Limited Long-Term Durability of the Cryolife O’Brien Stentless Porcine Xenograft Valve

Daisy Pavoni, MD; Luigi P. Badano, MD; Fabio Ius, MD; Enzo Mazzaro, MD; Romeo Frassani; Sandro Gelsomino, MD; Ugolino Livi, MD

Background—Despite the fact that early and midterm hemodynamic and clinical results of the Cryolife O’Brien (CLOB) stentless valve have been reported to be favorable, the long-term durability and clinical results of this valve are largely unknown. Accordingly, we analyzed 10-year outcomes after aortic valve replacement with this valve.

Methods and Results—From January 1994 to September 2004, 185 patients (67, 73, and 75 years, 25th, 50th, and 75th quartiles, respectively; 38% older than 75 years; 56% females) underwent aortic valve replacement with the CLOB valve. Sixty-eight percent of patients were in NYHA class 3 to 4. Standard EuroSCORE was 7.1±2.7. Pure aortic stenosis accounted for 42% (n=79), and pure insufficiency for 12% of cases (n=22). Concomitant surgery: 28% coronary artery bypass (n=51), 11% mitral valve replacement/annuloplasty (n=21), and 2% ascending aorta replacement (n=3). Sixty-one percent of patients received a 23-mm valve or smaller size. Follow-up was 100% completed, and cumulative follow-up was 65 months/patient. The 30-day mortality was 5.4% (none were valve related). Actuarial survival at 5 and 10 years were 68% and 40%, respectively. Actuarial freedom from structural valve deterioration was 91% at 5 years and dropped to 44% at 10 years. Actuarial freedom from reoperation was 94% at 5 years and declined to 57% at 10 years.

Conclusions—In a population with a high prevalence of elderly females with small aortic root, the CLOB valve demonstrated satisfactory clinical results till 8-years. Afterward, a significant increase in hazard for structural valve deterioration and reoperation occurred in late follow-up. (Circulation. 2007;116[suppl I]:I-307–I-313.)

Key Words: prostheses • follow-up studies • survival • valve surgery

S
tentless porcine aortic valve prostheses have been proposed to improve clinical outcomes after aortic valve replacement (AVR) due to improved hemodynamics.1–10 Early clinical studies of stentless valves showed hemodynamic parameters similar to homograft and even native aortic valves.3,5,6,8,10–13 It has been postulated that the superior hemodynamic performance of these valves will lead to enhanced durability attributable to lower mechanical stresses placed on the leaflet tissue.

The Cryolife O’Brien (CLOB) valve (Cryolife International, Atlanta, Ga) is a composite porcine stentless prosthesis first reported by O’Brien in 196714 and introduced into clinical practice in 1992.13 Satisfactory early and mid-term clinical and hemodynamic results after implant of the CLOB valve have been previously described, especially for elderly patients with a small aortic annulus.10,15,16 However, durability and long-term clinical results of the CLOB valve remain largely unknown.

Accordingly, the purpose of this study was to evaluate the long-term clinical outcomes and durability of the CLOB valve, by reviewing 10-year implants with this valve performed in our Institution.

Materials and Methods

Patients

Between January 1994 and September 2004, 185 patients underwent AVR with the CLOB valve. Patients risk stratification was performed according to the Standard European System for Cardiac Operative Risk Evaluation (EuroSCORE).18,19 Patients follow-up was 100% completed. One hundred fourteen patients were referred at our outpatient clinic for clinical examination and echocardiographic examinations scheduled at discharge, 6 months and 1 year since surgery, and yearly thereafter. The remaining 71 patients, who were followed at their referral hospitals using the same protocol, were contacted by means of telephone interview. For patients who were not followed at our outpatient clinic and had events, additional clinical data and echocardiographic reports were obtained from hospital records, family doctors, and referring cardiologists.

Inclusion criteria to implant the CLOB valve were:1 small aortic annulus,2 patient’s age greater than 65 years,3 or absolute contraindication to chronic anticoagulant therapy. Exclusion criteria for using the CLOB valve were:1 extensive calcification of the sinus aortic wall and root,2 annulus diameter >30 mm that precluded the use of a 29-mm valve, which is the largest available CLOB size,3 gross asymmetry of the aortic root,4 an extremely thin aortic wall,20

