Heart valves

Citation for published version (APA):

Document status and date:
Published: 01/01/1996

Publisher Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Heart valves: Facts and Visions
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WFW - rapport 96.126

September 1996
Technische Universiteit Eindhoven
Faculteit Werktuigbouwkunde
Vakgroep Fundamentele Werktuigkunde
ABSTRACT

The department WFW, Faculty of Mechanical Engineering of the Eindhoven University of Technology, has developed a new design for a heart valve prosthesis. This design comprises a trileaflet valve with EPDM-rubber as the matrix material, reinforced with polyethylene fibres. Prototypes of the new heart valve prosthesis are currently investigated. In order to meet the requirements for the 'perfect' heart valve prosthesis, detailed knowledge concerning the functioning and behaviour of the natural valve is necessary as well as the state of the art of heart valve prostheses.

A concise overview of current literature concerning heart valve prostheses is presented in this report. Main topics addressed include: anatomy and physiology of the natural (aortic) valve, the performance of current commercially available prosthetic heart valves and experimental data of synthetic prototypes. Problems, relevant to the development of a synthetic valve, are discussed and prior conditions for further progress are presented.
### CONTENTS

Abstract 

Contents 

I. Introduction 

II. The normal anatomic valve: anatomy & physiology 

III. Valve prostheses 
   3.1 Introduction 
   3.2 Design problems 
   3.3 Pericardial valves 
   3.4 Calcification 

IV. Synthetic valves 
   4.1 Design 
   4.2 Calcification 

V. Discussion 

References 

Appendix: Valve replacement, freestyle stentless valve 

Vocabulary

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>p. 1</td>
</tr>
<tr>
<td>Contents</td>
<td>p. 2</td>
</tr>
<tr>
<td>I. Introduction</td>
<td>p. 3</td>
</tr>
<tr>
<td>II. The normal anatomic valve: anatomy &amp; physiology</td>
<td>p. 6</td>
</tr>
<tr>
<td>III. Valve prostheses</td>
<td></td>
</tr>
<tr>
<td>3.1 Introduction</td>
<td>p. 13</td>
</tr>
<tr>
<td>3.2 Design problems</td>
<td>p. 15</td>
</tr>
<tr>
<td>3.3 Pericardial valves</td>
<td>p. 21</td>
</tr>
<tr>
<td>3.4 Calcification</td>
<td>p. 23</td>
</tr>
<tr>
<td>IV. Synthetic valves</td>
<td></td>
</tr>
<tr>
<td>4.1 Design</td>
<td>p. 25</td>
</tr>
<tr>
<td>4.2 Calcification</td>
<td>p. 28</td>
</tr>
<tr>
<td>V. Discussion</td>
<td>p. 30</td>
</tr>
<tr>
<td>References</td>
<td>p. 33</td>
</tr>
<tr>
<td>Appendix: Valve replacement, freestyle stentless valve</td>
<td>p. 37</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Human heart valves are passive devices that open and close in response to changes in pressure to maintain the unidirectional flow of blood through the heart. When functioning normally, they are extremely efficient, having minimal resistance to forward flow and allowing only trivial backflow when closed. In certain situations, the efficiency of the valves may be severely compromised. Pathological changes may result in a restriction of the free opening of a valve (stenosis) or loss of competence allowing backflow through the closed valve (regurgitation). In extreme cases, a valve may be both regurgitant and stenotic. Mitral and aortic valves are most frequently affected. In all instances, the work load for the heart is increased and, depending on the severity of the lesion and the ability of the heart to adapt to the increasing work, cardiac function may be compromised. For patients with severely symptomatic valve disease, valve replacement offers cardiovascular function, long-term survival and quality of life. Artificial heart valves were first used in the late 1950s and early 1960s. Following the success of these early implants, the replacement of diseased or damaged valves with prosthetic substitutes rapidly became accepted as a routine clinical procedure. During the next 30 years, the field of heart valve replacement became one of the major growth areas in cardiac surgery, and it is estimated that over 150,000 valves are replaced in the world each year. Following an initial steady increase in the number of implants, the requirement for valve substitutes in the United States and Europe is beginning to stabilize. World demand for these devices, however continues to expand at a rate of 10%-12% per year.

Since the introduction of the first mechanical prosthesis, the Starr-Edwards ball valve over 30 years ago and the first biological Hancock standard porcine prosthesis over 20 years ago, there have been extensive developments in mechanical and biological valvular substitutes. The advancements in mechanical prostheses, in design and materials, have been made to reduce the incidence of thromboembolism and thrombosis, and to eliminate the rare occurrence of deterioration of structural components. Heterografts tissue, namely porcine aortic valves and bovine pericardium, was utilized for valvular substitutes following the introduction of glutaraldehyde preservation by Carpentier and colleagues. Biological prostheses were popular in the 1970s because of the potential reduction of thromboembolism and anticoagulant related hemorrhage associated with mechanical prostheses. The durability of biological prostheses became a significant concern in the 1980s because of the presence of dystrophic calcification and stress related failures, and resulted in the resurgence of the use of mechanical prostheses with advanced designs and materials. The 1980s also brought new biological prostheses with advanced tissue preservation techniques and stent designs to control calcification and stress related fatigue injuries and to optimize hemodynamics. The main characteristics of the current available prosthetic valves are described schematically below.
Mechanical prostheses:  - ADVANTAGES:
  - superior and long-term durability
  - consistency of manufacture and high quality control

  - DISADVANTAGES:
  - unnatural form and fluid flow
  - patient usually requires long-term anticoagulant therapy
  - high incidence of thromboembolism
  - noise and mechanical dysfunction may be fatal

Biological protheses:  - ADVANTAGES:
  - more natural form and function
  - less need for long-term anticoagulant therapy
  - silent with central flow
  - low incidence of thromboembolism
  - reoperation may be safely predicted

  - DISADVANTAGES:
  - in vivo calcification and tear
  - consistency of manufacture and quality control more difficult
  - unproven long-term durability
  - generally not recommended for children

The autologous and homologous grafts are also biological prostheses. Allografts have superior hemodynamics in valve replacement. Due to shortage of suitable donor organs, availability of these valves is restricted mainly to infective endocarditis and aortic valve disease in young patients.

Direct comparison of the "total" performance of artificial heart valves is difficult, if not impossible. The precise definition of criteria used to benchmark valve performance varies from study to study. By the very nature of the goal of providing long-term performance, large numbers of patients and lengthy periods of observation are required, and during these periods there may be evolution in valve materials or design and in the medical treatment of patients with prosthetic heart valves.

The age of the patient at implantation and the underlying valvular heart disease(s) are extremely important factors in valve choice and longevity, as well. Furthermore, a valve design suited for the aortic position may not be appropriate for the mitral position. Nonetheless, clear characteristics of current valves can be identified. Mechanical valves tend to have greater durability at the expense of requiring life-long anticoagulant therapy because of their tendency toward thrombosis, while bioprostheses tend to deteriorate more rapidly due to degenerative processes but do not require anticoagulant therapy.

Consequently, it is not possible to categorize any particular valve as the best. Despite many improvements in the heart valve replacement surgery the choice of an artificial heart valve seems to remain confusing and depend on characteristics of the patient. Over the years, there have been many developments in valve design and several hundred different configurations have been considered. The majority of these have been abandoned due to problems discovered during preclinical evaluation. The ideal valve should be durable and efficient in terms of minimal resistance to forward flow and minimal backflow. In addition, it should not stimulate thrombosis or cause damage to the cellular or molecular components of the blood.
A solution could be a synthetic trileaflet heart valve with the durability of a mechanical and the hemodynamic performance of a biological valve without the need for anticoagulant therapy is. There have been already numerous studies on this subject, but no satisfactory results have been achieved yet.

At the Department of Mechanical Engineering of the Eindhoven University of Technology, a new design for a synthetic valve is developed. This is a trileaflet valve with EPDM rubber used as matrix material reinforced with polyethylene fibres. At this moment prototypes are investigated.
II. THE NORMAL AORTIC VALVE: ANATOMY & PHYSIOLOGY

When designing a prosthetic heart valve it is necessary to have knowledge about the structure and function of the natural valve. In this chapter a summary is given of the anatomic details and other factors which contribute to the behavior of the aortic valve.

The heart consists of two pumps in series: one to propel blood through the lungs for exchange of oxygen and carbon dioxide (pulmonary circulation) and the other to propel blood to all other tissues of the body (systemic circulation). The cardiac cycle can be divided into two parts: systole or ventricular contraction during which there is isovolumic contraction of the ventricle followed by the ejection phase of the ventricle of blood into the aorta and pulmonary artery, and diastole or ventricular relaxation during which there is isovolumic relaxation of the ventricle followed by filling phase of the ventricle with blood coming from the atrium (fig. 1). Two important structures can be distinguished when observing the aortic valve.

