CryoLife O’Brien aortic stentless prosthesis reoperations: clinical results and morphologic findings

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Abstract

OBJECTIVES: The CryoLife O’Brien (CLOB) stentless porcine aortic prosthesis has shown limited long-term durability, but its deterioration mechanisms have not yet been identified. The aim of this study was to review our experience with CLOB reoperations and to investigate the pathobiology of structural valve deterioration (SVD).

METHODS: Between March 1996 and December 2010, 35 patients underwent reoperation 82 ± 43 months after a CLOB implant. Patient records were retrospectively reviewed and follow-up was 100% complete. Nine valves explanted for SVD underwent pathological study.

RESULTS: Nineteen patients (54%) were operated on urgently for prosthetic valve replacement. No intraoperative technical complications occurred, and only one patient underwent aortic root replacement. One patient (3%) died in-hospital. Prosthesis dysfunction was due to SVD in 27 patients, caused by cusp commissural tearing in 22. All the nine explanted valves submitted to pathological examination showed calcifications and lipid insudation. At histology, eight prostheses disclosed cholesterol clefts and all showed a chronic inflammatory infiltrate. Transmission electron microscopy disclosed the presence of calcific deposits on cell debris and collagen fibres and confirmed the presence of cholesterol clefts. After a mean follow-up of 50 ± 33 months, survivals at 1, 5 and 7 years were 91 ± 5, 56 ± 9 and 38 ± 13%, respectively.

CONCLUSIONS: The CLOB reoperation is a feasible procedure, with satisfactory postoperative and mid-term survival results. Cusp tears, due to lipid and calcium deposits mostly targeting the commissures, seem to be the most important mechanism of SVD, resulting even in acute prosthetic incompetence and urgent reoperation.

Keywords: Heart valve • Stentless • Reoperation • Cardiac

INTRODUCTION

The CryoLife O’Brien (CLOB) stentless porcine aortic prosthesis (CryoLife International, Kennesaw, GA, USA) has shown good haemodynamic performance, a favourable effect on left ventricular mass regression and excellent mid-term durability, and for these reasons it has been employed widely in the past [1–3]. However, its long-term durability has recently been demonstrated to be unsatisfactory [4], and, following reports of unexpected paravalvular leaks due to abscess formation along the suture lines without evidence of pathogens [5, 6] and a subsequent survey of the French Authority of Health (www.afssaps.fr/Infos-de-securite/Retraits-de-lots-et-de-produits/), the CLOB has been withdrawn worldwide from the market in February 2010. As a consequence, many patients who received a CLOB are expected to undergo reoperation in the future. According to its design and implant technique, CLOB reoperations could be less technically challenging than reoperations in patients treated with other stentless porcine aortic prostheses, which have recently been recognized to be a hard procedure and to confer an increased risk of death [7]. In addition, the mechanisms of CLOB deterioration have not been investigated, but, similarly to the other porcine stentless prostheses, haemodynamics and mineralization along with evidence of a chronic inflammatory infiltrate could play an important role [8–10].

The aim of this study was to review our surgical experience with the CLOB reoperations, focusing on intra- and postoperative morbidity and mortality results, and to present the pathological findings of nine CLOB explanted for structural valve deterioration (SVD), in order to unveil the underlying pathobiological mechanisms.

METHODS

Patients and definitions of terms

Between March 1996 and December 2010, after a mean of 82 ± 43 months (range 1–158) from CLOB implant, 35 of 185...
Caucasian patients (19%), treated at our Institution between 1994 and 2004 with a CLOB [4, underwent reoperation, 32 (91%) at our Institution and the remaining 3 (9%) at 2 other hospitals. Actually, 39 patients (36% males, mean age 83 ± 9 years, range 41–98 years) still carry a CLOB prosthesis. Patient records were retrospectively reviewed and, after a mean of 50 ± 33 months (range 1.3–132 months) from CLOB explant, follow-up was 100% complete (1736 months) and was carried out by contacting surviving patients at home or their physician by phone. Preoperative patient characteristics are reported in Table 1.

