Oscillatory Ventilation During Exercise in Patients With Chronic Heart Failure*

Clinical Correlates and Prognostic Implications

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Study objectives: Although breathing disorders are often found in patients with chronic heart failure, exertional oscillatory ventilation (EOV) has been occasionally described. The aim of this study was to determine the prevalence, clinical characteristics, and outcome of patients with chronic heart failure and EOV.

Setting: Cardiology division at tertiary-care hospital.

Study population: We studied 323 patients with chronic heart failure and left ventricular ejection fraction (LVEF) < 40%.

Measurements and results: All patients performed a symptom-limited cardiopulmonary exercise test and were followed up for 22 ± 11 months (mean ± SD). EOV was defined as cyclic fluctuations in minute ventilation (VE) at rest that persist during effort lasting ≥ 60% of the exercise duration, with an amplitude ≥ 15% of the average resting value. Patients with EOV (12%), as compared to those without, showed higher New York Heart Association (NYHA) class (p < 0.05) and lower LVEF (p < 0.0001) and peak oxygen consumption (VO2) [p < 0.0001]. During the follow-up period, 53 patients died or underwent urgent cardiac transplantation; this group showed higher NYHA class (p < 0.05) and VE/VO2 slope (p < 0.0001) and lower LVEF (p < 0.0001), mitral Doppler early deceleration time (p < 0.01), and peak VO2 (p < 0.0001). EOV was more frequent in nonsurvivors than in survivors (28% vs 9%, p < 0.01). Multivariate analysis revealed peak VO2 (χ2, 51.5; p < 0.0001), EOV (χ2, 45.4; p < 0.0001), and LVEF (χ2, 20.6; p < 0.0001) as independent predictors of major cardiac events.

Conclusions: EOV is not unusual in patients with chronic heart failure, and is associated with worse clinical status, cardiac function, and exercise capacity. EOV is a powerful predictor of poor prognosis and, consequently, it may be considered a valuable guide in the management of patients with chronic heart failure and should suggest a more aggressive medical treatment policy when detected.

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Key words: exertional oscillatory ventilation; heart failure; prognosis

Abbreviations: AS = activity score; DT = Doppler-derived mitral deceleration time of early filling; EOV = exertional oscillatory ventilation; LVEDVI = end-diastolic left ventricular volume index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RER = respiratory exchange ratio; SR = sinus rhythm; VAT = ventilatory anaerobic threshold; VO2 = oxygen consumption

The management of patients with chronic heart failure represents a major challenge in the day-to-day medical practice in Western developed nations. Accurate risk stratification is crucial both for establishing prognosis and for the appropriate allocation of limited resources for advanced but expensive treatments including heart transplantation. Many clinical indexes have been used to estimate the severity of chronic heart failure, but all have limitations because of the heterogeneity and complexity of the syndrome.1 Evidence linking exercise capacity with outcome in patients with chronic heart failure has led to the frequent use of peak oxygen consumption (VO2) derived from maximal cardiopulmonary exercise testing in the prognostic assessment.2–4 Nevertheless, the prognostic power of peak VO2 is limited in patients with moderate-to-severe exercise

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limitation, and additional exertional gas exchange variables have been proposed to improve outcome prediction in this difficult but clinically important subset of patients. In this context, exertional hyperventilation, as defined by a steeper regression slope relating minute ventilation (VE) to carbon dioxide production (VCO$_2$), is associated both with the severity of the heart failure and, in combination with peak VO$_2$, may have independent prognostic implications. This and other features of the physiologic ventilatory response to exercise may have important physiologic meaning in understanding the cause of the heightened probability of death in these high-risk patients.

A distinct and abnormal pattern of ventilation, consisting of cyclic hyperpnea and hypopnea, has also been described both at rest and occurring during exercise in a small series of patients with severe chronic heart failure. This respiratory pattern can be evanescent or transient and can follow several distinct patterns: it has been observed in some throughout the entire exercise protocol, and in others occurring only at rest, before starting the exercise test, or disappearing during the early stages of exercise or indeed only disappearing at peak exercise.

