Clinical research

Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO₂ partial pressure

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Aims In chronic heart failure (CHF) patients, the ventilation (VE) needed to eliminate metabolically produced CO₂ during exercise (i.e. the VE/VCO₂ slope) is a strong prognosticator. VE/VCO₂ slope determinants are the dead space–tidal volume (VD/VT) ratio and the arterial CO₂ partial pressure (PaCO₂). We aimed at defining the respective prognostic role of these two variables.

Methods and results One hundred and twenty-eight stable CHF patients (average left ventricular ejection fraction 34 ± 10%) underwent cardiopulmonary exercise testing and blood gas analysis. The prognostic relevance of the VE/VCO₂ slope, Vb/Vt, and PaCO₂ at peak exercise was evaluated by the Kaplan–Meier approach with log-rank testing and by multivariate Cox regression analysis. During a mean period of 31.3 ± 20 months, 24 patients died from cardiac causes. In univariate analysis, predictors of death included the use of anti-aldosterone drugs, low peak VO₂, PaCO₂ at peak exercise was evaluated by the Kaplan–Meier approach with log-rank testing and by multivariate Cox regression analysis. During a mean period of 31.3 ± 20 months, 24 patients died from cardiac causes. In univariate analysis, predictors of death included the use of anti-aldosterone drugs, low peak VO₂, peak PaCO₂, and high VE/VCO₂ slope, and peak Vb/Vt. Multivariate analysis identified a low peak PaCO₂ (<35 mmHg) as the strongest independent prognostic indicator [hazard ratio 4.65, 95% confidence interval (CI) (1.695 – 12.751), P = 0.003] that primarily accounts for the VE/VCO₂ slope prognostic power.

Conclusion These findings imply that regulatory mechanisms involved in the tight control of ventilatory command and blood gas tension, rather than lung function abnormalities, play a critical pathophysiological role in the exercise ventilation inefficiency of CHF patients.

Introduction

Identification of chronic heart failure (CHF) patients at high risk for early death remains a basic challenge. This challenge has two major complementary approaches:

(i) the search for new and more sensitive prognostic indicators, and (ii) the refinement of already known prognostic markers through a more in-depth study and characterization of their determinants.

In recent years, there has been growing and convincing evidence that inefficient ventilation during physical performance is a very sensitive indicator of poor outcome in CHF patients.¹–⁷ Interestingly, a number of reports

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suggest that the excessive amount of ventilation (Ve) needed to eliminate metabolically produced CO₂ (i.e. the Ve/VCO₂ slope) is a prognostic indicator even more powerful than oxygen consumption measured at peak exercise (peak VO₂).²,³,⁷

The Ve/VCO₂ slope determinants are the physiological dead space–tidal volume (V₀/Vt) ratio and the arterial CO₂ partial pressure (PaCO₂). Studies investigating the pathophysiological basis for an increased Ve/VCO₂ slope in CHF have reported conflicting results. Some investigators have stressed the importance of an increased V₀/Vt secondary to ventilation/perfusion mismatching, especially in patients with moderate to severe heart failure with a preserved or minimally impaired neural control of ventilation.⁸,⁹ Others have provided evidence that overactive chemoreflex and ergoreflex responses drive the ventilatory pattern during exercise.¹⁰ Information regarding PaCO₂ changes during exercise is limited, and despite balanced evidence in favour for⁵,¹⁰–¹³ and against⁸,⁹,¹⁴ a significant decrease in PaCO₂ at peak exercise, the assumption is generally accepted that ventilation inefficiency occurs in the absence of significant changes in CO₂ tension.¹⁵

A salient point that has not been addressed before and that represents the primary objective of this study is the exploration of the relative contribution of V₀/Vt and PaCO₂ to the prognostic information provided by the Ve/VCO₂ slope. This may represent a step forward to a more precise identification of the mechanisms underlying an excessive exercise ventilation, and possibly toward more appropriate therapeutic interventions.

