The Distribution of the Blood Flow during Exercise in Chronic Heart Failure
Compensatory mechanism to the decreased cardiac output —

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TETSUYA KAKIMOTO, M.D., AND MITSUHIRO YOKOYAMAM.D.

To evaluate the blood flow distribution during exercise, 51 patients with chronic heart failure underwent ergometer exercise testing measuring cardiac output and leg blood flow. At the given workrate (10 watts and 25 watts) cardiac index (L/min/m²) was significantly lower in NYHA class III patients than class I patients (at 10 watts, 4.08 ± 1.05 in class I, 4.01 ± 1.29 in class II and 3.00 ± 0.89 in class III, p<0.05; I vs III), while leg blood flow (L/min/m²) was similar among 3 groups (at 10 watts, 1.19 ± 0.32, 1.29 ± 0.25 and 1.16 ± 0.29, ns). Consequently, residual blood flow (L/min/m²) was significantly lower in class III than class I (at 10 watts, 2.89 ± 0.92 and 2.78 ± 1.27 and 1.84 ± 0.71, p<0.05; I vs III). The results at 25 watts were similar. Serum noradrenaline was significantly higher in class III patients than class I patients at both 10 and 25 watts. We concluded that in severe heart failure, a greater blood flow is distributed to the working leg muscle as compared with less severe heart failure. And such an increased distribution of blood flow to working leg plays a role to compensate an insufficient cardiac output response in patients with severe heart failure.

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THE development of central and peripheral compensatory mechanisms which maintain systemic circulation when is cardiac function depressed is widely found in patients with chronic heart failure. One of the peripheral compensatory mechanisms in decreased cardiac output is a change of distribution of blood flow to the organs. Blood flow to the important organs such as brain and heart tends to be preserved even if cardiac output decreases; on the contrary, visceral, skin and muscular blood flow decreases when cardiac output decreases? These changes have been measured under resting conditions. However, blood flow distribution has rarely been examined during exercise in patients with chronic heart failure. Increase of blood flow to the working skeletal muscle is a major influence on the blood flow distribution during exercise. Recently, the reduced reserves of skeletal muscle blood flow were recognized as a limiting factor of exercise tolerance in patients with chronic heart failure. In addition, it is well known that cardiac output is greatly limited during exercise in chronic heart failure. Thus the relationship between skeletal muscle blood flow and cardiac output plays an important role in the development of the compensatory mechanism. In this study, we examined this relationship in regard to the severity of chronic heart failure.

METHODS

Subjects: Fifty one patients ranging in

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TABLE I THE RESULTS AT REST

<table>
<thead>
<tr>
<th>Class</th>
<th>n (cases)</th>
<th>VO2 (mL/min/m²)</th>
<th>Cardiac Index (L/min/m²)</th>
<th>Leg Flow (L/min/m²)</th>
<th>Residual Flow (L/min/m²)</th>
<th>Noradrenaline (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>23</td>
<td>128±22</td>
<td>2.79±0.69</td>
<td>0.26±0.08</td>
<td>2.52±0.65</td>
<td>0.19±0.06</td>
</tr>
<tr>
<td>Class II</td>
<td>19</td>
<td>131±17</td>
<td>2.78±0.85</td>
<td>0.26±0.10</td>
<td>2.52±0.80</td>
<td>0.28±0.16</td>
</tr>
<tr>
<td>Class III</td>
<td>9</td>
<td>139±24</td>
<td>2.24±0.45</td>
<td>0.32±0.35</td>
<td>1.93±0.47</td>
<td>0.36±0.14*</td>
</tr>
</tbody>
</table>

*p<0.05: Class I vs III.

TABLE II THE RESULTS AT 10 WATTS

<table>
<thead>
<tr>
<th>Class</th>
<th>VO2 (mL/min/m²)</th>
<th>Cardiac Index (L/min/m²)</th>
<th>Leg Flow (L/min/m²)</th>
<th>Residual Flow (L/min/m²)</th>
<th>Noradrenaline (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>285±65</td>
<td>4.08±1.05</td>
<td>1.19±0.32</td>
<td>2.89±0.92</td>
<td>0.26±0.09</td>
</tr>
<tr>
<td>Class II</td>
<td>299±45</td>
<td>4.01±1.29</td>
<td>1.29±0.25</td>
<td>2.78±1.27</td>
<td>0.41±0.28*</td>
</tr>
<tr>
<td>Class III</td>
<td>268±52</td>
<td>3.00±0.89*</td>
<td>1.16±0.29</td>
<td>1.84±0.71*</td>
<td>0.58±0.26*</td>
</tr>
</tbody>
</table>

