

Impairment of Ventilatory Efficiency in Heart Failure Prognostic Impact

F.X. Kleber, MD; G. Vietzke, MD; K.D. Wernecke, PhD; U. Bauer, MD; C. Opitz, MD;
R. Wensel, MD; A. Sperfeld, MD; S. Gläser, MD

Background—Impairment of ventilatory efficiency in congestive heart failure (CHF) correlates well with symptomatology and contributes importantly to dyspnea.

Methods and Results—We investigated 142 CHF patients (mean NYHA class, 2.6; mean maximum oxygen consumption [$\dot{V}O_{2\max}$], 15.3 mL O₂ · kg⁻¹ · min⁻¹; mean left ventricular ejection fraction [LVEF], 27%). Patients were compared with 101 healthy control subjects. Cardiopulmonary exercise testing was performed, and ventilatory efficiency was defined as the slope of the linear relationship of $\dot{V}CO_2$ and ventilation (VE). Results are presented in percent of age- and sex-adjusted mean values. Forty-four events (37 deaths and 7 instances of heart transplantation, cardiomyoplasty, or left ventricular assist device implantation) occurred. Among $\dot{V}O_{2\max}$, NYHA class, LVEF, total lung capacity, and age, the most powerful predictor of event-free survival was the VE versus $\dot{V}CO_2$ slope; patients with a slope $\leq 130\%$ of age- and sex-adjusted normal values had a significantly better 1-year event-free survival (88.3%) than patients with a slope $> 130\%$ (54.7%; $P < 0.001$).

Conclusions—The VE versus $\dot{V}CO_2$ slope is an excellent prognostic parameter. It is easier to obtain than parameters of maximal exercise capacity and is of higher prognostic importance than $\dot{V}O_{2\max}$. (*Circulation*. 2000;101:2803-2809.)

Key Words: prognosis ■ heart failure ■ ventilation

Ventilatory efficiency is defined by ventilation relative to CO₂ production. Its most important determinant is the matching of ventilation and perfusion. In most patients with congestive heart failure (CHF), as in normal control subjects, ventilatory efficiency improves with exercise. It correlates very well with exercise capacity respectively $\dot{V}O_{2\max}$ ¹ and closely relates to symptomatology.^{2,3} Both NYHA class and $\dot{V}O_{2\max}$ have been proven to be good predictors of prognosis in CHF. Therapy with ACE inhibitors known to improve prognosis also better ventilatory efficiency.³ Ventilatory efficiency can be derived from a moderate effort well before exhaustion and is highly reproducible.¹

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Therefore, we investigated the impact of ventilatory efficiency in CHF on outcome and compared it with other prognostic parameters like left ventricular ejection fraction (LVEF), NYHA class, and $\dot{V}O_{2\max}$. To maximize the physiological information from cardiopulmonary exercise testing (CPX), we normalized $\dot{V}O_{2\max}$ and the slope of ventilation (VE) versus $\dot{V}CO_2$ for age and sex using our own control population.^{4,5}

Methods

Patients

We monitored 142 consecutive patients (117 men, 25 women; mean age, 51.6 ± 10 years; range, 21 to 73 years) with CHF after performing CPX between June 1993 and November 1996. Mean and median follow-up until death or end of follow-up was 16 months. The cause of CHF was coronary artery disease (n=70), dilated cardiomyopathy (n=66), valvular heart disease (n=4), graft failure (n=1), and hypertensive heart disease (n=1). Eleven patients were in NYHA class IV, 78 in class III, and 45 in class II; 8 patients did not complain of symptomatic limitation (class I).

Symptoms were attributed to heart and not lung disease in all patients, albeit the mild abnormality of pulmonary function tests in some patients was thought to be secondary to heart disease. Current smoking status and smoking history are presented in Table 1.

Origin and severity of CHF were determined by echocardiography (n=130), chest radiograph (n=114), or cardiac catheterization (n=95). Inclusion criteria were a $\dot{V}O_{2\max} < 25$ mL O₂ · kg⁻¹ · min⁻¹ and either cardiothoracic ratio > 0.5 , echocardiographic left ventricular end-diastolic diameter ≥ 57 mm, or LVEF determined by contrast ventriculography or echocardiography $\leq 45\%$. Mean LVEF was 27% (median, 26%). One hundred nineteen patients were in sinus rhythm, 19 had atrial fibrillation, and 4 had pacemaker rhythm.

