

# Muscle Ergoreceptor Overactivity Reflects Deterioration in Clinical Status and Cardiorespiratory Reflex Control in Chronic Heart Failure

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**Background**—In chronic heart failure (CHF), overactivation of ergoreceptors (afferents sensitive to the metabolic effects of muscular work) may be a link between peripheral changes, sympathetic overactivation, and increased hemodynamic and ventilatory responses to exercise. The relationship between ergoreceptors, autonomic changes, and the progression of the syndrome has not yet been studied.

**Methods and Results**—Thirty-eight stable CHF patients (age,  $57 \pm 1$  years; ejection fraction,  $26 \pm 2\%$ ) were compared with 12 age-matched normal control subjects. The ergoreflex contribution to the ventilatory and hemodynamic responses to exercise, together with peripheral and central chemoreceptor sensitivity, arterial baroreflex sensitivity, plasma norepinephrine, epinephrine, and heart rate variability, were measured. Enhanced ergoreflex effects on ventilation ( $78 \pm 2\%$  versus  $50 \pm 8\%$ ), peripheral chemosensitivity ( $0.6 \pm 0.4$  versus  $0.2 \pm 0.1$  L/min per percent  $\text{SaO}_2$ ), and central chemosensitivity ( $2.9 \pm 0.2$  versus  $2.0 \pm 0.2$  L  $\cdot$  min $^{-1}$   $\cdot$  mm Hg $^{-1}$ ) and an impaired baroreflex function ( $4.1 \pm 0.6$  versus  $9.1 \pm 5.6$  ms/mm Hg) were confirmed in CHF compared with control subjects ( $P < 0.01$  in all comparisons). Ergoreceptor overactivity was associated with a worse symptomatic state (NYHA class,  $P < 0.05$ ), lower exercise tolerance (peak  $\text{VO}_2$ ,  $P < 0.05$ ), and pronounced exercise hyperventilation ( $\dot{V}_E/\text{VCO}_2$ ,  $P < 0.01$ ). It was also a strong predictor of increased central chemosensitivity (independently of clinical parameters), baroreflex impairment, and sympathetic activation (plasma catecholamines and heart rate variability indexes; all  $P < 0.05$ ). In multivariate analysis, among all reflexes studied, the ventilatory component of the ergoreflex was the only independent predictor of peak  $\text{VO}_2$  and  $\dot{V}_E/\text{VCO}_2$ .

**Conclusions**—In CHF, overactivation of the ergoreflex is associated with abnormal cardiorespiratory reflex control, independently of clinical severity. Among impaired reflexes, overactivation of the ergoreflex is an important determinant of exercise hyperventilation and reduced exercise tolerance. (*Circulation*. 2001;104:2324-2330.)

**Key Words:** baroreflex ■ chemosensitivity ■ ventilation ■ exercise

An increase in the ventilatory response to exercise is a well-described characteristic of chronic heart failure (CHF), associated with reduced exercise tolerance, autonomic dysfunction, progression of the disease, and poor prognosis.<sup>1</sup>

Overactivity of ergoreceptors (intramuscular afferents sensitive to metabolic products of skeletal muscle work) and peripheral and central chemoreceptors have been proposed as potential contributing factors to these changes in CHF.<sup>2,3</sup> Metabolic abnormalities in the skeletal muscles with early acidosis and accumulation of catabolites during exercise<sup>4</sup> may be responsible for enhanced ergoreflex activity. Initially, ergoreflex overactivation may be a beneficial compensatory mechanism, generating sympathetic stimulation, increased ventilation, and peripheral vasoconstriction in the nonexercising limbs, which may assist in the physiological response

to exercise. However, in a chronic disease state, excessive stimulation of these reflexes may be a source of the persistent sympathetic overactivity, reduced vagal activity, and blunted baroreflex control that are characteristic of the CHF syndrome.<sup>5</sup> The ergoreflex may play a key role not only in the origin of the limiting symptoms but also in the progression of the CHF syndrome by maintaining and stimulating compensatory mechanisms, which are deleterious in the long term.<sup>6</sup> Confirmation of this hypothesis has been elusive, although recent data point to the importance of the peripheral changes in the pathophysiological processes of progression of the syndrome.<sup>7</sup>

