

Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients

Non Peer-reviewed author version

Dos Santos Ribeiro, Gustavo; Deresz, Luís; Salvioni, Elisabetta; HANSEN, Dominique; Agostoni, Piergiuseppe & Karsten, Marlus (2022) Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients. In: INTERNATIONAL JOURNAL OF CARDIOLOGY, 360 (2022) p. 39-45.

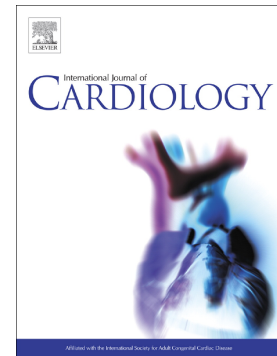
DOI: 10.1016/j.ijcard.2022.05.041

Handle: <http://hdl.handle.net/1942/37331>

Journal Pre-proof

Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients

Gustavo dos Santos Ribeiro, Luís Fernando Deresz, Elisabetta Salvioni, Dominique Hansen, Piergiuseppe Agostoni, Marlus Karsten



PII: S0167-5273(22)00753-7

DOI: <https://doi.org/10.1016/j.ijcard.2022.05.041>

Reference: IJCA 30324

To appear in: *International Journal of Cardiology*

Received date: 6 April 2022

Revised date: 17 May 2022

Accepted date: 18 May 2022

Please cite this article as: G. dos Santos Ribeiro, L.F. Deresz, E. Salvioni, et al., Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients, *International Journal of Cardiology* (2022), <https://doi.org/10.1016/j.ijcard.2022.05.041>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Elsevier B.V. All rights reserved.

Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients

Gustavo dos Santos Ribeiro¹, Luís Fernando Deresz², Elisabetta Salvioni³, Dominique Hansen⁴, Piergiuseppe Agostoni^{3,5}, Marlus Karsten^{1,6,7}

¹ Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil.

² Departamento de Educação Física, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, Brazil.

³ Centro Cardiologico Monzino, IRCCS, Milan, Italy.

⁴ Hasselt University (UHASSELT), Faculty of Rehabilitation Sciences, BIOMED REVAL, Hasselt, Belgium / Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium.

⁵ Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Milano, Italy.

⁶ Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Florianópolis, Brazil.

⁷ Programa de Pós-Graduação em Fisioterapia, UDESC, Florianópolis, Brazil.

Authorship statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Correspondence author

Marlus Karsten, Centro de Ciências da Saúde e do Esporte, Universidade do Estado de Santa Catarina (UDESC), Rua Pascoal Simone 358, CEP 88080-350, Florianópolis, SC, Brazil.

E-mail: marlus.karsten@udesc.br

Funding

This study was financed in part by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Sample CRediT author statement

Gustavo Ribeiro: Conceptualization, Methodology, Formal analysis, Writing - Original draft preparation. **Luís**

Fernando Derez: Conceptualization, Methodology, Writing - Original draft preparation. **Elisabetta Salvioni:**

Resources, Writing - Review & Editing. **Dominique Hansen:** Writing - Review & Editing, Supervision. **Piergiuseppe**

Agostoni: Resources, Writing - Review & Editing, Supervision. **Marlus Karsten:** Conceptualization, Methodology,

Writing - Review & Editing, Project administration.

Journal Pre-proof

Abstract

Background: Exercise oscillatory ventilation (EOV) shows a four-fold greater risk of adverse events. This study aims to analyze the sensitivity and specificity of three EOV diagnostic definitions to predict adverse outcomes at a 2-year follow-up and to compare its EOV prevalence and relations with the patient's profile.

Methods: Cardiopulmonary exercise tests from 233 heart failure patients were analyzed. Two blinded reviewers used a semiautomated software to identify EOV cases pattern according to the definitions of Ben-Dov, Corrà, and Leite. Data were grouped in EOV-positive or EOV-negative according to each definition. Baseline characteristics, EOV prevalence, relative risk, sensitivity, and specificity to predict 2-years of major adverse cardiovascular outcomes were analyzed.

