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HEMODYNAMIC BENEFITS OF THE TORONTO STENTLESS VALVE

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We report on 254 consecutive patients (170 male, 84 female) undergoing aortic valve replacement with the Toronto SPV Stentless Valve (St. Jude Medical, Inc., St. Paul, Minn.). Mean age (± standard deviation) was 62.1 ± 11.6 years. Three patients (1%) received sizes 21 or 22 mm, 24 (9%) received size 23 mm, and 227 patients (89%) received sizes 25, 27, or 29 mm. Serial echocardiography was used to assess valve performance during a 3-year follow-up. Mean gradient decreased by 35.8% ($p < 0.0001$; 95% confidence interval −39.6%, −31.7%) from postoperative values to the 3- to 6-month follow-up and by 6.1% ($p = 0.004$; 95% confidence interval −10.1%, −2%) at each subsequent interval; effective orifice area increased by 17.2% ($p = 0.0001$; 95% confidence interval 12.0%, 22.6%) initially and by 4.4% ($p < 0.001$; 95% confidence interval 1.8%, 7.0%) thereafter. At 2 years of follow-up, mean gradient was 3.3 ± 2.1 mm Hg and mean effective orifice area was 2.2 ± 0.8 cm^2. Studies on left ventricular mass were carried out on 84 patients. Left ventricular mass decreased by 14.3% (37.8 ± 57.9 gm; $p < 0.0001$; 95% confidence interval −53.7, −21.9 gm) and left ventricular mass index decreased by 15.2% (21.1 ± 30.5 gm/m^2; $p < 0.0001$; 95% confidence interval −29.5, −12.7 gm/m^2) from postoperative values to the 3- to 6-month follow-up interval. The reduction in residual gradient and potential regression in left ventricular hypertrophy may have a beneficial prognostic implication. We believe that the unique stentless design of the Toronto SPV Stentless Valve allows this to occur. (J Thorac Cardiovasc Surg 1996;112:1431-46)

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Cardiac myocytes, unlike cells from other organs, proliferate only in the fetal period; soon after birth they lose their ability to replicate deoxyribonucleic acid.[1, 2] However, adaptive growth of the heart must still occur in response to physiologic demands and pathologic states that increase cardiac work.[3] Postnatal cardiac development must therefore maintain proper allometric ratio of heart to body size and also allow matching of heart size to functional load during adaptation to altered hemodynamic requirements.

Ventricular hypertrophy is a physiologic response to an altered hemodynamic state; it can occur in several pathological conditions including valvular heart disease. The hypertrophic response is mediated by classic signal transduction mechanisms,[1, 2, 4-7] with activation of a specific family of genes[8, 9] that function as mediators of long term cellular responses.[4] The salient feature of transduction pathways is that the signal mechanisms must be sustained to maintain the process.

Aortic valvular disease is known to produce left ventricular hypertrophy (LVH). If signal transduction mechanisms are operational in the induction of LVH in human beings, then correction of the valve lesion, although it may alleviate symptoms, may not necessarily result in regression of LVH if a residual gradient exists. We have observed that transvalvular gradients decrease with time in patients who undergo aortic valve replacement (AVR) with a Toronto SPV Stentless Valve (SPV; St. Jude Medical, Inc., St. Paul, Minn.). The initial clinical results on this group of patients are reported elsewhere.[10] In this report, we focus on the hemodynamic changes to support the hypothesis that ventricular remodeling occurs after AVR with a stentless bioprosthesis.

Materials and methods

Patient population. In this cohort, 254 patients underwent AVR (with or without concomitant coronary bypass) with the SPV before December 31, 1995. For this report, the implanting centers were Sunnybrook Health Science Center ($N = 84$ patients) and Toronto Hospital ($N = 170$ patients) in Toronto, Ontario, Canada. All patients are part of an international phase II, multicenter, prospective clinical trial to assess the safety and efficacy of the SPV. Clinical patient characteristics are summarized in Table I.

Study valve. The SPV is a stentless porcine valve manufactured by St. Jude Medical (St. Paul, Minn.). It is an excised porcine aortic valve fixed in glutaraldehyde under low pressure. The SPV comprises only the valve and sufficient aortic wall tissue to support the commissures and leaflets. It is covered with a single layer of fine Dacron polyester fabric.[11, 12] Three colored sutures are placed at the base of the inflow at 120 degrees intervals to facilitate implantation. The SPVs were implanted with a technique that is similar to that originally described by Ross[13] for freehand homografts and has been previously described.[12, 14]

Echocardiography. All patients who underwent AVR with an SPV were followed up with serial echocardiography. The first examination was performed early in the immediate postoperative period, usually just before discharge. Subsequent follow-up examinations were done between 3 and 6 months, at 1 year, and annually thereafter. Transthoracic echocardiographic analysis of the leaflets and the left ventricular outflow tract (LVOT) and continuous-wave and color Doppler studies were performed at each examination and used to assess valve function.

Statistical methods. Data from each center participating in the ongoing clinical trial were collected and analyzed by St. Jude Medical. Statistical analyses were performed with SAS (Statistical Analysis System, Cary, N.C.) and BMDP 5V statistical software packages (SPSS Inc., Chicago, Ill.). Discrete variables are presented as counts and percentages. Continuous variables are presented as means (± standard deviation). Formulas for calculating mean systolic gradient, effective orifice area (EOA), and left ventricular mass are provided in the Appendix. Statistical significance was at the nominal α level of 0.05.

Mean gradient and EOA were modeled with the longitudinal methods of Laird and Ware.[15] For each response, logs of the five serial measurements for a patient (early postoperative period, 3 to 6 months, 12 months, 24 months, and 36 months) were assumed to be an approximately multivariate normal vector with general covariance structure. The Laird-Ware method permits missing data. Means in the log scale for each period are estimated, adjusting for the observed patterns of missing data, making use of the correlation among the longitudinal observations. Means (in the log scale) were estimated separately for each size. Regression models were used to estimate the amount of change in the measurement from early postoperative period to 3 to 6 months and the trend in changes from 3 to 6 months to 3 years. The covariates were evaluated for importance singly and in combination by means of stepwise procedures. Arithmetic means in the log scale transform back to geometric means in the original scale. Plots of the estimated medians (with associated confidence limits) are provided.

For complication rates, both the simple percentage of patients with early events (<30 days) and linearized rates for late events (>30 days) are reported. Linearized rates (in percent per patient-year) were calculated by dividing the number of events by patient-years of follow-up and multiplying by 100%. Survival was determined by the Kaplan-Meier product limit method.[16] The number of patients at risk is shown for each interval, along with 95% confidence limits for the estimates.

Data on left ventricular mass were obtained from patients who were operated on at the Sunnybrook Health Science Centre ($N = 84$). All left ventricular mass and gradient data for this subset were analyzed with the advice of the Department of Research Design and Biostatistics, Sunnybrook Health Science Centre, University of Toronto,