However, while the phenomenon of periodic breathing at rest, particularly overnight, has received great attention in the literature to date, no comprehensive data exist on the prevalence and clinical significance of oscillatory ventilation during exercise (exertional oscillatory ventilation [EOV]), which may start at rest but which is also seen during exercise. We hypothesized that this ventilatory pattern might reflect a marked alteration of the normal physiologic control systems important in cardiopulmonary responses and could, therefore, be useful as an adjunct in full and proper evaluation of patients with chronic heart failure. Thus, the aims of our study were: (1) to determine the prevalence of EOV in a large population of patients with clinically stable chronic heart failure, (2) to verify the reproducibility of EOV, (3) to describe the underlying clinical characteristics of patients exhibiting EOV, and (4) to investigate the prognostic value of EOV in this population.

### Materials and Methods

#### Study Population

We studied 390 patients with chronic heart failure due to ischemic or idiopathic dilated cardiomyopathy referred for cardiopulmonary exercise testing as part of a comprehensive heart failure evaluation between January 1996 and November 1998. All patients had a history of at least one unequivocal clinical episode of heart failure. All had been receiving stable medical optimized treatment for at least 1 month at the time of the study. Eligibility criteria were: (1) echocardiographic left ventricular ejection fraction (LVEF) ≤ 40%; (2) ability to perform a cardiopulmonary exercise test until exhaustion with a peak respiratory exchange ratio (RER) ≥ 1.05, in order to exclude poor motivation; and (3) exercise test stopped for fatigue and/or dyspnea. Patients were excluded if graphical breath-by-breath gas exchange data were uninterpretable due to technical difficulties. Patients were included in the study after their informed written consent was obtained.

#### Cardiopulmonary Exercise Testing

All patients underwent an incremental cardiopulmonary exercise test on a bicycle ergometer. After a 1-min warm-up period at 0-W workload, a ramp protocol of 10 W/min was started and continued until exhaustion. The pedaling rate was kept constant at 60 revolutions per minute. A 12-lead ECG was monitored continuously during the test (MAX-1; Marquette Electronics; Milwaukee, WI), and cuff BP was manually recorded every 2 min. Respiratory gas exchange measurements were obtained breath-by-breath using a computerized metabolic cart (Vmax29; Sensor Medics; Yorba Linda, CA). Before each test, oxygen and carbon dioxide analyzers and flow mass sensor were calibrated using available precision gas mixtures and a 3-L syringe, respectively. Peak VO$_2$ was recorded as the mean value of VO$_2$ during the last 20 s of the test and expressed in milligrams per kilogram per minute. Predicted VO$_2$ was determined by using a gender-, age-, height-, and weight-adjusted and protocol-specific formula outlined by Wasserman and colleagues. The ventilatory anaerobic threshold (VAT) was determined by the V-slope method. Ventilatory response to exercise was calculated as a linear regression function by plotting VE against VCO$_2$ obtained every 10 s of exercise (VE/VCO$_2$ slope); both VE and VCO$_2$ were measured in liters per minute. Medical treatment administered the day of exercise testing was recorded.

VE at rest and during exercise was displayed on an expanded time scale, and the presence of an oscillatory ventilation pattern was established according to the recommendations of previous studies. EOV was defined as cyclic fluctuations in VE lasting > 60% of the exercise protocol duration, with an amplitude of > 15% of the average amplitude of cyclic fluctuations at rest.

#### Activity Scoring System

Before exercise testing, patients’ level of weekly physical activity was scored by an interviewer-administered habitual physical activity scoring system, also taking into consideration deconditioning events. Details, objectivity, and applicability of the activity scoring system have described elsewhere. Five different levels of weekly physical activity intensity were identified, corresponding to an activity score (AS) of 1 to 5, and the final AS was reduced by 20% if a hospital admission had taken place during the month preceding the test, or by 10% if hospitalization(s) had occurred between 30 days and 120 days before the test.