Results: The Corrà definition led to the best prediction of 2-year major cardiovascular adverse outcomes (HR 2.46 [1.16 to 5.25]; $p = 0.019$, AUC = 0.618; $p = 0.007$). EOV prevalence was 17.2%, 17.2%, and 9.4% applying Ben-Dov, Corrà, and Leite definition, respectively. The main clinical differences between EOV-positive and EOV-negative patients were: MECKI score and VE/VCO₂ slope (all definitions), and BNP levels (Ben-Dov and Leite). BNP levels were correlated with amplitude ($\rho = 0.255$; $p = 0.033$) and cycle length ($\rho = 0.388$; $p = 0.002$).

Conclusion: Corrà definition was the only one that exhibited the capacity to predict major adverse cardiovascular outcomes at a 2-year follow-up. Regardless of its definition, EOV was more often prevalent in patients with a greater MECKI score and VE/VCO₂ slope values.

Keywords

Cardiology, Cardiovascular Diseases, Cardiopulmonary Exercise Test, Periodic Breathing, Prognosis.

1. Introduction

Exercise oscillatory ventilation (EOV) is an abnormal ventilatory pattern observed in chronic heart failure (HF) patients and is associated with disease severity and worse prognosis [1-3]. Cornelis *et al.* [4] reported a four-fold greater risk of adverse cardiovascular events in HF EOV-positive patients compared to their counterparts without EOV. Rovai *et al.* [5] highlighted that the presence of EOV is associated with a lower 2-year survival in HF patients with reduced or mid-range left ventricular ejection fraction, regardless of age and gender.

Although current evidence reinforces its predictive value, the EOV prevalence in HF is still controversial. Cornelis *et al.* [6] identified nine different EOV definitions based on EOV length and amplitude. It is not surprising that these different definitions lead to a wide range of EOV reported incidence, from 7 to 58% of HF patients [2, 6].

Although the American Heart Association has proposed the Corrà definition to screen for EOV cases [7], there is no consensus on the best EOV definition [4, 8]. Ingle *et al.* [9] were the first to evaluate the impact of different definitions on the prevalence and prognosis within EOV-positive patients. A similar prevalence between the Corrà and Leite definitions was observed (25 vs. 31%). However, EOV cases identified by the Corrà definition exhibited a greater hazard ratio (HR 6.3 [1.6 to 25.2]) to all-cause 12-month death than EOV cases identified by Leite definition (HR 4.9 [2.6 to 18.2]).

The different options to determine the EOV due to the lack of standardization, compromises the clinical applicability of EOV. Albeit likely, it is unclear whether and to what extent the different definitions exhibit distinct sensitivities and specificities to detect EOV, and to predict adverse outcomes. Among all the definitions available, we chose to compare Ben-Dov, Corrà, and Leite definitions because these definitions have different conceptual criteria in their development (e.g., high amplitude vs. longer duration) and have been frequently utilized in studies on EOV. These features may be linked to the HF aetiology (e.g., left or right HF) or clinical markers of hemodynamic impairment.

Therefore, this study aims to analyse the sensitivity and specificity to predict major adverse cardiovascular outcomes in a 2-year follow-up in HF patients, using three diagnostic definitions that apply distinct criteria to screen this phenomenon, and to compare the EOV prevalence and the clinical patient profile.

2. Methods

2.1 Study design

Retrospective anonymized single-centre data from 500 cardiopulmonary exercise tests (CPETs) performed between 2011 and 2014, and with a follow-up of at least 2 years, were analyzed. This study was approved by the Research Ethics Committee from the main author (referee 3.516.801/2019) according to current ethical standards.

2.2 Data sampling

CPETs of HF patients aged 40 to 90 years were included. Data from patients who performed a short CPET (< 6 minutes [10, 11]), with a too short registration (< 90 seconds) of the minute ventilation (VE) at rest, or tests that did not allow to apply the EOv definitions (corrupted file) were excluded. Patients with a follow-up < 2 years were also excluded.

2.3 Exercise test protocol

CPETs followed the hospital routine [12]. Briefly, a personalized ramp protocol was performed on an electronically braked cycle ergometer (Erg 800S; Sensor Medics, Yorba Linda, CA) [5, 13]. All subjects were instructed to perform a maximal effort (exercise peak near to 10 min). The tests were stopped when patients reported fatigue or in the presence of any cardiac abnormalities. The breath-by-breath data were collected and analysed using the 20-s smoothing average (Vmax[®] 12-3A Series, CareFusion, Yorba Linda, CA).

