Transcatheter aortic valve implantation of a second-generation valve for pure aortic regurgitation: procedural outcome, haemodynamic data and follow-up

Friederike Schlingloff, Ulrich Schäfer, Christian Frerker, Michael Schmoeckel and Ralf Bader

Department of Cardiac Surgery, Asklepios Klinik St. Georg, Hamburg, Germany
Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany
* Corresponding author. Abteilung für Herzchirurgie, Asklepios Klinik St. Georg, Lohmühlenstr. 5, 20099 Hamburg. Tel: +49-40-1818854150; fax: +49-40-1818854184; e-mail: f.schlingloff@asklepios.com (F. Schlingloff).

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Abstract

OBJECTIVES: The second-generation Jenavalve prosthesis (Jenavalve Technology, Inc., Munich, Germany) is the first transcatheter valve Conformité Européene (CE) marked for treatment of both aortic stenosis (AS) and pure aortic regurgitation (AR). Although the feasibility of the Jenavalve transcatheter aortic valve implantation (TAVI) in patients with pure AR has been described, haemodynamic and follow-up data are lacking.

METHODS: We report on a series of 10 transapical Jenavalve implantations for pure AR between December 2012 and September 2013. The patients were determined for TAVI by heart team decision at high surgical risk [log EuroSCORE (European System for Cardiac Operative Risk Evaluation) >20%], frailty or Charlson Comorbidity Index (CCI). Transaortic gradients and right heart haemodynamics were measured invasively before and after TAVI. Ventriculography and transoesophageal echocardiography were used to determine paravalvular regurgitation. All-cause mortality, NYHA functional class and echocardiographic measurements were followed up at 30 days and at 3, 9 and 12 months postoperatively.

RESULTS: Overall, mean age was 79 ± 9 years, mean left ventricular ejection fraction 50 ± 17% and mean log EuroSCORE 28.3 ± 17.1%. There were no perioperative complications. Paravalvular regurgitation immediately after implantation was graded none (n = 6), trace (n = 3) or mild (n = 1). Overall 30-day mortality was 30% (3/10). Three patients refused further treatment, such as haemodialysis or treatment of mitral regurgitation. Rate for pacemaker implantation was 2/10 (20%).

CONCLUSIONS: Intraprocedural success and haemodynamic data in our cases were good. The mortality in our group highlighted the importance of careful patient selection, especially for this pathology. The Jenavalve prosthesis proved to be suitable for treatment of AR in surgical high-risk patients.

Keywords: Pure aortic regurgitation • Transcatheter valve implantation • Second-generation valves • Haemodynamic data • VARC-2 Transcatheter aortic valve implantation

INTRODUCTION

Until recently, treatment of pure aortic regurgitation (AR) was restricted to conventional open heart surgery. Although transcatheter aortic valve implantation (TAVI) for aortic stenosis (AS) has been practiced since 2002, valves suitable for TAVI in (AR have only been available since 2012. Few implantations of the CoreValve (Medtronic, Inc., Minneapolis, MN, USA) have been reported [1–3] with satisfying results; however, because of increased risk for valve dislocation or annular rupture, experience has been limited. Two second-generation valves, such as the Jena Valve (Jenaavalve Technology, Inc., Munich, Germany) and the Engager (Medtronic, Inc), have been designed with a different anchoring mechanism that does not need calcification in the native valve. The Jena Valve comprises a self-expanding nitinol stent with a native porcine aortic valve. Three feelers that are deployed first during the implantation process, ensure an anatomically correct placement, while a special clipping mechanism then fixes the valve onto the native leaflets. The first promising results for the treatment of AS with the Jena Valve have recently been published [4]. Given several successful implantations in patients with AR [5–7], the Jena Valve is currently the only transcatheter valve Conformité Européene (CE)-marked for treatment of both AS and AR. Currently the Jena Valve delivery system can only be used for transapical (TA) access. A new delivery system for transfemoral use has been developed, has been successful in the first-in-man trial and will be available this year. A delivery system for transaortic access will be available from the beginning of next year.

Given that the transcatheter treatment of AR is a novel procedure, no recommendations have yet been made as to which
patients should be treated. At this stage, patients are selected using the same criteria as for conventional TAVI in AS: high surgical risk (log EuroSCORE ≥20), inoperability or frailty. However, the underlying pathology for AR is different from that of AS. Whereas AS is typically a result of degenerative calcification of the valve, AR develops as a consequence of structural abnormalities of the valve, the myocardium or the aortic root. AR causes a gradual dilation of the left ventricle with subsequent fibrosis and a decline in left ventricular function that might not be reversible in the late stages of the disease even after valve replacement.

