Midterm outcome after aortic root replacement with stentless porcine bioprostheses

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Abstract

Objective: Midterm clinical outcome was evaluated after aortic root replacement with Freestyle® stentless aortic root bioprostheses. Methods: Between April 1996 and December 2007, 301 patients underwent aortic valve replacement with stentless Medtronic Freestyle® bioprostheses in full-root technique at a single center. Concomitant coronary artery bypass grafting (CABG) was required in 96 patients (32%). In 94 patients (31%), the ascending aorta was replaced. The mean age was 71.6 ± 9.1 (range: 36–89) years. Follow-up was closed in October 2008, 99% complete and encompassed 916 patient-years. Results: Overall mortality within 30 days was 5%. A total of 62 patients died during the follow-up period. Overall survival at 5 and 9 years was 74 ± 4% and 53 ± 6%, respectively. Re-operations were required in three patients: in one patient due to structural valve deterioration, and in two patients due to prosthetic valve endocarditis. Non-structural dysfunctions were not observed. In eight patients, prosthetic valve endocarditis occurred, in most of them (N = 6) during the first year after surgery. Rate of freedom from re-operation, structural valve deterioration, prosthetic valve endocarditis, thrombo-embolic and major bleeding events at 9 years was 94 ± 6%, 94 ± 6%, 94 ± 3%, 87 ± 5%, and 95 ± 2%, respectively. The linearized rates of late adverse events in percent per patient-year were 0.35, 0.12, 0.83, 1.7, and 0.7, respectively, for re-operation, structural valve deterioration, prosthetic valve endocarditis, thrombo-embolic and major bleeding events. A little less than a quarter (22%) of the patients required anticoagulation therapy. Conclusions: Aortic root replacement with the stentless Freestyle® bioprosthesis provided a respectable short-term mortality, optimal valve durability and acceptable rates of valve-related complications within 9 years.

Keywords: Aortic valve replacement; Stentless valves; Aortic surgery; Follow-up studies; Survival

1. Introduction

Aortic valve replacement is the therapy of choice for symptomatic aortic valve disease with the intention to re-establish the function of the aortic valve, resulting in a regression of left-ventricular hypertrophy and prolonged life expectancy. However, the insertion of valve prostheses into the diseased aortic valves reduces the orifice area in comparison to the native valve [1]. As a consequence of this prosthesis–patient mismatch, higher transvalvular gradients can be observed, which, in turn, may result in less regression of left-ventricular hypertrophy and a decrease in survival after aortic valve replacement. There is an ongoing debate whether prosthesis–patient mismatch has a clinical impact or not [2]. However, recent studies relying on effective orifice areas actually measured by echocardiography in each single patient, instead of the calculated areas obtained from manufacturers or the literature, showed a reduced survival for patients with prosthesis–patient mismatch [3,4].

To avoid prosthesis–patient mismatch, especially in patients with small aortic roots, aortic ring enlargement procedures or full-root replacement with stentless valves are surgical options. Aortic ring enlargement may be technically difficult in fragile aortic roots frequently seen in elderly patients [5]. Superior hemodynamics and an inferior incidence of aortic valve regurgitations were observed after full-root implantation of stentless valves [5–8]. Although the full-root implantation technique is more demanding and is associated with prolonged myocardial ischemia, no increased
operative risk was found in comparison to sub-coronary implantation of stentless valves [8] or to supra-annular implantation of stented valves [5] in risk-adjusted analyses.

The aim of the study was to describe our experience over 10 years with replacement of the aortic root using stentless Freestyle® bioprostheses and to evaluate the short- and midterm outcomes.

2. Patients and methods

2.1. Patient population

Between 1996 and 2007, 4409 patients underwent aortic valve replacement at our hospital: 1780 mechanical valve prostheses, 956 stented bioprostheses, and 1667 with the Medtronic Freestyle® stentless bioprosthesis, whereas 301 of them were implanted using the full-root technique (Fig. 1).

Concomitant procedures and characteristics for patients receiving stentless valves using the full-root technique are listed in Tables 1 and 2, respectively.

Follow-up information was obtained by mailed questionnaires and completed by telephone interviews. Follow-up was closed in September 2008 with 99% complete for vital status and 96% complete for valve-related events. Five patients refused to answer, in five patients information concerning valve-related events could not be retraced after death and three patients were lost to follow-up. Valve-related events were reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions [9]. Structural valve deterioration was determined by re-operation [9].

The prospective follow-up study was approved by the Ethics Committee of the General Medical Council of the State of Baden-Württemberg (Germany). The approval incorporates written informed consents regarding participation in the study.

