

In-Vivo Experience with the Triflo Trileaflet Mechanical Heart Valve

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Background and aim of the study: The in-vivo performance of the Triflo trileaflet mechanical valve was evaluated in an ovine model. The aim of long-term follow up was to gather site-specific performance data demonstrating device safety, as required for regulatory approval of this new valve design, prior to its use in clinical trials.

Methods: The Triflo trileaflet valve was implanted in 26 sheep using 29-mm mitral (n = 8; animal body weight 63.3 ± 10.3 kg, age 112.0 ± 30.7 weeks) or 21-mm aortic mechanical valves (n = 19; body weight 73.0 ± 4.36 kg, age 112.6 ± 23.6 weeks) using standard techniques. Animals were allocated to 150- or 365-day survival cohorts. The 150-day cohort was further subdivided into mitral valve (n = 6) and aortic valve (n = 11) implants. The 365-day cohort was organized into aortic (n = 7) and mitral (n = 2) implants. Angiography, echocardiography, and pathology were performed to assess valve performance.

Results: Angiographically monitored pressure measurements for the trileaflet mitral valve at 150 and 365 days were within established ranges in terms of mean aortic pressure, systolic and diastolic aortic pressure, and left ventricular end-diastolic pressure. In animals receiving a mitral valve the transvalvular gradient was 3.5 ± 0.71 mmHg at 365 days, and 0.2 ± 0.4 mmHg at 150 days. The Triflo mitral valve had only mild (physiologic) regurgitation. Cardiac output was within normal limits in animals receiving the Triflo valve in the aortic position. Laboratory values reflected no ongoing infection or destruction of

blood cells as a result of device implantation. No significant abnormality was noted at necropsy in any animal, except for evidence of thromboembolic events in the kidneys (4-20%). Pathological evaluation was reflected by mild to moderate fibrous tissue formation at the inflow orifice (n = 15), and minimal growth was observed in the outflow tract of one valve. This was consistent with that seen in sheep implanted with a standard St. Jude Medical bileaflet valve.

Conclusion: The study results showed the Triflo valve to perform to safety levels comparable with those of the standard St. Jude Medical bileaflet design, when implanted in the aortic and mitral positions. Additional analysis of historic control data suggested that the trileaflet valve design may offer a reduction in outflow tract obstruction by allowing for a greater effective orifice area index when compared to an equal-sized-orifice bileaflet valve. Notably, the Triflo valve was associated with a statistically significant reduction in myocardial hypertrophy, further reducing the potential for patient-prosthesis mismatch. Overall, the Triflo valve appeared to more closely emulate the hemodynamic properties of the native tissue valve than the traditional bileaflet design. Hence, the trileaflet design may offer the function of a tissue valve while retaining the durability of the mechanical valve.

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Despite recent advances in prosthetic heart valve design, to date there is no valve that is comparable to the native human valve with regard to the risk of

thrombosis and overall hemodynamic function (1-3). The ideal prosthetic heart valve emulates the natural heart valve in terms of hemodynamic character and thrombogenicity, while maintaining durability (4,5). Whilst bioprosthetic devices mimic the native valve with regard to thrombogenicity, durability is of significant concern, notably among younger patients. Whereas approximately 45% of implanted bioprosthetic valves fail at 10 years (6), mechanical prostheses

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have a lower incidence of structural valve failure and are thus more often used in patients aged <65 years. The structural durability of mechanical valves, as characterized by Wernly and Crawford, is of 'lifetime durability' (6), and others have suggested that mechanical valves have an implantation life exceeding 20 years (5). While the mechanical valve addresses durability concerns associated with the bioprosthetic counterpart, significant hemodynamic and thrombotic issues have yet to be resolved. Specifically, the implantation of a mechanical valve may lead to an increased risk of thrombosis, increased transvalvular pressure, hemolysis, and infection (2,7).

Following the implantation of a prosthetic heart valve, complications and undesirable pathophysiology may arise due to prosthesis-patient mismatch. This pathological phenomenon is found when the effective prosthetic valve area, after insertion into the patient, is less than that of the normal human valve (8). The two-dimensional plane of the valve orifice through which blood actually flows is termed the effective orifice area (EOA), and valves with an EOA less than that of a typical human valve have demonstrated a deleterious impact on postoperative mortality, hemodynamics, and overall long-term survival (9).

