Clinical Investigation

Regression of Left Ventricular Mass

after Implantation of the Sutureless 3f Enable Aortic Bioprosthesis

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Left ventricular hypertrophy in aortic stenosis is considered a compensatory response for the maintenance of systolic function but a risk factor for cardiac morbidity and death. We investigated the degree of left ventricular mass regression after implantation of the sutureless Medtronic 3f Enable® Aortic Bioprosthesis.

We studied 19 patients who, from May 2010 through July 2011, underwent isolated aortic valve replacement with the 3f Enable bioprosthetic valve, with clinical and echocardiographic follow-up at 6 months. The mean age was 77.1 ± 5.1 years (range, 68–86 yr); 14 patients were women (73.7%); and the mean logistic EuroSCORE was 15.4% ± 11.8%. Echocardiography was performed preoperatively, at discharge, and at 6 months' follow-up. The left ventricular mass was calculated by means of the Devereux formula and indexed to body surface area.

The left ventricular mass index decreased from 146.1 ± 47.6 g/m² at baseline to 118.1 ± 39.8 g/m² at follow-up (P=0.003). The left ventricular ejection fraction did not change significantly. The mean transaortic gradient decreased from 57.3 ± 14.2 mmHg at baseline to 12.3 ± 4.6 mmHg at discharge and 12.2 ± 5.3 mmHg at follow-up (P <0.001), and these decreases were accompanied by substantial clinical improvement. No moderate or severe paravalvular leakage was present at discharge or at follow-up.

In isolated aortic stenosis, aortic valve replacement with the 3f Enable bioprosthesis results in significant regression of left ventricular mass at 6 months' follow-up. However, this regression needs to be verified by long-term echocardiographic follow-up. ***(Tex Heart Inst J 2015;42(2):117-23)***

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Left ventricular (LV) hypertrophy constitutes a risk factor for cardiac morbidity and death.[1,2] Prognostic studies have given rise to the hypothesis that regression of LV hypertrophy is the underlying determinant of human longevity after aortic valve replacement (AVR) for aortic stenosis (AS).[3-6] In most patients, LV afterload reduction results in regression of LV mass within one year after surgical AVR for AS. However, this regression remains incomplete in some patients.[7,8]

Sutureless aortic bioprosthetic valve implantation is a feasible alternative for high-risk patients with AS. Despite the relatively recent clinical application of the Medtronic 3f Enable® Aortic Bioprosthesis model 6000 (Medtronic, Inc.; Minneapolis, Minn), several reports already have shown promising results for this sutureless bioprosthetic valve in mortality and morbidity rates, and in hemodynamic performance.[9-12] Yet the impact of these bioprostheses on LV mass is still unknown.

The aim of this study was to investigate the degree of LV mass regression at 6 months' echocardiographic follow-up after 3f Enable implantation.

Patients and Methods

From May 2010 through July 2011, 31 high-risk patients with symptomatic aortic valve disease underwent elective AVR with the Medtronic 3f Enable sutureless aortic bioprosthesis at our hospital. Patient selection for this type of device was left to the discretion of the surgeon. Exclusion criteria were active infective endocarditis, irregular aortic annulus, or ascending aorta geometry. We analyzed 19 of these patients who presented with severe AS, with or without aortic regurgitation, without concomitant tricuspid, mitral, or coronal disease, and who subsequently underwent isolated AVR, with 6 months' follow-up. In regard to the other 12 patients, 9 also had procedures concomitant to AVR (5, coronary artery bypass grafting; 1, mitral valve replacement;

and 3, tricuspid valve replacement); the remaining 3 patients were eliminated from the study because they did not have 6 months of follow-up. Outcome analysis was approved by our local ethics committee, and individual consent was waived. Transthoracic echocardiography (TTE) was performed at baseline, before discharge from the hospital, and again at follow-up.

The follow-up, obtained by interviewing the surviving patients, was complete in regard to postoperative adverse events, actual functional status, and the results of echocardiographic examination.

