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Research Article

Bioprosthetic Valves with a Novel Support System with Heart Shape Commissural Posts

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Abstract

Background: Continuous improvement in the mechanics, preservation and anticalcification treatment made bioprostheses the standard mode of valve replacement in the aging population. A novel Support System with large openings at the Commissural posts has been developed and the performance and durability of bioprostheses constructed went under evaluation.

Methods: This stent was used to create Three trileaflet composite porcine valves of 23mm (titanium), 27mm and 31mm (POM-C) in diameter were constructed. and one 25mm (titanium) bovine pericardial valve. All valves were tested in a heart valve duplicator system. The porcine valves underwent fatigue accelerating testing.

Results: For the porcine valves the peak pressure was measured as 12.5mmHg, 9.1 mmHg and 7.3mmHg for the 23mm, 27mm and for the 31mm valve respectively and the valve area were 2.5 cm^2, 2.6 cm^2 and 2.7 cm^2 respectively. The 25mm pericardial valve showed a peak pressure of 5.5mmHg and a valve area of 3.1 cm^2. The durability test showed deterioration after $225x10^6$cycles for the 23mm, $265x10^6$ cycles for the 27mm and $240x10^6$ cycles for the 31 mm.

Conclusion: This novel stent for bioprosthetic valves offers excellent hydrodynamic performance for a variety of biological issues tested and above the standards durability.

Background

Since the introduction of Glutaraldehyde-fixed xenografts by Alain Carpentier [1], bioprosthetic valves have shown an advantage over the mechanical valves, such as no need for daily intake of anticoagulants, less incidence of thromboembolic episodes, hemorrhage and infectious endocarditis [2]. The main disadvantage, however, is that they do not last as long as the mechanical valves do. The bioprosthetic valves are derived either from porcine aortic valve, or bovine and equine pericardium [3-7]. Animal sources such as kangaroo [8] and seal tissues [9-11], have been proposed by various researchers as an alternative to the currently used xenograft tissues. The mode of failure of bioprosthetic valves is calcification and torn leaflets specifically at the commissural posts due to the increased forces applied on them during the cardiac cycle [12-15].

A novel support system (stent) with large heart shape openings at the commissural posts made either from acetal copolymer (POM-C) or grade 5 Titanium has been developed. Even if this stent was initially designed to accommodate aortic and pulmonary valves derived from marine mammal origin (Phoca Groenlandica), showing excellent hydrodynamic performance when tested in a steady flow system [11], its use was expanded to include porcine aortic valves and valves of bovine pericardium origin.

Methods

Stent

Two different stents were constructed. The "plastic form" (Figure 1) made out of acetal copolymer POM-C (Plastics International, 7600 Anagram Dr., Eden Prairie, MN, USA) and the "metallic form" (Figure 2) made out of grade 5 titanium (Columbia Metals Ltd, Union Street South, Halifax, England). The thickness of the plastic stent was 1 mm and that of titanium 0.25-0.30mm depending on the diameter (17mm up to 33mm).

A CO2-laser was used to cut the pipes to the desired design after which the produced stents were cleaned with two stage sand blasting. Both plastic and metallic stents were covered with thin Knitted Dacron cloth (C. R. Bard, Inc. Murray Hill, New Jersey, USA) (Figure 3).

Animal Source

Porcine aortic valve

Fresh porcine aortic valves were harvested from a local slaughter house and after cleaning and trimming the excess tissues, the valves were treated with 0.5% buffered glutaraldehyde for

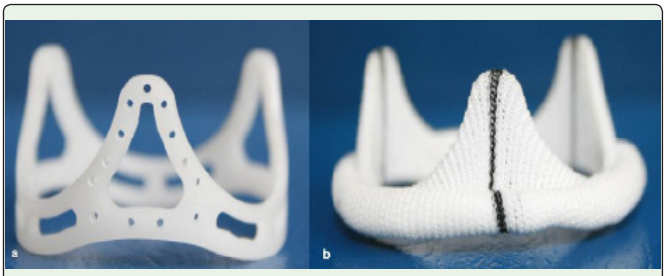

Figure 1: a) Stent made of POM-C, b) the same stent covered with Knitted - Dacron cloth.

Figure 2: a) Titanium stent, b) titanium stent from above showing the thin thickness and c) titanium stent covered with PTFE using the encapsulation technology.