#### Echocardiography

Complete two-dimensional and Doppler echocardiograms were performed using an imaging system (model 77622-A; Hewlett-Packard; Andover, MA) within 5 ± 2 days (mean ± SD) of cardiopulmonary exercise test in stable clinical and pharmacologic conditions. Left ventricular volume was calculated from orthogonal apical views using the area-length method, and LVEF was derived from the standard equation. Diastolic filling pattern was provided by Doppler-derived mitral flow velocity re-
Follow-up and Documentation of Cardiac Events

Patients were followed up at the outpatient clinic of our hospital, and patient’s status was determined from the medical records. The following events were defined as cardiac end points: sudden death (ie, unexpected death, occurring in or out of hospital within 1 h after the onset of, or change in, symptoms or during sleep in a patient who had been symptomatically stable during the previous 24 h); progressive heart failure (ie, progressive hemodynamic deterioration resulting in pulmonary edema or cardiogenic shock and death); acute myocardial infarction; and pulmonary embolism. Urgent heart transplantation (status I patients) was classified as equivalent to death for purposes of statistical analysis. Data from patients who survived until the end of the follow-up period or who died of noncardiac-related causes or who underwent nonurgent heart transplantation were evaluated as “censored.”

Statistics

Results are expressed as means ± SD. Student’s t test for nonpaired values was used to compare the means of groups for quantitative variables. For qualitative variables, the χ2 test with Yates’ correction or Fisher exact test, if necessary, was employed. The level of statistical significance was set at a two-tailed p value ≤ 0.05. The variables that showed a significant association with the outcome (p < 0.01) at univariate Cox regression analysis, were included in the regression analysis of survival data based on Cox proportional hazard model (multivariate analysis). Survival was estimated by the product-limit Kaplan-Meier method. Differences between survival curves were tested with the log-rank χ2 statistic. All calculations were performed using software (BMDP; Abacus Concepts; Berkeley, CA).

RESULTS

Sixty-seven patients were excluded from the study: 37 patients were unable to reach a peak RER ≥ 1.05; 26 patients were not limited by fatigue and/or dyspnea; and in 4 patients, the presence of artifacts rendered the breath-by-breath gas exchange data uninterpretable. Among proscribed patients, three patients had EOV, but their data were not included in subsequent analysis. Thus, 323 patients met the inclusion criteria and form the basis of this report. Patients’ demographics and clinical characteristics are shown in Table 1.

Thirty-eight (12%) patients exhibited EOV. Six patients showed oscillatory ventilation only at rest and were assigned to the nonoscillatory ventilation group.

Reproducibility of EOV

To assess the reproducibility of EOV, the cardio-pulmonary exercise test was repeated in 5 of 38 patients (13%) with EOV in stable clinical conditions within 1 month. In all repeated tests, the oscillatory ventilation during exercise was observed and fulfilled

