

Effects of Valve Replacement on Left Ventricular Function in Patients with Aortic Regurgitation and Severe Ventricular Disease

Julian Collinson¹, Marcus Flather¹, John R. Pepper³, Michael Henein²

¹Clinical Trials and Evaluation Unit, ²Department of Echocardiography, ³Department of Cardiac Surgery, Royal Brompton and Harefield NHS Trust and National Heart and Lung Institute, London UK

Background and aim of the study: Longstanding aortic regurgitation (AR) can result in left ventricular (LV) dysfunction that may reverse after aortic valve replacement (AVR). Stentless valves may result in a more rapid recovery in function due to a more physiological flow and lower outflow resistance.

Methods: The effect of AVR on LV function was studied in 47 patients who received either a stentless (n = 33) or stented (n = 14) valve for isolated AR. All patients had evidence of pre-existing LV dysfunction (end-systolic dimension (ESD) >50 mm). Patients were studied using transthoracic echocardiography at baseline, postoperatively, and at 2.5-year follow up.

Results: Preoperatively, there were no differences in LV dimensions. The end-diastolic dimension fell from 75 ± 10 mm to 61 ± 10 mm postoperatively and to 52 ± 10 mm at follow up in the stentless group (p <0.001), and ESD fell from 54 ± 10 mm to 36 ± 8 mm at follow up (p <0.001). There were no significant early changes in patients who received stented

valves, though LV dimensions fell at follow up. Fractional shortening (FS) increased from 25 ± 8% in the postoperative period to 31 ± 7% in the stentless group (p <0.001), but there was no change in the stented group (20 ± 7% versus 23 ± 8%). In the stentless group, LV mass fell from 366 ± 104 g to 276 ± 68 g postoperatively and to 219 ± 79 g at follow up (p <0.001); there was no postoperative change in the stented group, though a late reduction occurred, from 349 ± 51 g preoperatively to 265 ± 61 g at follow up (p = 0.06).

Conclusion: For patients with AR and LV dysfunction, AVR with a stentless prosthesis offers early reductions in LV dimensions, improved LV function, and regression of LV mass. In patients who received a stented valve, these improvements were delayed and less complete. Hence, for some patients with AR and LV dysfunction, a stentless prosthesis may be preferable.

The Journal of Heart Valve Disease 2004;13:722-728

Aortic regurgitation represents a combined pressure and volume overload to the left ventricle, with the excess volume ejected into the relatively high pressure aorta (1). When longstanding, these effects result in left ventricular (LV) dilatation and dysfunction (2). The degree of dysfunction may be underestimated, because severe regurgitation leads to an increase in ventricular fractional shortening (FS). Even poor ventricular function has been shown to be reversible after aortic valve replacement (AVR) (3). Accompanying the improvement in LV dysfunction is a regression of elevated LV mass, that may reflect a degree of LV modeling following surgery (4). However, the increased

pressure drop across both metallic and tissue stented valves, and the concomitant increase in ventricular wall stress, may delay improvement in ventricular function following valve replacement.

The hypothesis of the present study was that the use of valves with low pressure drops and a more physiological flow (5), including stentless valves (homograft and Toronto stentless porcine valve), may result in a more rapid functional recovery as well as more rapid and complete improvement in ventricular function, together with regression of raised LV mass.

Clinical material and methods

Patients

In a retrospective study, early changes in echocardiographic measurements of LV function were compared in patients who received stented or stentless valves.

The inclusion criteria were: (i) isolated aortic valve

Address for correspondence:
Michael Henein, Department of Echocardiography, Royal Brompton and Harefield NHS Trust, Sydney Street, London SW3 6NP, UK
e-mail: m.henein@rbh.nthames.nhs.uk

surgery required for significant valve regurgitation as assessed by Doppler echocardiography; (ii) depressed LV systolic function, with end-systolic dimension (ESD) >50 mm; and (iii) availability of complete pre-operative and postoperative echocardiography studies. Patients were excluded if they were undergoing re-do aortic valve surgery or any additional procedure (e.g. coronary artery bypass grafting, other valvular interventions). At the time of examination, all patients were in sinus rhythm. The results from these patients were compared with those from 21 normal subjects (mean age 58 ± 11 years) who were without evidence of cardiac, pulmonary or systemic disease.