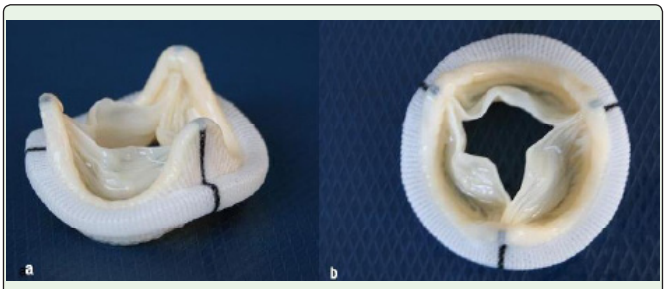

Figure 3: a) Trileaflet composite porcine aortic valve using POM-C stent and b) outflow view.

one month and then transferred to 0.25% buffered glutaraldehyde solution. Subsequently triple composite valves were manufactured from select porcine aortic valve cusps, using only cusps devoid of the septal muscle bar. The cusps were carefully matched for optimum leaflet coaptation and hemodynamics. Three trileaflet composite porcine valves of 23mm (titanium) (Figure 4), 27mm and 31mm (POM-C) in diameter were constructed (Figure 3).

Bovine pericardium

Fresh bovine pericardium was harvested and treated using the same protocol as for the porcine aortic tissue. One piece of pericardium 0.6mm in thickness was used to wrap a 25mm titanium stent and create a pericardial valve (Figure 5).

Heart valve pulse duplicator

A heart valve pulse duplicator Vivitro SPS3891 (Vivitro Systems Inc., Victoria, BC Canada) was used to measure hemodynamic parameters. All tests were performed with the standard FDA waveform. The test fluid temperature was 25°C and the density 1.000g/ml. The heart rate was set to 71.5/min, stroke volume 64.4 ml-73.0 ml, end systolic volume 110.2 ml-115.5 ml, cardiac output 5.2 l/min, systole/diastole ratio 0.561-0.571. Results were taken for an average of 10 cycles with 256 samples per cycle. Maximum transvalvular pressure was measured and the valve area was calculated.

Durability test

In collaboration with independent engineers in Athens Greece, we developed a six chamber device using a swash plate drive system to conduct heart valve fatigue testing (Figure 6). Up to six samples can be tested in six separate chambers. As the swash plate rotates, the bellows are compressed or extended causing fluid to flow through the valves. Test fluid dispersion into separate chambers enables pressure and temperature stabilization. The test frequency was set to 700-750 cycles/min, fluid temperature at 22°C, density at 1.000 g/ml and driving pressure at 100 mmHg. The valves were inspected daily by stroboscope for leaflet kinematic assessment and valve integrity. Every 50 millions cycles the valves were inspected using a light microscope with a 10x magnification.

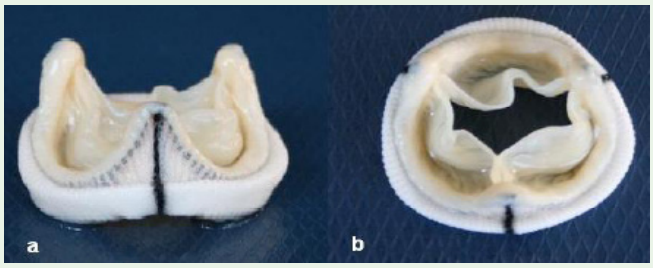

Figure 4: a) Trileaflet composite porcine aortic valve using titanium stent and b) outflow view.

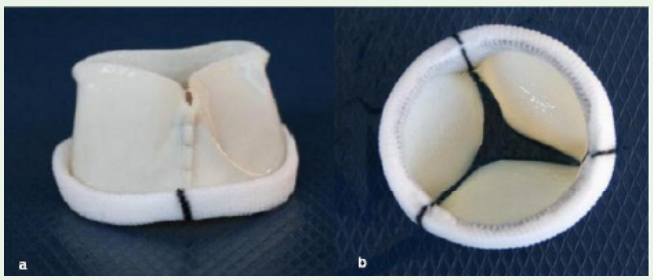

Figure 5: a) Pericardial valve using titanium stent and b) inflow view.

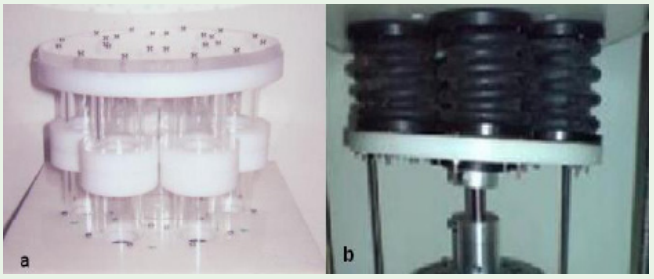

Figure 6: a) a six-chamber fatigue acceleration device and b) the underlying mechanism using a swash plate drive system.