The highest 20-s averaged oxygen uptake (VO_2) value registered was considered as the $\text{VO}_{2\text{PEAK}}$. The VE/ VCO_2 slope, a marker of ventilatory efficiency, was measured by applying the V-slope method, which is defined as the linear relationship between VE and carbon dioxide production (VCO_2), excluding the first minute of exercise and the period above the respiratory compensation point [5]. All measures were done following the hospital's expertise.

2.4 Clinical profile and MECKI score

The patient's clinical variables were obtained directly from the hospital's medical record. Data on body mass index, New York Heart Association (NYHA) functional classification, left ventricular ejection fraction (LVEF), right ventricular systolic pressure (RVSP), blood hemoglobin, and B-type natriuretic peptide (BNP) levels were recorded. All variables were collected on the day of the CPET or within the week before it. The MECKI score was used for calculating the risk of chronic systolic HF, estimated from six independent predictors (% of $\text{VO}_{2\text{PEAK}}$ predict, VE/ VCO_2 slope, blood hemoglobin, sodium, left ventricular ejection fraction, and modification of diet in renal disease [MDRD]) [14].

2.5 EOv definitions

The EOv was determined by the combined characteristics of the ventilatory pattern (amplitude, cycle length, and/or oscillatory time) according to the definitions of Ben-Dov [15], Corrà [16], and Leite [17]. Figure 1 shows the EOv-positive ventilatory pattern and illustrates the minimum of oscillatory cycles or duration recommended for each definition.

INSERT FIGURE 1

2.6 EOV identification

Two blinded reviewers used a semiautomated tool to identify EOV cases in a standardized way. The software EASY-EOV tool 1.0 is an open-access application developed to allow the EOV analysis from CPET raw data of any system (LabVIEW, National Instruments, US). In a validation study, a high intra-rater ($k \geq 0.82$) and inter-rater ($k \geq 0.83$) reliability was observed (unpublished data).

2.7 Follow-up data

Follow-up data were recorded by the hospital service from the completion of the CPET until the registration of death or a cardiovascular procedure – limited to 2-years for all patients. Cardiovascular death, urgent heart transplantation, or the need for left ventricular assist device implantation were included as major adverse cardiovascular outcomes. Subjects without cardiovascular death or need for cardiac procedure, and who had clinical follow-up less than 1 year after CPET, were excluded.

2.8 Statistical analysis

Data were separated in EOV-positive vs. EOV-negative patients according to each definition. To assess normality of data distribution, we used the Kolmogorov-Smirnov test. Baseline characteristics were compared between groups by the Mann-Whitney test or Fisher's exact test (EOV-positive vs EOV-negative) and Kruskal-Wallis test (EOV-positive between Ben-Dov, Corrà, and Leitão). Cochran's Q test and the McNemar post hoc were applied to compare the prevalence of EOV across different definitions. Furthermore, the interaction between EOV characteristics (amplitude, cycle length, and total oscillation time) and blood BNP levels was assessed by Spearman's correlations (ρ).

All patients were followed for two years. The risk of major adverse cardiovascular outcomes was calculated for each EOV definition. The sensitivity and specificity to predict major adverse cardiovascular outcomes were estimated by the Receiver-Operating Characteristic (ROC) curve. All baseline variables were inserted as possible predictors in the univariate model (removed variable if $p > 0.1$ or collinearity > 0.3) [9]. Multivariable Cox proportional-hazards regression analysis was used with the backward method to identify the best predictive model (entered variable if $p < 0.05$).

3. Results

Among 500 patients who performed a baseline CPET, 443 were HF patients. Of them, sixty-one records had less than 90 seconds of VE recording at rest, and 149 patients had too short or no clinical follow-up after CPET: these cases were excluded, leading to a study population of 233 cases. Table 1 shows the sample characteristics. EOV

prevalence was 17.2% (Ben-Dov), 17.2% (Corrà), and 9.4% (Leite). Ben-Dov and Corrà definitions identified 40 EOV cases each. Both definitions exhibited a greater prevalence than EOV cases identified by Leite ($p < 0.01$).

