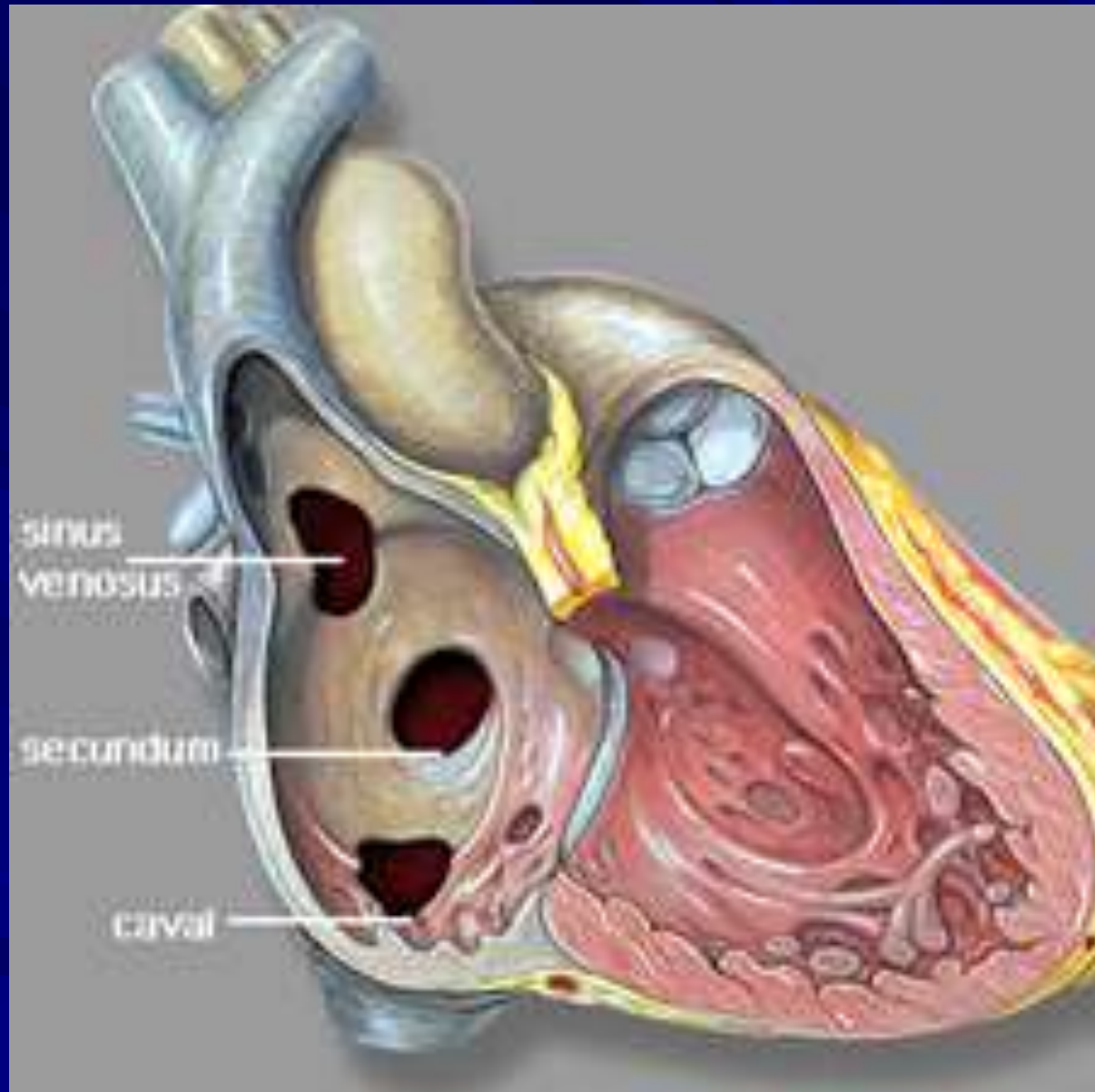
M4

JPEG

PAT T: 37.0C  
TEE T: 38.9C

91 bpm







# Natural History

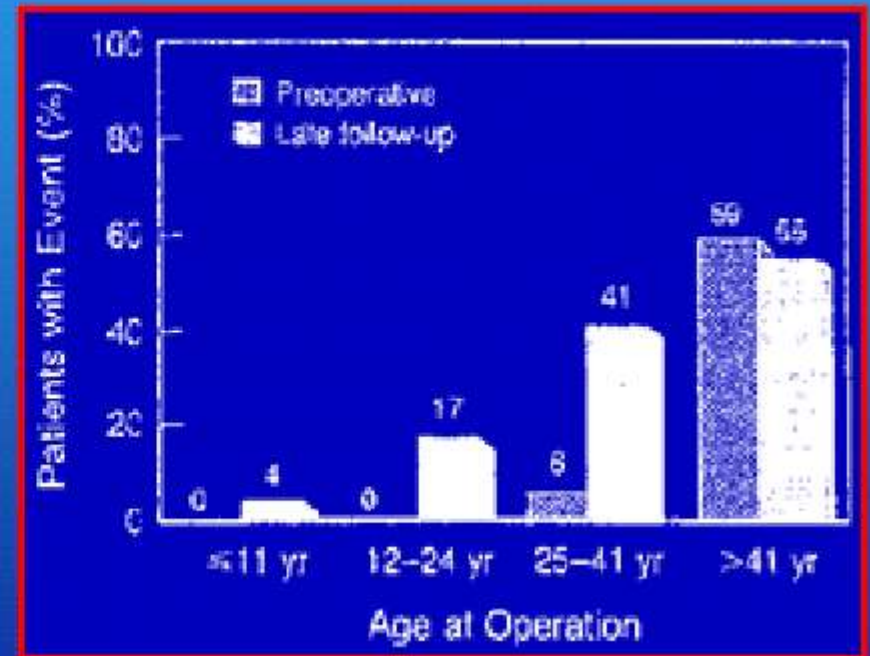
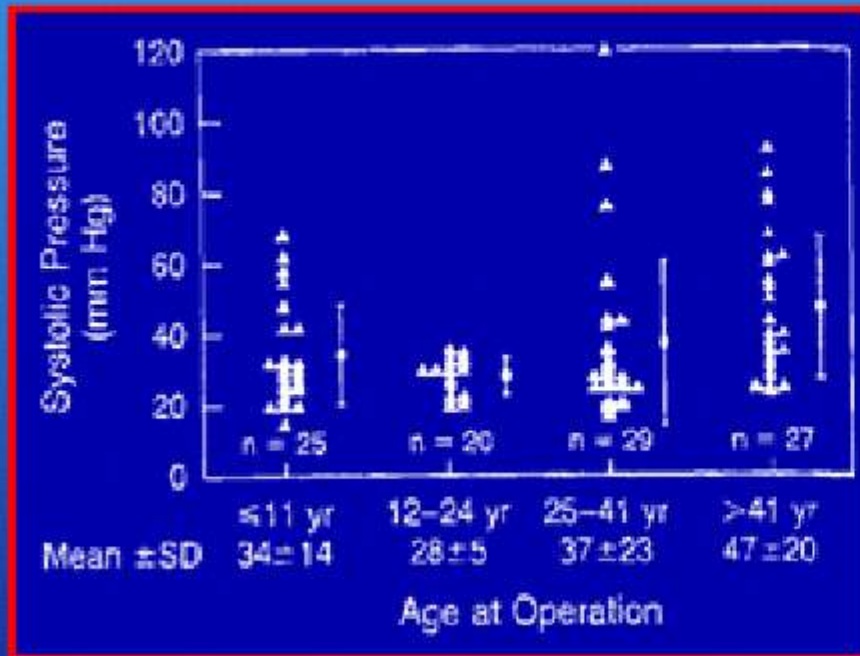
- 104 patients (average age 4.5 years at diagnosis) with isolated ASD  $>3$  mm in size;
- serial echocardiograms every 6 months.
- Spontaneous closure of the ASD occurred in only four patients (4 %)
- ASD diameter increased in 65 %;
- 30 % of patients had more than a  $>50$  % increase in diameter
- 12 % had an increase to  $>20$  mm.



# SECUNDUM ASD UNTREATED

↑ risk PHT

↑ risk A Fib





There are two main indications for closure of an  
ASD:  
the development of symptoms, and  
a high rate of shunt flow.



# Qp/Qs

- Qp/Qs >2:1
- Qp/Qs 1.7:1
- Qp/Qs 1.5:1 .
- **Absence** of severe fixed pulmonary hypertension, pulmonary vascular resistance >1200 dyne sec cm<sup>(-5)</sup> m<sup>2</sup> (15 Wood units)

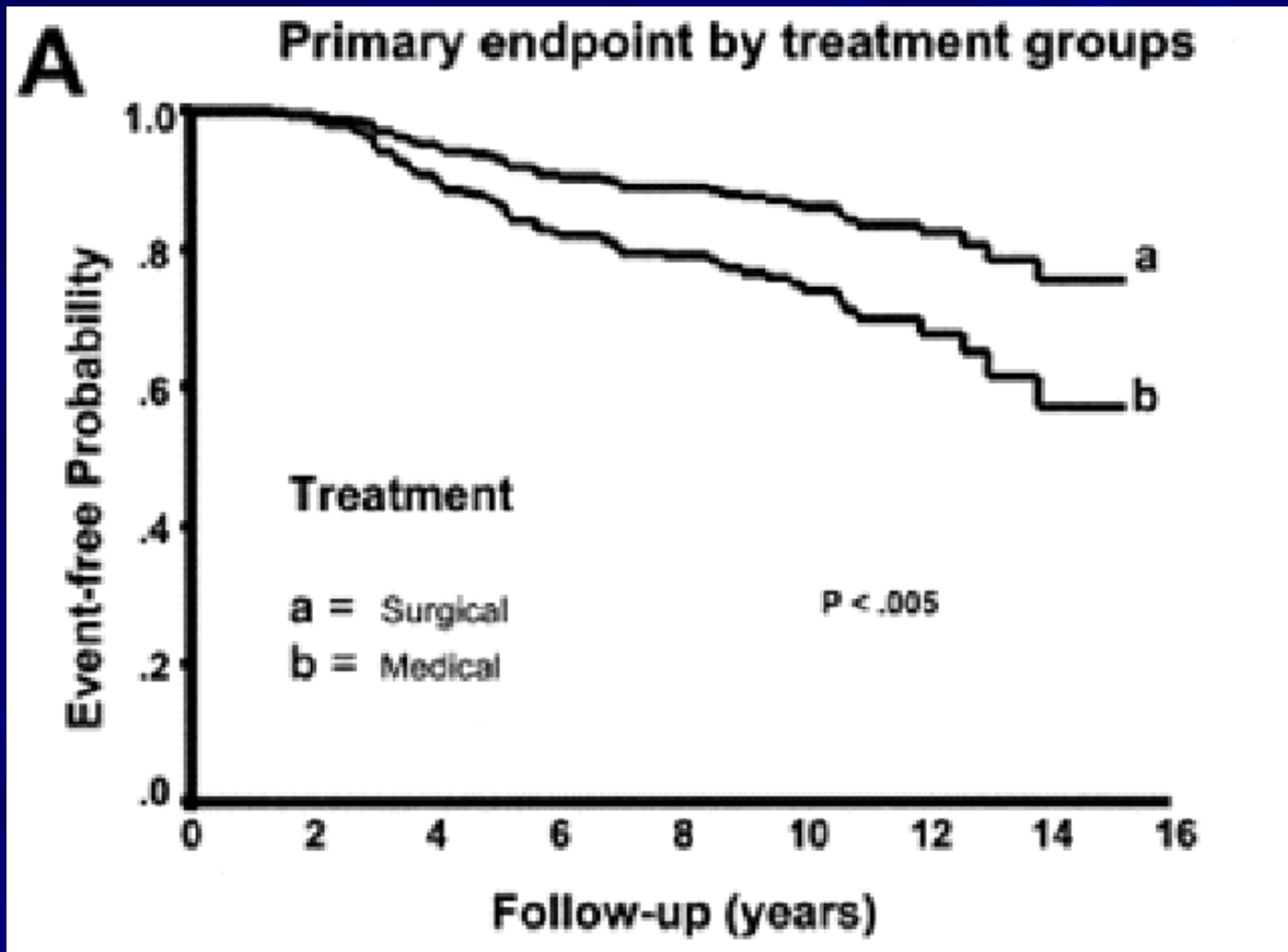




- randomized trial of 473 patients over age 40 (mean age 51)
- follow-up of 7.3 years
- The composite primary end point (21 versus 11 percent, hazard ratio 2.0) (recurrent pneumonia)
- On multivariate analysis a significantly higher mortality with medical management (hazard ratio 4.1).



## OVERALL BENEFIT: REDUCED EVENTS AND HOSPITALISATIONS WITH SURGICAL VS MEDICAL TREATMENT

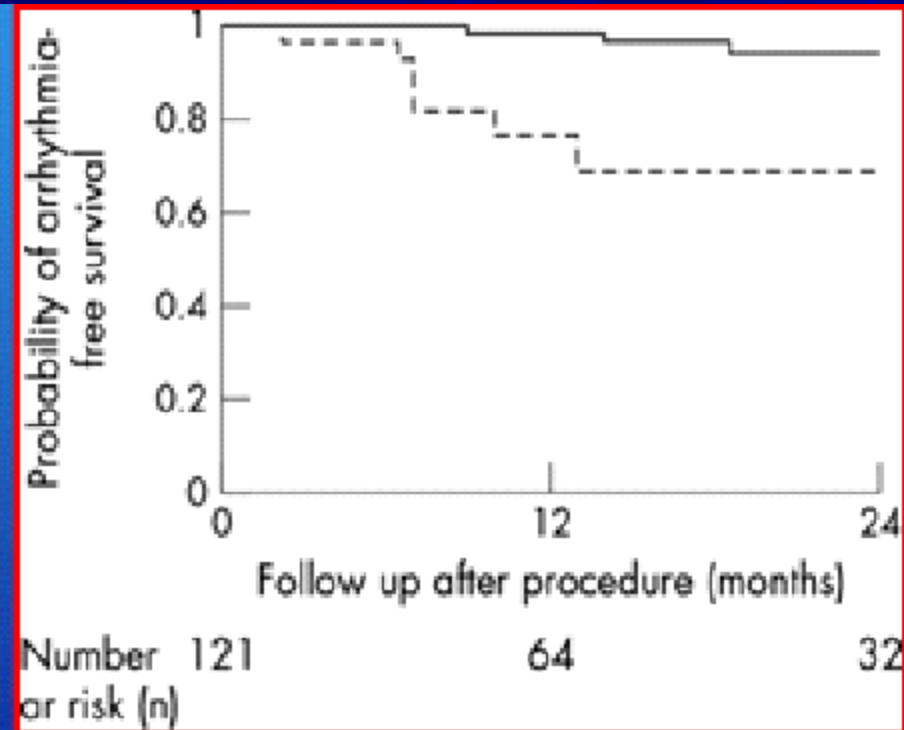
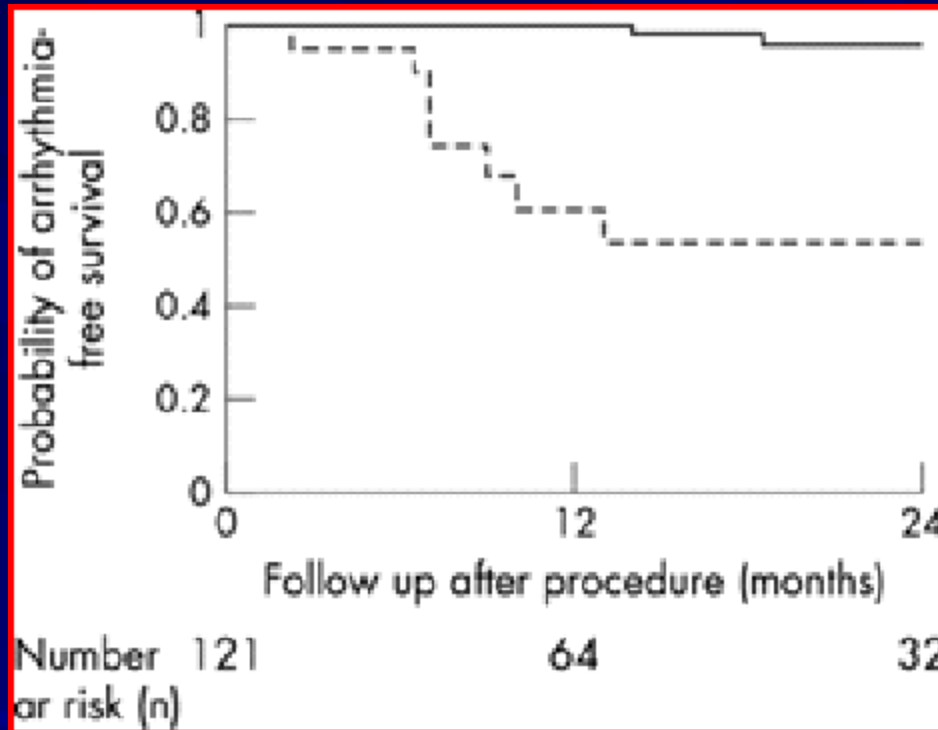




