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Review

An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation — A systematic review

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ABSTRACT

The variable "exercise oscillatory ventilation" (EOV), assessed during cardiopulmonary exercise test (CPET), recently became a fundamental prognostic parameter in patients with heart failure. In literature, various definitions are suggested, but an uniformly accepted description to identify EOV still lacks. We performed a systematic review of the literature in order to determine the different definitions and diagnostic techniques to assess EOV. A systematic search strategy was established and executed in seven databases (PubMed, Google Scholar, Cochrane Clinical Trials, Science Direct, Pedro, Web Of Science library and Medline (Ovid)) resulting in 605 citations after de-duplication. Full-text articles (n = 124) were assessed for eligibility, resulting in 75 citations. The review accounted 17,440 patients of whom 4,638 subjects presented EOV. Seven studies described EOV in a non-heart failure population accounting 168 EOV subjects. The definitions could be categorized in nine subdivisions of which four (n = 43) referred to an original description. The other subdivisions were combinations of the original definitions (n = 11), quantifications (n = 4), computational (n = 3), vaguely described (n = 8) or not defined (n = 6). Symptom limited maximal exercise tests were conducted to assess EOV, however the modes, protocols, software and data sampling were divers. Heterogeneity in the numerous definitions to identify EOV and the vaguely described assessment methods are hindering the evolution to a standardized uniformly accepted definition and technique to identify this abnormal breathing pattern. Unity in definition and international adopted assessment is warranted to strengthen its validity as a prognostic marker and could promote communication. It may facilitate clinical trials on pathophysiology and origin of EOV.

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1. Introduction

In a population with heart failure (HF), exercise oscillatory ventilation (EOV) emerges as a key prognostic parameter that tends to outperform the formerly suggested predictive cardiopulmonary exercise test (CPET) derived variables such as peak oxygen uptake (VO_2) and ventilation over carbon dioxide (VE/VCO_2) slope [1,2]. Furthermore, this oscillatory breathing pattern indicates general deterioration of other CPET derived prognostic values [2]. The reported incidence of this waxing and waning pattern in ventilation (VE) during exercise is 7 to 51% [3,4]. This broad interval originates as no universal definition is currently described to assess EOV [5,6]. The lack of a gold standard definition could arise from the wide variability within the EOV pattern characteristics e.g., amplitude, duration of the oscillations and period [7,8]. Moreover, assessment of EOV is mainly done by manual scoring or visual interpretation of at least one clinician, which is subjective and could therefore vary considerably between centers and individuals [8]. In 2010, the American Heart Association (AHA) [1] declared the definition adopted by most studies stated that oscillations were present for at least 60% of the exercise time with an amplitude ≥ 15% of the average resting value, in accordance to Corrà et al. [9]. This description was followed by a joint scientific statement of the AHA and the European Society of Cardiology (ESC) [5]. Moreover, many different CPET systems are available with each of its unique software for processing, analyzing and displaying data [1]. This software also determines data sampling and averaging, which the user can select. Modern CPET systems provide a wide variety of automated reports, causing a selection of the available data for the clinicians' interpretation and therefore significantly influencing the assessment of the test results and the data analysis. It is stated that there is an important need of standardization in data sampling e.g., breath by breath (BbB), the amount of breaths, moving

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averages or specific time intervals, as there is a misbalance in these methodologies between precision and variability. Especially in EOV, of which the assessment is based on pattern recognition, relates the difficulty in visualization of the signal for analysis. Visualization is commonly done by using a moving average filter which smooth the data and eliminate small variations [10]. The ESC and AHA council recommends to use 10 s averaged ventilation data for plotting [5]. Furthermore, each stadia of the test e.g., rest, warm-up, exercise and cool-down should be reported as well as the selected exercise protocol as both could influence the interpreted variables [1]. In a recent meta-analysis of our research group [2], it was stated that more research should be done on defining and assessing EOV in a more accurate and reproducible way. We found that difference in defining EOV influenced significantly the results. Despite, the mode of protocol was an independent parameter, all sub-group analyses were characterized by a high overall heterogeneity. Therefore we performed a systematic search strategy to provide an overview of the suggested definitions and assessment techniques used to analyze EOV. The purpose of this systematic review was to identify all the applied definitions of EOV through a symptom-limited exercise test (SLMT) and to summate the described test characteristics in literature independently from pathology. As the pathophysiology of EOV is not yet fully understood [7,11], analysis of EOV in other populations than HF could lead to new insights in this aspect.

2. Methods

This systematic review was registered in the PROSPERO database (registration number: CRD42013006712). A systematic search strategy was established: "exercise oscillatory ventilation" OR "exercise periodic breathing" OR "exertional periodic breathing" OR "exertional oscillatory ventilation" OR "exercise oscillatory breathing" OR "exertional oscillatory breathing". In the Pedro database only "exercise oscillatory ventilation" was searched as the other quotations were not found. As indicated in the specific database, the following filters were applied: only humans (PubMed and Science Direct) and journals (Science Direct), no reviews (Cochrane), no patents or citations (Google Scholar).

The following inclusion criteria were a priori established: (1) defining and/or investigating oscillatory minute VE during a CPET; (2) all populations; (3) all interventions; (4) humans; (5) English, French, German, Dutch, Spanish or Portuguese; (6) normal environmental conditions. The exclusion criteria were: (1) oscillations described during rest, sleep and/or steady-state exercise; (2) the study designs were reviews, meta-analyses or books; (3) high altitude. Expert opinions and recommendations on on-going studies or other relevant data were gathered. Conference proceedings, index lists, doctoral manuscripts, commentaries and editorials were screened and included if oscillations in minute VE were defined through exercise and if it concerned original research by the authors. Reference lists were checked for any topic-related studies. The corresponding author of a study was contacted if needed to obtain any missing information or data. If authors could not be reached or if the data was not available, the citation was excluded. The search included citations published up until October 24th 2014.

All citations identified by the above mentioned electronic databases were organized and the duplicates were deleted. Initially, two investigators (J.C. & T.V.) screened the results from the electronic searches in order to select potentially relevant citations based on titles and abstracts. Full-text articles were retrieved and evaluated based on the proposed in- and exclusion criteria. In case of uncertainty, a third investigator (C.V.) evaluated the citation and consensus was sought during a meeting. Although the authors were responsible for a specific step in the screening process, the final determination on whether an article was included or excluded was based on common agreement.

The following study characteristics were extracted, and if appropriate coded, from the articles by two researchers (J.C. & C.V.). Concerning the assessment of EOV by CPET, the variables rest, warm-up, mode, protocol, intensity, data sampling and data collection were retrieved. Furthermore, the described EOV definition was acquired. Secondary collected data concerned "population, study center, respiratory exchange ratio (RER), pathophysiology and incidence of EOV".

Methodological scoring nor Risk of Bias were performed as we only extracted data concerning the methodological analysis and applied definitions in order to evaluate EOV. This scoring would not give an additional value regarding the studies included in this review.

3. Results

3.1. Selection of the studies

Seven databases (PubMed, Google Scholar, Cochrane Clinical Trials, Science Direct, Pedro, Web Of Science library and Medline (Ovid)) were consecutively systematically searched, resulting in 751 citations. Five studies [3,12–15] were identified after manual reference list screening, resulting in 756 citations. After de-duplication, 605 articles were screened for eligibility on title and abstract, resulting in 124 citations. Ultimately, full text screening resulted in 75 studies (Fig. 1).

Since the group of Sun et al. reported on the same sample in two different studies, description of the population was only mentioned once [4,16].

3.2. Characteristics of the included studies

The 75 studies included in this review, accounted for 17,440 patients of which 4,638 (26.6%) presented EOV (Fig. 2). Seven of these included studies described EOV in another population than HF e.g., cardiac dysfunction [14,17,18], idiopathic dilated cardiomyopathy [19], total cavopulmonary connection after Fontan [20], liver transplantation [21] and congenital cardiac disorder [10], accounting 752 subjects of which 168 presented EOV. EOV was not reported in healthy control patients [12,22–27]. Ten of the included studies were conducted in a multicentre setting [4,16,28–35], totalling 113 centers, representing 8326 subjects with HF of which 2150 presented EOV. The lowest and highest reported incidence rate was 7% [36,37] and 64% [38], respectively.