![Diagram of heart cycle and pressures](image)

**Fig. 1** Left atrial, aortic, and left ventricular pressure pulses correlated in time with aortic flow, and ventricular volume for a complete cardiac cycle in a dog. (Ref. 4)
Leaflets

The cardiac valves consist of thin flaps of flexible, tough endothelium-covered fibrous tissue firmly attached at the base to the fibrous valve rings. The valve between the left ventricle and the aorta consists of three cuplike cusps (thickness: 0.1 mm) attached to a valve ring (annulus fibrosus) (fig.2+3). The leaflet supports the aortic diastolic pressure by virtue of its aortic attachment. Normal valve leaflets are made from a very pliable, spongy material that contains fibers resistant to stretch but not to compression.

The aortic leaflets consist of three layers (fig.4): *Fibrosa* is the dense collagenous layer near the aortic surface; *spongiosa* is the central layer containing mainly acid mucopolysaccharides and collagen fibres; and *ventricularis* is the layer at the ventricular surface and contains both elastin and collagen (according to Gross and Kugel). It is this low resistance to axial compressive forces that is likely responsible for the extreme pliability of the normal tissue. Movements of the valve leaflets are essentially passive, and the orientation of the cardiac valves is responsible for unidirectional flow of blood through the heart.

The shape of the aortic leaflet is of particular interest when its relationship to function is considered. During a human lifetime the aortic valve may open and close $3 \times 10^9$ times. The fact that medical science has been unable to duplicate this function suggests that we still do not understand the stress to which the normal valve is subjected.

Forces around the circumference of the aorta that are exerted in the leaflet attachments are balanced by the circular placement of the leaflets around the aortic wall.

Below the valve, the relaxed ventricular muscle affords little support (fig.3); the noncoronary leaflet receives the least since it rests principally on the thin anterior leaflet of the mitral valve. It is not surprising, therefore, that the arc of leaflet attachment is parabolic, since this is the optimum shape to resist a uniform stress parallel to its axis. This function is well suited to the tough, collagenous annulus fibrosus of which the attachment is formed. Cross sections taken through the leaflet in a plane at right angles to the axis of the paraboloid form circular arcs. Since the aortic diastolic pressure is evenly distributed at right angles to the leaflet surface, the circular cross section ensures an even distribution of tension throughout the leaflet.
The collagen bundles that form the annulus striae take an intermediate course, forming an angle of approximately 45 degrees to the line of attachment. This enables the bundles to transfer support from the attachment to the leaflet body and as well as to resist the diastolic pressure on the leaflet substance.

Natural leaflets routinely replace their substance, as radiographic observations demonstrated. The differences in the patterns of glycosaminoglycan or collagen protein elaboration and retention suggest that the two classes of substances turn over at different rates in response to separate functional stresses. The turnover of collagenous protein is hardly surprising in view of its stress bearing role. Indeed, in bioprosthetic valves where collagen replacement is not possible eventual disintegration of collagenous fibres is a notable feature of valve failure. What has been somewhat more surprising is the seemingly rapid replacement of tissue glycosaminoglycans. This suggest that these substances may be more important in normal tissue protection from stress than has perhaps been appreciated. The extensive functional changes in shape and position of the valve bring about significant stresses at the leaflet attachment sites. Some balance between the potentially destructive effects of the stresses and the need for maximal blood flow is achieved by combination of favorable structure (for example, effective thickness, semifluid components, etc) and capacity for repair. Repair seems particularly likely to be elicited by the high tensile stresses in the lamina fibrosa and by frictional stresses in the semifluid ground substance.

In the functioning human aortic valve, the leaflets usually have been considered to be under stress in the closed position and under no stress in the open position, responding passively to changes in the pressure gradients generated by the left ventricle.
Direct observations of the functioning valve, however, indicate that the open valve assumes a triangular orifice. This configuration implies that the open leaflet is under significant stress. The concept of normal aortic valve function is that the aortic root expands as the aortic valve opens and brings the leaflet orifice to triangular configuration. A slight shortening of the leaflets occurs, possibly acting as a shock absorber. As the pressure falls the aortic root radius decreases and the leaflets flex towards the axis of the aorta, resulting in valve closure. The relatively incompressible leaflet is protected from the fatigue of repeated lengthening and shortening by the changing dimensions of the aortic root. The leaflet suspended, from the aortic root, undergoes a relatively constant stress maintained during the cardiac cycle by motion of its supporting structure. This results in a considerable reduction in the fluctuation of the stresses placed on the leaflet and could explain how the thin leaflets last a lifetime under normal operating conditions. The leaflet must be quite elastic in the radial direction to maintain the sharp curvature at the coaptation intersection without producing large stresses. The bending stresses at the coaptation intersection line is further decreased by a very thin structure there.

The apposed portions form the lunulae (fig.5). Since they are not load bearing they are considerably thinner than the leaflet body proper, and because they lie in vertical radial plane they form no part of the paraboloid. Each lunula may be regarded as being composed of a series of unloaded hanging lines, running radially one beneath the other from the aorta to the nodulus aranti. The noduli aranti are thickenings at the middle of the free edge of the leaflet and are believed to play a role in valve closure. The lunula are smooth and miss the fibers present in the rest of the leaflet. By definition, the free margins of the closed leaflets should be catenary curves, in contrast to the lines of leaflet apposition, whose shape is determined by the geometry of the load-bearing portion of the leaflets. The leaflet margins start at their aortic attachments about 2mm higher than do the lines of apposition which mark the lower border of the lunula. This short distance is represented by that portion of the leaflet which shares a common attachment with the leaflet next to it. The added depth thereby given to the lunulae helps to form an efficient seal between the leaflets and aids in their stabilization.

Fig. 5 Frontal view of one leaflet of the aortic valve (McAlpine, 1975)
a. schematic drawing, b. photograph (Ref.101)
The large apparent redundancy of the coapting surfaces above load-carrying fiber lines through the point of the cylindrical section serves several purposes. First, this zone actually decreases in area as the pressure is increased. Second, as the leaflets fold back during systole, their length is such that the free edge of the open leaflets forms a circle providing a flow separation surface of maximum leaflet and flow stability against leaflet vibrations and local flow separations. There is also speculated that this geometry in the opening transition and the open state is critical in the development of the circulatory vortex flows in the sinuses.

Fig. 6 The mechanism of opening of the aortic valve. When pressure in the left ventricle equals the pressure in the aorta, the commissures move outward and thereby pull the leaflets to produce a stellate orifice. The arrows indicate the movement of the commissures. (Ref. 12)

**Aortic root**

Behind the aortic valve are small outpocketings of the aorta, called the sinuses of Valsalva. The presence of the sinuses of Valsalva does affect aortic valve function, because of the effects on fluid flow, as well as stress distribution on the leaflets. With the exception of their upper margins, the aortic sinuses are supported by the annulus fibrosus in a similar manner to the leaflets. Therefore, they act as a balance or counterweight to the force exerted on the valve leaflets, with the annulus fibrosus forming the pivot.

The importance of sinus curvature and its effect on stress distribution with the leaflets has been studied with the use of marker fluoroscopy techniques in dogs. It has been observed that the diastolic shape of the sinuses is nearly spherical and the shape of the leaflets is cylindrical (in the load-bearing area). By engineering analysis, the stress carried by the leaflets in diastole was calculated to be four times as high as the stress in the sinuses. If the leaflet stress was not shared with the sinuses, the sinus walls would be pulled inward during diastole. The marker studies demonstrated that the sinus walls move outward instead (fig.6), implying that part of the load on the leaflets is taken up by the sinus walls. This stress sharing decreases the stress and the wear on the leaflets.
It has been shown that both the fresh porcine and the human aortic root dilate by approximately 30% with 80 mmHg internal pressure and by approximately 45% with 120 mmHg internal pressure. In each cardiac cycle, when ventricular pressure equals aortic pressure, the intercommissural distances increase. This increase creates the tangential tension on the leaflets which pulls the leaflet open to produce a stellate orifice. The aortic valve initially opens without any detectable forward flow. Further opening of the valve is dependent on forward flow velocity. As forward flow increases the configuration of the valve orifice changes from stellate to triangular to circular (fig. 7). The increase in the commissure perimeter can be explained as follows. In diastole, tension in the leaflets, produced by the pressure gradient across the leaflets, is transmitted to the commissures and exerts an inward pull on the commissures.

![Graph showing relationship between leaflet displacement and velocity](image)

**Fig. 7** Relationship between the maximum aortic blood flow velocity and maximum leaflet displacement (percentage of full opening). The closed valve corresponds to 0 percent leaflet displacement. The initial valve orifice is stellate, and there is no detectable forward flow. As the blood velocity increases to 30 cm. per second, the orifice becomes circular. The greatest change in the valve orifice (leaflet displacement) occurs over a narrow range of blood flow velocity. The negative velocity with the stellate orifice indicates regurgitant flow. (ref.12)

In systole, the tension in the leaflets is reduced so that the commissures move outward, which causes the leaflets to separate and the valve to open. The ventricular side of the aortic root, especially the region between the line of attachment of the leaflets, would be governed by the difference between the left ventricular pressure and intrathoracic cavity pressure. In systole, the increase of the left ventricular pressure above the intrathoracic cavity pressure causes the aortic root to develop a greater intramural tension to sustain the increased pressure gradient across its wall. This would also result in the expansion of the aortic root during systole. When the root is not dilated the leaflets become redundant, function and geometry become abnormal and high open leaflet deformations occur. The failure to recognize that dilation of the aortic root and a normal leaflet geometry are essential to achieve good leaflet function has led to abnormal leaflet mechanics in both first and second generation frame mounted valves. This causes high open leaflet bending deformations that can lead to calcification.

