

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

Piotr Ponikowski, MD, PhD; Darrel P. Francis, MD, MRCP; Massimo F. Piepoli, MD, PhD; L. Ceri Davies, BSc, MRCP; Tuan Peng Chua, MD, MRCP; Constantinos H. Davos, MD, PhD; Viorel Florea, MD, PhD; Waldemar Banasiak, MD, PhD; Philip A. Poole-Wilson, MD, FRCP; Andrew J.S. Coats, DM, FRCP; Stefan D. Anker, MD, PhD

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 (\dot{V}_E/\dot{V}_{CO_2}) predicts poor prognosis in advanced CHF. Derangement of cardiopulmonary reflexes may trigger exercise hyperpnea. We assessed the relationship between cardiopulmonary reflexes and \dot{V}_E/\dot{V}_{CO_2} and investigated the prognostic value of \dot{V}_E/\dot{V}_{CO_2} 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 $\dot{V}O_2$) ≥ 18 mL \cdot kg⁻¹ \cdot min⁻¹ (age 56 years; left ventricular ejection fraction 28%; peak $\dot{V}O_2$ 23.5 mL \cdot kg⁻¹ \cdot 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 \dot{V}_E/\dot{V}_{CO_2} (ie, >34.0). During follow-up (49 \pm 22 months, >3 years in all survivors), 34 patients died (3-year survival 81%). High \dot{V}_E/\dot{V}_{CO_2} (hazard ratio 4.3, $P<0.0001$) but not peak $\dot{V}O_2$ ($P=0.7$) predicted mortality. In patients with high \dot{V}_E/\dot{V}_{CO_2} , 3-year survival was 57%, compared with 93% in patients with normal \dot{V}_E/\dot{V}_{CO_2} ($P<0.0001$). Patients with high \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} .

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 $\dot{V}O_2$ 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).¹ Poor exercise capacity, measured objectively by low peak oxygen consumption (peak $\dot{V}O_2$), predicts an unfavorable outcome independently of other clinical and hemodynamic parameters.¹⁻⁴ 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.^{5,6}

See p 916

We recently reported that an excessive ventilatory response to exercise, expressed as ventilation per unit of carbon dioxide production (ie, \dot{V}_E/\dot{V}_{CO_2} slope), is a marker of poor prognosis for patients with moderate to severe CHF.⁷ Because \dot{V}_E/\dot{V}_{CO_2} 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,⁸ but overactive reflexes from chemoreceptors and ergoreceptors may play a role.^{9,10}

Received July 20, 2000; revision received October 18, 2000; accepted October 20, 2000.

From the Cardiac Medicine Department, Imperial College, National Heart & Lung Institute, London, UK (P.P., D.P.F., M.F.P., C.D., T.P.C., C.H.D., V.F., P.A.P.-W., A.J.S.C., S.D.A.); the Cardiology Department, Clinical Military Hospital, Wroclaw, Poland (P.P., W.B.); and the Franz-Volhard-Klinik (Charité, Campus Berlin-Buch) at Max-Delbrück-Centrum, Berlin, Germany (S.D.A.).

Correspondence to Dr Piotr Ponikowski, MD, PhD, Clinical Cardiology, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY. E-mail piotrponikowski@hotmail.com

© 2001 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

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 $\dot{V}O_2 \geq 18$ mL · kg⁻¹ · min⁻¹.^{3,4} Considering NYHA functional classification as being fairly subjective, we decided to use peak $\dot{V}O_2$ as an objective measure of exercise capacity for selection of our patients. It has been demonstrated that peak $\dot{V}O_2$ 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.^{3,4} 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 $\dot{V}O_2$ 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 (\dot{V}_E), oxygen consumption ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) were measured by heated pneumotachograph and mass spectrometry (Amis 2000, Innovision, Denmark). The $\dot{V}_E/\dot{V}CO_2$ slope was calculated in every subject as the slope of the regression line relating \dot{V}_E to $\dot{V}CO_2$ during exercise testing and was used as an index of the ventilatory response to exercise.⁷ An abnormally high $\dot{V}_E/\dot{V}CO_2$ 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 method⁹ 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% O₂.⁹ Hypercapnic chemosensitivity was expressed in liters per minute per mm Hg of CO₂ (L · min⁻¹ · mm Hg⁻¹).

Cardiac Autonomic Control

After a 20-minute period of supine rest in a quiet room, 30-minute continuous recordings of heart rate (ECG) signal were performed.¹¹ Subjects breathed spontaneously and were asked to relax, but not to fall asleep. Stationary, 20-minute periods of recording were selected, and autoregressive power spectral analysis was applied to the RR interval time series.¹¹ The following spectral bands of heart rate variability (HRV) were identified: low-frequency (0.04 to 0.15 Hz, LF) and high-frequency (0.15 to 0.40 Hz). The areas below each peak were calculated in absolute units (ms²).

