Negative results - Valves

Early calcification of the aortic Mitroflow pericardial bioprosthesis in the elderly

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Abstract

Background: We report our experience in the elderly with aortic valve replacement using the Mitroflow A12 pericardial bioprosthesis.

Methods: From January 1993 to January 2006, 491 patients over the age of 70 years received an aortic Mitroflow A12 bioprosthesis implantation. Concomitant procedures included coronary artery bypass grafting in 20% of patients. All patients had routine postoperative Echo-Doppler studies at discharge, one month and a mean of 11.1 months after surgery and annually thereafter. Results: Twenty (4%) patients underwent a second aortic valve replacement due to bioprosthetic valve dysfunction (Group 2). Calcified stenosis was the most common finding at reoperation (98%). Median time to valve reoperation was 76 months. Of patients requiring reoperation, median age at first and second implantation was 73 (70–78) and 79 (76–83) years, respectively. For all patients, freedom from structural valve dysfunction (SVD) was 95 ± 3% at 5 years and 55.8 ± 2% at 10 years. Bioprosthetic valve deterioration was identified in 27 patients (Group 1). Median age of these patients at first operation and at diagnosis of deterioration by echo was 75 (70–84) and 77 (70–82) years, respectively. The median interval between operation and detection of bioprosthetic valve deterioration was 46 months. Among the total patient population, freedom from bioprosthetic deterioration was 85.7 ± 2% at 5 years and 33.5 ± 4% at 10 years. Conclusion: The Mitroflow A12 pericardial bioprosthesis provides less than optimal performance in elderly patients.

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Keywords: Elderly; Calcification; Mitroflow

1. Introduction

As the population ages, tissue heart valves are being used at an increasing rate to replace dysfunctional cardiac valves. Bovine pericardial bioprostheses combine an excellent hemodynamic performance [1, 2] with low thrombogenicity [3], but long-term durability of tissue heart valves is still uncertain and valve failure associated with calcification remains a concern [4]. Choice of appropriate aortic valve bioprosthesis is based on tissue valves durability, hemodynamic performance and aortic annulus size.

The latest generation of the aortic Mitroflow pericardial bioprosthesis (model A12, Sorin Group Inc, Mitroflow Division, Vancouver, Canada) was introduced in 1992; our experience with this bioprosthesis began in January 1993. A recently published study reported an 8-year follow-up demonstrating left ventricular mass regression with the new Mitroflow A12 [2] but contrary to expected findings, there was a trend in this series for increased metabolic valve dysfunction. In the current report, we document an early rate of calcification with the Mitroflow A12 in the elderly.

2. Material and methods

2.1. Patients

From January 1993 to January 2006, 585 patients underwent isolated aortic valve replacement with the Mitroflow A12 at our center. Of these, 491 patients over the age of 70 years were included in this study. Demographic data at time of aortic valve replacement are listed in Table 1. The size distribution of the bioprosthesis is presented in Table 2, with 83% of the patients receiving 21 or 23 mm valves. There were 132 patients (26.8%) taking statin drugs. No patients received infusions or chronic treatment with calcium. No patients with renal insufficiency prior or after surgery were present.

All patients were discharged from the hospital on a regimen of lifelong aspirin therapy, unless atrial fibrillation or other reasons indicated the need for anticoagulant treatment.
Table 1
Demographic data

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>76.5 ± 4 (70–89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/Male</td>
<td>261/230</td>
</tr>
<tr>
<td>New York Heart Association Class</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>139 (28.3%)</td>
</tr>
<tr>
<td>Class III</td>
<td>345 (70.2%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>295 (60%)</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>14 (2.8%)</td>
</tr>
<tr>
<td>Mixed lesions</td>
<td>182 (37%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>191 (39%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>74 (15%)</td>
</tr>
</tbody>
</table>

Table 2
Bioprosthesis size

<table>
<thead>
<tr>
<th>Valve size (mm)</th>
<th>All patients (%)</th>
<th>SVD (%)</th>
<th>BD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>41 (8.3)</td>
<td>1 (5)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>21</td>
<td>260 (52.4)</td>
<td>11 (55)</td>
<td>16 (59.2)</td>
</tr>
<tr>
<td>23</td>
<td>150 (30.5)</td>
<td>7 (35)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>25</td>
<td>40 (8.1)</td>
<td>1 (5)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Total</td>
<td>491</td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>

SVD, structural valve dysfunction; BD, bioprothetic valve deterioration.

2.2. Surgical technique

Aortic valve replacement was performed through a midline sternotomy, with moderate hypothermia (33 °C) cardiopulmonary bypass using anterograde blood cardioplegia. The bioprosthetic valves were inserted in the supra-annular position employing 2-0 mattress pledgeted sutures. Concomitant procedures included coronary artery bypass grafting in 20% of patients.

2.3. Follow-up

All patients were entered into a database at the time of the operation and were followed up prospectively at the Cardiac Surgery and Cardiology Services of the University Hospital with a follow-up visit on a yearly basis. Follow-up extended from 0 to 11.7 years (median time was 3.4 years) and was 98% complete.

