Hemodynamic Performance and Myosin Light Chain–1 Expression of the Hypertrophied Left Ventricle in Aortic Valve Disease Before and After Valve Replacement


Previously, we have reported on the selective accumulation of an atrial-like myosin light chain–1 (ALC1) in different forms of human ventricular hypertrophy. The present study involves the determination of ALC1 content in a control group and in patients with aortic stenosis or insufficiency before and 56±23 months after valve replacement and compares the hemodynamic and angiographic parameters. ALC1 was quantified densitometrically after two-dimensional electrophoretic resolution of biopsy specimens from the left ventricle and was expressed in percent of total ventricular light chain–1. The mean ALC1 content was 11.2±9.2% in preoperative aortic stenosis and 4.5±1.4% in aortic insufficiency, both being significantly (p<0.001) higher than the control value of 0.3±0.3%. After valve replacement, mean ALC1 content was lower than before, 4.2±3.3% (p<0.05) in stenosis and 3.4±3.1% (p=NS) in insufficiency. Left ventricular systolic pressure yields a significant (p<0.01) linear correlation (r=0.45) with the ALC1 content in all preoperative and postoperative patients. Patient group averages of ALC1 content correlate directly with left ventricular systolic and end-diastolic pressure and wall thickness (r=0.94–0.98) and, in an exponential fashion, with peak systolic circumferential wall stress (r=0.98) but not with muscle mass or any other parameter. The ventricular ALC1 binds to myosin in proportion to its occurrence in the myocardium. The content of the endogenous ventricular light chain–1 did not change under pathological hemodynamics. The response in expression of the ALC1 to pressure and volume overload suggests an adaptational process. This seems to be confirmed by its lower content in the postoperative patient groups with improved hemodynamic parameters. (Circulation Research 1992;70:1035–1043)

**Key Words** • myosin light chain • cardiac hypertrophy • aortic stenosis • aortic insufficiency • myocardial function

Ventricular hypertrophy is a compensatory mechanism in response to a variety of physiological and pathological stimuli. Under hemodynamic overload the heart tries to adapt to the increased external work by normalizing chamber wall stress. This may be affected by long-lasting adjustment of genetic expression, leading to quantitative and qualitative changes by specific activation and/or deactivation of selected genes.1–3 Under the persisting overload, these adaptive processes may prove insufficient, and cardiac failure may ensue eventually. The properties of contractile proteins of the sarcomere determine the limits for the mechanical performance. A direct correlation between contraction characteristics and particular protein isoforms, especially isoforms of myosin, has been established in animals (see References 4 and 5 for reviews). Myosin has two heavy chains (MHCs) and two pairs of light chains (MLCs), MLC1, also called the alkali or essential light chain, and MLC2, also called the 5,5′-dithiobis-(2-nitrobenzoic acid) or regulatory light chain. Two types of MHC isoforms are expressed in heart muscle cells, α-MHC and β-MHC. Homodimeric myosin with two α-MHCs has a high level of ATPase activity; homodimeric myosin with two β-MHCs has a low level of ATPase activity. Heterodimeric myosin, with one α-MHC and one β-MHC, has an intermediate level of ATPase activity. The expression of α-MHC and β-MHC in the ventricles of small laboratory animals has been shown to vary developmentally, in response to hormones and hemodynamic overload.6–8 Hemodynamic overload favors expression of β-MHC at the expense of α-MHC. Slow contraction characteristics with ββ-myosin allow for greater economy in force generation.9 In humans, normal ventricular muscle contains almost exclusively ββ-myosin. Therefore, there is no potential left for a significant shift in expression from α-MHC toward β-MHC to adapt to hemodynamic overload.10–12 The atria contain their characteristic light chain isoforms (ALC1 and ALC2), and the ventricles

From The Division of Cardiology, Medical Policlinic, and the Clinic of Cardiovascular Surgery, University Hospital, Zurich, Switzerland, and the Institute of Pharmacology, University of Zurich.

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Address for correspondence: M.C. Schaub, MD, PhD, Institute of Pharmacology, University of Zurich, Gloriastrasse 32, CH-8006 Zurich, Switzerland.

