Aortic Valve Tissue Engineering

Defining biomechanical endpoints for tissue engineered heart valve leaflets from native leaflet properties

W. David Merryman, George C. Engelmayr Jr., Jun Liao, Michael S. Sacks

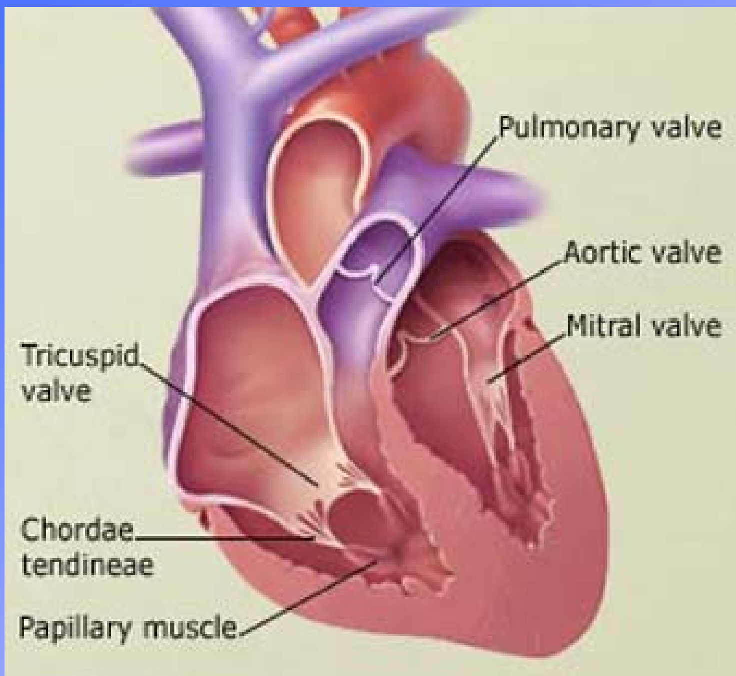
Progress in Pediatric Cardiology, 21 (2006), 153-160

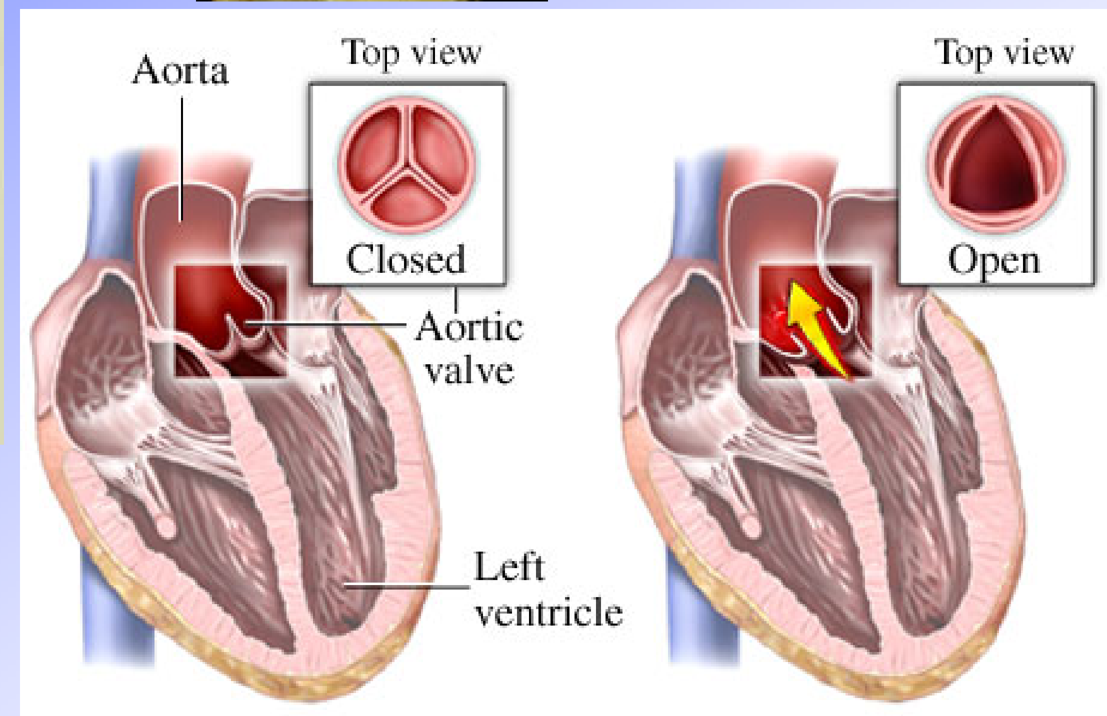
Discussion by Chi Zheng

Introduction

- Aortic valve: most commonly replaced valve ~63% of 95,000 in the U.S.
- Current procedure problematic in pediatric patients
  - Cryopreserved cadaver allograft
  - Ross procedure: pulmonary autograft and cadaver allograft
- Tissue engineering (TE) offers valve availability, appropriate size, growth potential, and immuno-compatibility.

