Improved Oxygen Utilization During Mild Exercise in Heart Failure

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In heart failure with low cardiac output, exercise tolerance is reduced despite modulated regional blood distribution and oxygen extraction. However, low cardiac output does not necessarily lead to reduced exercise tolerance especially during mild exercise. In the present study, in order to understand the mechanisms regulating exercise tolerance in heart failure, we measured oxygen consumption (\( \dot{V}O_2 \)) and cardiac output (CO) during both mild and intense exercise. Patients with heart failure were divided into 2 groups; group L (n=8) consists of patients with low anaerobic threshold (AT) <13 ml/min per kg and group H (n=7) consisting of patients with AT >13 ml/min per kg. At rest, \( \dot{V}O_2 \) was similar between groups L and H, whereas CO was lower in group L than in group H (3.5±0.3 vs 4.8±1.4 ml/min, p<0.01). Increase in \( \dot{V}O_2 \) during warm-up exercise was not significant between the 2 groups (7.4±0.5 (group L) vs 6.2±0.3 ml/min per kg (group H), ns), but increase in CO was lower in group L than in group H (2.5±0.6 vs 3.4±0.4 ml/min, p<0.01). After warm-up to the AT point, however, the increase in not only \( \dot{V}O_2 \) but also CO was markedly reduced in group L than in group H (\( \dot{V}O_2 \): 0.5±0.4 vs 3.7±0.8 ml/min per kg, p<0.01, CO: 0.2±0.3 vs 1.1±0.3 L/min, p<0.01). Based on these measurements, we calculated the arteriovenous oxygen difference (c(A-V)O2 difference) during exercise in individual patients using Fick’s equation. The c(A-V)O2 difference was markedly increased in severe heart failure during the warm-up stage, but between the end of warm-up and the AT point, it remained at the same level as that of group H. These results suggest the presence of a unique mechanism regulating the c(A-V)O2 difference in severe heart failure patients, activation of which may, at least during mild exercise, contribute to efficient oxygen delivery to the peripheral tissues thus compensating for the jeopardized exercise tolerance in those patients. (Jpn Circ J 1998; 62: 741 – 744)

Key Words: Chronic heart failure; c(A-V)O2 Difference; Exercise; Oxygen utility

The severity of chronic heart failure (CHF) has traditionally been assessed by the extent of breathlessness or fatigue, or the extent to which these symptoms limit effort tolerance. In an attempt to overcome these subjective and sometimes unreliable criteria, various parameters reflective of ventricular function have been developed. Unfortunately, few have been successful because parameters for ventricular function at rest do not necessarily reflect effort tolerance in heart failure.

Recently, exercise testing with expired gas analysis has become a mainstay in estimating exercise tolerance in CHF. The exercise ability in heart failure is estimated by many parameters including anaerobic threshold (AT), maximal oxygen uptake (max\( \dot{V}O_2 \)), or the ratio of increase in \( \dot{V}O_2 \) to increase in work rate (\( \dot{V}O_2/WR \)).

Weber et al have shown that the \( \dot{V}O_2 \) at the AT point and severity of heart failure are negatively correlated during ramp exercise;\(^1\) that is, during aerobic exercise, \( \dot{V}O_2 \) gradually increases along with the intensity of the exercise, which favors production of sufficient amount of adenosine triphosphate (ATP) for exercise. In heart failure, the \( \dot{V}O_2/WR \) is lower and the increase in peak \( \dot{V}O_2 \) during exercise is more reduced than in normal subjects.\(^1\)\(^-\)\(^3\)

During cardiopulmonary exercise testing, CHF patients can exercise freely until the end of the warm-up exercise without limiting symptoms. However, soon after ramp exercise is initiated, CHF patients reach the AT point and the endpoint of ramp exercise in a matter of minutes. Therefore, it seems likely that there exists in CHF patients an unknown mechanism that works during mild exercise but not after the AT point.

In heart failure, stroke volume is frequently decreased and the blood flow to the peripheral tissues is reduced. To compensate for decreased blood distribution to the skeletal muscles, the sympathetic nervous system is activated, which causes heart rate and cardiac output (CO) to increase. Constriction of the precapillary arteries also contributes to blood redistribution. These changes in the cardiovascular autonomic system in CHF may affect exercise tolerance to some extent.