Methods

Study population

The study comprised patients with CHF due to either ischaemic or idiopathic dilated cardiomyopathy, who were referred to the Cardiopulmonary Laboratory at San Paolo Hospital or at the Institute of Cardiology, University of Milan, for CHF evaluation. Assessment included echocardiography, lung function, and symptom-limited cardiopulmonary exercise testing.

We restricted the analysis to patients who had been in a stable clinical condition for at least 4 months before evaluation, and under a stable therapeutic regimen prescribed by the referring physician, which was optimized during the hospital stay. We excluded patients who presented with anginal symptoms, had undergone a coronary artery bypass procedure in the previous 6 months, had primary pulmonary disorders and/or a forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) ratio < 70% of the predicted normal value, had primary valvular heart disease, or had a history of smoking more than 10 cigarettes per day during one of the past 5 years. The primary endpoint was death for cardiac reasons.

To assess vital status we resorted to the combined use of administrative and clinical databases; records during re-admission and outpatient records during follow-up (most patients attended our outpatient clinic) were reviewed. When vital status could not be determined by these methods, patients or their families were interviewed by telephone.

Echocardiography

Two-dimensional and Doppler echocardiography was performed by standard methods. Left ventricular end-systolic and end-diastolic chamber dimensions and volumes were quantified by standard techniques, using the area–length method to measure ejection fraction.

Pulmonary function tests

Spirometry was performed with equipment (Vmax Spectra, Sensomedics, Yorba Linda, CA, USA) that met the American Thoracic Society performance criteria.¹⁶ To adjust for height, age, and sex, published prediction equations for FEV₁ and FVC were used. Lung diffusion capacity for carbon monoxide (Dl/CO) was determined twice with washout intervals of at least 4 min (the average was taken as the final result) with a standard single breath technique.

Cardiopulmonary exercise testing

Patients underwent symptom-limited cardiopulmonary exercise testing with a respiratory gas exchange measurement. A personal-ized ramp protocol was used.¹⁸ A 12-lead electrocardiogram, heart rate, and blood pressure were obtained at rest and at each minute during exertion. For breath-by-breath gas exchange measurements, a Sensor Medics metabolic cart (Vmax Spectra, Sensomedics, Yorba Linda, CA, USA) was utilized. Minute ventilation [Vₑ, BTPS (body temperature, atmospheric pressure saturated with water vapour)], O₂ uptake [VO₂, STPD (standard temperature and pressure dry)], CO₂ output (VCO₂, STPD), and other exercise variables were computer-calculated breath-by-breath, interpolated second-by-second, and averaged at 10 s intervals.

The V₀/Vt ratio was derived from PaCO₂, according to the following formula:¹⁹

\[
\frac{V₀}{Vt} = \frac{Paco₂ - PECO₂}{Paco₂ - Vapp} \frac{V₀}{Vt}
\]

where PECO₂ is the mean expiratory pressure of CO₂ and Vapp is the dead space of the breathing apparatus.

The Ve/VCO₂ slope was measured by linear regression, excluding the non-linear part of the data after the onset of ventilatory compensation for metabolic acidosis. Peak VO₂ was defined as the highest VO₂ observed during the exercise test. Age-, gender-, and weight-adjusted predicted VO₂ values were also determined by using the regression equations of Wasserman et al.¹⁸ Anaerobic threshold (AT) was determined using the V-slope method.²⁰

Blood gases (PaO₂, PaCO₂) and pH were measured at rest and just before peak exercise, on arterialized capillary blood samples from the hyperaemic earlobe.

Statistical methods

The prognostic value of Ve/VCO₂ slope, peak PaO₂ and peak VO₂/Vt, and other clinical variables (age, ejection fraction, drug therapy, peak VO₂, and peak Vt) were analysed by means of the Kaplan–Meier approach with log-rank testing and by univariate Cox regression analysis. Considering that, for the assessment of ventilatory efficiency, some authors have simply used the Ve/VCO₂ ratio at peak exercise²¹ or the Ve/VCO₂ ratio at AT,²¹,²² these two variables were also included in the univariate approach.

