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Left Ventricular Ejection Performance in Heart Failure.
— Assessment by Angiotensin II Loading and Follow-up Echocardiographic Studies —

Yoshio Takeuchi¹, Yoshiyuki Yokota², and Hiroya Kawai¹.

To elucidate the left ventricular ejection performance in patients with heart failure by changes in afterload stress, 14 patients with dilated cardiomyopathy were subjected. 1. Angiotensin II (AT II) loading test: Left ventricular end-systolic wall stress (WS), the time velocity integrals of left ventricular total filling (IT) and left ventricular forward ejection flow (IE), and their ratio (IE/IT) were measured by M-mode and Doppler echocardiography. Patients were given AT II intravenously and re-examined by echocardiography. The severity of mitral regurgitation by color Doppler (MR) was also assessed; 2. Follow-up study: The same echocardiographic variables were obtained before and after medical treatment (mean 6.1 months). Results: 1: By AT II, WS increased significantly, while, IE, IT, and IE/IT (an index of left ventricular ejection efficacy) decreased significantly (p < 0.01). 2: By medical treatment, all patients had symptomatic improvement. During the follow-up period, WS reduced significantly, IE and IE/IT increased significantly (p<0.01). IT tended to increase and MR reduced significantly (p<0.01) during the follow-up period.

In conclusion: Not only the depressed systolic function (afterload mismatch) but also the decreased left ventricular ejection efficacy due to enhanced MR plays an important role in the decrement of left ventricular forward ejection by increased afterload stress.

Key Words
Left ventricular ejection performance,
Dynamic MR,
Heart failure,
Left ventricular function,
Doppler echocardiography.

Introduction

Decrement of left ventricular forward output by increasing afterload stress is referred as "afterload mismatch", and an important factor of the progression of heart failure clinically (1-4). However, Left ventricle communicates to left atrium not only during diastole, but also during systole because most of failing heart have functional mitral regurgitation (MR) (5,6). Accordingly, in most of failing heart, left ventricular contraction induces both forward and backward blood flows. It is well known that the severity of MR grade changes by
Table 1. Clinical and echocardiographic data of subjects.

<table>
<thead>
<tr>
<th>NAME</th>
<th>AGE</th>
<th>SEX</th>
<th>NYHA</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
<th>Dd</th>
<th>Ds</th>
<th>%FS</th>
<th>MR</th>
<th>NYHA</th>
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<td>K.K.</td>
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<td>114</td>
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<td>85</td>
<td>75</td>
<td>71</td>
<td>5</td>
<td>3</td>
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</tr>
<tr>
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<td>M</td>
<td>3</td>
<td>103</td>
<td>74</td>
<td>91</td>
<td>73</td>
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<td>67</td>
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<td>0</td>
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<tr>
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<td>70</td>
<td>65</td>
<td>59</td>
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<td>68</td>
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<tr>
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<tr>
<td>Y.S.</td>
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<td>120</td>
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<tr>
<td>N.K.</td>
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<td>98</td>
<td>46</td>
<td>80</td>
<td>63</td>
<td>53</td>
<td>16</td>
<td>2</td>
<td>2</td>
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</table>

M 50.8  2.9  107.1  66.9  81.0  67.6  58.9  13.0  1.9  1.9  1.4
SD 12.1  0.8  9.7  12.8  12.7  5.0  5.5  4.2  1.1  0.4  1.0

DBP: diastolic blood pressure(mmHg), Dd: left ventricular end-diastolic dimension(mm), Ds: left ventricular end-systolic dimension(mm), F: female, %FS: percent fractional shortening, HR: heart rate(min), M: male, MR: severity of mitral regurgitation, NYHA: functional class of heart failure, SBP: systolic blood pressure(mmHg)

The loading condition (7,8). The purpose of this study is to elucidate the changes of left ventricular ejection performance associated with acute or chronic changes of left ventricular afterload in patients with heart failure.

Subjects and methods

Subjects

Fourteen patients with dilated cardiomyopathy (DCM) including 12 men and 2 women with a mean age of 51 ± 12 years were subjected. The diagnosis of DCM was based on the criteria of WHO/ISFC task force report (9). All of the subjects had marked impairment of myocardial contractility and dilatation of left ventricle (Table 1). All of the subjects were in normal sinus rhythm and did not have any other cardiac disease including aortic regurgitation demonstrated by color Doppler echocardiography.

Echocardiographic studies

All of the patients were examined by echocardiography in the lateral recumbent position. The ultrasound system used in this study combined a 2-dimensional mechanical sector with
Left ventricular ejection performance

a ranged-rated Doppler flow velocity meter (Toshiba model SSH 160A).

