Left ventricular mass: impact on left ventricular contractile function and its reversibility in patients undergoing aortic valve replacement

Kazuhiro Taniguchia,*, Toshiki Takahashia, Koichi Toda, Hajime Matsuea, Yasuhiro Shudoa, Hideo Shintanib, Masataka Mitsunob, Yoshiki Sawa

a Department of Cardiovascular Surgery, Osaka Rosai Hospital, Sakai, Japan
b Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Suita, Japan

Received 9 January 2007; received in revised form 27 June 2007; accepted 2 July 2007; Available online 8 August 2007

Abstract

Background: We examined the relationships of left ventricular (LV) contractile state with LV geometry and hypertrophy in patients with aortic valve disease, and investigated the reversibility of LV hypertrophy and contractility following aortic valve replacement. Methods: Preoperative data from quantitative cineangiography and pressure measurements in 132 patients with chronic aortic valve disease, of whom 82 aortic regurgitation (AR), 41 aortic stenosis (AS), and 9 had mixed stenosis and regurgitation (AS-AR), were reviewed. Late after surgery, 59 of the patients (39 with AR, 20 with AS) were studied to elucidate the postoperative reversibility of LV performance and regression of LV hypertrophy. Results: Preoperatively, multiple comparison tests found significant changes in the variables of LV volumes and dimensions in relation to LV contractile state. In stepwise regression analysis, the LV mass index was initially incorporated into a multivariate regression model as an important correlate of LV contractile state. LV geometric variables showed either no or a poor correlation with contractile state. Following aortic valve replacement, improvement of LV contractile dysfunction and regression of LV hypertrophy were limited in many of the patients who had severe preoperative hypertrophy (LV mass index ≥ 200% of normal or greater). Further, a close association between LV hypertrophy and LV contractility persisted postoperatively. Conclusion: Our results suggest that the development of LV hypertrophy in terms of an increase in LV mass index, in contrast to changes in geometric patterns, is significantly associated with deterioration in contractile function. LV hypertrophy may become irreversible and pathological at equivalent degrees of hypertrophy (LV mass index ≥ 200% of normal), regardless of the type of aortic valve lesion.


1010-7940/$ — see front matter © 2007 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ejcts.2007.07.003

1. Introduction

Preoperative left ventricular (LV) myocardial function is generally accepted as a major determinant of postoperative survival and LV functional recovery in patients undergoing aortic valve replacement, while preoperative LV hypertrophy is also viewed as a risk factor for cardiovascular morbidity and mortality [1—3]. Recently, understanding of the differences between physiologic and pathologic hypertrophy has increased, based on the results of experimental studies of organs, as well as cellular and genetic levels [4]. However, the relationship between LV hypertrophy and LV myocardial function in a clinical setting has not been sufficiently elucidated.

The goals of the present study were: (1) to examine the relationship between LV hypertrophy and LV myocardial function, (2) to define the degree of LV hypertrophy necessary to transition from normal to decreased contractility, and (3) to elucidate the postoperative reversibility of LV contractility and hypertrophy following aortic valve replacement.

2. Materials and Methods

2.1. Patients

The records of all patients who underwent cardiac catheterization at the Surgical Catheterization Laboratory,
First Department of Surgery, Osaka University Hospital, between July 1981 and May 1994, and then received an isolated aortic valve replacement or repair within 3 months of catheterization were reviewed. During the same period, a total of 146 patients underwent an aortic valve replacement or repair. Of those 146, 14 who underwent cardiac catheterization at another cardiac division or hospital were excluded, as were patients with mitral lesions or coronary artery disease. As a result, 132 patients with aortic valve disease were included in the present study. There were 104 males and 28 females, with a mean age of 48 ± 14 years old.

Eighty two of the patients had 'pure' aortic regurgitation (AR), which was defined as having a regurgitation grade ≥3/4, while 41 had 'pure' or nearly pure stenosis (AS), which was defined as having an aortic valve area <1.0 cm² and a regurgitation grade ≤2/4, and 9 had mixed aortic stenosis and regurgitation (AS-AR), which was defined as having an aortic valve area <1.0 cm² and regurgitation grade ≥3/4. All aortic valve lesions were consistent with the findings obtained during surgery. The mean New York Heart Association functional classification was 2.4 for the AS-AR group, 0.9 for the AR group, and 2.8 ± 1.0 for the AS group, and 3.1 ± 0.8 for the AS-AR group. Clinical and baseline hemodynamic data for these three groups are summarized in Table 1.