Current medication included ACE inhibitors (89%), diuretics (69%), nitrates (67%), digitalis (52%), anticoagulants (30%), and antiarrhythmics (6%). Ten percent were on calcium antagonists, mainly for rate control, and 31% were on aspirin for coronary disease.

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From Medizinische Klinik und Poliklinik I, Universitätsklinikum Charité, Arbeitsgruppe Medizinische Biometrie, Humboldt-Universität zu Berlin, Berlin, Germany.

Reprint requests to F.X. Kleber, MD, Professor of Medicine, Humboldt University, Berlin, Director Department of Internal Medicine, Unfallkrankenhaus Berlin, Warener Straße 7, 12683 Berlin, Germany. E-mail franz-xaverk@ukb.de

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TABLE 1. Lung Function Tests and Smoking Status

Test	Patients With VE vs \dot{V}_{CO_2} Slope		<i>P</i>
	≤130 pp	>130 pp	
TLC	98.6±15.3	92.0±14.1	0.026
FEV ₁	90.2±17.7	84.1±17.9	NS
IVC	91.4±14.4	84.1±14.3	0.01
D _{LO₂}	82.6±16.1	74.0±15.4	0.001
Current smokers	19/69	16/60	NS
Pack-years	17.9±23.2	15.1±16.8	NS

Univariate testing was done with the Mann-Whitney *U* test; smoking status was compared by the χ^2 .

Control Subjects

One hundred one healthy volunteers 16 to 75 years of age (mean, 37±14 years) underwent CPX testing to establish age- and sex-corrected normal values. Forty-five were female (weight, 60±8 kg; height, 165±6 cm), 56 were male (weight, 78±12 kg; height, 179±9 cm). Results have been published in part elsewhere.⁴ Linear regression analysis for age versus oxygen consumption and VE versus \dot{V}_{CO_2} slope revealed the following mean normal value formulas: VE versus \dot{V}_{CO_2} slope: $0.13 \times \text{age} + 19.9$ for men and $0.12 \times \text{age} + 24.4$ for women; \dot{V}_{O_2} at the gas exchange anaerobic threshold (\dot{V}_{O_2AT}): $-0.17 \times \text{age} + 28.6$ for men and $-0.16 \times \text{age} + 24.2$ for women; \dot{V}_{O_2max} : $-0.36 \times \text{age} + 51.5$ for men and $-0.34 \times \text{age} + 44.6$ for women.

For prognostic analysis, oxygen consumption and VE versus \dot{V}_{CO_2} slope values are presented as percent predicted (PP) from the individual age- and sex-corrected mean normal values.

Exercise Testing

In all patients and control subjects, a symptom-limited CPX test was performed according to the modified Naughton protocol⁶ with a Medical Graphics CPX/D system. Details of our test protocol have been published earlier.⁴

Great effort was undertaken not to stop exercise prematurely. However, indications to stop the test were a higher degree of AV block or ventricular tachycardia >5 consecutive beats at a rate >120/min, new atrial fibrillation, ST-segment depression >3 mm, or systolic blood pressure >260 mm Hg, as well as a progressive decrease in blood pressure.

\dot{V}_{O_2max} was defined as the peak \dot{V}_{O_2} measured, always occurring well beyond the anaerobic threshold. \dot{V}_{O_2} at \dot{V}_{O_2AT} was detected by the V-slope method,^{7,8} supplemented by simultaneous observation of end-tidal gas concentrations (PETO₂/CO₂).

Ventilatory efficiency on exercise was measured by plotting VE against \dot{V}_{CO_2} . This plot revealed a linear relationship ($r=0.98$ to 0.99). The ventilatory efficiency on exercise is represented by its slope. The nonlinear part of this relationship after onset of acidotic drive to ventilation⁸ was excluded.