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contain their light chain isoforms (VLC1 and VLC2). A gradual shift from ALC1 and ALC2 toward the VLC1 and VLC2 has been observed in both atria of humans in response to cardiac overload.13 Thus, the human atrial muscle is able to adapt to chronic overload by changing the expression of α-MHC toward β-MHC and of both types of MLCs toward the corresponding ventricular variety with a lower ATPase activity.14-16

ALC1 and ALC2 are normally only expressed in atrium and not found in adult human ventricle. However, ALC1 is transiently expressed in the fetal ventricle, disappearing within a few months after birth,17-19 but persists for several years in infants with tetralogy of Fallot.19 The close relation or identity between the fetal ventricular isoform and ALC1 in adult atrium in humans was suggested by their identical mobility in two-dimensional electrophoretic resolution20 and by peptide maps21 and has since been confirmed by identification and localization of their common single gene on the long arm of chromosome 17.22 ALC2 was not observed in ventricles either during development or under hemodynamic overload.12,16,18,19

When we examined biopsy samples from 52 patients with different types of cardiac hypertrophy including dilated cardiomyopathy, we found in the total tissue homogenate of the left ventricle an atrial-like MLC1 with percentages of total VLC content varying from 1% up to 30%.12 Percentages up to 8% of such an atrial-like MLC1 have also recently been reported in the ventricles of three patients with valve disease, dilated cardiomyopathy, or ischemic heart disease.23 In two further studies involving a limited number of patients with dilated cardiomyopathy, only traces24 or no atrial-like MLC25 was found in ventricles.

In the present study, the ALC1 content in left ventricles from 60 patients with aortic stenosis or aortic insufficiency before or after successful aortic valve replacement accompanied by significant hemodynamic improvement was compared with hemodynamic and angiographic data. The following questions were addressed: 1) Is there a common functional parameter in the two types of valve lesions that correlates with the ALC1 content in the left ventricle? 2) Does the postoperatively improved hemodynamic condition correlate with a lower content of ventricular ALC1? 3) Is the expression of ALC1 in the ventricle accompanied by a concomitant change in the expression of intrinsic ventricular VLC? 4) Does ALC1 bind to MHCs in proportion to its content found in the ventricular tissue?

Materials and Methods

Patient Population

Patients were divided into three groups (Table 1). The first group, preoperative group A, consisted of 27 patients (six women, 21 men; mean age, 53±13 years). Seventeen of the 27 patients had aortic stenosis, and 10 had aortic insufficiency (patients with combined aortic valve disease and a valve area ≤1.0 cm² were assigned to aortic stenosis). The second group, postoperative group B, consisted of 15 patients (two women, 13 men; mean age, 48±11 years) examined 16-99 (mean, 56±23) months after successful aortic valve replacement. The third group, control group C, consisted of 10 patients (five women, five men; mean age, 34±14 years) with normal hemodynamics. Seven of them were evaluated for atypical chest pain, and three were evaluated for quantification of a hemodynamically not relevant atrial septal defect. All patients were in sinus rhythm. None had significant coronary artery disease (≥50% narrowing), except for one patient in group A with 75% stenosis of the right coronary artery.

Hemodynamic data for the 15 group B patients were available both before (from preoperative catheterization) and after surgery. Preoperative and postoperative biopsy specimens were not available from the same patients. Therefore, group A consisted of 27 patients that had been selected from a pool of 60 patients (33 with aortic stenosis and 27 with aortic insufficiency) for hemodynamic and angiographic data that best matched the data of group B before surgery for the two types of valve disease (compare Tables 2 and 3).

Hemodynamics and Left Ventricular Angiography

Informed consent was obtained from all patients under a protocol approved by the human studies committee of the University Hospital. Right- and left-heart catheterization, high-fidelity left ventricular pressure measurements, biplane left ventricular angiography, and selective coronary arteriography were performed according to our standard techniques26 in group A and group B before surgery. After surgery, eight patients in group B were examined using all the above procedures, whereas seven had only right heart catheterization (ambulatory basis) with transeptal left ventricular mi-
### Table 2. Hemodynamic and Angiographic Data and Myosin Light Chain–1 Content in the Left Ventricle in Aortic Stenosis