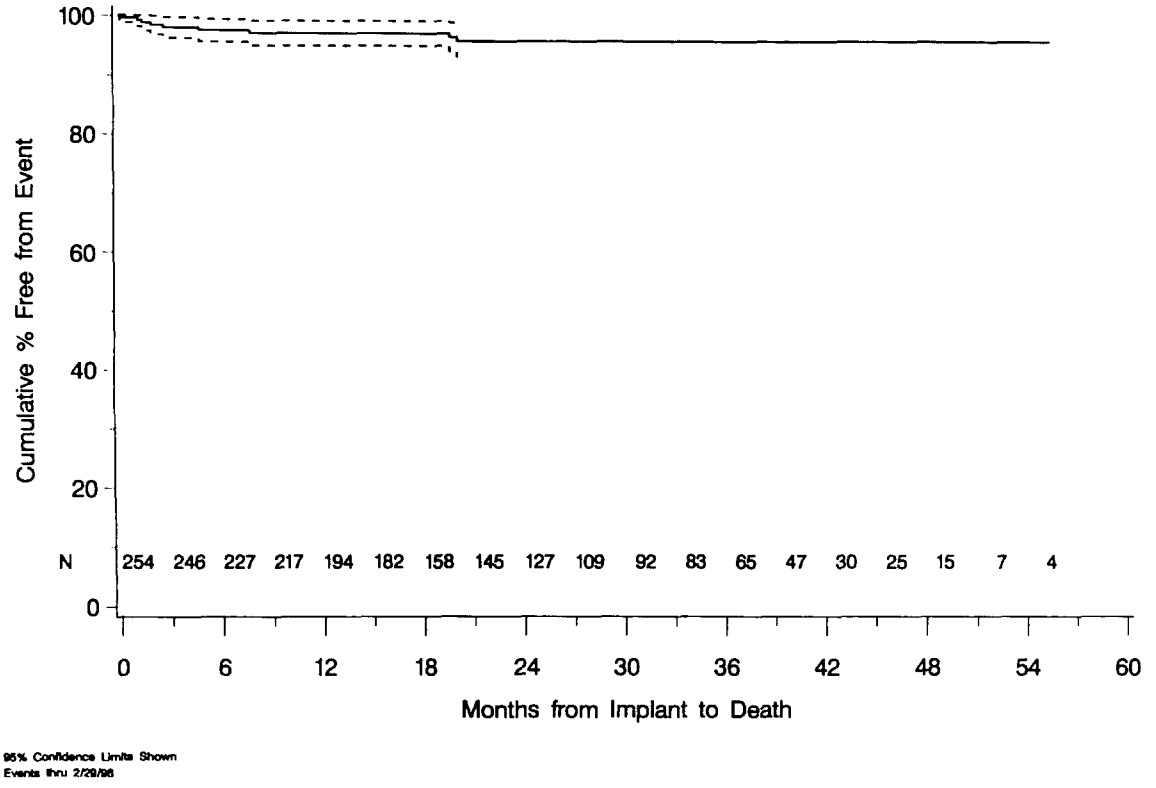


Fig. 1. Actuarial survival was determined by the Kaplan-Meier method. The number of patients at risk is shown along the *x*-axis. At 3 years after operation, survival was 95%.

Toronto, Canada. The initial change from postoperative period to the 3 to 6 month interval for the continuous variables (peak and mean gradient, EOA, thickness of intraventricular septum, posterior left ventricular wall thickness, left ventricular mass, and left ventricular mass index) was tested by matched pairs *t* test. Further analysis of left ventricular mass and gradient with time up to the 1-year interval was performed in two steps. Initially, a multivariate analysis of variance of both left ventricular mass and gradient up to the 1-year interval was applied to establish the statistical significance of the overall effect of time on both of the primary dependent variables (gradient and left ventricular mass) considered together. Subsequently, for each dependent variable one repeated measures analysis of variance with contrasts of each time interval with the postoperative baseline was used to establish change with time.

Results

Clinical outcome. Demographic, etiologic, and perioperative data are summarized in Table I. At the time of this report, 120 patients have reached the 2-year follow-up interval, 57 patients have reached the 3-year mark, and 14 have reached the 4-year mark. Although 84% of patients were in New York Heart Association functional classes II and III before operation, these proportions had changed to 92% in class I, 7% in class II, 1% in class III, and 0% in class IV at 3 to 6 months. At 1 year and at later visits, 99% or more patients were in classes I and II, with most being in class I.

Table II provides complication rates. There were two endocarditis events (both late), two patients had anticoagulant-related hemorrhages (both late), four had myocardial infarctions (three early, one late), and one had thrombosis (late, endocarditis-related) event. In addition, there were 11 thromboembolic events (four early and seven late), all of which were neurologic (transient ischemic attack or stroke).

There were nine deaths (one early and eight late) in this cohort, three of which were valve related. Two patients died of bacterial endocarditis (at 34 and 42 postoperative days), and one patient died of intracerebral hemorrhage 20 months after operation. This patient was receiving warfarin (coumadin) because of a previous transient ischemic attack. The six non-valve-related deaths were caused by right ventricular infarction from injury to the right coronary artery (at 2 days), cardiac arrhythmia or arrest (at 58 days), suicide (at 80 days), myocardial infarction from concomitant atherosclerosis (at 143 days),

Table I. *Patient characteristics (N = 254)*

Characteristic	*N*	*Mean + SD (continuous) or % (categoric)*	*Minimum*	*Maximum*
Sex				
Female	84	32.3%		
Male	170	67.7%		
Age group (yr)				
<40	19	7.5%		
40–49	25	9.8%		
50–59	43	16.9%		
60–69	103	40.6%		
70–79	60	23.6%		
≥80	4	1.6%		
Age (yr)	254	62.1 ± 11.6	33.3	93.4
Body surface area (m^2)	254	1.9 ± 0.2	1.4	2.5
Valve size implanted (mm)				
21	1	0.4%		
22	2	0.8%		
23	24	9.4%		
25	62	24.4%		
27	93	36.6%		
29	72	28.3%		
Preoperative NYHA class				
I	17	6.7%		
II	94	37.0%		
III	120	47.2%		
IV	23	9.1%		
NYHA class at 3–6 months				
I	210	92.1%		
II	16	7.0%		
III	2	0.9%		
IV	0	0.0%		
Aortic valve disease etiology				
Calcification	177	69.6%		
Congenital defect	100	39.3%		
Rheumatic disease	29	11.4%		
Endocarditis	4	1.5%		
Structural deterioration	1	0.3%		
Prosthesis dysfunction	7	2.7%		
Other etiology	6	2.3%		
Initial condition of the anulus				
Normal	10	3.9%		
Stenotic only	198	78.0%		
Enlarged/dilated only	12	4.7%		
Mixed	4	1.6%		
Other	2	0.8%		
Unknown	28	11.0%		
Condition of preexisting aortic valve				
Normal	1	0.4%		
Scarred or fibrosed leaflets	125	49.2%		
Leaflet torn or ruptured	12	4.7%		
Calcified leaflets	226	89.0%		
Infection	2	0.8%		
Commissural fusion	65	25.6%		
Bicuspid valve	123	48.4%		
Bioprosthesis dysfunction	2	0.8%		
Other	13	5.1%		
Previous cardiovascular operations				
Coronary artery bypass grafting	4	1.5%		
Permanent pacemaker insertion	5	1.9%		

Table I. *Cont'd*

Characteristic	*N*	*Mean + SD (continuous) or % (categoric)*	*Minimum*	*Maximum*
Aortic valve repair	0	0.0%		
Aortic valve replacement	4	1.5%		
Other cardiovascular operations	7	2.7%		
Concomitant coronary bypass	83	32.7%		
Cardiopulmonary bypass time (min)				
All patients	254	121.2 ± 40.0	58	277
Patients with no concomitant procedures	160	109.3 ± 32.0	58	190
Aortic crossclamp time (min)				
All patients	254	96.3 ± 40.8	46	253
Patients with no concomitant procedures	160	90.1 ± 27.7	46	171
Anticoagulant and antiplatelet therapies at discharge	253			
Aspirin or other platelet inhibitor	228	90.1%		
Dipyridamole	7	2.8%		
Coumadin	11	4.3%		
None	13	5.1%		

SD, Standard deviation; *NYHA,* New York Heart Association.

Table II. *Complication rates for primary and secondary events* (N = 254 patients)*

	Early events (≤30 days)		*Late events (>30 days)*		
Event	*No.*	*Simple %*	*No.*	*Patient-years at risk*	*Linearized rate† (%/patient-year, ± SE)*
Endocarditis	0	0.0	2	522.6	0.4 ± 0.3
Anticoagulant-related hemorrhage	0	0.0	2	521.9	0.4 ± 0.3
Myocardial infarction	3	1.2	1	516.4	0.2 ± 0.2
Thromboembolism	4	1.6	7	499.6	1.4 ± 0.5
Thrombosis	0	0.0	1	522.6	0.2 ± 0.2
Death (all causes)	1	0.4	8	522.6	1.5 ± 0.5

SE, Standard error.

*Both primary and secondary events are included (e.g., thrombosis secondary to endocarditis would be counted in both event categories).

†Linearized rates are calculated by dividing the number of events by the patient's years of follow-up × 100%.

Table IIIa. *Severity of aortic insufficiency by visit*

Visit	*No. echocardiographic examinations*	*Trivial*		*Mild*		*Moderate*		*Severe*	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Early	248	11	4.4	5	2.0	0	0.0	0	0.0
3–6 month	227	8	3.5	12	5.3	0	0.0	0	0.0
12 months	179	5	2.8	8	4.5	0	0.0	0	0.0
24 months	113	7	6.2	2	1.8	1	0.9	0	0.0
36 months	58	3	5.2	1	1.7	0	0.0	0	0.0
All visits	825	34	4.1	28	3.4	1	0.1	0	0.0

malignancy (at 235 days), and pneumonia (at 612 days). The Kaplan-Meier freedom from death at 3 years was 95.9% ± 1.4% (Fig. 1).