2.2. Surgical technique

The prostheses type was selected according to the major criteria of aortic valve selection proposed by American

Table 1. Cardiac procedures.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N</th>
<th>%</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated full root replacement</td>
<td>136</td>
<td>45</td>
<td>2.9% [0.1—5.7] N = 4</td>
</tr>
<tr>
<td>+ Ascending aorta replacement</td>
<td>69</td>
<td>23</td>
<td>3% [0—7.1] N = 2</td>
</tr>
<tr>
<td>+ Coronary artery bypass grafting</td>
<td>70</td>
<td>23</td>
<td>12.9% [4.9—20.9] N = 9</td>
</tr>
<tr>
<td>+ Ascending aorta replacement and coronary artery bypass grafting</td>
<td>25</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>+ Mitral valve reconstruction or replacement</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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College of Cardiology/American Heart Association (ACC/AHA) guidelines [10]. For biological valve substitution, stentless valves were preferably used, unless extensive calcification of the aortic wall or other anatomical findings made the implantation of a stentless valve difficult or dangerous. The application of stentless bioprostheses and the full-root technique increased with time and the development routines, but was influenced by the attitude and experience of individual surgeons, major changes in the surgical team and training of younger surgeons in aortic valve surgery (e.g., in year 2000, Fig. 1). The main indications for total root replacement were: (1) aneurysm of the ascending aorta and/or the aortic root, (2) diameter of aortic annulus <21 mm, and (3) patients with an assumed risk for prosthesis—patient mismatch (determined by projected effective orifice area for the respective prosthesis type and size divided by body surface area). The method of concomitant replacement of the ascending root was introduced in November 2001.

Normothermia, intermittent ante- and retrograde cold blood cardioplegia, and left atrial vent were routinely introduced. During the full-root technique, oversizing was often performed: the prostheses were one or two valve sizes introduced. During the full-root technique, oversizing was limited because the maximum size of the Freestyle® bioprosthesis is 29 mm. The Freestyle® bioprosthesis was rotated in a clockwise manner directing the higher part of the Dacron carrying the prosthesis's right coronary ostia toward the patient's non-coronary sinus. Part of the wall of the prosthesis non-coronary sinus, as well as the left coronary ostia, were excised as buttons with a size of approximately 0.5—1 cm. The residual coronary ostium of the Freestyle® valve directed to the non-coronary side was then oversewn. The prosthesis was connected to the left ventricular outflow tract by a running 4/0 polypropylene suture. In cases of fragile tissue, autologous pericardium was used to stabilize the anastomoses. The suture was pulled tight to prevent leakage. The coronary ostia were reattached to the prosthesis using a 4/0 polypropylene suture. The distal anastomosis of the Freestyle® aortic root was sutured either to the native aorta or to a vascular graft (Hemashield Platinum) using a 4/0 Prolene running suture. In cases of dilatation of the distal ascending aorta, the anastomoses of the vascular graft to the proximal aortic arch were performed in circulatory arrest, with protective hypothermia (28 °C) and antegrade cerebral perfusion.

2.3. Statistical analysis

Statistical analysis was performed using the software package Statistical Package for Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA). The data (Table 2) were obtained from a database for cardiosurgical quality assurance.

All continuous data were expressed as mean values (± one standard deviation) and compared by the Mann—Whitney test. Dichotomous variables were evaluated by the univariate chi² test and Fisher’s exact test. The survival and freedom from valve-related complications were estimated by Kaplan—Meier and lifetime table analysis. Predictors of survival time were determined using Cox regression. Late linearized rates were calculated as number of events occurring 30 days after surgery divided by the respective patient-years.

The logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was calculated according to the guidelines published on the website (http://www.euroscore.org). The Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (STS PROM) was computed using the regression coefficients of the STS 2008 risk model for isolated valve surgery [11] and for valve plus coronary bypass surgery [12].

3. Results

3.1. Operative mortality and midterm survival

Overall operative mortality (within 30 days) was 5.0% (15 patients); it was 6.3% and 2.2% for the full-root implantation technique and combined procedure with replacement of the ascending aorta, respectively. The mortality for the several procedures and their combinations is shown in Table 1.

The observed operative mortality after full-root replacement was lower than the mortality predicted by logistic EuroSCORE (observed/expected mortality (O/E): 0.59 (0.53—0.66)) and higher than predicted by STS score (O/E: 1.47 (1.35—1.58)) (Fig. 2). For the combined procedure with replacement of the ascending aorta, the observed mortality was also lower in comparison to the mortality predicted by EuroSCORE (O/E: 0.14 (0.07—0.21)) and similar to the mortality predicted by STS score (O/E: 1.02 (0.99—1.05)).