<table>
<thead>
<tr>
<th></th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>EDVI (ml/m²)</th>
<th>EF (%)</th>
<th>ΔP (mm Hg)</th>
<th>AVA (cm²)</th>
<th>RF (%)</th>
<th>LMMI (g/m²)</th>
<th>h₀₀ (cm)</th>
<th>S₀ (kDyne/cm²)</th>
<th>Total MLC₁ (mol/mol TM)</th>
<th>ALC₁ (% of total MLC₁)</th>
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<tr>
<td><strong>Aortic stenosis</strong></td>
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<tr>
<td><strong>Group A (n=17)</strong></td>
<td>214±35</td>
<td>17.1±7.2</td>
<td>121±29</td>
<td>57±10</td>
<td>71±17</td>
<td>0.70±0.21</td>
<td>18±13</td>
<td>173±47</td>
<td>1.23±0.15</td>
<td>501±40</td>
<td>3.36±0.26</td>
<td>11.2±9.2</td>
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<td><strong>Group B</strong></td>
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<tr>
<td>Before valve replacement (n=9)</td>
<td>193±20</td>
<td>15.9±8.1</td>
<td>127±38</td>
<td>54±15</td>
<td>67±16</td>
<td>0.69±0.20</td>
<td>13±12</td>
<td>191±60</td>
<td>1.23±0.14</td>
<td>477±70</td>
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<tr>
<td>After valve replacement (n=9)</td>
<td>141±20</td>
<td>12.0±3.1</td>
<td>100±23</td>
<td>59±15</td>
<td>9±5*</td>
<td>2.10±0.59†</td>
<td>...</td>
<td>92±16</td>
<td>0.86±0.10</td>
<td>444±125</td>
<td>3.16±0.22</td>
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<td><strong>Control</strong></td>
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<tr>
<td><strong>Group C (n=10)</strong></td>
<td>116±11</td>
<td>8.2±3.4</td>
<td>85±21</td>
<td>69±6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>83±13</td>
<td>0.76±0.12</td>
<td>308±115</td>
<td>2.80±0.32†</td>
<td>0.3±0.3†</td>
</tr>
</tbody>
</table>

**ANOVA test**

|                      |                |                |              |        |            |           |        |             |        |                |                          |                        |
| **Group A vs. group B after valve replacement** | p<0.001       | p=NS           | p=NS         | p=NS   | ...        | ...      | ...    | ...         | p<0.001 | p<0.001        | p=NS                     | p=NS       |
| **Group A vs. group C** | p<0.001       | p<0.01         | p<0.01       | p<0.05 | ...        | ...      | ...    | ...         | p<0.001 | p<0.001        | p<0.001                  | p<0.001    |
| **Group B after valve replacement vs. group C** | p=NS          | p=NS           | p=NS         | p=NS   | ...        | ...      | ...    | p=NS        | p=NS   | p<0.01         | p=NS                     | p=NS       |
| **Student's t test** |                |                |              |        |            |           |        |             |        |                |                          |                        |
| **Group A vs. group B after valve replacement** | ...           | ...            | ...          | ...    | p<0.001    | p<0.001 | ...    | ...         | ...    | ...            | ...                      | ...        |

Values are mean±SD. LVSP, left ventricular (LV) systolic pressure; LVEDP, LV end-diastolic pressure; EDVI, LV end-diastolic volume index; EF, LV ejection fraction; ΔP, mean pressure gradient; AVA, aortic valve area; RF, aortic regurgitation fraction; LMMI, LV muscle mass index; h₀₀, LV end-diastolic wall thickness; S₀, LV peak systolic circumferential wall stress; MLC₁, myosin light chain–1; TM, tropomyosin; ALC₁, atrial-like myosin light chain–1; ANOVA, analysis of variance; NS, not significant. Group A includes the preoperative group of patients; group B represents the postoperative patients with the corresponding data before and after aortic valve replacement.

* n=6; † n=5; ‡ n=18.
### Table 3. Hemodynamic and Angiographic Data and Myosin Light Chain–1 Content in the Left Ventricle in Aortic Insufficiency

