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Prosthetic Heart Valves

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ABSTRACT:
Prosthetic heart valves are amongst the most widely used cardiovascular implants across the world. Currently, 2 major types of heart valves are commercially available- mechanical heart valves & bioprosthetic heart valves. The structure, physiology & failure modes of natural heart valves are studied in detail. A historical perspective of the progress in heart valve research is presented along with a summary of the current state-of-art. The market for prosthetic heart valves is evaluated & the various socioeconomic factors involved in the rising demand for prosthetic heart valves are examined. The clinical issues faced by both mechanical & bioprosthetic heart valves are reported & contrasted. Solution approaches based on usage of polymeric materials as well as tissue engineering in developing new varieties of heart valves are discussed for the various issues encountered in the case of existing heart valve designs.

AIMS:
Natural heart valves are strong, flexible, self healing & can undergo cyclic loading for millions of cycles without failure. In the event of failure however, it becomes critical to replace natural valves with prosthetic implants so as to extend the lifetime of the affected person. The anatomy, physiology & biomechanics of natural heart valves are studied in detail to understand the structure-function relationships of natural heart valves. The proposed prosthetic implants must be able match the performance characteristics of natural heart valves as closely as possible. Further, the implants must be biocompatible & not cause any adverse reactions. Current research in tissue engineering, polymer engineering, & surface modification along with the development of innovative biomaterials have paved the way for significant improvement in biocompatibility & biostability. This paper aims to propose new viable solutions to the problems faced by current prosthetic valves to improve the success rate of long-term clinical implantation of prosthetic heart valves.

BACKGROUND:
Introduction:
The function of valves in the heart is to allow blood to flow unidirectionally in the heart. The human heart has 4 valves- the tricuspid valve & the mitral valve- which regulate the atrioventricular blood flow, & the aortic valve & the pulmonary valve- which regulate the blood flow out of the ventricles. The tricuspid & the pulmonary valves are situated in the right side of the heart, while the mitral & aortic valves are situated in the left side of the heart as shown in Fig 1.

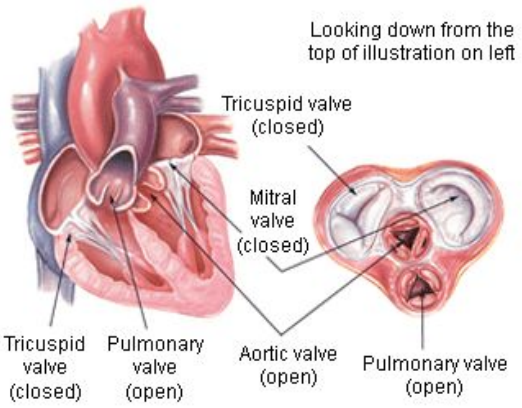

Fig 1: Illustration of natural heart valves- tricuspid valve(closed), mitral valve(closed), pulmonary valve(open) & aortic valve(open) at the stage of ventricular contraction [1]

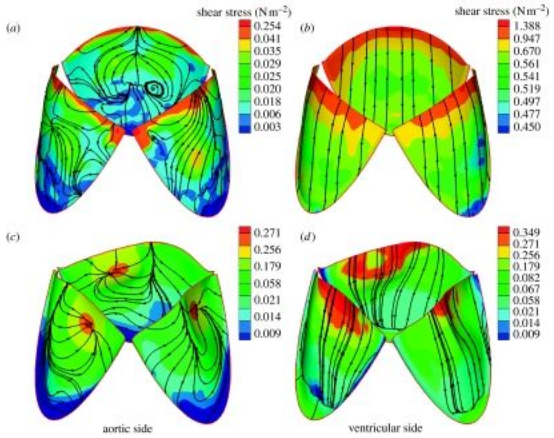

Fig 2: Instantaneous friction streamline & shear stress magnitude plots on the aortic (a,c) & ventricular (b,d) sides of the leaflets during the fully open (a,b) & early closing (c,d) phases of the cardiac cycle[2]

Structure of Natural Heart Valves:

The outermost layer of the heart valves are made up of endocardium & include leaflets or cusps which are thrust open to allow blood to flow & which then close shut to block blood from returning. The mitral valve has 2 cusps while all the other valves have 3 cusps.