# REDUCED INCIDENCE OF AF WITH PERCUTANEOUS CLOSURE

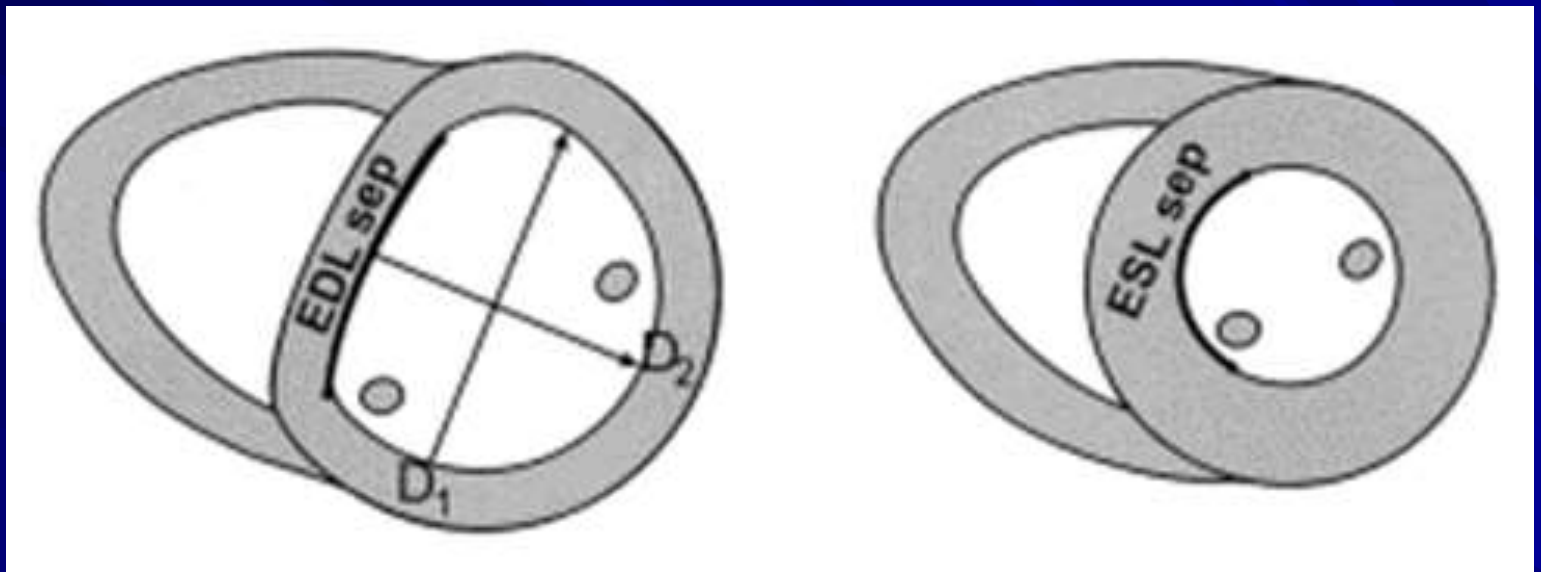
Correlation with past AF

Correlation with age





**Closure improves the geometry of the ventricles**  
**Decreases RV size**  
**Increases LVEF**



**Closure improves functional capacity**

**Walker RE, et al, Am J Cardiol 2004**



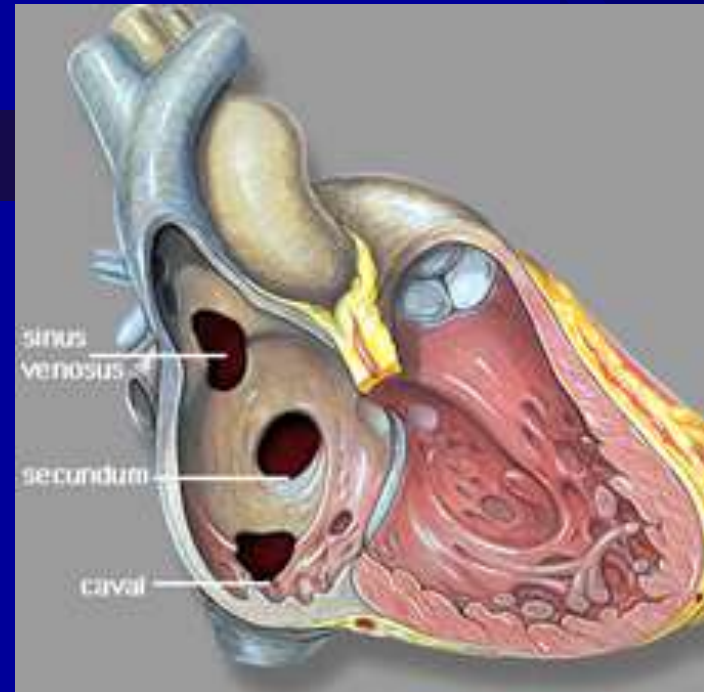
# Contra-indications to percutaneous treatment

- No evidence of right heart volume overload
- Insignificant shunt
- Non-secundum ASD
- Insufficient rim tissue (at least 5 mm)
- Nickel allergy (relative)

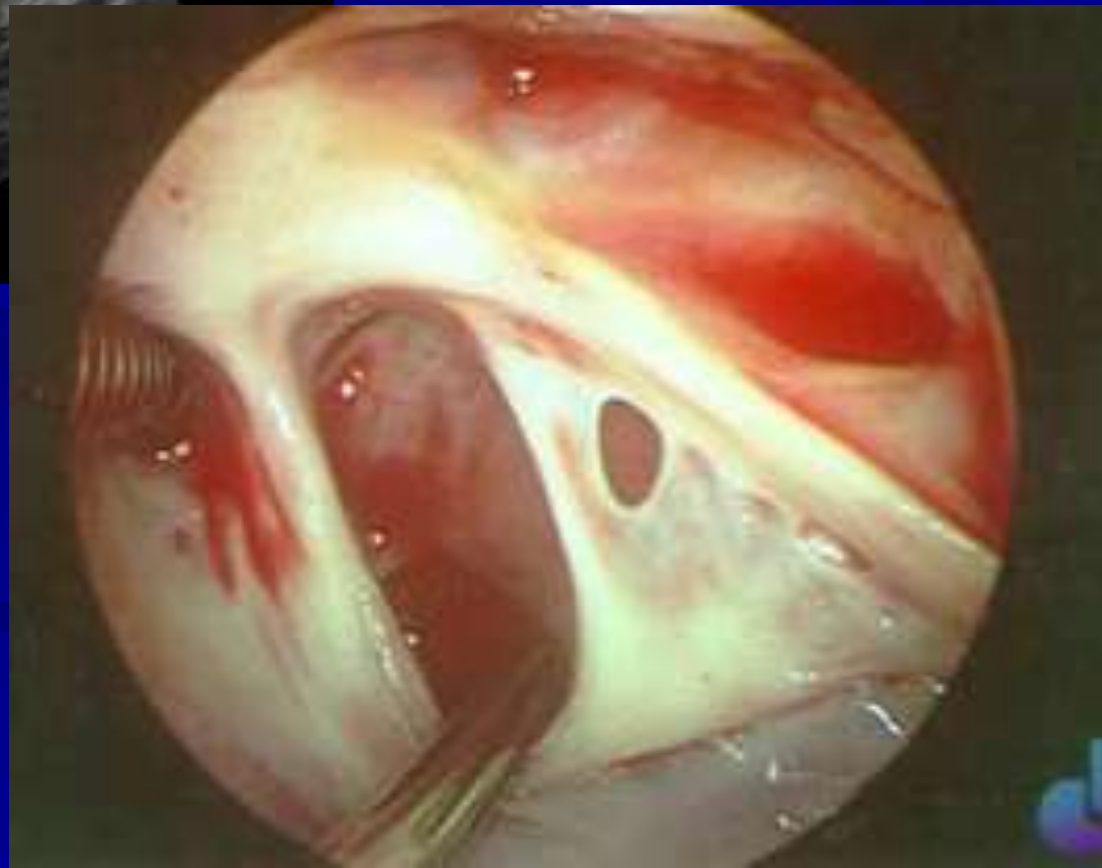
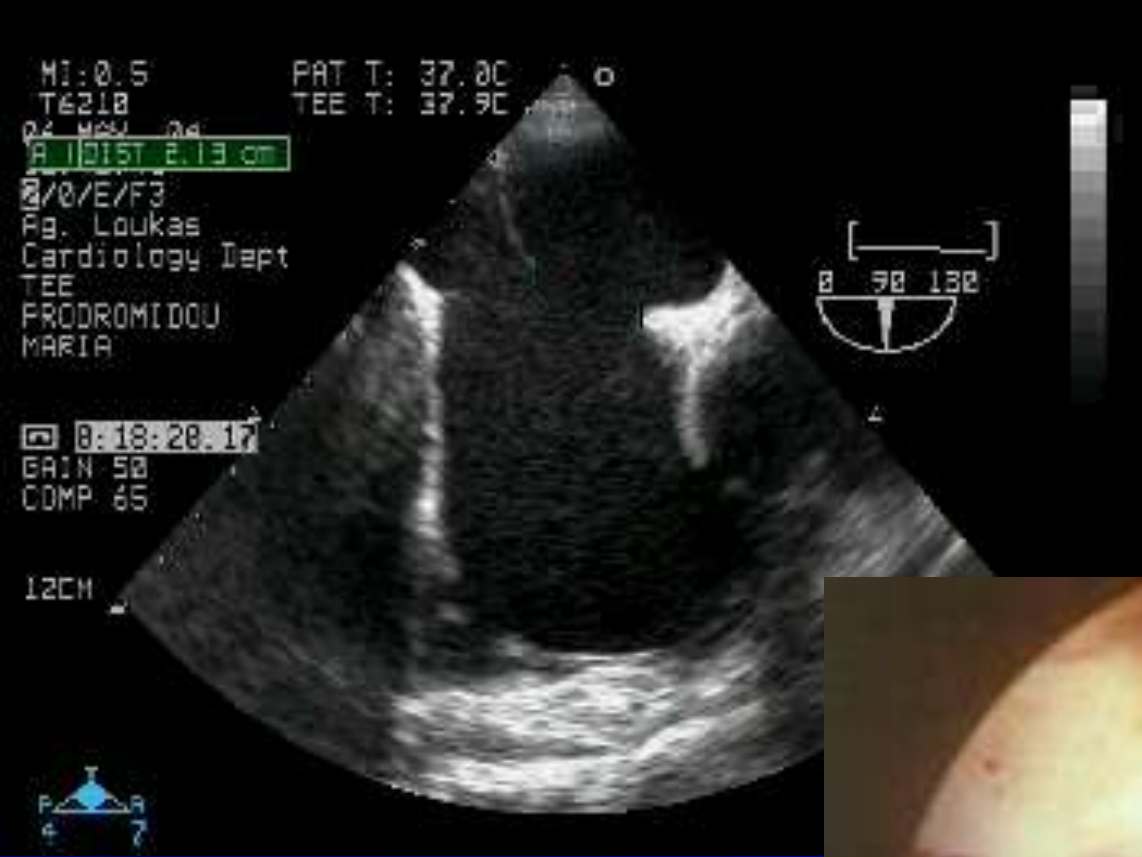


# Contra-indications to percutaneous treatment

- Non – secundum ASD



Secundum ASDs 70% of total ASDs

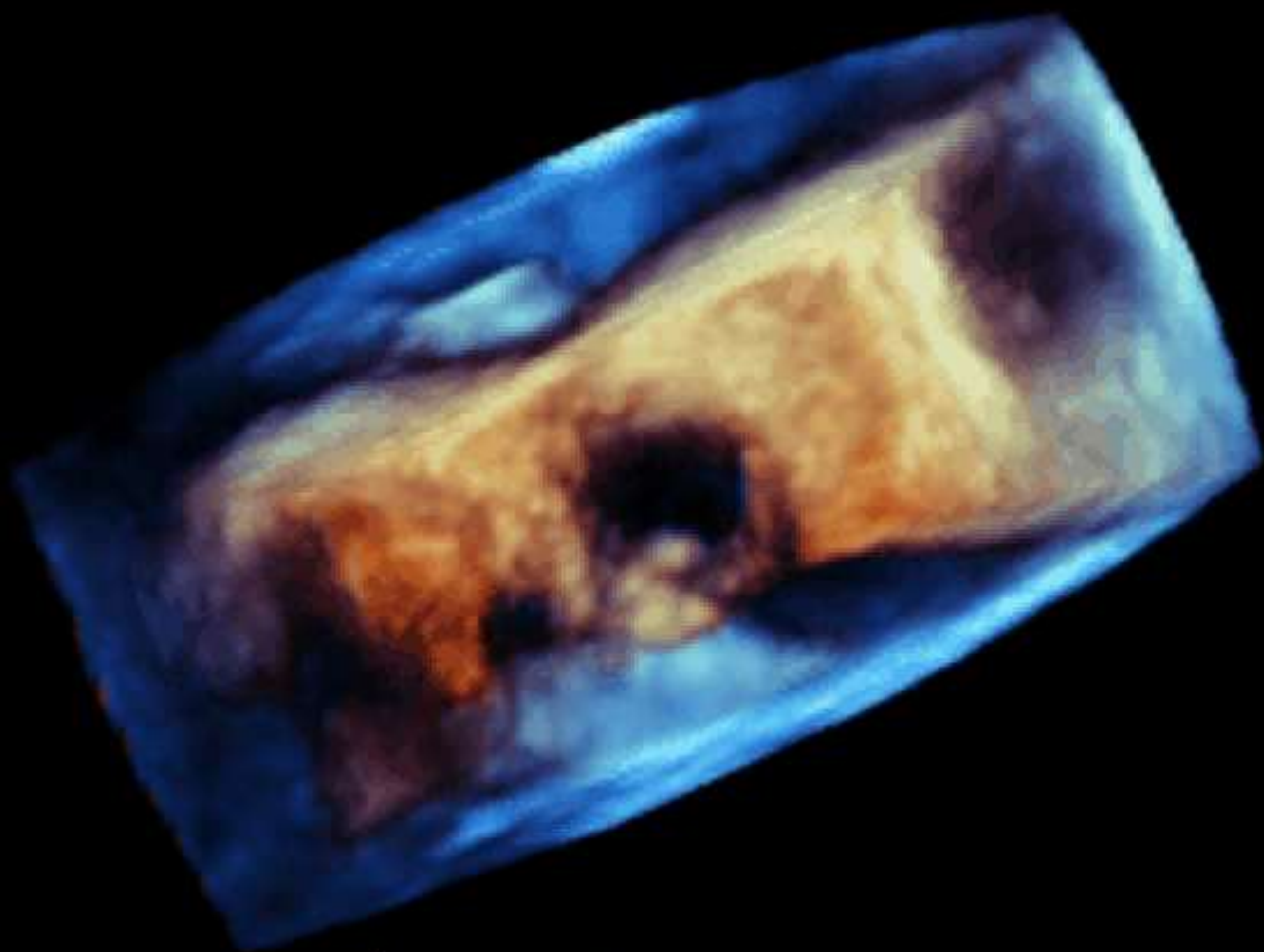




2007/11/15 04:28:53PM  
AGIOS LOUKAS

VR 17Hz  
5cm

Live 3D  
3D 51%  
3D 60dB



68 bpm





# Comparison with surgery

- 442 children and young adults Amplatzer ASD closure (median age 9.8 years)
- 154 surgery (median age 4.1 years)
- procedural success higher with surgery (100 versus 96 %)
- percutaneous closure group less complication rate (7 versus 24 %) and mean hospital stay (1.0 versus 3.4 days).
- No deaths

# Safety Summary

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	Device Patients N=442	Surgical Control N=154	p-value
Major Complications	7 (1.6%)	8 (5.2%)	0.030
Minor Complications	27 (6.1%)	29 (18.8%)	< 0.001
Overall Complications	32 (7.2%)	37 (24.0%)	<0.001

Unit of Analysis ="patient"





# Conclusions

**Proceed to catheterisation  
when there is:**

- **development of symptoms**
- **Right heart enlargement**

**Implant the device when:**

- **$Q_p:Q_s > 1.5:1.0$**
- **Pap < 70% systemic**
- **Appropriate septal anatomy**

