JACC Vol. 27, No. 3
March 1, 1996:650–7

Relation Between Chemosensitivity and the Ventilatory Response to Exercise in Chronic Heart Failure

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Objectives. **This study sought to establish the chemosensitivity of patients with chronic heart failure.**

Background. **The ventilatory response to exercise is often increased in patients with chronic heart failure, as characterized by the steeper regression slope relating minute ventilation to carbon dioxide output. We hypothesized that the sensitivity of chemoreceptors may be reset and may in part mediate the exercise hyperpnea seen in this condition.**

Methods. **Hypoxic and peripheral hypercapnic chemosensitivity were studied in 38 patients with chronic heart failure (35 men, 3 women; mean [±SE] age 60.2 ± 1.3 years; radionuclide left ventricular ejection fraction 25.7 ± 2.3%) and 15 healthy control subjects (11 men, 4 women; mean age 54.9 ± 3.0 years) using transient inhalations of pure nitrogen and single breaths of 13% carbon dioxide, respectively. The change in chemosensitivity during mild exercise (25 W) was assessed in the first 15 patients and all control subjects. Central hypercapnic chemosensitivity was also characterized in 25 patients and 10 control subjects by the rebreathing of 7% carbon dioxide in 93% oxygen. Cardiopulmonary exercise testing was performed in all subjects.**

Results. **Maximal oxygen consumption was 16.6 ± 0.9 versus 29.7 ± 2.2 ml/kg per min ($p < 0.0001$), and the ventilation–carbon dioxide output regression slope was 37.2 ± 1.5 versus 26.5 ± 1.4 ($p < 0.0001$) in patients and control subjects, respectively. Hypoxic and central hypercapnic chemosensitivity were enhanced in patients (0.707 ± 0.076 vs. 0.293 ± 0.056 liters/min per % arterial oxygen saturation [Sao_2], $p = 0.0001$ and 3.15 ± 0.41 vs. 2.02 ± 0.25 liters/min per mm Hg, $p = 0.025$, respectively) and correlated significantly with the ventilatory response to exercise. Hypoxic chemosensitivity was augmented during exercise in patients and in control subjects but remained higher in the former (1.530 ± 0.27 vs. 0.685 ± 0.12 liters/min per $\%Sao_2$, $p = 0.01$). The peripheral hypercapnic chemosensitivity of patients at rest and during exercise was similar to that in control subjects, consistent with its lesser contribution to overall carbon dioxide chemosensitivity.**

Conclusions. **Enhanced hypoxic and central hypercapnic chemosensitivity may play a role in mediating the increased ventilatory response to exercise in chronic heart failure.**

(J Am Coll Cardiol 1996;27:650–7)

Patients with chronic heart failure are often limited by exertional dyspnea and exercise intolerance. Although the survival of these patients has improved with vasodilator therapy, especially with angiotensin-converting enzyme inhibitors (1–4), the symptoms remain debilitating. The precise mechanisms underlying these symptoms are not known (5,6). There is little correlation between exercise tolerance and resting hemodynamic variables (7,8). Both pulmonary and peripheral factors (9), including skeletal myopathy (10–12) and impaired peripheral blood flow (13), may play a role in the genesis of these symptoms. The proportional increase in ventilation with work rate, oxygen consumption and carbon dioxide output is seen in patients with chronic heart failure during exercise as it is in normal subjects (14,15). This finding suggests that the stimulus to exercise ventilation may be humoral and that arterial chemoreceptors may play a central role. It has been documented previously that in normal subjects, the ventilatory response to exercise correlates positively with chemosensitivity (16,17). As a corollary to this, the increased ventilatory response to exercise seen in patients with chronic heart failure and characterized by the steeper regression slope relating minute ventilation to carbon dioxide output may be related to an increased chemosensitivity. On a more theoretic basis, it has also been suggested (18) that the generalized neurohormonal activation in chronic heart failure may not only be linked to a reduced input from inhibitory baroreceptors, but may also be caused by an increased input from excitatory chemoreceptors. On the basis of these considerations, we hypothesized that the sensitivity of chemoreceptors to arterial blood gases may be reset and may in part mediate the exercise hyperpnea seen in this condition. The purpose of this study was, therefore, to examine the chemosensitivity of patients with chronic heart failure, which hitherto has not been evaluated, and to assess its relation with the ventilatory response to exercise.

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Manuscript received July 19, 1995; revised manuscript received October 12, 1995, accepted October 17, 1995.

