Relationship Between Impaired Chronotropic Response, Cardiac Output During Exercise, and Exercise Tolerance in Patients with Chronic Heart Failure

Hisanori Samejima,1 MD, Kazuto Omiya,1 MD, Masato Uno,1 MD, Kohji Inoue,1 MD, Masachika Tamura,1 MD, Kae Itoh,1 MD, Kengo Suzuki,1 MD, Yoshihiro Akashi,1 MD, Atsushi Seki,1 MD, Noriyuki Suzuki,1 MD, Naohiko Osada,1 MD, Kazuhiko Tanabe,1 MD, Fumihiko Miyake,1 MD, and Haruki Itoh,2 MD

SUMMARY

The present study was undertaken to investigate the relationship between the extent of impaired chronotropic response and cardiac output during exercise, and exercise tolerance in patients with chronic heart failure. The subjects consisted of 24 patients (mean 60.1 ± 14.0 years) who had mild chronotropic incompetence. Cardiopulmonary exercise testing was performed in all patients, and heart rate (HR), anaerobic threshold (AT), maximum oxygen uptake (peak VO2), slope of the regression line relating the ventilatory equivalent to carbon dioxide output (VE/VCO2 slope), and exercise time were measured. Cardiac output (CO) was measured by a thoracic bioimpedance method and cardiac index (CI) was calculated. Plasma norepinephrine (NE) was measured at rest and immediately after the exercise test. The changes in HR, NE, and CI from the resting state to immediately after exercise were calculated as ∆HR, ∆NE, and ∆CI, respectively. The ∆NE was converted to a logarithmic scale and ∆HR/ln(∆NE) was used as a parameter of HR response to sympathetic nerve stimulation. The results were as follows: HR and NE in the resting state had no correlation with AT and with peak VO2. ∆HR/ln(∆NE) correlated positively with both AT and peak VO2, and negatively with the VE/VCO2 slope. ∆HR/ln(∆NE) correlated positively with peak CI, %∆CI, and ∆CI/exercise time. The data suggest that one of the mechanisms of low exercise tolerance in chronic heart failure patients was due to an inadequate increase in CO response against exercise caused by an impaired HR response to increased NE. (Jpn Heart J 2003; 44: 515-525)

Key words: Chronic heart failure, Impaired chronotropic response, Norepinephrine, Exercise tolerance, Cardiac output
In the 1970s, chronotropic incompetence, defined as an inadequate increase in heart rate (HR) from rest to a given level of exercise, was found to correlate with the extent of the presence of coronary artery disease. An increased incidence of sudden cardiac death was reported in middle-aged men who showed an impaired HR response in daily activities and during standard exercise stress testing.

Since the 1980s, a correlation between left ventricular dysfunction and chronotropic incompetence has been reported. It has been reported that chronotropic incompetence is complicated by severe left ventricular dysfunction and improved after completing a cardiac rehabilitation program. Although β-receptor downregulation or β-adrenergic receptor desensitization in the myocardium with high circulating catecholamines is recognized as a cause of chronotropic incompetence in chronic heart failure patients, the precise mechanisms of its effect on cardiac output, and on exercise tolerance remain unknown. The aim of the present study was to clarify the effects of impaired chronotropic response on exercise tolerance and on cardiac output dynamics during exercise by assessing HR response to sympathetic nervous activity in patients with chronic heart failure.

**METHODS**

**Subjects:** The subjects consisted of 24 patients with chronic heart failure or asymptomatic left ventricular dysfunction. There were 23 men and 1 woman ranging in age from 28 to 73 years (mean age, 60.1 ± 14.0 years). Inclusion criteria were a stable condition for at least 3 months in an outpatient department, normal sinus rhythm without evidence of significant atrio-ventricular conduction delay or ventricular arrhythmia at rest or during exercise, a left ventricular ejection fraction < 45%, and a maximum HR obtained during exercise test < 90% of age predicted maximum HR. The clinical characteristics of the patients are shown in Table I. Patients with New York Heart Association (NYHA) functional class IV, angina pectoris, uncontrolled arrhythmia, uncontrolled diabetes mellitus, or who were undergoing β-blockade therapy were not included.

The study protocol was approved by the Committee on Human Investigation of our University, and written informed consent was obtained from each patient before participation in the study.

