Impaired Chronotropic Response to Exercise in Patients With Congestive Heart Failure
Role of Postsynaptic \( \beta \)-Adrenergic Desensitization
Wilson S. Colucci, MD, Jorge P. Ribeiro, MD, Michael B. Rocco, MD, Rebecca J. Quigg, MD, Mark A. Creager, MD, James D. Marsh, MD, Diane F. Gauthier, RN, and L. Howard Hartley, MD

The mechanism responsible for the attenuated heart rate (HR) response to exercise in patients with congestive heart failure (CHF) was investigated in 46 normal subjects and 59 patients with CHF stratified by peak exercise oxygen consumption (\( \text{VO}_{2} \)). The peak exercise HR and the increment in HR from rest to peak exercise were decreased in CHF patients, and both correlated strongly with peak \( \text{VO}_{2} \) \((r=0.810, p<0.0001; r=0.863, p<0.0001, \text{respectively})\). Peak exercise norepinephrine level (NE) and the increment in NE from rest to peak exercise were not attenuated in CHF patients. Resting NE was elevated in CHF patients and correlated inversely with peak \( \text{VO}_{2} \) \((r=-0.595, p<0.001)\). However, no significant correlation occurred between peak \( \text{VO}_{2} \) and either peak exercise NE or the exercise increment in NE. The ratio of the exercise increments in HR and NE, an indirect index of sinoatrial node sympathetic responsiveness, was markedly reduced in CHF patients and was inversely related to the severity of exercise impairment. Likewise, the HR response to a graded isoproterenol infusion was markedly reduced in CHF patients. Age-matching of normal subjects and CHF patients did not affect the foregoing observations. Infusion of CHF patients with the phosphodiesterase inhibitor milrinone caused a significant increase in the ratio of the exercise increments in HR and NE. These data strongly suggest that the attenuated HR response to exercise in CHF patients is due, at least in part, to postsynaptic desensitization of the \( \beta \)-adrenergic receptor pathway. (Circulation 1989;80:314–323)

Peak heart rate response to exercise is determined primarily by the magnitude of increase in sympathetic drive to the heart and the ability of \( \beta \)-adrenergic receptors in the sinoatrial node to respond to catecholamines. In patients with congestive heart failure (CHF), the chronotropic response to peak exercise is reduced and may contribute significantly to the impaired cardiac output response to exercise.1–4

The mechanism responsible for a reduced chronotropic response to exercise in patients with CHF is not known. Although it is known that both the reflex stimulation of sympathetic nervous system activity5–8 and the postsynaptic responsiveness of the myocardium to \( \beta \)-adrenergic stimulation9–11 are reduced in patients with CHF, it is not known whether either (or both) of these abnormalities contributes to the attenuated chronotropic response to exercise in these patients. Indeed, previous studies have come to opposite conclusions regarding the sympathetic response to exercise in patients with CHF.4,12 Likewise, although it is well known that myocardium from patients with CHF is subsensitive to the contractile effect of \( \beta \)-adrenergic stimulation,9–11 the possibility that sinoatrial tissue is subsensitive to \( \beta \)-adrenergic stimulation has received little attention.

The purpose of this study was to evaluate the role of a reduced sympathetic outflow response compared with reduced end-organ responsiveness of the sinoatrial node to \( \beta \)-adrenergic stimulation as a cause for the attenuated chronotropic response to exercise in patients with CHF. Fifty-nine patients with New York Heart Association functional Class I–IV CHF were stratified by exercise capacity and were compared to 46 normal subjects without known
cardiac disease. The systemic sympathetic response to exercise was assessed by measuring plasma norepinephrine at rest and at 3-minute intervals during progressive workload, symptom-limited exercise. β-Adrenergic end-organ responsiveness of the sinoatrial node was evaluated by 1) quantitating the relation between plasma norepinephrine and heart rate during exercise and 2) by determining the heart rate response to a graded infusion of the β-adrenergic agonist isoproterenol.13

Methods

Study Population

The study population consisted of 46 subjects without a history of cardiac disease and 59 patients with symptomatic New York Heart Association functional Class I–IV CHF. Exercise testing was performed in 37 normal subjects and 51 CHF patients (Table 1). Isoproterenol infusion tests were performed in an additional nine normal subjects and eight CHF patients (Table 2).