Loading Cycle of Natural Heart Valves:

Valves in the heart are chiefly passive and are driven by forces wielded by the flowing blood & other cardiac muscles. With an estimated working lifecycle of about $3x10^9$ cycles, heart valves need to possess certain exceptional mechanical properties. The shear stresses on the heart valves during each stage of the cardiac cycle are shown in Fig 2. Considering the loading conditions, the cusps would need to have the following properties[2]:

- Highly tensile to withstand high Trans Valvular Pressures
- Low rigidity in bending to allow for passive interactions with the flowing blood
- Able to bear considerably high, rapid, directionally dependent strain when closing
- Allow swift cessation of strain after fully closing

Failure Modes of Natural Heart Valves:

Valvular heart disease refers to any flaw of the heart valves. It is principally seen in 2 forms:

- **Stenosis:** Narrowing of the valves
- **Regurgitation:** Allowing blood to flow in the reverse direction

Artificial Heart Valves:

Artificial heart valves are devices implanted in the diseased hearts of patients suffering from either of the above problems. They are required to replicate the functioning of a normal heart valve & should last throughout the lifetime of the patient. Prosthetic heart valves are of two main types- mechanical or bioprosthetic. Mechanical valves can be categorized based on their design as caged-ball valves, single-tilting disk valves or bileaflet valves. Bioprosthesic valves may be either heterografts(i.e. Cardiac tissue from cows or pigs), attached to a metal frame or homografts, which are preserved human aortic valves[3]. From the 1950s onwards, around 80 different types of artificial heart valves have been designed, tested & implanted

Materials used in Artificial Valves:

Mechanical heart valves are composed of several materials such as metals, polymers, & ceramics eg.: SS, Titanium, Pyrolytic Carbon(Pyrolyte), Alumina etc. Bioprosthetic valves are made from artificial materials, eg.: Teflon, Dacron etc. & substances of biological sources,eg.: bovine pericardium, porcine heart valves.[4]

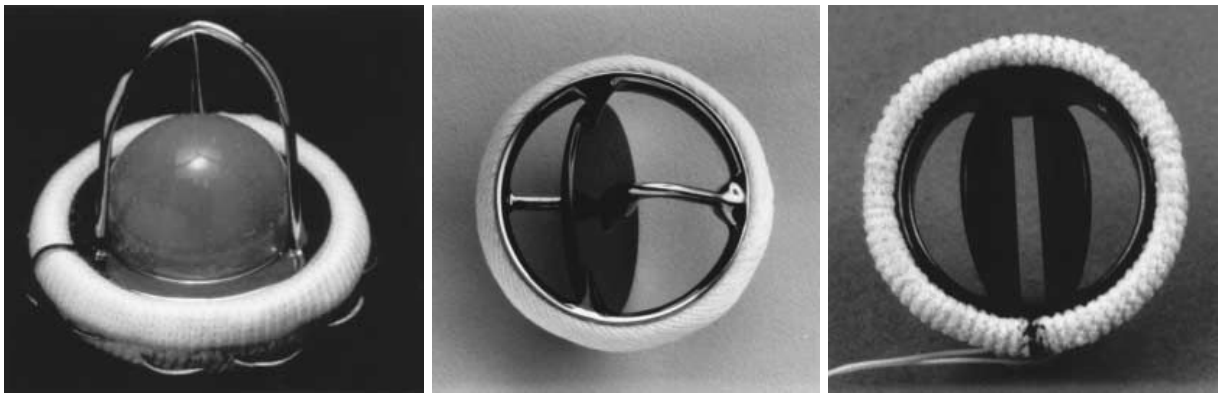

Fig 3: The Starr-Edwards caged ball valve, the Medtronic Hall tilting disc valve & the St. Jude's Medical bileaflet valve

The first caged-ball model was introduced by Starr-Edwards LifeSciences(Fig 3) in the 1960s in the USA. This used a titanium cage, a silastic ball, & a suture ring covered with teflon. The silastic ball of the valve had a tendency to absorb liquid which at times malformed it & resulted in jamming[5].

