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Review

Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation — A systematic review and descriptive meta-analysis☆

Justien Cornelis [a,*,1], Jan Taeymans [a,b,c,1], Wendy Hens [a,1], Paul Beckers [a,d,e,1], Christiaan Vrints [d,e,1], Dirk Vissers [a,1]

[a] Faculty of Medicine and Health Sciences, University of Antwerp, Department of Rehabilitation Sciences and Physiotherapy, Universiteitsplein 1, CDE S0.22, B-2610 Wilrijk, Belgium
[b] Bern University of Applied Sciences (Health), Murtenstrasse 10, CH-3008 Bern, Switzerland
[c] Faculty of Physical Education and Physical Therapy, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Elsene, Belgium
[d] Department of Cardiology, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Belgium
[e] Faculty of Medicine and Health Sciences, University of Antwerp, Department of Medicine, Universiteitsplein 1, B-2610 Wilrijk, Belgium

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ABSTRACT

The purpose of this review was to describe the occurrence of prognostic variables as derived from cardiopulmonary exercise testing (CPET) in patients with heart failure (HF), presenting exercise oscillatory ventilation (EOV) compared to patients without EOV. The effect of EOV on peak oxygen consumption (VO_2), minute ventilation/carbon dioxide production (VE/VCO_2) slope, oxygen uptake efficiency slope (OUES), rest and peak pulmonary end-tidal carbon dioxide pressure ($PETCO_2$) was meta-analysed. A systematic search strategy was performed in five databases (Pubmed, Cochrane Library, PEDro, Science Direct and Web of Science) assessing 252 articles for eligibility. Nineteen citations met the inclusion criteria totalling 3032 patients with HF (EOV = 1111; non-EOV = 1921). The risk of bias was assessed by two researchers. Extracted data were pooled using random or fixed effects meta-analysis, if appropriate. The level of significance was set at $p \leq 0.05$. Overall, the presentation of EOV significantly indicated aggravated prognostic markers. Subgroup analysis revealed left ventricular ejection fraction (LVEF) and mode of CPET protocol as independent factors, whereas defining EOV significantly influenced the results. A meta-analysis of studies reporting hazard ratios for cardiovascular events demonstrated that HF patients with EOV run a fourfold risk for an adverse event compared to HF patients without EOV. In general, these findings suggest that the presence of EOV in patients with HF is associated with a deterioration of the prognostic CPET parameters. Furthermore, EOV can occur in HF patients with reduced as well as preserved ejection fraction. Further research on defining and assessing EOV in a more accurate and reproducible way is required.

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1. Introduction

In clinical management and research of patients with heart failure (HF), the use of cardiopulmonary exercise testing (CPET) has become notable in providing information about aerobic capacity, ventilatory efficiency and diagnostic insights [1]. Accordingly, a wide range of CPET parameters demonstrated a considerable prognostic value in this population. Previously, researchers focussed mainly on the assessment of peak oxygen consumption (peak VO_2), and therefore this value was stated to be the key CPET parameter in prognosis of HF [1,2]. Nowadays, a shift arises towards the prognostic ability of the minute ventilation/carbon dioxide production (VE/VCO_2) slope [3,4], oxygen uptake efficiency slope (OUES) [5–7], pulmonary end-tidal carbon dioxide pressure ($PETCO_2$) [7,8] and exercise oscillatory ventilation (EOV) [9,10]. These parameters have received more attention in research and proved their striking independently as well as complementary prognostic contribution [1,3,4,7,11]. Those novelties and multi-variable approaches caused researchers to develop and validate broader risk scores to obtain optimal prognosis in patients suffering this chronic disease [7,10,12,13]. However, the clinical application of these tools seem to be difficult since there is an abundance of CPET-derived parameters [10], a wide range of applied CPET protocols [14] and a lack of general standardisation [10] mainly caused by the absence of gold standard definitions to describe the prognostic variables [11] and the diversity in proposed threshold values [7,10,15,16]. Despite investigation and clarity regarding these major features is needed in every suggested prognostic parameter, this study will focus on EOV as primary parameter. A recent meta-

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* Corresponding author at: Faculty of Medicine and Health Sciences, University of Antwerp, Department of Rehabiliation Sciences and Physiotherapy, Universiteitsplein 1, CDE S0.22, B-2610 Wilrijk, Belgium.
E-mail address: Justien.Cornelis@uantwerpen.be (J. Cornelis).

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analysis of Cahalin et al. [10] indicated EOV as very important variable in prognostic CPET assessment. This abnormal ventilatory pattern is currently manual determined by a researcher instead of automatically calculated by the software packages [10,11]. Therefore EOV could be left unnoticed by the clinician in many cases. Furthermore, many significant differences were seen between an EOV presenting (EOV+) and a non-EOV presenting (EOV−) population. HF patients presenting EOV would have an aggravated prognosis since cardiac events significantly occurred more in patients presenting EOV [9]. Significant differences such as decreased peak VO_2, increased VE/VCO_2 slope and decreased peak $PETCO_2$ were noted in this population [9,17]. It was stated that patients with EOV had a decreased exercise capacity, yet in multivariate models, EOV occurred as the strongest independent predictor of events [15,17,18] and was therefore independent to other prognostic variables [19]. It was assumed that EOV presentation is a warning sign for aggravation of the symptoms and prognosis of the HF population [19]. However, the pathophysiological mechanisms that induce EOV are not yet clarified [19] since increased circulatory delay, increased chemosensitivity, pulmonary congestion or ergoreflex signalling is suggested as possible triggers [11]. The presentation of EOV could be an indication for adjusted medication prescription, individualised modified cardiac rehabilitation [20], intensive follow-up of the patient and even heart transplantation (HTX) [18]. Therefore it seems interesting to perform a systematic search strategy to overview the baseline characteristics of an EOV+, compared to an EOV− group. A meta-analysis of the available published literature was executed to investigate the effect of EOV on other key-variables and its prognostic value in patients with HF.

2. Methods

This systematic review and descriptive meta-analysis was registered in the PROSPERO database (registration number: CRD42014010106). The meta-analysis process was performed according to the Cochrane Collaboration recommendations [21]. Following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, a systematic search strategy was performed.

Systematically searched databases were Pubmed, the Cochrane Library, PEDro, Web of Science and Science Direct. The following search strategy was conducted: (heart failure OR cardiac failure) and (exercise oscillatory ventilation OR exercise periodic breathing) in PEDro and Science Direct. In the other three databases, the medical subject heading for "heart failure" was used instead. The search included citations published up until May 14th 2014.

Inclusion and exclusion criteria were established a priori. Citations were included if (1) the population was diagnosed with heart failure and (2) was aged 18 years and older; (3) oscillatory ventilation during cardiopulmonary exercise was analysed as primary parameter; (4) a comparison in the characteristics of patients with and without EOV was made; and (5) the studies were published in English, Spanish, French, German and Dutch meeting the subsequent specifications. Cardiorespiratory and metabolic parameters were secondary parameters. Studies were excluded if (1) oscillatory ventilation was only presented during rest or sleep; (2) only normal ventilation was presented; (3) only other abnormal ventilatory patterns (e.g. apnoea, hyperventilation, hypoventilation) were described; (4) the EOV pattern was voluntarily simulated; (5) EOV was assessed in other pathologies; and (6) the study designs were reviews, editorials, doctoral manuscripts and conference proceedings. Reference lists were checked for any topic-related studies. Expert opinions and recommendations on on-going studies or other relevant data were gathered. The corresponding author of a study was contacted if needed to obtain any missing information or data [9,17,22–24]. If authors could not be reached [25] or if the data were no longer available, the trial was not included in this study.