INSERT TABLE 1

EOV patients had a worse functional class, MECKI score, ventilatory efficiency (VE/VCO₂ slope), and lower maximal workload, regardless of EOV definition. There was no difference in clinical characteristics among EOV-positive groups when calculated by the definitions of Ben-Dov, Corrà and Leite ($p > 0.05$). EOV-positive cases identified by the definitions of Ben-Dov and Leite presented higher levels of blood BNP than HF patients without EOV. Low to moderate correlations between BNP levels and amplitude ($\rho = 0.255$; $n = 933$) or cycle length ($\rho = 0.388$; $p = 0.002$) were found. No association with total oscillation time was observed ($\rho = -0.104$; $p = 0.229$).

Among all EOV cases, 16 patients were exclusively identified by the definition of Corrà and 12 patients by the definition of Ben-Dov. Both definitions shared 22 EOV cases. Leite's definition shared 15 positive cases with Corrà's definition and 19 with Ben-Dov's definition. Only one EOV patient was identified just by the definition of Leite. The overlap of EOV cases is presented in the Figure 1S. Regarding related diagnosis, blood BNP levels were greater when EOV was identified by the definition of Ben-Dov vs. the definition of Corrà (720 [411 to 1,067] vs. 260 [80 to 677] pg/mL; $p = 0.019$).

The relative risk for 2-year major adverse cardiovascular outcomes was significant applying Corrà's definition (2.9 [1.6, 5.2]; $p < 0.001$), and Ben-Dov's definition (1.9 [1.0, 3.7]; $p = 0.047$). However, Corrà's definition was the only one that showed a significant probability to predict 2-year major adverse cardiovascular outcomes (Table 2).

INSERT TABLE 2

Supplemental Table 1S shows the potential predictors for major adverse cardiovascular outcomes (univariate analysis). Four variables were entered in the predictive model after multivariate Cox analysis (R^2 -adjusted = 0.184; $p < 0.001$). Only two variables were significantly predictive: Corrà's definition (HR 2.46 [1.16 to 5.25]; $p = 0.019$) and age (HR 1.07 [1.03 to 1.12]; $p = 0.002$).

4. Discussion

The number of HF patients identified as EOV-positive ranged from 9.4 to 17.2% according to the applied definition. There was no difference in EOV prevalence (40 EOV cases) when applying Ben-Dov's vs. Corrà's definition. Of these 40 cases identified by the Ben-Dov and Corrà criteria, only 22 cases were identified by both criteria,

while the other 18 cases were identified exclusively by the Ben-Dov or by Corrà criteria. Moreover, the Corrà definition allowed us to identify EOVC cases with the greatest 2-years major adverse cardiovascular outcome rate. In contrast, the blood BNP levels were greater in cases identified exclusively by Ben-Dov's definition. Furthermore, a low-to-moderate correlation between blood BNP levels and amplitude or cycle length was observed.

To our knowledge, Ingle *et al.* [9] were the only that investigated the impact of different EOVC diagnostic definitions on prognosis. They evaluated 240 HF patients applying Corrà and Leite definitions. There was no difference in EOVC prevalence in both definitions (Corrà: 25% and Leite: 31%). However, Ingle *et al.* [9] observed that EOVC-positive cases identified by Corrà's definition were associated with a higher all-cause mortality at 1-year (HR 5.2 [2.8 to 9.9]; $p < 0.001$) in comparison to the cases identified by Leite's definition (HR 4.8 [2.8 to 8.8]; $p < 0.001$).

In the present study, we found a lower EOVC prevalence by all definitions, as well as a lower sensitivity to predict adverse outcomes applying the Corrà criteria, in comparison with other studies [9, 17]. Furthermore, Ben-Dov's and Leite's definitions did not show a sufficient sensitivity to predict 2-year major adverse cardiovascular outcomes. The difference between our and previous study outcomes could be related to: the different baseline characteristics (our sample was older and with lower VO_{2PEAK}), the difference in follow-up time (24 vs 12 months), and the use of a semiautomated tool to identify EOVC cases rather than manual scoring and/or visual interpretation (less subjective).