The ultrasound frequency of transducer used was 3.75 and 2.5 MHz.

By standard M-mode echocardiography, left ventricular end-systolic wall stress (WS) was calculated according to the following formula;

\[ WS = 0.59 \times SBP \times Ds/Ths, \]

where \( SBP \) = systolic blood pressure; \( Ds \) = left ventricular end-systolic dimension; \( Ths \) = left ventricular end-systolic wall thickness (4,10). Then using the apical long axis view, left ventricular filling and ejection flow velocity profiles were obtained by pulsed Doppler echocardiography. The sample volume was set in the center of the mitral annulus for the left ventricular filling flow, and left ventricular outflow tract for left ventricular ejection flow. The time velocity integrals of left ventricular total filling (IT) and the time velocity integral of left ventricular forward ejection flow (IE) were measured (Fig.1), and the ratio of IE and IT (IE/IT) was also calculated.

1. Angiotensin II loading echocardiography.

Angiotensin II (AT II) was infused intravenously at a rate of 4 ng/kg/min and gradually increased by 4 ng/kg/min until SBP was raised by 30% above the basal condition (10). Before and during AT II loading, pulsed Doppler echocardiograms were recorded. In case of progression of heart failure symptom during AT II loading, when SBP was not raised by 30% above the basal condition, increment of AT II administration was discontinued and echocardiographic examination was done (11). The

Figure 1.
Doppler echocardiographic measurements.
upper panel: A recording of left ventricular outflow tract doppler echocardiogram.
IE: time velocity integral of left ventricular forward ejection flow.
lower panel: A recording of transmitral flow Doppler echocardiogram.
IT: time velocity integral of left ventricular total filling.
severity of MR grade by color Doppler was also assessed before and during AT II loading \((12)\).

2. Follow-up study.

At the beginning of this study, 5 patients had mild functional limitation (NYHA class II) and the remaining 9 patients had moderate to severe func-
Table 2. Results of angiotensin II loading echocardiography.

<table>
<thead>
<tr>
<th></th>
<th>WS (g/cm²)</th>
<th>IE (cm)</th>
<th>IT (cm)</th>
<th>IE/IT</th>
<th>MR grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNT</td>
<td>299 ± 66.1</td>
<td>11.4 ± 2.34</td>
<td>11.1 ± 3.63</td>
<td>1.13 ± 0.38</td>
<td>1.54 ± 0.97</td>
</tr>
<tr>
<td>AT II</td>
<td>442 ± 83.6</td>
<td>7.9 ± 2.46</td>
<td>9.0 ± 2.85</td>
<td>0.97 ± 0.43</td>
<td>2.04 ± 1.08</td>
</tr>
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p value <0.01 <0.01 <0.01 <0.01 <0.01

AT II: angiotensin II loading, CNT: control, IE: time velocity integral of left ventricular forward ejection, IT: time velocity integral of left ventricular total filling, IE/IT: ratio of IE and IT, WS: left ventricular end-systolic wall stress

Table 3. Results of follow-up echocardiography.

<table>
<thead>
<tr>
<th></th>
<th>WS (g/cm²)</th>
<th>IE (cm)</th>
<th>IT (cm)</th>
<th>IE/IT</th>
<th>MR grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>321 ± 78.7</td>
<td>10.5 ± 2.31</td>
<td>10.2 ± 3.63</td>
<td>1.13 ± 0.38</td>
<td>2.9 ± 0.77</td>
</tr>
<tr>
<td>After treatment</td>
<td>258 ± 68.4</td>
<td>14.0 ± 3.26</td>
<td>11.4 ± 2.20</td>
<td>1.27 ± 0.37</td>
<td>1.9 ± 0.36</td>
</tr>
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</table>

p value <0.01 <0.01 <0.1 <0.05 <0.01

MR: mitral regurgitation, other abbreviations are same in Table 2.

tional limitation (class III to IV) (Table 1). All patients were treated with digitalis and diuretics. Vasodilator and/or β-blocker were administered to 10 patients. Echocardiographic examinations were carried out and same variables as those used in AT II loading study were obtained in each patients before and after long term medical treatment (mean follow-up period was 6.1 months).

All Doppler recordings were performed under stopping patient’s breathing following shallow expiration in order to avoid the influence of changes in respiration on Doppler flow velocities. For each subject, results from 5 cardiac cycles were aver-
aged for each measurement. The data were expressed as mean ± 1 standard deviation. The level of significance was p < 0.05.