Normal subjects had no history of cardiac disease, hypertension, myocardial ischemia, myocardial infarction, or valvular heart disease and were not receiving cardiac medications or medications that interact with the autonomic nervous system. Peak oxygen uptake in this group averaged 29±1 ml/min/kg. In all cases, exercise was limited by symptoms of fatigue or dyspnea, and no patient experienced angina, syncope, or claudication during exercise.

The CHF patients were all receiving conventional therapy with digitalis, diuretics, and vasodilators before entry into the protocol. In all cases, digitalis and diuretics were withheld on the morning of the day of exercise testing, and vasodilators were withheld.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal subjects</th>
<th>CHF patients (Exercise class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>37</td>
<td>A</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46±2</td>
<td>7</td>
</tr>
<tr>
<td>Sex (M/F)</td>
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<td>0</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
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<tr>
<td>III</td>
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<td>3</td>
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<td>0</td>
</tr>
<tr>
<td>Etiology of CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>ICM</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>—</td>
<td>20±5</td>
</tr>
<tr>
<td>RV</td>
<td>—</td>
<td>36±11</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>—</td>
<td>2.4±0.4</td>
</tr>
<tr>
<td>Left ventricular filling pressure (mm Hg)</td>
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<td>27±4</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/ml, rest, sitting)</td>
<td>291±18</td>
<td>386±72</td>
</tr>
<tr>
<td>VO₂ peak (ml/min/kg)</td>
<td>29±1</td>
<td>27±3</td>
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CHF, congestive heart failure; NYHA, New York Heart Association functional Class; IHD, ischemic heart disease; ICM, idiopathic cardiomyopathy; LV, left ventricular; RV, right ventricular.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal subjects</th>
<th>CHF patients</th>
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<tr>
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<td>8</td>
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<td>48±4</td>
</tr>
<tr>
<td>Sex (M/F)</td>
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<td>NYHA</td>
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<td>Cardiac index (l/min/m²)</td>
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<td>Left ventricular filling pressure (mm Hg)</td>
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<tr>
<td>Plasma norepinephrine (pg/ml, rest, sitting)</td>
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<td>514±118</td>
</tr>
<tr>
<td>VO₂ peak (ml/min/kg)</td>
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<td>15±2</td>
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</table>

CHF, congestive heart failure; NYHA, New York Heart Association functional Class; IHD, ischemic heart disease; ICM, idiopathic cardiomyopathy; LV, left ventricular.
held for at least 2 days before the exercise test. CHF was due to previous myocardial infarction (28 patients) or idiopathic cardiomyopathy (31 patients). All CHF patients were in normal sinus rhythm and without evidence of significant atrioventricular conduction delay at rest or with exercise. In no patient was there evidence of active myocardial ischemia, claudication, significant pulmonary disease, or musculoskeletal abnormalities that may limit exercise. Based on clinical assessment, CHF patients were classified as New York Heart Association functional Class I (one), II (seven), III (37), or IV (14 patients). The left ventricular ejection fraction measured by radionuclide ventriculography was less than 40% in all CHF patients.

CHF patients were stratified by peak exercise oxygen uptake according to the criteria defined by Weber et al as follows: class A, greater than 20 ml/min/kg (seven); class B, 16–20 ml/min/kg (eight); class C, 10–15 ml/min/kg (28); and class D, less than 10 ml/min/kg (eight patients).

Exercise Protocol

A short No. 18 polyethylene cannula was inserted into an antecubital vein at least 30 minutes before the start of the study and was kept patent by slow infusion of 5% dextrose in water. Before exercise, patients rested on the cycle ergometer in the sitting position for at least 10 minutes, after which venous samples were taken without the use of a tourniquet for the determination of plasma norepinephrine concentration by radioenzymatic assay and blood lactate by an enzymatic method. Blood samples were drawn immediately before the beginning of exercise, every 3 minutes during exercise, and at the end of the peak exercise level achieved.

