Conclusions

The Magna Ease valves demonstrated excellent durability and hydrodynamic performance after an equivalent of 25 years of wear. All study valves successfully endured one billion cycles of simulated wear, five times longer than the standard requirement for a tissue valve as stipulated in ISO5840.

Materials and Methods

In-vitro valve hydrodynamic performance, durability, and quantitative flow visualization were conducted in accordance with ISO 5840:2005 heart valve standard. The study valves were subjected to accelerated valve cycling to an equivalent of 25 years of wear. Hydrodynamic evaluations at intervals of 100 million cycles (2.5 years) were performed on the study valves. New un-cycled Magna Ease valves were used as hydrodynamic controls in this study. A quantitative assessment of the fluid motion downstream of the control and study valves was performed using Particle Image Velocimetry. The results between the test and control valves were compared to assess valve performance after an equivalent of 25 years of wear.

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All study valves met the ISO5840 requirements for effective orifice area, 1.81±0.06 cm² and 2.06±0.17 cm², and regurgitant fraction, 1.11±0.87% and 2.5±2.34%, for the 21mm and 23mm study valves, respectively. The flow characterization of the control valves and the billion-cycle valves demonstrated that the valves exhibited similar flow characteristics. The velocity and shear stress fields were similar between the control and study valves.

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Keywords: bioprostheses valve durability, tissue valve durability, valve, tissue valve, long-term performance

1. Introduction

The use of bioprosthetic heart valves (BHV) for valve replacement surgeries has increased in the recent past. In 2009, Brown et al. reported a 10-year study between 1996 and 2006 demonstrating a dramatic shift away from mechanical heart valves towards BHVs. In this work, Brown et al. showed that outcomes, including rates of death and stroke, have not only improved but are quite low for isolated aortic valve replacement surgery with BHVs (1). With the increasing use of BHVs, long-term durability and good hydrodynamic performance remain the paramount considerations in valve replacement surgery. Primary failure modes of BHVs take on many forms such as mechanical wear and tear, as well as calcific, non-calcific and fibrotic degeneration (2, 3), with calcification and mechanical modes accounting for the largest proportion of failures (4). Vesely et al. studied these two failure modes in BHVs and concluded that majority of the damage was occurring strictly due to mechanical reasons (5). Roselli et al. (2) conjectured that the advancements in the fixation techniques currently available reduce calcification in the biological milieu and hence mechanical wear could be a dominant mechanism for structural valve deterioration.

In this work, we focus on this dominant failure mechanism: mechanical wear and tear. An in vitro study can be used to isolate and evaluate the long-term mechanical durability of the bioprosthetic valve in the absence of calcification. Past studies have shown encouraging correlations between durability observed in vitro experiments and clinical in vivo durability of prosthetic heart valves (6, 7). Currently, the International Organization for Standardization (ISO) has mandated durability testing of BHVs in an in vitro setup up to 200 million cycles (equivalent to 5 years in vivo), as specified in the ISO 5840 International Heart Valve Standard (8). This mandate was established based on previous clinical data that demonstrated that in

Abstract

Background and Aim of Study

Durability and hemodynamic performance are top considerations in selecting a valve for valve replacement surgery. This study was conducted in order to evaluate the long-term mechanical durability and hydrodynamic performance of the Carpentier-Edwards® PERIMOUNT® Magna Ease™ Bioprostheses, through one billion cycles (equivalent to 25 years).

Materials and Methods

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an in vivo setting, the calcification cascade begins after 5 years, at which point mechanical testing would no longer be clinically relevant. However, in the light of new evidence that demonstrates the primary cause of valve deterioration as mechanical wear (5), it is now very important to perform durability tests of BHVs well past 200 million cycles. This need for long-term durability testing is further emphasized based on clinical studies that have demonstrated integrity and hemodynamic stability of BHVs up to 20 years post-implantation in patients (9, 10).