Following concepts suggested by Rahimtoola (8), Pibarot et al. showed that patient-prosthesis mismatch was a function of the EOA index (EOAI) and body surface area (BSA), and correlated directly with morbidity and mortality (9). When choosing an appropriate prosthetic heart valve for implantation, it is important to know the EOA (in cm²) of the valve, as well as patient's BSA (in m²) for correct sizing of the replacement valve. When the EOA of an aortic valve is too small to accommodate the cardiac output, the ensuing elevated transvalvular gradients may eventually lead to cardiac hypertrophy, congestive heart failure, and mortality (Fig. 1). Certainly, a similar pathophysiology occurred in patients where incorrectly sized mitral prosthetic mechanical valves were utilized (10).

Although the bileaflet mechanical valve remains the prosthesis of choice in some patients requiring a replacement aortic or mitral valve (11), a potentially superior mechanical valve with three leaflets has been developed. The Triflo valve (Triflo, Costa Mesa, CA, USA) was evaluated in the mitral and aortic positions with regard to its hemodynamic character, thrombogenicity, pathology, and overall durability. Recent studies by Gregoric et al. (1) showed the trileaflet valve to have hemodynamic properties similar to those of the native valve. Furthermore, it was postulated that the trileaflet valve would be less obstructive than an equally sized bileaflet valve due to an increased EOA, and that this would lead to a decrease in the obstructive physiology observed for replacement valves.

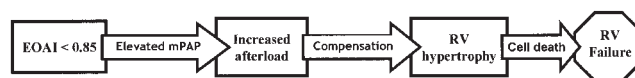


Figure 1: The proposed mechanism of right heart failure: The steps to right ventricular failure resulting from the use of a replacement valve with an inadequate effective orifice area index (EOAI). mPAP: Mean pulmonary artery pressure; RV: Right ventricle.

The aim of this preclinical in-vivo assessment of the Triflo valve was to evaluate the valve's performance characteristics in order to assess its safety, prior to commencing human clinical trials. Previous experience in the area of preclinical testing allowed for the observation that valve design must take into account the working conditions into which the valve is implanted - a concept referred to as 'site-specific testing' (12). Such testing, when conducted by Gregoric with the Triflo valve design in an aortic implantation study, showed that the small triangular windows of an earlier valve version caused high-shear micro-jets (13). These three jets induced a shear stress that activated platelets. A redesign of the valve ring without these windows eliminated the problem, which was not originally evident when the valve was implanted in the mitral position (Fig. 2). Following site-specific testing, the redesign prevented patients from exposure to an adverse event, product recall, or additional surgery. Fortunately, subsequent blood compatibility testing confirmed that the redesign did not unduly activate the clotting system (3).

The Triflo valve is very similar to the biological aortic valve with regard to flow dynamics and geometry. The geometric orientation of the Triflo valve's three

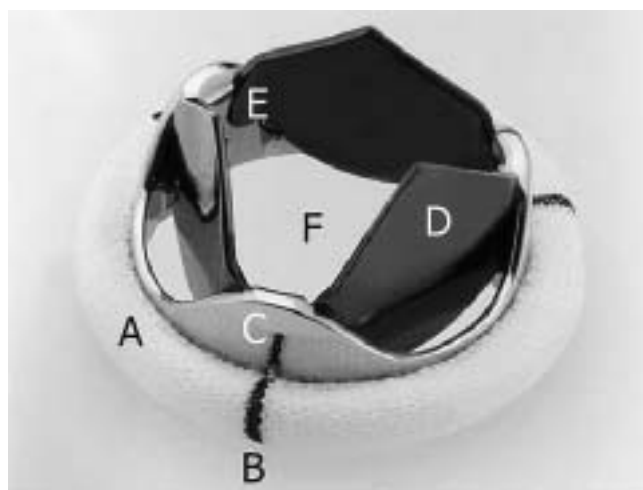


Figure 2: The redesigned Triflo trileaflet valve. A, sewing ring; B, orientation marker; C, valve strut; D, pyrolytic carbon leaflet; E, hinge region; F, central orifice.