No previous study has simultaneously assessed a wide range of reflex and autonomic abnormalities in patients with CHF with a spectrum of degrees of functional limitation. We therefore developed a prospective study to investigate how

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**TABLE 1. Clinical Characteristics of the Study Population**

Variables	CHF Patients	Control Subjects
Sex, M/F	36/2	10/2
Age, y	57.8±1.3	60.2±3.5
Origin of heart failure, n (%)		
IHD	28 (74)	NA
IDC	10 (26)	
NYHA class, n (%)		
II	23 (60)	NA
III	14 (37)	
IV	1 (2)	
LVEF, %	26.2±1.9	55.2±3.5‡
LVEDD, mm	69.8±1.7	45.6±2.5‡
RVEF, %	33.9±2.3	51.3±4.7‡
Peak V <sub>O<sub>2</sub></sub>		
mL · min <sup>-1</sup> · kg <sup>-1</sup>	19.0±1.0	27.9±3.3‡
% Predicted	58.5±3.0	93.9±4.4‡
VE/V <sub>CO<sub>2</sub></sub>	35.8±1.5	29.5±2.5*
Medications, n (%)		
Diuretics	38 (100)	0 (0)
ACE inhibitors	36 (95)	0 (0)
Digoxin	15 (39)	0 (0)

\*P<0.05, †P<0.01, ‡P<0.005 vs CHF.

IHD indicates ischemic heart disease; IDC, idiopathic dilated cardiomyopathy; and NA, not applicable. Values are mean±SEM or number of subjects (%) when appropriate.

the “muscle hypothesis” may contribute to the evolution of the CHF syndrome with the development of changes in functional capacity and cardiorespiratory reflex control. To this end, we investigated whether activation of muscle ergoreflex responses is associated with the severity of the clinical condition, exercise intolerance, neurohormonal changes, arrhythmic risk, autonomic control, and ventilatory abnormalities in CHF patients.

Furthermore, to gain insight into the complex pathophysiological process of autonomic derangement in CHF, we assessed the relationship between the ergoreflex and autonomic indexes (heart rate variability [HRV]) and reflexes (arterial baroreflex, peripheral and central chemoreflex), which are all important prognostic indicators in this syndrome.<sup>8,9</sup> Finally, we examined how strongly the overactivity of the muscle ergoreflex in CHF was related to well-recognized markers of functional limitation (exercise tolerance and abnormally elevated ventilatory response to exercise) compared with the strength of relationship shown by other autonomic indexes and reflexes.<sup>3,9</sup>

**Methods**

**Study Population**

We prospectively evaluated 38 patients (Table 1) who attended the outpatient CHF clinic of our tertiary referral hospital and who met the following criteria: ≥6-month history of CHF caused by idiopathic dilated cardiomyopathy or ischemic heart disease, left ventricular ejection fraction (LVEF) ≤45%, clinically stability for ≥1 month preceding the study, absence of signs of fluid retention with unchanged medication, and no acute coronary event within the 6

months preceding the study. Exclusion criteria included age >75 years, seriously limiting muscle-skeletal abnormalities or peripheral vascular disease, pulmonary disease, significant renal dysfunction, or treatment with β-blockers. This study was performed before use of β-blockers became established therapy for CHF in the United Kingdom. A control group of 12 age-matched normal volunteers was compared with the CHF patients. The local Ethics Committee approved the study protocol, and all subjects gave informed consent. These patients’ data have not appeared in any previous publication from our group.

First, the subjects were fully assessed clinically, including examination of the clinical status (NYHA functional classification). Then, they underwent radionuclide ventriculographic assessment, followed by evaluation of (1) cardiopulmonary exercise tolerance, (2) ergoreceptor activity, (3) peripheral and central chemosensitivity, (4) arterial baroreflex sensitivity, (5) sympathovagal balance and respiratory analysis, (6) 24-hour ECG Holter monitoring, and (7) hormonal assessment. All tests were performed on consecutive days, except for tests 3, 6, and 7, which were performed during the same session.