All citations identified by the aforementioned electronic databases were organised and the duplicates were deleted. Initially, one investigator (J.C.) 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 second and third investigator (D.V. and J.T.) 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 of 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 one researcher (J.C.): publication year, CPET protocol, definition of EOV, incidence of EOV, enrolment, follow-up, end point, event rate, hazard ratio (HR), study size, sex, age, body mass index (BMI), New York Heart Association (NYHA) class, left ventricle ejection fraction (LVEF), aetiology of HF, medication, peak VO_2 (ml/kg/min), VE/VCO_2 slope, OUES, rest and peak $PETCO_2$ (mm Hg).

The risk of bias of each eligible study was assessed by two researchers (J.C. & W.H.) using the Cochrane Collaboration's tool for assessing risk of bias [21]. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting were evaluated. Each category was assessed as low, unclear or high risk of bias and was overviewed in a table with a plus, question mark or minus sign respectively. Disagreements were resolved by mediation. If necessary, the citation was reviewed by a third author (D.V.) who made the final decision regarding risk of bias. In order to assess possible publication bias, a funnel plot and subsequently a classic (Rosenthal's)-fail-safe N algorithm was executed.

The extracted data were analysed using the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, NJ, USA). The Cochran's Q statistic and its corresponding p-value were calculated to assess the presence of heterogeneity across studies. To explain the part of the total observed variability that can be explained by true between-studies variability, Higgins' I^2 (%) was calculated. For all analyses, the limit for statistical significance was set at $p \leq 0.05$.

A meta-analysis with a random-effect model was a-priori chosen to examine the overall effect estimate of EOV on peak VO_2, VE/VCO_2 slope and peak $PETCO_2$. A fixed-effect model was opted in the meta-analysis on rest $PETCO_2$ and OUES since few studies described these parameters. The 95% confidence intervals [95% CI] were expressed around the weighted mean estimates. Cardiopulmonary exercise test values were reported in the same unit in the individual studies and therefore were expressed as raw mean differences in the present meta-analysis. However, because different units for peak $PETCO_2$ values were used in the individual studies, these values were standardised and used as standardised mean differences (SMD) in this analysis. Prognostic evaluation was conducted by extracting the HR for EOV from the citations. Endpoints were general death (D), cardiac related death (CD), heart transplantation (HTX) and/or implantation of a left ventricular assist device (LVAD).

Meta-regression analysis was conducted to assess the effect of the mean LVEF on the overall estimated change in peak VO_2 caused by EOV on the meta-analysis results. Subgroup analysis of mode of CPET protocol and applied EOV definition was performed in order to examine the effect of potential independent variables on the meta-analysis results.

3. Results

After the initial search, 252 articles were assessed for eligibility. Deduplication resulted in 191 articles. After screening on title, abstract and full-text, 19 citations fulfilled the a priori set inclusion criteria (Fig. 1).

The risk of bias of 18 studies was assessed (Table 1). Since the group of Sun et al. reported on the same sample in two different studies [22,23], description of the population was only mentioned once. The HR and OUES were the only supplementary values extracted from Sun et al. [23]. The most obvious risk of bias in all included citations was the non-random sequence generation and the lack of allocation concealment. The reason why sequence generation and allocation concealment were negative, was related to the study design and the presence of EOV in a population with HF. Thus, it imposed that only studies were included if the sample was divided in two groups depending on presence of EOV at a preliminary CPET. Furthermore, blinding techniques were unclear since it was often not stated in the article. However, assessment and interpretation of EOV was often done by two different researchers. Free of other bias was stated unclear when the study was a multicentre conducted study using other modes in the CPET protocol or when the study was retrospectively conducted. Description of the in- and exclusion criteria was stated unclear if at least one of both criteria was vaguely described in the citation. The funnel plot showed no asymmetry. The classic-fail-safe N analyses revealed that an additional 1149 non-significant studies would be needed to nullify the results ($p > 0.05$).

In the majority of the articles, an individualised breath-by-breath symptom limited exercise protocol was described. In order to make the data more interpretable, (moving-) averages were used. Peak VO_2 was assessed as the highest value or the mean achieved level during the last 15 s, 30 s or 60 s of the breath-by-breath symptom limited exercise protocol. The VE/VCO_2 slope was mainly calculated by plotting VE against VCO_2 every 10 s of exercise or by using the following regression ($y = mx + b$, m = slope). The OUES was defined as the slope of linear regression of VO_2 versus the log-transformed VE values for all exercise variables according following equation ($VO_2 = m\ (\log 10VE) + b$, m = slope). The peak $PETCO_2$ and rest $PETCO_2$ were described as the respectively highest or lowest averaged 10 s or 30 s values obtained at respectively peak exercise or at rest before exercise. In most studies, LVEF was assessed using two dimensional echocardiography combined with Doppler according to the Simpson's method. One study [26] also used