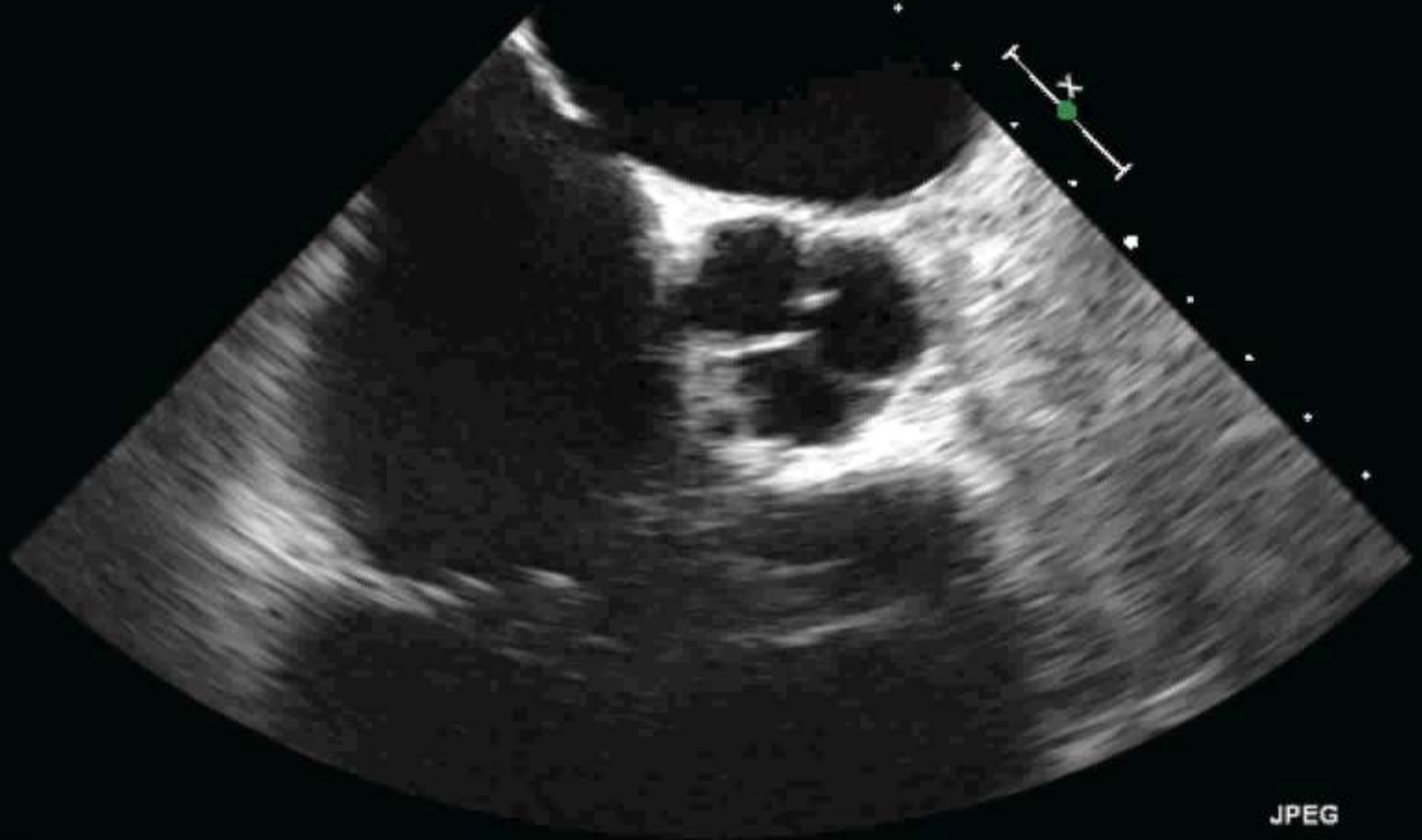


# ASD- RECURRENCE AFTER SURGERY

- 67 Y OLD MALE
- SURGICAL CLOSURE OF A LARGE ASD (NO RIM) 5 YEARS AGO
- RECURRENT PALPITATIONS LAST YEAR (AF)

PR 35Hz  
12cm

2D  
74%  
C 50  
P Off  
Gen



JPEG

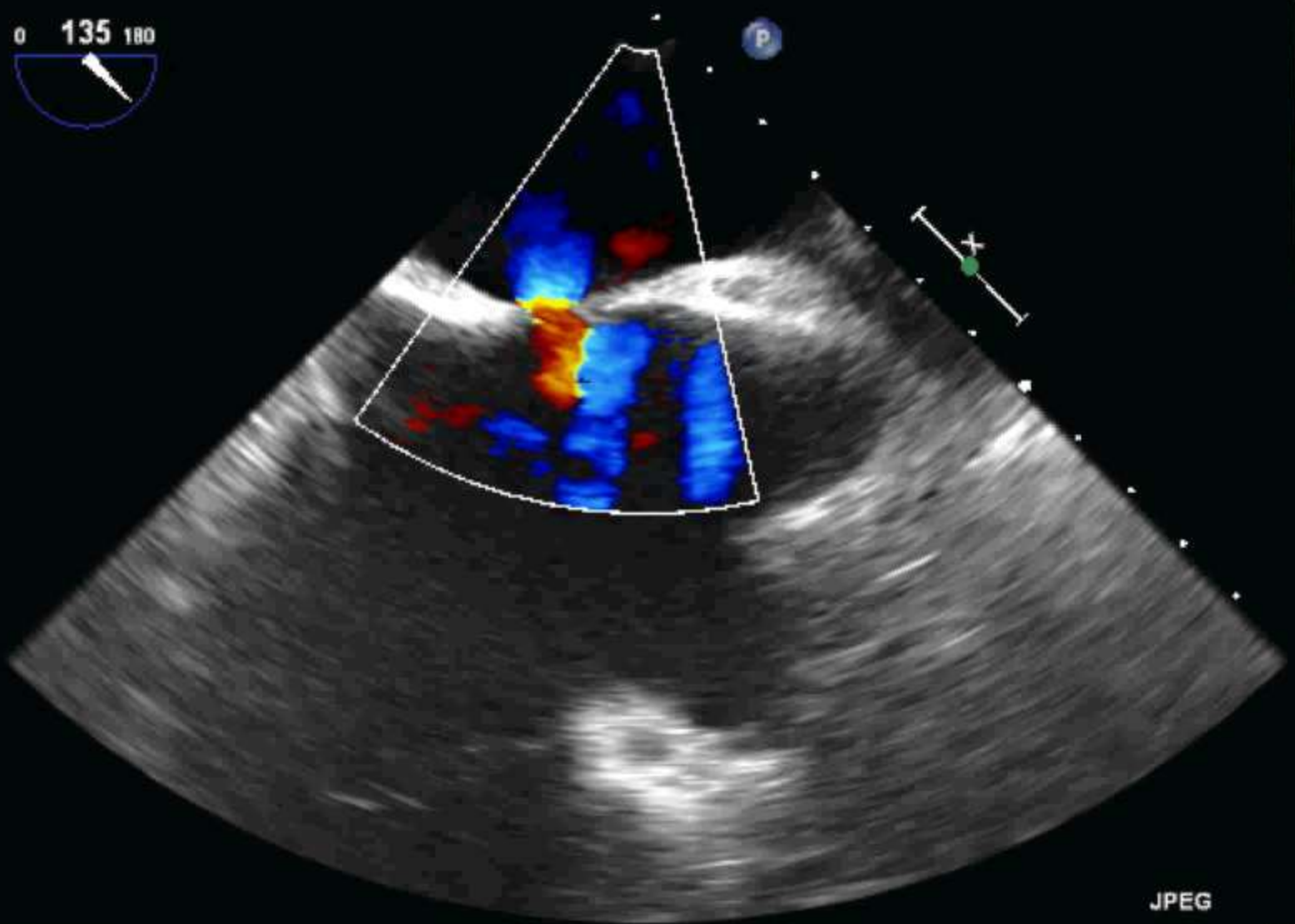
78 bpm

PAT T: 37.0C  
TEE T: 38.4C



FR 15Hz  
12cm

**2D**  
77%  
C 50  
P Off  
Gen  
**CF**  
63%  
4.4MHz  
WF High  
Med



JPEG

78 bpm

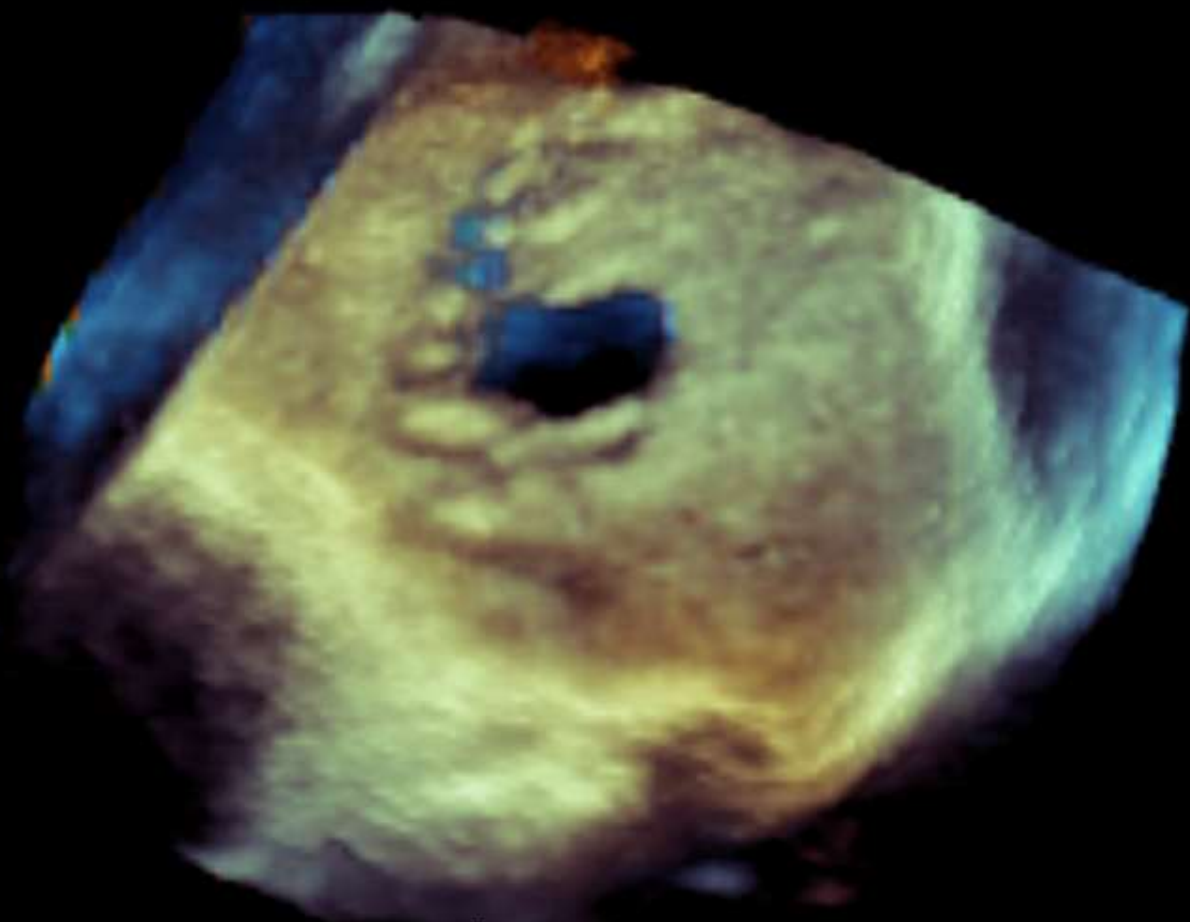
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TEE T: 37.5C



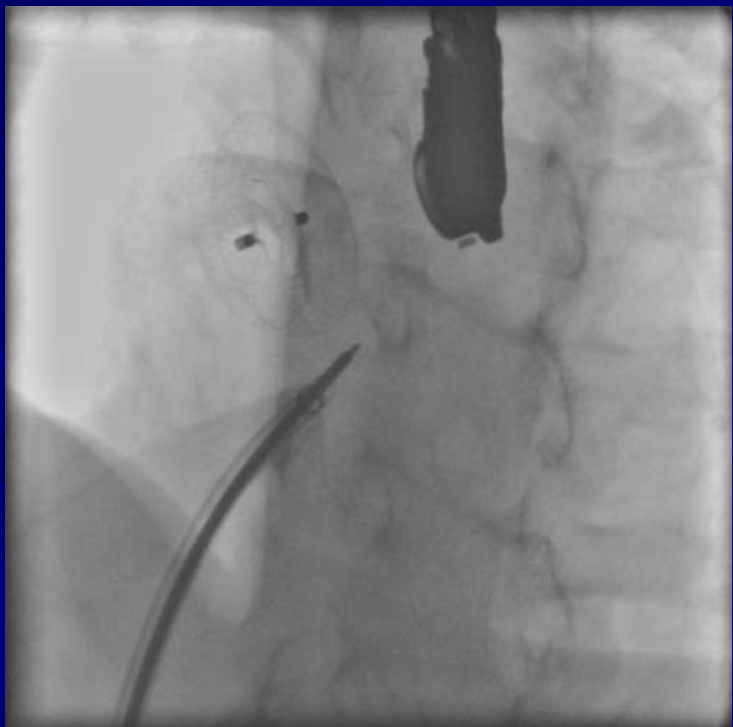
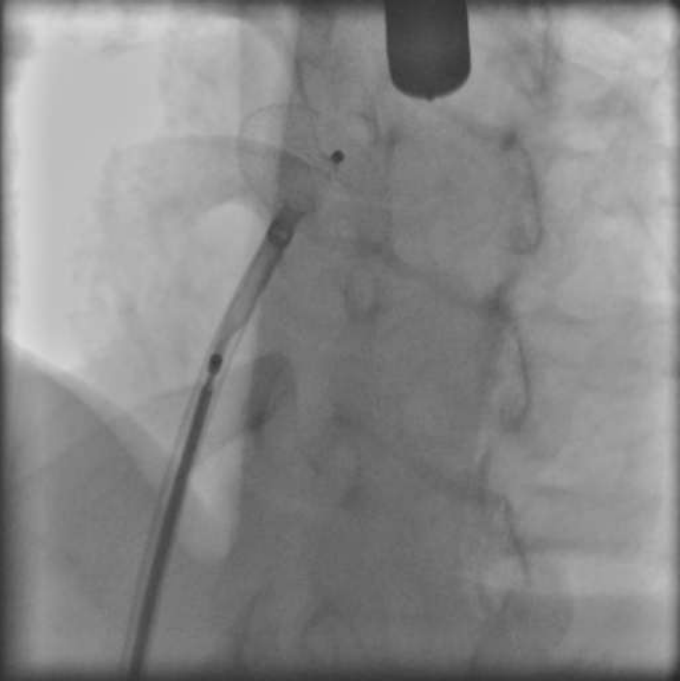
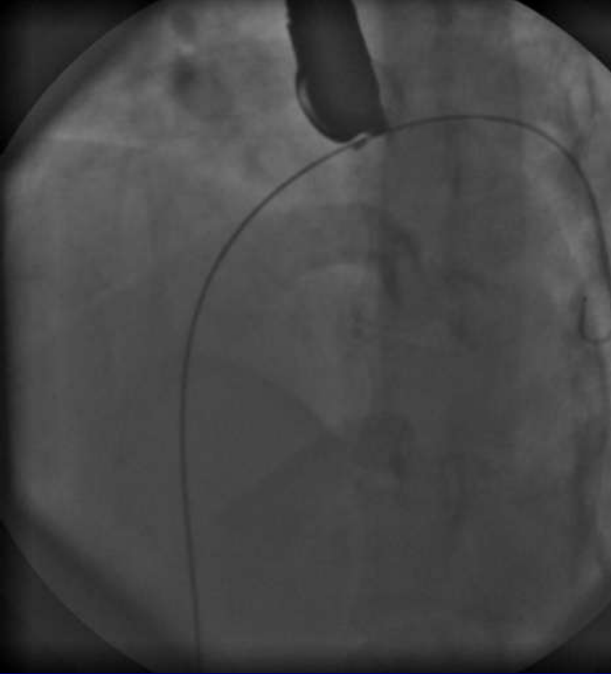
VR 12Hz  
6cm