**Data**

**Cardiopulmonary Exercise Testing**

All patients underwent symptom-limited cardiopulmonary exercise testing (modified Bruce protocol)<sup>1</sup> with assessment of minute ventilation (V<sub>E</sub>), oxygen consumption (V<sub>O<sub>2</sub></sub>), and carbon dioxide production (V<sub>CO<sub>2</sub></sub>) every 10 seconds by mass spectrometer (Amis 2000, Innovision; MedGraphics Cardio O<sub>2</sub> System). Patients were encouraged to exercise to exhaustion (V<sub>CO<sub>2</sub></sub>/V<sub>O<sub>2</sub></sub>>1.1), and all participants stopped exercise as a result of breathlessness and/or fatigue. V<sub>O<sub>2</sub></sub> at peak exercise was expressed as both milliliters per kilogram per minute (peak V<sub>O<sub>2</sub></sub>) and as a percentage of predicted peak V<sub>O<sub>2</sub></sub> accounting for age, sex, body weight, and height.<sup>10</sup> The slope of the relation between V<sub>E</sub> and V<sub>CO<sub>2</sub></sub> (V<sub>E</sub>/V<sub>CO<sub>2</sub></sub>) was calculated as the index of ventilatory response to exercise.<sup>1</sup>

**Ergoreflex Assessment Protocol**

The ergoreflex activity was assessed by the post-handgrip regional circulatory occlusion (PH-RCO) method.<sup>2</sup> The following data were acquired: heart rate (ECG), noninvasive blood pressure (Finapres, Ohmeda Monitoring System), ventilatory data (mass spectrometer), and right leg (nonexercising limb) blood flow (mercury-in-Silastic strain-gauge plethysmograph), whereas the corresponding leg vascular resistance (in arbitrary units) was computed. The contributions made specifically by the ergoreflex to the ventilatory and hemodynamic responses to exercise were derived by calculating (1) the absolute difference between PH-RCO and the recovery without PH-RCO and (2) the percentage of the exercise response maintained by PH-RCO.<sup>2,6,9</sup>

**Chemosensitivity**

Peripheral chemosensitivity was assessed by the transient hypoxic method (liters per minute per percent O<sub>2</sub> saturation), whereas central hypercapnic chemosensitivity was determined by the rebreathing of CO<sub>2</sub> method (slope relating V<sub>E</sub> to end-tidal CO<sub>2</sub>, L · min<sup>-1</sup> · mm Hg<sup>-1</sup>).<sup>3</sup>

**Arterial Baroreflex Sensitivity**

The phenylephrine method was used to calculate the slope of the regression line relating changes in RR interval to changes in systolic blood pressure (ms/mm Hg).<sup>11</sup>

**Sympathovagal Balance and Respiratory Analysis**

HRV analysis was performed in patients in the resting condition in the morning (9 AM to noon).<sup>11</sup> Simultaneous recordings of ECG and a respiratory signal (impedance plethysmography, Hokanson) were acquired by a computer program over 30 minutes. HRV was presented by SD and spectral power density in defining the following spectral bands: very low (<0.04 Hz [VLF]), low (0.04 to 0.15 Hz [LF]), and high frequency (0.15 to 0.40 Hz [HF]). Stationary, 20-minute periods of stable recordings were also used to identify

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oscillatory respiratory patterns producing an amplitude modulation in the breathing signal; the presence of periodic breathing was defined as a pattern of waxing and waning of ventilation.<sup>12</sup>

### Twenty-Four-Hour ECG Holter Monitoring

All patients underwent 24-hour ECG monitoring (Marquette Electronics Inc) to assess the presence of nonsustained ventricular tachycardia (NSVT), ie, >3 consecutive ventricular ectopic beats at a rate of >100 bpm.

### Hormonal Assessment

Blood samples were collected in the morning, between 9 and 10 AM, after a fasting period of >12 hours to assess resting plasma norepinephrine and epinephrine by high-performance liquid chromatography (sensitivity, 0.1 nmol/L).