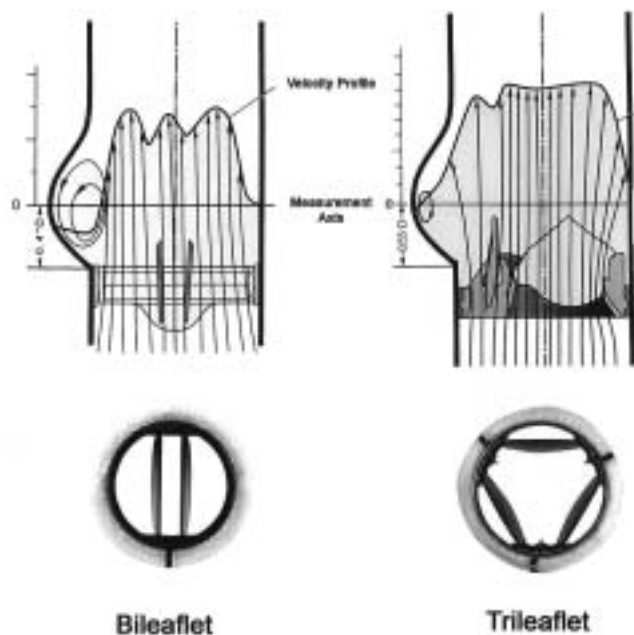


Figure 3: Velocity-profile of the Triflo (left) and St. Jude Medical (right) valves. Fluid flow through the Triflo valve has a curve which is more consistent with that of a tissue valve, whereas the bileaflet valve has three jets because of the two central struts.

leaflets complements the normal aortic root. When the trileaflet valve opens, central flow induces uniform counterclockwise vortices in the sinuses of Valsalva (14). The forward flow is similar to that of a tissue valve, where fluid flows through the central orifice fastest in the center and slowest at the edges. The leaflets initiate the closing motion when forward flow starts to decelerate in the systolic phase. The soft and early closure of the valve is facilitated by leaflets designed like aerofoils that take advantage of lift forces during systole. This design, as well as swirling eddies (vortices) in the sinuses, gently pushes the leaflets together earlier in the cycle, thereby allowing their early closure. Interestingly, because the hinges are at the edges of the valve, where the flow is less, there is proportionally less turbulent shear stress to activate platelets. In comparison, the typical bileaflet hinges are centrally located and the flow is directed into three jets (two leaflet jets and an interleaflet jet) (Fig. 3). These three jets have high-velocity shear gradients of approximately 1150-1500 dynes/cm², which is three- to five-fold the shear stress needed to activate platelets in a clinical laboratory study (15). In comparison, the counterclockwise vortices that form in the aortic sinuses oppose and delay closure of the bileaflet valve. This leads to a relatively large reverse flow being needed to close the bileaflets. Furthermore, the reverse flow accelerates bileaflet closure so that the valve creates a 'water hammer effect' that is attributed to the forma-

tion of cavitation (the high-speed jets and vortices cause the rapid formation of microbubbles, the sudden collapse of which generates shock waves, termed 'cavitation'). Cavitations not only cause pitting of mechanical valve surfaces, but can also activate platelets and the clotting cascade, with potential leaflet damage and microemboli formation (14).

Materials and methods

Animals

Adult sheep (23 females, three neutered males; age 3 years; mean body weight 70.9 ± 13.1 kg) were used in these studies. The animals received care in compliance with the *Guide for the Care and Use of Laboratory Animals*. Experimental protocols were approved by the University of Minnesota Animal Care and Use Committee. This study was completed in compliance with ISO-5840 (2005) guidelines which mandate that all devices used in an animal study be identical to that destined for clinical use with respect to design, manufacture, size, packaging and sterilization (Table I).

Surgical technique

Specific details of the surgical procedure used for valve implantation in the sheep model have been reported previously (16), and are briefly summarized here.

Mitral valve implantation

For mitral prosthesis implantation, a left atriotomy was performed and a Ross atrial retractor placed to expose the mitral apparatus. The native valve was excised and the chordae tendineae were dissected down to the papillary muscle. The prosthetic valve was then secured to the mitral annulus in the usual fashion using interrupted 3-0 braided polyester inverted mattress sutures. Once completed, the atrium was vented, the animal rewarmed and weaned from CPB in

Table I: Preclinical testing of implantable heart valves.

| |
|------------------------------|
| Valve verification: In vitro |
| Biologic safety |
| Device durability |
| Hydrodynamic testing |
| Fatigue assessment |
| Design specific testing |
| Valve validation: In vivo |
| Hemodynamic performance |
| Ease of surgical handling |
| Thromboembolism |
| Pannus formation |
| Structural deterioration |
| Valve-related pathology |

the usual fashion with the reinitiation of mechanical ventilatory support. All bypass cannulas were removed when the animal was stable and off CPB, and heparin was reversed with protamine. The pericardium and chest cavity were then closed, with temporary chest tubes being left in place.

Aortic valve implantation

The technique for aortic valve implantation in the sheep differed only slightly from that used for the mitral valve. Following heparin administration, the descending thoracic aorta and right atrial appendage were cannulated for CPB. Mechanical ventilation was discontinued upon the initiation of CPB, and the animal was cooled to 25°C. A cold cardioplegic arrest was then performed by infusing the cardioplegia solution through a 14-gauge catheter inserted into the aorta. The native valve apparatus was then exposed and removed through a transverse aortotomy. The prosthetic valve was implanted using interrupted inverted sutures. It should be noted that only the trileaflet valve could be positioned in a fashion that provided an orientation consistent with that of the native three-leaflet biological valve; that is, both the coronary and non-coronary leaflets were aligned. The remainder of the procedure was consistent with that used for mitral valve implantation.

