Development and evaluation of a novel artificial catheter-deliverable prosthetic heart valve and method for in vitro testing

THOMAS E. CLAIBORNE1, DANNY BLUESTEIN1, RICHARD T. SCHOEPHOERSTER2, 3

1 Biomedical Engineering Department, Stony Brook University, Stony Brook, New York, NY - USA
2 College of Engineering, The University of Texas At El Paso, El Paso, TX - USA
3 Florida International University Biomedical Engineering Department, Cardiovascular Engineering Center, Miami, FL - USA

ABSTRACT: Background: This work presents a novel artificial prosthetic heart valve designed to be catheter or percutaneously deliverable, and a method for in vitro testing of the device. The device is intended to create superior characteristics in comparison to tissue-based percutaneous valves.

Methods: The percutaneous heart valve (PHV) was constructed from state-of-the-art polymers, metals and fabrics. It was tested hydrodynamically using a modified left heart simulator (LHS) and statically using a tensile testing device.

Results: The PHV exhibited a mean transvalvular pressure gradient of less than 15 mmHg and a mean regurgitant fraction of less than 5 percent. It also demonstrated a resistance to migration of up to 6 N and a resistance to crushing of up to 25 N at a diameter of 19 mm. The PHV was crimpable to less than 24 F and was delivered into the operating LHS via a 24 F catheter.

Conclusion: An artificial PHV was designed and optimized, and an in vitro methodology was developed for testing the valve. The artificial PHV compared favorably to existing tissue-based PHVs. The in vitro test methods proved to be reliable and reproducible. The PHV design proved the feasibility of an artificial alternative to tissue based PHVs, which in their traditional open-heart implantable form are known to have limited in vivo durability. (Int J Artif Organs 2009; 32: 262-71)

KEY WORDS: Percutaneous, SIBS, Transcatheter, Polymer, Tissue, Minimally invasive

INTRODUCTION

With an estimated 2% to 4% of persons over the age of 65 in the developed world suffering from aortic valve stenosis, and the estimated mortality rate for aortic valve disease standing at 25% to 54%, heart valve prosthesis research and development remains an important public health endeavor (1, 2). Moreover, the rising costs of healthcare globally are driving innovation in terms of increasing the efficiency of medical practice; minimally invasive medical procedures are evidence of such innovation. The current gold standard in heart valve replacement is open-chest surgical implantation of a suture-fixed heart valve prosthesis in either mechanical or tissue forms (3). The procedure is highly invasive, costly (on average 120,000 USD), time consuming, and has significant risks, e.g., bleeding, stroke, infection, and death. Furthermore, up to one third of patients in need of aortic valve replacement are denied surgery due to significant comorbidities (4).

Catheter-based or percutaneous replacement of heart valves, first described by Andersen et al (5) and later developed for human use by Bonhoeffer et al (6) (pulmonary valve) and Cribier et al (4) (aortic valve), has the potential in the near-term to allow patients to have access to heart-valve replacement when they would otherwise be denied open-chest surgery due to significant comorbidities. In the long term, a percutaneous approach may supplant open-chest procedures as the gold standard.

All percutaneous heart valves (PHV) currently in clinical trials employ chemically fixed tissue valves, which are known to be vulnerable to in vivo degradation via calcification and to have relatively short usable life spans (7, 8). Ad-
ne-block-styrene))-polyester (SIBS) composite leaflet material developed by Schoephoerster et al (12, 13), super-elastic Nitinol wire (Small Parts, Inc., Miramar, FL, USA), and 4-0 Ethicon Ethibond Excel polyester sutures. Stent bonding was performed using thin-walled stainless steel hypodermic tubing (Small Parts, Inc., Miramar, FL, USA) and ethyl cyanoacrylate. The stent was constructed from three Nitinol wires. The Nitinol wires were annealed for shape setting (Fig. 1). The result produced three shape-set and oxidized super-elastic Nitinol wires for stent fabrication. Two of the stents were identical sinusoidal shapes with six turns each (proximal stents). The third or distal stent was designed with teardrop shaped loops in each of its six bends for added stiffness (14). The two proximal stents were designed to support the leaflet material, while the distal stent was designed to provide PHV fixation (Fig. 1). The height of each stent from top bend to bottom bend was approximately 12 mm.