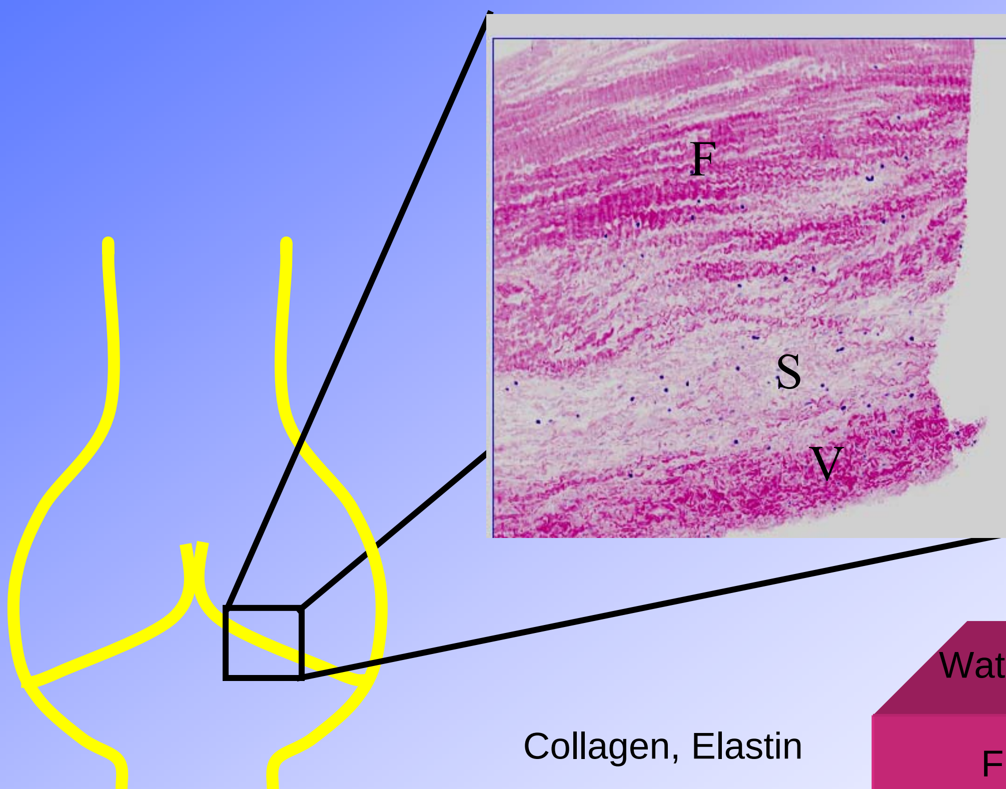
Background – Heart Anatomy

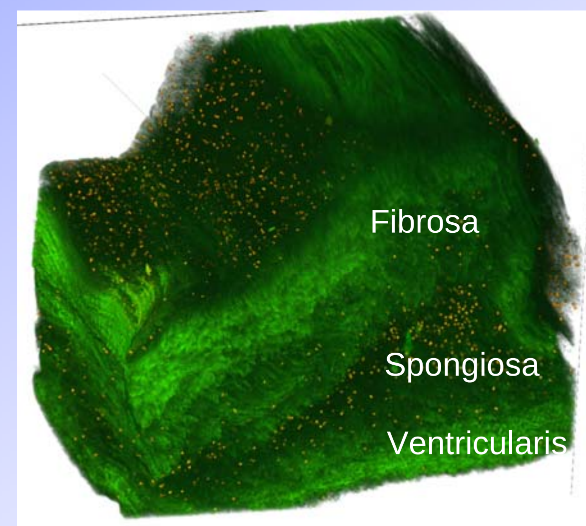


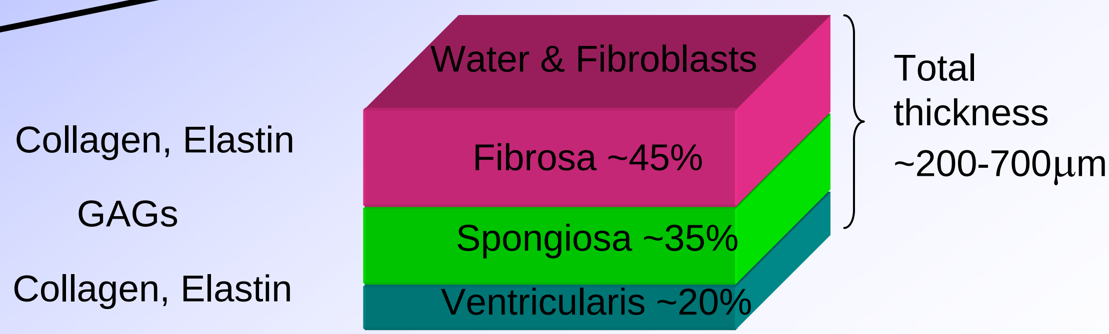


- “Lub-dub” caused by valves closing

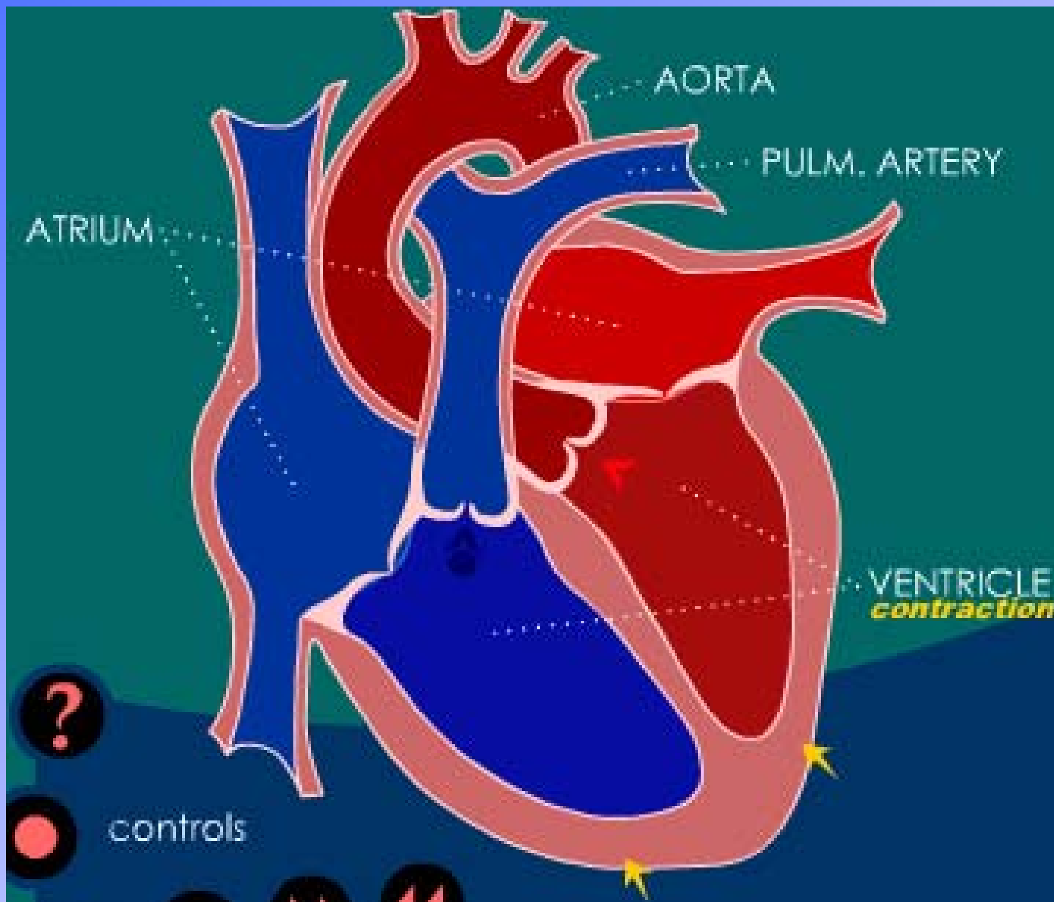
3 Layers of the Aortic Valve