Considering the increasing use of BHVs, the objective of this study was to assess the simulated long-term durability and hydrodynamic performance characteristics of the Magna Ease valve in an in vitro setting. This study evaluates the valves up to 1 billion cycles which is equivalent to 25 years of simulated in vivo wear. Three tests were conducted: a) Accelerated Wear Testing (AWT), b) Hydrodynamic evaluation, and c) Particle Image Velocimetry (PIV). The AWT enables the simulation of 25 years of mechanical wear (excluding calcification and other biological processes) on the valve within a relatively short amount of time by accelerating the beat rate. Hydrodynamic evaluation was used to quantify the performance of the valves and PIV was used to understand the specific flow field features of the valves. Hydrodynamic performance and flow field results of the wear tested study valves were compared to those of uncycled-control valves of same sizes.

2. Materials and Methods

2.1. Valve Selection

The valve selected for this study was the Magna Ease aortic valve which is one of the most commonly implanted and commercially available aortic valves. Three samples each of 21mm and 23mm of clinical quality valves were used as the study valves. These two sizes were selected because they represent the majority of implanted valves in the patient population. To determine how the performance of the study valves might change over time, three samples of the Magna Ease aortic valve of same sizes in the uncycled condition were used as the controls valves for hydrodynamic comparison to the 1-billion cycled study valves.

2.2. Valve Description

The Magna Ease model 3300TFX valve is a stented bovine pericardial tissue valve fixed using glutaraldehyde solution and treated with the proprietary ThermaFix processes. This is a proprietary fixation method to reduce calcification in the pericardial tissue. The stent is made from cobalt chromium covered with PTFE cloth.

2.3. Experimental Setup and Testing Methodology

The study met the requirements for test equipment, set-up, and test intervals as specified for hydrodynamic, durability, and flow visualization testing specified in the FDA Replacement Heart Valve Guidance and ISO 5840 International Heart Valve Standard. The accelerated wear tester (AWT) was used in this study to simulate wear of the valves within a relatively short amount of time by accelerating the beat rate. In this study, the tester was set to operate at a frequency between 800-1100 cp (cycles per minute) for a minimum of one billion cycles. The tester was tuned to peak differential closing pressure of greater than 95mmHg, where 5% of each cycle must be above this minimum pressure for 95% of all cycles per ISO5840 requirements. The AWT was also tuned to achieve complete valve opening and closing for each cycle, similar to the valve opening and closing observed in the pulse duplicator tuned to physiologic conditions. In order to meet both of these conditions, the average peak transvalvular differential pressure the valves were subjected to was approximately 120 mmHg.

Leaflet kinematics were evaluated using high-speed video during AWT and during hydrodynamic performance testing. Hydrodynamic performance testing was conducted using a pulse duplicator system consisting of an atrium, mitral section, ventricular drive, aortic section and peripheral compliance and resistance. The pulse duplicator system can be adjusted to simulate various physiologic flow and pressure conditions. Valves were evaluated for pressure drop, leakage, and Effective Orifice Area (EOA). The valves were subjected to hydrodynamic evaluation at nominal physiologic flow and pressure conditions (Cardiac Output (CO) 5 LPM, Heart Rate (HR) 70 BPM, and Mean Aortic Pressure (MAP) 100 mmHg). The study valve testing and valve inspections were conducted at specific intervals of 100 million cycles from time zero up to one billion cycles.

In order to characterize the fluid flow characteristics of the valves, Particle Image Velocimetry (PIV) was performed on the study valves and control valves. PIV is an instantaneous, non-intrusive, whole-field, optical flow diagnostic technique to measure global velocity field. Fluid mechanic metrics such as turbulence and shear stress fields can be derived using this velocity field information. The PIV experiments were conducted in the Cardiovascular Fluid Mechanics Laboratory at the Georgia Institute of Technology.

