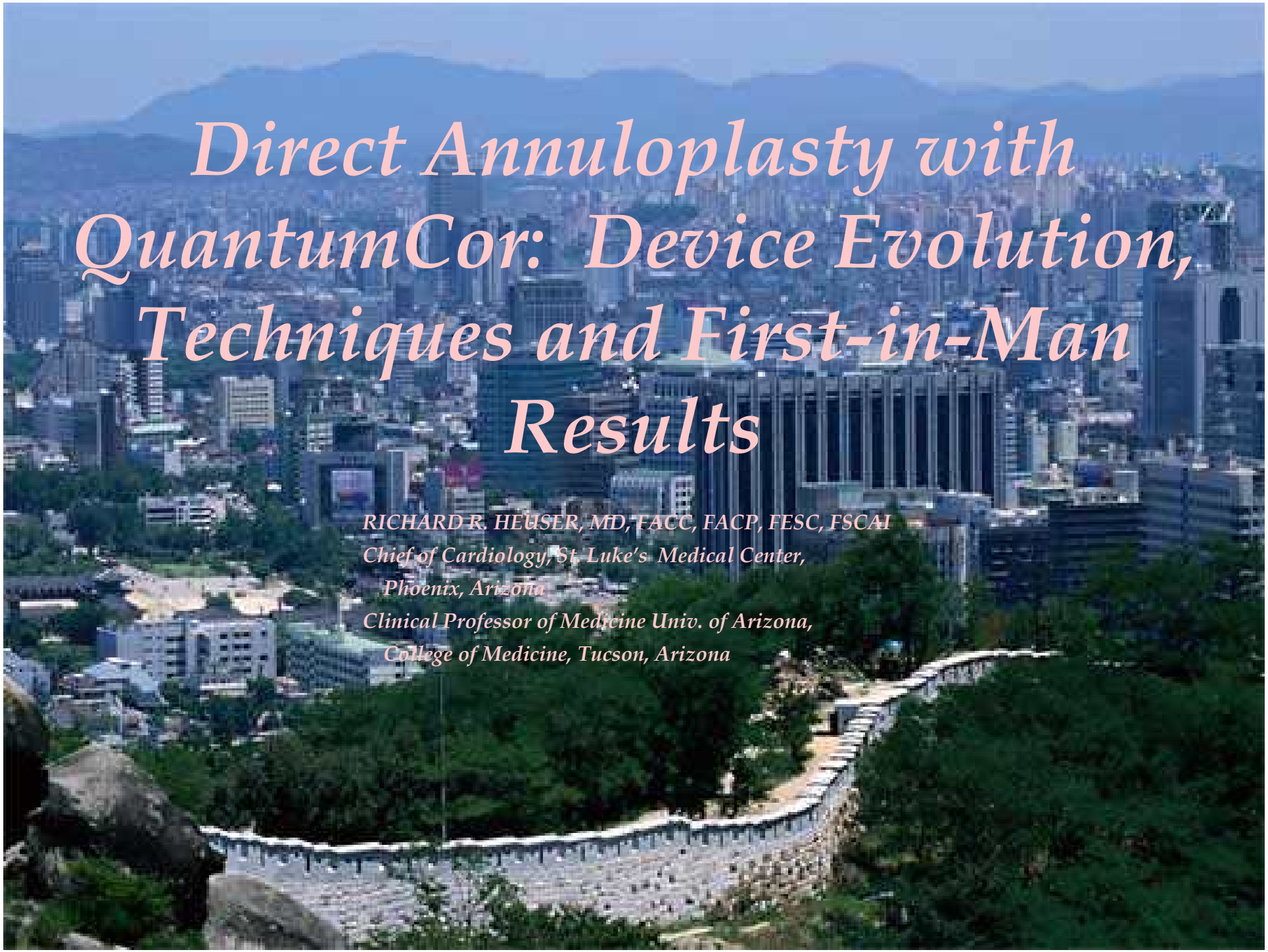

Direct Annuloplasty with QuantumCor: Device Evolution, Techniques and First-in-Man Results

RICHARD R. HEUSER, MD, FACC, FACP, FESC, FSCAI

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Phoenix, Arizona

Clinical Professor of Medicine Univ. of Arizona,

College of Medicine, Tucson, Arizona

Presenter Disclosure Information

Name: ***RICHARD R. HEUSER M.D.***

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Company Name	***Relationship***
QuantumCor	*Major Stock Holder/Medical Director*
Spectranetics, Inc.	*Honorarium*
CSI	*Stockholder*

Patents *-- RF, Snares, Wires, Balloon Catheters, Covered Stents, Devices for Arterial Venous Connection, Devices for LV and RV Closure, Sheaths*

I Am Presenting on Behalf of QuantumCor, Inc.

This work would not have been possible without the contributions of the following:

- *Thomas Witzel*
- *Duane Dickens*
- *Dr. Patricia Takeda*
- *Dr. Ramil Goel*
- *Dr. Shishir Murarka*

Ischemic Mitral Regurgitation

- Acute*
- Chronic**

* Tcheng JE, Jackman JD, Jr., Nelson CL:, Gardner LH, Smith LR, Rankin JS, et al. Outcome of patients sustaining acute ischemic mitral regurgitation during myocardial infarction.

** Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J. Cardiol 2003;91(5):538-43.

Coronary Angioplasty for Acute Mitral Regurgitation Due to Myocardial Infarction

A Nonsurgical Treatment Preserving Mitral Valve Integrity

RICHARD R. HEUSER, M.D.; GERRY L. MADDOUX, M.D.; JEROME E. GOSS, M.D.; BARRY W. RAMO, M.D.; GILBERT L. RAFF, M.D.; and NEAL SHADOFF, M.D.; Albuquerque, New Mexico

Annals of Internal Medicine. 1987;107:852-855.

Chronic Ischemic Mitral Regurgitation is found in 10-20% of patients with coronary artery disease and is a major cause of CHF after MI

AJGC. 2006;15:291-301.

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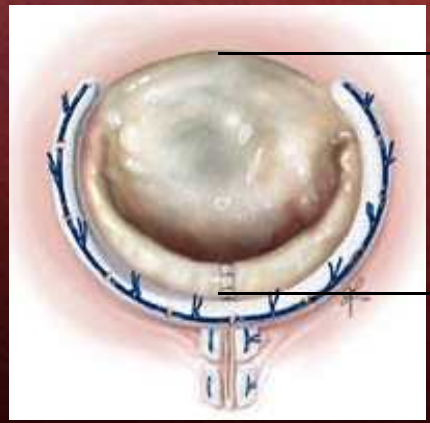
GAME CHANGER

AJGC. 2006;15:291-301.

Surgical Repair

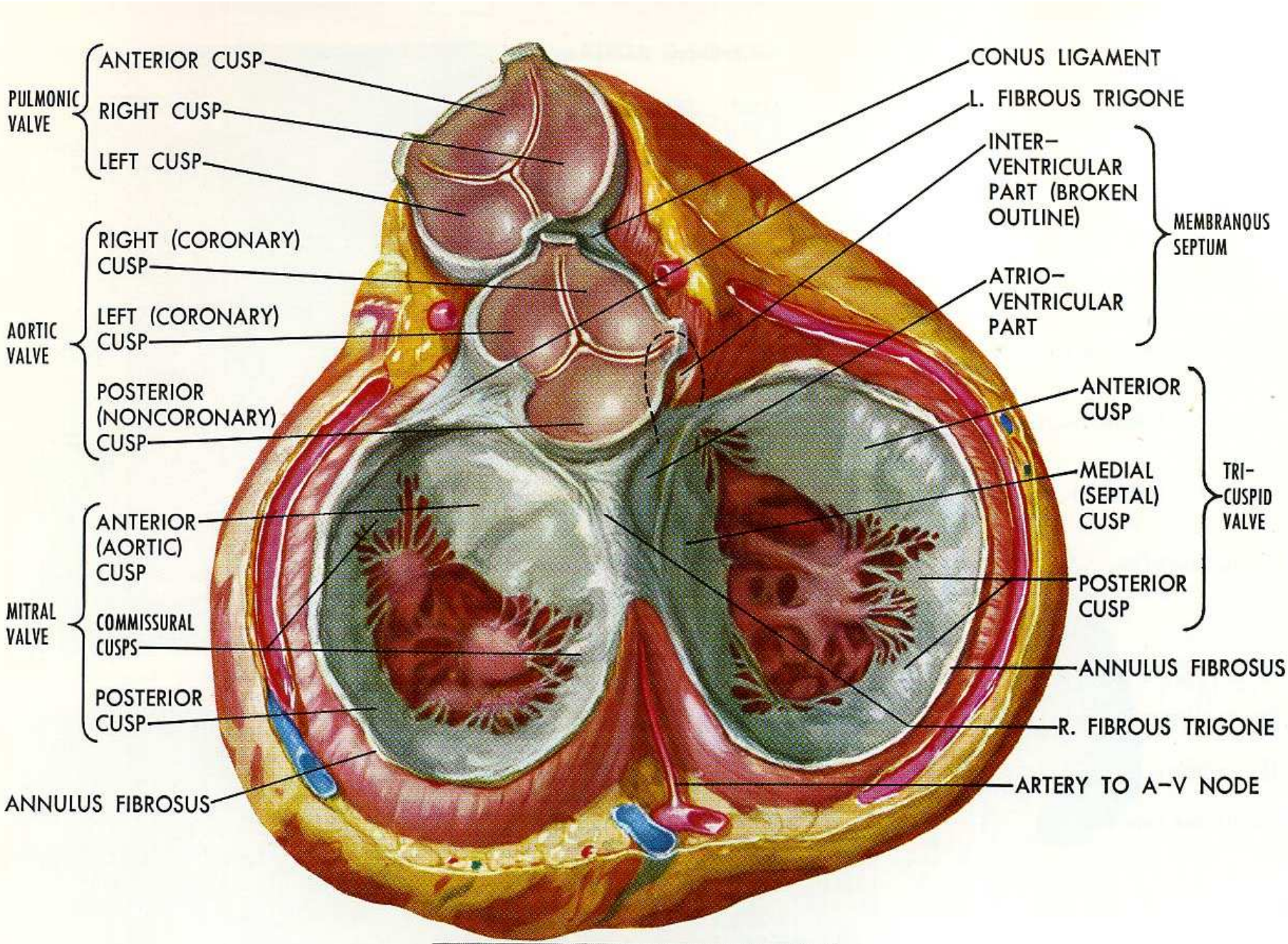


- *Surgical Procedure (Annuloplasty)*
  - ✓ *Surgeon resect posterior annulus*
  - ✓ *Reduce size of posterior annulus*
  - ✓ *<u>Objective:</u> Reduce distance between valve leaflets*
  - ✓ *<u>Goal:</u> Anterior posterior (A/P) reduction of <u>~ 20%</u>*

Percutaneous Mitral Valve

Treatment will need to be:

- Direct valve approach;
- Annular approach;
- Repeatable;
- Cannot preclude future mitral valve repair



THE HEART IN DIASTOLE: VIEWED FROM BASE WITH ATRIA REMOVED

Background

Mitral Annulus Slices

(Trichrome Stain)

Left, Posterior Leaflet Segment

Middle, Posterior Leaflet Segment

Right, Posterior Leaflet Segment

COLLAGEN CAN BE SHRUNK

-- The amount of shrinkage is dependent on time and temperature

-- First Shown in 1871

QUANTUMCOR

The QuantumCor™ Device Uses Radiofrequency (RF) Energy At Sub-ablative Temperatures To Produce Contraction Of The Mitral Valve Annulus And Theoretically Reduces Mitral Regurgitation.

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Safe Window of Collagen Heating is Possible

Shrinkage Rate Is Dependent On Temperature Level

- Wide Spectrum Of Temperatures Feasible With Rf.
- Important To Treat Annulus Within Brief Interval.
- Tendon Data Show 20% Shrinkage To Be Maximal, Without Loss Of Tensile Strength.
- QuantumCor Studies Show >20% Annular Shrinkage Is Feasible.

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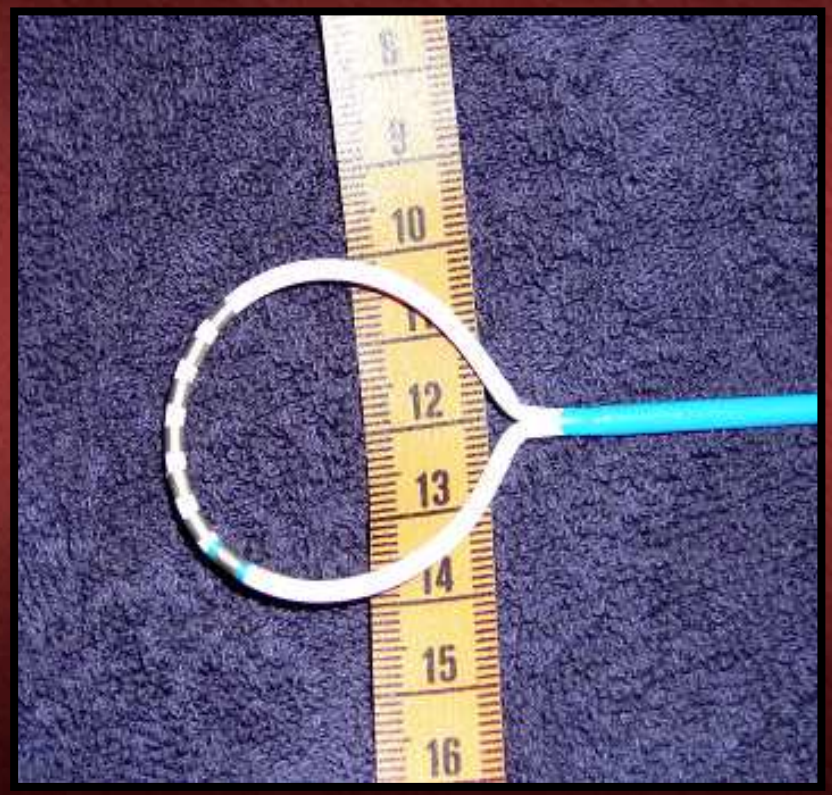
Method

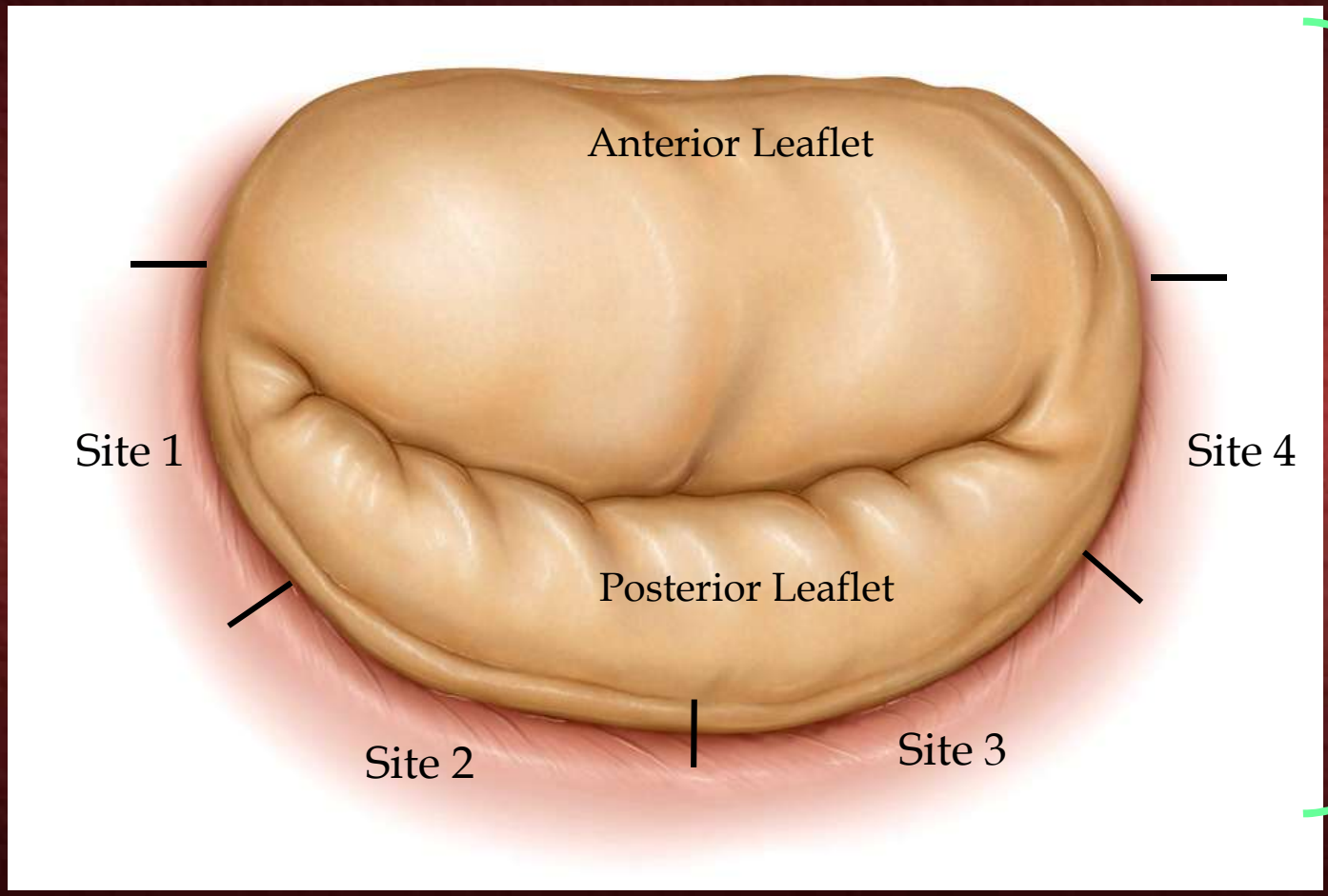
Method

Boa-Surg

- *7 Electrodes/14 Thermocouples*
- *3mm Length*
- *2mm Spacing*
- *40mm Loop Diameter*



Mitral Annulus Treatment Sites



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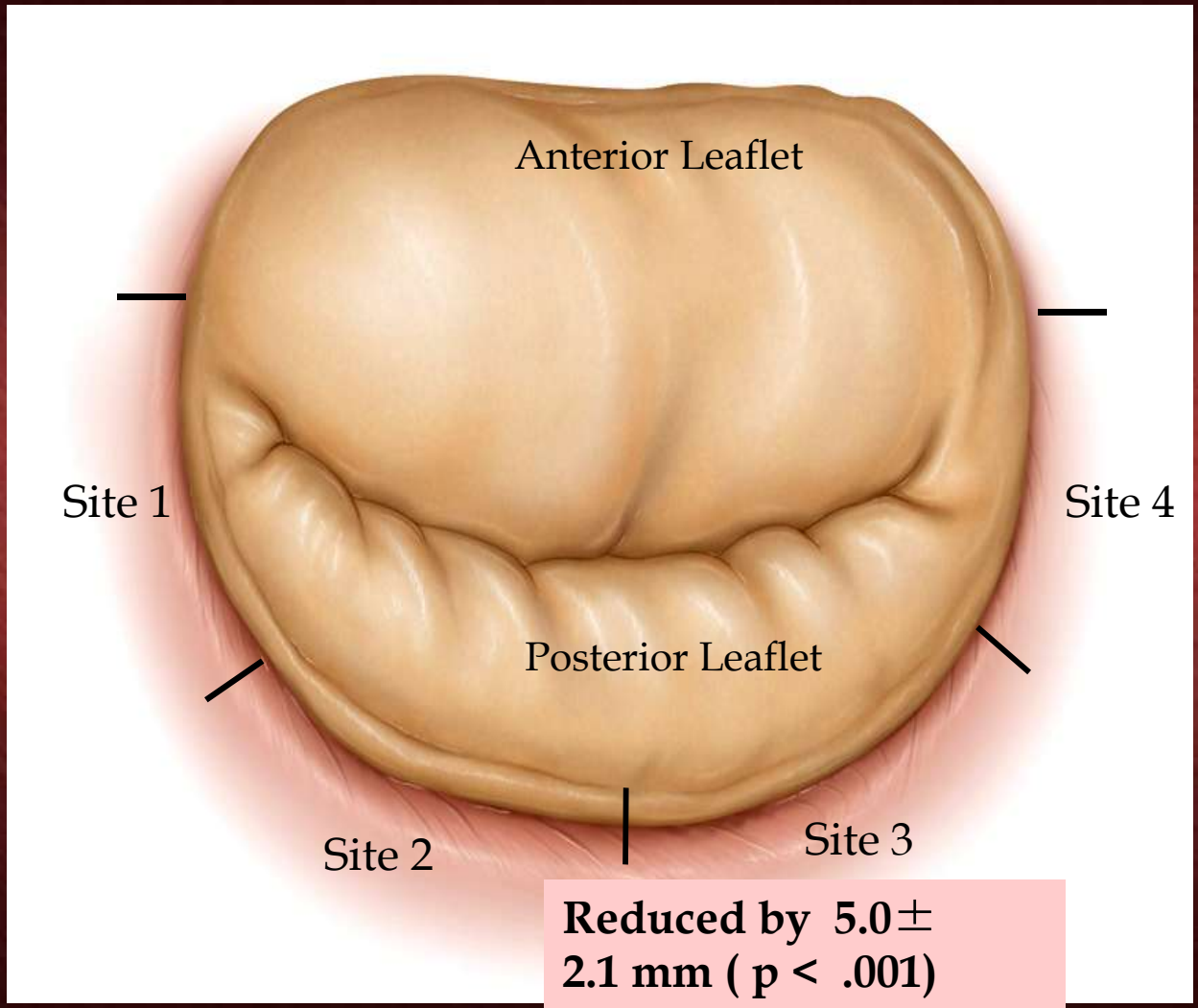
RESULTS

Mitral Annulus Treatment Sites



PA or Septal Lateral

Reduced by 5.0± 2.1 mm (p < .001)

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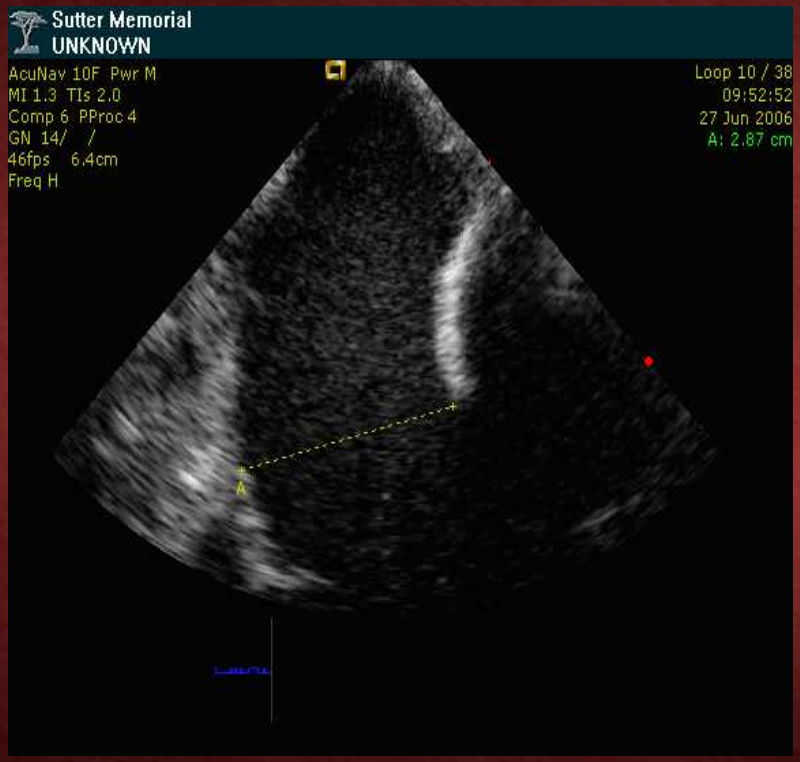
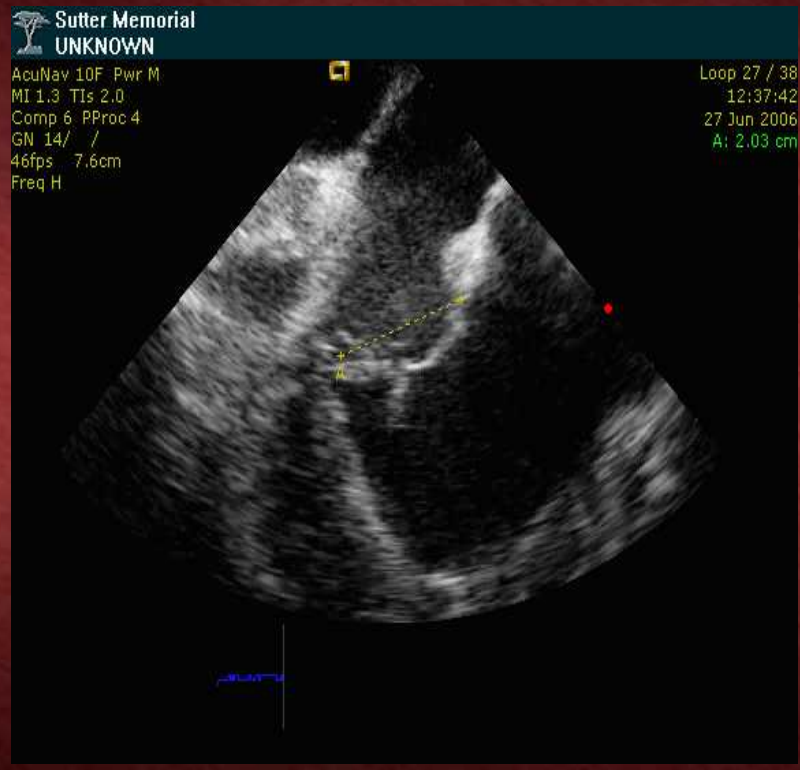
Intracardiac Echo ICE

Mitral valve pre-treatment



A/P diameter <u>28.7</u> mm

Mitral valve post-treatment



A/P diameter <u>20.3</u> mm

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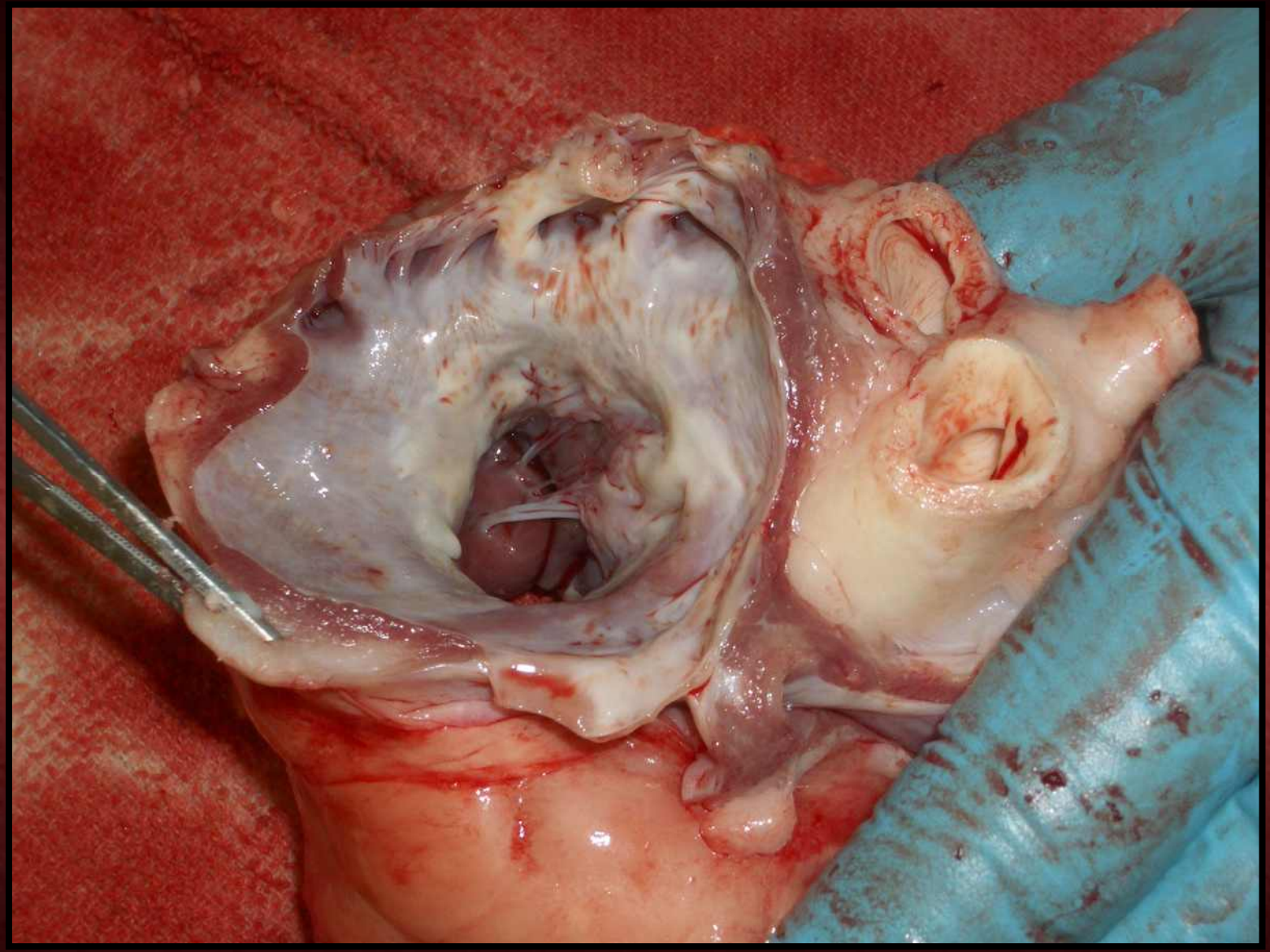