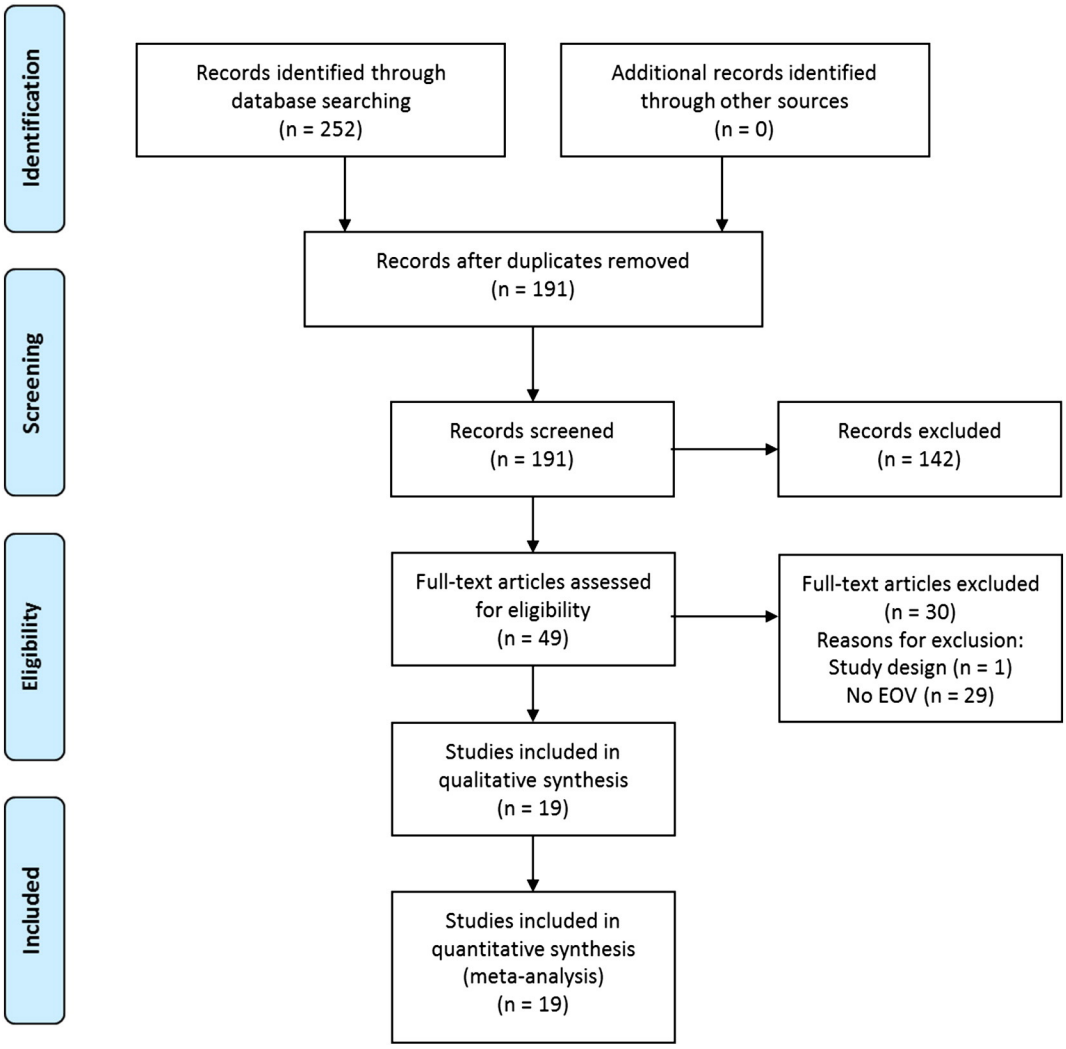


Fig. 1. Four-phase flow diagram of the systematic reviewing process.

Table 1
Overview of the risk of bias assessment using the Cochrane Collaboration's tool.

Author (year)	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective outcome reporting	Free of other bias	In- and exclusion criteria allocation described
Agostoni (2003)	−	−	?	?	+	+	+	+
Arena (2008)	−	−	?	?	+	+	+	?
Corrà (2002)	−	−	?	?	+	+	+	+
Corrà (2006)	−	−	?	?	+	+	+	+
Guazzi, A (2007)	−	−	?	?	+	+	?	?
Guazzi, M (2008)	−	−	?	?	+	+	?	+
Ingle (2009)	−	−	?	?	+	+	+	?
Kazimierczak (2001)	−	−	?	?	+	+	+	+
Koike (2003)	−	−	?	?	+	+	+	+
Kremser (1987)	−	−	?	?	+	+	+	+
Leite (2003)	−	−	?	?	+	+	+	+
Matsuki (2013)	−	−	?	?	+	+	+	?
Murphy (2011)	−	−	?	?	+	+	+	+
Olson (2008)	−	−	?	?	+	+	?	+
Schmid (2008)	−	−	?	?	+	+	?	+
Sun (2010)	−	−	+	+	+	+	+	?
Ueshima (2010)	−	−	?	?	+	+	+	?
Wang (2013)	−	−	?	?	+	+	+	+
Yajima (1994)	−	−	?	?	?	−	?	?

Summary of risk of bias for each trial, a judgement of Yes (+) indicated a low risk of bias, a judgement of No (−) indicated a high risk of bias, and an Unclear (?) judgement indicated an uncertain risk of bias, which meant there was insufficient information to permit a judgement of Yes (+) or No (−).

Table 2
General characteristics of the included studies.

Author and study year	Mode	Rest (min)	Warm-up (min)	Protocol	Definition	Incidence EOV (%)	Enrollment (m)	Follow-up (m) ±SD or (IQ)	End point	Event rate (%)	Hazard ratio (95% CI)
Agostoni 2003	B	3	3	Ramp SLMT; 8–12 min	Other	/	/	/	/	/	/
Arena 2008	T	/	/	Ramp; ↑ ± 2 ml O_2/kg/min in W every 30 s	Kremser	35.7	119	36	CD; HTX; LVAD	27.9	3.0 (1.6–5.5)
Corrà 2002	B	/	1; 0 W	Ramp SLMT; 10 W/min; 60 rpm	Kremser	11.8	34	22 ± 11	CD; HTX	16	/
Corrà 2006	B	/	1; 0 W	Ramp SLMT; 10 W/min; 60 rpm	Kremser	21.1	72	38.4 ± 20.7	CD; HTX	23.3	/
Guazzi 2007	BT	/	/	Ramp SLMT	Leite	35.1	74	20.8 ± 13	CD; HTX	22.6	5.5 (3.2–9.5)
Guazzi 2008	BT	/	/	Ramp SLMT; 8–10 min	Combined	34.2	107	13 (8–34)	CD; LVAD; HTX	15.7	5.5 (2.1–16.9) (diastolic); 2.5 (1.6–3.7) (systolic)
Ingle 2009	T	/	/	Bruce SLMT; 2.74 km/h; 0% gradient	Kremser Leite	36.3	/	46 (34–56)	D	18	6.3 (1.6–25.2)
Kazimierczak 2011	B	/	/	Ramp SLMT; 7–10 min	Leite	30.8	44	3	/	/	/
Kremser 1987	B	/	3 or 4; 0 W	Continuous ↑ in W or at 1 min interval; 6–10 W/min; 20–100 rpm	Kremser	19.4	30	/	/	/	/
Leite 2003	B	/	/	Ramp SLMT	Leite	29.8	/	11.3 (6.0–21.8)	CD	30.9	2.97 (1.34–6.54)
Matsuki 2013	B	/	3	Ramp SLMT; 10 W/min	Kremser	43.5	31	/	/	/	/
Murphy 2011	B	/	3; 0 W	Ramp SLMT; 5–15 W/min	Kremser	44.6	/	/	/	/	/
Olson 2008	T	/	/	2.0 mph; gradient ↑ every 2 min to 2 MET ↑	Kremser	7.0	/	/	/	/	/
Schmid 2008	B	/	3; 60 rpm	Ramp continuous or equivalent 0 W; 6–12 W/min; ±10 min	Kremser	15	48	/	/	/	/
Sun 2010	BT	3	3	SLMT; 5–15 W/min or 1 min step intervals; 6–15 min	Sun	51	/	6	D	3.7	5.54 (4.29–6.79)
Ueshima 2010	B	3	3; 10 W	Ramp SLMT; 15 W/min	Ben-Dov	28	/	6	/	/	/
Wang 2013	B	/	2; 0 W	SLMT; graded continuous ↑; 10 W/min	Leite	38.7	17	/	/	/	/
Yajima 1994	B	4	3; 20 W; 60 rpm	1 W/6 s ↑	Ben-Dov	10.4	/	/	/	/	/
Median						*30.8*	*46*			*20.3*	

Bicycle (B), treadmill (T), a combination of both (BT), minutes (min), load (W), symptom-limited exercise test (SLMT), months (m), standard deviation (±SD), interquartile (IQ), 95% confidence interval (95% CI), general death (D), cardiac related death (CD), left ventricular assist device (LVAD), pedalling rate expressed in revolutions per minute (rpm), miles per hour (mph), metabolic equivalent (MET) and heart transplantation (HTX).

scintigraphy, however only the echocardiography data was extracted in the analysis.

