

# Difference in prevalence of exertional oscillatory ventilation between healthy subjects and patients with cardiovascular disease

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## Abstract

Exercise oscillatory ventilation (EOV) is an ominous sign in heart failure due to reduced left ventricular ejection fraction

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Informed consent: An informed written consent was obtained from all participants, and the protocol was approved by the ICS Maugeri Central Ethics Committee.

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(HFrEF) whatever it is represented. But EOV is detected also in normal healthy individuals and in other cardiovascular disease (CVD) patients, however, its prevalence in these is not completely clear. The aim was to describe the occurrence of EOV in healthy subjects and the overall population all CVD patients who performing symptom-limited cardiopulmonary exercise testing (CPET). Healthy subjects were divided in athletes and normal subjects, while, CVD patients were subdivided into: i) those with preserved left ventricular ejection fraction (LVEF); ii) those with mild to moderate impairment of LVEF (41-49%); iii) those with severe impairment of LVEF ( $\leq 40\%$ ); iv) HFrEF or with preserved LVEF (HFpEF); and v) patients after heart transplantation (HXT). EOV was observed only in CVD patients and in those with depressed LVEF; the prevalence of EOV was observed 1.9% (3/55) those with mild to moderate impairment of LVEF (41-49%), 3.4% (56/1613) those with severe impairment of LVEF ( $\leq 40\%$ ), and 7.3% (214/2903) in HFrEF; no EOV was observed in CVD with preserved LVEF. Kremser's EOV was observed in patients, and, particularly, in those with systolic function impairment. Moreover, as EOV impacts prognosis in HFrEF, its occurrence can modify prognostic-decision models. Even though, EOV prevalence was derived from largest single center population, more studies are needed to tackle the EOV prevalence in different CVD conditions and in normal subjects.

## Introduction

Exercise oscillatory ventilation (EOV) is an atypical exertional respiratory response [1], characterized waxing and waning in ventilation (VE). EOV is frequently detected in heart failure due to reduced left ventricular ejection fraction (HFrEF) [2,3], and it is an ominous sign, whatever it is represented [3]. EOV is discovered also in normal healthy individuals [4] and in other cardiovascular disease (CVD) patients [5]. Though, EOV prevalence is not clear, yet.

The principal aims of this study were 1) to describe the occurrence of EOV in the overall population, healthy subjects and CVD patients, with or without history of heart failure (HF), performing symptom-limited cardiopulmonary exercise testing (CPET) 2) to assess of EOV prevalence in HFrEF, and resting factors that might predict this abnormal respiratory phenomenon.

## Patients and Methods

### Data source

This was a retrospective study of data collected prospectively for prognostic assessment purposes; here, follows data on EOV

prevalence. The study was based on patient medical records from the ergo-spirometry laboratory of the Istituti Clinici Scientifici Maugeri, IRCCS Scientific Institute of Veruno (NO), Italy; CPET data were recruited from September 15, 1995 to December 31, 2016 (12 years). All records originated from the ergo-spirometry laboratory of Veruno, and, subjects' and patients' documents and statistics were, anonymously, used. A note was kept about demographic, clinical, echocardiographic parameters, as well as about pharmacological treatment.

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). An informed written consent was obtained from all participants, and the protocol was approved by the ICS Maugeri Central Ethics Committee.

## Study population

Healthy subjects performed symptom-limited CPET for functional assessment, while, for CVD patients, CPET was executed for both functional and prognostic estimations. Those with HF were categorized, in order to the history or recent (<3 months) existence of signs or symptoms of HF, as described ESC guidelines [6]. CVD patients were subdivided, according left ventricular ejection fraction (LVEF) and symptoms/signs of HF. They were classified as follows: i) those with preserved left ventricular ejection fraction (LVEF =  $\geq 50\%$ ), those with mild to moderate impairment of LVEF (41-49%), and those with severe impairment of LVEF ( $\leq 40\%$ ); all above-mentioned patients had no HF symptoms or signs, ii) HF patients (these patients were characterized to have had symptoms or signs of HF, according ESC guideline) with reduced LVEF (HFrEF) or with preserved LVEF (HFpEF), iii) patients after heart transplantation (HXT). HXT patients were evaluated one month after surgery.

Exclusion criteria were: 1) myocardial infarction, myocardial revascularization or unstable angina, one month before the study; 2) ventricular arrhythmias induced by exercise (sustained ventricular tachycardia or fibrillation); 3) severe aortic valvular stenosis; 4) concomitant diseases that might limit the exercise capacity assessment (either in healthy subjects or CVD patients); 5) cardiac strategies scheduled; 6) unwillingness to provide informed consent.

