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# A method for determining exercise oscillatory ventilation in heart failure: Prognostic value and practical implications☆,☆☆

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ABSTRACT

*Background:* Exercise oscillatory ventilation (EOV) has been shown to be a powerful prognostic marker in chronic heart failure (CHF). However, EOV is poorly defined, its measurement lacks standardization and it is underutilized in clinical practice. The purpose of this pilot study was to investigate the prognostic value of a modified definition of EOV in patients with CHF.

*Methods:* Eighty-nine CHF patients (56.5 ± 8.4 years) (64% NYHA class III-IV) underwent cardiopulmonary exercise testing. EOV was defined as meeting all the following criteria: (1) ≥3 consecutive cyclic fluctuations of ventilation during exercise; (2) average amplitude over 3 ventilatory oscillations ≥5 L; and (3) an average length of three oscillatory cycles 40s to 140 s. Adverse cardiac events were tracked during 28 ± 19 months follow up. Cox proportional hazard analysis was used to determine the association between cardiac events and EOV.

*Results:* Forty-eight patients (54%) met all three criteria and were determined to have EOV. These patients exhibited significantly increased risk for adverse cardiac events [hazard ratio = 2.2, 95% CI (1.2 to 4.1), p = 0.011] compared to patients without EOV. After adjusting for age and established prognostic covariates (peak $VO_2$ and $V_E/VCO_2$ slope), the modified EOV definition was the only significant variable in the multivariate model [hazard ratio = 2.0, 95% CI (1.1 to 3.7), p = 0.035].

*Conclusions:* The proposed method for determining EOV was independently associated with increased risk for adverse cardiac events in CHF patients. While larger prospective studies are needed, this definition provides a relatively simple and more objective characterization of EOV, suggesting its potential application in clinical practice.



## 1. Introduction

Exercise oscillatory ventilation (EOV) is a cyclic fluctuating breathing pattern observed during cardiopulmonary exercise testing (CPX) and is related to disease severity and poor prognosis in patients with chronic heart failure (CHF) [1–4]. In some studies, the prognostic value of EOV has been reported to outperform traditional variables derived from CPX such as peak oxygen uptake (peak $VO_2$) and other markers of ventilatory efficiency (e.g. $V_E/VCO_2$ slope) [2]. A recent meta-analysis of 3032 CHF patients reported a 4-fold higher risk for adverse cardiovascular events in patients with EOV compared to patients without EOV [5]. Although these observations are clinically important, the prevalence of EOV ranged from 7% to 58%, which highlights the different methodologies applied and the lack of agreement between these studies for defining EOV [2,3,5].

Currently, definitions of EOV are considerably vague; some do not include length of oscillatory cycles while others use resting ventilation as a baseline for exercise oscillation. In addition, although the assessment of EOV tends to be complex, visual interpretation is often performed without standardized objective criteria [1–3,5,6]. These limitations are challenging for the implementation of EOV in clinical practice and therefore it is rarely utilized [1–3,5,7]. The aims of this study were: 1) to develop a simple, practical and objective definition of EOV; and 2) to assess the prognostic utility of this method in a pilot cohort of patients with CHF.

## 2. Methods

### 2.1. Subjects and study design

Eighty-nine adult patients with an established diagnosis of CHF [8] who were assessed with CPX at Stanford University between 2011

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and 2015 were considered for the study. Inclusion criteria consisted of: 1) diagnosis of CHF confirmed by history and left ventricular dysfunction as assessed by 2- dimensional echocardiography; and 2) age between 40 and 80 years. Patients (<40 or >80 years) or having hepatic, hematological and infectious conditions were excluded. All patients were evaluated in the outpatient clinic and were hemodynamically stable to perform exercise testing. CPX data were carefully evaluated for EOV by two individuals experienced in CPX and who were otherwise blinded to patient identity and other clinical information.

### 2.2. Cardiopulmonary exercise testing

CPX was performed according to established guidelines [7,9–13]. Standardized medical examinations were performed before testing, and medications were continued as prescribed. All patients underwent a symptom-limited maximal treadmill CPX to volitional exhaustion. In the absence of clinical indications for stopping, participants were encouraged to exercise to their individual maximum capacity, and the Borg 6–20 scale was used to quantify effort [10]. Cardiopulmonary responses were obtained using a Quark CPX metabolic system (CosMed, Rome, Italy), calibrated in a standard fashion according to manufacturer recommendations. Minute ventilation ($V_E$, BTPS), oxygen uptake ($VO_2$, STPD), carbon dioxide production ($VCO_2$, STPD), and other CPX variables were acquired breath by breath, reported in rolling 10-s intervals averaged over 30 s.