Among the patients ($n = 47$), the etiology of the aortic regurgitation was Marfan's syndrome ($n = 5$), previous endocarditis ($n = 4$), isolated rheumatic aortic valve disease ($n = 6$) and senile degeneration ($n = 32$). Patients underwent postoperative echocardiography at a median of 5 days (range: 3 to 7 days), and follow up echocardiography at a median of 2.4 years (range: 1.5 to 4 years). At the time of the postoperative assessment, patients were mobile and not receiving any intravenous medication (other than heparin).

All patients underwent preoperative, pre-discharge (at 5-7 days) and follow up (2.5 years) transthoracic echocardiography for the assessment of aortic valve and LV function.

Echocardiography

Doppler echocardiographic examinations were performed using a Hewlett-Packard echograph model 77020 A Sonos 1500 interfaced to a 2.5 MHz phased array transducer. Two-dimensional guided M-mode echocardiograms were obtained while the patient was lying in the semi-lateral position, together with a simultaneous electrocardiogram and phonocardiogram. Left ventricular minor axis recordings were obtained with the cursor by the tips of the mitral valve leaflets. From the apical four-chamber recordings, longitudinal dimensions of the ventricle were measured from a frozen image view as well as M-modes of the ventricular long axes, represented by mitral ring motion (6). The cursor was positioned at the left and septal sites of the ring. Transmitral forward-flow velocities were obtained using the same transducer in the pulsed-wave Doppler mode with the sample volume at the tips of the mitral valve leaflets, from the apical four-chamber view. Aortic valve flow velocities were obtained using the same imaging probe in the continuous-wave mode.

M-mode echocardiograms of the LV minor and long axes and Doppler traces were recorded separately on a strip chart recorder at a paper speed of 100 mm. All M-mode traces were digitized and analyzed using a dedicated computer program to obtain the peak rate of

shortening and lengthening of the LV minor and long axes (7).

Measurements

Left ventricular dimensions

Left ventricular transverse dimensions were measured using leading-edge methodology, the end-diastolic dimension (EDD) at the onset of the 'q' wave of the electrocardiogram and the ESD at the onset of the first high-frequency component of the second heart sound of the phonocardiogram (A2). Basal FS was then calculated as the percentage systolic decrease in transverse axis divided by EDD. Left ventricular mass was calculated using the American Society of Echocardiography (ASE) convention method: $LV\ mass = 0.8 \times \{1.04 \times [(EDD + posterior\ wall\ thickness\ in\ diastole + interventricular\ septal\ thickness\ in\ diastole)^3 - EDD^3]\} + 0.6g$.

The peak rate of transverse axis shortening and lengthening were measured from the digitized traces. The longitudinal LV dimensions were measured from the frozen four-chamber images, as the distance between the apical endocardial border and mitral ring center. Longitudinal fractional shortening (FS) was calculated in the same manner.

Long axis

Two long-axis sites were taken, namely the LV free wall and septal. Systolic long-axis excursion was taken as the amplitude of mitral ring movement between the outermost point at the time of the 'q' wave (end-diastole) to the innermost point at A2 (end-systole). Peak shortening and lengthening rates were measured from the digitized traces.

Doppler measurements

Aortic valve

Peak velocity and the presence of any aortic regurgitation were recorded from the Doppler traces. The modified Bernoulli formula, omitting the subaortic signal in the presence of a low preoperative gradient, was used.

Mitral valve

Peak early 'E' and late diastolic 'A' velocities were measured from the pulsed-wave Doppler traces, and the E/A ratio was then calculated.

Operative technique

Surgery was performed with the patient under general anesthesia, with cardiopulmonary bypass being routinely established through a medial sternal approach. Myocardial protection was afforded with cold blood cardioplegia. Stentless porcine valves and

aortic homografts were implanted using a free-sewn technique and interrupted sutures at the outflow. Mechanical or stented biological valves were implanted with an interrupted single suture line.