Lung Function Tests

Routine lung function tests, including total lung capacity (TLC), forced expiratory volume in 1 second (FEV₁), inspiratory vital capacity (IVC), and diffusion capacity for carbon monoxide (DLCO), were expressed as percent predicted of normal PP. Oxygen saturation was continuously measured percutaneously by pulse oximetry on the ear lobe. Breathing reserve was calculated as $100 - (100 \times VE_{max} / \text{resting FEV}_{1} \times 41)$.⁹

Follow-Up Data on Prognosis

Follow-up events included overall deaths, cardiac transplantation (HTX), implantation of a left ventricular assist device (LVAD), or cardiomyoplasty. Most patients had a follow-up of >1 year. Minimal follow-up was 6 months. One patient was lost to follow-up.

Statistical Analysis

Results are presented as mean±SD. For comparison between groups, the Mann-Whitney *U* test was used; to compare prognostic parameters, linear and logistic regression analyses were performed. Correlations were determined according to Bravais-Pearson or Spearman. The follow-up data were analyzed by Kaplan-Meier life-table analysis and the log-rank test. To define the cutoffs giving the best discrimination in defining the likelihood of event-free survival, univariate log-rank tests (Mantel-Haenszel)¹⁰ were used. A multiple Cox regression analysis was performed using LVEF, \dot{V}_{O_2max} , VE versus \dot{V}_{CO_2} slope, age, TLC, and NYHA class.¹¹

Classification trees (CART) were constructed with subgroups internally as homogeneous and externally as heterogeneous as possible, measured on the corresponding log-rank test.^{12,13} The successive splits of the tree correspond to the features with the greatest prognostic importance. For diagnostic testing sensitivity, accuracy and ORs were estimated.

Results

Exercise Testing

Eighty-nine patients terminated exercise because of dyspnea, 15 because of angina, 13 because of fatigue, 10 because of nonspecific symptoms like vertigo and anxiety, and 15 because of the above-defined criteria. All exercise tests in control subjects were limited by exhaustion.

\dot{V}_{O_2AT} and \dot{V}_{O_2max} were 10.7 ± 3.2 and 15.2 ± 4.7 mL O₂ · kg⁻¹ · min⁻¹ (median, 57 and 47 PP), respectively, in the patient group. The VE versus \dot{V}_{CO_2} slope was 39.3 ± 16.4 (median, 128 PP). There was no difference between the 2 major etiologic subgroups.

At termination of exercise, patients used $44 \pm 15\%$ of maximal breathing capacity; healthy volunteers, $59 \pm 12\%$. In patients and in all NYHA subgroups, \dot{V}_{O_2max} was reached earlier after \dot{V}_{O_2AT} than in normal subjects ($\dot{V}_{O_2AT}/\dot{V}_{O_2max}$ in patients, $71 \pm 11\%$; in normal subjects, $58 \pm 9\%$; $P<0.001$; see Table 2). Termination of exercise because of angina or by

TABLE 2. \dot{V}_{O_2} and VE versus \dot{V}_{CO_2} Slope in Subsets With Different Severity of CHF

	Control Subjects (n=101)	NYHA I (n=8)	NYHA II (n=45)	NYHA III (n=78)	NYHA IV (n=11)
\dot{V}_{O_2AT} , mL · kg ⁻¹ · min ⁻¹	20.7±5.1	13.5±2.7	12.0±2.7	10.3±2.9	6.8±2.0
\dot{V}_{O_2max} , mL · kg ⁻¹ · min ⁻¹ /M/F	39.5±7.8	19.5±2.0	17.3±4.0	14.5±4.4	9.2±2.3
\dot{V}_{O_2AT} of \dot{V}_{O_2max} , %	58±9	68±7	70±10	72±11	75±7
VE vs \dot{V}_{CO_2} slope, L · L \dot{V}_{CO_2}	26.2±4.0	29.4±3.4	33.1±4.8	41.0±18.0	60.0±19.3

Values are mean±SD. All parameters showed significant differences in NYHA classes vs control subjects with $P<0.05$. Within NYHA classes, \dot{V}_{O_2AT} , \dot{V}_{O_2max} , and VE vs \dot{V}_{CO_2} slope differed significantly in all pairwise comparisons except NYHA I vs II; \dot{V}_{O_2AT} in percent of \dot{V}_{O_2max} did not differ.

the physician did not influence the $\dot{V}_{O_2AT}/\dot{V}_{O_2max}$ ratio. Patients with normal and reduced ventilatory efficiency had similar $\dot{V}_{O_2AT}/\dot{V}_{O_2max}$ ratios ($71 \pm 11\%$ versus $72 \pm 10\%$).

