Dilated cardiomyopathy (DCM) is an important cause of morbidity and mortality among patients with heart failure. Left ventricular dilation is viewed as a compensatory response to maintain stroke volume, and left ventricular dilation is directly related to the increase of wall stress. However, only a few studies have examined whether wall stress can be a prognostic variable in patients with dilated cardiomyopathy. This study was designed to elucidate whether left ventricular systolic wall stress was related to the prognosis in patients with dilated cardiomyopathy. Twenty-five normal control subjects and 68 patients with dilated cardiomyopathy participated in this study. Hemodynamic parameters and left ventricular systolic wall stress were determined using echocardiography. In addition, the extent score determined by thallium-201 myocardial scintigraphy was measured as an index of cumulative loss of myocardium. During the 53-month follow-up period, 13 patients died of cardiac events. In a stepwise multivariable analysis, end-systolic wall stress and fractional shortening were significant predictors of survival. The extent score was markedly greater in the patients who died than in alive patients. There was a significant correlation between end-systolic wall stress and extent score (r=0.501, p=0.0001). Left ventricular end-systolic wall stress is an important predictor of mortality in patients with dilated cardiomyopathy.

**Key Words:** Dilated cardiomyopathy; End-systolic wall stress; Fractional shortening; Prognosis; Thallium-201 myocardial scintigraphy

**Methods**

**Study Population**

The study population consisted of 25 normal control subjects and 68 patients with DCM. Twenty-five subjects with chest pain syndrome (aged 28–71 years), who showed normal coronary arteries, served as the normal control subjects. In addition, none of the subjects in this group had significant heart disease. Sixty-eight patients (aged 27–77 years) were diagnosed as having DCM according to the report of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. Patients with moderate to severe valvular regurgitation were excluded. Ejection fraction assessed by left ventriculography in this group ranged between 7% and 47%. New York Heart Association functional class on diagnosis was 6 in class I, 18 in class II, 30 in class III and 14 patients in class IV. Sixteen patients were in atrial fibrillation. All subjects participated after giving informed consent.

**Echocardiographic Study**

M-mode and 2-dimensional echocardiography were
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ECHOCARDIOGRAPHIC STUDY

Arterial systolic blood pressure (SBP) was determined in duplicate using a cuff sphygmomanometer.

THALLIUM-201 MYOCARDIAL SCINTIGRAPHY AND DETERMINATION OF THE EXTENT SCORE

Thallium-201 myocardial scintigraphy at rest was performed in 53 of the 68 patients with DCM, using the method described previously. Briefly, subjects were examined in the morning after an overnight fast. Imaging at rest began 15 min after administration of 111MBq of 201Tl, and the imaging was repeated 5 h later. A scintillation camera was rotated for 90° for each 36 projections over 360° circular orbits. Energy discrimination was provided by a 15% window centered on the 72 keV photopeak of 201Tl.

The computerized 201Tl tomographic method proposed by Garcia et al was used to quantitate the size of the myocardial perfusion defects. To formulate a polar map, the normalized maximal count value at each point was compared with the normal value at the corresponding point. The extent polar map depicted the extent of points with subnormal counts below 2 standard deviations of the mean.

Univariate and multivariate Cox’s proportional-Hazards regression models were constructed to assess univariate and independent associations with survival. All calculations were performed on a personal computer using the statistical package StatView (Abacus Concepts, Inc, Berkeley, CA, 1994). A P-value <0.05 was considered significant.

RESULTS

CLINICAL PROFILES OF THE SUBJECTS

The profiles of the subjects are shown in Table 1. There were no significant differences in age, gender and SBP between control subjects and patients with DCM.

ECHOCARDIOGRAPHIC AND HEMODYNAMIC PARAMETERS

Table 2 shows the echocardiographic and hemodynamic parameters in the 2 groups. Left ventricular dimensions

