Early prosthetic valve degeneration with Mitroflow aortic valves: determination of incidence and risk factors†

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Abstract

OBJECTIVES: We describe a cluster of early valve degeneration (EVD) in a series of 281 Mitroflow valves implanted during 1999–2013. Patients with EVD were identified as having symptomatic stenosis or regurgitation within 6 years of implantation leading to reoperation.

METHODS: Freedom from reoperation was estimated by Kaplan–Meier actuarial analysis. Patient and valve characteristics in the EVD group were compared with those without using univariate and Cox proportional hazard multivariate regression analysis.

RESULTS: The rate of actuarial freedom from reoperation was 97% at 6 years and 92.5% at 10 years. The linearized rate of reoperation was 0.7% per patient-year. Ten patients required repeat surgery for EVD. Reoperation occurred from 2 years of implantation in patients with a mean age of 60, compared with 70 in those without EVD. Causes of explantation were stenosis (8), regurgitation (1) and mixed disease (1). The age was the only significant predictor of early degeneration; \( P = 0.03, \) hazard ratio = 2.89. Other factors analysed were atrial fibrillation, hypertension, chronic obstructive pulmonary disease, stroke, diabetes, preoperative angina, poor left ventricular function, renal dysfunction and extracardiac arteriopathy. There were no significant postoperative complications or operative mortality in those patients undergoing repeat surgery.

CONCLUSIONS: There is an unexplained incidence (3.6%) of EVD resulting in explantation in some patients at 2 years after surgery. Mitroflow valves may not be suited to a younger age population.

Keywords: Aortic valve replacement • Structural valve degeneration • Bioprosthetic valves

INTRODUCTION

Prosthetic valve degeneration is a recognized process following the implantation of biological prosthetic valves. Durability up to 15 years has been demonstrated with newer generation valves. The Mitroflow pericardial bioprosthesis valve (Sorin Group Canada, Inc., Mitroflow Division) has shown a low incidence of valve-related events and is recommended in patients above the age of 65. The rates of actuarial freedom from reoperation has been published in the literature at the 10-, 17- and 20-year follow-up, which demonstrate acceptable results [1–4]. Pericardial valves have been recommended by some to be used in an older patient population [5, 6]. Although European guidelines recommend the use of biological valves in patients aged 60–65, the national adult cardiac surgical database report has noted an observed increase in their use in younger age groups. Thus, it has been recommended that individual centres track outcomes [7, 8].

The main outcome measures of this study were to determine the incidence of early structural valve degeneration (SVD) and to identify possible risk factors within our patient population who have undergone aortic valve replacement with Mitroflow pericardial valves.

MATERIALS AND METHODS

We retrospectively analysed a prospectively collected database of 281 Mitroflow valves implanted in the aortic position during 1999–2013 at our institution. Valves were implanted in a standard surgical technique. All procedures were performed on standard cardiopulmonary bypass with cooling of the patient. The majority of our patient cohort received cold blood cardioplegia, while a minority received crystalloid fluid. Our study cohort was not limited to isolated aortic valve replacements.

The indication for surgery in all patients was SVD presenting as either stenosis, regurgitation or mixed disease. Surgical intervention was decided upon following collaboration between the cardiac surgeon and the cardiologist, thus both echocardiographic as well as clinical indications for redo surgery were present. Degenerative changes were confirmed during intraoperative visual examination, typically showing macroscopic calcification and architectural destruction of the valve itself.

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Multiple studies have shown acceptable durability of the Mitroflow valve at 10 years [1–4, 9]. We therefore included all patients undergoing redo surgical valve replacement for SVD within 10 years of implantation in our analysis (n = 15, Group 1). In this study, we classified cases of early valve degeneration (EVD) as those who needed redo surgery within 6 years of initial implantation (n = 10). Additionally, a subgroup analysis was performed in this cohort of patients. Both Group 1 and the subgroup were compared against all patients who had Mitroflow aortic valves implanted who did not require redo surgery for SVD (n = 266, Group 2). The study was carried out in accordance with the American Association for Thoracic Surgery/Society for Thoracic Surgeons/European Association for Cardio-Thoracic Surgery guidelines for reporting valve morbidity and mortality to the best of our abilities [10].