The general characteristics of the included studies are described in Table 2. The overall incidence of EOV amounted between 7% and 51% [22,27]. The population enrolment in the studies ranged from 17 to 119 months [9,24]. The follow-up range was between 3 and 46 months [26,28]. Event rates of the afore mentioned end-points ranged from 3.7 to 30.9% [22,26].

The characteristics of the EOV+ and EOV− population are described in Tables 3 and 4. The median age of the EOV+ and EOV−

Table 3
Characteristics of the EOV positive population.

Study year	Population (m/f)	Age (year)	Mean NYHA	Beta blockers (%)	Aetiology ischemic (%)	LVEF (%)	BMI (kg/m^2)
Agostoni 2003	10 (9/1)	67.3	3.0	/	50	26.1	25.3
Arena 2008	55 (31/24)	47.8	2.5	60.1	43.9	29.1	/
Corrà 2002	38 (35/3)	59	2.6	37	58	18.0	/
Corrà 2006	28 (26/2)	61.2	2.6	46.4	70.9	21.0	25.0
Guazzi 2007	101 (70/31)	56.1	2.6	52.1	53.1	29.3	/
Guazzi 2008	190 (134/56)	58.3	2.6	64.0	55	30.9	/
Ingle 2009	134	63	/	61.3	/	34	27
Kazimierczak 2011	12 (12/0)	67	2.6	100	75	28	28.4
Kremser 1987	6	/	/	/	/	/	/
Leite 2003	25 (20/5)	47.2	2.68	/	/	33.5	/
Matsuki 2013	20 (16/4)	65.6	3.0	25	100	41.3	24.0
Murphy 2011	25 (20/5)	56	/	100	36	29	29.2
Olson 2008	47 (34/13)	61	2.6	70	51	37	29.0
Schmid 2008	78 (76/2)	64.5	/	82	59	28.2	25.6
Sun 2010	258 (183/75)	64	3.0	/	/	25	29.1
Ueshima 2010	14 (9/5)	59	1.9	/	100	/	/
Wang 2013	65 (32/33)	61.9	/	92.1	55.5	37.6	24.7
Yajima 1994	5 (5/0)	55	2.0	/	20	30.7	27.4
Median	*33*	*61*	*2.6*	*62.7*	*55.3*	*29.2*	*27*

Male (m), female (f), New York Heart Association (NYHA) scale, left ventricular ejection fraction (LVEF) and body mass index (BMI).

group was respectively 61.0 and 57.1 years. The median percentage of subjects with an ischemic aetiology in both groups was 55.3% and 52.5% respectively. The median NYHA was respectively 2.6 and 2.2. The BMI was respectively 27.0 and 27.1 kg/m^2. The median percentage of the population that used beta-blocker medication was respectively 62.7% and 60.1%. The median LVEF was 29.2% and 33.2% respectively.

The peak VO_2 (ml/min/kg) of 1111 patients was described in de EOV+ group and in 1959 patients of the EOV− group (Tables 3 and 4). In one study [29] peak VO_2 was described in five patients in the EOV+ group and in 43 patients in the EOV− group, however patient characteristics (age, gender, BMI and LVEF) were only described in each group in five patients. Therefore, in Table 4 we reported five patients, however in meta-analysis the peak VO_2 value was considered in 43 patients of the EOV− group. In one study [19] characteristics and prognostic parameters of respectively 60 (Corrà criteria) and 74 (Leite criteria) EOV+ patients and 93 (Corrà criteria) and 79 (Leite criteria) EOV− patients were described separately. However, 47 EOV+ patients of which were diagnosed using both criteria, resulting in an overlap of these results. In reality only 87 patients were assessed. However, we opted to present and meta-analyse the parameters as described in the study, accounting 134 patients in the EOV+ group and 172 patients in the EOV− group. Therefore we overestimated 47 patients in the EOV+ and 19 patients in the EOV− group. In results concerning the clinical definition however, a split analysis was integrated. The numbers for gender presented in Tables 3 and 4 of this article are correct as we received also an acknowledgement of the original authors [9,15,24]. The medians of peak VO_2 were 12.7 and 16.1 ml/kg/min respectively (Table 5). In 1035 patients of the EOV+ group, the VE/VCO_2 slope was described. In the EOV− group, this slope was described in 1788 patients. The median value of the VE/VCO_2 slope was respectively 38.55 and 33.45. The parameter peak $PETCO_2$ was evaluated in 302 patients of the EOV+ group and 498 patients of the EOV− group. The median value was respectively 31.3 and 35.2 mm Hg. It should be noted that the value of one study [30] was not taken into account when calculating the median as it was expressed in another unit. $PETCO_2$ during rest was evaluated in 92 and 132 patients. The medians were respectively 31 and 33 mm Hg respectively. Only one study [23] described OUES, accounting for 258 patients in the EOV+ (1.105) and 250 patients in the EOV− (1.480) population. The numbers presented in this meta-analysis are correct; as the author wrote an acknowledgement there was an incorrect number presentation in the tables of both articles [22,23].

The meta-analysis results of the effect of EOV on peak VO_2 were described in 18 studies [9,15,17–19,22,24,26–36]. The overall random weighted estimate was −2.91 ml/kg/min (95% CI: −3.49 to −2.32; $p < 0.001$). Heterogeneity analysis showed significant high between studies heterogeneity (Cochran's Q = 44.1; degrees of freedom of Q, df(Q) = 17; $p < 0.001$; $I^2 = 61.4\%$) (Fig. 2).

The meta-analysis results of the effect of EOV on the VE/VCO_2 slope were extracted from 15 studies [9,15,17–19,22,26–28,31–33,35,36]. The overall random weighted estimate was 5.89 (95% CI: 4.59 to 7.19, $p < 0.001$). Heterogeneity analysis showed significant high between studies heterogeneity (Cochran's Q = 41.4; df(Q) = 14; $p < 0.001$; $I^2 = 66.2\%$) (Fig. 3).

The meta-analysis results of the effect of EOV on peak $PETCO_2$ were described in six studies [9,15,24,27,30,33]. The overall random weighted estimate was −0.56 mm Hg (95% CI: −0.75 to −0.37, $p < 0.001$). There was no significant difference in heterogeneity between studies (Cochran's Q = 7.6; df(Q) = 5; p = 0.180; $I^2 = 34.3\%$) (Fig. 4).

The meta-analysis results of the effect of EOV on rest $PETCO_2$ were described in three studies [26,27,33]. The overall fixed weighted estimate was −2.38 mm Hg (95% CI: −3.45 to −1.32, $p < 0.001$). There was no significant difference in heterogeneity between studies (Cochran's Q = 2.1; df(Q) = 2; p = 0.357, $I^2 = 2.8\%$) (Fig. 5).

Sun et al. [23] was the only study that evaluated the effect of EOV presence on the OUES. The overall fixed estimate was −0.38 (95% CI: −0.46 to −0.29; $p < 0.001$).

The hazard ratio (HR) was extracted from six studies [9,15,17,19,23,26]. In one study, the hazard ratios of the systolic and diastolic HF population were separately described [17]. Under random effects conditions this analysis showed that the overall weighted HR was 4.05 (95% CI: 2.88 to 5.72, $p < 0.001$). There was significant high heterogeneity between studies (Cochran's Q = 15.8; df(Q) = 6; p = 0.015, $I^2 = 62.1\%$).

