Blood Flow Redistribution During Exercise Contributes to Exercise Tolerance in Patients With Chronic Heart Failure

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Background It is widely known that blood flow redistribution is impaired in patients with chronic heart failure (CHF). However, the relationship between exercise tolerance and the degree of blood flow redistribution is not fully understood. Whole-body thallium-201 chloride (201Tl) scintigraphy can estimate blood flow distribution. This study will evaluate the relationship between exercise tolerance and blood flow redistribution using whole-body scintigraphy in patients with CHF.

Methods and Results Exercise stress whole-body thallium scintigraphy was performed in 19 patients with CHF (mean ejection fraction: 33.0%; peak oxygen uptake: 15.5 ml·min⁻¹·kg⁻¹). Blood flow redistribution was quantified by comparing the regional thallium count (count/pixel) in the thigh and arm. We then assessed the relationship between these parameters and parameters obtained from cardiopulmonary exercise testing. 201Thallium-chloride uptake in the thigh increased during exercise compared to rest (p<0.05), while its uptake in the arm was different between exercise and rest. Increased 201Tl uptake in the thigh during exercise was positively correlated with exercise tolerance (r=0.689). In contrast, 201Tl uptake in the arm was not correlated with exercise tolerance.

Conclusions By using this method, it is concluded that blood flow redistribution to the exercising muscle increases as the exercise tolerance increases in patients with CHF. (Circ J 2007; 71: 465–470)

Key Words: Blood flow redistribution; Chronic heart failure; Exercise

During exercise, blood vessel dilation is essential to meet oxygen demands of the working muscle. It has been reported that muscle blood flow increases linearly with work load during incremental exercise testing and is closely related to the oxygen demand of the exercising muscle! Therefore, it is assumed that if the increase in blood flow volume is insufficient during exercise, oxygen uptake is limited and exercise tolerance is impaired. Even though cardiac output is diminished, if blood flow volume is distributed selectively to the working muscle, exercise tolerance might be preserved. However, if blood flow is not properly redistributed to the working muscle, exercise tolerance will be impaired. It is known that as the severity of exercise intolerance increased, nutritive flow to skeletal muscle declined in patients with chronic heart failure (CHF)² Besides, Jondeau et al demonstrated that insufficient active muscle, not cardiac output, was the limiting factor for maximal exercise capacity in patients with severe heart failure, although exercise capacity in normal subjects and patients with mild to moderate heart failure was limited by cardiac output! However, it is methodologically difficult to evaluate the blood flow distribution of the whole body simultaneously if the exercise is like a daily activity.

Table 1  Patient Characteristics

<table>
<thead>
<tr>
<th>Patients' characteristics</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>65±10</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/16</td>
</tr>
<tr>
<td>NYHA functional class (II/III)</td>
<td>9/10</td>
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<tr>
<td>Etiology of CHF</td>
<td></td>
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<tr>
<td>DCM</td>
<td>9</td>
</tr>
<tr>
<td>ICM</td>
<td>10</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>33±4</td>
</tr>
<tr>
<td>Peak CO (L/min)</td>
<td>6.1±1.5</td>
</tr>
<tr>
<td>AT (ml·min⁻¹·kg⁻¹)</td>
<td>10±2</td>
</tr>
<tr>
<td>Peak VO₂ (ml·min⁻¹·kg⁻¹)</td>
<td>16±4</td>
</tr>
<tr>
<td>VE·VCO₂ slope</td>
<td>40±14</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; CHF, chronic heart failure; DCM, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy with prior infarction; LVEF, left ventricular ejection fraction; CO, cardiac output; AT, anaerobic threshold; VO₂, oxygen uptake; VE·VCO₂, minute ventilation-carbon dioxide output.

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with CHF and investigated how much abnormality of blood flow redistribution during exercise influenced exercise tolerance.