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n = 323)</th>
<th>Survivors (n = 270)</th>
<th>Nonsurvivors (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57 ± 9</td>
<td>57 ± 9</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>279/44</td>
<td>231/39</td>
<td>48/5</td>
</tr>
<tr>
<td>Etiology of heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>184 (57)</td>
<td>154 (57)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>139 (43)</td>
<td>116 (43)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>SR</td>
<td>284 (88)</td>
<td>239 (88)</td>
<td>45 (85)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 0.6</td>
<td>2.5 ± 0.9†</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>292 (90)</td>
<td>246 (91)</td>
<td>46 (87)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>306 (95)</td>
<td>253 (93)</td>
<td>53 (100)</td>
</tr>
<tr>
<td>β-Adrenergic blocking agents</td>
<td>100 (31)</td>
<td>90 (33)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>128 ± 48</td>
<td>121 ± 41</td>
<td>160 ± 63†</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24 ± 8</td>
<td>24 ± 8</td>
<td>19 ± 6†</td>
</tr>
<tr>
<td>DT, ms</td>
<td>157 ± 50</td>
<td>160 ± 52</td>
<td>138 ± 35†</td>
</tr>
<tr>
<td>Exercise data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂, mL/kg/min</td>
<td>14 ± 3</td>
<td>14.4 ± 3</td>
<td>11.7 ± 3†</td>
</tr>
<tr>
<td>% predicted peak VO₂</td>
<td>50 ± 16</td>
<td>52 ± 13</td>
<td>42 ± 11†</td>
</tr>
<tr>
<td>Exercise time, s</td>
<td>480 ± 160</td>
<td>498 ± 163</td>
<td>384 ± 138†</td>
</tr>
<tr>
<td>V̇e/V̇CO₂ slope</td>
<td>32 ± 8</td>
<td>31.6 ± 7</td>
<td>37 ± 11†</td>
</tr>
<tr>
<td>RER</td>
<td>1.19 ± 0.1</td>
<td>1.19 ± 0.1</td>
<td>1.19 ± 0.1</td>
</tr>
<tr>
<td>EOV</td>
<td>38 (12)</td>
<td>23 (9)</td>
<td>15 (28)†</td>
</tr>
<tr>
<td>Detectable VAT</td>
<td>217 (67)</td>
<td>189 (70)</td>
<td>28 (53)</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD or No. (%) of patients unless otherwise indicated. ACE = angiotensin converting enzyme.
†p < 0.05.
‡p < 0.01.
the definition criteria for EOV applied in this study. An example of the EOV pattern and its reproducibility is shown in Figure 1.

**Baseline Characteristics of Patients With Oscillatory Ventilation at Rest and During Exercise**

Age and gender were similar in patients with and without EOV, and the occurrence of this abnormal ventilatory pattern did not differ as regards the etiology of heart failure or the presence of sinus rhythm (SR; Table 2). Patients with EOV, as compared to those without, showed a higher New York Heart Association (NYHA) class (p < 0.05), a reduced AS (p < 0.0001), a lower LVEF (p < 0.0001), a greater end-diastolic left ventricular volume index (LVEDVI; p < 0.05), and a shorter DT (p < 0.0001) [Table 2]. In addition, patients with EOV had a reduced peak $\text{VO}_2$, percentage of predicted peak $\text{VO}_2$, and exercise duration (p < 0.0001), whereas peak RER was similar. $\text{Ve}/\text{VCO}_2$ slope was steeper (p < 0.0001), whereas peak VE was lower, as a consequence of lower functional capacity (Table 2). VAT was identified in 13 patients (34%) with EOV and in 207 patients (72%) without EOV (p < 0.05); the $\text{VO}_2$ at the VAT was lower in patients with EOV (8.0 ± 2 mL/kg/min vs 10.4 ± 3 mL/kg/min; p < 0.0001).

Mean furosemide daily dose was significantly higher in patients with EOV compared to patients with a normal ventilatory pattern on exercise (p < 0.01), whereas an equal percentage of patients in each group received angiotensin-converting enzyme inhibitors and $\beta$-adrenergic blocking agents (Table 2).

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21977/)
Follow-up

No patient was unavailable for the follow-up period, which lasted 22 ± 11 months. One patient died of noncardiac causes (cancer), and 49 patients died of cardiac causes: sudden death (n = 29), progressive heart failure (n = 17), myocardial infarction (n = 2), and pulmonary embolism (n = 1). Twenty-six patients underwent heart transplantation, and 4 of these patients were hospitalized for hemodynamic support and urgent heart transplantation (status I patients). Accordingly, 53 patients (16%) had major cardiac events (cardiac deaths and urgent heart transplantation). For patients without major cardiac events, the duration of follow-up was 22 ± 13 months; for those who died, the mean follow-up duration was 16 ± 11 months. Actuarial 1-year and 2-year survival rates were 91% and 86%, respectively.