Patients exercised according to the following protocol as described previously. Patients sat on an electronically calibrated cycle ergometer (Sensormedics, Anaheim, California) and pedalled at a rate of 60 rpm. Starting with a workload of 20 W (CHF patients) or 30 W (normal subjects), exercise intensity was increased at 3-minute intervals by 15-W increments for CHF patients or 30-W increments for normal subjects. All normal subjects and CHF patients stopped exercise because of profound fatigue, severe dyspnea, or both symptoms until they were unable to maintain a pedalling rate of 60 rpm. All normal subjects and CHF patients exercised beyond their anaerobic threshold as reflected by a respiratory quotient of 1.11±0.02 (n=79) at peak exercise, and an increase in blood lactate from 1.0±0.06 at rest to 5.6±0.3 mM (n=65) at peak exercise.

Heart rate and the 12-lead electrocardiogram were monitored continuously during exercise. Before the start of exercise and at the end of each exercise stage, systolic blood pressure was determined with an arm cuff. Before and during exercise testing, patients breathed through a three-way valve into a metabolic cart (Sensormedics Horizon System) that continuously measured ventilatory function, oxygen uptake, and carbon dioxide output. Hard copy printout was obtained at 15-second intervals. Immediately before exercise, the metabolic cart was calibrated with gas mixtures of known concentrations and volumes.

Milrinone Infusion

In a subgroup of 12 patients, either milrinone (Winthrop-Breon, Rensselaer, New York) or a similar-appearing placebo solution was administered 5 minutes before the start of exercise by a slow intravenous bolus during 45 seconds. The cardiovascular, metabolic, and ventilatory responses to exercise with placebo or milrinone in this subgroup were described previously in detail. Of the 14 patients initially reported, two were excluded from the present analysis because of paced heart rate (one patient) or a subtherapeutic milrinone level (one patient). The characteristics of this subgroup were very similar to the overall population of patients with class C or D exercise impairment (age, 57±3 years; men/women, 11/1; NYHA III, 10 patients; NYHA IV, two patients; etiology: ischemic heart disease, 10 patients; etiology: idiopathic cardiomyopathy, two patients; left ventricular ejection fraction, 0.20±0.03; resting plasma norepinephrine, 725±118 pg/ml; peak oxygen consumption, 11±1 ml/kg/min; cardiac index, 1.8±0.2 l/min/m²; left ventricular end-diastolic pressure, 29±2 mm Hg). The order of administration of placebo or milrinone was assigned randomly by the drawing of cards, and the two exercise tests were performed on subsequent days at the same time of day. The patient and physician conducting the exercise test were not aware of the true identity of medication. The dose of milrinone infused ranged from 25 to 75 μg/kg and was based on the dose that had produced an optimal hemodynamic response during a prior intravenous bolus administration of the drug.

Isoproterenol Infusion

Isoproterenol infusions were performed essentially as described by Yusuf et al. Subjects rested supine for at least 30 minutes before the start of the study. Heart rate was determined at least twice during the control period (separated by 3 minutes) and until subsequent determinations differed by less than 2 beats/min. The mean of the last two preinfusion values was taken as the control value. Heart rate was recorded continuously at 25 mm/sec on a strip chart recorder, and each determination was the average for a 1-minute recording period. Freshly prepared isoproterenol in 5% dextrose in water was infused by a constant infusion pump. The infusion was increased at 5-minute intervals according to the following schedule: 5, 10, 15, 20, and 25 ng/kg/min. Heart rate was determined during the last full minute at each infusion rate. The dose of isoproterenol that caused a 25-beats/min increase in heart...
rate over baseline (ISO$_2$) was determined by least squares linear regression.\textsuperscript{13}

**Statistical Analysis**

All data are presented as the mean±SEM. Significant differences among multiple observations for each variable were detected by two-tailed non-paired or paired \( t \) tests with Bonferroni’s method for multiple simultaneous comparisons such that statistical significance was assumed if the null hypothesis could be rejected at 0.05/\( n \) probability level where \( n \) is the number of comparisons.\textsuperscript{17}

Normal subjects and CHF patients were matched for age by arranging both groups in order of ascending ages. Beginning with the youngest normal subject, each was matched within 2 years of age to a CHF patient. In this way, it was possible to match 27 normal subjects and 27 CHF patients. For the matching process, CHF patients were identified only by a subject number and age and were therefore drawn randomly from the four CHF groups.