Our findings differ from other studies that used the Leite's definition to identify EOVC cases. In the original study, Leite *et al.* [17] observed a 30% EOVC prevalence and a 3-times greater risk for premature death within 2 years in patients with heart transplantation indications (HR 2.7 [1.34 to 6.54]; $p < 0.01$). Similarly, Vainshelboim *et al.* [18] found a higher prevalence (54%) and hazard ratio for major cardiac-related events at 5 years (HR 2.2 [1.2 to 4.1]; $p = 0.011$) applying Leite's modified criteria.

Regarding Corrà's methodology, the results are contradictory. The original study reported an EOVC prevalence slightly lower than ours (12%) [16]. Nevertheless, Guazzi *et al.* [19] found a higher EOVC prevalence in HF patients with a reduced (35%) and preserved ejection fraction (32%), beyond the greater hazard rate to overall mortality at four years (HR 2.0 [1.3 to 3.1]; $p < 0.001$ and 5.9 [2.1 to 16.9], $p < 0.001$). It should be noted that the exercise tests were performed both on a treadmill and cycle ergometer, making further inferences unfeasible since the specificity of the exercise mode can produce different physiological responses. In this sense, Guazzi *et al.* [19] observed 25% EOVC-positive cases among tests performed on a cycle ergometer and 41% of EOVC-positive cases among tests done on a treadmill.

Another point to be considered is the use of dichotomous EOVC detection: EOVC-positive or EOVC-negative. As the EOVC pathophysiology remains unknown [1, 3, 18], it is plausible to consider that the amplitude and/or length of each cycle differs from one patient to another, even with a confirmed EOVC diagnosis by two or three definitions (by Corrà and Ben-Dov, for example). The clinical impact of this variation is yet unknown. It seems that the cycle

amplitude would be related to hemodynamic impairments such as circulatory delay [20], a lower ventilatory efficiency [21], and higher blood BNP levels [21]. Thus, higher amplitudes would be related to worse outcomes in EOV patients. Nonetheless, this hypothesis yet needs to be confirmed.

Our data show the EOV-positive patients diagnosed by Ben-Dov's and Leite's definition have higher blood BNP levels than those identified by Corrà's definition, albeit with a lower mortality. Yamauchi *et al.* [21] also found a positive correlation between cycle amplitude and blood BNP levels when applying Leite's definition ($r = 0.615$; $p = 0.007$). However, they did not provide an explanation for this finding. An essential factor that may have influenced blood BNP levels is the right ventricular impairment, commonly seen in HF superimposed by pulmonary hypertension. Leuchte *et al.* [22] found that high blood BNP levels were directly related to high pulmonary capillary wedge pressures, pulmonary vascular resistance, and right atrial pressure, and were inversely correlated with cardiac index or VO_{2PEAK} . Indeed, Murphy *et al.* [20] observed an association between right ventricular ejection fraction and both amplitude ($r = -0.68$; $p < 0.001$) or cycle length ($r = -0.48$; $p = 0.02$), suggesting that these parameters would be related to a worse hemodynamic function in EOV-positive patients.

This is the first study that investigated the predictive capacity of three definitions for EOV with totally different conceptual characteristics: Ben-Dov, Corrà, and Leite. Indeed, Ben-Dov proposed the presence of two consecutive cycles with 30-60s of length and a cycle magnitude of near to 25% of the average VE for EOV diagnosis [15]. Corrà proposed that the oscillation would need to be present in at least 60% of total exercise time, with an amplitude above 15% of the VE at rest [16]. Finally, Leite proposed that EOV would be characterized by at least three regular oscillations with a minimal amplitude above 5 L/min [17].

In brief, Ben-Dov's and Leite's definitions imply a shorter oscillation time, but a larger amplitude compared to the Corrà's definition. It is unknown how these definitions are related to the patient hemodynamic impairment, albeit it is possible to speculate that a higher ventilation amplitude suggests a greater hemodynamic impairment [20, 21]. Nevertheless, the oscillation time seems to have a greater probability to predict adverse outcomes, which possibly would justify the better sensitivity of the Corrà's definition. Accordingly, the reasons behind the cessation of EOV during exercise, albeit at present unknown, are of major importance. The idea that EOV ceased during exercise due to the capability to improve cardiac output, or to divert more blood to the exercising muscles, both leading to an improved peripheral oxygen delivery (which in its turn allows reducing the metabolic and chemoreflex sites of activation) are attractive and maybe the link between the observed difference in EOV prognosis and definition.