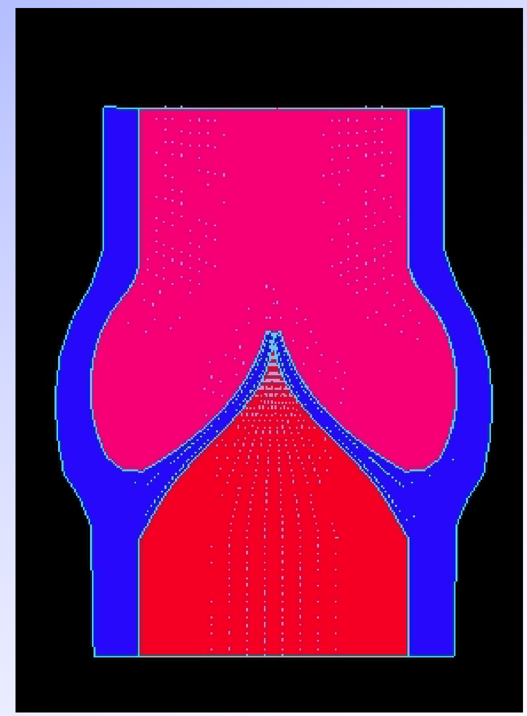


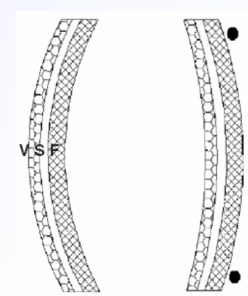




Cardiac Cycle 1

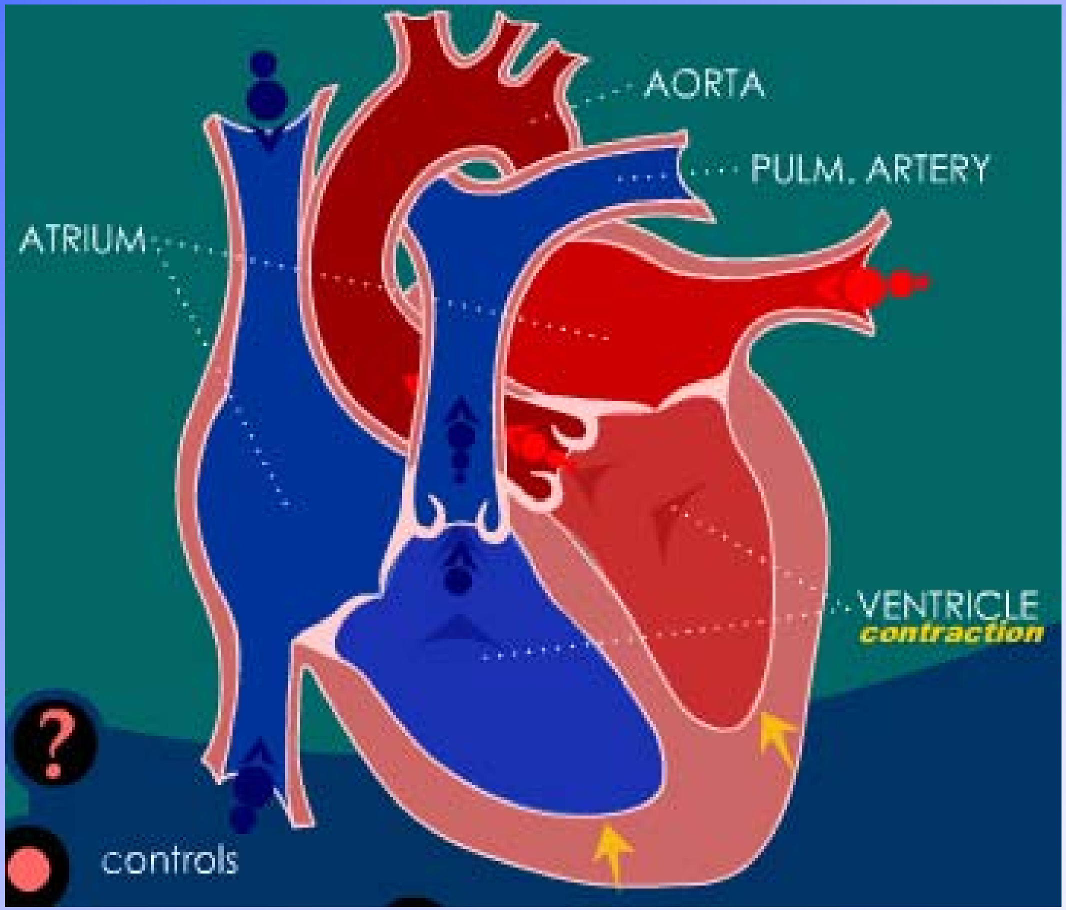


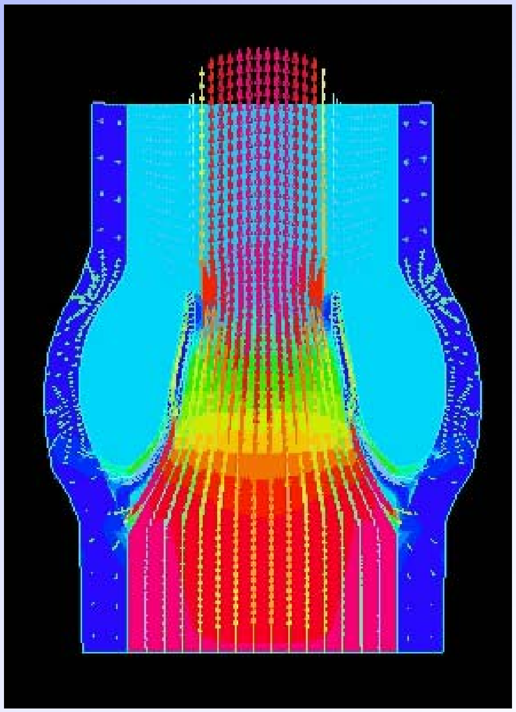




- Isovolumetric contraction: all valves closed
- Against-curvature planar tension on aortic valve