Statistical analysis

All values were expressed as mean \pm SD. Pre-operative, postoperative and follow up data were compared using a repeated measures ANOVA. When this was significant, individual values were compared using a paired *t*-test. Measurements between groups of patients or between patients and controls were compared using the unpaired Student's *t*-test. A *p*-value <0.05 was considered to be statistically significant.

Results

Patient data

Among a total of 223 aortic valve replacements performed for aortic regurgitation at the authors' institution between January 1993 and December 1997, 47 patients (29 males, 18 females; mean age 55 ± 12 years) fulfilled the eligibility criteria. Among these patients, 33 (mean age 56 ± 12 years) received a stentless valve, and 14 (mean age 53 ± 12 years) a stented valve. Three of the stented group (21%) and four of the stentless group (12%) were females. No patient had acute aortic regurgitation. Reasons for excluding patients from the study were: ESD <50 mm; atrial fibrillation at the time of assessment; requirement for permanent pacemaker; or incomplete postoperative echocardiogram. None of the patients had a history of coronary artery disease. There were no perioperative deaths, myocardial infarctions or other significant perioperative events in either group of patients. By the time of follow up at 2.5 years, there had been three deaths (9%) in the stentless group and one death (7%) in the stented group (none was closely related to the time of surgery). The type of

valve substitute used was at the free choice of the operating surgeon and details are listed in Table I. Methods of myocardial preservation, though chosen by the individual surgeon, did not differ between the two groups.

Clinical data

No patient in either group had more than mild aortic stenosis (defined as a peak aortic velocity of 2.5 m/s). Postoperatively, the peak aortic pressure drop was 12 ± 4 and 35 ± 5 mmHg in the stentless and stented groups, respectively, and no patient had more than trivial aortic regurgitation. Two of the patients with Marfan's syndrome underwent additional aortic root replacement. There were no differences preoperatively in cardiac medications taken by the patients, though those who received a mechanical valve took anti-coagulants postoperatively.

Left ventricular function

Minor axis

Left ventricular transverse axis dimensions at end-diastole and end-systole were increased at baseline, and FS was reduced compared to that in controls. These values did not differ between the two groups (Table II). Soon after surgery, patients receiving a stentless valve showed a significant decrease in mean EDD, from 75 ± 10 mm to 61 ± 10 mm ($p < 0.001$), and in ESD from 54 ± 10 mm to 46 ± 11 mm ($p < 0.001$) (Fig. 1). At later follow up, the EDD was 52 ± 10 mm and the ESD 36 ± 8 mm, a reduction of 31% and 33% respectively compared with preoperative values, the latter dimensions being similar to those in controls. There was no change in FS during the postoperative period ($27 \pm 8\%$ preoperatively versus $25 \pm 8\%$ postoperatively), but at follow up FS had increased to $31 \pm 7\%$ ($p < 0.001$); this was also not significantly different to that in controls. By contrast, in the stented group, no significant change was seen in LV dimensions early postoperatively, but

Table I: Valve substitutes used in the studies.

Valve type	Total used (n)	Valve diameter (mm)			
		23	25	27	29
Stentless (n = 33)					
Homograft	14*				
Toronto	18	-	7	10	1
Freestyle	1	-	-	1	-
Stented (n = 14)					
St. Jude Medical	7	-	2	3	2
Starr-Edwards	5	1	1	3	-
Carpentier-Edwards	2	-	-	2	-

*Includes two patients undergoing root repair for Marfan's syndrome.

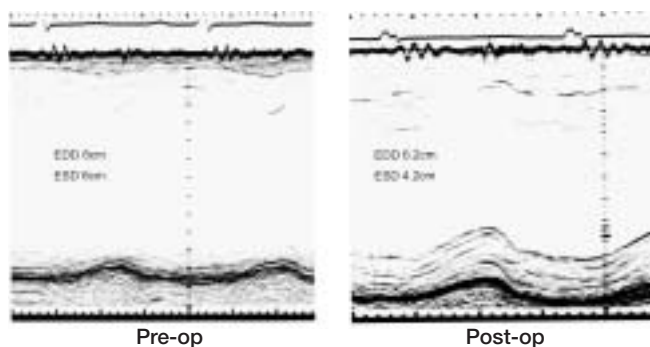


Figure 1: Left ventricular M-mode recording of the minor axis in a patient before (left) and after (right) aortic valve replacement with a homograft. Note the marked regression in the increased left ventricular dimensions and improved fractional shortening after surgery. EDD: End-diastolic dimension; ESD: End-systolic dimension.