To evaluate a possible confounding effect of the LVEF (%) on the weighted estimates, a fixed effect meta-regression of the individual studies weighted estimates over LVEF was conducted. LVEF was described in 16 studies [9,15,17–19,22,24,26–29,31–33,35,36]. The slope regression coefficient was −0.05 [95% CI: −0.12 to −0.02] indicating that LVEF is not confounding the presence of EOV. Thus, the difference in results between the two groups was not associated with the ejection fraction.

The CPET was performed on a bicycle (n = 12), on a treadmill (n = 3) or a combination of the two modes (n = 3). The latter was especially presented in multicentre studies. Rest and warm-up were registered in respectively four and 11 studies. The commonly used registration period in those separate phases was 3 min and warm-up was mainly executed without resistance (0 W). A subgroup analysis was made based on the mode of the applied CPET protocol. Studies were classified in

Table 4
Characteristics of the EOV negative population.

Study year	Population (m/f)	Age (year)	Mean NYHA	Beta blockers (%)	Aetiology ischemic (%)	LVEF (%)	BMI (kg/m^2)
Agostoni 2003	20 (17/3)	60.5	2.5	/	25	33.4	27.1
Arena 2008	99 (66/33)	50.1	2.0	64	34	30.1	/
Corrà 2002	285 (244/41)	57	2.1	31	57	25	/
Corrà 2006	105 (99/6)	57.1	2.2	55.7	61.7	24	24.7
Guazzi 2007	187 (125/62)	55.0	1.9	54.1	73.3	33.7	/
Guazzi 2008	366 (262/104)	55.8	2.2	67.3	67.3	31.8	/
Ingle 2009	172	58	/	56.2	/	35.5	27.5
Kazimierczak 2011	27 (27/0)	59	2.3	0	96	33	30.7
Kremser 1987	25	/	/	/	/	/	/
Leite 2003	59 (45/14)	44.1	/	/	/	35.3	/
Matsuki 2013	26 (16/10)	59.3	/	23	0	50.5	22.6
Murphy 2011	31 (24/7)	62	/	90	48	31	27.3
Olson 2008	47 (33/14)	55	2.1	70	30	35	29
Schmid 2008	78 (76/2)	64.4	/	82	62	30.2	25.3
Sun 2010	250 (183/67)	63	2.9	/	/	27	29.7
Ueshima 2010	36 (28/8)	54	1.8	/	0	/	/
Wang 2013	103 (53/50)	61	/	92.4	58.6	36.3	24.2
Yajima 1994	5 (2/3)	56	/	/	20	36.6	22.2
Median	*68.5*	*57.1*	*2.2*	*60.1*	*52.5*	*33.2*	*27.1*

Male (m), female (f), New York Heart Association (NYHA) scale, left ventricular ejection fraction (LVEF) and body mass index (BMI).

Table 5
Thresholds of the EOV positive population compared with the EOV negative population.

Study year	Peak VO_2 (ml/kg/min)		VE/VCO_2 slope		Peak $PETCO_2$ (mm Hg)		Rest $PETCO_2$ (mm Hg)		OUES	
	EOV+	EOV−	EOV+	EOV−	EOV+	EOV−	EOV+	EOV−	EOV+	EOV−
Agostoni 2003	11.1	16	46.6	33.3	/	/	/	/	/	/
Arena 2008	12.7	16.1	38.1	34.2	36.8	38.5	/	/	/	/
Corrà 2002	11.2	14.4	41	31	/	/	/	/	/	/
Corrà 2006	12.7	14.9	38	32	/	/	/	/	/	/
Guazzi 2007	13.5	16.7	39.5	32.7	31.7	35.2	/	/	/	/
Guazzi 2008	12.1	16.2	39	34.6	/	/	/	/	/	/
Ingle 2009	19.3	21.5	36.3	33.8	/	/	/	/	/	/
Kazimierczak 2011	11.4	14.9	41.1	31.2	/	/	/	/	/	/
Kremser 1987	11.7	16.1	/	/	/	/	/	/	/	/
Leite 2003	13.0	16.5	48.7	39.5	/	/	34.2	37.8	/	/
Matsuki 2013	11.9	13.9	36.0	30.4	31.3	36.3	30.7	32.4	/	/
Murphy 2011	11.3	13.2	41.6	36.6	/	/	/	/	/	/
Olson 2008	16	20	40.2	34	30	34	31	33	/	/
Schmid 2008	14.6	15	38	32.8	/	/	/	/	/	/
Sun 2010	11	13.1	37.4	33.6	/	/	/	/	/	/
Sun 2012	11	13.1	37.4	33.6	/	/	/	/	1.105	1.480
Ueshima 2010	15.3	18.8	32.9	30.0	5.8 (%)	6.0 (%)	/	/	/	/
Wang 2012	13.7	18.1	/	/	31.2	30.9	/	/	/	/
Yajima 1994	23.0	22.0	/	/	/	/	/	/	/	/
Median	*12.7*	*16.1*	*38.55*	*33.45*	*31.3*	*35.2*	*31*	*33*	*1.105*	*1.480*

Exercise oscillatory ventilation presenting group (EOV+), exercise oscillatory ventilation negative (EOV−), oxygen consumption (VO_2), minute ventilation/carbon dioxide production (VE/VCO_2), pulmonary end-tidal carbon dioxide pressure ($PETCO_2$), and oxygen uptake efficiency slope (OUES).

"treadmill-only studies" (T), "bicycle-only studies" (B) or the combination of "treadmill and bicycle" (TB). The bike fixed effect and the treadmill fixed effect analyses revealed overall weighted estimates of −2.83 ml/kg/min (95% CI: −3.34 to −2.32; $p < 0.001$) and −2.62 ml/kg/min (95% CI: −3.40 to −1.84; $p < 0.001$) respectively. The overall fixed weighted estimate was −2.86 (95% CI: −3.17 to −2.54; $p < 0.001$). There was significant high overall heterogeneity (Cochran's Q = 44.1; df(Q) = 17; $p < 0.001$; $I^2 = 61.4\%$). The total between studies heterogeneity was not significant (Cochran's Q = 0.6; df(Q) = 2; p = 0.754).