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0735-1097/96/$15.00
0735-1097(95)00523-4

Table 1. Characteristics of Normal Subjects and Patients With Chronic Heart Failure

	Normal Control Subjects (n = 15)	Patients With CHF (n = 38)
Age (yr)	54.9 ± 3.0	60.2 ± 1.3
Male:female	11:4	35:3
Height (cm)	169.5 ± 2.4	172.1 ± 1.2
Weight (kg)	73.9 ± 4.1	79.5 ± 2.4
Spirometry		
FEV_1 (% predicted)	105.9 ± 4.6	85.3 ± 2.9
FVC (% predicted)	112.1 ± 2.9	89.2 ± 2.7
Etiology of CHF		
IHD		22
DCM		12
Other*		4
NYHA functional class		
I		1
II		19
III		16
IV		2
Treatment		
Diuretic drugs		38
Dose of furosemide (mg) or its equivalent†		64.2 ± 5.2
ACE inhibitors		35
Digoxin		10
LVEF (%)		25.7 ± 2.3
Max O_2 consumption (ml/kg per min)	29.7 ± 2.2	16.6 ± 0.9
V_E-V_{CO_2} slope	26.54 ± 1.40	37.15 ± 1.50

*Two patients had valvular heart disease, and one had alcohol-related and one hypertension-related cardiomyopathy. †One milligram of bumetanide was taken as equivalent to 40 mg of furosemide. Data presented are mean value ± SE or number (%) of patients. ACE = angiotensin-converting enzyme; CHF = chronic heart failure; DCM = idiopathic dilated cardiomyopathy; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; Max = maximal; NYHA = New York Heart Association; V_E-V_{CO_2} slope = regression slope relating minute ventilation to carbon dioxide output.

Methods

Subjects. Thirty-eight patients with chronic heart failure between 40 and 75 years of age (mean age [±SE] 60.2 ± 1.3 years; 35 men, 3 women) participated in the study. Patients with a known history of pulmonary and neurologic disease were excluded from the study. All patients had been in heart failure for >3 months. They were all treated with diuretic drugs, and most received angiotensin-converting enzyme inhibitors. Nineteen patients were in New York Heart Association functional class II, and 16 in class III. No patient was limited by angina. Patient characteristics are summarized in Table 1. A control group of 15 healthy subjects (31 to 73 years old, mean age 54.9 ± 3.0 years; 11 men, 4 women) was also studied.

Hypoxic and peripheral hypercapnic chemosensitivity, both mediated by the carotid chemoreceptors, was assessed at rest in all subjects. The first 15 consecutive patients with chronic heart failure recruited into the study also had these assessments made during mild exercise on a cycle ergometer (Tunturi) at 25 W for 10 min on two separate occasions to evaluate the change in chemosensitivity on exercise. A fixed external work rate was used based on the observation that for a particular work rate, patients with chronic heart failure have a higher ventilatory response than normal subjects (14). In addition, central hypercapnic chemosensitivity was assessed in 10 control subjects and 25 patients to assess the role of central (medullary) chemoreceptors. All subjects performed cardiopulmonary exercise testing to assess the ventilatory response to exercise. Subjects were told to avoid caffeinated products on the morning of the tests. The study had been approved by the local ethics committee, and all subjects gave written informed consent.

Transient hypoxic ventilatory response test. There are three principal methods of assessing hypoxic chemosensitivity using steady state (19), progressive (20,21) and transient (22) hypoxia, respectively. The absolute values obtained from each method are different, but relatively, they reflect the same indexes of chemosensitivity (23,24). The transient hypoxic method was chosen in this study for practical and safety reasons because patients were not subjected to prolonged episodes of hypoxia, especially during exercise, and the depressant effects of prolonged hypoxia on central respiratory drive are also avoided.

The transient hypoxic chemosensitivity test was performed while subjects were seated and after a period of quiet breathing. Each subject wore a nose clip and breathed through a pneumatic respiratory valve (Innovision), which separated the expirate from the inspirate. The inspirate port was further connected to a T-valve placed behind the subject, and, depending on the position of the T-valve, the subject breathed either room air or pure nitrogen from a 4-liter reservoir bag that was quietly refilled from a gas cylinder containing pure nitrogen. Minute ventilation was measured breath by breath using a heated pneumotachograph, and continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry (Amis 2000, Innovision). The pneumotachometer and mass spectrometer were calibrated before each test. Arterial oxygen saturation was measured using a pulse oximeter (model N-200E, Nellcor), set at fast mode with a response time of 2 to 3 s and a lightweight ear probe clipped gently on the subject's right earlobe. After the subject breathed room air for several minutes, the T-valve was turned surreptitiously during the expiratory phase of the previous breath so that pure nitrogen was inhaled for two to eight breaths. This was repeated 10 to 15 times to provide a wide range of arterial oxygen saturations from 70% to 100%, with ~2-min intervals of air breathing between exposures to allow arterial oxygen saturation and end-tidal carbon dioxide to return to the subject's baseline. The maximal minute ventilation after each period of nitrogen inhalation was obtained by averaging the two largest consecutive breaths. We found the two-breath period optimal in maintaining sensitivity and reproducibility of the transient hypoxic test, as did Edelman et al. (25). The maximal ventilation was then plotted against the lowest arterial oxygen saturation reached for every period of nitrogen inha-