The cut-off values for high Ve/VCO₂ slope, peak Ve/VCO₂ ratio, Ve/VCO₂ ratio at AT, age, V₀/Vt, and those for low EF, peak VO₂, and peak Vt were based on median values derived from the
heart failure cohort. Selection of median values as cut-off was motivated by the lack of an established clinical predictive cut-off for exercise peak PaCO2 and peak Vo2/VT (this is the first study investigating the prognostic power of these variables).

Multivariate Cox regression models together with Shoenfeld residual analysis was used to assess the prognostic relevance of the VE/VCO2 slope, of its determinants PaCO2 and Vo2/VT, and of other possible predictors. Model construction was based on a backward approach with initial selection of covariates on the basis of results of univariate analyses.

In order to evaluate the independent prognostic value of VE/VCO2 slope, of peak PaCO2 and peak Vo2/VT, two multivariate Cox regression analyses were carried out. Specifically, the first model was performed in order to confirm the VE/VCO2 slope prognostic power. As VE/VCO2 is a function of Vo2/VT and PaCO2, the second analysis was performed by excluding VE/VCO2 and including its two determinants PaCO2 and Vo2/VT. Both models were adjusted for the clinical variables statistically significant at the univariate analysis.

Four Kaplan-Meier curves for 6.5 year survival were plotted: one, for the patients with normal and for those with high VE/VCO2 slope (Figure 1); two, using as the discriminatory parameter peak PaCO2 (Figure 2) and peak Vo2/VT (Figure 3), respectively; one relating survival to the combination of both peak PaCO2 and peak Vo2/VT (Figure 4).

The Student’s t-test for unpaired values was used to compare the means of groups for quantitative variables. Data are presented as means ± SD. The level of statistical significance was set at two-tailed P value < 0.05.

Results

Follow-up on survival

One hundred and twenty-eight consecutive patients who met the entry criteria were selected for follow-up. No patients were lost to follow-up. The mean duration of follow-up was 31.3 ± 20 months (median 25 months). During this period there were 24 deaths for cardiac reasons. Three patients with an implantable cardioverter defibrillator (ICD) had ventricular fibrillation successfully terminated by the ICD. None of the patients underwent heart transplantation.

Baseline characteristics

Table 1 reports the clinical characteristics of the patient population. Mean age of participants was 60 ± 9 years and left ventricular ejection fraction averaged 34 ± 10%. Ischaemic cardiomyopathy was the predominant (56%)
cause of CHF. All patients had symptomatic heart failure with a mean New York Heart Association (NYHA) class of 2.0 ± 0.8. Current medical therapy included ACE-inhibitors (76%), digoxin (34%), diuretics (72%), β-blockers (30%), amiodarone (32%), and aldosterone antagonists (33%).

**Lung function test and blood gases**

The mean FEV$_1$, FVC, and DLco were 85, 75, and 76% of predicted normal value, respectively. When patients were grouped according to the median value of peak VO$_2$ (0.22) and of peak PaCO$_2$ (35 mmHg), significant differences in FEV$_1$, FVC, and DLco were detected between the two groups ($P < 0.05$; Tables 2 and 3). In the whole population, average values of arterial blood gases both at rest and at peak exercise were within normal limits. However, when patients were grouped according to the median peak Vo/VT and peak PaCO$_2$ cut-off, there were significant differences in PaCO$_2$ and pH at peak exercise (Tables 2 and 3).

