Transapical approach for sutureless stent-fixed aortic valve implantation: experimental results

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Received 26 October 2005; received in revised form 16 January 2006; accepted 30 January 2006

Abstract

Objective: Percutaneous aortic valve implantation has been performed in patients with severe aortic stenosis judged as nonsurgical candidates. We evaluated a facilitated transapical antegrade approach for potential use in surgical high-risk patients. Methods: A pericardial xenograft fixed within a 23-mm stent (Cribier—Edwards aortic prosthesis, Edwards Inc., Irvine, CA, USA) was implanted using a transapical approach in fifteen 35—45 kg pigs. A limited or a full sternotomy was used to transapically introduce a crimped valve through a 24-F sheath. Deployments were performed on the beating heart either with ventricular unloading using femoro-femoral cardiopulmonary bypass (CPB) or rapid ventricular pacing (RVP), all under fluoroscopic and echocardiographic visualization. Results: All valves were successfully deployed at the target site with acceptable visualization of the noncalcified annulus. Valve migration occurred in six procedures (three distal and three retrograde) secondary to inadequate reduction of ventricular output, unfavorable annular anatomy, excessive crimping of the valve, and dislodgement by the delivery balloon. Exact positioning of the valve into the target area was confirmed by autopsy at the end of the procedures. Paravalvular leak was noted in five implants. Conclusions: The transapical approach provides a safe, accurate, and effective route for facilitated antegrade delivery of a stent-fixed valve. Advanced stent design will lead to better stability of the implant and may minimize the risk of paravalvular leakage in future. Identifying the appropriate population for human feasibility trials remains a challenge.

Keywords: Aortic valve replacement; Stent-fixed aortic valve; Transapical approach; Beating heart cardiac surgery

1. Introduction

Surgery is indicated according to standard guidelines in patients with symptomatic aortic valve disease [1]. Aortic valve replacement (AVR) is performed applying standard surgical techniques and results in the successful treatment of most patients. Prosthetic heart valves have evolved as reliable devices with good long-term function since their initial development in the 1960s. Major therapeutic options are conventional stented or stentless xenografts or mechanical prostheses. In parallel to these favorable developments, there has been a steady increase in operative age of about 1 year annually along with the presence of additional comorbidities leading to a clinically relevant increase of the individual’s operative risk.

In 2003, approximately 10,000 patients received isolated AVR in Germany. In-hospital mortality was 2.4% after mechanical and 3.8% after xenograft implantation [2]. Subgroups, especially octogenarians have a higher risk of up to 10% during aortic valve surgery. According to the STS database, the operative mortality after AVR was 4% in a total of 32,968 patients operated in 2004 in the United States. Concomitant coronary artery bypass graft (CABG) surgery lead to further increase in mortality up to 6.8%, 6.6% in patients with diabetes, 7.6% with previous cardiac surgery, and 17% in patients with end stage renal disease. These data are a clear indicator for a significant increase in perioperative risk in presence of patient-related comorbidities.

Application of the numeric and logistic EuroSCORE allows the preoperative estimate of perioperative risk [3,4]. A subgroup of patients with aortic valve disease carries a risk of 15% or above and some have even been considered nonsurgical candidates. In this high risk group percutaneous aortic valve implantation has been performed as a treatment option [5—7]. In order to further reduce the invasiveness of standard surgical AVR, we evaluated a facilitated transapical...
antegrade approach for potential use in high-risk surgical patients.

2. Materials and methods

Experimental application was performed on 15 pigs after institutional review board approval. A total of eight animals were operated at Edwards Lifesciences Biological Resource Center, Irvine, CA, USA (IR) and other seven animals at the experimental animal laboratory, Heart Center Leipzig, Department of Cardiac Surgery, Leipzig, Germany (LE). All animals received human care in compliance with standard guidelines (1996 NRC Guide for the Care and Use of Laboratory Animals. Available at: http://www.nap.edu/readingroom/books/labrats/contents.html).

Anesthetic induction was per standard techniques, using ketamine (2.2 mg/kg), xylazine (1.1 mg/kg), and tiletamine/zolazepam (Telazol®) (4.4 mg/kg) IM (IR) or atropine (0.02 mg/kg) azaperone (Stresnil®) (2 mg/kg) IM plus intravenous thiopental (Trapanal®) (4 mg/kg) and fentanyl (LE) for induction. This was followed by endotracheal intubation, controlled ventilation using isoflurane and intravenous access. All procedures were performed in the dorsal recumbent position.