The mean age of the 19 patients in our study group was 77.1 ± 5.1 years (interquartile range, 68–86 yr). Arterial hypertension occurred in 94.7% of the patients. The preoperative mean aortic valve pressure gradient was 57.3 ± 14.2 mmHg (range, 44–79 mmHg), and the mean logistic EuroSCORE was 15.4% ± 11.8%. Baseline characteristics of the patients are listed in Table I.

Technology

The 3f Enable aortic bioprosthesis (model 6000) consists of the following: 1) a 3f aortic bioprosthesis (model 1000) assembled from 3 equal sections of equine pericardial material that have been cross-linked with formulations of low concentration glutaraldehyde within specific limits of time, pH, and temperature; 2) a self-expanding nitinol frame covered with polyester fabric on its inflow aspect; and 3) a polyester flange. Three equal equine pericardial leaflets are assembled into a tubular structure with the aid of locking sutures (Fig. 1). The self-expanding nitinol frame contributes partly to the fixation of the device in the deployed location, by virtue of outwardly emitted radial forces inherent in the nitinol material. The polyester flange has been incorporated into the inflow aspect of the device in order to minimize the potential of perivalvular leaks and migration, and the flange apposes well to the aortic annulus, without blocking the coronary ostia. The bioprosthesis is available in sizes from 19 mm to 29 mm.

TABLE I. Baseline Characteristics of the 19 Patients

Variable	Value
Age (yr)	77.1 ± 5.1
Female	14 (73.7)
Body surface area (m^2)	1.8 ± 18.5
Body mass index (kg/m^2)	29.9 ± 5.9
Hypertension	18 (94.7)
Diabetes mellitus	5 (26.3)
COPD	7 (36.8)
Hyperlipidemia	10 (52.6)
Chronic renal failure	1 (5.3)
Peripheral vascular disease	3 (15.8)
Atrial fibrillation	4 (21)
Logistic EuroSCORE (%)	15.4 ± 11.8

COPD = chronic obstructive pulmonary disease

Data are presented as mean ± SD or as number and percentage.

Fig. 1 *The Medtronic 3f Enable® aortic sutureless bioprosthesis.*

Operative Procedures

A standard median sternotomy was performed in the first 3 patients; the other 16 patients underwent a minimally invasive approach to AVR, via an upper partial ministernotomy (n=13) or a right anterior minithoracotomy (RT) (n=3). For the first 3 patients who underwent the new sutureless prosthesis AVR implantation at our center, we preferred conventional sternotomy as the approach. Thereafter, we implanted the 3f Enable via minimally invasive surgery.

Before surgery, all patients underwent imaging with use of a Toshiba Aquilion™ 64-slice computed tomographic scanner (Toshiba Medical Systems; Tokyo, Japan), without contrast enhancement, to evaluate aortic calcification, as well as the spatial relationships between the aortic valve, the sternum, and the intercostal spaces. Patients were judged suitable for RT if, at the level of the main pulmonary artery, 1) more than half of the ascending aorta was located on the right with respect to a vertical line drawn from the right sternal border to the ascending aorta and 2) the distance from the ascending aorta to the sternum did not exceed 10 cm.[13] Intraoperative data are reported in Table II. Cardiopulmonary bypass (CPB) was instituted with aortic–atrial cannulation and with induction of cardioplegia by anterograde administration of normothermic blood solution. A transverse aortotomy was performed approximately 2 cm above the commissures, and the aortic valve was inspected. The native aortic valve was excised,

the aortic annulus decalcified, and the 3f Enable bioprosthesis implanted. The rising and folding processes of the prosthesis and the implantation technique have been described by Martens and colleagues.[11] The aortotomy was closed with a continuous 5-0 Prolene suture, and the patient was weaned from CPB. Immediately thereafter, the positioning and functioning of the prosthesis were evaluated by means of intraoperative transesophageal echocardiography.