At the end of the reduced ejection phase of ventricular systole, there is a brief reversal of blood flow toward the ventricles (shown as a negative flow in the phasic aortic flow curve) that snaps the cusps
together and prevents regurgitation of blood into the ventricles (fig. 1). During ventricular systole the cusps do not lie back against the walls of the aorta but float in the bloodstream approximately midway between the vessel walls and their closed position. Under no load the cusps furl up in the axial direction. Cusps furl up to provide sufficient clearance between the cusp free-margins and the distal end of the sinuses to generate vortices of optimal strength. In the sinuses of Valsalva, eddy currents develop that tend to keep the valve cusps away from the vessel walls. The orifices of the right and left coronary arteries are located behind the right and left cusp, respectively, of the aortic valve. The coronary arteries provide the entire blood supply to the heart muscle. Were it not for the presence of the sinuses of Valsalva and the eddy currents developed herein, the coronary ostia could be blocked by the valve cusps.

![Diagram](image)

**Fig. 8** Drawing of vortex patterns in the sinuses of the model aortic valve. Mid-systole is shown above, late systole below (side view is shown on the left, the end view on the right). The sinuses are numbered 1-3. (Ref. 14)

Vortices have an complex role to play in controlling the aortic valve during systole (fig. 8). The vortices provide both a control mechanism for the valve and additional thrust to aid closure in the latter part of the systole. At peak systole, blood flowing into the sinuses is matched by blood flowing out, and the aortic pressure-gradient vanishes. Thus the cusps are balanced between the sinus vortices and aortic flow. When the aortic flow decelerates, pressure in the aorta at the level of the distal end of the sinuses exceeds that at the proximal end. Since blood enters the sinuses from the distal end, the average pressure in the sinuses exceeds that in the aorta, and the cusps respond to this pressure-difference by moving slowly towards closure, with blood flowing into the sinuses, but no longer out. In the absence of a control mechanism, the thin cusps would frequently be caught out of position at the end of the systole (because of anatomic and flow asymmetries) and would experience huge shock loads when closed rapidly by reversed aortic flow. A small amount of reversed flow is required to seal the valve 14.
III. VALVE PROSTHESES

3.1 Introduction

Valves are subjected to 40 million cycles per year in the heart, and patients and physicians expect prosthetic heart valves to perform satisfactorily for at least 400 million cycles\textsuperscript{15}. To meet this demand there are a few considerations one should acknowledge when designing a valve. Design, biocompatibility, hemodynamic performance etc. are important features of a prosthetic valve. Many attempts have been made to develop the perfect valve. What is the state of art at the moment, which were the problems in the past and their solutions? Answering these questions provide insight in the complexity of designing a valve substitute.

Even after 30 years of experience, problems associated with heart valve prostheses have not been eliminated. The most serious complications are: 1) thrombosis and thromboembolism, 2) anticoagulation-related hemorrhage, 3) tissue overgrowth, 4) infection, 5) paravalvular leaks due to healing defects, and 6) valve failure due to material fatigue or chemical change.

In terms of these complications related to heart valve design, the basic engineering concerns are hemodynamics, structural mechanics, and material; the biological response to the prosthetic implant also remains a key issue\textsuperscript{16}.

Hemodynamic aspects:

1) Pressure gradient - Since the heart must supply the work necessary to maintain adequate blood flow through a prosthetic valve, good valve design requires that flow not to be significantly impeded - implying that the magnitude of pressure gradient across the valve be as small as possible. Bioprosthetic valves, which better mimic natural valve geometry and motion, have relatively lower pressure gradients for a larger diameter valves, but small sizes generally have higher pressure gradients than their mechanical counterparts. While the clinical importance of pressure gradient in predicting long-term performance is not clear, the fact that these gradients are a manifestation of energy losses resulting from viscous-related phenomena implies that minimizing the pressure gradient magnitude across an artificial valve is highly desirable.

2) Regurgitation - Regurgitation, arising from reverse flow created during valve closure and from backward leakage once closure is effected, reduces the net flow through a valve. Closing regurgitation is closely connected to the valve shape and closing dynamics, and the percentage stroke volume that succumbs to this effect is reported to range from 0.2% to 7.5% for mechanical valves, while that for bioprosthetic valves is typically less-ranging between 0.1% and 1.5%\textsuperscript{17}. Leakage, which depends upon how well the orifices are "sealed" upon closure, has a reported incidence of 0% to 10% in mechanical valves and 0.2% to 5% in bioprosthetic valves\textsuperscript{17}. The overall tendency is for regurgitation to be less for the trileaflet, bioprosthetic heart valve than for mechanical devices.

3) Fluid dynamic stress - Fluid dynamic viscous stresses result when spatial velocity gradients occur in a flow field. Turbulent flow produces so-called Reynolds stresses as a consequence of momentum transport resulting from fluctuating velocities. While these Reynolds stresses
are not viscous stresses within themselves, they produce local spatial velocities gradients that
ultimately result in viscous stresses. Mechanical stresses induced by flow phenomena can have
profound effect on cells in blood and tissue. Shear stresses in the order of 150 to 400 Pa can
cause lethal damage to red blood cells (RBC)\footnote{18}, and in the presence of foreign surfaces
stresses in the range of 1 to 10 Pa may be lethal\footnote{19}. While the exact mechanism of turbulence
stress damage to the cell is not precisely known, there is no disagreement that the cell damage
can be created by high turbulent stresses; minimizing these is conducive to better valve
performance, both from the standpoint of hemolysis and from energy loss considerations.
Platelets are also affected by fluid dynamic shear stresses. Evidence that platelet activation,
aggregation, and thrombosis are induced by fluid shear forces has been generated
predominantly by viscometric studies performed under well-defined fluid mechanical
conditions.

Flow separation - In addition to high shear stresses being potentially detrimental in heart valve
flow fields, unusually low wall shear stresses may also be of great concern. Arteries in a
variety of mammalian species adapt their diameters to prevailing blood flow conditions such
that the mean wall shear stress is in relatively narrow range of 1 to 2 Pa\footnote{20}, and changes in
artery diameter in response to altered flow conditions appear to be mediated by endothelial
cells. Flow separation, defined as a phenomenon in which fluid elements moving near and
approximately parallel to a surface abruptly follow trajectories away from the surface, may
create a zone that contains areas of low wall shear stress and relatively long residence time
of cellular elements. Since low shear has been associated with intimal proliferations, these
regions may experience tissue growth\footnote{20}.

The ideal heart valve design from the hemodynamic point of view will (i) produce minimal pressure
gradient, (ii) yield relatively small regurgitation, (iii) minimize production of turbulence, (iv) not
induce regions of high shear stress, and (v) contain no stagnation or separation regions in its flow
field, especially adjacent to the valve superstructure. No valve design as yet, other than normal, native
valves, satisfies all these criteria\footnote{16}.

Materials and structural mechanics factors:
Several factors pertinent to prosthetic valve performance are related to structural mechanics. The
design configuration affects the load distribution and dynamics of the valve components, which, in
conjunction with the material properties, determine durability - notably wear and fatigue life.

Choice of valve materials is closely related to structural factors, since the fatigue and wear
performance of a valve depend not only on its configuration and loading but on the material
properties as well. Additionally, the issue of biocompatibility is crucial to the prosthetic valve design
- and biocompatibility depends not only upon the material itself but also on its in vivo environment.

Mechanical durability depends on the material properties and the loading cycle, and examples of
degradation include fatigue cracks, abrasive wear, and biochemical attack on the material\footnote{16}.
3.2 Design problems

As mentioned before, the design of the valve has a major influence on its function. In this section, problems will be reviewed which are also of concern to designing a synthetic leaflet valve. Mainly bioprostheses will be discussed, because they show the most similarity with the synthetic leaflet valve. The long-term performance of bioprosthetic valves is limited by fatigue failure and calcification of the leaflets. Problems with calcification and durability have remained major obstacles, and 20% to 40% of patients require valve replacement within 10 years.

In attempt to limit mechanical tissue damage, much attention has been focused on improving the mechanical characteristic of bioprosthetic tissues.

Fixation-treatment
The tissue of bioprostheses is usually treated with gluteraldehyde for preservation and to reduce antigenicity. When such tissue is fixed with gluteraldehyde, it becomes up to four times stiffer than fresh tissue. Gluteraldehyde-treated tissue and fresh tissue respond differently to bending as shown by Vesely and colleagues. Strips of gluteraldehyde-tested tissue always buckled more than fresh tissue.