To elucidate the postoperative reversibility of LV contractile dysfunction and hypertrophy, we investigated 59 of the patients (39 with AR, 20 with AS) at 29 ± 26 months (range 6—140 months) after undergoing aortic valve replacement. The indications for postoperative catheterization were not selective, though all patients were free of any signs of perioperative myocardial infarction and coronary artery disease during the follow-up period. The purposes of the investigation as well as the invasive nature of the tests were explained in detail to all patients, and only those who gave informed consent were studied. Regarding postoperative catheterization, we obtained approval for the study from our institutional ethics committee on human research. None of the patients had complications from either preoperative or postoperative catheterization.

2.2. Cardiac catheterization and measurements

Our pre- and postoperative cardiac catheterization and quantitative cineventriculography techniques have been described [5], and were performed using the same equipment and catheter manometer systems reported previously. Postoperatively, the left ventricle was catheterized using a transseptal technique in all the patients. None had a significant paravalvular leak or developed significant coronary artery disease.

LV end-diastolic volume (EDV) and end-systolic volume (ESV) were obtained using the area-length method, as were LV minor-axis dimensions from the same left ventriculograms. LV dimensions were determined in the present study, as they were able to provide data comparable with those obtained by echocardiography. LV mass and wall thickness were also determined, while LV volume and mass were indexed based on body surface area. As an index of the pattern of LV hypertrophy, the ratios of LV minor-axis radius to wall thickness and of LV mass to volume were calculated. Circumferential mid-wall stresses were also routinely obtained using Mirsky’s formula [6]. All measurements and calculations were routinely processed using a digital plotting table connected to a personal computer.

2.3. Assessment of left ventricular contractile performance

LV contractile state was assessed using the ejection fraction-end-systolic stress (EF-ESS) relationship and the

<table>
<thead>
<tr>
<th>Gender (female/male)</th>
<th>AR (n = 82)</th>
<th>AS (n = 41)</th>
<th>AS-AR (n = 9)</th>
<th>Control (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45 ± 14</td>
<td>55 ± 14</td>
<td>50 ± 9</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>58 ± 7</td>
<td>55 ± 6</td>
<td>57 ± 7</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>77 ± 18</td>
<td>76 ± 18</td>
<td>73 ± 10</td>
<td>77 ± 14</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.96 ± 0.81</td>
<td>2.82 ± 0.87</td>
<td>3.01 ± 1.18</td>
<td>3.68 ± 1.03</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>143 ± 23</td>
<td>202 ± 29</td>
<td>162 ± 33</td>
<td>120 ± 17</td>
</tr>
<tr>
<td>AoSP (mmHg)</td>
<td>143 ± 23</td>
<td>126 ± 18</td>
<td>136 ± 33</td>
<td>120 ± 17</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>16 ± 8</td>
<td>17 ± 11</td>
<td>13 ± 4</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>ESS (kdyn/cm²)</td>
<td>212 ± 42</td>
<td>143 ± 47</td>
<td>190 ± 55</td>
<td>160 ± 23</td>
</tr>
<tr>
<td>EDVI (kdyn/cm²)</td>
<td>422 ± 79</td>
<td>423 ± 76</td>
<td>412 ± 76</td>
<td>332 ± 43</td>
</tr>
<tr>
<td>EF</td>
<td>0.49 ± 0.10</td>
<td>0.56 ± 0.18</td>
<td>0.47 ± 0.11</td>
<td>0.65 ± 0.05</td>
</tr>
<tr>
<td>ESS/ESVI (kdyn/cm²/µl)</td>
<td>2.31 ± 0.96</td>
<td>3.32 ± 1.55</td>
<td>2.32 ± 0.63</td>
<td>5.82 ± 0.99</td>
</tr>
<tr>
<td>EDVI (cc/m²)</td>
<td>207 ± 64</td>
<td>122 ± 55</td>
<td>160 ± 36</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>ESVI (cc/m²)</td>
<td>110 ± 56</td>
<td>63 ± 55</td>
<td>87 ± 32</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>LV mass index (g/m³)</td>
<td>233 ± 82</td>
<td>208 ± 71</td>
<td>226 ± 54</td>
<td>96 ± 13</td>
</tr>
<tr>
<td>LV mass/volume ratio</td>
<td>1.13 ± 0.20</td>
<td>1.82 ± 0.51</td>
<td>1.42 ± 0.32</td>
<td>1.22 ± 0.17</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>76 ± 8</td>
<td>61 ± 10</td>
<td>68 ± 5</td>
<td>54 ± 4</td>
</tr>
<tr>
<td>EDS (mm)</td>
<td>58 ± 10</td>
<td>45 ± 14</td>
<td>52 ± 7</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>11.1 ± 2.0</td>
<td>12.7 ± 2.3</td>
<td>12.1 ± 2.3</td>
<td>8.5 ± 1.0</td>
</tr>
<tr>
<td>LV radius/thickness</td>
<td>3.50 ± 0.53</td>
<td>2.49 ± 0.99</td>
<td>2.92 ± 0.54</td>
<td>3.23 ± 0.38</td>
</tr>
</tbody>
</table>