Postoperative care

Immediate postoperative and long-term care was completed at the University of Minnesota under the direction of licensed veterinarians. All animals were extubated postoperatively and transferred to the veterinary intensive care unit, where the chest tubes were removed promptly to assist in early mobilization of the animal. Each animal received 2000 units heparin sulfate per day subcutaneously for two days after the procedure. No additional anti-coagulation was administered during the remainder of the study.

Angiography and echocardiography

On completion of the designated study period, animals were instrumented for angiography, assessed by echocardiography, and ultimately electively euthanized. Angiography with pressure measurement recording allowed the cardiac output to be determined, using a thermodilution technique with an American Edwards Laboratories (model #9520A) cardiac output computer. Angiography was performed after injection of radiographic contrast (40-60 ml). The regurgitant volume was graded independently using Sellars' classification as: 1+ = mild; 2+ = moderate; 3+ = moderately severe; and 4+ = severe. Two-dimensional echocardiography, as well as color flow and pulsed Doppler studies, were performed using a Hewlett-

Table II: Criteria in pathologic evaluation

| |
|---|
| Pathological evaluation |
| General findings |
| Critical organs |
| Surgical sites |
| Inflow/outflow tracts |
| Topography |
| Cause of death (model- or device-related) |
| Histopathology |
| Bacteriology |

Packard SONOS 5500 ultrasound imaging system via a transthoracic approach. Imaging was obtained from the right and left periaxillary windows.

Post-mortem studies

On completion of the hemodynamic assessment, the animals were euthanized using an approved standard protocol. A formal necropsy was then performed by a licensed veterinary pathologist. Particular care was directed at the gross evaluation and photographic documentation of all prosthetic valves. The heart, liver, spleen, brain and kidneys underwent gross and microscopic examination (Table II). Swabs were collected from the valve inflow and outflow for microbiological studies.

Statistical analysis

Results were reported with respect to published normal values in sheep as established in Gross' Animal Models in Cardiovascular Medicine (17). Statistical analyses were performed using the SPSS v11.0 software package; data were presented as mean ± SD.

Table III: Pressure measurements at angiography: Mitral valve.

| Parameter | Group 1 | Group 2 |
|----------------------------|------------------------|--------------|
| Population (n) | 6 | 2 |
| Survival (days) | 150 | 365 |
| Ao _{Sys} (mmHg)* | 85.7 ± 17.0 | 118.0 ± 22.6 |
| Ao _{Dias} (mmHg)* | 70.0 ± 14.6 | 93.5 ± 10.6 |
| Ao _{Mean} (mmHg)* | 78.5 ± 15.0 | 102.5 ± 12.0 |
| LV _{Peak} (mmHg)* | 87.7 ± 10.4 | 116.0 ± 11.3 |
| LV _{End} (mmHg)* | 6.8 ± 3.2 | 14.0 ± 2.8 |
| Wedge (mmHg)* | 6.5 ± 3.9 | 17.5 ± 2.1 |
| TV gradient (mmHg)* | 0.2 ± 0.4 | 3.5 ± 0.71 |
| Regurgitation* | 0.9 ± 0.9 ⁺ | 2.5 ± 2.1 |

*Values are mean ± SD.

⁺Four sheep only.

Ao_{Dias}: Aortic pressure diastolic; Ao_{Mean}: Mean aortic pressure; Ao_{Sys}: Aortic pressure systolic; LV: Left ventricular; LV_{End}: Left ventricular end-diastolic pressure; LV_{Peak}: Left ventricular peak pressure TV: Transvalvular.

Kaplan-Meier calculations were made using MedCalc v8.1.1.0 statistical software.

Results

The results of pressure measurements during angiography for the trileaflet mitral valve at 150 days and 365 days (Table III) were within established ranges for sheep, based on historic controls from the present authors' laboratory, with respect to mean aortic pressure, systolic and diastolic aortic pressure and left ventricular end-diastolic pressure (LVEDP). Wedge pressures in animals implanted with a trileaflet valve for 150 and 365 days were 6.5 ± 3.9 mmHg and 17.5 ± 2.1 mmHg, respectively. Animals implanted for 365 days showed a transvalvular gradient of 3.5 ± 0.7 mmHg, while those implanted for 150 days had a transvalvular gradient of 0.2 ± 0.4 mmHg.

