

Sutureless Stented Aortic Valve Implantation Under Direct Vision: Lessons From a Negative Experience in Sheep

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ABSTRACT *Background and Aim of the Study:* Percutaneous aortic valve replacement has been proposed as a valid alternative to surgery in selected cases; however, it still has many problems. As a less radical preliminary step, we implanted a balloon-expandable stented aortic valve under direct vision in sheep. *Methods:* Under cardiopulmonary bypass (CPB) and through a transverse aortotomy, an aortic valve mounted in a long tubular balloon-expandable stent was implanted in six acute sheep. The leaflets were not excised and no anchoring sutures were used between stent and native annulus. Epicardial, two-dimensional color Doppler echocardiography was used to assess the function of the stented valve followed by macroscopic inspection at necropsy. *Results:* Direct visualization of the entire annulus when the collapsed, valved stent was placed within the aortic root was difficult in all animals. Valve deployment took less than 1 minute. The surgical procedure resulted in major complications in all cases. Migration (3/6), paravalvular leak (2/6), mitral conflicts resulting in mitral regurgitation (1/6), and coronary ostia obstruction (2/6) were the major events at the origin of the failure. Only three animals could be weaned from CPB but did not recover enough to survive the procedure. *Conclusions:* Sutureless implantation of a stented aortic valve through standard CPB and aortotomy is far more complex than expected. Changes in stent design and surgical approach are indicated. doi: 10.1111/j.1540-8191.2007.00337.x (*J Card Surg* 2007;22:13-17)

The success of percutaneous stenting for coronary and peripheral vessels has encouraged the search for successful methods of percutaneous valve intervention. Although pulmonary valve replacement within a failed root conduit has shown consistently satisfactory clinical results¹ and several mitral valve repair devices have reached the level of clinical trials, percutaneous aortic valve replacement (PAVR) is still at an experimental stage. Some clinical PAVR have been reported; however, the success rate has been low and sporadic. The high-pressure environment, presence of coronary ostia, and a calcified valve are specific problems that are difficult to overcome. Surprisingly, despite these obvious problems, few in vitro and in vivo experimental studies have been reported. This situation suggested the need for a systematic approach that would address each problem separately.

One of the main problems of PAVR is that the majority of candidates for the procedure suffer from calcified aortic stenosis. In these cases, balloon dilation, with its inherent risk of embolism, is required to crack open the valve. The crushed valve remnants also represent an

irregular base for anchoring the stented valve, resulting in the nearly constant presence of residual paravalvular leaks. Difficulties in the correct orientation and placement of the stent in the outflow tract compound the problem. We hypothesized that the sutureless implantation of the stented valve under direct vision might solve some of these issues. Contrary to our expectations, the negative results of this study revealed serious problems that question the validity of this approach.

MATERIALS AND METHODS

The stented aortic valve

Previous measurements of the aortic valve annulus diameter in adult Targhee sheep weighing 45 to 55 kg averaged 19 mm. For this study, two different types of valves were used.

The first valve was manufactured from a porcine aortic root (21 mm diameter). The wall of the aortic root was trimmed down, leaving a ± 2 -mm scalloped rim. The proximal ventricular aspect of the root was also trimmed down, leaving a horizontal plane tubular orifice.

The second valve was manufactured as reported by Goetz et al.,² from a flat piece of fresh sheep pericardium. The fat and fibrous strands of the mediastinal

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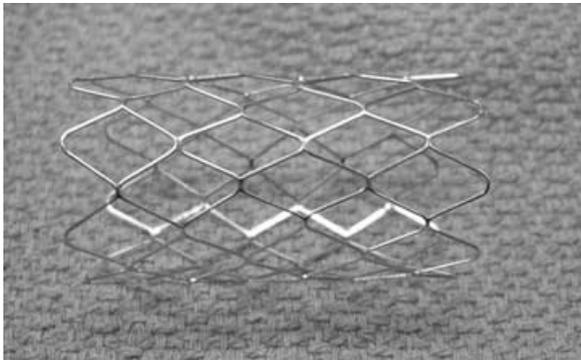