An urgent operation was defined as an operative procedure performed during the same hospital admission for diagnostic evaluation and an emergency operation as a procedure performed on unstable patients before the start of the next working day. Prolonged hospital stay was defined as a hospital stay requiring ≥ 14 days and prolonged mechanical ventilation time as a ventilation support requiring ≥ 96 h. Descriptions of morbidity and mortality were based on guidelines for reporting morbidity and mortality after cardiac valve surgery [11]. The occurrence of SVD and non-structural valve dysfunction events was definitely determined by intraoperative valve inspection.

Unlike a recent survey of the Working Group for Aortic Valve Surgery of the German Society of Thoracic and Cardiovascular Surgery [12], the term ‘cusp’ was preferred to ‘leaflet’ at the ventricular-arterial junction. At our Institution, in the absence of an international consensus document, the term ‘cusp’ is usually adopted at this level and the term ‘leaflet’ at the atrio-ventricular junction. Moreover, the term ‘bicuspid’ instead of ‘bi-leaflet’ is usually used to describe a native aortic valve with two components. Concerning the meaning of commissural tear, ‘commissure’ is intended to be the point where two cusps or leaflets come closer and, at the ventricular-arterial junction, corresponds to the top apex of the intercuspal triangle. Finally, the term native aortic ‘annulus’ refers to the basal part of the cusp, corresponding to the lowest cuspal hinge.

The study was approved by the hospital ethical committee that waived the need for patient consent to the study.

Pathological examinations

Nine CLOB explanted at reoperation were fixed in 10% formalin and sent to the Cardiovascular Pathology Unit of the University of Padua for detailed X-ray, gross, histological, ultra-structural and atomic absorption spectroscopy (AAS) examinations (Table 2).

The study protocol consisted of gross examination, photography with a stereoscope and X-ray for semi-quantitative analysis of Ca²⁺ deposits (0–4 score, defined as follows: 0: none; 1: mild; 2: moderate; 3: severe and 4: massive calcium deposits) [13]. A histopathological study with haematoxylin–eosin, Heidenhain-trichrome, elastic-van-Gieson and Von-Kossa stains was then performed. The presence of calcification, inflammatory infiltrates, foreign body reaction, foam cells and cholesterol clefts was carefully assessed. In particular, the presence of cholesterol clefts was semi-quantitatively evaluated on the histological sections at >80 magnification fields with a 0–4 score according to the area extent of lipid infiltration: grade 0: none; grade 1: ≤ 25%; grade 2: 25–50%; grade 3: 50–75%; grade 4: >75–100%.

For transmission electron microscopy, ultra-thin sections were stained with uranyl acetate and lead citrate. Residual cusp tissue underwent AAS analysis of calcium (Ca²⁺) and phosphorus (P) content (mg/g dry weight).

Data analysis

This study was a retrospective analysis of prospectively collected data. SPSS for windows release 20.0 (SPSS, Chicago, IL, USA) was used to perform data analysis. Categorical and continuous variables are summarized as percentages and means ± SD, respectively. The non-parametric two-sample Wilcoxon rank-sum test was used to compare the CLOB and new prosthesis diameters. Survival estimates were calculated by the product-limit method of Kaplan–Meier and their 70% confidence interval (CI) reported. The primary end point was mortality for any cause, and secondary end point, prolonged hospital stay (≥14 days). Univariate associations with mortality and prolonged hospital stay for pre-, intra- and perioperative variables were obtained using the Fisher’s exact test for categorical variables, and the non-parametric Mann–Whitney test for the continuous variables and two-tailed P-values ≤ 0.05 were considered significant.