Transthoracic Echocardiography

According to the Echocardiography Working Group of the Italian Society of Cardiology, ensuring the accuracy, reliability, and reproducibility of Doppler echocardiographic measurements is necessary to diagnosis, decision-making, and the reduction of repeated examinations, especially during a clinical trial.[14,15] With that goal in mind, we established an echocardiographic laboratory at our institution (Fondazione Toscana G. Monasterio, Massa), in order to ensure the best data quality by standardizing image acquisition and minimizing the variability of measurements. Dedicated cardiologists and sonographers have been trained, in accordance with current guidelines, to obtain reproducible Doppler echocardiographic measurements of cardiac structure and function. Finally, our echocardiographic laboratory is certified by the Italian Society of Cardiovascular Echocardiography.

With the patient in the left lateral decubitus position, 2-dimensional TTE was performed with use of a Philips iE33 xMATRIX Echocardiography System (Philips Electronics, N.V.; Best, The Netherlands). Echocardiographic measurements of cardiac structure and function were performed in accordance with the standards of the Echocardiography Working Group of the Italian Society of Cardiology.[14] Left ventricular dimensions were obtained from the parasternal long-axis view, by measuring end-diastolic interventricular septal thickness, LV posterior-wall thickness, and LV end-diastolic and end-systolic internal diameters just below the tips of the anterior mitral leaflet. Left ventricular mass was calculated by means of the Devereux formula and indexed to body surface area (LV mass index, LVMI).[16] Left ventricular hypertrophy was defined as LVMI greater than 115 g/m^2 for men and LVMI greater than 95 g/m^2 for women. Relative wall thickness (RWT) (calculated as 2 × LV posterior-wall thickness/LV end-diastolic diameter) was considered abnormal when it exceeded 0.42 mm.[17] The RWT and LVMI were used to evaluate LV geometry. Patients were categorized as having normal geometry (normal RWT–normal LVMI); concentric remodeling (increased RWT–normal LVMI); eccentric hypertrophy (normal RWT–increased LVMI); or concentric hypertrophy (increased RWT–increased LVMI). Left ventricular end-diastolic and end-systolic volumes were obtained from the apical view and were indexed to body surface area. The LV ejection fraction was calculated by means of the biplane modified Simpson rule. Transaortic peak velocity and mean gradient were measured with use of continuous-wave Doppler echocardiography through the native or prosthetic aortic valve. The Doppler signal was acquired from multiple views, after optimal alignment with the direction of transaortic blood flow had been achieved.

TABLE II. Intraoperative Data for the 19 Patients

Variable	Value
Valve size (mm)	
19	4
21	9
23	3
25	3
Surgical approach	
Sternotomy	3 (15.8)
Ministernotomy	13 (68.4)
Right anterior minithoracotomy	3 (15.8)
Aortic cross-clamp time (min)	65.9 ± 18
Cardiopulmonary bypass time (min)	99.4 ± 22.9

Data are presented as mean ± SD or as number and percentage.

Statistical Analysis

Statistical analysis was performed with use of SPSS 17.0 statistical software (IBM Corporation; Armonk, NY). Continuous variables are presented as mean ± SD and categorical variables are presented as frequencies and percentages. In order to evaluate differences between baseline, discharge, and 6-month follow-up values for continuous variables, a one-way analysis of variance for repeated measurements was used, followed by a post hoc Bonferroni method of multiple comparisons. The same approach was used for ordinal variables, assuming a constant difference between values. If variables were not normally distributed, differences were evaluated by means of nonparametric tests for 3 related samples (Friedman test). For comparisons between 2 time points, a paired-sample *t* test or a Wilcoxon signed rank test was used for normally distributed or skewed data, respectively. A 2-sided *P* value of less than 0.05 was considered statistically significant.

Results

There were no deaths in the hospital or at follow-up. The prosthesis sizes implanted were 19 mm (n=4), 21 mm (n=9), 23 mm (n=3), and 25 mm (n=3). The cardiopulmonary bypass and aortic cross-clamp (ACC) times were 99.4 ± 22.9 min (range, 61–136 min) and 65.9 ± 18 min (range, 41–96 min), respectively (Table II). The median hospital stay was 8 days (interquar-

tile range, 5–28 d). One patient developed acute renal failure that necessitated short-term dialysis. Temporary pacemaker placement was necessary in one patient. Finally, 2 patients needed sternal rewiring to correct deep wound infection and sternal diastasis. One of these 2 patients had a logistic EuroSCORE of 14.2% with important clinical predictors of infection (diabetes mellitus, obesity, and postoperative transfusions); the other patient had a logistic EuroSCORE of 18.4% with diabetes mellitus, hemodynamic instability, preoperative renal failure on dialysis, and postoperative transfusions.