2.4. Pulsatile Left Heart Simulator

The Georgia Tech Left Heart Simulator (GTLHS) was used as the pulsatile flow loop for the PIV studies. This loop consists of a fluid reservoir, a mechanical mitral valve, a bladder pump, a valve chamber, a compliance chamber, and a resistance element. The bladder pump, driven by compressed air and solenoid valves is used to simulate ventricular (11). A water-glycerin solution containing 36% glycerin by volume was used as a blood analog fluid to match the density and viscosity of blood (kinematic viscosity of 3.51 cP) and to minimize optical distortion during PIV experiments.

The flow conditions used for these experiments were the nominal physiological cardiac output and stroke volume of 5.0 L/min and 70 mL per beat at a mean arterial pressure of 100 mmHg. The cardiac output, ventricular and aortic pressures through the cardiac cycle were measured at 500 Hz for all valves, using a custom LabView program for 200 cycles before and after each experimental run. Measurements of the velocity field were acquired at 20 time points during the cardiac cycle. A higher temporal resolution during systole was chosen with
a uniform time spacing of 25 ms (over 400 ms centered about peak systole), yielding 16 time points and 4 other discrete time points were chosen during diastole (Figure 1).

2.5. PIV Instrumentation

PIV is a quantitative, optical based method of flow analysis which has been extensively used to study velocity and shear stress fields of aortic valve prosthesis in vitro simulators (11, 12). Two dimensional PIV was used to understand the flow field downstream of the valve models. The time spacing between laser pulses and image acquisition was optimized at each time point during the cardiac cycle to ensure that the average displacement of particles between images was approximately 25% of the final interrogation window size. Velocity measurements were acquired along the center line of the valve assembly such that one commissure post and line of leaflet coaptation was aligned with the imaging plane and the opposing leaflet was aligned perpendicular to the same plane (Figure 1C).

2.6. Definition of Calculated Quantities- Principal Reynolds Shear Stress

Shear stress has been correlated to blood cell damage and can serve as a predictor of potential areas where platelet activation or damage may occur (12). Reynolds shear stresses (RSS) is a measure of the average momentum flux in a flow field due to temporal variations in the velocity field, which arises due to cycle-to-cycle variations as well as fluctuations in turbulent flow. The principal RSS is defined as follows:

$$RSS = \rho \sqrt{\frac{(u'w')^2 + (v'w')^2}{2}}$$

Please refer to (13) for more details on the computation and interpretation of this metric.

3. Results and Discussion

3.1. AWT and Hydrodynamic Performance

Representative opening and closed images of a 23mm study valve in the pulsatile flow tester and AWT at zero and one billion cycles test interval are shown in Figure 2. In general, the only observable difference between the images is the diminishing size of the central gap caused by leaflet relaxation over time. The valves were taken out of the AWT at 100 million cycle test intervals for detailed inspection. Minor tears in the cloth were observed near the top of the stent posts on two of the size 23mm valves. These tears are known to be a test artifact. Cloth tears are not observed clinically, likely because the deposition of blood proteins and eventual ingrowth of host tissue eliminate the direct contact between the leaflet and cloth.

One of the size 23mm valves developed a pin hole in the leaflet after approximately 500 million cycles (equivalent to approximately 12.5 years) caused by the loose cloth from the cloth tear that came into contact with the open leaflet a few millimeters below the commissure tip immediately adjacent to the stent post (Figure 3). This valve remained fully functional through one billion cycles, meeting the acceptance criteria for effective orifice area and regurgitant fraction in ISO 5840. X-ray evaluation of the study valves verified that all structural components for all valves remained intact over the one billion cycle duration of the AWT study. Valve kinematic evaluations verified leaflet function from full opening to closure throughout the duration of the study. Hydrodynamic testing results of the study and control valves, EOA and RF, are presented in Table 1. EOA shows approximately 12% increase for the 23mm study valves and approximately 10% increase for the 21mm study valves through one billion cycles. The increase in EOA of the study valves may be due to leaflets becoming more flexible from the repeated pressure loading in the accelerated wear tester over time (14). Both the study and control valves display EOA values (1.81 cm² and 1.60 cm² for the 21 mm, respectively, and 2.06 cm² and 1.70 cm² for the 23 mm valves) well above the ISO minimum EOA requirement of 0.85 cm² for 21 mm valves and 1.00 cm² for 23 mm valves. The supplementary movie submitted along with the paper qualitatively illustrates the similarities in performance between the two valves.