In the present study, in order to understand the difference between mild and intense exercise in CHF, we measured \( \dot{V}O_2 \) and CO at rest, warming-up and at the AT point. We further calculated the difference in arteriovenous \( O_2 \) content (c(A-V)O2) by using Fick’s equations.\(^2\) We hypothesized that an increase in c(A-V)O2 in CHF patients during exercise may be a compensatory mechanism that favors exercise tolerance in heart failure.
In brief, after a 4-min rest on the bicycle ergometer, patients started pedaling at the intensity of 20 watts for 4 min (warm-up), then performed an incremental (10 watts/min) exercise test until exhaustion.

During exercise testing, breathed gas was continuously collected through the tubing, and respiration rate, tidal volume, \( \text{VO}_2 \) and carbon dioxide production (\( \text{VCO}_2 \)) were measured breath by breath. A face mask was used to collect gas samples, which were analyzed using a gas analyzer (AE280S, Minato Ikagaku Co, Tokyo, Japan). The AT was determined by the V-slope method.

Blood pressure was measured every minute with an automatic sphygmomanometer (STB-780, Collin Co Ltd, Tokyo, Japan). Electrocardiogram was also monitored during exercise.

**Difference in Arteriovenous Oxygen Content**

The \( c(A-V)O_2 \) difference was calculated using Fick’s equation as follows:

\[
\text{VO}_2 = \text{CO} \times c(A-V)O_2 \\
\text{ie, } c(A-V)O_2 \text{ difference } = \frac{\text{VO}_2}{\text{CO}}.
\]

**Statistics**

Parameters were compared using the unpaired Student’s t-test. Values are expressed as mean ± SD. Differences were considered significant at \( p<0.05 \).

**Methods**

**Patients**

Fifteen consenting patients with heart failure (NYHA classification I–III) were enrolled. Basal cardiac diseases were old myocardial infarction (n=8) and dilated cardiomyopathy (n=7). Patients were divided into 2 groups according to their exercise tolerance: groups H and L. The AT of group H was more than 13 ml/min per kg, and that of group L was less than 13 ml/min per kg using Weber et al’s evaluation of CHF. The mean age of group H and group L was 56.4±7.2 and 61.8±6.7 (ns), respectively. Left ventricular ejection fraction (LVEF) was 50.9±18.5% (group H) and 57.1±17.4 % (group L, ns) (Table 1). LVEF was measured by transthoracic M-mode echocardiography.

**Cardiac Output**

Cardiac output at rest and during exercise was measured by the dye-dilution method with indocyanine green injection from the upper arm. No side effects from the injection were observed. Cardiac output was calculated by a dye-dilution cardiac output calculator (Nihon Koden, Tokyo, Japan).

**Cardiopulmonary Exercise Testing (CPX)**

Patients performed a symptom-limited ramp exercise test (10 watt/min) on a bicycle ergometer (CPE2000 Medgraphics, St Paul, MA, USA). Exercise protocol and gas exchange analysis were performed according to the method previously described by Ito et al. In brief, after a 4-min rest on the bicycle ergometer, patients started pedaling at the intensity of 20 watts for 4 min (warm-up), then performed an incremental (10 watts/min) exercise test until exhaustion.

During exercise testing, breathed gas was continuously collected through the tubing, and respiration rate, tidal volume, \( \text{VO}_2 \) and carbon dioxide production (\( \text{VCO}_2 \)) were measured breath by breath. A face mask was used to collect gas samples, which were analyzed using a gas analyzer (AE280S, Minato Ikagaku Co, Tokyo, Japan). The AT was determined by the V-slope method.

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**Fig 3.** Changes in VO₂, CO and c(A-V) difference during exercise in both groups (Table 2). VO₂ was increased from rest to the end of the warm-up in both groups in a similar manner. However, c(A-V)O₂ between rest and the end of the warm-up showed no difference between the two groups. Patients with increased exercise tolerance (group H), on the other hand, showed an increase in CO with a proportionate increase in the c(A-V)O₂ difference. Therefore, we suggest that the increase in the c(A-V)O₂ difference during intense exercise may play an important role as a compensatory mechanism to enhance the maxVO₂ uptake.

**Discussion**

In the present study, we demonstrated that patients with unknown exercise tolerance had a marked increase in the c(A-V)O₂ difference between the rest and the end of the warm-up exercise, whereas the rate of increase in CO was less than the c(A-V)O₂ difference. Patients with increased exercise tolerance (group H), on the other hand, showed a significant increase in CO with a proportionate increase in the c(A-V)O₂ difference. Therefore, we suggest that the increase in the c(A-V)O₂ difference during intense exercise may play an important role as a compensatory mechanism to enhance the maxVO₂ uptake.