Pressure measurements taken during catheterization at the time of angiography in sheep with Triflo aortic valves (Table IV) were comparable to baseline values. Notably, there was an elevated LVEDP (24.5 ± 7.8 mmHg) in sheep implanted for 365 days. The regurgitant volume was slightly higher (2+) in the sheep surviving for 365 days compared to those surviving for 150 days (Table V). The Triflo mitral valve had only mild (physiologic) regurgitation as measured at the study end-points (Fig. 4).

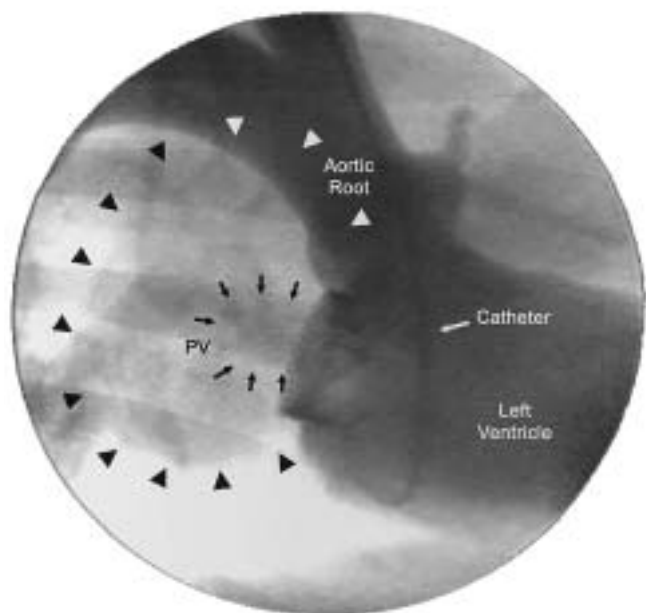


Figure 4: Angiography of the Triflo valve. Mild regurgitation to moderate regurgitation was demonstrated in Triflo mitral valves at 365 days. Arrowheads outline the left atrium with a blanching of the contrast at a pulmonary vein orifice (PV). The arrows outline mild systolic regurgitation of the Triflo valve.

Table IV: Pressure measurements at angiography: Aortic valve.

| Parameter | Group 1 | Group 2 |
|----------------------------|---------------------------|-------------|
| Population (n) | 6 | 2 |
| Survival (days) | 150 | 365 |
| Ao _{Sys} (mmHg)* | 107.0 ± 28.9 | 102.0 ± 2.8 |
| Ao _{Dias} (mmHg)* | 87.3 ± 23.4 | 88.0 ± 1.4 |
| Ao _{Mean} (mmHg)* | 96.2 ± 24.6 | 94.5 ± 2.1 |
| LV _{Peak} (mmHg)* | 127.8 ± 29.4 ⁺ | 129.5 ± 0.7 |
| LV _{End} (mmHg)* | 11.6 ± 6.4 ⁺ | 24.5 ± 7.8 |
| Wedge (mmHg)* | 5.4 ± 4.0 ⁺ | 3.5 ± 3.5 |
| TV Gradient (mmHg)* | 31.2 ± 23.2 ⁺ | 27.5 ± 2.1 |
| Regurgitation* | 0.9 ± 1.2 ⁺ | 2.0 ± 1.4 |

*Values are mean ± SD.

⁺Five sheep only.

Abbreviations as Table III.

Echocardiographic data available for comparison was limited to cardiac output and heart rate. Evaluation of the heart rate and cardiac rhythm for both the 150- and 365-days groups in the mitral and aortic studies showed no abnormalities or arrhythmia. Cardiac output data in both 150- and 365-day mitral valve studies was consistent with a baseline value of 7.2 ± 1.6 l/min. By contrast, cardiac output in animals receiving the Triflo valve in the aortic position was 9.7 ± 2.3 and 10.0 ± 2.1 l/min in the 150-day and 365-day groups, respectively.

Laboratory values for red and white blood cell counts and hematocrit appeared within normal ranges (Table VI). Among mitral valve-implanted animals, the haptoglobin concentration was highest in the 150-day sheep, there being no detectable levels in the 365-day sheep. In sheep receiving aortic valve implantations, haptoglobin levels were highest preoperatively (14.37 ± 27.4 mg/dl), with levels of 1.51 ± 3.5 and 0.57 ± 1.5 mg/dl in the 150- and 365-day animals, respectively.

Bacteriological studies

Cultures from the inflow and outflow surfaces of the valves (n = 27) were negative for bacterial growth.