### Cardiopulmonary exercise testing

As shown in Table 1, patients presented with a moderate exercise limitation (average peak VO$_2$: 16.5 ± 4.4 mL·min$^{-1}$·kg$^{-1}$ corresponding to 60% of maximum predicted). Again, when patients were grouped according to peak Vo/VT and peak PaCO$_2$ median value, those with the lower Vo/VT and higher PaCO$_2$ presented with significantly higher peak VO$_2$, Vo$_2$ at AT O$_2$ pulse and peak tidal volume, and lower peak

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**Table 1** Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Gender, M/F, %</td>
<td>79/21</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169 ± 7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 ± 12</td>
</tr>
<tr>
<td>Ischaemic, non-ischaemic, %</td>
<td>56/44</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.0 ± 0.8</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>34 ± 10</td>
</tr>
</tbody>
</table>

Therapy distribution, %

- Digoxin: 34
- Diuretics: 72
- ACE-inhibitors: 76
- Nitrates: 16
- β-blockers: 30
- AT blockers: 8
- Aldosterone antagonists: 33
- Amiodarone: 32

Pulmonary function

- FEV$_1$, L: 2.4 ± 0.6
  - % predicted: 85 ± 17
- FVC, L: 3.0 ± 0.7
  - % predicted: 75 ± 15
- DLco, mL·min$^{-1}$·mmHg$^{-1}$: 20 ± 6
  - % predicted: 76 ± 20

Blood gases

- PaCO$_2$ at rest, mmHg: 39.5 ± 5
- PaO$_2$ at rest, mmHg: 104 ± 8
- pH at rest: 7.43 ± 0.02
- Peak PaCO$_2$, mmHg: 38 ± 5
- Peak PaO$_2$, mmHg: 110 ± 15
- pH at peak exercise: 7.37 ± 0.03

Cardiopulmonary exercise testing

- Heart rate at rest, b.p.m.: 80 ± 17
- Heart rate at peak exercise, b.p.m.: 139 ± 30
- Peak VO$_2$, mL·min$^{-1}$·kg$^{-1}$: 16.5 ± 4.4
  - % predicted: 60 ± 16
- VO$_2$ AT, mL·min$^{-1}$·kg$^{-1}$: 10 ± 3.0
- Peak O$_2$ pulse, mL·beat$^{-1}$: 9.5 ± 2.9
- Ve$_c$, L: 49 ± 19
- Peak Vo/VT: 0.22 ± 0.05
- Peak Vo/Vo$_2$: 44 ± 10
- Ve$_c$/VCO$_2$ AT: 39 ± 9
- Peak Ve/VCO$_2$: 40 ± 8
- Ve$_c$/VCO$_2$ slope: 34 ± 8

Data are presented as means ± SD.
Table 3 Pulmonary function, cardiopulmonary exercise testing data, and arterial blood gases in the study population according to exercise peak PaCO2 median value