Eligibility criteria were: 1) the ability to perform a CPET, limited by fatigue or dyspnea, with a peak respiratory exchange ratio (RER)  $\geq 1.00$  [7], and 2) for CVD/HFrEF patients, clinical/pharmacological stability 1 month before CPET.

## Cardiopulmonary exercise testing

CPET was performed on a bicycle ergometer with a ramp protocol for all, healthy subjects and CVD patients. For health subjects, a 20 Watts, every one-minute ramp protocol was managed, while for CVD patients a 10 Watts every one minute was arranged. The CPET was conducted with breath-by-breath respiratory gas exchange (Sensormedics, Vmax 29, Yorba Linda, CA, USA).

Peak  $\text{VO}_2$  was recorded as the mean value of  $\text{VO}_2$  during the last 60 seconds of the test, while the relationship between ventilation (VE) and carbon dioxide ( $\text{VCO}_2$ ) was computed as a linear regression function from the whole exercise period (VE/ $\text{VCO}_2$  slope) [8], and percentage of predicted peak  $\text{VO}_2$  ( $\text{VO}_2\%$ ) was processed, according to Wasserman *et al.*'s formula [9]. In the post-test phase,

VE (L/min.) was displayed on an expanded time scale, and EOv was launched, applying Kremser *et al.*'s criteria [10]. We traditionally adopted Kremser's method (mainly for outcome reasons, in HFrEF patients); we persisted to use this procedure to harmonize CPET data. This method implies i) cyclic fluctuations in VE lasting longer than 66% of the whole exercise duration, and ii) amplitude of each single VE oscillation more than 15% of the average value at rest. A typical EOv pattern is shown in Figure 1.

Blood pressure was measured manually at rest, every 3 min during incremental exercise, and at peak of exercise, while electrocardiogram and heart rate were monitored at rest and throughout exercise with at 1-min intervals. All CPETs were conducted on medical therapy.

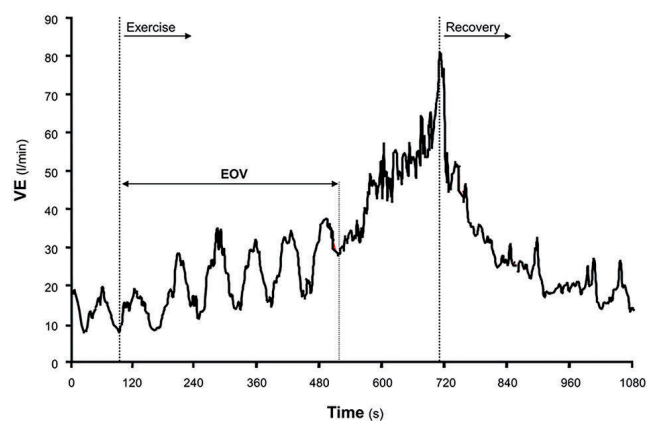
CPET results were interpreted and revised by experienced and qualified cardiologists.

## Echocardiographic evaluation

Trans-thoracic echocardiograms were performed within 4-6 days of CPET, and LVEF and trans-mitral deceleration time (DecT.) were calculated as described [11].

## Statistical analysis

Continuous data was expressed as means  $\pm$  standard deviation (SD). Student's *t*-test for non-paired values was used to compare the means of groups for quantitative variables. For qualitative variables, the  $\chi^2$  test with Yates' correction or Fisher's exact test, if necessary, was employed. Logistic regression univariate and multivariable analysis for EOv was performed in HFrEF; for multivariable inquiry, we used significant resting variable at univariate analysis. The level of statistical significance was set p-value  $< 0.05$ .



**Figure 1. Representation of exertional oscillatory ventilation (EOV). Exercise represents when incremental exercise phase is organized (ramp fashion; 10 watts/1 min for patients; 20 Watts/1 min for healthy subjects). The exercise phase is anticipated by a warm-up pedaling period, usually lasting 1-2 min. The recovery phase is when incremental exercise is stopped. This phase lasts 6 min: it is composed by 1-min pedaling phase at 10 watts, followed by a 5-min resting phase, in setting position. VE, ventilation in l/min; Time, time of exercise phase in seconds.**

All calculations were performed using the STATA®10 system (StataCorp, College Station, TX, USA).