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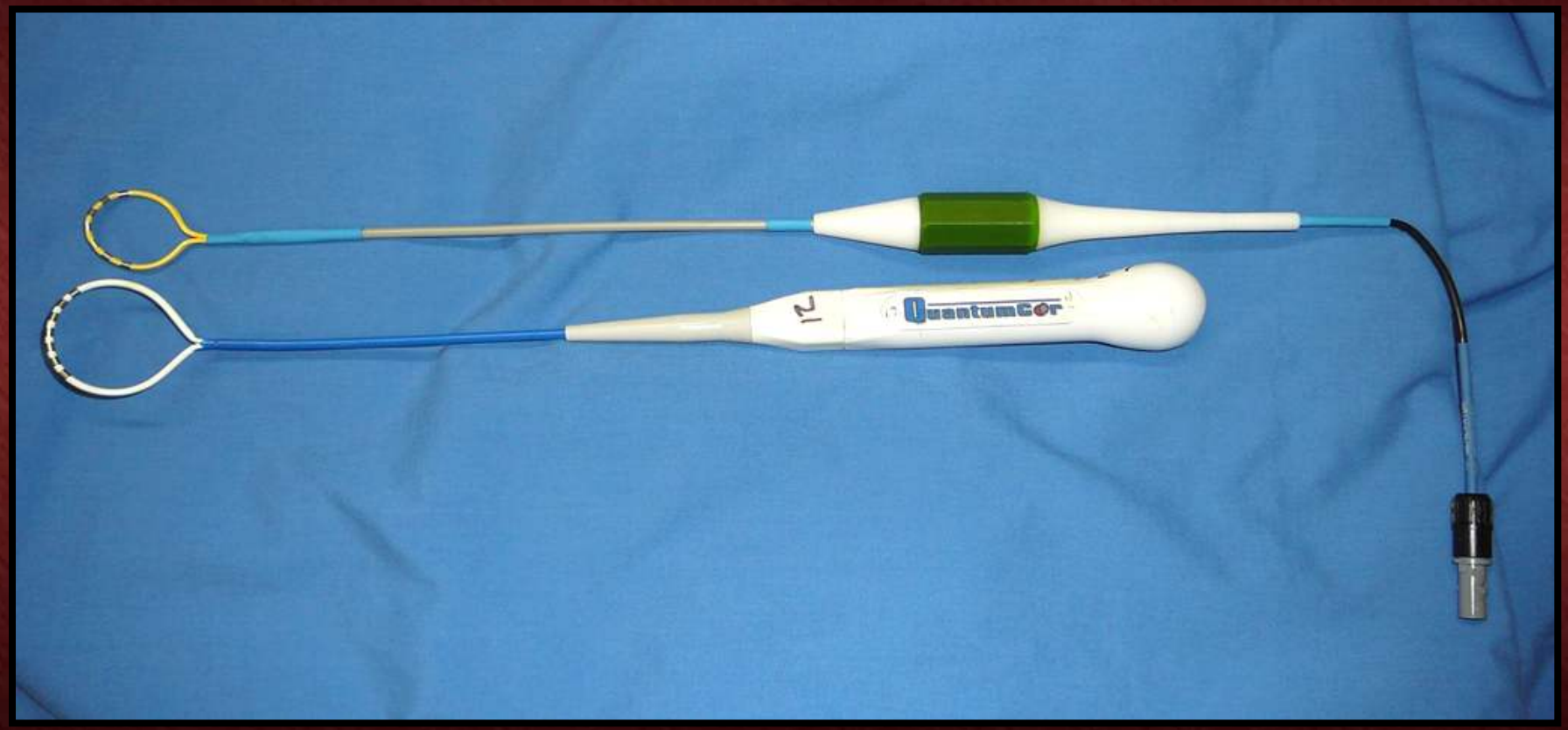
Acute Histopathology Results

- *No damage to the valve leaflets.*
- *No damage to the coronary sinus.*
- *No damage to the coronary arteries.*

BOA-SURG Probe



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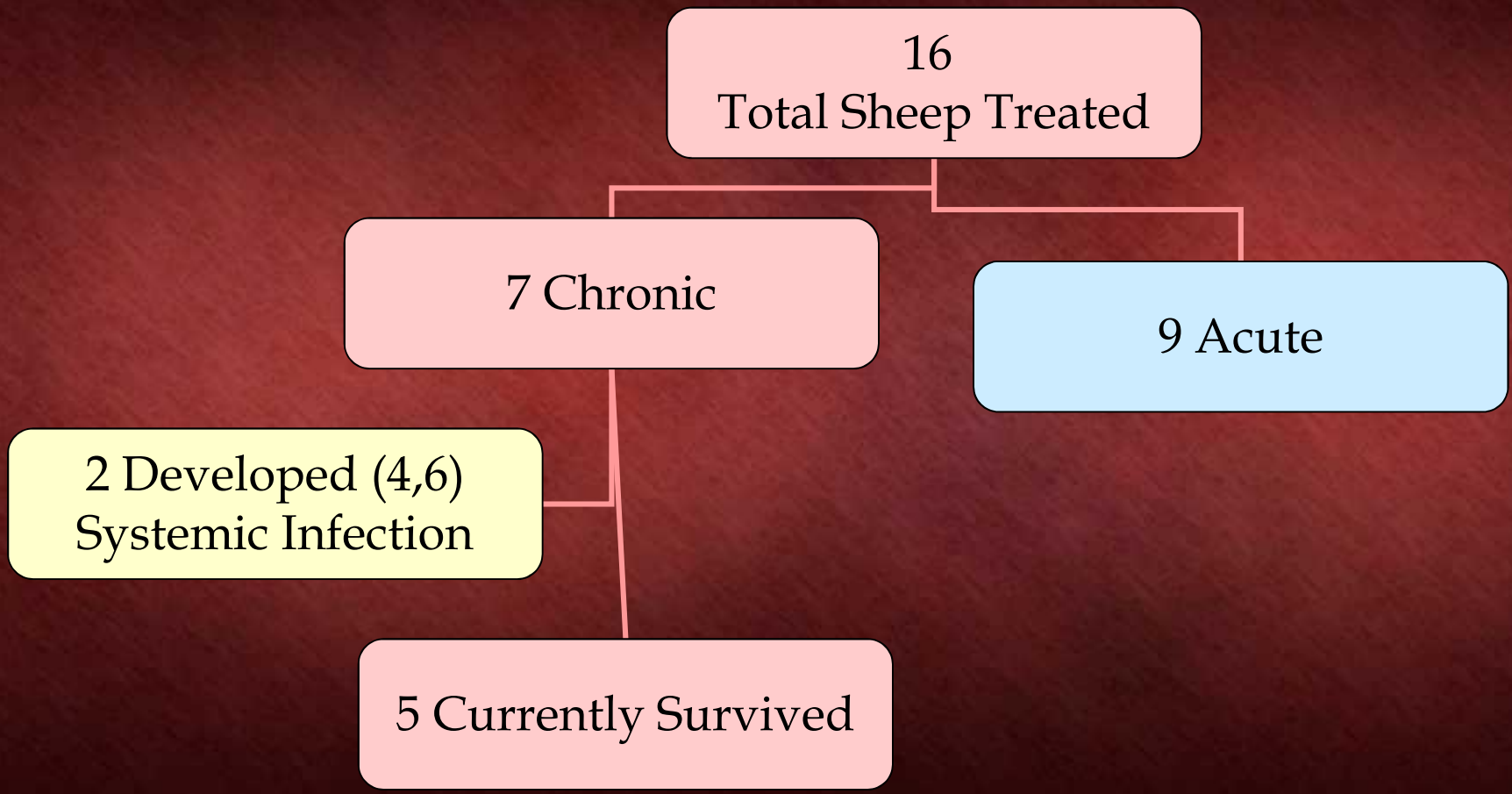
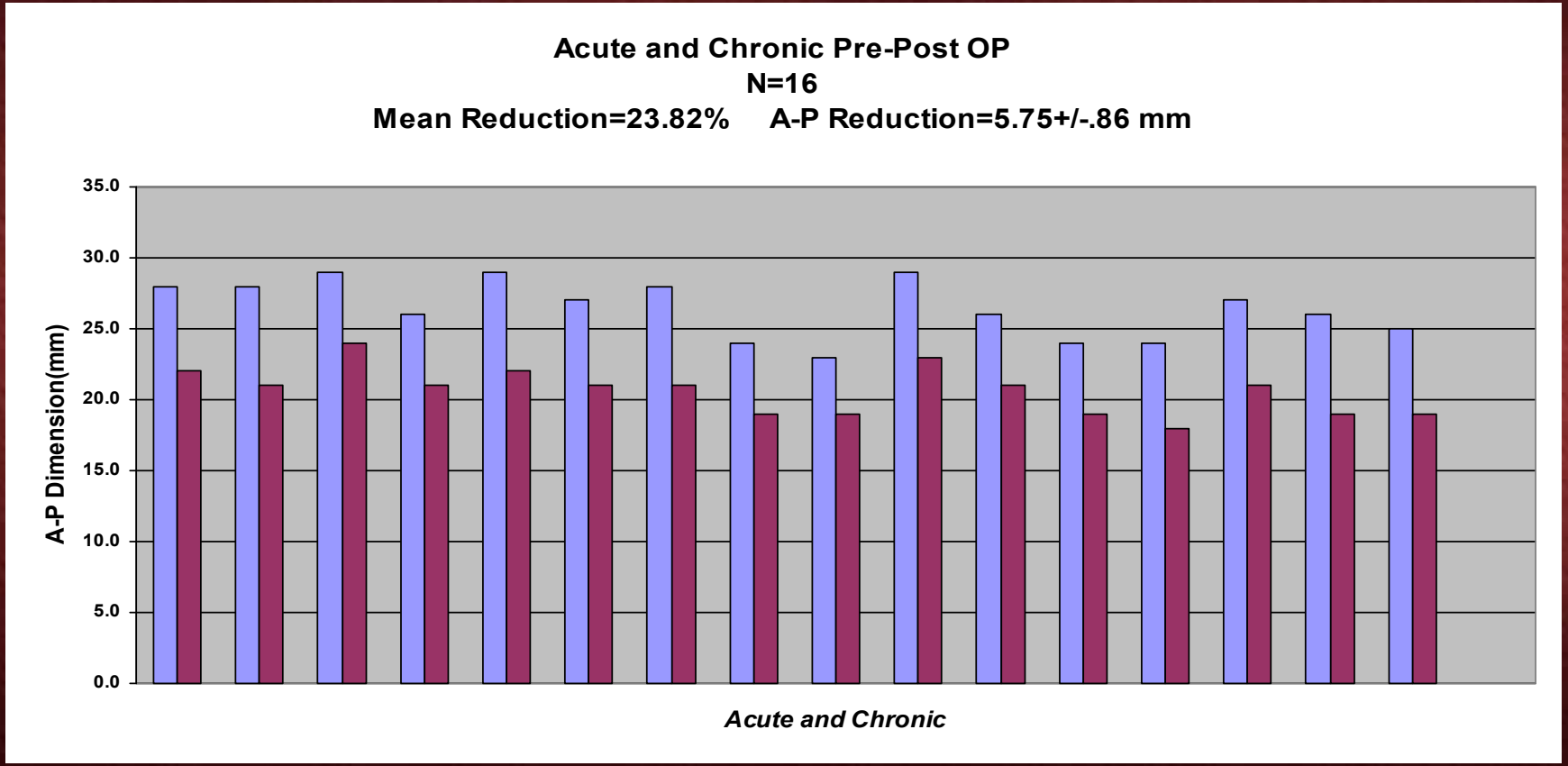
Animal Study Summary



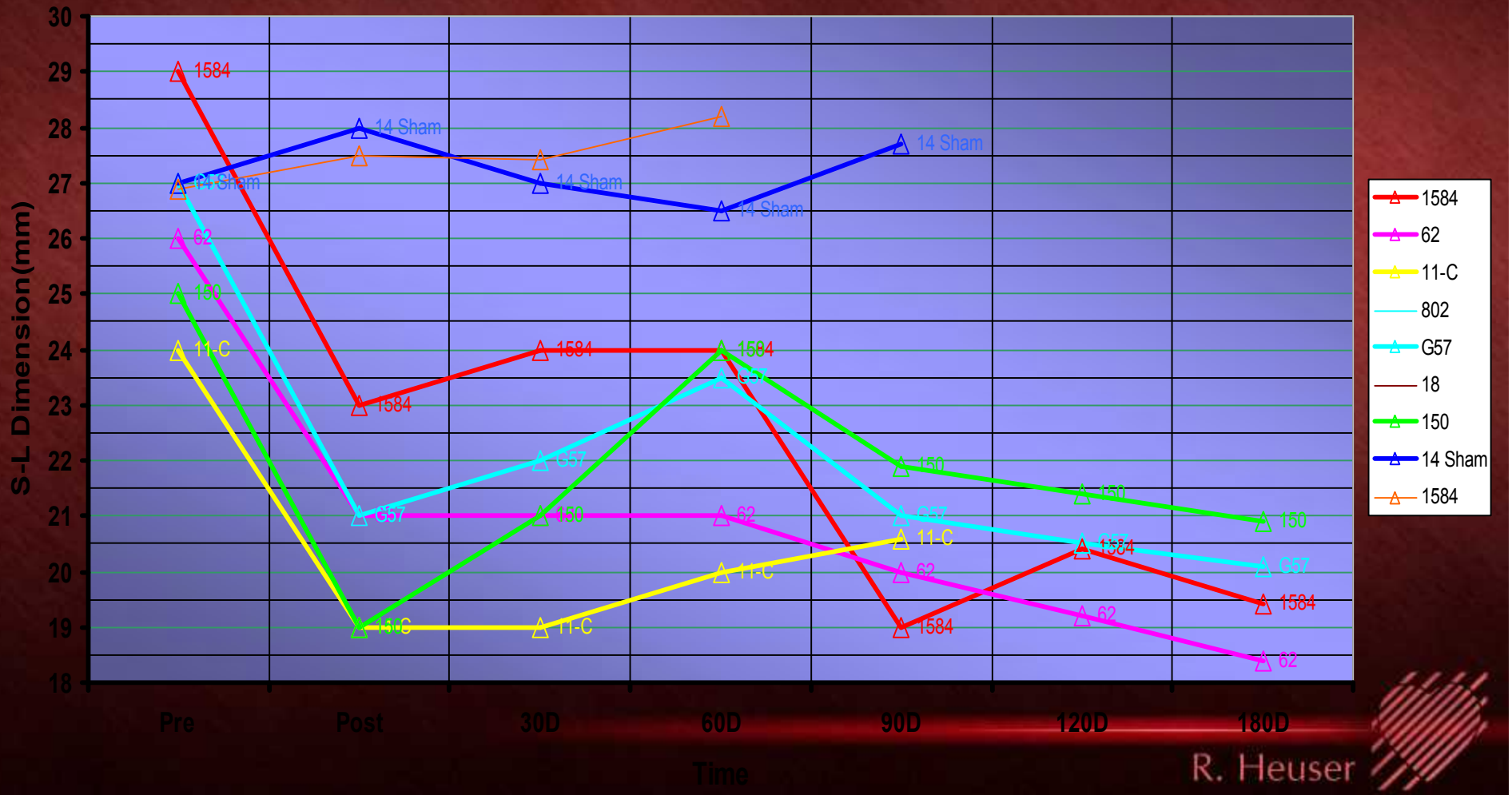
Acute Success in All Animals



RESULTS

QuantumCor

Chronic Animal Series S-L Shrinkage Durability



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180 Day Chronic Treatment Histology Summary

- *Chronic lesions did not compromise the structural integrity of the atrium or mitral leaflets.*
- *Extramural coronary arteries (Circumflex) were not involved in the thermal lesions and were microscopically normal.*

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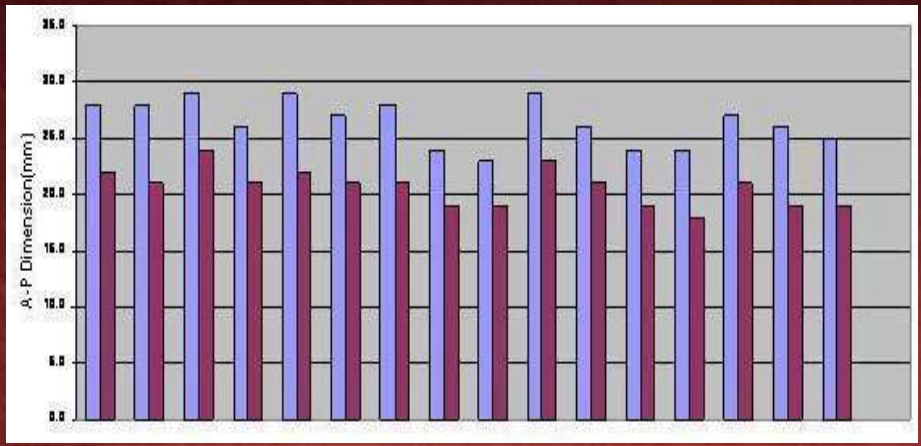
Live Animal Studies



Acute

- Remodeling successful in all animals
- Remodeling consistent with clinical and surgical expectations
- Average remodeling 21.7%

Chronic

- Remodeling maintained for six months
- Remodeling continued, at six months averaged 26.4%

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Collagen Differences Across Species And Across Humans

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Ovine Closely Packed Bundles

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Human Sheets Or Very Large Bundles

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Human Heart Project

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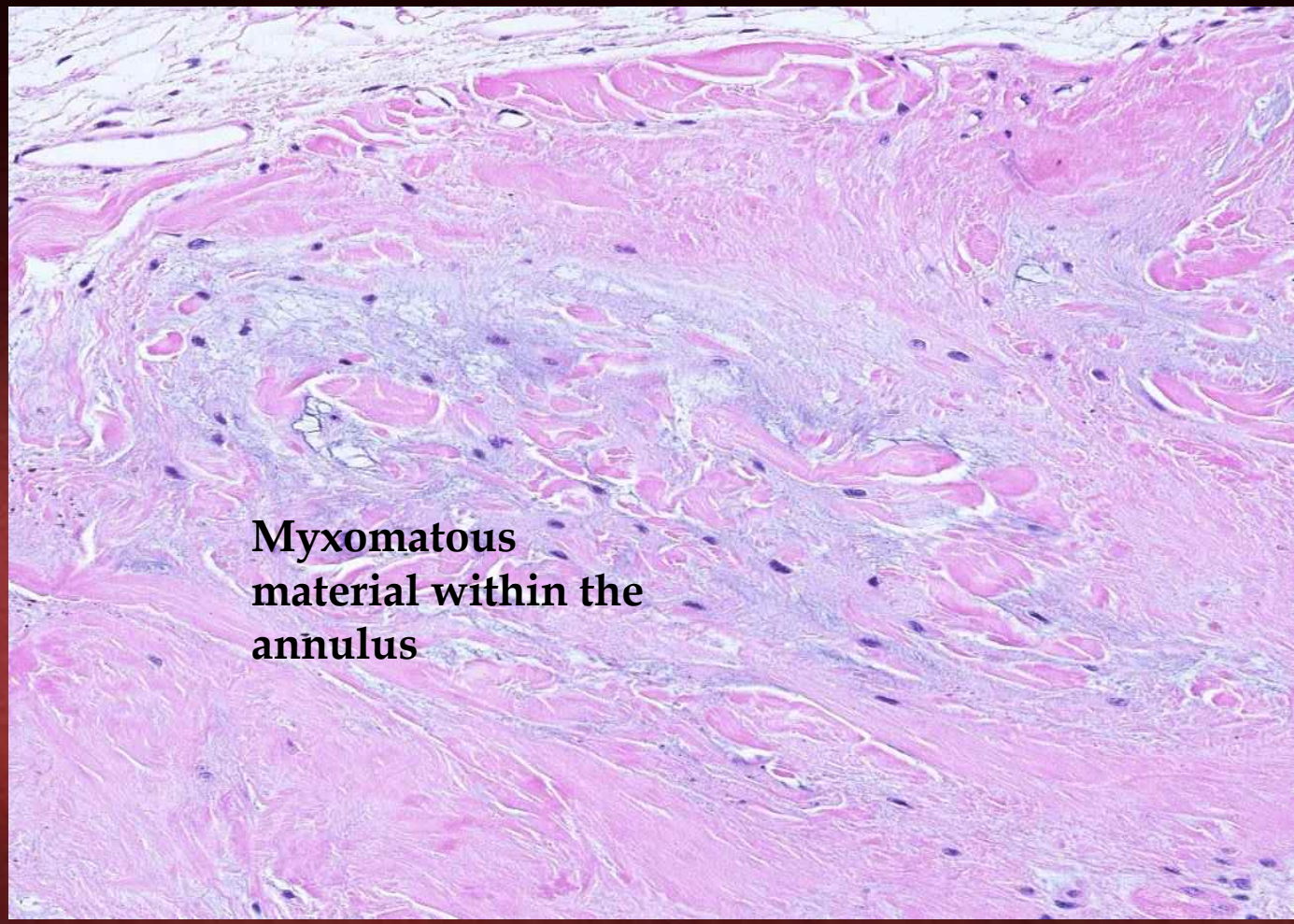

Lateral Portion of the Anterior Leaflet of the Mitral Valve – H&E Stain at 20x magnification. The annulus contains myxomatous material.

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Medial Scallop of the Posterior Leaflet of the Mitral Valve – Trichrome Stain at 10x magnification. The annulus contains small areas of calcification.

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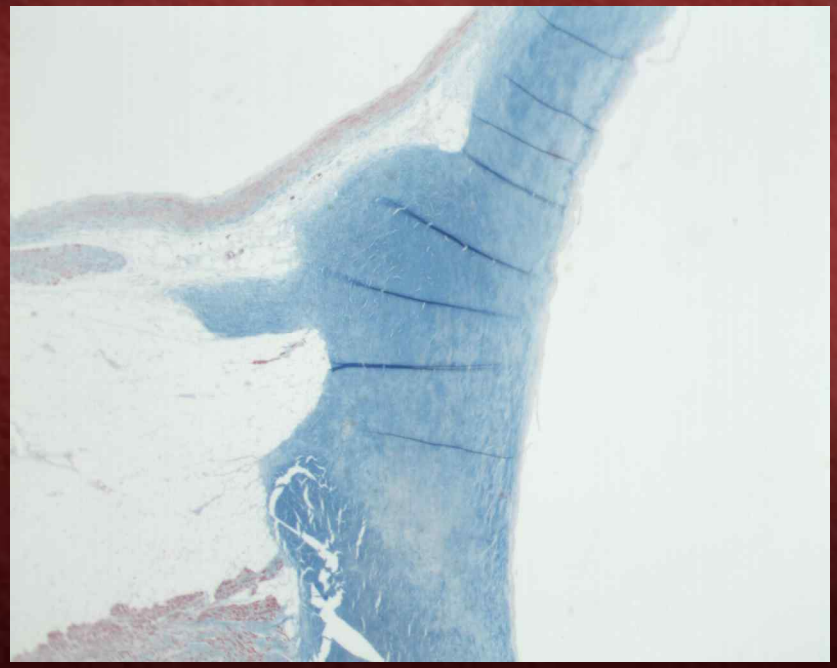
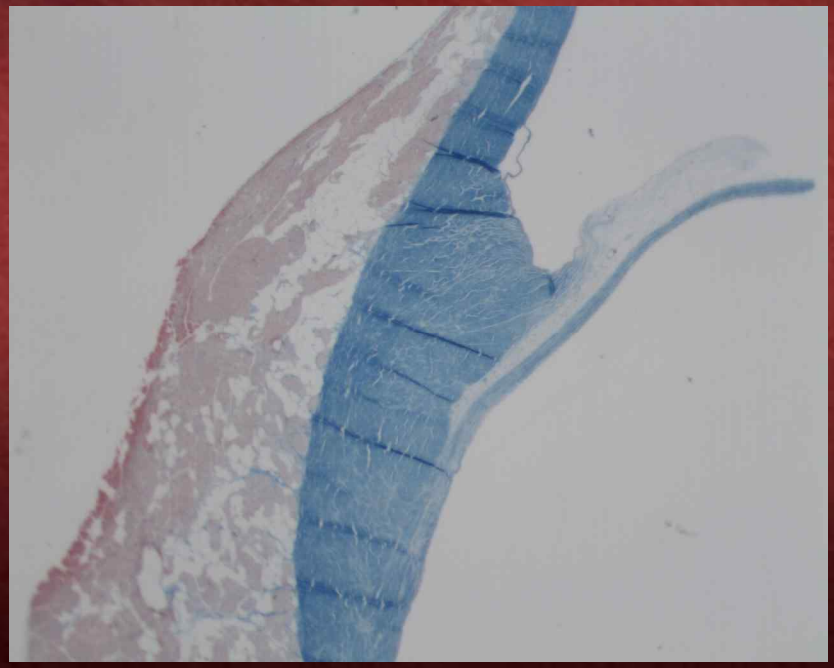
Histological Comparison of Mitral Valve Annulus: Human VS Ovine

Human Mitral Annulus X-section



Sheep Mitral Annulus X-section



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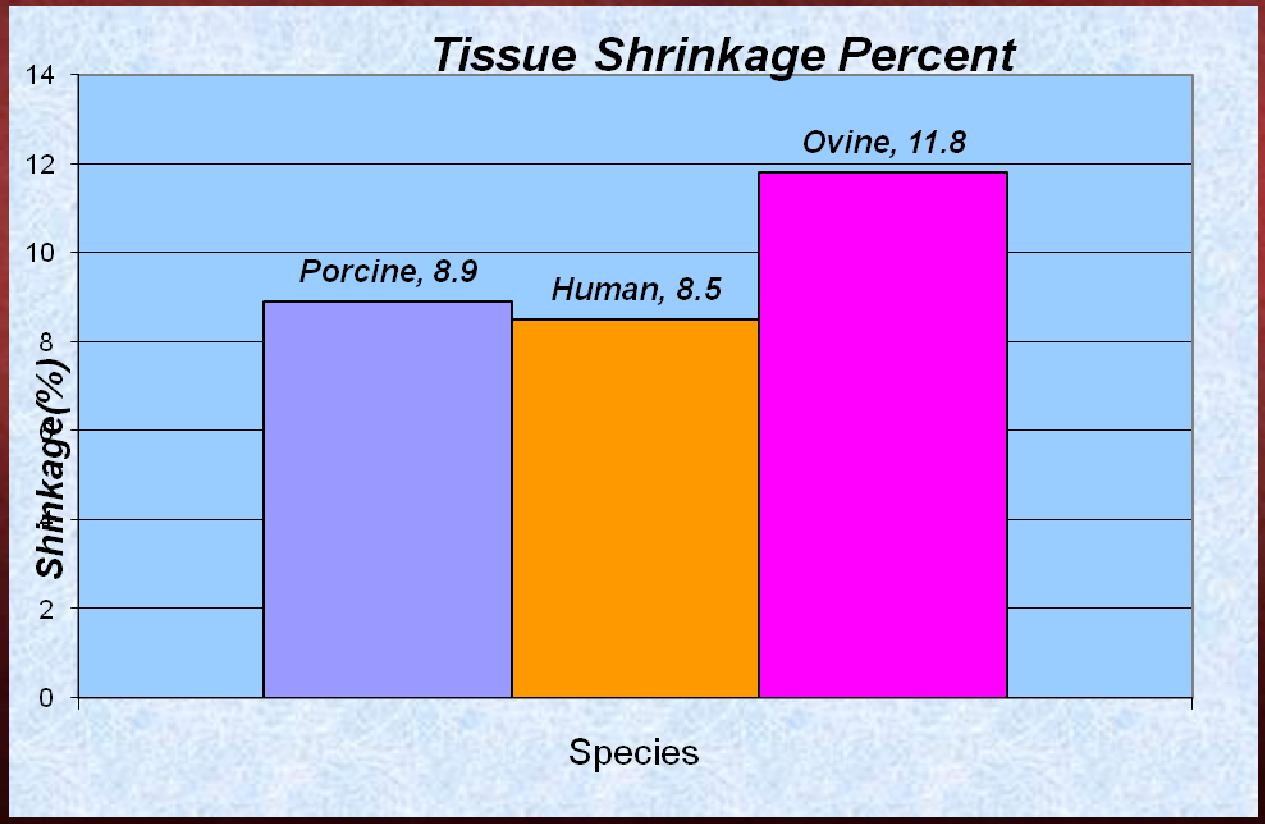
Annulus Linear Shrinkage

Porcine (In situ), Human (In situ) and Ovine (In vivo)



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Histological Comparison of MV Annulus

Human vs. Ovine

CONCLUSION:

- *Overall structure of the mitral valve annulus of human and Ovine sections are comparable.*
- *Both the annular segment and histology studies validate that the human results should be similar to what was seen in the Chronic Ovine series.*

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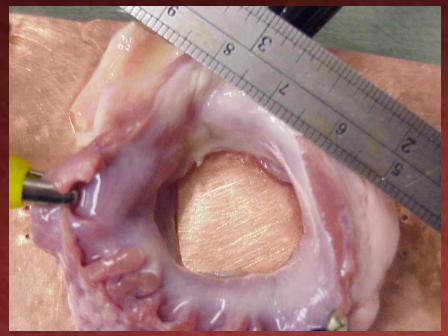
Annulus Contraction in Sheep and Pig Hearts



- *Annuluses treated circumferentially*
- *Temperatures set at 65 ℃*
- *Image analysis used to compute changes in dimensions*

1

Area 11%
Perimeter 6%

2

Area 17%
Perimeter 10%

3

Area 21%
Perimeter 12%

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The RF Approach to Treating Mitral Regurgitation: The QuantumCor System

A Repeatable Less Invasive Option May Be Desirable.