In the late 1960s a new material-pyrolytic carbon was used to replace the silastic ball so as to reduce the ball wear. However, the harder ball & softer titanium cage caused the struts to wear & sometimes also break. Bokros found that highly polished Pyrolyte was the most thromboresistant material as it would not react with Heparin[6]. The fabrication of pyrolytic carbon was a

milestone breakthrough in mechanical heart valve development & it became the primary biomaterial for almost all mechanical heart valves.

In the mid 1970s, the tilting disc valves came into existence. The fundamental composition of the design was a thin metal strut that acted as a guide for a tilting disc made of Pyrolyte during opening & closing of the valve[5]. This was popularised by Medtronic(Fig 3) with more than 300,000 successful implants performed over the course of the last 40 years.

Just after the era of tilting disc models, the bileaflet heart valve model was introduced in 1979. Two semicircular leaflets rotating about struts connected to a Teflon coated ring was the key feature of this design[5]. St. Jude's Medical(Fig 3) were one of the pioneers of development of these valves.

The TTK Chitra valve was developed in Sri Chitra Institute in Trivandrum & first implanted in December 1990. This valve was composed of a tilting disc made of ultra-high molecular-weight PE and enclosed in an integrally machined cobalt-based ally cage, with a polyester suture ring[5]. More than 75000 have been implanted.

Currently, there are several companies manufacturing both mechanical & bioprosthetic heart valves such as Abbott Healthcare, TTK healthcare, St. Jude's Medical, Medtronic Inc., Boston Scientific Corporation, ValveXchange Inc., etc.

Market Evaluation:

Socioeconomic factors such as lifestyle-induced dietary habits, physical inactivity & other habits such as smoking have led to an increasing prevalence of heart valve diseases. These factors, in addition to the growing life expectancy of the geriatric population, has led to a substantial growth in the global heart valves market. The number of mitral valve surgeries performed in the USA keeps increasing year on year(Fig 4)[7]. Currently, a 4.84 billion USD market, the prosthetic heart valves segment is projected to reach 8.86 billion USD by 2022[8].

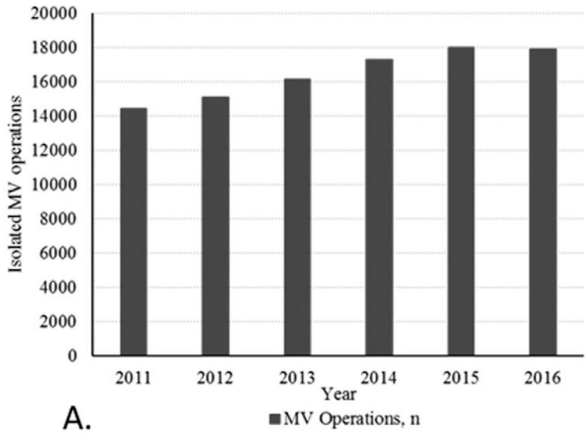

Fig 4: Number of isolated mitral valve operations performed every year(2011-2016)

CURRENT ISSUES IN THE PRODUCT:

The key characteristics of any prosthetic valve are durability (longevity), thrombogenicity & haemodynamic profile.

Durability: It is generally not a concern in case of mechanical prosthetic valves, usually lasting 20 to 30 years. However, bioprostheses have a reduced life, with 10 to 20 percent of homograft bioprostheses & 30 percent of heterograft bioprostheses requiring replacement within 10 to 15 years of implantation[3].