3.3. Assessment

Assessment through a SLMT was performed in all included studies, yet characteristics were only described in 68 citations (n = 68) (Table 1). The RER varied between 1.00 [33,39] and 1.10 [21,40], mainly set ≥ 1.05 [9,29,35] for inclusion. The selected mode of protocol in these studies was bicycle (n = 38), treadmill (n = 11) or a combination of both modes (n = 7). The passive rest, active (un)loaded warm-up and the recovery phase during one to three minutes after SLMT was registered in 18, 25 and five articles, respectively [19,41–44]. The (modified) ramp protocol was selected in the majority of the studies using a bicycle. In treadmill, a (modified) Bruce protocol was often selected. Twenty-two different CPET devices of 12 manufactures were used to collect the data. Generally, BbB data were collected. In order to assess EOV, a moving or fixed averaging method was often applied. In the majority of the articles, SLMT was conducted during 8–12 min. In a few articles, other limits were obtained such as 7–10 min [45] and 6–15 min [4,16].

3.4. Definitions

The definitions described in the included studies (n = 75) could be categorized in nine subdivisions of which four (n = 44) referred to an original definition as suggested by Kremser et al. [12] (n = 23), Leite et al. [23] (n = 13), Ben-Dov et al. [46] (n = 6) and Sun et al. [4] (n = 2) (Table 2; Fig. 2). The other subdivisions were combinations of the original definitions (n = 11), quantifications (n = 4), computational (n = 3), vaguely defined (n = 8) or undefined (n = 6). One study [47] compared the difference in EOV incidence upon two definitions [9,46]. When the reported original definitions were applied, EOV

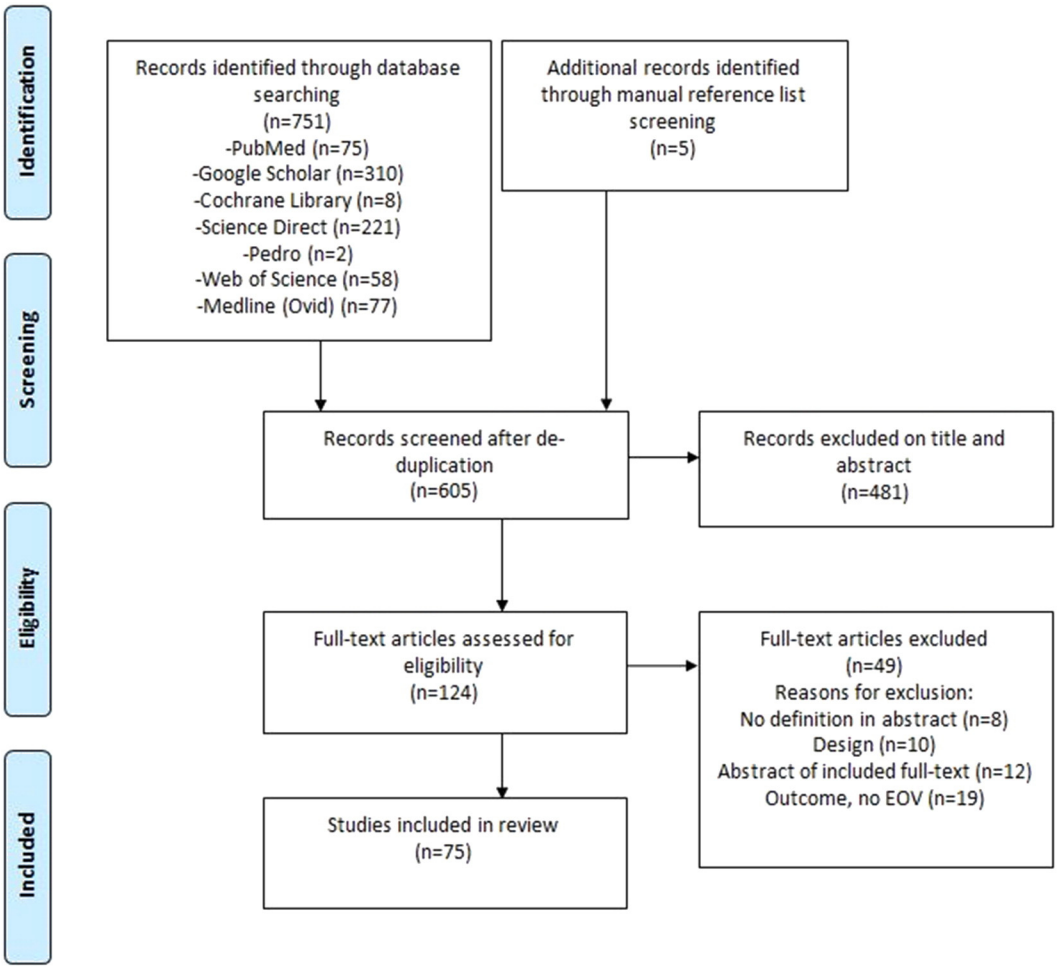


Fig. 1. Four-phase flow diagram of the systematic reviewing process.

was visually determined [21,37,48–50] or quite rapidly manual calculated [32,51,52] by at least one clinician. In seven studies, EOV was determined by quantification or by computational techniques. One study [53] reported the use of a familiarization test to confirm the presence of EOV.

4. Discussion

To our knowledge, this systematic review is the first to provide a full overview of the applied definitions and diagnostic methods to assess EOV. An important finding is the wide variety of definitions applied to describe EOV. Four original descriptions with many modifications were suggested [4,12,23,46]. Attempts to quantify EOV [13,15,24,54] without proposed cut-off value were performed and authors aimed to assess this abnormal breathing pattern with specific computer techniques [10,25,55]. Moreover, numerous CPET protocols, data collection approaches and data sampling procedures were applied in the included studies.

Exercise oscillatory ventilation is especially recognized in HF, however this review indicates EOV can appear in other cardiac related

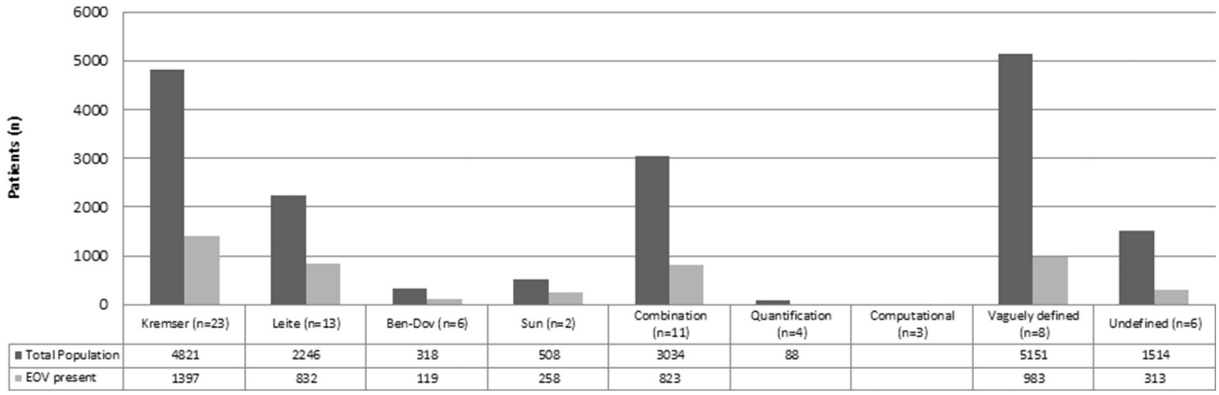


Fig. 2. Overview of the total amount of patients and subjects with exercise oscillatory ventilation (EOV) in the included studies according the amount of studies that quoted the definition.

Table 1
An overview of the applied symptom limited maximal test (SLMT) characteristics and data sampling.