RESULTS

Operative data

The indication for surgery was prosthetic valve incompetence in 29 patients and steno-incompetence in 6. Operative results

<table>
<thead>
<tr>
<th>Table 1: Preoperative and operative characteristics (35 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative variable</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
</tr>
<tr>
<td>Standard EuroSCORE</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>NYHA Class</td>
</tr>
<tr>
<td>Native bicuspid aortic valve</td>
</tr>
<tr>
<td>Second time reoperation</td>
</tr>
<tr>
<td>Implanted CryoLife 300 prosthesis size &lt; 23 mm (n, %)</td>
</tr>
<tr>
<td>Implanted CryoLife 300 prosthesis size ≥ 23 mm (n, %)</td>
</tr>
</tbody>
</table>

Operative variable

- Cardiopulmonary bypass time (min): 169 ± 71 (range: 119–250)
- Cross clamp time (min): 119 ± 53
- Operative priority: Elective 16 (46); Urgent 19 (54); Emergent 0
- Implanted prosthesis size (mm, median): 21
- Implanted prosthesis size < 23 mm (n, %): 25 (74); Implanted prosthesis size ≥ 23 mm (n, %): 9 (26)
- Associated procedures: CABG: 5 (14); Mitral valve surgery: 4 (11); Bentall: 1 (3); Separate aortic valve + ascending aorta replacement: 1 (3)

CABG: coronary artery bypass graft.

Values are expressed as mean ± SD or n (%).
### Table 2: Clinical, pathologic, X-ray and AAS data of nine CLOB explanted for SVD

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at implant (years)</th>
<th>Sex</th>
<th>Year of intervention</th>
<th>CLOB Size (mm)</th>
<th>Time in place (months)</th>
<th>Dysfunction</th>
<th>Gross pathology</th>
<th>X-ray (Ca^{2+} scores 0–4)a</th>
<th>Cholesterol clefts (scores 0–4)b</th>
<th>Foreign body reaction</th>
<th>Foam cellsc</th>
<th>Cusp haematoma</th>
<th>Ca^{2+} content (mg/g dry weight)</th>
<th>P content (mg/g dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>Female</td>
<td>1995</td>
<td>21</td>
<td>133</td>
<td>AR</td>
<td>Commissural tear RC-LC, fraying</td>
<td>2</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>11.8</td>
<td>11.4</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>Male</td>
<td>1995</td>
<td>25</td>
<td>127</td>
<td>AR</td>
<td>Commissural and basal tear LC</td>
<td>3</td>
<td>3</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>94.4</td>
<td>56.6</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>Female</td>
<td>1995</td>
<td>25</td>
<td>132</td>
<td>AR</td>
<td>Commissural tear RC, fraying</td>
<td>2</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>22.5</td>
<td>16.2</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>Male</td>
<td>2003</td>
<td>21</td>
<td>53</td>
<td>AR</td>
<td>Commissural tear NC-RC, fraying, cusp perforation</td>
<td>2</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>4.4</td>
<td>7.9</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>Male</td>
<td>1998</td>
<td>25</td>
<td>114</td>
<td>AR</td>
<td>Commissural tear RC-NC</td>
<td>4</td>
<td>3</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>33</td>
<td>6.2</td>
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<tr>
<td>6</td>
<td>50</td>
<td>Male</td>
<td>1996</td>
<td>21</td>
<td>145</td>
<td>AR</td>
<td>Commissural tear NC</td>
<td>3</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>174.4</td>
<td>99.5</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>Female</td>
<td>1997</td>
<td>27</td>
<td>147</td>
<td>AR</td>
<td>Commissural tear NC</td>
<td>2</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>59.2</td>
<td>33.5</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>Female</td>
<td>1997</td>
<td>21</td>
<td>158</td>
<td>AR</td>
<td>Commissural tear NC</td>
<td>2</td>
<td>3</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>6.6</td>
<td>9.8</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>Male</td>
<td>2002</td>
<td>27</td>
<td>97</td>
<td>AR</td>
<td>Commissural tear NC-RC</td>
<td>2</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

AR: aortic regurgitation; LC: left coronary cusp; NC: non-coronary cusp; RC: right coronary cusp.

aCalcium score: grade 0 = none; grade 1 = mild; grade 2 = moderate; grade 3 = severe and grade 4 = massive calcium deposits.

bCholesterol clefts: grade 0 = none; grade 1 ≤ 25%; grade 2 = 25–50%; grade 3 = 50–75%; grade 4 = 75–100%.

c×100 magnification field.
are reported in Table 1. Nineteen patients (54%) were operated on urgently: 12 patients (34%) presenting at hospital admission with acute heart failure and pulmonary oedema, 2 (6%) with a diagnosis of acute endocarditis, 3 (9%) with chronic heart failure and worsening dyspnoea and 2 (6%) with unstable angina.