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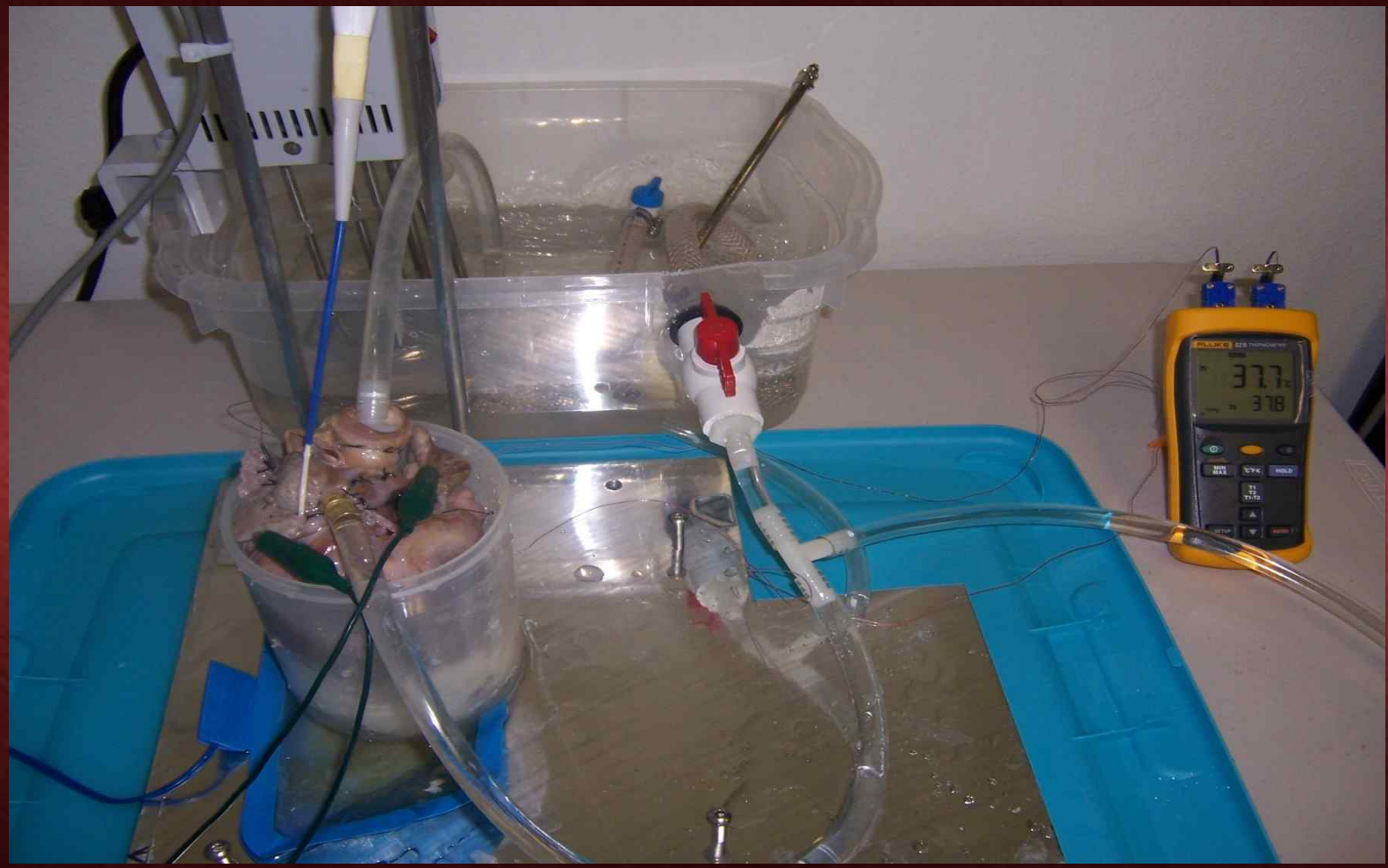
Bench Studies



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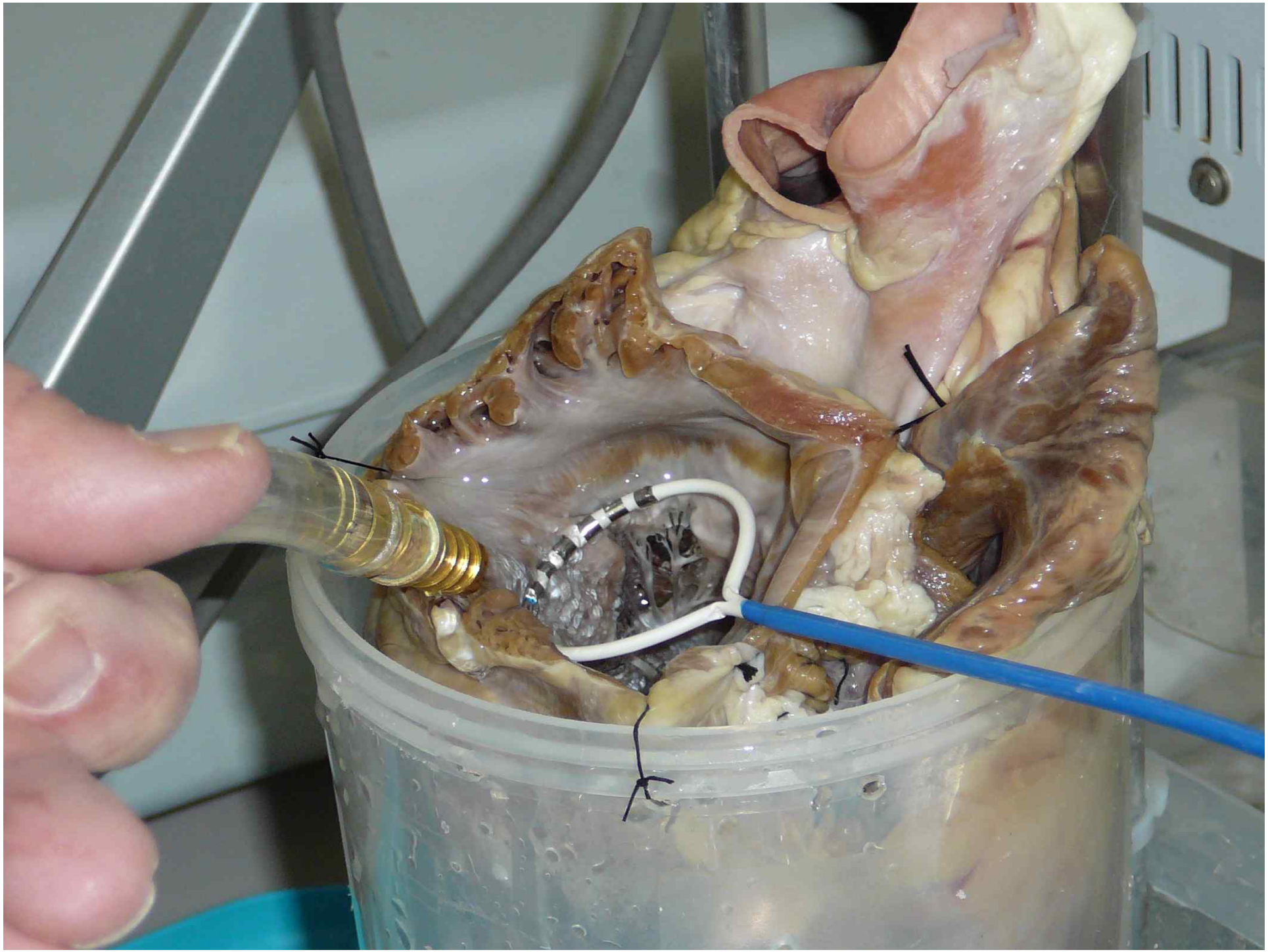

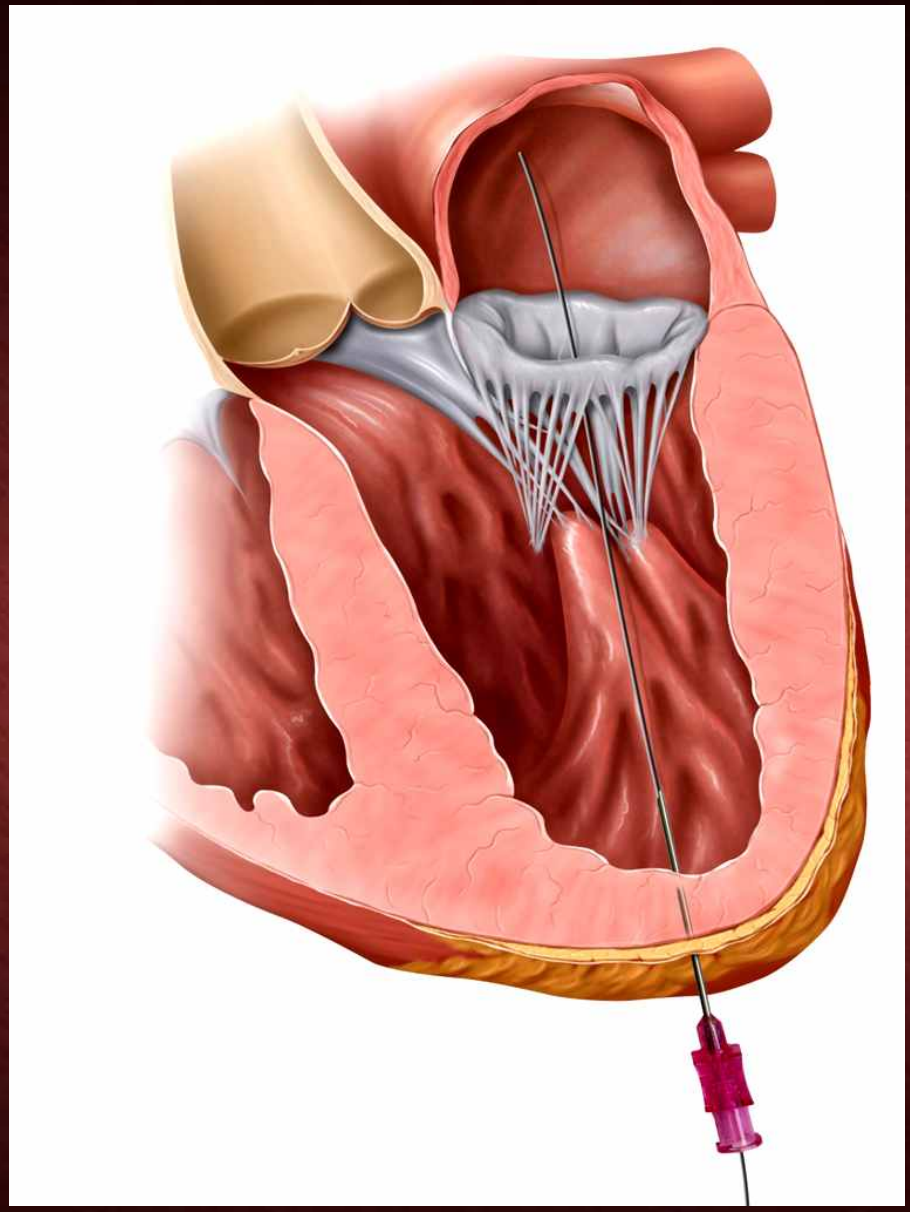

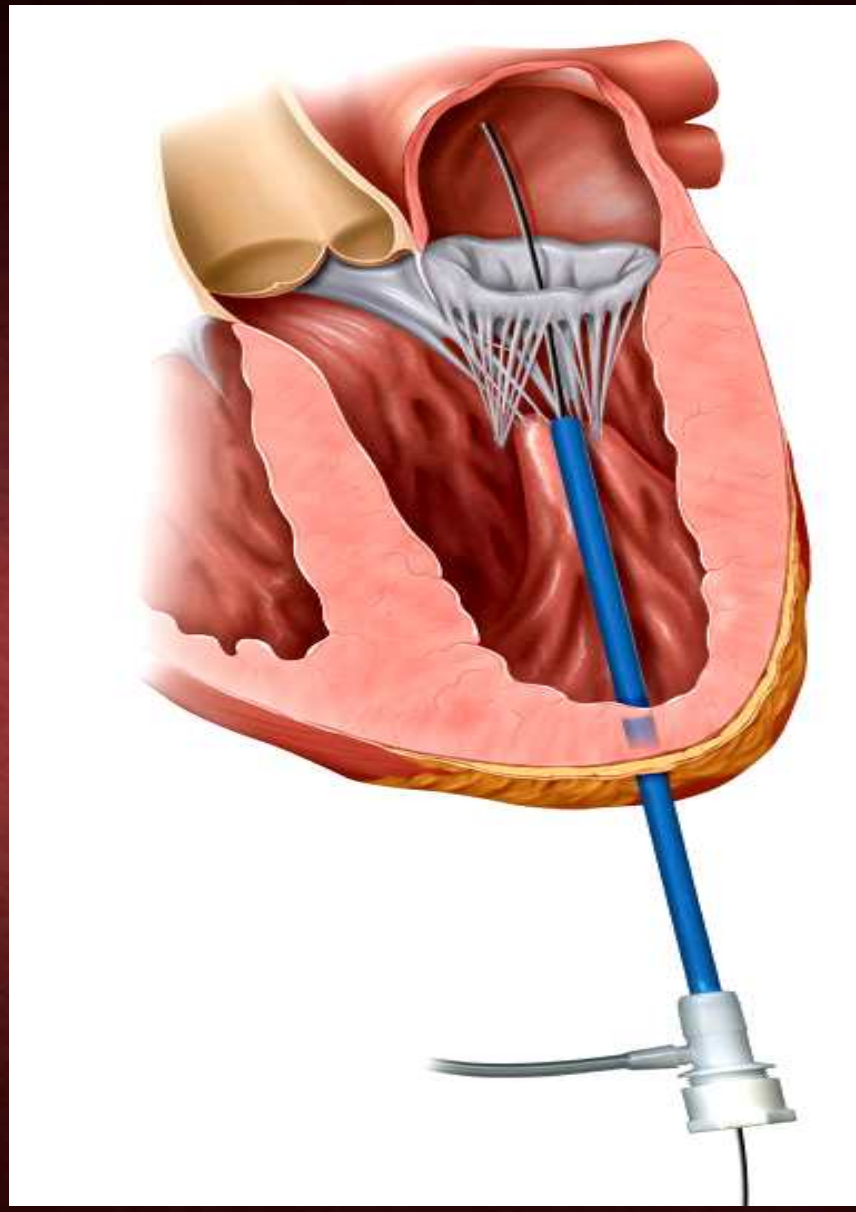

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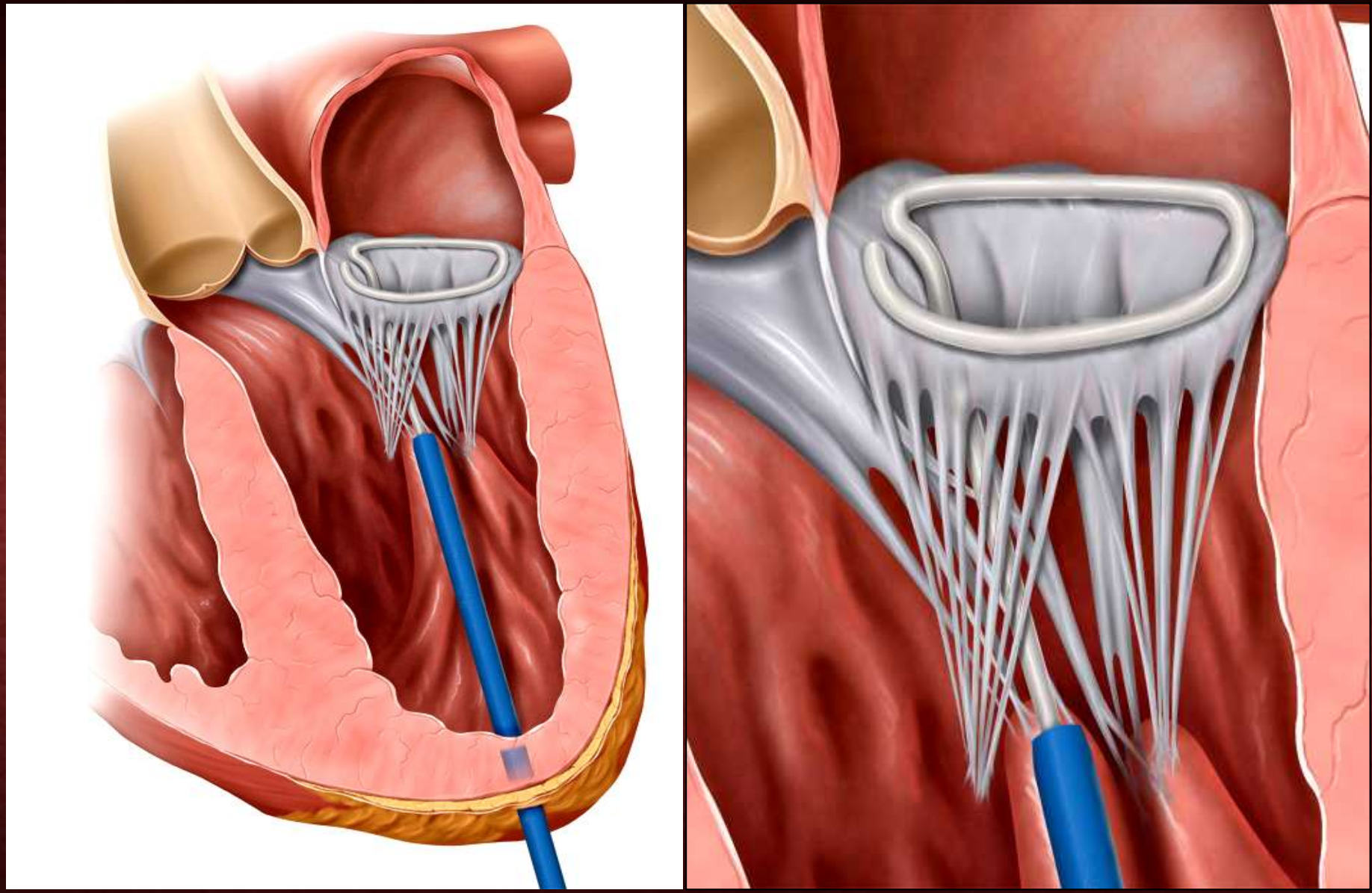
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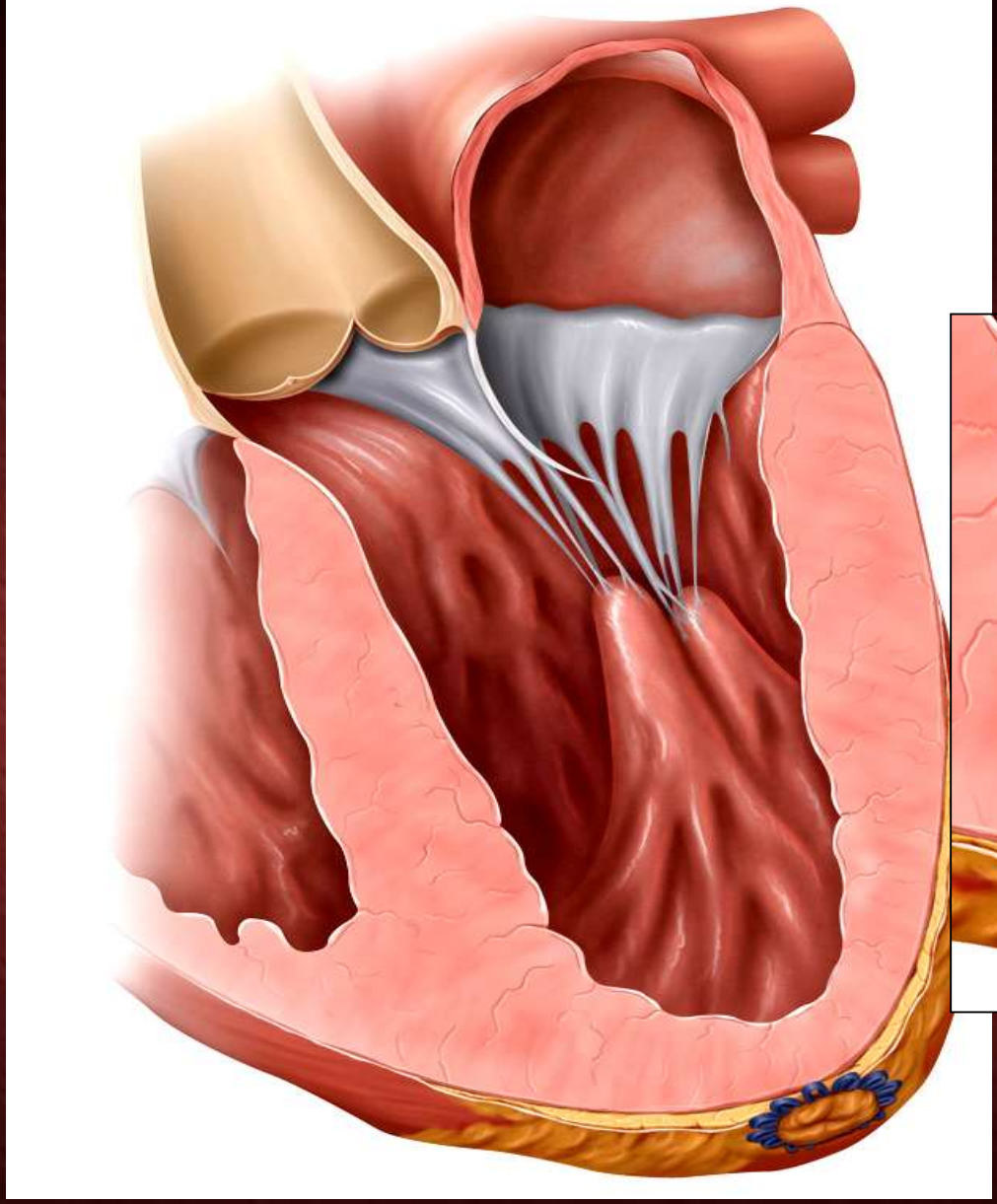
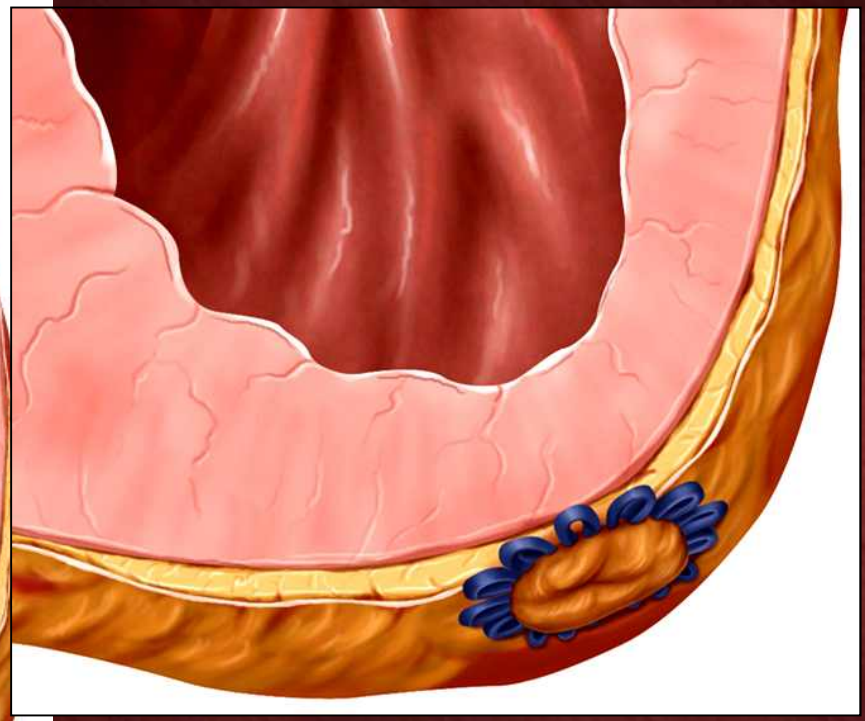
Starclose





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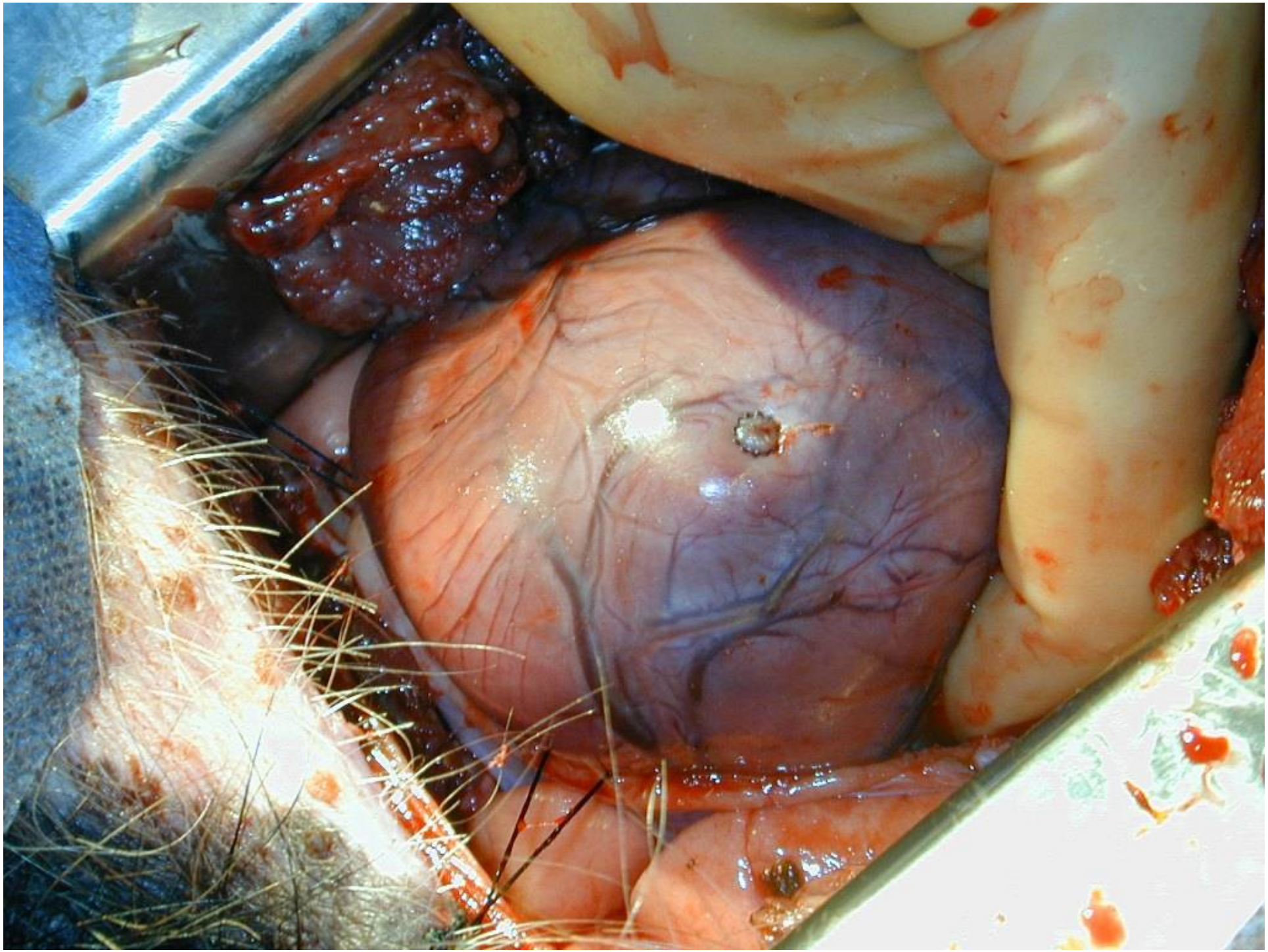

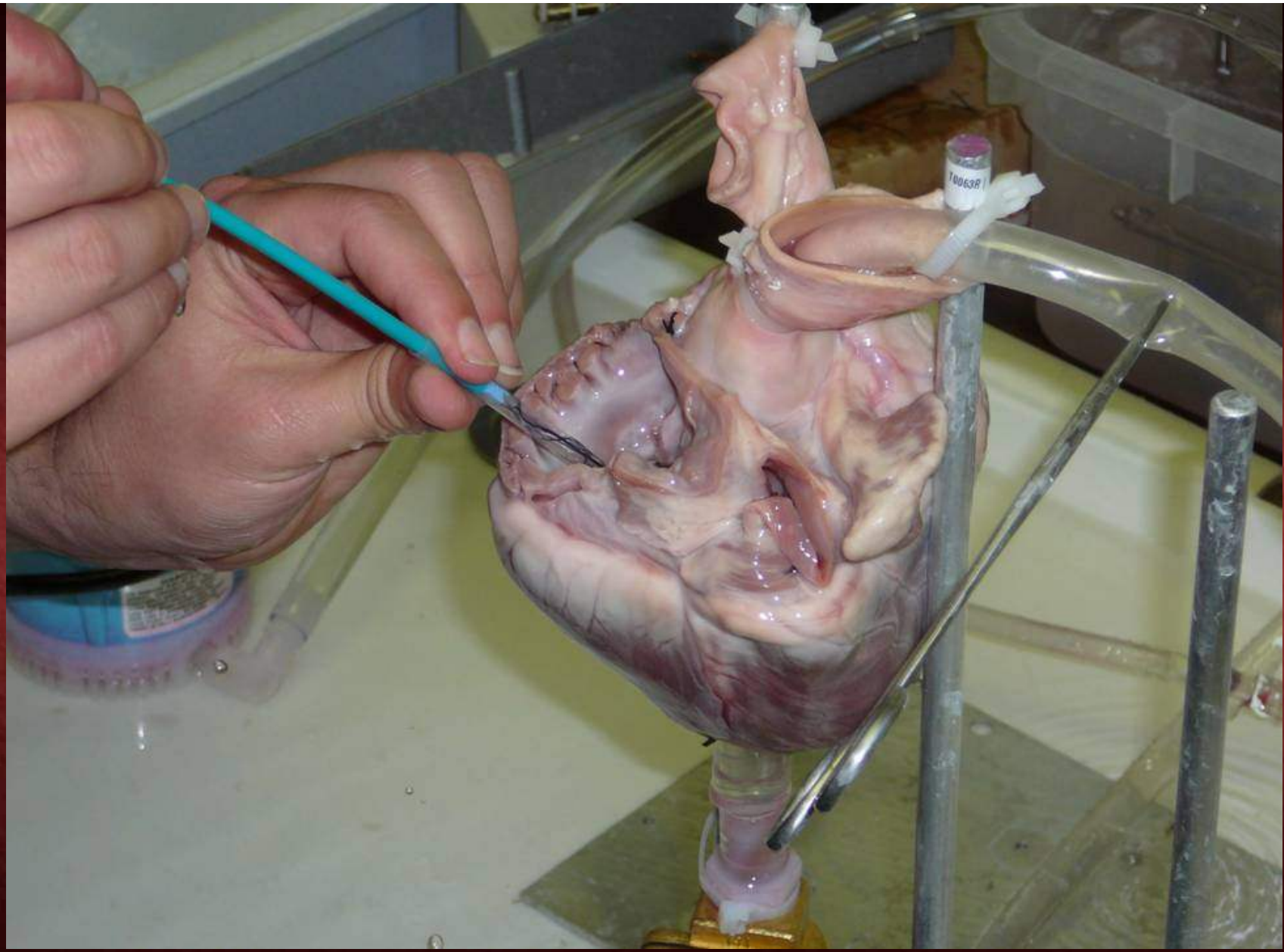

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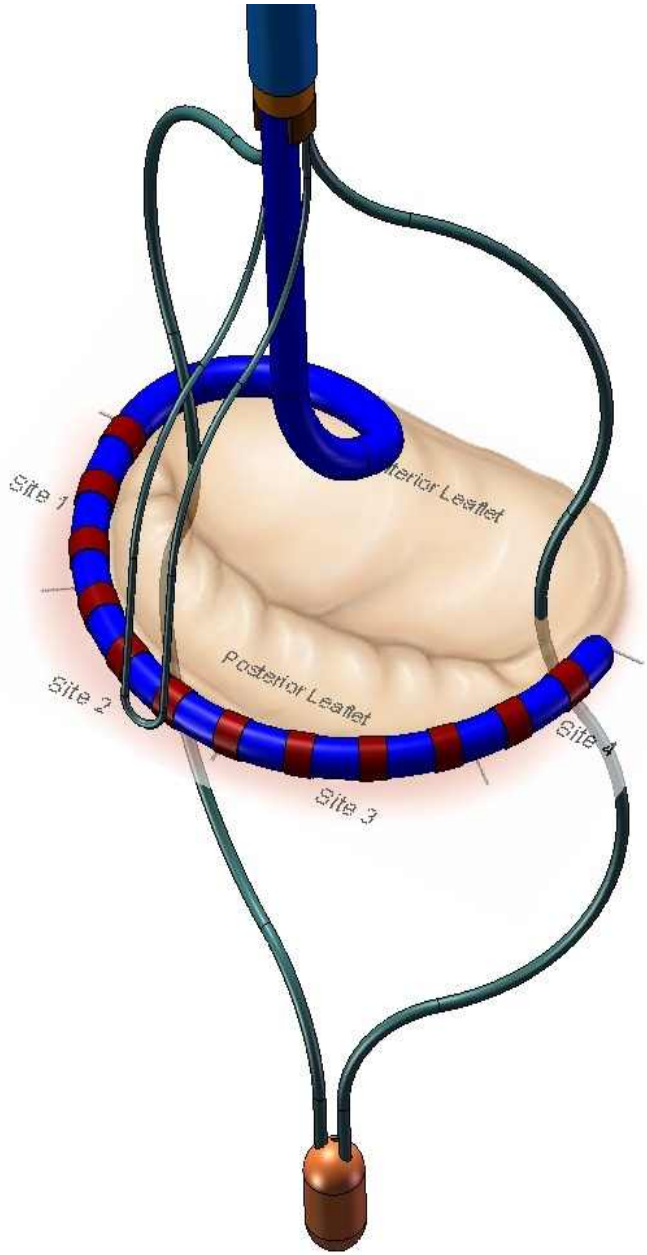