Oxygen Desaturation and Lung Function Testing

In 6 of 142 patients, a significant decrease in oxygen saturation ($\geq 4\%$) was found (mean, 96% to 87%). Five of these were in NYHA class III, and 1 was in class IV. One had a small atrial septum defect, and 1 had suspected pulmonary embolism with extremely elevated VE versus \dot{V}_{CO_2} slope (140) normalized at reevaluation. The other 4 had severe CHF (\dot{V}_{O_2AT} , 4.7 to 9.0; \dot{V}_{O_2max} , 6.1 to 11.2 mL O₂ · kg⁻¹ · min⁻¹; VE versus \dot{V}_{CO_2} slope, 57 to 85), and all 4 died within 2 years. Lung function and smoking status are given in Table 1.

Relationship Between Ventilatory Efficiency, Symptoms, and Exercise Capacity

Ventilatory efficiency was impaired (VE versus \dot{V}_{CO_2} slope >35) in 46% of patients. Patients with reduced ventilatory efficiency had lower LVEF ($20 \pm 7\%$ versus $25 \pm 8\%$; $P < 0.001$) and \dot{V}_{O_2max} (12.2 ± 3.6 versus 17.8 ± 3.9 ; $P < 0.001$) than patients without reduced ventilatory efficiency.

Results in various NYHA classes are presented in Table 2. The VE versus \dot{V}_{CO_2} slope but not \dot{V}_{O_2AT} or \dot{V}_{O_2max} was significantly different in all NYHA classes ($P < 0.05$), but the correlation between VE versus \dot{V}_{CO_2} slope and NYHA class was not very good ($r = 0.44$; $P < 0.001$). Exercise ventilatory efficiency correlated with \dot{V}_{O_2AT} ($r = -0.70$, $P < 0.001$), \dot{V}_{O_2max} ($r = -0.70$; $P < 0.001$), and exercise time ($r = -0.53$; $P < 0.001$) but only weakly with LVEF ($r = -0.17$; $P = 0.048$).

The correlations between exercise capacity and ventilatory efficiency were similar using the PP values (\dot{V}_{O_2max} PP and slope PP: $r = -0.64$; $P < 0.001$; \dot{V}_{O_2AT} PP and slope PP: $r = 0.65$; $P < 0.001$).

Follow-Up of Vital Status

Thirty-seven deaths occurred during follow-up. An additional 7 patients survived HTX, cardiomyoplasty, or LVAD implantation. Eight deaths occurred at various time intervals after prior HTX, LVAD, or cardiomyoplasty. Median event-free survival was 38 months (overall survival, 39 months). Univariate Kaplan-Meier analysis of event-free survival revealed significant survival differences (log-rank test) with cutoff points for \dot{V}_{O_2AT} at 10 mL · kg⁻¹ · min⁻¹ or 30, 45, and 50 PP; \dot{V}_{O_2max} at 10, 12, and 14 mL · kg⁻¹ · min⁻¹ or 45 PP; and VE versus \dot{V}_{CO_2} slope at 35 and 40 L/L CO₂ or 125 and 130 PP.

Figure 1 shows the event-free survival for the total group, and Figure 2a and 2b shows Kaplan-Meier life-table analyses (event-free survival) for the best cutoffs, ie, \dot{V}_{O_2max} (>45 versus ≤ 45 PP) and VE versus \dot{V}_{CO_2} slope (≤ 130 versus >130 PP). The best cutoff for \dot{V}_{O_2AT} was >50 versus ≤ 50 PP (life table not shown).

In a multivariate Cox regression analysis, the following items were included: age, LVEF, NYHA class, \dot{V}_{O_2max} , VE versus \dot{V}_{CO_2} slope, and TLC. The analysis revealed the VE versus \dot{V}_{CO_2} slope to be the most powerful predictor of event-free survival, followed by \dot{V}_{O_2max} . \dot{V}_{O_2max} did not substantially improve the predictive value of the model. Classification trees were used to estimate the practical use-