<table>
<thead>
<tr>
<th></th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>EDVI (ml/m²)</th>
<th>EF (%)</th>
<th>ΔP (mm Hg)</th>
<th>RF (%)</th>
<th>LMMI (g/m²)</th>
<th>hₑₑ (cm)</th>
<th>Sₚ  (kdyn/cm²)</th>
<th>Total MLC₁ (mol/mol TM)</th>
<th>ALC₁ (% of total MLC₁)</th>
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<tr>
<td>Group A (n=10)</td>
<td>138±17</td>
<td>13.6±6.9</td>
<td>204±38</td>
<td>62±7</td>
<td>5±12</td>
<td>58±8</td>
<td>189±37</td>
<td>1.02±0.16</td>
<td>483±108</td>
<td>2.99±0.17</td>
<td>4.5±1.4</td>
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<td>Group B</td>
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<tr>
<td>Before valve replacement (n=6)</td>
<td>140±25</td>
<td>16.1±10.3</td>
<td>232±56</td>
<td>60±9</td>
<td>7±15</td>
<td>59±10</td>
<td>201±35</td>
<td>1.02±0.08</td>
<td>524±121</td>
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</tr>
<tr>
<td>After valve replacement (n=6)</td>
<td>127±7</td>
<td>9.3±3.1</td>
<td>143±74</td>
<td>55±12</td>
<td></td>
<td></td>
<td>126±52</td>
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<td>3.11±0.14</td>
<td>3.4±3.1</td>
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<tr>
<td><strong>Control</strong></td>
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<tr>
<td>Group C (n=10)</td>
<td>116±11</td>
<td>8.2±3.4</td>
<td>85±21</td>
<td>69±6</td>
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<td>308±115</td>
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<td>0.3±0.3*</td>
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**ANOVA test**

Group A vs. group B after valve replacement

<table>
<thead>
<tr>
<th></th>
<th>p=NS</th>
<th>p=NS</th>
<th>p&lt;0.05</th>
<th>p=NS</th>
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<th>p=NS</th>
<th>p=NS</th>
<th>p=NS</th>
<th>p=NS</th>
<th>p&lt;0.001</th>
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Group A vs. group C

<table>
<thead>
<tr>
<th></th>
<th>p=NS</th>
<th>p=0.001</th>
<th>p=NS</th>
<th>...</th>
<th>p&lt;0.001</th>
<th>p&lt;0.01</th>
<th>p=NS</th>
<th>p&lt;0.01</th>
<th>p=NS</th>
<th>p&lt;0.001</th>
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Group B after valve replacement vs. group C

<table>
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<th></th>
<th>p=NS</th>
<th>p=NS</th>
<th>p&lt;0.05</th>
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<th>p=NS</th>
<th>p=NS</th>
<th>p=NS</th>
<th>p&lt;0.001</th>
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</table>

Values are mean±SD. LVSP, left ventricular (LV) systolic pressure; LVEDP, LV end-diastolic pressure; EDVI, LV end-diastolic volume index; EF, LV ejection fraction; ΔP, mean pressure gradient; RF, aortic regurgitation fraction; LMMI, LV muscle mass index; hₑₑ, LV end-diastolic wall thickness; Sₚ, LV peak systolic circumferential wall stress; MLC₁, myosin light chain–1; TM, troponymosin; ALC₁, atrial-like myosin light chain–1; ANOVA, analysis of variance; NS, not significant. Group A includes the preoperative group of patients; group B represents the postoperative patients with the corresponding data before and after aortic valve replacement. *ₙ=18.
crominator-tipped pressure transducers and contrast ventriculography. Drawings of left ventricular end-diastolic and end-systolic silhouettes obtained from biplane left ventricular cineangiograms served to estimate intracardiac volumes according to the area–length method and to determine biplane ejection fraction. Left ventricular hypertrophy was assessed by estimation of left ventricular muscle mass index. Left ventricular peak systolic circumferential wall stress was calculated according to Gaasch et al.

**Biopsy and Autopsy Material**

Left ventricular endomyocardial biopsies (three to five samples) were taken in groups A and B from similar regions of the anterolateral wall as described elsewhere. Biopsy material was available from 18 patients; this material was obtained by catheterization (from three patients of hemodynamic control group C), at coronary surgery (from patients with normal cardiac function), or at necropsy (from accident victims with normal cardiac anatomy). The necropsy samples were removed within 8 hours from victims of traffic accidents who showed no cardiac involvement. Additional samples were available from two patients, one with an end-stage dilated cardiomyopathy and heart transplantation and one with a history of long-standing hypertension with pronounced secondary hypertrophy.