**Results**

**Relation Between Oxygen Consumption and Heart Rate During Exercise**

Heart rate increased linearly in relation to absolute VO$_2$ in normal subjects and CHF patients (Figure 1A). Heart rate was higher at rest and at any given VO$_2$ in CHF patients. However, peak heart rate was decreased in CHF patients compared with normal subjects: The severity of this impairment was least in class A patients and was progressively more severe in class B, C, and D patients, respectively (Figure 2). The increment in heart rate from rest to peak exercise likewise decreased progressively in class A, B, C, and D CHF patients, respectively (Figure 2).

Normalization of VO$_2$ as a percentage of peak exercise VO$_2$ showed further the progressive attenuation in the heart rate response to exercise in the CHF patients (Figure 1B). There was a mild depression of this relation in patients with class A exercise impairment, and the severity of impairment increased progressively in class B, C, and D patients, respectively.

For the whole study population, peak VO$_2$ was strongly correlated with both peak heart rate obtained during exercise (\( r=0.810, p<0.0001 \)) and the increase in heart rate from rest to peak exercise (\( r=0.863, p<0.0001 \)) (Figure 3A). These correlations were also apparent when only the CHF patients were analyzed (\( r=0.718 \) and 0.828, for peak heart rate and increment in heart rate, respectively).

The increase in systolic blood pressure with exercise and the heart rate–blood pressure double-product at peak exercise were progressively reduced in class A, B, C, and D patients, respectively (Figure 4).

**Relation Between Oxygen Consumption and Plasma Norepinephrine**

Resting plasma norepinephrine increased progressively in class A, B, C, and D patients, respectively.

**FIGURE 1. Plots of relation between heart rate and oxygen uptake during exercise in normal subjects (NL) and congestive heart failure patients with class A, B, C, or D exercise impairment according to the criteria of Weber et al.\textsuperscript{4} Panel A: Oxygen uptake is expressed in absolute terms. Panel B: Oxygen uptake is expressed as a percentage of peak oxygen uptake.**

**FIGURE 2. Bar graphs of heart rate and plasma norepinephrine at rest and peak exercise and the increments in heart rate and norepinephrine with peak exercise in normal subjects and congestive heart failure (CHF) patients with class A, B, C, or D exercise impairments. $^*p<0.0125$ vs. normal subjects.**
FIGURE 3. Plots of relation between peak exercise oxygen consumption and the increments in heart rate (Panel A) and plasma norepinephrine (Panel B) with exercise. CHF, congestive heart failure.

(Figure 2). Peak VO₂ correlated inversely with resting plasma norepinephrine in both the CHF patients ($r=-0.441$, $p<0.001$), and the whole study population ($r=-0.595$, $p<0.001$). Plasma norepinephrine increased with exercise in both normal subjects and CHF patients, achieving similar peak values (Figures 2 and 5A). At any given VO₂, norepinephrine was higher in CHF patients (Figure 5A). However, the increment in norepinephrine from rest to peak exercise was of similar magnitude in normal subjects and in all of the CHF groups (Figure 2). When VO₂ was normalized as a percentage of peak VO₂, the relation between VO₂ and norepinephrine was similar in normal subjects and all of the CHF groups, although for any given percentage of peak VO₂, the CHF patients tended to have a higher plasma norepinephrine (Figure 5B).