Figure 1. *Cylindrical stent.*

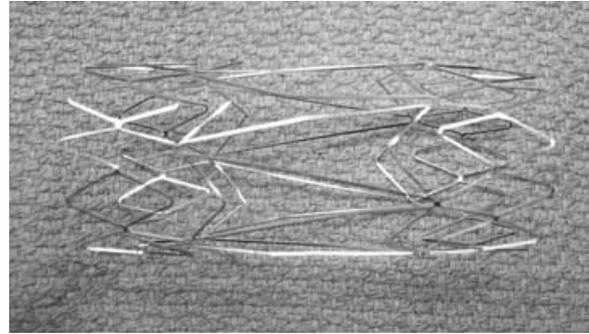


Figure 2. *Symmetrical stent.*

surface of the pericardium were cleaned. The tissue was then treated with 0.6% buffered glutaraldehyde for 10 minutes and rinsed with 0.9% sodium chloride. A flat template with a trapezoidal shape of the appropriate size was placed on the treated pericardium. The pericardium was then cut into a trapezoidal flat piece. The location of the future equidistant commissures were marked with three 5-0 polypropylene sutures placed on the longer (outflow) length of the pericardium. The pericardium was wrapped over a 21-mm diameter plastic holding cylinder, and its lateral sides were sutured together with running 5-0 polypropylene to convert the flat pericardium into an inverted, truncated cone with smaller inflow and larger outflow orifices.

Two different customized stents (Medtronic, Inc., Minneapolis, MN, USA) were used. The stents were designed for implantation with the base at the level of the annulus, the middle part at the level of the sinuses of Valsalva, and the top at the level of the sinotubular junction. The stent dimensions were calculated from the aortic root ratios originally reported by Swanson et al.³ and modified according to our previous sonometric studies.⁴

For a diameter of 19 mm, the length of both stents was 32 mm. The first, cylindrical, stent was made of diamond intersections of thin, cobalt-nickel wires (Fig. 1). The second, symmetrical, stent was designed with three different kinds of diamond intersections (Fig. 2). The valves were attached to the stents at the level of the base with running 5-0 polypropylene sutures. The tips of the commissures of the porcine valve or the previously marked three equidistant points of the pericardial valve were sutured with a single polypropylene 5-0 stitch at the corresponding metal intersections.

Surgical protocol

Adult Targhee sheep underwent the sutureless implantation of a bioprosthetic aortic valve mounted in a balloon-expandable stent. A left jugular catheter was placed, and the animal was premedicated with intravenous (IV) administration of ketamine 1.0 mg/kg, atropine 0.03 mg/kg, and propofol 4.0 mg/kg. The animal was intubated, and ventilation was maintained with a volume respirator (North American Drager, Telford, PA,

USA) supplemented with oxygen at 4 L/min. Anesthesia was maintained with intermittent propofol and continuous isoflurane (1.5% to 2.5%). The heart was exposed with a standard left thoracotomy through the fourth intercostal space. The pericardium was incised, and the heart was suspended in a pericardial cradle. In preparation for cardiopulmonary bypass (CPB), a 300 U/kg bolus of IV heparin was injected, with a target activated clotting time of 480 seconds or more. The aortic arch and the brachiocephalic trunk were cannulated with #16 Fr and #12 Fr arterial cannulae. The right atrium was cannulated with a #32 Fr venous cannula. CPB was instituted, and a vent line was inserted into the left ventricular (LV) apex. The ascending aorta was cross-clamped, and cold blood cardioplegia was infused into the aortic root. The ascending aorta was then opened with a transverse aortotomy above the sinotubular junction. The native aortic annulus was sized with a Duran spherical sizer. The prosthetic aortic valve enclosed within the crimped stent was mounted on a balloon catheter (Z-MED II™, diameter 22 mm, NuMED, Inc., Hopkinton, NY, USA). The base of the stented valve was placed at the level of the native annulus and oriented so as to avoid any conflict between the coronary ostia and the commissures. The balloon was inflated with sterile water at 2 atm and then deflated after 20 seconds. The position of the stented valve and its relationship between the native leaflets and the coronary ostia were checked. A running 5-0 polypropylene suture was used to close the aortotomy. Air was purged from the ascending aorta and LV, and the aortic cross-clamp was removed. CPB flow was decreased and then stopped if possible. Epicardial, two-dimensional color Doppler echocardiography was used to assess acute function of the stented prosthetic valve in the beating heart. Aortic valve regurgitation (central or paravalvular), mitral valve regurgitation, early device migration, and leaflet movements were observed. The animal was euthanized with a ventricular injection of potassium chloride, and the heart was removed (including the ascending aorta). Transverse ventriculotomy and aortotomy were performed to expose both ends of the stent, followed by a longitudinal incision along the entire length of the outflow tract and aortic root. The location of the base of the stent in relation to the aortic annulus and the mitral valve was

observed. Coronary ostia appearance and position of the native leaflets were also verified. All animals were cared for in accordance with the "Principles of Laboratory Animal Care" formulated by the National Society of Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Animal Resources, National Research Council, and published by the National Academy Press, revised 1996. The protocol for the use of the animals for this project was also reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of The University of Montana.