Live 3D  
3D 47%  
3D 40dB



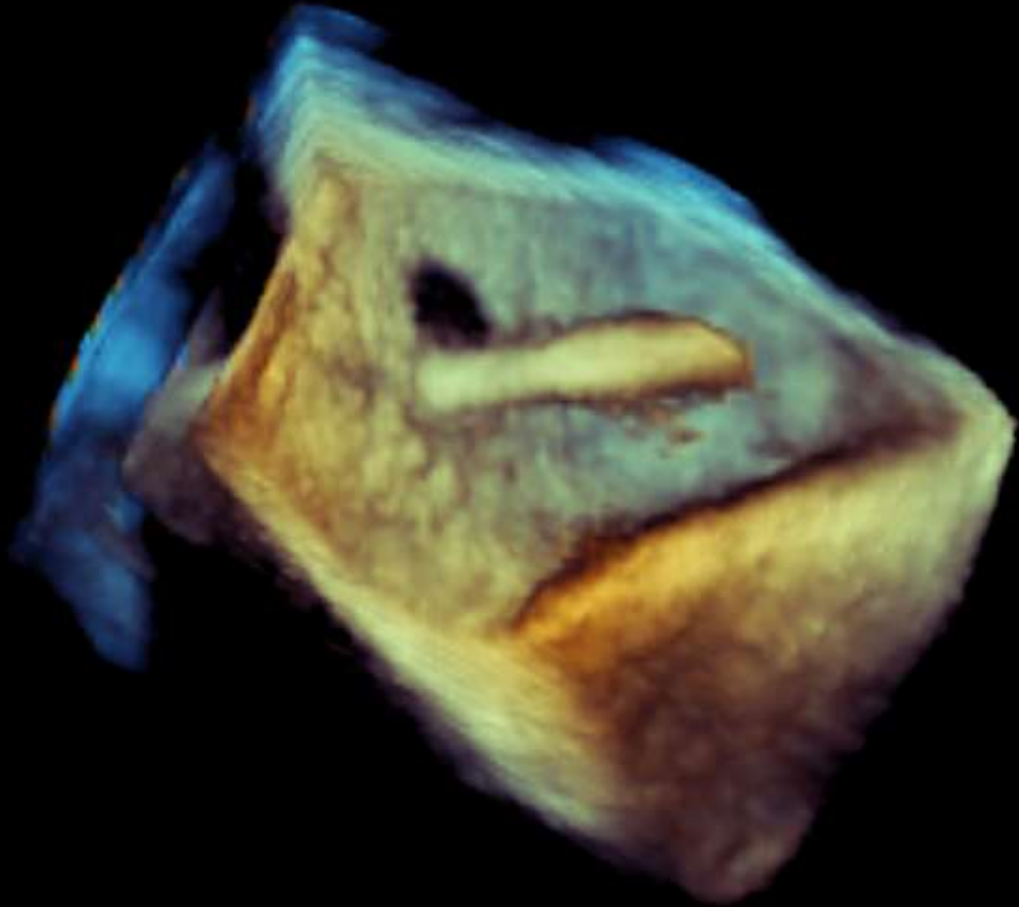
0 bpm



VR 10Hz  
5cm



Live 3D  
3D 13%  
3D 40dB

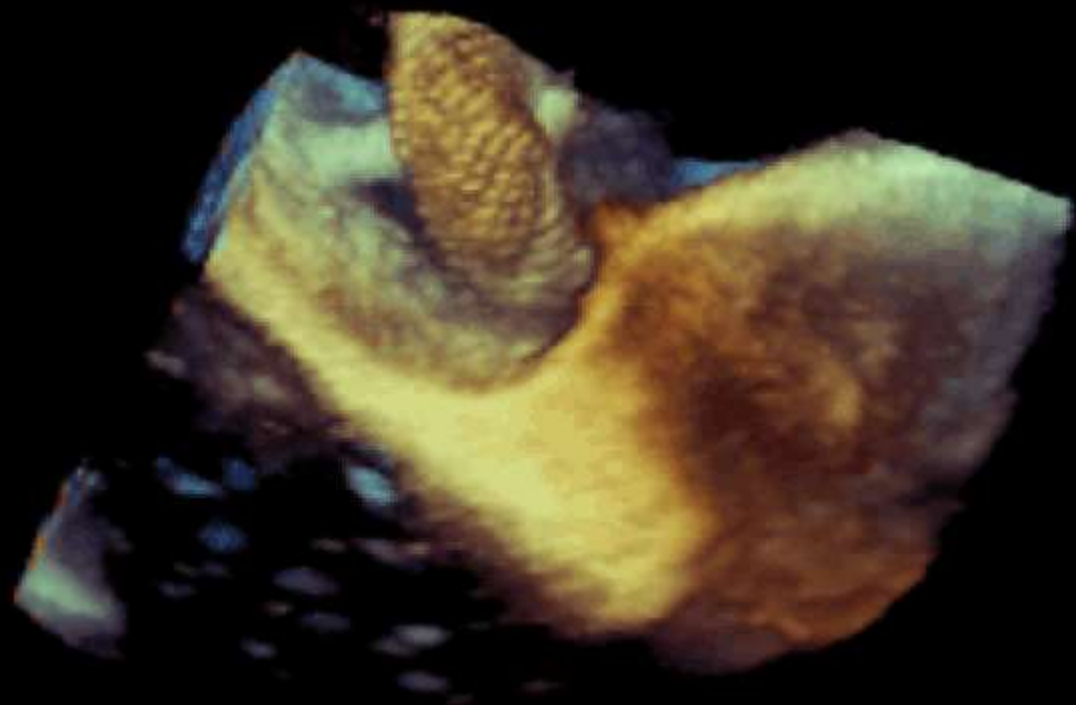


0 bpm

VR 10Hz  
5cm



ive 3D  
D 11%  
D 40dB

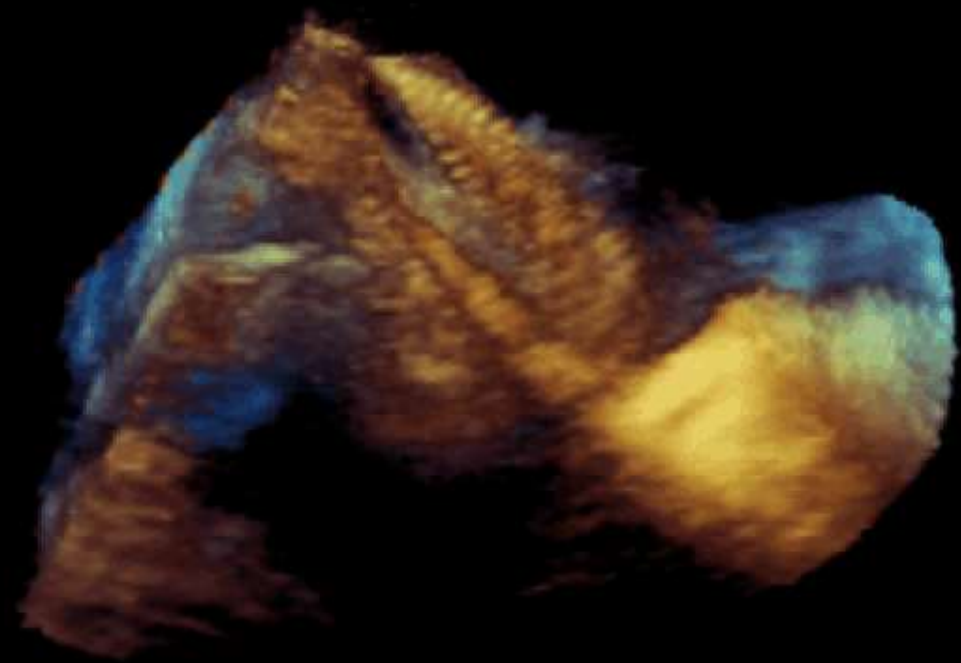


0 bpm

VR 10Hz  
5cm



Live 3D  
3D 11%  
3D 40dB



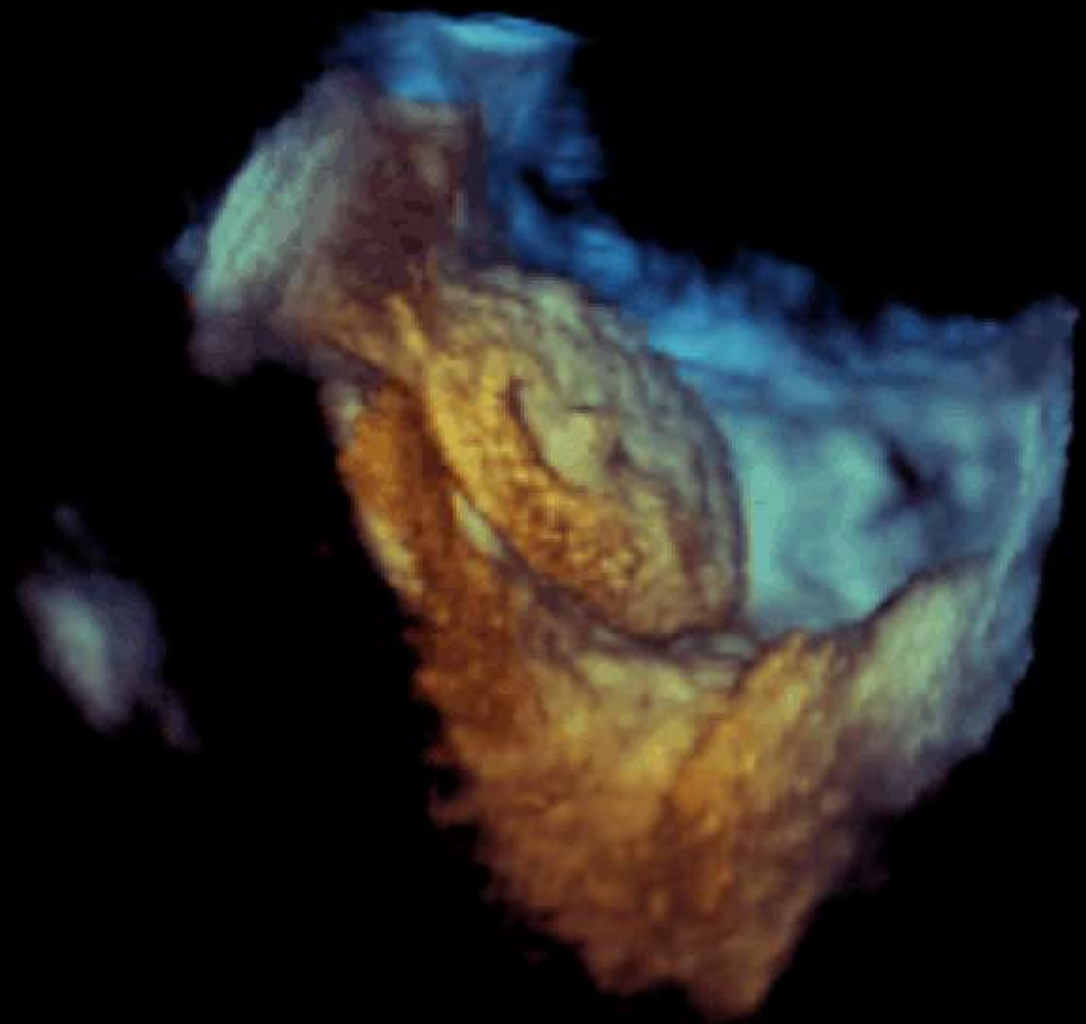
3D↑



0 bpm



VR 7Hz  
5cm  
Live 3D  
3D 1%  
3D 40dB

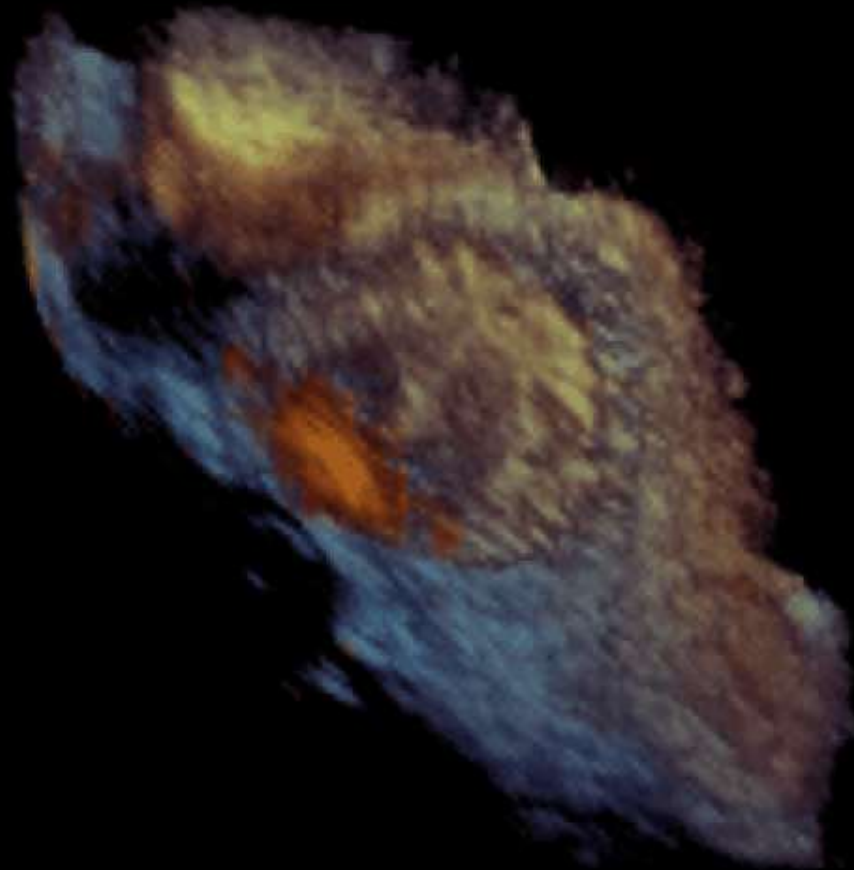


0 bpm

VR 7Hz  
5cm



Live 3D  
3D 2%  
3D 40dB



0 bpm



# PFO CLOSURE

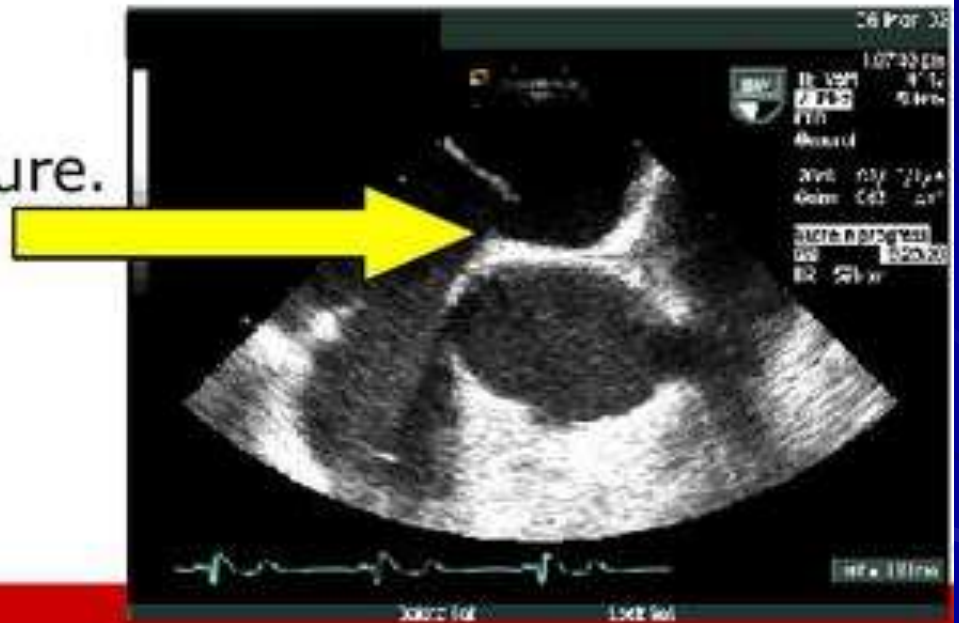


## Patent foramen ovale :

Prevalence of  $\pm 25\%$  (19-36%).  
Remnant of fetal circulation.

Mischievous potential.

