

# Enhanced Sympathetic and Ventilatory Responses to Central Chemoreflex Activation in Heart Failure

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**Background**—Sympathetic activation and respiratory abnormalities may each be implicated in the pathophysiology of congestive heart failure (CHF). Chemoreflexes are an important mechanism regulating both sympathetic drive and breathing. We therefore tested the hypothesis that chemoreflex function is altered in CHF.

**Methods and Results**—We compared ventilatory, sympathetic, heart rate, and blood pressure responses to hypoxia, hypercapnia, and the cold pressor test in 9 patients with CHF and 9 control subjects matched for age and body mass index. Baseline muscle sympathetic nerve activity (MSNA) was higher in the patients with CHF compared with control subjects ( $47 \pm 8$  versus  $23 \pm 3$  bursts per minute,  $P < 0.01$ ). During hypercapnia, patients with CHF had greater increases in minute ventilation ( $6.7 \pm 1.4$  versus  $2.7 \pm 0.9$  L/min,  $P = 0.03$ ) and heart rate ( $7.0 \pm 2.1$  versus  $0.6 \pm 1.2$  bpm,  $P = 0.02$ ). Despite higher ventilation, which inhibits sympathetic activity, the MSNA increase in patients with CHF was also greater than that in control subjects ( $58 \pm 12\%$  versus  $21 \pm 9\%$ ,  $P = 0.03$ ). Ventilatory, autonomic, and blood pressure responses to hypoxia and the cold pressor test in CHF patients were not different from those in control subjects.

**Conclusions**—Chronic heart failure is characterized by a selective potentiation of ventilatory and sympathetic responses to central chemoreceptor activation by hypercapnia. (*Circulation*. 1999;100:262-267.)

**Key Words:** hypercapnia ■ hypoxia ■ reflex ■ nervous system ■ heart failure

Activation of the sympathetic nervous system is an important component of the pathophysiology of chronic heart failure.<sup>1-5</sup> Direct intraneural recordings have shown that heart failure is accompanied by increased efferent sympathetic nerve activity to skeletal muscle.<sup>6-9</sup> The cause of the heightened sympathetic drive is not known. Possible mechanisms include impaired inhibitory cardiac and arterial baroreflex function,<sup>9,10</sup> abnormalities in central neural control,<sup>1</sup> and augmented sympathetic excitatory chemoreceptor<sup>11-15</sup> and somatic reflexes.<sup>1,16</sup>

The role of chemoreflex mechanisms in heart failure has recently received considerable attention.<sup>11-14,17,18</sup> Chemoreflexes are the dominant control mechanisms regulating ventilatory responses to changes in arterial oxygen and CO<sub>2</sub> content.<sup>19-22</sup> The peripheral chemoreceptors, located in the carotid bodies, respond primarily to hypoxia.<sup>23,24</sup> Central chemoreceptors, located on the ventral surface of the medulla, respond primarily to hypercapnia.<sup>25</sup> Both these chemoreceptor mechanisms also exert powerful influences on neural circulatory control, especially in situations involving marked changes in arterial oxygen and/or CO<sub>2</sub>. Chemoreflex activation causes increases in sympathetic activity, heart rate (HR), blood pressure, and minute ventilation.<sup>26,27</sup> Increased minute ventilation and increased blood pressure inhibit the sympathetic

response to chemoreflex activation.<sup>26-28</sup> Thus, chemoreflexes elicit several cardiovascular and respiratory responses, with complex interactions between the responses themselves. To define any abnormalities in chemoreflex function, it is therefore crucial to consider the individual contributions of the key components of the integrated chemoreflex response.

Previous studies examining chemoreflex function in congestive heart failure (CHF) have examined almost exclusively the ventilatory responses and are inconclusive.<sup>11-14,17</sup> Sympathetic and hemodynamic responses to peripheral and central chemoreflex activation in patients with CHF are not known.

We tested the hypothesis that chemoreflex function is altered in CHF. We measured ventilatory, sympathetic, and hemodynamic responses to peripheral chemoreceptor activation by hypoxia and to central chemoreceptor activation by hypercapnia in patients with heart failure. These responses were compared with those obtained in normal control subjects matched for age, body mass index (BMI), and sex. To ensure that any abnormalities in chemoreflex function did not represent a generalized and nonspecific abnormality in response to excitatory stimuli, we also compared the responses to the cold pressor test, which served as an internal control.<sup>29,30</sup>