There were 15 early and 47 late deaths. Causes of early death were cardiac failure (seven), stroke (one), sepsis (three), mesenteric vascular occlusion (two), and bleeding events (two). Of the 47 late deaths, seven were valve-related, 13 were cardiac, 19 were non-cardiac, and eight were unknown. The causes of valve-related deaths were endocarditis (one), re-operation due to endocarditis (two), neurological events (two), and bleeding events (two).

The overall survival rate was 74 ± 4% and 53 ± 6% at 5 and 9 years, respectively (Fig. 3). Predictors of survival time were age per 10 years (hazard ratio (HR): 1.611 (1.07—2.43)), diabetes mellitus (HR: 1.97 (1.12—3.46)), ejection fraction
per 10% decrease if the ejection fraction is smaller than 50% (STS definition) (HR: 1.03 (1.01—1.06)) and emergency procedure (HR: 5.89 (2.28—15.2)). In Fig. 3, the overall survival after full-root replacement was compared to an age- and sex-matched example from the general German population and to the survival of low-risk patients undergoing full-root replacement. After excluding operative mortality and patients with identified risk factors, such as emergency procedures and an ejection fraction <50%, defined as low-risk patients, survival was quite similar to that of men and women of the general German population of the same age of 71 years (Fig. 3).

Because the characteristics for patients undergoing full-root replacement and the combined procedure with replacement of the ascending aorta were very different (Table 2), the survival for the subgroups presented in Fig. 4 is adjusted by the above-described predictors of survival time.

### 3.2. Valve-related events

#### 3.2.1. Re-operation

Three patients required re-operations at the aortic position. The causes for re-operations were prosthetic valve endocarditis (PVE) (two) and structural valve deterioration after 8 years (one). Of the three patients undergoing re-operation, in two patients the Freestyle® valve was explanted and replaced by a Freestyle® aortic root using the full-root technique or by a Tissuemed aortic root. These two patients died within 30 days. In one patient, the valve leaflets were excised and a mechanical valve was implanted. This patient was still alive 2 years later.

The 5-, 7- and 9-year actuarial freedom from aortic valve re-operation and structural valve deterioration was 99.2 ± 0.5%, 99.2 ± 0.5%, and 93.6 ± 5.5% and 100%, 100%, and 94.3 ± 5.6%, respectively. The late linearized rates of adverse events were 0.35% per patient-year and 0.12% per patient-year for re-operation and structural valve deterioration, respectively.

#### 3.2.2. PVE

There were eight endocarditis episodes. Endocarditis occurred between 15 days and 63 months with a mean interval of occurrence of 16 ± 20 months. Two patients underwent re-operation. Four patients died. The 5-, 7-, and 9-year actuarial freedom from endocarditis was 97.2 ± 1.1%, 94.4 ± 2.9, and 94.4 ± 2.9%, respectively. The late linearized rate was 0.83% per patient-year.

#### 3.2.3. Thrombo-embolic events

Thrombo-embolic events were observed in 17 patients. Three patients died. The late linearized rate was 1.7% per patient-year. Actuarial freedom from thrombo-embolic events at 5, 7, and 9 years was 93.2 ± 2.5%, 87.0 ± 4.8%, and 87.0 ± 4.8%, respectively.

#### 3.2.4. Bleeding events

Bleeding events occurred in 13 patients. Five of them (38%) were on anticoagulation medication at the time of the occurrence of the bleeding event. The late linearized rate was 1.18% per patient-year and for major bleeding events 0.71% per patient-year. Actuarial freedom from major bleeding events at 5, 7, and 9 years was 95.4 ± 1.7%. A little less than a quarter (21%) in (22%) of the patients required anticoagulation therapy due to generalized atherosclerotic disease or chronic atrial fibrillation presenting pre- or postoperatively.

Valve thrombosis and non-structural dysfunction was not observed.

### 4. Discussion

The present study describes the experience of a single center with replacement of the aortic root using stentless Freestyle® bioprostheses. Short- and midterm outcomes were evaluated. The overall 30-day mortality after full-root replacement was 5%. These rates were similar to previously reported mortality rates after full-root replacement, which varied between 5% (in-house mortality) [5] and 6% [13,14].

The mortality predicted by the logistic EuroSCORE was much higher than the observed mortality (Fig. 1), whereas the observed mortality after isolated full-root replacement was higher than predicted by the STS Score but within the range of the confidence limits. It has been previously
demonstrated that the EuroSCORE overestimates the operative risk [15], whereas the STS Score predicts the operative mortality more accurately [16]. In previous studies, no significantly increased operative risk after full-root replacement in comparison to the sub-coronary implantation technique [8], and to the implantation of stented bioprostheses was found after adjustment for different risk factors by propensity scores [5].