Methods

Subjects

We studied 19 patients with CHF (16 male and 3 female, 47–78 years of age, mean age: 65±10 years, mean ± standard deviation). Entry criteria included a history of daily exertional dyspnea associated with moderate to severe stable CHF (New York Heart Association functional class II and III) and left ventricular dysfunction with an echocardiographic left ventricular ejection fraction (EF) <45% (mean EF: 33±6%). The underlying cause of heart failure was idiopathic dilated cardiomyopathy in 9 patients and ischemic cardiomyopathy with prior infarction in 10 patients (Table 1). All patients were clinically stable, with no worsening of heart failure during the study. Patients with primary pulmonary disease, residual myocardial ischemia or arrhythmias during exercise, renal disease or exercise intolerance for any reason other than fatigue or dyspnea were excluded from the study. All subjects gave informed consent to participate in the study that had been approved by the Institutional review Board of the Gunma Prefectural Cardiovascular Center.

Exercise-Stress Scintigraphy

Exercise-stress 201Tl myocardial scintigraphy is being used to evaluate patients with suspected or known coronary artery disease. When we examine exercise-stress 201Tl myocardial scintigraphy in each subject, we drew regions of interest to not only around the heart but also whole body. The exercise test was performed in the upright position on a cycle ergometer. The protocol was started at 25 W and increased by 25 W every 3 min. Leads V5, II, aVF were monitored continuously, with 12-lead electrocardiograms and arterial blood pressure recorded every minute. At the time the patient felt exhaustion or their heart rate reached 85% of the maximal predicted value, 201Tl (111.0 MBq) was injected intravenously. Exercise was then continued for an additional minute at the same or lower workload when it was impossible to continue at the same workload. The first image was acquired 10 min later (exercise-imaging), and the second image was acquired 3–4 h later (rest-imaging). Single photon emission computed tomographic images were acquired using the PRISM3000 (Picker, Cincinnati, OH, USA) 3-headed single photon emission computed tomography system with low-energy, high resolution, parallel-hole collimators. The detector system was interfaced to a dedicated nuclear medicine computer. Regions of interest were drawn around the mediastinum, the left arm and the left thigh. Thallium-201 chloride (201Tl) counts in the left arm and left thigh were normalized to counts in the mediastinum. 201Tl uptake in the exercising muscle (thigh) during exercise imaging is increased compared to that in the rest imaging.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed using a ramp protocol. The equipment used included a cycle ergometer (MedGrafics, St. Paul, MN, USA), breath-by-breath gas analyzer (MINATO 300S, Minato Ikagaku, Osaka, Japan), and electrocardiograph recorder (Fukuda Denshi, Tokyo, Japan). A face mask was used to collect gas samples, and oxygen uptake, carbon dioxide output, tidal volume and respiratory rate were measured. The exercise test began with a 3-min resting period on the ergometer followed by 3 min of warm-up exercise, and then the load was increased incrementally by 1 W every 6 s. Blood pressure measurements were obtained every minute. The electrocardiogram was monitored throughout the test. The anaerobic threshold was determined by using the V-slope method. Peak oxygen uptake was defined as the highest oxygen uptake attained during a 15-s period during incremental exercise. The slope of the ventilatory equivalent to the carbon dioxide relationship was assessed by linear regression analysis of the breath-by-breath plot as previously reported.

All 19 patients also gave informed consent for the measurement of cardiac output at peak exercise. Cardiac output was measured by the echocardiography at rest and the indication dye method using 5 mg of indocyanine green at peak exercise.
Statistical Analysis

Data are expressed as mean±standard deviation. The difference in 201Tl uptake between exercise imaging and rest imaging was assessed by the unpaired t-test. Linear regression analysis was performed to evaluate the relationship between 201Tl uptake in the exercise muscle and other parameters measured in cardiopulmonary exercise testing. Values of p<0.05 were considered statistically significant.

Results

All patients performed exercise-stress scintigraphy and cardiopulmonary exercise testing without any complications. The mean values of the anaerobic threshold, peak oxygen uptake, and the slope of the ventilatory equivalent to the carbon dioxide relationship were moderately impaired, as summarized in Table 1. The mean cardiac output at peak exercise during cardiopulmonary exercise testing was also decreased compared with normal subjects9,10.