### Statistical Analysis

Data are expressed as mean±SEM. The mean values of results for the 2 groups of subjects were compared by use of ANOVA and Fisher's post hoc test. Simple linear regression (least-squares method), multivariate analysis, and stepwise regression analyses were performed to assess factors independently predicting the ergoreceptor parameters (expressed in percentage terms). A value of  $P<0.05$  was considered significant.

## Results

### Clinical Parameters

Patients had reduced left and right ventricular systolic function and increased left ventricular dimensions (Table 1). During cardiopulmonary exercise testing, CHF patients had reduced peak  $\dot{V}O_2$  and elevated  $\dot{V}E/\dot{V}CO_2$  slope compared with control subjects.

### Autonomic Reflexes and Sympathovagal Balance

Compared with healthy subjects, patients had elevated ventilatory and hemodynamic (blood pressure, nonexercising limb vascular resistance) responses to ergoreceptor activation during exercise (No effect on HR was observed in either group; Table 2). These were associated with augmented peripheral and central chemosensitivity and impaired baroreflex sensitivity. Sympathovagal balance (HRV) was also altered in CHF patients: flattening of the time domain variability (SD) and a reduction in both LF and HF oscillations, whereas the VLF component was pronounced. The neurohormonal assessment showed elevated catecholamine levels in CHF.

NSVT was observed in 34% and periodic breathing in 60% of the patients, whereas no significant ventricular arrhythmia or respiratory abnormalities were detected in the control group.

### Clinical Condition

Patients with a more severe clinical condition (defined by NYHA functional classification, reduced peak  $\dot{V}O_2$ , or increased  $\dot{V}E/\dot{V}CO_2$  slope) were characterized by more marked ergoreflex component in the ventilatory and hemodynamic responses to exercise (Table 3). The presence of either periodic breathing or NSVT was associated with greater ergoreflex-dependent ventilatory response to exercise. Patients with CHF of ischemic origin tended to have a more abnormal ergoreflex activity compared with those with a nonischemic origin.

**TABLE 2. Neurohumoral, Respiratory, and Arrhythmic Indices in the Study Population**

Variables	CHF Patients	Control Subjects
Ergoreflex activity		
Ventilation		
L/min	9.4±0.9	3.5±0.8*
%	61.0±2.3	50.2±8.4*
Systolic pressure		
mm Hg	38.5±3.5	25.9±3.7*
%	62.0±5.4	53.2±9.7*
Leg vascular resistance		
Units	36.9±4.1	27.4±3.0*
%	60.7±4.2	47±4†
Peripheral chemosensitivity, L·min <sup>-1</sup> ·%SaO <sub>2</sub> <sup>-1</sup>	0.6±0.4	0.2±0.1†
Central chemosensitivity, L·min <sup>-1</sup> ·mm Hg	2.9±0.2	2.0±0.2*
Baroreflex sensitivity, ms/mm Hg	4.1±0.6	9.1±5.6†
R-R interval, ms	849±21	851±37
Sympathovagal balance		
SD, ms	30±12	128±24‡
VLF, ms <sup>2</sup>	827±117	425±212‡
LF, ms <sup>2</sup>	79±15	215±41‡
HF, ms <sup>2</sup>	23±3	183±32‡
Norepinephrine, nmol/L	3.0±0.2	1.9±0.2†
Epinephrine, nmol/L	0.9±0.2	0.5±0.0*
Periodic breathing, n (%)	23 (60)	0 (0)
NSVT, n (%)	13 (34)	0 (0)

Values are mean±SEM or number of subjects (%) when appropriate. VLF/LF/HF indicate very low/low/high frequency power; NSVT, nonsustained ventricular tachycardia.

### Resting Cardiac Status and Exercise Physiology

In the CHF population, ergoreflex activity was correlated with objective functional (peak  $\dot{V}O_2$ ), subjective capacity (NYHA class), and ventilatory response to exercise ( $\dot{V}E/\dot{V}CO_2$  slope) (Figure 1), but not with resting ventricular function (LVEF, right ventricular ejection fraction [RVEF], or left ventricular end-diastolic diameter [LVEDD]; Table 4). This preferential relationship with exercise capacity was also seen with the other specific reflexes studied (central and peripheral chemoreflex and arterial baroreflex,  $P<0.05$ ).