The prosthesis was replaced in 34 patients (17 with biological and 17 with mechanical valve prostheses) (97%) and re-sutured in 1 (3%). In the latter case, who underwent reoperation in 1996, 22 months after the original procedure, the prosthesis appeared partially detached at the level of the left and non-coronary cusps without any sign of infection and with preserved and pliable leaflets, favourable for an easy resuture. In addition, at that time, no CLOB SVD had been yet reported.

After median re-sternotomy and removal of pericardial adhesions, cardiopulmonary bypass was instituted by canulating for venous drainage the right atrium in 30 patients (86%) and the superior and inferior caval veins separately in the remaining 5 (14%), and for arterial return, the ascending aorta in 25 patients (72%), a femoral artery in 5 patients (14%) and the aortic arch in 5 (14%). Surgery was carried out under moderate body hypothermia, after antegrade and retrograde infusion of cold crystalloid cardioplegia (St. Thomas). Through an aortic transverse incision, the CLOB prosthesis was carefully inspected and the pathological findings were recorded. In most cases, only the cusps were removed. The new prosthesis was implanted by passing stitches through the native aortic annulus and, whenever possible, the CLOB porcine aortic wall component, which had been previously used to suture the CLOB to the native aorta in a supra-annular position, after its decalcification in eight patients (23%). In three patients (9%), the decalcification procedure was more complex, requiring the suture of an aortic wall tear at the level of the left coronary sinus in one case. Operative technical complications were reported in three patients (9%): two cardiopulmonary bypass re-institutions (one aortotomy repair and one additional aorto-coronary bypass) and one right subclavian artery repair, dissected during an unsuccessful cannulation attempt at the beginning of operation.

Mean new prosthesis size was 21 ± 2 mm (range 17–27, median size 21 mm), significantly smaller than the mean previously implanted CLOB size of 24 ± 2 mm (range 21–29) (P = 0.0003, at the two-sample Wilcoxon rank-sum test). No patient underwent aortic annulus patch enlargement. At the pre-discharge echocardiographic evaluation, peak and mean pressure gradients (mmHg) were 22 ± 9 (range 12–51) and 11 ± 5 (range 6–29), respectively. Two patients, who received a 19 mm mechanical prosthesis, presented with high prosthesis pseudo-gradients, with an indexed aortic valve area of 0.76 and 0.79 cm²/m², respectively, which were stable at last echocardiographic control.

Pathological findings

According to the intraoperative prosthesis inspection, 27 patients (77%) underwent reoperation because of SVD and 8 patients (23%) because of a non-structural valve dysfunction. Among these last eight patients, three patients presented a paravalvular leak without evidence of infection, two patients a severe prosthesis regurgitation due to lack of central cusp coaptation related to aortic root ectasia and three patients a preoperative echocardiographic evidence of prosthesis endocarditis, not confirmed at intraoperative inspection, with the explanted prostheses showing no signs of infection. In these last three patients, in contrast to the French Authority of Health survey, prosthesis dysfunction was due to the presence of a peri-prosthetic abscess cavity not involving the suture line (n = 2) and to the detachment of a patch employed to close an abscess cavity during the previous operation for acute endocarditis and to which the CLOB had been sutured (n = 1). Mean time to valve replacement or re-suture in patients with non-structural valve dysfunction was 31 ± 29 months (range 1–78).

