Regression of left ventricular hypertrophy during 10 years after valve replacement for aortic stenosis is related to the preoperative risk profile

Ole Lund*, Kristian Emmertsenb, Inge Dørupb, Finn T. Jensen, Christian Fløc

*Department of Thoracic and Cardiovascular Surgery, Aarhus University Hospital in Skejby, Aarhus, Denmark
bDepartment of Cardiology, University Hospital in Skejby, Aarhus, Denmark
cDepartment of Clinical Physiology and Nuclear Medicine, Aarhus University Hospital in Skejby, Aarhus, Denmark

Background Previous studies have suggested that regression of hypertrophy may be the underlying determinant of longevity and left ventricular function after valve replacement (AVR) for aortic stenosis (AS). The potential for hypertrophy regression could therefore be related to the preoperative risk profile.

Methods Ninety-one consecutive patients with AS had a 'project' Doppler-echo and radionuclide ventriculography in addition to the standard investigation programme prior to AVR with a disc valve (19–29 mm, n=82), a caged ball valve (26–29 mm, n=8), or a stented porcine valve (26 mm, n=1); 49 (group A) were selected for a serial follow-up study while 42 served as controls (group B). Forty-two group A patients took part in a 1.5-year examination while 47 (26 group A, 21 group B) patients were studied at 10 years.

Results Groups A and B were comparable as regards all pre- and intra-operative data including left ventricular mass index (LVMi). A previously developed preoperative prognostic index (PI) separated the patients into groups with low (n=23), intermediary (n=19) and high risk (n=49) with 10-year survivals of 87%, 58% and 43% (P<0.01). LVMi dropped from 202±58 g/m² preoperatively to 152±45 g/m² (P<0.0001) at 1.5 years, and 139±40 g/m² (P<0.0001) at 10 years (three and six patients, respectively, with paravalvular leak or mitral regurgitation excluded). PI correlated with preoperative (r=0.51, P<0.001), 1.5-year (r=0.46, P<0.01), and 10-year LVMi (r=0.41, P<0.01). Also preoperative left ventricular ejection fraction correlated with the three LVMi measurements. Patients with systemic hypertension had higher LVMi at 1.5 years (193±42, n=6 vs 144±42, n=33, P<0.05) and 10 years (175±39, n=12 vs 124±31 g/m², n=29, P<0.001). Patients with low, intermediary or high PI, excluding those with hypertension, had 1.5-year LVMi of 110±35 (n=8), 134±43 (n=9) and 164±33 g/m² (n=16; P<0.01), respectively, and 10-year LVMi of 116±25 (n=17), 126±27 (n=6), and 146±41 g/m² (n=6; P<0.05), respectively. There was no relation between LVMi at 1.5 or 10 years and peak or mean Doppler gradient, prosthetic valve size, or valve size index.

Conclusions Left ventricular hypertrophy regression for patients who survived up to 10 years after AVR for AS is dependent on the preoperative risk profile indicating that irreversible myocardial disease is the underlying factor. Systemic hypertension is an important factor in its own right.

© 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

KEYWORDS
Aortic stenosis; Valve replacement; Left ventricular hypertrophy; Prognosis; Hypertension
Introduction

Prognostic studies have given rise to the hypothesis that regression of left ventricular hypertrophy is the underlying determinant of longevity after aortic valve replacement (AVR) for aortic stenosis (AS). Other authors have predominantly seen incomplete hypertrophy regression as a consequence of suboptimal haemodynamic function of the prosthetic aortic valve. However, just like survival, also left ventricular systolic and diastolic function measured 12 years after AVR could be described by preoperative risk models. An ensuing 3-year observational study showed that left ventricular diastolic dysfunction, related to residual hypertrophy, was the prime predictor of cardiac related deaths. The above hypothesis may thus be expanded to encompass the importance of hypertrophy regression also for left ventricular systolic and diastolic function. Accordingly, it seems pertinent to analyse if hypertrophy regression is related to the preoperative risk profile.