Since there is a wide range of definitions described in the literature, we opted to subdivide them into five categories. EOV was described using the definition of Kremser et al. (1987) (n = 9), Leite et al. (2003) (n = 5), Ben-Dov et al. (1993) (n = 2), a combination of Kremser et al. and Leite et al. (n = 1) or classified as "others" (n = 2). In one study [31], EOV could not be addressed to a specific definition since EOV was described as "presence of exercise-induced oscillations". In another study [22], an accurate definition of EOV was given but was classified as "other" because this definition was only used in one study. A split was applied on one study [19] as the authors applied two definitions (Kremser and Leite) to describe the groups. The Ben-Dov and Kremser weighted estimates under fixed effect conditions were −2.10 ml/kg/min (95% CI: −4.59 to 0.38; $p < 0.001$) and −2.52 ml/kg/min (95% CI: −3.05 to −1.99; $p < 0.001$) while the combined weighted estimate was −4.10 ml/kg/min (95% CI: −4.93 to −3.27; $p < 0.001$). The Leite fixed weighted estimate was

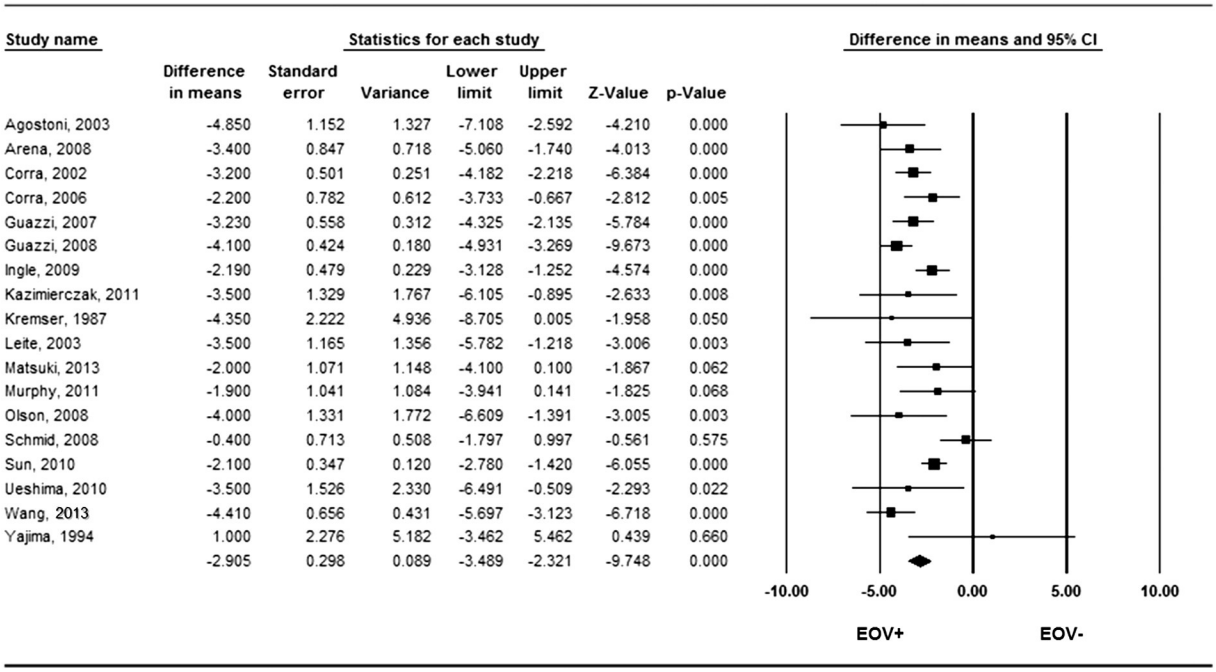


Fig. 2. Meta-analysis results of peak VO_2 (ml/kg/min) in a population with and without EOV.

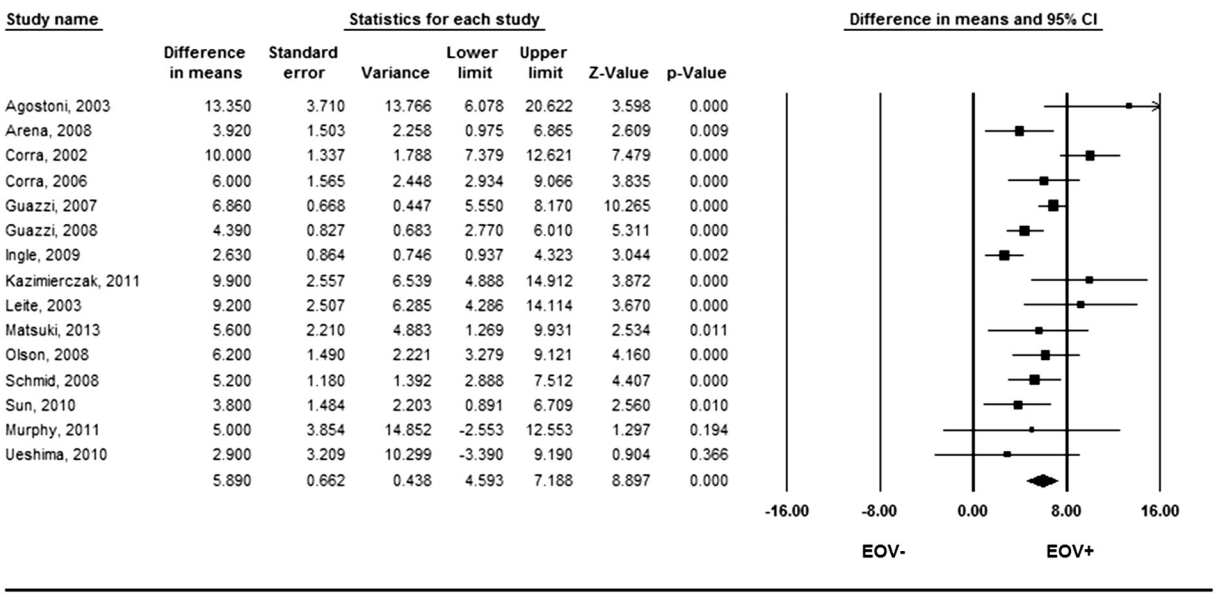


Fig. 3. Meta-analysis results of VE/VCO_2 slope in a population with and without EOV.

−3.18 ml/kg/min (95% CI: −3.83 to −2.53; $p < 0.001$). The "other" fixed weighted estimate was −2.33 ml/kg/min (95% CI: −2.98 to −1.68; $p < 0.001$). The overall fixed weighted estimate was −2.86 ml/kg/min (95% CI: −3.18 to −2.54; $p < 0.001$). There was significant high overall heterogeneity (Cochran's Q = 45.2; df (Q) = 18; $p < 0.001$; $I^2 = 60.2$). There was significant between studies heterogeneity (Cochran's Q = 14.0; df (Q) = 4; p = 0.007).

4. Discussion

To our knowledge, this systematic review and descriptive meta-analysis is the first to investigate the differences in cardiorespiratory parameters based on the presence of EOV in patients with heart failure.

The key findings include in general worsened prognostic CPET parameters in the EOV population compared to a non-EOV population. Thus, in EOV presenting HF patients, a significant decrease in peak VO_2, peak $PETCO_2$, rest $PETCO_2$ and OUES was apparent. A significant increase was visible in VE/VCO_2 slope. Mode of the exercise protocol, LVEF and definition used to describe EOV were investigated as possible confounders, identifying only the latter as dependent variable. A remarkable finding was the major hazard ratio that reflected the risk for a cardiac event associated with EOV presentation.

The prognostic value of EOV is well identified in recent literature [18,19,22,35] and might even exceed other established prognostic markers such as peak VO_2 [9], VE/VCO_2 slope [15], peak $PETCO_2$ [37], rest $PETCO_2$ [38] and OUES [23]. It is recognised that towards prognostic assessment of patients suffering from HF, a multiparametric approach would be preferred in order to estimate prognosis [13,15]. Indeed, a recent meta-analysis conducted by Cahalin et al. [10], supported this multivariable evaluation and stated that especially the combination of peak VO_2 together with VE/VCO_2 slope and EOV might provide a better insight in this feature. The possibility to predict whether somebody will present EOV is not explored yet. However, systematic worsened prognostic CPET markers might signal severe affected patients and could indicate the need for specified individualised care. Therefore, the current meta-analysis is novel as it compares multiple parameters in an EOV and non-EOV presenting population and therefore evaluating the influence of a waxing and waning breathing pattern on exercise capacity, disease severity and prognosis.