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The QuantumCor Device May Offer An Option For Some Patients With Mitral Regurgitation

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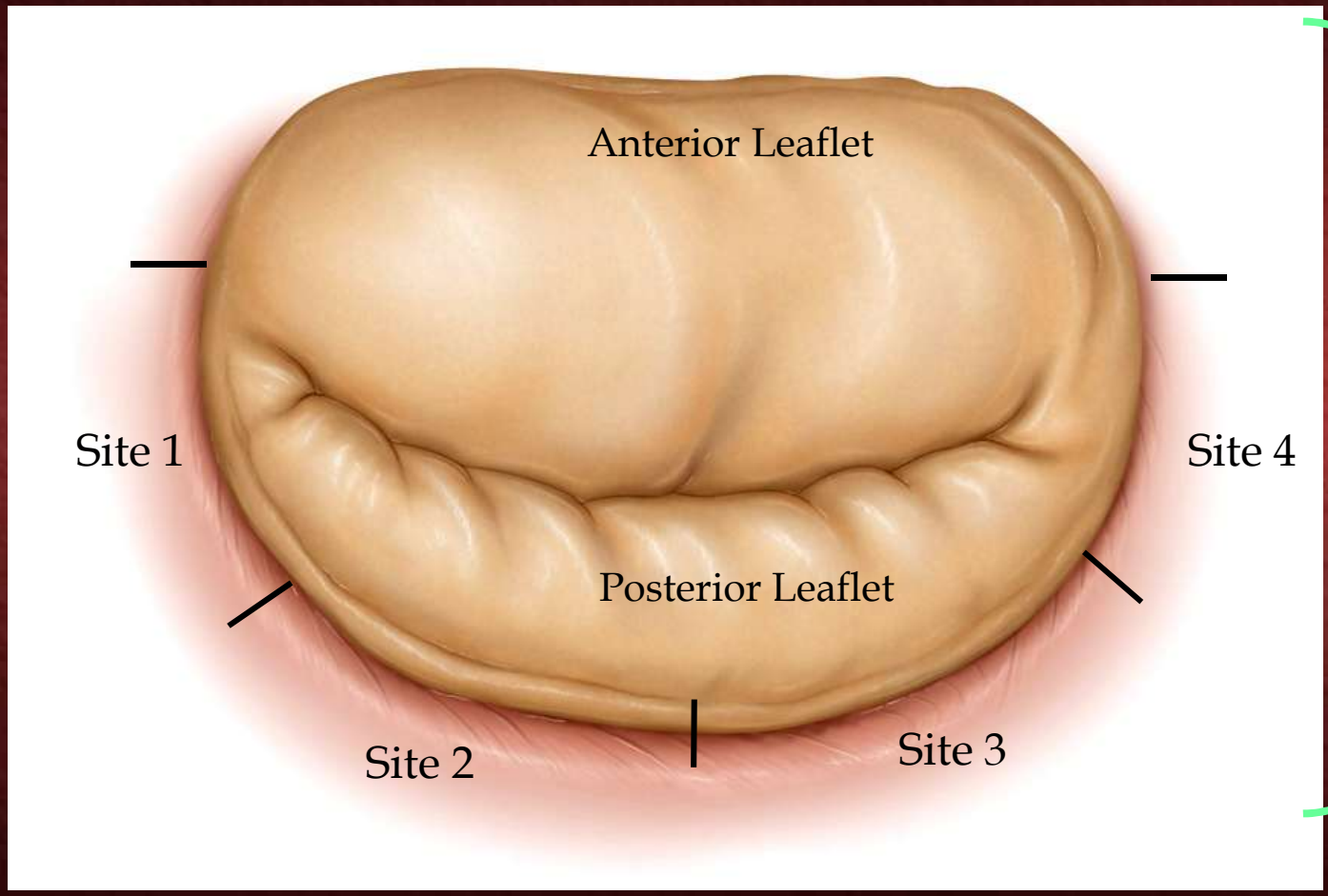
Mitral Annulus Treatment Sites



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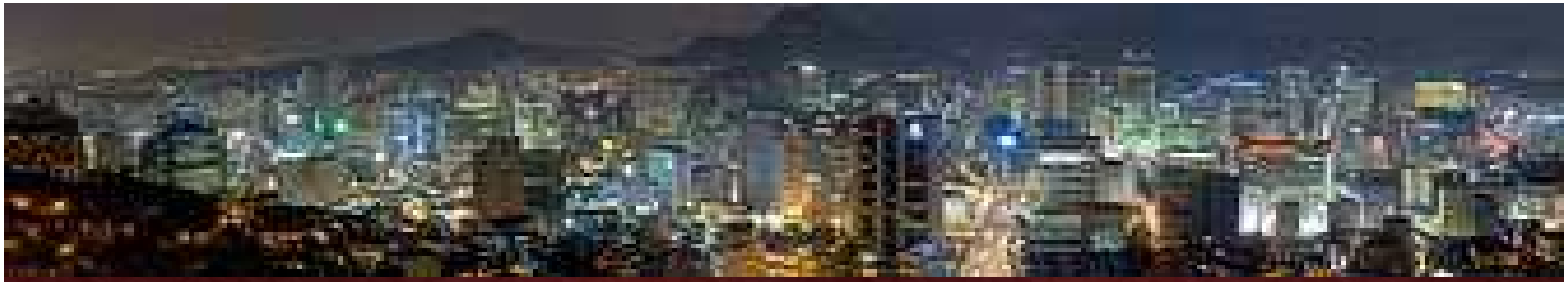

1ST IN THE OPERATING ROOM

Eventually As A Percutaneous Treatment For Mitral Regurgitation That Could Be Performed With Standard EP RF Consol In The Catheterization Laboratory

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Percutaneous Mitral Valve in the Future

Treatment will need to be:

- Direct valve approach;
- Annular approach;
- Repeatable;
- Cannot preclude future mitral valve repair

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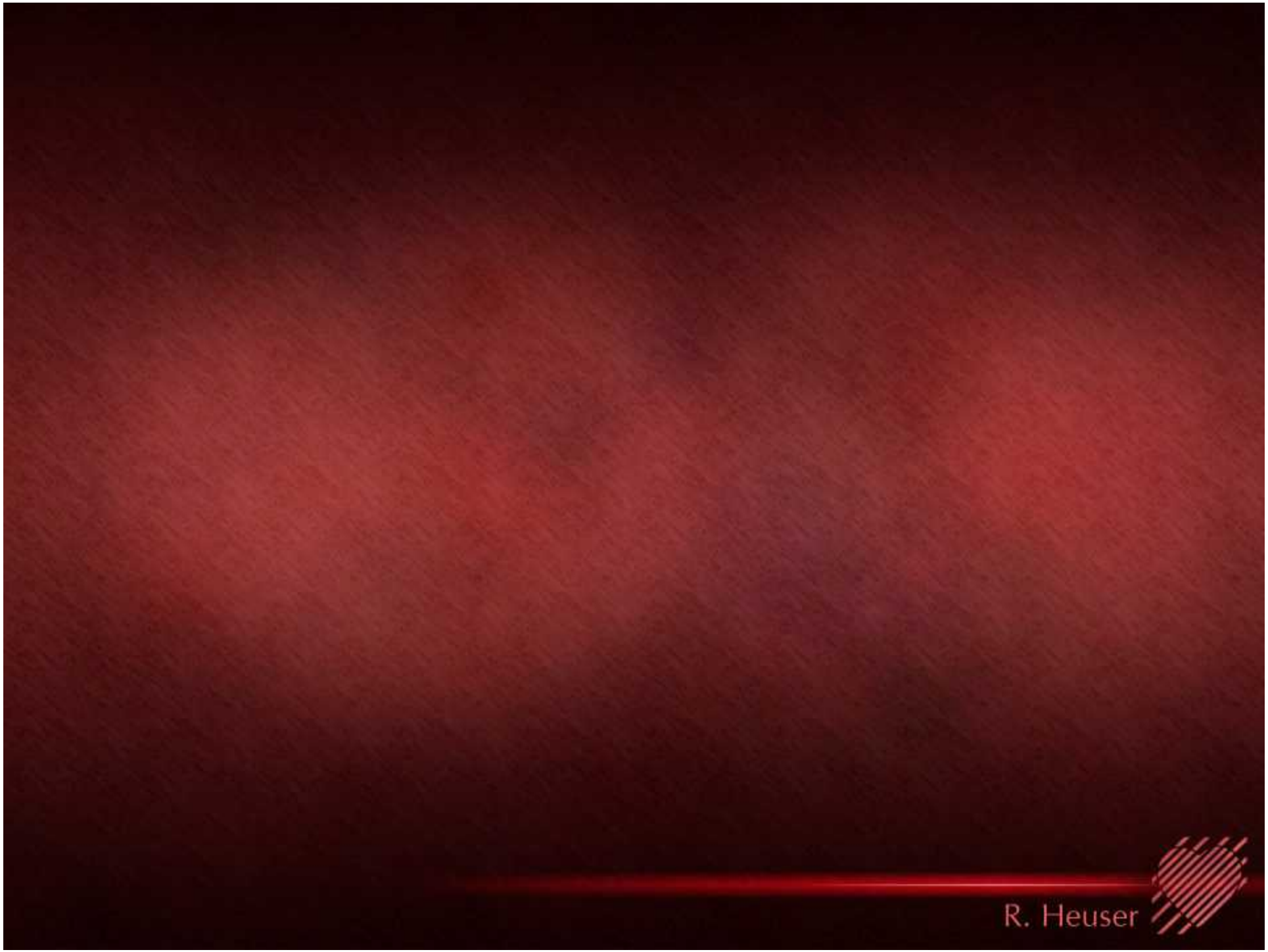
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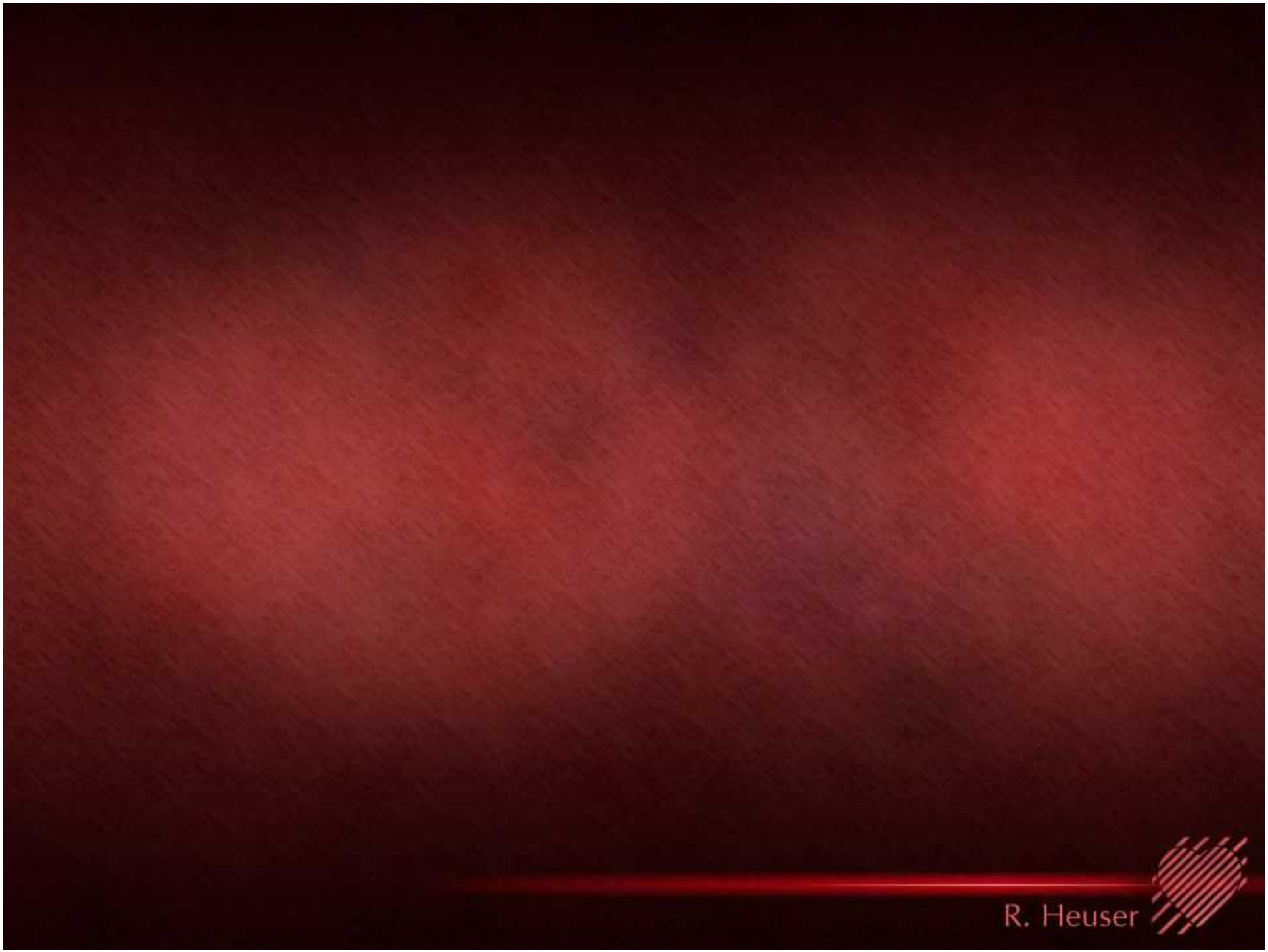
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Product Evolution

Surgical Device

- *Surgical market limited and not expanding*
- *Surgeons slow to change practice patterns*
- *Institutional investors will not fund a surgical device*

Percutaneous Device

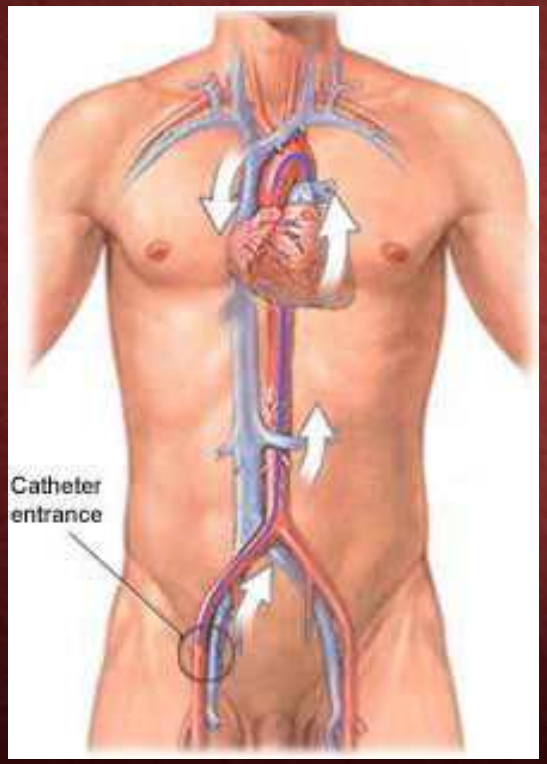
- *Percutaneous Mitral Valve Repair (PMVR) market potential is huge*
- *Interventional Cardiology eagerly waiting for PMVR devices*
- *Minimally invasive structural heart repair (including PMVR) is the new "hot area"*

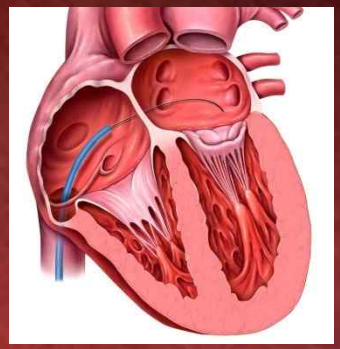
Direct Annuloplasty with QuantumCor: Device Evolution, Technique, and First-in-Man Results

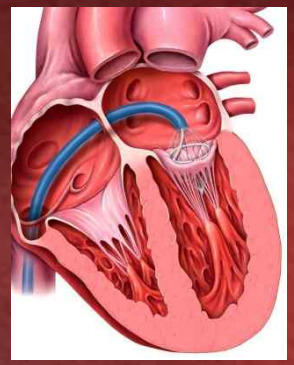
RICHARD R. HEUSER, MD, FACC, FACP, FESC, FASCI
Director Of Cardiology, St. Luke's Medical Center, Phoenix, Arizona
Clinical Professor of Medicine Univ. of Arizona, College of Medicine, Tucson, Arizona

QuantumCor -- Procedure

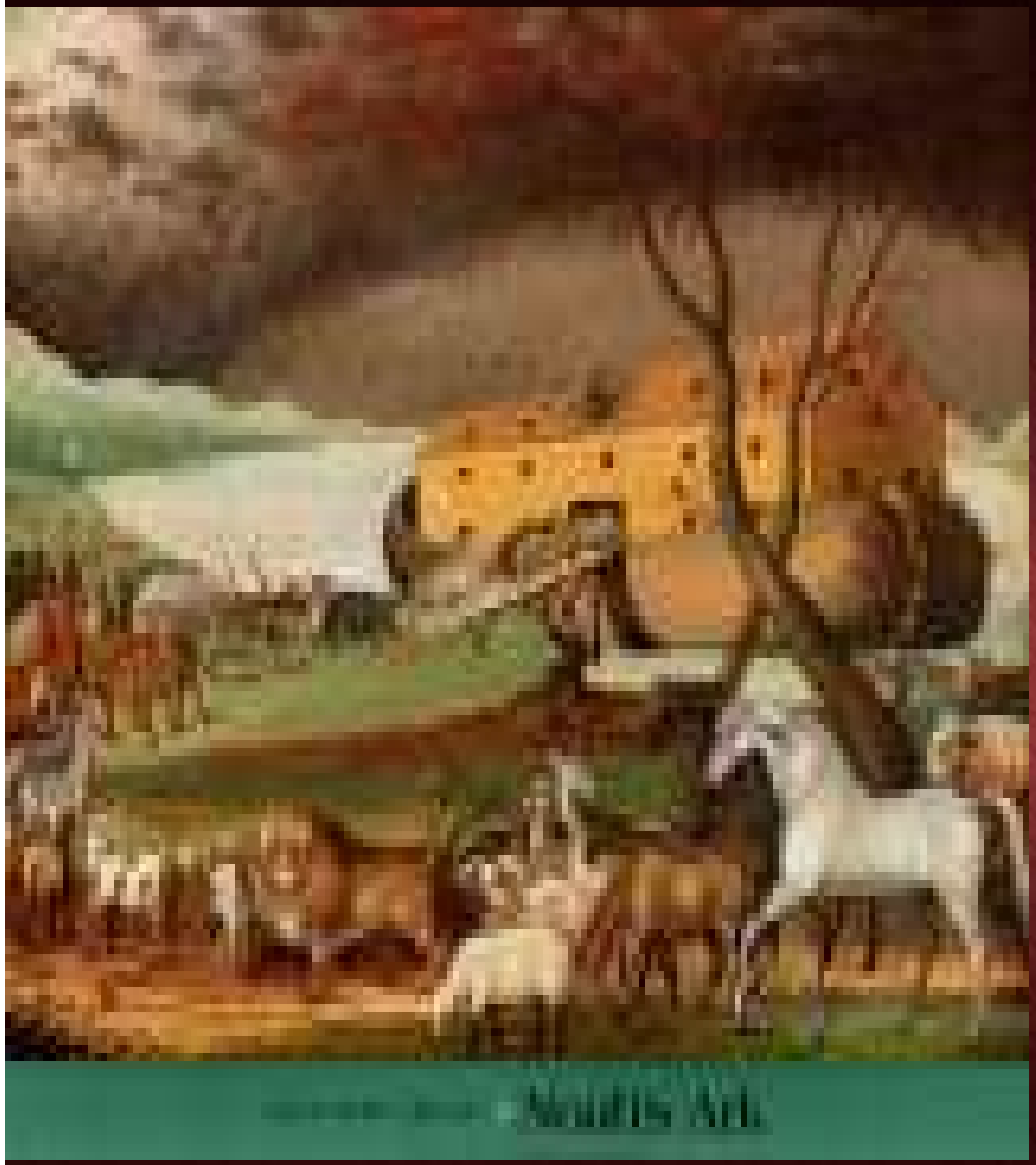
Percutaneous Mitral Valve Repair







- *Catheter device positioned*
- *RF energy applied to valve annulus*
- *Collagen shrinkage (remodeling) is immediate*
- *Verify remodeling using ICE and color flow doppler*
- *Send the patient home*



CROSS SPECIES PROJECT

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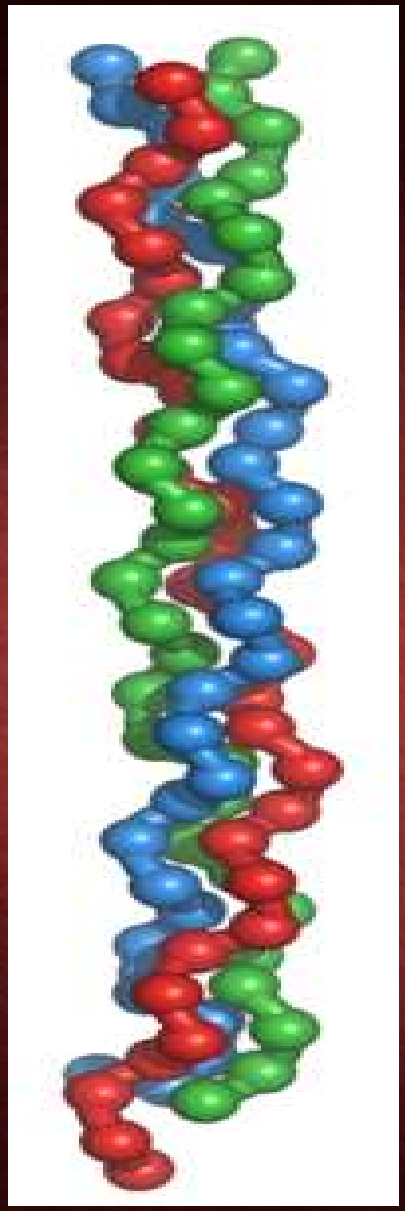

Everything You Wanted To Know About Collagen, But You Were Afraid To Ask

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Percutaneous Mitral Valve Repair

- *Obvious Strategy for PMVR is to combine direct valvular procedure with a percutaneous annuloplasty technique*
- *Mimics what is done surgically*

RESULTS

Percutaneous Treatment for Mitral Regurgitation

TOO EARLY TO TELL

- *With RF Energy Applied To The Mitral Annulus It May Be Possible To Treat A Larger Population Of Patients With Mitral Regurgitation.*
- *If You Don't Succeed You Can Repeat The Procedure.*
- *Treat Without Affecting The Coronary Sinus.*
- *Use In Conjunction With Leaflet Procedures.*

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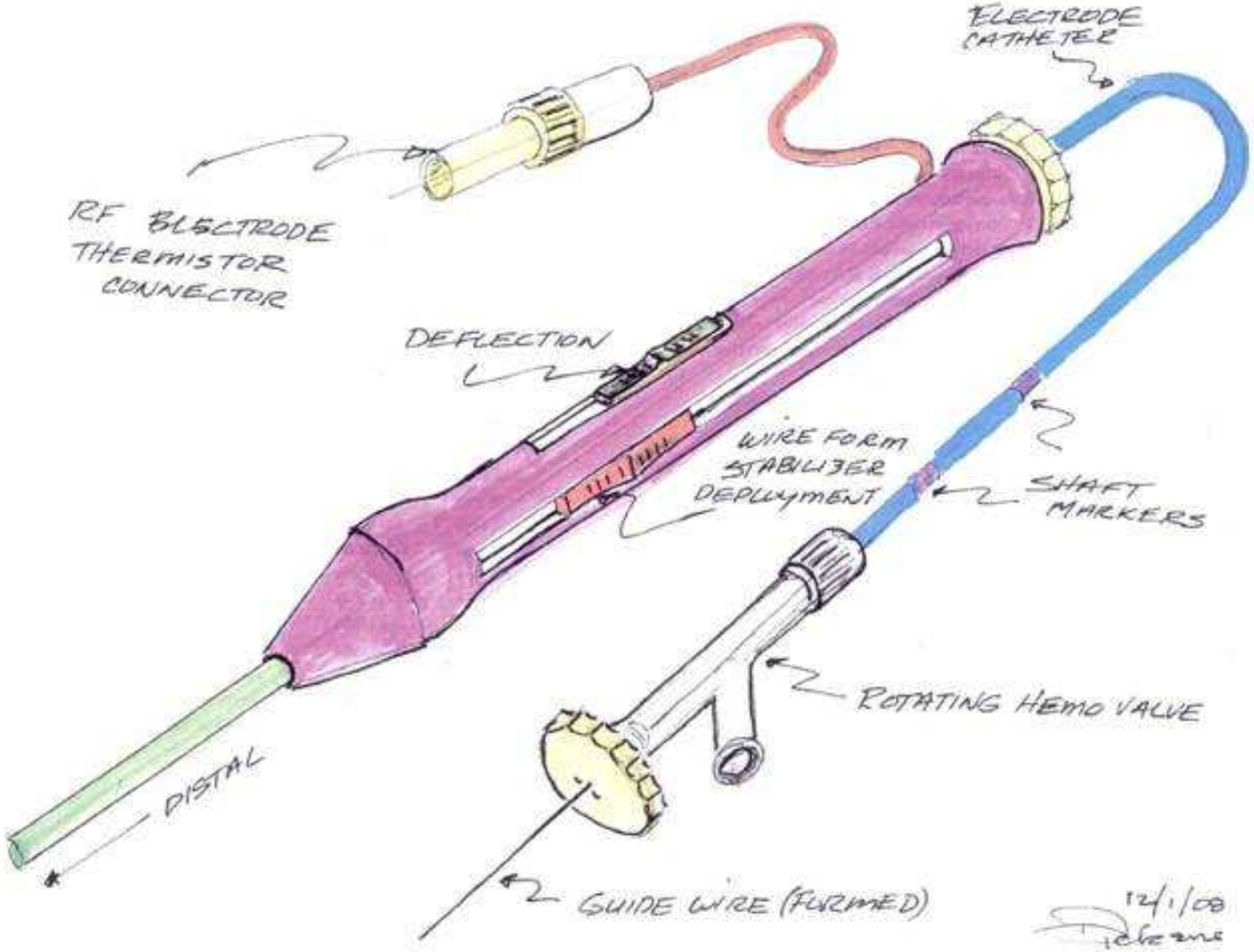
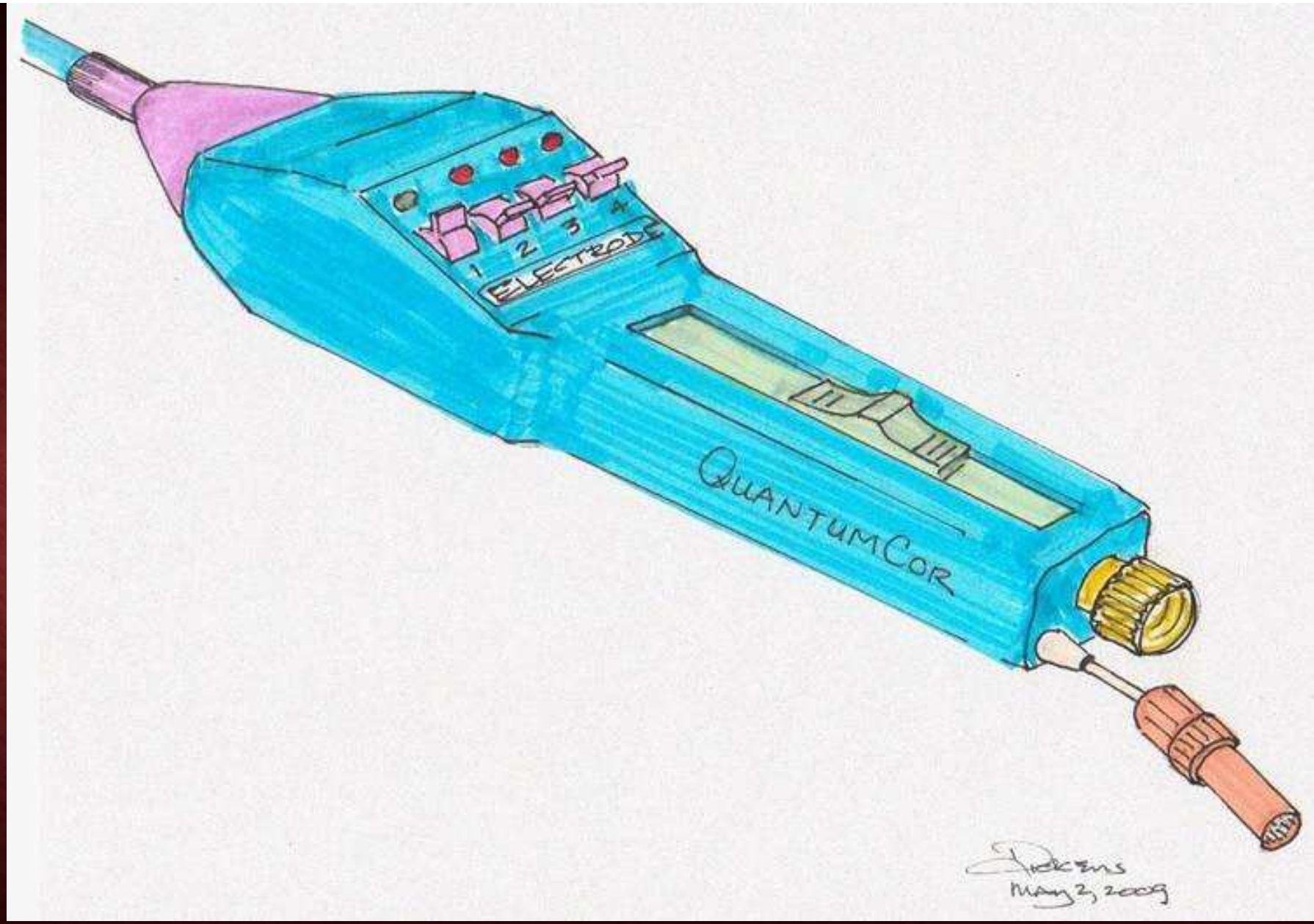
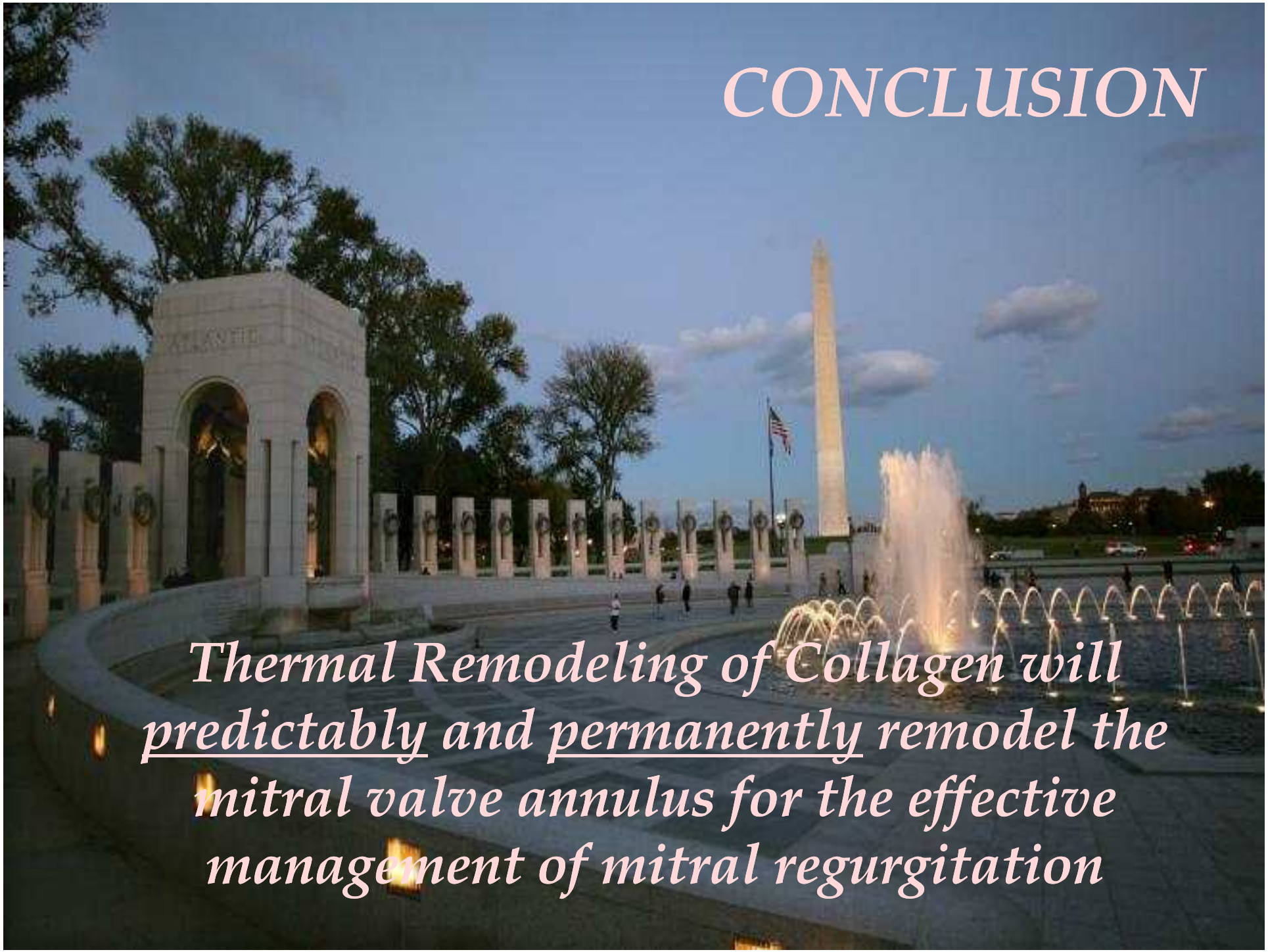