At present, the EOV definition described by Corrà [16], i.e., oscillation presence of at least 60% of loaded exercise with a minimal amplitude above 15% of VE at rest, seems to be the best choice to link EOV to prognosis.

4.1 Limitations

The present study has a few limitations which need to be acknowledged. Firstly, our sample size was small as limited in the number of major adverse cardiovascular outcomes, which may be related to the optimal treatment offered in a high-level cardiology centre. In this regard, bigger studies with a larger HF population that includes different phenotypes are definitively essential. Secondly, we re-analyzed CPET previously done in a single centre with mainly a low-ejection fraction HF phenotype. Therefore, our data should not be applied to different HF populations such as in mid-range or preserved ejection fraction patients [5].

5. Conclusion

The Corrà definition for EOVS was the only one that exhibited the capacity to predict major adverse cardiovascular outcomes at a 2-year follow-up. The choice of EOVS definition seems to affect the number of identified cases (ranging from 9.4 to 17.2%). Regardless of the definition, EOVS was more often prevalent in patients with a greater MECKI score and VE/VCO₂ slope values. There were no differences in the clinical characteristics among EOVS-positive groups. The positive correlation of blood BNP levels with amplitude and cycle length, the main features of the Ben-Dov and Leite definitions, suggests a link between these features with a clinical impairment marker.

References

- [1] Agostoni P, Salvioni E. Exertional Periodic Breathing in Heart Failure: Mechanisms and Clinical Implications. *Clin Chest Med.* 2019;40:449-57.
- [2] Agostoni P, Corra U, Emdin M. Periodic Breathing during Incremental Exercise. *Ann Am Thorac Soc.* 2017;14:S116-s22.
- [3] Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M. Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis. *Eur J Prev Cardiol.* 2021.
- [4] Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis. *Int J Cardiol.* 2015;182:476-86.
- [5] Rovai S, Corra U, Piepoli M, Vignati C, Salvioni E, Bonomi A, et al. Exercise oscillatory ventilation and prognosis in heart failure patients with reduced and mid-range ejection fraction. *Eur J Heart Fail.* 2019;21:1586-95.
- [6] Cornelis J, Beckers P, Vanroy C, Volckaerts T, Vrints C, Vissers D. An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation - a systematic review. *Int J Cardiol* 2015;190:161-9.
- [7] Balady G, Arena R, Sietsema K, Myers J, Cokelet C, Fletcher G, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122:191-225.
- [8] Panagopoulou N, Karatzanos E, Dimopoulos C, Tasoulis A, Tachliabouris I, Vakrou S, et al. Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure. *Eur J Prev Cardiol.* 2017;24:825-32.
- [9] Ingle L, Isted A, Witte K, Cleland J, Clark A. 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.* 2009;16:451-6.
- [10] Hansen D, Bonn  K, Alders T, Hermans A, Copermans K, Swinnen H, et al. Exercise training intensity determination in cardiovascular rehabilitation: Should the guidelines be reconsidered? *Eur J Prev Cardiol.* 2019;26:1921-8.
- [11] Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R, et al. Work-rate affects cardiopulmonary exercise test results in heart failure. *Eur J Heart Fail.* 2005;7:498-504.
- [12] Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. *International journal of cardiology.* 2019;288:107-13.