The meta-analysis ascertained a stupendous four times greater risk to an event when presenting EOV. However, the HR demonstrated

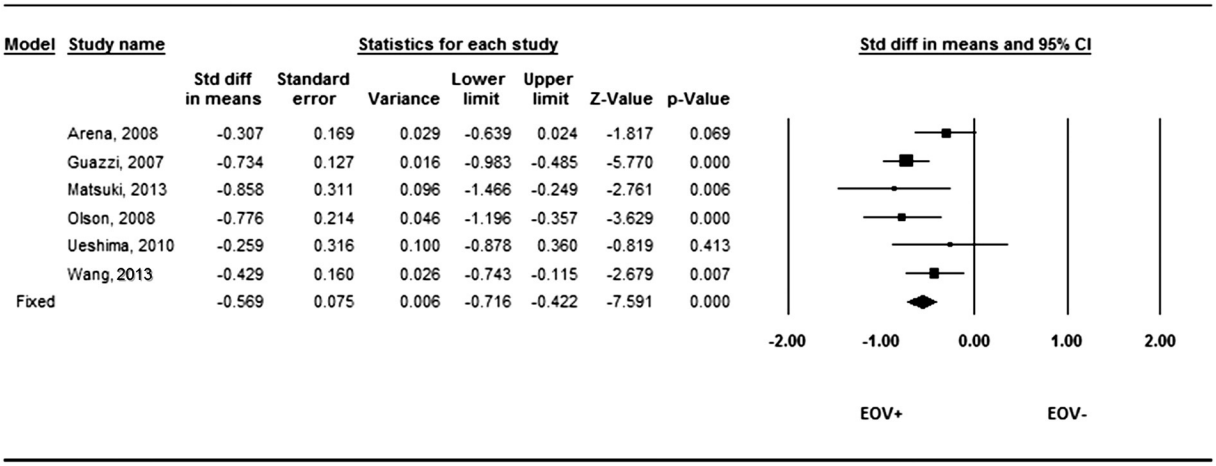


Fig. 4. Meta-analysis results of peak $PETCO_2$ (mm Hg) in a population with and without EOV.

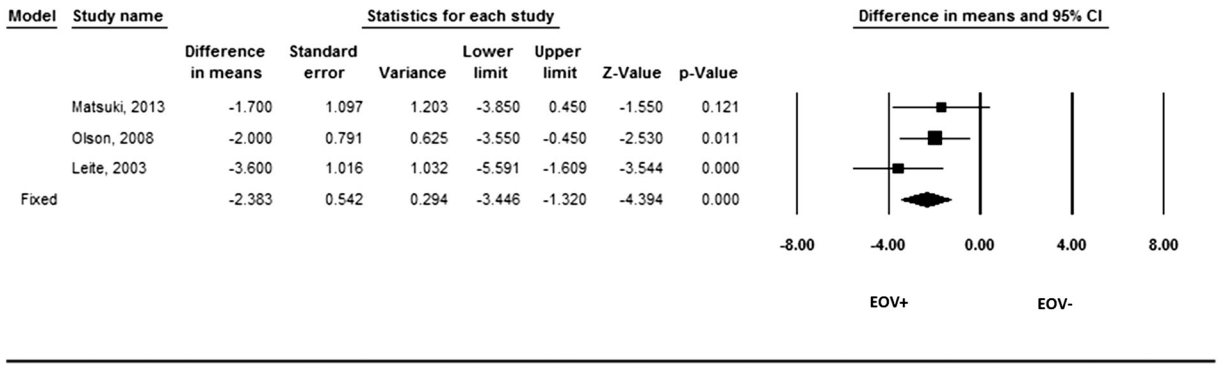


Fig. 5. Meta-analysis results of rest $PETCO_2$ (mm Hg) in a population with and without EOV.

high heterogeneity. This might be caused by the diversity in end-points during follow-up e.g. cardiac death, overall mortality, (un)censored heart transplantation or left ventricle assist devices. In general, all end-points were classified as major cardiac events. Furthermore, EOV is indicated in multivariate regression analysis as absent or present, whereas other prognostic markers had more specified thresholds [15,19]. It might be possible that with appearance of EOV a crucial prognostic burden is exceeded, with severe consequences towards pathophysiology, exercise capacity and quality of life. Thus, the prodigious HR clearly implicates the need for systematic analysis, assessment and identification of this atypical breathing pattern in clinical settings. Therefore, EOV should be a standard incorporated parameter in each multiparametric prognostic analysis.

Clinical guidelines by the American Heart Association and the American College of Cardiology provide guidance on class recommendations and levels of evidence for CPET in patients with HF in a narrowly focused fashion [2]. Given the new CPET paradigm proposed, that is supported strongly by research in this article, revision to and expansion of class recommendations and associated levels of evidence are warranted. It is clear that several application-specific class recommendations and associated levels of evidence are appropriate. In a recent article [39], Arena et al. proposed that the primary prognostic recommendation for CPET should be restored to a Class I recommendation at a level of evidence "A" for three primary variables in patients with HF and reduced ejection fraction (HFrEF): (1) the VE/VCO_2 slope, (2) EOV and (3) peak VO_2. To their knowledge, the body of evidence clearly justifies this recommendation. Although it is not the purpose of this meta-analysis, they also stated that the prognostic value of patients with HF and preserved ejection fraction (HFpEF) showed initial promise, in particular, the VE/VCO_2 slope, peak VO_2 and EOV can be useful in providing prognostic information in patients with HFpEF. They suggested a Class IIa recommendation at a level of evidence "B" for these three variables.

A possible explanation for the under investigation of EOV might be the absence of a gold standard definition but also the lack in automated registration of EOV. However, a recent report recognised this hiatus and presented a new registration method based on Fourier analysis [40]. Although, the EOV signal might be also accurately analysed by other automated methods, since there is no consensus in defining this pattern. Essential in further research would be the development of a gold standard definition, as our results proved that the way of describing EOV is a strong dependent variable. The lack in consistency towards identification might be the reason our results presented in general a moderate to high heterogeneity. The American Heart Association International Guidelines confirmed that criteria for EOV are not yet established, however they proposed to assess EOV using the Corrà definition, as it is mostly cited in literature [13]. Although less rigorous, it resembled mainly the Kremser definition in our study. To our knowledge none of the definitions showed to have superior diagnostic characteristics, as limited studies compared definitions. In our study, the Kremser definition was cited in 9 studies. The difference in defining between the lowest and highest value for peak VO_2 (1.99 ml/kg/min) was clinical significant if 14 ml/kg/min is seen as cut-off for severe deteriorate prognosis in HF [10]. One study [19] described a 6% higher incidence using the Corrà definition [18] compared to the Leite definition [26]. Thus, the remarkable large reported interval in incidence (12%–51%) [18,22] could be mainly influenced by the applied definition. Therefore, more suggested descriptions might be compared and evaluated.