EDD and ESD fell by 14% and 8% respectively at later follow up. Fractional shortening in the stented group also remained depressed at follow up ($23 \pm 8\%$). Both postoperatively and at follow up, FS was significantly higher in the stentless group than in the stented group ($p < 0.001$ for the comparison). In the stentless group, the calculated LV mass fell from 366 ± 104 g to 276 ± 68 g soon after surgery, and fell further to 219 ± 79 g at follow up ($p < 0.001$). In the stented group, there was no significant change postoperatively, although LV mass fell at follow up (from 349 ± 51 g preoperatively to 265 ± 61 g at follow up; $p = 0.04$). At follow up, the LV mass was significantly lower in the stentless group than the

stented group ($p < 0.01$).

Longitudinal dimensions

Compared to control values, the longitudinal dimensions of the left ventricle measured at end-systole and end-diastole were increased in both groups, and the proportional change in dimensions was reduced (Table III). At follow up, the dimensions remained raised in both groups, although end-systolic lengths had fallen from 103 ± 14 mm preoperatively to 90 ± 15 mm at follow up ($p < 0.05$) in patients receiving stentless valves. In those receiving stented valves, end-systolic lengths were 98 ± 10 mm and 88 ± 10 mm, respectively. The proportional change between systole and diastole (longitudinal shortening fraction) improved from $4.1 \pm 3.6\%$ preoperatively to $6.3 \pm 3.3\%$ at follow up (values were similar to those of controls), but there was no significant change in the stented group ($3.6 \pm 2.9\%$ and $5.3 \pm 1.6\%$ respectively; $p = 0.33$).

Long axis

Preoperative, postoperative and follow up assessments were performed in 22 of the stentless group, and in 11 of the stented group. Preoperative LV free wall and septal excursion, peak shortening and peak lengthening rates were reduced in the two patient groups compared to normal values (Table IV). There was no change in septal values for either group. In the two patient groups, there were no significant early changes in LV long axis excursion, peak shortening or peak lengthening rates during the postoperative period. At follow up, excursion and peak shortening rate

Table II: Left ventricular minor axis data.

Parameter	Normal (n = 21)	Stentless (n = 33)			Stented (n = 14)		
		Preoperative	Postoperative	Follow up	Preoperative	Postoperative	Follow up
Left ventricle							
EDD (mm)	48 ± 5	75 ± 10	$61 \pm 10^{**}$	$52 \pm 10^{**\dagger}$	71 ± 5	67 ± 7	$61 \pm 10^{\dagger}$
ESD (mm)	33 ± 5	54 ± 10	$46 \pm 11^{\dagger}$	$36 \pm 8^{**\dagger}$	52 ± 7	53 ± 8	48 ± 11
Peak shortening rate (cm/s)	9.0 ± 3.0	9.7 ± 3.2	$6.7 \pm 2.1^{**}$	7.3 ± 2.0	9.6 ± 2.8	5.7 ± 2.4	7.5 ± 3.5
Peak lengthening rate (cm/s)	10.4 ± 2.6	9.6 ± 3.9	7.0 ± 3.4	6.0 ± 3.9	7.8 ± 3.9	6.0 ± 4.5	5.8 ± 3.2
Fractional shortening (%)	30 ± 10	27 ± 8	25 ± 8	$31 \pm 7^{\dagger}$	27 ± 7	20 ± 7	23 ± 8
LV mass (g)	163 ± 9	366 ± 104	$276 \pm 68^{\dagger}$	$219 \pm 79^{**}$	349 ± 51	320 ± 64	265 ± 61
Mitral Doppler							
'E'-wave (m/s)	0.7 ± 0.1	0.7 ± 0.3	0.6 ± 0.3	0.5 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.5 ± 0.3
'A'-wave (m/s)	0.5 ± 0.1	0.5 ± 0.3	0.6 ± 0.4	0.6 ± 0.2	0.7 ± 0.2	0.5 ± 0.3	0.7 ± 0.2
E/A ratio	1.4 ± 0.4	1.8 ± 1.3	1.5 ± 1.2	$1.0 \pm 0.7^{\dagger}$	1.0 ± 0.5	1.3 ± 1.0	0.9 ± 0.6

