Enhanced Ventilatory Response to Exercise in Patients With Chronic Heart Failure and Preserved Exercise Tolerance
Marker of Abnormal Cardiorespiratory Reflex Control and Predictor of Poor Prognosis

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Background—In patients with chronic heart failure (CHF) and preserved exercise tolerance, the value of cardiopulmonary exercise testing for risk stratification is not known. Elevated slope of ventilatory response to exercise (VE/VO2) predicts poor prognosis in advanced CHF. Derangement of cardiopulmonary reflexes may trigger exercise hyperpnea. We assessed the relationship between cardiopulmonary reflexes and VE/VO2 and investigated the prognostic value of VE/VO2 in CHF patients with preserved exercise tolerance.

Methods and Results—Among 344 consecutive CHF patients, we identified 123 with preserved exercise capacity, defined as a peak oxygen consumption (peak VO2) $\geq 18$ mL · kg$^{-1}$ · min$^{-1}$ (age 56 years; left ventricular ejection fraction 28%; peak VO2 23.5 mL · kg$^{-1}$ · min$^{-1}$). Hypoxic and hypercapnic chemosensitivity (n = 38), heart rate variability (n = 34), baroreflex sensitivity (n = 20), and ergoreflex activity (n = 20) were also assessed. We identified 40 patients (33%) with high VE/VO2 (ie, >34.0). During follow-up (49±22 months, >3 years in all survivors), 34 patients died (3-year survival 81%). High VE/VO2 (hazard ratio 4.3, $P$ <0.0001) but not peak VO2 ($P$ =0.7) predicted mortality. In patients with high VE/VO2, 3-year survival was 57%, compared with 93% in patients with normal VE/VO2 ($P$ <0.0001). Patients with high VE/VO2 demonstrated impaired reflex control, as evidenced by augmented peripheral ($P$ =0.01) and central ($P$ =0.0006) chemosensitivity, depressed low-frequency component of heart rate variability ($P$ <0.0001) and baroreflex sensitivity ($P$ =0.03), and overactive ergoreceptors ($P$ =0.003) compared with patients with normal VE/VO2.

Conclusions—In CHF patients with preserved exercise capacity, enhanced ventilatory response to exercise is a simple marker of a widespread derangement of cardiovascular reflex control; it predicts poor prognosis, which peak VO2 does not. (Circulation. 2001;103:967-972.)

Key Words: heart failure ■ ventilation ■ respiration ■ prognosis

Cardiopulmonary exercise testing with gas-exchange measurement has become well established in routine clinical evaluation and risk stratification of patients with chronic heart failure (CHF). Poor exercise capacity, measured objectively by low peak oxygen consumption (peak VO2), predicts an unfavorable outcome independently of other clinical and hemodynamic parameters. Among CHF patients with preserved exercise tolerance, however, the role of cardiopulmonary exercise testing for predicting prognosis has not been evaluated. Despite recent advances in the management of CHF, the annual mortality in this group is still unacceptably high, and risk stratification remains an important clinical challenge.

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We recently reported that an excessive ventilatory response to exercise, expressed as ventilation per unit of carbon dioxide production (ie, VE/VO2 slope), is a marker of poor prognosis for patients with moderate to severe CHF. Because VE/VO2 can be measured readily from the data routinely acquired during cardiopulmonary exercise testing, it has the advantage of universal availability at no additional cost or patient inconvenience. The mechanisms responsible for exercise hyperpnea have not yet been fully elucidated, but overactive reflexes from chemoreceptors and ergoreceptors may play a role.

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A derangement of cardiopulmonary reflexes occurs in CHF and may not be restricted to advanced stages of the disease. In less symptomatic patients, it may underlie the enhanced ventilatory response to exercise, because in this group, increased ventilation is not closely associated with functional and hemodynamic impairment. In these patients, abnormal control of the cardiorespiratory reflexes may also reflect a greater disruption of the physiological milieu, which in turn has the potential to be an early marker of poor outcome.