ratio of end-systolic stress to end-systolic volume index (ESS/ESVI). Preoperative contractility was grouped into three contractile subgroups using the EF-ESS relationship. LV contractility was categorized as normal (Group I) if the patient had values that were above the lower 70% confidence limit (one standard deviation) of the normal EF-ESS relationship for control subjects, intermediate (Group II) if the value was between the lower 70% and lower 95% confidence limits, and depressed (Group III) if the value was below the lower 95% confidence limit of the normal EF-ESS relationship. In addition, the vertical distance (\(D_{EF}\)) of each individual EF-ESS coordinate above or below a previously published regression line of the normal (control) group was computed and presented as the contractile state index (CS index), by dividing by the standard deviation at the same ESS value (Fig. 1). This method was a modification of that reported by Lang et al. [7].

2.4. Surgery and implanted valve size

Of the 132 patients studied, 130 underwent an isolated aortic valve replacement and 2 an aortic valvuloplasty. With the implanted valve sizes utilized, particular effort to insert a larger prosthesis was made because the concept of prosthesis-patient mismatch is well recognized. As a result, 13 patients received 21-mm valves (9 St Jude Medical bileaflet mechanical valves, 1 Bjork-Shiley tilting disc valve, and 3 Carpentier- Edwards pericardial bioprostheses), 28 received 23-mm valves (6 St Jude Medical valves, 18 Bjork-Shiley valves and 4 Carpentier- Edwards bioprostheses), 54 received 25-mm valves (5 St Jude Medical valves, and 49 Bjork-Shiley valves), and the remaining 35 received a larger size Bjork-Shiley valve (27, 5, and 3 patients received 27, 29, and 31-mm valves, respectively). All but three patients over 70 years old received a bioprosthetic valve. The body surface area (BSA) for the entire group ranged from 1.17 to 2.05 m² (mean, 1.62 ± 0.18 m²), while that for patients who received a small valve (21 or 23 mm) ranged from 1.17 to 1.79 m² (mean 1.49 ± 0.16 m²). Although it was not determined, the effective orifice area index (EOAI) was considered to be greater than 0.90 cm²/m² in all patients [8, 9].

2.5. Normal subjects

Normal values for LV angiographic and function data were obtained from 30 control patients who were referred to us for cardiac catheterization to evaluate atypical chest pain syndrome [5].

2.6. Statistics

All data are expressed as the mean ± 1 standard deviation. Comparisons between two groups were performed with an unpaired t-test, while multiple comparisons between more than two groups were performed using a Bonferroni test. Correlations between variables were tested with multiple correlation analysis. Preoperative variables thought to correlate with LV contractile state were subjected to univariate analysis and then to stepwise multiple regression analysis (Appendix A). Pre-, intra- and postoperative variables were also used to examine the postoperative decrease in LV mass using stepwise multivariate analysis (Appendix B). Comparisons of pre- and postoperative data were performed with a paired t-test. Linear regression analysis using a least squares method was performed using control patient data to obtain 70 and 95% confidence limits for the normal EF-ESS relationship. Statistical analysis was done using the statistical package StatView J 4.11, (Avacus Concept Inc., CA.).

3. Results

3.1. Stratification of patients based on assessment of contractile state

As shown in Fig. 2, 41 patients (16 with AS, 24 with AR, 1 with AS-AR) had a normal contractile state (Group I), and 64 patients (16 with AS, 41 with AR, 7 with AS-AR) had a depressed contractile state (Group III), while the remaining 27 patients (9 with AS, 17 with AR, 1 with AS-AR) fell between the lower 70% and lower 95% confidence limits of the normal EF-ESS relationship, and were classified as having an
intermediate contractile state (Group II). Table 2 shows the baseline hemodynamic data for all 132 patients divided into these three contractile groups.