<table>
<thead>
<tr>
<th>Pulmonary function</th>
<th>Peak PaCO2 ≥ 35 (n = 64)</th>
<th>Peak PaCO2 &lt; 35 (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, L</td>
<td>2.5 ± 0.7</td>
<td>2.2 ± 0.4 *</td>
</tr>
<tr>
<td>% predicted</td>
<td>88 ± 15</td>
<td>80 ± 17 *</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.1 ± 0.7</td>
<td>2.8 ± 0.7 *</td>
</tr>
<tr>
<td>% predicted</td>
<td>78 ± 15</td>
<td>71 ± 15 *</td>
</tr>
<tr>
<td>DLco, mL·min⁻¹·mmHg⁻¹</td>
<td>21 ± 6</td>
<td>19 ± 5 *</td>
</tr>
<tr>
<td>% predicted</td>
<td>80 ± 20</td>
<td>72 ± 18 *</td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO2 at rest, mmHg</td>
<td>40 ± 4</td>
<td>39 ± 5</td>
</tr>
<tr>
<td>PaO2 at rest, mmHg</td>
<td>105 ± 7</td>
<td>102 ± 8</td>
</tr>
<tr>
<td>pH at rest</td>
<td>7.44 ± 0.03</td>
<td>7.42 ± 0.02</td>
</tr>
<tr>
<td>Peak PaCO2, mmHg</td>
<td>38 ± 5</td>
<td>33 ± 5 *</td>
</tr>
<tr>
<td>Peak PaO2, mmHg</td>
<td>112 ± 7</td>
<td>109 ± 8</td>
</tr>
<tr>
<td>PaO2 at peak exercise</td>
<td>7.38 ± 0.03</td>
<td>7.28 ± 0.02 **</td>
</tr>
<tr>
<td>Cardiopulmonary exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate at peak</td>
<td>80 ± 17</td>
<td>80 ± 18</td>
</tr>
<tr>
<td>Heart rate at exercise</td>
<td>143 ± 32</td>
<td>136 ± 29 *</td>
</tr>
<tr>
<td>Peak V O2, mL·min⁻¹·kg⁻¹</td>
<td>17.6 ± 4.0</td>
<td>15.4 ± 4 *</td>
</tr>
<tr>
<td>% predicted</td>
<td>63 ± 15</td>
<td>57 ± 16 *</td>
</tr>
<tr>
<td>VO2 AT, mL·min⁻¹·kg⁻¹</td>
<td>10.8 ± 2.5</td>
<td>9.7 ± 2.6 *</td>
</tr>
<tr>
<td>Peak O2 pulse, mL·beat⁻¹</td>
<td>9.7 ± 2.8</td>
<td>9.1 ± 3.0 *</td>
</tr>
<tr>
<td>VCO2, L</td>
<td>49 ± 15</td>
<td>49 ± 23</td>
</tr>
<tr>
<td>Tidal volume, L</td>
<td>1.8 ± 0.4</td>
<td>1.6 ± 0.3 *</td>
</tr>
<tr>
<td>Peak VO2/V Ti</td>
<td>0.21 ± 0.05</td>
<td>0.23 ± 0.05 *</td>
</tr>
<tr>
<td>Peak VE/VO2</td>
<td>38.5 ± 6.5</td>
<td>50.0 ± 9.5 **</td>
</tr>
<tr>
<td>VE/VO2 AT</td>
<td>34 ± 5</td>
<td>43 ± 10 **</td>
</tr>
<tr>
<td>Peak VE/VCO2</td>
<td>34.7 ± 5.5</td>
<td>44 ± 8 **</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>30.6 ± 4.6</td>
<td>38 ± 9 **</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.
*P < 0.05 vs. PaCO2 ≥ 35.
**P < 0.01 vs. PaCO2 ≥ 35.

Table 4 Univariate predictors of death (n = 24)

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>SE</th>
<th>z</th>
<th>P &gt; z</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.4429</td>
<td>0.6001</td>
<td>0.882</td>
<td>0.378</td>
<td>0.638–3.260</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>3.1776</td>
<td>1.5021</td>
<td>0.014</td>
<td>0.014</td>
<td>1.258–8.025</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>0.3685</td>
<td>0.2478</td>
<td>−1.295</td>
<td>0.195</td>
<td>0.2419–1.336</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>0.6185</td>
<td>0.3153</td>
<td>0.942</td>
<td>0.346</td>
<td>0.2277–1.680</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>3.2992</td>
<td>1.3842</td>
<td>2.845</td>
<td>0.004</td>
<td>1.449–7.508</td>
</tr>
<tr>
<td>Peak VO2, mL·min⁻¹·kg⁻¹</td>
<td>2.5426</td>
<td>1.1599</td>
<td>2.046</td>
<td>0.041</td>
<td>1.039–6.217</td>
</tr>
<tr>
<td>VE/VCO2 AT</td>
<td>2.2093</td>
<td>0.9939</td>
<td>1.762</td>
<td>0.078</td>
<td>0.914–5.335</td>
</tr>
<tr>
<td>Peak VE/VCO2</td>
<td>2.2090</td>
<td>1.0458</td>
<td>1.674</td>
<td>0.094</td>
<td>0.873–5.587</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>7.7488</td>
<td>4.7896</td>
<td>3.313</td>
<td>0.001</td>
<td>2.307–26.023</td>
</tr>
<tr>
<td>Peak VE/VO2</td>
<td>2.6249</td>
<td>1.1996</td>
<td>2.112</td>
<td>0.035</td>
<td>1.071–6.429</td>
</tr>
<tr>
<td>Tidal volume, L</td>
<td>1.6629</td>
<td>0.7038</td>
<td>1.202</td>
<td>0.230</td>
<td>0.725–3.811</td>
</tr>
<tr>
<td>Peak VO2/V Ti</td>
<td>2.2356</td>
<td>0.9694</td>
<td>1.855</td>
<td>0.064</td>
<td>0.955–5.229</td>
</tr>
<tr>
<td>Peak PaCO2, mmHg</td>
<td>1.6629</td>
<td>2.6360</td>
<td>3.207</td>
<td>0.001</td>
<td>1.892–14.043</td>
</tr>
</tbody>
</table>

