Prosthetic Heart Valves

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Natural Heart Valves

- Allow unidirectional flow of blood in the heart
- 4 Valves in the human heart- Tricuspid, Mitral, Pulmonary & Aortic
- Incorporate leaflets or cusps which are pushed open to allow blood flow & which then close together to seal & prevent backflow

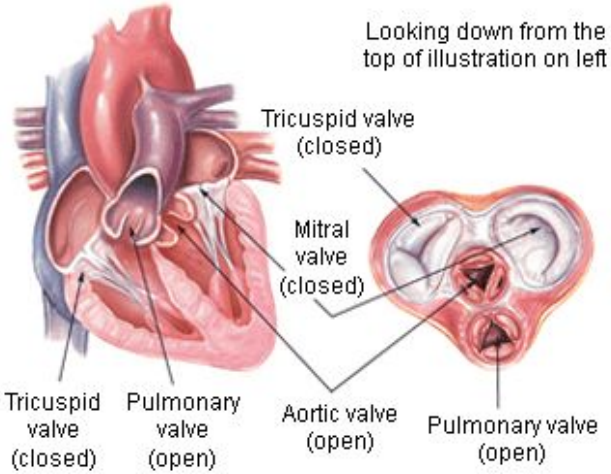


Fig: Illustration of Natural Heart Valves†

†http://www.yourheartvalve.com/heartbasics/pages/heartvalves.aspx

Loading Cycle of Natural HVs

- HVs are primarily passive structures that are driven by forces exerted by the surrounding blood & heart
- HVs must replicate their cyclic function over an entire lifetime, with an estimated functional demand of at least $3x10^9$ cycles

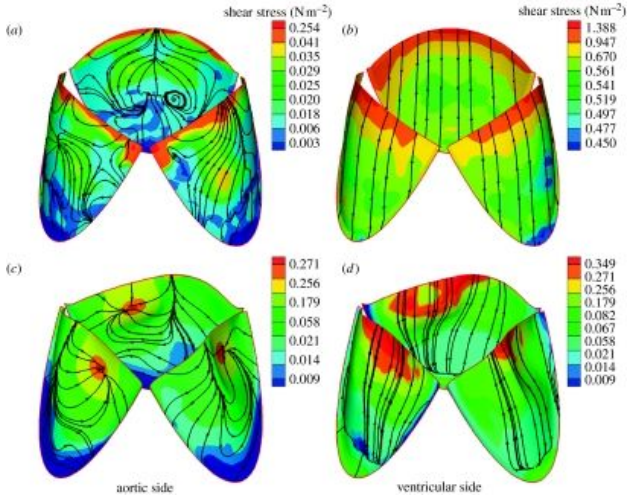


Fig: Instantaneous friction streamline & shear stress magnitude plots on the aortic (a,c) & ventricular (b,d) sides of the leaflets during the fully open (a,b) & early closing (c,d) phases of the cardiac cycle[†]

[†]M.S. Sacks, A.P Yoganathan, "*Heart valve function: a biomechanical perspective*", Philosophical Transactions of the Royal Society, 2007 Aug 29; 362(1484): 1369–1391

Properties of Natural HVs

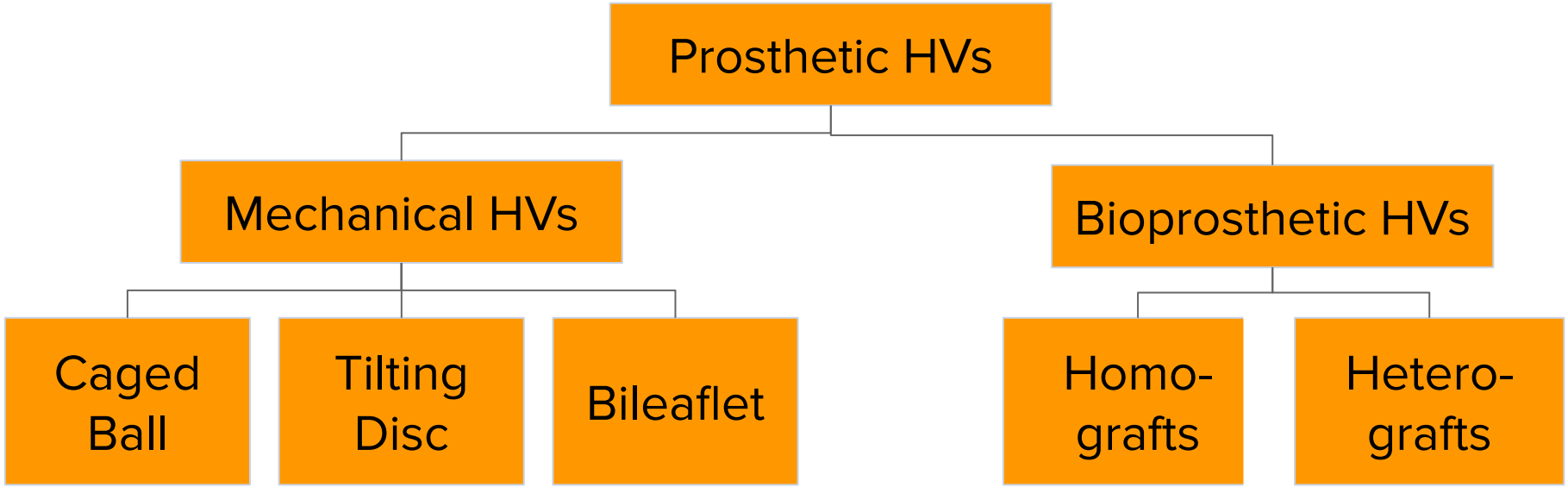
- High tensile strength to resist high Trans Valvular Pressures
- Very low flexural rigidity to allow for passive interactions with the surrounding blood
- Undergo large, rapid, directionally dependent strain when in the process of closing
- Allow for rapid cessation of strain when closed