The present study reports our experience with the implantation of the Jenavalve in patients with pure AR.

MATERIALS AND METHODS

Study design and patient population

Between December 2012 and September 2013, a total of 10 patients with severe AR underwent TAVI at our institution (Table 1). Of these, 7 of 10 (70%) had a high surgical risk according to risk scores or were deemed inoperable. One patient (1/10) absolutely refused conventional surgical cardiothoracic surgery and had already left another surgical department without being treated, being admitted a few days later at our institution with acute congestive heart failure. Two patients (2/10) did not have a high surgical risk according to risk scores, but were deemed high-risk patients by the heart team, which took aspects such as frailty or a high score on Charlson Comorbidity Index (CCI) into consideration. Patients with severe mitral regurgitation underwent MitraClip implantation in the same session. In 1 patient with severe paravalvular regurgitation after mechanical mitral valve replacement (MVR), the leak was closed with two Amplatzer vascular plugs (St Jude Medical, St Paul, MN, USA) in the same session. All procedures were performed in a hybrid operating room under general anaesthesia by an interdisciplinary team of cardiac surgeons, interventional cardiologists and anaesthesiologists. The antegrade TA approach was used because the Jenavalve was only available for the TA approach at that time. A trans-septal approach was used for the MitraClip implantation (Fig. 1), whereas the Amplatzer occluder was implanted through the TA approach (Fig. 2). Preoperative measurements of the aortic valve and annulus were conducted in transoesophageal echocardiography and multislice CT (MSCT) in all patients. The 3mensio software (3mensio Medical Imaging BV, Bilthoven, Netherlands) was used to determine optimal access site, angulation of the device and exact valve area, which is important especially in patients with oval annulus (Fig. 3). Following the manufacturers’ recommendations, a 23-mm prosthesis was chosen for an aortic annulus of 21–22.9 mm, a 25-mm prosthesis for an aortic annulus of 23–24.9 mm and a 27-mm prosthesis for an aortic annulus of 25–27 mm.

All patients received acetylsalicylic acid (100 mg), which was started before the procedure and continued indefinitely. A 600-mg loading dose of clopidogrel was administered the day before the procedure, followed by 75 mg daily for 1 month. If patients were taking warfarin or new oral anticoagulants before the procedure, they received only clopidogrel in addition. Standard antibiotic prophylaxis with intravenous cefazolin was started before the procedure and continued for 3–5 days. During the intervention, 100 IU/kg of heparin was administered to achieve an activated clotting time of 250–300 s.
Valve implantations were guided by fluoroscopy. Two pigtail catheters were placed into a cusp of the native valve each for better visualization. The valve was deployed in three different steps. Once the delivery system was introduced through the apex, it was advanced through the native valve into the ascending aorta. The positioning feelers were released and placed into the corresponding sinuses of the aortic root (Step 1). After correct orientation verified in two different fluoroscopic angulations, the lower stent part was released (Step 2), resulting in the clipping and attachment of the leaflets to the device. The stent was then fully expanded (Step 3). Once the valve was deployed, aortic root angiography and transoesophageal echocardiography were used to verify optimal placement and check for paravalvular leakage. No rapid pacing was needed during the implantation. In this series, there was no need for pre- or postimplantation dilatation because there was only rare calcification. Invasive haemodynamic recordings [transvalvular gradient, left ventricular end-systolic/end-diastolic pressure (LVEDP), systemic arterial and pulmonary arterial pressure, pulmonary capillary wedge pressure and cardiac output] were taken during the procedure. Immediately after the procedure, the patients were extubated and the temporary pacemaker removed, if possible. All patients were fully informed about the procedure and the off-label use and signed written consent forms.

Data collection

All clinically relevant baseline and follow-up variables were recorded and entered into a database. Procedural success was defined as stable device placement and function as assessed by angiography and echocardiography, according to Valve Academic Research Consortium-2 (VARC-2) criteria [8]. Invasive haemodynamic data were obtained immediately before and after valve implantation. During the follow-up visits at 30 days and 3 months, postprocedural regurgitation, reverse remodelling (LVEDP), left ventricular function and transvalvular pressure gradients were assessed by transthoracic echocardiography.

Statistical analysis

Continuous data were described as means and standard deviation (SD). Differences between variables pre- and post-TAVI intervention were tested with the non-parametric Wilcoxon signed rank test. Categorical data were described with absolute and relative frequencies.