Statistical analysis was performed using MedCalc for Windows (MedCalc Software, Ostend, Belgium). Continuous variables were analysed using unpaired t-tests and categorical variables analysed using either the χ² test or Fisher’s exact test for values <5 within a contingency table. Freedom from reoperation was estimated by Kaplan–Meier actuarial analysis. Patient characteristics in both the 10-year and 6-year groups were compared with those who had Mitroflow valves inserted and not requiring re-replacement. Analysis was performed using univariate analysis and Cox proportional hazard multivariate regression analysis. Preoperative factors included in the Cox regression model included the following: angiography, previous myocardial infarction, previous cardiac surgery, diabetes, smoking history, hypertension, chronic obstructive pulmonary disease (COPD), extracardiac arteriopathy, atrial fibrillation, poor left ventricular (LV) function, elevated creatinine (>120 μmol/l) and age >65. Odds ratios (ORs) were calculated from standard logistic regression analysis and hazard ratios (HRs) were calculated from Cox regression analysis with 95% confidence intervals (CIs). A P-value of <0.05 was considered statistically significant. The linearized rate of reoperation was calculated as the number of events per 100 patient-years in the cumulative follow-up.

RESULTS

A total of 1495 tissue valves were implanted in the aortic position at our institution over the past 14 years. This comprised 275 (18%) Mitroflow valves. There were 15 (5%) cases of patients returning to the theatre for redo aortic valve replacement due to SVD within 10 years of implantation. A substantially high number (n = 10, 67%) of these degenerated within 6 years, resulting in clinical symptomatic deterioration necessitating redo aortic valve replacement. Three valves degenerated within the second year of insertion, one in the fourth, two in the fifth and four in the sixth. The median age in Group 1 was 60 (interquartile range (IQR): 46–71) and 74 in Group 2 (IQR: 66–78). The median time to reoperation in our series was 5.9 years (±1.9). Further preoperative demographics are displayed in Table 1.

The most common native valve pathology was degenerative disease: 73 and 82% in Groups 1 and 2, respectively. The commonest cause for explantation in Group 1 was stenosis (n = 11, 71%). This remained unchanged in our subgroup at 6 years (n = 8, 80%). The sizes of explanted valves were as follows: 19 mm = 2 (7.5), 21 mm = 5 (33), 23 mm = 5 (33) and 25 mm = 3 (20%).

Intraoperatively, there were no differences between the two groups. A majority received cold blood cardioplegia (n = 12, 80% and n = 201, 76%) and were cooled to ~30° (mean 31 ± 1.8 and 29.3 ± 3°) for Groups 1 and 2, respectively. Additionally, there were no statistically significant differences in the mean bypass time (Group 1 = 96.9 min ± 43.8, Group 2 = 106.9 min ± 40.9, P = 0.47, CI = −10.9 to 22.4) and the mean cross-clamp time (Group 1 = 63.8 min ± 27.4, Group 2 = 106.9 min ± 40.9, P = 0.43 CI = −16.6 to 36.7) in both groups.

Postoperatively there were no significant in-hospital events in Group 1, thus making comparison in this regard insignificant. There were no in-patient deaths in Group 1. In Group 2, there were 5 in-patient deaths; these cases were not counted in our actuarial freedom from SVD analysis. As the main purpose of this study was to evaluate preoperative risk factors specifically for SVD, further analysis towards postoperative complications was not conducted.

The median effective orifice area index (EOAI) of explanted Mitroflow valves was 1.3 cm²/m² (IQR: 1.1–1.65). There were no identified cases with an EOAI <0.85 cm²/m². Therefore, we do not feel that patient–prosthesis mismatch was a potential risk factor for early SVD in our series.