The aim of this study was to assess whether an abnormal ventilatory response to physical stress could predict poor prognosis in CHF patients with preserved exercise tolerance. Furthermore, in the attempt to elucidate the physiological basis of this elevated ventilation, the relationship between cardiorespiratory reflexes and ventilatory response to exercise was assessed.

Methods

Patients
Consecutive CHF patients who were referred to our laboratory between January 1993 and March 1997 for cardiopulmonary exercise testing and met the following criteria were considered for the study: >6-month history of CHF, clinically stable for >1 month preceding the study, with no signs of fluid retention, and with preserved exercise tolerance, as evidenced by peak VO2 ≥18 mL · kg⁻¹ · min⁻¹. Considering NYHA functional classification as being fairly subjective, we decided to use peak VO2 as an objective measure of exercise capacity for selection of our patients. It has been demonstrated that peak VO2 values ≥18 mL · kg⁻¹ · min⁻¹ identify CHF patients who have only mildly impaired or nearly normal exercise capacity and are considered to imply uniformly good outcome. Therefore, this cutoff value was chosen as a selection criterion. Exclusion criteria included significant pulmonary disease and musculoskeletal disorders.

To assess the supplementary question of whether indices derived from cardiopulmonary exercise testing may have a different prognostic usefulness in patients with less-well-preserved exercise capacity (peak VO2 between 14 and 18 mL · kg⁻¹ · min⁻¹), we separately analyzed a supplementary group of patients in this range who were studied in our institution within the same period.

The local Ethics Committee approved the study protocol.

Exercise Testing
Patients underwent symptom-limited treadmill exercise testing with respiratory gas exchange analysis. Minute ventilation (Ve), oxygen consumption (Vo2), and carbon dioxide production (Vco2) were measured by heated pneumotachograph and mass spectrometry (Amis 2000, Innovision, Denmark). The Ve/VCO2 slope was calculated in every subject as the slope of the regression line relating Ve to VCO2 during exercise testing and was used as an index of the ventilatory response to exercise. An abnormally high Ve/VCO2 slope was defined as above the mean+2 SD of our previously reported age-matched control group (ie, >34.0).7

Assessment of Cardiopulmonary Reflex Control
The evaluations of cardiopulmonary reflexes were performed in the morning (9 to 12 AM) in a quiet laboratory environment. Patients were asked not to smoke or drink caffeine on the study day.

Hypoxic Chemosensitivity Evaluation
Hypoxic chemosensitivity was assessed by the transient hypoxic method6 and expressed in liters per minute per percent O2 saturation (L · min⁻¹ · %SaO2⁻¹).

Hypercapnic Chemosensitivity Evaluation
Hypercapnic chemosensitivity was assessed by the standard method using rebreathing from a 6-L bag initially containing 7% CO2 and 93% O2. Hypercapnic chemosensitivity was expressed in liters per minute per mm Hg of CO2 (L · min⁻¹ · mm Hg⁻¹).

Cardiac Autonomic Control
To measure the ergoreflex response, the subjects performed dynamic handgrip followed by posthandgrip regional circulatory occlusion (PH-RCO). This protocol, which has been described and validated elsewhere, allows the metabolic state of the muscle to be fixed and prolongs the activation of the ergoreceptors. Ergoreflex activity was assessed and quantified as the percentage ventilatory response to exercise, which was maintained by PH-RCO compared with recovery without PH-RCO (%V).

Follow-Up
Patients were regularly seen by the study investigators at the outpatient CHF clinic, with a follow-up duration of ≥3 years in all who survived. Information regarding survival (as of March 31, 2000) was obtained from the hospital information system and from the UK Office of National Statistics, where all patients of the Royal Brompton Hospital are flagged for follow-up. No patient was lost to follow-up. The primary end point of the study was all-cause mortality.

Statistical Analysis
Data are expressed as mean±SD. For statistical analysis, the LF components HRV, BRS, and hypoxic and hypercapnic chemosensitivities were logarithmically transformed to correct for a skewed distribution. The unpaired Student’s t test was used to compare differences between groups. Univariate and multivariate regression analyses were applied to assess factors that independently predicted Ve/Vco2 slope. A value of P<0.05 was considered significant. The relationship of baseline variables with survival was assessed by Cox proportional-hazards analysis (univariate and multivariate analysis). To estimate the influence of risk factors on early (6-month) and long-term (3-year) survival, Kaplan-Meier cumulative survival curves were constructed and compared by the Mantel-Haenszel log-rank test.