Within-group comparisons analyzed with repeated measures ANOVA. If significant, a paired *t*-test was applied. Between-group comparisons analyzed using an unpaired *t*-test was applied.

$^{\dagger}p < 0.05$, $^{\ddagger}p < 0.01$, $^{**}p < 0.001$ compared with preoperative values.

$^{\ddagger}p < 0.05$ compared with stented group at follow up.

EDD: End-diastolic dimension; ESD: End-systolic dimension.

Table III: Left ventricular longitudinal dimensions.

Parameter	Normal (n = 11)	Stentless (n = 33)			Stented (n = 14)		
		Preoperative	Postoperative	Follow up	Preoperative	Postoperative	Follow up
EDL (mm)	81 ± 7	107 ± 14	103 ± 13	96 ± 14 [†]	102 ± 12	108 ± 7	93 ± 12*
ESL (mm)	76 ± 7	103 ± 14	97 ± 14	90 ± 15*	98 ± 10	103 ± 7	88 ± 10
Proportional change (%)	5.6 ± 2.2	4.1 ± 3.6	5.1 ± 3.4	6.3 ± 3.3*	3.6 ± 2.9	4.2 ± 2.1	5.3 ± 1.6

Values compared using repeated measures ANOVA, where significant then compared using paired *t*-test.

**p* <0.05, †*p* <0.01 compared with preoperative values.

EDL and ESL measured from the mitral valve ring to the endocardial surface of the apex.

Proportional change = (EDL - ESL)/EDL.

EDL: End-diastolic length; ESL: End-systolic length.

had increased towards normal in both groups. Follow up values were not significantly different to normal.

No significant difference in mitral Doppler was seen in either early or late diastolic flow velocities, or in the E/A ratio.

Discussion

Among patients with aortic regurgitation and poor LV systolic function in the absence of coronary artery disease, those who received a stentless valve (with a low pressure drop) had earlier and more complete improvement of LV function. Following valve replacement, both ESD and EDD fell during the early postoperative period, and fell further at follow up. However, whereas FS and ejection fraction in the stentless valve group improved to within the normal range, these measures remained depressed in patients who received stented valves, even at follow up. Linked with these observed changes in ventricular function was an apparent fall in LV mass. Again, this occurred earlier and was more complete in patients with stent-

less valves. The LV longitudinal dimensions followed the same pattern in both the stentless and stented valve groups. These findings were observed in patients for whom the peak aortic valve velocity was higher postoperatively and at follow up and who received a stented valve rather than a stentless valve.

Initially, the left ventricle adapts to longstanding aortic regurgitation by increases in both wall motion velocity and end-diastolic volume. The eventual effects of aortic regurgitation are manifested by an increase in end-systolic volume. Although symptoms have always been considered as a sensitive marker for the timing of surgical intervention (8), the development of symptoms does not necessarily correlate with the degree of LV dysfunction. The consensus is to recommend presymptomatic valve replacement to guard against irreversible LV disease (9). Surgery for acute aortic regurgitation with a normal ventricular cavity size has been shown to be successful in preserving long-term pump function (10). In the presence of significant LV dysfunction, the evidence for the effect of valve replacement is more controversial (11). In this

Table IV: Left ventricular long axis data.