2.1. Technical equipment

Both laboratories were equipped to perform routine cardiac surgical operations including a standard cardiopulmonary bypass (CPB) system; access was obtained via the femoral vessels. ECG, arterial blood pressure, and central venous pressures were routinely monitored. Functional hemodynamic monitoring was performed using intracardiac ultrasound (IR) with the probe advanced via the right internal jugular vein or standard transesophageal or epicardial echocardiography (LE).

Additional equipment to perform fluoroscopic examinations was available in both laboratories. This consisted of a mobile C-arm (GE Stenoscop 9000+) allowing for conventional monoplane visualization (IR). In the other laboratory (LE) a monoplane fluoroscopic angiography system (Axiom Sensis, Siemens, Munich, Germany) was used. Fluoroscopy should ideally be performed to give a perpendicular view of the aortic root. This allows for optimal delineation of the level of the aortic annulus in relation to the aortic sinuses together with imaging of the coronary ostia. After testing multiple angulations of the system, the preferred visualization of the aortic root was achieved at a left anterior oblique 35° and cranial 15° position of the system.

2.2. Sutureless stent-fixed aortic valve

A 23-mm Cribier–Edwards equine pericardial valve (model 9000) mounted on a stainless steel stent was used. The valve has three cusps and three commissures as is seen with other pericardial xenografts. The stainless steel stent has a very low profile when fully expanded. The lower inflow portion of the valve is covered with polyethylene terephthalate (PET) cloth. This is the same device as used in recent clinical percutaneous approaches [4–6]. One size was available for implantation fitting all annular sizes up to 23 mm (Fig. 1). The sutureless stent-fixed aortic valve was prepared for antegrade delivery under sterile conditions in the operating room by a technician just prior to implantation. The delivery catheter was flushed with a heparinized saline solution. The deployment balloon was primed with a mixture of saline and contrast, free of air. A balloon-sizing ring was used to determine the exact amount of volume needed to expand the balloon to 22 mm. The valve was crimped onto the deployment balloon so that it was equidistant between two radiopaque markers and was able to be passed through the 24-F delivery sheath; this was performed immediately prior to delivery. All valve deployments were performed using standard volumetric inflation of the balloon.

2.3. Transapical AV placement procedure

Access to the apex of the heart was obtained via a partial inferior [8] or a complete sternotomy [7]. The smaller incision was sufficient in all cases; the larger one was only performed to be able to perform additional epicardial echocardiographic visualization of the implantation procedure.
A surgical cut down was performed to cannulate the right internal carotid artery for placement of a calibrated angiography catheter (pigtail). Echocardiography was performed to aid with annular sizing, implantation, and evaluation of valve performance. After opening the pericardium at the apex, a double purse string suture of 3-0 Prolene was placed. Anticoagulation was performed using 300 IU/kg of heparin. Cineangiography of the aortic root with a calibrated catheter was then performed to size the aortic annulus; landmarks were used to identify the noncalcified porcine annulus.

A 0.35" super-stiff guidewire was placed transapically and across the aortic valve down the descending thoracic aorta using the Seldinger technique. Balloon dilatation of the aortic valve was performed in order to mimic the situation of clinical use in potential patients with aortic valve stenosis. The 24-F introducer sheath was then placed into the LV below the aortic valve under fluoroscopic guidance. The crimped valve on the delivery catheter (Fig. 2) was then introduced through the delivery sheath into the LV. After cardiac unloading the valve was positioned so that the annulus bisects the stent. Control angiography confirmed exact valve position (Fig. 3). The heart was loaded and the guidewire and sheath retrieved, the apex was safely secured using the purse-string sutures. Valve function was assessed using cineangiography and echocardiography after eventually weaning off CPB. The animals were then sacrificed and pathological examination of the heart performed.

2.4. Statistical evaluation

Results are given in a standard fashion expressed as mean ± SEM. The two-tailed Student’s t-test or Mann—Whitney U-test were applied as appropriate. Statistical analysis was performed using a SPSS 13.0 statistical package. A p-value of <0.05 was considered to indicate statistical significance.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Irvine</th>
<th>Leipzig</th>
<th>p</th>
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<tr>
<td>N</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td>n.s.</td>
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<tr>
<td>Body weight (kg)</td>
<td>41.8 ± 3.2</td>
<td>41.7 ± 2.1</td>
<td>41.9 ± 3.9</td>
<td>n.s.</td>
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<tr>
<td>Annulus—echo (mm)</td>
<td>20.2 ± 0.9</td>
<td>19.8 ± 0.9</td>
<td>20.6 ± 0.7</td>
<td>n.s.</td>
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<tr>
<td>Annulus—fluoro (mm)</td>
<td>19.9 ± 1.4</td>
<td>19 ± 1.15</td>
<td>20.7 ± 1</td>
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*Echo = echocardiographic measurements, intracardiac echo in Irvine and transesophageal and epicardial echo in Leipzig; fluoro = fluoroscopic measurements; p indicates statistical significance between echocardiographic and fluoroscopic measurements.*