ELECTRODE CATHETER
RF ELECTRODE THERMISTOR CONNECTOR
DEFLECTION
WIRE FORM STABILIZER DEPLOYMENT
SHAFT MARKERS
ROTATING HEMO VALVE
DISTAL
GUIDE WIRE (FORMED)
12/1/08


1 2 3 4
ELECTRODE
QUANTUMCOR
May 3, 2009

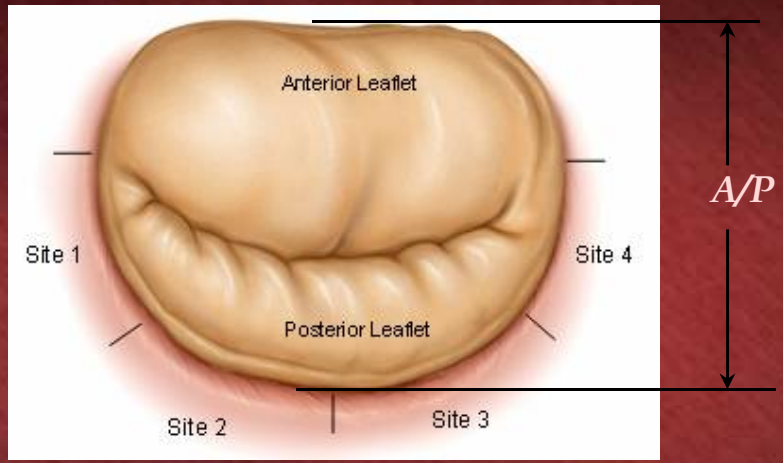


CONCLUSION

Thermal Remodeling of Collagen will predictably and permanently remodel the mitral valve annulus for the effective management of mitral regurgitation

Clinical Objective

- *Apply RF energy to sites 1,2,3,4*
  - *Shrink collagen fibers ~ 10% per site*
  - *Reduce A/P dimension ~20%*
  - *Allowing valve leaflets to close properly*



Method

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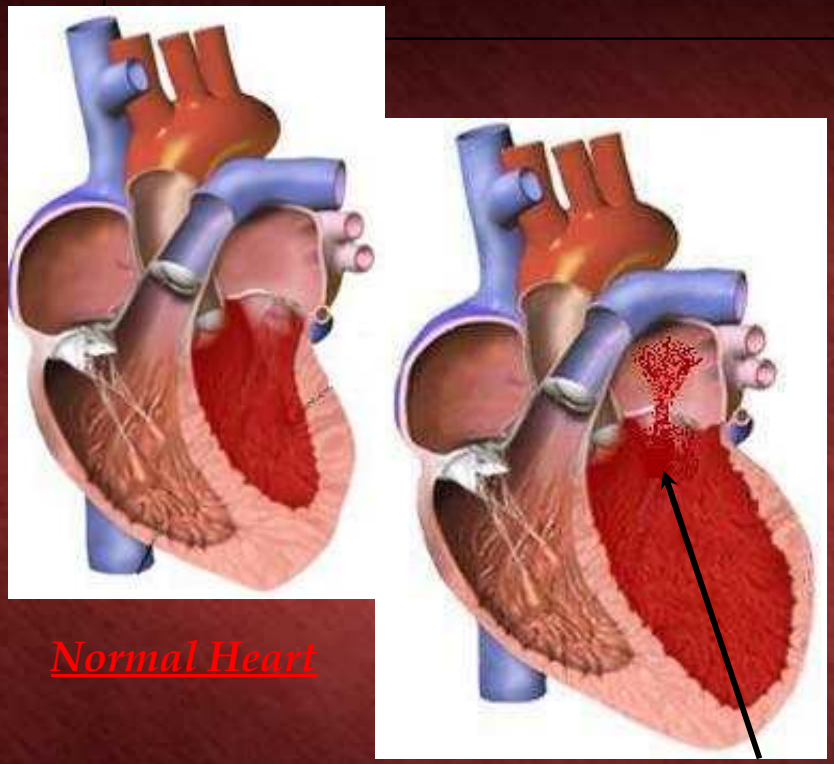
Mitral Valve Regurgitation



Normal Heart

Diseased Heart

Mitral Regurgitation

- Valve annulus stretches leaflets can't close properly
  - Blood regurgitates back into the left atrium
    - ✓ Reducing cardiac output
    - ✓ Elevating left atrial pressure
    - ✓ Compromising pulmonary function
    - ✓ Contributes to Congestive Heart Failure (CHF)

The Question

Today, less than 4% of patients suffering from mitral valve regurgitation are being treated… … ….

WHY??

Millennium Research Group 2007 Heart Valve Report

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Mission

To revolutionize mitral valve repair in the same way that angioplasty and stents revolutionized the treatment of coronary artery disease

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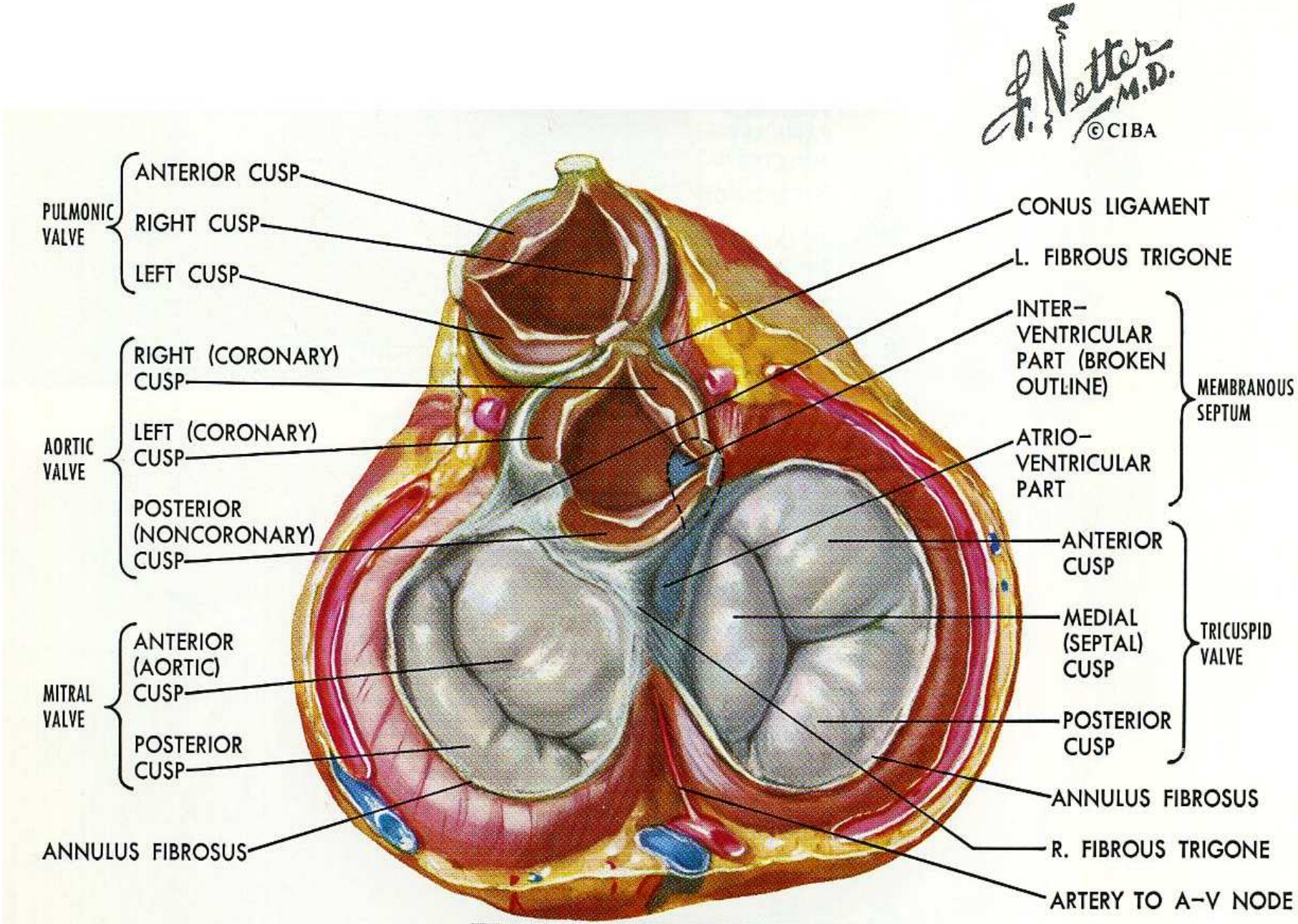
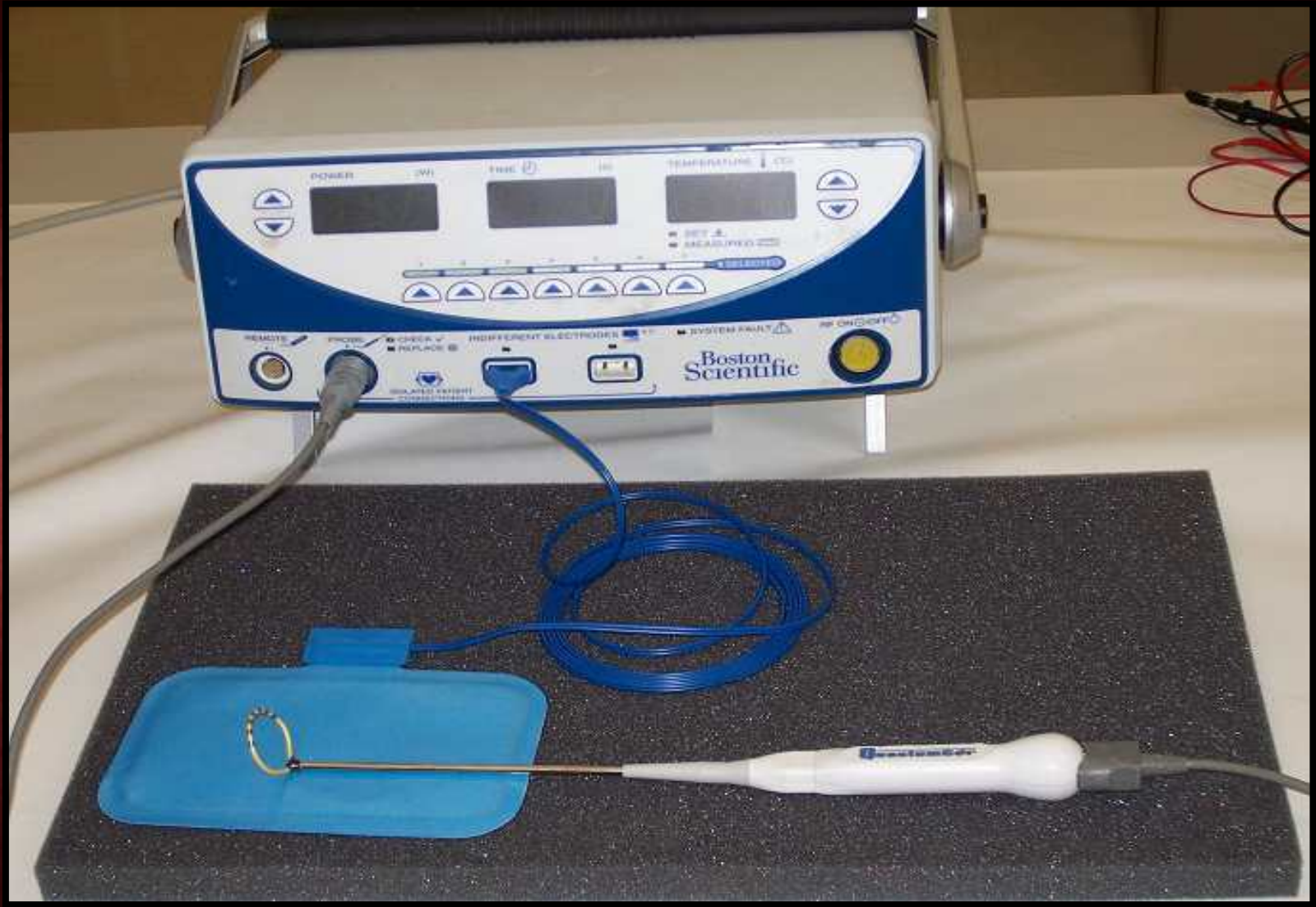


THE HEART IN SYSTOLE: VIEWED FROM BASE WITH ATRIA REMOVED

Method



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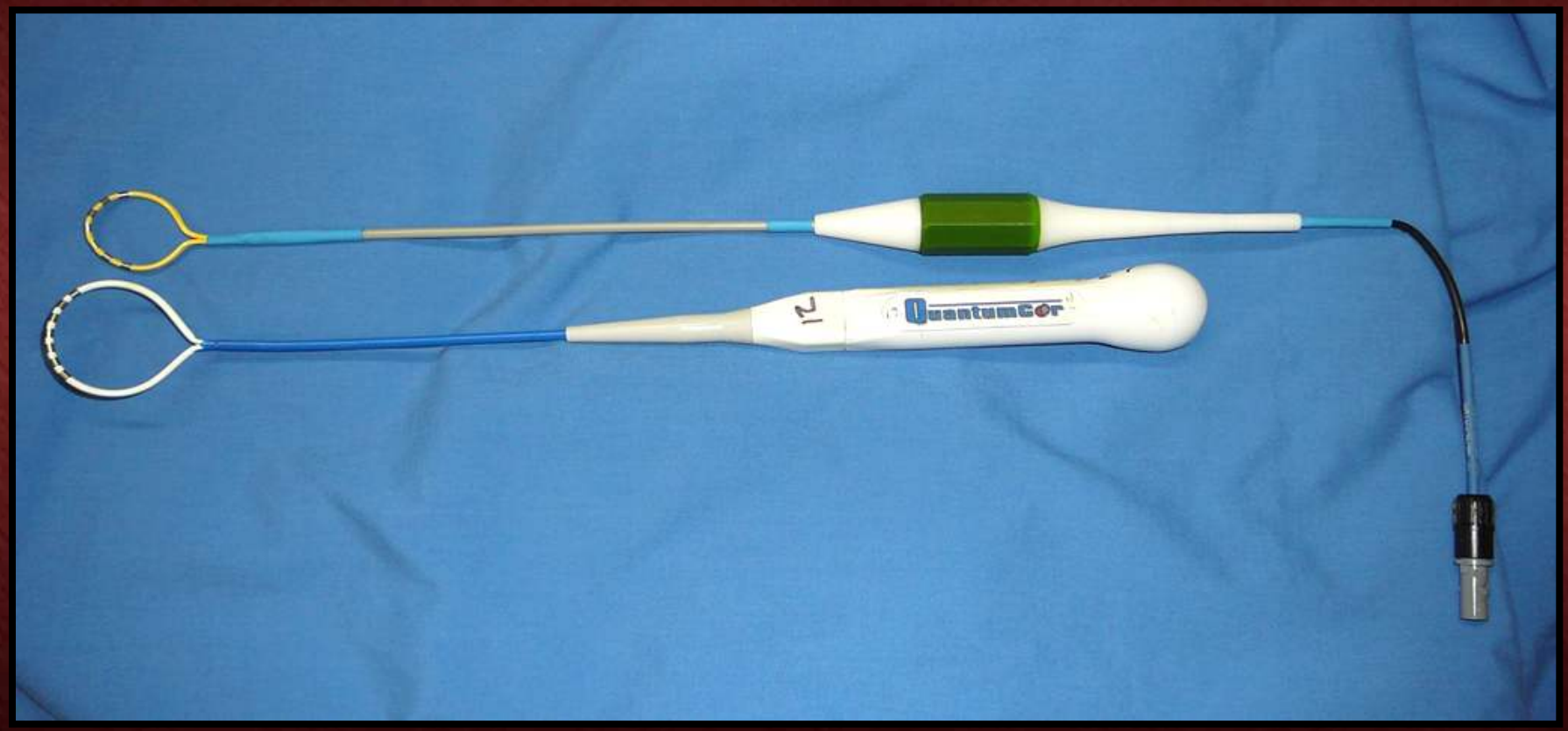
BOA-SURG Probe



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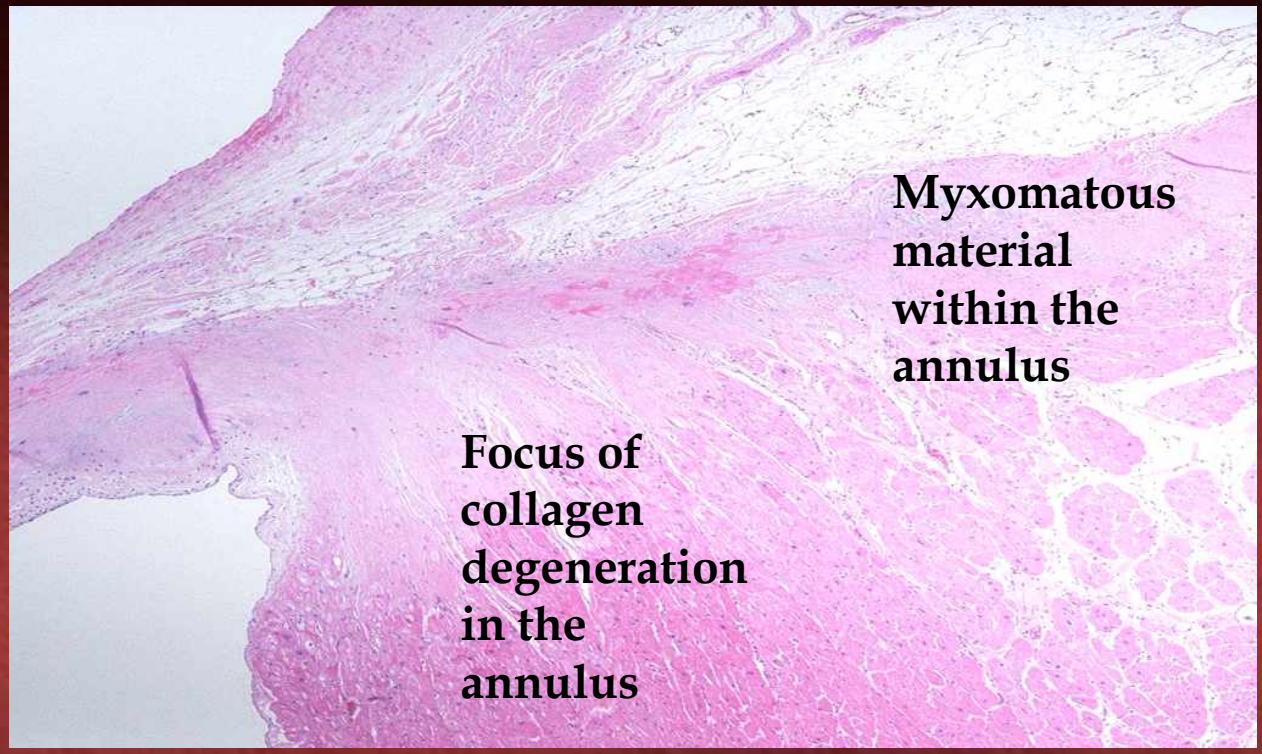

Lateral Portion of the Anterior Leaflet of the Mitral Valve – H&E Stain at 4x magnification. The annulus contains myxomatous material, collagen degeneration and calcification.

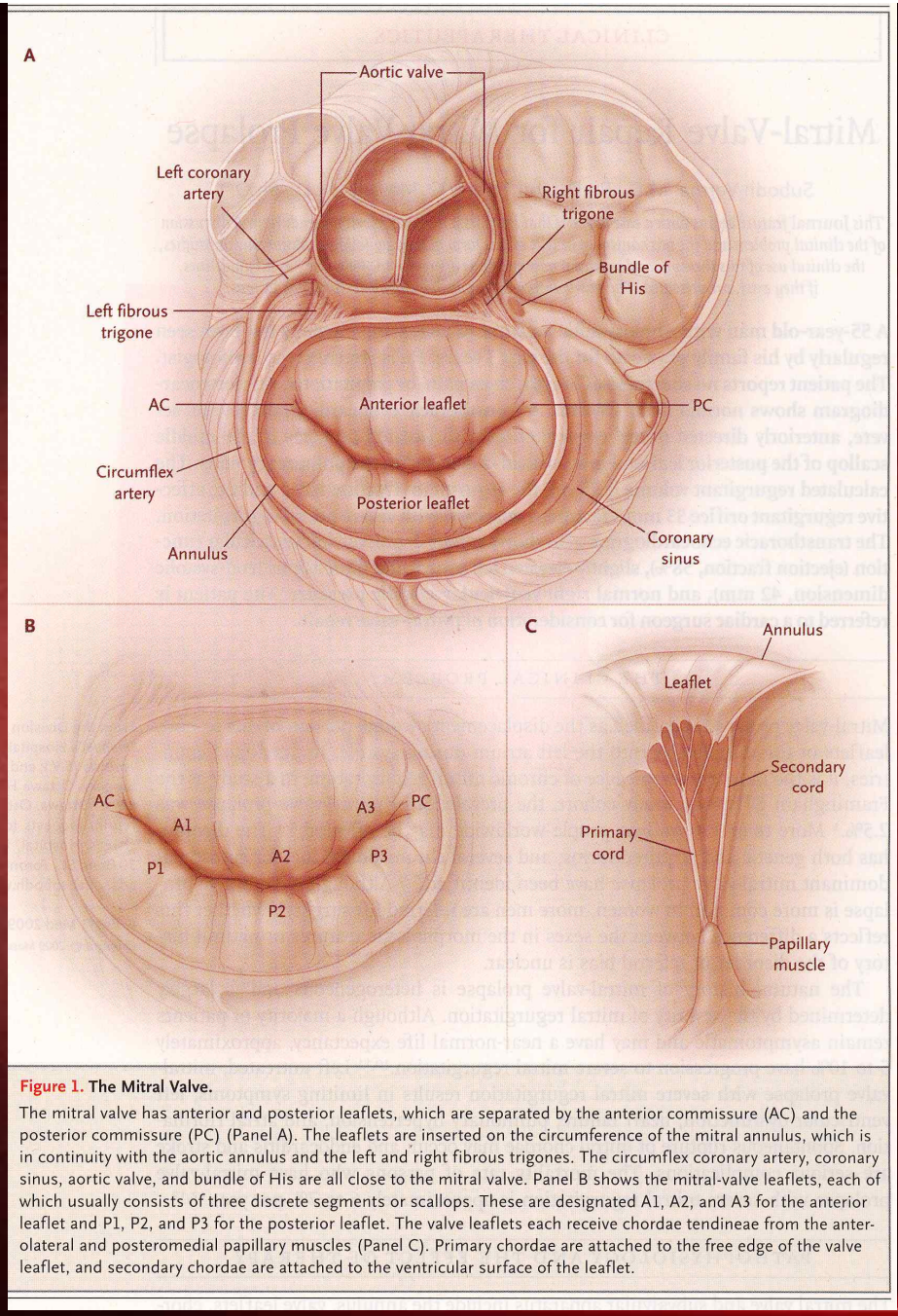

Figure 1. The Mitral Valve.

The mitral valve has anterior and posterior leaflets, which are separated by the anterior commissure (AC) and the posterior commissure (PC) (Panel A). The leaflets are inserted on the circumference of the mitral annulus, which is in continuity with the aortic annulus and the left and right fibrous trigones. The circumflex coronary artery, coronary sinus, aortic valve, and bundle of His are all close to the mitral valve. Panel B shows the mitral-valve leaflets, each of which usually consists of three discrete segments or scallops. These are designated A1, A2, and A3 for the anterior leaflet and P1, P2, and P3 for the posterior leaflet. The valve leaflets each receive chordae tendineae from the anterolateral and posteromedial papillary muscles (Panel C). Primary chordae are attached to the free edge of the valve leaflet, and secondary chordae are attached to the ventricular surface of the leaflet.

N Engl J Med 2009;361:2261-9.

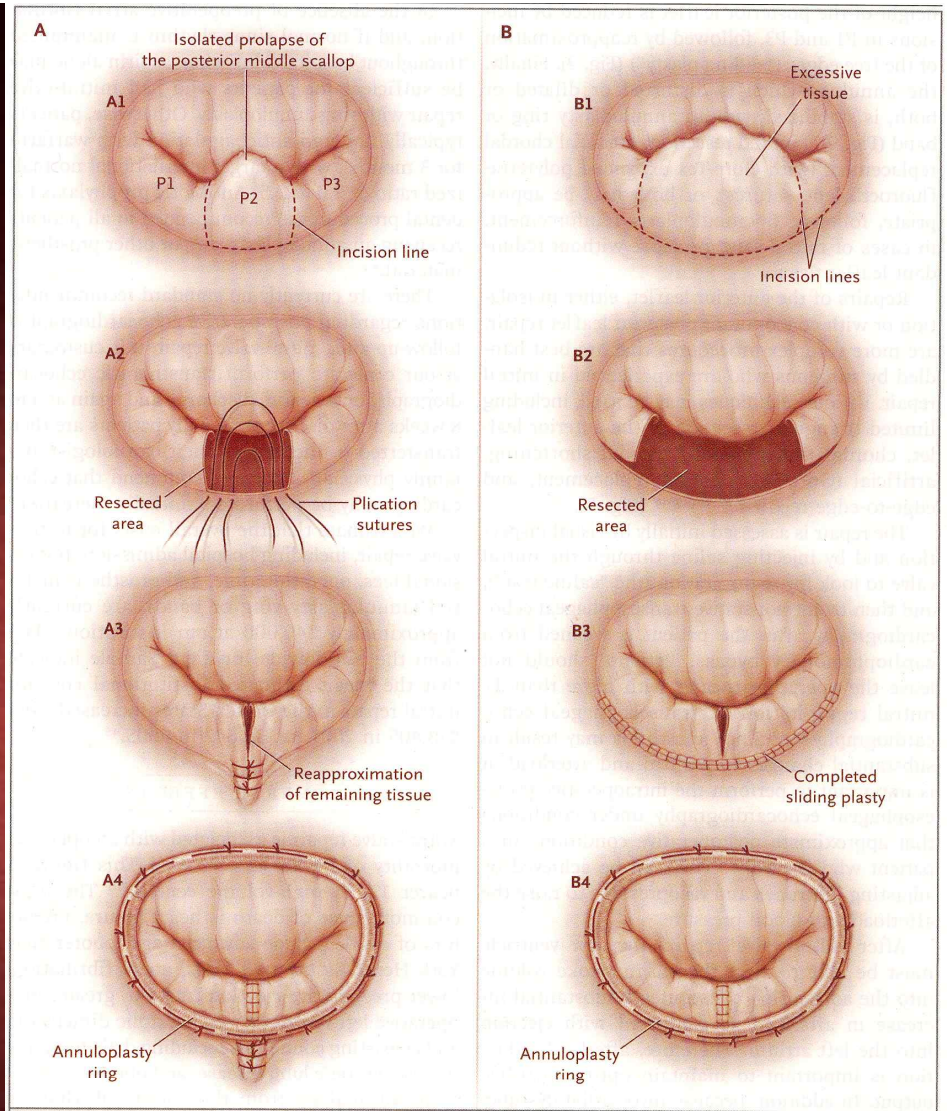

Figure 2. Mitral-Valve Prolapse.

The most common leaflet abnormality seen in mitral-valve prolapse is isolated prolapse of the posterior middle scallop (P2) (Panel A1). In patients with isolated prolapse of P2, repair usually involves limited resection of this scallop by means of a quadrangular or triangular incision (Panel A2). The remaining parts of the posterior leaflet, namely P1 and P3, are then brought together (Panel A3). After the leaflet repair is complete, an annuloplasty ring or band is used to reinforce and stabilize the annulus, thus preventing progressive dilatation (Panel A4). If excessive posterior leaflet tissue is present (Panel B1), the height of the posterior leaflet is reduced by incising P1 and P3 from the annulus (Panel B2), followed by reapproximation of the free edges ("sliding plasty") (Panel B3). After the leaflet repair is complete, an annuloplasty ring or band is inserted (Panel B4).

N Engl J Med 2009;361:2261-9.