The leaflet dimensions were determined using a formula and constants defined by Thubrikar (15). Based on the desired valve diameter (d) of 19 mm, the ideal valve height (H) was taken to be \( H = \frac{d}{2} \times \sqrt{1.245} \approx 12 \text{ mm} \). The stent height (h) was then \( h = 2 \times H \approx 24 \text{ mm} \). The constant 1.245 was based upon ideal human anatomy. A rectangular piece of leaflet material was cut to approximately 65 X 18 mm, with the length \( L = d \times \pi + 5 \approx 65 \text{ mm} \), and the width \( w = H + H/2 \approx 18 \text{ mm} \). The extra width was used as an outer cuff during PHV assembly, and the extra length was used to create a cylinder.

The PHV was assembled using 4-0 Ethicon Ethibond Excel suture. The distal portion of the leaflet material was attached to the proximal stents at three equidistant bends in order to create a trileaflet valve. Once the PHV was assembled, three 9.525 mm stainless steel ball bearings and a 19 mm diameter aluminum cylinder were used to anneal a semilunar shape into the leaflet material.

The PHV delivery system was designed to deliver and deploy the PHV via peripheral arterial access, thus via retrograde approach. Furthermore, the function of remote tip

**Fig. 1** - Shows: (a) the composite leaflet material in its configuration prior to being mounted to the stent; (b) the plate utilized to create the composite leaflet material; (c) the jig utilized for shape setting the Nitinol wire; (d) the Nitinol wire in its final stent configuration; (e) the tool created to crimp and load the PHV into the delivery catheter; (f) the delivery system hand piece used to steer the catheter and deploy the PHV.
Development and evaluation of PHV

deflection or steering was added to the design. Medical grade fluorinated ethylene propylene (FEP) tubing was donated by Zeus Industrial Products, Inc. (Orangeburg, SC, USA) and used as a catheter. The outer diameter of the tubing was 8 mm or 24 F and the inner diameter was 7 mm. It was sufficiently flexible to navigate a mock aorta made of polycarbonate tubing with an inner diameter of 25.4 mm. A catheter tip was machined from Delrin and functioned to facilitate atraumatic intravascular navigation, passage of a guide wire, and anchorage of the catheter’s internal support wire. The internal support wire was a length of 1.27 mm diameter super-elastic Nitinol wire. A PHV crimping tool was designed to crimp and hold the PHV for loading into the catheter (Fig. 1). Finally, a hand piece was designed to allow remote control of catheter tip deflection and PHV deployment (Fig. 1).

Each of the 14 PHV prototypes was hydrodynamically tested using a SuperDup’r Left Heart Simulator (LHS) (Vivitro Systems, Inc., Victoria, BC, Canada) modified to accommodate the mounting of the tested PHVs, according to the following procedure. An artificial aortic conduit was molded from Sylgard 184 (Dow Corning, Midland, MI, USA) and placed inside the aortic chamber of the LHS, thus replacing the glass sinus of Valsalva and bypassing the characteristic aortic compliance chamber of the LHS. The mold was designed so that the wall thickness of the silicone aortas could be varied and the elasticity or compliance of the tubes could be further altered via changing the elastomer to the curing agent ratio (Fig. 2). The compliance of the silicone tubes was measured via observed changes in diameter during LHS testing and on the bench top using digital calipers and a sphygmomanometer. The inner diameter of each tube was 19 mm, and none contained sinuses of Valsalva.

Prior to each PHV test, values were recorded of the flow characteristics of the silicone tubes alone in order to gage their influence on the results. Baseline data was recorded with the LHS manufacturer recommended assembly before any PHV testing began. The first benchmark included testing a 25 mm diameter bileaflet St. Jude Medical mechanical heart valve.