3. Results

All procedures were completed as planned. Conduct of anesthesia was uneventful. As the Cribier—Edwards stent-fixed valve was available in size 23 mm only, animal selection was made in order to obtain an annular diameter between 18 and 23 mm; therefore, animals with a body weight between 35 and 45 kg were selected.

Eight procedures were performed at IR and seven procedures at LE. Mean body weight of the animals was 41.8 ± 3.2 kg. The mean aortic annulus diameter was 19.9 ± 1.4 mm on fluoroscopy and 20.2 ± 0.9 mm by echocardiographic measurements. This slight difference was statistically not significant. Thus, adequate measurements were obtained using either method. Similarly, there were no significant differences between the experiments performed in IR and LE. Detailed results on the parameters of the experimental model are given on Table 1.

Valve placement was performed without ventricular unloading in two, using rapid ventricular pacing (RVP) in seven and using CPB in six animals. During both applications where no ventricular unloading was used, distal embolization of the prosthesis occurred. Therefore, this approach was no longer pursued. Presently the authors believe that in the
4. Discussion

Transapical aortic valve placement is a relatively new approach that is under evaluation at present. New iterations of the valve and delivery system are under development.

4.1. Literature results

Percutaneous AVR has been performed in selected patients [5–7]. Besides successful implantations, problems have arisen with regard to trans-septal puncture and the rather long distance to the aortic valve, impairing the positional stability of the prosthesis during implantation [6,8]. Furthermore, femoral access is problematic in patients with peripheral arterial occlusive disease. All patients included into clinical trials so far had been rejected by two independent cardiac surgeons [5–7]. There are reports identifying 'nonsurgical candidates’, with some even talking about large cohorts of untreated patients. Depending on the individual clinician indications and attitudes to this disease, this may be rather surprising. Given the good results of conventional aortic valve surgery, therapy should not be denied to those suffering from symptomatic aortic valve disease. However, with the increasing number of individual patients with higher surgical risks, the search for less invasive techniques, the wish to be open minded towards new approaches and an attitude to adopt new techniques the transapical approach may be an option in future.

Different experimental approaches for direct aortic valve replacement have been published. Hubers group successfully implanted a prototype-valved stent in 12 pigs with transapical delivery [9]. Similar valves with nitinol Z-stents had been previously evaluated in the pulmonary and mitral position by the same group [10,11]. Percutaneous resection of calcified structures before valve implantation has been studied experimentally [12]. However, for implantation of the Cribier–Edwards prosthesis resection is not required. Good coronary flow has been proven for a self-expanding nitinol stent in the aortic position [13,14]. In comparison to that device, the steel stent-based Cribier–Edwards valve should not cover the coronary ostia and thus not lead to an impairment of coronary flow in presence of a normal (human) length of the aortic root. Bonhoeffer's group deserves the credit for their large clinical experience with percutaneous valve placement, even though not in the aortic but in the pulmonary position [15].

4.2. Team approach

Traditionally AVR is a surgical task. The prostheses developed over the past 45 years and have reached a high level of perfection allowing patients to continue a rather healthy life with significant improvement in their quality of life [16,17]. When applying any new technology, an interdisciplinary research group with a wide variety of experiences, including cardiologists and cardiac surgeons, is helpful. Joint collaborative efforts and experiences will provide maximum benefit for potential patients.

4.3. Experimental model

The porcine model used is similar to human anatomy, but it differs in several critical features. Specifically the aortic annulus was pliable because annular and leaflet calcification was not present. Thus, anchoring of the prosthesis is not comparable to that which is potentially possible in the presence of equally distributed calcification as in a human clinical situation. In addition, the relationship of the coronary ostia to the annulus and to the mitral valve annulus was closer. No ideal animal model mimicking aortic valve stenosis together with adequate calcification is known.