Echocardiographic studies. Transthoracic echocardiography was used to assess both the clinical performance of the valve (leaflet function, insufficiency, thrombosis) and the hemodynamics (transvalvular mean gradient and EOA). In the early postoperative period, 94% showed no insufficiency;

Table IIIb. *Severity of aortic insufficiency categorization*

	Ratio of area of jet to area of LVOT (short-axis view)	*Ratio of height of jet to height of LVOT (long-axis view)*
Trivial	<4	<24
Mild	4–<25	24–<45
Moderate	25–<60	45–<65
Severe	≥60	≥65

Table IV. *Mean gradient and effective orifice area by postoperative visit*

		Mean gradient (mm Hg)		*EOA (cm^2)*	
Valve size (mm)	*Postoperative visit*	*N*	*Mean ± SD*	*N*	*Mean ± SD*
23	Early	24	8.4 ± 3.8	24	1.29 ± 0.42
	3–6 month	22	5.4 ± 3.4	21	1.56 ± 0.63
	12 months	15	5.5 ± 2.6	15	1.49 ± 0.45
	24 months	7	4.2 ± 2.2	7	1.55 ± 0.38
	36 months	5	4.7 ± 4.3	5	1.80 ± 0.84
25	Early	61	6.7 ± 3.0	60	1.44 ± 0.43
	3–6 months	57	5.2 ± 2.9	56	1.61 ± 0.55
	12 months	45	4.9 ± 2.8	45	1.70 ± 0.78
	24 months	29	4.4 ± 2.8	29	1.73 ± 0.58
	36 months	12	4.4 ± 3.6	11	2.22 ± 1.40
27	Early	86	6.0 ± 2.6	86	1.64 ± 0.47
	3–6 months	79	3.7 ± 1.9	79	2.06 ± 0.65
	12 months	66	3.7 ± 2.1	66	2.12 ± 0.66
	24 months	42	3.0 ± 1.7	42	2.33 ± 0.71
	36 months	20	2.5 ± 1.4	20	2.62 ± 0.90
29	Early	69	4.8 ± 2.6	69	2.07 ± 0.60
	3–6 months	64	3.2 ± 1.9	64	2.45 ± 0.86
	12 months	50	2.4 ± 1.4	50	2.70 ± 1.03
	24 months	33	2.4 ± 1.2	33	2.70 ± 0.85
	36 months	19	2.5 ± 1.2	19	2.70 ± 1.02
All	Early	240	6.1 ± 3.0	239	1.68 ± 0.57
	3–6 months	222	4.1 ± 2.5	220	2.01 ± 0.77
	12 months	176	3.8 ± 2.4	176	2.12 ± 0.89
	24 months	111	3.2 ± 2.1	111	2.23 ± 0.81
	36 months	56	3.1 ± 2.4	55	2.49 ± 1.06

Data are presented as mean ± standard deviation.

Table V. *Estimated percentage changes for mean gradient and EOA*

	Mean gradient (mm Hg)		*EOA (cm^2)*	
Period	*% change*	*p for Z statistic*	*% change*	*p for Z statistic*
Relative change from early postoperative period to 3–6 months	−35.8 (−39.6, −31.7)	<0.0001	17.2 (12.0, 22.6)	<0.0001
Slope from 3–6 months to 3 years (change per period)	−6.1 (−10.1, −2.0)	0.004	4.4% (1.8%, 7.0%)	<0.0001

The 95% confidence intervals are given in parentheses.

the other 6% showed trivial or mild insufficiency. At subsequent follow-up visits, fewer than 9% of the patients showed trivial or mild insufficiency. The degree of insufficiency by visit is given in Table III.

Table IV presents the means of mean systolic gradient and EOA for each postoperative visit. Table V gives the estimated percentage change in mean systolic gradient and EOA from early postoperative period to 3 to 6 months and the trend (slope) for 3 to 6 months to 36 months. Overall, the mean gradient decreased 35.8% in the early postoperative period to 3- to 6-month period and decreased approximately 6.1% each period thereafter. EOA increased 17.2% from the early postoperative period to the 3- to 6-month period and increased approximately 4.4% each period thereafter. All changes were in the direction of improvement and were highly statistically significant. Plots of the estimated medians for each valve size are given in Figs. 2 through 9.

Table VI reports the results from the longitudinal multiple regression models used to evaluate the effects of the covariates. These covariates included valve size, hospital where implantation was performed, age at implantation, sex, date of implantation, body surface area, preoperative New York Heart Association functional class, whether the valve replaced was stenotic or enlarged/dilated before operation, and whether other cardiac procedures were performed concomitantly

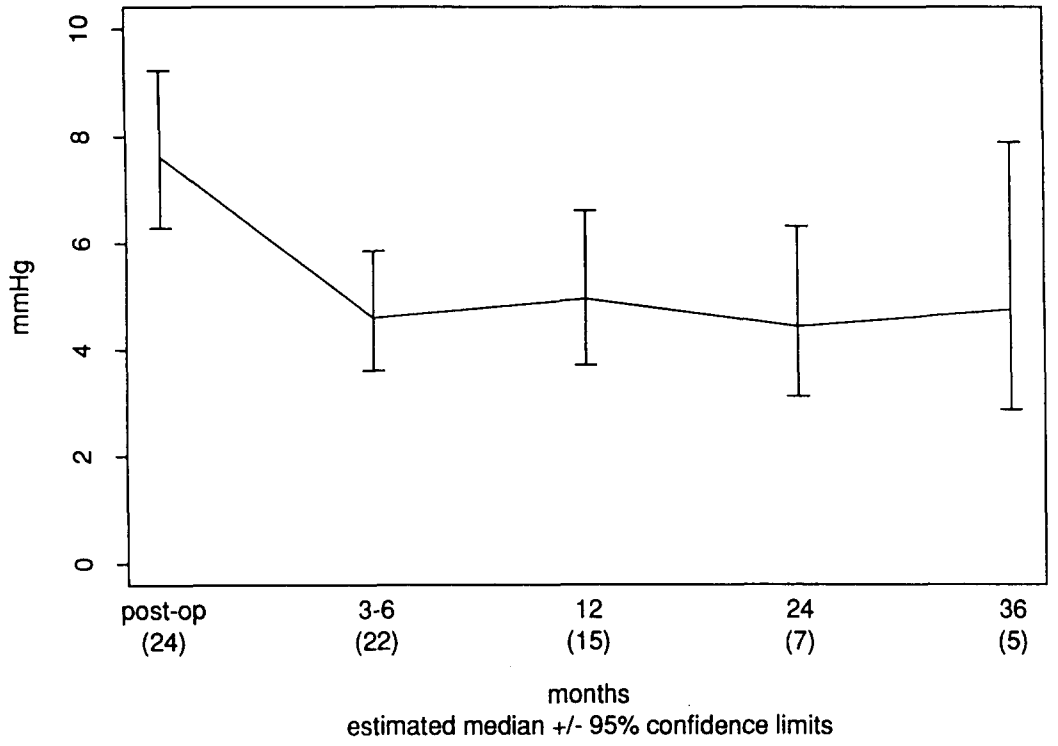


Fig. 2. Change in mean valvular gradient as a function of time for valve size 23 mm. Numbers of patients at each follow-up interval are shown in parentheses.