All patients had routine postoperative Echo-Doppler studies at discharge, one month and one year post-surgery and yearly until bioprosthetic deterioration was detected; when deterioration was detected, follow-up was more frequent (> once per year). All patients had more than one Echo-Doppler examination.

Valve-related complications are reported according to the guidelines for reporting morbidity and mortality after cardiac valvular operations [5]. Operative death was defined as any death in the hospital or at home within 30 days after operation.

Bioprosthetic valve deterioration (BD) was defined as any morphological change documented by Echo-Doppler (calcification, gradual increase in gradients obtained on previous ECHO, opening leaflet decrease). The patients with BD (Group 1) were asymptomatic.

Structural valve dysfunction (SVD) was defined as any clinically relevant valvular stenosis (area <0.8 cm², mean gradient at rest >40 mmHg) or insufficiency documented by Echo-Doppler with bioprosthetic calcification confirmed at reoperation. Patients with SVD (Group 2) were advised to go under reoperation if they were symptomatic. Radiographic evaluation was performed on all explanted tissue valves to confirm intrinsic calcification.

An experienced pathologist performed histopathologic analysis of the removed bioprosthesis.

2.4. Statistical analysis

Data are reported as median and range deviation. Survival analysis was performed using Kaplan–Meier and Cox regression analysis using the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL). Cumulative survivals are expressed as mean. A P-value of 0.05 in a two-tailed test was considered significant.

3. Results

Demographic data at the time of aortic valve replacement are listed in Table 1. The size distribution of bioprostheses is presented in Table 2, with 83% of the patients receiving 21 or 23 mm valves. Follow-up ranged from 0 to 11.7 years (median 3.4 years) and was 98% complete.

At present, 20 (4%) patients have undergone a second aortic valve replacement because of SVD (Group 2). The median age of these patients at first operation and at reoperation was 73 (70–78) and 79 (76–83) years, respectively. Stenosis due to calcification of the tissue valve was the most common finding at reoperation (98%). Five cases with early endocarditis were excluded; there were no patients with prolonged postoperative subclinical infection. Median time between the first operation and the reoperation was 76 months (range 46 to 98 months). The median interval between the first echocardiographic sign of BD and reoperation due to SVD was 32 months. The bioprosthetic size distribution in these patients is presented in Table 2; 55% of patients receiving 21 mm valves.

Of the 20 patients undergoing reoperation, one died before leaving the hospital (5%). Echocardiographic parameters are shown in Table 3; no significant periprosthetic leaks were detected. Long-term freedom from SVD is shown in Fig. 1. Freedom from reoperation for SVD was 95 ± 3% at 5 years and 55.8 ± 2% at 10 years. Linearized rate of SVD was 0.74%/patient/year.

Macroscopic findings of the explanted bioprosthesis included the following: extensive calcification, noticeable rigidity of the leaflets due to diffuse intrinsic calcifications, leaflet thickness greater than normal and granular calcification on the commissures. On radiographic analysis, that all explanted bioprostheses had one leaflet more calcified than the others; in most cases, the right coronary leaflet was the most calcified (14/20) (Fig. 2).

Histologic findings included: collagen fibers degeneration with fragmentations of collagen bundles, cholesterol clefts and linear areas of intrinsic calcifications.

Preoperative serum levels of cholesterol were 179 mg/dl (111–210), triglycerides 129 mg/dl (60–206), lipoprotein A 6.6 mg/dl (1–19) and calcium 9 (8–10.1).

Tissue valve deterioration was present in 27 patients (Group 1). The median age of these patients at first
Table 3

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>First year after operation</th>
<th>Before reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gradients (at rest) mmHg</td>
<td>19</td>
<td>21 ± 6</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>16 ± 7</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>12 ± 3</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>Orificial surface area (cm²)</td>
<td>19</td>
<td>1.08 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>1.52 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>1.69 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>1.72 ± 0.32</td>
</tr>
</tbody>
</table>

operation was 75 (70–84) years; median age at diagnosis of degeneration by echo was 77 (70–82) years. Mean time between operation and detection of BD was 46 months (range, 22 to 95 months). Patients with BD (Group 1) were asymptomatic.

Actuarial freedom from BD is shown in Fig. 3. Freedom from BD was 85.7 ± 4% at 5 years and 33.5 ± 12% at 10 years. Linearized rate of BD was 1.04%/patient/year.

The first sign of deterioration was a decrease in the opening of one of the leaflets. Later, there was an appearance of dot-like calcifications; lastly a gradual increase in transvalvular gradients is detected. All these signs were observed preoperatively in all reoperated patients.

The overall patient survival rate was 86.5 ± 3%, 82 ± 5%, 74 ± 5% and 39.5 ± 7% at 1, 3, 5 and 10 years, respectively (Fig. 4). There were 66 late deaths (Table 4).