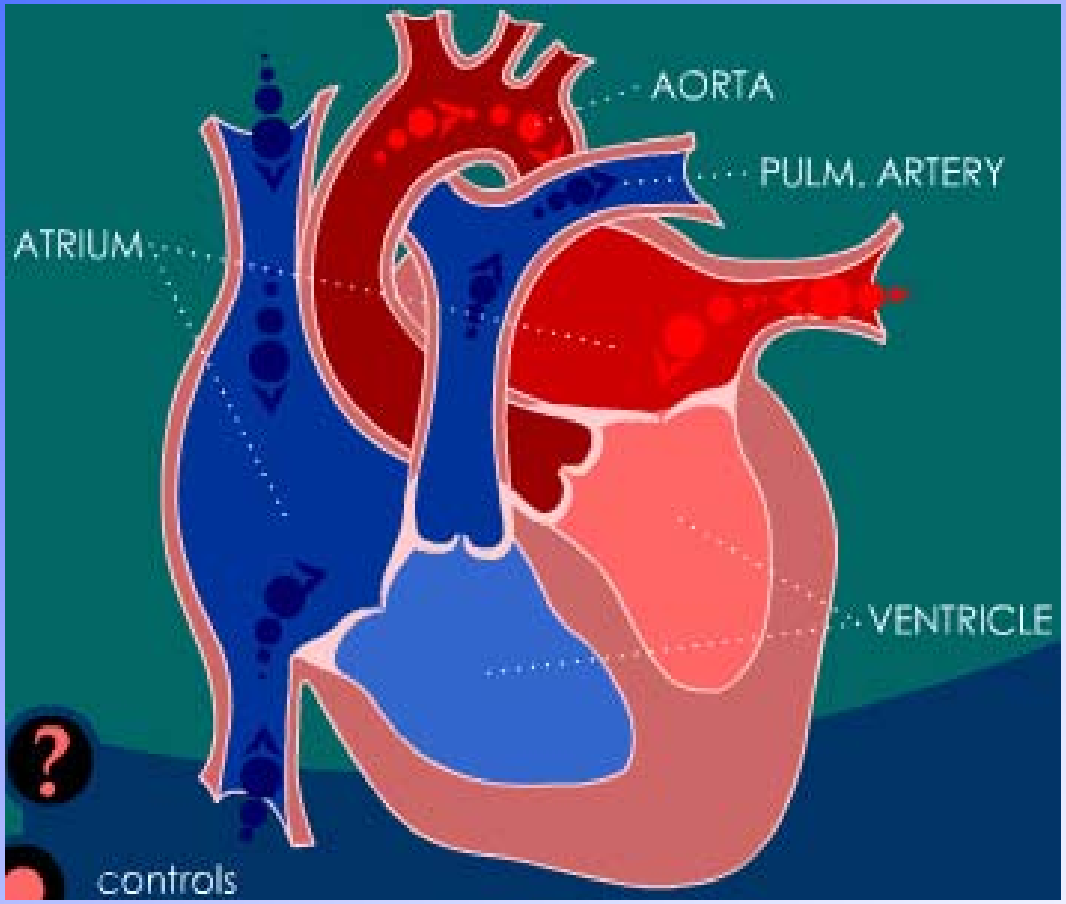
Cardiac Cycle 2

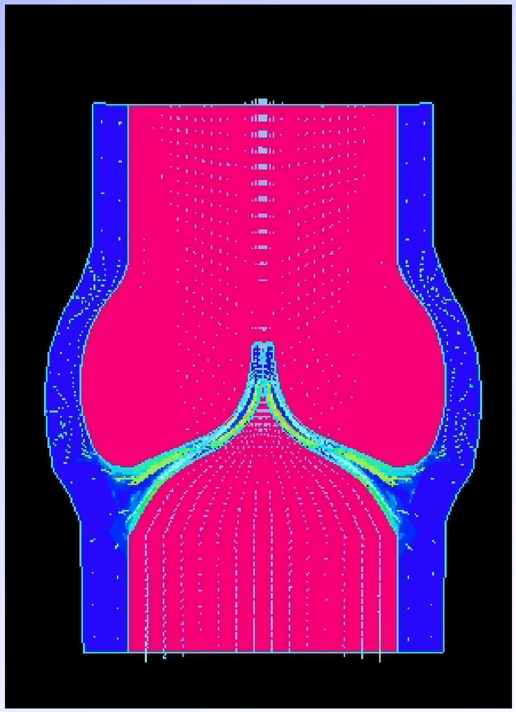




- Ejection/systemic systole: aortic valve open
- Flexure and shear on aortic valve