Thrombogenicity: A major complication that occurs when a prosthetic valve is implanted is thrombosis i.e. blocking of blood flow due to a blood clot formation inside the blood vessel [9]. All foreign materials introduced in the cardiovascular system, including heart valves are thrombogenic in nature. Prosthetic-valve thrombosis refers to the formation of thrombus on the surface of the prosthesis, leading to impaired functioning of the valve [10]. Impaired function can cause reduced motion of the valve leaflets, thickening of the valve leaflets, changes in effective prosthesis orifice area (which leads to stenosis or regurgitation)[11,12]. The rate of prosthetic-valve thrombosis incidents has been reported to be 0.1 to 5.7 percent per patient-year [3]. Currently, this complication is managed by keeping the patient on long term anticoagulant therapy as a preventive measure. Moreover, the currently popular anticoagulant, warfarin which is a Vitamin K Antagonist (VKA) has well described disadvantages such as extensive food drug interaction & necessity for regular anticoagulant monitoring. Although Novel Oral Anticoagulants (NOACs) are gaining popularity, adoption into clinical practice has been slow due to factors such as uncertainty about dosing in certain patient populations & drug cost[13].

Structural Failure: Structural failure of mechanical prosthetic valves is rare but there have been reports of incidences of fracture of the valve ring strut. Strut fracture leads to embolization of the disk & is manifest as cardiovascular collapse, dyspnea or loss of consciousness. Structural failure is more common in bioprosthetic valves with about 30 percent of heterograft bioprosthetic valves & 10 to 20 percent of homograft valves requiring replacement within 10 to 15 years [14][15][17-19]. Bioprosthetic heart valves are susceptible to calcification which causes the cusps of the valve becoming rigid & eventually rupturing, leading to severe regurgitation & in some cases even severe valvular stenosis.

Embolization: An embolus is an unattached mass that through the bloodstream which is capable of clogging arterial beds at a point distal to the point of its origin when the blood vessels become thin. The incidence of embolization is roughly 4 percent per patient-year in the absence of antithrombotic therapy. However, this statistic goes down to 2 percent per patient-year with antiplatelet therapy, & 1 percent per patient-year with warfarin therapy [21]. Majority of

embolizations manifest themselves as cerebrovascular events [22,23]. In particular, the risk of embolization is increased in case of caged-ball type valves & mitral valve prosthesis [21,24].

Haemolysis: Haemolysis is the rupture or destruction of red blood cells. A prosthetic valve implant can cause trauma to the red blood cells leading to haemolysis. A common cause for haemolysis is paravalvular regurgitation. This condition manifests itself as anemia, congestive heart failure, fatigue, jaundice, dark urine, & a regurgitant murmur [25].

Paravalvular Regurgitation: Although uncommon, paravalvular regurgitation is a serious complication of prosthetic valve implants. One of the reasons for this condition is improper implantation of the valve. In case of mild paravalvular leaks, the patient may be asymptomatic or have mild haemolytic anaemia. Paravalvular leaks occur with an incidence rate of 2–10% in the aortic position & 7–17% in the mitral position.

PROPOSED SOLUTIONS:

From the above discussion, it can be seen that both mechanical heart valves as well as bioprosthetic heart valves have their drawbacks. Mechanical heart valves though durable, are accompanied by an increased risk of thrombosis whereas bioprosthetics though less likely to cause thrombosis, are not as durable as mechanical valves requiring a replacement surgery after some time.

Exploring Polymeric Materials:

The idea of using polymeric materials for heart valves is now gaining interest as it shows promise in combining the durability of the mechanical heart valves with the biocompatibility of the bioprosthetic heart valves. Early clinical results were unsatisfactory, mainly due to limited durability and hence polymeric heart valves did not reach commercialisation. Advances in design and fabrication methods of heart valves have the potential to tackle the durability issue and lead to heart valves that can be used for long lasting implantation.

Attempts at using synthetic polymers as heart valve materials have been done since the 1950s, however, initial setbacks have rendered R&D of prosthetic heart valves made of polymeric materials to be slow. Advances in material sciences, though, have resulted in superior polymers which has drawn attention back to research on polymeric heart valves. Progress in polymer synthesis methods and nanotechnology has given rise to many biostable polymers with improved properties, making them attractive candidates as prosthetic valve material.