Table 1 Patient Profiles

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Age on diagnosis (years)</th>
<th>M/F</th>
<th>HR (beats/min)</th>
<th>SBP (mmHg)</th>
<th>Follow-up (months)</th>
<th>CTR (%)</th>
<th>NYHA functional class I–II/III–IV</th>
<th>Atrial fibrillation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>25</td>
<td>52.4±12.2</td>
<td>19/6</td>
<td>65±11</td>
<td>118±10</td>
<td>48±5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DCM (total)</td>
<td>68</td>
<td>54.0±11.5</td>
<td>58/10</td>
<td>74±15*</td>
<td>115±16</td>
<td>53±50</td>
<td>57±9*</td>
<td>24/44</td>
<td>23.5</td>
</tr>
<tr>
<td>Alive</td>
<td>55</td>
<td>53.6±10.9</td>
<td>46/9</td>
<td>73±14</td>
<td>117±16</td>
<td>57±53</td>
<td>56±7</td>
<td>22/33</td>
<td>23.6</td>
</tr>
<tr>
<td>Dead</td>
<td>13</td>
<td>56.1±14.0</td>
<td>12/1</td>
<td>78±15</td>
<td>106±15*</td>
<td>37±27</td>
<td>59±5</td>
<td>2/11</td>
<td>23.1</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01 compared with normal, ‘P<0.05 compared with alive; HR, heart rate; SBP, systolic blood pressure; CTR, cardiothoracic ratio; NYHA, New York Heart Association; DCM, dilated cardiomyopathy.

Table 2 Echocardiographic and Hemodynamic Data in Control Subjects (Normal) and Patients With DCM

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LAD (mm)</th>
<th>LVDd (mm)</th>
<th>LVDs (mm)</th>
<th>FS (%)</th>
<th>PWTd (mm)</th>
<th>PWTs (mm)</th>
<th>PSWS (×10³ dynes/cm²)</th>
<th>ESWS (×10³ dynes/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>32.7±4.2</td>
<td>47.6±3.3</td>
<td>29.8±2.6</td>
<td>37.4±2.9</td>
<td>8.0±0.7</td>
<td>14.5±1.1</td>
<td>146.7±28.1</td>
<td>52.0±8.1</td>
</tr>
<tr>
<td>DCM (total)</td>
<td>43.2±6.5</td>
<td>67.8±7.5</td>
<td>56.5±8.8</td>
<td>17.0±6.1</td>
<td>8.5±1.5</td>
<td>12.3±2.3</td>
<td>211.1±46.1</td>
<td>145.6±40.9</td>
</tr>
<tr>
<td>Alive</td>
<td>42.5±6.4</td>
<td>67.6±7.6</td>
<td>55.4±8.2</td>
<td>18.4±5.7</td>
<td>8.7±1.4</td>
<td>12.9±2.7</td>
<td>208.8±48.6</td>
<td>135.4±37.7</td>
</tr>
<tr>
<td>Dead</td>
<td>46.6±6.2</td>
<td>68.6±7.0</td>
<td>61.1±7.4</td>
<td>11.0±4.0</td>
<td>7.6±1.3</td>
<td>10.9±2.3</td>
<td>220.9±33.9</td>
<td>178.5±36.5</td>
</tr>
</tbody>
</table>

Values are the mean±standard deviation; *P<0.01 compared with normal, **P<0.05, ***P<0.001 compared with alive; DCM, dilated cardiomyopathy; LAD, left atrial dimension; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; FS, fractional shortening; PWTd, posterior wall thickness at end-diastole; PWTs, posterior wall thickness at end-systole; PSWS, peak-systolic wall stress; ESWS, end-systolic wall stress.
were significantly larger in patients with DCM than in control subjects, but PWTs was thinner in patients with DCM than in control subjects.

**Relationship Between FS and PSWS and ESWS**

There was no significant correlation between PSWS and FS. There was a negative correlation between ESWS and FS in normal control subjects (y=47.966–0.203x, r=–0.569, p=0.0030), and in patients with DCM (y=30.076–0.091x, r=–0.608, p<0.0001). Comparison of the 2 regression slopes in normal control subjects and DCM patients was significantly different (p<0.05).

**Comparisons of Clinical Profiles and Hemodynamic Parameters Between Alive Patients and Those Who Died**

The average of the follow-up period in patients with DCM was 53±50 months, ranging between 3 and 186 months. During the follow-up period, 13 patients died of cardiac events (4 of sudden death and 9 of progressive congestive heart failure). In alive patients, the use of diuretics, digitalis, angiotensin converting enzyme inhibitors, beta-blocker and mexiletine was 55%, 85%, 91%, 31% and 11%, respectively. However, the use of these drugs in the patients who died was 85%, 100%, 85%, 15% and 31%, respectively. Except for digitalis, there was no significant difference in the frequency of the use of other drugs between the 2 groups.

In the clinical profiles on diagnosis between the alive group and died group, only SBP was significantly lower in the died group than in the alive group (Table 1). In the hemodynamic parameters estimated on diagnosis in the alive and died groups, LVDd was greater in the died group. FS was smaller in the died group. Left ventricular PWTd and PWTs were significantly thinner in the died group than in the alive group (Table 2).

