Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis

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Objectives: The aim of this study was to investigate the long-term clinical and hemodynamic outcomes after aortic valve replacement with the Carpentier-Edwards Perimount bioprosthesis (Edwards Lifesciences, Irvine, Calif), which has been used in our institution since 1984.

Methods: From January 1984 to December 1995, the Carpentier-Edwards pericardial bioprosthesis was used for aortic valve replacement in 254 patients (male/female ratio 117:137) with a mean age of 71 years (range 25-87 years). Before the operation, 216 patients (85%) were in New York Heart Association functional class III or IV. The predominant diagnosis was aortic stenosis ($n = 219$, 86%). Associated surgical procedures included coronary artery bypass grafting in 130 cases (51%), mitral valve replacement in 11 cases (4%), and tricuspid or mitral valve repair in 12 cases (5%). Previous cardiac operations had been performed in 36 cases (14%). Follow-up was 100% complete at a mean of 60 ± 31 months. Univariate estimates of time-related cumulative probabilities were calculated by the Kaplan-Meier method. Multivariable adjustment was performed by Cox proportional hazards regression. Echocardiography was performed in 61% of long-term survivors.

Results: There were 11 early deaths (4%) and 58 late deaths. Actuarial survivals at 5, 10, and 12 years were $80\% \pm 3\%$, $50\% \pm 8\%$, and $36\% \pm 9\%$, respectively. At 12 years the freedom from cardiac death was $73\% \pm 7\%$, the freedom from valve-related death was $84\% \pm 11\%$, the freedom from valve reoperation was $83\% \pm 9\%$, the freedom from primary tissue failure was $86\% \pm 9\%$, the freedom from thromboembolism was $67\% \pm 13\%$, and the freedom from endocarditis was $98\% \pm 1\%$. Echocardiography was performed on long-term survivors (mean follow-up 67 ± 25 months) and showed that transvalvular peak and mean pressure differences measured with Doppler echocardiography were 23.2 ± 9.6 and 12.3 ± 4.8 mm Hg, respectively. Aortic regurgitation was found by Doppler echocardiography to be none or trivial, mild, moderate, and severe in 64%, 30%, 3%, and 1% of patients, respectively. Mean left ventricular mass index was 107.2 ± 35.3 g/m² (118.9 ± 40.2 g/m² in men and 98.8 ± 28.8 g/m² in women) at late follow-up. One third of all patients, regardless of sex ($n = 26/64$ women and $n = 14/45$ men), had evidence of left ventricular hypertrophy. However, our analyses indicate that the residual left ventricular hypertrophy was not caused by valve mismatch but was probably multifactorial.

Conclusion: The Carpentier-Edwards Perimount bioprosthesis has provided satisfactory clinical and hemodynamic outcome. However, at long-term follow-up about one third of the patients being investigated still had left ventricular hypertrophy examined by echocardiography.

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The Carpentier-Edwards Perimount (CEP) bioprosthesis (Edwards Lifesciences, Irvine, Calif) has been in clinical use since 1980 in Canada. We began using it in 1984. The long-term clinical results have previously been reported to be excellent, and this valve is regarded the bioprosthesis of choice by many surgeons.¹⁻⁴ This study reviews our experience with the CEP bioprosthesis and also examines its late hemodynamic performance.

Material and Methods

Patients

From January 1984 to December 1995 the CEP pericardial bioprosthesis (model 2900; Edwards Lifesciences, Irvine, Calif) was used for aortic valve replacement (AVR) in 254 patients with a mean age of 71 years (range 25-87 years). The clinical profile and the operative data of these patients are summarized in Tables 1 and 2, respectively.

From 1984 to 1989, all patients undergoing valve replacement with the CEP were discharged from the hospital with a regimen of daily warfarin sodium for the first 3 months after the operation, followed by lifelong aspirin therapy. This practice was changed in 1990, after which patients were discharged with a regimen of lifelong aspirin therapy only, with the exception of those in need of warfarin sodium for other indications, such as chronic atrial fibrillation or a concomitant mitral valve procedure.