Failure Modes of Natural HVs

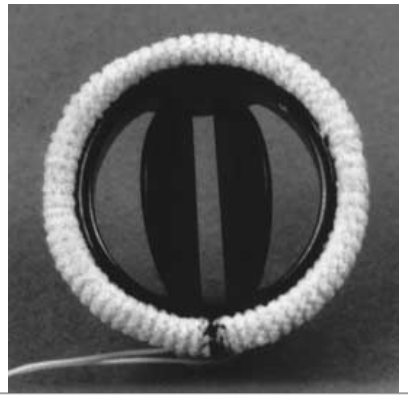
Regurgitation	Stenosis
• Leaflets of the valve fail to coapt correctly	• Narrowing of the valves
• Allows blood to flow in the reverse direction	• Prevents adequate outflow of blood

Artificial Heart Valves

Prosthetic heart valves are required to replicate the functioning of a normal heart valve & should last throughout the lifetime of the patient



Mechanical HVs

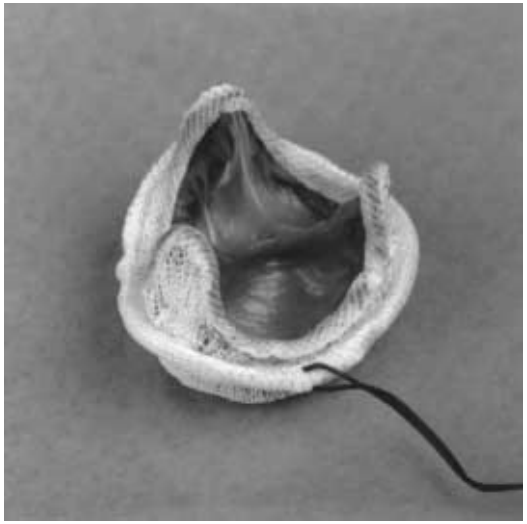


Starr-Edwards Caged Ball Valve(1960s)†	Medtronic Hall Tilting Disc Valve(1970s)†	St. Jude's Medical Bileaflet Valve(1979)†
A titanium cage, a silastic ball, & a suture ring covered with teflon	A tilting pyrolytic carbon disc with a central perforation for a thin metal strut	Two semicircular leaflets that rotate about struts attached to the valve housing

†W. Vongpatanasin, L.D. Hillis, R.A. Lange, " *Prosthetic Heart Valves*", The New England Journal of Medicine 1996; 335:407-416

Bioprosthetic HVs

- **Homografts:** Preserved human aortic valves
- **Heterografts:** Composed of bovine or porcine tissue(pericardial or valvular), mounted on a metal support



Carpentier-Edwards Porcine Bioprosthesis[†]

[†]W. Vongpatanasin, L.D. Hillis, R.A. Lange, " *Prosthetic Heart Valves*", The New England Journal of Medicine 1996; 335:407-416

Prosthetic HVs Materials

- **Mechanical Heart Valves**
  - Metals - Stainless Steel, Titanium
  - Ceramics - Titanium Dioxide, Pyrolytic Carbon†
  - Synthetic Materials- Silicone
- **Bioprosthetic Heart Valves**
  - Natural Materials - Bovine & Porcine tissue
  - Synthetic Materials - PTFE, Dacron

†C.R. Gentle, "*The use of ceramics in prosthetic heart valves",* Journal of Engineering in Medicine, Volume 16, Issue 2, 1987, p.no: 115-117

Market Evaluation

- Increase in valvular disease due to:
  - Socioeconomic factors
  - Growing life expectancy
- Currently a 4.84 billion USD market, the prosthetic HV market is projected to reach 8.86 billion USD by 2022*
- Abbott Healthcare, Edwards LifeSciences Corp., St. Jude's Medical, Medtronic PLC, & Boston Scientific Corp. are the major players in this segment