All P-values are two-sided. A P-value lower than 0.05 was considered significant. All calculations were performed with the statistical analysis software SAS (SAS Institute, Inc., version 9.2, Cary, NC, USA).
RESULTS

Overall baseline characteristics are summarized in Table 1. Mean age was 79.1 ± 9.3 years; mean log EuroSCORE was 28.3 ± 17.1% and STS-PROM score 6.7 ± 11.1%. Ninety percent of the patients (9/10) were in NYHA functional class III or IV. One patient was in NYHA class II. All patients had severe AR. Three patients also had moderate to severe mitral regurgitation. The mean transvalvular pressure gradient was 8.6 ± 4.3 mmHg and mean calculated valve orifice area was 2.6 ± 0.6 cm² (Table 2).

Procedural success

All implantations were successful, and there were no intraprocedural complications. Cardiopulmonary bypass was not required and conversion to open heart surgery was not performed in any case. No apical haemorrhage or vascular bleeding was encountered, and no reoperation for bleeding or tamponade was required. No paravalvular leak was observed in 6 patients (60%).

A paravalvular leak qualifying as ‘trace’ was observed in 3 patients (30%) and mild paravalvular regurgitation in 1 patient (10%). Mean procedure time was 152 ± 43 min and mean time of fluoroscopy was 26 ± 15 min. Mean amount of contrast fluid used was 132 ± 74 ml.

Three patients died during the 30-day follow-up period in hospital. One 80-year-old patient refused treatment of concomitant severe mitral regurgitation by MitraClip implantation a few days postoperatively and died of cardiac failure. A 90-year-old patient refused haemodialysis for acute on chronic renal failure. One patient, who had a log EuroSCORE of 63% preoperatively, also suffered from acute on chronic renal failure and from acute respiratory failure after extubation. It had been discussed with his family before the intervention not to escalate treatment in face of further complications. One patient died 35 days after the procedure because of respiratory failure from atypical pneumonia. The log EuroSCORE and STS score were not predictive for mortality in our series ($P = 1.0$).

Haemodynamic and valvular function was satisfactory in all patients. Mean transvalvular gradient was 7.2 ± 4.3 mmHg after TAVI. Cardiac output remained stable throughout the procedure, whereas left ventricular systolic pressure increased and LVEDP decreased (Table 2). Mean aortic pressure also increased significantly ($P = 0.003$).

Two pacemaker implantations (20%) were necessary, one for postoperative bradyarrhythmia in long-standing persistent atrial fibrillation and one for AV-block III°.

Mean length of stay in intensive care was 6.1 ± 2.9 days and mean length of stay in hospital was 12.7 ± 2.9 days. There were no cerebrovascular events.

Follow-up clinical results

Follow-up at 30 days, 3, 6 and 12 months was performed by clinical examination and transthoracic echocardiography and complete at 30 days in 6 out of 10 patients (60%), at 6 months in 5 patients (50%) and 12 months in 2 patients (20%). One patient was alive but lost to follow-up because of lack of compliance. One patient died 42 days postoperatively from pneumonia and respiratory failure. Three patients died postoperatively at our institution (Table 1). There was no paravalvular leak in all patients. At 30 days,

| Table 2: Intraprocedural hemodynamic data before and after TAVI |
|---------------|------------------|
|                | Before TAVI      | After TAVI      | $P$   |
| P mean (mmHg) | 8.6 ± 4.3        | 7.2 ± 4.3       | 0.007 |
| Valve orifice (cm²) | 2.6 ± 0.6   | 3.2 ± 0.5       | 0.015 |
| LVsys (mmHg)  | 104.6 ± 27.6     | 112.3 ± 25.9    | 0.037 |
| LVEDP (mmHg)  | 15.4 ± 7.9       | 13.5 ± 6.7      | 0.220 |
| AO mean (mmHg)| 62.4 ± 15.6      | 73.7 ± 12.7     | 0.003 |
| Cardiac output (l/min) | 4.4 ± 1.2 | 4.4 ± 1.1       | 0.828 |
| PCWP (mmHg)   | 20.9 ± 6.1       | 20.2 ± 7.6      | 0.753 |
| PAPmean (mmHg)| 31.3 ± 9.8       | 31.1 ± 8.1      | 0.765 |

Data are expressed as mean values ± standard deviation (n = 10).
Pmean: mean transvalvular pressure gradient; LVsys: left ventricular end-systolic pressure; LVEDP: left ventricular end-diastolic pressure; AO mean: mean aortic pressure; PCWP: pulmonary capillary wedge pressure; PAPmean: mean pulmonary arterial pressure; TAVI: transcatheter aortic valve implantation.