Results
Among 344 consecutive CHF patients who underwent cardiopulmonary exercise testing, we identified 123 (36%) who met the study criteria and had preserved exercise capacity (peak VO2 ≥18 mL · kg⁻¹ · min⁻¹); their mean age was 56±9 years; 110 (89%) were in New York Heart Association (NYHA) class I to II, and 13 (11%) were in NYHA class III; their mean left ventricular ejection fraction (LVEF, measured by nuclear ventriculography, n=90) was 28±11%; and CHF etiology was ischemic heart disease in 65 patients (53%), idiopathic dilated cardiomyopathy in 52 (42%), and other
heart disease in 6 (5%). In all patients, the respiratory gas exchange ratio (VCO2/VO2) exceeded 1.0 at peak exercise, indicating adequate exertion. The patients’ mean peak VO2 was 23.5±5.0 mL·kg⁻¹·min⁻¹, and the mean VE/VCO2 slope was 31.4±8.5.

Thirty-five (28%) of the 123 patients in this report were also prospectively entered into a prognostic study of cardiopulmonary reflexes in CHF, which is reported separately.¹²

Forty patients (33%) demonstrated an abnormally high ventilatory response to exercise (VE/VCO2 slope >34.0) and had a lower peak VO2 (21.8 versus 24.2 mL·kg⁻¹·min⁻¹, P=0.01) and LVEF (25% versus 30%, P=0.04) compared with 83 patients with a normal VE/VCO2 slope.

Cardiopulmonary Reflexes in Patients With High Ventilatory Response to Exercise

Forty-eight patients agreed to have the assessment of cardiopulmonary reflexes. They did not differ significantly in clinical parameters from the whole population studied (peak VO2 22.8 mL·kg⁻¹·min⁻¹, LVEF 27%).

Patients with a high VE/VCO2 slope demonstrated abnormal cardiorespiratory reflex control compared with those with a normal VE/VCO2 slope, as evidenced by augmented hypoxic and hypercapnic chemosensitivity (P=0.012 and P=0.0006, respectively), lower values of the LF component of HRV (P<0.0001), reduced BRS (P=0.034), and elevated ergoreflex contribution to ventilation (P=0.003) (for full details see the Table).

There were significant correlations between VE/VCO2 slope and hypoxic (r=0.33, P=0.047) and hypercapnic (r=0.58, P=0.0003) chemosensitivity, the LF component of HRV (r=−0.60, P=0.0001), BRS (r=−0.52, P=0.026), and the ergoreflex contribution to ventilation (r=0.54, P=0.014) (Figure 1). In the multivariate analysis, hypercapnic chemosensitivity and the LF component of HRV predicted VE/VCO2 independently of peak VO2 and LVEF (P=0.01 and P=0.02, respectively).

Predictors of Mortality Among Patients With Preserved Exercise Capacity

At the end of follow-up (mean follow-up duration 49±22 months, range 2 days to 84 months, >3 years in all who survived), there were 34 deaths (28%) (mean time to death 24±19 months, range 5 days to 63 months). The cumulative survival of all patients was 91% at 1 year, 86% at 2 years, and 81% at 3 years. There was no difference in treatment, age, CHF etiology, NYHA functional class, and peak VO2 between those who died and those who survived (all P>0.2). Patients who died had a lower LVEF (24±11% versus 30±11%, respectively, P=0.015) and higher VE/VCO2 (36.9±9.8 versus 29.3±6.9, respectively, P<0.0001) than survivors.

The following factors were considered in the univariate Cox proportional-hazards analysis: age, sex, CHF etiology, NYHA functional class, LVEF peak VO2, and VE/VCO2 slope. We found that age (χ²=0.5), sex (χ²=0.3), CHF etiology (χ²=0.4), NYHA functional class (χ²=0.3), and peak VO2

<table>
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<td>Baroreflex sensitivity, ms/mm Hg (n=20)</td>
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LF indicates spectral low frequency component of heart rate variability; Ergo, percentage ventilatory response to exercise that was maintained by PH-RCO vs recovery without PH-RCO.