Author (year)	Mode	Rest (min)	Warm-up		Protocol; intensity	Data collection (averaging); software
			Time (min)	Load (W); rpm		
Agostoni [22]	B	3	3	0	Ramp	BbB; Vmax[a]
Agostoni [53]	B	–	1	0; 60	Continue ↑6–12 W/min 60 rpm	BbB; Vmax[a]
Agostoni [28]	BT	–	–	–	Ramp (B) & Modified Bruce (T)	BbB
Agostoni [29]	BT	–	–	–	Ramp	BbB
Apostolo [62]	B	>5	>3	0	Ramp; ↑5–10 W/min	BbB; Vmax[a]
Arena [63]	T	–	–	–	Conservative ramp; ↑ ± 2mlO_2/kg/min in workload every 30 s	BbB (10 s)
Arena [64]	T	Yes	–	–	Conservative treadmill protocol	BbB (10 s); Vmax29[a]
Ben-Dov [23]	BT	Short (T)	2–3	0 (B)	Naughton modified ↑ every 2 min from 1 mph 0% to maximum 3.5 mph 16% or Ramp ↑10–15 W/min or ↑ in 1 min steps	BbB (8 breath moving); System 2001[b] or CPX[b]
Cahalin [41,65]	B	–	–	–	Ramp	BbB (30 s, printed rolling averages 10 s); Vmax[a]
Callegaro [54]	T	–	–	–	Ramp; 2.4 km/h 2% with ↑ every 20 s in speed and slope	BbB; Metalyzer3B[c]
Castro [66]	B	–	–	–	↑5 W every minute 60 rpm	BbB; Vmax229[a]
Corrà [9,48,37,49]	B	–	1	0	Ramp; 10 W/min 60 rpm	BbB; Vmax29[a]
Corrà [67]	B	2–3	1	0	Ramp; 10 W/min 60 rpm	BbB; Vmax29[a]
Dall'Ago [13]	T	–	–	–	Ramp; 2.4 km/h 2%, ↑ every 20 s of speed 0.1–0.2 km/h and ↑ every 60 s 0.5%–1.0% in slope	(20 s mean aliquots); TEEM 100[d]
Feld [3]	–	–	–	–	–	(8-breaths confirmed by converting data to BbB); System 2001[b]
Francis [24]	T	Short	–	–	Bruce; Modified initial stage 0.5 mph 5%	BbB on-line; Amis 2000[e]
Francis [25]	T	–	–	–	Bruce; Modified initial stage 1 mph 5%	BbB on-line (different moving windows 15 s, 30 s, 60 s); Amis 2000[e]
Guazzi [30]	BT	–	–	–	Ramp	BbB (30 s, printed in rolling averages 10 s)
Guazzi [68–70]	B	–	–	–	Ramp	VE collected continuously; CPX-D[b]
Guazzi [31]	BT	–	–	–	Ramp	BbB (30 s, printed in rolling averages 10 s); CPX-D[b] or Vmax[a]
Guazzi [71]	B	–	–	–	Ramp	BbB (30 s, printed in rolling averages 10 s); Vmax[a]
Guazzi [32]	BT	–	–	–	Ramp	BbB (30 s, printed in rolling averages 10 s); CPX-D[b] & Vmax29[a]
Guazzi [72]	B	–	–	–	Ramp	VE collected continuously at rest and throughout exercise; CPX-D[b]
Guazzi [51,52]	B	–	–	–	Ramp	BbB (30 s, printed in rolling averages 10 s); Vmax29[a]
Guazzi [43]	B	3	–	–	Ramp	BbB (10 s); Vmax Spectra[a]
Guazzi [73]	B	–	2	0; 60	Ramp	BbB (30 s, printed in rolling averages 10 s); Vmax29[a]
Ingle [47,60]	T	–	–	–	Bruce; Modified initial stage 2.74 km/h 0%	Oxycon Delta[f]
Joho [56]	B	–	3	0	Progressive ↑5–10 W/min	BbB (EOV cycles displayed on an expanded time scale); AE-300[g]
Kato [18]	B	4	4	0 or 20; 60	↑1 W/6 s (10 W/min)	BbB (interpolated to SbS values; calculated as successive 3 s averages translated to 5 point moving average); AE-300 s[g]
Kazimierczak [45]	B	–	–	–	Ramp	BbB (10 s); ZAN680[h]
Koike [17]	B	4	4	10 or 20	↑1 W/6 s (10 W/min) 60 rpm	BbB 4 min before start and until end of exercise (5 point moving); AE-280[g]
Kremser [12]	B	–	3–4	0	Continuous ↑6–10 W/min or at 1 min interval 20–100 rpm	BbB (30 s; breaths with a tidal volume <250 ml were not analyzed)
Lasso [44]	B	3	3	0	Naughton & San Ignacio 20 ↑20 W/min	Vacu Med-Vista mini CPX (software Turbofit 5.12)[b]
Leite [46]	B	–	–	–	Ramp	BbB (8 breaths moving average); CPX[b]
Lim [74]	T	–	–	–	Ramp	Powercube[i]
Matsuki [75]	B	yes	3	–	Ramp; 10 W/min	AE310[g]
Miyagi [14]	B	–	3	0	↑3–15 W/min	BbB; AE280[g]
Muneuchi [20]	T	–	3	0	↑15%/min	BbB
Murphy [26]	B	–	3	0	Ramp; continuous ↑5–15 W/min	BbB (1 min); Medgraphics[b]
Neviere [21]	B	2	2	0	Ramp; 10 W/min	BbB (10 s moving); Medisoft ErgoCard[j]
Okumura [19]	B	3	3	<10	Ramp; 10 W/min	–
Oldenburg [76]	B	–	–	–	10 W and continuous ↑10 W/min	BbB (1 min)
Olson [36]	T	–	–	–	2.0 mph 0%; ↑ every 2 min to yield an approximate 2MET per work level	BbB (averages obtained over the final 30 s of each workload); Medgraphics[b]
Olson [8]	B	10	–	–	–	BbB; CPX/D[b]
Ribeiro [77]	B	–	–	–	0 W ↑15 W every 3 min 60 rpm	BbB; Sensormedics Inc[a]
Roche [40]	B	2	–	–	10 W ↑10 W progressively 60 rpm	(Every 15 s); ExpAir Soft[j]
Sato [78,79]	B	–	–	–	Ramp	BbB; AE-300S Aeromonitor[g]
Scardovi [33,39]	B	–	–	–	Ramp	BbB (10 s intervals); Vmax29[a]
Schmid [34]	B	–	3	0; 60	Ramp or ramp equivalent (load ↑/min; 0 W ↑6–12 W/min)	BbB (10 s); Vmax[a] or Oxycon Alpha[k]
Sperandio [42]	B	–	3	0; 50 ± 5	Ramp; 5–10 W/min 50 ± 5 rpm	BbB (arithmetic mean of 20 s); CardiO_2 System[b]
Sun [4,16]	BT	3	3	0	Ramp; 5–15 W/min (usually 10 W/min) or 1 min step intervals	BbB (10 s bins); 6 different systems
Ueshima [50]	B	3	3	10	Ramp; 15 W/min	AE-280[g]
Vangesselen [10]	T	–	–	–	4.8 km/h <6 years or 5,6 km/h >6 years; 0% ↑2%/min; severe cardiac impairment adapted protocol initial 1 km/h/min ↑2%/min	–

Table 1 (*continued*)

Author (year)	Mode	Rest (min)	Warm-up		Protocol; intensity	Data collection (averaging); software
			Time (min)	Load (W); rpm		
Wang [57]	B	–	2	0	Continuous ↑10 W/min	BbB; MasterScreen CPX[l]
Winkelmann [15]	B	–	–	–	–	BbB; Metalyzer3B[c]
Yajima [27]	B	4	3	20;60	↑1 W/6 s	BbB (5 breath moving); RM-300[g]
Zurek [35]	B	yes	3	0	Ramp	BbB (rest & warm-up 60 s; exercise 30 s); Oxycon Alpha[k] & Vmax29C[a]

Bicycle (B); Treadmill (T); Bicycle & Treadmill (BT); minute (min); watt (W); rates per minute (rpm); second (s); Breath-by-Breath (BbB); ventilation (VE); Second-by-Second (SbS).
[a] SensorMedics, Yorba Linda, CA, USA or SensorMedics, Homestead, FL, USA.
[b] Medical Graphics Corporation, St Paul, MN, USA or Medgraphics, Minneapolis, MN, USA.
[c] Cortex, Leipzig, Germany.
[d] Aerosport, Ann Arbor, Michigan, USA.
[e] Innovision, Odense, Denmark.
[f] ViaSys Healthcare Inc, Philadelphia, Pennsylvania, USA.
[g] Minato Medical Science, Osaka, Japan.
[h] nSpire Health Inc, Hertford, UK.
[i] Ganshorn, Medizin Electronic, Neuenkirchen, Germany.
[j] Medisoft, Dinant, Belgium.
[k] Jaeger-Toennies, Höchberg, Germany.
[l] CareFusion Corp, San Diego, USA.

populations [10,14,17–20]. The most striking finding is the presence of EOV in liver transplant patients [21]. However, it is not clear whether the subjects presenting EOV in that study had no underlying cardiac pathology. It could be assumed that EOV is a patient related pathophysiologic indicator as it was not mentioned in normal subjects yet [22,26].