**Electrophoretic Resolution of Myosin Light Chains**

Tissue samples were frozen in melting isopentane (−159°C) and stored at −70°C. After homogenization of 1–8 mg tissue in a micro tissue grinder, total homogenate was resolved by two-dimensional gel electrophoresis: isoelectrofocusing followed by electrophoresis in sodium dodecyl sulfate. Gels were then fixed, stained with Coomassie brilliant blue, destained, and densitometrically evaluated as described elsewhere. MLCs were quantified relative to tropomyosin by using their chemical molecular mass. VLCs appeared in a double spot because of partial phosphorylation (Figure 1). No allowance was made for possible differences in dye uptake by the different proteins. Crude myosin was prepared from 50–70 mg myocardium by high salt extraction. Such preparations still contain some residual tropomyosin and actin serving as internal standards for orientation in two-dimensional electrophoresis (Figure 1D). Protein concentrations were estimated by microassay standardized by the biuret method.

**Statistical Analysis**

Reported values are mean±SD. Data from the three study groups (preoperative group A, postoperative group B, and control group C) were compared by single-classification analysis of variance; if significant (p<0.05), Scheffe’s procedure was applied. Unpaired Student’s t test (with p<0.05 denoting significance) was used for comparing preoperative data of group A and group B before surgery, for comparing aortic valve area and pressure gradient between preoperative and postoperative groups with aortic stenosis, and for comparing group A with aortic stenosis versus group A with aortic insufficiency. Regression analyses were performed to examine correlations between the ALC content and the various parameters. Linear curve transformations were performed by the least-squares methodology. Partial correlation analysis was performed according to Reference 37.

**Results**

**Hemodynamic and Angiographic Data**

Mean values of the hemodynamic, angiographic, and biochemical data including statistics are listed for aortic stenosis in Table 2 and for aortic insufficiency in Table 3. No differences are evident in the hemodynamic and angiographic data between group A and group B before valve replacement either in aortic stenosis or in aortic insufficiency (all p>0.05; not shown). In patients with aortic stenosis (Table 2), all hemodynamic and angiographic data differed from those of control group C. Left ventricular systolic pressure (LVSP), mean pressure gradient, left ventricular muscle mass index (LMMI), and left ventricular end-diastolic wall thickness (hOD) were significantly lower after rather than before valve replacement. The aortic valve area increased threefold. The left ventricular peak systolic circumferential wall stress (S) was only slightly reduced after surgery and was still significantly higher than in control group C.

Patients with aortic insufficiency (Table 3) showed an increase in LVSP, end-diastolic volume index, LMMI, hOD, and S, when compared with control group C. Left ventricular end-diastolic pressure and ejection fraction were not changed. Only end-diastolic volume index and LMMI were lower in the postoperative than in the preoperative cohort. The postoperative values again approached those of the control group with the exception of ejection fraction, which attained a lower value.

**Isosforms of Myosin Light Chain–1**

The main finding in total myocardial tissue homogenates was the variable occurrence of an additional polypeptide migrating with a higher apparent molecular mass and a slightly more acidic isoelectric point than the proper VLC. Its electrophoretic position seems to coincide with that of MLCs from atrial tissue (Figure 1). Increasing admixtures of atrial to ventricular tissue homogenate (Figure 2) demonstrates its identical electrophoretic mobility with ALC. The admixture of atrial tissue with its ALC (Figures 2C–2F) led to a gradual increase of the ALC-like protein spot relative to the VLC, yielding a straight line with a correlation coefficient of 0.99. This ALC-like protein that appears in hypertrophied ventricles will thus be referred to as ventricular ALC. A significant amount of this ventricular ALC is associated with myosin (Figure 1D). Its proportion bound to myosin is in fact similar to that found in the total tissue homogenate (compare panels C and D in Figure 1). Densitometric evaluation indicated a contribution of 28.5% for the ventricular ALC in the homogenate as compared with 23.3% in the crude myosin preparation that still contained some actin and tropomyosin.