RESULTS

Six Targhee sheep (average weight 45.7 ± 8 kg) underwent sutureless implantation of an aortic bioprosthesis mounted within a balloon-expandable stent. The first stent model, holding a pericardial valve, was implanted in three sheep. The second stent model, holding two porcine valves and one pericardial valve, was implanted in the other three sheep.

Surgical findings at implantation

In all sheep, the transverse aortotomy above the sinotubular junction did not provide good visualization of the entire native annulus when the collapsed device was placed within the aortic orifice. Inflation of the balloon and delivery of the expanded stented valve took less than 1 minute. Using direct observation through the transverse aortotomy, the deployed stented valve was judged to be in the correct position in five sheep. In one sheep, the inflow orifice of the stent was too far below the native annulus. In this animal, the device was then removed, re-crimped onto the collapsed balloon, and successfully redeployed. After device delivery, all coronary ostia were free but seemed to be stretched. The native leaflets were sandwiched between the aortic wall of the sinuses of Valsalva and the stent, but they did not cover the coronary ostia in any sheep. The aortotomy closure was difficult in four of six sheep because the top of the stent interfered; it had to be reinforced with pledgeted sutures. After unclamping the aorta, the native aortic root appeared stretched and cylindrical in shape. The average aortic cross-clamp time was 41 ± 5 minutes.

Surgical findings post implantation

Three sheep were unable to be weaned from CPB. In one sheep, irreversible ventricular fibrillation occurred immediately after unclamping the aorta despite multiple electric shocks and drug administration. Another sheep had severe paravalvular regurgitation, as assessed by epicardial echocardiography. The third animal presented an ST-segment elevation on the electrocardiogram (EKG) and could not support viable hemodynamics without mechanical support. These three sheep were sacrificed by potassium chloride injection after more than 2 hours of assistance.

The three remaining animals were successfully weaned from CPB after a perfusion time of 94 ± 29

minutes. In one animal, epicardial echocardiography showed severe paravalvular regurgitation; another presented a junctional rhythm that required a pacemaker; and the third one was successfully weaned from CPB despite an ST segment elevation on the EKG. These three sheep presented irreversible cardiac rhythms and LV dilation in the hour after CPB was discontinued; therefore, they were sacrificed.

Findings at necropsy

In three sheep, the stented valve was misplaced. In two cases, the inflow of the entire extremity of the stent had migrated into the LV outflow tract (an anterior mitral chord was entrapped in one of them). The third case had a partial retro-migration below the native annulus at the level corresponding to the left coronary sinus. Two coronary obstructions occurred: in one, the right coronary orifice was totally obstructed by the base of the device; in the other, the left coronary ostium was partially blocked by a commissure of the device. In two cases, the device was found correctly placed; however, the coronary ostia appeared to be stretched.

Despite the small sample size in this study, no correlation was found between the findings and the type of valve or stent used. Migration, paravalvular leaks, and significant EKG changes occurred at least once with both stents and both valves.

DISCUSSION

Orthotopic aortic valve replacement has been performed in humans since the early 1960s, when Harken⁵ and Starr⁶ developed the very successful prosthetic ball valves. In an attempt to reduce the implantation time when myocardial protection was at its infancy, Magovern et al.⁷ developed an ingenious system of retractable hooks placed along the skirt of a ball valve that secured it to the annulus by simply turning the supporting valve holder. Magovern reported 728 patients implanted with this device between 1962 and 1988, with 11% operative mortality before 1981 and 4.9% after 1981. However, the attractive rapidity of implantation was off balanced by the difficulty of its correct location prone to paravalvular leaks. This prosthesis was displaced by the safer technique of placing the sutures around the aortic annulus under direct vision before bringing the prosthesis into the operative field. In the beginning of the 1980s, a new porcine bioprosthesis (Tascon valve) with a detachable sewing ring was designed to facilitate insertion and removal; but even if the valve's screw locking mechanism worked very well, this device did not have the expected success.⁸ Since then, the surgical technique for aortic valve replacement has not changed substantially. Research and development has been limited to improvements of the different prostheses. Recently, the success of percutaneous coronary and peripheral vascular stenting has stimulated the application of these endovascular techniques to valve repair and replacement. While this approach shows promising results for pulmonary valve replacement^{1,9} and possibly for mitral valve repair,¹⁰ PAVR has so far shown rather poor results.^{11,12}

The first human PAVR was performed by Cribier in 2002.¹³ In June 2005, the only published results in English from this team reported eight patients, and only five were followed echocardiographically for more than one month.¹⁴ At an April 2005 meeting,¹⁵ they presented 40 cases of PAVR using the Edwards PVT device but did not report early results or follow-up. At the same meeting, Ruiz et al.¹² reported 10 patients with 50% mortality at 11 days but "no complications related to the CoreValve™ device." Nine of these patients were reported to be operable.