Changes in LV dimensions, mass, and geometry are shown in Table III. Interventricular septal and LV posterior-wall thickness decreased significantly at follow-up. In addition, at mid-term follow-up, the LV mass index decreased from 146.1 ± 47.6 to 118.1 ± 39.8 g/m^2 (P=0.003), and RWT decreased from 0.49 ± 0.1 to 0.43 ± 0.08 mm (P=0.012). However, the percentage of patients with LV hypertrophy, RWT greater than 0.42, or both did not change significantly. Concentric remodeling and concentric and eccentric hypertrophies remained unchanged at 6 months after sutureless bioprosthesis implantation. The LV systolic function did not change significantly. However, a significant clinical improvement was observed in the majority of patients at follow-up: New York Heart Association (NYHA) functional class improved from 2.8 ± 0.5 to 1.7 ± 0.9 (P <0.001), and no major cerebral or cardiovascular events were described.

The mean pressure gradient decreased significantly from a preoperative value of 57.3 ± 14.2 mmHg to 12.2 ± 5.3 mmHg at follow-up (P <0.001). The mean peak transvalvular jet velocity decreased significantly from a preoperative value of 457.4 ± 92.1 cm/s to 213.6 ± 46.4 cm/s at follow-up (P <0.001).

At discharge, mild paravalvular leakage occurred in 2 patients (10%), and persisted in one patient at follow-up (Table IV).

Discussion

This study shows a significant regression in LV mass at the 6-month follow-up after sutureless bioprosthesis implantation in 19 patients undergoing isolated AVR. We showed that implantation of the 3f Enable bioprosthesis in high-risk patients is a safe and feasible procedure associated with low morbidity and mortality rates and with excellent hemodynamic performance at short-term follow-up. This is confirmed by several previous reports.[9-12] Santarpino and colleagues[18] described LV mass regression at a mean 13.5 ± 7.3 months' follow-up after the implantation of a Perceval S sutureless bioprosthesis (SORIN Group; Saluggia, Italy). However, the impact of the 3f Enable bioprosthesis on LV mass at short-term follow-up has never before been analyzed.

Aortic valve disease is associated with substantial hemodynamic stresses on the LV in the form of pressure and volume overload.[19] To adapt to the particular stress that is sustained, the LV undergoes hypertrophy in a fashion that maintains systolic wall stresses at or near normal levels, and it dilates in response to diastolic stresses. With AVR, there is a reduction in the degree of hemodynamic stress faced by the LV as the severely stenotic or regurgitant native valve is replaced with a prosthetic valve that has only a relatively stenotic orifice. The compensatory response to the volume and pressure

TABLE III. Left Ventricular Echocardiographic Data

Variable	Baseline	Hospital Discharge	6-Month Follow-Up	*P* Value: Baseline vs Discharge	*P* Value: Discharge vs Follow-Up	*P* Value: Baseline vs Follow-Up
LV Dimensions						
Septal wall thickness (mm)	14.1 ± 2.4	13.4 ± 2.9	12.3 ± 2.4	0.05	0.014	<0.001
Posterior wall thickness (mm)	11.8 ± 1.7	11.2 ± 1.6	10.7 ± 1.1	0.03	0.26	0.003
LVIDD (mm)	50.2 ± 8.9	49.7 ± 8.5	50 ± 8.7	0.27	1.15	0.55
LVIDS (mm)	32.4 ± 8.6	32.8 ± 8.5	33.1 ± 9.2	0.48	0.41	0.03
LVED volume index (cm^3/m^2)	122.4 ± 46.1	129.1 ± 49.4	132.1 ± 49.5	0.003	0.005	<0.001
LVES volume index (cm^3/m^2)	50.8 ± 24.9	55.2 ± 24.7	58 ± 24.5	0.008	0.005	0.001
LV mass						
LV mass (g)	260.1 ± 85.7	257.9 ± 85.9	210.8 ± 69.1	0.64	0.003	0.003
LV mass index (g/m^2)	146.1 ± 47.6	143.8 ± 48.4	118.1 ± 39.8	0.68	0.003	0.003
Relative wall thickness*	0.49 ± 0.1	0.45 ± 0.1	0.43 ± 0.08	0.08	0.13	0.012
LV function						
LV ejection fraction	0.58 ± 0.6	0.57 ± 0.34	0.55 ± 0.54	0.91	0.76	0.37