**Left Ventricular Wall Stress and Extent Score**

As shown in Table 2, there was no significant difference in PSWS between the 2 groups. However, ESWS was significantly higher in the died group.

As shown in Fig 1, the extent score was significantly greater in the died group than in the alive group (alive 25±15%, died 48±18%, p<0.0001). Fig 2 shows the relation between the extent score and ESWS in patients with DCM.

**Table 3 Cox Proportional-Hazards Analysis: Predictors of Survival**

<table>
<thead>
<tr>
<th>Predictive Variable</th>
<th>Univariate model</th>
<th>Multivariate model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA classification</td>
<td>3.331 0.0680</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.518 0.4716</td>
<td></td>
</tr>
<tr>
<td>CTR</td>
<td>0.385 0.5350</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.648 0.4208</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>2.812 0.0936</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>1.757 0.1851</td>
<td></td>
</tr>
<tr>
<td>LVDd</td>
<td>0.029 0.8642</td>
<td></td>
</tr>
<tr>
<td>LVDs</td>
<td>2.951 0.0858</td>
<td></td>
</tr>
<tr>
<td>PWTd</td>
<td>5.981 0.0145</td>
<td></td>
</tr>
<tr>
<td>PWTs</td>
<td>10.409 0.0012</td>
<td></td>
</tr>
<tr>
<td>FS</td>
<td>11.651 0.0006</td>
<td>4.152 0.0416</td>
</tr>
<tr>
<td>PSWS</td>
<td>2.226 0.1356</td>
<td></td>
</tr>
<tr>
<td>ESWS</td>
<td>11.099 0.0009</td>
<td>6.523 0.0106</td>
</tr>
<tr>
<td>Extent score*</td>
<td>6.163 0.0130</td>
<td></td>
</tr>
</tbody>
</table>

*n=53. See Table 1 and 2 for Abbreviations.

There was a significant positive correlation between the 2 variables (r=0.501, p=0.0001). There was also a significant relation between the extent score and FS (r=–0.452, p=0.0007).

**Predictors of Survival in DCM**

Univariate and multivariate analyses were performed to determine predictors of survival, and their results are shown in Table 3. Multivariate analysis were performed on 53 of the 68 patients for whom complete clinical, hemodynamic and extent score data were available. Left ventricular PWTd and PWTs, FS, ESWS and the extent score were significantly related to survival in patients with DCM in the univariate model. On the other hand, in a stepwise multivariable analysis, ESWS and FS were significant predictors of survival.

**Kaplan-Meier Lifetime Analysis**

Patients with DCM were stratified into 2 groups on the basis of the median value of FS (16%), and cumulative survival curves were constructed according to the Kaplan-Meier survival method. Survival rates, as evaluated by Kaplan-Meier survival analysis, were significantly lower in patients with a FS of <16% (p=0.0083), as shown in Fig 3A. In the subgroup with a FS <16% (the basis of the
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Median value of FS, patients with DCM were stratified into 2 groups on the basis of the median value of ESWS (150×10^3 dynes/cm^2). Fractional shortening in 2 subgroups with FS <16% and ESWS <150×10^3 dynes/cm^2, and FS <16% and ESWS ≥150×10^3 dynes/cm^2 were 11.4±3.9% and 13.3±2.3%, respectively. There were no significant differences in FS. Survival rates were significantly lower in patients with an ESWS of ≥150×10^3 dynes/cm^2 (p=0.0383), as shown in Fig 3B.

Discussion

The present study indicates that ESWS and FS were powerful predictors of survival in patients with DCM. Of the patients whose FS was less than 16%, the patients with a higher ESWS had an adverse prognosis. In addition, there was a positive correlation between ESWS and the extent score. Thus, the cumulative loss of myocardium may be closely related to the high value of ESWS and to the prognosis in patients with DCM.

Estimation of Left Ventricular Wall Stress

Left ventricular wall stress is directly related to chamber dimension, internal pressure and wall thickness. PSWS and ESWS are representative wall stress clinically applied. PSWS is the maximal left ventricular systolic wall force and ESWS is a measure of the maximal load that can be sustained by the myocardial fibers at end-systole. PSWS is used as a marker of oxygen consumption and ESWS represents the force (afterload) that the shortened myocardial fibers cannot overcome; the relation between ESWS and FS sensitively reflects the contractile state.