Values are mean±SD; P for normal vs high VE/VCO2 slope.

*n=24; †n=14; ‡n=23; §n=11; ¶n=13; ‡n=7.
(χ²<0.1, all P>0.2) did not predict prognosis in this group of patients.

Only VE/V̇CO₂ slope and LVEF predicted poor survival in univariate Cox proportional-hazards analysis: for VE/V̇CO₂ slope, RR 4.3 (95% CI 2.1 to 8.5, P<0.0001) when dichotomized at 34.0 and RR 1.10 (95% CI 1.06 to 1.13, P=0.0001) when analyzed as a continuous variable, and for LVEF, RR 0.95 (95% CI 0.91 to 0.99, P=0.008).

In multivariate analysis VE/V̇CO₂ slope was related to outcome independently of LVEF (RR 2.8, 95% CI 1.2 to 6.3, P=0.01 when dichotomized at 34.0 and RR 1.08, 95% CI 1.03 to 1.13, P=0.0009 for continuous variable). LVEF did not predict survival independently of VE/V̇CO₂ slope (P=0.08).

Kaplan-Meier analysis was performed for early (6-month) and late (3-year) survival. Early and late survivals were 80% (95% CI 68% to 92%) and 57% (95% CI 42% to 73%), respectively, for the 40 patients with high VE/V̇CO₂ compared with 98% (95% CI 94% to 100%) and 93% (95% CI 87% to 99%) in the 83 CHF patients with normal values of VE/V̇CO₂ (P=0.0008 and P<0.0001, respectively) (Figure 2).

Exercise Parameters as Predictors of Mortality Among Patients With Less-Well-Preserved Exercise Capacity
Supplementary to the main study, we analyzed the data of CHF patients who were investigated at the same time in our institution but demonstrated less-well-preserved exercise tolerance (peak VO₂ between 14 and 18 mL · min⁻¹ · kg⁻¹; see Methods). There were 131 such patients, and they had the following characteristics: mean age 61 years; 5 (4%) in NYHA class I, 50 (38%) in class II, 66 (50%) in class III, and 10 (8%) in class IV; mean LVEF=23% (n=104); and CHF etiology was ischemic heart disease in 79 (60%) and nonischemic in the remaining 52 (40%). The patients’ mean peak VO₂ was 15.8±1.2 mL · kg⁻¹ · min⁻¹, and the mean VE/V̇CO₂ slope was 37.2±8.7.

At the end of follow-up (mean duration: 43 months), 59 patients (45%) had died. In univariate Cox proportional-hazards analysis, we found that among nonexercise parameters, only age (χ²=6.9, P=0.009) and ischemic heart disease as CHF etiology (χ²=4.1, P=0.04) were markers of poor prognosis. Survival was also predicted by peak VO₂ (RR 0.74, 95% CI 0.59 to 0.93, P=0.009) and VE/V̇CO₂ slope (RR 1.9, 95% CI 1.1 to 3.4, P=0.03 when dichotomized at 34.0 and RR 1.03, 95% CI 1.0 to 1.06, P=0.02 when analyzed as a continuous variable). In multivariate analysis, both peak VO₂ and VE/V̇CO₂ slope were related to outcome independently of each other and of remaining parameters (age and CHF etiology): P=0.02 for peak VO₂ and P=0.01 for VE/V̇CO₂ slope.

Discussion
This study shows that abnormal enhancement of the ventilatory response to exercise indicates disruption of cardiorespiratory reflex control and predicts poor outcome in CHF patients whose exercise tolerance is well preserved and who would otherwise be classified as having uniformly low risk.