LV = left ventricular; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; LVIDD = left ventricular internal diameter at end-diastole; LVIDS = left ventricular internal diameter at end-systole

*Relative wall thickness = 2 × (posterior wall)/(LV end-diastolic diameter).

Data are presented as mean ± SD. P <0.05 was considered statistically significant.

TABLE IV. Aortic Valve Echocardiographic Data and Clinical Status

Variable	Baseline	Hospital Discharge	6-Month Follow-Up	*P* Value		
				Baseline vs Discharge	Discharge vs Follow-Up	Baseline vs Follow-Up
Aortic valve function						
Mean aortic gradient (mmHg)	57.3 ± 14.2	12.3 ± 4.6	12.2 ± 5.3	<0.001	0.7	<0.001
Peak aortic velocity (cm/s)	457.4 ± 92.1	215.2 ± 44.1	213.6 ± 46.4	<0.001	0.65	<0.001
Paravalvular leakage	—	—	—	—	0.15	0.15
Mild	0	2 (10)	1 (5)	—	—	—
Moderate	0	0	0	—	—	—
Severe	0	0	0	—	—	—
NYHA functional class	2.8 ± 0.5	1.9 ± 0.6	1.7 ± 0.9	—	—	<0.001

NYHA = New York Heart Association

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ was considered statistically significant.

overload sustained by the LV develops over a prolonged period involving many years, even decades, as the body grows and the disease progresses. The rate and extent of postoperative regression of the patterns of hypertrophy and dilation seen with these disorders has not been established.

In our patients, the regression of LV mass after AVR was a prolonged process, with substantial change in the intermediate postoperative period, and with further change late after reduction in ventricular load. Monrad and colleagues[7] studied 21 patients who had either AS or aortic insufficiency preoperatively; the results were collected after an intermediate period (1.6 ± 0.5 yr), and again late (8.1 ± 2.9 yr) after aortic valve replacement, then were compared on each occasion with results in 11 control patients. At the intermediate postoperative study, the LV muscle mass index remained significantly higher in those with preoperative aortic insufficiency (128 ± 29 g/m^2) and in those with AS (114 ± 27 g/m^2), as opposed to the control subjects ($P < 0.01$). By the time of the late postoperative study, there were no longer any significant differences in LV muscle mass index.[7] Lund and associates[20] analyzed LV hypertrophy regression during 10 years after AVR with disc valves, caged ball valves, and stented porcine valves implantations for AS. The mean LVMI was 202 ± 46 g/m^2 preoperatively, 157 ± 48 g/m^2 at 1.5 years ($P < 0.0001$), and 159 ± 70 g/m^2 at 10 years ($P < 0.0001$). Doss and co-authors[21] compared pulmonary autografts with mechanical prostheses (group 1); stentless bioprostheses with mechanical prostheses (group 2); and stentless with stented bioprostheses (group 3). They concluded that, at 6 months' follow-up in group 1, the mean LVMI decreased from 185 ± 42.3 g/m^2 and 179 ± 38.6 g/m^2 at baseline to 149 ± 34.1 g/m^2 and 141 ± 35.4 g/m^2; in group 2, from 181 ± 40.9 g/m^2 and 182 ± 39.2 g/m^2 to 143 ± 34.2 g/m^2 and 145 ± 32.8 g/m^2; and in group 3, from 174 ± 34.3 g/m^2 and 180 ± 40.5 g/m^2 to 130 ± 31 g/m^2 and 132 ± 36.1 g/m^2. None of these changes reached statistical significance.[21] Santarpino and colleagues[18] described a regression, after the implantation of Perceval S sutureless bioprostheses, from 148.4 ± 46 g/m^2 at baseline to 119.7 ± 38.5 g/m^2 at follow-up (mean, 13.5 ± 7.3 mo) ($P = 0.002$). In our experience with the implantation of sutureless 3f Enable aortic bioprostheses, the results at the 6-month follow-up were encouraging: the mean LVMI decreased from 146.1 ± 47.6 g/m^2 at baseline to 118.1 ± 39.8 g/m^2 at follow-up ($P = 0.003$). Regression was incomplete, but that can be explained by incomplete follow-up data. Moreover, our patients, because of their advanced age, had been exposed to the harmful effects of severe AS for many years: long-standing LV hypertrophy eventually becomes irreversible, due to myocardial fibrosis.[20,22] In addition, 94.7% of patients had a history of hypertension. Postoperative medications were β-blockers in 15 patients (79%), angiotensin-converting enzyme inhibitors/angiotensin-1 receptor blockers in 11 (58%), calcium antagonists in 5 (26%), and diuretics in 10 (53%). Despite optimal medical therapy, reduced systemic arterial compliance might have contributed to the incomplete regression of LV mass.[23] Finally, genetic factors could have played a role.[24] In another study, [25] Kennedy and associates observed a significant reduction in LV mass but found, 1.5 years postoperatively, that significant hypertrophy remained, in comparison with a with control group.