- [13] Campodonico J, Mapelli M, Spadafora E, Ghilardi S, Agostoni P, Banfi C, et al. Surfactant proteins changes after acute hemodynamic improvement in patients with advanced chronic heart failure treated with Levosimendan. *Respir Physiol Neurobiol*. 2018;252-253:47-51.
- [14] Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, 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*. 2013;167:2710-8.
- [15] Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis*. 1992;145:776-81.
- [16] Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJS, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: Clinical correlates and prognostic implications. *Chest*. 2002;121:1572-80.
- [17] Leite J, Mansur A, De Freitas H, Chizola P, Bocchi E, Terra-Filho M, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol*. 2003;41:2175-81.
- [18] Vainshelboim B, Amin A, Christle JW, Hebbal S, Ashley EA, Myers J. A method for determining exercise oscillatory ventilation in heart failure: Prognostic value and practical implications. *Int J Cardiol*. 2017;249:287-91.
- [19] Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J*. 2008;29:2751-9.
- [20] Murphy R, Shah R, Malhotra R, Pappagianopoulos P, Hough S, Systrom D, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. *Circulation*. 2011;124:1442-51.
- [21] Yamauchi F, Adachi H, Tomono I, Toyoda S, Iwamatsu K, Sakuma M, et al. Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure. *Heart Vessels*. 2016;31:1659-68.
- [22] Leuchte HH, Holzapfel M, Baumgartner RA, Ding I, Neurohr C, Vogeser M, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. *J Am Coll Cardiol*. 2004;43:764-70.

Figure legends

Fig. 1. EOV-positive ventilatory pattern. EOV, exercise oscillatory ventilation. VE, minute ventilation. CPET, cardiorespiratory exercise test. SD, standard deviation.

Journal Pre-proof

Table 1. Clinical characteristics stratified by EOv definition

Variable/Definition	Ben-Dov [15]		Corrà [16]		Leite [17]	
	EOV-positive	EOV-negative	EOV-positive	EOV-negative	EOV-positive	EOV-negative
Sample, n (%)	40 (17.2)	193 (82.9)	40 (17.2)	193 (82.9)	22 (9.4)	211 (90.6)
Male gender, n (%)	35 (87.5)	156 (80.8)	31 (77.5)	160 (82.9)	21 (95.5)	170 (80.6)
Age, years	69 [66 – 72]	68 [67 – 70]	74 [69 – 76]*	68 [66 – 69]	69 [63 – 75]	68 [67 – 70]
Body mass index, kg/m ²	24.8 [23.8 – 27.4]	26.6 [25.4 – 27.2]	24.8 [24.2 – 27.0]	25.6 [25.1 – 27.3]	24.2 [22.3 – 27.0]*	26.6 [25.4 – 27.3]
NYHA class III-IV, n (%)	22 (55.0)*	67 (34.7)	22 (55.0)*	67 (34.7)	13 (59.1)*	76 (36.0)
LVEF, %	32.9 [30.2 – 36.4]	32.7 [32.0 – 35.2]	32.8 [29.2 – 37.3]	32.9 [32.0 – 35.0]	31.9 [24.7 – 36.4]	33.0 [32.1 – 35.2]
RVSP, mmHg	36.0 [33.0 – 46.0]	35.0 [32.0 – 37.0]	39.0 [34.0 – 46.0]	35.0 [33.0 – 37.0]	42.0 [31.0 – 49.0]	35.0 [33.0 – 37.0]
MECKI score, %	8.1 [6.0 – 11.5]*	3.7 [2.9 – 4.8]	7.4 [4.8 – 12.6]*	3.8 [3.1 – 4.9]	11.1 [3.1 – 16.1]*	4.0 [3.3 – 5.2]
Hemoglobin, mg/dL	13.9 [12.7 – 14.7]	13.9 [13.7 – 14.3]	13.6 [12.8 – 14.2]	14.0 [13.7 – 14.3]	13.9 [12.6 – 14.8]	13.6 [13.7 – 14.2]
BNP, pg/mL	550 [372 – 737]*	267 [200 – 322]	330 [272 – 549]	272 [221 – 398]	514 [282 – 987]*	275 [224 – 379]
CPET time, s	533 [486 – 572]	532 [517 – 562]	492 [477 – 572]	539 [521 – 563]	538 [470 – 652]	530 [515 – 556]
VO _{2PEAK} , ml.kg.min ⁻¹	12.7 [11.9 – 14.7]*	14.0 [13.4 – 14.8]	12.2 [11.1 – 13.5]*	14.3 [13.5 – 15.0]	12.6 [9.8 – 14.9]	14.0 [13.2 – 14.8]
VE/VCO ₂ slope	36.3 [32.9 – 40.5]*	29.6 [28.8 – 30.6]	36.0 [32.0 – 40.0]*	30.0 [28.8 – 31.0]	37.6 [32.0 – 42.7]*	30.0 [29.0 – 31.0]
Maximal workload, w	61 [46 – 80]*	69 [64 – 75]	48 [37 – 64]*	71 [68 – 79]	56 [33 – 80]*	70 [64 – 74]
Major adverse outcome, n (%)	10 (25.0)	25 (13.0)	13 (32.5)**	22 (11.4)	6 (27.3)	29 (13.7)