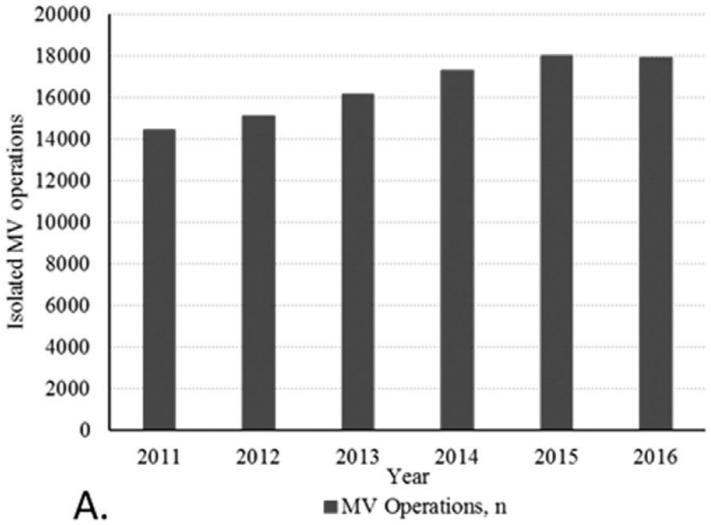


Fig: Total number of isolated mitral valve operations performed every year in 1143 major US hospitals (2011-2016)†

*https://www.marketsandmarkets.com/Market-Reports/prosthetic-heart-valve-market-245407958.html

†J.S. Gammie et al, "*Isolated Mitral Valve Surgery: The Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis*", The Annals of Thoracic Surgery, September 2018,Volume 106, Issue 3

Issues with Prosthetic HVs

- **Durability**
  - Mechanical HVs: Life of 20 to 30 years
  - Bioprosthetic HVs: Require replacement within 10-15 years[†]
- **Thrombogenicity**
  - Reduced leaflet movement, thickening of valve leaflets, changes in effective prosthesis area (stenosis or regurgitation)
  - Mechanical HVs: Highly thrombogenic; Long term anticoagulant therapy (warfarin) required
  - Bioprosthetic HVs: Less thrombogenic

[†]W. Vongpatanasin, L.D. Hillis, R.A. Lange, " *Prosthetic Heart Valves"*, The New England Journal of Medicine 1996; 335:407-416

Issues with Prosthetic HVs

- **Structural Failure**
  - Mechanical HVs: Rare
  - Bioprosthetic HVs: Calcification leads to cusps becoming rigid and rupturing
- **Embolization**
  - An unattached mass clogs arterial beds at a point distal to its origin. Eg: Thromboembolism
- **Paravalvular Regurgitation**
  - Improper implantation, sutures give way over time
  - Causes trauma to blood cells;leads to hemolysis

Solutions- Polymeric Materials

- Combine durability & strength of mechanical HVs and biocompatibility of bioprosthetic HVs
- Polyurethane (PU) is attractive option:
  - Hard (crystalline) and soft (elastomeric) segments
  - Proportion determines features like stiffness
  - Favourable mechanical and hemodynamic properties, resistance to thrombus formation
- Drawbacks: Susceptibility to degradation & risk of calcification;

Solutions- Polymeric Materials

- Soft segments are modified - three variant polymers of PU
- Polyester urethane
  - Soft segments were easily hydrolysed; hence unsuitable for long term implantation
- Polyether urethane
  - Resistant to hydrolysis but susceptible to oxidative degradation and cracking under env. stress *in vivo*
- Polycarbonate urethane
  - Resistant to oxidative degradation
  - Biodegradation is limited to peripheral layer

Solutions- Polymeric Materials

- Modification of chemical structure
  - Linking biodegradation resistant molecules
    - Eg: polydimethylsiloxane (thermal and oxidative stability)
  - Attempts to link anticalcification agents into the polymer structure
    - Eg: covalent binding of bisphosphonate (2-hydroxyethane bisphosphonic acid [HEBP])[†]

[†]Hossein Ghanbari, Helene Viatge, "*Polymeric heart valves: new materials, emerging hopes",* Colloids and Surfaces B: Biointerfaces

Solutions- Endothelialization

- Provide a coating of endothelial cells on prosthesis surface so as to reduce risks of thrombosis and autoimmune reactions
- Two techniques - Tissue Engineering & Surface Modification
- **Tissue Engineering:** Seeding of cells on the polymer surface and proliferating them *In vitro*
  - Need for providing the cell culture
  - Risk of infection

Solutions- Endothelialization

- **Surface Modification:** Modify surface of polymer so as to promote adhesion of endothelial progenitor cells (EPCs) *in situ*†
  - Application of short peptide sequences recognized by cell receptors
  - Low concentration of EPCs; Need for a **selective** surface
  - The tripeptide Arg-Gly-Asp (RGD) has been in common use
    - Also recognized by platelet integrin receptors
  - Tetrapeptide Arg-Glu-Asp-Val (REDV) is shown to have high selectivity towards human endothelial cells

†Beata A.Butruk-Raszeja, Magdalena S.Dresler, Aleksandra Kuzminska, Tomasz Ciach, "*Endothelialization of polyurethanes: surface silanization and immobilization of REDV peptide, Colloids and Surfaces*"

Conclusions

- Proposed design involves the use of Polycarbonate urethane, structurally modified by linking biodegradation resistant molecules and anti calcification molecules
- Further, surface modification techniques used to enhance affinity of human endothelial progenitor cells (EPCs) towards the prosthesis
- Expected to have longer life as a result of reduced risks of biodegradation and calcification
- Also expected to be less susceptible to thrombosis and autoimmune reactions due to endothelialization


THANK YOU