Baroreflex Sensitivity Assessment

Baroreflex sensitivity (BRS) was assessed by the bolus phenylephrine method¹¹ and was expressed in units of milliseconds per mm Hg.

Ergoreflex Assessment Protocol

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.¹⁰ 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 \pm SD. For statistical analysis, the LF components HRV, BRS, and hypoxic and hypercapnic chemosensitivity 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 $\dot{V}_E/\dot{V}CO_2$ 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 $\dot{V}O_2 \geq 18$ 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 $28 \pm 11\%$; and CHF etiology was ischemic heart disease in 65 patients (53%), idiopathic dilated cardiomyopathy in 52 (42%), and other

Characteristics of Patients With Normal (Normal \dot{V}_E/\dot{V}_{CO_2} Slope) and Elevated Ventilatory Response to Exercise (High \dot{V}_E/\dot{V}_{CO_2} Slope)

	Normal \dot{V}_E/\dot{V}_{CO_2} Slope (n=83)	High \dot{V}_E/\dot{V}_{CO_2} Slope (n=40)	P
Age, y	55±10	57±8	NS
Cause of heart failure, n			NS
Ischemic	39	26	
Nonischemic	44	14	
Medications, n			NS
ACE inhibitors	73	35	
Diuretics	51	30	
Digoxin	20	11	
LVEF, % (n=90)	30±11	25±11	0.04
Peak \dot{V}_{O_2} , mL · kg ⁻¹ · min ⁻¹	24.2±5.5	21.8±3.2	0.01
\dot{V}_E/\dot{V}_{CO_2} slope	26.5±3.8	41.4±6.4	<0.0001
Hypercapnic chemosensitivity, L · min ⁻¹ · mm Hg ⁻¹ (n=38)	2.04±0.70*	3.58±1.85†	0.0006
Hypoxic chemosensitivity, L · min ⁻¹ · %SaO ₂ ⁻¹ (n=38)	0.46±0.25*	0.74±0.36‡	0.012
LF, ms ² (n=34)	4.4±0.9‡	2.3±1.9§	<0.0001
Baroreflex sensitivity, ms/mm Hg (n=20)	5.5±2.8	2.5±3.1¶	0.034
Ergo, %V (n=20)	37±18	65±14¶	0.003

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 \dot{V}_E/\dot{V}_{CO_2} slope.

*n=24; †n=14; ‡n=23; §n=11; ||n=13; ¶n=7.

heart disease in 6 (5%). In all patients, the respiratory gas exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) exceeded 1.0 at peak exercise, indicating adequate exertion. The patients' mean peak \dot{V}_{O_2} was 23.5±5.0 mL · kg⁻¹ · min⁻¹, and the mean \dot{V}_E/\dot{V}_{CO_2} 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 (\dot{V}_E/\dot{V}_{CO_2} slope >34.0) and had a lower peak \dot{V}_{O_2} (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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_{O_2} 22.8 mL · kg⁻¹ · min⁻¹, LVEF 27%).

Patients with a high \dot{V}_E/\dot{V}_{CO_2} slope demonstrated abnormal cardiorespiratory reflex control compared with those with a normal \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} independently of peak \dot{V}_{O_2} 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 \dot{V}_{O_2} 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 \dot{V}_E/\dot{V}_{CO_2} (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 \dot{V}_{O_2} , and \dot{V}_E/\dot{V}_{CO_2} slope. We found that age (χ^2 =0.5), sex (χ^2 =0.3), CHF etiology (χ^2 =0.4), NYHA functional class (χ^2 =0.3), and peak \dot{V}_{O_2}