Among the 27 patients operated on for SVD, the most common dysfunction mechanism was cusp or commissural tear (22 patients, 81%). Calculifications, mostly involving the suture line, and cusp prolapse of the non-coronary cusp were observed macroscopically in 15 and 3 cases, respectively. Mean times to SVD diagnosis and to valve replacement were 89 ± 33 months (range 11–147) and 97 ± 34 months (range 12–158), respectively.

Clinical, pathological, X-ray and AAS data of the nine CLOB explanted prostheses are reported in Table 2. At gross and X-ray examination, calcification was identified in all nine explanted CLOB and was massive (4+) in one, severe in two (3+) and moderate (2+) in six, involving in all the commissures (Fig. 1). Lipid insudation in the form of yellow spots was observed by the naked eye in all nine explants. Cusp commissural and belly tearing were observed in all explants, thus accounting for incompetence as a dysfunction mechanism. It was related at histology to calcium deposits in all and to lipid insudation, with cholesterol clefts, and lipid-laden macrophages (foam cells) in eight (Fig. 1). Additionally, mononuclear inflammatory cell infiltrate was observed in all explants, giant-cell foreign-body reaction in five, and dissecting haematomata of a cusp in one.

Transmission electron microscopy disclosed the presence of calcific deposits on cell debris and collagen fibres and confirmed the presence of cholesterol clefts (Fig. 2). The mean Ca²⁺ and P content at AAS was 50.6 ± 64.7 mg/g dry weight (range 3.3–174.4) and 30.1 ± 32.8 mg/g dry weight (range 6.2–99.5).

Perioperative morbidity and mortality results

Perioperative morbidity results are reported in Table 3. Eleven patients (31%) showed no major or minor complications postoperatively, but 16 patients (46%) showed a prolonged (≥14 days) postoperative course, 6 patients requiring 30 days or longer. No preoperative or intraoperative variable showed a statistically significant association with prolonged hospital stay. No intraoperative or early (<30 days) deaths were reported. One patient (3%) died in hospital as a consequence of postoperative complications, almost 3 months after the reoperation. After a mean follow-up of 50 ± 33 months, there were 15 late deaths (43%), 11 being cardiac-related, i.e. due to chronic heart failure and 7 valve-related (1 due to haemorrhagic stroke; 2 to aortic prosthesis endocarditis, only 1 necropsy-confirmed; 1 to chronic heart failure worsened by bioprosthesis dysfunction; the remaining 3 patients died suddenly at home). At 1, 5 and 7 years, survival was 91 ± 5% (70% CI, 84–95%), 56 ± 9% (70% CI, 46–65%) and 38 ± 13% (70% CI, 24–51%), respectively (Fig. 3). Among pre-, intra- or perioperative variables, only chronic congestive heart failure showed a significant association with mortality for any cause (P = 0.036).
DISCUSSION

Even if the CLOB has recently been withdrawn from the market following the survey of the French Authority of Health and is no longer employed worldwide, patients who received a CLOB in the past are still at risk of developing SVD requiring reoperation and could benefit from the messages that may be extrapolated from this study.

In comparison with the stented counterparts, few case series on stentless valve reoperations have been reported so far [7, 14, 15]. Reoperations in patients with porcine stentless prostheses showed increased technical and operative challenges, with a high incidence of aortic root replacement procedures, mainly due to severe calcification of the stentless valve and surrounding root and adhesions between the subcoronary stentless valve and the native aortic wall, which often required extensive dissection with the risk of damaging the coronary ostia, aortic wall and annulus, with a high perioperative mortality risk [7]. In contrast, no intraoperative complications specific to CLOB explant were reported in our study, and only one patient

Figure 1: Gross, X-ray and microscopic findings of a CLOB valve explanted for SVD after 127 months because of incompetence (Case 2, Table 2). (A–C) gross features of left, right and non-coronary cusps: note the yellow appearance of the cusps due to lipid insudation. (D–F) corresponding X-ray appearance: note the bright signal at the level of commissural calcifications. (G–I) Von-Kossa stain histological sections of the corresponding cusps: note calcium deposits (black) and the cholesterol clefts and lipid deposits (white). Original magnification ×100.