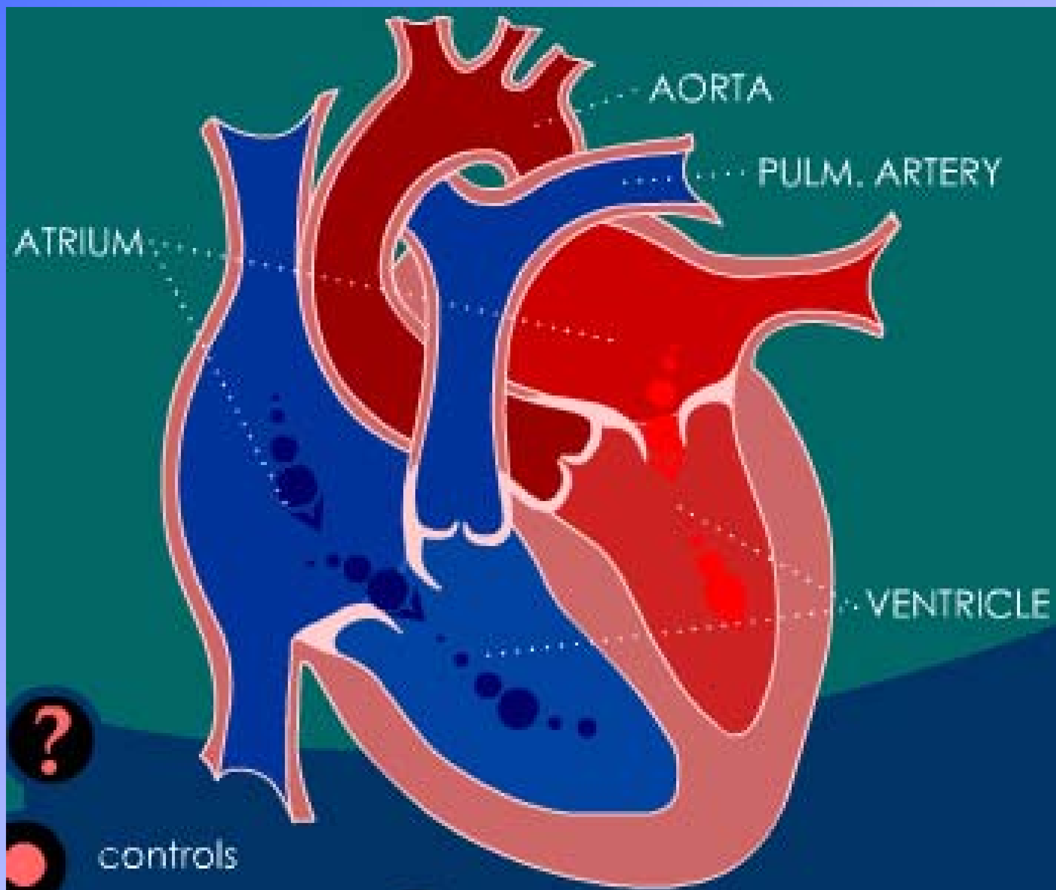
Cardiac Cycle 3

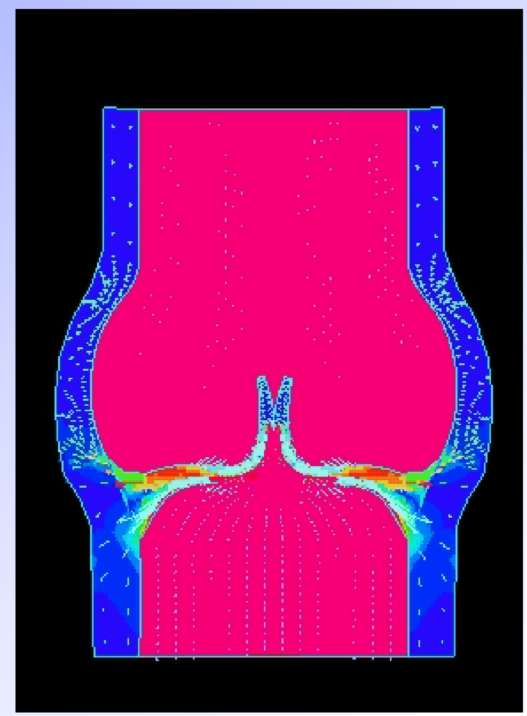


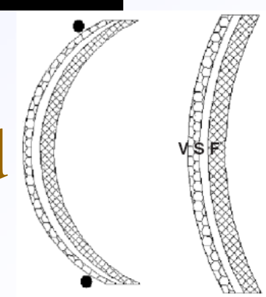


- Isovolumetric relaxation: all valves closed
- Flexure on aortic valve

Cardiac Cycle 4

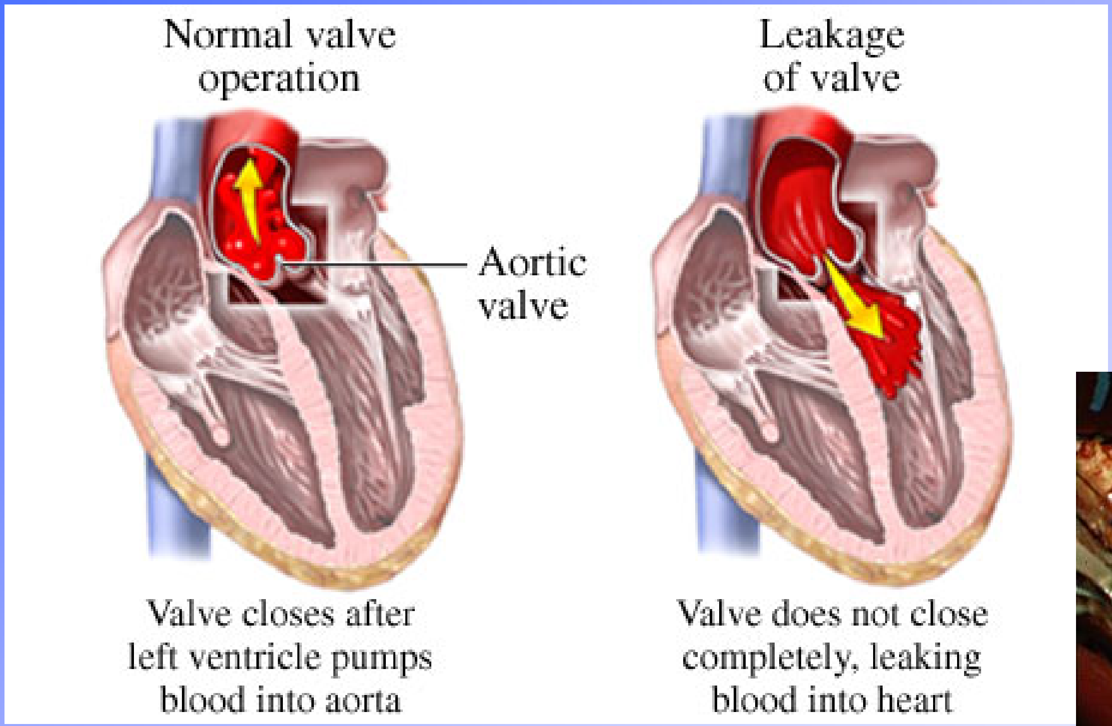


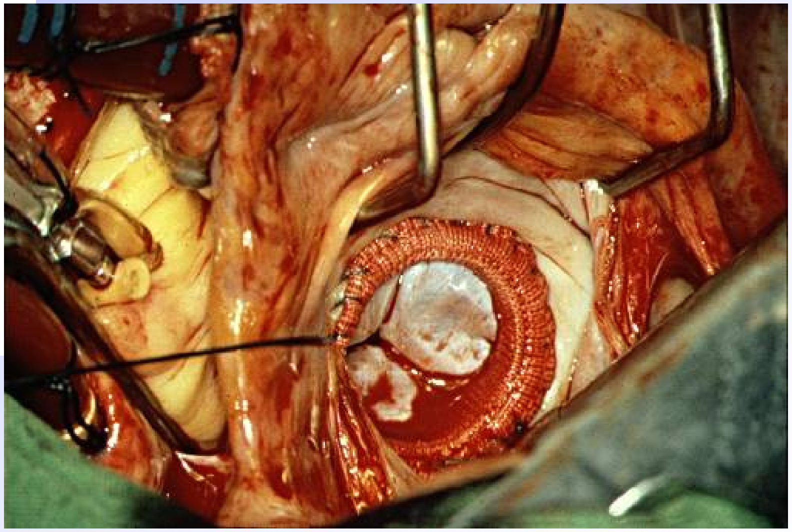




- Ventricular filling/systemic diastole: aortic closed
- With-curvature planar tension on aortic valve