Buckling is the deformation of composite material in such a way that length and compressive stresses are reduced in exchange for local structural collapse, and is commonly observed when such familiar materials as cardboard, sponge rubber, or leather are bent to high curvatures. For these materials, buckling appears as the crinkling of the surface on the inside of the bend.

Fig. 9 Technique used to fix the tissue strips in a bent configuration. The radius of curvature varied between specimens and was measured after the sections were mounted on slides and stained. The corrugated surface of the tissue when sectioned perpendicular to the major collagen bundles in the fibrosa is evident. (Ref. 6)

Buckling produces large stresses in individual fibres and if it occurs in bioprosthetic valves, such buckling would likely be the first site of mechanical fatigue and fibre breakage. Although fresh tissue buckled in bending tests (fig.9), it did so only during very sharp reverse bending to curvatures much greater than those experienced in vivo. Reverse bending is defined as bending with the fibrosa (aortic surface of the valve) on the outside. It appears, therefore, that normal leaflets are unlikely to buckle at all during aortic valve function because reverse curvatures do not usually occur and normal bending does not lead to buckling.
Since buckling of bioprosthetic tissue results mainly from reverse curvatures, it seems advisable that these deformations be kept to a minimum.

The difference in buckling between the fresh tissues and the treated tissues may be explained in part by altered shear properties of the bioprosthetic tissues. Prosthetic tissue has been shown to shear less than fresh tissue and is therefore likely to experience greater compressive stresses and buckle more because of the restricted motion of the fiber layers. During the reverse bending of circumferential fibers induced by valve design, the collagen-dense fibrosa resides on the outside of the tissue bend. Since little elongation is possible in the stretch-resistant fibrosa, very large compressive deformation must occur in both the weaker ventricularis and the central spongiosa. The ventricularis is unable to decrease its length substantially because of its own elevated compressive resistance; hence buckling occurs. When the same tissue is bent to natural curvatures, the fibrosa and ventricularis reverse roles. If the ventricularis cannot stretch sufficiently to facilitate bending, the outer layers of the fibrosa must compress and eventually buckle.

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**Fig. 10** Diagram of the aortic aspects of a partially open aortic xenograft. The diagram defines the areas of the leaflet that experience natural and reverse circumferential bending during valve opening. Sites of sharp bending correlate well with the documented areas of leaflet tearing. 

(N = natural curvature; R = reverse curvature)

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Because the mounting frame for these prosthetic valves cannot expand with the aortic root during opening as observed for a normal valve, the valve leaflets must fold back on themselves and experience the reversals of leaflet shown in Fig. 11.
**Stent design**

Bioprostheses are mounted on stents to prevent annulus deformation and to aid the surgeon with the implantation of the valve substitute.

Recent studies have shown that frame-mounted porcine valves currently used have abnormal (nonphysiologic) neutral leaflet geometries and that these abnormal leaflet geometries result in high open-leaflet bending deformations at the commissures, an area prone to calcification and failure 25-27.

Today it is believed that these abnormal geometries are results of flaws in valve design. Extensive functional changes in shape and position of the valve bring about significant stresses at the leaflet attachment sites.

Most bioprosthetic valves are mounted on rigid metallic or synthetic supporting frames or stents without prior dilation of the gluteraldehyde-fixed root to physiological diameters (30 to 40% greater). They are simply sewn into the stents in their contracted, relaxed states.

The base of the stent has a fixed diameter and the stent posts generally do not move outward during systolic valve opening. Consequently the diameter of the supporting aortic wall is much smaller than its natural state which effectively means the leaflets are too long for their frame support and have an abnormal leaflet geometry. This may have beneficial effect when the leaflet is in its closed position as it is likely to reduce the tensile stresses created by the high pressure difference across the leaflet. However, in the open position the extra length of the leaflet causes high bending deformations and a resultant high levels of strain at the free edge of the leaflet particularly at the commissural region 28, 29.

The aortic valve with expansile leaflet attachment opens initially because of the increase in the distances between the commissures. This mode of opening results in a stellate orifice at the commencement of valve openings. In this opening process, flexion in the leaflets is minimized. From these results one can hypothesize the consequences of an aortic valve with nonexpansile leaflet attachments (fig 12).

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**Fig. 12** A schematic representation of a cross-section of the aortic valve showing the leaflet profiles during valve opening for expansile (I) and nonexpansile (II) leaflet attachments. Leaflet profiles during progressive openings are marked by the arrows 1, 2, 3 and 4 between the closed valve and the maximally open valve. The commissures of the valve I move from positions ABC to A'B'C' as the valve goes from the closed position to the open position. The valve I initially has a stellate orifice. The valve II has a central circular opening from the beginning of the opening. In this case the other arrows indicate the areas of increased flexion. (Ref. 12)
In this case, the valve would open in response to the flow of blood from the left ventricle into the aorta. This mode of opening would result in an initial circular orifice. In this process the leaflets are subjected to additional flexion. Because of the restriction of the external frame, opening of a porcine bioprosthesis is associated with acute leaflet buckling both at the commissures and at the midpoint of the free edge of the leaflet. Thus, an increase in flexural rigidity is likely to be accompanied by an increase resistance to opening. Examination of the opening characteristics of porcine xenografts has shown two areas of high bending that correlate well with sites of leaflet tearing and calcification. These are the free edge and near the attachments of the leaflets to the aortic root.

In stent-mounted bioprostheses the expansile characteristics are undefined. Even if the stents are flexible, they are not attached to and therefore do not become part of the aortic root. This causes further deviation in the expansile characteristics of bioprostheses from those of the normal aortic valve. Decreased or absent systolic expansion of the stent will lead to increased flexion of the leaflets and to premature flexion failure of the bioprosthetic leaflets.

Most importantly, the stent is obstructive, which causes high pressure gradients across the valve prostheses (a measure of the degree of stenosis associated with the valve). These pressure gradients will ultimately cause fatigue failure of the valve substitutes.

The need to improve flexibility of bioprostheses has long been recognized. The pressure of a rigid stent contributes to a poor hemodynamic profile secondary to a reduction in the effective orifice area. Furthermore, the mechanical stress along the line of cusp movement may lead to premature valve dysfunction.

The performance of stentless porcine aortic valve bioprostheses has recently been of interest. Many studies investigated the superiority of a stentless valve. In stentless aortic valve replacement the aortic root is used as a "physiological" stent. It is considered the best stent for the aortic valve. As a result increased durability is expected from the higher annular flexibility. Calcification of stentless valves was almost absent experimentally in comparison with severe calcification of conventional bioprostheses. The stentless porcine valve has shown to cause less resistance to ejection in systole. The lower ejection velocities and flexible commissure may theoretically reduce the rate of cusp degeneration over time.

Early results suggest that the use of biologic aortic valves without the traditional stent as aortic valve substitutes offers two major hemodynamic advantages because of the lack of a rigid support. First, part of the mechanical stress to which the leaflets are exposed during the cardiac cycle may be dampened by the wall of the surrounding native aortic root, with potential for better long-term durability. Second, the greater flexibility and size of the valvular orifice may allow better hemodynamic performance when compared with the traditional bioprostheses in the aortic position. This is not surprising in view of the stent elimination and considering that the internal orifice of the stentless is the same as that of a two-size larger stented valve (e.g. 23 mm stentless has the same internal orifice as a 25 mm stented valve). However, in small diameters this is not fully confirmed.

Long-term studies are necessary in order to prove whether the stentless valve can live up to its expectations. Compared with the stented valve, a stentless valve is technically demanding to insert, requires longer aortic cross-clamp time, and can potentially give rise to aortic regurgitation, all of which may increase operative risk. But with gaining experience, implantation will require less cross-clamp time. Aorta insufficiency (regurgitation) after implantation of stentless biological valves is common. This is
probably related to the technical capability and experience of the surgeon, because the spatial relationships of the three commissures are crucial to proper leaflet coaptation and hence to aortic valve competence after implantation. Although the aorta insufficiency is usually mild, it may however predispose the valve to premature failure because of either increased mechanical stress or infective endocarditis.

Research suggests that the pattern of the leaflet stress in the prosthetic valves can be influenced by the stent design. From this point of view it is probably interesting to mention the research done by Vesely, Krucinski, et al. on the effect of different stent designs. Three examples of stent design were simulated with the finite element method to examine the effects of rigid, pliable and expansile stents on the distribution of leaflet stresses.

Rigid stent: In the closed position, a tensile major principal stress of 350 kPa was observed in the commissural region. Such stresses are induced at the commissures due to the tension that is generated in the valve leaflets in the closed position. In the fully open configuration, a compressive major principal stress of 250 kPa was observed, again in the commissural region. This compressive stresses induced by leaflet flexure are, therefore, of magnitude comparable to tensile stresses and likely contribute to material failure through a compressive buckling phenomenon.

Pliable stent: In diastole, inward deflection of the pliable stent induced significant compressive stresses near the central coaptation area. This was accompanied by some wrinkling of the leaflet free edge. In systole, this stent produced compressive stress at the commissural region very similar to that of the rigid stent. This simulation has, therefore, demonstrated that the very simple flexible stent design not only disturbed the coaptation process but also restrained the outward radial motion of the valve cusps. Such a stent design, therefore, offers no appreciable reduction in compressive stresses during the opening phase of this type of valve.