The preoperative demographics analysed as potential risk factors included age <65, atrial fibrillation, hypertension, chronic obstructive pulmonary disease, stroke, diabetes, preoperative angina, poor LV function, previous cardiac surgery, renal dysfunction (serum creatinine >120 μmol/l), smoking and extracardiac arteriopathy. Comparison of Groups 1 and 2 demographics by univariate analysis demonstrated age <65 to be a statistically significant predictor of SVD at 10 years (OR: 3.74, CI: 1.38–10.1, P = 0.01). This was also significant in Cox proportional multivariate analysis (HR: 2.9, CI: 1.0–7.7, P = 0.03). In our subgroup analysis at 6 years, age <65 trended towards significance in univariate analysis only (OR: 3.18, CI: 0.96–10.49, P = 0.057). No other preoperative demographics were shown to be predictors of EVD. These results are summarized in Tables 2–5.

### Table 1: Preoperative demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group 1, n = 15</th>
<th>Group 2, n = 266</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (%, SD)</td>
<td>60 (46–71)</td>
<td>74 (66–78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Angina</td>
<td>10 (66%)</td>
<td>131 (49%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2 (13%)</td>
<td>52 (20%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>1 (7%)</td>
<td>13 (5%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (7%)</td>
<td>45 (17%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (47%)</td>
<td>123 (46%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (53%)</td>
<td>162 (61%)</td>
<td>0.56</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (13%)</td>
<td>37 (14%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Extracardiac arteriopathy</td>
<td>2 (13%)</td>
<td>18 (7%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (13%)</td>
<td>32 (12%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Poor LV function</td>
<td>2 (13%)</td>
<td>20 (8%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>1 (7%)</td>
<td>45 (17%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>27.8 (4.9)</td>
<td>28.8 (19.9)</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean additive</td>
<td>6.7 (3.1)</td>
<td>8 (2.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>9.7 (8.3)</td>
<td>11.8 (9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean logistic EuroSCORE</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

EOAI: chronic obstructive pulmonary disease; EuroSCORE: European system for cardiac operative risk evaluation; LV: left ventricular; MI: myocardial infarction; BMI: body mass index.

Continuous variables expressed as the median (interquartile range) and categorical variables given as a number (percentage).
DISCUSSION

The incidence rate of SVD was 5% at 10 years since implantation and 3.6% at 6 years since implantation. Our rate of actuarial freedom from reoperation for SVD was 97 at 6 years and 92.5% at 10 years (Fig. 1). Our linearized rate of reoperation was 0.7% patient-year for all age groups (CI: 0.9–1.2), 1.8%/patient-year for those 65 and younger (CI: 0.9–3.4) and 0.3%/patient-year for those older than 65 (CI: 0.1–0.7). Yankah et al. [9] demonstrated a rate of actuarial freedom from SVD of 89.5 at 10 years and 71.8% at 20 years in their large analysis of 1513 Mitroflow pericardial valves. Additionally, their linearized rate of degeneration was 1.4% per patient-year. Their large series supported the conclusion that Mitroflow valves were comparable to other types of available bioprosthetic valves.

The only significant predictor of SVD within 10 years of implantation was age. On initial comparison between Groups 1 and 2, a statistically significant difference existed with regard to age. However, we feel this is due to the fact that younger patients with SVD are more likely to be offered higher-risk redo surgery and this was our primary indicator for SVD. Those aged <65 had roughly a 3-fold increase in their risk for developing SVD, with a majority of these cases developing SVD within the first 6 years.
The rate of actuarial freedom from SVD in those aged >65 was 95% but only 85% in those aged <65 (Fig. 2). Our linearized rate of degeneration went from 0.3 to 1.8/patient-year once age became >65. The pathogenesis of how or why this occurs is still uncertain. A study involving microscopic analysis of explanted valves revealed the presence of calcification, pannus, thrombus and inflammatory cells as well as collagen disruption [11]. It is hypothesized that differences in the shape, structure and dynamic function place pericardial valves in a different risk category from their porcine counterparts. In an earlier study performed at the same centre, Yankah et al. found that the 10-year rate of actuarial freedom from SVD was 87%. Additionally, they found that a younger age (<50) was found to be a significant risk factor for SVD at univariate analysis [12].