Results

1. Results of AT II loading (Table 2, Fig. 2).

By AT II loading, left ventricular end-systolic wall stress (WS), an index of afterload, increased significantly (p < 0.01). Left ventricular forward ejection (IE) and total filling (IT) decreased significantly (p < 0.01) by AT II loading. In interest, the IE/IT, an index of left ventricular ejection efficacy, decreased significantly (p < 0.01). Whereas the severity of MR significantly increased after AT II loading (p < 0.05).

2. Results of follow-up study (Tables 1, 3, Figs. 2, 3).

All of the patients in this study had symptomatic improvement during follow-up period. Left ventricular afterload (WS) was significantly smaller, while left ventricular forward ejection (IE) and IE/IT were significantly larger after treatment than before treatment, respectively, (p < 0.01 for each) (Table 3). Left ventricular total filling (IT) increased during follow-up period. The severity of MR grade by color Doppler ameliorated in 9/14 patients and unchanged in others during follow-up period (Fig. 2). Representative change of the severity of MR grade is shown in Fig. 3.

Discussion

Decrement of left ventricular forward output by increasing afterload stress in heart failure is referred as "afterload mismatch". It is an important factor of the progression in heart failure occurred by the depression of systolic function due to the limit of preload reserve (1-4). However, left ventricle communicates to left atrium not only during diastole, but also during systole because most of failing heart have functional MR (5,6). Thus, in most of failing heart, left
ventricular contraction results in both forward blood flow into systemic circulation and backward blood flow into left atrium. It is reported that the severity of MR grade changes by the loading condition (7-8). Namely, preload (8) or afterload (7) reduction decreases MR in failing heart. It means that in failing heart forward ejection decreases and backward ejection (MR) increases with afterload augmentation. Similarly in our study, the severity of MR grade increased by acute afterload augmentation (AT II loading) and decreased by chronic afterload reduction (reduction of WS) during follow-up periods. But, it is semi-quantitative evaluation. In order to assess quantitative left ventricular ejection performance, the time velocity integrals of left ventricular forward flow (IE) and total filling (IT) was measured in the setting of loading condition.

Exactly to assess the amount of blood flow, cross sectional area of Doppler sample volume is required. Total filling volume can be calculated by the product of IT and mitral valve annular area (MVA), forward ejection volume can be calculated by the product of IE and aortic valve annular area, and MR volume can be calculated by these difference in patients without aortic regurgitation. Thus, if we assume MR is ineffective on left ventricular ejection, left ventricular ejection efficacy (LVEf) is expressed as following formula: LVEf = IE × AVA/IT × MVA (12). If AVA/MVA is constant in this formula, one get; LVEf = IE/IT × K, where K = AVA/MVA (Fig.4). However, although it is reported that aortic annular area is relative constant because of its firm construction, mitral valve annular area is not constant by the changes of loading condition. Borgenhagen (13) reported that mitral valve annular area increased by afterload stress in mitral regurgitant dog. It suggests that K (AVA/MVA) decreases by increasing afterload stress. Because K decreases by increasing afterload stress, the decrement of IE/IT directly means the decrement of left ventricular ejection efficacy itself.

In our study, acute afterload augmentation with AT II loading decreased IE/IT, indicating the decrement of left ventricular ejection efficacy, and chronic afterload reduction by medical treatment increased it. Furthermore, the severity of MR grade enhanced by acute afterload and reduced after the treatment. These results indicate that, in heart failure, decrement of left ventricular forward output is caused not only by the depressed left ventricular systolic function with elevated afterload (so-called “afterload mismatch”) but also by the decrement of left ventricular ejection efficacy due to enhanced MR.

**Limitation**

A few limitation before our conclusion may be noteworthy. We might be able to calculate the quantative blood volume using AVA and MVA. The calculation of aortic or mitral valve anular area, total filling volume, and forward ejection volume are usually made by following formulas; aortic or mitral valve anular area = π × (aortic or mitral valve annular diameter)², total filling volume = MVA × IT, forward ejection volume = AVA
Figure 4.
Schematic calculation of left ventricular ejection efficacy.
MVA: mitral valve annular area, A VA: aortic valve annular area, FSV: forward stroke volume, TFV: total filling volume, R: rapid filling wave, A: atrial filling wave, Other abbreviations are same in Fig.1 and Table 1.

\[
\text{left ventricular ejection efficacy} = \frac{FSV}{TFV} = \frac{IE \times AVA}{IT \times MVA} = k \times \frac{IE}{IT} \quad (k = \frac{AVA}{MVA})
\]
\( \times \) IE (Fig.4) However, it is difficult to estimate total filling volume because of phasic changes of mitral annular area (5) and non-circular mitral annular shape (14). These problems enhance the technical error and may lead incorrect results. This is the reason why we did not use aortic and mitral valve annular areas.

References

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