Table V: Regurgitation data.

| Valve | Population size (n) | Survival (days) | Regurgitation (Sellars' class) |
|---------|---------------------|-----------------|--------------------------------|
| Mitral | | | |
| Group 1 | 5 | 150 | 1+ |
| Group 2 | 2 | 365 | 2+ |
| Aortic | | | |
| Group 1 | 6 | 150 | 1+ |
| Group 2 | 5 | 365 | 1+ |

Pathology

In the 150-day study, all mitral valves showed slight pannus overgrowth which occluded their inflow by between 2% and 16%. Mild vegetations developed over the hinge area on the inflow surface (n = 5), and thrombotic deposits were noted on the stent posts on the outflow side of the valve (n = 3). The Triflo aortic valves had mild to moderate pannus growth obstructing the inflow (Fig. 5). Jet lesions and endocardial scars due to turbulent flow were occasionally observed (n = 4). One Triflo aortic valve had a leaflet that failed to close due to deposit formation in the hinge region. Small renal infarcts due to thrombotic or embolic occlusion were observed in one sheep implanted with a Triflo aortic valve.

Pathological findings for the aortic and mitral valves at 365 days were comparable to those tested for 150 days. Paravalvular leaks were observed in one mitral and one aortic valve. Both the mitral and aortic valves

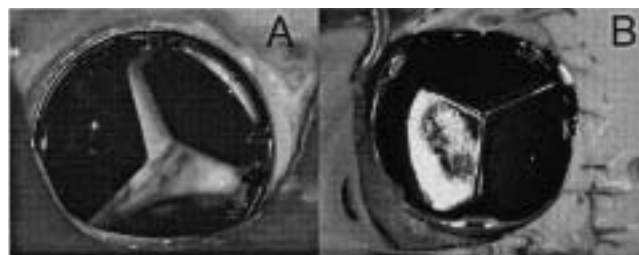


Figure 5: Aortic inflow and outflow orifices. Macrographs taken at the time of necropsy of the inflow (A) and outflow (B) of the Triflo trileaflet valve in the aortic position. The valve is well-seated and intact. The sewing cuff sutures, visible on the outflow surface, are regularly seated, and the tissue valve interface is sealed with fibrous tissue. The inflow orifice sewing cuff is covered with thin, shiny white-semi-transparent tissue. The outflow orifice sewing cuff is covered with thick, white tissue. Tissue overgrowth is present on the top rim of the outflow from 12:30 and 2 o'clock.

Table VI: Selected laboratory values.

| Parameter | Preoperative | Group 1 | Group 2 |
|---------------------------------------|-----------------------------|----------------------------|---------------|
| Mitral valve group | | | |
| Population (n) | 8 | 6 | 2 |
| Survival (days) | - | 150 | 365 |
| Preoperative weight (kg) | - | 63.33 ± 10.33 | 81.00 ± 16.97 |
| Weight at sacrifice (kg) | - | 64.33 ± 9.31 | 90.00 ± 15.56 |
| RBC count (×10 ⁶ /μl) | 12.14 ± 1.4 | 10.77 ± 1.9 | 12.05 ± 0.8 |
| WBC count (×10 ³ /μl) | 4.71 ± 2.0 | 3.8 ± 0.6 | 4.0 ± 1.0 |
| Platelet count (×10 ³ /μl) | 376.57 ± 182.8* | 371.0 ± 125.0 | 207.5 ± 24.8 |
| Prothrombin time (s) | 16.88 ± 1.1 | 16.2 ± 0.4 | 14.75 ± 1.5 |
| Plasma Hb (mg/dl) | 23.14 ± 29.5 | 11.0 ± 7.0 | 8.10 ± 0.9 |
| Hematocrit (%) | 37.96 ± 2.9 | 38.6 ± 3.4 | 42.20 ± 4.2 |
| Haptoglobin (mg/dl) | 5.14 ± 8.1 | 28.0 ± 46.0 | 0 |
| Calcium (mg/dl) | 10.0 ± 0.4 | 9.8 ± 0.5 | 10.35 ± 0.1 |
| Phosphate (mg/dl) | 5.85 ± 1.6 | 6.1 ± 0.9 | 5.50 ± 0.1 |
| Aortic valve group | | | |
| Population (n) | 18 | 11 | 7 |
| Survival (days) | - | 150 | 365 |
| Preoperative weight (kg) | - | 73.00 ± 4.36 | 73.71 ± 21.44 |
| Weight at sacrifice (kg) | - | 75.91 ± 10.55 | 97.71 ± 15.64 |
| RBC count (×10 ⁶ /μl) | 11.75 ± 1.1 [†] | 11.73 ± 1.0 | 11.85 ± 1.3 |
| WBC count (×10 ³ /μl) | 6.22 ± 2.2 | 4.52 ± 1.5 | 4.83 ± 1.8 |
| Platelet count (×10 ³ /μl) | 330.86 ± 181.7 [†] | 339.82 ± 83.5 [‡] | 498.7 ± 338.0 |
| Prothrombin time (s) | 21.1 ± 12.5 | 17.58 ± 2.1 | 18.47 ± 2.1 |
| Plasma Hb (mg/dl) | 8.13 ± 4.5 [†] | 25.15 ± 34.8 | 53.03 ± 87.0 |
| Hematocrit (%) | 36.68 ± 2.9 [†] | 38.95 ± 3.5 | 40.70 ± 4.77 |
| Haptoglobin (mg/dl) | 14.37 ± 27.4 | 1.51 ± 3.5 | 0.57 ± 1.5 |
| Calcium (mg/dl) | 9.67 ± 0.4 | 9.93 ± 0.41 | 9.80 ± 0.44 |
| Phosphate (mg/dl) | 6.18 ± 1.2 | 6.19 ± 1.9 | 6.54 ± 1.9 |