A second benchmark was created for the purpose of comparing the new design to an existing PHV, by constructing an artificial version of the Edwards Lifesciences Sapien-Cribier PHV (Fig. 3). This PHV was assembled in a manner similar to our PHV using 4-0 Ethicon Ethibond Excel suture. No modifications were made to the suture itself.

Each PHV prototype was run for 12 consecutive 30-second tests according to the FDA guidelines (16). Heart rates of 45, 70, 100, and 120 bpm were used and target mean flow rates of 2.3-11.4 l/min were attempted. Flow rates were recorded using a Carolina Medical Square Wave electromagnetic flow sensor and flow meter, and transvalvular pressures were recorded using two Mikro-Tip catheter transducers (Millar Instruments, Huston, TX, USA) with one each in the left ventricle and the distal aortic chamber. LHS test measurements were recorded using a PC running AcqKnowledge 3.2.3 software and a MP100A data acquisition system (Biopac Systems, Inc., Santa Barbara, CA, USA), which was connected to the flow meter and pressure transducer units. The heart rate was
set using a Tri-Pack TP 2001 Square Wave Generator. The flow was generated using a Superpump SPA3891 Servo Power Amplifier connected to a Superpump Piston-in-Cylinder System (all from Vivitro Systems, Inc., Victoria, BC, Canada). Characteristic waveforms of the Vivitro system with a 25 mm St. Jude bileaflet mechanical valve are shown in Figure 4. A blood analog solution composed of 35% glycerin and 65% deionized water by volume with 9 grams of sodium chloride per liter was used during LHS testing. The resulting solution had a density of 1.133 g/mL and a viscosity of 3.2 cP, which was similar to whole blood.

The ability of the PHVs to resist migration and collapse in situ was tested using a Bose ELF 3200 (Bose Corporation, Eden Prairie, MN, USA) and two separate custom built fixtures. PHV fixation testing was performed using a method similar to that described in a 2007 paper by Zhou et al, in which they tested the displacement force of aortic stent grafts by deploying the grafts into animal aortic segments and pulling the grafts axially (17). The tests in this work were conducted by anchoring a silicone aorta to the mobile top anchor of the Bose ELF 3200 via #1 Ethicon Ethibond Excel suture and tethering the PHV, deployed inside the tube, to the bottom fixed anchor of the system. The suture attached to the PHV was separated and held parallel to the wall of the tube via an aluminum disc so that no bending moments were applied to the PHV during the test. The silicone tube and the PHV were both wetted with the blood analog solution used in the LHS. The force required to make the PHV slip was termed the fixation force.

Radial compression tests were performed using a Teflon sheet that was cut into a shape that would allow the Bose ELF 3200 to convert linear motion into rotational motion, meaning, as the machine increased the linear distance between its two anchors, the Teflon sheet loop would decrease in diameter. Therefore, the force measured was taken to be the hoop force, $F_\theta$, of the PHV. The hoop force was converted to radial force, $F_r$, using the relationship $F_r = F_\theta 2\pi$. The starting diameter of the Teflon sheet loop was set to 21 mm at the beginning of each test using a stainless steel cylinder of the same diameter.

An F-scale sizing block was designed and machined from Delrin for the purpose of testing the crimpability of each prototype PHV. It contained holes varying in size from 24 F to 12 F.

The delivery system was qualitatively tested via verification tests that included bench top and in situ active LHS loading, deflection, and deployment. For the bench top tests, a simple 25.4 mm diameter polycarbonate tube was utilized. For active LHS tests, a mock aortic conduit was fabricated and attached to the LHS. The external circuit redirected the LHS flow through the mock aorta and arterial system. An access port was added to the circuit in order to allow distal introduction of the delivery catheter into the LHS. The simulated delivery system employed a retrograde approach.

Data for all tests were collected and qualitatively analyzed for trends. The valvular pressure gradient data recorded during LHS testing was altered by subtracting the mean pressure gradients recorded for the silicone tubes without in situ PHVs. This “tube factor” was utilized to adjust pressure readings influenced by the
Development and evaluation of PHV

Both the modified Sapien and our final optimized PHV design exhibited initial slippage forces greater than 6 N, which was approximately equivalent to twice the normal diastolic pressure (160 mmHg) over the cross-sectional area of a 19 mm rigid conduit.