Using serial follow-up investigations 10 days, 3 months and 1.5 years after AVR for AS we have previously shown that insufficient regression of left ventricular hypertrophy was related to preoperative indices of advanced myocardial disease which also precluded functional ventricular improvement despite a successful AVR. Incomplete hypertrophy regression was, furthermore, related to preoperative myocardial histological abnormalities gauged from intraoperative transmural left ventricular biopsies. In accordance, sub-normal left ventricular ejection fraction after AVR was related to residual hypertrophy and was predominantly predicted by the preoperative “starting value” as was also noted by Hwang et al. The present study now presents the analysis following completion of a 10-year post-AVR investigation programme in our serial follow-up population. The aim was to chart left ventricular hypertrophy regression during 10 years after AVR for AS and to perform a dedicated analysis of the relation to preoperative risk profile. The latter was quantitated by a validated prognostic index (PI) with strong predictive powers as regards long-term post-AVR survival.

Material and methods

The study population includes 91 prospectively enrolled adult patients with AS, no or insignificant regurgitation, with (n=38) or without coronary artery disease (CAD) and no other associated heart disease, who had their entire preoperative investigation programme done at the present centre, and who underwent AVR during August 1988 to October 1990. We initially enrolled 100 patients consecutively when referred for surgery (December 1987 to January 1990) planning to allocate 50 (group A) to a sub-study involving an intraoperative left ventricular transmural biopsy and a serial follow-up investigation programme 8 days, 3 months and 1.5 years postoperatively with the remaining patients serving as a control group (group B). Eight patients, however, died awaiting surgery and one was excluded (revision of aortic root angiogram showed significant regurgitation) leaving 91 for study. The allocation of eventually 49 patients to group A was done consecutively immediately preoperatively upon the patients informed consent during 12 months from November 1988 leaving 42 patients in group B including seven who declined the group A sub-study. The surgical waiting time was 5.3±3.1 months in group A and 5.9±3.3 in group B (NS). All patients were followed with annual contact. The study was approved by the Ethical Committee of Aarhus County.

Preoperative invasive data and prognostic index

All patients underwent standard left sided heart catheterization including aortic root and coronary angiographies. The peak-peak aortic valve gradient (PPAVG) was measured directly in 82 patients and estimated in the remaining nine (a catheter could not be passed retrogradely through the valve): PPAVG=24+0.69×peak echo-Doppler gradient (from a previously published correlation study: r=0.68, P<0.001). A preoperative prognostic index (PI) which was previously developed for patients with AS undergoing AVR was calculated for each patient: PI=−0.012×PPAVG+5.075×CTI+0.585×LVF+0.726×POD15−0.026×age+0.415×sex+0.760×VEB+0.342×AAM. CTI is cardiothoracic index; LVF is clinical left ventricular failure (pulmonary vascular stasis or oedema within a year before the operation); POD15 is prosthetic valve orifice diameter ≤15 mm; VEB is ventricular ectopic beats in ≥10% of beats in resting ECG; and AAM is anti-arrhythmic or anti-arrhythmic medication (nitrates, beta blockers, calcium channel inhibitors, amiodarone, other anti-arrhythmic drugs excluding digoxine); PPAVG (Table 1), CTI (0.5±1.05), and age (Table 1) were entered with their discrete value, while LVF (Table 1), POD15 (n=4), VEB (n=10), and AAM (n=49) were entered with a value of 1 if present and 0 if not; sex (Table 1) had a value of 1 for men and 0 for women. PI cut into 8 equidistant intervals identified eight risk groups where low risk groups I–III each had sex and age specific normal long-term survival (to 20 years), intermediate risk group IV had late excess mortality relative to their matched background population, and high risk groups V–VIII had increasing excess mortalities throughout their follow-up. PI was probably valid for any adult population with symptomat AS which was unpinned by prospective application in the present patients (Fig 1) and in an up-dated AS population including 500 patients more (operated later) than the 690 of the original study population. For the present 91 patients we divided the patients into three PI groups (Table 1, Fig 1): PI group 1 (n=23; PI≤3.42) corresponding to above mentioned low risk groups I–III with presumed normal survival, PI group 2 (n=19, PI 3.43–3.9) corresponding to intermediate risk group IV, and PI group 3 (n=49; PI>3.9) corresponding to high risk groups V–VIII.