Operative survivors were followed up by telephone or questionnaire between October 1998 and January 1999. The follow-up was 100% complete. The mean follow-up was 60 ± 31 months (range 1-167 months), and 1214 patient-years of follow-up were available for analysis.

Doppler Echocardiography

Transthoracic echocardiography with continuous-wave, pulsed-wave, and color flow Doppler studies were performed with a Hewlett Packard 1000, 1500, 2500, or 5500 Ultrasonoscope (Hewlett-Packard Company, Palo Alto, Calif) equipped with a 2.5-MHz transducer. Sixty-one percent of survivors ($n = 109/178$) had an echocardiogram performed at our hospital between December 1998 and May 1999. The mean follow-up for these studies was 67 ± 25 months (range 7-172 months). Those patients who did not undergo echocardiography either lived too far away from the hospital or were too old and in too fragile a condition to come without great difficulty.

For further details about measurements and calculations, see the Appendix. Left ventricular hypertrophy (LVH) was defined as a left ventricular mass index (LVMI) higher than 131 g/m^2 for men and higher than 100 g/m^2 for women.⁵

Definitions and Statistics

This report was based on the guidelines for reporting morbidity and mortality after cardiac valvular operations.⁶ Survival and time-related event analyses were performed with the Kaplan-Meier method. Multivariable analyses of risk factors for survival and time-related events were done by Cox regression methods previously described. The term *actuarial survival* was used to describe

TABLE 1. Clinical characteristics

No. of patients	254
Age (y, mean $\pm$ SD)	71.3 $\pm$ 8.8 (25-87)
Sex (No.)	
Male	117 46%
Female	137 54%
Electrocardiogram (No.)	
Sinus	226 89%
Atrial fibrillation	17 7%
Heart block	11 4%
NYHA functional classification	
Class I	2 1%
Class II	36 14%
Class III	127 50%
Class IV	89 35%
Aortic valve lesion	
Stenosis	155 61%
Insufficiency	35 14%
Mixed	64 25%
Mitral valve lesion	
Stenosis	7 3%
Insufficiency	10 4%
Mixed	1 0.5%
Coronary artery disease	
None	126 50%
1-Vessel	41 16%
2-Vessel	35 14%
3-Vessel	52 20%
Left ventricular function	
> 0.54	79 31%
0.40-0.54	111 44%
0.20-0.40	47 18%
< 0.20	5 2%
Endocarditis	12 5%
Reoperation	36 14%
Previous AVR	27 11%
Previous coronary artery bypass grafting	15 6%
Previous mitral valve replacement	2 1%
Previous other	3 1%

time-related analysis for that event and not to describe the type of analysis performed. Differences were tested for statistical significance with 1-way analysis of variance. When the *F* test revealed a significant difference, each pair of means was compared with the Scheffé test.

Results

Patient Survival

There were 11 operative deaths (4%). Eight of the 11 patients (73%) had undergone combined AVR and coronary artery bypass grafting. There were 58 late deaths (23%). Thirty-five of the 58 patients (60%) had undergone combined AVR and coronary artery bypass grafting. Operative mortality and morbidity and late mortality are shown in Table 3. The actuarial survival is shown in Figure 1. Multivariate analysis showed that preoperative New York Heart Association (NYHA) functional class III or IV (odds ratio

TABLE 2. Operative data

No. of patients	254	
Valve sizes implanted (mm, mean $\pm$ SD)	22.4 $\pm$ 2.3 (19-29)	
19 mm (no.)	13	5%
21 mm (no.)	101	40%
23 mm (no.)	85	33.5%
25 mm (no.)	46	18%
27 mm (no.)	8	3%
29 mm (no.)	1	0.5%
Associated procedures		
Coronary artery bypass grafting	130	51%
Mitral valve replacement	11	4%
Mitral valve repair	10	4%
Tricuspid valve repair	4	1.5%
Miscellaneous	11	4%
Aortic crossclamp time (min, mean $\pm$ SD)	86.5 $\pm$ 31.0 (45-236)	
Cardiopulmonary bypass time (min, mean $\pm$ SD)	118.4 $\pm$ 43.1 (61-335)	