lation. The transient hypoxic chemosensitivity was obtained as the slope of the best-fit line that related ventilation to arterial oxygen saturation, calculated by least-squares linear regression analysis and expressed in terms of liters per minute per percent oxygen saturation (liters/min per $\%Sao_2$). For the transient hypoxic test during exercise, on average, only six episodes of transient hypoxia were given in view of the duration of the exercise. A delay of 3 min after the onset of exercise was given before the hypoxic chemosensitivity testing to allow steady state (26,27). For safety reasons, the degree of arterial oxygen desaturation was deliberately kept >80%. All patients were monitored electrocardiographically during exercise.

Single-breath carbon dioxide ventilatory response test. Peripheral hypercapnic chemosensitivity was assessed using the single-breath carbon dioxide test as described by McClean et al. (28). The apparatus including the T-valve was the same as that described before. A smaller 2-liter reservoir bag was used, which was quietly refilled after each inhalation with a gas mixture containing 13% carbon dioxide in air. After a period of quiet breathing, the T-valve was turned during the expiratory phase of the previous breath so that the subject inhaled a single breath of 13% carbon dioxide in air. On average, 10 breaths were administered at ~2-min intervals. As before, minute ventilation was measured, with continuous monitoring of carbon dioxide done at the mouth. The mean minute ventilation of the preceding five breaths before the stimulus carbon dioxide breath was calculated and taken as the control ventilation [$\dot{V}(C)$]. The mean end-tidal fraction of carbon dioxide of these breaths was also calculated and taken as the control end-tidal fraction of carbon dioxide [$F_{ETCO_2}(C)$]. The response ventilation after the stimulus carbon dioxide breath [$\dot{V}(S)$] was calculated by averaging the two largest consecutive breaths but, unlike before, within 20 s after the stimulus breath. Breaths beyond this time limit were assumed to be affected by central chemoreceptors and therefore excluded from analysis (28). The end-tidal carbon dioxide concentration of the stimulus breath was considered the stimulus end-tidal fraction of carbon dioxide [$F_{ETCO_2}(S)$]. The single-breath carbon dioxide response was calculated using the previous variables as follows:

$$\text{Single-breath } CO_2 \text{ response} = \frac{\dot{V}(S) - \dot{V}(C)}{[F_{ETCO_2}(S) - F_{ETCO_2}(C)] \times (P_B - 47)}$$

where P_B is the atmospheric pressure (mm Hg), and 47 is the saturated water vapor pressure (mm Hg). The mean of 10 responses was considered the subject's single-breath carbon dioxide response at rest and expressed in liters per minute per millimeter Hg (liters/min per mmHg). For the 10-min exercise period at 25 W on the cycle ergometer, an average of six single breaths of carbon dioxide were administered at shorter time intervals in view of increased minute ventilation and circulation during exercise. These were given 3 min after the onset of exercise to allow steady state.

Carbon dioxide rebreathing technique. Central hypercapnic chemosensitivity was assessed using rebreathing of carbon dioxide (29). During the test, expired carbon dioxide is constantly returned to the lungs, and as carbon dioxide accumulates, this provides a progressive carbon dioxide stimulus to ventilation. After a period of quiet breathing, subjects rebreathed through a 6-liter bag containing a gas mixture of 7% carbon dioxide in oxygen for 4 min; the test was stopped sooner if they were too breathless to continue or if P_{ETCO_2} exceeded 10%. It has been shown (29) that by rebreathing of 7% carbon dioxide (which approximates to venous $P(\bar{v})_{CO_2}$) in oxygen, a P_{CO_2} equilibrium is developed rapidly in the mixed venous blood, arterial blood, gas in the lung and gas in the breathing bag. Thus, the $P(\bar{v})_{CO_2}$ in any one of these compartments is representative of the other compartments, including the brain tissue. With the high oxygen concentration, the peripheral hypercapnic response is known to be very small or negligible (30,31). Minute ventilation was measured breath by breath, and continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry. The central hypercapnic chemosensitivity was obtained as the slope that related minute ventilation to P_{ETCO_2} calculated by linear regression analysis and expressed in terms of liters per minute per millimeter Hg (liters/min per mm Hg). We did not perform this test during exercise because of the uncertainties of P_{CO_2} equilibrium during exercise in all the compartments (mixed venous blood, arterial blood, gas in the lung and gas in the breathing bag) using the same mixture of 7% carbon dioxide in oxygen.