To our knowledge, the first authors to describe the oscillations in ventilation were Kremser et al. in 1987 [12]. Since then, investigators tried to discover the best possible way to define and assess those oscillations. Up until now, no gold standard was proposed [11], causing a wide variety of suggested definitions for EOV. Recently, the AHA and ESC council [1,5] published guidelines in which the definition by Corrà et al. [9] was elected to define EOV. In Table 2 is shown that this definition is a modified description of the proposed criteria by Kremser et al. [12]. Only one third of the citations included in this review used this description to assess EOV. It is unclear why the guidelines suggest that definition in particular. Furthermore, it remains elusive why the majority of the authors refer to Corrà et al. [9] and only a few to Kremser et al. [12], although the latter was published 15 years earlier. Furthermore, it seems that two definitions were used in Corrà et al. [9,48]. After contacting the authors [9], they confirmed that the second description (>60% duration; amplitude >15%) is the one to follow, not corresponding to the suggested definition in the AHA and ESC guidelines (≥60% duration; amplitude ≥15%). We could assume that the proposed definition in the guidelines slightly misquoted the original author.

Lately, Sun et al. [4] analyzed oscillations in other parameters in addition to VE in order to define EOV. However, it was stated [25] that the oscillations in VO_2, VCO_2 and RER were proportionally smaller than those in VE, and were also different in phase. Therefore, it is questionable if oscillations in other cardiorespiratory parameters simulate the same underlying pathophysiologic processes.

Apart from the wide variety of definitions also many different interpretations were mentioned concerning the mathematical terms and characteristics within the described definitions. Regarding the cycle length, many descriptions were given such as the distance between two nadirs [26], the period of observed oscillation divided by the number of oscillation [56] and the interval from peak to peak for each cycle at rest expressed as mean value [18]. Moreover, different values were proposed for the duration of the cycle length such as approximately 60 s [57], 40 s–140 s [4,16], 30 s–60 s [23] or a percentage of the average [46]. Furthermore, the total duration of the oscillations could also vary. Suggested durations were >66% of the exercise protocol [12], > or ≥60% [9], ≥50% [58], 2 or 3 regular oscillations [23,46]. Sometimes these characterizations were measured at a specific point in time such as at 50% peak exercise [36,38]. Concerning the amplitude, numerous descriptions were suggested. The amplitude was described as the difference between the peak VE of the oscillation and the average of the VE of the two surrounding nadirs [26]; by calculating the variation coefficient of VE [35]; by assessing the correlation coefficient of VE [36]; or expressed as a percentage of the mean of the rest VE [18]. In addition, "a nadir", mentioned in numerous definitions [17,26], is neither a mathematical nor a medical term, but rather a term used in physics. We assumed to interpret this term as local minima. A recent meta-analysis [2] stated that the presence of EOV depended upon the proposed definition. Therefore it is important to describe these above mentioned subcharacteristics unambiguously.

Regarding computational techniques to define EOV, there is an uncertainty about the interpretation of the signal using a Fourier transformation [8,25] as the researchers assumed EOV is a stationary signal. However, other investigators [10] indicated that EOV is a non-stationary signal and therefore Fourier would not be the ideal transformation to apply in a clinical individualized setting as assessment in a frequency domain is not useful for clinical application. These authors applied a calculation of the mean BbB variability in respiratory gas exchange [10]. These developed software algorithms are promising to bring new insights in the analysis of EOV. We assume that up until now no clear detection methods other than visualization during data collection or chart review were effectively applied. These techniques are characterized by a high heterogeneity as medical charts typically only provide summarized information and hand scoring could vary considerably between individuals and centers. Moreover, some authors tried to quantify the oscillations and thus obtained to describe an amount, recognized by a number [13,24,54]. However, no clear cut-off values to quantify the oscillations were suggested. Yet, the authors [54] make clear that it is a different approach compared to the other studies in which the presence of EOV is analyzed by YES/NO criteria. In general, more research towards defining EOV is mandatory.

In the majority of the included studies, data sampling techniques were described. Twelve different unique software systems, of which a few are validated [14], were applied to register and analyze the data. In literature is stated that those devices are not always interchangeably in order to assess peak VO_2 and VE [59]. This attests the possibility that towards analyzing EOV, there is a lack of congruence between the devices, contributing to a higher heterogeneity [1]. Furthermore, it was suggested that both in clinical practice and in research publications data from patients ought to be accompanied by details of the averaging technique used [1]. This was stated as important as knowing whether the exercise is on a treadmill or a bicycle and the protocol used. This information would assist in interpreting discrepancies between findings from different centers [25]. In the majority of the studies presented, the data was recorded BbB. Consequently a data averaging method

Table 2
An overview of the different descriptions used to define exercise oscillatory ventilation (EOV).

Description		Citations quoting the description
Original definition of Kremser et al. (1987) [12]: Ventilatory oscillations lasting >66% of the exercise protocol, with an amplitude >15% of the average value at rest.		
Modified	>60% duration; amplitude >15%	[9,48,37,49,47,19,20,80]
	≥60% duration; amplitude ≥15%	[9,48,74,63,64,52,73,32,69,70,51,72,81,75,82]
	Cyclic fluctuations in minute VE at rest that persist during effort ≥50% of the exercise duration	[58]
Original definition of Leite et al. (2003) [46]: ≥3 regular oscillations (i.e., clearly discernible from inherent data noise) in VE; Regularity was defined if the SD of 3 consecutive cycle lengths (time between 2 consecutive nadirs) was within 20% of the average; minimal average amplitude of ventilatory oscillation ≥5 l (peak value minus the average of 2 in-between consecutive nadirs).		[47,33,35,21,30,68,45,60,57,56]
Modified	≥3 regular oscillations in ventilation	[83]
	Amplitude of oscillation >30% of the mean value for VE, VO_2 or VCO_2, ≥3 consecutive oscillations with amplitude of ≥5 L/min for VE and ≥3 ml/kg/min for VO_2 or VCO_2.	[40]
Original definition of Ben-Dov et al. (1992) [23]: Marked oscillations of 30–60 s duration. Magnitude (Δ) VE (Δ = (peak-nadir)/mean over the time period of the oscillation) ≥25% in ≥2 consecutive cycles (nadir to nadir) during exercise visually and normalized to 360°.		
Modified	Regular oscillations of VE amplitude >25% of mean amplitude VE.	[38]
	≥2 consecutive cycles of clear ventilatory oscillations at rest or warm-up period. The mean of the differences between the peak and nadir of oscillating VE is >30% of the mean value of VE.	[50,17]
	≥3 consecutive cycles of clear ventilatory oscillations were noted from the beginning of rest until the end of the warm up. Thereafter, the mean of the differences (amplitudes) between the peak and nadir of oscillating VE at rest and the mean resting VE was calculated. Amplitude was >40% of mean VE.	[18]
	Clear regular cyclic waxing and waning of VE without apnea, an amplitude of VE > 30% of the mean VE at cycle peak and ≥3 consecutive cycles at rest and during exercise. The same 3 cycles were used for the measurement of amplitude (the difference between peak and nadir of a cycle and averaged over 3 consecutive cycles) and period (the time interval between 2 consecutive nadirs or 2 consecutive peaks and averaged over 3 consecutive cycles). Quantifications were also obtained and Fourier analysis was also conducted.	[8]
Original definition of Sun et al. (2010) [4]: ≥3 consecutive cyclic fluctuations of VE. To be defined as positive, the amplitude of oscillatory ventilation >30% of concurrent mean VE with a complete oscillatory cycle within 40 s–140 s. Oscillations of similar frequency must also be visible in ≥3 or more of the following variables: oxygen pulse, VO_2, VCO_2, VE/VCO_2, RER (i.e., VCO_2,/VO_2), $PetO_2$ or $PetCO_2$.		
Modified	≥3 consecutive cyclic fluctuations of VE or ≥60% of entire CPET period.	[16]
Combinations of the above stated definitions		
≥3 regular oscillatory fluctuations in VE, with minimal average amplitude of ≥5 l/min persisting for ≥60% of the entire exercise time.		[65,41,71]
>60% duration; amplitude of >30% of the mean VE.		[34,53]
Oscillations ≥60% of entire exercise data at an amplitude >15%; amplitude of VE ≥5 l/min; a regular oscillation as defined by a SD of 3 consecutive cycle lengths within 20% of the average.		[31,43,42]
Cyclic fluctuation of VE at rest and during exercise with amplitude swings >30% of the mean VE, >15% for ≥60% of incremental exercise duration.		[62]
≥3 consecutive, regular oscillations in VE during exercise with oscillation amplitude ≥25% of average VE, persisting for ≥60% of exercise duration.		[26]
≥25% variation of the amplitude of VE, persisting for ≥60% of exercise duration.		[36]
Quantifying oscillations		
Oscillatory breathing at rest and during CPET. For each cycle of oscillation, the mean and amplitude (half the difference between peak and trough) was calculated. The relative amplitude (α) as the ratio between amplitude and mean e.g., if VE varied between 15 and 25 l/min, the mean 20 l/min was defined; than amplitude would be 5 l/min and αVE would be 5/20 = 0.25		[24]
The relative amplitudes of oscillations (α) in VE, VO_2 and VCO_2 were calculated for every 20-s period as the ratio between amplitude and its respective mean throughout the test.		[13]
For every 2 adjacent 20-s period of VE, the amplitude of oscillation was calculated as difference between the 2 points divided by their mean. This value was again divided by the mean to obtain the relative amplitude, and the values of the entire test were averaged to convey in a single ratio.		[15,54]
Computational		
Computational analysis using the theorem of Fourier.		[55,25]
Computational analysis calculating the mean BbB variability in respiratory variables.		[10]
Vaguely defined (referred to)		
Exercise-induced periodic oscillation in VE, VO_2, VCO_2 and the RER.		[22]
Cyclic fluctuations of ventilation ([48]).		[28,29]
Oscillatory ventilation during exercise is characterized by a TV that acts as a crescendo-decrescendo pattern without apnoea period ([68,46,4,84,85]).		[44]
Visual oscillations.		[77]
Ventilatory oscillations ([23]).		[27]
Cyclic pattern of respiration confirmed on two separate occasions in each patient.		[3]
An oscillatory hyperventilation pattern.		[14]
Not defined (referred to)		
Scardovi [39] ([46]); Oldenburg [76] ([9]); Castro [66] ([46,47]); Corrà [67] ([12]); Sato [78,79]		