Correlation Between 201Tl Uptake and Parameters of Exercise Tolerance

201Tl chloride uptake in the thigh during exercise imaging was significantly greater than that during rest imaging (45.8±11.8 vs 33.8±4.8 counts/pixel, p=NS). Fig 2 shows the correlation between 201Tl uptake in the thigh during exercise imaging and parameters of exercise tolerance obtained from cardiopulmonary exercise testing. 201Tl uptake in the thigh was correlated positively with both anaerobic threshold and peak oxygen uptake (r=0.658, p<0.01 and r=0.689, p<0.01, respectively). 201Tl uptake in the thigh was inversely correlated with the slope of the ventilatory equivalent to the carbon dioxide relationship (r=–0.544, p<0.05). Fig 3 illustrates the correlation between 201Tl uptake in the arm during exercise imaging and parameters of exercise tolerance. Although 201Tl uptake in the arm also showed a significant correlation with the anaerobic threshold (r=0.475, p<0.05), there were no correlations between 201Tl and peak oxygen uptake as well as the slope of the ventilatory equivalent to the carbon dioxide relationship (r=0.373, p=NS and r=–0.453, p=NS, respectively).

Correlation Between Exercise/Rest (E/R) Ratio for 201Tl Uptake and Parameters of Exercise Tolerance

To evaluate the change in the 201Tl uptake ratio between exercise imaging to rest imaging, we assessed the E/R ratio, which is calculated as follows: 201Tl-uptake at exercise/201Tl-uptake at rest. Fig 4 demonstrates the correlation

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**Fig 2.** Correlation between parameters of exercise tolerance and thallium-201 chloride (201Tl) uptake in the thigh in exercise imaging. VE-VCO₂, minute ventilation-carbon dioxide output.

**Fig 3.** Correlation between parameters of exercise tolerance and thallium-201 chloride (201Tl) uptake in the arm in exercise imaging. VE-VCO₂, minute ventilation-carbon dioxide output.
between the E/R ratio of the thigh and parameters of exercise tolerance. The E/R ratio was positively correlated with the anaerobic threshold and peak oxygen uptake ($r=0.586$, $p<0.01$ and $r=0.579$, $p<0.01$, respectively). In contrast, the E/R ratio of the arm was not correlated with parameters of exercise tolerance (Fig 5).

**Correlation Between Cardiac Output and Anaerobic Threshold or Peak Oxygen Uptake**

The correlations between anaerobic threshold or peak oxygen uptake and cardiac output at peak exercise are shown in Fig 6. Both anaerobic threshold and peak oxygen uptake were correlated positively with cardiac output at peak exercise ($r=0.561$, $p<0.05$ and $r=0.531$, $p<0.05$, respectively). The slope of the ventilatory equivalent to the carbon dioxide relationship also correlated with cardiac output at peak exercise ($r=-0.674$, $p<0.01$).

**Discussion**

The main finding of the present study is that in patients with CHF, $^{201}$Tl uptake during exercise is augmented only in the exercising muscle, not in the non-exercising muscle. We were able to show differences in blood flow perfusion simultaneously using whole-body $^{201}$Tl scintigraphy. Also, the degree of $^{201}$Tl uptake in exercising muscle was correlated positively with exercise tolerance. Because $^{201}$Tl uptake by the muscle is strongly related to blood perfusion,
the degree of $^{201}$TI uptake is a parameter of how much blood perfusion is present. Thus, the present study revealed that the blood flow volume during exercise increases approximately 2-fold in exercising muscle as compared with resting muscle. This value was smaller than the value of normal subjects. Therefore, blood flow volume might be one of the regulators of exercise tolerance in CHF patients. Moreover, the E/R ratio of exercising muscle is also positively correlated with parameters of exercise tolerance. We conclude that the greater the increase in blood flow during exercise is, the greater the exercise tolerance.