Parameter	Normal	Stentless (n = 22) (n = 21)			Stented (n = 11)		
		Preoperative	Postoperative	Follow up	Preoperative	Postoperative	Follow up
Left ventricle free wall							
Excursion (cm)	1.5 ± 0.25	1.2 ± 0.3	1.0 ± 0.3	1.4 ± 0.3 [†]	1.1 ± 0.4	1.1 ± 0.3	1.3 ± 0.4
Peak shortening rate (cm/s)	8.0 ± 1.5	6.4 ± 1.7	5.6 ± 2.2	7.5 ± 2.1 [†]	5.6 ± 2.0	6.0 ± 2.2	9.3 ± 4.4 [†]
Peak lengthening rate (cm/s)	10.0 ± 2.5	6.5 ± 2.9	6.6 ± 3.5	6.6 ± 3.2	5.7 ± 2.7	6.9 ± 2.9	5.0 ± 2.4
Left ventricular septum							
Excursion (cm)	1.5 ± 0.3	1.0 ± 0.3	0.7 ± 0.3	0.9 ± 0.2	1.1 ± 0.4	0.8 ± 0.4	0.8 ± 0.3
Shortening velocity (cm/s)	7.5 ± 1.2	4.7 ± 1.6	3.5 ± 1.3	3.8 ± 1.1	5.3 ± 2.1	2.6 ± 1.8	2.0 ± 2.4
Lengthening velocity (cm/s)	9.0 ± 1.5	4.6 ± 1.6	4.2 ± 1.4	4.5 ± 1.5	5.6 ± 2.6	3.3 ± 2.5	2.5 ± 2.8

Values compared using repeated measures ANOVA, where significant then compared using paired *t*-test.

†*p* <0.01 for follow up values compared with postoperative values.

retrospective study, the aim was to address this question in a group of patients undergoing surgery for aortic regurgitation and who had significant LV dysfunction.

Among the present patients there was evidence of an adverse LV remodeling process prior to surgery, as shown by the increase in LV dimensions on both axes and the increase in LV mass. The study results suggest that this remodeling is not irreversible and that, following surgery, the left ventricle is 'refashioned'. In patients with aortic regurgitation and remodeling, there is evidence that the proto-oncogene *c-Myc* is implicated in the pathogenesis, and this is associated with increases in myocardial cell diameter and fibrous content (12). In endomyocardial biopsies taken from patients with aortic regurgitation or stenosis, changes in the collagen architecture (increased cross-hatching or endocardial fibrosis) were associated with altered systolic function and passive diastolic function (13). Likewise, persistent elevation of the LV mass was associated with continued high fibrous content (14). In a study of 67 patients, the failure of LV function to recover was predicted by myocardial fiber hypertrophy, a moderate to severe increase in interstitial fibrous tissue, or reduced levels of myofibrillar adenosine triphosphate (15). The present findings confirm an early recovery of ventricular function with stentless valves, and late recovery with stented valves. In either case, the outcome suggests that the presence of significant interstitial fibrosis hindering the recovery of function is unlikely in these patients.

Measurements of LV function in patients with aortic regurgitation are complicated by the fact that the regurgitant volume tends to exaggerate systolic measures such as FS and ejection fraction. It has been shown that aortic valve replacement can be performed safely in patients with LV dysfunction and aortic regurgitation, albeit with an increased operative risk and no guarantee of postoperative improvement (15). In patients with normal LV function, the use of stentless valves has been associated with more complete regression of LV hypertrophy and recovery of function (16). It appears that homografts and stentless xenografts provide similarly good results (17).

The present results suggest that LV dysfunction can improve significantly following aortic valve surgery for aortic regurgitation. In addition, the reduction in LV mass and the fall in longitudinal LV diameter suggest that LV refashioning occurs soon after surgery and continues during the years of follow up. In the present study, the greatest effects were seen in patients who received a stentless valve, and these effects also occurred earlier than in those patients who received a stented valve. The extent of this early change is likely to correlate with prompt relief of the volume overload,

along with the loss of outflow tract resistance. The greater changes in the stentless group may be secondary to the greater reduction in the pressure overload. Although the left ventricle is dilated and apparently poorly functioning, it still maintains the ability for a rapid normalization of structure and function when a physiologically more normal valve is implanted.