No significant correlation was found between peak VO₂ and peak norepinephrine obtained during exercise in the CHF patients ($r=0.073$) or the whole study population ($r=0.154$). Likewise, no significant correlation was found between peak VO₂ and the exercise increment in norepinephrine in CHF patients ($r=0.270$) or the whole group ($r=0.265$) (Figure 3B).

Relation Between Heart Rate and Norepinephrine During Exercise

Compared with normal subjects, the heart rate was lower in CHF patients for any given level of

FIGURE 4. Bar graphs of the increment in systolic blood pressure with exercise (Panel A) and the peak exercise double-product (Panel B) in normal subjects and congestive heart failure (CHF) patients. *$p<0.0125$ vs. normal subjects.

FIGURE 5. Plots of the relation between plasma norepinephrine and oxygen uptake during exercise in normal subjects (NL) and class A, B, C, or D congestive heart failure patients. Panel A: Oxygen uptake is expressed in absolute units. Panel B: Oxygen uptake is expressed as percentage of peak oxygen uptake.
plasma norepinephrine during exercise (Figure 6A). The reduction in heart rate relative to plasma norepinephrine was least in class A patients and was most profound in class D patients. The same stratification was found when the relative increases in heart rate and norepinephrine were compared at three different exercise levels (Figure 6B). Thus, for an increase in norepinephrine of 1,000 pg/ml over baseline, heart rate increased by approximately 85 beats/min in normal subjects and by 63, 46, 30, and 21 beats/min in class A, B, C, and D patients, respectively (Figure 6B).

The ratio of the increment in heart rate divided by the increment in norepinephrine from rest to peak exercise was used as an index of chronotropic sympathetic responsiveness. This ratio 1) decreased progressively in class A through D patients (Figure 7), 2) correlated with VO₂ peak \( r = 0.356, p = 0.010 \), and 3) was inversely related to the resting level of plasma norepinephrine \( r = -0.348, p = 0.041 \) in CHF patients.

**Effect of Age on Heart Rate and Norepinephrine Responses to Exercise**

To control for the possible effect of age on the heart rate and norepinephrine responses to exercise,\(^*\) 27 normal subjects and 27 CHF patients were matched for age within 2 years (Table 3). Peak VO₂ in the age-matched normal subjects and CHF patients were 28±1 and 15±1 ml/min/kg, respectively.

In the CHF patients, resting heart rate was higher, and both peak exercise heart rate and the increment in heart rate with exercise were lower than in age-matched normal subjects (Table 3). As in the whole study population, resting norepinephrine was higher in CHF patients, and peak exercise norepinephrine and the increment in norepinephrine with

**Table 3. Comparison of the Changes in Heart Rate and Plasma Norepinephrine From Rest to Peak Exercise in Age-Matched Normal Subjects and Patients With Congestive Heart Failure**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal subjects</th>
<th>CHF patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>49±1</td>
<td>49±2</td>
<td></td>
</tr>
<tr>
<td>VO₂ peak (ml/min/kg)</td>
<td>28±1</td>
<td>15±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>72±3</td>
<td>90±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak</td>
<td>168±3</td>
<td>136±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change</td>
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<td>+46±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Norepinephrine level (pg/ml)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>316±19</td>
<td>569±46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak</td>
<td>2,069±182</td>
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<td>Change</td>
<td>+1,753±179</td>
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<td>&lt;0.796</td>
</tr>
<tr>
<td>Change heart rate/ Change norepinephrine</td>
<td>0.076±0.011</td>
<td>0.038±0.005</td>
<td>&lt;0.0005</td>
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</table>

CHF, congestive heart failure.
exercise were identical in normal subjects and CHF patients. Likewise, the ratio of the increments in heart rate and norepinephrine from rest to peak exercise was markedly decreased in the CHF patients.