**Quantification of Ventricular ALC**

The content of the ventricular ALC of total tissue homogenates was expressed as percentage of total MLC. In preoperative group A, the mean ALC content was 11.2% in aortic stenosis (Table 2) and 4.5% in...
aortic insufficiency (Table 3). Both values differed significantly from the control value of 0.3% ALC1. After valve replacement, the corresponding values were lower (4.2% in aortic stenosis and 3.4% in aortic insufficiency) but still higher than the control values. The scatter of individual values is high in the different disease groups; e.g., it ranges from 1.0% to 32.4% in preoperative aortic stenosis. However, ALC1 content never exceeded 1.2% in controls. Separate analyses could be done in three cases on subendocardial, midwall, and subepicardial myocardium. The different myocardial layers gave similar results. The same correspondence was found in seven cases where two or three muscle specimens taken from different sites (but all from the anterolateral region of the left ventricle) were analyzed. We never found evidence for the occurrence of ALC2 in left ventricular tissue samples.

The total ventricular MLC1 content (i.e., VLC1 plus ALC1), expressed as moles of light chain per mole of tropomyosin, is highest in preoperative aortic stenosis, intermediate after valve replacement, and lowest in the control group (Table 2). Plotting the total MLC1 content of all 42 patients, irrespective of the type of valve disease and irrespective of the stage before or after surgery, versus the relative ALC1 content (not shown) yields a regression line with a correlation coefficient r of 0.45 (p<0.01). This indicates direct proportionality between the two parameters. In Table 4, the 42 cases are grouped according to increasing ALC1 content and listed along with ALC1 content of 18 controls and the mean total MLC1 content for the same groups. Plotting the averages of absolute ALC1 content versus the excess of total MLC1 (amount above that of the controls) yields a regression line with a correlation coefficient r of 0.96 and a slope of 0.87 (Table 4). The slope of −1 suggests that ALC1 is expressed in the ventricle in addition to the endogenous VLC1 and accounts for the increase in total MLC1.

**Correlation Between Ventricular ALC1 Isoforms and Hemodynamic and Angiographic Parameters**

Regression analysis of the ALC1 content with all other parameters was performed for the 42 patients taken individually and irrespective of the type of valve disease before and after surgical intervention. No significant correlation was found. However, when the patient group averages of the ALC1 content were compared with the

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**Figure 1.** Two-dimensional electrophoresis of total tissue homogenates from left ventricular myocardium (panels A and C), from ventricle and atrium together (panel B), and from isolated crude ventricular myosin (panel D). A, actin; T, α-tropomyosin; A1, atrial and atrial-like myosin light chain−1; A2, atrial myosin light chain−2; V1, ventricular light chain−1; V2, ventricular light chain−2. Gels are presented with the basic pH range in electrophoresis to the left and decreasing molecular weight in sodium dodecyl sulfate electrophoresis from top to bottom. Details are given for the region of actin and the myosin light chains. Panel A: Ventricle of 29-year-old male without cardiovascular impairment displaying no A1. Panel B: Coelelectrophoresis of ventricle and atrium of same subject as in panel A. Panel C: Ventricle of 66-year-old male patient with aortic stenosis displaying A1 in the ventricle. Panel D: Crude myosin extracted from ventricle of patient with aortic stenosis with A and T as internal markers. Stain, Coomassie brilliant blue.

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**Figure 2.** Two-dimensional electrophoresis of total tissue homogenates from ventricle and from atrium, separately and in coelectrophoresis, of a 20-year-old male with dilated cardiomyopathy. T, α-tropomyosin; V, ventricular light chain−1; A (and arrowhead), atrial and atrial-like myosin light chain−1. Presentation of gels is as described in Figure 1. Details are given for the region of tropomyosin and myosin light chain−1. Panel A: Ventricle displaying some A protein in addition to V. Panel B: Atrium. Panels C–F: Constant amount of ventricular tissue as in panel A throughout, with increasing admixtures of 25%, 50%, 75%, and 100% of atrial tissue based on protein estimates. Stain, Coomassie brilliant blue.
averages of the functional parameters including control group C, linear correlations were found with the following three parameters: LVSP, left ventricular end-diastolic pressure, and $h_{od}$. All three have correlation coefficients $r$ between 0.94 and 0.98 and significance levels between $p<0.02$ and $p<0.01$ (Figures 3 and 4). LVSP and $h_{od}$ are both ascertained in terms of the stress parameter $S_p$. The best correlation found by the least-squares procedure criterion with $S_p$ was exponential ($r=0.98$ and $p<0.01$). A partial correlation analysis was then performed on the interdependence of ALC$_1$ content with both LVSP and $h_{od}$. The partial correlation coefficients stratified for ALC$_1$, LVSP, and $h_{od}$ were 0.55, 0.83, and 0.92, respectively. The