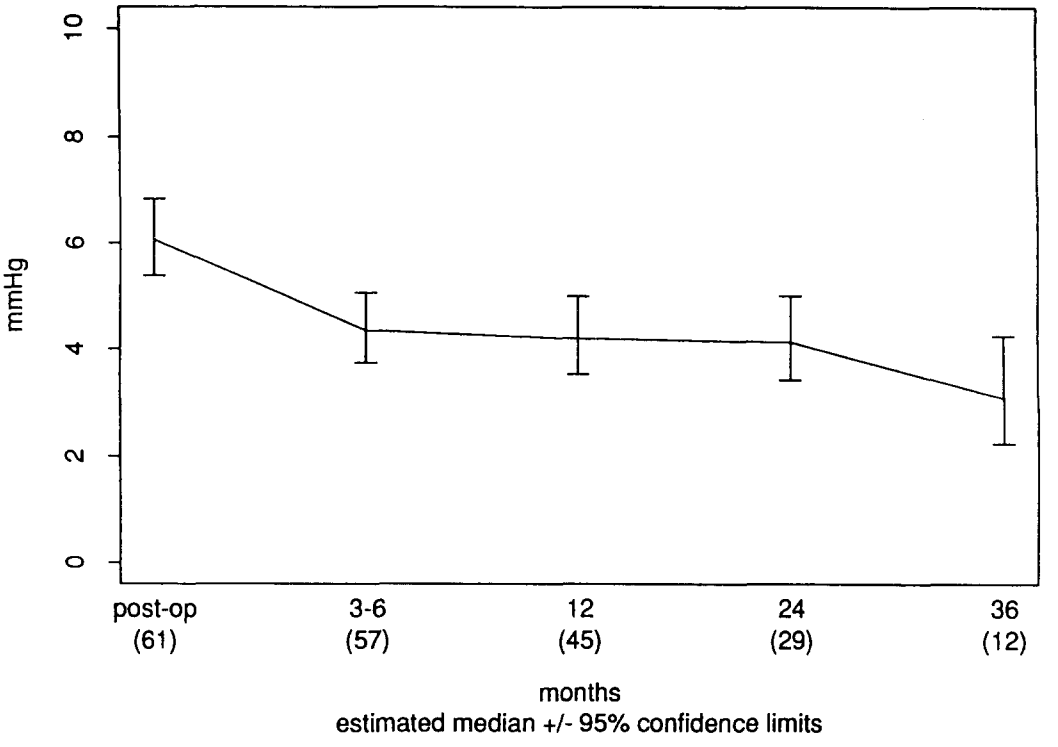


Fig. 3. Change in mean valvular gradient as a function of time for valve size 25 mm. Numbers of patients at each follow-up interval are shown in parentheses.

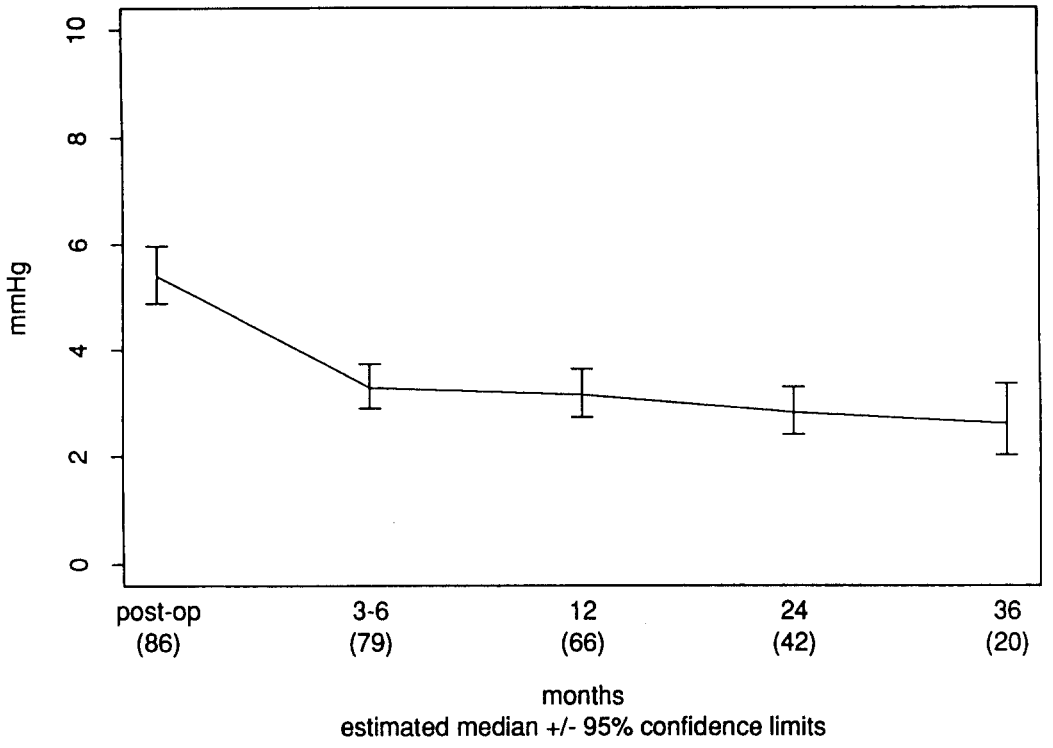


Fig. 4. Change in mean valvular gradient as a function of time for valve size 27 mm. Numbers of patients at each follow-up interval are shown in parentheses.

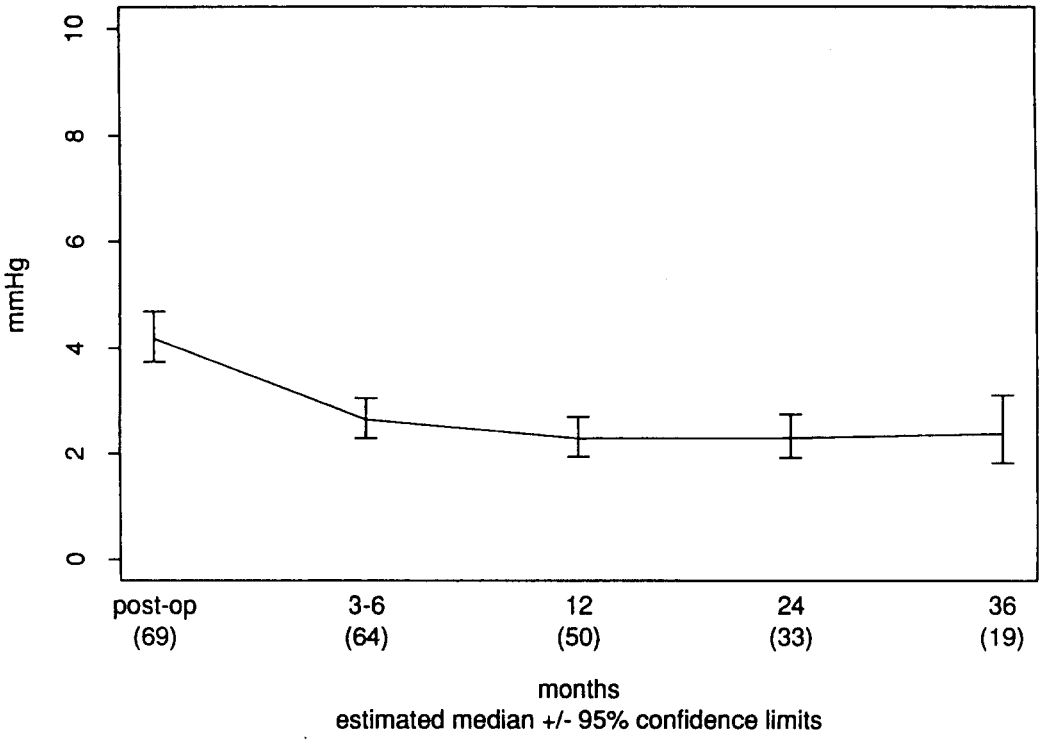


Fig. 5. Change in mean valvular gradient as a function of time for valve size 29 mm. Numbers of patients at each follow-up interval are shown in parentheses.

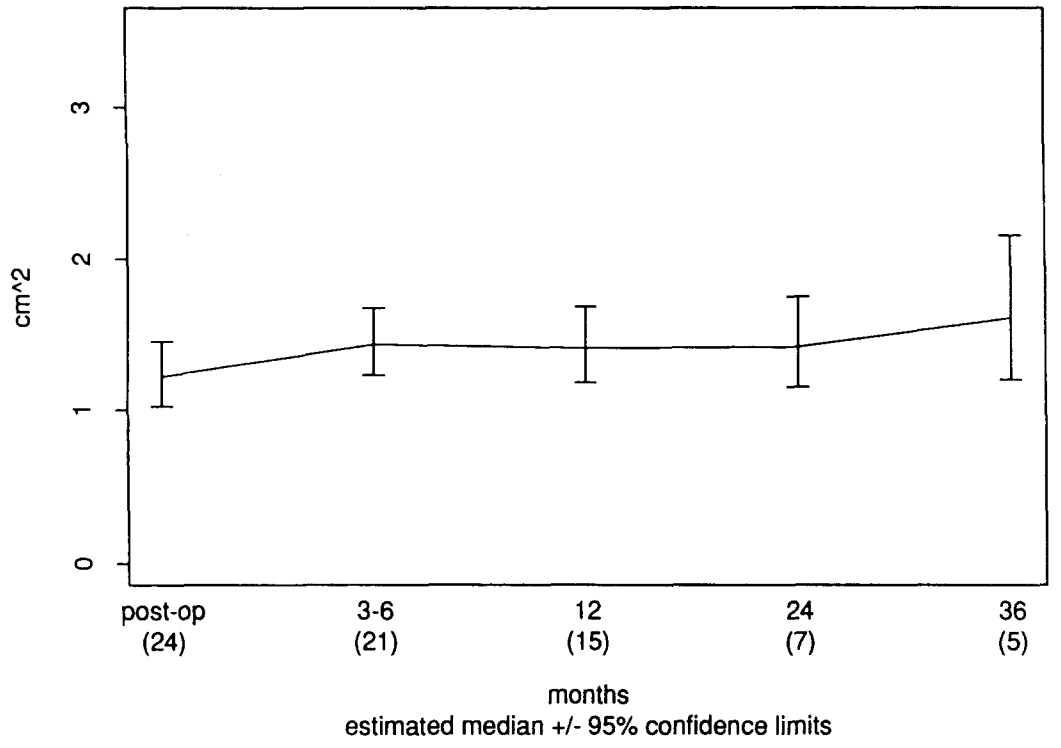


Fig. 6. Change in EOA as a function of time for valve size 23 mm. Numbers of patients at each follow-up interval are shown in parentheses.