Exercise testing with gas-exchange analysis has become a routine clinical tool for the evaluation of patients with CHF and remains the gold standard for risk stratification. In moderate and severe CHF, peak VO₂ constitutes an integral part of patients’ pretransplant assessment, with some various...
cutoff values having been proposed for decision-making. The prognostic strength of peak VO2 measurements, however, lies predominantly in patients with advanced symptoms and at least moderate functional impairment, as previously known from several studies and confirmed by our supplementary analysis of patients with less-well-preserved exercise tolerance. Yet data from large trials show that death is not rare in patients with mild symptoms: annual mortality ranges from 8% to 10%, and sudden death is not uncommon. Despite these epidemiological data, evidence-based guidelines are not established for risk assessment in such patients.

The present study demonstrates that the measurement of the ventilatory response to exercise (Ve/VCO2 slope), which can be easily derived from any routine cardiopulmonary exercise test data, carries important prognostic information in CHF patients with preserved exercise tolerance. This information is independent of conventional risk markers, such as peak VO2 and LVEF. Indeed, peak VO2 itself does not predict poor outcome within this group of patients. Measurement of the Ve/VCO2 slope and application of the 95th percentile of normal individuals as a cutoff identified a subset of 40 patients (33%) with unexpectedly high mortality over 3 years, despite their mean peak VO2 of 22 mL · min⁻¹ · kg⁻¹, which would otherwise be considered to imply low risk. Of this ill-fated subset, 20% died by 6 months and nearly 50% by 3 years (in contrast to 2% and 7%, respectively, of those with normal ventilatory response to exercise). These optimally treated patients with only mild symptoms and objectively documented good exercise capacity had far poorer outcome than might have been expected from conventional considerations.

The mechanisms responsible for excessive ventilatory response to exercise may well be multifactorial, but in principle, impairment in hemodynamic status or an abnormal control of ventilation can be involved. The link between this easily measured abnormality and multiple aspects of the pathophysiology of heart failure supports its potential value in the clinical assessment of the whole spectrum of CHF patients. It may have a special clinical meaning among patients with preserved exercise tolerance in whom an increased ventilatory response to exercise reflects not an advanced stage of the disease but rather a specific hypersensitivity of ventilatory reflex control, including augmented peripheral and central chemosensitivity or activated muscle ergoreceptors. In fact, derangement in cardiopulmonary reflex control occurs early in the course of CHF. In a pattern reminiscent of that seen with neurohormonal systems, these initially compensatory mechanisms can have damaging effects on cardiovascular function from long-term overactivity. Sympathetic overactivation and impairment in the arterial baroreflex response are known to be ominous signs. Augmented peripheral chemosensitivity is related to severe autonomic imbalance and high prevalence of ventricular arrhythmias. In a separate prospective investigation that included 80 CHF patients (35 reported in this study), we found that hypersensitivity of the peripheral chemoreceptors constitutes an independent, adverse prognostic marker in CHF. Also, enhanced activity of central chemoreceptors, which was recently documented in mild CHF, may contribute to increased sympathetic drive. It is possible that in CHF patients with preserved exercise capacity, an augmented ventilatory response to exercise may be closely tied to a spectrum of reflex abnormalities, which in turn may explain the prognostic usefulness of Ve/VCO2 slope.

The findings of the present study confirm that among patients with preserved exercise tolerance, an abnormally enhanced ventilatory response to exercise is the tip of an iceberg of deranged cardiopulmonary reflex control. It was evidenced by augmented peripheral and central chemosensitivity, impaired sympathovagal balance with sympathetic predominance, depressed baroreflex control of circulation, and higher activity of peripheral muscle ergoreceptors in those with an abnormally high Ve/VCO2 slope. The relationship between enhanced Ve/VCO2 slope and disruption of sympathovagal balance, hypersensitivity of central chemoreceptors, and muscle ergoreceptors was independent of conventional clinical parameters. These findings suggest that at least in patients with preserved exercise capacity, an elevated ventilatory response to exercise may be related to abnormal reflex responses from the periphery. Further support for this mechanism comes from therapeutic studies that show that changes in the activity of chemoreceptors (with oxygen or opiates) or muscle ergoreceptors (with exercise training) can favorably affect the ventilatory response to exercise.