Expansile stent posts (by pivoting): the results of this simulation showed that an outward movement of the stent posts, equivalent to a 10% radial expansion of the commissural diameter, considerably reduced the circumferential leaflet curvatures at the commissures when the valve was fully open. Compared with a major principal stress of 250 kPa for a rigid stent, this simulation produced a major principal stress of 150 kPa, a reduction of 40%. This reduction in compressive stress, however, was not accompanied by an increase in tensile stress at the centre of the cusp free edge, as would be expected if the radial movement of the stent posts produced leaflet tension. Perhaps, the best stent would be one that functions in harmony with the patient's aortic root. Ideally, the tops of the stent posts should be fastened to the recipient aortic root such that the expansion of the aorta during the ventricular contraction will pull the tops of the stent posts outward with it.

Besides these models Vesely, Krucinski et al. also modeled the opening and closing sequence of a trileaflet bovine pericardial valve with an expansile stent during valve opening using the infinite element analysis. A stent was designed with pivoting stent posts. The stent posts were assumed to be rigid, and were prescribed to pivot outward about a rigid base during systolic valve opening. During diastole, the stent posts returned to their vertical position as aortic pressure dropped. Such action could easily be simulated in the real valve by affixing the tops of the stent posts to the recipient aorta. Conclusion from the simulations was that pivoting stent posts that move outward during systole can reduce the compressive flexural stresses normally associated with the function of existing pericardial bioprostheses. It appeared that any expansion beyond 15% produced excessive tensile stresses in the leaflets. It should be noted that flexible stent posts that deflect inward during diastole, as featured in some existing valves, play no role in reducing these flexural stresses.
Mathematical modeling of biologic tissues, however, is still in its infancy. Although the model may be realistic enough to produce a qualitative assessment of leaflet stresses, it is still very simplistic and should be applied to quantitative analyses with care. It does not simulate the interactions between the valve leaflets and the pattern of fluid flow through the valve.

The influence of the stent height of bioprosthetic valves on the leaflet stresses was investigated. Carpentier et al (1982) suggested several attractive features which may result from reducing the stent height of bioprosthetic valves. Reducing the stent height would minimize protrusion of the struts into the aorta and it was thought to be an important consideration in reducing turbulence. However, Hamid et al (1986) showed that a reduction of stent height also results in increased stresses upon the closed cusps. The advantages of improved hemodynamic derived from reducing stent height, therefore, may be mitigated somewhat by the disadvantages of increased leaflet stresses.

Carbomedics developed a prosthetic valve (fig. 13) with a new fixation technique and an improved design. On one hand, a valve requires a stiff stent to prevent annulus deformation. On the other hand, it requires a flexible stent to assure good hemodynamic motion of the leaflets. The Carbomedics valve consist of two stents. The outer stent, very stiff and corrosion-resistant, is to deter deformation after implantation, whereas the second, inner titanium stent is flexible. This flexibility minimizes the leaflet stress and enhances the opening and closing of the valve leaflets within the valve. Both stents are radiopaque.

![Fig. 13 The Carbomedics pericardial bioprosthesis Photo f. (Ref. 53)](image-url)
3.3 Pericardial valves

Because there was concern regarding the comparatively obstructive nature of the stented porcine bioprostheses, particularly in small sizes, the so-called pericardial valves, constructed of bovine pericardium, were designed in the 1970s to improve hemodynamic performance. The first generation of pericardial valves has been withdrawn from the market because of excessive high rates of premature failure, characterized by leaflet tears. The most widely used pericardial valve at that time were the Ionescu-Shiley valves. In these models, the leaflets are secured inside the valve post by a fixation or coaptation suture. The method of manufacture in the IS version allows for two potential problems: It tends to limit the degree of leaflet opening and consequent orifice size, and it permits a predictable mode of failure in cases of leaflet disruption. These valves showed early primary failure, in which leaflet disruption clearly began at the coaptation suture site inside the strut. Pericardial valves failing mainly because of damage sustained during valve closure, whereas porcine bioprosthetic valves appeared to be damaged mainly during the opening phase of the cardiac cycle. Whereas calcification of porcine valves appears to be related to areas of maximum stress on the leaflet, leaflet tears of Ionescu-Shiley pericardial valves are mostly related to the holding commissural suture at the summit of the stent. The abrasion was caused by the leaflet being pulled over the (Dacron) cloth at the edge of the frame when the valve was in the closed position, and it was greatest where the tension in the leaflet was presumably high.

The second generation of pericardial valves show some improvements. Carpentier-Edwards designed a pericardial valve with the tissue leaflets attached behind the struts without the need for anchoring sutures because the pericardial cusp was mounted by drawing it into the stent from below. Strut flexibility was achieved with an Elgiloy wire (a corrosion resistant alloy of cobalt and nickel). The Mitroflow prosthesis is constructed from a single sheet of glutaraldehyde-preserved bovine pericardium sutured onto a Dacron cloth-covered flexible Delrin stent. The stent is designed to optimize cusp shape at low profiles. The sewing ring consist of tungsten powder-loaded silicone elastomer for radiographic opacity. The manufacturing process incorporates matching tissue thickness to stent diameter to ensure proper operation of the cusps and pulsatile flow testing at both high and low rates to ensure proper closure at all physiologic flow rates. The Dacron used in the manufacture of the Mitroflow valve has a ribbed side and a smooth side. The originally manufactured Mitroflow valve had the ribbed side in potential contact with the pericardium, and it has been shown that the abrasions are actually due to the ribbing of the Dacron. The current model of the valve with smooth side potentially in contact with the pericardium has shown with in vitro studies that the abrasion factor has been significantly reduced by the alteration of the Dacron. It is conceivable that either altering the Dacron or the covering the Dacron with pericardium could extend the durability of the prosthesis.

Sorin developed a valve consisting of two pericardial sheets. One sheet forms the three leaflets and is sutured to the second sheet which lines the inner surface of the stent. This particular design was developed in order to achieve better distribution of mechanical stress and to avoid mechanical injury by direct leaflet-to-fabric contact. The two-sheet design was also used in a stentless pericardial valve of Sorin. The valve is comprised of an external scalloped cylinder that contains an internal cylinder forming three valvular cusps and the inflow rim (fig. 14). In general, the elimination of the stent and suture ring which are obstructive to the flow should provide better hemodynamics. The direct suturing of stentless valves to the aortic root without the interposition of the less elastic and compliant stent may offer the potential for increased durability.
Furthermore, the absence of polymeric fabrics may provide a greater resistance to recurrent infection, particularly when valve replacement is required in presence of active endocarditis 48.

The key point about pericardial valves is that they are constructed and as a result of that, each valve stands on its own merit due to differences in design. This makes it difficult to draw conclusions about pericardial valves in general. The importance of the design was shown in the study by Carrera San Martin and colleagues 65. Their object was to determine the durability of the pericardial membrane by means of a real fatigue assay, and thus establish the safety margins confronted by design engineers in their attempt to achieve indefinite duration of the valves (50 years). Maximum work stress was found to range between 0.363 MPa if the valve leaflet had the shape of an elliptic paraboloid and 0.206 MPa when it was spherical. Likewise, with the equation it was determined that it would take 336 and 4924 years for the pericardium to reach these work loads respectively. This important variation in the calculated durability clearly indicates the relevance of the geometric design of the bioprosthesis, and probably the need to imitate the morphology of the natural valves which absorb a maximum of force with the minimum of stress fatigue. The durability of the pericardial membrane is not directly correlated with that of the bioprosthesis. This is not only because of problems in design, but rather the complex integration of the membrane in a structure (leaflet, suture, ring, etc.). The role of the suture as a generator of zones of lower resistance is well known. This is why the theoretical durability is much greater than the real durability of the prostheses.

At present time, pericardial valves seem to perform comparable with the porcine prostheses. Nevertheless, calcification and valve failure appears to be unavoidable with time in both porcine and pericardial bioprostheses, stented or stentless.
3.4 Calcification:

The main failure mode of implanted trileaflet valves, manufactured from treated porcine or bovine tissue and synthetic material such as polyurethane, is fatigue failure and calcification of the leaflets. Calcification has been shown to occur preferentially in the commisural region of the leaflets, and is believed to be accelerated by high bending deformations that occur in this region when the valve leaflets are fully open or by high tensile stresses which can occur in this region in the fully closed valve.

Extensive studies have been done on calcification of tissue, especially of the pericardial tissue since the first generation of pericardial valves had such an early failure mode. The relationship between mechanical stress and calcification is supported by reports that implants in the right-side of the heart are less subject than the left-side implants (aortic and mitral valve replacement) and that stress levels on closed valves are greater in the mitral than in the aortic position.