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The Valve

The Model 300 of the CLOB valve is a composite design, constructed from noncoronary leaflets of 3 porcine aortic valves. Leaflets are carefully excised from valves already fixed in a 0.35% glutaraldehyde solution under a very low pressure (<2 mm Hg). Further dissection is necessary to remove the remnant ventricle muscle. Individual leaflets are critically matched for size and symmetry to ensure competence, maximal coaptation, and synchronous opening. The composite valve is not treated by any antimicrobial process. Initial interrupted and then running sutures are placed along the free edges of the aortic wall, carrying the sutures to the full length of the leaflet commissures. A blanket stitch is placed to secure the inflow surface of the valve. The CLOB valve is implanted in a supraannular position, and this affords good exposure especially in the small aortic root, and provides a most effective central flow and a less obstructive orifice with low transvalvular gradients. At the time of valve introduction, the absence of additional synthetic materials (Dacron reinforcement) represented a significant difference with other stentless valves.

Surgical Technique

Operations were performed according to the standard technique described previously by Dr O’Brien. The CLOB valve was secured to the patient’s aortic root with a single continuous running suture. The patient aortic annulus was intraoperatively measured with a Hegar probe, and the selected valve was 1 size larger than the measured host annulus. Because the valve takes a supraannular position, the aortic annulus dimension indicates the internal diameter of the valve to be selected and the commercial size of the CLOB valve represents the external diameter of the valve. Thus, for an aortic annulus of 25 mm one should select a stentless valve of 27 mm, which offers an inflow diameter of 25 mm.

Echocardiographic Studies

Complete echocardiographic studies were performed using commercially available ultrasound machines (Hewlett-Packard Sonos 5500, HP, and VIVID 7 Dimension, GE Healthcare). The structural valve deterioration at echocardiographic study was defined in accordance with the definition of Edmund et al as presence of new onset significant prosthesis regurgitation, leaflet calcification, leaflet tear, or significant reduction of prosthesis effective orifice area.

Data Analyses

Descriptions of valve-related events and mortality were based on guidelines for reporting morbidity and mortality after cardiac valve surgery. SPSS for windows release 12.0 (SPSS, Inc) was used to perform data analyses. Continuous variables were summarized as means±SD. Discrete variables were presented as percentages. Repeated ANOVA measures were performed, where appropriate, to make comparisons among the various assessment points. Death and event-free survival estimates were calculated by the product-limit method of Kaplan and Meier and reported with 95% confidence interval. With this method, patients who die without ever having an event are regarded as those who might have suffered the condition had they lived. The log rank test was used to test the hypothesis that there was no difference in survival among groups. In all cases probability values lower than 0.05 were considered significant.

Responsibility

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Preoperative patients’ characteristics are summarized in Table 1. As expected, our study population was composed of elderly and overweight patients. Thirty-eight percent of patients were over 75 years old, and 11% were over 80 years old. Thirteen percent of patients were obese (ie, body mass index ≥30 Kg/m²). Patients were generally highly symptomatic (Table 1). Concomitant coronary artery disease was found in 78 patients (42%). The main indication for AVR was mixed aortic valve stenosis and regurgitation (Table 1). The aortic valve pathology at surgical inspection was degenerative in 160 cases (86%), rheumatic in 9 cases (5%), and acute endocarditis in 15 cases (8%). Only in 1 patient the cause of replacement was a prosthetic valve dysfunction. In 30 patients (16%) the native aortic valve was bicuspid. Among bicuspid valve patients, mean age at time of operation was 67±11 years; preoperative valve lesion was 43% pure aortic stenosis and 3% pure incompetence.

Operative data are summarized in Table 2. Sixty-one percent of patients received a 23-mm or a smaller size CLOB valve. Standard EuroSCORE was 7.1±2.7. At the time of AVR, 38% of patients underwent concomitant surgical interventions (Table 2). The most frequent early postoperative complication was atrial fibrillation (33%). Less frequent postoperative complications were mediastinitis (4%), bleeding (3%), low cardiac output (2%), cerebral ischemia (2%), and respiratory insufficiency (2%).

In 21 patients (12%) a trivial regurgitation of the CLOB valve was seen at predischarge echocardiogram; in 1 patient the prosthetic regurgitation was judged to be moderate. Among the 21 cases with trivial regurgitation, a progression toward moderate-severe regurgitation was documented in 7 patients. The causes of regurgitation progression were cusp thickening and calcification with retraction in 2 cases, cusp tears in 4 cases, and cusp prolapse in 1 case. In 16 patients...
(9%) a periprosthetic leak was detected at predischarge study. In 2 patients the leak was scored moderate, in the other cases it was classified as trivial.