Dynamic anatomic structure.  
(Valsalva)





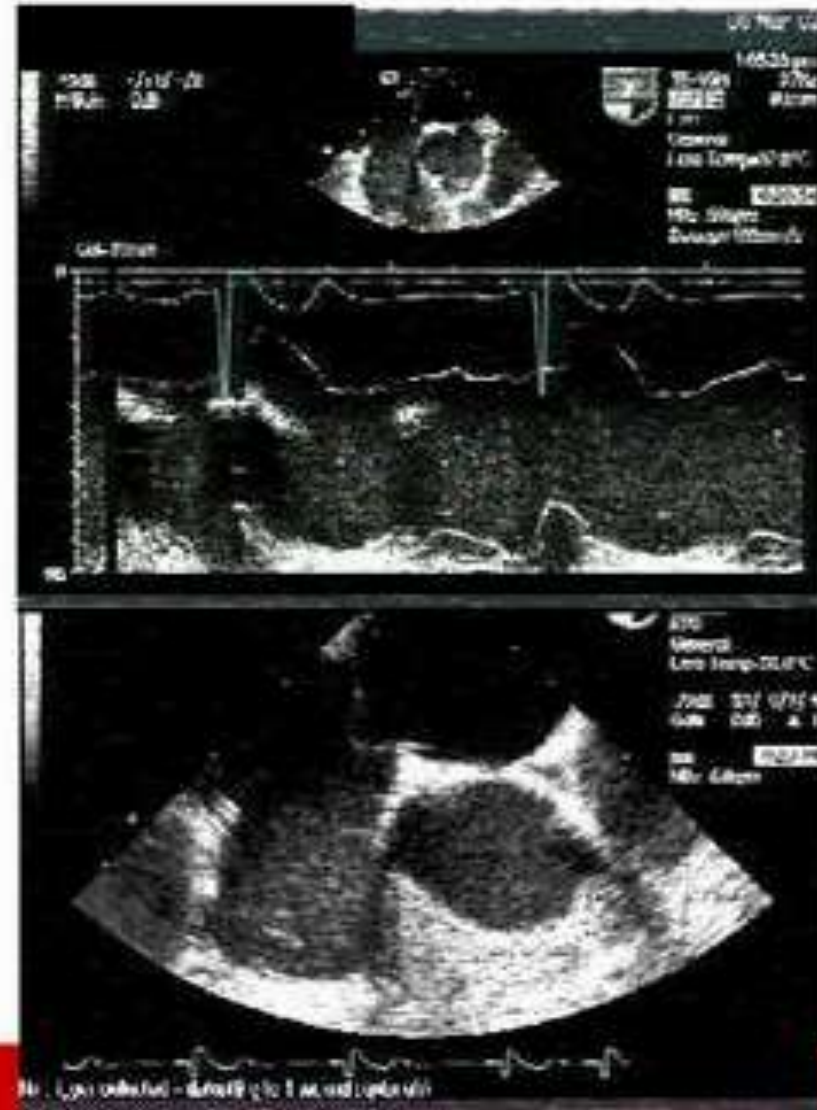
# Atrial septal aneurysm : (ASA)

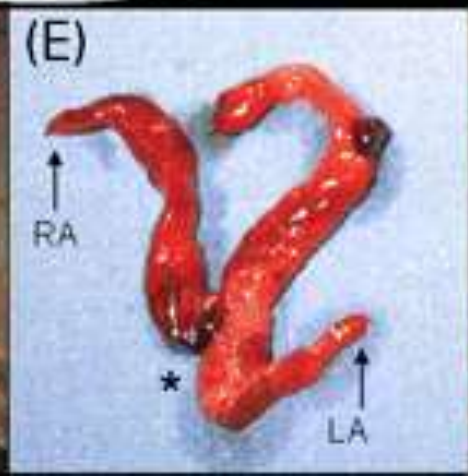
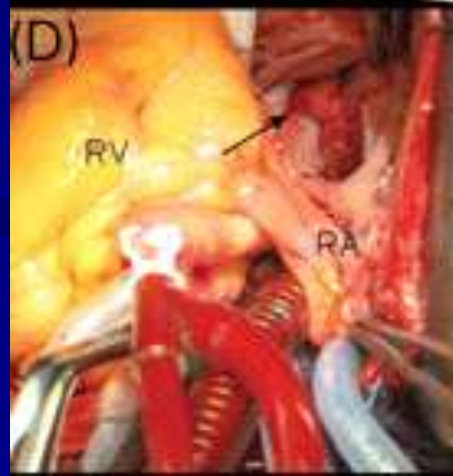
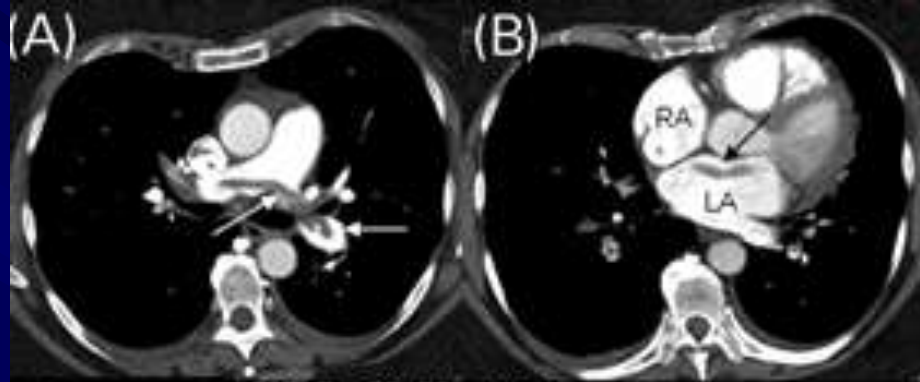
Prevalence  $\pm$  1%.

Prevalence on TEE :

1.9% : excursion  $\geq$  10mm

0.22% : excursion  $\geq$  15mm





# General Population

- PFO is NOT a significant predictor of stroke in the general population
  - Meissner I. et al: J Am Coll Cardiol 47:440-445, 2006
    - N=585
    - PFO in 140 and 12 had stroke (none had ASA): OR 1.46(95% CI 0.74-2.88, p=0.28)
    - ASA 11 and 2 had stroke but none had PFO: OR 3.72(95% CI 0.88-15.71, p=0.07)
  - Petty G. et al: Mayo Clin Proc 81:602-608, 2006
    - N=1072
    - 519 random population controls without CVA
      - PFO in 20.8%
    - 262 controls without CVA referred for other cardiac reasons
      - PFO in 8.4% - OR of 0.47 (95% CI 0.26-0.87)
    - 158 with non-cryptogenic CVA
      - PFO in 10.8% - OR of 0.69 (95% CI 0.37-1.29)
    - 133 with cryptogenic CVA
      - PFO in 16.5% - OR of 1.10 (95% CI 0.63-1.90)



## Prevalence of PFO in patients with "cryptogenic" stroke

	Cryptogenic Stroke	Control	P
• Lechat 1988	54%	10%	< 0.01
• Webster 1988	50%	15%	< 0.01
• De Belder 1992	13%	3%	< 0.01
• Di Tullio 1992	47%	4%	< 0.01
• Hausmann 1992	50%	11%	< 0.01
• Cabanes 1993	56%	18%	< 0.01
• PICCS Trial 2002	39%		
• PICCS Trial ( <u>known stroke type</u> )		30%	<0.02



# Heart Disease and Stroke Statistics

**2008 Update:** Circulation 117; January 29, 2008

- 2.6% of population >18 years of age have a history of stroke
  - 17.8% of the population over 45 years of age reported at least 1 stroke symptom.
- The prevalence of silent cerebral infarction between 55 and 64 years of age is approximately 11% and increases to 43% above 85 years.



Common Disorders intersecting create the perfect storm.

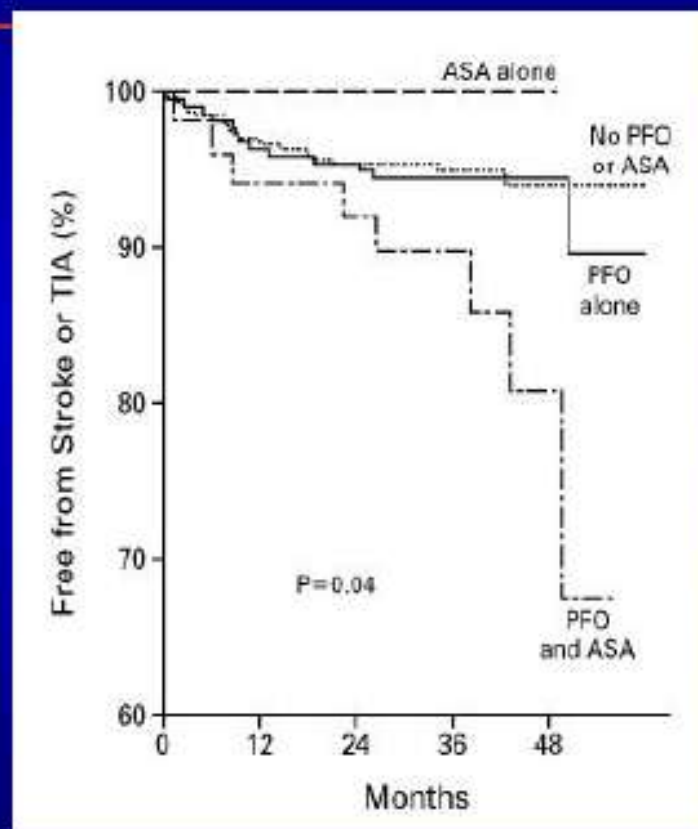


**PFO Prevalence:**  
>20% general population  
>40% cryptogenic stroke population



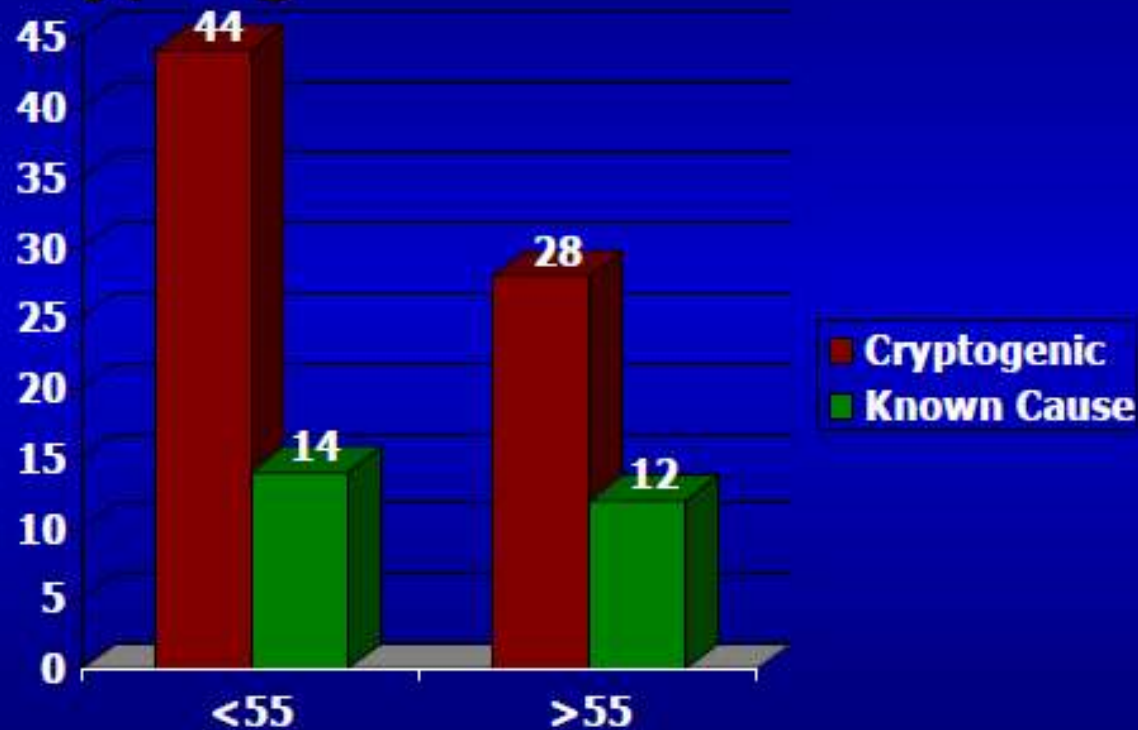
## Recurrent Cerebrovascular Events Associated with PFO, Atrial Septal Aneurysm, or Both

- 581 patients with cryptogenic CVA
- ASA 300 mg/day
- 4 year F/U





## Patent Foramen Ovale and Older Cryptogenic Stroke Patients



N Engl J Med 2007;357:2262-8.

Force M et al., Clin Neurol Neurosurg. 2008 Jun



## Patent Foramen Ovale and Stroke

- In a general population the presence of PFO is not an independent risk factor for stroke
- Pts with a history of stroke and large PFO and ASA are at sig risk for recurrent events if just on aspirin
- Atrial septal aneurysm without a PFO is not a risk factor for recurrent stroke



## Optimal Treatment to Prevent strokes in patients with a PFO

- Currently there are no established treatment options
- Options available:
  - Antiplatelet therapy
  - Anticoagulant treatment
  - Surgical Closure
  - Percutaneous Closure



# Transcatheter Closure vs Medical Therapy PFO and Presumed Paradoxical Thromboemboli

10 Transcatheter Closures Studies

1355 Patients

6 Medical Management Studies

895 Patients

Recurrent neuro event @ 1 Yr

0 - 4.9%



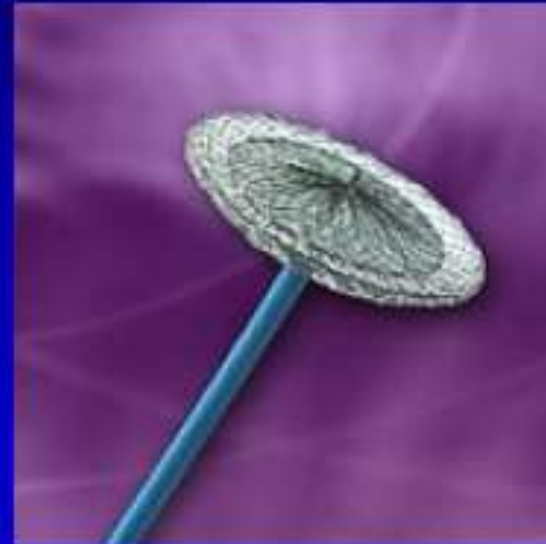
3.8% - 12%



# Techniques of Closure PFO Occluder in Clinical Trial



**STARFlex (NMT Med)**



**PFO occluder (AGA Med)**



**Helex Septal Occluder (Gore )**



# Ongoing PFO Stroke Trials

Trial	Respect	Closure I	Reduce
N	500+	900	664
Device (Company)	Amplatzer (AGA)	StarFlex (NMT)	Helex (Gore)
Inclusion	Stroke	Stroke or TIA	Stroke or MRI TIA
Primary Endpoint	Stroke	Stroke or TIA	Stroke or MRI TIA
Key Secondary Endpoints	? Migraine	? Migraine	MRI WMLs

**Completed enrollment**

Different Populations, Devices, Endpoints  
Essential to Building a Body of Evidence

# CLOSURE I: Study Flow (Superiority Study)

- Age 18-60yrs
- Documented Cryptogenic Stroke Or TIA
- PFO

**Device Group:**  
Starflex Septal  
Occuder and Aspirin

Aspirin 2 years  
Clopidogrel 6 mths

## Primary End points

- All case death at 30 days
- 2 year Stroke or TIA
- Neurological death >30 days

R

910 patients  
Enrolled between  
June 2003 and  
October 2008

**Control Group:**  
Aspirin and/or  
Coumadin 2 years

iv h no m1

iv h no m6

fi \$ v r aey 1

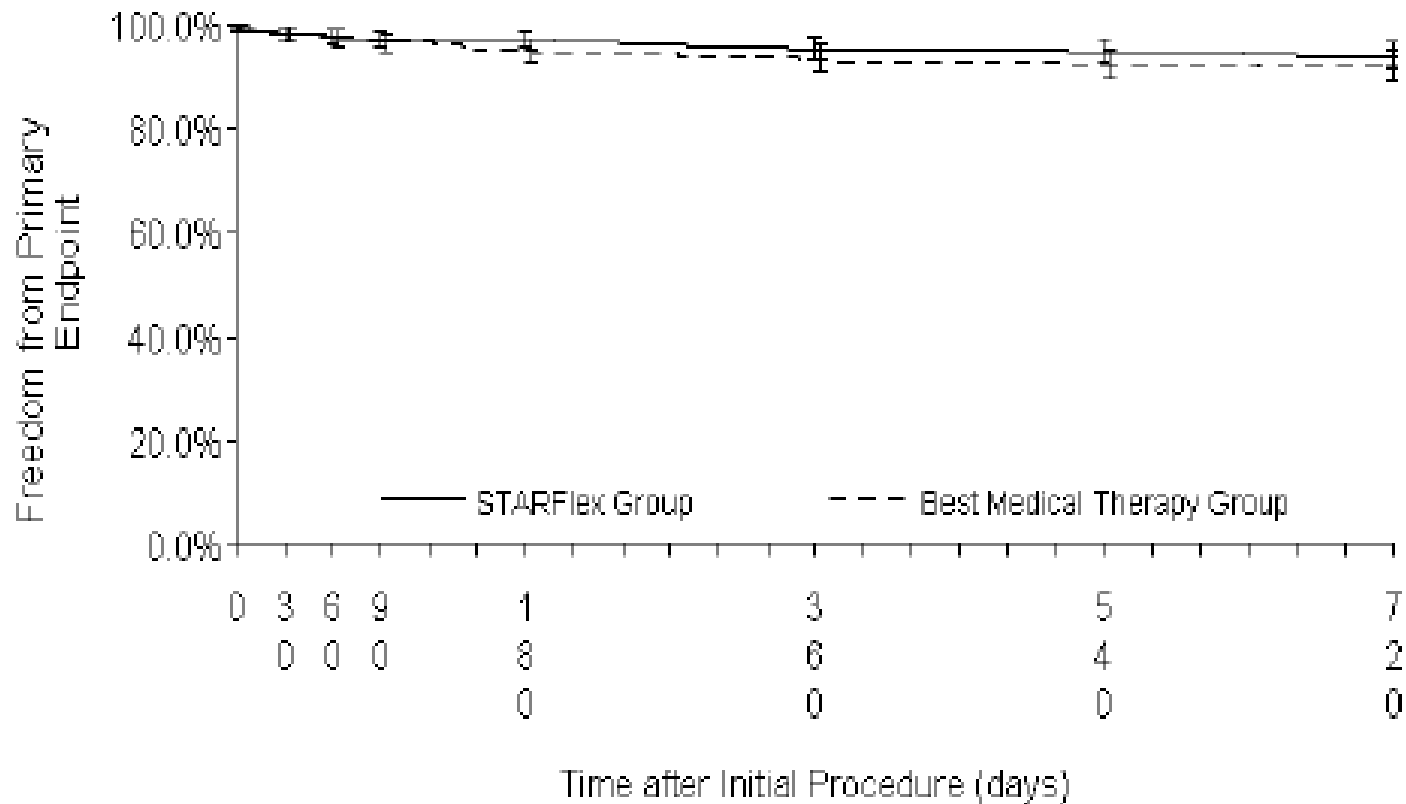
fi \$ v r aey 2

## Baseline Characteristics ITT

	STARFlex	Medical	P value
N randomized	447	462	
Mean Age	46.3 (18-61)	45.7(18-61)	
Male	52.1%	51.5%	
White	89%	90%	
Index cryptogenic stroke	73%	71%	
Mod/substantial shunt*	58% (231/400)	51% (228/451)	0.04
ASA $\geq$ 10 mm*	38% (151/400)	35% (160/451)	0.49