Interrelationships were seen between the neural reflexes; an increased ergoreceptor contribution to ventilation was a strong predictor of arterial baroreflex desensitization and central chemosensitivity but not of peripheral chemosensitivity (Figure 2). Sympathetic status was also related to ergoreflex activity in catecholamines levels and HRV indexes (LF, depressed SD).

In the control population, ergoreflex activity did not correlate with exercise capacity, ventilatory response to exercise, or indexes of sympathetic tone; among the reflexes studied, it predicted only baroreflex sensitivity ( $r=-0.49$ ,  $P<0.05$ ).

**TABLE 3. Differences in Ergoreflex Activity in Heart Failure Population According to Clinical Status (NYHA Class, Peak VO<sub>2</sub>, VE/VCO<sub>2</sub>), Presence of Periodic Breathing, NSVT, or Etiology**

	Ergoreflex Contribution to	
	Ventilation, %	Systolic Pressure, %
NYHA class II vs III-IV	55.6±6 vs 68.4±5*	54.0±5 vs 70.0±6*
Peak VO <sub>2</sub>		
> vs <19.0 mL · min <sup>-1</sup> · kg <sup>-1</sup>	39.0±6 vs 73.8±4†	40.4±4 vs 72.6±4†
> vs <50% predicted	53.3±5 vs 71.6±6*	55.5±5 vs 68.0±6*
VE/VCO <sub>2</sub> (> vs. <35.8)	73.3±4 vs 48.2±4†	65.2±5 vs 56.2±6
Periodic breathing, presence vs absence	65.4±5 vs 54.2±7*	61.0±5 vs 60.2±7
NSVT, presence vs absence	68.0±6 vs 47.4±8*	64.0±7 vs 59.0±5
Origin, ischemic vs idiopathic	65.0±4 vs 49.9±9	64.3±4 vs 50.7±9

\*P<0.05, †P<0.01.

**Multivariate Correlation Analysis**

To determine whether the relationship between the ergoreflex and central chemoreflex was a result of a confounding effect of age, NYHA class, VE/VCO<sub>2</sub> slope, or peak VO<sub>2</sub>, we performed a series of bivariate regression analyses (Table 5). The results showed that this relationship was independent of all other variables considered. When we tested which of the neural reflexes (ergoreflex, peripheral or central chemoreflex, baroreflex) was an independent predictor of the reduced peak VO<sub>2</sub> and increased VE/VCO<sub>2</sub> slope, the ventilatory component of ergoreflex was the only one.

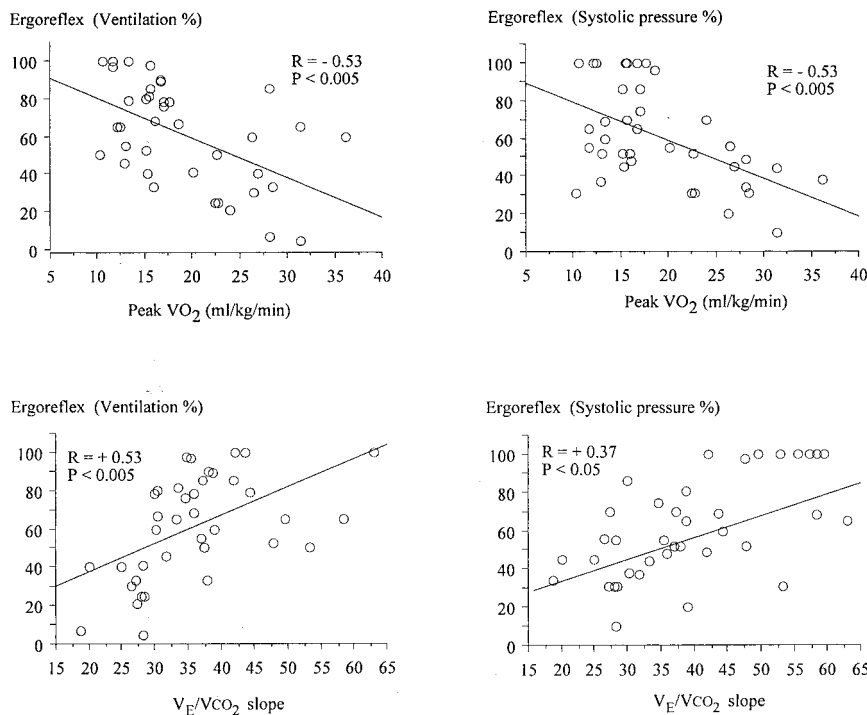
**TABLE 4. Univariate Correlation Analysis Between Ergoreceptor Activity and Indexes of Exercise Tolerance and Autonomic and Hemodynamic Function in Heart Failure Population**