### Table 4. Preoperative and Postoperative Groups With Aortic Stenosis and Aortic Insufficiency Sampled According to Percentage of Atrial-like Myosin Light Chain–1 Content in Left Ventricle in Comparison With Control Group

<table>
<thead>
<tr>
<th>Patients</th>
<th>Range (%)</th>
<th>ALC$_1$ Average (%)</th>
<th>Absolute content (mol/mol TM)</th>
<th>Total content (mol/mol TM)</th>
<th>Excess of total ALC$_1$ over controls (mol/mol TM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n=8$</td>
<td>9.5–32.4</td>
<td>18.2±8.90</td>
<td>0.651</td>
<td>3.57±0.21</td>
<td>0.77</td>
</tr>
<tr>
<td>$n=9$</td>
<td>6.1–8.3</td>
<td>7.36±0.85</td>
<td>0.236</td>
<td>3.20±0.14</td>
<td>0.40</td>
</tr>
<tr>
<td>$n=12$</td>
<td>3.3–5.7</td>
<td>4.65±0.91</td>
<td>0.143</td>
<td>3.08±0.21</td>
<td>0.28</td>
</tr>
<tr>
<td>$n=13$</td>
<td>1.0–2.9</td>
<td>1.85±0.75</td>
<td>0.056</td>
<td>3.05±0.13</td>
<td>0.25</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n=18$</td>
<td>0–1.2</td>
<td>0.33±0.34</td>
<td>0.009</td>
<td>2.80±0.56</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Values are mean±SD, where applicable. ALC$_1$, atrial-like myosin light chain–1; TM, tropomyosin; MLC$_1$, myosin light chain–1 (total MLC$_1$=ALC$_1$+ventricular light chain–1). The 42 surgical patients are grouped according to increasing ALC$_1$ content. A plot of the averages of absolute ALC$_1$ content versus excess of total MLC$_1$ yields a regression line with correlation coefficient $r=0.97$, slope=0.87, and significance level of $p<0.01$.

### Figure 3. Relation between atrial-like myosin light chain–1 (ALC$_1$) content in the left ventricle and left ventricular systolic pressure (LVSP, top panel) and left ventricular end-diastolic pressure (LVEDP, bottom panel). LC, light chain. The mean values of the patient and control groups are plotted. Regression line for LVSP has a correlation coefficient $r=0.98$ and $p<0.01$; regression line for LVEDP has $r=0.94$ and $p<0.02$. Open circles indicate the group with aortic stenosis; closed circles, the group with aortic stenosis after valve replacement; open squares, the group with aortic insufficiency; closed squares, the group with aortic insufficiency after valve replacement; closed triangles, the control group.

### Figure 4. Relation between atrial-like myosin light chain–1 (ALC$_1$) content in the left ventricle and left ventricular end-diastolic wall thickness ($h_{od}$, top panel) and peak circumferential wall stress ($S_p$, bottom panel). LC, light chain. The mean values of the patient and control groups are plotted. Regression line for $h_{od}$ has a correlation coefficient $r=0.96$ and $p<0.02$; regression line for $S_p$ has $r=0.98$ and $p<0.01$. In the bottom panel the ALC$_1$ content is plotted on a logarithmic scale. Open circles indicate the group with aortic stenosis; closed circles, the group with aortic stenosis after valve replacement; open squares, the group with aortic insufficiency; closed squares, the group with aortic insufficiency after valve replacement; closed triangles, the control group.
results indicate that LVSP and \( h_{ed} \) do not depend on each other but are separately correlated with the ALC\(_1\) content. This is further borne out by plotting the group averages of \( h_{ed} \) versus LVSP (Figure 5, top panel). This yields two straight lines both with a correlation coefficient \( r=1.00 \) with higher slope in aortic insufficiency.

It is worth mentioning that LMMI does not correlate with the ALC\(_1\) content at all (Figure 5, bottom panel). The ALC\(_1\) content is significantly higher in aortic stenosis than in insufficiency, whereas LMMI is similarly high in both types of overload. In addition, in aortic insufficiency, LMMI is significantly lower after valve replacement than before, yet the ALC\(_1\) content after surgery was only slightly lower than the value before surgery. In addition, the ALC\(_1\) content correlated neither with end-diastolic volume index nor with ejection fraction.