TABLE 3. Operative morbidity and mortality and late mortality

	No.	%
Operative morbidity		
Reexploration for bleeding	15	6
Reexploration for cardiac arrest	2	1
Perioperative myocardial infarction	7	3
Perioperative stroke or transient ischemic attack	10	4
Mediastinitis	4	2
Permanent pacemaker implantation	16	6
Operative mortality	11	4
Cardiac arrest	2	
Low cardiac output syndrome	5	
Sepsis	2	
Multiple organ failure	1	
Other	1	
Late mortality	58	23
Valve related	5	
Stroke	3	
Endocarditis	2	
Cardiac related	24	
Congestive heart failure	6	
Myocardial infarction	10	
Sudden death	5	
Other	3	
Noncardiac	26	
Unknown	3	
Total early and late deaths	69/254	27

1.49, 95% confidence interval 1.02-2.18, $P = .04$) and the presence of coronary artery disease (odds ratio 2.08, confidence interval 1.26-3.44, $P = .004$) were independent risk factors for late death.

Valve-Related and Cardiac-Related Deaths

The actuarial freedoms from valve-related death at 5, 10, and 12 years were 98% $\pm$ 1%, 96% $\pm$ 2%, and 84% $\pm$ 11%, respectively. The actuarial freedoms from cardiac death at 5, 10, and 12 years were 87% $\pm$ 2%, 73% $\pm$ 7%, and 73% $\pm$ 7%, respectively.

Complications

Thromboembolism. Thromboembolic events were observed in 17 cases (14 strokes and 3 transient ischemic attacks). The freedoms from thromboembolism at 5, 10, and 12 years were 93% $\pm$ 2%, 88% $\pm$ 3%, and 67% $\pm$ 13%, respectively. The linearized rate for thromboembolic events was 1.4% $\pm$ 0.1% events/100 patient-years. At the last follow-up 38 of 178 patients (21%) were taking warfarin sodium and 140 (79%) were taking aspirin daily. Multivariate analysis showed that age (odds ratio 1.11, 95% confidence interval 1.02-1.20, $P = .01$) was an independent risk factor for thromboembolism.

Structural valve dysfunction. Structural valve deterioration occurred in 4 patients, and they were reoperated on after 8, 9, 9, and 13 years of follow-up. All 4 patients had cusp tears: 2 had commissural tears and 2 had midcusp tears. In addition, 3 patients had calcification of the cusps. The actuarial freedoms from structural valve dysfunction at 5, 10, and 12 years were 100%, 86% $\pm$ 9%, and 86% $\pm$ 9%, respectively (Figure 2). The actual freedoms from structural valve dysfunction at the corresponding intervals were 100%, 92% $\pm$ 6%, and 92% $\pm$ 6%, respectively (Figure 2). There were no valve failures in patients older than 65 years.

Bioprosthetic valve endocarditis. Five patients had bioprosthetic valve endocarditis that was diagnosed at 22 days, 4 months, 6 months, 3 years, and 3.5 years after the operation. Two patients were treated with antibiotics and replacement of the bioprosthesis, after which both survived. Three patients were treated with antibiotics alone; 1 survived and 2 died. The patient who survived after treatment with antibiotics alone had only mild aortic regurgitation on echocardiography at follow-up. The actuarial freedoms from bioprosthetic valve endocarditis at 5, 10, and 12 years were 98% $\pm$ 1%, 98% $\pm$ 1%, and 98% $\pm$ 1%, respectively.

Reoperations. Six patients underwent reoperation, and all survived. The indications for reoperation were structural valve deterioration in 4 cases and endocarditis in 2 cases. The actuarial freedoms from reoperation at 5, 10, and 12 years were 99% $\pm$ 1%, 83% $\pm$ 9%, and 83% $\pm$ 9%, respectively.

Other complications. Only 1 patient had a serious anti-coagulant-related hemorrhage, even though 21% of the patients were receiving oral anticoagulation. Four patients needed late pacemaker implantation. Eight patients had a late acute myocardial infarction.

Figure 1. Actuarial survival. Data points represent mean; error bars represent SEM.

Figure 2. Actuarial (circles) and actual (squares) freedoms from structural valve degeneration (SVD).