There are many studies in the literature that have shown an acceptable rate of SVD in Mitroflow valves. It is ideally suited to elderly patients with multiple comorbidities [13]. In a study by Pomar et al. [3] 161 Mitroflow valves were implanted over a 10-year period. They found the linearized rate of degeneration higher in their younger cohort of patients. The rate of developing SVD was 3.13%/patient-year in the 60–69 age group and 1.2%/patient-year in the >70 age group. A retrospective analysis of 152 patients (mean age of 79.5) by Sjögren et al. [14] demonstrated a rate of actuarial freedom from SVD of 99 at 5 years and 82% at 10 years. Another retrospective study by Jameson’s group demonstrated that the rate of actuarial freedom from SVD at 10 years for those aged over 65 was 85% [15]. These findings are similar to our own. Minami et al.’s [4] large study of 1044 patients showed a 10-year actuarial freedom rate from SVD of 77.6% in all patients but this improved to 85.8% in those aged >70 with a valve diameter ≤23 mm. Pomar’s group similarly found Mitroflow valves to be preferable in patients older than 70 when compared with those in their 60s. Their rate of developing SVD was 3.13 vs 1.2%/patient-year, respectively [5]. Favourable long-term results of Mitroflow valves have been validated in other studies up to 20 years, also advocating their use in patients older than 70 years of age [12, 16, 17]. Benhameid’s group looked at outcomes after 15 years in 161 patients. The rate of actuarial freedom from SVD at 15 years was 80.8% in patients older than 70 but only 62% in those in the 60–69 age group [18].

In contrast, there have also been published papers demonstrating poor functional outcomes with the use of Mitroflow valves. Examination of explanted valves by Lenardri’s group identified that collagen degeneration was an important causative factor. Additionally, there were lipid infiltration, pannus growth and atheromatous reactions. They state that the mode of failure originates from a tear occurring near the commissure, leading to further structural changes within the cusp tissue. The incidence rate of SVD was ~13% in their study [19]. Similar morphological changes have been seen in smaller studies and concerns have been raised regarding the methods of valve production including but not limited to harvesting, processing and preservation [11]. Additionally, Alvarez et al. [20] looked at 491 patients for a median follow-up of 3.4 years. Despite their older patient population (median age 76.5), the incidence rate of SVD was 4% with a median time to reoperation of 6.3 years. The Carpentier-Edwards pericardial valve has a documented rate of actuarial freedom from SVD of 98 and 96% at 5 and 10 years, respectively. In a comparative study between Carpentier-Edwards and Mitroflow valves, superior performance was observed in the latter with regard to durability (SVD rate of 2.3 vs 5.4%/patient-year) [21].

The main purpose of this study was to evaluate our centre’s experience with Mitroflow valves as we had noticed a fairly high incidence of early SVD within our patient population. Additionally, we wished to see if we could identify any potential risk factors for EVD. Despite analysing a variety of comorbidities, age <65 was the only statistically significant risk factor. Regression analysis showed it to be a highly significant predictor in SVD within 10 years of implantation and tended towards significance in 6 years of implantation. We suspect this would have been significant in a larger cohort of patients. This is relevant as there are specific groups of patients younger than 65 who may require biological valve replacement to avoid warfarinization or those who refuse by choice. Additional limiting factors in this study are as follows. Owing to absent data, we were unable to obtain the size of all Mitroflow valves implanted. This would have aided in further subgroup analysis as there is evidence to support better performance of this valve in smaller aortic roots [4]. And finally, due to a lack of up to date survival data, the actual freedom from SVD could not be accurately calculated, thus limiting the extent we can report on this valve.

**CONCLUSION**

There is an unexplained incidence of EVD resulting in explantation in some patients at 2 years after surgery. Mitroflow valves may not be suited to a younger age population. Further evaluation with a larger sample size is needed to draw more definite conclusions.

**Conflict of interest**: none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr J. Pepper (London, United Kingdom): Early structural degeneration of tissue valves in the 21st century is unusual. You say the patients you chose were between the ages of 60 and 65; I assume you mean over the age of 60 or 65, because otherwise it’s a very narrow age limit. My concern is that although the statistics have been done carefully, exactly what factors were chosen as potential incremental risks in your Cox regression is not clear. And I would like to ask you some specific questions about how these operations were done.