	R, Ergoreflex Contribution to	
	Ventilation	Systolic Pressure
Age	+0.41†	+0.37*
NYHA class	+0.39*	+0.39*
Peak VO <sub>2</sub>	-0.53‡	-0.53‡
VE/VCO <sub>2</sub> slope	+0.53‡	+0.37*
LVEF	-0.12	-0.10
RVEF	-0.14	-0.15
LVEDD	+0.11	+0.12
Reflexes		
Central chemoreflex	+0.52‡	+0.41*
Peripheral chemoreflex	+0.05	+0.16
Arterial baroreflex	-0.48†	-0.55‡
Hormonal assessment		
Norepinephrine	+0.35*	+0.33*
Epinephrine	+0.44†	+0.35*
HRV		
SD	-0.26	-0.31*
VLF	+0.10	+0.20
LF	-0.18	-0.38*
HF	-0.11	-0.11

\*P<0.05, †P<0.01, ‡P<0.005.

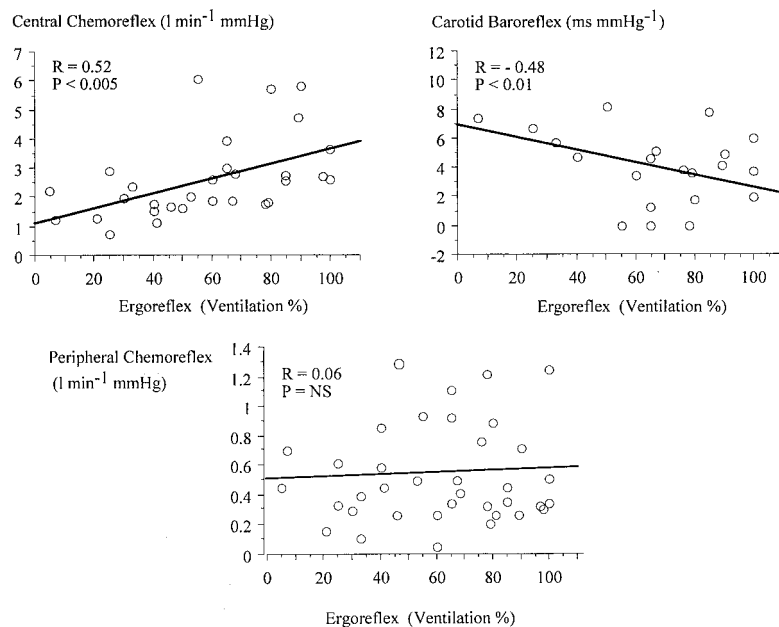
**Discussion**

The new findings of this study are the following. First, ergoreflex activation in CHF is closely related to the severity of exercise intolerance, as assessed subjectively by the



**Figure 1.** Regression analyses between ergoreflex component to ventilation and systolic pressure responses to exercise vs peak O<sub>2</sub> consumption (peak VO<sub>2</sub>) and slope of relation between VE and VCO<sub>2</sub> (VE/VCO<sub>2</sub>) in heart failure. Ergoreceptor responses are determinant of exercise tolerance and exercise hyperventilation.





**Figure 2.** Regression analyses between ergoreflex component of ventilatory response to exercise and chemoreflex activity (central and peripheral) and arterial baroreflex in heart failure. Increased ergoreceptor response of ventilation is strong predictor of central chemosensitivity activation and baroreflex desensitization but not of activity of peripheral chemoreceptors.