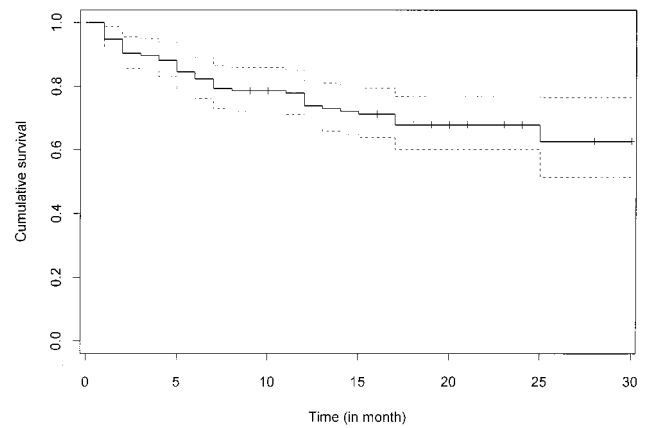


Figure 1. Event-free survival for total patient group.

fulness of the model to predict 1-year overall and event-free survival. Of the 141 patients, 105 were survivors of the first year of follow-up, and 103 survived without an event. According to the best discriminating variable and cutoffs in the log-rank statistics, we included the following parameters/cutoffs in the CART analysis: \dot{V}_{O_2AT} cutoff, 50 PP; VE versus \dot{V}_{CO_2} slope, 130 PP; NYHA functional class, I/II versus III/IV and I to III versus IV; \dot{V}_{O_2max} cutoff, 45 PP; age, 65 years; and LVEF, 25%. The VE versus \dot{V}_{CO_2} slope had by far the highest log-rank test value (25.65; $P < 0.0001$),

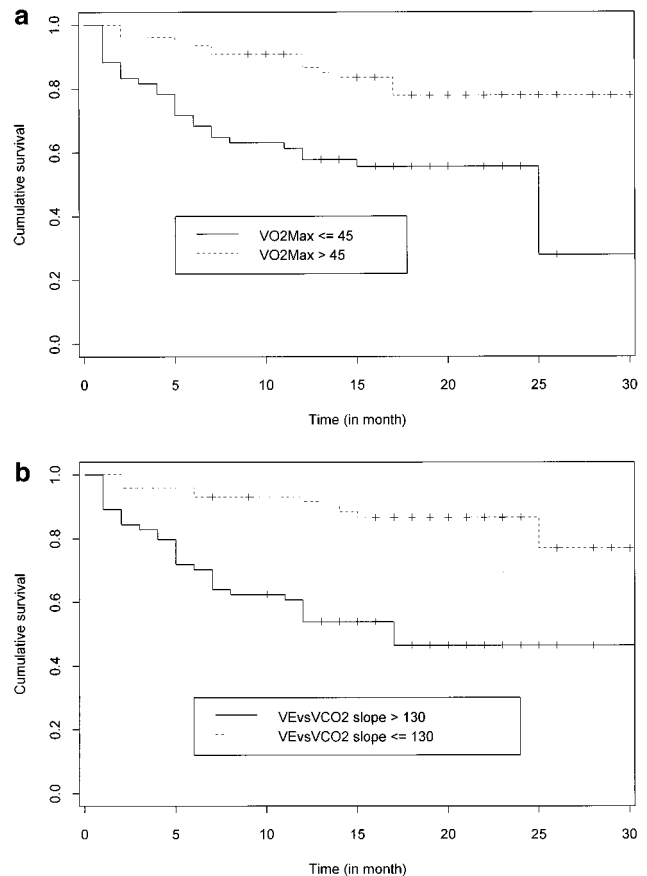


Figure 2. Kaplan-Meier life-table analysis for $\dot{V}_{O_2max} >45\%$ vs $\leq 45\%$ predicted (a) and for VE vs \dot{V}_{CO_2} slope $\leq 130\%$ vs $>130\%$ predicted (b).