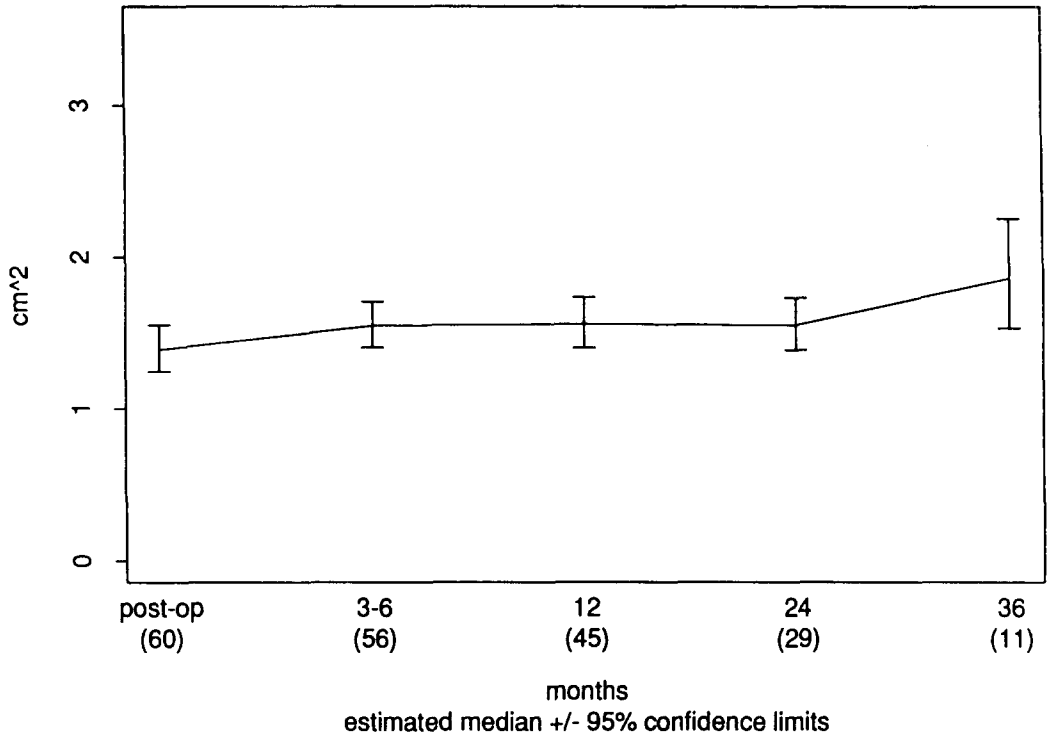


Fig. 7. Change in EOA as a function of time for valve size 25 mm. Numbers of patients at each follow-up interval are shown in parentheses.

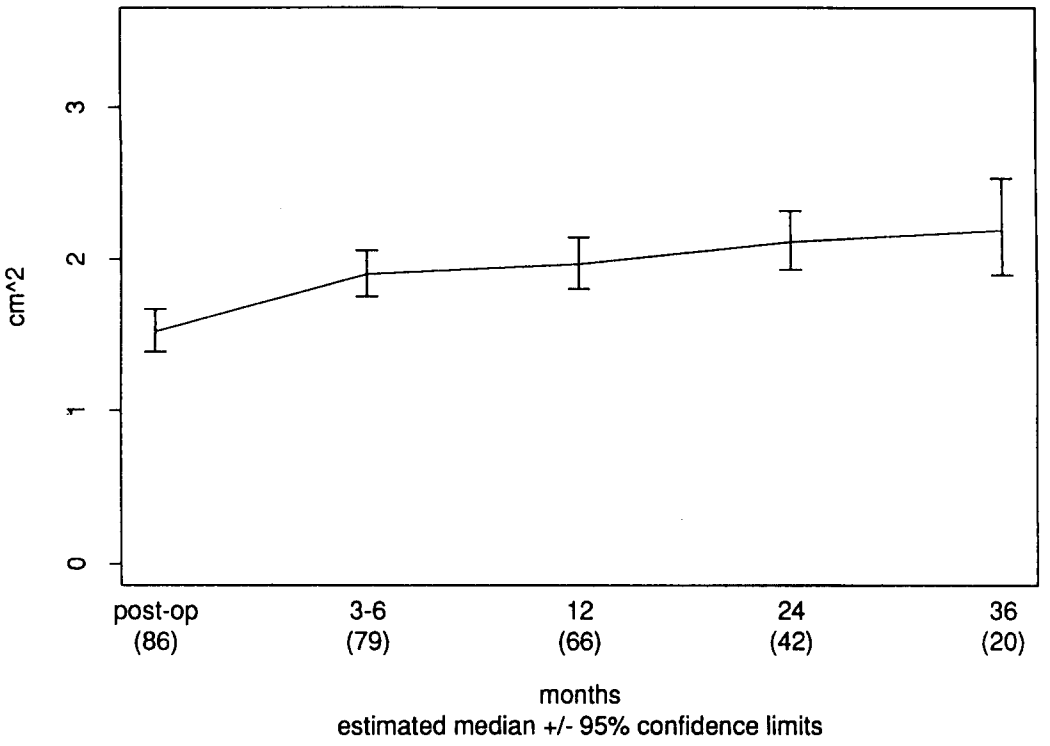


Fig. 8. Change in EOA as a function of time for valve size 27 mm. Numbers of patients at each follow-up interval are shown in parentheses.

with the valve operation. The estimates and 95% confidence intervals in Table VI give estimated percentage changes from the postoperative period to 3- to 6-month follow-up interval and estimated percentage changes from the 3- to 6-month interval to 3 years for mean transvalvular gradient and for EOA. Entries marked with asterisks are estimates of statistically significant effects included in the model and based on the results of the stepwise procedure. Unmarked entries are estimated effects determined by adding that term alone to the stepwise model. None of the covariate effects are as large as the overall effects.

Table VII examines the changes in hemodynamics and left ventricular mass for patients operated on at Sunnybrook Health Science Centre. These data demonstrate a significant reduction in thickness of both the intraventricular septum and the posterior wall of the left ventricle from the postoperative period to the first follow-up visits. These changes resulted in a net decrease in left ventricular mass of 37.8 ± 57.9 gm (14.3%) and a reduction in left ventricular mass index of 21.1 ± 30.5 gm/m^2 (15.2%) during this period.

Multivariate analysis of variance demonstrated a statistically discernible relationship between transvalvular gradient and left ventricular mass through a 1-year period ($p < 0.001$) in the Sunnybrook subset ($N = 84$). Subsequent univariate analysis of variance for each dependent measure established robust effects for time (up to 1 year) and for each interval when compared with the postoperative baseline value ($p < 0.001$ for all). These results during this interval replicate the previous analysis on the entire cohort ($N = 254$, Table V). Changes in left ventricular mass with time are illustrated in Fig. 10.