Effect of Phosphodiesterase Inhibition on the Heart Rate and Norepinephrine Responses to Exercise

Twelve CHF patients received intravenous milrinone or placebo in a random order on subsequent days as part of a double-blind, cross-over study of the effects of milrinone on exercise capacity. Milrinone administration had no effect on resting heart rate, resting plasma norepinephrine, or peak exercise norepinephrine (Table 4). However, despite similar plasma norepinephrine concentrations at peak exercise, the peak exercise heart rate was significantly higher during milrinone administration. Likewise, there was a significant increase in the ratio of the increments in heart rate and plasma norepinephrine during milrinone administration. Milrinone administration resulted in a significant increase in peak \( VO_2 \). The respiratory exchange ratio and blood lactate at peak exercise were similar during placebo and milrinone administration, indicating comparable exercise efforts.

Heart Rate Response to Isoproterenol Infusion

Baseline heart rate was higher in the CHF patients (normal subjects, 62±5 beats/min; CHF patients, 87±5 beats/min; \( p < 0.01 \)). In normal subjects, isoproterenol infusion at rates from 5 to 25 ng/kg/min caused a linear progressive increase in heart rate (Figure 8). The infusion rate of isoproterenol that caused a 25 beats/min increase in heart rate (ISO25) for normal subjects was 17±3 ng/kg/min. In CHF patients, the heart rate response to isoproterenol was markedly attenuated such that the heart rate increase at each infusion rate was significantly less than in normal subjects. Likewise, the ISO25 in CHF patients (45±9 ng/kg/min) was more than twice that in normal subjects (\( p < 0.02 \) vs. normal subjects). To allow for the potential effect of age on the heart rate response to isoproterenol, \( ^{15} \) ISO25 doses were compared in four normal subjects and four CHF patients who could be age matched. The ISO25 in these subgroups (23±5 and 40±8 ng/kg/min, respectively) were similar to those in the respective whole groups and were significantly different from each other (\( p < 0.05 \)). Baseline systolic blood pressures, diastolic blood pressures, and pulse pressures were similar in normal subjects and CHF patients (Table 5). At the highest isoproterenol infusion rate (25 ng/kg/min), systolic and pulse pressures increased significantly, and diastolic pressure decreased significantly in both normal subjects and CHF patients. The increases in systolic and pulse pressures were attenuated in the CHF patients.
Discussion

The major goal of this study was to elucidate the basis for the attenuated heart rate response to peak exercise in patients with CHF. Prior work in patients with CHF has shown that there is attenuation of both the stimulation of systemic sympathetic outflow by reflex mechanisms \(^5\)-\(^8\) and the end-organ responsiveness of the myocardium to the contractile effects of \(\beta\)-adrenergic stimulation.\(^9\)-\(^11\) These experiments were designed to assess the possible roles of attenuated sympathetic outflow or end-organ responsiveness in limiting the peak exercise heart rate response of patients with CHF.

Although there is ample evidence that resting sympathetic nervous system activity is increased in patients with CHF,\(^4\),\(^6\)-\(^7\),\(^12\),\(^19\) there is relatively little information available regarding the systemic sympathetic response to exercise in patients with CHF. Chidsey et al\(^12\) found that for comparable multiples of basal oxygen consumption, plasma norepinephrine was higher in patients with CHF than in normal subjects, and they concluded that compared with normal subjects, patients with CHF have an augmented sympathetic outflow response to exercise. The interpretation of that study was limited, however, because nine of the 10 patients had aortic or mitral valve disease as the basis for CHF, and no effort was made to achieve a peak exercise effort.\(^12\)

More recently, Francis et al\(^4\),\(^20\) compared the plasma norepinephrine response with exercise in patients with CHF and normal subjects by normalizing oxygen consumption as a percentage of peak oxygen consumption. Using this approach, it was found that the slope of the rise in norepinephrine with exercise was reduced in patients with CHF, and it was suggested that the sympathetic outflow response to exercise in CHF was attenuated.\(^4\)