\* modified ITT

## Kaplan-Meier for Primary Endpoint ITT



## Composite Primary Endpoint Baseline Shunt and Atrial Septal Aneurysm (TEE)

	STARFlex N=400	Medical N=451	P value
Trace shunt	7.0% (n=8/114)	8.0% (n=10/126)	0.75
Moderate shunt	5.3% (n=7/132)	8.4% (n=12/143)	0.31
Substantial shunt	3.6% (n=3/84)	5.3% (n=3/57)	0.62
No atrial septal aneurysm	6.4% (n=15/236)	8.5% (n=20/236)	0.38
Atrial septal aneurysm	4.9% (n=7/142)	6.5% (n=9/139)	0.58

# Adverse Events

	STARFlex N=402	Medical N=458	P value
Major vascular complications*	3.2% (n =13)	0.0%	<0.001
Atrial fibrillation	5.7% (n= 14/23 periprocedural)	0.7% (n=3)	<0.001
Major bleeding	2.6% (n=10)	1.1% (n=4)	0.11
Deaths (all non endpoint)	0.5% (n=2)	0.7% (n=3)	ns
Nervous system disorders	3.2% (n=12)	5.3% (n=20)	0.15
Any SAE	16.9% (n=68)	16.6% (n=76)	ns

\*Perforation LA (1); hematoma >5cm at access site (4); vascular surgical repair (1); peripheral nerve injury (1); procedural related transfusion (3);retroperitoneal bleed (3)

# STARFlex Technical Success

	STARFlex n=402	95% CI
Procedural success	90.0%	(86.7%,92.8%)
Thrombus by TEE	1.0% (n=4; stroke in 2 at days 4, 52)	
Effective closure	No recurrent stroke or TIA in patients with residual leaks	
TEE 6 mos	86.1% closed	(82.1%,89.4%)
TEE 12 mos	86.4% closed	(82.5%,89.8%)
TEE 24 mos	86.7% closed	(82.8%,90.0%)

**Procedural success** was defined as successful delivery of one or more STARFlex devices to the site during the index procedure, deployment of the device at the intended site, and removal of the delivery system without a major procedural complication prior to discharge. **Effective closure** was defined as procedural success with either grade 0 (none) or 1 (trace) residual shunt by TEE.

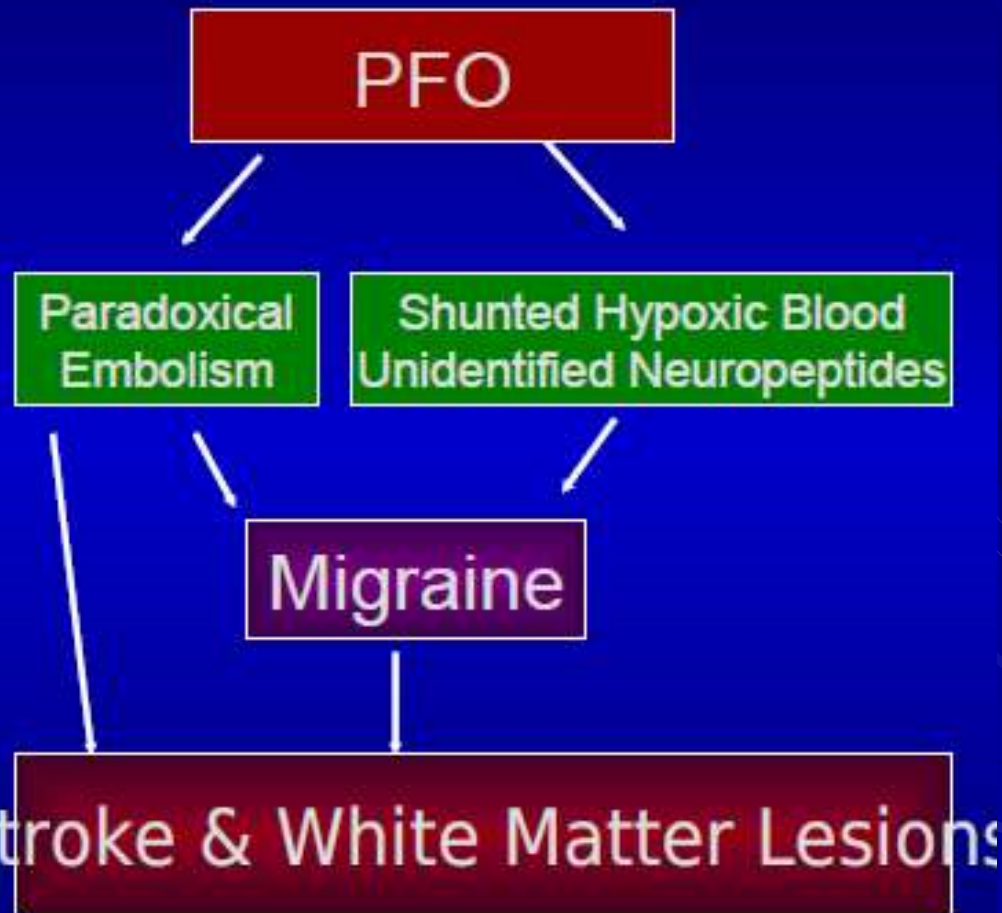
## Aspirin versus Warfarin

	<b>Aspirin alone (n=243)</b>	<b>Warfarin alone (n=139)</b>	<b>P value</b>
<b>Composite</b>	<b>6.7%</b> (n=14)	<b>8.1%</b> (n=9)	<b>0.63</b>
<b>Stroke</b>	<b>3.9%</b> (n=8)	<b>2.7%</b> (n=3)	<b>0.67</b>
<b>TIA</b>	<b>2.9%</b> (n=6)	<b>6.3%</b> (n=7)	<b>0.09</b>



# Migraine and PFO

- 1) Association of Migraine and PFO
- 2) Association of migraine and stroke
- 3) PFO closure reduced headaches in stroke pts with a history migraine





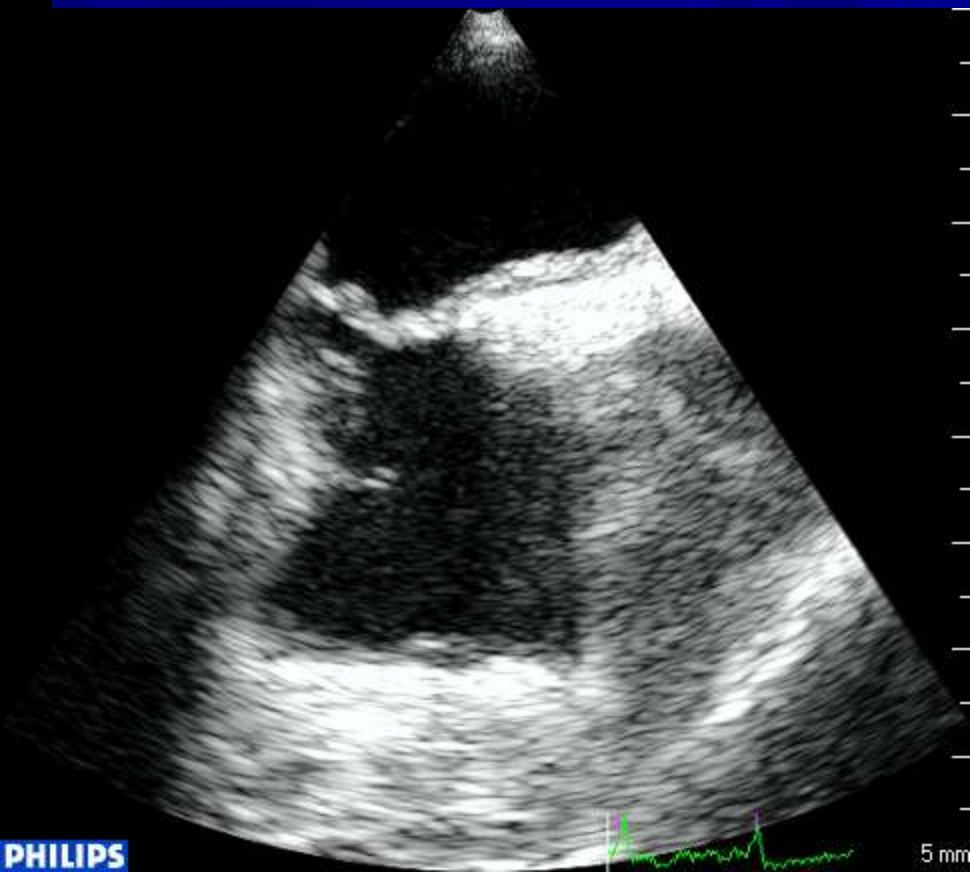
# MIST Trial

- **135 Migraine with Aura pts** with PFO randomized
- **Primary Endpoint:** Cessation of Migraine attack(MHA)
  - 3 pts in device and 3 in control group
- **Secondary Endpoint:** 50% reduction of MHA days
  - Device : 42% of pts
  - Control: 23 % of pts

**$p < 0.04$**
- **PFO closure effectiveness** data: controversial



PHILIPS



PHILIPS

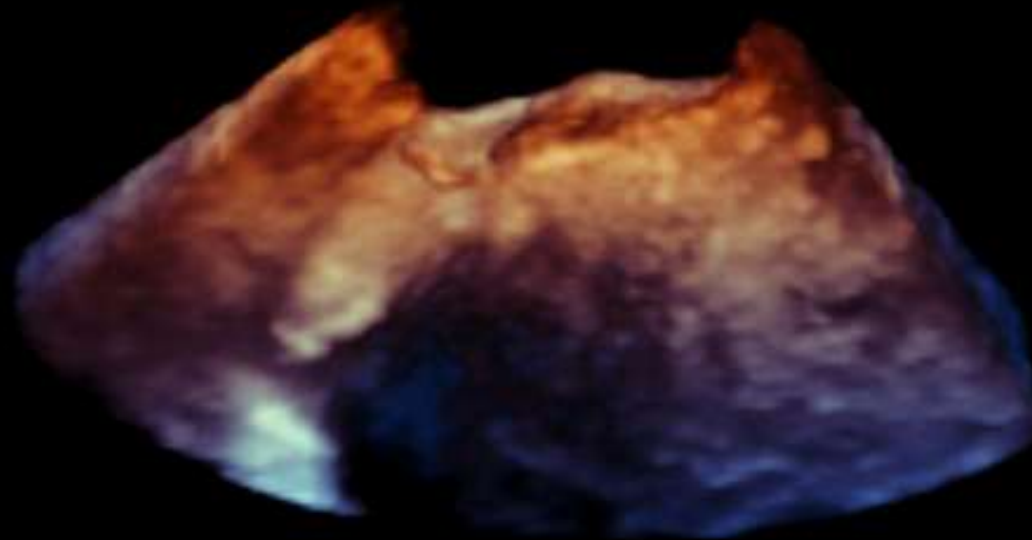
5 mm



2007/10/30 06:18:56PM  
AGIOS LOUKAS

VR 16Hz  
7cm

Live 3D  
3D 47%  
3D 40dB



3D↑



70 bpm

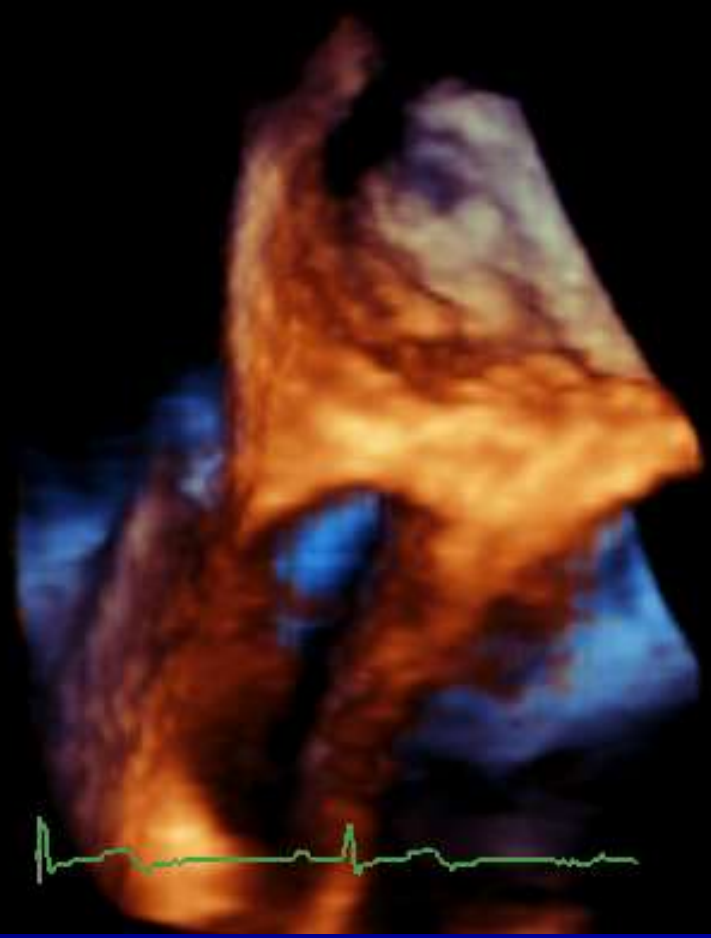
PHILIPS



2007/11/02 10:15:15AM  
AGIOS LOUKAS

VR 26Hz  
6cm

Live 3D  
3D 47%  
3D 40dB



56 bpm

FR 52HZ  
12cm

2D  
79%  
C 50  
P Off  
Gen



JPEG



PAT T: 37.0C  
TEE T: 39.0C

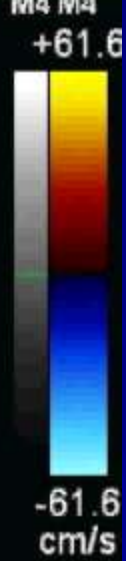
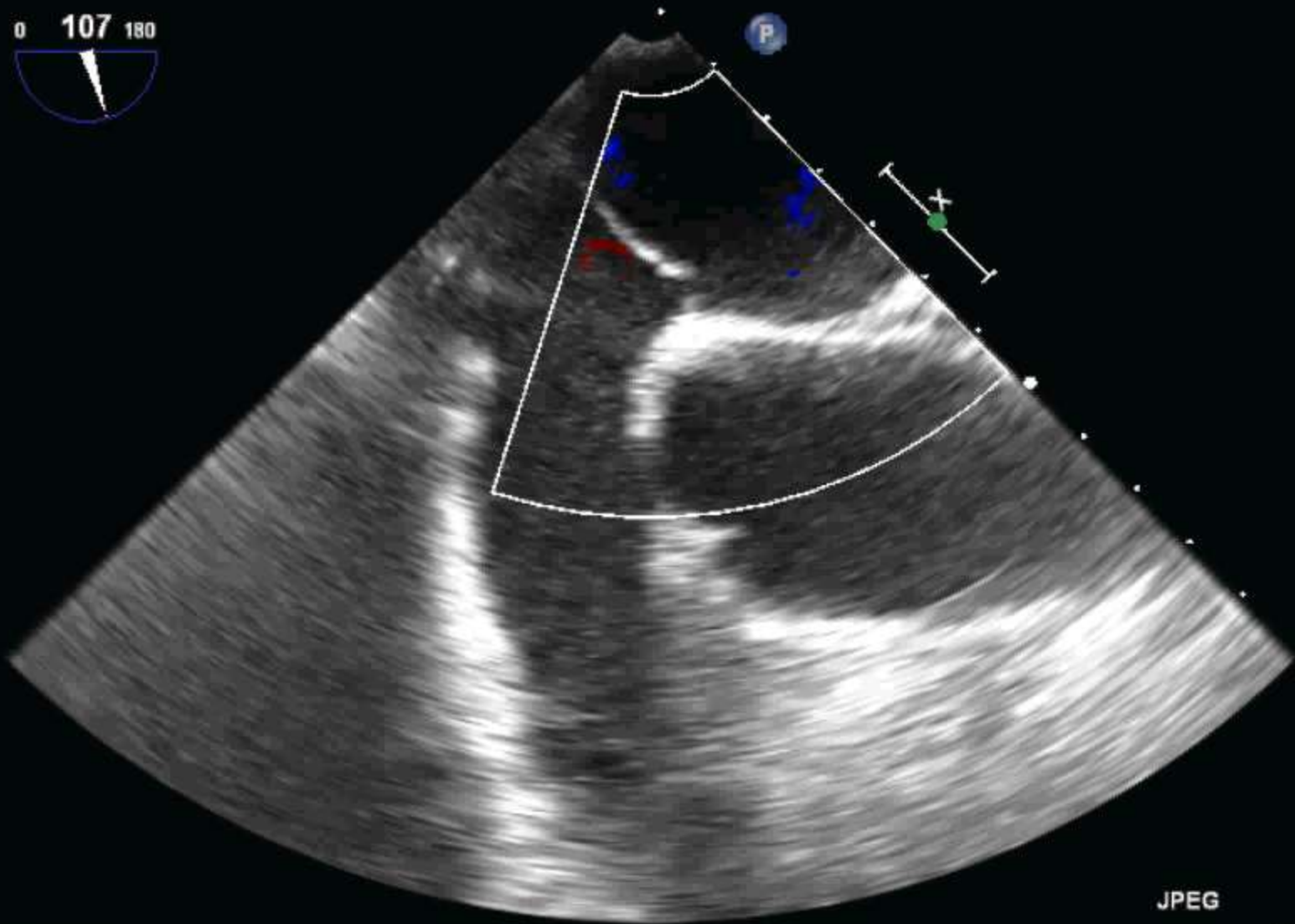
\*\*\* bpm