Studies of reproducibility. The transient hypoxic, single-breath carbon dioxide and rebreathing carbon dioxide tests were repeated in seven healthy control subjects and five patients with chronic heart failure to assess reproducibility and the coefficient of variation. There was good agreement between repeated measurements ($r = 0.93$, 0.69 and 0.97, respectively, $p < 0.05$ for all three tests), with the mean coefficient of variation of the respective tests being 21.4 ± 3.0%, 21.0 ± 4.9% and 14.6 ± 4.4%, accordingly, comparable to other studies (24,28,29). Similarly, the mean value of the respective tests in our control subjects compared favorably with previous data (24,25,28,29).

Cardiopulmonary exercise testing. Cardiopulmonary exercise testing was performed in all subjects on a separate day to determine the exercise ventilation. All exercised to exhaustion (respiratory exchange ratio > 1.1) using the Bruce protocol (32), with the addition of a "stage 0" at 1.0 mph and 5% gradient for the patients with chronic heart failure. Respiratory gas exchange analysis was carried out by means of a respiratory mass spectrometer (Amis 2000, Innovision) using the inert gas dilution technique (33). The slope of the regression line relating minute ventilation to carbon dioxide output was used as an index of the ventilatory response to exercise (15).

Statistical analysis. Results are presented as mean value ± SE. Two-tailed Student *t* test was used where appropriate to assess the significance of results. The relation between variables was assessed using linear regression analysis; $p < 0.05$ was considered significant.

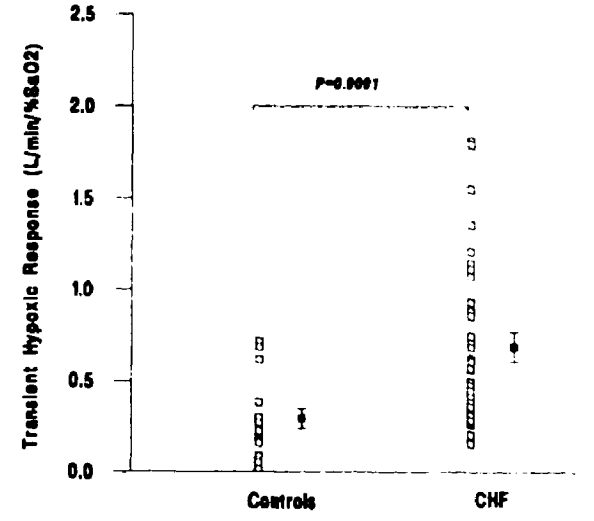


Figure 1. Transient hypoxic chemosensitivity in patients with chronic heart failure (CHF) versus normal subjects. SaO2 = arterial oxygen saturation.

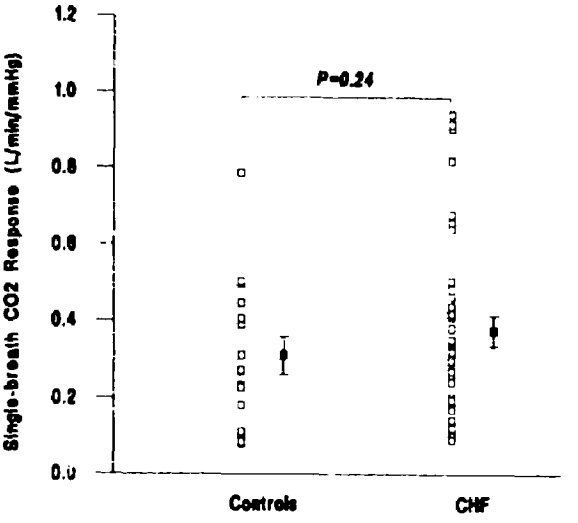


Figure 2. Single-breath carbon dioxide (CO2) response in patients with chronic heart failure (CHF) versus normal subjects.