Clinical applications of the prosthesis in the presence of calcified structures may be easier than in this experimental
model as visualization will be better due to the calcium and fixation of the steel stent will be enhanced after pressing the calcium to the side. Calcification will, in addition, lead to reduced pliability of the aortic annulus and the aortic root and thus to better valve fixation. Another important aspect is the distance between the aortic annulus and the coronary ostia. This was rather short (7–8 mm) in the experimental model, leading to a higher risk of coronary artery obstruction after positioning of the prosthesis. However, in humans the geometry of the aortic root is different with a larger distance between 12 and 15 mm leading to a significantly lower risk of coronary ostia obstruction in potential clinical applications. Furthermore, better visualization in presence of some annular and ostial calcifications will be present. This study was performed solely to address the feasibility of the delivery technique and not the valve itself. Accurate placement of the same valve without migration has been documented by the percutaneous approach in animals. Thus, the migration of valve we encountered in our study, we feel, is a reflection of the animal model and not the valve or the delivery technique.

4.4. Sutureless stent-fixed aortic valve prosthesis

The Cribier–Edwards stent-fixed aortic valve prosthesis has been applied in the clinical setting using a percutaneous approach. This design will allow for sufficient hemodynamic performance as proven during experimental testing and from initial clinical results. Durability may be sufficient, especially in higher risk patients who may have a limited life expectancy. From the valve design standpoint, the stent is minimally covered with cloth and there is no cuff around the outer side. This may theoretically allow for optimal fixation in a calcified annulus. However, in presence of some irregularities at the annular level, typical paravalvular as well as trans-stent leakage may occur [4–8]. The latter would be directed from the central flow area through the stent depending of the position of the valve in relation to the native aortic root. Adding a cuff or skirt to the stent may reduce this risk. In the experimental model we observed aortic incompetence in several cases due to lack of backpressure. Further evaluation in the clinical setting is warranted. We strongly believe that it is important, whenever new prostheses are developed and applied, to aim at achieving the present high level of good clinical results with conventional devices. Minimal incompetence is acceptable in high-risk patients if a safer way to implant the prosthesis is available. However, a higher degree of valvular incompetence may not be tolerated by a ventricle used to aortic valve stenosis and should not be accepted.

4.5. Access for transapical AVR

Access to the apex of the heart was sufficiently obtained via a partial small inferior sternotomy in this model. Transposing these results into potential human practice and considering the different anatomies an anterolateral minithoracotomy in the fifth or sixth intercostal space would be feasible. This would even be true in the presence of cardiac adhesions during potential redo operations.

4.6. What is the ideal candidate for transapical AVR?

Transapical AVR is a procedure in its infancy. Early experimental data are promising and limited access beating heart aortic valve placement may become a reality in selected patients. However, there is no consensus yet as to who may be an ideal patient. Equally distributed calcification of the aortic annulus and the native valve cusps is important to safely position and anchor the valve. Larger eccentric plaques may lead to uneven opening of the valve or potential paravalvular leakage. Presence of bicuspid aortic valve disease or fusion of one of the commissures should be considered carefully. Transesophageal echocardiographic visualization is the standard for an exact preoperative diagnosis. In addition, CT scanning to delineate the amount of calcium in the aortic root may be helpful. Complete equal opening of the commissures without fusion with some annular and cusp calcification may be optimal. Patients with previous coronary artery bypass graft surgery with open grafts including a patent left internal mammary artery (LIMA) may be ideal candidates. Redo aortic valve surgery usually poses patients at an increased surgical risk due to advanced age and additional risk factors. Open bypass grafts would provide an additional safety margin in case of a short distance between the annulus and the coronary ostia. Other suitable candidates would be patients with porcelain aorta without any surgical option at an acceptably low perioperative risk. A stiff and calcified aortic root would be an additional help to safely anchor a sutureless stent-fixed aortic valve prosthesis under such circumstances. Patients carrying a higher surgical risk profile would be candidates to receive beating heart minimally invasive aortic valve placement with femoro-femoral CPB backup. Recent clinical experiences indicate that using an ‘oversized’ valve technique of approximately 3 mm will be important. Therefore, the 23 mm device should be used for patients with rather small aortic annuli of 19 mm to maximal 21 mm. If available, a larger 26-mm device could be considered for patients having an aortic annulus up to 24 mm.

5. Conclusion

In summary, the transapical approach allows for safe placement of a stent-based aortic valve prosthesis in the porcine model with potential applications for high risk surgical patients. An animal model to completely determine valve performance in the native calcified annulus is not available.