FR 13Hz  
12cm

**2D**  
81%  
C 50  
P Off  
Gen



**CF**  
59%  
4.4MHz  
WF High  
Med



JPEG

PAT T: 37.0C  
TEE T: 39.0C

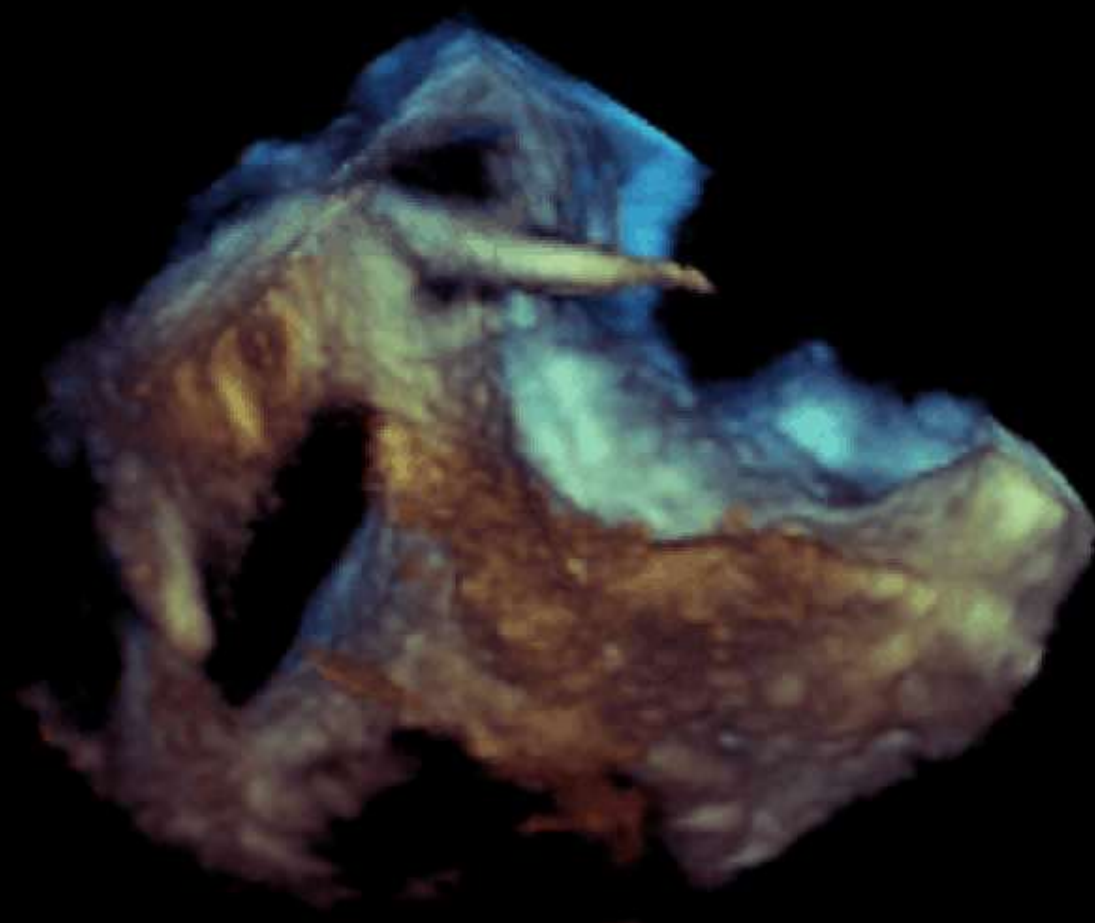
\*\*\* bpm



VR 6Hz  
5cm



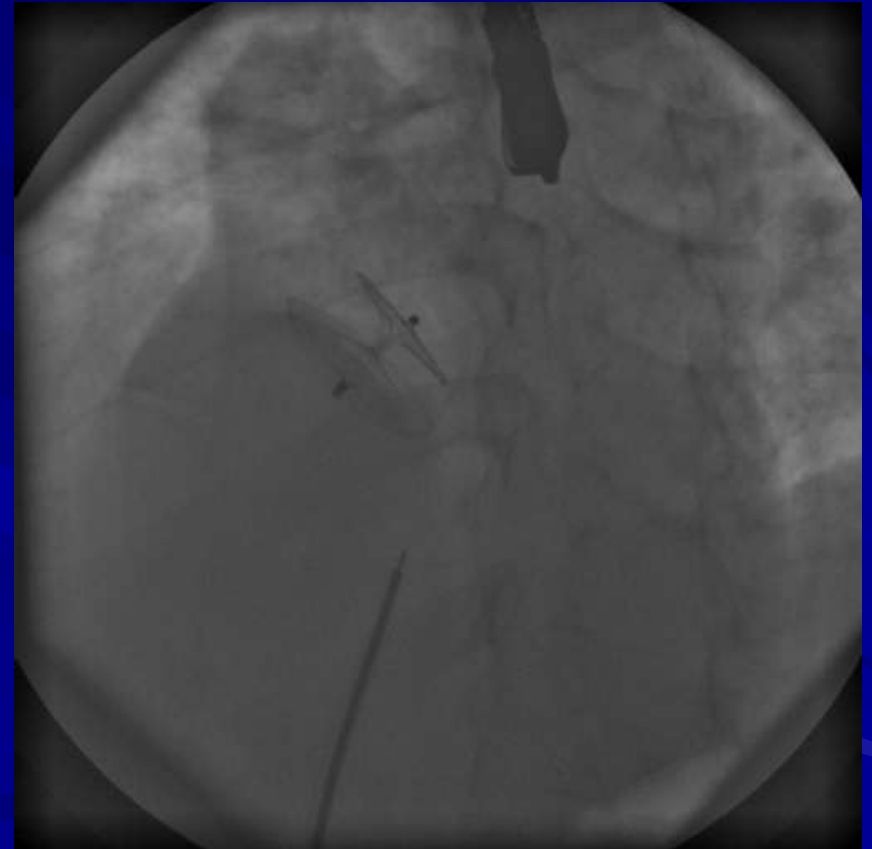
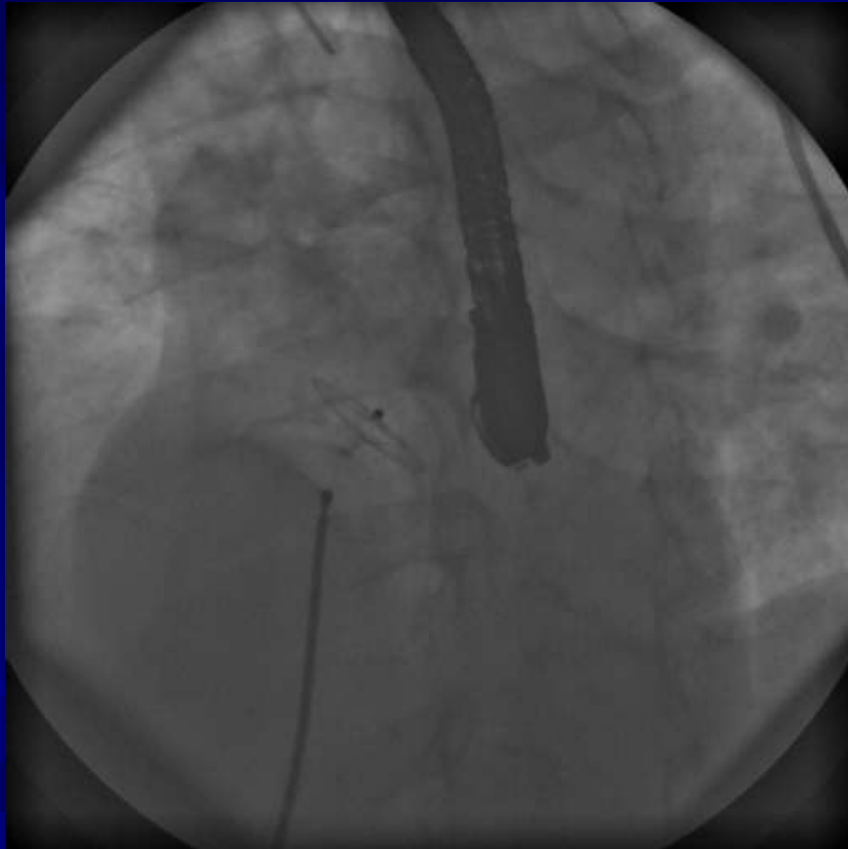
Live 3D  
3D 14%  
3D 40dB



0 bpm



# PFO + ASAneurysm

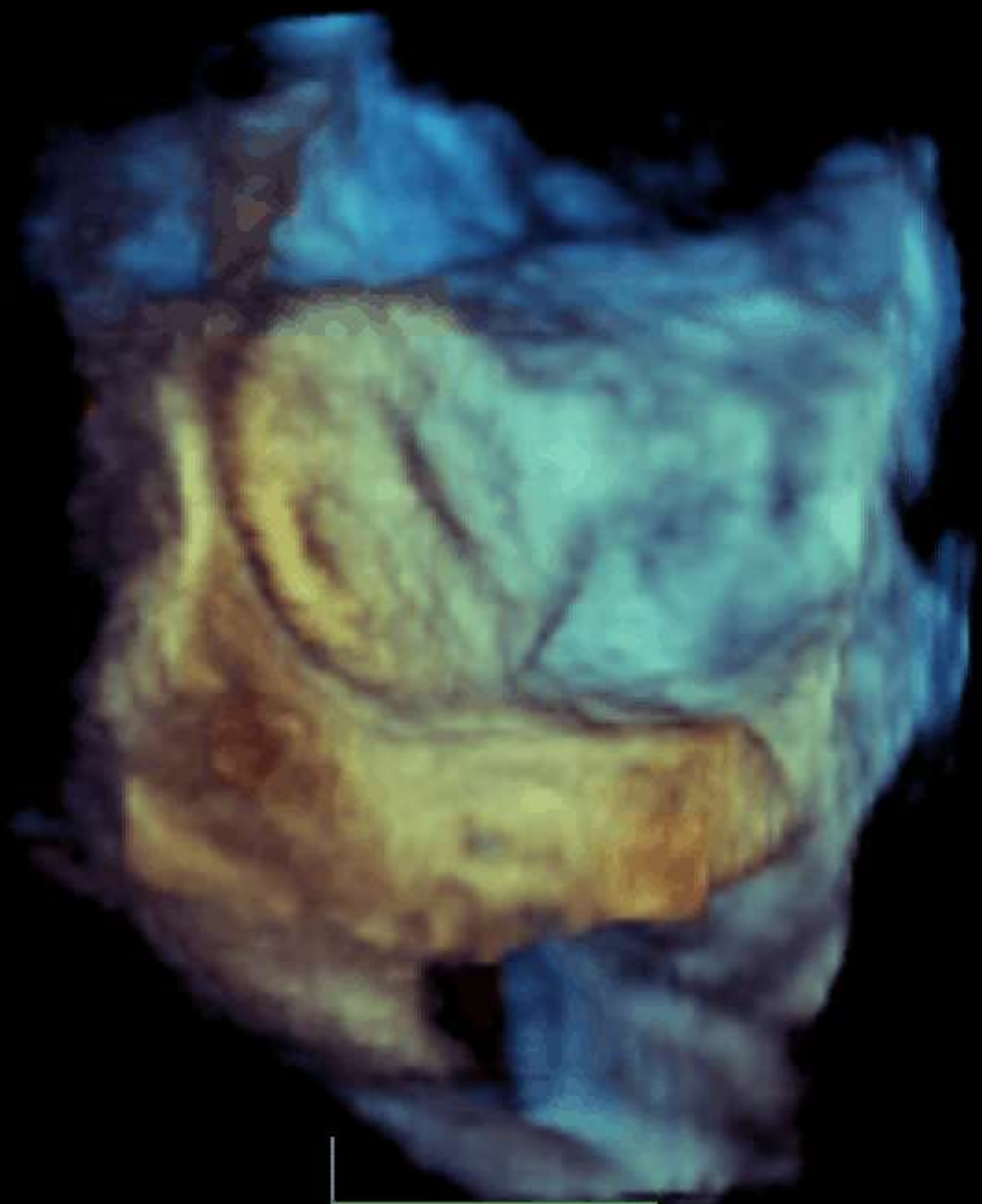


VR 8Hz  
6cm

0 80 180



Live 3D  
3D 1%  
3D 40dB



0 bpm



# Cassano set for heart surgery with Milan braced to miss forward for months

In a statement the club said: 'The player will undergo a small surgical cardiological intervention in the coming days and the recovery time will be better defined after the surgery, but it will probably be a few months.'

Cassano was reportedly joking with teammates on the plane, before suddenly developing problems with his **vision, speech and movement**, but the Italian champions' statement said he was feeling much better.



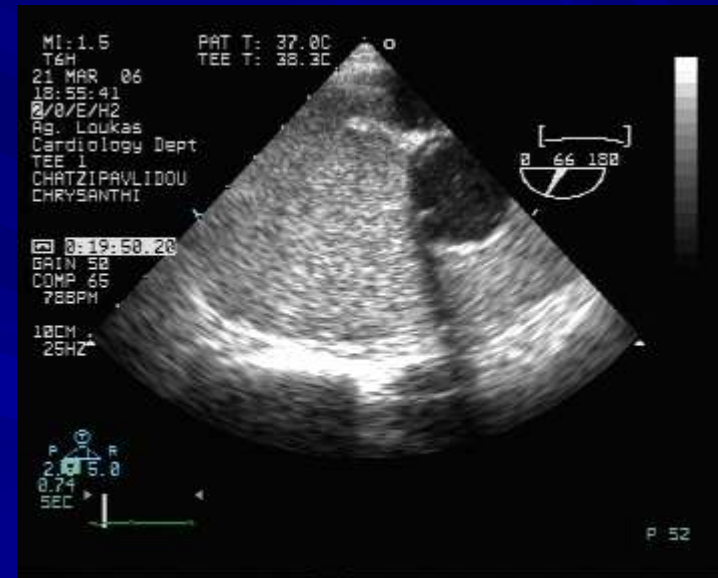
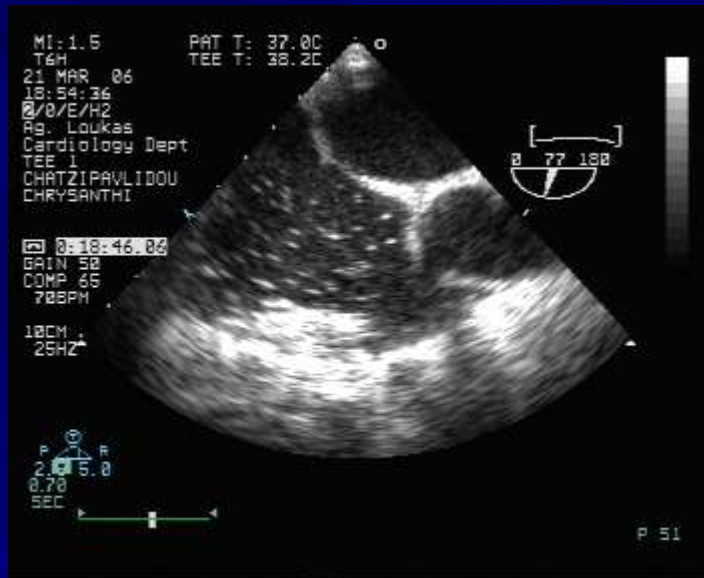
# IN CONCLUSION

- Secundum ASD closure is both feasible and safe in a wide range of sizes
- PFO closure as a reason for cryptogenic stroke is feasible but the indication needs further research
- New imaging modalities (3D TEE) offers a new window into the heart and makes complex procedures feasible





# Bubble test .... Should be adequate and sufficient



## 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
- **Major vascular complications in 3% of device arm**
- **Significantly higher rate of atrial fibrillation in device arm (5.7%)**
  - 60% periprocedural

## CONCLUSIONS

- **2 year stroke rate essentially identical in both arms (3%)**
  - cryptogenic stroke includes multiple etiologies
  - diagnostic criteria for paradoxical embolism are imprecise
  - potential efficacy of PFO device closure in well 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  $\leq$  age 60 presenting with cryptogenic stroke or TIA and a PFO**