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## Methods

### Subjects

We studied 9 patients with chronic heart failure (8 men and 1 woman; mean age, 43±9 years; mean BMI, 28±7 kg/m<sup>2</sup>). All patients had supporting clinical, chest roentgenographic, and echocardiographic evidence of impaired ventricular function. The cause of heart failure was idiopathic dilated cardiomyopathy in 7 patients, valvular heart disease in 1 patient, and alcohol-related cardiomyopathy in 1 patient. In all patients, angiography was performed to rule out coronary artery disease as an underlying cause of heart failure. Left ventricular ejection fraction, determined by a resting radionuclide ventriculogram, was 28±4% (mean±SEM). One patient was in NYHA functional class I, 5 were in class II, and 3 were in class III. All patients were treated with diuretics. Six patients received ACE inhibitors, 5 patients were treated with digitalis, and 2 patients received carvedilol. For reasons of patient safety, medications were not withheld for the purpose of this study. No patients had Cheyne-Stokes breathing or history suggestive of obstructive sleep apnea.

We also studied 9 sex-, age- and BMI-matched healthy control subjects (mean age, 41±6 years; mean BMI, 28±6 kg/m<sup>2</sup>). No control subjects were receiving any medications or had any chronic disease. Informed written consent was obtained from all subjects. The study was approved by the Institutional Human Subjects Review Committee.

### Measurements

HR was measured continuously by an ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-Control Corp). Oxygen saturation was monitored with a pulse oximeter (Nellcor Inc). End-tidal CO<sub>2</sub> was monitored with a Hewlett-Packard 47210A Capnometer. Minute ventilation was determined by use of a KL Engineering S430 monitor. Breathing was via a mouthpiece with a nose clip to ensure exclusive mouth breathing. Muscle sympathetic nerve activity (MSNA) was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity to muscle blood vessels, measured from a muscle nerve fascicle in the peroneal nerve posterior to the fibular head as described previously.<sup>31</sup>

### Protocol and Procedures

The protocol used to determine chemoreflex responses to isocapnic hypoxia and hyperoxic hypercapnia was identical to that used in previous studies.<sup>26,27</sup> In brief, subjects were exposed to a hypoxic gas mixture to induce peripheral chemoreflex activation (10% O<sub>2</sub> in N<sub>2</sub> with CO<sub>2</sub> titrated to maintain isocapnia) and a hypercapnic gas mixture to induce central chemoreflex activation (7% CO<sub>2</sub>/93% O<sub>2</sub>). During hypoxic stimulation of peripheral chemoreceptors, perturbation of central chemoreceptors was minimized by the maintenance of isocapnia.<sup>27</sup> During hypercapnic stimulation of central chemoreceptors, perturbation of peripheral chemoreceptors was minimized by hyperoxia.<sup>26</sup> The sequence of hypoxic and hypercapnic interventions was randomized. At least 15 minutes separated the end of 1 intervention from the beginning of the next.

Baseline measurements were taken during a 5-minute period of stable ventilation while subjects breathed room air with a mouthpiece. Then, with a 3-way valve, subjects were exposed to either the hypoxic or hypercapnic stressor for 3 minutes. We were unable to obtain stable nerve recordings in 1 patient with CHF. Consequently, sympathetic responses to hypoxia and hypercapnia were obtained in 8 CHF patients and 9 control subjects. Seven CHF patients and 8 control subjects underwent a subsequent cold pressor test. The cold pressor test, a stimulus for ventilation and sympathetic excitation, involves immersing the subject's hand in ice water for 2 minutes.<sup>29,30</sup>

### Analyses

Sympathetic bursts were identified by careful inspection of the voltage neurogram. The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and expressed as units per minute.

**TABLE 1. Resting Measurements in Free-Breathing Normal Control Subjects and Patients With CHF**

Measurement	Normal Control Subjects	Patients With CHF	<i>P</i>
Oxygen saturation, %	98.2±0.4	95.7±0.8	0.02
SBP, mm Hg	111±5	111±5	0.98
DBP, mm Hg	68±4	69±3	0.86
MAP, mm Hg	84±4	83±4	0.96
HR, bpm	61±4	78±4	0.01
MSNA, bursts/min	23±3	47±8	0.01
MSNA, bursts/100 beats	39±4	61±10	0.047

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and MAP, mean arterial pressure.

Measurement of nerve activity at baseline before each intervention was expressed as 100%. Changes in integrated MSNA allow evaluation of within-subject changes in sympathetic traffic during the same recording session. Sympathetic activity was also expressed as bursts per minute and bursts per 100 heartbeats, which allows comparison of sympathetic discharge between individuals, thus permitting a comparison of resting MSNA between CHF patients and control subjects.