The mechanical properties of the leaflet tissue influence both the operational and durability characteristics of the valve substitute. Pericardium is a composite of collagen and elastin fibers embedded in a gel-like amorphous matrix. The fibers in a biologic composite are designed to support tension and reduce the probability of failure by crack propagation. The fibers will fail under compression by buckling. Whereas the chemically modified pericardium is flaccid in its undeformed state, under load the material is relatively stiff. In pure bending the neutral plane (fig.15) is coincident with the midplane of the material and does not change its dimension. All tissue below this plane is compressed (the stresses are compressive), whereas above the neutral plane the material is stretched (the stresses are tensile).

Collagen is better able to withstand tensile than compressive stresses. High tensile stresses concentrating at the commissural stitches may also have an effect. All moving parts of the valve leaflets, regardless of surface, calcified more than static areas, again indicating the importance of dynamic stresses in the calcification process. Moreover, in pure bending the free edges of a pericardial sheet would move toward one another. The leaflets of pericardial heterografts are attached to a relatively rigid stent and the leaflet boundaries are fixed. As a consequence, the process of pressure loading and resultant flexure as the valve closes causes the midplane of the leaflet to be...
stretched. This tension is constant throughout the thickness of the cusp. If the midplane tension is greater than the maximum compressive stress induced by bending, then the entire leaflet will be in tension; otherwise compressive stresses will be present in the tissue. Theoretical studies have shown that the site and magnitude of compressive stresses in the leaflet are determined by the attachment conditions at the stent. In particular, restraint of leaflet rotation at the stent can lead to high compressive stresses along the hinge line.

In a study by Grabenwöger et al, morphologic examination of tissue biopsies excised from the margin of cuspal tears showed severe tissue deterioration by calcium deposits and invading macrophages. It is therefore suggested that cuspal tears are not primarily fatigue-induced but a consequence of severe tissue degeneration. Beside the commissural area, the cuspal base was shown to be an area of severe tissue degeneration (fig. 16). Mechanical stress seems to be only an accelerating factor in dystrophic valve calcification, since even subcutaneous implants in rats, which clearly are not subjected to mechanical stress, calcify intensively. A modification of implant microstructures by glutaraldehyde pretreatment is therefore suggested to be essential factor causing calcification.

![Fig. 16 Frequency of calcific deposits radiologically evaluated in the four locations of valvular leaflets of 17 porcine bioprosthetic heart valves: basal area, central area, free margin, and commissural attachment. (Ref. 108)](image)

The initial calcium deposition, in subcutaneous implants as well as explanted bioprostheses, is suggested to occur in cellular remnants. Although mineralization of cellular debris was found, too, the observations favor the interfibrillar space of the collagenous network as well as the collagen fibril itself as the predominant area of initial calcium deposition.

In the Sheffield Explanted valve Study which was set up in 1984. Since that time a total of 570 valve shave been received: 504 biological and 66 mechanical valves. The study shows that the leaflets of both pericardial and porcine valves undergo significant morphological changes in vivo, even in the absence of tearing or calcification. Changes observed include loss of collagen crimp, loss of proteoglycans and infiltration of plasma constituents into the leaflet tissues. In addition, pericardial leaflets show thickening, stretching and changes in mechanical properties.
Creating a prosthetic heart valve has proved to be an arduous challenge because no currently available biomaterial duplicates the flexibility and hemocompatibility of natural valves. Akutsu et al (1959) implanted the first synthetic heart valve in an animal. The development of synthetic valves has been impeded by problems of manufacturing relatively thin leaflets of sufficient strength. The major problems with synthetic valves have been: 1) tearing of the leaflets due to poor mechanical strength; 2) poor flexibility of the leaflets and 3) thrombus deposition and calcification of the leaflets. Synthetic valves can be manufactured relatively inexpensively compared to mechanical or tissue valves.

Thrileaflet valves manufactured from synthetic materials such as polyurethanes are presently used only in ventricular assist devices and artificial heart as a bridge to transplant. Functional requirements of valves are: low pressure differences during forward flow, rapid synchronous leaflet opening, and low regurgitation and leakage. These requirements are highly influenced by design and construction of the valve and the characteristics of the material used.

4.1 Design

One of the primary design considerations will be to reduce the level of stress and tissue deformation that occurs at the free edge of the leaflets. The manufacturing technique of valves is one of the major factors that contribute to high levels of stress in the leaflets. Polyurethane trileaflet valves are most commonly manufactured by dip-coating a shaped mandrel in polyurethane. When comparing dip cast valves with film-fabricated valves, dip cast valves perform better in the durability tests. In dip cast valves, the leaflets are fully integrated to the frame during the dipping process and debonding of the leaflet from the frame has not been found. By securely bonding the leaflet to the edge of the frame stability is achieved. This method enables the development of valve designs with the required amount of material in the leaflet to allow full opening but without the high bending deformations associated with the excess material present in the existing porcine valve leaflets. However, when the leaflets are closed there is less material present in the leaflet and the valve may be subjected higher strains resulting from the pressure difference across the leaflet. Corden et al (1995) compared dip-cast valves and film-fabricated polyurethane valves on each valve closing almost simultaneously. The dip-cast valves were superior and showed a very symmetrical pattern with all three leaflets. For both the film-fabricated valves and the dip-cast valves the leaflets take about five times longer to close than they take to open, and the leaflets were observed to gradually fold inwards until they finally buckled into the fully closed position. For both valve types the leaflet deformation during the closing phase were less severe than those observed during valve opening. Jansen et al suggested that minimization of stresses within the valve leaflets is achieved by manufacturing the valve leaflets shapes as flat as possible in a medium open position. The design of a leaflet geometry is a compromise between the open and closed positions. While it is desirable to reduce the length of the leaflet in the circumferential direction with respect to the diameter of the frame to reduce the leaflet curvatures and strains in the open position, this cannot be
shortened too much as it can compromise the level of coaptation and stability, and increase the level of stress in the closed valve leaflet.

Optimization of synthetic leaflet geometries requires careful analysis of stresses and strains in both the open and closed leaflets. In the case of the dip-coated polyurethane valves, in which the leaflet shape is well defined, this allows a reasonably accurate method of determining stresses. Numerical analyses of porcine valve leaflets are more difficult, and at present the influence of dilation of the aortic root and the resulting different geometries have not been studied.

In a numerical study by Corden et al (1995) a method has been developed in order to investigate the bending deformations present in open valve leaflets, which quantifies the degree of curvature along the leaflet free edge. This method has been applied to a new design of polyurethane valve and various commercially available porcine and pericardial valves. The polyurethane valves all deformed into a similar shape in both steady flow and at peak systole in pulsatile flow. At steady flow and at pulsatile flow the difference between the mean bending radius at the post and the mean bending radius at the middle of the leaflet was statistically significant. The porcine valves had very small bending radii, the prototype prepared with aortic root dilation as well as the pericardial valve had larger bending radii which lower bending strains.

The values of strain in the open leaflet configuration can be compared to values of stress and strain obtained from the analyses of polyurethane valves in the closed position. In the closed position the valves leaflets are subjected to a static pressure of the order of 100 mm Hg. The leaflets act as membranes and the stresses are mainly membrane stresses acting in the circumferential and radial direction rather than compressive and tensile stresses resulting from leaflet bending. The largest deformations occur in the areas of the commissures and at the positions where the leaflet is attached to the valve frame. It is interesting to note that the levels of stress predicted in the closed polyurethane valve were higher than the maximum stress obtained experimentally in the open polyurethane valve. It is not known what are acceptable levels of strain or stress for a polyurethane heart valve leaflet, or precisely how the stress levels influence the fatigue life and biological degradation process. The acceptable levels will clearly depend on the material used.

In a study by Leat et al (1994) a new leaflet configuration called an 'alpharabola' has been investigated. The performance of this new leaflet geometry (fig 17) has been compared experimentally in synthetic leaflet heart valves manufactured of polyurethane to that of a spherical leaflet geometry. The leaflet was designed such that the radius of curvature of the leaflet increased continuously away from the centre of the valve leaflet at the free edge, towards the base of the valve and towards the posts. Valves were tested under both steady and pulsatile flows in the aortic position. The introduction of the alpharabola leaflet geometry where the radius of curvature of leaflet increased away from the centre of the valve towards the base of the leaflet, reduced the opening pressures by 40%, and leaflets with a thickness of 180 μm had an opening pressure drop of less than 1 mm Hg. The alpharabola leaflet opening showed initial deformation in the base of the leaflet where the radius of curvature was greatest. The overall hydrodynamic function of the alpharabola valve was found to be acceptable and superior in terms of forward flow pressure drop to the latest design of porcine bioprosthesis. In the study of Leat all the leaflets on one valve had constant thickness. The effect of changing the thickness also had a marked effect on opening pressure. The manufacture of a leaflet with reduced thickness in the base could also assist leaflet opening. Results of durability tests have not been reported in this article. This valve with new geometry design has reduced the pressure drops required to open the leaflets, reduced the flows at which all these leaflets are fully open and produced smooth rapid leaflet opening.
However, previous experimental studies\textsuperscript{72,78} have shown that the leaflet dynamics and opening characteristics in polyurethane valves can be considerably worse than in tissue valves, due to higher elastic modulus of the material used. The leaflet material was found to be quite stiff and thick and consequently this had detrimental effect on the opening. The pressure required to open the valve leaflets has been identified as an important parameter in bioprosthetic valves in the mitral position, where pressure drops and flows are often at a low level\textsuperscript{79,80}. It is of course necessary to determine the pressure needed to open valve leaflets under steady flow conditions\textsuperscript{78} in order to eliminate the inertial effects associated with the acceleration of the fluid under pulsatile flow situations. The resistance to opening or buckling pressure of a heart valve is proportional to the elasticity of the leaflet, the cube of the leaflet thickness and inversely proportional to the cube of the radius of curvature. As the elastic modulus of the polyurethane is at least one order of magnitude greater than that of the fresh tissue at low strains, it is necessary to consider variations in leaflet thickness and geometry in order to obtain acceptable opening characteristics\textsuperscript{77}.