The final PHV design exhibited approximately 25 N of radial force or a stiffness of about 130 kPa at a crushed diameter of 19 mm. In contrast, the theoretical radial crushing force exerted via the typical arterial segment of 30 mm in length was calculated to be approximately 10 N (19).

The delivery system performed as intended during verification testing, both on the bench-top and inside the functioning LHS. Briefly, the prototype PHV was loaded into the delivery catheter using the crimping tool; the catheter was flexible enough to navigate a tortuous path and stiff enough to be pushed through the test conduit; the PHV was deployed using the delivery system hand piece, and the catheter tip was “steered” or deflected from the outer wall of our mock aorta into the center of the test conduit lumen (Fig. 9).

Discussion

Catheter deliverable or percutaneous heart valve (PHV) prostheses have been developed recently and promise to be a safe and effective minimally invasive alternative to open-heart valve replacement surgery. There has been significant interest among interventional cardiologists and cardio-thoracic surgeons in this emerging technology since the first successful pulmonary PHV human trial by Bonhoeffer et al in 2000, and the first successful aortic PHV human trial by Cribier et al in 2002 (6, 2). Development of PHV’s has rapidly advanced since then, primarily in the hands of private industry, with limited public availability of peer-reviewed medical, scientific, and engineering analyses of the technology. The rapid and incongruous development of PHV’s has caused concern among medical professionals who have recommended standardization of practices and a tempered pace of development, which alone justifies peer-reviewed scientific investigation into PHV technology (20). For example, to date one relevant peer-reviewed engineering analysis of PHVs has been published and this occurred after a 21% rate of stent fracture was reported during clinical trials of the Bonhoeffer-Medtronic Melody pulmonary PHV (21).

All of the relevant PHVs designed for percutaneous delivery currently in development and/or in human trials are...
Fig. 6 - Illustration of the optimization process by progressive improvement in the performance of selected successive prototypes compared to a 25 mm St. Jude Bileaflet Mechanical valve. A positive slope was expected.

Fig. 7 - Illustration of the optimization process by progressive improvement in the performance of selected successive prototype compared to a 25 mm St. Jude Bileaflet Mechanical valve. A negative slope was expected, however the systemic resistance of the LHS had to be decreased to achieve higher cardiac outputs, which caused regurgitation to increase in some cases.

based on tissue valves, which in their open-heart implantable form are known to exhibit limited durability. Moreover, the effects of crimping and deploying tissue PHVs have just begun to be investigated. A percutaneous heart valve must be able to withstand the crimping and deployment procedure without sustaining damage to the blood contacting surfaces. For this reason, chemically fixed xenograft valves, specifically, pericardial or porcine valves, may not be ideal due to the nature of the tissue structure and its inability to repair any incidental damage caused during crimping and deployment. Moreover, percutaneous heart valves that require balloon dilatation are likely to experience additional destructive forces when dilated in vivo. For example, Ruiz et al recognized the inability of chemically fixed xenografts to regenerate, and experimented with decellularized tissue (8). They harvested small intestinal submucosa (SIS) and constructed a PHV. Once deployed in vivo, the SIS valve began to be populated by endothelial cells and became a
Development and evaluation of PHV