Demographic data and baseline characteristics were compared by use of an unpaired *t* test. Responses to hypoxia, hypercapnia, and the cold pressor test were analyzed by repeated-measures ANOVA with time (baseline versus intervention) as within-factor and group (the CHF patients versus the control subjects) as between-factor variables. The key variable was the group-by-time interaction. Data are presented as mean±SEM. A value of *P*<0.05 was considered significant.

## Results

### Resting Values

Compared with normal control subjects, CHF patients had lower oxygen saturation, faster HR, and increased MSNA (Table 1). Blood pressures in CHF patients were similar to values obtained in the control subjects (Table 1).

### Responses to Hypercapnia

The baseline levels and increases in end-tidal CO<sub>2</sub> during hypercapnia were similar in CHF patients and control subjects (Table 2). Hypercapnia induced significant HR increases in CHF patients but not in control subjects (Table 2 and Figures 1 and 2). Patients with CHF and control subjects both showed increases in minute ventilation, blood pressure, and MSNA during hypercapnia. However, the increases in minute ventilation and MSNA during hypercapnia were significantly greater in the CHF patients (Table 2 and Figures 1 and 2).

### Responses to Hypoxia

The change in oxygen saturation during hypoxia was similar in patients with CHF and control subjects (Table 3). Autonomic, ventilatory, and blood pressure changes during hypoxia in the CHF patients were not significantly different from those observed in control subjects (Table 3).

### Effects of the Cold Pressor Test

The ventilatory, HR, blood pressure, and MSNA responses to the cold pressor test were similar in the CHF patients and control subjects (Table 4).

TABLE 2. Effects of Hypercapnia in Control Subjects and Patients With CHF

Measurement	Normal Subjects		Patients With CHF		Interaction, Group-by-Time P
	Baseline	Hypercapnia	Baseline	Hypercapnia	
Oxygen saturation, %	98.7±0.4	99.9±0.1	97.1±0.7	99.6±0.3	0.10
End-tidal CO <sub>2</sub> , mm Hg	36±2	51±1	36±1	50±1	0.52
Minute ventilation, L/min	7.4±0.5	10.1±0.8	7.2±0.6	13.9±1.9	0.03
HR, bpm	61±2	62±4	79±4	86±5	0.02
MAP, mm Hg	84±3	90±4	85±4	94±4	0.34
MSNA, bursts/min	24±3	23±2	42±8	50±8	0.01
Integrated MSNA, %	100	121±9	100	158±12	0.03

MAP indicates mean arterial pressure. Baseline values were obtained immediately before hypercapnia while subjects breathed room air with a mouthpiece. Probability values are for the group-by-time interaction term (ANOVA). Values are mean±SEM.

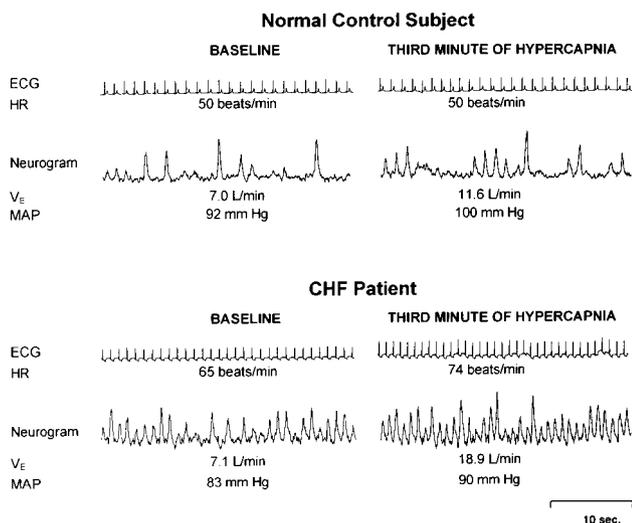
### Discussion

One novel finding of this study is that CHF is associated with potentiation of central chemoreflex sensitivity. This is evident in the increased ventilatory, HR, and sympathetic neural responses to hypercapnia. Second, responses to both peripheral chemoreflex activation and the cold pressor test are not altered in patients with CHF. Thus, potentiation of chemoreflex function in CHF is selective for the central chemoreflex.