All values are mean ± SD (unless otherwise indicated).

*Six sheep only.

[†]17 sheep only.

[‡]Seven sheep only.

Hb: Hemoglobin; RBC: Red blood cell; WBC: White blood cell.

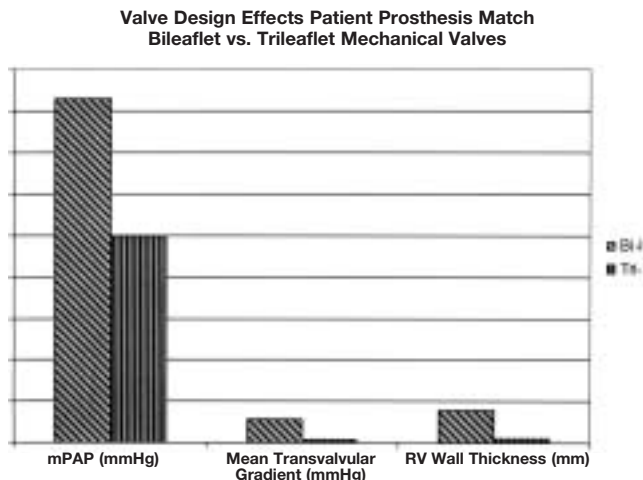


Figure 6: Comparison of orthotopic mitral implantation of a novel trileaflet mechanical valve to historic data from equal-sized mitral valves. The trileaflet mechanical design is postulated to be less obstructive, and there is a corresponding reduction in pathophysiological changes compared to the bileaflet design. Given the significant increase in hemodynamic parameters with the associated increase in right ventricular (RV) wall thickness, it is concluded that the equally sized mitral bileaflet valve is obstructive to flow, likely due to a reduced effective orifice area and 'patient-prosthesis mismatch'. mPAP: Mean pulmonary artery pressure.

demonstrated pannus formation which obstructed the inflow or outflow ($n = 7$). Three sheep implanted with aortic valves showed pathology consistent with renal infarcts. Thrombi deposition over the hinge regions was also observed equally between the two valves ($n = 4$). At necropsy, all valves ($n = 27$) were structurally intact. Overall, the pathological features were comparable between the two valve types, irrespective of their duration of implantation.

In summary, there was mild to moderate fibrous tissue formation at the inflow orifice ($n = 15$), and minimal growth was also observed in the outflow tract of one valve. All valves appeared structurally intact at the time of removal, and of the 27 valves used in this study only one valve was not functioning correctly due to deposits in the hinge area which obstructed leaflet movement. At 150 and 365 days after implantation, 96% and 81% of sheep respectively were free from any renal embolus event at necropsy, as determined by Kaplan-Meier analysis. Thus, without anticoagulation the risk of thromboembolism with the trileaflet design implanted between 150 and 360 days ranged from 4 to 20%.