3.2. Relationships of LV geometry and hypertrophy to contractile state

To examine the relationships of LV geometry and hypertrophy with the development of contractile dysfunction, changes in the same variables from the normal contractile group (Group I) to the depressed contractile group (Group III) were determined for each type of valve lesion (Fig. 3). Data from the AS-AR patients were excluded because of the small number.

Both EDVI and ESVI showed a progressive increase from Group I to III, though the increase in volume from Group I to Group II was slight. However, there was a marked increase from Group II to Group III. The ratio of LV mass to volume showed a tendency to increase from Group II to III for patients with AR, whereas there was a tendency to decrease from Group II to III for those with AS. LV end-diastolic dimension (EDD) showed a small increase from Group I to II and a marked increase from Group II to III. End-systolic dimension (ESD) demonstrated a progressive increase from Group I to II and then from Group II to III. The ratio of LV radius to thickness showed a tendency to decrease from Group II to III for patients with AR, whereas there was a tendency to increase from Group II to III for those with AS. Notably, there was a significant difference in these variables between patients with AR and those with AS within the same contractile group (Fig. 3).

LV mass index demonstrated a progressive increase from Group I to III. Interestingly, despite the lack of increase in EDVI from Group I to Group II, there was a significant increase in LV mass index, whereas there was no difference in LV mass index between patients with AS and those with AR in all three contractile groups (Fig. 4). These results indicate that the amount of LV hypertrophy, in contrast to type of aortic valve disease, is strongly associated with deterioration of LV contractile state. Notably, in Group II patients with an intermediate contractile state, the mean value of LV mass index was $189 \pm 27 \text{ g/m}^2$ for those with AS and $187 \pm 31 \text{ g/m}^2$ for those with AR, which were approximately two times higher than the value for the controls ($96 \pm 13 \text{ g/m}^2$).

Of the tested variables, LV mass index showed a close correlation with LV contractile state (partial correlation coefficient $= -0.73$, $p < 0.001$), and was initially incorpo-

---

### Table 2

Multiple comparisons (ANOVA) of variables among all patients classified by normal, intermediate and depressed contractility

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I ($n = 41$)</th>
<th>Group II ($n = 27$)</th>
<th>Group III ($n = 64$)</th>
<th>$p$ value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>70 ± 15</td>
<td>79 ± 20$^*$</td>
<td>79 ± 16$^*$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CI (l/min/m$^2$)</td>
<td>3.07 ± 0.86</td>
<td>3.26 ± 0.83</td>
<td>2.68 ± 0.79$^*$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>165 ± 37</td>
<td>169 ± 46</td>
<td>158 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>AoSP (mmHg)</td>
<td>137 ± 23</td>
<td>141 ± 26</td>
<td>136 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>14 ± 6</td>
<td>13 ± 6</td>
<td>19 ± 10$^*$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS (kdy/cm$^2$)</td>
<td>179 ± 58</td>
<td>187 ± 55</td>
<td>196 ± 52</td>
<td>NS</td>
</tr>
<tr>
<td>PSS (kdy/cm$^2$)</td>
<td>430 ± 88</td>
<td>421 ± 69</td>
<td>417 ± 74</td>
<td>NS</td>
</tr>
<tr>
<td>EDS (kdy/cm$^2$)</td>
<td>45 ± 23</td>
<td>42 ± 26</td>
<td>39 ± 33$^*$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EF</td>
<td>0.63 ± 0.07</td>
<td>0.56 ± 0.06$^*$</td>
<td>0.41 ± 0.10$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESS/ESVI (kdy/cm$^2$/cc/m$^2$)</td>
<td>3.86 ± 0.96</td>
<td>3.07 ± 0.81$^*$</td>
<td>1.69 ± 0.65$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDVI (cc/m$^2$)</td>
<td>133 ± 43</td>
<td>147 ± 52</td>
<td>219 ± 70$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESVI (cc/m$^2$)</td>
<td>51 ± 23</td>
<td>67 ± 29</td>
<td>132 ± 58$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index (g/m$^2$)</td>
<td>159 ± 33</td>
<td>190 ± 30$^*$</td>
<td>279 ± 70$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass/volume ratio</td>
<td>1.30 ± 0.51</td>
<td>1.46 ± 0.59</td>
<td>1.35 ± 0.35</td>
<td>NS</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>65 ± 8</td>
<td>67 ± 10</td>
<td>76 ± 10$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>44 ± 8</td>
<td>49 ± 9$^*$</td>
<td>61 ± 11$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>10.2 ± 1.9</td>
<td>11.4 ± 2.0$^*$</td>
<td>12.6 ± 21.9$^*$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV radius/thickness ratio</td>
<td>3.26 ± 0.77</td>
<td>3.09 ± 0.87</td>
<td>3.09 ± 0.61</td>
<td>NS</td>
</tr>
</tbody>
</table>