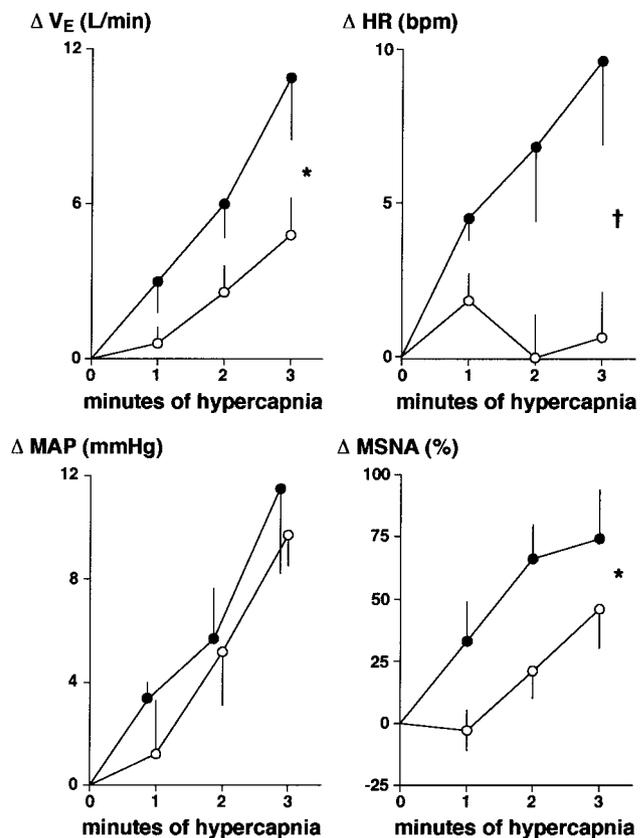
The increased sympathetic drive during hypercapnia in heart failure was evident despite significant increases in blood pressure (8±2 mm Hg) and despite the potentiated ventilatory response. Increases in blood pressure and minute ventilation would each be expected to attenuate the sympathetic response to hypercapnia.<sup>32,33</sup> Very high baseline levels of sympathetic activity would also be expected to limit further increases in sympathetic drive.<sup>34</sup> Despite these considerations, hypercapnia elicited a >50% increase in the already-high levels of sympathetic nerve traffic in the CHF patients. The hypercapnic stimulus therefore represents a very

potent mechanism for sympathetic activation in the setting of CHF.

Although our data are consistent with prior studies of the ventilatory response to hypercapnia,<sup>11,12</sup> we did not observe any potentiation of ventilatory responses to hypoxia. Several factors may be implicated in the discrepancy between our results and those of previous studies.<sup>12-14</sup> First, the studies reporting increased peripheral chemoreflex sensitivity in CHF<sup>12-14</sup> used transient inhalations of pure nitrogen. In this



**Figure 1.** ECG tracings and sympathetic neurograms at baseline and during third minute of hypercapnia. Recordings are shown in normal control subject (top) and patient with CHF (bottom). Hypercapnia induced greater increases in HR, minute ventilation (V<sub>E</sub>), and MSNA in patient with CHF. MAP indicates mean arterial pressure.



**Figure 2.** Changes in minute ventilation (V<sub>E</sub>), mean arterial pressure (MAP), HR, and MSNA during hypercapnia in control subjects (○) and patients with CHF (●). Increases in minute ventilation, HR, and MSNA were significantly greater in patients with CHF. \*P<0.05, †P<0.001 for group-by-time interaction. Data are mean±SEM.

**TABLE 3. Effects of Hypoxia in Control Subjects and Patients With CHF**

Measurement	Normal Subjects		Patients With CHF		Interaction, Group-by-Time P
	Baseline	Hypoxia	Baseline	Hypoxia	
Oxygen saturation, %	98.3±0.4	88.3±1.8	96.4±0.5	86.4±1.6	0.95
End-tidal CO <sub>2</sub> , mm Hg	37±2	37±2	36±1	36±1	0.74
Minute ventilation, L/min	7.0±0.6	10.3±0.9	7.3±0.7	11.2±1.7	0.79
HR, bpm	61±4	69±5	81±4	87±4	0.57
MAP, mm Hg	84±5	85±4	85±5	88±4	0.23
MSNA, bursts/min	20±2	21±2	43±8	47±8	0.57
Integrated MSNA, %	100	139±16	100	120±10	0.35

MAP indicates mean arterial pressure. Baseline values were obtained immediately before hypoxia while subjects breathed room air with a mouthpiece. Probability values are for the group-by-time interaction term (ANOVA). Values are mean±SEM.

transient hypoxic chemosensitivity test, based on the 2 largest consecutive breaths after nitrogen inhalation, both oxygen saturation and ventilatory response may give rise to errors,<sup>12</sup> especially in the setting of periodic or Cheyne-Stokes breathing, which is common in CHF patients.<sup>35</sup> Second, the steady-state method of chemoreflex activation used in the present study enhances the likelihood of increased CO<sub>2</sub> inducing changes in the cerebrospinal fluid necessary for activation of the brainstem central chemoreceptors. Furthermore, the methodology for chemoreflex activation used in the present study has been shown to be highly reproducible.<sup>36</sup> Third, it has been suggested that augmentation of peripheral chemoreflex sensitivity is associated with the severity of chronic heart failure.<sup>14</sup> For reasons of subject safety, most of our patients were in NYHA class II and did not have significant cardiac ischemia. Thus, we cannot rule out the possibility that the potentiated ventilatory responses to hypoxia may be evident in patients in very severe heart failure and/or ischemic heart disease. It is also conceivable that the relatively small sample size may have obscured a difference in the hypoxic response, which may have been evident in a larger, more varied heart failure population.