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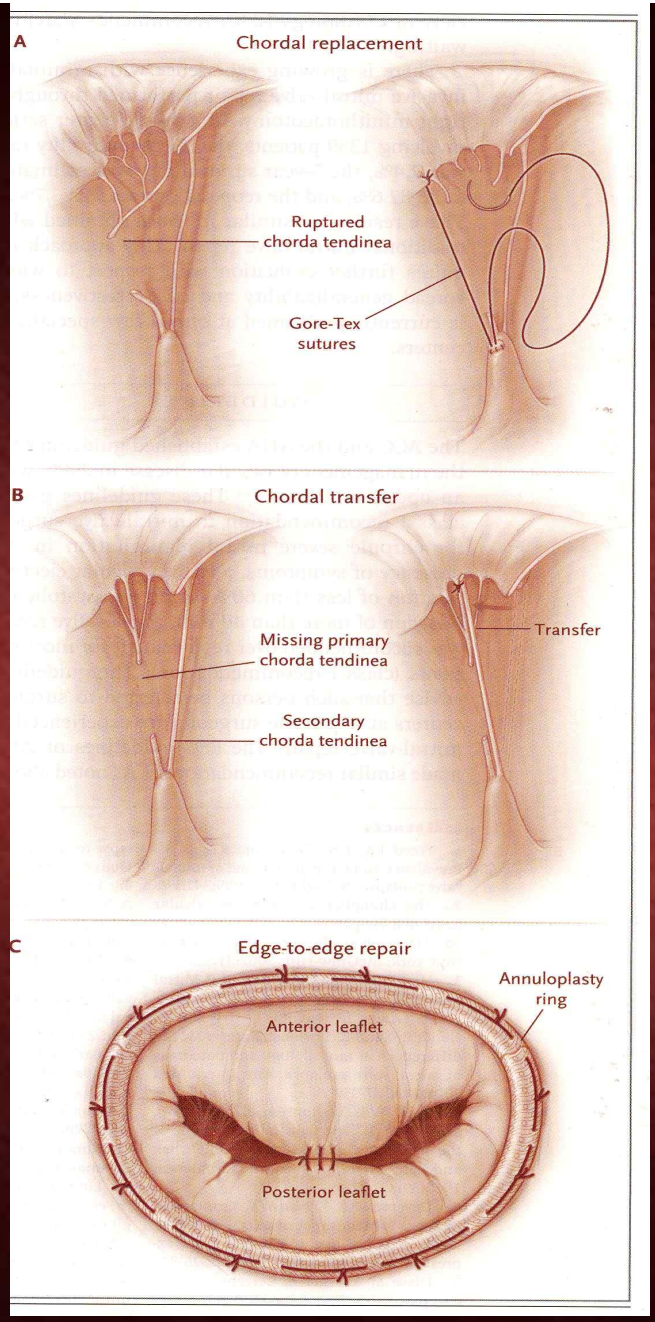

Special Repair Techniques.

Ruptured chordae tendineae can be replaced with artificial substitute (Gore-Tex expanded polytetrafluoro-ethylene sutures) (Panel A). Ruptured or surgically severed primary chordae can e replaced with secondary chordae, a process called chordal transfer (Panel B). Edge-to-edge repair (Panel C) is performed by sewing the anterior and posterior leaflets together at the central points of their middle scallops, which corrects the prolapse while leaving two functional valve orifices on each side.

N Engl J Med 2009;361:2261-9.

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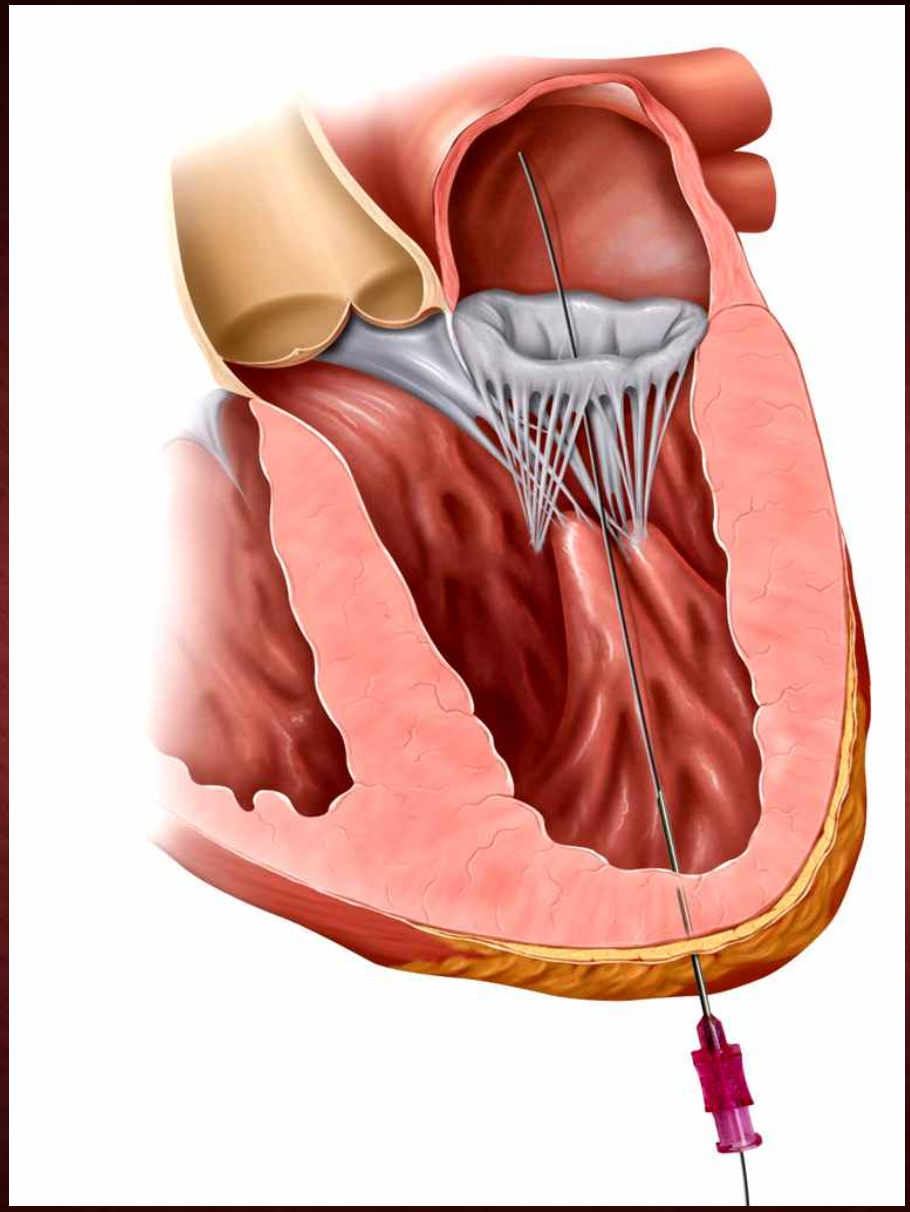

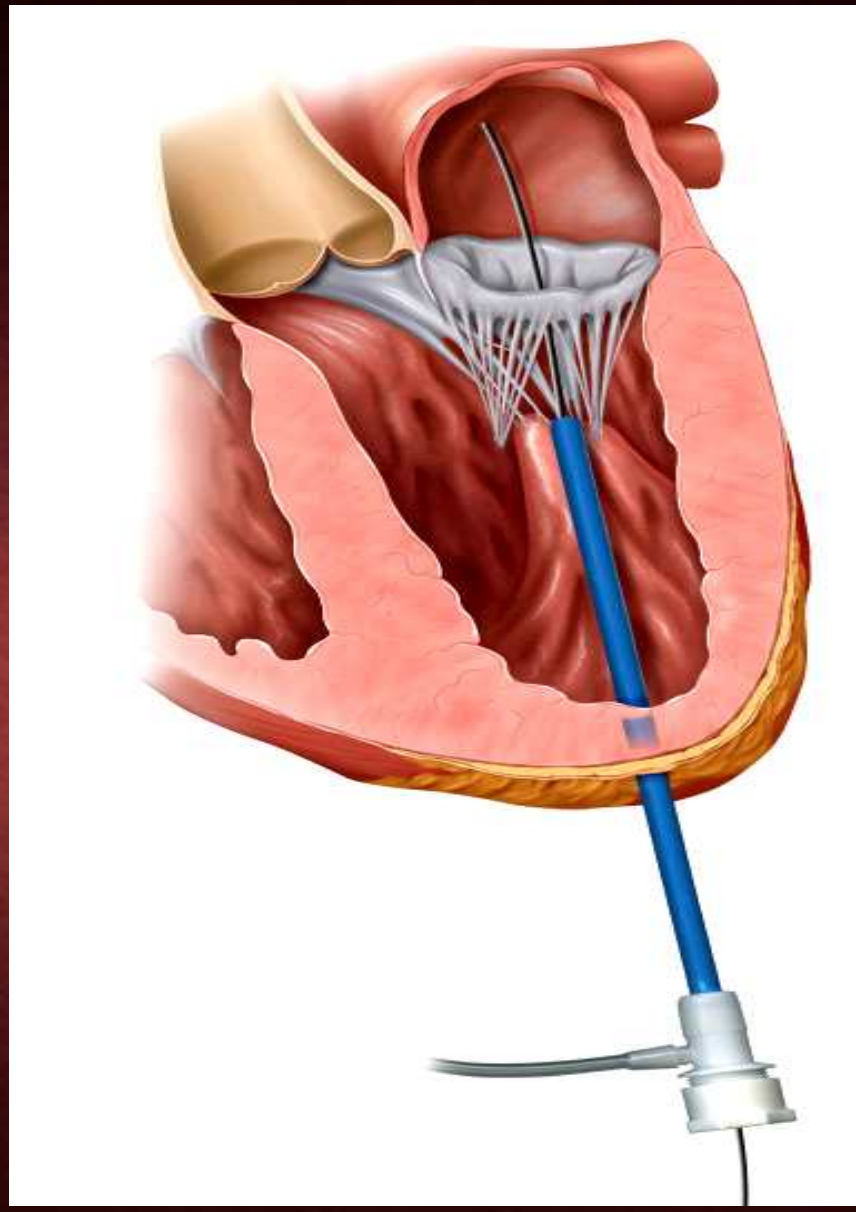

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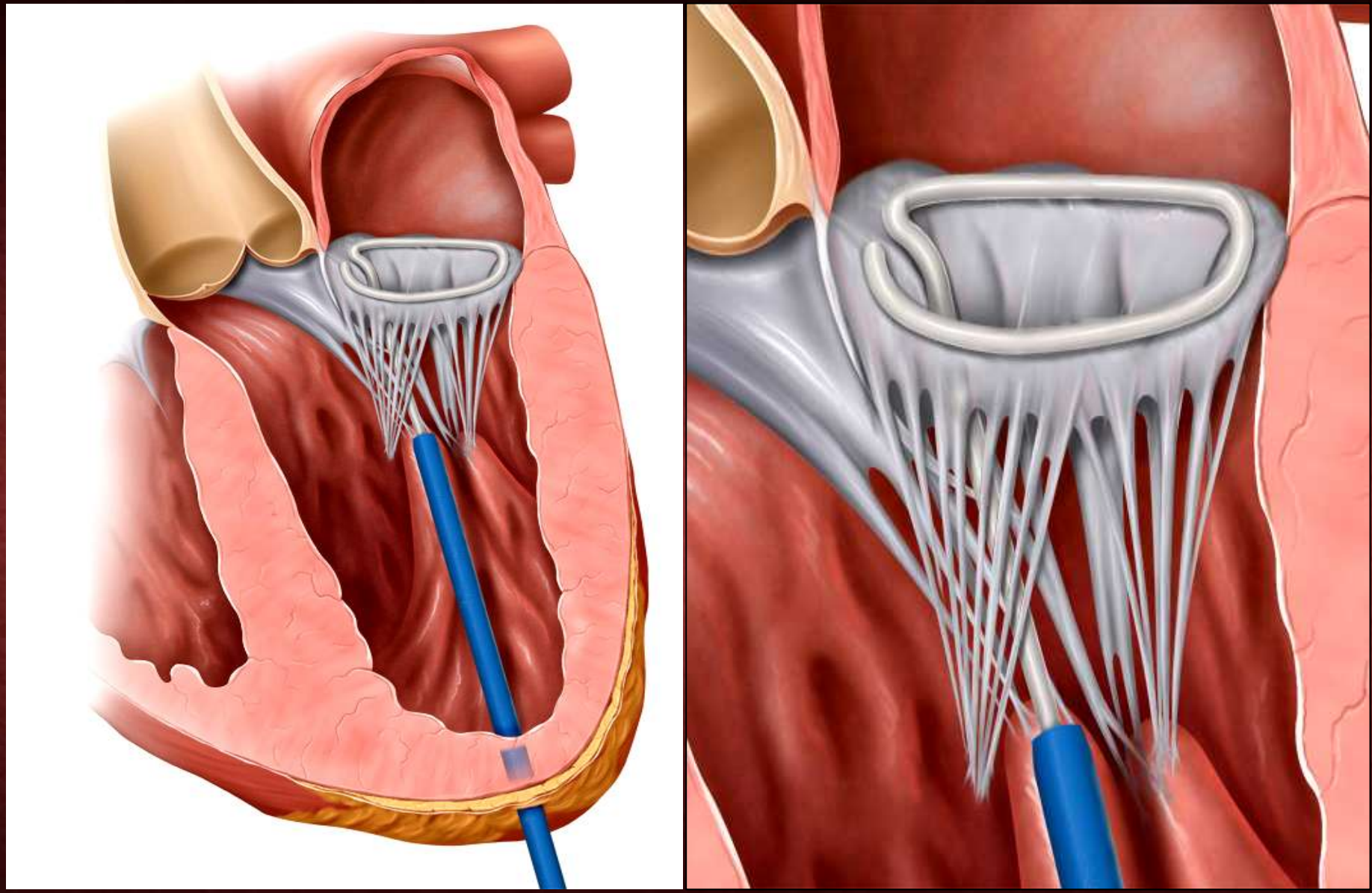
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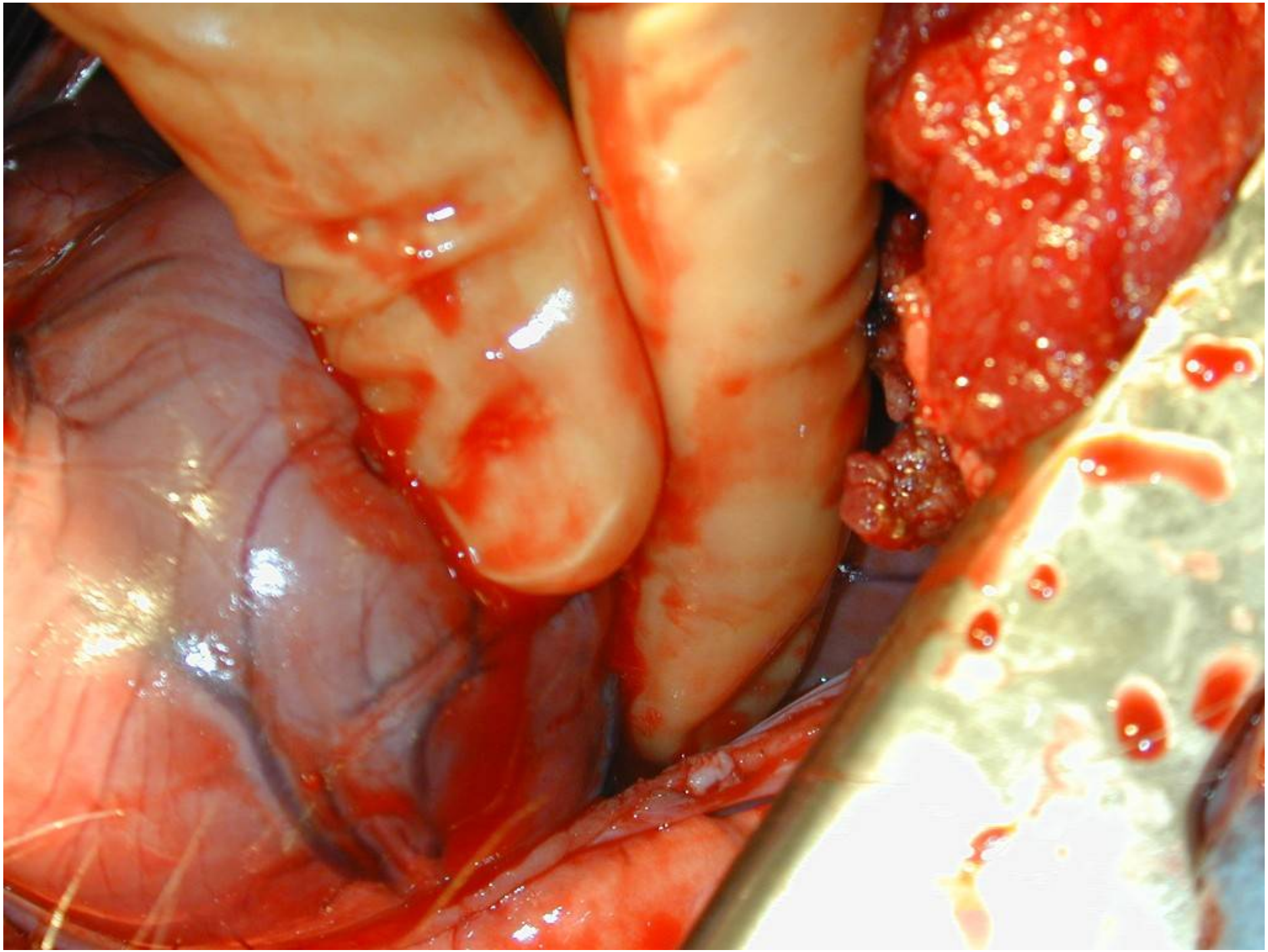
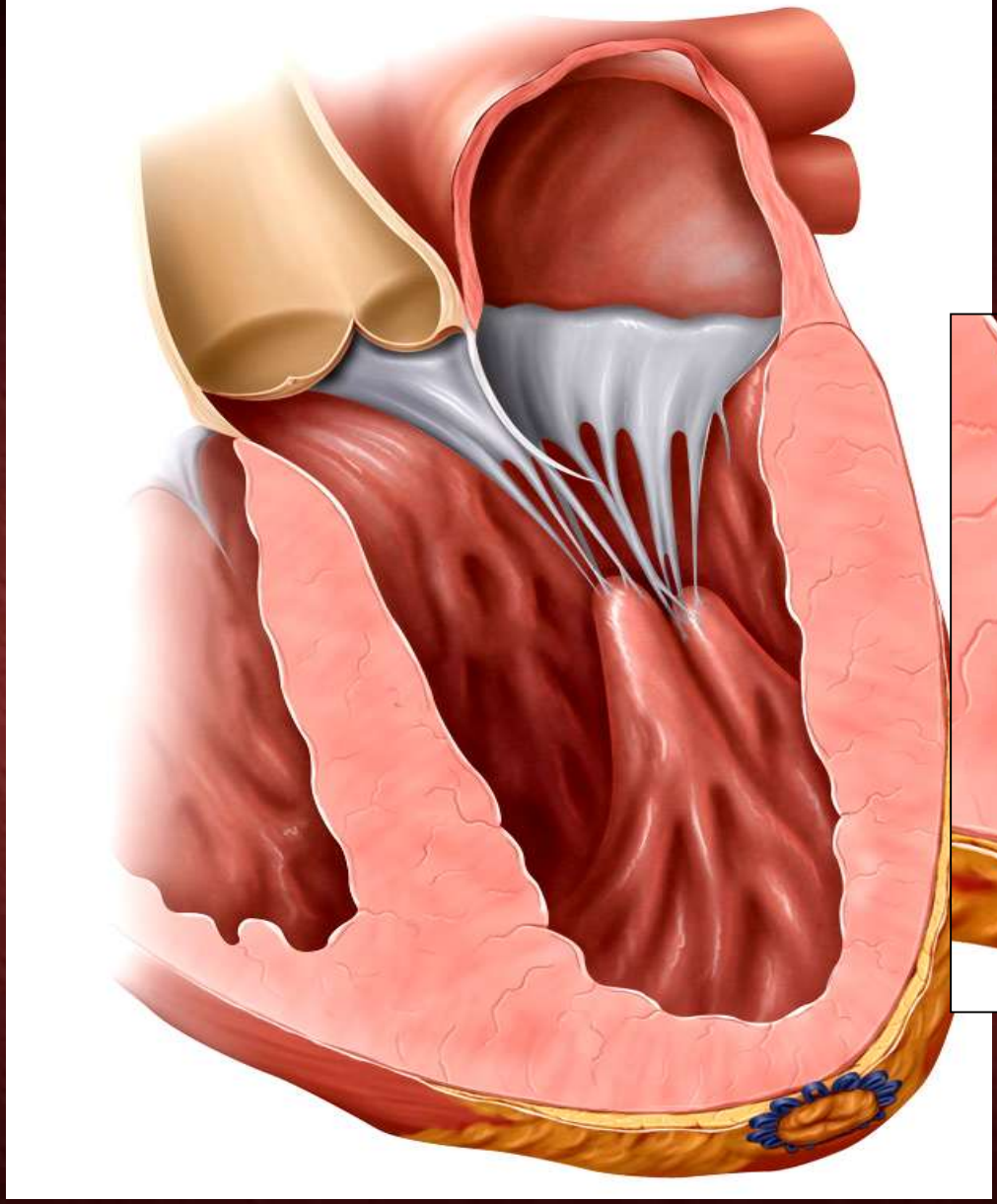
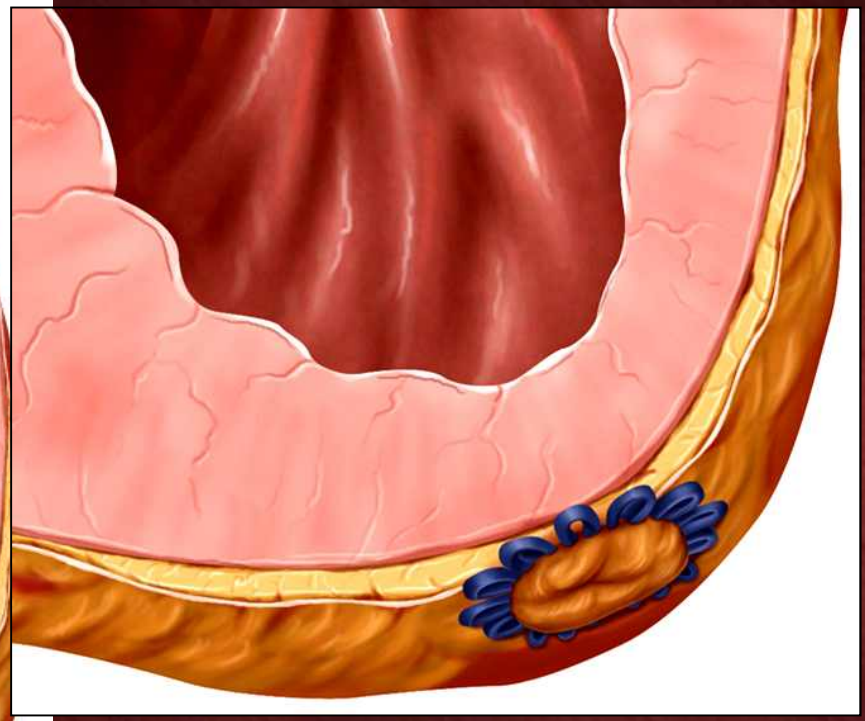


Starclose





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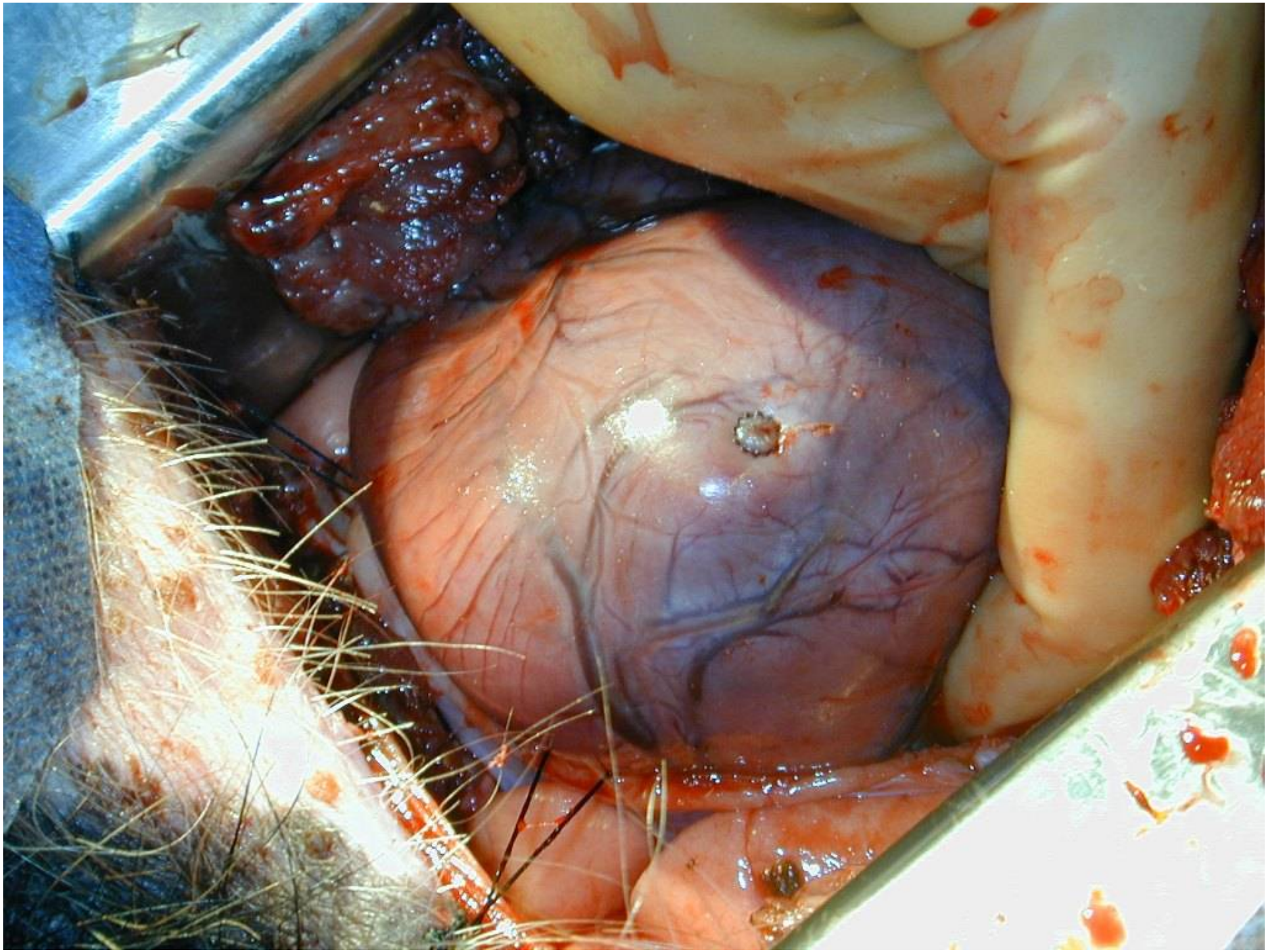

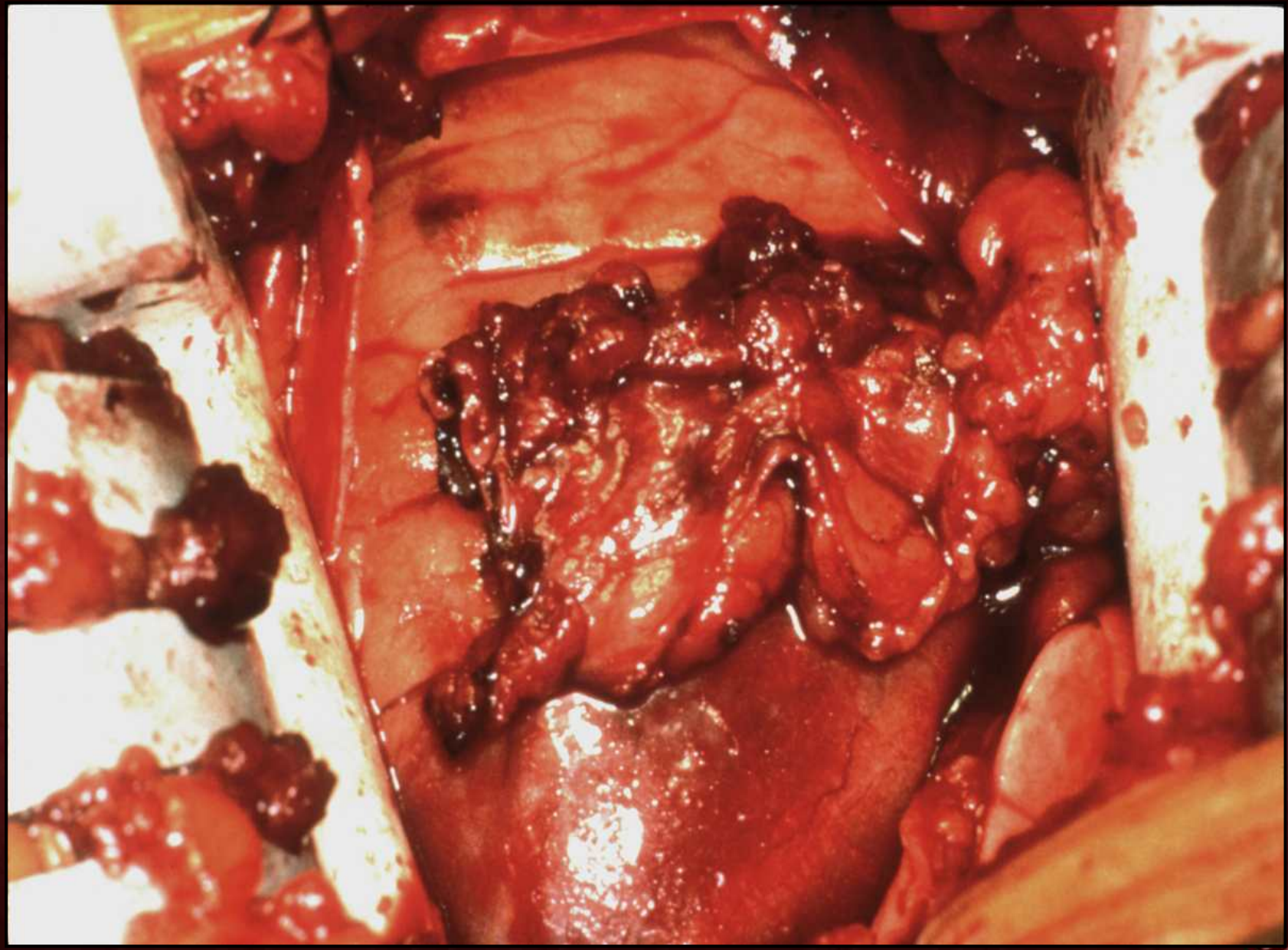

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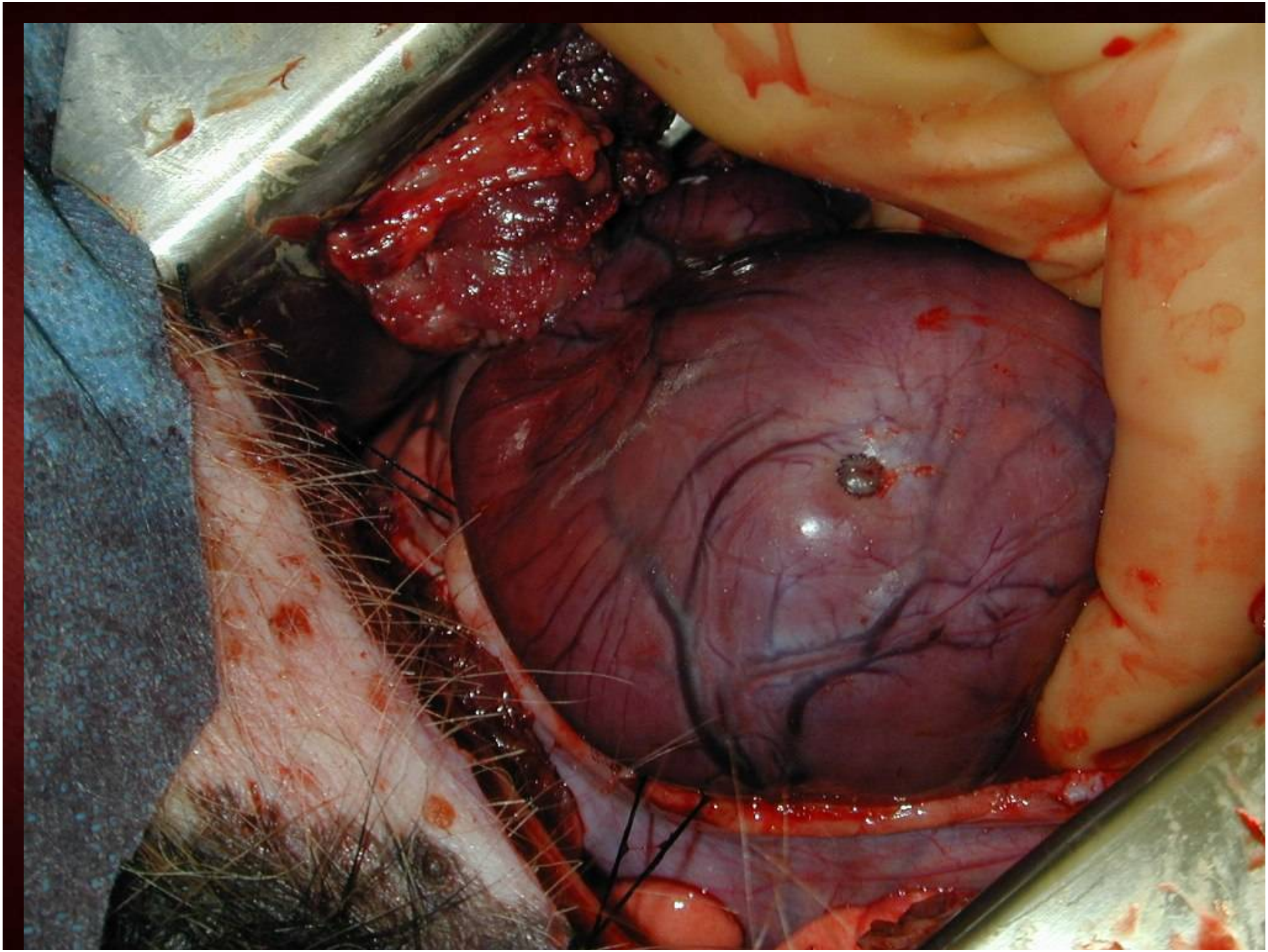
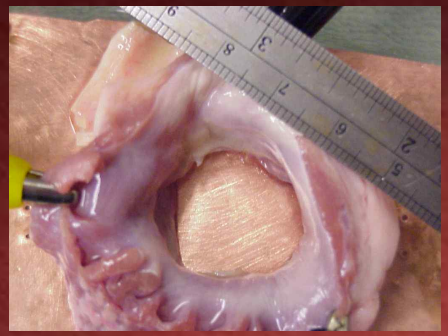


Annulus Contraction in Sheep and Pig Hearts



- *Annuluses treated circumferentially*
- *Temperatures set at 65 ℃*
- *Image analysis used to compute changes in dimensions*

1

Area 11%
Perimeter 6%

2

Area 17%
Perimeter 10%

3

Area 21%
Perimeter 12%

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The RF Approach to Treating Mitral Regurgitation: The QuantumCor System

A Repeatable Less Invasive Option May Be Desirable.