---

$a p < 0.05$: Group I versus II.

$b p < 0.01$: Group I versus III.

$c p < 0.05$: Group I versus III.

$d p < 0.01$: Group II versus III.

$e p < 0.01$: Group I versus II.
rated into the stepwise multivariate regression model as an independent correlate of LV contractile state. In contrast, LV geometric variables showed either no or a poor correlation with contractile state (CS index).

### 3.3. Postoperative reversibility of left ventricular function

The exact point at which adaptive and reversible hypertrophy with normal myocardial function becomes pathologic hypertrophy with irreversible myocardial dysfunction remains unknown. Based on the relationship of LV contractile dysfunction to the degree of LV hypertrophy, we hypothesized that impairment of LV contractile function supervenes when the increase in LV mass index is about 200% of the normal value or greater (LV mass index ≥192 g/m²), which might represent the transitional stage from physiologic to pathologic hypertrophy. Therefore, the patients were classified into those with a preoperative LV mass index less than 192 g/m² (group A) and those with that equal to or greater than 192 g/m² (group B). Postoperatively, the ejection fraction for group A patients was increased and then returned to normal from 0.56 ± 0.05 to 0.63 ± 0.07 in those with AR (n = 11, p < 0.05), and from 0.63 ± 0.10 to 0.64 ± 0.08 in those with AS (n = 8, p = ns). The ejection fraction for group B was also increased and then returned to normal or near normal from 0.43 ± 0.09 to 0.54 ± 0.14 in those with AR (n = 28, p < 0.01), and from 0.44 ± 0.18 to 0.57 ± 0.16 in those with AS (n = 12, p < 0.01). ESS/ESVI, which has been used by others to estimate contractile state, increased and then returned to a normal range in group A patients from 3.0 ± 0.9 to 4.7 ± 0.9 kdyn/cm²/ml/m² in those with AR (p < 0.01), and from 4.2 ± 0.8 to 5.4 ± 1.9 kdyn/cm²/ml/m² in those with AS (p < 0.01) (Fig. 5). However, in group B patients, ESS/ESVI increased and then remained substantially lower than normal in both those with AR (from 1.6 ± 0.7 to 3.4 ± 1.3 kdyn/cm²/ml/m², p < 0.01) and AS (from 2.3 ± 1.0 to 3.4 ± 1.4 kdyn/cm²/ml/m², p < 0.01), despite their undergoing successful aortic valve replacement (Fig. 5). The CS index for group A changed from −0.92 ± 1.14 to −0.71 ± 1.46 in patients with AR (p = ns), and from −1.19 ± 1.81 to −0.82 ± 1.35 in patients with AS (p = ns), which were not significant. In group B patients, the CS index increased and then remained abnormal in both AR (from −3.92 ± 1.91 to −2.52 ± 2.55, p < 0.01) and AS (from −4.32 ± 3.21 to −2.41 ± 3.10, p < 0.01) postoperatively.

### 3.4. Postoperative regression of left ventricular hypertrophy

LV mass index tended to decrease significantly and did not return to a normal range in any of the groups. In group A, LV mass index decreased from 172 ± 19 to 134 ± 21 g/m² in those with AR (p < 0.01) and from 169 ± 23 to 124 ± 32 g/m² in those with AS (p < 0.01), with mild hypertrophy persisting in both groups after surgery. The LV mass index for group B decreased from 310 ± 100 to 190 ± 68 g/m² in AR patients (p < 0.01) and from 244 ± 45 to 173 ± 35 g/m² in AS patients (p < 0.01), and severe hypertrophy persisted after surgery.