Non-invasive preoperative and 1.5 and 10 year follow-up studies

For the present analysis we included the 1.5-year postoperative (1.5 year date±2 weeks) out-patient clinic investigation of group A; 42 out of 45, who were alive, attended. Forty-seven out of 52 patients who were alive (26 of 27 in group A; 21 of 25 in group B) consented to attend a 10-year study which took place an average of 10.4 (range 10.0–11.5) years after the operation. The five non-attenders had end-stage pulmonary emphysema (n=1), bilateral above knee amputation (n=1), meningoc-encephalitis (n=1), or chronic psychoses (n=2). Systemic hypertension was recorded in case of a positive history and specific antihypertensive medical treatment. No preoperatively normotensive group A patient attending the 1.5 year study had developed new-onset hypertension but five group A patients and four group B patients had been started on antihypertensive medication prior to the 10-year study. All untreated patients had diastolic blood pressure below 90 mmHg at the 1.5- and 10-year studies.
Transthoracic Doppler echocardiography\textsuperscript{16,17} and ECC gated radionuclide left ventriculography\textsuperscript{18–20} were performed on the day before the operation and at the 1.5- and 10-year follow-up studies. The echocardiographic examination were done by one experienced observer using standard equipment. Peak and mean Doppler aortic valve gradients were calculated using the Bernoulli equation.\textsuperscript{16} The left ventricular mass index (LVMi; g/m\textsuperscript{2}) was calculated as \(1.04[(EDD+EDPWTh+EDSWTh)^3−EDD^3]−14)/\text{body surface area}\) where EDD is the end-diastolic dimension, EDPWTh and EDSWTh the end-diastolic posterior wall and septum wall thickness, respectively, from ventricular M-mode recordings guided by two-dimensional images employing the Penn convention.\textsuperscript{21} Aortic paravalvular and mitral valve regurgitation (grade 3–4 of 4; P-M leak) at the 1.5- and 10-year studies were semi-quantitated with standard colour Doppler technique. The ECG gated radionuclide left ventriculography has been previously validated\textsuperscript{18–20} and described in detail.\textsuperscript{14} For the present study

\begin{table}[h]
\centering
\caption{Preoperative data in relation to Prognostic Index (PI) groups 1–3 (see text)}
\begin{tabular}{llll}
\hline
 & PI group 1 (n=23) & PI group 2 (n=19) & PI group 3 (n=49) \\
\hline
Age (years)\textsuperscript{a} & 47±13 & 61±9 & 68±8 \\
Age ≥70 years\textsuperscript{b} & 4\% (1) & 21\% (4) & 47\% (23) \\
Female gender & 57\% (13) & 37\% (7) & 35\% (17) \\
NYHA class\textsuperscript{a} & & & \\
II & 61\% (14) & 47\% (9) & 6\% (3) \\
III & 39\% (9) & 48\% (9) & 71\% (35) \\
IV & 0 & 5\% (1) & 23\% (11) \\
Clinical left ventricular failure\textsuperscript{a} & 0 & 11\% (2) & 63\% (31) \\
Coronary disease\textsuperscript{c} & & & \\
1-vessel & 0 & 21\% (4) & 18\% (9) \\
2-vessel & 9\% (2) & 5\% (1) & 20\% (10) \\
3-vessel/left main stem & 0 & 11\% (2) & 20\% (10) \\
Peak-peak aortic valve gradient (mmHg)\textsuperscript{b} & 101±25 & 82±22 & 76±24 \\
Valve type & & & \\
St. Jude bileaflet & 96\% (22) & 95\% (18) & 86\% (42) \\
Starr–Edwards ball & 4\% (1) & 5\% (1) & 12\% (6) \\
St. Jude xenograft & 0 & 0 & 2\% (1) \\
Valve size (mm) & 22.8±1.9 & 23.7±2.8 & 23.2±2.4 \\
Body surface area (m\textsuperscript{2}) & 1.78±0.23 & 1.84±0.19 & 1.86±0.20 \\
Alive at 10 years\textsuperscript{c} & 87\% (20) & 58\% (11) & 43\% (21) \\
\hline
\end{tabular}
\end{table}

Data are mean±standard deviation or % of patients (number in parenthesis).
\textsuperscript{a}P<0.0001.
\textsuperscript{b}P<0.001.
\textsuperscript{c}P<0.01.

Fig. 1  Cumulative survival in relation to prognostic index (PI) groups 1–3 (see text and Table 1).
we used the left ventricular ejection fraction (LVEF; stroke volume in percent of end-diastolic volume) and fast filling fraction (LVFFFF; filling volume during first half of diastole in percent of total filling volume).

**Operation**

Standard techniques as described previously including extracorporeal circulation with general hypothermia (30°C), topical cooling, and crystalloid cardiopulmonary arrest were used in all 91 patients. A standard St. Jude bileaflet disc valve (19–29, mean 22.8 mm) was implanted in 82 patients, a Starr–Edwards model 1260 silastic ball valve (26–29, mean 27.0 mm) in eight and a St. Jude Bioimplant stented xenograft (26 mm) in one. All except the latter patient received life-long warfarin treatment.