Survival
The final clinical end points were determined on October 15, 2006. The mean follow-up period was 64±41 months (range 0 to 149 months). Cumulative follow-up was 65 months per patient. The early (30-day) mortality rate was 5.4%. Of the early deaths, no case was valve related, 6 cases were cardiac related (2 sudden deaths, 3 ruptures of the aorta, and 1 acute myocardial infarction), and 4 were non–cardiac-related (1 multiorgan failure, 1 respiratory insufficiency, and 2 sepsis).

Standard EuroSCORE was 9.1±3.7 in patients who died early. There were 64 late deaths (34%). Among late deaths, 20 were cardiac related, and 5 were valve related (Table 2). Standard EuroSCORE of patient who died late was 7.9±2.7. Actuarial survival curve of the whole study population is shown in Figure 1. No statistical difference was seen in survival stratified by sex, age, by presence of preoperative coronary artery disease, and by preoperative valve lesion (P=0.05 by the log rank test). Freedom from valve-related mortality at 5 and 10 years was 98% (95% CI 96% to 100%) and 90% (95% CI 80% to 100%), respectively. Freedom from cardiac-related mortality at 5 and 10 years was 89% (95% CI 85% to 94%) and 73% (95% CI 62% to 86%), respectively.

Nonfatal Valve Events
Structural valve deterioration was diagnosed in 33 patients. Seventeen patients underwent reoperation, whereas the other 16 patients remained under strict clinical and echocardiographic follow-up, because stable clinical conditions or because reoperation was considered to be a high risk procedure. Freedom from structural valve deterioration at 5 and 10 years was 91% (95% CI 86% to 97%) and 44% (95% CI 28% to 60%), respectively (Figure 2). The mean time of structural valve deterioration appearance was 74±33 months. Of the 33 patients with structural valve deterioration, 25% had a native bicuspid valve, and 24% showed a trivial aortic regurgitation of the bioprostheses at discharge. Nonstructural valve deterioration was diagnosed in 11 cases. Freedom from nonstructural valve deterioration at 5 and 10 years was 95% (95% CI 92% to 98%) and 94% (95% CI 86% to 97%), respectively.

Valve reoperation was required in 29 patients. Surgical gross examination was available for all these valves (Table 3). The most frequent reason for valve reoperation was leaflet

### Table 2. Operative and Follow-Up Data

<table>
<thead>
<tr>
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<th>(n=185)</th>
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<tbody>
<tr>
<td>Pump time, min</td>
<td>159±60</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>124±43</td>
</tr>
<tr>
<td>Prosthesis size, mm</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>59 (32%)</td>
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<tr>
<td>23</td>
<td>54 (29%)</td>
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<tr>
<td>25</td>
<td>50 (27%)</td>
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<td>27</td>
<td>16 (9%)</td>
</tr>
<tr>
<td>29</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Concomitant surgery*</td>
<td>70 (38%)</td>
</tr>
<tr>
<td>CABG</td>
<td>51 (28%)</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Mitral or tricuspid annuloplasty</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>Ascending aorta replacement</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>64±41</td>
</tr>
<tr>
<td>Range, months</td>
<td>0–149</td>
</tr>
<tr>
<td>All deaths</td>
<td>74 (40%)</td>
</tr>
<tr>
<td>Valve related</td>
<td>5/74 (7%)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>26/74 (35%)</td>
</tr>
</tbody>
</table>

Data are summarized as mean±SD and percentages. CABG indicates coronary artery by-pass graft.

*Some patients underwent more than one concomitant surgical procedure.
tear, which was observed in 48% of cases (14 of 29). Leaflet tears were all localized within the body of the leaflet (Figure 3); the most frequent culprit leaflet with a tear was the right coronary cusp (7 out of 14).

Five and 10-year freedom from valve reoperation for any cause was 94% (95% CI 90% to 97%) and 57% (95% CI 42% to 72%), respectively (Figure 4). The mean time of reoperation was 70±40 months. No statistical difference was seen in freedom from structural valve deterioration and from reoperation, when patients were stratified by native valve morphology (bicuspid versus tricuspid valve; \( P < 0.05 \) by the log rank test), by preoperative valve lesion (stenosis versus insufficiency versus mixed lesion; \( P > 0.05 \) by the log rank test), by year of operation and valve size (\( P > 0.05 \) by the log rank test). The mean time between structural valve deterioration detection and consequent reoperation or death was 11±14 months. Five and 10-year freedom from valve reoperation for SVD was 94% (95% CI 86% to 100%) and 19% (95% CI 5% to 40%), respectively (Figure 5).