*p<0.05: Class I vs II, *p<0.01: Class I vs III, *p<0.05: Class II vs III

TABLE III THE RESULTS AT 25 WATTS

<table>
<thead>
<tr>
<th>Class</th>
<th>VO2 (mL/min/m²)</th>
<th>Cardiac Index (L/min/m²)</th>
<th>Leg Flow (L/min/m²)</th>
<th>Residual Flow (L/min/m²)</th>
<th>Noradrenaline (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>388±77</td>
<td>4.77±1.07</td>
<td>1.65±0.44</td>
<td>3.12±0.94</td>
<td>0.33±0.12</td>
</tr>
<tr>
<td>Class II</td>
<td>407±59</td>
<td>4.61±1.37</td>
<td>1.75±0.42</td>
<td>2.85±1.36</td>
<td>0.60±0.35</td>
</tr>
<tr>
<td>Class III</td>
<td>370±58</td>
<td>3.54±0.78*</td>
<td>1.56±0.32</td>
<td>1.98±0.68*</td>
<td>0.79±0.29*</td>
</tr>
</tbody>
</table>

*p<0.05: Class I vs II, *p<0.01: Class I vs III, *p<0.05: Class II vs III

The mean age from 34 to 69 years (mean 54) were studied. All patients were stable clinically, and had NYHA class I chronic heart failure in 23 cases (class I), class II in 19 cases (class II) and class III in 9 cases (class III). The cause of heart failure was myocardial infarction in 35 cases, dilated cardiomyopathy in 10 cases and regurgitant valvular heart disease in 6 cases. Patients with obstructive valvular disease, angina pectoris, anemia, and peripheral vascular disease were excluded from this study. The risks of the study were explained fully to the patients and informed written consent was obtained.

Exercise Protocol: Exercise testing was performed with the subjects in the supine position using an bicycle ergometer (Siemens Elema 380B). The exercise was a 3 min incremental multi-stage protocol. The work rate at the initial stage was 10 watts, the next stage was 25 watts, followed by 25 watts increases every 3 min. The endpoint of the exercise was severe fatigue or dyspnea.

Measurement: Respiratory gases, right sided cardiac pressure, arterial pressure, blood oxygen content, arterial noradrenaline concentration and leg blood flow were measured at rest and during exercise. Oxygen intake (VO2) was measured using breath by breath technique (Minato RM-300). The value was averaged every 30 sec. Cardiac index (CI) was calculated as VO2 derived by arterio-venous oxygen difference and body surface area (Fick's law). Leg blood flow was measured using a thermodilution technique. A 5 french thermodilution catheter was inserted via the femoral vein with a check valve sheath. The tip of the sheath was positioned at the level of the inguinal ligament and the thermister was 5 cm distal from the sheath. Leg blood flow was measured by rapid injection of an iced dextrose.

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TABLE IV  THE RESULTS AT PEAK EXERCISE

<table>
<thead>
<tr>
<th></th>
<th>VO2 (mL/min/m2)</th>
<th>Cardiac Index (L/min/m2)</th>
<th>Leg Flow (L/min/m2)</th>
<th>Residual Flow (L/min/m2)</th>
<th>Noradrenaline (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>731 ± 123</td>
<td>6.77 ± 1.20</td>
<td>3.02 ± 0.79</td>
<td>3.74 ± 1.02</td>
<td>1.14 ± 0.49</td>
</tr>
<tr>
<td>Class II</td>
<td>660 ± 51*</td>
<td>5.59 ± 1.34*</td>
<td>2.42 ± 0.59*</td>
<td>3.17 ± 1.24</td>
<td>1.25 ± 0.60</td>
</tr>
<tr>
<td>Class III</td>
<td>420 ± 58*</td>
<td>3.83 ± 0.65*</td>
<td>1.82 ± 0.43*</td>
<td>2.01 ± 0.71*</td>
<td>1.11 ± 0.39</td>
</tr>
</tbody>
</table>

*p<0.05: Class I vs II, *p<0.01: Class I vs III, *p<0.05: Class II vs III

Fig. 1. The relation between cardiac index and leg flow during exercise. NYHA class III patients showed the left side shift of this relation. This indicates that the blood flow distributes to the leg more extensively against the impaired cardiac output.

The results showed that the VO2 and cardiac index were significantly lower in class III than in class I and II. The leg flow and residual flow were lower in class III than in class I and II. The noradrenaline level was significantly higher in class III than in class I and II.

RESULTS

Clinical Feature of the Subjects: Average age was similar in 3 groups (53 ± 8 years in class I, 54 ± 10 years in class II and 55 ± 10 years in class III). Average left ventricular ejection fraction was 58 ± 9% in class I, 43 ± 13% in class II and 34 ± 18% in class III. It was significantly different between the 3 groups (p<.05). Average hemoglobin was similar in 3 groups.

Resting Value (Table I): At rest, a significant difference was found only in serum noradrenaline. It was significantly higher in class III than other groups. VO2, CI, leg blood flow and residual blood flow were similar in the 3 groups.

Results at the Matched Workrate (Table II and Table III): The results were compared at 10 watts and 25 watts workrate. VO2 was similar in all groups. CI was significantly lower in class III than class I at both workrates. Leg blood flow was similar in all groups. Residual blood flow was significantly lower in class III than class I at 25 watts. Serum noradrenaline was significantly higher in class III than class I at both workrates and was higher in class II than class I at 25 watts.

Results at Peak Exercise (Table IV): At peak exercise, significant differences in VO2, CI and leg blood flow were found between the groups. Residual blood flow was significantly lower in class III than class I and II. Serum noradrenaline was not significantly different.