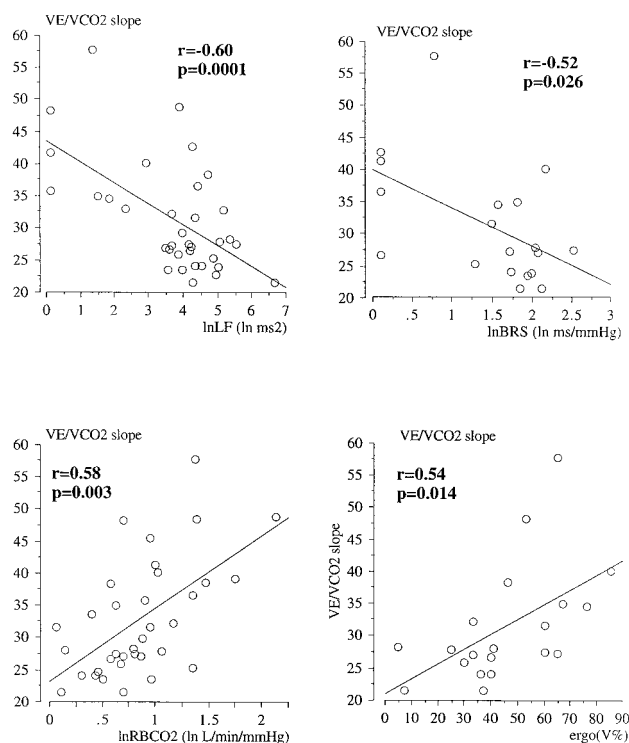


Figure 1. Linear regressions between \dot{V}_E/\dot{V}_{CO_2} slope and cardiorespiratory reflexes in CHF patients: LF, $n=34$; BRS, $n=20$; RBCO₂, hypercapnic chemosensitivity, $n=38$; and ergo ($V\%$), ventilatory response to ergoreflex activation, $n=20$.

($\chi^2=0.1$, all $P>0.2$) did not predict prognosis in this group of patients.

Only \dot{V}_E/\dot{V}_{CO_2} slope and LVEF predicted poor survival in univariate Cox proportional-hazards analysis: for \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} compared with 98% (95% CI 94% to 100%) and 93% (95% CI 87% to 99%) in the 83 CHF patients with normal values of \dot{V}_E/\dot{V}_{CO_2} ($P=0.0008$ 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 \dot{V}_{O_2} between 14 and 18 $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$; see Methods). There were 131 such patients, and they had the

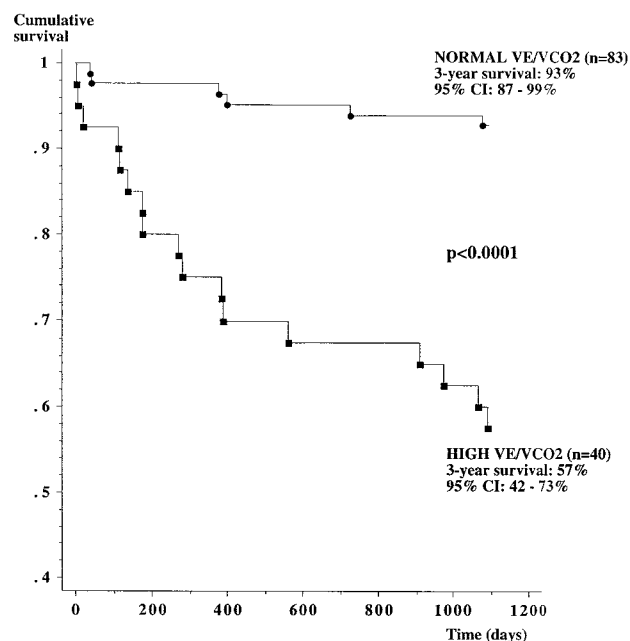


Figure 2. Kaplan-Meier survival curves for 3-year survival showing a significant difference ($P<0.0001$) in survival in patients with normal \dot{V}_E/\dot{V}_{CO_2} slope compared with those with high \dot{V}_E/\dot{V}_{CO_2} slope.

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=25% ($n=104$); and CHF etiology was ischemic heart disease in 79 (60%) and nonischemic in the remaining 52 (40%). The patients' mean peak \dot{V}_{O_2} was $15.8 \pm 1.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and the mean \dot{V}_E/\dot{V}_{CO_2} 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 ($\chi^2=6.9$, $P=0.009$) and ischemic heart disease as CHF etiology ($\chi^2=4.1$, $P=0.04$) were markers of poor prognosis. Survival was also predicted by peak \dot{V}_{O_2} (RR 0.74, 95% CI 0.59 to 0.93, $P=0.009$) and \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_{O_2} and \dot{V}_E/\dot{V}_{CO_2} slope were related to outcome independently of each other and of remaining parameters (age and CHF etiology): $P=0.02$ for peak \dot{V}_{O_2} and $P=0.01$ for \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_{O_2} constitutes an integral part of patients' pretransplant assessment, with some various

cutoff values having been proposed for decision-making.^{2-4,13} The prognostic strength of peak $\dot{V}O_2$ measurements, however, lies predominantly in patients with advanced symptoms and at least moderate functional impairment, as previously known from several studies^{1,3,4} 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.^{5,14} 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 ($\dot{V}_E/\dot{V}CO_2$ 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 $\dot{V}O_2$ and LVEF. Indeed, peak $\dot{V}O_2$ itself does not predict poor outcome within this group of patients. Measurement of the $\dot{V}_E/\dot{V}CO_2$ 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 $\dot{V}O_2$ of $22 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, 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.⁸ 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 chemosensitivity⁹ or activated muscle ergoreceptors.¹⁰ In fact, derangement in cardiopulmonary reflex control occurs early in the course of CHF.^{15,16} 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.¹⁷⁻¹⁹ Augmented peripheral chemosensitivity is related to severe autonomic imbalance and high prevalence of ventricular arrhythmias.¹¹ 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.¹² Also, enhanced activity of central chemoreceptors, which was recently documented in mild CHF,¹⁶ may contrib-