Patients were not treated with warfarin sodium unless there was persistent atrial fibrillation or flutter (22% of cases; \( n = 41 \)). Thromboembolic events occurred in 13 patients (7%), with bleedings in 6 patients (3%). Actuarial freedom from thromboembolism at 5 and 10 years was 94% (95% CI 91% to 98%) and 89% (95% CI 83% to 95%), respectively.

Bacterial endocarditis occurred in 7 cases, and 6 of them underwent reoperation. Actuarial freedom from endocarditis at 5 and 10 years was 96% (95% CI 93% to 99%) and 95% (95% CI 91% to 99%), respectively. Among the 7 patients who experienced infective endocarditis of the prosthesis, 3 (43%) had a history of endocarditis.

**Discussion**

Since 1992, the CLOB valve has been widely used in a number of institutions and several studies reported excellent hemodynamic performance and midterm durability of the valve.\(^{10,15,16,20,25,26}\) The CLOB valve showed a low transvalvular gradient, large effective orifice area, and patients receiving the valve experienced a significant regression of left ventricular hypertrophy in the early postoperative period.\(^{10,15,20,25,26}\) A follow-up study of 402 patients by O’Brien et al\(^{20}\) showed only 1 SVD requiring reoperation over a mean follow-up of 4.3 years. In the same study, the actuarial 8-year freedom from reoperation due to all causes was 96.7%±2.3%, and the freedom from valve explantation was 97.8%±2.1%.\(^{20}\) Martinovic et al\(^{26}\) found only 2 hemodynamic significant aortic regurgitations among 206 patients implanted with the CLOB valve and followed for a mean 4.8 years. However, Luciani et al\(^{11}\) have reported unsatisfactory early outcomes with the CLOB valve relative to 2 other

<table>
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<tr>
<th>TABLE 3. Presentation of Nonfatal Events</th>
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<tr>
<td>SVD (n=33)</td>
</tr>
<tr>
<td>Reoperation (n=29)</td>
</tr>
<tr>
<td>Conservative management (n=22)</td>
</tr>
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</table>

SVD indicates structural valve disease.

* 5 tears, 9 tears and calcifications, and 3 commissural calcifications.

† 3 perivalvular leak and 3 sinusolobular dilatation.

‡ 4 tears, 7 tears and calcifications, 3 commissural calcifications, and 2 diffuse valve calcification.

§ Perivalvular leak with moderate aortic regurgitation in asymptomatic patients.
stentless xenografts, although midterm survivals after stentless AVR were good with all 3 xenografts. At present, studies of long-term survival using the CLOB valve are not available. Therefore, the long-term durability and clinical performance of this valve remain largely unknown.

Our results show that in a population with a high prevalence of elderly females with small aortic annulus, followed for 10 years after AVR, the freedom from SVD was 91% at 5 years and dropped to 44% at 10 years. Particularly, a dramatic increase in the prevalence of SVD was noted after 8 years from valve implant. A SVD occurred in 21 patients of 115 (18%) before 8 years, and in 12 patients of 33 (36%) after the eighth year. The fact that degenerative changes in the CLOB valve occur relatively late after AVR may explain the apparent conflict of data with the previous reports which analyzed patients with a mean follow-up up to 5 years. However, our data are significantly different from those reported by O’Brien et al, who reported 10-year results of 402 implants with the CLOB valve during a comparable follow-up length, 17 of 185 of our study patients underwent reoperation for SVD in comparison to only 1 of 402 reported by O’Brien et al. A possible explanation may be the different way of assessing SVD used by O’Brien et al who defined it on the basis of reoperation, whereas in the present study it was based on echocardiographic and clinical findings.

A percent freedom from SVD of 44% at 10 years may be considered unacceptable by most surgeons, as it compares unfavorably with outcomes of other stentless bioprostheses. By comparison, freedom from SVD and from reoperation at 10 years for the Freestyle valve were 90 and 92%, respectively. Moreover, Desai et al reported a 10-year freedom from SVD and from reoperation for the St Jude Toronto valve of 78% and 78%, respectively. These data raise the issue of the long term durability of the CLOB stentless porcine valve.