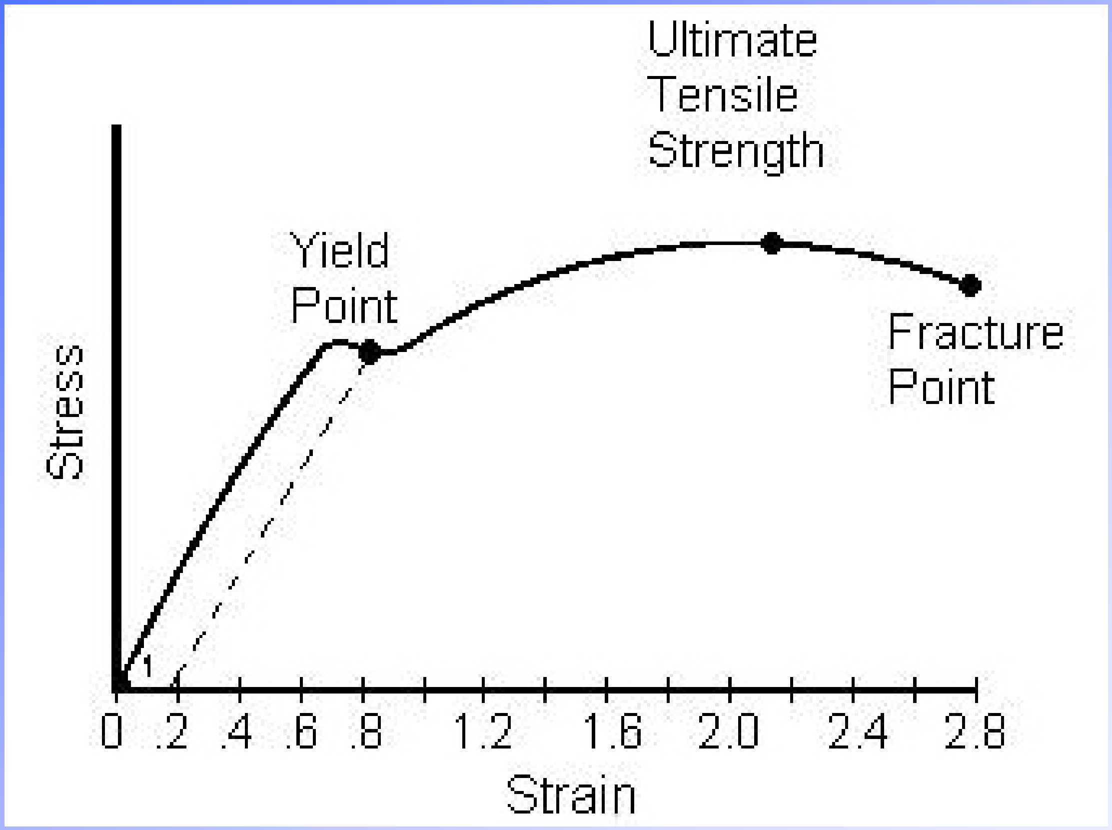
Valve Replacement





- Calcification, stenosis, infection, flexural fatigue ($3x10^9$ times/lifetime)

Background – σ-ε relationship



Stress

$$\sigma = \frac{Force}{Area}$$

Strain

$$\varepsilon = \frac{\Delta length}{length_0}$$

σ-ε relationship

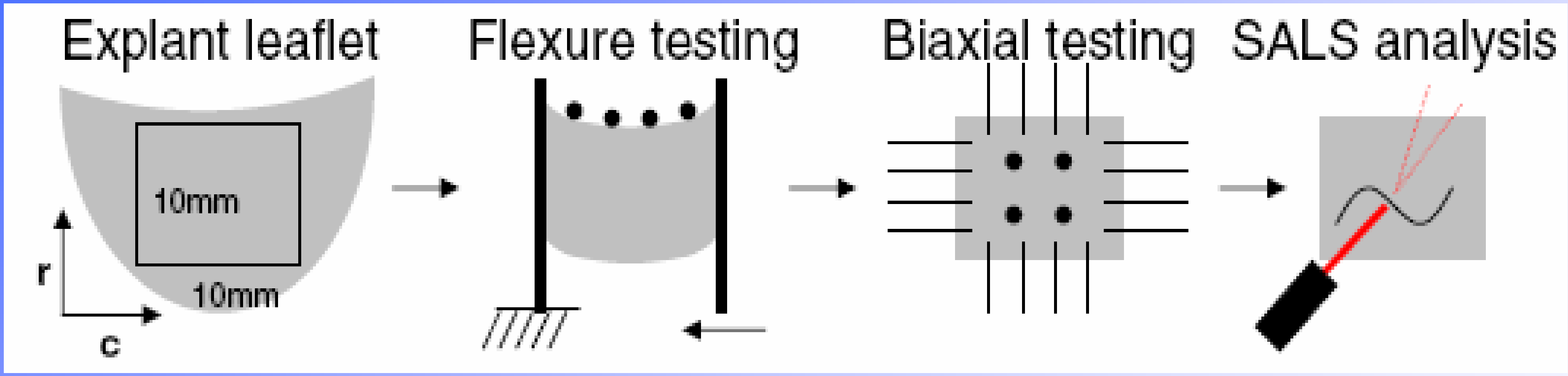
$$\varepsilon = \frac{1}{E}\sigma$$

- Tissue: non-linear elastic regime, biaxial tension, rarely reach fracture point