# REDUCE Trial

- 40 sites enrolling( Europe and US)
- Approximately 15% enrolled
- Unique Features of the Trial
  - 2:1 randomization
  - 5 year follow up required
  - MRI for all patients at 2 years
  - Medical arm: Antiplatelet therapy( Aspirin preferable)



# RESPECT Trial

- >600 pts enrolled
- Design is event driven not patient driven
- Medical arm
  - Aspirin or coumadin, or Clopidogrel, Aggrenox
- Device Arm:
  - Aspirin for 6 months, Clopidogrel for 1 mth



# Immediate and late procedural complications

## Group I

### ■ Complications

■ Severe arrhythmias	0
■ Transient palpitations	5 (11%)
■ Device embolization	0
■ Hemopericardium	1 (2%)
■ Thrombus formation	0
■ Device failure	0
■ Endocarditis	0



# Follow-up results

	Group I	Group II	P
■ <b>Incidence of embolic events</b>			
■ TIA	1/48 (2.05%)	6/44 (6.85%)	0.001
■ CVA	0	7/44 (7.95%)	0.0004
■ <b>Incidence of hemorrhagic events</b>			
■ Major	0	2/44 (4.5%) <sup>†</sup>	0.48
■ Minor	0	4/44 (9%) <sup>§</sup>	0.001



# 6 MONTHS LATER

2007/10/30 05:18:17 PM  
AGIOS LOUKAS

VR 16Hz  
4cm

Live 3D  
3D 42%  
3B 40dB



PHILIPS



Endothelialized Amplatzer®  
Septal Occluder





# TRANSCATHETER CLOSURE VERSUS MEDICAL THERAPY OF PATENT FORAMEN OVALE AND CRYPTOGENIC STROKE

**Basil D. Thanopoulos MD, Petros Dardas MD, FESC\*, Nicholas Eleptherakis,  
Evangelos Karanasios, Nick. E. Mezilis MD, FESC\*, Vasilios Votzas**  
*Catheterization and Cardiovascular Intervention, 2006*

ΝΟΣ. ΠΑΙΔΩΝ ΑΓΙΑ ΣΟΦΙΑ, ΑΘΗΝΑ  
ΚΛΙΝΙΚΗ ΑΓΙΟΣ ΛΟΥΚΑΣ, ΘΕΣΣΑΛΟΝΙΚΗ



# Patient characteristics

	INVASIVE Group I	non- INVASIVE Group II	P
N	<b>48</b>	<b>44</b>	NS
Age (years)	43±11	40±12	NS
Female/male	21/27	23/21	NS
Hypertension	12.5% (6/48)	13% (6/44)	NS
Hypercholesterolemia	25% (12/48)	29% (13/44)	NS
Diabetes mellitus	4% (2/48)	2% (1/44)	NS
Oral contraceptives	6% (3/48)	9% (4/44)	NS
Coronary artery disease	4% (2/48)	2% (1/48)	NS
Current smoker	12% (6/48)	11% (5/44)	NS
<b>Embolic events</b>			
CVA	73% (35/48)	61% (27/44)	NS
TIA	27% (13/48)	34% (15/44)	NS
Average incidence of events/year	4.7% (113)	4% (88)	NS
ASA	13/48 (27%)	10/44 (23%)	NS
<i>Degree of R to L shunt (Number of bubbles)</i>			
Large	53% (25/48)	66 % (29/44)	NS
Small	47% (23/48)	34% (15/44)	NS

## Baseline Characteristics

- No statistical differences between STARFlex versus medical therapy
  - medical history
  - prior events
  - stroke risk factors
- CLOSURE I patient population is representative of patients  $\leq$  age 60 with cryptogenic stroke/TIA and a PFO

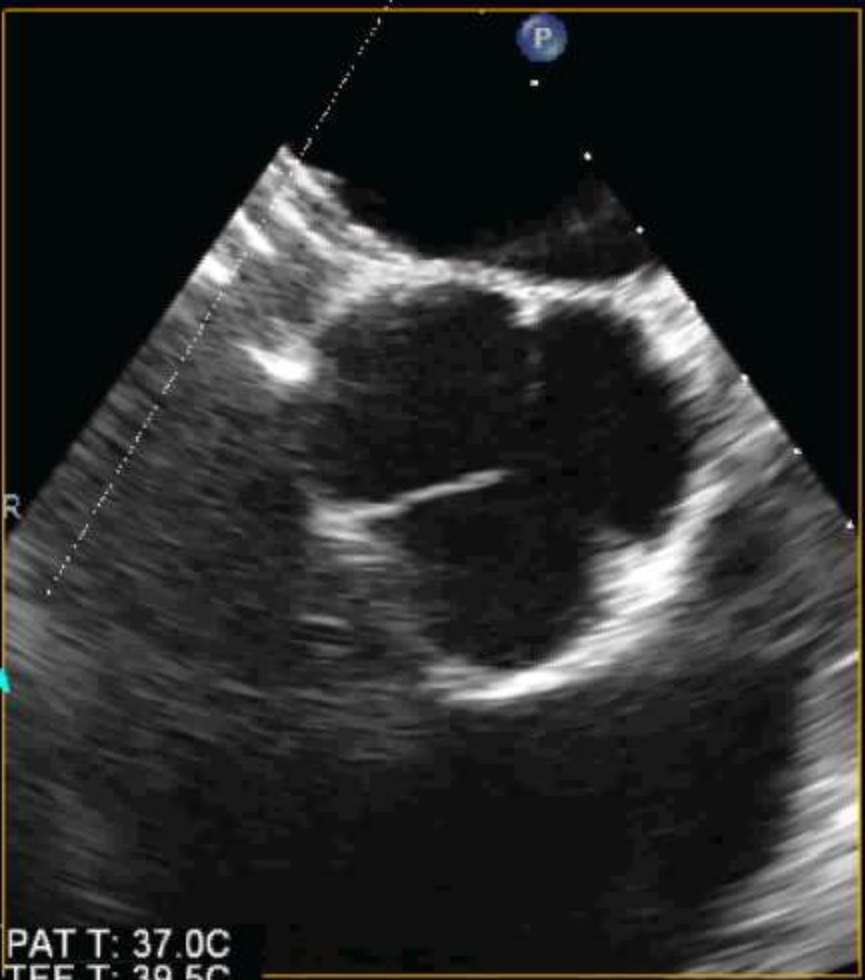
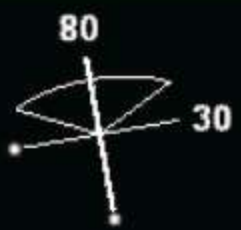
## 2 Year Primary Endpoint ITT

	<b>STARFlex</b> n = 447	<b>Medical</b> n = 462	<b>P value*</b>
<b>Composite</b>	<b>5.9%</b> (n=25)	<b>7.7%</b> (n=30)	<b>0.30</b>
<b>Stroke</b>	<b>3.1%</b> (n=12)	<b>3.4%</b> (n=13)	<b>0.77</b>
<b>TIA</b>	<b>3.3%</b> (n=13)	<b>4.6%</b> (n=17)	<b>0.39</b>

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

FR 36HZ  
12cm

xPlane  
71%  
71%  
50dB  
P Off  
Gen



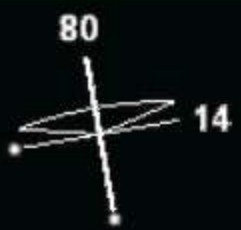
PAT T: 37.0C  
TEE T: 39.5C



FR 7/Hz  
12cm

**xPlane**  
73%  
73%  
50dB  
P Off  
Gen

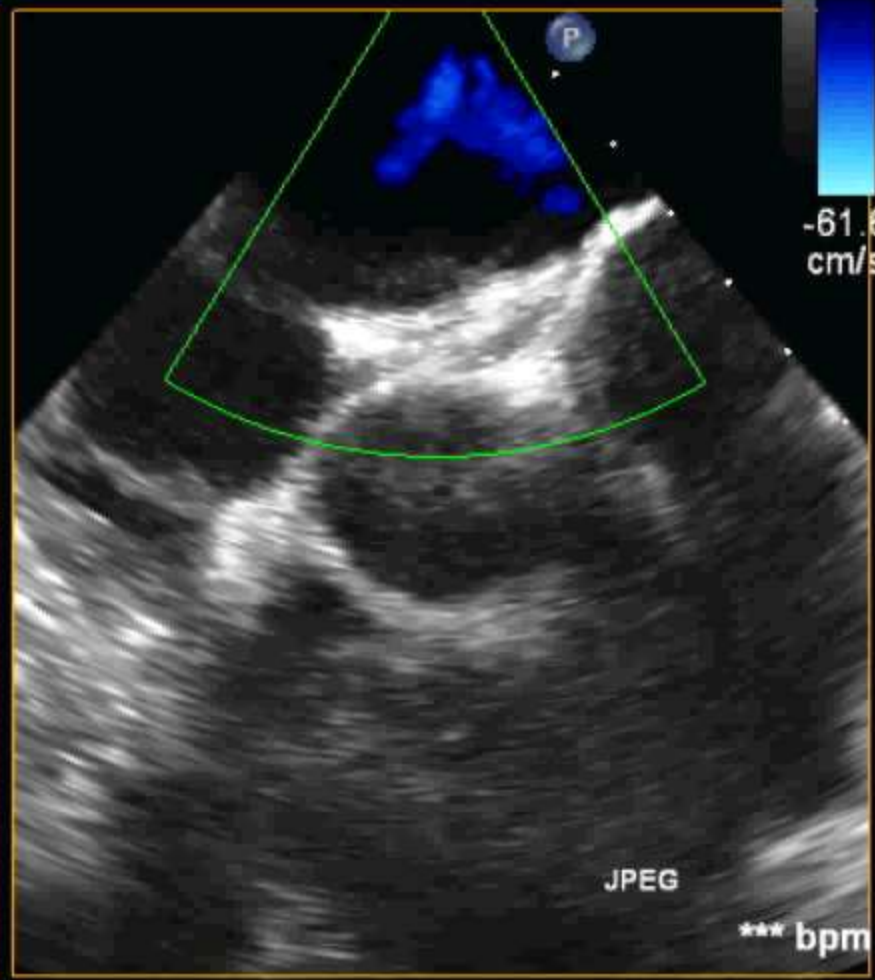
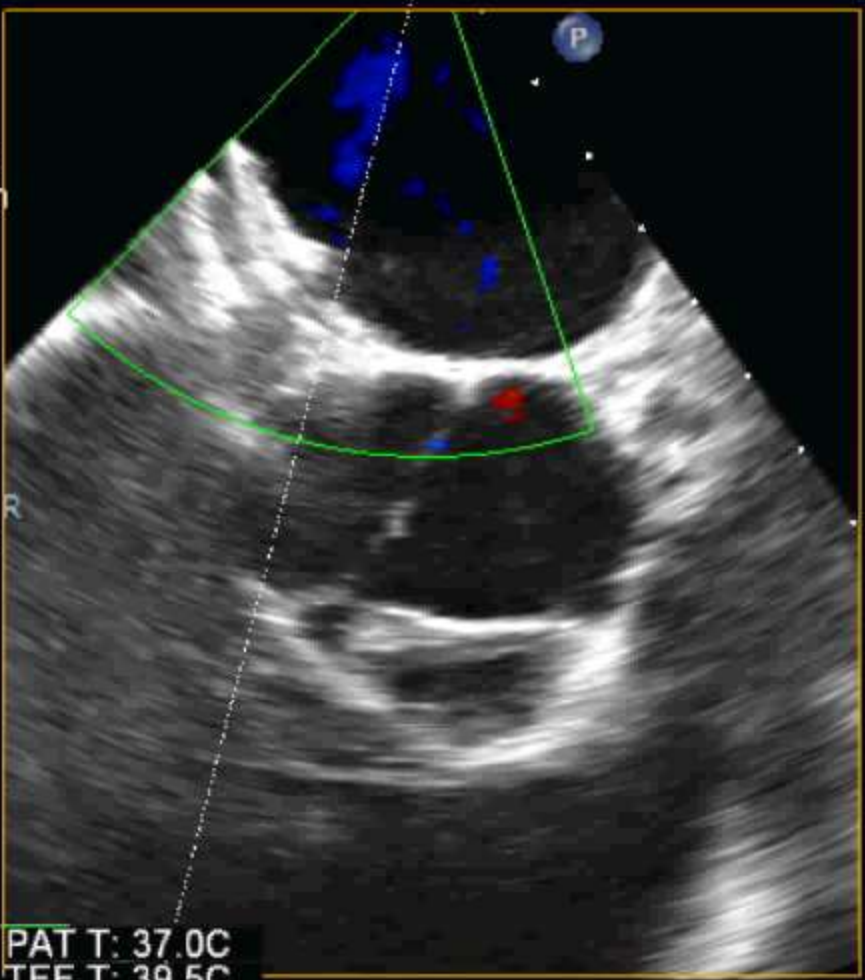
**CF**  
59%  
4.4MHz  
WF High  
Med



M4 M4  
+61.6



-61.6  
cm/s



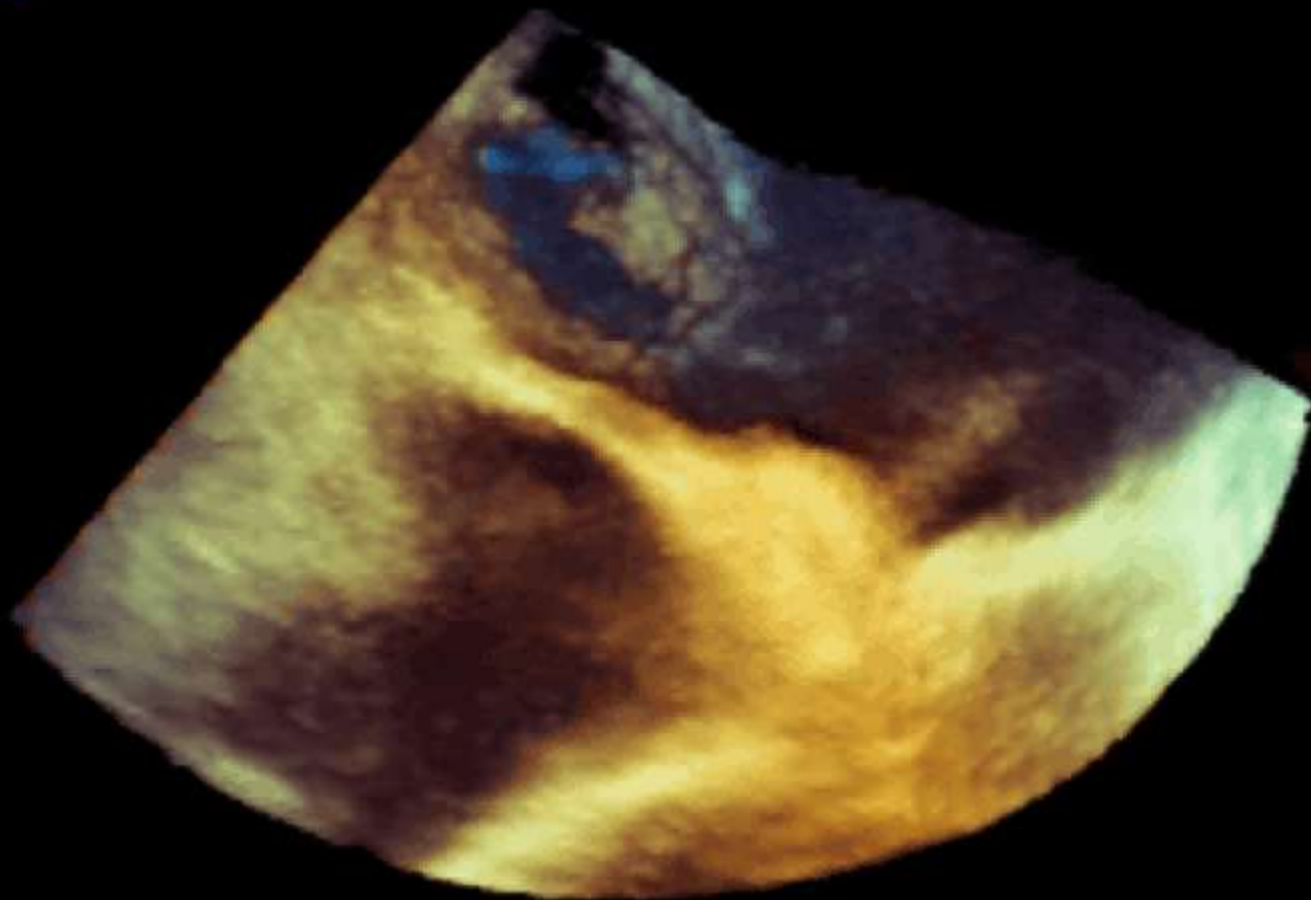
PAT T: 37.0C  
TEE T: 39.5C



VR 10Hz  
4cm



ive 3D  
D 35%  
D 40dB



0 bpm