NYHA classification or objectively by cardiopulmonary exercise testing (peak  $\dot{V}O_2$ ), in agreement with a recent study.<sup>10</sup> Meanwhile, ventricular function is poorly related not only to exercise capacity<sup>13</sup> but also to the neural reflexes here studied (ie, ergoreflex, chemoreflex, and carotid baroreflex), consistent with the concept of CHF as a complex multisystemic syndrome. The common symptoms of impaired exercise capacity (dyspnea, early fatigability) seem to be related to neurohumoral derangement than to heart impairments although the latter has been the original disruption.

**TABLE 5. Multivariate Analysis Testing of Which Clinical Parameter (Age, NYHA Class,  $\dot{V}E/\dot{V}CO_2$  Slope, Peak  $\dot{V}O_2$  Was Affecting the Relationship Between Ergoreflex and Central Chemoreflex Showed That This Relationship Was Independent of All Considered Variables**

Covariate	<i>P</i>
Age	
Age	0.03
Ergoreflex (ventilation)	0.01
NYHA class	
NYHA class	0.04
Ergoreflex (ventilation)	0.01
Peak $\dot{V}O_2$	
Peak $\dot{V}O_2$	0.40
Ergoreflex (ventilation)	0.02
$\dot{V}E/\dot{V}CO_2$ slope	
$\dot{V}E/\dot{V}CO_2$ slope	0.20
Ergoreflex (ventilation)	0.03
All	
Age	0.08
NYHA	0.12
Peak $\dot{V}O_2$	0.40
Ergoreflex (ventilation)	0.03

Second, the ergoreflex sensitivity predicts autonomic and reflex regulatory disturbances such as baroreflex attenuation, altered HRV, and increased central chemoreflex and catecholamines, consistent with the hypothesized presence in CHF of enhanced activatory sympathetic inputs and impaired vagal tonic reflex.<sup>5</sup> This is also supported by the HRV data showing an impaired vagal index (SD) and an increased sympathetic one (LF).

Third, the positive correlation between ergoreceptor sensitivity and the central chemoreflex suggests a possible causative link between these 2 reflexes. The most plausible explanation for this would be a common mechanism of activation. Periodic breathing, in whose pathophysiology enhanced chemoreflex plays an important role, was particularly prevalent in the subjects with an enhanced ergoreflex.

Finally, the overactive muscle ergoreflex in CHF was more closely related to exercise tolerance and an abnormally elevated ventilatory response to exercise than were other autonomic indexes or reflexes. These data are consistent with a key role of the muscle ergoreflex in symptom generation and disease progression—the muscle hypothesis of heart failure.<sup>6</sup>

In CHF damage to the heart and disturbance of central hemodynamics activate compensatory mechanisms, including neurohumoral and autonomic changes, with consequent peripheral vasoconstriction and tachycardia. These changes may be beneficial at the beginning to maintain adequate arterial pressure and circulation to the more vital territories, but in the longer term, they induce modifications in many organ systems of the body, including peripheral skeletal muscle structure metabolism. A predominance of glycolytic over oxidative metabolism with ultrastructural modifications in muscle composition (fiber type, mitochondrial and endothelial function) has been demonstrated.<sup>4,14</sup> Consequently, early acidosis and depletion of high-energy compounds develop during exercise, which in turn triggers other mechanisms that would, in normal individuals, maintain skeletal muscle performance.

These compensatory mechanisms include stimulation of various afferents, including both central and peripheral chemoreceptors and skeletal muscle ergoreceptors. The latter receptors are poorly defined intramuscular receptors that are sensitive to the product of muscle work and linked to small myelinated and unmyelinated fibers; once activated, they directly stimulate sympathetic drive, ventilation, and vasoconstriction in the nonexercising limbs, the combined effect of which has the beneficial effect of diverting more well-oxygenated blood to the working skeletal muscles. But in the long term, overactivation of the ergoreflex system may be harmful because it maintains an abnormal neurohormonal and vasoconstrictor milieu that favors progression of the disease.<sup>5,6</sup> In the literature, a correlation between sympathetic activation and exercise intolerance has been demonstrated, which would be consistent with a role for overactive sympathoexcitatory neural reflexes in symptom generation in CHF.<sup>3,9,10</sup> In addition, the findings from this study support the muscle hypothesis in CHF.