**Study Protocol:** Cardiopulmonary exercise test: Subjects underwent a cardiopulmonary exercise test on a treadmill (MAT-2500, Fukuda Denshi Co., Tokyo) with a one minute incremental protocol which was designed to obtain an approximate 3.5 mL/min/kg VO₂ increase every minute. After a 3 minute rest on the treadmill, exercise was started with a 3 minute warm-up period (speed: 1.0 mile/h, grade: 0%) and the load was increased every minute thereafter. Twelve-lead
electrocardiographs were monitored with a stress system (ML-5000, Fukuda Denshi Co.), and blood pressure was measured at 1-min intervals with an automatic indirect manometer (STBP-780, Colin Co., Aichi, Japan). The end-point of exercise testing was that of the American College of Sports Medicine.\textsuperscript{12} Expired gas was analyzed on a breath-by-breath basis with a respiro-monitor (AE-280, Minato Co., Osaka, Japan), and anaerobic threshold (AT), peak oxygen uptake (peak VO\textsubscript{2}), slope of the regression line relating the ventilatory equivalent (VE) to carbon dioxide output (VCO\textsubscript{2}) (VE/VCO\textsubscript{2} slope), exercise time from the start to end of the incremental exercise, and heart rate (HR) were measured. AT was determined according to conventional criteria.\textsuperscript{13}

**Measurement of cardiac output:** Cardiac output (CO) during exercise was measured by a thoracic bioimpedance method using an NCCOM3-R7 cardiac output monitor (Biomed Medical Instruments Co., Irvine, CA, USA). The measurement of CO with the thoracic bioimpedance method has been described elsewhere.\textsuperscript{14,15} Briefly, thoracic bioimpedance was used to measure the pulsatile change in resistance to injected microcurrents for the calculation of stroke volume. Cardiac index (CI) was calculated as CO/body surface area, calculated on a beat-by-beat basis and represented as the average of 16 accepted beats.

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>60.1 ± 14.0</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.7 ± 7.4</td>
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<tr>
<td>Weight (kg)</td>
<td>69.4 ± 8.1</td>
</tr>
<tr>
<td>Etiology of chronic heart failure</td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>14</td>
</tr>
<tr>
<td>DCM</td>
<td>10</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37.3 ± 13.3</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>60.2 ± 5.4</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>diuretics</td>
<td>15/24</td>
</tr>
<tr>
<td>nitrates</td>
<td>15/24</td>
</tr>
<tr>
<td>calcium channel blockers</td>
<td>8/24</td>
</tr>
<tr>
<td>ACEIs</td>
<td>14/24</td>
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</tbody>
</table>

DCM = dilated cardiomyopathy; NYHA; New York Heart Association; LVEF = left ventricular ejection fraction; LVDD = left ventricular diastolic dimension, ACEIs = angiotensin converting enzyme inhibitors.
NE was measured as an index of sympathetic nervous activity. Samples were obtained before and immediately after the exercise from an 18G catheter inserted into the antecubital vein. The samples were ice-cooled immediately and centrifuged at 3000 G and 4°C for 10 minutes, thereby separating the plasma, which was stored at −70°C until the day of analysis. NE was extracted by alumina absorption and then measured by high-performance liquid chromatography.

**HR and CO responses to sympathetic nervous stimulation:** The changes in HR, NE, and CI from the resting state to immediately after exercise are presented as ΔHR, ΔNE, and ΔCI, respectively. The plasma NE concentration ratio was converted to a logarithmic scale since NE increases exponentially against the increase in VO2.16) ΔHR/logΔNE was used as the HR response to sympathetic nervous stimulation.7,11) Peak CI, %ΔCI, and ΔCI/exercise time were calculated as the CO response during exercise. %ΔCI was calculated as follows; (peak CI-rest CI)×100/rest CI.

**Statistical analysis:** All data are expressed as the mean ± SD. The paired t-test was used for within-group comparisons. Patient characteristics were analyzed by an unpaired t-test or χ² test as needed. Regression analysis (least-squares linear estimation) was used for correlation analysis between ΔHR/logΔNE and AT, peak VO2, VE/VCO₂ slope, and CO responses. A P value of < 0.05 was considered significant.

**RESULTS**

**Exercise testing and exercise-induced changes in plasma NE and CI (Table II):**

Exercise testing was terminated upon symptoms of fatigue or dyspnea in all subjects, and no patient experienced angina or syncope. None of the patients showed ischemic ST-T changes or severe arrhythmia. The gas exchange ratio (carbon

<table>
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<tr>
<th>Table II. Exercise Test Parameters</th>
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<tbody>
<tr>
<td>AT (mL/min/kg)</td>
</tr>
<tr>
<td>Peak VO₂ (mL/min/kg)</td>
</tr>
<tr>
<td>Exercise time (sec)</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
</tr>
<tr>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>BP (mmHg)</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
</tr>
<tr>
<td>NE (pg/mL)</td>
</tr>
</tbody>
</table>

AT = anaerobic threshold; VO₂ = oxygen uptake; VE = minute ventilation; VCO₂ = carbon dioxide output; HR = heart rate; BP = blood pressure; CI = cardiac index; NE = norepinephrine.
dioxide output (\(\dot{V}O_2\)) in all patients reached 1.15 or more, an exercise level sufficient to evaluate maximum HR. The results from exercise testing are shown in Table II.