Late Functional Classification

At the latest follow-up 178 patients were alive and had the original CEP bioprosthesis in place. Seventy-two patients (41%) were in NYHA functional class I, 63 (35.5%) were in class II, 41 (23%) were in class III, and 1 (0.5%) was in class IV.

Echocardiography

Echocardiography of long-term survivors (mean 67 ± 25 months) showed that peak and mean gradients for all valve sizes were 23.2 ± 9.6 mm Hg (range 11-66 mm Hg) and

12.3 ± 4.8 mm Hg (range 5-31 mm Hg), respectively. Table 4 shows Doppler-echocardiographic data according to valve sizes at late follow-up. Smaller valves had statistically significantly higher transvalvular peak ($P = .02$) and mean ($P = .003$) gradients than did larger valves. Mean aortic valve area for all valves was 1.3 ± 0.3 (range 0.5-2.36 cm²), and area increased significantly with increasing valve size ($P = .0001$). Also, aortic valve areas were significantly larger in 27-, 25-, and 23-mm valves than in 19- and 21-mm valves (Table 4). However, 22 patients (20%) had an aortic valve area smaller than 1 cm² at late follow-up.

TABLE 4. Doppler echocardiographic results of CEP aortic valve bioprosthesis according to valve size at follow-up

Valve size (mm)	No. of patients	P_{peak} (mm Hg)	P_{mean} (mm Hg)	EOA (cm ²)	CI (L · min ⁻¹ · m ⁻²)	BSA (m ²)
19	5	38.4 ± 17.4	19.4 ± 7.6	0.95 ± 0.2	3.5 ± 1.2	1.59 ± 0.1
21	45	24.7 ± 10.2	13.0 ± 5.0	1.1 ± 0.2	2.7 ± 0.5	1.66 ± 0.2
23	33	21.4 ± 7.2	11.2 ± 3.6*	1.5 ± 0.3†‡	2.6 ± 0.9	1.82 ± 0.1‡
25	22	20.1 ± 7.3§	11.2 ± 4.3*	1.4 ± 0.3†‡	2.4 ± 0.7	1.87 ± 0.2‡
27	4	19.0 ± 10.8	10.1 ± 4.5	1.6 ± 0.4†	2.5 ± 0.8	1.84 ± 0.14
All sizes	109	23.2 ± 9.6	12.3 ± 4.8	1.3 ± 0.3	2.7 ± 0.7	1.76 ± 0.2

All values are expressed as mean ± SD. Significant differences between valve sizes according to Scheffé test are indicated by symbols. P_{peak} , Maximum pressure difference; P_{mean} , mean pressure difference; EOA, effective orifice area, CI, cardiac index; BSA, body surface area.

* $P < .05$, sizes 25 and 23 versus size 19 mm.

† $P < .05$, sizes 27, 25, and 23 versus size 19 mm.

‡ $P < .05$, sizes 25 and 23 versus size 21 mm.

§ $P < .05$, size 25 versus size 19 mm.

M-mode Doppler measurements and calculations of left ventricular mass and LVMI are shown in Table 5. In a general linear model there were significant increases in left ventricular end-diastolic dimension ($P = .03$) and interventricular septum ($P = .04$) with increasing valve size. However, there was no significant difference in posterior wall measurement ($P = .42$) with increasing valve size. The only statistically significant difference seen between valve sizes was that left ventricular end-diastolic dimension was increased in patients with 25-mm valves relative to those with 21-mm valves (Table 5). Mean left ventricular mass and LVMI were 189.0 ± 70.5 g (range 90-518 g) and 107.2 ± 35.3 g/m² (range 53-245 g/m², male 118.9 ± 40.2 g/m², female 98.8 ± 28.8 g/m²), respectively. Left ventricular mass and LVMI increased statistically significantly with increasing valve size ($P = .0001$ and $P = .01$, respectively). Body surface area also increased significantly with increased valve size ($P = .0001$). One third of all patients, regardless of gender (26/64 of the women and 14/45 of the men), had evidence of LVH. Valve sizes correlated for body surface area (indexed valve size) in patients with LVH were similar to those in patients without LVH (Figure 3). This suggests that valve mismatch was not the reason for LVH seen at long-term follow-up in this subgroup of patients. Indexed valve area stratified according to valve size showed a trend toward higher mean indexed valve sizes for larger valves, which might suggest a relative mismatch for smaller valve sizes (Figure 4). However, LVMI increased with larger valve sizes, again indicating that valve size or valve mismatch was not the final determinant of LVMI or LVH. At follow-up, 69% ($n = 75/109$) had normal systolic left ventricular function, whereas 25% ($n = 28/109$) of the patients had mildly impaired left ventricular function, 3% ($n = 3/109$) had moderately impaired left ventricular function, and 3% ($n = 3/109$) had severely impaired left ventricular function.