### Autonomic Indexes and Cardiorespiratory Reflexes

In CHF, ergoreceptor activation was associated with autonomic abnormalities compatible with sympathetic activation and vagal withdrawal: elevation of plasma catecholamine concentrations and a reduction in HRV, its SD, and the LF component. VLF rhythms are more rather than less prominent in patients with an enhanced ergoreflex. This is, however, in keeping with the known association of VLF rhythm with a poorer autonomic state. In fact, in very advanced CHF, modulation of HRV at the LF and HF rhythms is almost absent, and the principle remaining modulation is at the VLF band.<sup>15</sup>

In our evaluation of the interaction between chemoreflexes and baroreflexes in CHF, we saw a mutually antagonistic relationship for which there is confirmation in animal physiology.<sup>16,17</sup> Modulation of chemoreceptor activity affects autonomic control of the heart.<sup>18</sup> It has been hypothesized that the blunted baroreceptor response in CHF may result in a loss of this inhibitory interaction, leading to a further increase in excitatory activity of the muscle receptors.<sup>5</sup> To the best of our knowledge, however, there are no data on the association between ergoreceptor sensitivity and autonomic imbalance or baroreflex sensitivity in patients with CHF. Also, the interaction between the chemoreflex and ergoreflex systems has not been studied in either animals or humans. This is the first documentation of a direct correlation between ergoreflex and central chemoreflex activity and an inverse correlation between the ergoreflex and baroreflex.

The mechanisms causing the tight relationship between chemoreceptors and ergoreceptors remain obscure. We may speculate that in CHF the altered modulating effect of chemoreflexes on the ventilatory response to exercise determines an augmented ventilatory response to exercise; consequently, the response to ergoreflex stimulation is abnormally great.

### Arrhythmia and Respiratory Abnormalities

A higher prevalence of ventricular arrhythmia (NSVT) was observed in those patients with higher ergoreflex activity.

This reflex has been shown to contribute to autonomic control, inducing sympathetic activation.<sup>2</sup> In our study a direct correlation was also seen between ergoreflex activation and neurohormonal indexes of sympathetic activation. It may therefore be hypothesized that together with enhanced ergoreflex, there is a degree of sympathetic activation, which may have a proarrhythmic effect.<sup>19</sup>

The increased prevalence of periodic breathing in those patients with elevated ergoreflex activity suggests a peripheral origin for this respiratory pattern. An important contribution of chemoreflex activation has been hypothesized in our laboratory for this abnormal respiratory pattern.<sup>12,20</sup> The present study suggests that the peripheral abnormalities may also contribute to the respiratory pattern through the muscle ergoreflex.

### Study Limitations

We compared a reflex activated by muscle exercise with basal resting measurements of autonomic state—respiration. However, in CHF, tonic activation of the ergoreflex even at low-level exercise has been observed experimentally in association with significant increases in blood concentration of vasoactive hormones (norepinephrine, renin, vasopressin), with increased sympathetic and renal vasoconstrictive drives.<sup>21</sup> In the more advanced stage of the syndrome, even the slightest daily activities may stimulate the ergoreflex, producing a status of permanently increased sympathetic drive that persists after exercise. This may favor the alteration in autonomic state, ventilation, and increased arrhythmia observed here to be associated with increased muscle ergoreflex and the progression of the syndrome.

### Conclusions

We should be careful to differentiate between hemodynamic derangement and a disruption in integrated physiology in CHF: Patients who appear to be mild on the basis of ventricular function criteria may be severe in physiological terms and vice versa. Indeed, new scoring systems may be warranted to ensure that neurohormonal and reflex mechanisms involved in syndrome progression are adequately represented.

The mechanisms by which exercise training improves physiology in CHF are not clear; this intervention has been shown to partially reverse early muscle acidosis and peripheral hemodynamic changes.<sup>4,14</sup> Improving muscle function can reduce the stimulus to the ergoreflex, thus allowing the physiological balance to improve.<sup>2</sup> A specific agent is not yet available to do this, but if one were developed, it may be a highly attractive therapeutic strategy.

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