The average measured regurgitant fraction (RF) of the study valves and control valves are presented in Table 1. The results generally show similar regurgitant fractions between the study
The next major hurdle to overcome for BHVs is calcification. Several clinical and in vitro studies have reported about the different means calcification can develop on BHVs (15, 16). Kheradvar et al. (15, 16) discuss that calcification can occur on BHVs not only via chemical/biological mechanisms but also due to mechanical reasons such as micro-injury and stress. The ability to reduce calcification clinically has the potential to extend the mechanical durability of bioprosthetic surgical valves in patients.

3.2. PIV Results

Figure 1B illustrates a sample velocity vector field for the 21 mm control valve at peak systole (T = 230 ms). It also indicates the locations at which the velocity profiles were extracted (15, 25, 35, 45, and 55 mm downstream from the valve annulus) for all the valves tested in this work.

Figure 4 illustrates the velocity profiles at 5 locations downstream from the valve annulus measured at peak systole for the 21 mm and 23 mm valves. For the 21 mm valve a comparison between the control and study valve shows that the velocity profiles and peak velocity magnitude are quantitatively similar (difference 0.1 m/s) proximal to the valve annulus. However, the velocity fields of the two valves differ with respect to the velocity profile (difference 0.5 m/s) distal from the valve (Figure 4B). This could imply that the momentum of the flow through the study valve was not sustained at the downstream locations when compared to the control valve. The increase in EOA observed for the study valve could be responsible for the observed reduced velocity. For the 23 mm valves (control and

<table>
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<th>Pulse Duplicator Full Opening</th>
<th>Inflow View</th>
<th>Outflow View</th>
<th>45° View</th>
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Figure 2: Representative 23mm control and study valves opening and closing in the pulsatile tester, and photo inspection of 23mm study valve at time 0 and at 1 billion cycles.

Figure 3: 23mm study valve with hole in leaflet near right commissure.

and control valves. Both the study and control valves display regurgitant fraction values well below the minimum regurgitant fraction requirement in ISO5840.

The results presented above show that the Carpentier Edwards Magna Ease valves are able withstand the mechanical environment of aortic valves for up to 25 years and perhaps even longer. This in-vitro AWT study demonstrates that the size 21 and 23 mm Magna Ease study valves (N=3) maintained structural integrity and good hydrodynamic performance up to 25 years of simulated accelerated wear. These results support the clinical findings of Johnston et al. who showed that the cumulative incidence of explant/year for structural valve deterioration was just 5.45% at 20 years (10).
Table 1: Summary of Effective Orifice Area and Regurgitant Fraction Results, EOA = effective orifice area; ISO = International Organization for Standardization; RF = regurgitant fraction

<table>
<thead>
<tr>
<th>Valve size</th>
<th>Control Valve (0 cycles)</th>
<th>Study Valve (1 Billion cycles)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EOA (cm²)</td>
<td>RF (%)</td>
</tr>
<tr>
<td>21 mm (n=3)</td>
<td>1.60±0.07</td>
<td>1.59±0.80</td>
</tr>
<tr>
<td>ISO 5840:2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 mm minimum requirement</td>
<td>≥0.85</td>
<td>≤10%</td>
</tr>
<tr>
<td>23 mm (n=3)</td>
<td>1.70±0.06</td>
<td>2.08±0.90</td>
</tr>
<tr>
<td>ISO 5840:2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 mm minimum requirement</td>
<td>≥1.00</td>
<td>≤10%</td>
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Figure 4: Velocity profile at 5 downstream locations from the valve annulus at peak systole in the center plane: A) 21 mm 0 cycle B) 21 mm 1 billion cycles C) 23 mm 0 cycle D) 23 mm 1 billion cycles.
a greater plug flow velocity profile was observed when compared to the 21 mm valves (Figure 4). The combination of valve size and chamber size (here the chamber size was held fixed, while the valve size changed), could be responsible for this observation. Furthermore, the 23 mm valves exhibit the same trends as that of the 21 mm valves with respect the variation of velocity profile at distal locations from the valve.