There was no difference in age, gender, etiology of heart failure, or percentage of patients in SR between survivors and nonsurvivors (Table 1). However, those who died were in a higher NYHA functional class (p < 0.05), showed a lower LVEF (p < 0.0001), a larger LVEDVI (p < 0.0001), a shorter DT (p < 0.01), a reduced peak VO₂, percentage of predicted VO₂, and exercise duration (p < 0.0001), and a higher Ve/VCO₂ slope (p < 0.0001). Finally, the EOV pattern was more frequent in nonsurvivors than in survivors (28% vs 9%, p < 0.01; Table 1).

In the univariate Cox proportional hazard model, NYHA functional class, DT, detectable VAT, LVEF, peak VO₂, Ve/VCO₂ slope, exercise duration, and EOV were all significant prognostic predictors (p < 0.01). Multivariate Cox proportional hazard analysis revealed peak VO₂, EOV, and LVEF as the only independent and additional predictors of cardiac death (Table 3). Total mortality was significantly higher according to functional capacity impairment: 38% of the 49 patients with peak VO₂ ≤ 10 mL/kg/min died, as opposed to only 2% of the 55 patients with peak VO₂ ≥ 18 mL/kg/min (p < 0.0001). The cumulative 1-year mortality rate was 20% in patients with peak VO₂ ≤ 10 mL/kg/min, and 0% in those with peak VO₂ ≥ 18 mL/kg/min (p < 0.0001). In contrast, no difference in mortality rate was found among the 219 patients with intermediate exercise capacity: 16% in patients with peak VO₂ > 10 to ≤ 14 mL/kg/min vs 14% in those with peak VO₂ > 14 to 18 mL/kg/min. Survival according to functional capacity is shown in Figure 2, top, a.

Oscillatory Ventilation

Patients with EOV had a worse prognosis as compared to those without EOV (40% vs 14% deaths, p < 0.0001): the cumulative 1-year mortality rate was 34% in patients with EOV vs 4% in those without EOV in the total population (p < 0.0001; Fig 2, middle, b). One of six patients (16%) with oscillatory ventilation only at rest died during the follow-up period. Among patients with peak VO₂ between 10 mL/kg/min and 18 mL/kg/min, those with EOV (n = 26, 12%) still had a significantly higher total mortality rate than those without EOV (37% vs 12% deaths; p < 0.0001). The cumulative 1-year mortality rate was 33% in patients with EOV vs 4% in those without EOV (p < 0.0001; Fig 2, bottom, c).

**Table 2—Clinical Characteristics of Patients According to Ventilatory Pattern During Exercise**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Oscillatory Ventilation</th>
<th>Normal Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>38</td>
<td>285</td>
</tr>
<tr>
<td>Age, yr</td>
<td>59 ± 7</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>35/3</td>
<td>244/41</td>
</tr>
<tr>
<td>Etiology of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>22 (58)</td>
<td>162 (57)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>16 (42)</td>
<td>123 (43)</td>
</tr>
<tr>
<td>SR</td>
<td>32 (84)</td>
<td>252 (88)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.6 ± 0.5</td>
<td>2.1 ± 0.61</td>
</tr>
<tr>
<td>AS (1–5)</td>
<td>1.44 ± 0.5</td>
<td>1.60 ± 1.11</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>34 (89)</td>
<td>258 (90)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>38 (100)</td>
<td>268 (94)</td>
</tr>
<tr>
<td>Diuretic daily dose, μg</td>
<td>150 ± 132</td>
<td>66 ± 63</td>
</tr>
<tr>
<td>β-Adrenergic blocking agents</td>
<td>14 (37)</td>
<td>86 (31)</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD or No. (% of patients unless otherwise indicated. See Table 1 for expansion of abbreviation.*

Follow-up

Although oscillatory ventilation as a mild form of Cheyne-Stokes respiration has been described some