aDiscrete dummy variable ‘high vs. low’.
bDiscrete dummy variable ‘low vs. high’.
cDiscrete dummy variable ‘no vs. yes’.

Univariate analysis

Results of the univariate analysis of factors known to influence prognosis are reported in Table 4. Ve/VCO2 slope and peak exercise PaCO2 emerged as stronger predictors. Among the therapeutic drug regimen, aldosterone antagonists were found to be the only significant predictors of survival.

Multivariate analyses

Tables 5 and 6 report the results of the Cox regression analysis and Shoenfeld test of proportional hazard assumption. Two models have been used: the first model (Table 5) included ejection fraction, use of aldosterone antagonists, peak VE/VO2, and peak VO2; an abnormally steep Ve/VCO2 slope was found to be the only predictor of death [HR 5.84, CI (1.692–20.197), P = 0.005]. In the second model (Table 6), after adjusting for ejection fraction, aldosterone antagonist therapy, peak VE/Vo2, peak PaO2, and peak VO2/Vr, the strongest independent predictors of death were peak PaCO2 [HR 4.65, CI (1.69–12.751), P = 0.003], peak VO2/Vr [HR 2.51, CI (1.067–5.931), P = 0.035] and ejection fraction [HR 2.96, CI (0.151–7.646), P = 0.024].

Survival analysis

The Kaplan–Meier 6.5-year survival approach evidenced a survival of 38% for patients with a Ve/VCO2 slope median value ≥32.6 compared with 94% survival for those with a median value <32.6 (Figure 1). When analyses were performed according to the Ve/VCO2 slope determinants, PaCO2 and Vo2/Vt at peak exercise, the survival was 40% (Figure 2) and 46% (Figure 3), respectively. Remarkably,
survival of patients with both a low peak exercise PaCO2 and a high peak VD/VT was as low as 25% (Figure 4).

Correlation analyses

As shown in Figure 5A, a strong inverse correlation was found between VE/VCO2 slope and peak PaCO2 ($r = -0.69; P = 0.0001$); 85% of non-survivors were distributed in the area with a lower peak PaCO2 ($<35$ mmHg) and a higher VE/VCO2 slope ($\geq 32.4$). A weaker positive correlation was found between VE/VCO2 slope and peak VO2/Vt ($r = 0.37; P = 0.001$) (Figure 5B); 58% of non-survivors were distributed in the area with a higher peak VO2/Vt ($0.22$) and a higher VE/VCO2 slope ($\geq 32.4$) (Figure 5B). No correlation was found between peak PaCO2 and peak VO2/Vt ($r = -0.152, P = 0.086$).

Discussion

There are two novel findings in the present study. First, a low peak exercise PaCO2 and an elevated peak VO2/Vt are strong independent predictors of mortality in stable CHF patients. Second, a low peak exercise PaCO2 is the more significant determinant of the prognostic value of a steep VE/VCO2 slope.