The 38 patients with CAD had concomitant bypass grafting performed with 1–5, mean 1.9 distal anastomoses.

**Statistical analysis**

All tests were performed using the BMDP Dynamic release 7.0 software package. Univariate comparisons between groups were performed using a standard Pearson chi-square test, a non-paired t-test, or a one-way analysis of variance as appropriate. Paired comparisons were done with a paired t-test. Linear relations were checked with a standard least-squares linear regression analysis. Cumulative survival was assessed with Kaplan–Meier’s product limit method and comparison between groups done with a log-rank and a Gehan test. Quantitative data are given as mean±standard deviation. P<0.05: not significant (ns).

**Results**

Groups A (n=49) and B (n=42) were comparable as regards all preoperative data including age (61±13 vs 61±12 years), female gender (39% vs 41%), New York Heart Associations functional classes III–IV (73% vs 71%), hypertension (12% vs 10%), LVEF (59±15 vs 60±14), peak-peak aortic valve gradient (84±24 vs 84±27 mmHg), LVMi (203±56 vs 200±61 g/m²), prognostic index (3.95±0.91 vs 3.91±0.95), PI groups 1, 2, and 3 (22%, 22%, and 56% vs 29%, 19%, 52%), and survival at 10 years (55% vs 59%).

**Hypertension, valvular regurgitation and hypertrophy regression**

LVMi was 202±46 g/m² preoperatively (n=91), 157±48 g/m² at 1.5 years (n=42, P<0.0001), and 159±70 g/m² at 10 years (n=47, P<0.0001). Three out of 42 patients had significant aortic paravalvular leak at 1.5 years; one had a minimal reduction of LVMi, the other two an increase (Fig. 2) and all three had died before 10 years. One out of 47 patients had significant paravalvular leak at 10 years while five had significant mitral valve regurgitation; the echo-Doppler examination indicated primary mitral valve disease with annular and cusp calcification and degeneration in two with LVEF of 34 and 36% and NYHA class II status; the remaining three were judged to have secondary (functional) regurgitation with hugely dilated left ventricles, LVEF of 14–21%, NYHA class III status and monstrous left ventricular hypertrophy (Fig. 2, Table 2). All four group A patients with valvular leak had an increase in LVMi from 1.5 to 10 years (Fig. 2) and all three with secondary mitral regurgitation and one with primary had 10-year LVMi greater than the preoperative value. The patients with left sided regurgitation (hereafter referred to as P–M leak) had the highest LVMi at both 1.5 and 10 years (Fig. 2, Table 2).

Ten patients had hypertension preoperatively, six of whom (group A) attended the 1.5-year study (average LVMi drop 33 g/m², NS; Fig. 2) and 3 the 10-year study (one with primary mitral regurgitation; Fig. 2); all had an increase in LVMI between 1.5 and 10 years. Five group A patients had developed new hypertension between 1.5 and 10 years with LVMi increase from 130±37 to 175±45 g/m² (P<0.05) even though one had a minor drop (Fig. 2). Two group B patients with preoperative hypertension and three with new hypertension attended the 10-year study. A total of 12 patients without P–M leak were thus treated for hypertension at the 10-year study; they had no significant LVMi drop from the preoperative value (average 25 g/m²; ns) and hypertensive patients had significantly higher LVMi at both 1.5 and 10 years than normotensive patients (Fig. 2, Table 2). There were no relations between systolic or diastolic blood pressure and the simultaneously measured LVMi.

**Prognostic index and hypertrophy regression**

Preoperative data in relation to PI groups 1–3 are given in Table 1. The groups were comparable as regards prosthetic valve size and body surface area. The remaining data indicated a worsening of preoperative risk profile from group 1 to group 3 and survival to 10 years behaved accordingly (Fig. 1, Table 1).