## Results

We screened 5741 CPETs: 834 patients were excluded, because due to other limiting symptoms than other than fatigue or dyspnea (n=197), peak RER lower <1.00 (n=439), clinical/pharmacological stability not accomplished (n=198). The remaining

4907 CPETs formed the study population: 14 CVD patients had a LVEF  $\geq 50\%$ , 157 CVD patients had LVEF between 41-49%, and 1613 CVD patients showed a LVEF  $\leq 40\%$ . HFrEF and HFpEF patients were 2903 and 55, respectively. Finally, HXT patients were 101 recipients (Table 1). Moreover, 64 healthy subjects (of these 35 were athletes) were screened. Overall, EOv was observed in 273 patients, 5.5% of total population: 1.9% in CVD patients with mild to moderate impairment, in 3.4% in those with severe left ventricular dysfunction and 7.3% in HFrEF patients (Table 1). Therefore, EOv was witnessed only in CVD with LVEF impairment (LVEF < 50%) or in HFrEF patients.

**Table 1. Etiology and EOv occurrence in the overall study population.**

	Total number	EOv (%)
Total CPETs analyzed and n (%) of EOv	4907	273 (5.5)
Athletes	35	0 (0)
Other healthy subjects	29	0 (0)
CVD with preserved LV systolic function (LVEF $\geq 50\%$ )	14	0 (0)
HFpEF (LVEF $\geq 50\%$ )	55	0 (0)
CVD with mild to moderate impairment of LV systolic function (LVEF >40 and <50%)	157	3 (1.9)
CVD with severe impairment of LV systolic function (LVEF $\leq 40\%$ )	1613	56 (3.4)
HFrEF (LVEF $\leq 40\%$ )	2903	214 (7.3)
Recent HXT	101	0 (0)

Values reported for continuous data are mean  $\pm$  SD, for raw data: number of patients (percentage of total). EOv, exertional oscillatory ventilation; CPET, cardiopulmonary exercise testing; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; HF, heart failure; HFpEF, heart failure with preserved LVEF; HFrEF, heart failure with reduced LVEF; HXT, heart transplantation.

**Table 2. demographic, clinical, echocardiographic, CPET and medical characteristic of HFrEF patients with and without EOv.**

	With EOv (n=214)	Without EOv (n=2694)	p
Age (years)	61 $\pm$ 9	58 $\pm$ 10	0.0015
Male (%)	213 (91)	2347 (80)	0.0661
BMI (kg/m <sup>2</sup> )	25 $\pm$ 3	26 $\pm$ 4	0.0016
Etiology of HF			
IHD (%)	128 (8)	1510 (92)	
ICD (%)	83 (7)	1162 (93)	0.2143
VHD (%)	3 (15)	17 (85)	
NYHA class	2.0 $\pm$ 0.6	2.3 $\pm$ 0.5	<0.0001
NYHA class - Categories			
NYHA 1 (%)	10 (2)	463 (98)	
NYHA 2 (%)	112 (7)	1667 (93)	<0.0001
NHYA 3 (%)	92 (13)	564 (86)	
Sinus rhythm (%)	193 (82)	2475 (84)	<0.0001
LVEF (%)	22 $\pm$ 8	27 $\pm$ 8	<0.0001
DecT (msec)	147 $\pm$ 47	171 $\pm$ 54	<0.0001
Beta-blockers: n (%)	148 (63)	2013 (75)	0.0002
ACE-inhibitors: n (%)	214 (92)	2452 (93)	0.8140
Loop diuretics: n (%)	220 (94)	2401 (89)	0.0134
Loop diuretics daily dose	50 $\pm$ 12	37 $\pm$ 8	0.2013
Peak VO <sub>2</sub> (ml/kg/min)	12.9 $\pm$ 3	15.3 $\pm$ 4	<0.0001
Percentage of predicted peak VO <sub>2</sub> (%)	48 $\pm$ 14	55 $\pm$ 14	<0.0001
VE/VCO <sub>2</sub> slope	32 $\pm$ 6	38 $\pm$ 10	<0.0001
Peak RER	1.13 $\pm$ 0.09	1.14 $\pm$ 0.09	0.6061

Mean value  $\pm$  SD for continuous values or percentage for categorial values. CPET, cardiopulmonary exercise testing; EOv, exertional oscillatory ventilation; BMI, body mass index; NYHA, New York Heart Association; HF, heart failure; IHD, ischemic heart disease; ICD, idiopathic cardiomyopathy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction; DecT, trans-mitral deceleration time; ACE, angiotensin converting enzyme; VO<sub>2</sub>, oxygen consumption; VE/VCO<sub>2</sub> slope, exertional relationship between ventilation (VE) and carbon dioxide (VCO<sub>2</sub>); RER, respiratory exchange ratio (*i.e.*, peak VO<sub>2</sub>/VCO<sub>2</sub> ratio).