On univariate analysis, age and hypertension retained prognostic significance, whereas on multivariate analysis, only age (Hazard ratio 0.73, 95% CI 0.59–0.89, P = 0.002) was retained as having independent prognostic significance in relation to SVD.

4. Discussion

Pericardial valves have been used in clinical practice for >30 years [6] and the Mitroflow pericardial valve bioprosthesis (Sorin Group Inc, Mitroflow Division, Vancouver, Canada) was introduced into clinical use in 1982. Its design demonstrated excellent hemodynamic performance, particularly in the small aortic annulus [7]. However, early and mid-term mechanical failures, due to abrasion, were documented [8]. The latest generation of aortic Mitroflow pericardial bioprosthesis (model A12) was introduced in
1992 in an attempt to remedy this problem. It was decided to reverse the Dacron cloth that covered the frame of the valve such that the non-ribbed side would be in contact with the pericardial tissue.

With this change, bioprosthetic valve durability showed considerable improvement; their principal limitation remains the development of calcifications, structural valve deterioration and failure over time. The rate of structural valve deterioration is lower in the elderly patients [9] but the exact age threshold for choosing a bioprosthesis remains the subject of debate; Rahimtoola [10] proposed that the cut-off ages should be 60–65 years. In 1007 patients aged 70 years and over, Pupello and colleagues [11] reported a 9-year freedom from structural dysfunction of 94.3% with stented porcine xenograft prostheses; Banbury and colleagues [12] reported an actuarial freedom from SVD at 5, 10 and 15 years of 99%, 94% and 77% with the Carpentier–Edwards aortic pericardial bioprosthesis in a patient-population whose mean age was 65 years. Minami and associates [13] studied the long-term results of the Mitroflow Synergy bioprosthesis for aortic valve replacement in 1516 patients, reporting an actuarial freedom from structural valve deterioration at 5, 10 and 15 years of 99%, 82% and 62%, respectively. They recommended that implantations should be rigorously restricted to patients older than 75 years. The freedom from SVD in our patients with an aortic valve replacement with the Mitroflow A12 bioprosthesis was worse than in these previous reports, although the mean age in our patients was 76.5 years.

These previous reports showed a lower number of SVD than in our study. This figure could be an underestimation because dysfunction was considered only if reoperation was needed and patients who did not undergo reoperation, despite having structural valve deterioration, were not included. Structural valve deterioration is a process occurring over a prolonged period of time and the real incidence may have been less than the rate that would be detected by periodic echocardiographic studies. In the present study, we included both patients who underwent reoperation (Group 2) and those with echocardiographic evidence of valve deterioration (Group 1).

Despite the development of new generations of bioprosthetic valves, their principal problem remains the development of SVD over time; this structural failure of the pericardial valves is characterized by calcification. The onset of calcification has been postulated by Herrero et al. [14] to originate from an electrostatic attraction between the acid phospholipids of the connective tissue and calcium. In a more recent article, Cunanan and colleagues [15] found a correlation between the phospholipids content of tissues and calcification. They also found that the Mitroflow tissues developed significantly more calcifications than other commercial valves.

We performed radiographic and histologic analysis of the explanted bioprosthesis and found that all valves showed severe calcification of the leaflets and granular calcification on the commissures. There may be other mechanisms that also contributed to the bioprosthetic calcification, but in our patients a casual relationship was not found. While we expected good results in our patient cohort [2], there was a trend towards increased metabolic valve dysfunction. We therefore conclude that the Mitroflow A12 pericardial bioprosthesis provides less than optimal performance in the elderly patients.

References

So, the increase of age means the increase of risks. Elderly patients suffer scoring methods consider age as a risk factor for mortality and morbidity.

Valvular calcification is common in chronic renal disease, and is closely associated with findings of intimal arterial disease. The presence of inflammation and the duration of dialysis treatment contribute to this complication [4].

One of the issues is osteopontin which is found to be related to calcification of bioprosthetic valves. Osteopontin is a heavily phosphorylated and acidic pro-inflammatory glycoprotein with strong calcium-binding properties that stimulates differentiation of myofibroblasts and regulates the deposition of calcium by osteoblasts. Increased levels of plasma osteopontin are found to be associated with the presence of aortic valve calcification and stenosis [5]. This finding suggests that osteopontin might play a functional role in the calcification of bioprosthetic valves as well as native calcific valves.

It should be clarified whether bioprosthetic valve calcification is related only to the valve itself or to other factors. We know that bioprosthetic valve preservation is essential for the prevention of calcification. Various pretreatment methods of bioprosthetic valves are being applied with different chemicals. In this paper [1], it is not clear whether the total valve deterioration and the structural valve dysfunction are subjected to only the valve itself or to a comorbid condition. On the other hand, it would be better to know whether survival of this cohort is fairly different than the expected survival of a normal population at this advanced age. This cohort consisted of almost all aortic stenosis (97%) [1]. Hence, it should be kept in mind that patients with aortic stenosis have a higher tendency to calcification than the normal population.

References


