An Unexpected Risk Factor for Early Structural Deterioration of Biological Aortic Valve Prostheses

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Background. **An alarming rate of early failure has been recently reported for the LivaNova (previously Sorin) Mitroflow (LivaNova, London, UK) bioprosthesis. Here, we aimed at verifying if this possible underperformance is confirmed in a large, single-center experience and identifying the risk factors associated with early deterioration.**

Methods. **In all, 459 Mitroflow valves have been implanted from July 2009 to December 2013 (patients' mean age 73 years; 204 women). Surviving patients have undergone yearly clinic and echocardiographic follow-up. Dysfunction was defined as moderate if the mean gradient was more than 30 mm Hg or severe if it exceeded 40 mm Hg. The population was divided on the basis of a dimensional mismatch, the model of the prosthesis (LX or DL: follow-up to 4 years), and patient's age at the time of implantation.**

Results. **Cumulative freedom from moderate valve dysfunction was 81% ± 3% at 60 months. It was lower with patient-prosthesis mismatch (71% ± 5% versus 92% ± 3%; $p = 0.0065$) and with the more recent DL model (at 42 months: 78% ± 6% versus 96% ± 2%; $p < 0.0001$). Cumulative freedom from severe dysfunction was 93% ± 2% at 5 years. Again, it was inferior among patients with a mismatch (86% ± 4% versus 100%; $p = 0.0013$) and for the DL model (42 months: 92.5% ± 3% versus 98.5% ± 1%; $p = 0.0309$). Smaller prostheses showed higher rates of early degeneration.**

Conclusions. **The LivaNova Mitroflow valve appears to be prone to early deterioration. Smaller size prostheses should be used cautiously and avoided with patient-prosthesis mismatch. The DL model anticalcification treatment seems unable to prevent early degeneration, and possibly contributes to even earlier failure.**

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Bioprosthetic heart valves for aortic valve replacement have recently had a rebirth owing to the enhanced hemodynamic performance and extended durability reported previously [1]. Moreover, the possibility of performing a percutaneous valve-in-valve implantation in the case of primary structural valve degeneration (SVD), thereby avoiding a reoperation, has contributed to expansion of their range of application even in patients of relatively younger age [2]. Among these third-generation bioprostheses, the LivaNova (previously Sorin) Mitroflow (London, UK) valve has been used worldwide in a large number of patients [3, 4]. The main feature of the valve design is the positioning of a bovine pericardium sheet on the outside part of a Delrin (DuPont, Wilmington, DE) stent [5]. The purpose was to achieve a larger effective orifice area and less mechanical obstruction to left ventricular ejection. Lower gradients across the prosthesis would mean less turbulence and mechanical stress on the leaflets and quicker regression of left ventricle hypertrophy [6], whereas a larger orifice area should limit patient-prosthesis mismatch (PPM) and guarantee better efficiency in patients with a small aortic annulus.

Several models of this prosthesis have been introduced over time to improve the performance, and the last model, called DL, incorporates also an anticalcification treatment based on phospholipids removal from the pericardium by means of octanediol to delay or even prevent SVD [7, 8]. Organic solvents using an opportune mixture of ethanol, 1,2-octanediol, or octanol have been applied during bioprosthetic valve manufacturing to extract cell membrane phospholipids, trying to reduce the chances of calcification [7]. The earlier reports showed good results in terms of hemodynamics and durability of the prosthesis [9, 10], although some recent studies highlighted an impressively high rate of early deterioration, characterized by a very rapid increase of transprosthetic gradients [11, 12].

These findings are not shared by the entire scientific community and necessitate further investigation. With this in mind, we decided to review the outcome of our large population to verify whether the underperformance

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of the Mitroflow valve is confirmed and to identify any possible further risk factor for early deterioration. More in detail, we wanted to verify whether the anticalcification treatment of the Mitroflow DL can significantly affect the durability of the valve, although its introduction on the market is relatively recent (2012).

Patients and Methods

Patients

From July 2009 to December 2013, 459 consecutive patients underwent routine, ethically approved with patient's consent, aortic valve replacement with a Mitroflow bioprosthesis at our institution. The mean age of our patient population was 73 ± 8 years (range, 21 to 90 years), and 204 (44%) were women. All patients signed an informed consent agreement before undergoing the operation and agreed to provide their clinical data during the follow-up exclusively for the intent of the study. Our Institutional Review Board and Ethical Committee approved the study.