With hypertensive patients and those with 1.5- and 10-year P–M leak excluded, LVMi dropped from 200±60 g/m² preoperatively (n=81) to 134±41 g/m² at 1.5 years (n=33, P<0.0001) to 124±31 g/m² at 10 years (n=29, P<0.0001; Table 2). Preoperative PI correlated significantly with both preoperative, 1.5-year, and 10-year LVMi with hypertensive patients included, and the correlation coefficients rose when hypertensive patients were excluded (Fig. 3). There were similar correlations between preoperative LVEF and preoperative (r=−0.33, P<0.001), 1.5-year (r=−0.40, P<0.05) and 10-year LVMi (r=−0.40, P<0.01). Exclusion of patients with hypertension and P–M leak revealed a significant increase in LVMi across the three PI groups for both the preoperative, 1.5-year, and 10-year LVMi with hypertensive patients included, and the correlation coefficients rose when hypertensive patients were excluded (Fig. 3). There were similar correlations between preoperative LVEF and preoperative (r=−0.33, P<0.001), 1.5-year (r=−0.40, P<0.05) and 10-year LVMi (r=−0.40, P<0.01). Exclusion of patients with hypertension and P–M leak revealed a significant increase in LVMi across the three PI groups for both the preoperative, 1.5-year, and 10-year measurements (Table 2, Fig. 2) and significant reductions in LVMi at 1.5 years in both PI group 1 (P<0.01, n=8), group 2 (P<0.01, n=9) and group 3 (P<0.001, n=16) for patients with paired values. There were no further change in LVMi between 1.5 and 10 years. The preoperative PI and the related changes in LVMi also seemed to indicate LVEF and LVFFFF at the three measurement times (Table 2). There were no relations between preoperative CAD, prosthetic valve size or valve size index (valve orifice diameter divided by body surface area) and LVMi at any of the three measurement times. Peak Doppler gradient across the prosthetic valve at 1.5 years (18±6 mmHg; mean gradient was not measured) did not correlate with 1.5-year LVMi (patients with P–M leak
excluded) with or without hypertensive patients included. Peak (24±10 mmHg) or mean Doppler gradient (10±5 mmHg) at 10 years were not related to 10-year LVMi. Age was not related to any of the LVMi measurements (P–M leak excluded, hypertension included).

Men and women did not differ significantly as regards preoperative, 1.5-year, or 10-year LVMi.

Nine of 10 patients with preoperative LVMi ≤140 g/m² were alive at 10 years (including a 1.5- and 10-year study non-attender) without functional mitral regurgitation.
Table 2  Left ventricular mass index (LVMi), ejection fraction (LVEF), and fast filling fraction (LVFFF) preoperatively and 1.5 and 10 years after the operation in relation to prognostic index (PI) groups 1–3, systemic hypertension (SHyp) and significant left sided regurgitation (P–M leak; see text and Table 1)

<table>
<thead>
<tr>
<th></th>
<th>LVMi (g/m²)</th>
<th>LVEF (%)</th>
<th>LVFFF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperatively (n=91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI groups 1–3 (n=81)</td>
<td>200±60b,i</td>
<td>58±17b,i</td>
<td>60±14b,i</td>
</tr>
<tr>
<td>PI group 1 (n=21)</td>
<td>161±41c,i</td>
<td>71±7c,i</td>
<td>67±8c,i</td>
</tr>
<tr>
<td>PI group 2 (n=19)</td>
<td>176±44</td>
<td>67±8</td>
<td>60±11</td>
</tr>
<tr>
<td>PI group 3 (n=41)</td>
<td>232±58</td>
<td>42±16</td>
<td>55±16</td>
</tr>
<tr>
<td>SHyp (n=10)</td>
<td>212±46d,ns</td>
<td>67±5d,1</td>
<td>61±12ns</td>
</tr>
<tr>
<td>P–M leak (n=0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.5 years (n=42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI groups 1–3 (n=33)</td>
<td>144±42b,h</td>
<td>63±17b,h</td>
<td>53±14b,i</td>
</tr>
<tr>
<td>PI group 1 (n=8)</td>
<td>110±35c,i</td>
<td>75±4c,i</td>
<td>68±11c,h</td>
</tr>
<tr>
<td>PI group 2 (n=9)</td>
<td>134±43</td>
<td>74±6</td>
<td>56±11</td>
</tr>
<tr>
<td>PI group 3 (n=16)</td>
<td>164±33</td>
<td>51±16</td>
<td>45±12</td>
</tr>
<tr>
<td>SHyp (n=6)</td>
<td>193±42d,i</td>
<td>73±10ns</td>
<td>61±8ns</td>
</tr>
<tr>
<td>P–M leak (n=3)</td>
<td>230±24c,1</td>
<td>65±6ns</td>
<td>71±22ns</td>
</tr>
<tr>
<td>10 years (n=47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI groups 1–3 (n=29)</td>
<td>124±31b,h</td>
<td>62±7b,1</td>
<td>60±14b,ns</td>
</tr>
<tr>
<td>PI group 1 (n=17)</td>
<td>116±25c,i</td>
<td>63±7c,ns</td>
<td>66±10c,1</td>
</tr>
<tr>
<td>PI group 2 (n=6)</td>
<td>126±27</td>
<td>62±6</td>
<td>55±14</td>
</tr>
<tr>
<td>PI group 3 (n=6)</td>
<td>146±41</td>
<td>57±7</td>
<td>49±15</td>
</tr>
<tr>
<td>SHyp (n=12)</td>
<td>175±39d,h</td>
<td>54±12d,1</td>
<td>53±22ns</td>
</tr>
<tr>
<td>P–M leak (n=6)</td>
<td>297±76e,8</td>
<td>31±19e,1</td>
<td>62±21ns</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation or % of patients (number in parenthesis).