Stepwise multivariate regression analysis showed that the postoperative LV mass index was predicted by the equation 0.46 (preoperative LV mass index in g/m²) − 0.44 (interval from surgery to postoperative catheterization in months) + 62.8 (r = 0.83, p < 0.0001). There was a strong inverse correlation between postoperative LV mass index and postoperative ESS/ESVI ratio (r = −0.64, p < 0.0001), and also with postoperative CS index (r = −0.55, p < 0.001), indicating that a close relationship between LV hypertrophy and contractile dysfunction persists following aortic valve replacement.

Multivariate analysis also showed that the magnitude of decrease in LV mass index after surgery was correlated with the equation 0.23 (preoperative LV mass index in g/m²) + 10.2 (manufacturer’s labeled valve size in mm) − 230 (r = 0.53, p < 0.0001). The magnitude of decrease in LV mass index after surgery was also weakly but significantly correlated with postoperative PSS (r = −0.27, p = 0.043) and postoperative stroke volume index (r = −0.28, p = 0.036). These findings indicate that a postoperative regression of LV hypertrophy may be influenced by the size of the implanted prosthetic valve as well as postoperative medical treatment.

### 4. Discussion

Preoperative LV function is accepted as a key determinant of surgical outcome in patients with valvular heart disease, while LV hypertrophy is recognized as an independent cardiac risk factor [1–3]. However, the relationship between LV
dysfunction and hypertrophy in a clinical setting is not fully understood, and few indices derived from LV hypertrophy are included in guidelines or recommendations for aortic valve surgery [10].

A major finding of the present study was that the amount of hypertrophy (LV mass index), in contrast to the geometric pattern of hypertrophy, was more importantly associated with LV contractile state when stratified by the EF-ESS relationship. An association between the development of hypertrophy and contractile dysfunction was reported by Wisenbaugh et al. [11], and our findings confirm those results and also suggest that contractile dysfunction develops at similar degrees of hypertrophy, regardless of the type of aortic valve lesion. In the present study, the AS and AR subgroups within the same contractile group had equivalent amounts of hypertrophy (increased LV mass index), though they showed distinctly different hemodynamic characteristics and geometric patterns of hypertrophy. The mean values of LV mass index for the AS and AR subgroups in the intermediate contractile group were about 200% of the normal value of the controls. Therefore, we concluded that LV contractile dysfunction supervenes in many patients with aortic valve disease when the increase in LV mass index is twice the normal value or more. Further, we speculate that a two-fold increase in LV mass, presumably accompanied by structural alterations of the myocardium at the microscopic level [12] and changes in specific proto-oncogene expression at the gene level [13], may be the turning point in the course of both eccentric and concentric hypertrophy processes.

We also observed that contractile dysfunction and substantial hypertrophy persisted late after successful aortic valve replacement in many patients, particularly in those with AR and AS, in whom the increase in preoperative LV mass index was severe (200% of normal or greater). Persistent postoperative hypertrophy after aortic valve replacement was also correlated closely with persistent postoperative contractile dysfunction. These findings indicate that irreversibility or, at best, partial reversibility of both myocardial dysfunction and hypertrophy may already be present prior to aortic valve replacement. Other investigators have also observed partial reversibility of ventricular hypertrophy and dysfunction following aortic valve replacement in AR [5,14] as well as AS patients [15]. The present results extend those of previous studies, and also provide new data showing that preoperative LV mass (≥200% of normal) is strongly associated with persistent postoperative hypertrophy and persistent postoperative contractile dysfunction.

4.1. Study limitations

We recognize that the major limitation of the present study is the outdated method utilized for calculating LV volumes and mass. Recently, echocardiography has largely replaced angiography for measurements of LV function and hypertrophy, while magnetic resonance imaging has become the gold standard for calculating LV mass and wall stress. Therefore, the practical usefulness of the results is limited. Serial echocardiography studies are required to precisely determine the degree and type of LV hypertrophy that constitute a pathologic irreversible state, as well as the functional consequences of the regression of hypertrophy after aortic valve surgery. However, the validity of quantitative cineventriculography for measuring LV mass has been established, and it is unlikely that the use of newer techniques would have led to different conclusions. In the present study, the intraobserver (K.T.) and interobserver (K.T. and M.M.) variabilities of LV mass measurements were evaluated using end-diastolic frames of 60 ventriculograms, and were shown to be 3.6 ± 2.8% and 6.5 ± 3.5%, respectively.