Continuous data are expressed as median [95% confidence interval (CI)] and categorical data as absolute (n) and relative (%) frequencies. EOv, exercise oscillatory ventilation.

EOV-positive, patients with a confirmed diagnosis. EOv-negative, patients with a negative diagnosis. NYHA, New York Heart Association. LVEF, left ventricular ejection fraction.

RVSP, right ventricular systolic pressure. BNP, B-type natriuretic peptide. CPET, cardiopulmonary exercise test. VO_{2PEAK}, peak oxygen uptake. VE/VCO₂, minute ventilation-carbon dioxide production. *p < 0.05 Mann-Whitney Test (EOV-positive vs EOv-negative). **p < 0.01 Fisher's exact test (EOV-positive vs EOv-negative).

Table 2. Sensitivity and specificity to predict 2-year major cardiovascular adverse outcomes.

Definition	AUC	95% CI	p-value	Sensitivity	Specificity
Ben-Dov	0.567	0.487 to 0.647	0.100	28.57	84.85
Corrà	0.618	0.533 to 0.702	0.007	37.14	86.36
Leite	0.545	0.479 to 0.611	0.179	17.14	91.92

EOV, exercise oscillatory ventilation. AUC, area under the ROC curve. CI, confidence interval.

Author Agreement Form – International Journal of Cardiology

Manuscript Title: Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients

List of all Authors: Gustavo S Ribeiro, Luís Fernando Deresz, Elisabetta Salvioni, Dominique Hansen, Piergiuseppe Agostoni and Marlus Karsten

Corresponding Author: Marlus Karsten (marlus.karsten@udesc.br)

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. *Int. J. Cardiol.* 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

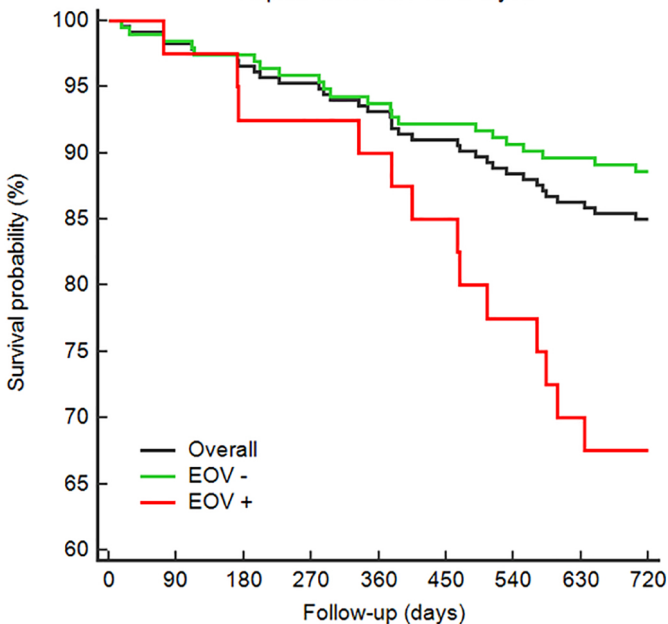
All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

Highlights

- Exercise oscillatory ventilation is a phenomenon associated with a worse prognosis.
- There is no consensus on the best EOV definition to be applied.
- EOV prevalence is higher when Ben-Dov or Corrà definitions are applied.
- BNP levels are associated with amplitude and cycle length.
- Corrà definition has the better capacity to predict 2-year mortality.

Journal Pre-proof

Kaplan-meier survival analysis



Overall

233 229 225 222 217 212 206 201 198

EOv -

193 190 188 185 181 178 175 173 171

EOv +

40 39 37 37 36 34 31 28 27

Figure 1