### 2.3. Exercise oscillatory ventilation

The method used in the current study to evaluate the presence of EOV was developed by modifying criteria that have been suggested [1, 14,15]. *EOV was defined as meeting all the following criteria* (Fig. 1); *1*) *≥ 3 consecutive cyclic fluctuations of ventilation during exercise* [15]; *2*) *an average amplitude of three ventilatory oscillations ≥ 5 L* [14]; *and 3*) *an average length of three oscillatory cycles between 40s and 140 s* [15]. For each exercise test, data were analyzed by plotting minute ventilation (in liters) on the Y axis versus time (in seconds) on the X axis using excel spreadsheets. The nadirs and the peaks of three consecutive oscillation cycles were marked for ventilation and time. Oscillatory amplitude was calculated from nadir to peak ventilation for each of the three oscillations and then averaged [3,4], while oscillatory cycle length was measured from nadir to nadir of the three oscillations and then averaged [3,4] (Fig. 2).

### 2.4. End-points

Patients were followed for major cardiac-related events for up to 60 months after completing their CPX. Events were captured through review of electronic medical records. A composite outcome of cardiac-related hospitalizations, left ventricular assist device implantation, heart transplantation and cardiac-related death was used.

### 2.5. Statistical analysis

Statistical analyses were conducted using SPSS v.23 software (IBM, Chicago, IL, USA). The significance level was set at $p < 0.05$. Continuous data are reported as mean ± SD, while categorical data are reported as percentage or frequency. Unpaired *t*-tests and chi-square tests were used to compare continuous and categorical variables, respectively, between subjects who met the EOV definition and those who did not. Cox proportional hazards analysis was used to assess the prognostic utility of EOV and other CPX variables. Kaplan-Meier curves using a log-rank test were utilized to compare patients who met the definition for EOV and those who did not. The proportional hazards assumption was evaluated graphically for paralleled function and confirmed using the scaled Schoenfeld residuals.

## 3. Results

Clinical and physiological characteristics of the sample are summarized in Table 1. The mean age was 56.5 ± 8.4 years, 70% were male, left ventricular ejection fraction was 47.2 ± 11.8%, 64% of the sample were in New York Heart Association classes III and IV and peak oxygen uptake (peak $VO_2$) was 14.7 ± 6.1 mL/kg/min. Forty-eight patients (53.9%) were determined to have EOV. During a mean follow-up of 28.3 ± 18.9 months, patients who met the EOV definition exhibited a significantly higher risk for adverse cardiac events [Hazard Ratio (HR) = 2.2, 95% confidence interval (CI) (1.2 to 4.1), p = 0.011] compared to patients who did not meet the EOV definition. After adjusting for age and established prognostic covariates (peak $VO_2$ and $V_E/VCO_2$ slope), EOV was the only variable in the model that remained significantly associated with cardiac events [HR = 2.0, 95% CI (1.1 to 3.7), p = 0.035] (Table 2). Kaplan-Meier curves confirmed the poorer outcomes among those who met the criteria for EOV (Fig. 3). A subgroup analysis of patients who met at least one or two of the three criteria for EOV (n = 47) showed a trend for increased risk of cardiac events, p = 0.061 (Table 2).

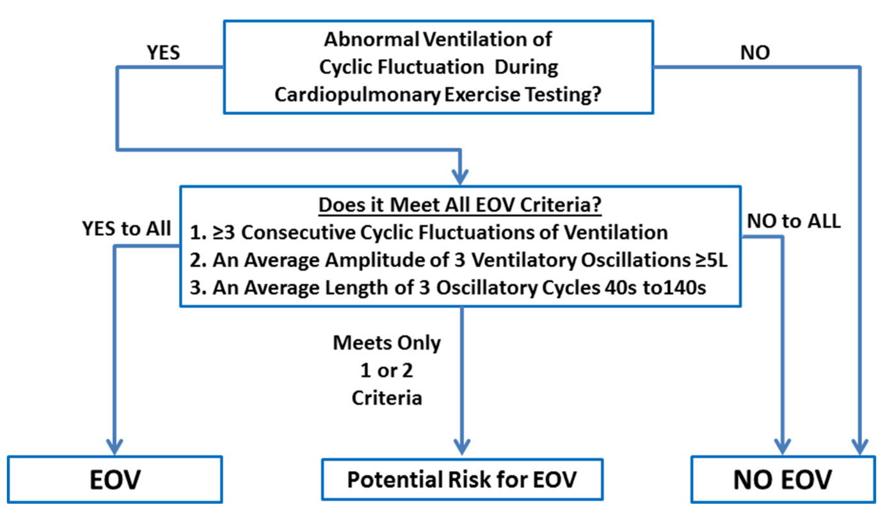


**Fig. 1.** A modified definition of exercise oscillatory ventilation. EOV; exercise oscillatory ventilation.

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