Successful PAVR will require solution of the following problems: 1) selection of the appropriate tissue valve; 2) stent design and materials; 3) interference with coronary flow; 4) device anchoring system; 5) device migration; 6) delivery system; 7) handling of the native valve; and 8) development of cardiopulmonary support systems. Attempts at jumping directly from limited animal testing into clinical implantation are bound to fail. A slower but safer approach should be identifying a particular problem and then designing a specific study to address it.

Attempting to follow this philosophy, we decided to explore the possible advantage of the sutureless implantation of a stented valve under direct vision using standard open heart techniques. This hybrid approach is familiar to all surgeons. It also would not only reduce ischemic time but, more importantly, it also would allow resection of the calcified native valve under direct vision, which is impossible with present endovascular technology. This method would also avoid the problems of peripheral access, delivery systems, and correct positioning of the stented valve. Furthermore, this theoretically simpler approach would allow us to study the different stent designs and tissue valves in an animal model.

We, therefore, implanted two porcine aortic valves and four pericardial valves sutured to two types of balloon-expandable stents in sheep. Under standard CPB and transverse aortotomy beyond the sinotubular junction, the stented valve was positioned under direct vision. To mimic a percutaneous procedure, the native aortic valve cusps were not resected. The collapsed, stented valve was oriented so that the valve commissures did not interfere with the coronary ostia and so that the stent inflow orifice was lying approximately 5 mm below the bases of the native cusps. Surprisingly, in all cases, identification of the coronary orifices and base of the cusps was difficult when the collapsed balloon and valve were in place. This information is important because it disqualifies one of the expected advantages of this approach. In one case, this limited visibility was responsible for the immediate malposition of the device, requiring its removal and redeployment. A possible solution to this problem, as suggested by Quijano,¹⁶ is the placement of one or more guiding sutures passed through the native annulus and stented valve. However, our limited experience with retrograde and LV apical approaches (not reported here) has shown that a combination of fluoroscopy and epicardial echocardiography might provide better landmarks of the LV outflow tract and root than direct surgical vision.

In our sheep model, the surgical procedure resulted in major complications. Migration (3/6), paravalvular leak (2/6), mitral conflicts resulting in mitral regurgitation (1/6), and coronary ostia obstruction (2/6) were found in all cases as the cause of failure. Our results significantly differ from the unpublished report of Quijano,¹⁶ successfully performed in six swine and in humans in January 2005. To facilitate correct implantation of the device, they placed one or more sutures through the native annulus and stent before deployment.

In our study, coronary flow interference by the device could be due to a variety of mechanisms. To mimic PAVR, we did not remove the native leaflets and chose to over-expand our stented valves from 19 mm to 22 mm to avoid migration and paravalvular regurgitation.^{17,18} This overexpansion resulted in a cylindrical shape of the aortic root, with distortion of the sinuses of Valsalva and stretched coronary ostia. Early stent migration in one case and malrotation placing a commissure close to a coronary ostium in another resulted in the reduction of coronary flow. Our findings were not so different from percutaneous or transapical results previously reported.¹⁹⁻²³ All these results approached 50% failure. These poor results, particularly when compared to standard aortic valve surgery, highlight the need for extensive *in vitro* and *in vivo* studies before PAVR continues to be tested in humans. The present animal study and its negative results emphasize this need.

Limitations of the study

The small sample size of our experiment represents an obvious limitation. Two different stents and two different types of valve were used for the experiment, but the same types of complications were observed with both stents and both valves. The use of CPB and cardioplegia in sheep might have increased the mortality in our study but should have facilitated the stented valve implantation. The sheep model is probably not the perfect model for aortic valve replacement because of the shortness and narrow diameter of the ascending aorta. However, this was primarily a feasibility study attempting to determine the advantages and disadvantages of sutureless aortic valve implantation.

CONCLUSIONS

PAVR is now performed in humans with results far inferior to standard aortic valve surgery. As an intermediate phase between both techniques, we explored the feasibility of sutureless implantation of a stented valve using a transaortic approach. In our experience, this procedure does not facilitate a safe and accurate implantation. For human delivery, according to the position statement of the Society of Thoracic Surgeons, the American Association for Thoracic Surgery, and the Society for Cardiovascular Angiography and Interventions, "our collective enthusiasm for new, less-invasive cardiovascular approaches should not divert us from the importance of evaluating these devices in the context of controlled clinical trial environment."²⁴⁻²⁷ More

in vitro and in vivo studies should be undertaken before considering any human clinical trial.

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