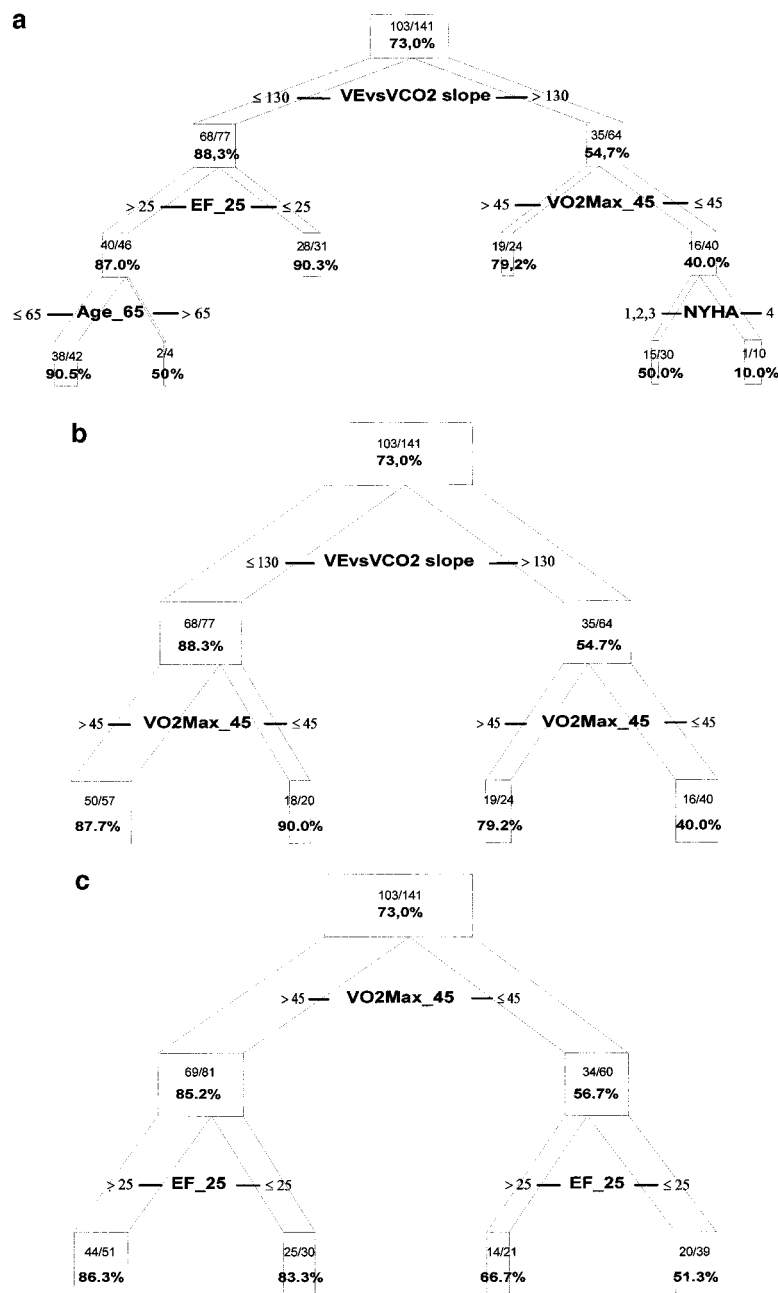


Figure 3. CART analysis with successive splits according to greatest prognostic importance of variables with respect to 1-year event-free survival (a) and CART analyses with successive splits according to various clinical decisions with respect to 1-year survival (b through e).

followed by $\dot{V}O_2\text{max}$ (with a log-rank test value of 7.57; $P=0.0059$). The VE versus $\dot{V}CO_2$ slope was therefore used as the first parameter to dichotomize the patients. Analysis for event-free and overall survival revealed essentially the same: both the VE versus $\dot{V}CO_2$ slope in PP and the $\dot{V}O_2\text{max}$ PP represented important information for the prognosis. Patients with a VE versus $\dot{V}CO_2$ slope ≤ 130 PP had a significantly better 1-year event-free survival (88.3%) than patients with a slope > 130 PP who had a 1-year event-free survival of only 54.7% (overall survival, 88.3% versus 57.8%).

Patients with a VE versus $\dot{V}CO_2$ slope > 130 PP but a $\dot{V}O_2\text{max}$ > 45 PP had a 79.2% 1-year event-free survival. No other parameters were useful to further characterize the prognosis of patients with a VE versus $\dot{V}CO_2$ slope ≤ 130 PP who had a good prognosis. For details, see Figure 3.

The sensitivity and specificity of a VE versus $\dot{V}CO_2$ slope with a cutoff of 130 PP for survival were 70.3% and 63.5%; positive and negative predictive values were 40.6% and 85.7%, accuracy was 65.3%, the OR was 4.1, and the 95% CI was 1.9 to 9.0.