a) Patients with SHyp and P–M leak excluded.
b) Test of PI groups 1–3 combined versus SHyp group versus P–M leak group.
c) Test of PI groups 1–3.
d) Test of SHyp group versus PI groups 1–3 combined.
e) Test of P–M leak group versus PI groups 1–3 combined.
f) Test of PI group 1 versus groups 2–3 combined.
g) P<0.0001.
h) P=0.001.
i) P<0.01.
j) P<0.05. ns: not significant.

The one who died had developed aortic paravalvular leak at 1.5 years compared with 54% (n=38) of 71 with LVMi of 141–279 g/m² and two of 10 with LVMi≥280 g/m² (five died, three with functional mitral regurgitation; Fig. 4). The prognostic impact of LVMi at the 1.5-year investigation (excluding three patients with P–M leak) is shown in Table 3. Those with 1.5-year LVMi ≤120 g/m² had experienced the highest hypertrophy regression during the preceding 1.5 years and had the best prognosis during the ensuing 8.5 years. The functional status in relation to PI group, hypertension, and P–M leak at 10 years is given in Table 4. The majority of PI group 1 patients were asymptomatic while all in group 3 had class II and half with P–M leak class III symptoms.

Discussion
The present paper is the first to chart hypertrophy regression and its impact on longevity and patient functional status in a substantial and representative group of adult patients in the long term after AVR for AS. "Cleaned" for patients with development of left sided valvular regurgitation or hypertension the time course and rules determining changes in LVMi postoperatively seemed quite clear. There was a highly significant LVMi reduction during the first 18 months. We have previously shown that this is a continuing process in the early postoperative phase with reduction in LVMi from 10 days to 3 months and 3 months to 1.5 years. This accords well with other studies indicating that the majority of hypertrophy regression has taken place during the first 12 months. However, the present study indicates that no further change in LVMi took place between 1.5 and 10 years. Previous long-term studies have analysed only 11 and 10 patients who were alive 8.1 (±2.9) and 7.4 (±1.8) years, respectively, after AVR for AS. At odds with the present results, both studies seemed to indicate that hypertrophy regression is a continuing process over many years and that some late residual hypertrophy was related to increased afterload caused by the prosthetic valve. However, such results may be explained by the small number of patients and the fact that patients who died before the late study, perhaps due to less regression of hypertrophy, were not analysed. However, the process of left ventricular mass regression may be separated into hypertrophy regression proper, i.e. regression of myocyte contractile elements which seems to happen early after relief of the pressure load, and remodelling of the
interstitial collagen matrix, which may take place over years and have bearing on maintenance of some diastolic stiffness.27 The present study obviously cannot address the issue of collagen matrix remodelling but can only conclude that left ventricular mass reduction in simple and absolute terms, whether predominantly related to myocyte or interstitial tissue, seems to be complete within the first 1.5 years. The diastolic fast filling fraction of our patients remained primarily unchanged thereafter up to 10 years (Table 2) despite the fact that the filling fraction is inversely related to advancing age.20 Finally, studies of remodelling of the collagen matrix in the long term after AVR for AS have employed endomyocardial catheter biopsies,27 and the endomyocardium may not be representative of the full wall thickness of functioning myocardium.10