**Table 3—Multivariate Predictors of Cardiac Events (Cardiac Deaths or Urgent Heart Transplantation)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Improvement</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x²</td>
<td>p Value</td>
</tr>
<tr>
<td>LVEF</td>
<td>21.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>EOV</td>
<td>10.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td>7.1</td>
<td>0.007</td>
</tr>
</tbody>
</table>
200 years ago, breathing disorders in patients with chronic heart failure detected during wakefulness, sleep, or exercise are a modern area of study. Oscillatory ventilation during exercise has been occasionally and anecdotally described and, to our knowledge, this is the first study evaluating the clinical and prognostic value of oscillatory ventilation during exercise in a large cohort of patients with chronic heart failure. Our data indicate that the occurrence of EOV is a reproducible breathing phenomenon, not unusual in patients with chronic heart failure, especially in those with advanced clinical status, severe hemodynamic dysfunction, and reduced functional capacity, and is not

![Log rank results](chart.png)

**Figure 2.** Cumulative survival without major cardiac events according to peak VO₂ values (top, a) and to the presence of EOV in the total population (middle, b) and in patients with peak VO₂ between 10 mL/kg/min and 18 mL/kg/min (bottom, c). NV = normal ventilation at rest and during exercise, n.s. = not significant.
related to the etiology of chronic heart failure. Furthermore, our data provide evidence that the presence of EOV gives additional and independent prognostic information. Importantly, the EOV has still additional prognostic power among patients with moderate-to-severe functional impairment (peak VO₂ between 10 mL/kg/min and 18 mL/kg/min) in whom peak VO₂ has limited prognostic value.

Few reports have reviewed the clinical hallmarks of patients with chronic heart failure exhibiting EOV, and the prevalence varies from 10 to 33%.9–13,23 We observed EOV in 12% of patients in the total population; in 23% of patients with LVEF ≤ 20%; in 19% of those with peak VO₂ ≤ 14 mL/kg/min; and in 20% of those in NYHA functional class III and IV. Moreover, patients with EOV had a lower AS, indicating an increasing limitation of daily physical activity, which has been demonstrated to progressively decrease with worsening of heart failure symptoms.17 Previous small studies documented that EOV correlates with the severity of heart failure and with an impaired functional capacity in 6 of 31 patients with dilated cardiomyopathy,10 in 5 of 32 patients with chronic heart failure in NYHA functional class III and IV,9 and in 9 of 37 patients with peak VO₂ between 500 mL/min and 799 mL/min.23 By contrast, Yajima et al.,12 noticing EOV in 5 of 48 consecutive patients with chronic heart failure with moderate exercise intolerance, found similar mean LVEF and peak VO₂ in patients with and without EOV. However, in the study by Yajima et al.,12 all patients were in SR, in NYHA functional class II, and peak VO₂ was significantly higher compared to our population, indicating that they were less severely affected.

**Prognostic Significance of EOV**

Our results confirm previous reports2–4 that mortality in patients with chronic heart failure is commensurate with functional capacity. Among exercise variables, peak VO₂ was the strongest independent predictor. In particular, a peak VO₂ ≤ 10 mL/kg/min identified high-risk patients, whereas a peak VO₂ ≥ 18 mL/kg/min identified low-risk patients. We also endorsed the finding of other investigators8–4 that the prognostic and decisional value of peak VO₂ in patients with moderate-to-severe functional impairment (peak VO₂ between 10 mL/kg/min and 18 mL/kg/min) is limited. It is in patients with this intermediate exercise ability range of exercise intolerance that clinical assessment and risk quantification with conventional functional staging is least reliable, therefore representing a group where supplementary prognostic variables are most needed. An integrated analysis of peak VO₂ and exercise-related ventilatory abnormalities may help to predict outcome. Chua et al.7 proved that a Ve/Vco₂ slope > 34 selects high-risk patients with chronic heart failure and is an independent prognostic marker. In addition, MacGowan et al.8 demonstrated that Ve/Vco₂ measured at the VAT gives additional prognostic information in patients with a peak VO₂ ≤ 15 mL/kg/min. In the present study, Ve/Vco₂ slope and other functional variables, including NYHA class and DT, were related to mortality at univariate analysis, but they did not emerge as independent predictors of survival in the multivariate analysis. In contrast, EOV emerged as a significant predictor of mortality, independent of other factors affecting survival, such as peak VO₂ and LVEF. Interestingly, we also documented the impact of EOV on survival in patients with peak VO₂ in the range 10 to 18 mL/kg/min, suggesting that this abnormal ventilatory pattern may be a valuable guide in the decisional approach in this important subgroup of patients.