Results

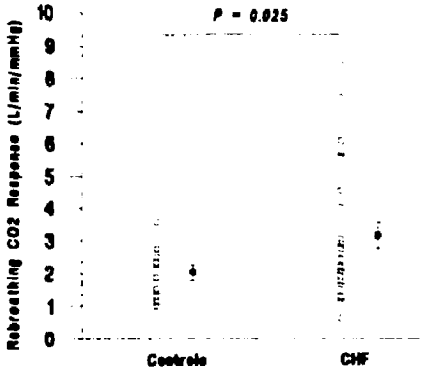
Cardiopulmonary exercise testing. Mean age, height and weight of control subjects and patients with chronic heart failure did not differ significantly (Table 1). Also shown in Table 1, patients with chronic heart failure had a lower maximal oxygen consumption ($p < 0.0001$) and higher ventilatory response to exercise as judged by the higher ventilation–carbon dioxide output regression slope compared with that for control subjects ($p < 0.0001$). There was no significant difference in maximal oxygen consumption (16.4 ± 0.8 vs. 17.3 ± 2.3 ml/kg per min), ventilation–carbon dioxide output regression slope (38.13 ± 1.70 vs. 34.60 ± 3.40) or left ventricular ejection fraction (27.1 ± 2.8 vs. 22.7 ± 4.5%) between patients with chronic heart failure from ischemic heart disease and idiopathic dilated cardiomyopathy who participated in the study.

Hypoxic chemosensitivity. Figure 1 shows a significantly higher transient hypoxic ventilatory response in patients with chronic heart failure (0.707 ± 0.076 liters/min per $\%Sao_2$) than in control subjects (0.293 ± 0.056 liters/min per $\%Sao_2$). When the results of the transient hypoxic ventilatory test were analyzed separately for patients with chronic heart failure from ischemic heart disease and idiopathic dilated cardiomyopathy, there was no significant difference between the two groups (0.642 ± 0.088 vs. 0.819 ± 0.14 liters/min per $\%Sao_2$, $p = 0.3$).

Hypercapnic chemosensitivity. The peripheral hypercapnic chemosensitivity was higher in patients with chronic heart failure (0.388 ± 0.04 vs. 0.310 ± 0.051 liters/min per mm Hg), but this did not reach statistical significance (Fig. 2). On the contrary, when central hypercapnic chemosensitivity was assessed in 25 of the patients with chronic heart failure, there was a significant difference between patients and control subjects (3.15 ± 0.41 vs. 2.02 ± 0.25 liters/min per mm Hg, $p = 0.025$) (Fig. 3). These 25 patients had similar age (57.3 ± 1.7 years), maximal oxygen consumption (17.8 ± 1.1 ml/kg per min), ventilation–carbon dioxide output regression slope (37.8 ± 2.0) and left ventricular ejection fraction (23.4 ± 2.8%) when compared with the total patient group studied. Fourteen patients had ischemic heart disease, and nine had idiopathic cardiomyopathy. There was no difference in central hypercapnic chemosensitivity between these two groups of patients (3.20 ± 0.51 vs. 3.27 ± 0.83 liters/min per mm Hg, $p = 0.95$). Of these 25 patients, 11 were in New York Heart Association functional class II and 13 in class III.

Chemosensitivity, functional impairment and exercise ventilatory response. To see whether there was any relation between hypoxic and central hypercapnic chemosensitivity and functional impairment, we compared the respective chemosensitivity in patients in functional classes II and III, as shown in Figure 4. Although the hypoxic chemosensitivity was higher in

Figure 3. Central hypercapnic chemosensitivity as measured by carbon dioxide (CO2) rebreathing in patients with chronic heart failure (CHF) versus normal subjects.



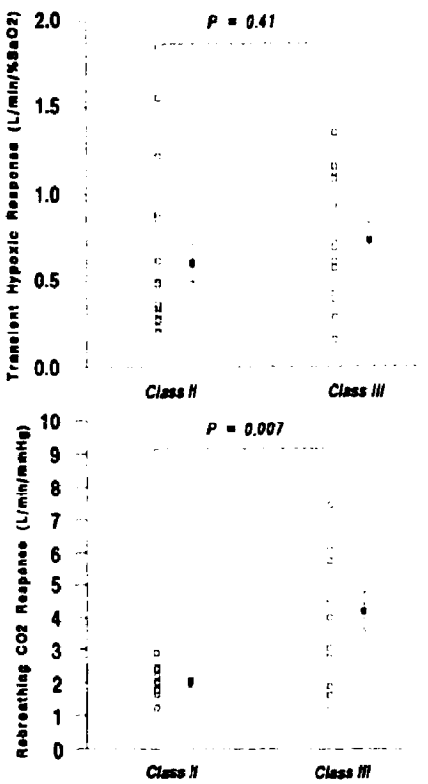
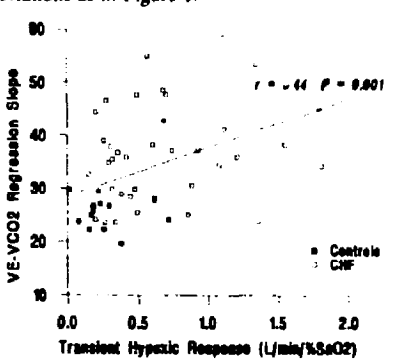