AT in one patient was not detectable and CIs in 2 patients were not measurable because of technical problems.

**Relationship of HR and plasma NE concentration to exercise tolerance:** HR at rest had no correlation with either AT (r = -0.13, NS) or peak VO\(_2\) (r = -0.24, NS). No correlation was obtained between resting plasma NE concentration and AT (r = -0.24, NS) and peak VO\(_2\) (r = -0.25, NS).

**Correlations between \(\Delta HR/\log \Delta NE\) and exercise tolerance (Figures 1 and 2):** Correlations between \(\Delta HR/\log \Delta NE\) and AT, and between the former and peak VO\(_2\) are shown in Figure 1. The correlation between \(\Delta HR/\log \Delta NE\) and the VE/\(\dot{V}CO_2\) slope is shown in Figure 2. \(\Delta HR/\log \Delta NE\) correlated positively with both AT (r = 0.52, \(P < 0.01\)) and peak VO\(_2\) (r = 0.56, \(P < 0.01\)), and inversely correlated with VE/\(\dot{V}CO_2\) slope (r = -0.51, \(P < 0.01\)).

**Correlations between \(\Delta HR/\log \Delta NE\) and CO responses (Figures 3 and 4):** \(\Delta HR/\log \Delta NE\) correlated positively with both peak CI (r = 0.63, \(P < 0.01\)) and %\(\Delta CI\) (r = 0.58, \(P < 0.01\)). \(\Delta HR/\log \Delta NE\) also correlated positively with \(\Delta CI/\text{exercise time}\) (r = 0.50, \(P < 0.05\)).

![Figure 1](image-url)  
*Figure 1.* Correlations between \(\Delta HR/\log \Delta NE\) and AT (left) and peak VO\(_2\) (right). Abbreviations as in Table II.
Figure 2. Correlation between $\Delta HR/\log \Delta NE$ and $\dot{V}E/\dot{V}CO_2$ slope. Abbreviations as in Table II.

Figure 3. Correlations between $\Delta HR/\log \Delta NE$ and peak CI and $%\Delta CI$. CI = cardiac index; Other abbreviations as in Table II.
DISCUSSION

Impaired heart rate response in chronic heart failure patients: Although impaired HR responses against exercise in chronic heart failure patients have been reported by several investigators, the definition of chronotropic incompetence remains controversial. Strictly speaking, the phenomenon reported by Sullivan, et al should not be categorized as chronotropic incompetence, because HR at rest was significantly higher in the control state than that after training, whereas the peak HR was equal. HRs at resting state and peak exercise in our study population are comparable and reasonable because they are almost equal or less than those of previous reports.

\[ \Delta HR/\log \Delta NE \]

\[ n = 22 \]
\[ r = 0.50 \]
\[ p < 0.05 \]

The \( \Delta HR/\log \Delta NE \) used in this study correlated with AT, peak \( \dot{V}O_2 \), and the \( \dot{V}E/\dot{V}CO_2 \) slope, and is promising as a marker of impaired chronotropic response in patients with low functional capacity. \( \Delta HR/\log \Delta NE \) has been used as an indirect index of sinoatrial nodal sympathetic responsiveness and it decreased progressively from mild chronic heart failure patients whose exercise tolerance was good (peak \( \dot{V}O_2 \) 27 ± 3 mL/min/kg) or moderate (18 ± 1, 12 ± 1) to severe chronic heart failure (9 ± 1). \( \Delta HR/\log \Delta NE \) might decrease in patients with a low left ventricular ejection fraction (LVEF), but it has no correlation with LVEF itself. It was also reported that there is no significant difference in LVEF between patients

Figure 4. Correlation between \( \Delta HR/\log \Delta NE \) and \( \Delta CI/exercise \) time. Abbreviations as in Figure 3, Table II.
with and without chronotropic incompetence, although peak VO2 was significantly low in patients with chronotropic incompetence. Also in the present study, ΔHR/logΔNE had no correlation with LVEF (r = 0.24, NS), which is the same result as these previous reports. ΔHR, which is used as a convenient marker of HR reserve, would seem to be not applicable to such a small study population because it will be strongly influenced by age or gender differences.