Discussion

Dyspnea and Ventilatory Efficiency

The most widely used scale to measure dyspnea in CHF is the NYHA classification, which, in contrast to the Borg scale and pulmonary function tests, has been shown to contribute prognostic information independently of left ventricular function.^{14,15}

One of the most prominent features of dyspnea in CHF is hyperpnea, ie, an increase in ventilation relative to gas

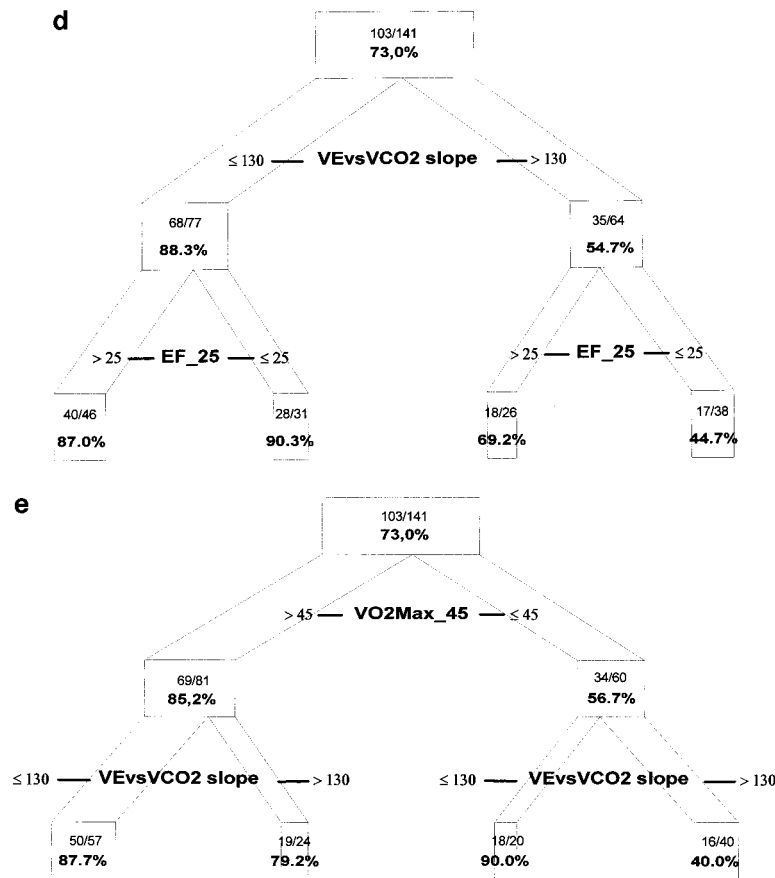


Figure 3. Continued.

exchange. It is caused by early anaerobic metabolism, an increase in anatomical dead space by increased breathing rate and low tidal volumes caused by secondary restrictive physiology or respiratory muscle fatigue,¹⁶ a decreased PaCO₂ set point resulting from acidosis, disturbances of diffusion,¹⁷ activation of muscle ergoreceptors,¹⁸ and respiratory muscle deoxygenation.¹⁹ The most important cause of hyperpnea, however, is the increase in physiological dead space by alveolar hypoperfusion.^{20,21} Therefore, we investigated the prognostic importance of ventilatory efficiency in patients with CHF and compared it with other currently used prognostic parameters like LVEF,^{22,23} NYHA class,^{24,25} and \dot{V}_{O_2max} .

Population Under Study

Patients suffered mainly from coronary disease or dilated cardiomyopathy similar to recently reported patients.²⁶ All patients had an LVEF ≤45%; all NYHA I patients had an LVEF <35%.

There was no difference in smoking status in patients with reduced compared with normal ventilatory efficiency. Differences in pulmonary function tests were small and thought to be secondary to CHF. Lungs were somewhat smaller in patients with reduced ventilatory efficiency, as has been shown in normal subjects under exercise²⁷ and in persons susceptible to high-altitude pulmonary edema.²⁸ This might contribute to \dot{V}/\dot{Q} mismatch by making a small ventilation-perfusion inequality more important. The slight decrease in TLC in our patients, however, is unlikely to contribute to a

larger extent to the decrease in ventilatory efficiency. Forty-six percent of patients had reduced ventilatory efficiency (median, 128 PP).