Study limitations

The present study was limited by its retrospective, non-randomized structure, and relatively small sample size. A few patients with poor LV function were excluded because postoperative echocardiography was unavailable. The assessment of aortic regurgitation was based on echocardiographic markers of LV activity and the peak aortic-LV pressure drop. Although this method may yield some variability of measurement, the two patient groups were assessed in the same manner. It is impossible to ensure that the duration of aortic regurgitation was similar in both patient groups, though the time between diagnosis of severe aortic regurgitation and surgery was not materially different.

In conclusion, it is considered that the use of stentless valves in patients with severe aortic regurgitation and poor LV function may result in more a rapid functional recovery and earlier beneficial refashioning relative to similar patients receiving a mechanical or stented biological valve. Larger prospective studies are under way to determine whether these early structural and functional changes might impact on long-term clinical outcomes.

References

1. Carabello BA. The changing unnatural history of valvular regurgitation. *Ann Thorac Surg* 1992;53:191-199
2. Yousof AM, Mohammed MM, Shuhaiber H, Cherian G. Chronic severe aortic regurgitation: A prospective follow-up of 60 asymptomatic patients. *Am Heart J* 1988;116:1262-1267
3. Bach DS, David T, Yacoub M, et al. Hemodynamics and left ventricular mass regression following implantation of the Toronto SPV stentless porcine valve. *Am J Cardiol* 1998;82:1214-1219
4. Jin XY, Gibson DG, Yacoub MH, Pepper JR. Perioperative assessment of aortic homograft, Toronto stentless valve, and stented valve in the aortic position. *Ann Thorac Surg* 1995;60:S395-S401
5. Yacoub MH, Kilner PJ, Birks EJ, Misfeld M. The aortic outflow and root: A tale of dynamism and crosstalk. *Ann Thorac Surg* 1999;68:S37-S43
6. Jones CJH, Raposo L, Gibson DG. Functional importance of the long axis dynamics of the human

- left ventricle. *Br Heart J* 1990;63:215-220
7. Gibson DG, Brown D. Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* 1973;35:1141-1149
 8. Hoshino PK, Gaasch WH. When to intervene in chronic aortic regurgitation. *Arch Intern Med* 1986;146:349-352
 9. Nishimura RA, McGoon MD, Schaff HV, Giuliani ER. Chronic aortic regurgitation: Indications for operation. *Mayo Clin Proc* 1988;63:270-280
 10. Carabello BA, Usher BW, Hendrix GH, Assey ME, Crawford FA, Leman RB. Predictors of outcome for aortic valve replacement in patients with aortic regurgitation and left ventricular dysfunction: A change in the measuring stick. *J Am Coll Cardiol* 1987;10:991-997
 11. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Aortic regurgitation complicated by extreme left ventricular dilatation: Long-term outcome after surgical correction. *J Am Coll Cardiol* 1996;28:798-799
 12. Taketani S, Sawa Y, Taniguchi K, et al. C-Myc expression and its role in patients with chronic aortic regurgitation. *Circulation* 1997;96:II-7
 13. Villari B, Campbell SE, Hess OM, et al. Influence of collagen network on left ventricular systolic and diastolic function in aortic valve disease. *J Am Coll Cardiol* 1993;22:1477-1484
 14. Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation* 1989;79:744-755
 15. Donaldson RM, Florio R, Rickards AF, et al. Irreversible morphological changes contributing to depressed cardiac function after surgery for chronic aortic regurgitation. *Br Heart J* 1982;48:589-597
 16. Jin XY, Zhang Z-M, Gibson DG, Yacoub MH, Pepper JR. Effects of valve substitute on changes in left ventricular function and hypertrophy after aortic valve replacement. *Ann Thorac Surg* 1996;62:683-690
 17. Ali A, Lim E, Halstead J, Ashrafian H, Ali Z, Khapley Z, Theodorou P, Chamageorgakis T, Kumar P, Jackson C, Pepper J. Porcine or human stentless valves for aortic valve replacement? Results of a 10-Year Comparative Study. *J Heart*

Valve Dis 2003;12:430-435