Recent years have witnessed a strong trend towards favouring stentless xenografts (and allografts) over stented xenografts and mechanical prosthetic aortic valves due to theoretical advantages as regards haemodynamic function and hypertrophy regression.24,25 One non-randomized study analysing 39 patients with an allograft, 72 with a stentless xenograft, 13 with a stented xenograft and 13 with a bileaflet disc valve examined serially to 3 years seemed to prove the point.23 However, a prospective study randomizing 100 patients to a stentless or a stented xenograft found no difference in haemodynamic function or LVMi 3 months or 1 year postoperatively.26 Two large non-randomized studies analysing stentless xenografts, stented xenografts, and bileaflet disc valves,28,29 and one large prospective randomized comparison of three contemporary disc valves30 also failed to elucidate any impact of valve type, size or haemodynamic function on post-AVR hypertrophy regression, in full accordance with the present results. Obviously, reversal of the hypertrophy process depends on the total reduction in outflow tract obstruction. The failure to elucidate any clear impact of stentless xenografts over modern stented xenografts and mechanical valves may simply be explained by reported mean Doppler gradients averaging 5–8 mmHg,24,26,29 7–14 mmHg,26,29 and 12 mmHg,29 respectively, 1 to 2 years postoperatively, and 10 mmHg at 10 years for the present patients. Such differences may be irrelevant when compared with the preoperative gradients being several magnitudes greater.

Preoperative risk profile and not the prosthetic valve seems to be the dominant factor. One main result of this paper is the strong and clear correlation between preoperative PI and not only preoperative but also both 1.5-year and 10-year LVMi. The main rule governing

---

**Fig. 3** Connection (linear regression) between preoperative (preop.) prognostic index and left ventricular mass index (LVMi; g/m²) measured preoperatively and at the 1.5- and 10-year postoperative studies. Patients with aortic paravalvular leak or primary or secondary mitral valve regurgitation (see text, Table 2, and Fig. 2) at the 1.5- and 10-year studies were excluded. x: patients with systemic hypertension; o: patients without. In each panel the statistics in the upper left corner is for all patients and in the lower right corner with hypertensive patients excluded.
hypertrophy regression can thus be added to the time course elucidated above. Patients with a favourable preoperative risk profile had less pronounced left ventricular hypertrophy preoperatively but also more complete regression 1.5 years after the operation than patients with a worse risk profile. This advantage was maintained at 10 years when the vast majority was alive with normal left ventricular function. Patients in PI group 3, on the other hand, had the highest preoperative LVMi and the least hypertrophy regression at 1.5 and 10 years.

**Table 3** Prognostic impact of left ventricular mass index (LVMi) at the 1.5-year investigation

<table>
<thead>
<tr>
<th>LVMi ≤120 g/m^2 (n=11)</th>
<th>LVMi 121–170 g/m^2 (n=13)</th>
<th>LVMi ≥171 g/m^2 (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ-LVMi (g/m^2)^a</td>
<td>82±36</td>
<td>55±39</td>
</tr>
<tr>
<td>Alive at 10 years^a,b</td>
<td>91% (10)</td>
<td>77% (10)</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation or % of patients (number in parenthesis). Δ-LVMi: preoperative minus 1.5-year LVMi.

^aP<0.05.

^bChi-square test for linear trend.

**Table 4** Ten-year functional status in relation to prognostic index (PI) groups 1–3, systemic hypertension (SHyp) and significant left sided regurgitation (P–M leak; see text and Table 1 and Table 2)

<table>
<thead>
<tr>
<th>NYHA class^a</th>
<th>PI–1 (n=17)</th>
<th>PI–2 (n=6)</th>
<th>PI–3 (n=6)</th>
<th>SHyp (n=12)</th>
<th>P–M leak (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>77% (13)</td>
<td>67% (4)</td>
<td>0</td>
<td>58% (7)</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>23% (4)</td>
<td>33% (2)</td>
<td>100% (6)</td>
<td>34% (4)</td>
<td>50% (3)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8% (1)</td>
<td>50% (3)</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are % of patients (number in parenthesis).

^aP<0.0001.
when only some 40% were alive. All patients with signifi-
cant mitral regurgitation at 10 years were, furthermore, recruited from PI group 3.