Exercise tolerance in heart failure depends on the amount of oxygen utilization during exercise. The maxVO₂ during exercise testing is known to be correlated with the peak cardiac index. Thus the exercise tolerance of heart failure patients is determined by the peak maxVO₂ during exercise. However, measuring the maxVO₂ is often difficult, especially in severe CHF patients because exercise testing may induce arrhythmia or heart failure. Furthermore, the maxVO₂ is dependent on the patient’s will to continue the exercise. Therefore, we suggest that the increase in the c(A-V)O₂ difference may function as one such mechanism.

In the present study, the increase in VO₂ from rest to the end of the warm-up was similar between groups L and H. However, the increase in CO during the warm-up stage was lower in group L (severe heart failure) than in group H (mild heart failure), which indicates the presence of a compensatory mechanism in severe CHF that increases VO₂ during exercise even in the presence of an attenuated CO increase. We demonstrated in this study that the increased c(A-V)O₂ difference may function as one such mechanism.

However, after the warm-up stage, this compensatory mechanism does not seem to function during more intense exercise in severe heart failure because the c(A-V)O₂ difference did not increase then. Because of the failure of this compensatory mechanism during intense exercise, patients with severe CHF very quickly reach the AT point without increasing VO₂ or CO.

The reason why the c(A-V)O₂ difference in severe heart failure patients is increased during mild exercise is not known. One explanation may be as follows: when CO is low and precapillary arteries are constricted, the blood velocity in the skeletal muscles could be slow, causing oxygen to be incorporated into muscles, thus reducing venous oxygen content.

In chronic heart failure, mitochondrial enzyme activity has been reported to be decreased. Because of these structural changes, the skeletal muscles are dysfunctional in incorporating and using oxygen. In severe heart failure, anaerobic metabo-

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**Results**

**Cardiac Output**

The increase in CO paralleled exercise intensity in both groups (Table 2), but was significantly lower in group L at rest and at the end of both the warm-up and the AT point. The increase in CO from rest to the end of warm-up was significantly lower in group L than in group H (2.5±0.6 vs 3.4±0.4 ml/min per kg, NS) (Fig 1). Conversely, between the end of the warm-up and the AT point, there was no significant increase in CO, although it tended to be higher in group H than in group L.

**Exercise Tolerance**

There was no difference in VO₂ at rest and during warm-up between the two groups (Table 2). VO₂ was increased from rest to the end of the warm-up in both groups in a similar manner and VO₂ between rest and the end of the warm-up showed no difference between the two groups (7.4±0.5 vs 6.2±0.3 ml/min per kg, NS). However, VO₂ between the end of the warm-up and the AT point was significantly lower in group L than that in group H (0.5±0.4 vs 3.7±0.8 ml/min per kg, p<0.01) (Fig 2).
lism is important for the production of sufficient ATP even at moderate exercise levels. But our results in this report have shown that during low intensity exercise (around 3 Mets (metabolic equivalents)), anaerobic metabolism is not necessarily induced during mild exercise. Instead, ATP can be produced aerobically by increasing the c(A-V)O2 difference.

Stringer et al previously reported that the c(A-V)O2 difference increases proportionally to the %VO2max (VO2/max VO2×100) and this relationship is unaltered regardless of the underlying heart disease and the severity of heart failure;14 for example, at maxVO2, the c(A-V)O2 difference should be the maximal, and at 50% of maximum VO2, the c(A-V)O2 difference should be half the value of maximal c(A-V)O2 difference. This is not necessarily inconsistent with our results. When heart failure is severe, the end of the warm-up exercise is close to the AT point, which is also close to the peak exercise with maxVO2.

Stringer et al showed the individual values of c(A-V)O2 difference as a function of %VO2max. We presented the individual values of the c(A-V)O2 difference depending on the stage of exercise, such as rest, the end of warm-up and the AT point. The interval from rest to the end of the warm-up or the interval from the end of the warm-up to the AT point varies among subjects because they change depending on the severity of the heart failure. Therefore, when heart failure is severe, peak exercise occurs soon after the end of the warm-up and at the AT point. Furthermore, VO2 during warm-up is almost the same in severe and mild heart failure, but the maxVO2 is generally lower in severe heart failure than in mild. This discrepancy leads to a higher %VO2max at the end of the warm-up exercise in severe heart failure.

From these results, we conclude that in severe heart failure the oxygen utilization by skeletal muscle is improved during mild exercise by increasing the c(A-V)O2 difference. During intense exercise at the AT point, this compensatory mechanism seems to be limited, which, together with low CO2, results in attenuated VO2 and reduced exercise tolerance.

References