Figure 3: (A) Amplatzer device in situ after implantation of Jenavalve (angiography). (B) Amplatzer plug in situ after implantation (3-D-echocardiography).
The low transvalvular gradients immediately after implantation and especially at 30 days seem promising. Given that there are currently no other data from transcatheter valves used for this pathology, we can only refer to transvalvular gradients observed in patients with TAVI for AS. Treede et al. [4] observed transvalvular gradients for the Jenavalve of 10 mmHg post-procedural in patients with AS. Holzhey et al. [9] report transvalvular gradients of 11.5 mmHg at 30 days and 13.9 mmHg at 6 months for the Engager valve, also in patients with AS, which corresponds well with a postoperative gradient of 7.2 mmHg in our study.

There was a low rate of paravalvular leakages observed in this study. Only 1 patient (1/10, 10%) had a mild paravalvular leak directly after implantation, whereas 6 patients (6/10, 60%) had no leak and 3 patients (3/10, 30%) only ‘trace’. At 30-day follow-up, no paravalvular leak was observed at all (6/6, 100%), even in those patients, where a paravalvular leak qualifying as trace or mild was documented directly after implantation. This might be explained by the observation that the nitinol stent of the valve often further expands during the first days after implantation. These numbers are very small, and future experience will show whether the results are reproducible. Considering that paravalvular leaks qualifying as mild or moderate have been observed in between 5.7 and 16% after TAVI for AS with first-generation valves in several centres [10–12] and the effects of paravalvular leakage on long-term survival are well known, this result could be noted as a fundamental advantage of the new valve design of second-generation transcatheter valves. Long-term data will have to prove this outcome.

The rate of pacemaker implantation for complete AV-block in this study (10%) is comparable with others reported for second-generation valves (Treede, 7.6%) [9]. The patient who developed a complete atrophicventricular (AV) block in our study had received the largest valve size (27 mm) currently available by Jenavalve. Bleiziffer et al. [13] report a 2-fold increased rate for pacemaker implantation if a large valve is implanted into a small annulus. On 3mensio measurements, the annulus of our patient had been measured as 25.9 cm², which makes a mistake by choosing a valve sized too large unlikely. Future results will show whether the pacemaker implantation rate is lower in patients with AR compared with patients with AS, because there are usually no calcified plaques pushed into the annulus and onto conductive tissues by the valve, or if plaques might protect the conductive tissue from pressure damage.

However, the mortality of 30% at 30 days observed in this study is high compared with the 30-day mortality reported recently for TA TAVI for AS (10%, Holzhey [11]; 9%, Walther [10]; 7%, Beckmann [14]) or AR (Seiffert et al.: 0% of 5 patients [6]). One reason might be that patients in our group were mostly those with an excessively high risk for surgery, with a log EuroSCORE of more than 30% in 4 patients and more than 40% in 2 patients. Mean age in our group was almost 80 years (79.1), whereas it was considerably lower, for example, in the group reported by Seiffert et al. (66.6 years) [6]. Another reason might be that we performed combination procedures in 3 of 10 patients (30%), because mortality reported for double transcatheter procedures is considerably higher than for single TAVI (22%, Beckmann [14]). Given that no death was valve related and there had been no intra-procedural complications or later complications with valve function, we attribute the high mortality at the beginning of our series to the need to gain more experience regarding patient selection. Pathology in AR is different from that in AS; therefore, different criteria for patient selection might be applicable. We have seen in our study that log EuroSCORE and STS-PROM score were not predictive for

The major finding of this series is the technical feasibility of treating pure AR with transcatheter valve implantation. Given the design of the second-generation valve used in this study, there were no complications during implantation, such as malpositioning, obstruction of coronary arteries or embolization of the valve. The feelers and the clip mechanism enable anatomically correct positioning and seem to make the implantation process safe and reproducible. The results of the Engager valve (Medtronic, Inc.), which has a very similar design, have shown an equally low rate of intra-procedural complications [9].
mortality. In our experience, one factor that reduces mortality is the treatment of mitral regurgitation in the same session if present. Although we lost the second patient after the procedure because of cardiac decompensation in untreated mitral regurgitation, Patients 4, 7 and 10 recovered well from the procedure, where we simultaneously implanted MitraClip or Amplatzer occluder for mitral regurgitation and/or paravalvular leakage.

Therefore, it has been shown that the treatment of AR by a TA TAVI approach with the Jenavalve is technically feasible with satisfying short-term results concerning haemodynamics and device success. Future results now have to show which patients can profit from this intervention and at which stage of their disease.

LIMITATIONS

This is an observational study of a small group of patients in a single centre. Our results are clearly compromised by the very high mortality observed. In this regard, patient selection seems to be of utmost importance. The follow-up period is currently short and long-term data are needed before expanding indications for the treatment of AR with the Jenavalve.

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Conflict of interest: Ralf Bader is a clinical proctor for JenaValve Technology, Inc.

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