Figure 5 illustrates the principal RSS fields for the 21 mm and 23 mm valves at peak systole ($T = 230$ ms). For both the 21 mm and 23 mm valves, a comparison between the control and study valve shows that peak magnitudes of RSS ($\sim 250$ N/m$^2$) are comparable across the whole flow field. However, the spatial distribution of the RSS field is different between the control and the study valves (in both 21 mm and 23 mm). It should be noted that the outer edges of the flow field in PIV data measurements are usually noisy and hence should be taken into account while drawing any conclusions.

Both study valves exhibited larger RSS values close to the leaflets. This is expected due to fluctuations/flutter of the individual leaflet tips (due to wear) during systole. The fluctuations of the leaflets thus translate into higher turbulence in the flow field, which manifest themselves as higher RSS values. It is interesting to note, that the larger spatial extent of the RSS field (Figure 5A and 5B) appears to be correlated to the noticeable reduction in the phase average velocity profile (Figure 4A and 4B) at distal locations from the annulus of the valve.

The PIV analysis performed in this work was used to evaluate the platelet damage potential of the study valve and to determine if it was quantitatively different from the control valve. RSS is an extensively used metric that has been experimentally correlated to the shear induced damage to platelets. All valves tested fell far below the determined threshold for platelet damage between the range of 600 N/m$^2$ and 200 N/m$^2$ for exposure times between 5 and 15 ms (12). This indicates there was no difference between the study and control valve with respect to cell damage potential. Prior in vitro studies on a porcine bioprosthetic aortic valve by Lim et al. (17) also reported similar maximum principal RSS values in the range of 250 - 500 N/m$^2$. The blood damage potential of the valves observed in this study appears to be within the standard reported and accepted ranges.

4. Study Limitations

The primary limitation of this study is the in vitro nature of the study. The pulse duplicators used in this work were fabricated using rigid tubing with lumped compliance and resistance elements. The ascending aorta and sinus was axisymmetric and idealized, but were designed based on previous anatomic measurements. Similarly, the AWT system used for this study is idealized; however, the hemodynamic environment in which the valves were tested matched the worst case scenarios of in vivo conditions. Furthermore, planar PIV measurements do not provide the third velocity component; however, in the bulk jet flow from the aortic valve the third component should be minimal.
5. Summary and Conclusions

With recent clinical evidence of BHVs maintaining structural integrity and hydrodynamic stability to around 20 years in patients, it is imperative that these valves be tested for mechanical wear and tear. The results from this work demonstrate that the study valves remained functional throughout the completion of one billion cycles (~25 years) under an average transvalvular pressure of approximately 120 mmHg; approximately five times longer and at a pressure 25% higher than the standard requirements for a tissue valve in ISO 5840. All the structural components of the study valves remained intact and the hydrodynamic results were functionally equivalent to the zero cycled control valves. At the time of this publication, the study valves are continuing to be cycled beyond 1.2 billion cycles without failure. All the valves also met the acceptance criteria for regurgitant fraction and effective orifice area per ISO5840 guidelines at the completion of one billion cycles. Furthermore, PIV results indicate that the study valves exhibited similar flow field characteristics as the control valves. The above results demonstrate that in the absence of calcification the study valves exhibited superior long-term mechanical durability and stable hydrodynamic performance. Therefore, the authors speculate that the ability to reduce calcification clinically has the potential to further extend the mechanical durability of bioprosthetic surgical valves in patients.

6. Acknowledgments

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