**Whole-Body $^{201}$TI Scintigraphy**

$^{201}$Thallium-chloride has physical characteristics similar to those of potassium. As $^{201}$TI is taken up by the cytosol when cellular function is not impaired, the amount of uptake is determined by blood flow around cells. A decrease in $^{201}$TI uptake and its diagnostic usefulness has been reported in patients with occlusive arterial disease. Whole-body $^{201}$TI scintigraphy has the major advantage of comparing several regions of interest simultaneously. Asanoi et al assessed the blood flow redistribution in healthy subjects using non-invasive whole-body $^{201}$TI scintigraphy by evaluating $^{201}$TI activity in the exercising leg compared to that in the non-exercising leg during extensor exercise of 1 foot, and showed that changes in $^{201}$TI uptake during exercise is highly correlated with that determined by plethysmography. The limitation of this method is that the $^{201}$TI uptake does not indicate the absolute blood flow volume.

**Blood Flow Redistribution**

The main mechanisms responsible for exercise intolerance in patients with CHF are low cardiac output and skeletal muscle dysfunction, as was shown by several studies, in which low blood flow to skeletal muscle is present at rest and during exercise in CHF patients. It is assumed that the cause of impaired nutritive flow to skeletal muscle is the attenuated vasodilatation of exercising muscle and the attenuation of sympathetic vasoconstriction of non-exercising muscle. In the present study, blood flow to the exercising muscle was correlated positively with parameters of exercise tolerance. In contrast, blood flow to the non-exercising muscle was not correlated with parameters of exercise tolerance.

**Blood Flow Increases During Cardiopulmonary Exercise Testing and Exercise Tolerance**

In the present study, $^{201}$TI uptake in exercising muscle was significantly greater than that at rest, while that of non-exercising muscle was not increased and the E/R ratio of exercising muscle was positively correlated with parameters of exercise tolerance. We hypothesize that not only are abnormalities of blood flow redistribution to exercising muscle present, but also that the level of blood flow redistribution in response to exercise will influence exercise tolerance in patients with CHF. Wada et al also reported blood flow redistribution to exercising and resting skeletal muscle in patients with CHF using whole-body thallium scintigraphy and found that thallium activity of the exercising muscle and the thallium ratio between exercising and resting muscle declines with the reduction of exercise tolerance. Their study utilized 1-leg exercise. The present study compared exercising legs and non-exercising arms, and we showed similar results. Moreover, in the present study, we showed a difference in the correlation between blood flow in the exercising and non-exercising muscle. That is, $^{201}$TI uptake in the exercising muscle was significantly increased compared to that at rest, while that in the non-exercising muscle is not increased and $^{201}$TI uptake in the exercising muscle during exercise is significantly correlated with parameters of exercise tolerance while $^{201}$TI uptake in the non-exercising muscle showed little correlation. Our data suggest that blood flow distribution to the exercising muscle increases as the exercise tolerance was more preserved in patients with CHF. Moreover, blood flow maldistribution is one of the important mechanisms responsible for exercise intolerance in patients with CHF.

**Slope of the Ventilatory Equivalent to the Carbon Dioxide Relationship**

The ventilation response to exercise is increased in patients with CHF and the high minute ventilation relative to carbon dioxide production is observed during exercise. It is well known that the slope of the ventilatory equivalent to the carbon dioxide relationship correlates with peak oxygen uptake during cardiopulmonary exercise testing. In the present study, although $^{201}$TI uptake in the thigh, $^{201}$TI uptake in the arm, and the $^{201}$ TI uptake E/R ratio of the thigh were inversely correlated with the slope of the ventilatory equivalent to the carbon dioxide relationship, the correlation was weaker compared to the anaerobic threshold or peak oxygen uptake. The reason for this is thought to be that an elevated slope of the ventilatory equivalent to carbon dioxide relationship is strongly linked to decreased pulmonary perfusion and cardiac output. Therefore, we believe that it is possible to use this method and compare each subjects’ results when the same protocol is used for all subjects.

**Conclusion**

We conclude that blood flow redistribution to the exercising muscle was better as the exercise tolerance was more preserved in patients with CHF. Exercise-stress whole-body $^{201}$TI scintigraphy is a useful method to estimate the severity of blood flow maldistribution of exercising and non-exercising muscle simultaneously in patients with CHF.
References