Discussion

This report details the hemodynamic results of 254 patients enrolled in the ongoing multicenter trial of the SPV. The clinical results of a subset of these patients are reported elsewhere.[10]

The excellent hemodynamic performance of stentless bioprostheses has been repeatedly demonstrated by several investigators.[10, 11, 14, 17-22] In a recent study comparing the SPV with a conventional stented heterograft, we demonstrated that it is possible to implant significantly larger valves in patients matched for body surface area and clinical characteristics if the SPV is used.[14] In that study, patients in whom the SPV was used received a prosthesis on average 2.4 sizes larger than that used in patients

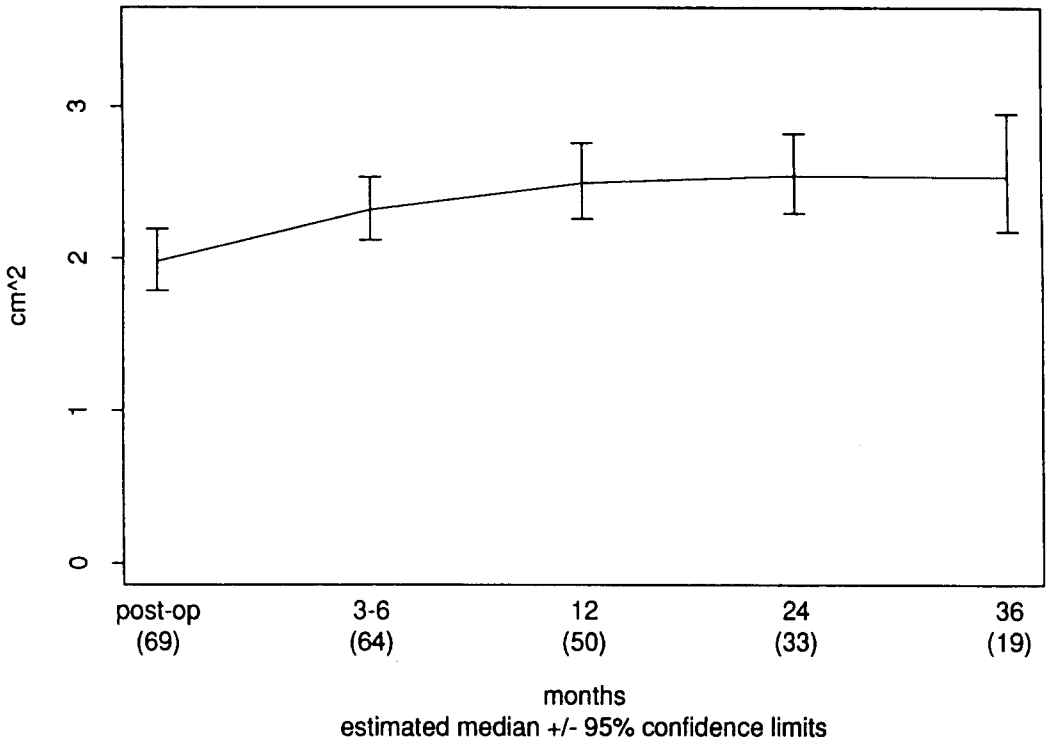


Fig. 9. Change in EOA as a function of time for valve size 29 mm. Numbers of patients at each follow-up interval are shown in parentheses.

who received conventional stented bioprostheses was used. In repeated studies, we have observed that postoperative gradients after AVR with the SPV were significantly lower than postoperative gradients seen when a conventional stented valve was used.[11, 14] The elimination of the stent and sewing ring allows the implantation of a larger bioprosthesis in any given root. Furthermore, the leaflets of the stentless heterograft may open more fully because the commissural areas are pulled apart during systole as the sinuses of Valsalva act as the functional "stents" for a nonstented bioprosthesis. In comparisons of a stentless valve with a conventional stented prosthesis, these differences in valve design probably account for the superior hemodynamics in the immediate postoperative period.

We have also reported that transvalvular gradients after AVR with the SPV decrease with time, and we hypothesized this was a result of ventricular remodeling.[10, 14] This study of a much larger group of patients confirms our previous results. Follow-up serial echocardiograms have demonstrated that the postoperative transvalvular gradients decrease with time (Table V). It has been suggested that this occurrence may be a result of regression of postoperative tissue edema or hematoma, and it has been observed with both the SPV[14] and the Medtronic Freestyle[21] bioprosthesis (Medtronic, Inc., Minneapolis, Minn.) implanted with the partial scallop aortic inclusion technique. However, we believe the major reason for this decrease in gradients with time is ventricular remodeling, and that this remodeling is specifically dependent on the unique design of stentless bioprostheses. If changes in transvalvular gradients were simply a result of resorption of a perivalvular hematoma, one would not expect to see continued decreases in the transvalvular gradient beyond the early postoperative period (3 to 6 months). In contrast, if this phenomenon were dependent on ventricular remodeling and regression of LVH, one would anticipate that continued decreases in transvalvular gradients could extend well beyond the early postoperative period. Our results (Table V) clearly support the latter hypothesis.

Transvalvular gradient is a function of both the velocity in the aorta as well as in the LVOT (Appendix). Concentric hypertrophy will decrease the size of the LVOT and produce a functional subaor-

Table VI. *Estimated percentage changes for mean gradient and EOA*

	Mean gradient (mm Hg)		*EOA (cm^2)*	
Covariate	*% Change early postoperative period to 3–6 months*	*Slope from 3–6 months to 3 years (%)*	*% Change early postoperative period to 3–6 months*	*Slope from 3–6 months to 3 years (%)*
Size (mm)				
23	**−3 (−15, 10)***	7 (−3, 18)	1 (−10, 13)	−3 (−8, 3)
25	**13 (3, 24)***	−2 (−8, 5)	−5 (−12, 3)	0 (−4, 3)
27	**−3 (−15, 10)***	−3 (−8, 3)	5 (−2, 13)	2 (−2, 5)
29	**−4 (−12, 5)***	−2 (−8, 4)	−1 (−9, 7)	2 (−2, 5)
Toronto Hospital	**−17 (−26, −7)***	0.2 (−9, 10)	8 (−2, 19)	1 (−5, 6)
Age (yr)	**−0.08 (−0.57, 0.42)***	**−0.32 (−0.62, −0.03)***	**0.03 (−0.36, 0.41)***	**0.28 (0.12, 0.45)***
Female sex	4 (−9, 19)	−4 (−11, 4)	−10 (−18, −1)*	2 (−2, 7)
Date of implantation (days)	**0.023 (0.008, 0.038)***	**0.012 (0.0006, 0.023)***	**−0.018 (−0.029, −0.007)***	−0.005 (−0.012, 0.002)
BSA (m^2)	−11 (−33, 19)	4 (−14, 25)	2 (−22, 34)	−5 (−15, 6)
Preoperative NYHA class	2 (−5, 9)	2 (−3, 7)	−1 (−7, 5)	−1 (−4, 20)
Preoperative aortic stenosis	−7 (−22, 10)	−1 (−10, 9)	7 (−4, 1)	−0.5 (−6, 5)
Enlarged or dilated before operation	**−22 (−39, −1)***	−13 (−36, 19)	15 (−6, 40)	14 (−8, 40)
Concomitant procedures	3−(−8, 15)	−2 (−9, 6)	−6 (−14, 3)	0 (−4, 4)

Point estimates for percentage change, along with 95% confidence intervals are provided in parentheses. If stepwise procedure included slope term in model, percentage change from early postoperative period to 3–6 months was always included in model. *BSA,* Body surface area; *NYHA,* New York Heart Association.

*Statistically significant changes at $\alpha = 0.05$ (boldface type).

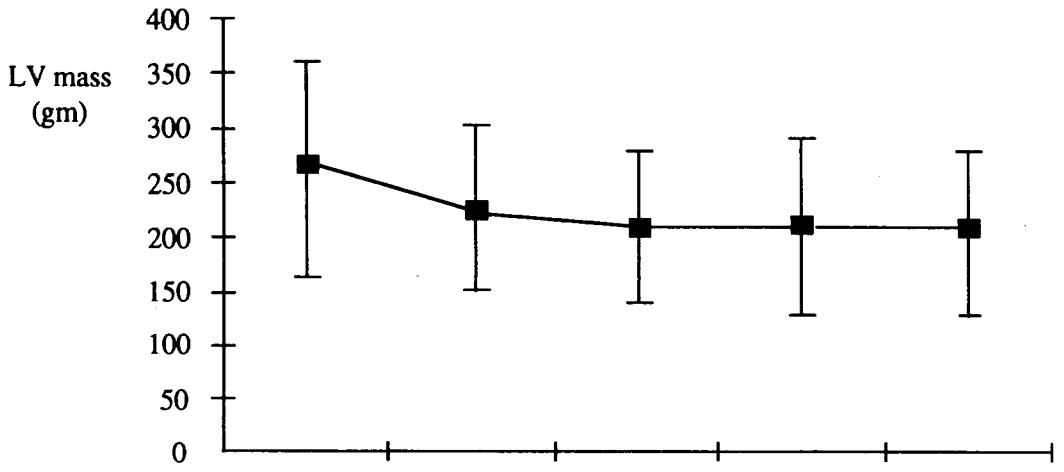
Table VII. *Hemodynamic and left ventricular mass changes for Sunnybrook patients (N = 84)*