Goals and Objectives

- Define endpoint criteria for TE aortic valve
- Develop constitutive model to adequately characterize TE aortic valve and supporting scaffold for clinical evaluation
- Biomechanical testing: flexural, biaxial tension
- Structural analysis: small angle light scattering (SALS) laser

Method



- Explant 10x10mm square specimen from native porcine or TE valve leaflet
- CCD cameras and cyanoacrylate marker record deformations (i.e. change in curvature, strain) during biomechanical testing

Method (cont'd)

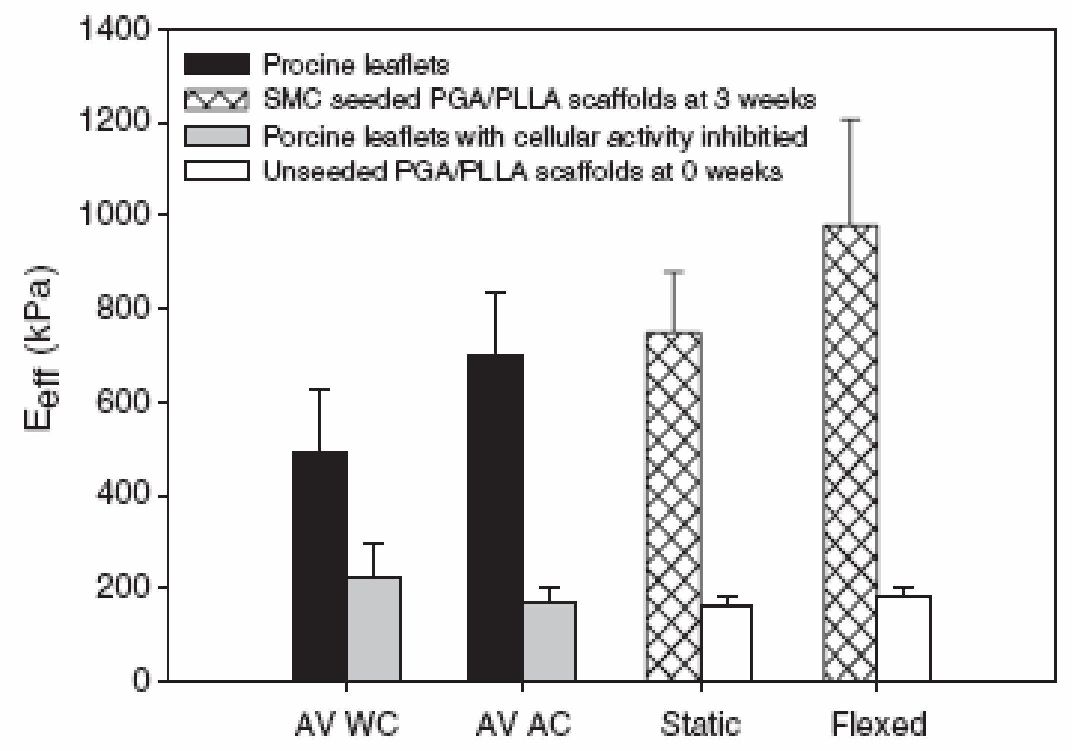
- Flexural testing yield E_{eff} (effective stiffness) for wide range of stress

  Bernouli-Euler Equation: $M = E_{eff} I \Delta \kappa$

- Biaxial testing yield stress-strain relationships at high-speed physiological strain rates
- SALS light scattering analysis reveals
  - Preferred connective tissue fiber direction
  - Fiber distribution
  - Orientation index (OI), more aligned to handle increase in tension