The ΔHR/logΔNE was reported to be significantly lower in chronic heart failure patients with a high VE/VCO2 slope (more than 34) than a low VE/VCO2 slope (less than or equal to 34). In recent years, it was reported that the VE/VCO2 slope can be used as a strong predictor of severity and mortality in chronic heart failure patients as well as peak VO2. In our data, the mean VE/VCO2 slope was 34.0, similar to the value reported by Oikawa et al, and this is just at the upper limit. From this, it is clear that the conditions of the subjects in the present study were not overly severe. ΔHR/logΔNE may be used as an another predictor in chronic heart failure, for it was correlated with both peak VO2 and the VE/VCO2 slope.

The slope of the logNE-HR line was found to be significantly less steep in patients with dilated cardiomyopathy whose mean fractional shortening (FS) was 14% and a nonfailing heart with valvular disease (aortic regurgitation, FS:33%) than in normal subjects (FS:33%). Although the protocol and the posture during exercise employed were different from ours, they used graded exercise with a supine cycle ergometer for their study. ΔHR/logΔNE can be measured under both protocols and used to determine chronotropic incompetence.

Mechanism of impaired chronotropic response: Endogenous adenosine has been shown to blunt the β-adrenoreceptor-mediated inotropic response in hypoperfused canine myocardium, and that it acts as a cardioprotector in the ischemic myocardium. The myocardial ischemia-induced inotropic response did not play a role in our study, because no subject experienced an ST-T segment change or symptoms of angina during exercise testing.

Currently, β1-receptor downregulation or β-adrenergic receptor desensitization in the myocardium with high circulating levels of catecholamines is recognized as a cause of chronotropic incompetence in patients with chronic heart failure. In a previous study, a 50% to 56% reduction in β-adrenergic receptor density in the left ventricles from heart transplant recipients, a 45% reduction in maximal isoproterenol-mediated adenylate cyclase stimulation, and a 54% to 73% reduction in maximal isoproterenol-stimulated muscle contraction were observed. They concluded that a decrease in β-receptor density leads to subsensitivity of the β-adrenergic pathway and decreases β-agonist-stimulated muscle contraction.
Other investigators reported that an increase in plasma NE after exercise occurred in both normal subjects and chronic heart failure patients, reaching similar levels, and that graded isoproterenol and phosphodiesterase inhibitor administration affected the HR response. They concluded that the attenuated HR response to exercise in chronic heart failure patients was due to postsynaptic desensitization of the $\beta$-adrenergic receptor pathway. In addition, they also concluded when VO\textsubscript{2} was standardized as a percentage of peak VO\textsubscript{2}, the relation between VO\textsubscript{2} and NE was similar between normal subjects and chronic heart failure patients, but for any given percentage of peak VO\textsubscript{2}, the chronic heart failure patients tended to have a higher plasma NE level.

In the present study, $\beta_1$-receptor downregulation may have led to a decrease in the CO response against exercise which was induced by an impaired HR response to increased NE. $\Delta$HR/log$\Delta$NE may be useful for evaluation of the grade of chronotropic incompetence in chronic heart failure patients who have an impaired chronotropic response because it correlates both parameters of exercise tolerance and CO response. Impaired chronotropic response during exercise, which was described as a strong predictor of severity of heart failure, may play an important role in the development of chronotropic incompetence in chronic heart failure patients.

**Study limitations:** First, the present study population was relatively small and there was no control group. Moreover, the disease severity in our patients seemed to be mild, the NYHA classification was relatively low, and the mean plasma NE level at rest was within the normal range (from 100 to 450 pg/mL). This may have been caused by the inclusion criterion was relatively mild (< 90% of age predicted maximum HR) for impaired chronotropic responses obtained during exercise testing. Further studies with more advanced chronic heart failure patients and a control group are needed.

It should be considered that $\Delta$CI/exercise time, will be the highest when exercise test is terminated near AT which is not enough level to evaluate exercise tolerance, because the CO increase will become less steep above AT than that below AT. In the present study, the data of $\Delta$ CI/exercise was comparable since all patients completed much higher exercise level whose gas exchange ratio greater than 1.15, almost near maximum exercise level for patients with chronic heart failure.

Furthermore, CO in the present study was measured by thoracic bioimpedance, a non-invasive method that is not the “gold standard”. CO measurement by an invasive method, the direct Fick method, or thermodilution, seemed to be difficult to perform during an exercise test in an outpatient department. Although the reliability of thoracic bioimpedance has been reported in two of our previous
studies, CO measurement using an invasive method is recommended in order to arrive at more definite conclusions.

CONCLUSIONS

The data suggest that one of the mechanisms of low exercise tolerance in chronic heart failure patients was due to an inadequate increase in CO response against exercise caused by impaired HR response to increased NE.

REFERENCES