None or trivial, mild, moderate, and severe aortic insufficiencies were found in 65% ($n = 71/109$), 31% ($n = 34/109$), 3% ($n = 3/109$), and 1% ($n = 1/109$) of the patients, respectively. Mitral regurgitation at follow-up was none or trivial in 28% of the patients ($n = 31/109$), mild in 49% ($n = 53/109$), moderate in 19% ($n = 21/109$), and severe in 4% ($n = 4/109$). There was no significant difference in mitral regurgitation between patients with and without preoperative coronary artery disease ($P = .3$). Furthermore, when patients were stratified according to both preoperative aortic insufficiency and mitral regurgitation at follow-up, there was no significant difference in LVMI between groups (Figure 5). However, a trend toward higher LVMI was seen in patients with preoperative aortic insufficiency and more than mild mitral regurgitation at follow-up echocardiography.

Discussion

The use of glutaraldehyde-treated bovine pericardial valves for AVR was introduced in 1971 by Ionescu and associates.⁷ Those valves were at the time superior to porcine valves from a hemodynamic point of view⁸ but showed signs of limited durability in fatigue tests, a problem that was later confirmed clinically.^{9,10} The CEP aortic valve was introduced after several design changes, which included improved tissue preservation, a more flexible stent, a modified shape of the cusps, and modified tissue-mounting of the pericardium in the stent. Early clinical and hemodynamic studies showed excellent results.^{11,12} Several studies have shown excellent long-term durability with CEP valves,¹⁻⁴ which seems to be related to a lower risk of primary tissue failure than seen with older porcine and bovine pericardial valves.

In this report of clinical and hemodynamic late outcomes after AVR with the CEP bioprosthesis, we confirm previous studies indicating good results comparable to newer porcine

Figure 3. Valve size indexed to body surface area (BSA) and LVMI stratified for patients with (squares) and without (circles) LVH.

TABLE 5. M-mode echocardiographic results and calculations of CEP aortic valve bioprosthesis according to valve size at follow-up

Valve size (mm)	No. of patients	LVEDD (mm)	IVS (mm)	PW (mm)	LVM (g)	LVMI (g/m ²)	LVH (No.)
19	5	41.0 ± 10.9	13.1 ± 1.9	10.5 ± 1.5	166.6 ± 69.7	103.2 ± 35.5	2 (40%)
21	45	42.1 ± 6.0	11.6 ± 2.6	10.3 ± 2.2	161.1 ± 51.8	97.0 ± 29.4	14 (31%)
23	33	45.6 ± 5.9	12.6 ± 2.2	10.4 ± 1.8	192.2 ± 53.7	105.7 ± 28.0	11 (33%)
25	22	49.1 ± 9.4*	13.7 ± 3.3	11.1 ± 1.9	243.4 ± 94.2*	129.7 ± 46.0*	11 (50%)
27	4	44.4 ± 3.6	13.8 ± 3.8	11.8 ± 1.7	219.2 ± 76.1	119.7 ± 43.1	2 (50%)
All sizes	109	44.6 ± 7.4	12.5 ± 2.7	10.5 ± 2.0	189.0 ± 70.5	107.2 ± 35.3	40 (37%)

All values are expressed as mean ± SD. (Significant differences between valve sizes according to Scheffé test are indicated by symbols.) LVEDD, Left ventricular end-diastolic dimension; IVS, interventricular septum; PW, posterior wall; LVM, left ventricular mass; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy.