The clear lack of potentiation of the sympathetic response to hypoxia in the present study is consistent with the results of our previous study examining the effects of chemoreflex deactivation on sympathetic traffic in patients with heart failure.<sup>18</sup> In that study, hyperoxia did not elicit any reduction in muscle sympathetic nerve activity, indicating that elevated sympathetic traffic in patients with CHF was unlikely to be explained by tonic activation of excitatory peripheral che-

moreflex afferents.<sup>18</sup> Nevertheless, in light of our present data, we cannot exclude the possibility that tonic central chemoreflex activation may contribute to elevated sympathetic activity in heart failure.

Important strengths of this study include first that both ventilatory and sympathetic responses to hypercapnia were shown to be increased, despite the inhibitory effects of ventilation on sympathetic activity. Thus, the enhanced ventilatory response represents a chemoreflex response rather than hyperventilation caused by hypercapnic stimulation of upper airway afferents. Second, ventilatory and autonomic responses to hypercapnia exclusively, not to hypoxia or the cold pressor test, were potentiated in heart failure. Hence, our findings do not represent a nonspecific potentiation of responses to stressful stimuli in general. Third, CHF patients and control subjects were closely matched for sex, age, and blood pressure, each of which may influence measurements of chemoreflex sensitivity.<sup>37-40</sup> The potential influence of these confounding variables was therefore eliminated.

It is tempting to speculate on the mechanisms and clinical implications of our findings. Regarding mechanisms, leptin may be involved in enhancing the central chemoreflex response. Leptin-deficient *ob/ob* mice have reduced hypercapnic ventilatory sensitivity, even before development of obesity.<sup>41</sup> Thus, leptin may act to potentiate central chemoreflex sensitivity. Patients with chronic heart failure have high leptin levels,<sup>42</sup> suggesting the intriguing possibility that elevated leptin in heart failure may contribute to the increased hypercapnic response in these patients. The clinical implications of an enhanced sympathetic response to CO<sub>2</sub> relate first to the

**TABLE 4. Effects of Cold Pressor Test in Control Subjects and Patients With CHF**

Measurement	Normal Subjects		Patients With CHF		Interaction, Group-by-Time P
	Baseline	CPT	Baseline	CPT	
Minute ventilation, L/min	7.3±0.6	8.4±0.6	7.2±0.4	8.3±1.1	0.98
HR, bpm	59±4	62±4	80±4	86±5	0.20
MAP, mm Hg	89±4	100±6	85±5	95±8	0.88
Integrated MSNA, %	100	236±33	100	178±32	0.42

MAP indicates mean arterial pressure. Baseline values were obtained immediately before cold pressor test (CPT) while subjects breathed room air with a mouthpiece. Probability values are for the group-by-time interaction term (ANOVA). Values are mean±SEM.

high prevalence of obstructive sleep apnea in heart failure.<sup>43</sup> Nocturnal CO<sub>2</sub> retention and consequent potentiated sympathetic vasoconstriction in heart failure may contribute to sleep apnea-related increases in norepinephrine and decreased ejection fraction in heart failure.<sup>44</sup> Second, our findings of an increased ventilatory and sympathetic response to CO<sub>2</sub> in CHF suggest a mechanistic explanation for the recent report by Andreas et al<sup>45</sup> demonstrating that nocturnal supplementation of both oxygen and CO<sub>2</sub> in CHF patients with Cheyne-Stokes respiration improved Cheyne-Stokes respiration but resulted in a marked and paradoxical increase in plasma norepinephrine.<sup>45</sup>

In summary, this is the first study to test the integrated autonomic, hemodynamic, and respiratory responses to chemoreflex activation in heart failure and to demonstrate that chronic heart failure is characterized by a potentiation of ventilatory and sympathetic responses to hypercapnia. In contrast, responses to hypoxia and to the excitatory cold pressor stimulus are not altered. This selective potentiation of central chemoreflex sensitivity may be implicated in the pathophysiology of CHF.

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