prior to crimping and deployment into a pulse duplicating bioreactor. This pre-treatment of the PHV produced less damage to the valve than otherwise, but they reported an inability to prevent infection with their technique. While showing certain promise, the complexities of such techniques preclude their use for practical applications in the viable living valve; however, over time the valve continued to thicken, which may prove detrimental in the long term. Stock et al also studied this phenomenon in an effort to mitigate tissue damage via tissue engineering techniques (9). They performed an in vitro study, in which they constructed an SIS valve, and seeded the valve with endothelial cells prior to crimping and deployment into a pulse duplicating bioreactor. This pre-treatment of the PHV produced less damage to the valve than otherwise, but they reported an inability to prevent infection with their technique. While showing certain promise, the complexities of such techniques preclude their use for practical applications in the viable living valve; however, over time the valve continued to thicken, which may prove detrimental in the long term. Stock et al also studied this phenomenon in an effort to mitigate tissue damage via tissue engineering techniques (9). They performed an in vitro study, in which they constructed an SIS valve, and seeded the valve with endothelial cells prior to crimping and deployment into a pulse duplicating bioreactor. This pre-treatment of the PHV produced less damage to the valve than otherwise, but they reported an inability to prevent infection with their technique. While showing certain promise, the complexities of such techniques preclude their use for practical applications in the
near term. Attmann et al demonstrated the phenomenon of tissue calcification in PHVs via animal studies of a pulmonary PHV composed of a bovine jugular vein segment with in situ venous valve and a Nitinol stent (9). Therefore, we speculate that the known limited performance characteristics of chemically fixed xenograft valves designed for open-heart implantation coupled with the latest tissue PHV data creates a strong case for the continued development of artificial valve materials, especially for percutaneous delivery, where the valve must endure the additional stresses of crimping and deployment. However, these stresses and their effects were not investigated in this study.

The purpose of this work was to develop and evaluate an artificial aortic PHV with characteristics that are superior to the current tissue based PHVs, and to develop a reliable in vitro testing methodology. The PHV developed during the course of this work utilized a state-of-the-art “super-biostable” polymer and polyester fabric composite valve material developed at Florida International University in conjunction with Innova, LLC that may be superior to tissue in terms of durability and equivalent in terms of hemocompatibility (12, 13). The PHV was designed to be self-expanding, to mimic the natural valve (trileaflet), and to remain in place via spring force and friction. While stainless steel or other rigid alloy stents may exert a higher initial radial force, a Nitinol stent will tend to slowly reshape the lumen of the vessel in which it resides to a larger diameter due to its chronic outward force (19). Furthermore, a less elastic alloy could be reduced in diameter over time by the cyclic loading applied by the muscular and dynamic aortic root.

The mean values of the hydrodynamic test results for each prototype PHV were compared to one another via one-way ANOVA, to a St. Jude 25 mm diameter bileaflet mechanical valve, and to a modified Edwards-Sapien PHV fabricated with the composite leaflet material. The results showed that the mean performance of each prototype was significantly different (p>0.001). Tukey’s post-hoc test indicated that there was no significant difference between the modified Sapien and the best PHV prototype (p=1.000), or between the St. Jude valve and the optimized PHV prototype (p=0.611). Additionally, there was no difference between the best PHV prototype and the St. Jude valve or the modified Sapien PHV according to the ACC/AHA heart valve performance scale (22). By comparison, a midterm study of the Sapien PHV showed a mean transvalvular pressure gradient of 10 mmHg with an average valve area of 1.7 cm², and 0 to +2 regurgitation (23). Our best hydrodynamically performing PHV prototype had an adjusted mean pressure drop of 14.4 mmHg with an EOA of 1.14 cm² and a regurgitation of 3.24%, which is essentially 0 on the ACC scale. When compared to a 30-day trial of the CoreValve where a mean pressure gradient of about 10 mmHg and regurgitation of 0 to +2 was reported, our PHV compares favorably (24, 25). Notably, the delivery catheters used by the CoreValve were 21 F and 18 F. However, a significant limitation to these comparisons was that our data was entirely in vitro whereas the literature data was entirely from clinical studies. To date, there have been no known relevant in vitro studies published for comparison.

These statistical results indicated that the final PHV design was at least comparable to competitors. However, only one prototype of each valve design iteration was constructed and tested, therefore N=1 for the statistical analysis which precluded the inclusion of error bars in the charts.