A consistent association between increased levels of ventilation and cardiovascular mortality has been documented in several studies across different population groups.1–7 Mostly, it has been shown that an abnormally high VE/VCO2 slope predicts an increased risk of death among CHF patients to an even greater degree than peak VO2.2,3,6,7 The relationship between a high VE/VCO2 slope and survival has been further strengthened by the recent landmark finding that even in patients with normal exercise performance and peak VO2 ($\geq 18$ mL·min$^{-1}$·kg$^{-1}$), an abnormal exercise ventilation significantly discriminates survival.4 In addition, the VE/VCO2 slope is independent of motivation, showing minimal variability at 30, 60, and 100% of exercise capacity,23 and retains a high prognostic power when measured at submaximal constant workloads.24 The current study confirms that VE/VCO2 slope is a stronger predictor than peak VO2, and expands, in some important respects, information provided by previous reports. In fact, it is the only study aimed at analysing the prognostic significance of the physiological determinants of ventilation in CHF patients. Furthermore, when peak PaCO2, peak VO2/Vt, and peak VO2 were considered together, the ventilatory variables emerged

**Table 5** Multivariate predictors of death: results of Cox regression analysis (model 1) and Shoenfeld test of proportional hazard assumption after adjusting for clinical variables significant in the univariate approach

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>SE</th>
<th>z</th>
<th>P &gt; z</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>2.2066</td>
<td>1.0640</td>
<td>1.641</td>
<td>0.101</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>5.8464</td>
<td>3.6979</td>
<td>2.792</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak VO2, mL·min$^{-1}$·kg$^{-1}$</td>
<td>2.0988</td>
<td>0.9694</td>
<td>1.605</td>
<td>0.108</td>
</tr>
</tbody>
</table>

**Table 6** Multivariate predictors of death: results of Cox regression analysis (model 2) and Shoenfeld test of proportional hazard assumption after adjusting for clinical variables significant in the univariate approach

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>SE</th>
<th>z</th>
<th>P &gt; z</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>2.9677</td>
<td>1.4330</td>
<td>2.253</td>
<td>0.024</td>
</tr>
<tr>
<td>Peak PaCO2, mmHg</td>
<td>4.6502</td>
<td>2.2934</td>
<td>2.986</td>
<td>0.003</td>
</tr>
<tr>
<td>Peak VO2/Vt</td>
<td>2.5168</td>
<td>1.1009</td>
<td>2.110</td>
<td>0.035</td>
</tr>
</tbody>
</table>

a Discrete dummy variable ‘low vs. high’.
b Discrete dummy variable ‘high vs. low’.
as stronger and independent predictors of death, indicating that they are not simply a function of lower workload achieved.

Increased \( V_{E}/V_{CO_2} \) slope: pathophysiological bases

The precise pathophysiological substrates that predispose to, and sustain an excessive ventilation in, CHF patients remain controversial.\(^{15}\) Mathematically, the \( V_{E}/V_{CO_2} \) slope is determined by three factors: the rate of \( CO_2 \) production, the physiological \( V_d/V_t \), and the \( PaCO_2 \). Therefore, for a given \( V_{CO_2} \), an increased \( V_{E}/V_{CO_2} \) slope has multiple possible substrates: (i) an augmented central and/or peripheral command to ventilation, which drives the \( PaCO_2 \) below the physiological range; (ii) a large dead space which requires an increase in ventilation to maintain a normal \( PaCO_2 \); and (iii) an early occurrence of metabolic acidosis which demands ventilatory compensation. Initial studies by Sullivan et al.\(^8\) reported that an increased \( V_d/V_t \), in the face of a preserved neural control of ventilation and normal blood gases, is responsible for the augmented \( V_{E}/V_{CO_2} \) slope. In 130 patients with different CHF severity, Wasserman et al.\(^9\) reproduced the same findings, identifying structural changes intrinsic to the lung (restrictive lung changes) and reduced lung perfusion, as responsible for the occurrence of a high \( V_d/V_t \) and consequent ventilation/perfusion mismatch. In these reports, changes in pH and \( PaCO_2 \) between rest and peak exercise were minimal, suggesting no differences in the \( PaCO_2 \) set point compared with healthy subjects. In contrast, other studies in CHF patients have reported a significant reduction in \( PaCO_2 \) at peak exercise.\(^{5,10,11,13}\) Notably, in a population similar to ours, Hachamovitch et al.\(^{12}\) reported a significant reduction in \( PaCO_2 \) even during a submaximal constant workload at 50 W. The link, however, between an increased \( V_d/V_t \) and a reduced \( PaCO_2 \) remains elusive. In the present report, both an increased \( V_d/V_t \) and a reduced peak exercise \( PaCO_2 \) were documented and for both of them a significant correlation with \( V_{E}/V_{CO_2} \) slope was found.