In an attempt to precise the assessment of EOV and to acquire accuracy among clinical research centres, the reported exercise protocols were evaluated and compared. There is a wide range of reported exercise protocols concerning mode (bicycle, treadmill or both), recording time of rest and warm-up, interval or continuous increase during exercise and applied load. Even using the same mode, results in maximal oxygen uptake and dynamics of gas exchange could differ [41]. Moreover, important towards the assessment of EOV, many different filter methods were used e.g. 10-s moving average and 30-s moving average. Assessing raw data instead of filtered data could achieve standardisation in evaluation. The meta-analysis of the applied mode of protocol showed to be an independent parameter in assessing EOV. This could be expected since the main differences between these two modes are the higher peak ventilation and peak oxygen consumption reached using treadmill rather than a difference in parameters during the incremental exercise test [41,42].

Considering the EOV population, our results confirmed a significant meaningful lower peak VO_2 and increased VE/VCO_2 slope. As these parameters are established prognostic markers [4], they indicate aggravated prognosis. Significant notable reduced $PETCO_2$ during rest and exercise reflects a lower exercise capacity and decreased cardiac output response [8,37]. $PETCO_2$ has been seen as prognostic CPET parameter and predictor of cardiac-related events [43]. Therefore, assessment of $PETCO_2$ has been integrated in prognostic CPET scores [44]. Also OUES has showed to be an independent strong predictor of cardiac events [5], however it is questionable if its prognostic power is superior to other variables [45]. Furthermore, in risk scores, threshold values are integrated in order to describe worsen prognosis for all prognostic variables. Rest $PETCO_2 < 33$ mm Hg, peak $VO_2 \leq 14$ ml/kg/min, VE/VCO_2 slope ≥ 34 and OUES < 1.4, thus in this meta-analysis the EOV + group presented median values of respectively 31; 13.37; 38.55 and 1.105 indicating severe deteriorate prognosis and disease progression [44,46,47].

These results reflect the assumption that HF patients presenting EOV have in general a major decreased exercise capacity in comparison with non-EOV patients. Deconditioning may indicate cardiovascular, pulmonary, neural and/or peripheral skeletal muscle dysfunction [48]. This mind-set corresponds to the suggested pathophysiologic mechanism of EOV such as circulatory delay, increased chemosensitivity, increased pulmonary congestion and/or elevated ergoreflex signalling [11]. As changes in the complex exercise response are caused by the central

nervous system [48], one specific explanation for the initiation of EOV cannot be pointed out at this moment. Therefore, it might be assumed that low daily physical activity [18,33] and/or quality of life in general could be a warning signal for the presentation of EOV in an early stage of the disease [49]. The fact that EOV also appears in other populations such as liver transplant patients [50] supports this idea. Moreover, it indicates that circulatory delay is not the crucial factor leading to EOV as cardiac output was not decreased in that specific population [50]. Furthermore, our results state that LVEF is an independent parameter in development of EOV. Before, this was only assumed by analysing the presence of EOV in heart failure patients with reduced or preserved LVEF [17,51]. Pathophysiology of EOV might be explained by research in broader populations. In order to analyse and possibly detect this abnormal breathing pattern in several populations, the definition and method to detect EOV, as mentioned before, should be more described. Moreover, manual and visual detection is very time consuming and less accurate. There should be aimed to automate and integrate analysis of EOV into existing CPET software, thus this pattern could be accurate registered in all clinical research facilities all over the world. This alignment would provide researchers more information concerning pathophysiology and even prevention of EOV. Moreover, management of EOV could be more individualised and specialised. It is suggested that the presentation of this atypical breathing pattern is an indicator for application of more aggressive therapy [20,50]. Thus, servoventilation [28,52], sildenafil intake [53], inhalation of acetazolamide and carbon dioxide [54], milrinone application and heart transplantation [55] showed to be effective in blunting EOV. However, re-occurrence of EOV in comparison with quality of life after these interventions is not properly investigated yet. Supporting the idea of deconditioning, physical activity in the form of aerobic exercise leaded to a remarkable 71.2% disappearance of EOV [20]. Exercise as non-pharmacological therapy in patients with heart failure cannot be underestimated [56]. This accompanies the fact that a wide range of modalities of physical training improves exercise capacity and tolerance in patients with heart failure [57–60]. More research should be done towards the effect of diverse training modalities, frequency and intensity on the prognosis, exercise intolerance and quality of life in patients suffering from EOV. Supervised home-care rehabilitation, adjustments in daily living and coaching could be useful as adjuvant therapy in this strong deconditioned population [61,62]. The reoccurrence of EOV during follow-up after cardiac rehabilitation might be evaluated.

4.1. Limitations

Doctoral manuscripts, editorials and conference proceedings were not included in this meta-analysis. It can be opted to screen these study designs. In general, the results showed often a high and significant between studies heterogeneity. This could be caused by the study design, often unclear or retrospectively and/or multicentre conducted studies. Moreover, the inclusion criteria selected in the citations may contribute to this high heterogeneity. Also, criteria for NYHA class inclusion, assessment of LVEF percentage, differences in age, aetiology of HF and definition used to describe EOV could contribute to this heterogeneity.

Moreover, the regression analyses were limited to peak VO_2. As peak VO_2 provided the biggest population, it was assumed that the same estimates should be reflected in the other prognostic parameters. It is plausible that when performing regression analyses of other prognostic parameters, definition would be also a dependent parameter whereas LVEF and mode of protocol would be independent.

Citations concerning this topic often try to investigate the prognostic value of EOV and therefore evaluate many (in)dependent parameters. However, we decided to limit this meta-analysis towards the prognostic CPET parameters, simply because the majority of the parameters are only mentioned once. Moreover, CPET has shown to be a good and accurate diagnostic tool in heart failure and useful in cardiac rehabilitation. More (in)dependent cardiopulmonary and echocardiography parameters could be investigated in further research.

Many echocardiography variables could be described in order to reveal the pathophysiology and more specific the haemodynamic response [35]. However, we did not aim to investigate the complex physiology behind this unusual pattern, however we aimed to deliver warning signs and insight in the overall physical condition of a heart failure person with EOV presence. Our research question aimed to point out the importance of EOV recognition in clinical practice. Many questions towards the origin of this kinetic symptom and the benefits of abolishment towards follow-up and survival are still unanswered.

5. Conclusions

In conclusion, prognostic CPET parameters such as peak VO_2, peak $PETCO_2$ and rest $PETCO_2$ were aggravated in heart failure patients with EOV, where VE/VCO_2 slope and OUES were significantly increased. Sub-study analysis revealed LVEF and CPET mode of protocol as independent factors, whereas the use of different EOV definitions significantly affected the results. A meta-analysis of studies reporting hazard ratios for cardiovascular events demonstrated that HF patients with EOV run a fourfold risk for an adverse event compared to HF patients without EOV. In general, these findings suggest that the presence of EOV in patients with HF is associated with a deterioration of the prognostic CPET parameters. Furthermore, EOV can occur in HF patients with reduced as well as preserved ejection fraction. Further research on defining and assessing EOV in a more accurate and reproducible way is required.

Conflicts of interest

None.

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