The fixation test was modeled after a study published by Zhou et al wherein an abdominal aortic aneurysm stent graft was deployed into a segment of bovine aorta and the force required for slippage was measured. Their results showed initial displacement forces between 3 N and 33 N depending on the type of graft and the magnitude of over-sizing (5-20%) (17). In this work, silicone aortas were utilized in lieu of a bovine aortic segment and the Bose ELF 3200 was more sophisticated than the force gauge utilized by Zhou. Additionally, the silicone aorta was wetted with the blood analog solution used in hydrodynamic testing of the PHVs to reduce friction. Theoretically, the valve was capable of resisting up to 160 mmHg of diastolic pressure, which is well above normal physiological diastolic pressures even for hypertensive individuals. The radial force tests indicated that the final PHV design could withstand greater than 25 N of radial force. Therefore, the PHV was predicted to be able to overcome the estimated 10 N crushing force of the aorta and expand to the desired diameter or to the elastic limit of the vessel (19).

The delivery system was designed to deliver and deploy the PHV retrograde via peripheral arterial access into the operating LHS with an added steering feature. The consensus in the medical literature indicates that such an approach is advantageous as compared to an antegrade approach, which is more technically challenging and has the potential of causing damage to the mitral valve and which may cause cardiac perforation or other serious complications during the valve deployment (26). Moreover, Edwards Lifesciences (Irvine, CA, USA) had recently developed a steerable PHV catheter for use with its Sapien PHV (27). The delivery system prototype designed and fabricated during the course of this work functioned as intended in verification bench-top testing and in dynamic delivery. Deployment testing was performed inside a mock aortic flow
Development and evaluation of PHV

However, the FEP tubing was less than ideal as a PHV delivery catheter because it kinked when navigating the curvature of the simulated aortic arch segment. Additionally, it took a considerable amount of force to retract the catheter sheath due to the tight fit of the PHV inside the 21 F lumen of the catheter. Accordingly, optimization of the delivery system design is warranted. Regardless, our results indicate the feasibility of testing in vitro PHV delivery.

Others have attempted to create artificial PHVs but have had limited success in animal trials for various reasons (28-32). However, we believe that we have created a viable alternative to tissue-based PHVs.

The work presented here is in the early stages of development, and durability and animal tests will be required to prove the design’s ultimate feasibility as a future candidate for human trials and eventual commercialization. However, it demonstrates the feasibility of an artificial composite PHV based on the natural anatomy of semilunar valves, which may become the best choice for the future of PHV development. Future work will include further optimization of the in vitro testing method; durability testing of the PHV and design optimization; in vitro biocompatibility testing; computer modeling of the PHV; and animal testing.

CONCLUSIONS

A novel catheter-deliverable artificial trileaflet aortic heart valve prosthesis and in vitro test method were developed and evaluated. The results demonstrate the feasibility of this technology by showing that an optimized polymer PHV prototype was equivalent to the existing PHV technology currently in clinical trials. Additionally, the in vitro test methodology proved to produce reliable and reproducible results. The delivery system functioned as intended by delivering and deploying our PHV on the bench top and inside the functioning Vivitro LHS. The final PHV design proved to be capable of resisting migration and crushing forces exceeding those expected in vivo.

ACKNOWLEDGEMENTS

This work was performed at Florida International University in Miami, Florida in the Department of Biomedical Engineering’s Cardiovascular Engineering Center and was funded by a grant from the W.H. Coulter Foundation.

The SIBS polymer was developed for heart valve applications and provided by Innovia, LLC of Miami, Florida. Leon Gibson of A-1 Precision Machining in Hialeah, Florida performed prototype machining. The authors wish to thank Siobhain Gallocher and Qiang Wang for their assistance.

Conflict of interest statement

Funding was provided by a Wallace H. Coulter Foundation grant given to Florida International University Biomedical Engineering Department Miami, Florida. The authors Claiborne and Schoephoerster have an intellectual property agreement and pending patent with Florida International University concerning the technology described herein. Dr. Schoephoerster has collaborated with Innovia, LLC, the commercial developer of the SIBS polymer.

This work was presented at the 24th Southern Biomedical Engineering Conference at the University of Texas at El Paso on April 19, 2008, and the conference proceedings were published in the International Journal of Medical Implants and Devices.

Address for correspondence:
Thomas E. Claiborne, III
Stony Brook University
Department of Biomedical Engineering
HSC T18, RM, 030
Stony Brook, NY 11794-8181
e-mail: tclai001@fiu.edu

REFERENCES