Minute ventilation (VE); standard deviation (SD); oxygen uptake (VO_2); carbon dioxide output (VCO_2); respiratory exchanger ratio (RER); ventilation over carbon dioxide (VE/VCO_2); liter per minute (l/min); second (s); Breath-by-Breath (BbB); tidal volume (TV); percentage (%); pulmonary end-tidal oxygen uptake ($PetO_2$); pulmonary end-tidal carbon dioxide output ($PetCO_2$); cardiopulmonary exercise test (CPET).

was often reported. These researchers averaged the data assumingly out of practical consideration or to visualize the oscillations more. These features indicate a high heterogeneity in data sampling techniques which could lead to a higher variability and lower precision in assessing EOV [1]. The recommended [5] 10 s averaging VE data technique was only applied in ten of the included studies. However, it is unclear why this would be the advised data sampling technique in order to estimate EOV. The effects of data averaging (using different periods from 10 s to 90 s) on the size of the oscillations as well as on the noise-to-signal ratio was already investigated [25], recommending a standardized averaging period similar to the length of the typical periodic breathing cycle, i.e., 60 s regardless of whether breathing is periodic or stable. These authors suggested this would improve the physiological validity of the value obtained in subjects with periodic breathing, without adverse effects in

subjects with stable breathing. Moreover, they assumed that ideally assessment of EOV should be made on raw data before 60 s averaging, as filters eliminate small variations in gas exchange parameters and clarifies the trend in a set of data [10,25]. Since in practice the exact period of oscillatory breathing may vary between patients, no single rectangular window can be guaranteed to eliminate oscillations in metabolic parameters [25]. Furthermore, it is important to evaluate this phenomenon objectively and therefore preferable without excluding these small variations in gas exchange [10].

In the included citations, often large databases were screened over many years. A variety on CPET protocols and data collection methods were suggested. The adopted modes in the SLMT were generally reported. Bicycle as well as treadmill were applied. In the multicentre studies included in this review, those two modes were often used interchangeably. Some investigators declared the results were correctly registered irrespective the mode of exercise [30,31]. However, the EOV prevalence was 25% among patients tested on a bike and 41.3% among those tested on a treadmill [31]. In future studies, both modes could be compared in the same sample of patients to accurately investigate the difference in EOV incidence. Concerning the applied protocol, it was expressed that each stadia of the exercise test (rest, warm-up, exercise and recovery) should be reported in a study assessing cardiac patients [1]. Especially in EOV, this data is of great importance to the authors [9,12], as the investigators defined EOV by comparing oscillations in rest data before the actual exercise test. However, this data was rarely mentioned in the included studies. One can argue if oscillations during rest should be classified as periodic breathing or as exercise oscillatory ventilation. Therefore, it is unclear if defining EOV requires analysis of the oscillations during rest or only during warm-up and exercise [60]. However, it could be interesting to evaluate the oscillations during recovery, as assessed in other prognostic parameters after submaximal exercise testing [61]. Many researchers stated and included the clinical test as maximal if a RER of 1.05 or even 1.00 was reached. However the guidelines described RER $\geq$ 1.10 as cut-off [1]. One could state that EOV can be assessed by submaximal exercise testing, making the RER value inferior to other characteristics of the exercise test. However, even this should be standardized as Scardovi et al. [39] presented a high percentage of EOV in female patients with HF using a 1.00 cut-off for RER, while in the majority of the included articles more male subjects were described. These features confirmed that despite the unpredictability of EOV, there is a need of standardized CPET protocols and data collection to assess EOV in prospective conducted studies.

4.1. Study limitations

We obtained to categorize the wide variety on descriptions, mentioned in literature to define EOV, in nine sub groups to provide a clear overview. In order to create these sub groups, the definitions were classified as modified or originally stated. Whether the definition was a modified or an original description was based on the publication date, the references made to the applied definition in the articles and the personal interpretation by two researchers (J.C. and C.V.). However, the nine sub groups in definition provide a clear general overview of all descriptions stated in literature, a general definition for EOV is mandatory. This overview does not provide a gold standard definition.

The lack of transparency towards assessment, the major variation on data sampling techniques and the diversity of the conducted studies, does not allow us to make a clear statement on which mode, protocol and data sampling technique should be used to assess a patient with EOV. Further research towards defining and assessing EOV is required.

5. Conclusions

Heterogeneity in the numerous definitions to identify EOV and the vaguely described assessment methods are hindering the evolution to a standardized uniformly accepted definition and technique to identify this abnormal breathing pattern. Unity in definition and international adopted assessment is warranted to strengthen its validity as a prognostic marker and could promote communication. It may facilitate clinical trials on pathophysiology and origin of EOV.

Conflicts of interest

None.

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References

[1] G.J. Balady, R. Arena, K. Sietsema, J. Myers, L. Coke, G.F. Fletcher, D. Forman, B. Franklin, M. Guazzi, M. Gulati, S.J. Keteyian, C.J. Lavie, R. Macko, D. Mancini, R.V. Milani, Amer Heart Assoc Exercise C, Council Epidemiology P, Council Peripheral Vasc D, Interdisciplinary Council Q, Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association, Circulation 122 (2) (2010) 191–225, http://dx.doi.org/10.1161/CIR.0b013e3181e52e69.

[2] J. Cornelis, J. Taeymans, W. Hens, P. Beckers, C. Vrints, D. Vissers, Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation — a systematic review and descriptive meta-analysis, Int. J. Cardiol. 182 (0) (2015) 476–486, http://dx.doi.org/10.1016/j.ijcard.2015.01.029.

[3] H. Feld, S. Priest, A cyclic breathing pattern in patients with poor left ventricular function and compensated heart failure: a mild form of Cheyne–Stokes respiration? J. Am. Coll. Cardiol. 21 (4) (1993) 971–974, http://dx.doi.org/10.1016/0735-1097(93)90355-5.

[4] X.G. Sun, J.E. Hansen, J.F. Beshai, K. Wasserman, Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure, J. Am. Coll. Cardiol. 55 (17) (2010) 1814–1823, http://dx.doi.org/10.1016/j.jacc.2009.10.075.

[5] M. Guazzi, V. Adams, V. Conraads, M. Halle, A. Mezzani, L. Vanhees, R. Arena, G.F. Fletcher, D.E. Forman, D.W. Kitzman, et al., Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations, Eur. Heart J. 33 (2012) 2917–2927.

[6] S. Pardaens, P. Calders, E. Derom, J. De Sutter, Exercise intolerance in heart failure: update on exercise parameters for diagnosis, prognosis and therapeutic interventions, Acta Cardiol. 68 (5) (2013) 495–504.