Similar to Veterans Administration Heart Failure Trial (V-HeFT) findings,²⁹ mean \dot{V}_{O_2max} was 15.2 mL · kg⁻¹ · min⁻¹, and cardiocirculatory limitation was confirmed by the high breathing reserve at the end of exercise, low rate of oxygen desaturation, and absence of pulmonary disease.

The lack of any important correlation to LVEF is not unexpected,^{23,30} and an LVEF ≤30% might not give very useful information regarding prognosis.^{14,31} More than 70% of our population had an LVEF ≤30%.

Follow-Up of Vital Status and CHF Events

Prognostic parameters in CHF²⁴ include symptoms,^{25,32,33} hemodynamics, LVEF, cardiothoracic ratio,²⁹ neurohormones,^{34,35} electrolytes,³⁶ and \dot{V}_{O_2max} .^{31,37,38} We used \dot{V}_{O_2} PP derived from our own large control population. Among LVEF, NYHA class, age, and TLC, the VE versus \dot{V}_{CO_2} slope was the most powerful indicator of prognosis in a multivariate analysis.

VE/ \dot{V}_{CO_2} ratio and slope are known to correlate to \dot{V}_{O_2max} .³⁹ Our results demonstrate that the VE versus \dot{V}_{CO_2} slope contains prognostic information in addition to and beyond the measurement of \dot{V}_{O_2max} : Patients with a VE versus \dot{V}_{CO_2} slope >130 PP had a 1-year mortality >40%, and even if \dot{V}_{O_2max} were preserved, 1-year mortality was >20%. Ventilatory efficiency is easier to obtain than \dot{V}_{O_2max} and can be derived from a submaximal exercise test. The high

negative predictive value of a normal ventilatory efficiency (ie, slope ≤ 130 PP) is of special clinical relevance for patients with low $\dot{V}_{O_2\max}$ or those who cannot exercise until exhaustion.

Underlying Physiology and Study Limitations

This study lacks an explanation of how ventilatory efficiency affects prognosis in CHF. Although normal ventilatory control in CHF⁴⁰ has been shown, an uncoupling of ventilation from CO₂ production⁴¹ has also been reported and thought to be due to activation of muscle ergoreceptors. However, substantial changes in arterial CO₂ tension have not been found,^{40,42,43} and the changes in physiological dead space suggested by increased ventilation^{40,42,43} and near-normal PCO₂ would thus be secondary.

An alternative explanation is that the increase in physiological dead space is directly caused by alveolar hypoperfusion⁴⁴ resulting from impaired endothelial vasodilatory capacity^{45–47} or neuroendocrine activation.^{35,48} If this theory is correct, the “muscle hypothesis” would not easily fit in.

A major diffusion disturbance^{17,49} is an unlikely explanation for the derangement of ventilatory efficiency because CO₂ diffuses much more easily than oxygen and a decrease in oxygen saturation has not been found in >95% of our patients. It might become important in severe CHF with prominent congestion.

Another limitation of our study is that not all patients stopped exercise for dyspnea or fatigue. This might introduce a considerable error through ischemic pump dysfunction. However, the reluctance to include patients with angina would not have reliably excluded silent ischemia, nor would it be meaningful to disregard some contribution of ischemia in a setting of CHF, whose leading cause is ischemic heart disease. Furthermore, dyspnea might be the only symptom of angina. Thus, in any exercise testing of CHF patients, ischemia is likely to play some part. The VE versus \dot{V}_{CO_2} relationship should, on the contrary, be of special value in this population, because it is measured well before the onset of angina or ischemia. Furthermore, the exclusion of patients who stopped exercise before the onset of dyspnea or fatigue led to a similar ratio of $\dot{V}_{O_2\max}/\dot{V}_{O_2AT}$. This indicates that our patients did not stop because of angina; rather, ischemia concurred with the limitation by CHF at the end of exercise in some of them.

Despite these limitations, our results show that measurement of the VE versus \dot{V}_{CO_2} relationship offers a unique way of estimating the prognosis of patients with CHF. During preparation of this article, similar results have been obtained by an independent group.⁵⁰ Given the possibility of therapeutic influences on ventilatory efficiency,³ this might also provide a useful tool to guide therapy, especially in severe CHF.

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