R. Heuser

Percutaneous Mitral Valve Repair

- *Obvious Strategy for PMVR is to combine direct valvular procedure with a percutaneous annuloplasty technique*

- *Mimics what is done surgically*

RESULTS

Percutaneous Treatment for Mitral Regurgitation

- *With RF Energy Applied To The Mitral Annulus It May Be Possible To Treat A Larger Population Of Patients With Mitral Regurgitation.*
- *If You Don't Succeed You Can Repeat The Procedure.*
- *Treat Without Affecting The Coronary Sinus.*
- *Use In Conjunction With Leaflet Procedures.*

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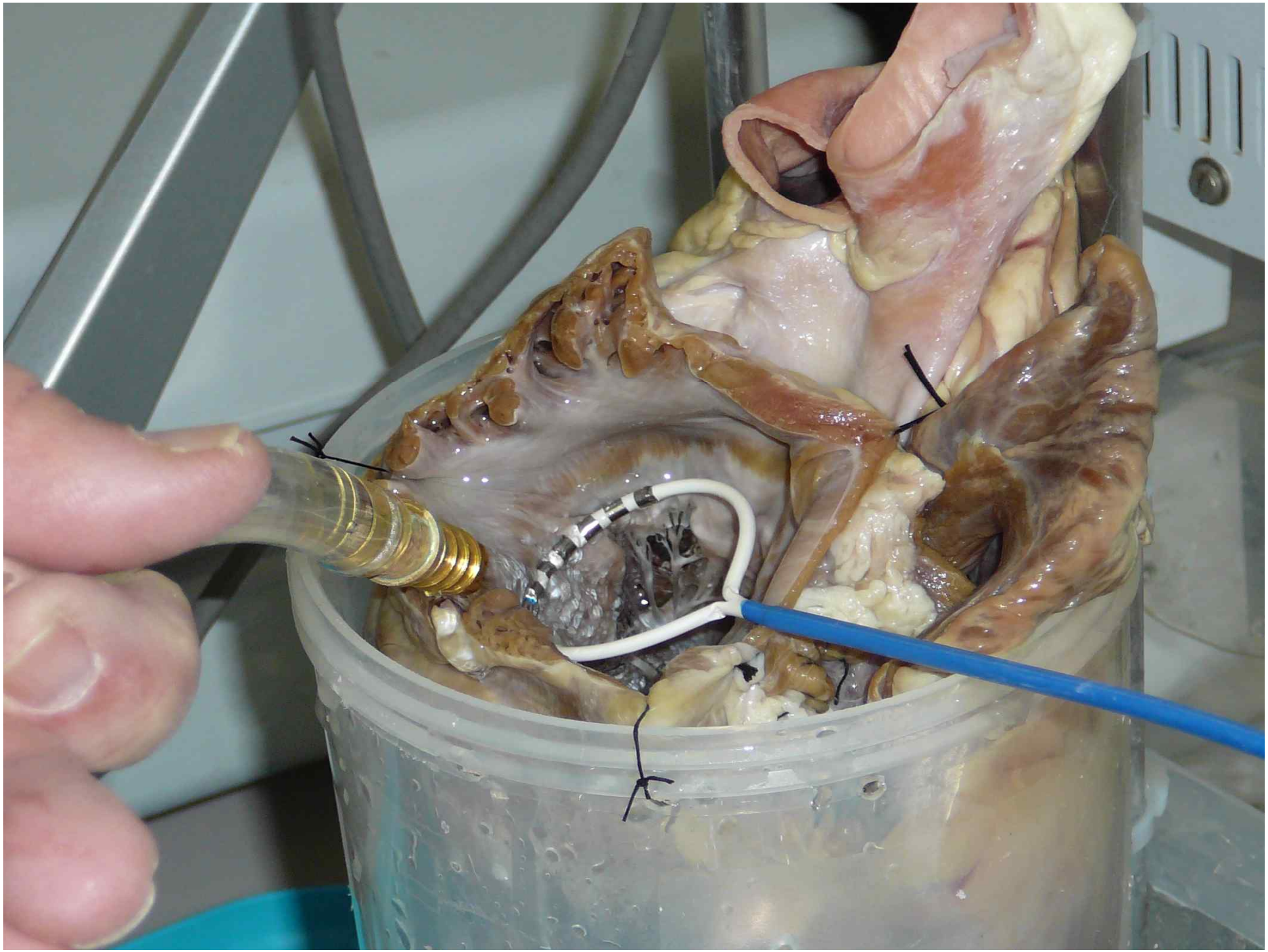
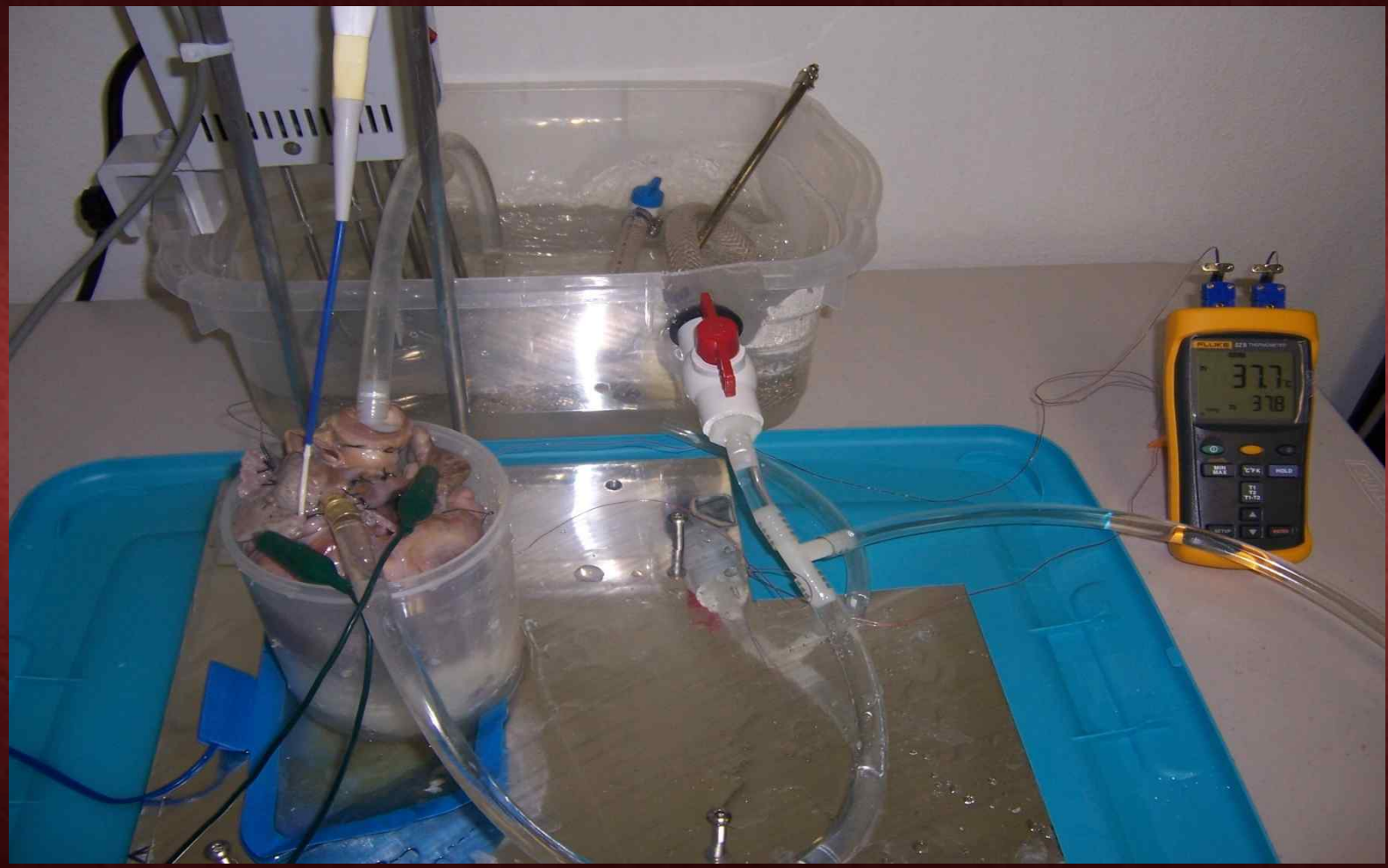


Bench Studies



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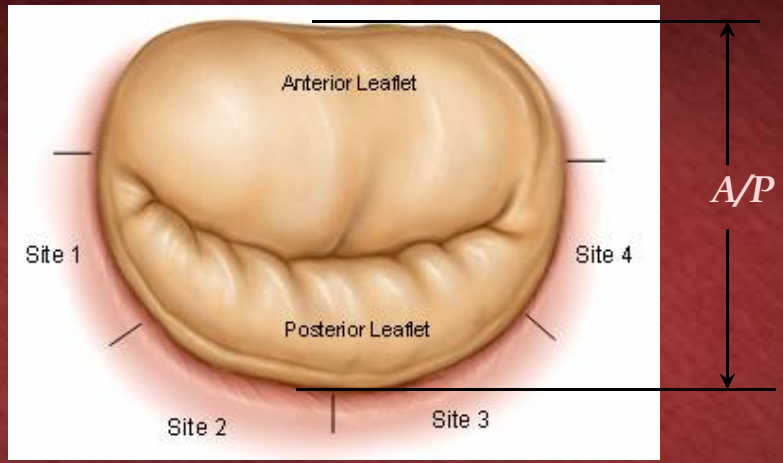
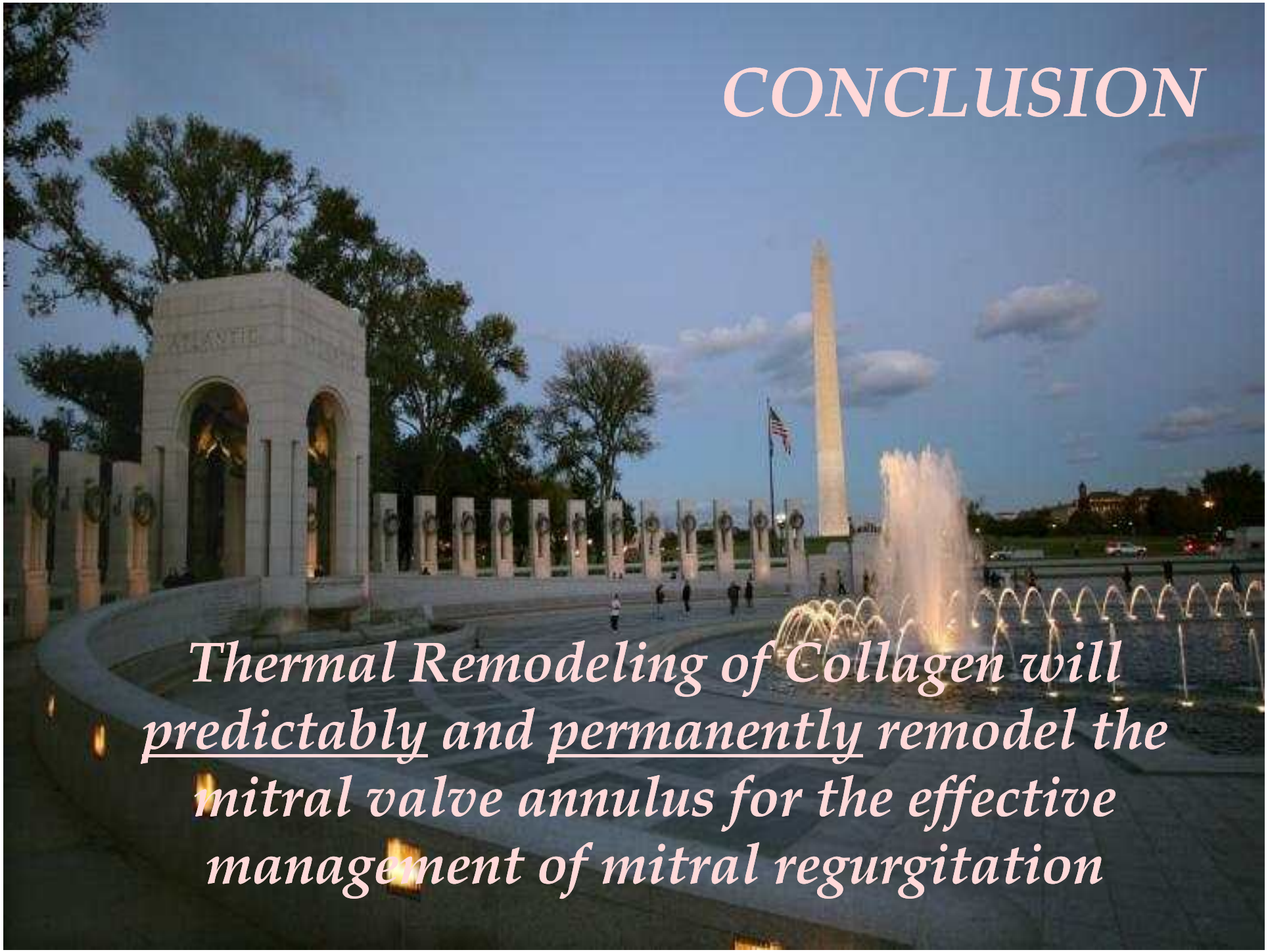
Clinical Objective

- *Apply RF energy to sites 1,2,3,4*
  - *Shrink collagen fibers ~ 10% per site*
  - *Reduce A/P dimension ~20%*
  - *Allowing valve leaflets to close properly*



CONCLUSION

The QuantumCor Device May Offer An Option For Some Patients With Mitral Regurgitation



CONCLUSION

Thermal Remodeling of Collagen will predictably and permanently remodel the mitral valve annulus for the effective management of mitral regurgitation

1ST IN THE OPERATING ROOM

Eventually As A Percutaneous Treatment For Mitral Regurgitation That Could Be Performed With Standard EP RF Consol In The Catheterization Laboratory

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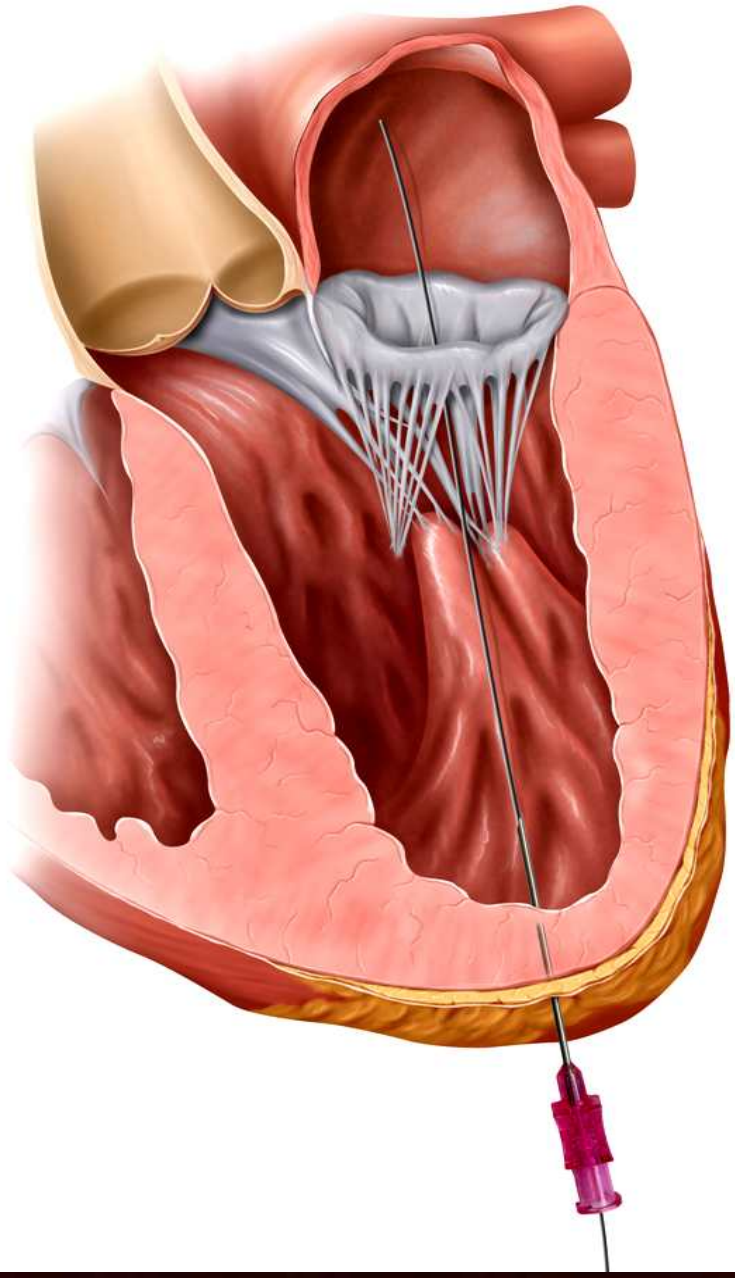

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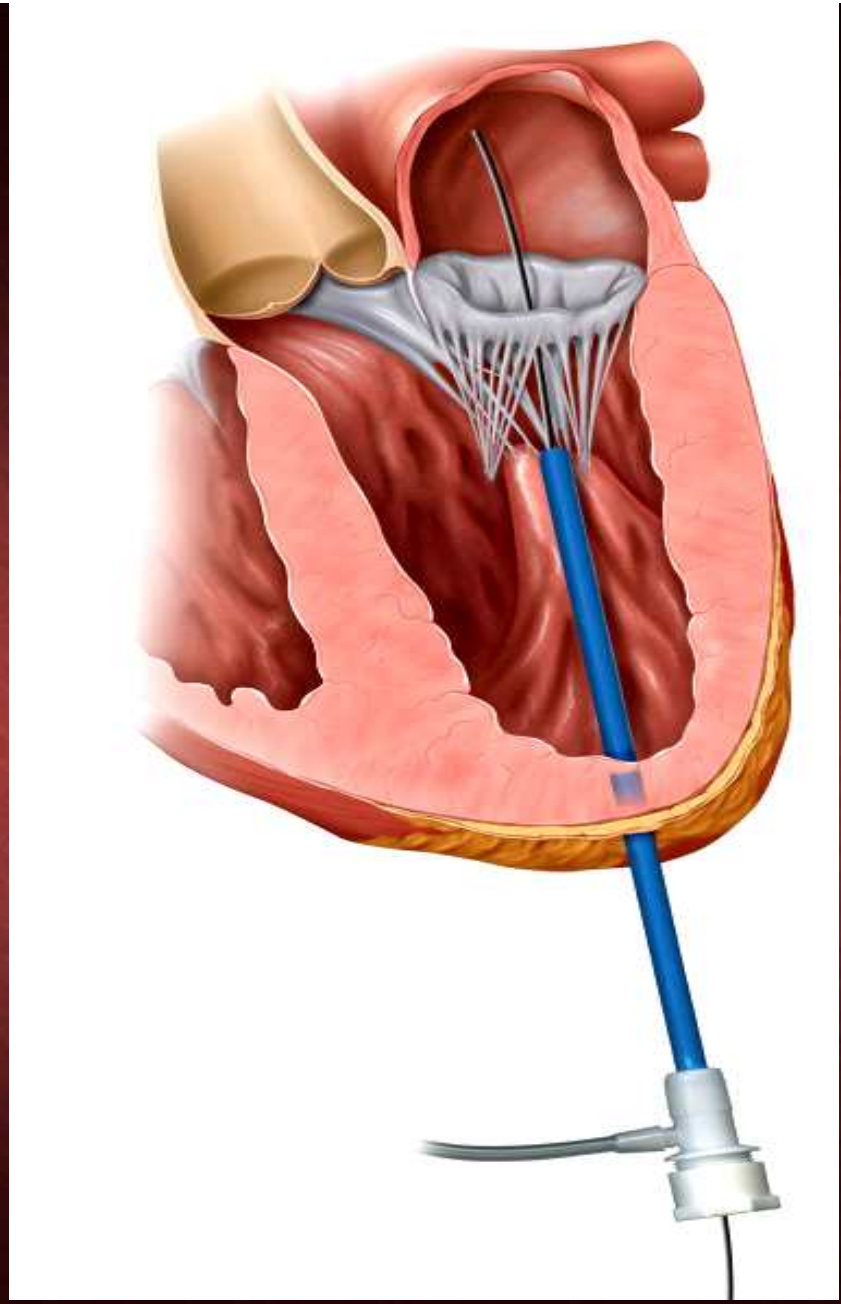

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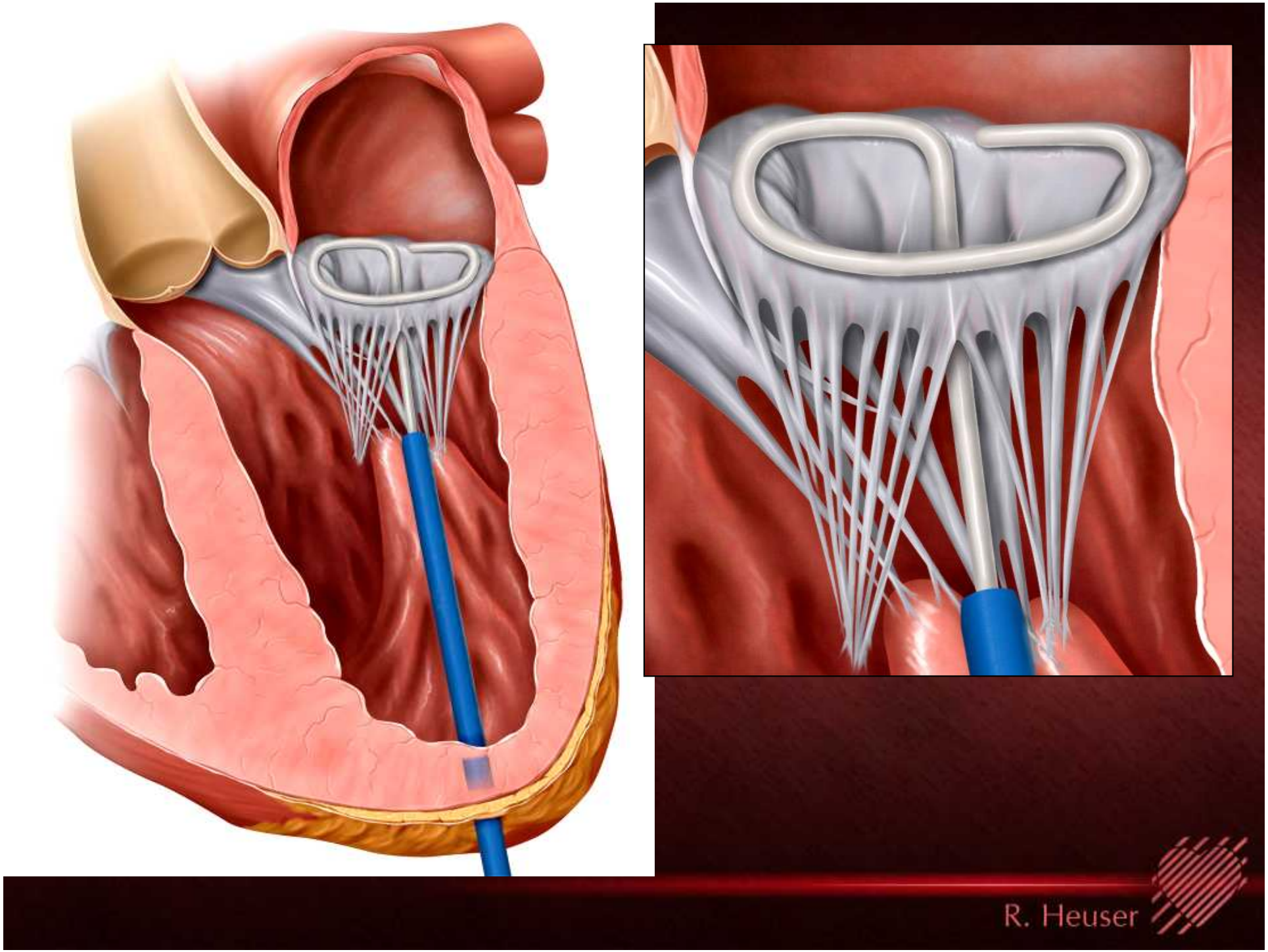
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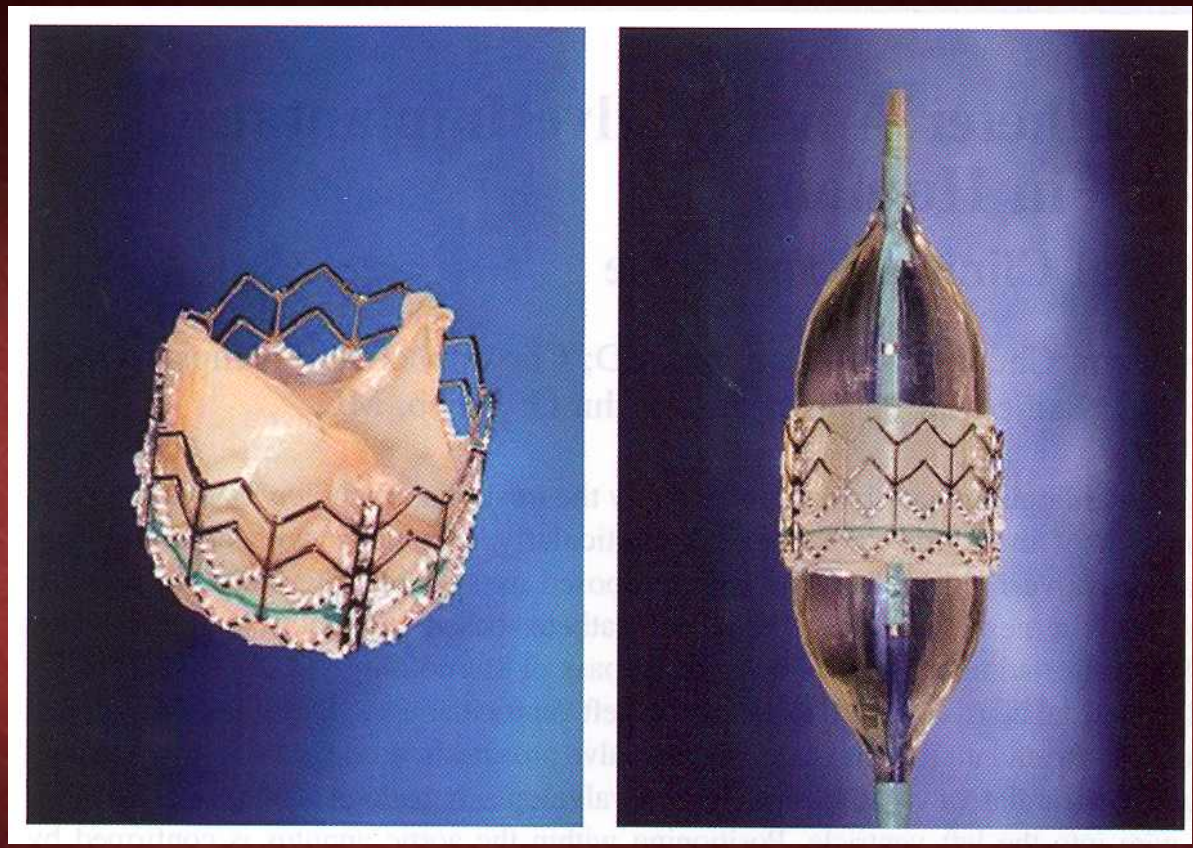

Circulation. 2006; 114:533-535.