Figure 4. $Tc_{\dot{V}}$. Relation between hypoxic chemosensitivity and functional capacity showing a higher chemosensitivity in New York Heart Association functional class III, although not statistically significant because of much overlap between patients in classes II and III. **Bottom,** Relation between central hypercapnic chemosensitivity and functional capacity. Abbreviations as in Figures 1 and 2.

functional class III than class II, this was not statistically significant (0.724 ± 0.10 vs. 0.600 ± 0.11 liters/min per % Sao_2, p = 0.41). In contrast, central hypercapnic chemosensitivity tended to be more discriminatory, with patients in functional class III having a significantly higher chemosensitivity than

Figure 5. Relation between ventilation–carbon dioxide output (VE-VCO2) regression slope and transient hypoxic chemosensitivity at rest. Other abbreviations as in Figure 1.



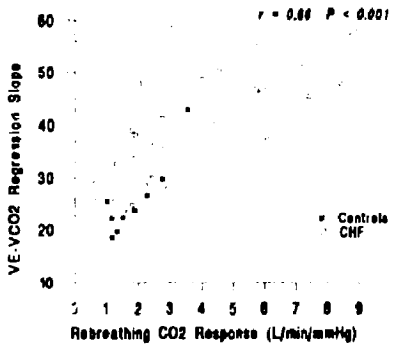


Figure 6. Relation between ventilation-carbon dioxide output regression slope and central hypercapnic chemosensitivity. Abbreviations as in Figures 2 and 5.

those in class II (4.17 ± 0.66 vs. 2.00 ± 0.14 liters/min per mm Hg, p = 0.007) (also shown in Fig. 4).

A significant correlation was seen between the ventilatory response to exercise and hypoxic chemosensitivity, as shown in Figure 5 (r = 0.44, p = 0.001). There was also a significant correlation between the ventilatory response to exercise and central hypercapnic chemosensitivity, as shown in Figure 6 (r = 0.66, p < 0.001). There was no correlation between the ventilatory response to exercise and the peripheral hypercapnic chemosensitivity (r = 0.08, p = 0.94).

Chemosensitivity during mild exercise. The 15 patients with chronic heart failure who had their chemosensitivity assessed during mild exercise showed similar baseline characteristics (age 60.7 ± 1.3 years; maximal oxygen consumption 17.9 ± 1.4 ml/kg per min; ventilation–carbon dioxide output regression slope 34.13 ± 2.30; left ventricular ejection fraction 27.5 ± 3.6%) compared with all patients with chronic heart failure as a group. As shown in Table 2, the transient hypoxic

Table 2. Summary of Chemosensitivity Results at Rest and During Mild Exercise in Normal Control Subjects and Patients With Chronic Heart Failure

Chemosensitivity	Normal Control Subjects (n = 15)	Patients With CHF (n = 15)	p Value
Transient hypoxia (liters/min per % Sao_2)			
Rest	0.293 ± 0.056	0.684 ± 0.130	0.01
Mild exercise (25 W)	0.685 ± 0.120	1.530 ± 0.270	0.01
Mean augmentation during exercise*	3.05 ± 0.62	2.66 ± 0.37	NS
Single-breath CO_2 (liters/min per mm Hg)			
Rest	0.310 ± 0.051	0.324 ± 0.046	NS
Mild exercise (25 W)	0.507 ± 0.052	0.534 ± 0.084	NS
Mean augmentation during exercise*	2.51 ± 0.42	2.05 ± 0.43	NS

*Mean value of all individual augmentation during mild exercise expressed as a fraction of rest value. Data presented are mean value ± SE. CHF = chronic heart failure; CO_2 = carbon dioxide; Sao_2 = arterial oxygen saturation.

response during exercise in these 15 patients was 1.530 ± 0.270 liters/min per $\%Sao_2$ compared with 0.685 ± 0.120 liters/min per $\%Sao_2$ in normal subjects. Despite augmentation of the hypoxic chemosensitivity during exercise in both control subjects and patients with chronic heart failure, the transient hypoxic response remained significantly higher in patients. Also shown in Table 2, the peripheral hypercapnic chemosensitivity was also augmented during exercise in control subjects and patients, but there was no significant difference between the two groups.

When the hypoxic chemosensitivity measured during mild exercise was correlated with ventilation–carbon dioxide output regression slope, the relation between these two variables remained intact, with a correlation coefficient of 0.41 ($p = 0.024$). A weak association between the single-breath carbon dioxide response during exercise and ventilation–carbon dioxide output regression slope was also seen ($r = 0.34$, $p = 0.07$).