**Discussion**

An atrial-like MLC\(_1\) has been reported to occur in various forms of human left ventricular hypertrophy,\(^{12,23-25}\) It is rarely observed in adult ventricles under hemodynamically compensated conditions.\(^{12,13,19,23-25}\) However, it is present during gestation and disappears rapidly post partum except in overloaded right ventricles, where it may persist for several years.\(^{19}\) In humans as opposed to most other mammals, ALC\(_1\) migrates with a higher apparent molecular mass in sodium dodecyl sulfate electrophoresis than does VLC\(_1\),\(^{38,39}\) From its electrophoretic mobility, ventricular ALC\(_1\) does not represent a degradation product of any of the atrial or ventricular MLCs. In two-dimensional resolution, it comigrates perfectly with atrial MLC\(_1\) without affecting the shape of the protein spot (Figure 2). Identical two-dimensional electrophoretic mobility indicates a close relation between the two proteins. Proof of identity awaits further study. The selective reappearance of ventricular ALC\(_1\) in amounts up to over 30% of total MLC\(_1\) in adult hypertrophied ventricles then indicates that this tissue has preserved its potential to reexpress its fetal MLC\(_1\) isofrom. It is expressed in addition to the intrinsic VLC\(_1\) in the ventricle, and it seems to be bound to myosin in proportion to its occurrence in the tissue.

The aim of the present study was to test the occurrence of left ventricular ALC\(_1\) under two different but hemodynamically well-defined pathological conditions, aortic stenosis and aortic insufficiency. The former is characterized by pressure overload; the latter, by predominant volume overload. For both types of disease, a patient cohort was studied after successful valve replacement with corresponding hemodynamic improvement (Tables 2 and 3). The individual scatter of the left ventricular ALC\(_1\) content was large in the different patient groups before and after valve replacement. Nevertheless, the ALC\(_1\) content did not exceed 1.2% of total ventricular MLC\(_1\) in hemodynamically compensated controls. Regression analyses between patient group averages revealed significant linear correlations of ALC\(_1\) with the pressure parameters, LVSP and left ventricular end-diastolic pressure, and, in an exponential manner, with \( S_p \) (Figures 3 and 4). In the latter case, the correlation function fit the equation \( y=ab^x \), indicating that circumferential wall stress \( S_p \) represents a mechanical parameter common to both disease groups that relates to the occurrence of the ventricular ALC\(_1\). Furthermore, the improved hemodynamic conditions after valve replacement coincided with a lower ALC\(_1\) content, approaching that of the control group.

The linear relation with LVSP and left ventricular end-diastolic pressure indicated that the pressure component in the stress formula\(^{31}\) might be the main determinant in both valvular disease groups for induction of the expression of ALC\(_1\) (Figure 3). The ALC\(_1\) content was also linearly related to the wall thickness \( h_{ed} \) (Figure 4, top panel). We show here that, at a given LVSP value, \( h_{ed} \) remained higher in aortic insufficiency than in aortic stenosis (Figure 5, top panel). Therefore, the wall thickness had to bear a lower pressure component in aortic insufficiency than in stenosis. This coincided with a significantly lower ALC\(_1\) content in preoperative aortic insufficiency than in stenosis. This finding still favors the hypothesis that the pressure component is the main determinant for the expression of ALC\(_1\) and, in particular, pressure in combination with a low relative wall thickness \( h_{ed} \). No correlation was found with end-diastolic volume index, ejection fraction, or LMMI. This latter is of interest because it indicates that the ALC\(_1\) content does not simply reflect

![Figure 5](http://circres.ahajournals.org/DownloadedFrom)
the increase in hypertrophic muscle mass. After valve replacement, the hemodynamic conditions have not fully reverted to the control level. This is accompanied by a still elevated ALC1 content. In addition, structural abnormalities in the left ventricle, such as interstitial fibrosis, muscle fiber diameter, and ventricular fibrous content, have been reported to persist over several years after valve replacement in patients with aortic stenosis and insufficiency.  

In conclusion, it may be hypothesized that the selective reexpression of ALC1 in the hypertrophied left ventricle is induced by mechanical stress on the muscle. It represents a chronic feature that is related to the severity of hemodynamic impairment. Whether ALC1 affects the contractile properties in the hypertrophied ventricle is not known at present.

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