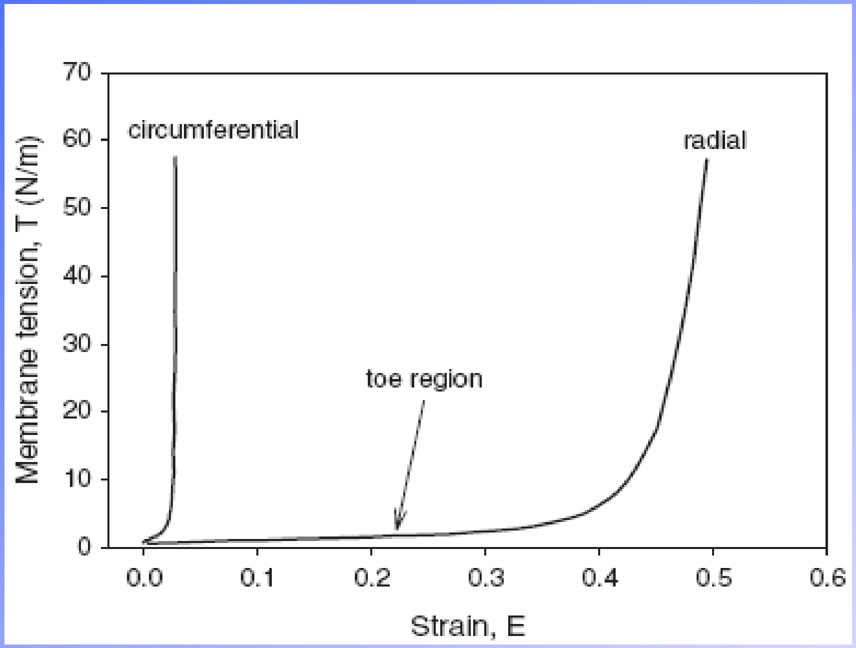
Flexural Response

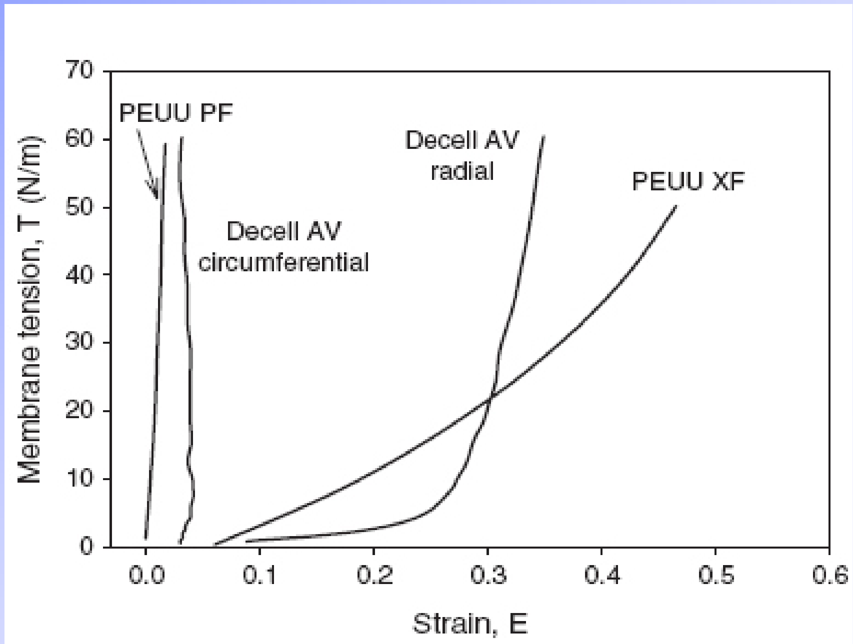
- Similar response between
  - native leaflet and smooth muscle seeded on polyglycolic acid/poly L-lactic acid scaffold
  - thapsigargin inhibited native leaflet and unseeded scaffold



- Lack of cellular activity results in loss in collagen
- Flexed or mechanical stimulated TE leaflet exhibited higher stiffness indicating increased cellular activity

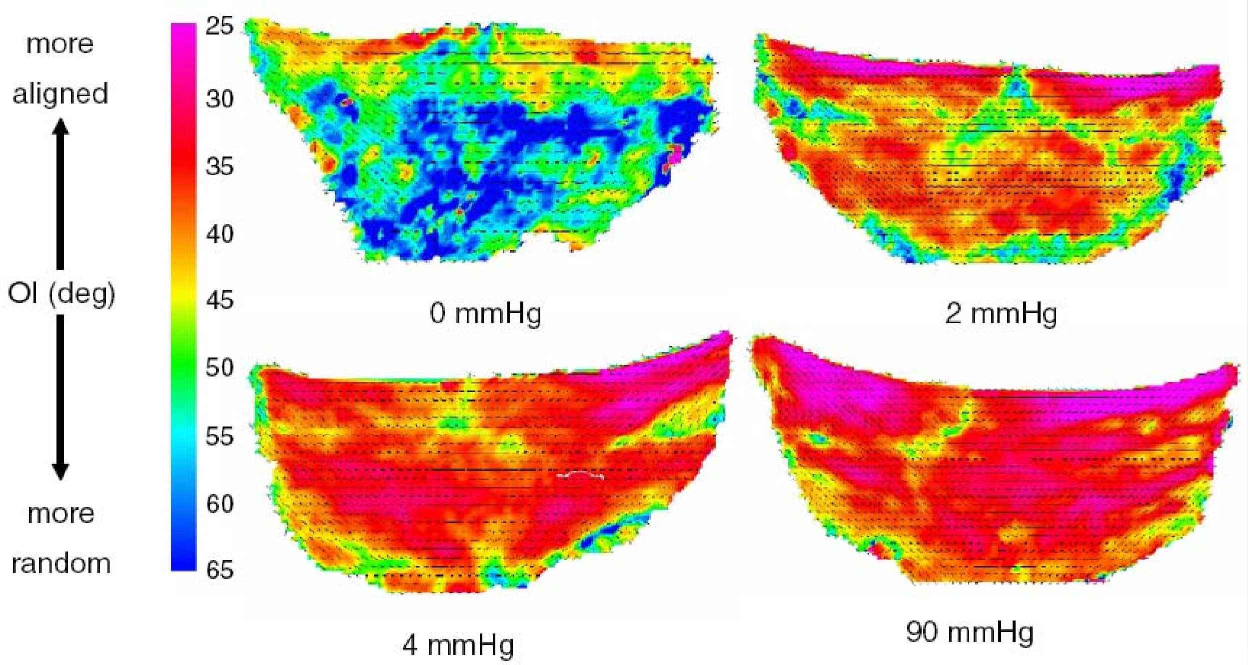
Biaxial Response





- Native: gradual radial response confirms fewer aligned collagen fiber (all stretch and remain coapted during tension)
- Decelled porcine and electrospun polyurethane urea TE scaffold exhibit similar stress-strain relationship

SALS Analysis



- SALS analysis confirm fiber alignment and straining occur during initial tension
- May help guide scaffold fabrication, not necessary to replicate

Conclusion

- Biomechanics comparison of native and TE leaflet performance show promising similarity
- Need to integrate flexural layer-specific data with biaxial coupling response
- SALS evaluates the structural architecture needed to emulate native performance
- Constitutive model needed to relate structure to function

Future Directive

- Data at cellular level may reveal more about its structure-function relationship
- Cell remodeling, mechanical fatigue, biodegradation must be examined in-vivo
- Ross procedure: pulmonary valve adapt to a higher mechanical demand. Is the reverse valid?

References

Technical content

- Merryman et al. Defining biomechanical endpoints for tissue engineered heart valve leaflets from native leaflet properties. Progress in Pediatrics Cardiology 2006. 21: 153-160
- Engineering.com. Stress strain relationship. 2000-2006. Accessed 05.29.2006. http://www.engineering.com/content/ContentDisplay?contentId=41005028

References (cont'd)

Photos

- http://webcenter.health.webmd.netscape.com/NR/rdonlyres/448D9A61-0A27-403A-941E-A4C13D856D84.jpeg
- http://images.webmd.com/images/hw/media67/medical/hw/nr551516.jpg
- http://heartlab.robarts.ca/dissect/aortic_valve.jpg
- http://images.webmd.com/images/hw/media67/medical/hw/nr551535.jpg
- http://images.encarta.msn.com/xrefmedia/sharemed/targets/images/pho/t012/T012497A.jpg
- http://www.cvgs.k12.va.us/Nuclear/Stress-Strain%20Curve.JPG

Animations

- http://medlib.med.utah.edu/kw/pharm/hyper_heart1.html
- http://www.childrenshospitalla.org/mpeg/aortic.valve.avi

¿QUESTIONS?

zheng4@gmail.com
chz14@pitt.edu