[7] M. Guazzi, Abnormalities in cardiopulmonary exercise testing ventilatory parameters in heart failure: pathophysiology and clinical usefulness, Curr. Heart Fail. Rep. 11 (1) (2014) 80–87, http://dx.doi.org/10.1007/s11897-013-0183-3.

[8] T.P. Olson, B.D. Johnson, Quantifying oscillatory ventilation during exercise in patients with heart failure, Respir. Physiol. Neurobiol. 190 (2014) 25–32, http://dx.doi.org/10.1016/j.resp.2013.09.008.

[9] U. Corra, A. Giordano, E. Bosimini, A. Mezzani, M. Piepoli, A.J. Coats, P. Giannuzzi, Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications, Chest 121 (5) (2002) 1572–1580.

[10] S. Vangesselen, M. Weymans, L. Mertens, M. Gewillig, T. Reybrouck, A Java software for calculating mean breath-by-breath variability in gas exchange parameters: application in young cardiac patients with exercise-related periodic breathing, Comput. Methods Prog. Biomed. 80 (1) (2005) 89–92, http://dx.doi.org/10.1016/j.cmpb.2005.06.008.

[11] B.P. Dhakal, R.M. Murphy, G.D. Lewis, Exercise oscillatory ventilation in heart failure, Trends Cardiovasc. Med. 22 (7) (2012) 185–191, http://dx.doi.org/10.1016/j.tcm.2012.07.018.

[12] C.B. Kremser, M.F. O'Toole, A.R. Leff, Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy, Am. J. Cardiol. 59 (8) (1987) 900–905.

[13] P. Dall'Ago, G.R.S. Chiappa, H. Guths, R. Stein, J.P. Ribeiro, Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial, J. Am. Coll. Cardiol. 47 (4) (2006) 757–763, http://dx.doi.org/10.1016/j.jacc.2005.09.052.

[14] K. Miyagi, H. Asanoi, S. Ishizaka, T. Kameyama, S. Sasayama, Limited value of anaerobic threshold for assessing functional capacity in patients with heart failure, Clin. Cardiol. 16 (2) (1993) 133–137.

[15] E.R. Winkelmann, G.R. Chiappa, C.O. Lima, P.R. Viecili, R. Stein, J.P. Ribeiro, Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness, Am. Heart J. 158 (5) (2009)http://dx.doi.org/10.1016/j.ahj.2009.09.005 (768 e761-767).

[16] X.G. Sun, J.E. Hansen, W.W. Stringer, Oxygen uptake efficiency plateau best predicts early death in heart failure, Chest 141 (5) (2012) 1284–1294, http://dx.doi.org/10.1378/chest.11-1270.

[17] A. Koike, N. Shimizu, A. Tajima, T. Aizawa, L.T. Fu, H. Watanabe, H. Itoh, Relation between oscillatory ventilation at rest before cardiopulmonary exercise testing and prognosis in patients with left ventricular dysfunction, Chest 123 (2) (2003) 372–379.

[18] J. Kato, A. Koike, M. Hoshimoto-Iwamoto, O. Nagayama, K. Sakurada, A. Sato, T. Yamashita, K. Wasserman, K. Aonuma, Relation between oscillatory breathing and