**Plausible Rationale for the Prognostic Impact of Oscillatory Ventilation**

This study was not designed to investigate the pathophysiologic mechanisms of EOV in patients with chronic heart failure. Nevertheless, several hypotheses have been suggested, and these may be conveniently grouped into ventilatory and metabolic-hemodynamic theories.24 EOV can be hypothesized as a consequence of instability of the ventilatory control system, which may include delay in information transfer function of homeostatic reflexes, an increase in controller gain, and a reduction in system damping.25 In heart failure, all the components of the ventilatory control system are altered: a prolonged circulatory time, overactivity of chemoreceptors, ergoreceptors, cardiopulmonary and arterial baroreflex impairment have all been described. The alternative metabolic-hemodynamic theory suggests that underlying oscillation in cardiac output or tissue metabolic rate can determine EOV.11,12 Recently, Piepoli et al.24 have developed a unifying general hypothesis: the mechanistic pathways envisage a link between left ventricular dysfunction, skeletal and respiratory muscle myopathy, and exercise hyperventilation (steeper Ve/Vco₂ slope) and/or oscillation. Thus, EOV which is associated with more pronounced clinical and hemodynamic deterioration, may represent an advanced derangement of the ventilatory control system and gives additional and independent prognostic advice.
Limitations of the Study

An occasional observation of EOV during cardiopulmonary exercise testing to assess prognosis has some limitations because EOV may change during the follow-up period, as a consequence of the long-term effect of medical therapy for heart failure. However, our data suggest that patients with EOV should be considered at higher risk for adverse outcome whenever this abnormal exertional ventilatory pattern is documented. Moreover, we described EOV as recommended in the literature, thus the application of the prognostic implication to different arbitrary definition of EOV is not justified.

Our results advocate further investigations. The clinical usefulness of EOV in the selection of heart transplantation candidates and whether EOV has different pathophysiologic and prognostic significance other than breathing disorders occurring at rest or in sleep have not yet been established. Peculiarly, oscillatory ventilation at rest during the emotional and stressful phase that precedes exercise is an intriguing feature; whether preexercise resting oscillatory ventilation resembles breathing disorders during wakefulness and the reason for recovering with exercise in some patients is unknown. Unfortunately, in our study, the number of patients that showed resting oscillatory ventilation that disappears with effort was not adequate to provide further insights. Finally, although we demonstrated that EOV, as described in the literature, is a valuable prognostic index, an extensive examination of oscillatory ventilation during exercise including information about frequency, amplitude, and duration may theoretically help to better underscore its pathophysiologic nature, which might be coupled with improved therapeutic prospects.

CONCLUSION

Oscillatory ventilation during exercise is not unusual in patients with chronic heart failure, and is associated with a more advanced clinical status, cardiac functional impairment, and reduced exercise capacity, and may reflect a more severe derangement of the ventilatory control system, perhaps as an important feature of neuroautonomic instability. The presence of EOV can be used as an additional index of clinical instability and hemodynamic deterioration that has independent and additional prognostic power. Consequently, the EOV pattern may be considered a valuable guide in the decisional modus operandi in patients with chronic heart failure, and should suggest a more aggressive medical treatment policy when detected.

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