Discussion

In recent years, mechanical heart valves have evolved from caged-ball, non-tilting-disk, to tilting-

disk, to bileaflet, and now to trileaflet (18). Each design change has led to sequential improvements in the performance of the mechanical valve (19). Concordantly, design advancements have generally resulted in reductions in the risk of thromboembolism by further minimizing the high-shear stresses that activate platelets (15). Today, the trileaflet design is the most innovative mechanical valve in preclinical studies (20). The ultimate goal for this design is to minimize the risk of thromboembolism, thereby allowing the use of antiplatelet agents such as aspirin rather than requiring a need for warfarin anticoagulation. Current data from the Veterans' Affairs trial for patients with aortic and mitral mechanical valves who were receiving anticoagulation, have shown the 15-year risk of thromboembolism with bileaflet valves to be approximately $18 \pm 4\%$ (21). Therefore, in order to recommend the use of this valve in human trials without anticoagulation, the design must achieve at minimum this rate of thrombus-free performance.

In the present study, the sheep did not receive daily anticoagulation of any kind following implantation. Ultimately, necropsy demonstrated a 20% per year risk of thromboembolism, based on the observed rate of thrombus discovered at necropsy, within the kidneys of the sheep. Although no animal died as a result of these observed thromboembolic events, their occurrence cannot be neglected. Furthermore, although direct comparison of the thromboembolic activity in sheep to that of humans has been questioned, this system currently represents the best comparison available in the preclinical setting. Hence, although (based upon this series) the design appears to be safe within the setting of no anticoagulation, clinical trial patients should receive anticoagulation in order to protect them against thromboembolic events following Triflo valve implantation, at least until a better determination of the true thromboembolic risk in humans has been determined.

In recent years, the present authors' laboratory has currently amassed a large repository of historic data for multiple valve designs. In order to gain a better understanding of the potential improvements in the function of the trileaflet design, the decision was taken to compare the mitral implantation of a trileaflet mechanical valve ($n = 6$) with selected historic data from bileaflet mitral mechanical valves ($n = 42$) implanted in sheep. Using a two sample t -test, an analysis of the hemodynamic and pathological parameters revealed a significantly greater mean transvalvular gradient (1.11 versus 0.16 mmHg, $p = 0.03$), pulmonary artery pressure (PAP) (16.6 versus 10 mmHg, $p = 0.01$) and mean right ventricular wall thickness (1.55 versus 0.23 mm, $p = 0.04$) in the bileaflet relative to the trileaflet valve (Fig. 6). Given the significant increase in hemodynamic parameters with the

associated increase in right ventricular wall thickness, based upon clinical studies of mitral stenosis, it is believed that the equally sized bileaflet valve is obstructive and might even aggravate right heart failure (22-25). From this retrospective comparison it is predicted that, in clinical studies, the trileaflet mechanical design will result in a greater reduction in right ventricular hypertrophy following mitral valve replacement compared to an equally sized bileaflet mechanical valve.

In the present study, the ovine model was used as a patient surrogate for valve implantation. This was in contrast to other studies which used a bovine (calf) model for implantation of the Triflo valve (1,2,26). Traditionally, sheep have been the preferred model for preclinical heart valve testing (27), one reason being that they have relatively little somatic growth as compared to the calf. For example, a 4- to 6-month-old calf weighing 80-110 kg has a cardiac output of up to 12 l/min and a BSA of 1.9-2.4 m² (BSA, in m², of calves calculated as: $(10.5 \times [\text{body weight (kg)} \times 1000]^{2/3})/10,000$) (28). As the calf grows for three months, it may gain ~1 kg per day for a final weight of 170-200 kg and a BSA of 3.2-3.6 m². The estimated EOAI of a 21-mm standard St. Jude Medical aortic valve in a 6-month-old calf is 0.50-0.56 cm²/m² (normal range: 0.85 to 0.90 cm²/m²). (The EOA of the standard aortic St. Jude valve is based upon published tables (15).) In comparison, the EOAI in the average 80-kg sheep used in the present study with the same-sized Triflo valve was 1.29 cm²/m² (same formula used to calculate BSA for calves as for sheep). The lack of 'patient-prosthesis mismatch' in the present study provided further justification for use of the ovine model in preclinical studies for heart valve evaluation.

In conclusion, the aim of the present preclinical study was to assess the site-specific safety profile of the Triflo valve, before its implantation in human trials. The Triflo aortic and mitral valves were explanted at 150 and 365 days, thereby allowing for a longitudinal assessment of a new mechanical leaflet design. The safety and performance of the valve was based upon site-specific in-vivo testing in an accepted standard ovine model. The trileaflet design performed to the same high degree of safety as the standard St. Jude Medical bileaflet mechanical valve in both the aortic and mitral positions over a 365-day period of observation. In addition, statistical analysis using historic data suggested that the trileaflet design might offer superior hemodynamic performance as a result of the greater EOAI from the same size of valve orifice. Thus, it is concluded that relocation of the valve apparatus away from the central flow to the periphery of the valve housing was the most likely reason for this finding.

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