Echocardiography is currently the most widely accepted noninvasive tool used for the assessment of left ventricular wall thickness and chamber size. Using M-mode echocardiographic technique, Wilson et al. noninvasively measured PSWS and ESWS. Recently, Dujardin et al. reported that for assessing left ventricular remodeling, the left ventricular diameter measured by M-mode echocardiography allows an acceptable estimation of wall stress. Thus, in the present study we measured PSWS and ESWS using the method of Wilson et al. [14]

Predictive Variables of the Prognosis in DCM

Left ventricular dilatation can be viewed as a response to left ventricular dysfunction associated with the loss of contractile myocardium. Although augmenting the left ventricular cavity size can restore stroke volume, this dilatation would also augment the diastolic and systolic wall stress through the operation of Laplace’s law and thereby stimulate further ventricular enlargement. When the cumulative loss of myocardium is large, a vicious cycle can be created; that is, ‘dilatation begets more dilatation.’ This augmentation in wall stress of the dilated ventricle can serve as a stimulus for additional myocyte hypertrophy, which can offset the increased wall stress. However, this cellular hypertrophy is usually inadequate to fully compensate for the degree of myocyte loss. Thus, in treating patients with left ventricular dysfunction, it is very important to attenuate the wall stress. In fact, it is well recognized that left ventricular wall stress is one of the most important determinants relating to the change of left ventricular remodeling after myocardial infarction.

In our study, PSWS was not significantly related to the prognosis, but ESWS was a powerful predictor of the survival of patients with DCM. As shown in Table 2, there was no significant difference in LVDd between the alive and died groups, but a significant difference in LVDs was observed between the 2 groups. The increase in the noncontractile region of myocardial tissue may be related to the increase of LVDs in the died group and thereby result in the marked increase of ESWS. In our study, SBP was lower in the died group than in the alive group, which may be mainly due to the decrease of stroke volume. In addition, this decrease in SBP may contribute to the attenuation of the ESWS. Juillière et al. reported that mean systemic arterial pressure was a predictor of the prognosis of DCM. In our study, DCM patients with a higher systemic pressure had a better prognosis, which supports our understanding about blood pressure in our patients.

In DCM patients whose FS was less than 16%, the prognosis was markedly worse in patients whose ESWS was more than 150×10^3 dynes/cm^2 than in patients whose ESWS was less than 150×10^3 dynes/cm^2. A marked increase of the ESWS means that the heart can not eject sufficient flow because of the markedly suppressed contractile state. The value of 150×10^3 dynes/cm^2 of ESWS, which is almost 3-fold of normal control subjects, seems to be a critical point. A previous echocardiographic
study in patients with DCM showed that the prognosis in patients with a higher degree of wall thickness was favorable. This finding seems to be mainly due to the attenuation of wall stress associated with a higher degree of wall thickness.

Our results also indicate that FS is another independent risk factor of survival in patients with DCM. A previous report has already elucidated that patients who died of congestive heart failure had a more reduced systolic function. Several studies suggest that the extent of left ventricular fiber shortening is determined by both the ESWS and the contractile state. An increase in wall stress is known to reduce myocardial fiber shortening so FS may also be dependent on the left ventricular contractile state.

Relation Between the ESWS and Extent Score

It is uncertain whether the left ventricular wall thickness at the base of the left ventricle estimated by echocardiography exactly reflects the extent of myocardial insults in DCM patients. Thus, in this study we tried to evaluate the abnormality of the myocardium using 201Tl myocardial scintigraphy. 201Tl myocardial perfusion abnormalities in patients with DCM have been previously reported. In those studies the assessment of myocardium loss by myocardial scintigraphy was subjective, whereas we estimated the myocardial loss by the extent score, proposed by Garcia et al., for a quantitative assessment. Bulkley et al. reported that constant perfusion defects seen on thallium scans of patients with DCM may represent areas of myocardial fibrosis and scarring. Shiotani et al. reported that persistent defect segments in DCM patients corresponds to severe wall motion abnormality, and that the prognosis of patients with persistent defect is poor.

In our study, the extent score in the patients who died was greater than that in the alive patients. In addition, there was a linear correlation between ESWS and the extent score in DCM patients. Our results indicate that the extent of the cumulative loss of myocardium was significantly larger in the dead patients than in those still alive. In addition, this increase in the cumulative loss of myocardium may be closely related to the increase in ESWS. In DCM patients whose FS is less than 16%, those with a higher ESWS had a poorer prognosis, despite the same FS. Thus, ESWS seems to be a very strong index of the prognosis of patients with DCM.

References