* $P < .05$, size 25 versus size 21 mm.

valves.^{2,3,13} Banbury and associates² and Neville and associates⁴ reported similar 5- and 10-year survivals, although in somewhat younger patient populations than in our study, for the CEP bioprosthesis in the aortic position. Table 6 shows survivals and freedoms from structural valve degeneration in earlier reported studies of the CEP pericardial bioprosthesis. Poirier and coworkers³ have reported excellent survival rates in a younger patient population than ours. Survivals for our patient population with the CEP bioprosthesis were lower than in our population with the Hancock II porcine bioprosthesis.¹³ However, our patients with the CEP bioprosthesis were significantly older than those with the Hancock II porcine bioprosthesis (Table 6). We have previously shown that advanced age, male sex, advanced left ventricular dysfunction, coronary artery disease, and advanced NYHA functional class are independent predictors of mortality among patients with AVR.¹⁴ Our patient pop-

ulation was in general older and had more coronary artery disease than in other studies.^{1-4,11,13} Considering the risk factor profile in our study, the survival must be considered satisfactory. As anticipated, the multivariate analysis from our study showed that coronary artery disease and NYHA class III or IV were risk factors for late death and for cardiac non-valve-related death.

Our study confirms that the CEP bioprosthesis is associated with a low incidence of structural valve dysfunction comparable to earlier reports¹⁻⁴ (Table 6). In our population, no patient older than 65 years has required reoperation because of structural valve degeneration. Some authors have even indicated that the CEP bioprosthesis may be superior to stented porcine bioprostheses in terms of structural valve dysfunction.² When the CEP valve is compared with the Hancock II, a second-generation porcine aortic valve, however, the risk of degeneration appears to be

Figure 4. Mean valve size indexed to body surface area (BSA) for all aortic valve sizes. *Darkest shading, 27 mm; second darkest, 21 mm; median shading, 19 mm; second lightest, 25 mm; lightest, 23 mm.*

Figure 5. LVMI stratified for preoperative aortic insufficiency (AI) and mitral regurgitation (MR) on follow-up echocardiogram. *Dark bars, Aortic insufficiency value of 1; light bars, aortic insufficiency value of 0.*

similar. In our experience the Hancock II was used in a younger patient population, and the freedom from valve degeneration was similar to that of the CEP valve. The clinical and hemodynamic data of the CEP and Hancock II valves are similar according to our experience.¹⁵ Transvalvular gradients and aortic valve areas for the CEP appear to be slightly worse than those of the Hancock II according to retrospective studies. However, neither of these valves has as good hemodynamic data as the Toronto SPV or the Freestyle bioprosthesis.^{16,17} There are a few long-term reports with echocardiography on the CEP. Frater and co-

workers¹¹ reported aortic valve areas somewhat similar to those found in our study after a mean follow-up of 67 months.

We found that LVH was still present at long-term follow-up in about a third of the patients. In contrast, as previously reported by our group,¹⁶ only 8% of the patients with a Toronto SPV had LVH by echocardiography after a similar mean follow-up of 5 years. However, we have also showed that sex, hypertension, cause of valve disease, and presence of coronary artery disease,¹⁶ as well as genetic factors,¹⁸ influence both the preoperative degree of LVH

TABLE 6. Survival and structural valve degeneration data for CEP bioprosthesis

Reference	No. of patients	Mean age (y)	Survival			Freedom from structural valve degeneration		
			5 y	10 y	12 y	5 y	10 y	12 y
Pericardial (Carpentier-Edwards)								
Pellerin et al, ¹ 1995	124	64.9 ± 13.6			50% ± 7%	100%	100%	100%
Banbury et al, ² 1998	310	64.2 ± 10.8	83% ± 2%	47% ± 3%	34% ± 3%	100%	91% ± 3%	82% ± 4%
Poirier et al, ³ 1998	812	64	80% ± 2%	69% ± 3%	68% ± 3%	99% ± 0.5%	93% ± 2%	80% ± 5%
Neville et al, ⁴ 1998	787	68.3 ± 10.8			53% ± 0.5%	99% ± 1%	94% ± 4%	94% ± 4%
Current study	254	71.3 ± 8.8	80% ± 3%	50% ± 8%	36% ± 9%	100%	86% ± 9%	86% ± 9%
Porcine (Hancock II)								
David et al, ¹³ 1998	723	65 ± 12	79% ± 2%	61% ± 3%	54% ± 4%	100%	97% ± 1%	94% ± 2%