Figure 2: Transmission electron microscopy findings (same case as Fig. 1). (A) Cholesterol clefts (*); (B) cholesterol cleft (*) and calcific deposits on collagen and cell debris.
Table 3: Perioperative morbidity (35 patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation time (days)</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>Intensive care unit stay (days)</td>
<td>6 ± 10</td>
</tr>
<tr>
<td>Postoperative hospital stay (days)</td>
<td>18 ± 15</td>
</tr>
<tr>
<td>Revision for bleeding</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Low cardiac output</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Strokes</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Sternal wound infection</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Limb ischaemia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>New dialysis</td>
<td>2 (6)</td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Intra-aortic balloon pump (IABP)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or n (%).

Figure 3: Actuarial survival. Patients still at risk are reported under the x-axis.

Although our population presented a high preoperative surgical risk, hospital mortality compares favourably with more recent series on stented prosthesis reoperations, which reported a hospital mortality ranging from 2 up to 15.5% [16-19]. In contrast, the worse postoperative morbidity in comparison with the stented case series could be explained by the higher number of patients who underwent operation urgently, among which 12 patients with SVD presented acute pulmonary oedema at hospital admission, due to an abrupt cusp tear with severe prosthesis regurgitation. In addition, since the presence of chronic heart failure due to or worsened by CLOB dysfunction was associated with a poorer long-term survival, patients with a CLOB prosthesis are currently followed-up at our institution by echocardiography twice a year and are encouraged to refer to the cardiologist or cardiac surgeon as soon as the signs of heart failure or deterioration appear. Since 2006, when the limited CLOB long-term durability was recognized and this follow-up strategy implemented, the number of urgent reoperations due to SVD has been significantly reduced from 75% (12 out of 16 patients) before 2006 to 36% (4 out of 11 patients) thereafter (P = 0.045).

Similarly to other porcine stentless prostheses [7, 14], the mechanisms leading to CLOB dysfunction are still debated. Paravalvular leak due to an unusual prosthetic-valve infective endocarditis [6] was not the most important prosthesis dysfunction mechanism in our case series, in contrast to the French Authority of Health survey [5]. In this last case, most paravalvular leaks were detected in prostheses implanted after 2004, when CLOB production moved from USA to Brazil, while all the CLOB explanted at our Institution were implanted before 2004. However, according to the company, no manufacture modification had been introduced at that time and this problem has not been reported in other worldwide case series so far. Moreover, the prevalence of endocarditis was lower in the CLOB case series (8.5%) than in other stentless reoperation series (12%) [7]. Thus, other mechanisms triggering a CLOB dysfunction should be investigated. Prosthesis distortion at the time of implant and progressive dilation of the ascending aorta, especially of the sinotubular junction, over the years have been proposed as possible mechanisms that could promote prosthesis SVD and regurgitation in patients with a Toronto SPV (St. Jude Medical, St. Paul, MN, USA), because of increased haemodynamic stress over the cusps [20]. This hypothesis can be extended also to patients with a CLOB, since implant symmetry is far more important with CLOB than with the Toronto SPV. Moreover, 9 patients in our case series showed some degree of ascending aorta ectasia and 12 had a native bicuspid aortic valve, which is usually associated with progressive aortic root dilation. Unfortunately, no serial diameters of the sinotubular junction were available in our series.