The Distribution of the Blood Flow: Fig. 1 shows the relationship between cardiac index and leg blood flow during exercise. An excellent linear relationship was found in these 2 parameters. The curve of patients with class III was shifted to the left side.
compared with the other groups. This indicates that in patients with severe heart failure a blood flow to the working leg is maintained by the distribution of blood flow in spite of insufficient cardiac output response during exercise.

DISCUSSION

During exercise, skeletal muscle consumes ATP and oxygen to produce external work. Consequently, the oxygen requirement of the working skeletal muscle increases, and the leg blood flow increases in order to supply this oxygen. In this study, leg blood flow at the workrate of 10 watts and 25 watts showed similar levels among 3 groups. On the other hand, cardiac index was significantly lower in class III than class I at the given workrate. This indicates that as the chronic heart failure was more severe, the response of cardiac output to exercise was smaller. As a result, residual blood flow was smaller in class III than class I. Thus, our results showed that there was a greater blood flow distribution to the working leg in patients with severe chronic heart failure.

In this study, we measured leg blood flow using a thermodilution technique. This method is most popular for measuring directly the leg blood flow during exercise, and is reliable. In our laboratory, comparison between known flow and measured flow by this technique using the roller pump method showed a linear relationship. Cardiac output was determined by a direct Fick's method. If we measured both cardiac output and leg blood flow using thermodilution method, the change of blood temperature should be influenced by injected solution from femoral vein, which causes a wrong measurement of cardiac output. Thus, cardiac output must be measured by Fick's method in our study.

There is increasing evidence that exercise intolerance in patients with chronic heart failure relates to the impaired blood flow reserve of the working skeletal muscle. Our results agreed with these reports. However it has been not clearly understood yet what is the mechanism of impaired blood flow reserve in the working muscle. Since leg blood flow uses almost all of the increment of cardiac output during maximal exercise, it is reasonable to consider that limited cardiac output should reduce the leg blood flow reserve in patients with chronic heart failure. However, Wilson et al. reported that peak leg blood flow was not improved after single administration of a vasodilating agent even if peak cardiac output increased. They concluded that impaired leg blood flow reserve is caused not by impaired cardiac output reserve but by impaired vasodilating reserve of the skeletal muscle. Sullivan et al. reported that the heart failure preferentially maintains arterial pressure and blood flow to non exercising region at the expense of leg hypoperfusion during exercise. Our results showed that cardiac index was smaller in class III patients compared with class I patients at the given workrate, which agreed with the previous report. However, leg blood flow was at the same level in all 3 groups at the given workrate, which is compatible with similar oxygen consumption level in all groups at this workrate. This indicates that the nutritive blood flow to the working muscle is compatible with the oxygen consumption, even though a cardiac output decreases. Thus, in patients with severe chronic heart failure, the blood flow shifted to the working leg from the residual portion to a greater compared with less severe chronic heart failure. This phenomenon may indicate a compensatory mechanism to maintain exercise metabolism when cardiac function is impaired.

The mechanism causing the change of blood flow distribution in class III patients was analyzed from the viewpoint of sympathetic activation during exercise. The autonomic nervous system is one of the most important mechanisms to produce the rapid change of blood flow to various organs. Exercise causes sympathetic activation, and this increases the vessel tone. However, during exercise, the accumulation of local metabolites in the working skeletal muscle abolishes the sympathetic vasoconstriction. In our study serum noradrenaline was significantly higher in class III than class I at the low level of given workrate (10 watt and 25 watt). This may cause more strict vasoconstriction in inactive organs in class III, while in working skeletal muscle vasodilating stimulation continues. Consequently, leg blood flow was maintained during exercise, while residual
blood flow decreased in patients with class III who had small exercise cardiac output. This result is opposite to the concept of Sullivan et al. A possible factor to explain this difference is that Sullivan et al compared normal subjects with patients with heart failure, while we compared 3 groups with different degrees of heart failure. We consider that normal subjects may have different exercise blood flow distribution to patients with chronic heart failure. As normal subjects can achieve a greater workrate, a larger amount of blood flow concentrates to the leg at peak exercise. This should make a larger blood flow distribution to the working leg in normal subjects.

Clinical Implication: Recently, therapeutic approaches to chronic heart failure have advanced. Vasodilator therapy is one of the useful managements of chronic heart failure. However, recent studies have proved that acute administration of a vasodilator is ineffective in improving exercise tolerance in chronic heart failure, but chronic use has an advantage. Our result explains this phenomenon, that is, acute administration of vasodilator may disrupt the compensatory regulation of blood flow distribution, which resulted in blood flow shift from skeletal muscle to inactive organs during exercise. It may take certain period to produce new homeostasis after vasodilator administration.

Conclusion: Our study showed that leg blood flow was similar even though cardiac output was decreased in NYHA III compared with NYHA I group at the given workrate. The result indicates the compensatory mechanism of blood flow distribution during exercise to maintain the exercise metabolism against the impaired cardiac function in severe chronic heart failure.

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