In contrast to the findings of Francis et al\(^4\),\(^20\) we found that at peak exercise and at comparable percentages of peak oxygen consumption, plasma norepinephrine was similar to or greater in patients with CHF compared with age-matched normal subjects (e.g., Figure 5 and Table 3). The major difference between our study and that of Francis et al\(^4\) appears to be in the peak plasma norepinephrine values achieved in CHF patients. Thus, the plasma norepinephrine value achieved by our normal subjects (average, 2,008 pg/ml) is similar to values observed by Francis et al\(^4\) and in several prior studies.\(^21\),\(^22\) However, the peak plasma norepinephrine in our patients with CHF (1,927–2,181 pg/ml in the four groups), although similar to that in our normal subjects, is substantially higher than the values of approximately 1,700 and 1,400 pg/ml observed by Francis et al\(^4\) in patients with mild and moderate CHF, respectively. The higher peak plasma norepinephrine achieved in our CHF patients may relate to the more gradual exercise protocol used in our study, the lack of age matching in the study of Francis et al\(^4\), or a more consistent achievement of a maximal exercise effort in our patients. Regardless of the reason for the higher peak plasma norepinephrine in our CHF patients, these data strongly argue that a generalized attenuation of the sympathetic nervous system outflow response to exercise does not account for attenuation of the peak heart rate response to exercise in patients with CHF.

An alternate possibility for the attenuated chronotropic response to exercise is end-organ desensitization of the \(\beta\)-adrenergic pathway in the sinoatrial node. During exercise, the heart rate at any given norepinephrine level was found to be less in CHF patients, and more important, the increase in heart rate for any given increase in norepinephrine was markedly reduced (e.g., Figures 6A and 6B). Because increases in heart rate above the intrinsic heart rate are mediated primarily by the action of the sympathetic nervous system on \(\beta\)-adrenergic receptors,\(^23\) these data suggest that the sinoatrial node may be less sensitive to \(\beta\)-adrenergic stimulation in CHF patients. Although desensitization of ventricular myocardium of CHF patients to the contractile and adenylate cyclase stimulating actions of \(\beta\)-adrenergic agonists has been shown,\(^9\)-\(^11\) desensitization of the sinoatrial node has received very little attention.

To examine more directly the role of end-organ \(\beta\)-adrenergic desensitization, the chronotropic response to a graded infusion of isoproterenol was studied. The dose-response relation for the chronotropic effect of isoproterenol was shifted markedly to the right in patients with CHF (Figure 8). Thus, for any given infusion rate of isoproterenol, the heart rate increase of the CHF patients was only approximately half of that in normal subjects, and the concentration of isoproterenol that caused a 25-beats/min increase in heart rate (\(\text{ISO}_{25}\)) was more than twice that required for normal subjects. These data therefore are consistent with the observations on heart rate relative to norepinephrine during exercise and more directly support the conclusion that postsynaptic desensitization of the \(\beta\)-adrenergic pathway contributes to the attenuated chronotropic responsiveness in CHF patients. This finding also agrees with a recent report of Erne et al\(^24\) that showed that the chronotropic response to isoproterenol was depressed in patients with CHF, whereas the response to forskolin, a direct activator of the catalytic subunit of adenylate cyclase, was preserved.

Certain limitations of this study warrant comment. First, the use of plasma norepinephrine as an index of sympathetic outflow may be misleading because plasma norepinephrine is regulated by multiple factors.\(^25\) Furthermore, changes in systemic sympathetic activity possibly do not reflect local changes in sympathetic activity at the heart.\(^26\) Consequently, we cannot exclude the possibility that although plasma norepinephrine increased normally with exercise in CHF patients, sympathetic activity at the sinoatrial node may have been reduced.
A second consideration in the interpretation of these data is the possibility that the heart rate response to isoproterenol was modified by reflex-mediated changes in autonomic tone. In normal subjects, the continuous infusion of isoproterenol, as done in this study, causes an increase in vagal tone that opposes the chronotropic action of \( \beta \)-adrenergic stimulation.27 However, in our patients with CHF, this reflex is attenuated for at least two reasons. First, baroreceptor sensitivity is reduced in patients with CHF.5-8 Second, the hemodynamic stimulus for this reflex (e.g., the increases in pulse pressure and systolic blood pressure with isoproterenol, see Table 5) was reduced in the patients with CHF. Consequently, the degree of \( \beta \)-adrenergic desensitization of the sinoatrial node in patients with CHF (vs. normal subjects) is probably underestimated by our methods.