A thorough look into the analyses of the relationship between Ve/VCO2 slope and reflex impairment revealed 2 interesting findings worthy of being addressed. First, although enhanced ventilatory response to exercise correlated significantly with central and peripheral chemosensitivity, such a relationship was much stronger for central chemoreceptors. This finding is in agreement with recent work by Narkiewicz et al showing a selective potentiation of central chemosensitivity in NYHA class I and II CHF patients. In CHF patients with well-preserved exercise capacity, central chemoreceptors may be involved in the regulation of ventilation, whereas peripheral chemoreceptors become more important in those with more compromised CHF symptoms. Second, we observed an inverse relationship between the LF component of HRV and Ve/VCO2 slope. Previous studies demonstrated that worsening in CHF was linked to a decrease or even an absence of LF oscillations in heart rate and in muscle sympathetic nerve activity. It may represent the stage when the sympathoeactivation with accompanying deterioration in baroreceptor function abolishes the ability of the cardiovascular system to modulate heart rate and blood pressure, resulting in a reduction of oscillatory components of heart rate and blood pressure variability. In this context, van de Borne et al suggested reduced rhythmic oscillations of autonomic outflow to be responsible for a depressed LF component. Thus, our study demonstrated that some CHF patients with mild symptoms but impaired autonomic balance also show an abnormally elevated ventilatory response to exercise.

Reduced ventilatory function is a common finding in CHF that may partially account for augmented ventilatory response to exercise. Although we had excluded CHF patients whose principal pathological condition was determined to be airway or pulmonary disease, we also decided to address the question.
of whether those with high Ve/VCO₂ slope might have had significantly greater impairment of lung function. We analyzed contemporaneous spirometric data on forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) that were available in 90 (75%) of the patients in the study. We found only mildly impaired ventilatory function (mean values of FEV₁, FVC, %FEV₁, and %FVC being 3.2 L, 4.1 L, 92%, and 93%, respectively), which did not correlate with Ve/VCO₂ slope (r values: 0.22 for FEV₁, 0.16 for FVC, 0.17 for %FEV₁, and 0.11 for %FVC). We therefore believe that among patients included in our study, abnormal pulmonary function was not a major determinant of augmented Ve/VCO₂ slope.

Quantification of the ventilatory response to exercise is quick and inexpensive and does not oblige the patient to undergo any additional testing, because it is calculated from the same metabolic exercise test data that are used for evaluation of peak VO₂. These features, in association with its prognostic value independent of conventional characteristics, would appear to commend it as an efficient and effective clinical parameter in the assessment of CHF patients with preserved exercise tolerance. In addition, an estimate of Ve/VCO₂ slope can be obtained even in patients who do not reach a valid peak VO₂ value.

### Study Limitations

Some information regarding the clinical usefulness of Ve/VCO₂ slope and potential responsible mechanisms is already available. To our best knowledge, however, none of the previous studies have focused on CHF patients with preserved exercise tolerance, and none have attempted to place the different observations into a coherent whole.

We detected a strong association between abnormal ventilatory response to exercise and reflex abnormalities. This relationship is presented as evidence in support of, but of course not proving, a hypothesized mechanism linking deregulations in reflex control to abnormal ventilatory regulation during exercise. The physiological assessment of cardiorespiratory reflexes was performed only in a subset of patients, who did not differ in clinical characteristics from the remaining patients. Further systematic studies, however, are necessary to fully elucidate the real nature of association between reflex abnormalities and augmented ventilatory response to exercise.

Because the variation of peak VO₂ within this group is smaller than that in unselected patients with CHF, it may not be surprising that peak VO₂ is not a useful prognostic indicator within this group. The aim of this study, however, was to identify prognostic markers within a subgroup of CHF patients in whom the best prognostic marker in CHF (peak VO₂) was unlikely to be helpful.

In summary, in CHF patients with well-preserved exercise capacity, an abnormally elevated ventilatory response to exercise allows the identification of those at high risk of death. In these patients, peak VO₂ itself provides no clinical information for risk stratification. The ventilatory response to exercise can be readily identified from routine cardiopulmonary exercise testing and is a simple window into the plethora of disordered cardiopulmonary reflex regulation patterns that can be seen in some patients with mild CHF symptoms.

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