	Peak gradient (mm Hg)	*Mean gradient (mm Hg)*	*EOA (cm^2)*	*IVS (mm)*	*LV_{post} (mm)*	*LV mass (gm)*	*LV mass index (gm/m^2)*
Postoperative	19.4 ± 7.7 (81)	11.0 ± 4.6 (75)	1.81 ± 0.59 (74)	13.2 ± 2.5 (66)	12.8 ± 2.4 (66)	264.7 ± 96.9 (66)	139.1 ± 45.3 (66)
3–6 months	14.9 ± 6.6 (72)	8.3 ± 4.0 (66)	1.96 ± 0.67 (67)	12.1 ± 2.2 (62)	11.4 ± 1.9 (62)	223.4 ± 74.7 (62)	118.3 ± 35.0 (62)
Δ (change from postoperative)	−4.7 ± 6.9 (68)	−3.0 ± 4.0 (60)	0.15 ± 0.42 (60)	−1.2 ± 1.7 (51)	−1.4 ± 1.9 (51)	−37.8 ± 57.9 (51)	−21.1 ± 30.5 (51)
95% confidence limit for Δ	−6.34, −3.06	−4.01, −1.99	0.04, 0.26	−1.67, −0.73	−1.92, −0.88	−53.7, −21.9	(−29.5, −12.7)
p	<0.0001	<0.0001	0.0092	<0.0001	<0.0001	<0.0001	<0.0001

All data presented as mean ± standard deviation. The number of patients examined is shown in parentheses. *IVS,* Thickness of intraventricular septum, *LV_{post}* thickness of the posterior wall of the left ventricle *(LV);* Δ, change in parameter from immediately after operation to first follow-up visit (3–6 months). Statistical significance determined by matched pairs *t* test such that each patient served as his or her own control.

tic stenosis. By removal of the stimulus for cardiac hypertrophy, however, we believe the ventricle undergoes remodeling. Figs. 2 through 5 and Tables V and VI examine the rate of decrease of transvalvular gradient for different valve sizes. If gradient decrease is a biologic process, one may hypothesize that the rate of gradient regression should be the same for all valve sizes, provided that the stimulus to induce hypertrophy was successfully blocked in all cases. The results demonstrated that although the initial gradient is smaller with the larger valve sizes, the change in gradient with time is similar across valve sizes. By 36 months after operation, mean transvalvular gradient becomes physiologic, with an average gradient of about 3.1 mm Hg for all valve sizes. These results are consistent with the hypothesis that gradient regression is indeed a biologic process and likely the result of remodeling of the ventricle after AVR with the SPV.

Table VI also indicates several significant predictors of mean gradient and EOA. For mean gradient, the valve size 25 mm appeared to be associated with a slower decline between the early postoperative period and 3 to 6 months than for other sizes. Older patients had greater improvements in gradient from 3 to 6 months to 3 years. In addition, Toronto Hospital patients had somewhat greater improvement in gradient from the early postoperative pe-



Time Interval	Post-op	3-6 months	1 year	2 years	3 years
Patients (N)	66	62	35	14	10
LV mass	264.7 ± 96.9	223.4 ± 74.7	209.7 ± 69.4	210.3 ± 80.4	208.8 ± 76.1
Maximum	538.4	510.0	397.7	373.0	355.7
Minimum	97.2	120.8	109.7	113.6	113.6
p		< 0.0001	< 0.0001	0.2	0.6

Fig. 10. Changes in left ventricular *(LV)* mass with time. Data presented as mean ± standard deviation.

riod to 3 to 6 months than did patients at the Sunnybrook Health Science Centre. The extent of the change in gradient beyond the initial follow-up and extending to 3 years, however, was the same at both sites. The initial differences may be related to case selection or to case mix. Furthermore, patients who underwent implantation later in the study had lesser improvements in gradient, which may also be the result of different patient enrollment through time. The decrease in mean gradient was consistent across all levels of the remaining covariates.

For EOA, all valve sizes were associated with increases at the same rates, and there were no site-dependent differences (Toronto Hospital vs Sunnybrook). Surprisingly, older patients had greater increases in EOA from 3 to 6 months to 3 years. Female patients had smaller changes than their male counterparts from early postoperative period to 3 to 6 months. Likewise, patients with later dates of implantation had smaller increases during the early postoperative period to 3- to 6-month period. The increase in EOA was consistent across all levels of the remaining covariates.

As previously discussed, ventricular hypertrophy is a physiologic response to an altered hemodynamic state. Animal studies have demonstrated that the hypertrophic response is mediated by classic signal transduction mechanisms[1, 2, 4-6] involving protooncogene activation and intracellular signaling through a classic protein kinase C pathway.[7] The human heart has also been shown to undergo molecular adaptation to pressure overload.[23] Induction of LVH, both in experimental models and in human beings, can be mediated by the renin-angiotensin system.[24, 25] The salient feature of transduction pathways is that to maintain the process the signal mechanisms must be sustained. If classic transduction pathways are operational in the development and maintenance of LVH in human beings in response to aortic valve pathology, then correction of the valve lesion may not necessarily result in resolution of LVH if there is a persistent and significant residual transvalvular gradient. On the other hand, elimination of or significant reduction in transvalvular gradient may abolish the stimulus for the maintenance of LVH and subsequently allow ventricular remodeling and regression of ventricular hypertrophy to occur.

This hypothesis is supported by mathematic mod-

els of ventricular geometry and function. Dumesnil and coworkers[26] developed a model to study the dynamic geometry of the left ventricle. They demonstrated that ejection fraction not only is dependent on the contraction of the circumferential and longitudinal fibers of the myocardium but also is related to the specific R/h ratio of the ventricle, where R is the mid-wall radius and h is the wall thickness. This phenomenon is particularly relevant when studying ventricles with variable R/h ratios, as may occur with LVH. In subsequent work, these investigators demonstrated that for two ventricles with identical preload the ejection fraction will be higher in the ventricle that has undergone LVH than in the normal ventricle.[27] These results predict that flow velocity across the aortic valve would be higher in patients with LVH than in normal patients. To extend this concept, a regression of LVH with time would result in a decreased flow velocity across the valve, which in turn would result in a decrease in transvalvular gradient.

If changes in gradient are indeed the result of ventricular remodeling, one would expect to see a parallel reduction in left ventricular mass. Our data clearly demonstrate a reduction in both left ventricular mass and in left ventricular mass index with time (Table VII). Furthermore, the results of the multivariate analysis of variance revealed the presence of a statistically discernible relationship between transvalvular gradient and left ventricular mass as a function of time. In addition, the analysis of variance demonstrated that for each of the dependent measures (left ventricular mass, gradient) there was a statistically significant decrease in their means through three time intervals (postoperative, 3 to 6 months, 1 year). Whether left ventricular mass regression continues beyond 1 year after AVR with the SPV cannot be ascertained from currently available data. Finally, our results and hypotheses are supported by a recent clinical study demonstrating reversal of hypertension-induced LVH with medical therapy[28] and by the work of Jin and associates,[29] who performed a comparative study on patients who received an aortic homograft, an SPV, or a conventional stented prosthesis. Left ventricular mass regression was comparable in patients receiving SPVs and homografts; patients who received a stented valve (either tissue or mechanical) did not have the same extent of mass regression.

We believe that valve design may play an important role in these findings. In contrast to the stentless valve, the effective valve orifice in a conventional stented valve is fixed by the supporting stent and sewing ring. Postoperative transvalvular gradients are therefore fixed by the supporting ring. This point is particularly important if there is a mismatch between the valve size and the patient's body size. If too small a stented valve is implanted, the residual postoperative gradient may be quite significant, making regression of hypertrophy and ventricular remodeling unlikely.