A third consideration in the interpretation of these data is the effect of age on \( \beta \)-adrenergic responses.18 Because the mean age of the normal subjects was lower than that of the CHF patients in this study, it was important to exclude the possible influence of age on both the sympathetic nervous system and the \( \beta \)-adrenergic end-organ responses to exercise. Indeed, we found a significant inverse relation between age and the ratio of heart rate to norepinephrine during exercise (\( r = -0.353, p = 0.011 \)). However, age-matched CHF patients continued to have a markedly reduced heart rate response to exercise despite a comparable increment in norepinephrine (Table 3). Matching for age also had no effect on the marked impairment of the chronotropic response to isoproterenol infusion. These data therefore indicate that chronotropic incompetence of patients with CHF in this study cannot be attributed to age alone and that the presence of CHF is a strong independent determinant of an attenuated chronotropic response to exercise and \( \beta \)-adrenergic stimulation.

Infusion of the phosphodiesterase inhibitor milrinone just before exercise had no effect on resting heart rate, resting norepinephrine, or peak exercise norepinephrine but caused a significant increase in peak heart rate that was associated with a significant increase in the heart rate/norepinephrine ratio at peak exercise. This finding is consistent with substantial in vivo data showing potentiation of \( \beta \)-adrenergic cardiovascular responses by phosphodiesterase inhibitors29 including milrinone29 and is analogous to our recent observation that the attenuated contractile response in patients with CHF is partially corrected by preinfusion of milrinone.11 Because milrinone also increases myocardial contractility and causes vasodilation,30 whether or not the increased peak heart rate, per se, contributed to the increase in exercise capacity is not clear. Nevertheless, these data indicate that the peak heart rate response in patients with CHF can be increased by pharmacologic means.

These data do not allow conclusions to be made regarding the mechanism of postsynaptic \( \beta \)-adrenergic desensitization in the sinoatrial node of patients with CHF. The significant inverse relation between resting plasma norepinephrine and the chronotropic response to exercise suggests that postsynaptic \( \beta \)-adrenergic desensitization of the sinoatrial node is associated with increased sympathetic tone. In patients with CHF, plasma norepinephrine is inversely related to the severity of CHF,6 and likewise, there is evidence that the density of myocardial \( \beta \)-adrenergic receptors is decreased in inverse proportion to the coronary sinus norepinephrine concentration.10 Thus, chronotropic incompetence is probably associated with decreased \( \beta \)-adrenergic receptor density in the sinoatrial node. Also, dysfunction of the sinoatrial node may be due to a nonspecific mechanism such as fibrosis. However, a number of observations argue against this possibility. First, sinus node recovery time, a measure of intrinsic sinoatrial node function, is normal in CHF patients.31,32 Second, increasing the maximal heart rate response to exercise was possible by the preinfusion of milrinone. Third, after cardiac transplantation, the chronotropic response to isoproterenol in the native sinoatrial node is similar to that in normal subjects,13 suggesting that chronotropic incompetence to \( \beta \)-adrenergic stimulation may be reversible.

These observations on the heart rate response to exercise and isoproterenol have potentially important implications for the therapy of CHF patients. They suggest that postsynaptic desensitization of the \( \beta \)-adrenergic pathway in sinoatrial tissue may have a significant effect on the exercise capacity of CHF patients. This desensitization may be secondary to the increased sympathetic activity that is frequent in CHF patients and that is related to impaired cardiac performance. \( \beta \)-Adrenergic receptor desensitization can be prevented or reversed by reducing the interaction of \( \beta \)-adrenergic receptors and agonists in vitro.33 Therefore, it will be of interest to determine whether interventions that directly34 or indirectly6,11 decrease the stimulation of sinoatrial node \( \beta \)-adrenergic receptors lead to resensitization of the \( \beta \)-adrenergic pathway and an improvement in the chronotropic response to exercise.

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