cardiopulmonary function during exercise in cardiac patients, Circ. J. 77 (3) (2013) 661–666, http://dx.doi.org/10.1253/circj.CJ-12-0925.
[19] T. Okumura, A. Hirashiki, S. Yamada, R. Okamoto, N. Shinoda, Y. Kono, K. Takeshita, Y. Bando, X.W. Cheng, T. Murohara, Prognostic value and mechanisms of exercise oscillatory ventilation in patients with idiopathic dilated cardiomyopathy, Eur. Heart J. 32 (2011) 977–978.
[20] J. Muneuchi, K. Joo, K. Yamamura, M. Watanabe, E. Morihana, Y. Imoto, A. Sese, Exertional oscillatory ventilation during cardiopulmonary exercise test in Fontan patients with total cavopulmonary connection, Pediatr. Cardiol. 30 (4) (2009) 452–457, http://dx.doi.org/10.1007/s00246-008-9358-1.
[21] R. Neviere, J.L. Edme, D. Montaigne, E. Boleslawski, F.R. Pruvot, S. Dharancy, Prognostic implications of preoperative aerobic capacity and exercise oscillatory ventilation after liver transplantation, Am. J. Transplant. 14 (1) (2014) 88–95, http://dx.doi.org/10.1111/ajt.12502.
[22] P. Agostoni, G. Cattadori, M. Bianchi, K. Wasserman, Exercise-induced pulmonary edema in heart failure, Circulation 108 (21) (2003) 2666–2671, http://dx.doi.org/10.1161/01.CIR.0000097115.61309.59.
[23] I. Ben-Dov, K.E. Sietsema, R. Casaburi, K. Wasserman, Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure, Am. Rev. Respir. Dis. 145 (4 Pt 1) (1992) 776–781, http://dx.doi.org/10.1164/ajrccm/145.4_Pt_1.776.
[24] D.P. Francis, L.C. Davies, M. Piepoli, M. Rauchhaus, P. Ponikowski, A.J. Coats, Origin of oscillatory kinetics of respiratory gas exchange in chronic heart failure, Circulation 100 (10) (1999) 1065–1070.
[25] D.P. Francis, L.C. Davies, K. Willson, R. Wensel, P. Ponikowski, A.J. Coats, M. Piepoli, Impact of periodic breathing on measurement of oxygen uptake and respiratory exchange ratio during cardiopulmonary exercise testing, Clin. Sci. (Lond.) 103 (6) (2002) 543–552, http://dx.doi.org/10.1042/.
[26] R.M. Murphy, R.V. Shah, R. Malhotra, P.P. Pappagianopoulos, S.S. Hough, D.M. Systrom, M.J. Semigran, G.D. Lewis, Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise, Circulation 124 (13) (2011) 1442–1451, http://dx.doi.org/10.1161/CIRCULATIONAHA.111.024141.
[27] T. Yajima, A. Koike, K. Sugimoto, Y. Miyahara, F. Marumo, M. Hiroe, Mechanism of periodic breathing in patients with cardiovascular disease, Chest 106 (1) (1994) 142–146.
[28] P. Agostoni, U. Corrà, G. Cattadori, F. Veglia, R. La Gioia, A.B. Scardovi, M. Emdin, M. Metra, G. Sinagra, G. Limongelli, et al., Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis, Int. J. Cardiol. 167 (2013) 2710–2718.
[29] P. Agostoni, U. Corrà, G. Cattadori, F. Veglia, E. Battaia, R. La Gioia, A.B. Scardovi, M. Emdin, M. Metra, G. Sinagra, et al., Prognostic value of indeterminable anaerobic threshold in heart failure, Circ. Heart Fail. 6 (2013) 977–987.
[30] M. Guazzi, R. Arena, A. Ascione, M. Piepoli, M.D. Guazzi, Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value, Am. Heart J. 153 (5) (2007) 859–867, http://dx.doi.org/10.1016/j.ahj.2007.02.034.
[31] M. Guazzi, J. Myers, M.A. Peberdy, D. Bensimhon, P. Chase, R. Arena, Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights, Eur. Heart J. 29 (22) (2008) 2751–2759, http://dx.doi.org/10.1093/eurheartj/ehn437.
[32] M. Guazzi, P. Boracchi, R. Arena, J. Myers, M. Vicenzi, M.A. Peberdy, D. Bensimhon, P. Chase, G. Reina, Development of a cardiopulmonary exercise prognostic score for optimizing risk stratification in heart failure: the (P)e(R)i(O)dic (B)reathing during (E)xercise (PROBE) study, J. Card. Fail. 16 (10) (2010) 799–805, http://dx.doi.org/10.1016/j.cardfail.2010.04.014.
[33] A.B. Scardovi, R. De Maria, A. Ferraironi, L. Gatto, A. Celestini, S. Forte, M. Parolini, S. Sciarretta, R. Ricci, M. Guazzi, A case for assessment of oscillatory breathing during cardiopulmonary exercise test in risk stratification of elderly patients with chronic heart failure, Int. J. Cardiol. 155 (1) (2012) 115–119, http://dx.doi.org/10.1016/j.ijcard.2011.02.033.
[34] J.P. Schmid, A. Apostolo, L. Antonioli, G. Cattadori, M. Zurek, M. Contini, P. Agostoni, Influence of exertional oscillatory ventilation on exercise performance in heart failure, Eur. J. Cardiovasc. Prev. Rehabil. 15 (6) (2008) 688–692, http://dx.doi.org/10.1097/HJR.0b013e32830fdfdb.
[35] M. Zurek, U. Corra, M.F. Piepoli, R.K. Binder, H. Saner, J.P. Schmid, Exercise training reverses exertional oscillatory ventilation in heart failure patients, Eur. Respir. J. 40 (5) (2012) 1238–1244, http://dx.doi.org/10.1183/09031936.00167011.
[36] L.J. Olson, A.M. Arruda-Olson, V.K. Somers, C.G. Scott, B.D. Johnson, Exercise oscillatory ventilation: instability of breathing control associated with advanced heart failure, Chest 133 (2) (2008) 474–481, http://dx.doi.org/10.1378/chest.07-2146.
[37] U. Corra, A. Mezzani, A. Giordano, E. Bosimini, P. Giannuzzi, Exercise haemodynamic variables rather than ventilatory efficiency indexes contribute to risk assessment in chronic heart failure patients treated with carvedilol, Eur. Heart J. 30 (24) (2009) 3000–3006, http://dx.doi.org/10.1093/eurheartj/ehp138.
[38] T.Y. Chon, B.D. Johnson, R.F. Rea, A.C. Clavell, V.K. Somers, D.L. Hayes, L.J. Olson, Cardiac resynchronization therapy attenuates exercise periodic breathing in patients with advanced heart failure, J. Card. Fail. 10 (4) (2004) S65-S65, http://dx.doi.org/10.1016/j.cardfail.2004.06.172.
[39] A.B. Scardovi, R. De Maria, A. Ferraironi, M. Renzi, F. Turi, M. Parolini, T. Di Giacomo, R. Ricci, Prognostic value of cardiopulmonary exercise test in elderly women with heart failure and reduced or preserved ejection fraction, World J. Cardiovasc. Dis. 2014 (2014).
[40] F. Roche, D. Maudoux, Y. Jamon, J.-C. Barthelemy, Monitoring of ventilation during the early part of cardiopulmonary exercise testing: the first step to detect central sleep apnoea in chronic heart failure, Sleep Med. 9 (4) (2008) 411–417, http://dx.doi.org/10.1016/j.sleep.2007.06.012.
[41] L.P. Cahalin, R. Arena, V. Labate, F. Bandera, C.J. Lavie, M. Guazzi, Heart rate recovery after the 6 min walk test rather than distance ambulated is a powerful prognostic indicator in heart failure with reduced and preserved ejection fraction: a comparison with cardiopulmonary exercise testing, Eur. J. Heart Fail. 15 (5) (2013) 519–527, http://dx.doi.org/10.1093/eurjhf/hfs216.
[42] P.A. Sperandio, M.F. Oliveira, M.K. Rodrigues, D.C. Berton, E. Treptow, L.E. Nery, D.R. Almeida, J.A. Neder, Sildenafil improves microvascular O2 delivery-to-utilization matching and accelerates exercise O2 uptake kinetics in chronic heart failure, Am. J. Physiol. Heart Circ. Physiol. 303 (12) (2012) H1474–H1480, http://dx.doi.org/10.1152/ajpheart.00435.2012.
[43] M. Guazzi, M. Vicenzi, R. Arena, Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study, Eur. J. Heart Fail. 14 (1) (2012) 82–90, http://dx.doi.org/10.1093/eurjhf/hfr147.
[44] J.I. Lasso, Ventilación oscilatoria durante el ejercicio incremental en pacientes con falla cardíaca, Rev. Colomb. Neumol. 24 (2012) 8–12.
[45] A. Kazimierczak, K. Krzyzanowski, R. Wierzbowski, R. Ryczek, P. Smurzynski, D. Michalkiewicz, Z. Orski, G. Gielerak, Resolution of exercise oscillatory ventilation with adaptive servoventilation in patients with chronic heart failure and Cheyne-Stokes respiration: preliminary study, Kardiol. Pol. 69 (12) (2011) 1266–1271.
[46] J.J. Leite, A.J. Mansur, H.F. de Freitas, P.R. Chizola, E.A. Bocchi, M. Terra-Filho, J.A. Neder, G. Lorenzi-Filho, Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation, J. Am. Coll. Cardiol. 41 (12) (2003) 2175–2181.
[47] L. Ingle, A. Isted, K.K. Witte, J.G. Cleland, A.L. Clark, Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure, Eur. J. Cardiovasc. Prev. Rehabil. 16 (4) (2009) 451–456, http://dx.doi.org/10.1097/HJR.0b013e32832a4f54.
[48] U. Corra, M. Pistono, A. Mezzani, A. Braghiroli, A. Giordano, P. Lanfranchi, E. Bosimini, M. Gnemmi, P. Giannuzzi, Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence, Circulation 113 (1) (2006) 44–50, http://dx.doi.org/10.1161/CIRCULATIONAHA.105.543173.
[49] U. Corra, A. Giordano, A. Mezzani, M. Gnemmi, M. Pistono, R. Caruso, P. Giannuzzi, Cardiopulmonary exercise testing and prognosis in heart failure due to systolic left ventricular dysfunction: a validation study of the European Society of Cardiology Guidelines and Recommendations (2008) and further developments, Eur. J. Prev. Cardiol. 19 (1) (2012) 32–40, http://dx.doi.org/10.1177/1741826710393994.
[50] K. Ueshima, N. Kobayashi, T. Yamazaki, M. Saitoh, M. Nakamura, K. Nakao, Clinical significance of awake oscillatory ventilation in patients with heart failure and effects of open-heart surgery, Clin. Cardiol. 33 (7) (2010) E20–E23, http://dx.doi.org/10.1002/clc.20572.
[51] M. Guazzi, P. Boracchi, V. Labate, R. Arena, G. Reina, Exercise oscillatory breathing and NT-proBNP levels in stable heart failure provide the strongest prediction of cardiac outcome when combining biomarkers with cardiopulmonary exercise testing, J. Card. Fail. 18 (4) (2012) 313–320, http://dx.doi.org/10.1016/j.cardfail.2012.01.006.
[52] M. Guazzi, V. Labate, L.P. Cahalin, R. Arena, Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction, Eur. J. Prev. Cardiol. 21 (7) (2014) 847–854, http://dx.doi.org/10.1177/2047487313476962.
[53] P. Agostoni, A. Apostolo, R.K. Albert, Mechanisms of periodic breathing during exercise in patients with chronic heart failure, Chest 133 (1) (2008) 197–203, http://dx.doi.org/10.1378/chest.07-1439.
[54] C.C. Callegaro, D. Martinez, P.A. Ribeiro, M. Brod, J.P. Ribeiro, Augmented peripheral chemoreflex in patients with heart failure and inspiratory muscle weakness, Respir. Physiol. Neurobiol. 171 (2010) 31–35.
[55] D.P. Francis, L.C. Davies, K. Willson, M. Piepoli, S.R. Seydnejad, P. Ponikowski, A.J.S. Coats, Impact of periodic breathing on V-O2 and V-CO2: a quantitative approach by Fourier analysis, Respir. Physiol. 118 (2–3) (1999) 247–255, http://dx.doi.org/10.1016/s0034-5687(99)00074-2.
[56] S. Joho, R. Ushijima, T. Akabane, Y. Oda, H. Inoue, Adaptive servo-ventilation improves exercise oscillatory ventilation and ventilatory inefficiency in patients with heart failure and central sleep apnea, IJC Metab. Endocr. 1 (2013) 20–26, http://dx.doi.org/10.1016/j.ijcme.2013.11.001.
[57] J.S. Wang, T.C. Fu, C.H. Wang, S.L. Chou, M.H. Liu, W.J. Cherng, Exertional periodic breathing potentiates erythrocyte rheological dysfunction by elevating pro-inflammatory status in patients with anemic heart failure, Int. J. Cardiol. 167 (4) (2013) 1289–1297, http://dx.doi.org/10.1016/j.ijcard.2012.03.170.
[58] C. Passino, A. Giannoni, L. Pastormerlo, M. Fontana, A. Gabutti, R. Poletti, C. Mammini, G. Vergaro, L. Masi, M. Emdin, Exertional periodic breathing is frequent in heart failure patients: correlation with clinical status and neuro-hormonal activation, Eur. Heart J. 29 (2008) 553-553.
[59] P. Van de Walle, C. Vanroy, J. Roeykens, T. Sannen, D. Kaat, D. Vissers, Devices to measure oxygen cost of walking are not interchangeable, Gait Posture 39 (2014) S119–S120, http://dx.doi.org/10.1016/j.gaitpost.2014.04.165.
[60] L. Ingle, A.S. Rigby, R. Sloan, S. Carroll, K.M. Goode, J.G. Cleland, A.L. Clark, Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure, Heart 100 (10) (2014) 781–786, http://dx.doi.org/10.1136/heartjnl-2013-304614.
[61] C.R. Cole, J.M. Foody, E.H. Blackstone, M.S. Lauer, Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort, Ann. Intern. Med. 132 (7) (2000) 552–555.
[62] A. Apostolo, P. Agostoni, M. Contini, L. Antonioli, E.R. Swenson, Acetazolamide and inhaled carbon dioxide reduce periodic breathing during exercise in patients with chronic heart failure, J. Card. Fail. 20 (4) (2014) 278–288, http://dx.doi.org/10.1016/j.cardfail.2014.01.007.