Results

The hydrodynamic results using a Vivitro heart valve pulse duplicator are listed on Table 1. The results of the fatigue acceleration testing for the porcine valves are listed in Table 2 along with the mode of failure for each valve. The pericardial valve did not undergo a durability test as it was constructed at a later stage and due to a lack at that time of a supporting annulus in the machine. Air bubble formation in the chambers was a problem as we had not yet developed an air evacuation system, during this preliminary testing, and these bubbles may have accelerated the destruction of the valves. Pressure transducers were not used for monitoring transvalvular pressure drop.

Table 1: Hydrodynamic values for the valves tested.

	23mm Porcine Titanium	25mm Pericardial Titanium	27mmPorcine POM-C	31mm Porcine POM-C
Heart rate/min	71.6	71.5	71.6	71.5
Stroke volume (ml)	72.1	73.0	70.5	64.4
End systolic volume (ml)	114.5	115.5	112.7	110.2
Cardiac output (l/min)	5.2	5.2	5.2	5.2
Systole/diastole ratio	0.561	0.569	0.571	0.571
Mean Pressure values (mmHg) Aortic left ventricle left atrium	 99.6 45.6 8.5	 99.6 44.2 8.5	 99.8 45.2 8.5	 99.8 44.5 8.7
Mean pressure gradient (mmHg)	2.0	1.2	1.7	1.5
Maximum pressure gradient (mmHg)	12.5	5.5	9.1	7.3
Pressure gradient at peak flow (mmHg)	11.3	3.7	7.5	5.5
Flow volume (ml) Forward Closing Closed Leakage (ml/s)	 75.6 -1.4 -1.6 -5.9	 76.2 -1.6 -0.5 -2.2	 75.2 -1.6 -1.2 -2.5	 75.0 -1.8 0.0 -3.8
Calculated valve areas (cm^2)	2.5	3.1	2.6	2.7
Ventricular energy per cycle (Joules)	1.015	0.785	0.987	0.836

Discussion

All cardiac surgeons are very well trained to be capable of replacing cardiac valves in their patients. During their career they come across hundreds or even thousands of valve replacements. Nevertheless, when it is a case of creating a heart valve and especially a bioprosthesis, then they would probably look at this as a very challenging proposition. They would have to address and develop techniques in tissue harvesting from an animal slaughter house, ideal transport methods to the lab, meticulous cleaning and trimming of the excess tissues around the valve, creating all the chemicals for stabilization and fixation of the tissues, creating a new anticalcification treatment for the tissues, finding the proper material as regards Dacron cloth and stitches, obtaining artistic techniques for mounting the valve (a very demanding procedure) on a Dacron covered stent (another demanding procedure) and creating a sterilization protocol. On top of these very demanding steps, the challenge would be magnified if someone had to design and create a new stent from various materials

Table 2: Fatigue accelerating results at 700-750 cycles/min.

	23mm Porcine Titanium	27mm Porcine POM-C	31mm Porcine POM-C
Number of cycles at failure ($x10^6$ Cycles)	225	265	240
Mode of failure	Increased collagen deterioration of one leaflet leading to stiffness	Deformity of the valve due to cut suture. Loose leaflet attachment	Increased collagen deterioration of one leaflet leading to stiffness

to compete with the existing perfect stents, available in the market from the heart valve industry, and even develop testing devices such as a steady flow system or a fatigue accelerating machine and be able to work with them.

We faced all these challenges when we first came up with the idea of using aortic and pulmonary valves from Canadian Harp Seals (Phoca Groenlandica) as a new animal source for bioprosthetic valves [10,11]. For this reason we created this novel stent with large heart shape openings at the commissural posts to accommodate the Harp Seal aortic and pulmonary valves. Along with this stent we developed all other aforementioned steps using a lot of patience, experimentation, communication with different kind of industries, a lot of studying, imagination, and countless hours in the lab. A lot of try-fail-success stories have been involved during the past few years and we experienced alternating emotions such as disappointment due to failure and happiness thanks to success.