Although the patients were prospectively identified, the data were obtained by means of a cardiac catheterization report review; thus this study has limitations inherent to retrospective studies. A relatively small number of patients with different types of aortic valve disease were evaluated and patients with potential confounding factors, such as coronary artery disease, hypertension, and renal disease requiring hemodialysis, were not included in the study. These limitations may have caused a selection bias. Further, postoperative studies were performed in only half of the patients. Also, the patients were not randomized with respect to either valve type or valve size. In addition, medications may have had influences on postoperative LV function and hypertrophy. Although we cannot exclude the possible effects of these factors on our results, we believe that selection bias and medical treatment did not affect our conclusions to a significant degree.

The influences of prosthetic valve type and size, and time following surgery on postoperative outcomes have been demonstrated in previous studies [9,16—21]. In the present series of patients, only mechanical or stented biologic prostheses were implanted. The effective orifice area (EOA) of these prostheses is always less than that of a normal human valve, which means that a certain degree of prosthesis-patient mismatch was likely present in the majority of our patients, though the expected EOA of was more than 0.90 cm²/m² in all. Therefore, our results may not be applicable for patients without a prosthesis-patient mismatch who receive a stentless aortic bioprosthesis, or a more efficient aortic valve substitute that has favorable hemodynamic performance [16,22].

The important influence of time following surgery on the regression of LV hypertrophy was demonstrated in a study by Monrad et al. [21], who noted that the postoperative regression of LV mass is a slow process that may continue for many years. It is possible that a further regression of LV hypertrophy will occur in some of our patients over an extended period of time.

Gender-related factors have also been found to influence the adaptive and recovery responses of the left ventricle to pressure and volume overload [23], as well as aortic valve replacement [24]. This issue could not be addressed in the present study, because of the relatively small number of female patients. In addition, the impacts of other patient-related factors, particularly systemic blood pressure, and cardiac rhythm and function [25], on the postoperative regression of LV hypertrophy were not sufficiently evaluated because the amount of data was limited.

As this study focused on LV hypertrophy and contractile function, the conclusions are very theoretical. Clinical correlates such as NYHA functional class, heart failure symptoms and survival after surgery were not examined [25].
Nevertheless, our findings confirm the strong association of LV hypertrophy with contractile function and provide a new cut-off value for LV mass index that may constitute irreversible LV contractile dysfunction [1—3].

In conclusion, our results suggest that progression from adaptive compensated hypertrophy to pathologic hypertrophy with irreversible contractile dysfunction in a clinical setting is supervised when the increase in LV mass index is 200% or greater of normal, regardless of the type of aortic valve lesion. Serial measurements of LV mass using magnetic resonance imaging or echocardiography may be useful for assessing the efficacy of therapeutic intervention, and may also be helpful in determining the timing of surgery for patients with chronic aortic valve disease. A prospective investigation with modern techniques is now required.

Acknowledgements

The authors wish to thank Hikaru Matsuda, MD, the Emeritus Professor of Surgery, as well as Susumu Nakano, MD, Kei Sakai, MD, Tomohide Kawamoto, MD, Shigehiko Sakaki, MD, Takashi Ueda, MD, Satoru Kuki, MD, Takafumi Masai, and colleagues from the Surgical Catheterization Laboratory, First Department of Surgery, Osaka University Graduate School of Medicine, for their valuable cooperation in this study.

References


Appendix A. List of tested variables

Age, cardiothoracic ratio, heart rate, cardiac output index, stroke volume index, LV systolic pressure, LV end-diastolic pressure, aortic systolic pressure, ESS, PSS, EDS, EDVI, ESVI, LV mass index, LV mass-to-volume ratio, EDD, ESD, LV wall thickness, LV radius-to-thickness ratio, and New York Heart Association functional class.

Appendix B. List of tested variables

Age, cardiothoracic ratio, heart rate, cardiac output index, stroke volume index, LV systolic pressure, LV end-diastolic pressure, aortic systolic pressure, ESS, PSS, EDS, EDVI, ESVI, LV mass index, LV mass-to-volume ratio, ejection fraction.
fraction, ESS/ESVI, CS index, New York Heart Association functional class, prosthetic valve size (mm), EOAI (cm²/m²), interval from aortic valve surgery to postoperative catheterization (months), and the same postoperative hemodynamic variables. The manufacturer’s indicated size was used to express prosthetic valve size. The EOA of the prosthesis was provided by the valve manufacturer or derived from the previous reports that measured EOA by means of Doppler echocardiography or hemodynamic studies. Individual EOAI values were calculated as the EOA divided by the BSA of the patient.