The higher incidence of SVD of the CLOB valve found during long-term follow-up studies in comparison to other stentless valves is difficult to explain. First, the function of stentless valves is strictly dependent on the integrity of the aortic valve-root complex, as the prosthesis is anchored to the native aortic root. Jin and Westaby have shown that progressive dilatation of the sinotubular junction, which frequently occurs with aging, may cause progressive prosthetic valve insufficiency attributable to reduced leaflet coaptation. Dysfunction of the stentless valve may, in turn, be associated with an increased shear stress and premature valve deterioration. However, in our study, only in 3 cases (9%) the cause of valve dysfunction can be ascribed to sinotubular junction dilatation. Therefore, other factors, such as an immunoresponse to the xenograft or the gluteraldehyde residuals on the cusp tissue (therefore irrespective of valve design) may have played a predominant role in our study patients.

Figure 3. Outflow surface of a the Cryolife O’Brien from a 79-year-old female at 7.5 years from aortic valve replacement. One cusp shows a large tear with calcification around the margins. The outflow surface shows a ridge of calcification (arrowheads) close to one commissure.

Figure 4. Actuarial freedom from valve reoperation for any cause. Thin lines represent 95% confidence limits. Number of patients at risk and number of patients undergoing valve reoperation for any cause are shown just above the x axis.
Interestingly, contrary to what occurs with stented bioprostheses, the structural deterioration of the CLOB valve is mainly characterized by progressive stiffening and rupture, often abrupt, localized within the body leaflet or at the commissures, with or without the concomitant presence of microcalcifications. Structural deteriorations found in our study population were independent on native valve lesion (stenosis or regurgitation), anatomy (tricuspid or bicuspid aortic native valve), and presence/absence of trivial regurgitation at pre-discharge echocardiography. Similar findings were reported by Luciani et al, who found that the modality and rate of SVD were similar among the 3 different valve models tested: Toronto SPV, Biocor PSB, and CLOB. Therefore, there may be a single mechanism leading to failure, common to some stentless xenografts, which reflects prosthetic valve engineering. Porcine xenografts valves are low pressure fixed in gluteraldehyde. Previous studies with porcine tissue have shown that low-pressure fixation causes significant loss of transverse cuspal ridges and collagen crimp. In addition, both the Toronto SPV and the CLOB valves are not treated with any antimineralization technique, which may also increase the rate of calcific degeneration. Notably, the Freestyle valve (ie, the valve with the lowest percentage of SVD at 10 years) was the only one treated with antimineralization technique.

The difference in percentage of SVD between the CLOB valve and the Toronto valve may also be explained by the different implant technique of these valves and the different study population. In comparison to the patients implanted with the Toronto valve, our study population was older (mean age 65 versus 72 years, respectively), with higher prevalence of female gender (34% versus 56%, respectively) and of renal insufficiency (3% versus 18%, respectively). Finally, the single-suture supraannular implant of the CLOB valve is more technically demanding for surgeons than the subcoronary implant of the Toronto valve, and the former may have resulted in some cases in a not optimal symmetry of leaflets of the implanted valve which, despite being hemodynamically and morphologically unapparent at the time of surgery, may have hampered the long-term durability of the CLOB valve.

In our high-risk population of elderly women with elevated standard EuroSCORE (ie, 73% of patients with Standard EuroSCORE ≥6), the lack of durability of the CLOB valve did not affect survival. Actuarial survival of our study population was 68% and 40% at 5 and 10 years, respectively. This figure compares favorable with the data reported by O’Brien et al in patients implanted with the same valve.

Study Limitations
This study reports a single institutional experience with the CLOB valve in aortic position. Our data suggest that after 8 years from implant, patients with the CLOB valve experience a dramatic increase of the rate of SVD. The need for reoperation appears to be higher than previously reported for the same valve. Small sample sizes and relatively high event rate in late years of the study may have overestimated the true rate of SVD. Because of the well known detrimental impact of technical factors related to stentless valve surgery, it is possible that minor mishaps with the implant technique, undetected at the time of operation, may have translated into relevant valve dysfunction with time in our patients. However, only in 22 patients (12%) a trivial aortic valve regurgitation at the predischarge echocardiogram was seen; among these, 7 patients showed a progression toward a moderate-severe.

Conclusions
Our study is the first to report a long-term clinical follow-up of the CLOB valve. Our data about reduced long-term durability of this valve may have important clinical implications because the acceleration of the SVD rate that occurs in
the CLOB valve after 8 years from implant warrants a close echocardiographic follow-up of these patients and planning of reintervention once a new hemodynamic significant aortic regurgitation has been found. However, because of the midterm good hemodynamic performance and satisfactory durability of the valve, and easy implantation technique, this valve may remain a reasonable choice in very elderly patients with degenerative aortic stenosis and small aortic root.

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Disclosures
None.

References
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