In addition to the existing, since the early 1970's, US marine mammal protection act, a major blow came for our research program with the European Community (EU) law in 2010 and finalized in 2014, banning marine mammals import into the EU. Since the two major world markets were now closed, we used our experience gained over all these years and tried to create bioprostheses from existing and "accepted" animal sources, such as of porcine and bovine origin, using the same stent that we had developed for the Harp Seals. Our preliminary results are presented in this study.

Natural pig valves have a muscle shelf attached to the right coronary cusp, which, even if meticulously trimmed, may produce an obstruction to the flow through the valve. Bioprostheses made from untreated native pig valves result in bulky valves and show high transvalvular gradients. Hancock [3] introduced the replacement of the muscle-bound right coronary leaflet with a nonmuscular cusp from another valve, thus producing a valve with better hemodynamic performance. The trileaflet composite valve technique was introduced by O'Brien [16] using only cusps devoid of the septal muscle bar, carefully matched for optimum leaflet coaptation and hemodynamics. We adapted this technique to create our valves with very good hydrodynamic performance as is evident from our results from the heart valve pulse duplicator.

Bovine pericardium is very easily handled and treated. Caution is taken that the pericardium chosen has uniform thickness all around. Then using the wrapping technique around the stent, as this was introduced by Mitroflow (Sorin Group Canada inc., Mitroflow Division), creates a valve with the advantage of a larger effective orifice area and supreme hemodynamics. Care must be taken so the edges of the pericardium cover the top of the commissure by 1-2mm, eliminating

the forces applied on the top of the commissure during the cardiac cycle. We produced such a pericardial valve wrapped around a 25mm titanium stent giving superior hydrodynamic performance such as measured with the low peak transvalvular pressure and increased effective orifice area. We started producing this kind of valve late during our research and durability tests will be performed at a later stage.

Bioprosthetic heart valves fabricated from biologically derived heterograft continue to be the dominant replacement valve modality, either as a conventional prosthetic design or more recently for percutaneous delivery [17]. Regardless of the specific design, long-term fatigue resilience remains a major limitation in the durability of any device utilizing these biomaterials. Leaflet calcification, with or without leaflet tearing, and mechanical fatigue, are two primary processes in limiting the bioprosthetic cardiac valve lifetime.

Fatigue damage independent of calcification has been shown to be a cause of structural damage to the leaflets of bioprostheses [18], indicating that tissue structural damage independent of calcification is a mechanism of deterioration [18,19]. Moreover, after chemical fixation the entire extracellular matrix is highly bonded, inducing an increase in tissue stiffness [20], as well as essentially eliminating the ability for tissue fibers to slide relative to each other.

Given the long term clinical expectations for replacement heart valves (at least 15 patient years, or about 600 million cycles), durability evaluations need to be conducted for millions of cycles. This is accomplished using accelerated fatigue testing, wherein fully intact and functioning valves are subjected to hydrodynamically induced opening/closure cycles at rates of 13–25 Hz. Generally, tissue valves are tested for 200 million cycles (the FDA recommend level, equivalent to 5 patient years), with the effects of tissue fatigue described after visual inspection at the end of the test [21].

All our porcine bioprosthetic valves, using this novel stent with large commissural openings, passed the durability test according to ISO/DIS 5840 [International Organization for Standardization, 2014/04/10]. Two of the valves failed due to increased stiffness at one of the leaflets because of collagen deterioration and one valve failed due to suture rupture producing a loose leaflet attachment and flail valve. These failures could be explained as lack of experience and a not yet perfected state of the art for manufacturing bioprosthetic valves. A non perfect matched leaflet would lead to a less desirable result, due to worse kinematic and increased forces applied on the leaflet, making it susceptible to collagen deterioration. A non- symmetrically placed suture could lead to mechanical failure for the same reasons.

This low profile novel stent with large heart shape openings at the commissural posts, offers a larger, than the conventional stents, area for distributing the forces applied on the commissure during the cardiac cycle. This area allows the commissure a slight in and out movement, avoiding the stiffness of a rigid stent. A question was raised, if these large open areas would offer a sufficient support for the valve. During the durability tests we did not notice any “crimping” of the valve at the commissures. The Dacron cloth, manufactured nowadays by the industry, is strong enough to support the back of the commissure without the need for extra support. In addition, a modification of this stent using encapsulation technology (C. R. Bard, Inc. Murray Hill, New Jersey, USA) can be used as well (Figure 2c). This technique may be suitable for the pericardial valves. More research and testing are needed to establish the safety of these valves for human implantation.

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