In the Kennedy study,[25] the regression of myocardial hypertrophy was associated with a significant reduction in the pattern of concentric hypertrophy, a pattern that persisted even into the authors' follow-up study, 9 years postoperatively. In the Monrad study,[7] the regression of hypertrophy was characterized by a reduction in left-ventricular wall thickness that was less than the reduction in chamber size, in such a manner that the chamber assumed a more concentric pattern.[7,26] Although concentric anatomy is itself a risk factor for death in patients with severe AS, our study was underpowered to detect its prognostic impact on 6-month

mortality rates. These changes in myocardial mass and configuration were associated with substantial improvements in resting hemodynamic values and in clinical status (NYHA class improved from 2.8 ± 0.5 to 1.7 ± 0.9; $P < 0.001$) at the 6-month follow-up.

Sutureless bioprostheses present an innovative approach to surgical AVR and have been designed to enable faster implantation, reducing CPB and ACC times. This is an advantage for all patients, regardless of risk profile. Therefore, sutureless aortic valve implantation might be an alternative treatment option for patients at high risk for death and morbidity after open-heart surgery. In our experience, mean CPB and ACC times were longer than expected but similar to those reported in other studies.[9-12] Our ACC time in sutureless implantation is not different from a standard AVR; this could be related to our learning curve. In the first 7 patients who underwent isolated AVR with the 3f Enable through ministernotomies, the mean ACC time was 71.8 ± 21.5 min. In the subsequent 6 patients, the ACC time was 61.2 ± 14.8 min, an improvement in operative time. Additional modifications to the polyester flange of the 3f Enable, enabling broader coaptation with the native annulus and better positioning of the valve, could further reduce procedural time. We think that greater experience of the surgeons, together with future evolution of this device, could reduce implantation time. Furthermore, we must consider that most of the bioprostheses were implanted via a minimally invasive approach, in which operative times are normally longer. As described by our study, in addition to these several advantages, the 3f Enable bioprosthesis results in excellent hemodynamic performance and a significant regression in LV mass at follow-up.

Some additional limitations exist in our report. Admittedly, this retrospective study involves a small series of patients. Yet we believe our series to have been of reasonable size under the circumstances, because we were investigating LV mass regression after the implantation of a new device. A possible weakness in our investigative method is that we left patient selection for this type of device to the discretion of the surgeon. Finally, our follow-up period is very short.

In conclusion, our experience with the 3f Enable sutureless valve showed favorable clinical and hemodynamic results. Our initial echocardiographic data show a significant regression of LV mass. Our study needs confirmation with long-term follow-up evaluation of these same patients, which we intend to do.

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