Acknowledgements

We acknowledge the support of Jane Olin, DVM, Mark Dehdashtian, Mark Konno, and all other employees at the Biological Resource Center at Edwards Lifesciences, Irvine. In Leipzig, we thank Petra Böske, DVM, Cris Ullmann, PhD, and Fabian Emrich for their valuable support to successfully perform these evaluations. This study was supported by Edwards Lifesciences.
References


Appendix A. Conference discussion

Dr M. Krason (Zabrze, Poland): I would like to ask you what is your positioning, let’s say tactics, and what is your oversizing tactics in this area of self-expanding stents, or balloon-expanding stents? Could you give us some more ideas, having in mind that there were so many displacements of the device?

Dr Walther: It is a very important question. We aim at some oversizing. In the animal model that is difficult, because the annulus is very flexible; it is noncalcified. I would expect that in humans with a calcified annulus there is more rigidity. So the anchoring of the valve would be easier. We measured the annulus in these animals on echo and on fluoroscopy, and we had an annulus of 19.8 mm on echo and 20.1 mm on fluoroscopy and we implanted a 23 mm valve. So we aim at something like 3 mm oversizing of the prosthesis.

Dr A. Böning (Kiel, Germany): Could you comment on the removal of the original aortic valve leaflets?

Dr Walther: Well, in the animal we didn’t remove them. In patients, we would really look for patients who have an equally distributed calcification, and we think that the calcification will help us to anchor the valve. As far as I heard from initial experiments in the 1990s from Heartport that they tried to do research on aortic valve implantation and tried to remove the whole calcium and they failed because they weren’t able to safely remove all that, and we think that the calcium may be a kind of anchor mechanism for the stent to be better seated within that calcified annulus. But we would exclude at present patients who have one big bunch of calcium at one commissure, for example. It needs to be equally distributed.

Dr Böning: May I make a comment? We started a pathological analysis in human aortic valves, and in 20–30% of the humans, the leaflets fall against the coronary ostia, if you push them towards the aortic wall. So you have a very high risk in a lot of patients to block the coronary arteries. I think we should start to work on the problem of valve leaflet removal.

Dr Walther: Well, it depends. There may be patients who have a somewhat enlarged sinus and the coronary ostia are a bit more away, the stent only dilates about 13 mm. There may be patients who require reoperative surgery as it was mentioned in your talk, and those who have open bypass grafts would maybe be ideal candidates for such an approach. It is just theoretical. We don’t have that much experience on that. It is just an experimental study so far.

Dr M. Deja (Katowice, Poland): Have you considered what happens if you implanted this in humans and then you need to remove it?

Dr Walther: Well, I think that is something you don’t want to have happen, but if it happens, of course, you have to go in and do the conventional approach, which is a very high risk, because I said our intention is to use such an approach for very high risk patients, even for patients whom some surgeons would consider as nonsurgical candidates. But of course, you then have to offer the patient some option because you don’t have a retrieval mechanism with this kind of prosthesis. Once it is deployed, it is deployed. That is a shortcoming, actually.

Dr R. Cesnjevar (Erlangen, Germany): You used rapid ventricular pacing for unloading and cardiopulmonary bypass. Which do you think is more effective? And secondly, as I understood the angiograms, the nitinol stent is not really close completely. How do you expect thrombus formation on this? It is just free-standing in the aortic root?

Dr Walther: Starting with the second, I don’t really expect thrombus because there is enough blood flow probably, and patients will get some aspirin. That should be fine. It is not a nitinol, it is a steel stent, so it doesn’t really close completely.

Regarding the unloading technique we realized that both are effective, when using rapid ventricular pacing the heart comes back, even in the animal; initially we were a bit anxious that they would keep on fibrillating but they came back, we used this technique because it is much easier. However, I personally think by now that both together is the best way to a hundred percent unload the heart so that you can position the valve at the very best place you want to have it.

Dr P. Kappetein (Rotterdam, The Netherlands): Do you think that a problem could occur with the chordae of the mitral valve, or haven’t you seen this?

Dr Walther: Well, with the mitral valve it really depends on the anatomy. In the animals we had about 2–3 mm distance below the annulus, the lower edge of the valve was sitting about 2–3 mm below the mitral valve annulus at the level of the anterior mitral leaflet. But the anatomy is very much different in the animals. We had a distance of the aortic annulus to the left coronary ostium of 7 mm, something like that, and in humans it is 12–15. So there is much more space, and in the other direction there should be more space as well. So I think it should be all right for human application.

Dr C. Mestres (Barcelona, Spain): You should define what is a real high risk patient, because EuroSCORE 9 is not really a great deal, at least in this part of the world.