Now, you mentioned your limitations. You don’t know the size of all the Mitroflow valves. I mean that’s fairly serious. You must know the size of the valves that were inserted. So that’s the first question. The second question is: Was transesophageal echo used during these operations, and do you know what the effective orifice area was after these valves were inserted?

The next point I’d just like to make is that when you use stented bioprothethic valves, you’re not in too small a valve, you’re going to get problems. And the last thing I’d like to ask you, What was your policy for anticoagulation? Did you anticoagulate these patients briefly, or was it restricted only to patients who had another indication such as atrial fibrillation?

Dr Joshi: The first question was about the selection of risk factors?

Dr Pepper: Well, yes, the selection of risk factors, how did you go about that?

Dr Joshi: Well, primarily, it was based on my literature review of other papers to see what had been found in other studies, and also what information was available. Our main limiting factor is that it is a retrospective study, and in our database there were a few other issues. For example, history of MI or peripheral vascular disease which, to the best of my knowledge, have not been found to be predictors in other studies, but I thought I would include them in our analysis to see whether or not there could be any potential.

Dr Pepper: Well, I would suggest that knowing the size of the valve is quite important.

Dr Joshi: Yes.

Dr Pepper: And also, how did you insert the valve? Did you use everting mattress sutures? Did you use continuous sutures? All these things make quite a difference, particularly if you used everting mattress sutures. Do you know the answer to that? Probably not, if you don’t even know the size of the valves.

Dr Joshi: I would be guessing if I did.

Dr Pepper: And what about the echo, do you have transesophageal echo data from the patients at operation?

Dr Joshi: We do have up to a certain time period. The problem is because this study goes back to 1999, getting that data for all patients in order to, I think, show any significant results, it was not possible.

Dr Pepper: And the last thing was, did you have a policy for anticoagulation? I mean some people anticoagulate for 2 or 3 months in all bioprosthetic valves; did you do that?

Dr Joshi: In our centre the only drug that they’re on is aspirin.

Dr Pepper: So you didn’t. Okay.

Dr Joshi: No.

Dr H. Vetter (Wuppertal, Germany): I think one point about a Mitroflow valve, the first model of which was introduced in 1984, is that everybody hoped that this would be the pericardial valve bioprosthesis with good long-term durability. However, we got results, long-term results, rather late. Do you agree with that?

Dr Joshi: I would agree with that. But for our particular study we only looked at short-term results. That was the main focus of this. In terms of long-term results, perhaps it’s something we could potentially look at. But I think one of the limitations is obviously that our patient cohort is very small. It’s not a very big centre. But perhaps in the future it’s something that we could add.

Dr M. Deja (Katowice, Poland): It’s more a comment than a question. I find it personally disturbing that there was a shift in the literature. In the beginning, we used to report structural valve deterioration, looking at the echo results. Nowadays, you are talking about structural valve deterioration, and although you actually acknowledge that this is based on reoperation, and I guess, therefore, on patients’ symptoms rather than echo findings, you use SVD all the time. And this causes confusion because a lot of reports recently are mainly about reoperation rates and they are being compared with the results on real SVD from other reports, suggesting that the newer valves are actually better than the older valves which may not necessarily be the case.

Dr J. Kluin (Utrecht, Netherlands): Was the Mitroflow the only valve you were using in your institution? Maybe you told us at the beginning, but I missed it.

Dr Joshi: No, it’s not the only valve. In total, it was probably about 20% of the biological valves that were put in over the time period.

Dr Kluin: But you didn’t look at the other valves, if they had the same problem, I mean, in this age group?

Dr Joshi: We have not looked into other valves in our centre. It was just simply noted through observation that Mitroflow valves had degenerated early which was what prompted this study.

Dr Kluin: So it becomes more a Mitroflow thing now, but maybe it’s a biological valve problem, in general I mean.

Dr Joshi: It could be. Yes. Perhaps. But if we did look at all of the biological valves we might see similar outcomes.

Dr Vetter: Did you use the Mitroflow in the small annuli?

Dr Joshi: That’s, again, one of the limiting issues. Because I don’t know the size of the aortic roots. And there is evidence that shows that it is beneficial and it has better outcomes than those when it’s implanted in size 23 mm or less. It would have been useful. Unfortunately, I have not included it in the study.