Data are mean ± SD when available.

and its regression. Thus many confounding factors exist between the previously mentioned studies, which makes it difficult to safely conclude anything regarding the degree of LVH at late follow-up. Maybe the most surprising finding of the late follow-up echocardiography was that 23% of the patients had moderate or severe mitral regurgitation. However, we were not able to show that either mitral regurgitation or preoperative aortic insufficiency was significantly more common among patients with LVH than among those without LVH.

Limitations of the Study

This study was retrospective, and therefore the valve-related complication rates were probably underestimated because follow-up was only obtained once for this population. However, the follow-up was 100% complete and reliable with respect to survival, reoperation, and echocardiographic data. The last, however, must be interpreted with caution, because the analysis was performed retrospectively and only included about 60% of the population who were alive at the time of the study.

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Appendix

Doppler Echocardiography

Color flow Doppler echocardiography was used to assess aortic insufficiency in the parasternal long- and short-axis views and in the apical 5- and 3-chamber views. Two-dimensional guided and

stand-alone continuous-wave Doppler modes were used to interrogate flow through the aortic valve from multiple positions. Pulsed-wave Doppler was used to assess flow in the left ventricular outflow tract (LVOT).

The peak ($V_{AV_{max}}$) and mean ($V_{AV_{mean}}$) systolic flow velocities (in meters per second) across the aortic valve were recorded with continuous-wave Doppler, and those proximal to the aortic valve in the LVOT ($V_{LVOT_{max}}$ and $V_{LVOT_{mean}}$) were recorded with pulsed-wave Doppler. The average of three consecutive cardiac cycles in sinus rhythm or of 10 cardiac cycles in atrial fibrillation was used to calculate transaortic velocities and velocity time integrals (VTI_{AV} and VTI_{LVOT} , in centimeters). Peak ($PLVOT_{peak}$ and PAV_{peak}) and mean (PAV_{mean} and $PLVOT_{mean}$) pressure differences (in millimeters of mercury) were calculated according to the modified Bernoulli equation¹:

$$P_{peak} = 4 \times (V_{AV_{max}}^2 - V_{LVOT_{max}}^2)$$

$$P_{mean} = PAV_{mean} - PLVOT_{mean}$$

$$PAV_{mean} - PLVOT_{mean} = 4 \times (V_{AV_{mean}}^2 - V_{LVOT_{mean}}^2)$$

The LVOT diameter (D , in centimeters) was determined in midsystole from the parasternal long-axis view. The effective orifice area (EOA , in centimeters) was calculated with the continuity equation¹:

$$EOA (cm^2) = 3.14 \times 2D/4 \times VTI_{LVOT}/VTI_{AV}$$

Cardiac output (CO , in liters per minute) was calculated as the product of stroke volume and heart rate (HR , in beats/min)¹:

$$CO = HR \times (3.14 \times 2D/4 \times VTI_{LVOT})/1000$$

Measurements of interventricular septum (IVS) and posterior wall (PW) thicknesses (in centimeters) and left ventricular end-diastolic dimension ($LVEDD$, in centimeters) were obtained with 2-dimensional echocardiography in a standard fashion. Left ventricular mass (LVM , in grams) was calculated from IVS and PW thicknesses and the $LVEDD$ according to the American Society of Echocardiography cube method²:

$$LVM = 0.8 \times 1.04 \times [(IVS + PW + LVEDD)^3 - (LVEDD)^3] + 0.6$$

The left ventricular mass index was calculated by dividing LVM by body surface area.

Aortic insufficiency was assessed with color flow Doppler and CW and PW Doppler in any view.³ The ejection fraction was determined according to the Simpson rule and left ventricular function was classified by ejection fraction as grade 1 (>60%), grade 2 (40%-60%), grade 3 (20%-40%), or grade 4 (<20%).¹

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