[63] R. Arena, J. Myers, J. Abella, M.A. Peberdy, S. Pinkstaff, D. Bensimhon, P. Chase, M. Guazzi, Prognostic value of timing and duration characteristics of exercise oscillatory ventilation in patients with heart failure, J. Heart Lung Transplant. 27 (3) (2008) 341–347, http://dx.doi.org/10.1016/j.healun.2007.11.574.
[64] R. Arena, M. Guazzi, J. Myers, P. Chase, D. Bensimhon, L. Cahalin, M.A. Peberdy, E. Ashley, E. West, D.E. Forman, Exercise oscillatory ventilation reflects diminished quality of life and perceived functional capacity in patients with heart failure, Int. J. Cardiol. 153 (2) (2011) 213–214, http://dx.doi.org/10.1016/j.ijcard.2011.09.072.
[65] L.P. Cahalin, R. Arena, V. Labate, F. Bandera, M. Guazzi, Predictors of abnormal heart rate recovery in patients with heart failure reduced and preserved ejection fraction, Eur. J. Prev. Cardiol. 21 (7) (2014) 906–914, http://dx.doi.org/10.1177/2047487313475892.
[66] R.R. Castro, L.M. Antunes-Correa, L.M. Ueno, M.U. Rondon, C.E. Negrao, A.C. Nobrega, Reversal of periodic breathing after aerobic training in heart failure, Eur. Respir. J. 35 (6) (2010) 1409–1411, http://dx.doi.org/10.1183/09031936.00177209.
[67] U. Corrà, A. Giordano, A. Mezzani, M. Pistono, M. Gnemmi, K. Kamiya, P. Giannuzzi, Prognostic significance of peak oxygen consumption ≤ 10 ml/kg/min in heart failure: Context vs. criteria, Int. J. Cardiol. 168 (2013) 3419–3423.
[68] M. Guazzi, R. Raimondo, M. Vicenzi, R. Arena, C. Proserpio, S.S. Braga, R. Pedretti, Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients, J. Am. Coll. Cardiol. 50 (4) (2007) 299–308, http://dx.doi.org/10.1016/j.jacc.2007.03.042.
[69] M. Guazzi, J. Myers, M.A. Peberdy, D. Bensimhon, P. Chase, S. Pinkstaff, R. Arena, Echocardiography with tissue doppler imaging and cardiopulmonary exercise testing in patients with heart failure: a correlative and prognostic analysis, Int. J. Cardiol. 143 (3) (2010) 323–329, http://dx.doi.org/10.1016/j.ijcard.2009.03.053.
[70] M. Guazzi, J. Myers, M. Vicenzi, D. Bensimhon, P. Chase, S. Pinkstaff, R. Arena, Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant chronic obstructive pulmonary disease, Am. Heart J. 160 (5) (2010) 900–905, http://dx.doi.org/10.1016/j.ahj.2010.07.014.
[71] M. Guazzi, K. Dickstein, M. Vicenzi, R. Arena, Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights, Circ. Heart Fail. 2 (6) (2009) 549–555, http://dx.doi.org/10.1161/CIRCHEARTFAILURE.109.881326.
[72] M. Guazzi, J. Myers, M.A. Peberdy, D. Bensimhon, P. Chase, R. Arena, Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure–normal ejection fraction, J. Cardiopulm. Rehabil. Prev. 30 (2010) 165–172.
[73] M. Guazzi, L.P. Cahalin, R. Arena, Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure, J. Card. Fail. 19 (7) (2013) 461–467, http://dx.doi.org/10.1016/j.cardfail.2013.05.005.
[74] H.S. Lim, M. Theodosiou, Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure, J. Card. Fail. 20 (9) (2014) 650–657, http://dx.doi.org/10.1016/j.cardfail.2014.06.355.
[75] R. Matsuki, T. Kisaka, R. Ozono, H. Kinoshita, Y. Sada, N. Oda, T. Hidaka, N. Tashiro, M. Takahashi, K. Sekikawa, Y. Ito, H. Kimura, H. Hamada, Y. Kihara, Characteristics of patients with severe heart failure exhibiting exercise oscillatory ventilation, Clin. Exp. Hypertens. 35 (4) (2013) 267–272, http://dx.doi.org/10.3109/10641963.2013.780071.
[76] O. Oldenburg, T. Bitter, R. Lehmann, S. Korte, Z. Dimitriadis, L. Faber, A. Schmidt, N. Westerheide, D. Horstkotte, Adaptive servoventilation improves cardiac function and respiratory stability, Clin. Res. Cardiol. 100 (2) (2011) 107–115, http://dx.doi.org/10.1007/s00392-010-0216-9.
[77] J.P. Ribeiro, A. Knutzen, M.B. Rocco, L.H. Hartley, W.S. Colucci, Periodic breathing during exercise in severe heart failure. Reversal with milrinone or cardiac transplantation, Chest 92 (3) (1987) 555–556.
[78] T. Sato, H. Yamauchi, Y. Kanno, S. Suzuki, A. Yoshihisa, T. Yamaki, K. Sugimoto, H. Kunii, K. Nakazato, H. Suzuki, et al., Comparisons of prognostic factors between young and elderly patients with chronic heart failure, Geriatr. Gerontol. Int. 15 (4) (2015) 435–442, http://dx.doi.org/10.1111/ggi.12293 [Epub 2014 Apr 15].
[79] T. Sato, H. Yamauchi, S. Suzuki, A. Yoshihisa, T. Yamaki, K. Sugimoto, H. Kunii, K. Nakazato, H. Suzuki, S.I. Saitoh, Y. Takeishi, Serum cholinesterase is an important prognostic factor in chronic heart failure, Heart Vessel. (2014)http://dx.doi.org/10.1007/s00380-014-0469-8.
[80] N. Panagopoulou, S. Dimopoulos, A. Tasoulis, L. Karatzanos, O. Papazachou, G. Tzanis, V. Sousonis, C. Kapelios, Z. Margari, S. Nanas, Beneficial effects of exercise training rehabilitation in periodic breathing in chronic heart failure: P1453, Eur. J. Heart Fail. 2 (May 2014) 285.
[81] I. Giverts, M. Poltavskaya, O. Dikur, A. Doletskiy, V. Sedov, V. Sviridenko, P. Chomakhidze, E. Yakubovskaya, A. Syrkin, Characteristics of chronic heart failure patients presenting with exercise oscillatory ventilation, Eur. J. Heart Fail. 12 (2013) S106-S106.
[82] N. Ikeda, A. Kuribara, Y. Ugata, H. Wada, Y. Sugawara, J. Ako, S. Momomura, Exercise oscillatory ventilation prognosticate early mortality and morbidity in chronic heart failure.: P164, Eur. J. Prev. Cardiol. 20 (1) (April 2013).
[83] Y. Oda, S. Joho, R. Ushijima, D. Harada, T. Hirai, H. Inoue, Periodic breathing during asleep and exercise in patients with heart failure, Circulation 122 (21) (2010).
[84] J.L. Fleg, Breathing not properly during exercise prognostic implications in heart failure, J. Am. Coll. Cardiol. 55 (17) (2010) 1824–1825, http://dx.doi.org/10.1016/j.jacc.2009.12.039.
[85] T.D. Bradley, The ups and downs of periodic breathing: implications for mortality in heart failure, J. Am. Coll. Cardiol. 41 (12) (2003) 2182–2184, http://dx.doi.org/10.1016/S0735-1097(03)00470-4.