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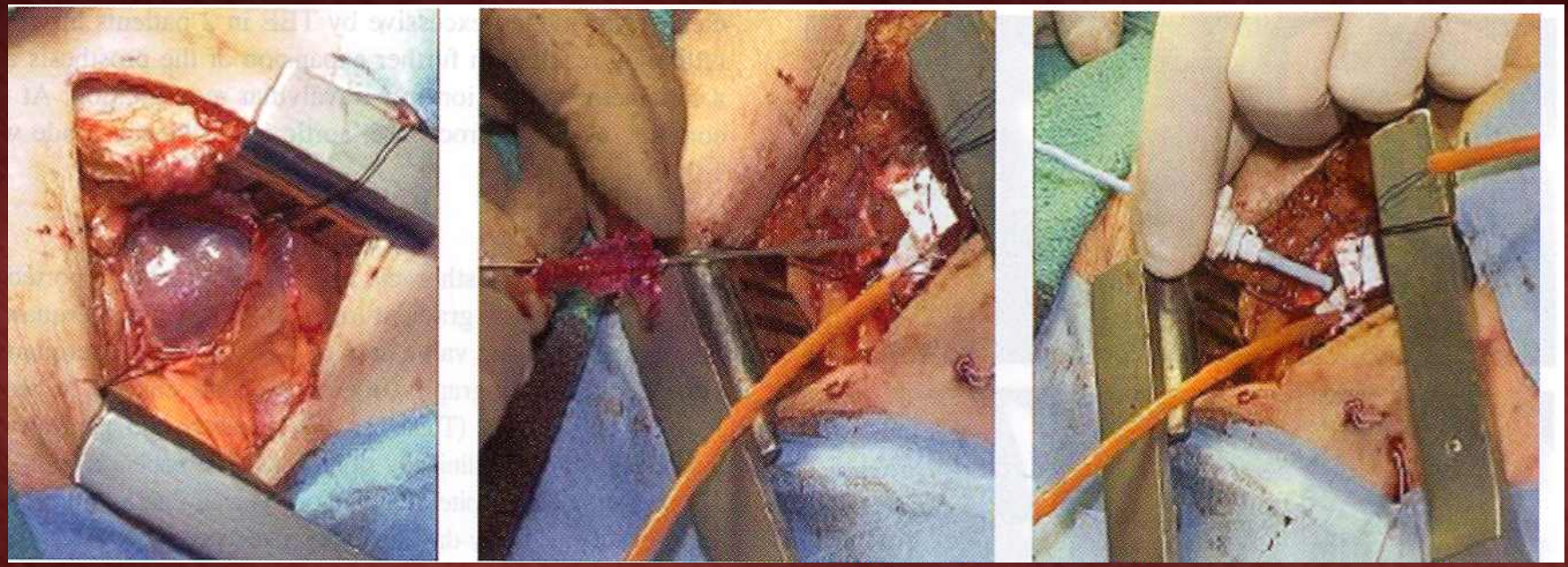

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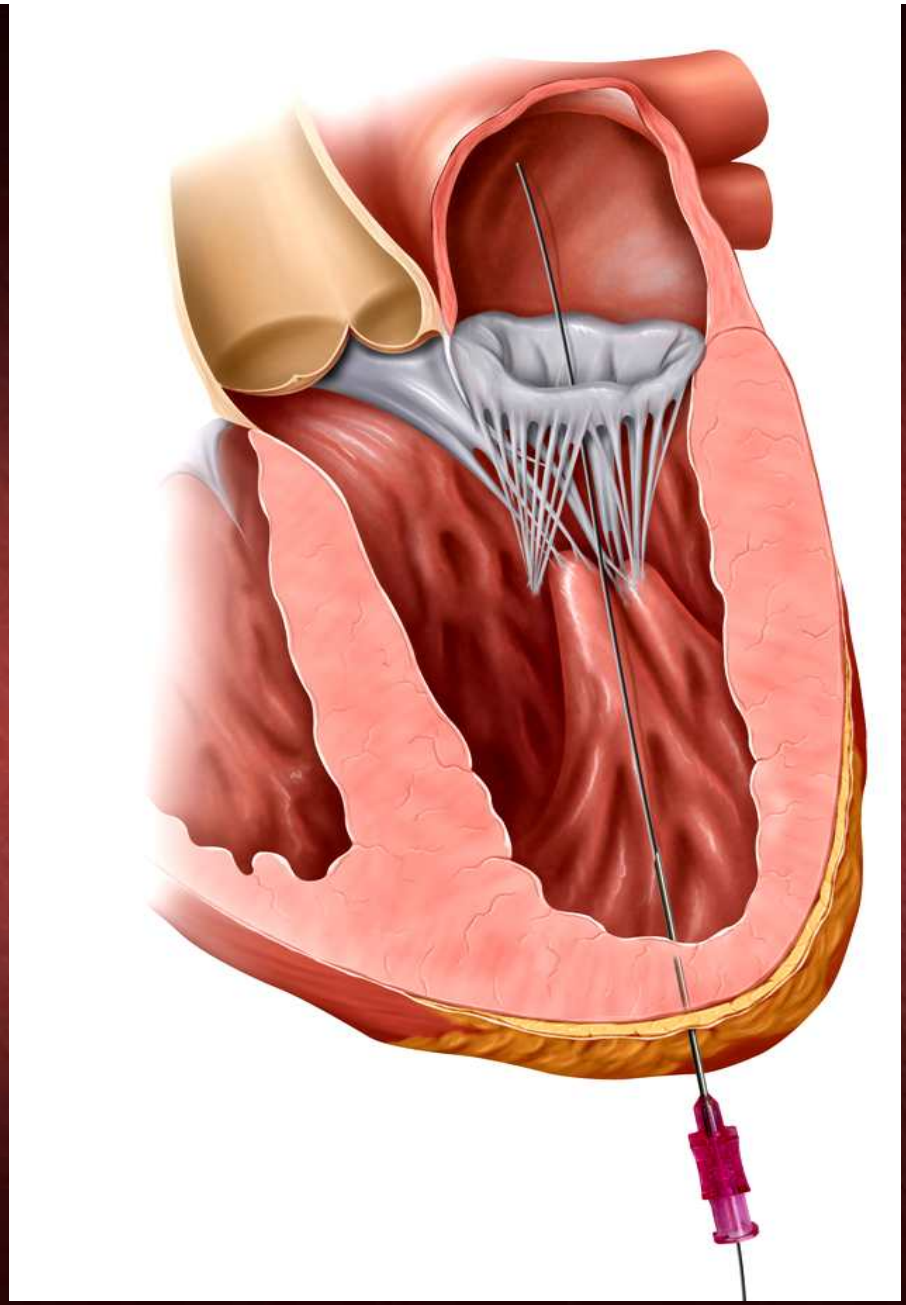

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Self-expanding AV Prosthesis
CoreValve

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Selfexpanding AV Prosthesis CoreValve (Delivery)

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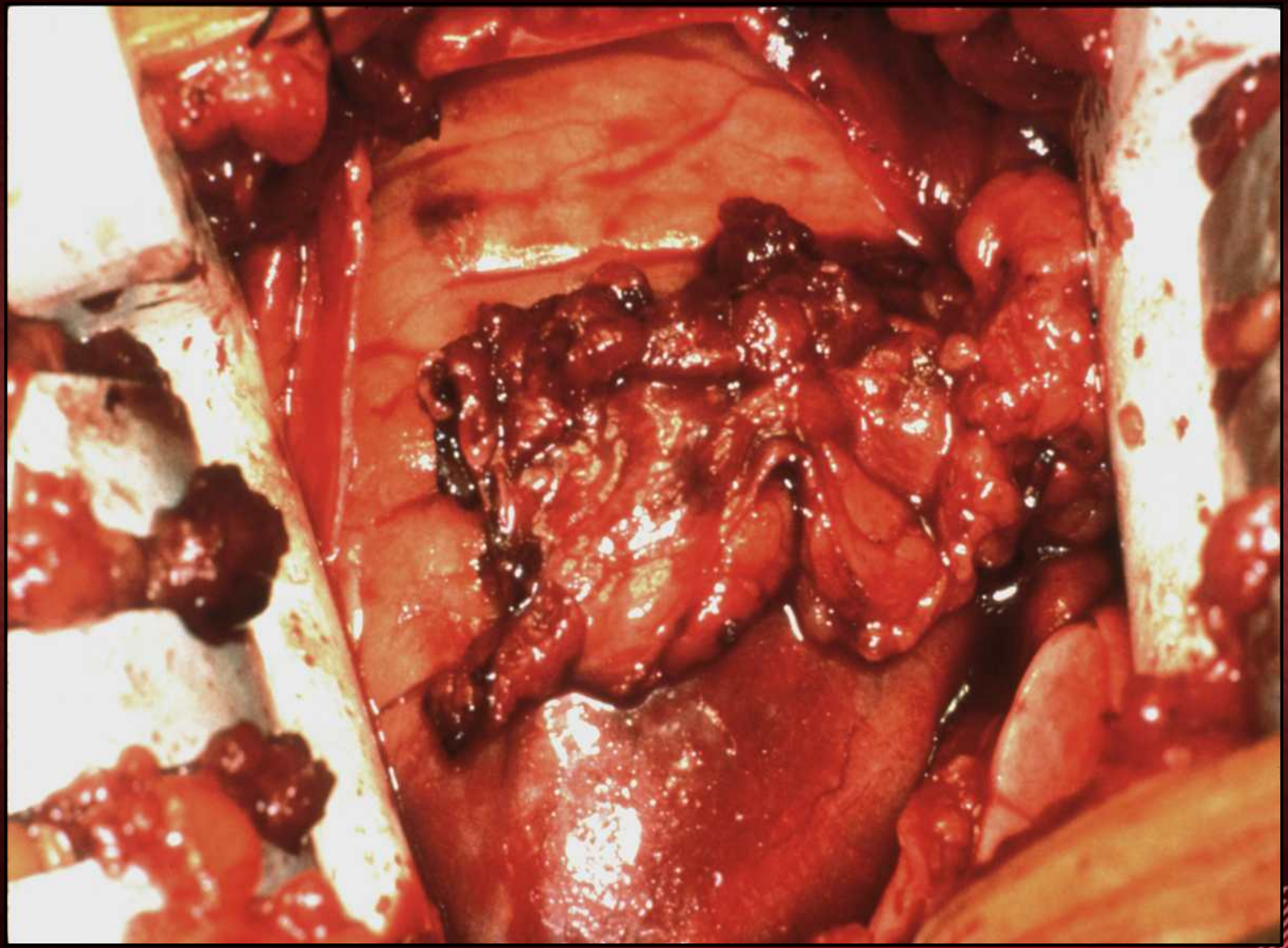

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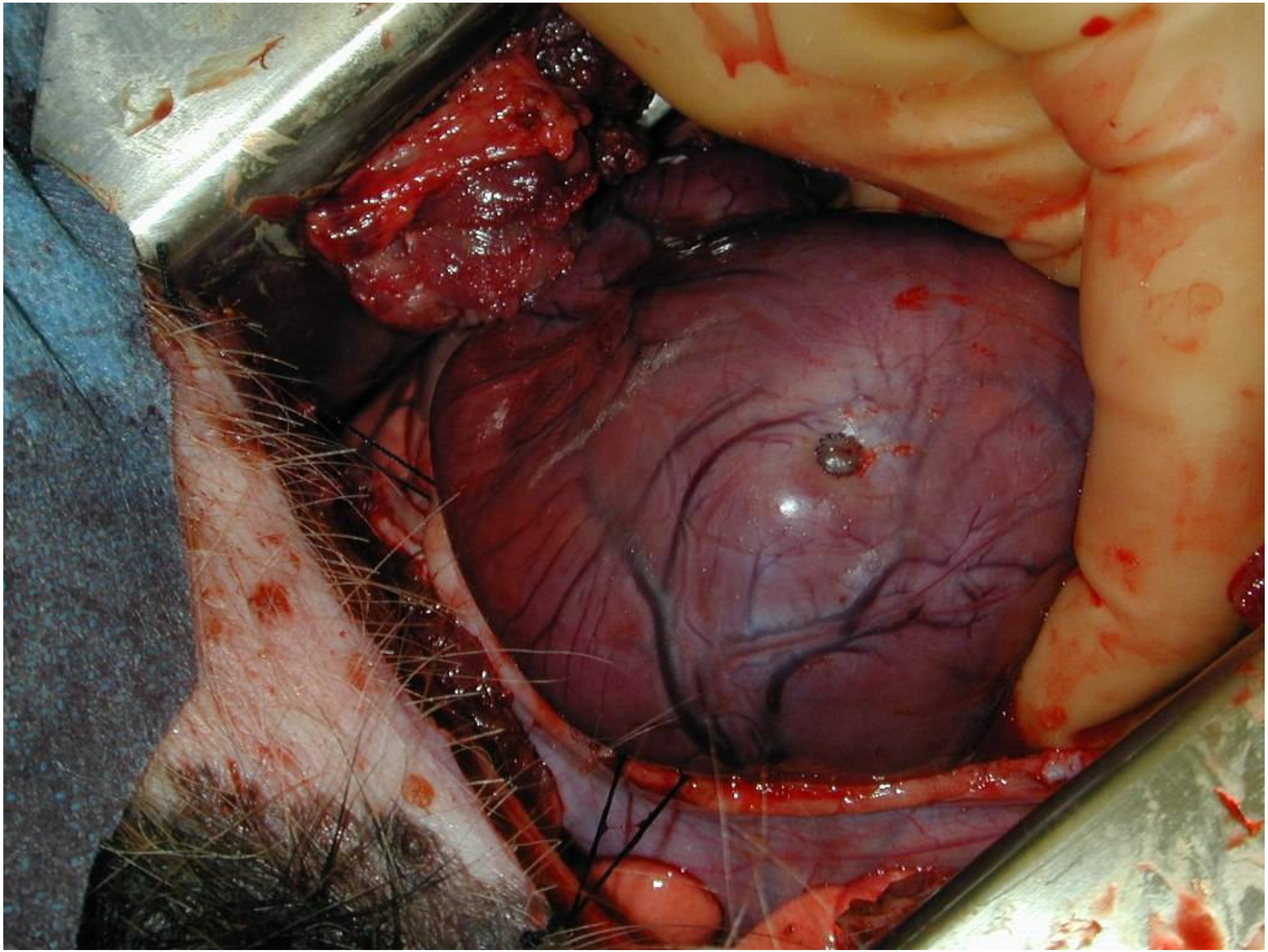

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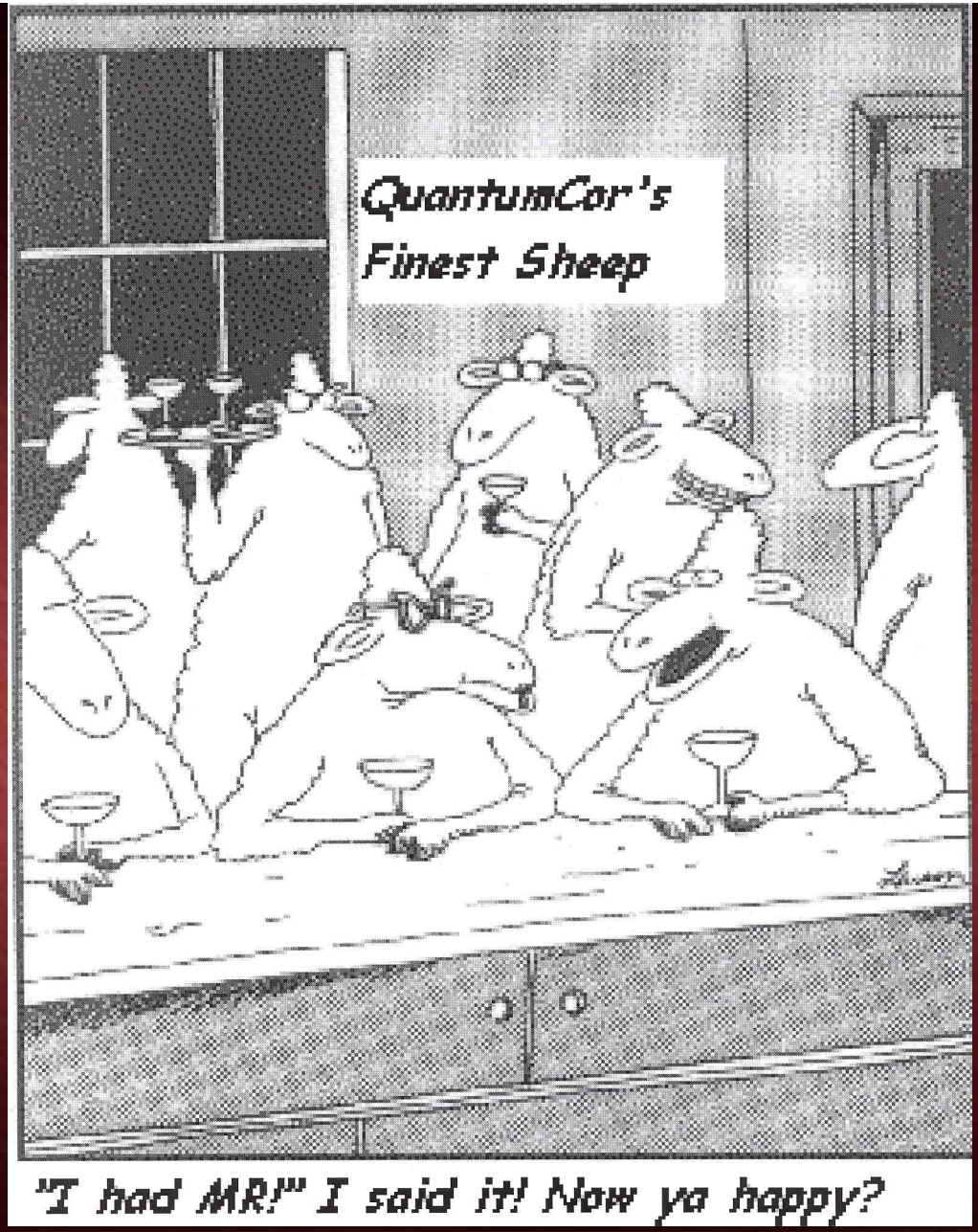
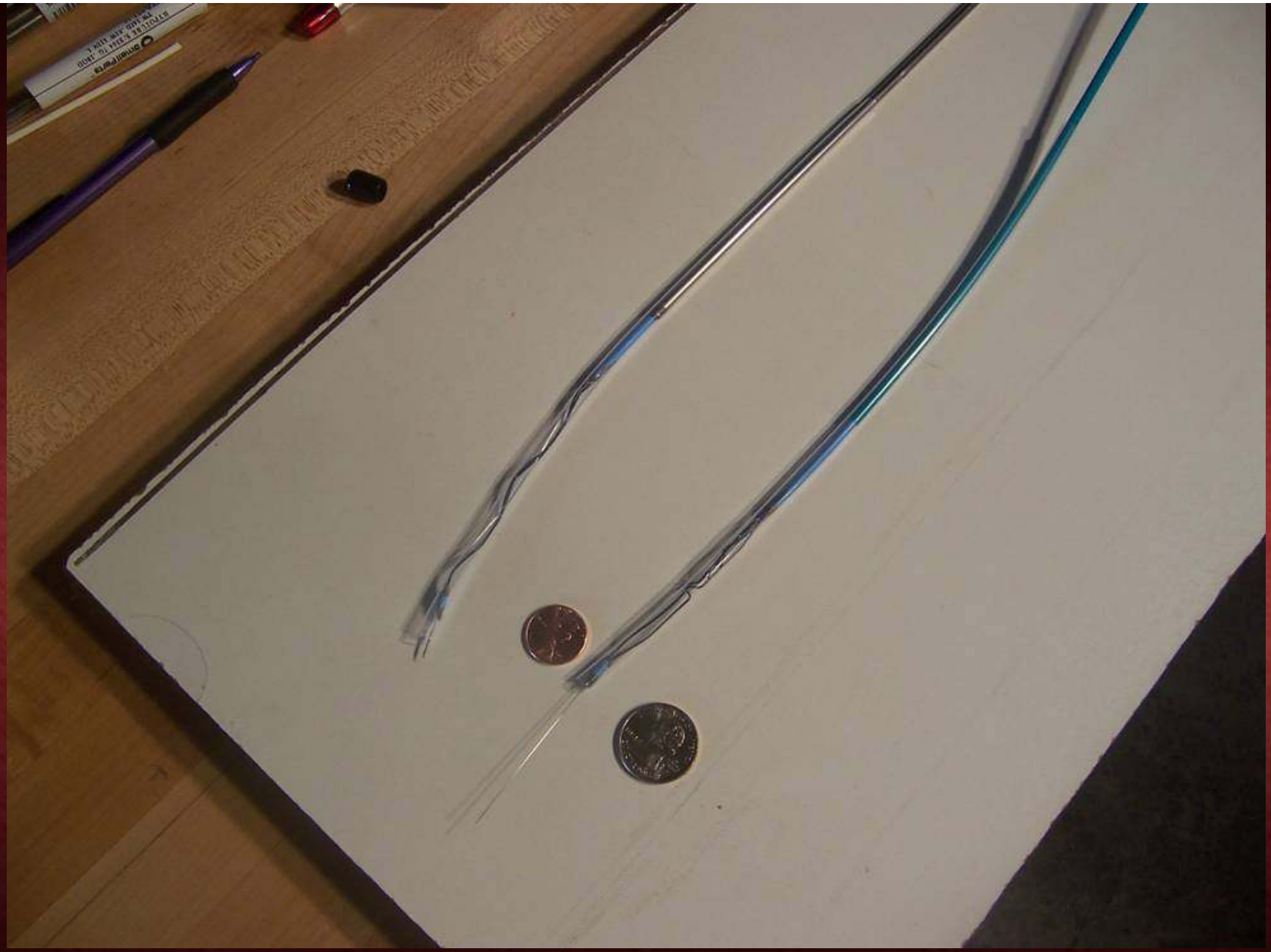
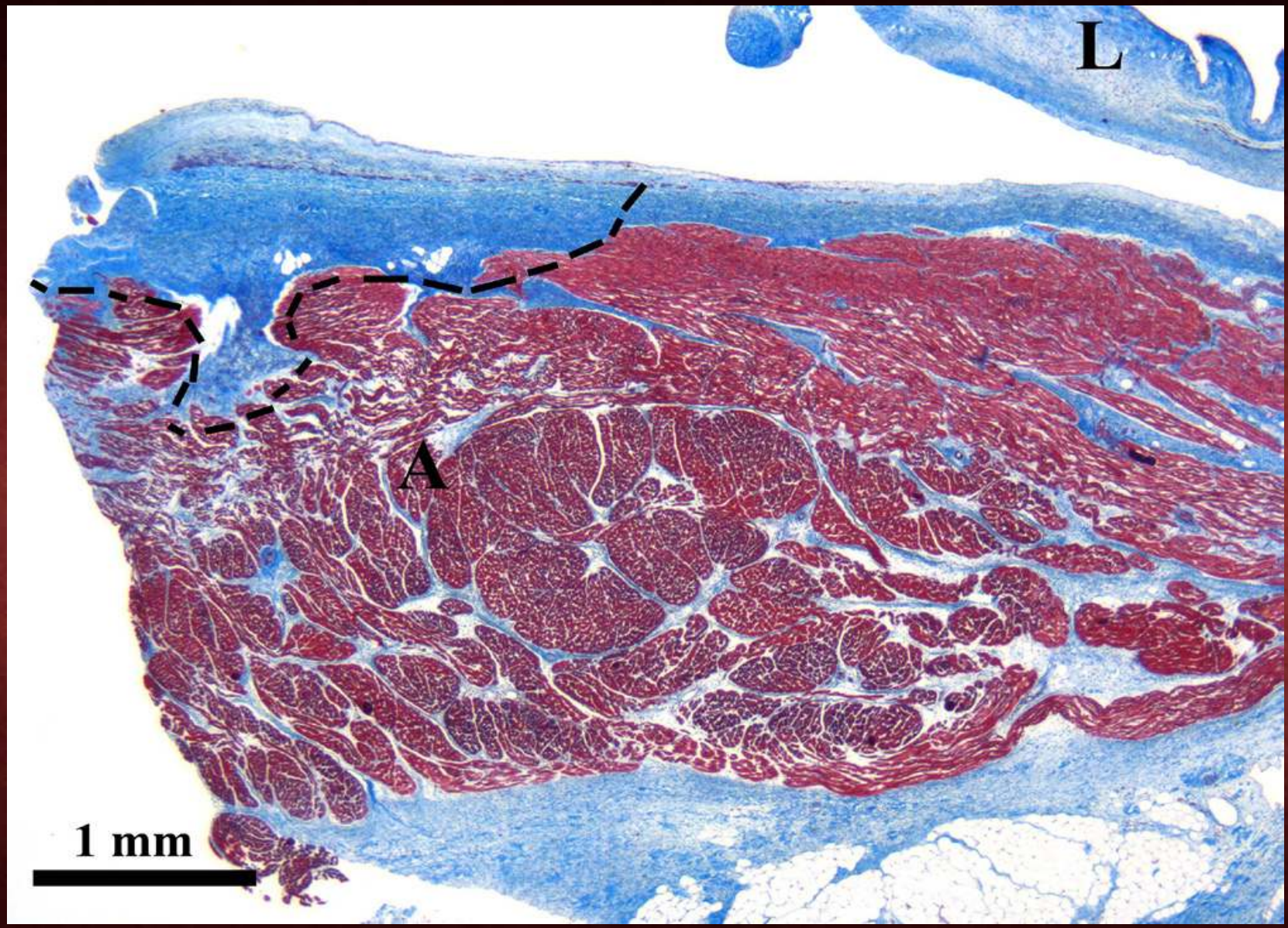

QuantumCor's
Finest Sheep
"I had MR!" I said it! Now ya happy?



Ischemic mitral regurgitation is a complication of myocardial infarction and a predictor of poor outcome.*

- Most frequently seen after inferior MI (38% of cases)
- Anteroseptal MI (10% of cases)

* Kumanohoso T, Otsuji Y, Yoshifuku S, Matsukida K, Koriyayma A, et al. Mechanism of higher incidence of ischemic mitral regurgitation in patients with inferior myocardial infarction: quantitative analysis of left vntricular and mitral valve geometry in 103 patients with prior infarction. J. Thorac Cardiovasc Surg 2003;125(1):135-43.



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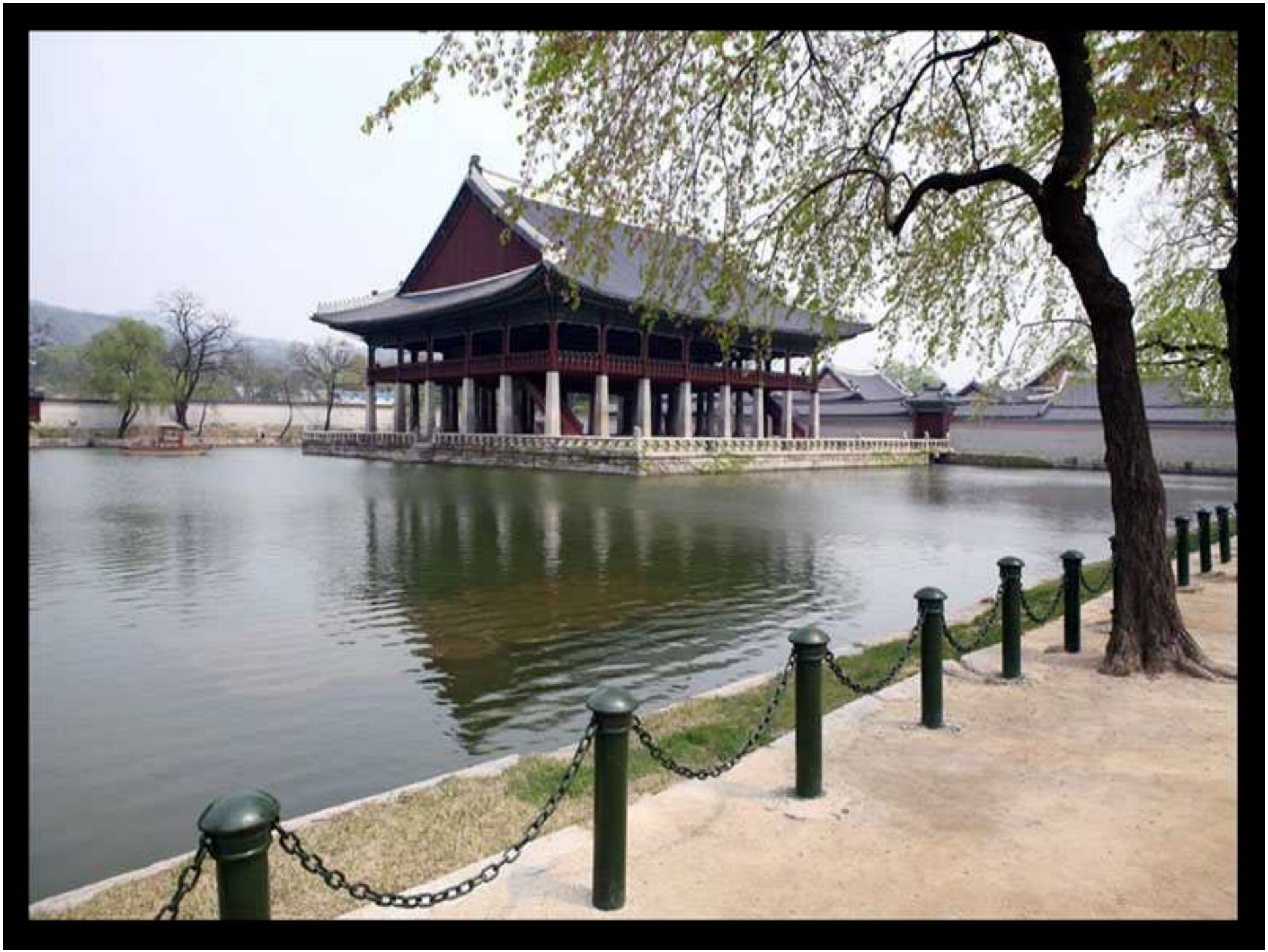

- Human collagen differences
  - -- Young normals
  - -- Old normals
  - -- MR patients

- *Human collagen differences*
  - *-- Young normals*
  - *-- Old normals*
    - *-- More collagen fibrinoid degeneration and myxomatous material*
  - *-- MR patients*
    - *-- More collagen fibrinoid degeneration and myxomatous material*

R. Heuser

We are not sure why more collagen fibrinoid degeneration in humans

R. Heuser