Operative Technique

Complete midline sternotomy, normothermic cardiopulmonary bypass, and intermittent warm blood cardioplegia were used in all cases. The valve was implanted in a supraannular position by means of 2-0 polyester U-shaped stitches, each reinforced with a Teflon (Impra Inc, subsidiary of C.R. Bard, Tempe, AZ) pledget on the ventricular side. Before implantation, the valve was immersed in a saline solution and rinsed for 3 minutes. Intraoperative transesophageal echocardiography was performed in all patients to verify proper placement of the prosthesis, absence of perivalvular leaks, and measurement of acceptable transvalvular gradients, as well as recovery of cardiac function and complete removal of air bubbles from the cardiac chambers. The intraoperative variables are described in Table 1.

Follow-Up

All survivors (100%) underwent transthoracic echocardiography between January 1 and March 31, 2016. All patients (100%) had a predischarge and 1-month echocardiogram. All survivors with 2-year follow-up could exhibit the 1-year control and went on to the second year control in our institution or provided their personal examination if they lived out of town. Patients with 3-year follow-up had all three echocardiograms available in 98% of the cases. Patients with 4-year follow-up had all four examinations in 94% of the cases. Surviving patients with 5-year follow-up were able to present all five echocardiograms in 89% of the cases.

The annual clinical examination with transthoracic echocardiography was required for any single patient as part of our follow-up protocol for valvular patients. The transthoracic echocardiograms obtained outside our center were reviewed for this study in our laboratory, and in case they were judged incomplete or of insufficient quality, they were repeated to obtain comprehensive and consistent data. The follow-up closure date was March 31, 2016.

Definitions

Moderate valve dysfunction (MVD) was defined as an increase of mean transvalvular gradients more than 30 mm Hg but less than 40 mm Hg. Severe valve dysfunction or structural valve deterioration was defined as the new onset of a mean transvalvular gradient that exceeded 40 mm Hg or an intraprosthesis regurgitation of at least moderate degree (ie, pressure half time less than 500 ms).

The effective orifice area for each prosthesis size was obtained directly by the manufacturer and indexed for the body surface area of the receiving patient. An indexed effective orifice area between 0.85 and 0.65 cm^2/m^2 identified moderate PPM, whereas a value less than 0.65 cm^2/m^2 was considered an indicator of severe PPM [13].

Finally, the left ventricular mass (LVmass) was calculated using the formula suggested by the American Society of Echocardiography:

$$\text{LVmass} = 0.83\,[(d + t) - 3d] + 0.6$$

where "d" is the left ventricular telediastolic diameter and "t" is the sum of the telediastolic thickness of the interventricular septum and the posterior wall [14].

Statistical Analysis

Categoric variables are reported as an absolute value and the corresponding percentage; continuous variables are reported as mean ± 1 SD. The primary endpoints of the study were the probability of freedom from death, reoperation, MVD, and SVD, calculated by means of the Kaplan-Meier method, for the entire population and for subgroups identified as follows: presence or absence of PPM, more than or less than 70 years of age at the time of implantation, size of the implanted prosthesis (19 mm to 25 mm), and DL or LX Mitroflow model (with or without anticalcification pretreatment, respectively). For the first three subgroups, the follow-up period was extended up to 5 years, whereas for the latter it was limited to a 42 months of comparison as the DL model was introduced only in 2012. Differences between curves were compared using the Mantel-Cox log rank test. The Cox proportional hazards model was used to identify independently predictive risk factors for prosthetic dysfunction and reoperation. An alpha error less than 0.05 was used to identify statistically significant differences.

Results

Early Results

The clinical characteristics of the patients' cohort are reported in Table 2. The baseline echocardiography variables are reported in Table 3. In 270 cases (59%), the aortic valve replacement was associated with other major surgical procedures. The operative mortality was 3% (6 of 189) for isolated aortic valve replacement and 6.7% (18 of 270) for the combined operations, for a global mortality rate of 5%. The incidences of the main nonfatal complications are