**Table 3. Logistic regression analysis for EOV prediction in HFREF, using significant resting variables.**

	$\chi^2$	p	OR	95% CI
LVEF	24.45	<0.0001	0.942	0.920-0.968
DecT	5.19	0.0226	0.996	0.992-0.999
Age	8.95	0.0028	1.027	1.009-1.044
BMI	4.42	0.0355	0.965	0.925-0.997
Sinus rhythm	14.11	0.0002	0.490	0.266-0.660
NYHA class	14.89	<0.0001	1,729	1.309-2.848

OR, odds ratio; CI, confidence of interval; see also Table 2 for abbreviations.

At univariate analysis in HFREF, EOV (214 patients) was discovered more frequently in those with advanced age and NYHA class, with more compromised systolic and diastolic function. Finally, in EOV was associated to worst exercise capacity (Table 2), *i.e.* in those with more reduced mean peak  $\text{VO}_2$ , and steeper  $\text{VE}/\text{VCO}_2$  slope (EOV was also found in 4% of CVD patients with LVEF dysfunction in class NYHA I with preserved mean peak  $\text{VO}_2$ : mean peak  $\text{VO}_2$  was =19±4,7 ml/kg/min.)

At multivariable logistic analysis for EOV in HFREF patients. Five resting clinical variables were selected: age, LVEF, DecT, NYHA class, body mass index, and cardiac rhythm at the moment of CPET (Table 3). EOV was more commonly seen in older patients, in advanced NYHA class, in those with more depressed LVEF, and shorter DecT, and in sinus rhythm.

## Discussion

Main findings were: 1) Kremser's EOV was noticed only in CVD and HFREF patients; 2) of note, EOV was observed only in patients with impaired left ventricular (LV) systolic function; 3) percentage of EOV was superior in HFREF patients; 4) rarely, EOV occurs in HFREF patients with preserved exercise capacity (peak  $\text{VO}_2 > 14$  ml/kg/min.); 5) at multivariate analysis in HFREF, demographic and clinical variables were selected, and those with older age, advanced NYHA class, more depression of systolic and diastolic function in the presence sinus rhythm at time of CPET were more prone to develop EOV.

Only one experience calculated EOV prevalence, though in healthy subjects with a broad range of cardiovascular risk factors: in the EURO-EX trial [4], EOV was detected in 17%, and it was associated with a poor CPET performance and altered gas exchange profile. Although not proven, EOV can "unmask" a higher level of risk, not readily apparent when assessing aerobic capacity [4]. In our experience, a mixture of healthy subject and CVD patients was enrolled, with healthy subject less represented. In contrast with EURO-EX trial, EOV definition and CPET interruption criteria were dissimilar. Thus, these two experiences are poorly comparable; nevertheless, EOV was detected only in CVD patients with LV dysfunction and/or in HFREF. Thus, we confirm that EOV might be related to hemodynamic derangement or ventilatory instability during exercise [12-15].

EOV has been shown to be a strong predictor of mortality in HFREF [1-3]. In this setting, prevalence is widespread, ranging from 7 to 51% [16-28]. The variance of EOV might originate from the heterogeneity of its definition and different techniques of measures [29]: four original EOV descriptions [10,17,26,29] have been rec-

ommended but many modifications are allowed. These four original EOV accounts have been reported in 23, 13, 6 and 2 experiences, respectively, with a mean prevalence of 28%, 37%, 35% and 50%.

A "relatively" low prevalence of EOV was documented in HFREF, in our study. Generally, we used to prescribe CPET when clinical stable condition, early mobilization or exercise training, and HF-saving therapeutic goals have been attained [30-32]. On the contrary, CPET is postponed in more disabled patients, *i.e.* in those with overt HFREF or those with concomitant diseases, with advanced disease, disable and with complex clinical status or altered acid-base/ionic disequilibrium [12-14,33]. Thus, CPET is usually recommended only for the 'best' ones.

EOV was also noticed in those with preserved exercise capacity, with mean peak  $\text{VO}_2$  of more than 14 ml/kg/min.: these shocking findings solicitate further investigations. Finally, EOV appears more frequently in elderly HFREF patients [33].

## Limitations

Limitations deserve mention: i) EOV was defined, according to Kremser *et al.*'s criteria [10]; other EOV definition's criteria might produce different rate of occurrence; ii) prevalence recorded from a single center data-base could be limited, as CPET protocol modality, execution type and criteria of for exercise testing termination were homogeneous.

## Conclusions

Kremser's EOV was observed in patients, and in those with CVD and systolic function impairment. Moreover, as EOV impacts prognosis in HFREF patients, its occurrence can modify prognostic-decision models; in HFREF, it is important to identify those are more prone EOV. However, more studies are needed to tackle the EOV prevalence in different CVD conditions and in normal subjects.

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