Discussion

General findings. Little is known about chemosensitivity in chronic heart failure. It has been documented that central hypercapnic chemosensitivity is enhanced in patients with chronic heart failure with central sleep apnea, but hypoxic chemosensitivity was not studied (34). We demonstrated in the present study that there is increased hypoxic and central hypercapnic chemosensitivity in patients with chronic heart failure. We showed that patients in functional class III had a higher chemosensitivity than those in class II, although this was not statistically significant with respect to hypoxic chemosensitivity. The lack of differentiation may be because there is much overlap in hypoxic chemosensitivity between patients in functional classes II and III, or perhaps hypoxic chemosensitivity is less associated with the functional capacity of patients. It has to be acknowledged that even in normal subjects, both hypoxic and hypercapnic chemosensitivity may vary considerably between subjects (35). However, the central hypercapnic chemosensitivity was significantly higher in patients in a higher functional class and may therefore relate more to the severity of chronic heart failure.

The absence of a significant increase in single-breath carbon dioxide response in patients with chronic heart failure is surprising although not totally unexpected. The single-breath carbon dioxide response test measures the peripheral hypercapnic chemosensitivity. Functional hypercapnic chemosensitivity is predominantly mediated by the central chemoreceptors. Some studies (30) have shown that the peripheral hypercapnic chemosensitivity accounts for only about one tenth of overall carbon dioxide chemosensitivity.

Mechanisms causing increased chemosensitivity. There are several possible mechanisms causing increased hypoxic chemosensitivity in patients with chronic heart failure. It is recognized that there are neurohormonal changes (36,37) in patients with chronic heart failure, and these include increased catecholamine levels. Catecholamines are known to potentiate chemosensitivity (38,39). Peripheral blood flow is also known to be reduced in chronic heart failure (13), and this may be related to reduced cardiac output or increased vasomotor tone. It has been previously suggested that a decrease in chemoreceptor blood flow, causing an ischemic hypoxia, may also mediate an increase in chemosensitivity (40).

Mechanisms causing altered central hypercapnic chemosensitivity are more obscure. Alteration in central neurogenic input or signals from muscle ergoreceptors (41,42) may induce changes in central hypercapnic chemosensitivity. Alternatively, signals from muscle ergoreceptors may feed directly into the respiratory control centers, causing central augmentation of both medullary and carotid chemoreceptor input. We have recently shown that the contribution of ergoreceptors to the ventilatory response to exercise is higher in patients with chronic heart failure than in control subjects (43). Early lactic acidosis during exercise may reduce the buffering ability in patients with chronic heart failure with consequent increased chemoreceptor activity, but this cannot explain the increased chemosensitivity at rest. Perhaps the interaction of carbon dioxide with other ventilatory control mechanisms may offer clues. It may be that the respiratory control centers are similarly and nonspecifically more responsive to various stimuli including carbon dioxide and exercise (44).

Relation between chemosensitivity and exercise ventilation. The role of chemosensitivity in mediating the ventilatory response to exercise is not known in chronic heart failure. In normal subjects, it has been shown in one study that carbon dioxide chemosensitivity, as measured by the rebreathing method, is related to the ventilatory response to exercise (16). In another study, exercise ventilation has been shown to be positively correlated with both hypoxic and hypercapnic chemosensitivity in healthy subjects (17). The mechanisms by which chemoreceptors may mediate exercise hyperpnea remain unclear, because there is little fluctuation in arterial blood gases, the putative stimuli, during exercise. Suggested mechanisms include an increased gain in chemosensitivity during exercise (45,46). Augmentation in chemosensitivity during exercise has been well documented in normal subjects (38,47). In other words, for a given partial pressure of arterial blood gases, it represents a higher stimulus to ventilation than otherwise, had the chemosensitivity not been enhanced. Thus, the absence of significant hypoxemia or hypercapnia does not exclude the existence of increased chemosensitivity. In our study, we showed an increase in rest hypoxic and central hypercapnic chemosensitivity in patients with chronic heart failure compared with that in normal subjects. There was also a significant degree of correlation between resting chemosensitivity and the ventilatory response to exercise. Hypoxic and hypercapnic (at least the peripheral component) chemosensitivity were shown to be augmented in patients with chronic heart failure during exercise. The augmentation in chemosensitivity during exercise may be explained by a further increase in catecholamines during exercise (38), elevation of arterial potassium level (48) or perhaps early lactic acidosis during exercise. Increased oscillations in arterial carbon dioxide, oxygen and pH caused by exercise and exaggerated in heart