The coupling of LVMi measured preoperatively and 1.5 and 10 years later with the preoperative PI, calculated from heart related variables and with a clear ability to predict and sub-stratify long-term survival, thus strongly indicates a preoperatively established basis in the left ventricular myocardium for the two related occurrences, hypertrophy regression and survival. This was previously indicated more directly by relating histological myocardial abnormalities to hypertrophy regression (in the short term) and long-term survival. This accords well with experimental animal studies showing that regression of hypertrophy occurs unless the myocardium has suffered structural damage.31

Two related findings of the present study should be pointed out. Only the very highest preoperative LVMi’s (≥280 g/m²) predicted a very poor prognosis and the lowest (≤140 g/m²) a very good prognosis. In the large intermediary range LVMi on its own had poor prognostic value. However, a far better and graded risk stratification was obtained by looking at the 1.5-year LVMi: by cutting at 120 and 170 g/m² we identified three nearly equally large groups with survival during the ensuing 8.5 years ranging from excellent via intermediary to poor. The important point is, that low LVMi at 1.5 years was related to the highest degree of regression (∆LVMi) to 1.5 years and vice versa. Thus, the absolute degree of left ventricular hypertrophy preoperatively is important but the regression potential is crucial as it is related both to the preoperative risk profile and postoperative longevity.

We chose to include LVEF and LVFFF in the present results since both have been shown to be independent predictors of post-AVR survival.14 The preoperative dependency of both LVEF and LVFFF upon the risk profile (PI) was maintained at the 1.5-year LVMi: by cutting at 120 and 170 g/m² we identified three nearly equally large groups with survival during the ensuing 8.5 years ranging from excellent via intermediary to poor. The important point is, that low LVMi at 1.5 years was related to the highest degree of regression (∆LVMi) to 1.5 years and vice versa. Thus, the absolute degree of left ventricular hypertrophy preoperatively is important but the regression potential is crucial as it is related both to the preoperative risk profile and postoperative longevity.

It should come as no surprise that systemic hypertension had a strong impact. Preoperatively, the influence of hypertension ‘drowned’ in the impact of left ventricular pressure load related to the valvular stenosis. At the 1.5- and 10-year investigations the influence was clear. Hypertensive patients had less hypertrophy regression and higher LVMi than normotensive patients. All hypertensive patients with paired values including all but one with newly diagnosed hypertension in the interim had an increase in LVMi between the 1.5- and 10-year studies. The one patient with new hypertension and a decrease in LVMi could represent a faulty diagnosis or optimal impact of antihypertensive treatment. Could the different LVMi profiles be the cause of hypertension in some patients? Not likely since patients with significant LVMi reduction to 1.5 years subsequently suffered significant LVMi increase to 10 years after contracting new hypertension. It seems clear that meticulous antihypertensive control and treatment is extremely important after AVR for AS.

The development of aortic paravalvular leak with significant volume load of the left ventricle is an obvious detrimental factor which highlights a meticulous intraoperative sewing technique and postoperative endocarditis prophylaxis. Given the dismal prognosis without reoperation, the latter should be strongly considered. Significant mitral valve regurgitation with a pronounced impact on LVMi at 10 years is a bit more interesting. Two patients had probable primary mitral valve disease which in a 10-year observation initiated by operation for calcified AS is probably not just coincidental. Mitral valve surgery is indicated if the patients age and general status allow it. The three patients with secondary or functional mitral regurgitation, on the other hand, had reached the last station before death with severe end-stage dilated but none-the-less hypertrophic cardiomyopathy. Heart transplantation would be the only treatment option.

A short-coming of our study resides in the fact that we did not initially plan (or have the capacity to) recruit also group B patients for the 1.5-year investigation. However, groups A and B were comparable as regards preoperative findings and risk profile as well as survival to 10 years. We may thus assume that the patients who did attend the 1.5-year study were representative of the entire cohort. At 10 years there were less difference in LVMi across PI groups 1 to 3 than at 1.5 years. The few patients of group 3 who were alive at 10 years tended to have lower LVMi than the larger group analysed at 1.5 years. The explanation probably is that the preoperative PI is not an accurate tool and that the few group 3 patients who were alive 10 years later were ‘selected’ due to some potential for hypertrophy regression despite a high risk profile.

In conclusion, left ventricular hypertrophy regression up to 10 years after AVR for AS is dependent on the preoperative risk profile indicating that varying degrees of irreversible myocardial disease is the underlying factor. Operative intervention early in the natural course of AS would thus ensure more complete hypertrophy regression and thereby improve long-term survival. Systemic hypertension, unlike the prosthetic valve, is an important detrimental factor in its own right.

Acknowledgements

The Danish Heart Foundation, St. Jude Medical Inc., and Baxter Healthcare Corporation are thanked for financial support.

References