For example, the Abiomed polyurethane valve\textsuperscript{72} showed superior reverse flow function, with significant lower closing regurgitation and leakage volumes compared to bioprosthetic and mechanical valves. However, the overall energy loss was still inferior to the other valves. As in other studies\textsuperscript{77,81} investigating the hemodynamic performance of polyurethane valves, the pressure drop necessary to open all the polyurethane valve leaflets was far greater than the accepted values of 1 to 3 mmHg for bioprostheses (6 mmHg in the case of the Abiomed valve). In studies done by Jansen et al\textsuperscript{75,76} and by Chandran et al\textsuperscript{71} polyurethane valves compare more favorably with the hemodynamic performance of tissue valves.
The elastic modulus of polyurethane is typically up to ten times greater than the elastic modulus of fresh tissue at low strains. This can introduce a larger resistance to deformation and dynamic changes in geometry between the open and closed positions, during both opening and closing of the leaflets. With similar thickness to fresh tissue (0.1 - 0.5 mm) this will produce very poor hemodynamic performance. However, a reduction of the leaflet thickness will result in an increase in the membrane stresses developed in the leaflets when the valve is closed, thus reducing the expected life span of the valve.

In a comparative study at the Helmholtz Institut by Herold et al, the pressure drop of individual polyurethane valves showed that even the thin polyurethane in this study gives a higher pressure drop than the pericardial valves (fig. 18).

Fig. 18 Comparison in pressure drop of individual HIA-PUR-valves with several bioprostheses. (BI = Bioimplant Canada Porcine, HAPO = Hancock Porcine, CES = Carpentier Edwards Supra-annular Porcine, BIPO = Biocor Porcine, CEPE = Carpentier Edwards Pericardial, HAPE = Hancock Pericardial, MI = Mitroflow Pericardial, ISA = Ionescu-Shiley Supraannular Porcine, ISLP = Ionescu-Shiley Low Profile Pericardial, IS3M = Ionescu-Shiley 3M Porcine).

4.2 Calcification

The failure of trileaflet designs has been shown in numerous studies to occur preferentially at the commissural region where the leaflets are attached to their supporting stents or posts; these tears often start at the free leaflet edge of the valve.

Reported failure of polyurethane valves is less common since they are only used for a limited period of time. But such leaflet tears as the primary cause of failure has been reported in long-term fatigue tests in laboratories, and also in explanted polyurethane valves used in animal studies in which high levels of calcific deposits have been observed on the valve leaflets in the commissural region. Prosthetic heart valve leaflets fabricated from synthetic polymeric materials have failed after long-term trials as a result of leaflet stiffening, tearing, thrombosis, and calcification.
Studies of polyurethane valved conduits implanted from the left ventricle to the descending thoracic aorta in calves reported two distinct types of calcification\textsuperscript{89,93}: macroscopic calcification in regions of mechanical strain (leaflet flexure) and in regions of low flow (leaflet commissures) and microscopic deposits on the leaflets and conduits walls proximal and distal to the prosthetic valve. These findings suggest that a relationship exist between modifications of the polyurethane surface and calcification, since plaque-like deposits were uniformly distributed over the leaflet surface and appeared to be independent of surface defects. It is not known whether the polyurethane surface modifications occur as a direct consequence of a casting procedure, the use of chemical adjuncts (such as antioxidants incorporated into the polyurethane), polymer processing and finishing procedures, or mechanical stresses induced within the leaflet. Calcification related to alterations in physiochemical properties of the polyurethane may develop independently of surface thrombotic material, fibrous sheath formation, and the degeneration of cells, or may be aggravated by these biological changes.

Leaflet flexure may also contribute to the calcification of polyurethane. A relationship between leaflet motion and calcification is suggested by the observation of macroscopic calcific nodules in the vicinity of the free edge and the commissural regions of the explanted valves\textsuperscript{91}.

In experimental models in a study by Bernacca et al (1995)\textsuperscript{94}, polyurethanes calcified to a much lesser degree than bovine pericardium under similar conditions. The polyurethane in this study were observed to fail in two main ways by developing holes in the central leaflet area towards the base of the coaptation junction and less often, tearing in the vicinity of the leaflet commissures. The few and inconsistent commissural tears they observed were thought to be related to irregularities in the leaflet in the leaflet thickness and may be improved by careful adaptation of the dipping procedure. It is likely that the repeated bending and buckling of the central portion has led to the tears in the leaflet centre. The pattern of calcification is not the same as that previously seen in biological material equivalent of the polyurethane valves, the bovine pericardial valve\textsuperscript{66}. In these valves, the pattern of calcification was shown to be associated with the commissural regions and with the area that bent over the central frame of the valve (stent-related?)

The damage and calcification occurring at the central coaptation point of one leaflet seemed to accelerate damage to its neighbours. This might be expected due to abrasive, calcified locus rubbing on its neighbour.

It is uncertain how great a role the thrombogenicity of the polyurethane plays in the calcification process. Some in vitro studies point to the existence of intrinsic calcification of polyurethanes, although the driving concentrations of calcium and phosphate are rather higher than would be physiological\textsuperscript{95}. Most in vivo studies, however, suggests that the calcification seen is largely extrinsic and associated with thrombus\textsuperscript{76,81,86}. Spectroscopic analysis of calcified leaflets suggests a process of intrinsic calcification involving, at least, the ether functional groups of the polyurethane. The degree of calcification may be related, primarily, to small molecular weight components of the polymer, which could be removed or reduced by solvent extraction processes. It seems likely, however, that, in the longer term, the primary structure of the polymer itself would also calcify. The performance of the polyurethanes is much better, however, than the similar bioprosthetic valves in term of calcification\textsuperscript{94}. 

V. DISCUSSION

The mechanism of the natural valve is extremely complex. There are many extrinsic and intrinsic factors contributing to a smooth performance of the heart valve. All these factors should be taken into account when developing a new synthetic heart valve. The perfect valve should have an indefinite durability, optimal performance and should lack the need for additional medication. Upon reviewing the literature on heart valves and valve prostheses, it becomes obvious that the perfect heart valve prosthesis does not exist. Current artificial valves have either the disadvantage of the need for lifelong anticoagulation therapy (mechanical valves) or are susceptible to biodegradation with limited durability due to calcification (bioprostheses). Aortic allografts have superior hemodynamics in aortic valve replacement. Due to the shortage of suitable donor organs, availability of these valves is restricted mainly to infective endocarditis and aortic valve disease in young patients.

Many research groups recognised the potential of a synthetic valve. Trileaflet valves manufactured from synthetic materials, such as polyurethane, offer a promising alternative to current clinical valve designs. They have a central orifice design which ensures minimal disturbance to the blood flow and can be manufactured from synthetic materials which offer the potential of substantially improved fatigue characteristics to glutaraldehyde-treated animal tissues. Synthetic heart valves are currently used in ventricular assist devices, but do not play a role in clinical cardiac implantation. Up till now they are not able to meet the high demands for a lifetime performance in an environment in which many different forces are exerted upon the valves. The parameters of the cardiac cycle vary widely: the cardiac output of the left ventricle in rest is about 5 liters per minute but can rise to 25 to 30 liters per minute during strenuous exercise; pressures in the heart and the cardiovascular system change during the different phases of the cardiac cycle (systole/diastole) and depend on age, exercise, diseases, stress etc.

There are two major problems in designing a synthetic trileaflet heart valve prosthesis. The first problem is the choice of the right material, which is closely related to structural factors, since the fatigue and wear performance of a valve depend not only on its configuration and loading but on the material properties as well. Synthetic materials have limited flexibility compared with the almost ideal slackness of natural tissue. This limitation has to be compensated for by preventive design features. Additionally, the issue of biocompatibility is crucial to prosthetic valve design and biocompatibility depends not only upon the material itself but also on its in vivo environment.