Conclusion

Clinical experience with the SPV to date is encouraging, and we remain enthusiastic about its use as a bioprosthesis. Low-pressure fixation, glutaraldehyde cross-linking, and the stentless design, which allows the dissipation of shear forces into the sinuses during diastole, may all contribute to an improvement in valve longevity compared with conventional stented valves. Furthermore, the hemodynamic performance of the valve is excellent and may have important prognostic implications. Persistence of LVH was shown in the Framingham study to be an important predictor of mortality.[30] We believe that the unique stentless design of the SPV removes the stimulus that maintains LVH in aortic valve disease–induced hypertrophy, thereby permitting remodeling to occur. Despite the slightly increased difficulty in implantation, the initial clinical results have been favorable and warrant continued clinical investigation.

We greatly appreciate the invaluable assistance of Dr. John Paul Szalai (Director) and Mr. Marko Katic of the Department of Research Design and Biostatistics, Sunnybrook Health Science Centre, University of Toronto, Toronto, Canada, in the analysis of left ventricular mass and gradients on the Sunnybrook subset, and that of Ms. Lisa McCallum (Supervisor of Biostatistics) and Dr. Kinley Larntz (consultant statistician), St. Jude Medical, Inc., in the analysis of gradients and EOA on the entire cohort. We are deeply indebted to Ms. Jeri Sever, Database Manager, Division of Cardiovascular Surgery, Sunnybrook Health Science Centre, for her countless hours of work, without which this article would not have been possible. D. D. R. personally thanks Dr. Jean Dumesnil, Quebec Heart Institute, and Mr. John Pepper, Royal Brompton Hospital, for their helpful discussions and for supplying their manuscripts. We also acknowledge Drs. C. Feindel, R. D. Weisel, and H. E. Scully, who contributed data on their patients to this series.

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Discussion

Dr. Delos M. Cosgrove *(Cleveland, Ohio).* You have done an excellent job reporting the hemodynamic performance of the you report little or no aortic regurgitation. This is a tribute to the excellent surgery and the surgical technique of implantation that has been developed. Secondly, you have carefully recorded the hemodynamic performance of this new prosthesis, recording both gradient and EOA. Unfortunately, the reporting of valve gradient is not as useful a descriptor of valve function as valve orifice area. This is because the gradient continues to increase as flow across the valve increases. Recorded valve orifice area data allow us to compare the performance of the currently available bioprostheses. Comparison by size of the SPV with published data for the Carpentier-Edwards standard, supraannular, and pericardial valves shows that all porcine valves have similar valve orifice areas but that the pericardial valve is slightly larger.

Your data give us the opportunity to compare different types of stentless prostheses. A multivariant trial of the Prima Edwards stentless valve has recently been published. The EOAs of this valve obtained at 12 months compare almost identically with those at 12 months as presented today, suggesting that there is little difference between these two types of prostheses.

The third important observation is the report of the decreasing left ventricular mass with time. It is well recognized that LVH begins to diminish immediately, but it has never been so well documented, nor has the fact that the majority of the resolution of the hypertrophy takes place in the first 6 months to a year been so apparent.

Fourth, a major observation has been made that EOA and gradient appear to improve with time, with most of the change occurring in the first 6 months. A similar trend was observed in the published performance of the Prima Edwards stentless valve. How is it possible, then, that a glutaraldehyde-treated, cloth-enclosed porcine prosthesis can increase in size? I suggest that this change is a result of changes in the LVOT. Echocardiography depends on measuring the velocity of flow in the LVOT and the aorta to obtain hemodynamic performance of the valve. With resolution of the hypertrophy, the LVOT enlarges, causing a decrease in its velocity. This, I believe, is the reason for the changes in the EOA, as opposed to actual changes in the valve structure. I would be interested in your thoughts on the reasons for this apparent change in EOA with time.

Dr. Del Rizzo. We actually have looked at what you are talking about. I think the answer to your question about why the gradients change with time is multifactorial. We hypothesized that annular expansion may be part of this (J Card Surg 1994;9:379-85), and subsequent reports by Dr. Westaby on the Medtronic Freestyle valve (Ann Thorac Surg 1995;59:857-62) and by Dr. Mohr on the SPV valve (Ann Thorac Surg 1995;60:171-6) suggested that our hypothesis may be correct. Furthermore, there is experimental evidence to suggest that the anulus is a dynamic, rather than a static, structure. Work out of the University of Western Ontario (London, Ontario, Canada) on an isolated porcine heart model (J Cardiovasc Surg 1991;6: 482-9) has shown that in a heart at normal pressure, in contrast to a cardioplegia-arrested heart, the anulus expands by approximately 40%. This, I think, is part of the answer, but it is not the entire answer. The other part, as you alluded to, is changes in hemodynamics. Dr. Dumesnil and colleagues from the Quebec Heart Institute looked at ventricular geometry and its effect on ejection fraction. They demonstrated that for equal volume load, a hypertrophied heart has a higher ejection fraction than a normal heart, and that this will translate into a higher transvalvular velocity. If this is correct, then changes in gradient should follow changes in transvalvular velocity. Dr. Dumesnil postulated that transvalvular gradient is determined by two factors. One is the EOA, as you yourself have pointed out, and the other is the change in the transvalvular velocity (Eur J Cardiothorac Surg 1992[suppl 1]:534-8). We performed a regression analysis in which we compared changes in gradient against changes in transvalvular velocity, and showed that this was a highly significant linear relationship ($r = 0.09$, $p < 0.0001$). I repeated the analysis looking at changes in the cross-sectional area of the LVOT versus changes in gradient, and also at changes in the velocity within the LVOT against changes in gradient, and found no relationship.

Dr. Colleen F. Sintek *(Los Angeles, Calif.).* I congratulate you on your large series of patients receiving stentless valves and your excellent results. Since January 1993, our group has implanted 83 of the Freestyle valves manufactured by Medtronic, and like you we have seen significant decreases in the transvalvular gradients and significant increases in the EOAs during the first year of follow-up for all valve sizes. In addition, we have seen lesser degrees of improvement in hemodynamics between 1 and 2 years.

We have found this valve to be especially useful in the elderly patient with a small aortic root. The excellent hemodynamics that we have seen with even the size 19 valves has allowed us to avoid aortic root enlargement procedures in this group of patients in whom we oftentimes see calcification. In fact, one third of our 83 patients received size 19 or size 21 valves. I want to say right now that we oversized our valves by about 2 mm, so that a patient who would get a size 19 stented valve would receive a size 21 Freestyle stentless valve. We implanted eight size 19 and 21 size 21 valves, with EOAs at 1 year of 1.3 and 1.6 cm^2, respectively.

Dr. Pennington. Dr. Sintek, we are interested in your information. Do you have any questions?

Dr. Sintek. Yes, I do. About the size, we really feel that the advantage of the stentless valve is in the patient with a small aortic root. I was curious that your valve sizes were much larger than those in the patients with whom we are dealing. Do you think that this is because of a difference in our populations? Our average age was 76 years, and most of our patients were women. Or do you think it has to do with your technique of oversizing significantly? Do you tilt the valve? Do you enlarge the aortic roots on your patients?

Dr. Del Rizzo. I think in part it is the fact that we have younger patients and more of our patients are male. That may be part of the reason why we are implanting larger valves. The other, as I alluded to previously, probably has to do with implantation technique. We size the valve to the sinotubular junction, rather than to the aortic anulus, and this tends to give us a larger size. As I mentioned before, we are probably oversizing our valves, which may contribute to why we are getting such large valves in. We do not tilt the valve, and we do not do an aortic root enlargement procedure.

Appendix

The mean systolic gradient and EOA are calculated by the following equation:

$$\text{Mean systolic gradient} = 4[(0.65V_2)^2 - (0.65V_1)^2] \quad (1)$$

$$\text{EOA} = \frac{0.8 \times (0.65V_1) \times A_{LVOT} \times 100}{100 \times \sqrt{[(0.65V_2)^2 - (0.65V_1)^2]}} \quad (2)$$

where V_1 is the maximum velocity in LVOT (m/sec), V_2 is the maximum velocity in the aortic valve (m/sec), D is the inner diameter of the LVOT (cm), and A_{LVOT} is the area of the LVOT (cm^2).

The left ventricular (LV) mass (gm) is calculated by the following equation:

$$\text{LV mass} = 0.00083\,[(LV_{post} + IVS + LV_{end})^3 - (LV_{end})^3] + 0.6 \quad (3)$$

where LV_{post} is the LV posterior wall thickness at end-diastole (mm), IVS is the thickness of the intraventricular septum at end-diastole (mm), and LV_{end} is the LV end-diastolic size (mm).

The LV mass index (gm/m^2) is calculated by the following equation:

$$\text{LV mass index} = \text{LV mass/BSA} \quad (4)$$

where BSA is the body surface area (m^2).