We cannot exclude a slightly increased operative risk in comparison to aortic valve replacement; however, the difference is small (~2%), and to show the significance of a difference of that level would require a sample size of more than 1800 patients in each group. However, the 30-day mortality after full-root replacement was between the 30-day mortality rates for isolated aortic valve replacement (3.4%) and aortic valve replacement with concomitant bypass surgery (6.8%) reported by the quality assurance of all German centers of cardiothoracic surgery for the year 2009.

The 30-day mortality separately for each procedural subgroup (Table 1) is of limited validity because the number of patients is small in each subgroup resulting in a wide variation of the confidence intervals. However, a lower mortality after combined replacement of the aortic root and the ascending aorta emerges, which may be explained by differences in the patient characteristics: patients with aortic aneurysm were younger, had less co-morbidities such as diabetes or peripheral artery disease, and were rarely emergent cases (Table 2), which is also supported by the lower STS Score for this patient group. Furthermore, after adjustment for the risk factors, the survival curves of both groups were equal (Fig. 4).

A respectable 9-year survival after full-root replacement of the aortic valve could be shown. In patients without an increased risk, that is, patients with a normal left-ventricular ejection fraction or not requiring emergency procedures, survival similar to that of the German general population of the same age was observed (Fig. 3). The survival rate at 5 years of 74% was quite similar to previously reported rates after full-root replacement in patients with a mean age of 70–72 years, varying between 73.5% and 77.8% [6,7,13]. A longer survival of 10 years was previously reported in 178 patients by Bach et al. [17], which, at 47.3%, was quite similar to the rate observed in the present study of 53% at 9 years. The reported survival rates at 10 years after biological aortic valve replacement in patient groups with a mean age over 70 years varied between 36.6% and 44% [17,18]. In younger patients receiving biological or mechanical aortic valves (mean age between 56 and 68 years), survival rates at 10 years between 58% and 74% were observed [20–23]. A wide variation in survival rates between different study cohorts will be observed due to differences in patient age and in the prevalence of co-morbidities.

The observed rate for freedom from re-operation at 9 years was similar to the rates found in other studies for the stentless Freestyle® bioprosthesis or for stented biological valves, which varied between 92% [17] and 94.6% [18,20,22] at 10 years. Freedom from re-operation and structural valve deterioration at 10 years was lower after replacement with stentless valves such as Cryolife O’Brien, at 57% and 19% [19], respectively, or Toronto SPV, at 85% and 86% [23], respectively. Reported freedom from PVE varied between 95% and 96% at 10 years for stentless bioprostheses [19,23] with linearized rates between 0.2% per patient-year for mechanical prostheses [21] and 0.4% per patient-year for stented bioprostheses [18,22,24]. Whereas the values for actuarial freedom from PVE were quite similar to the observed freedom in this study, the reported linearized rates were lower. Whether the higher linearized rate for PVE observed in this study is caused by the shorter follow-up time, where most of the endocarditis episodes occurred within 2 years, or by an increased risk with full-root replacement should be verified in studies with longer follow-up times.

Previously published linearized rates of major bleeding events varied between 0.4% per patient-year, whereas, in this study, only morbid events were reported [18], and 2.7% after mechanical aortic valve replacement [21], largely depending on the quality of anticoagulation treatment and the proportion of patients requiring anticoagulation.

Furthermore, a wide variation in the linearized rate of thrombo-embolic events after valve replacement can be found in the literature: 0.3% per patient-year after Carpentier–Edwards-pericardial aortic valve replacement in patients with a mean age of 74 years (morbidity only) [18], 1.3% per patient-year [22] and 2.3% per patient-year [24] after porcine stented valve replacement with a mean patient age of 69 years, 1.9% per patient-year after mechanical valve replacement (mean age 64 years) [21], and 2.7% per patient-year after stentless biological replacement (mean age 72 years) [17,25]. The rate of thrombo-embolic events mainly depends on age and patient-related risk factors for stroke such as diabetes mellitus, hypertension, atrial fibrillation and left-ventricular hypertrophy. Because the prevalence of these risk factors may differ throughout the different studies, a wide range of published thrombo-embolic rates results.

Although the full-root implantation technique is demanding, a respectable outcome was achieved with short- and midterm mortality rates similar to those reported after aortic valve replacement. Especially in patients with small aortic roots, full-root replacement represents a valid surgical option to avoid prosthesis–patient mismatch. We have previously shown that the proportion of severe mismatch is much lower after full-root replacement in comparison to aortic valve replacement with other biological or mechanical valve prostheses [4].

After combined aortic root and ascending aorta replacement with stentless bioprostheses, the short- and midterm mortality was very low, indicating that such biological substitutes may be an alternative to conventional mechanical composite grafts in the treatment of diseased valves and dilated or severely calcified ascending aortas.

References