Polyurethane has been the material of choice in synthetic heart valves, since it showed good biocompatibility in a number of blood-contact devices. But the elastic modulus of polyurethanes is generally much higher than the modulus of fresh tissue at low strains introducing larger resistance. Calcific deposits also form adjacent and external to experimental polyurethane valves. Calcification that stiffens and frequently causes cuspal tears is the major cause of aortic bioprosthetic failure. It is not clear yet what causes the calcification in the polyurethane valves. In these cases, the mineral is extrinsic to the implanted material and is believed to be related to inflammatory cells adjacent to the blood-contacting surface. Morphologic changes of polyurethane surface have been observed. It is not determined yet whether this morphologic change resulted from the adsorption of proteins and...
mineralization on the leaflet surface, a polymeric structural change related to the leaflet motion, or an alteration of the polyurethane by the biological environment. Calcification in heart valve implants is most pronounced in areas of leaflet flexion, where deformations are maximal (i.e., cuspal commissures and bases). Calcification in polyurethane valves is probably a multifactorial process in which both mechanical and chemical influences play their part.

The second problem is the design of the valve itself. The design influences the stresses and strains exerted on the valve tissue, and determines the hemodynamic performance and consequently the life-span of the valve prosthesis.

In the natural aortic valve stress reducing mechanisms are found to be present. In the natural situation, dimensional changes occur in the valve configuration during the cardiac cycle. The load bearing part of the aortic valve leaflet can be regarded as an elastic grid, reinforced with collagen fibres and bundles. These bundles and the placement in and interaction of the leaflets with the aortic root form an unique mechanism to enable the valve to open and close with minimal stresses.

Stresses within the valve leaflet due to design are believed to be a major factor in triggering calcification and leaflet tearing. Minimization of stresses within the valve leaflets through design improves durability and could reduce platelet activation and calcification.

According to some researchers, the natural design of the valve and its capacity for repair are features against which the development of artificial valves has continually to be considered. This implies a trileaflet design with optimal flexibility of the prosthesis. Engineers attempt to improve flexibility in current biologic valve prostheses, by removing the stent in which the valve was mounted. These stentless valves seem to have improved hemodynamic performance, but no long-term results are available yet to prove that the stentless valves are more durable.

When constructing a valve, as is the case in synthetic trileaflet valves, it is quite a problem to get rid of the stent. To obtain and keep proper leaflet coaptation and thus avoid regurgitation, the proportional distances between the commissures of the valve should not change. In stented valves these distances are well defined. In a flexible stentless valve it will become much more difficult to predict the in vivo leaflet motion. Even if the valve is attached to the aortic wall and leaflet motion is in concert with the dimensional changes in the aortic root during the cardiac cycle, anatomical dimensions of the aortic root vary widely in human beings. This means the surgeon has to be technically very capable to insert such a valve. In the current stentless bioprostheses, this problem is partly solved by inserting the entire root (freestyle valves, appendix).

The solution for a polymeric synthetic valve is probably either a valve with flexible leaflets mounted in a rigid structure, ensuring maintainance of the spatial relationships of the commissures on the condition that optimal hemodynamic performance can be provided, or a totally flexible valve duplicating the freestyle valves.

The design of the valve leaflet itself should also be taken into account. The shape (spherical, alpharabolic) and the thickness (or thickness distribution) influence the characteristics of leaflet motion.

Conventional prostheses comprise a suture ring and/or pieces of Dacron cloth to facilitate proper implantation of the prosthesis. The rigid circular orifice ring is a non-physiological configuration for a heart valve, since the natural valve responds to the large range of motion of the heart itself (e.g., the native mitral valve has an elliptically shaped annulus that changes its shape during the cardiac cycle). Besides that, the ring reduces the inflow orifice.
Suture rings and Dacron cloth obstruct the inflow tract, thus giving rise to higher transvalvular pressure gradients. Adding these structures to the valve design should be minimized.

Summarizing the clinical and experimental observations described in the literature, the ideal heart valve prosthesis should:
- provide life-time performance
- have excellent hemodynamic characteristics
- give no rise to thrombosis, calcification and fibrous sheating
- avoid the need for additional medication
- be easy to insert in all kinds of anatomical settings
- not exceed the costs of the currently available heart valve prostheses
REFERENCES


33


34


36
APPENDIX

Aortic valve replacement with the Freestyle stentless valve (according to Westaby et al, 1995)

Fig 1. (A) The aortic valve is approached with a transverse aortotomy 2 to 3 mm above the sinotubular junction. Stay sutures are applied above the right coronary ostium in the middle of the noncoronary sinus and to the distal aorta. The valve is excised and the annulus size determined. (B) Subcommissural simple sutures are inserted first and then further simple sutures placed to maintain the inflow in a single plane. The valve is oriented so that the porcine coronary arteries proximate to the human coronary ostia. (C) The porcine coronary arteries are excised to align directly with the human coronary ostia and the height of the valve cylinder is trimmed to equate with the depth of the human aortic sinuses. (D) The outflow suture line is performed with a single double-armed 4/0 Prolene suture, which forms the crest to the Freestyle valve with the crest of the transected aorta. The suture line is brought beneath the coronary ostia, but if the right coronary artery is occluded proximally the porcine right coronary sinus is not excised.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Allograft</td>
<td>A graft of tissue between individuals of the same species but of disparate genotype (graft: any tissue or organ for implantation or transplantation)</td>
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<tr>
<td>Anticoagulant</td>
<td>Preventing blood clotting</td>
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<td>Antigenicity</td>
<td>The property of being able to induce the specific immune response or the degree to which a substance is able to stimulate an immune response</td>
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<tr>
<td>Autologous</td>
<td>Originating within an organism itself</td>
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<td>Biocompatibility</td>
<td>The quality of not having toxic or injurious effects on biological functions</td>
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<tr>
<td>Biodegradation</td>
<td>The series of processes by which living systems render chemicals less noxious to the environment</td>
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<tr>
<td>Coaptation</td>
<td>To coapt= to approximate</td>
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<tr>
<td>Collagenous</td>
<td>Pertaining to collagen. Collagen=the protein substance of white fibers of skin, tendon, bone cartilage, and all other connective tissue</td>
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<tr>
<td>Commissure</td>
<td>A site of union of corresponding parts</td>
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<td>Coronary arteries</td>
<td>The blood vessels that supply the heart muscle</td>
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<tr>
<td>Coronary ostia</td>
<td>The openings in the aortic sinus which mark the origins of the left and right coronary arteries</td>
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<tr>
<td>Diastole</td>
<td>The dilatation, or period of dilatation, of the heart, especially of the ventricles</td>
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<tr>
<td>Elastin</td>
<td>The essential constituent of the yellow elastic connective tissue</td>
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<tr>
<td>Endocarditis</td>
<td>Inflammatory alterations (infection) of the endocardium (= the endothelial lining membrane of the cavities of the heart)</td>
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<tr>
<td>Endothelium</td>
<td>The layer of epithelial cells the lines the cavities of the heart and the blood and lymph vessels</td>
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<tr>
<td>Extrinsic</td>
<td>Coming from or originating from outside</td>
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<tr>
<td>Fibrous</td>
<td>Composed or containing fibers</td>
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<tr>
<td>Glutaraldehyde</td>
<td>A disinfectant, effective against vegetative gram-positive, gram-negative, and acid-fast bacteria, bacterial spores, some fungi, and viruses. Also used as a tissue fixative because of its preservation of fine structural detail and localization of enzyme activity</td>
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<tr>
<td>Glycosaminoglycan</td>
<td>A group of polysaccharides which contains hexosamine, which may or may not be combined with protein and which, dispersed in water, form many of the mucins. Called also mucopolysaccharides</td>
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<tr>
<td>Hemocompatibility</td>
<td>The quality of being compatible with the blood</td>
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<tr>
<td>Hemolysis</td>
<td>Disruption of the integrity of the red blood cell membrane causing release of hemoglobin</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>The escape of blood from the vessels; bleeding</td>
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<tr>
<td>Heterograft</td>
<td>See xenograft</td>
</tr>
<tr>
<td>Homologous</td>
<td>In transplantation biology, denoting individuals (or tissues) that are of the same species but antigenically distinct</td>
</tr>
<tr>
<td>Intimal proliferation</td>
<td>The reproduction or multiplication of the cells of the inner layer of the blood vessels</td>
</tr>
<tr>
<td>Intrinsic</td>
<td>Situated entirely within or pertaining exclusive to a part</td>
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</table>
Lunula: a small crescent or moon-shaped area (in this case of the leaflets of the aortic valve)
Mitral valve: valve between the left atrium and ventricle
Proteoglycan: any group of substances found primarily in the matrix of connective tissues and synovial fluid etc. Contains glycosaminoglycan chains.
Radiopaque: not penetrable by rontgen rays or forms of radiant energy; radiopaque areas appear light or white on the exposed film
Regurgitation: the backward flowing of the blood into the heart, or between the chambers of the heart when the a valve is incompetent
Stenosis: narrowing or stricture of a duct or canal (in this case a narrowing of the aortic orifice of the heart or the aorta itself)
Striae: streaks or lines
Systole: the contraction, or period of contraction, of the heart, especially that of the ventricles
Thromboembolism: obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel
Thrombogenicity: the property of producing a clot, or coagulum
Thrombosis: the formation or development, or presence of a thrombus. a thrombus is a aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements
Xenograft: a graft of tissue transplanted between animals of different species