Similarly to the stented counterparts, it seems that the substrate underlying SVD should be searched at the microscopic level. In a case series of nine explanted Medtronic Freestyle (Medtronic Inc., Minneapolis, MN, USA) stentless aortic valves (mean duration 4.5 years), a chronic inflammatory infiltrate with macrophages both at the cuff and at the porcine aortic wall tissue was found in eight prostheses [8] and led to medionecrosis with disruption of elastic lamellae and smooth muscle cells. As a consequence, the porcine aortic root can dilate and prosthesis regurgitation develop, accounting for an increased haemodynamic stress on the cusps already weakened by the inflammatory reaction, which can eventually lead to cusp tear [8, 9]. In another series of 30 explanted Toronto SPV with a mean implant duration of 100.7 ± 27.8 months, 27 prostheses (90%)

underwent aortic root and ascending aorta replacement with a composite graft according to the Bentall technique due to aortic root and ascending aorta ectasia. The absence of technical challenges could be related to the particular CLOB design. In comparison with other porcine stentless aortic prostheses, the CLOB, constructed from non-coronary cusps of three different porcine aortic valves matched for size and symmetry, does not present any additional synthetic material, porcine muscular shelf and aortic root tissue corresponding to the Valsalva sinuses, thus explaining the absence of extensive calcifications and adhesions between the prosthesis and the aortic root. In addition, the CLOB is implanted in a suprannular position with a single suture line, thus excluding the need for patch enlargement procedures at reoperation. In contrast, the use of smaller new prosthesis diameters, in our experience, could be related to the common annular rigidity at reoperation, which prevents oversizing of the most frequently employed partially intra-annular seating prostheses. However, not all patients received an undersized new prosthesis, depending on the new prosthesis type (stented vs stentless), and the degree of decalcification and removal of the CLOB suture line.
showed SVD characterized by tissue degeneration, cusp tears, calcification and lipid insudation [21].

Similarly, in our experience, dystrophic calcification and lipid insudation with commissural tearing represented the main causes of CLOB SVD, jeopardizing its long-term durability. As previously demonstrated in stented bioprostheses [22], nuclei of mineralization were identified on cell debris and collagen at microscopy. Moreover, lipid insudation, which was evident even by the naked eye and confirmed at light and electron microscopic examination, may have favoured calcification [23]. In addition, signs of a chronic inflammatory reaction were detected in different amounts in all explanted prostheses (Table 2).

Even if clinical studies are discordant on the role of statins in slowing SVD, pathological studies show a constant relationship between lipid insudation, chronic inflammatory infiltrate and dystrophic calcification and suggest that SVD should share some affinities with atherosclerosis. In a recent study on 18 Medtronic Freestyle explanted for SVD due to cusp tear, it was suggested that the accumulation of oxidized LDL within the bioprostheses leaflets might have attracted and activated macrophages, which led to the formation of foam cells, and to the production of inflammatory cytokines and metalloproteinases, which in their turn accounted for collagen breakdown, a decreased leaflet resistance to haemodynamic stress and a greater susceptibility to tear formation [10]. These features suggest that serum lipid control with statins along with anticalcification strategies should be pursued to increase the durability of porcine valve xenografts.

However, the benefit of statins in slowing the evolution towards SVD has not yet been straightforwardly demonstrated [24] and randomized control trials are required.

The following study limitations can be identified in this study. The study population was reoperated on along a time span of 15 years with an incidence of 2.3 patients/year, and the small number of patients reoperated on per year could have influenced the postoperative morbidity results. However, this case series is one of the biggest re-operative case series concerning a single type of stentless prostheses.

Moreover, only 9 out of 27 explanted prostheses (33%) were available for pathological analysis. However, we started analysing the explanted prostheses only in 2006, when we became aware of the limited long-term durability of CLOB. Unfortunately, it was not possible to retrieve tissue from prostheses explanted before 2006 either at our Institution or elsewhere.

In conclusion, reoperation in patients with a CLOB prosthesis showed no operative complications related to the valve explant procedure. Valve in valve’ transcatheter aortic valve implant, already performed successfully in a patient with a CLOB [25], might be a reliable alternative option to reoperation. Strict clinical and echocardiographic follow-up is needed for preventing urgent procedures and to refer patients to surgery before the signs of heart failure appear or worsen, in order to reduce the perioperative morbidity and improve survival. Finally, the observation of commissural calcification in all cases with commissural tearing indicates a potential role of computed tomography of the aortic root for the identification of CLOB prostheses at risk of impending rupture.

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