The characteristics of a viable heart valve alternative are biostability, haemocompatibility, anti-thrombogenicity, resistance to degradation and calcification and good endothelial cell affinity. Since 1950s, several materials synthetic materials have been investigated as materials for valve leaflets. Some of the materials tested are silicone and polyolefin rubbers [26-31].

However, these did not turn out to be viable because of but were low durability and were thus disregarded as materials for heart valves. Polytetrafluoroethylene (PTFE), commonly known by the name of 'Teflon', was also tested but it turned out to be thrombogenic and susceptible to calcification [27].

Polyurethane (PU) has been one of the most successful and popular biomaterials [32-34] because of its favourable properties. Polyurethane has a unique microstructure consisting of hard and soft segments. The soft segments are elastomeric whereas the hard segments are crystalline in nature. Furthermore, the proportion of these segments regulates critical features of like stiffness. It is particularly attractive as a material for cardiovascular devices because of its favourable mechanical and hemodynamic properties as well as its resistance to thrombus formation [35,36]. However, the drawbacks related to polyurethane are susceptibility to degradation, and risk of calcification which continues to be a hurdle in using it as a material for a long-term implant [34].

Attempts have been made to address these issues by modifying its two phase microstructure. The soft segments are more vulnerable [37] and hence these have been modified based on which there are currently three types of PUs - polyester urethane, polyether urethane and poly carbonate urethane that have been developed and tested.

The earliest variants of PUs were polyester urethanes. However, the modification of soft segments meant that they were quickly hydrolysed. Hence, these turned out to be inappropriate for implantation for long periods. Next, were developed, polyether urethanes or PEUs which were exceptionally resistant to hydrolysis and substituted polyester urethanes for two decades [38]. However, it has been shown recently that the soft segments of this polymer are susceptible to oxidative degradation and cracking under environmental stress *in vivo* [39,40]. Following this, there was the development of polycarbonate urethanes (PCUs) which overcame the problem of PEUs with enhanced oxidative stability [41-42]. PCUs are also less biodegradable and moreover, this degradation is restricted to a thin peripheral layer [39].

Attempts have also been made to increase biostability by making substitutions to the chemical structure of PUs. An efficient way to increase the biostability of PU is by linking biodegradation resistant molecules to the material. Although, the integration of anti calcification agents into the polymer structure has also been tried, there is not enough data available currently to provide evidence of this method in long-term *in vivo* applications [43-44].

Surface Modification:

Interactions between a biomaterial and the biological system is governed by the surface characteristics of the biomaterial and these interactions in turn govern the biocompatibility of the biomaterial. The factors that govern the biological reactions at the interface are the chemical

properties, physical properties, morphology and topology[45]. The important advantage that surface modification techniques present is their ability to selectively alter surface properties of the polymeric materials while still preserving the bulk properties [46].

For instance, the affinity of a surface to particular cells, such as endothelial cells can be increased by methods like plasma immersion ion implantation [46,47], cholesterol [48] and peptide modifications [49]. This will result in the formation of a layer of endothelial cells around the surface which is extremely desirable as this can safeguard the material against autoimmune reactions as well as enhance the hemocompatibility [50].

CONCLUSION:

It is proposed that a synthetic polymeric material such as polycarbonate urethane be chosen for the prosthetic heart valve material and its characteristics be further improvised by making substitutions to the chemical structure of the material. Polycarbonate urethane has already proven its hemocompatibility and durability. Subsequent substitutions, can lead to a material that is hemocompatible, durable and resistant to biodegradability. Moreover, substitutions with anti calcification agents can reduce the susceptibility to calcification and thus prevent tears and ruptures, although this still lacks clinical evidence in the form of *in vivo* studies. This material can then be endothelialized using surface modification techniques described above so as curtail the threat of autoimmune reaction.

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