failure may also be a possible mechanism of augmentation of chemosensitivity during exercise. The potential importance of such oscillations as a mechanism by which chemoreceptors may affect exercise hyperpnea has been documented previously (49,50). In chronic heart failure, the increased ventilatory response to exercise is often attributed to the increase in dead space ventilation (51). However, it remains to be answered how this dead space is sensed by the body, particularly if arterial blood gases remain little changed in chronic heart failure (52). Increased physiologic dead space and ventilation–perfusion mismatch may well increase the amplitude of oscillations in blood gases that is sensed by chemoreceptors. They may therefore also be important in mediating the effects of increased dead space and ventilation–perfusion mismatch in chronic heart failure.

Conclusions. The increase in chemosensitivity may serve as a compensatory mechanism producing an increase in ventilatory response during exercise and thereby preserving blood gas homeostasis, including maintaining arterial oxygen concentration. In fact, it has been shown (53) that increasing inspired oxygen concentration during exercise improves breathlessness and reduces minute ventilation in these patients. Other investigators (54) have reported mechanisms such as increased erythropoiesis that directly improve arterial oxygen content in chronic heart failure patients to compensate for reduced systemic arterial oxygen delivery.

In conclusion, there is increased hypoxic and central hypercapnic chemosensitivity in patients with chronic heart failure. Both hypoxic and hypercapnic chemosensitivity appear to correlate well with the ventilatory response to exercise. Although this association does not necessarily mean causation, arterial chemoreceptors may mediate the exercise hyperpnea seen in patients with this condition. The control of ventilation during exercise is complex, probably more so in chronic heart failure. Therefore, although increased chemosensitivity may play a role in the exercise hyperpnea in chronic heart failure, there are likely to be other factors involved. Furthermore, although this study shows the association between enhanced chemosensitivity and the increased ventilatory response to exercise, it should be emphasized that the latter is not synonymous with the sensation of dyspnea. It thus remains to be seen whether drugs that suppress chemosensitivity, such as mild opiates (55), would be of therapeutic benefit in relieving the debilitating symptoms of breathlessness in chronic heart failure.

Limitations of the study. With the transient hypoxic chemosensitivity test, both the arterial oxygen desaturation and the resultant ventilatory response are fleeting in nature. The measurement of arterial oxygen saturation and the use of a two-breath period to define maximal minute ventilation in such conditions, although necessary under the constraints of the method, may give rise to errors. However, a pulse oximeter (Nellcor N-200E) with a fast response time of 2 to 3 s was used in our study. Previous studies have demonstrated the accuracy (±3%) and reliability of arterial oxygen saturation obtained by pulse oximeter of this particular model in comparison to direct measurement of arterial blood samples (56,57). Furthermore, as shown by Shaw et al. (24), the transient method can give as good an index of hypoxic chemosensitivity as the progressive method.

From the results of the first 15 consecutive patients with chronic heart failure, we found that the hypoxic chemosensitivity was significantly higher in chronic heart failure, both at rest and during exercise. We therefore discontinued assessing the exercise chemosensitivity of the remaining patients, primarily because hypoxia during exercise was unpleasant to patients and had a certain associated risk. These 15 patients had similar age, exercise capacity, radionuclide ejection fraction and resting chemosensitivity compared with all the patients with chronic heart failure we studied as a whole. Despite only a randomly chosen subgroup of subjects having had the carbon dioxide rebreathing test, we were able to demonstrate that the central hypercapnic chemosensitivity was increased in patients with chronic heart failure. We did not attempt to measure central hypercapnic chemosensitivity during exercise, for the reasons stated, which may have otherwise added more information to our study.

Finally, because of the obvious limitation of using ventilatory changes to quantitate chemosensitivity, it is not possible to distinguish whether the increased ventilatory responses to hypoxia or hypercapnia are solely related to an increased gain in intrinsic chemoreceptor function or whether they reflect the altered kinetics caused by an increased dead space in heart failure. However, as discussed earlier, there are several abnormalities in chronic heart failure that may cause an increased chemosensitivity, thus making it unlikely that the results in this study are largely caused by an increased dead space. Furthermore, there is a fundamental difference between the ventilatory response to metabolic changes during exercise and the ventilatory response to hypoxia or hypercapnia, as in the tests of chemosensitivity, in relation to dead space. The ventilatory response to exercise represents a response to an endogenous load, whereas the latter represents that to an external stimulus. An increased dead space may actually diminish the level of the external stimulation reaching the arterial chemoreceptors. That there was an increase in chemosensitivity therefore suggests that there is an inherent change in chemoreceptor function.

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