Chua et al.\(^{25}\) observed that an augmented ventilatory response to exercise in CHF is significantly correlated with an impaired central and peripheral control of ventilation. The same group of investigators has expanded these observations providing impressive evidence of an abnormal cardiorespiratory reflex control, related to both activation of chemoreceptors and fibres originating from the working muscle (i.e. ergoreflex stimuli),\(^{26,27}\) and an abnormal autonomic baroreflex control of circulation.\(^{28}\)

\( PaCO_2 \) vs. \( V_d/V_t \) at peak exercise: prognostic insights

It is remarkable that in CHF the only link between augmented exercise ventilation and prognosis is provided by studies assessing the ergoreflex and chemoreflex activation.\(^{1,4,27}\) In these reports, however, neither were blood gas measurements obtained, nor peak exercise \( V_d/V_t \) calculated, and their possible relationship with survival has remained undefined. Our study sheds light on the prognostic power of these variables, and multivariate Cox regression analysis has identified both arterial \( PaCO_2 \) and \( V_d/V_t \) at peak exercise as survival predictors. \( PaCO_2 \) at peak exercise, however, retained a greater prognostic significance than peak \( V_d/V_t \) and was associated with a higher hazard ratio (4.65 vs. 2.51). The decrease in peak exercise \( PaCO_2 \) may be both the trigger (development of metabolic acidosis due to inadequate cardiac output), or the consequence (excessive ventilatory response to increasing \( CO_2 \) output) of the increased ventilatory response to exercise. It is very likely that these two mechanisms were additive in influencing \( PaCO_2 \) changes. Although we cannot rule out an excessive ventilatory drive secondary to chemoreflex and/or ergoreflex activation, it is noteworthy that patients who developed hypocapnia and metabolic
acidosis were exposed to a higher risk of death. Whatever the underlying mechanisms, our data are in favour of a peripheral substrate, rather than of a pulmonary ventilation/perfusion mismatching as a determinant of the prognostic significance of the ventilatory response to exercise in CHF.

Study limitations

The number of patients in this study was relatively small. It should be considered, however, that the average follow-up was quite long. The analysis included only CHF patients who were in stable clinical conditions and were able to perform a symptom-limited exercise test. However, this was an unselected ambulatory CHF population. The average peak VO\(_2\) of 16.5 ± 4.4 mL·min\(^{-1}\)·kg\(^{-1}\) reflected a mild to moderate exercise limitation, and results might not apply to advanced CHF. Nevertheless, because patients with advanced CHF and severe exercise limitation may exhibit hypocapnia and metabolic acidosis from the very early exercise stages, it is conceivable that an abnormally low arterial PaCO\(_2\) at peak exercise may bear an even more significant prognostic power in this subset of patients.

Conclusions

An excessively low peak exercise PaCO\(_2\) and an abnormally high peak VO\(_2\)/V\(_{\text{E}}\) (the two determinants of ventilation for a given CO\(_2\)) are both strong predictors of death among stable CHF patients and their prognostic value is independent of peak VO\(_2\).

PaCO\(_2\) emerges as the more significant determinant of the VE/VCO\(_2\) slope, suggesting that regulatory mechanisms involved in the tight control of ventilatory command and blood gas tension, rather than lung function abnormalities, play a critical pathophysiological role in the exercise ventilation inefficiency of CHF patients.

Acknowledgements

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References