ute 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 $\dot{V}_E/\dot{V}CO_2$ 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 $\dot{V}_E/\dot{V}CO_2$ slope. The relationship between enhanced $\dot{V}_E/\dot{V}CO_2$ 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)²⁰ or muscle ergoreceptors (with exercise training)¹⁰ can favorably affect the ventilatory response to exercise.

A thorough look into the analyses of the relationship between $\dot{V}_E/\dot{V}CO_2$ 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 al¹⁶ 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 $\dot{V}_E/\dot{V}CO_2$ 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.^{21,22} It may represent the stage when the sympathoexcitation 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.²¹ In this context, van de Borne et al²² 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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_E/\dot{V}_{CO_2} 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 \dot{V}_{O_2} . 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 \dot{V}_E/\dot{V}_{CO_2} slope can be obtained even in patients who do not reach a valid peak \dot{V}_{O_2} value.

Study Limitations

Some information regarding the clinical usefulness of \dot{V}_E/\dot{V}_{CO_2} 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 derangements 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 \dot{V}_{O_2} within this group is smaller than that in unselected patients with CHF, it may not be surprising that peak \dot{V}_{O_2} 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 \dot{V}_{O_2}) 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 \dot{V}_{O_2} 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.

Acknowledgments

Dr Ponikowski was supported by a research fellowship from the European Society of Cardiology; Dr Anker by a postgraduate fellowship from the Max-Delbrück-Centrum, Berlin, Germany; Dr Francis by the British Heart Foundation; Dr Davies by the Robert Luff Foundation; Dr Piepoli by the Wellcome Trust; and Dr Coats by the Viscount Royston Trust.

References

1. Stevenson LW. Selection and management of candidates for heart transplantation. *Curr Opin Cardiol*. 1996;11:166–173.
2. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778–786.
3. Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med*. 1998;129:286–293.
4. Opasich C, Pinna GD, Bobbio M, et al. Peak exercise oxygen consumption in chronic heart failure: toward efficient use in individual patient. *J Am Coll Cardiol*. 1998;31:766–775.
5. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. *N Engl J Med*. 1992;327:685–691.
6. Cowburn PJ, Cleland JGF, Coats AJS, et al. Risk stratification in chronic heart failure. *Eur Heart J*. 1998;19:696–710.
7. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 1997;29:1585–1590.
8. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol*. 1996;28:1092–1102.
9. Chua TP, Clark AL, Amadi AA, et al. The relationship between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 1996;27:650–657.
10. Piepoli M, Clark AL, Volterrani M, et al. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure. *Circulation*. 1996;93:940–952.
11. Ponikowski P, Chua TP, Piepoli M, et al. Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation*. 1997;96:2586–2594.
12. Ponikowski PP, Chua TP, Piepoli MF, et al. Augmented peripheral chemosensitivity better than depressed baroreflex sensitivity predicts poor outcome in patients with chronic heart failure. *Circulation*. 1998;98:1–210. Abstract. Submitted for publication as Ponikowski P, Chua TP, Piepoli M, et al. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure.
13. Pina IL. Optimal candidates for heart transplantation: is 14 the magic number? *J Am Coll Cardiol*. 1995;25:1143–1153.
14. Kjekshus J. Arrhythmias and mortality in congestive heart failure. *Am J Cardiol*. 1990;65:421–481.
15. Mancía G, Seravalle G, Giannattasio C, et al. Reflex cardiovascular control in congestive heart failure. *Am J Cardiol*. 1992;69:17G–23G.
16. Narkiewicz K, Pesek CA, van de Borne PJ, et al. Enhanced sympathetic and ventilatory responses to central chemoreflex activation in heart failure. *Circulation*. 1999;100:262–267.
17. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819–823.
18. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:1645–1650.
19. Mortara A, LaRovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation*. 1997;96:3450–3458.
20. Chua TP, Harrington D, Ponikowski P, et al. Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 1997;29:147–152.
21. Mortara A, La Rovere MT, Signorini MG, et al. Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation. *Br Heart J*. 1994;71:422–430.
22. Van de Borne P, Montano N, Pagani M, et al. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. *Circulation*. 1997;95:1449–1454.