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Software development to standardize the clinical diagnosis of exercise oscillatory ventilation in heart failure Peer-reviewed author version

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#### Software Development to Standardize the Clinical 1

### **Diagnosis of Exercise Oscillatory Ventilation in** 2 **Heart Failure** 3

- 4
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#### 27 Abstract

- 28 Background: Exercise oscillatory ventilation (EOV) is characterized by periodic oscillations of minute
- 29 ventilation during cardiopulmonary exercise testing (CPET). Despite its prognostic value in chronic heart failure
- 30 (HF), its diagnosis is complex due to technical limitations. An easier and more accurate way of EOV
- 31 identification can contribute to a better approach and clinical diagnosis. This study aims to describe a software
- 32 development to standardize the EOV diagnosis from CPET's raw data in heart failure patients and test its
- 33 reliability (intra- and inter-rater).

- 1 Methods: The software was developed in the "drag-and-drop" G-language using LabVIEW<sup>®</sup>. Five EOV
- 2 definitions (Ben-Dov, Corrà, Kremser, Leite, and Sun definitions), two alternative approaches, one smoothing
- 3 technique, and some basic statistics were incorporated into the interface to visualize four charts of the
- 4 ventilatory response. EOV identification was based on a set of criteria verified from the interaction between
- 5 amplitude, cycle length, and oscillation time. Two raters analyzed the datasets. In addition, repeated
- 6 measurements were verified after six months using about 25% of the initial data. Cohen's kappa coefficient ( $\kappa$ )
- 7 was used to investigate the reliability.
- 8 Results: Overall, 391 tests were analyzed in duplicate (inter-rater reliability) and 100 tests were randomized for
- 9 new analysis (intra-rater reliability). High inter-rater ( $\kappa > 0.80$ ) and intra-rater ( $\kappa > 0.80$ ) reliability of the five
- 10 EOV diagnoses were observed.
- 11 Conclusion: The present study proposes novel semi-automated software to detect EOV in HF, with high inter
- 12 and intra-rater agreements. The software project and its tutorial are freely available for download.
- 13

### 14 Keywords

- 15 Cardiology, Cardiovascular Diseases, Cardiopulmonary Exercise Test, Periodic Breathing,
- 16 Prognosis
- 17

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- 27 Marlus Karsten: Conceptualization, Methodology, Writing Review & Editing, Project administration.
- 28 29

### 1 Introduction

Exercise oscillatory ventilation (EOV) is a phenomenon originally described in chronic heart failure
(HF) patients, characterized by periodic oscillations of the minute ventilation (VE) during exercise testing [1-3].
Current evidence suggests that HF patients with EOV have a four-fold increased risk of adverse cardiovascular
events, and deterioration in all prognostic parameters from the cardiopulmonary exercise test (CPET) [4].
Agostoni and Salvioni [1] claimed that EOV can be considered as an independent marker of worse prognosis,
with better prognostic predictability than peak oxygen consumption (*V*O<sub>2.peak</sub>) and ventilatory efficiency
(*VE*/*V*CO<sub>2</sub> slope) [5, 6].

9 Although the prognostic value is clinically relevant, this marker is not commonly used in clinical 10 practice due to the absence of consensus on the best EOV definition [2, 4, 7], and the lack of standardized data 11 processing techniques. Cornelis et al. [7] highlighted at least nine conceptual variations to identify EOV by the 12 combination of different characteristics of the VE response during CPET: amplitude (h), cycle length ( $\lambda$ ), and 13 oscillation time ( $\Delta t$ ). Furthermore, the EOV identification depends on the manual data calculation or visual 14 interpretation of the VE response, impacting the diagnosis reliability due to the inter-rater variability [7]. 15 Cornelis et al. [8] developed a graphical interface to automatically detect the ventilatory pattern 16 characteristic of EOV. Different smoothing techniques were applied to remove noise from the breath-by-breath 17 VE signals and the four most common EOV definitions were included in this interface [9-12]. The EOV 18 diagnosis has become faster and less affected by the inter-rater variation. Even though this was a precursor 19 initiative for standardizing EOV identification, it is not clear whether this tool will be made available to 20 manufacturers of all metabolic carts, or if it will be available for a broader application. 21 To better incorporate the EOV assessment into clinical practice and spread its applicability, we believe 22 that it is necessary to simplify its analysis and improve the inter-rater agreement. Therefore, this study aims to 23 develop a semi-automated tool to standardize the identification of EOV from the CPET exported raw data and 24 test its reliability (intra- and inter-rater). We hypothesize that our tool will be able to support the EOV 25 identification and show a good inter-rater agreement improving the evaluation and follow-up of EOV patients. 26

# 1 Methods

## 2 Study design

3	This cross-sectional study based on retrospective data was approved by the local ethics committee
4	(referee 3.516.801/2019 and 4.558.550/2021). A novel resource was developed to standardize the EOV
5	diagnosis. Data from 500 CPETs performed in a specialized center were selected to initial screening. Only data
6	from HF patients were used to test the tool's reliability (inclusion criteria). Records with exercise time lower
7	than six minutes or resting time lower than 90 seconds were excluded from the analysis for making two EOV
8	definitions unfeasible (exclusion criteria). All CPETs used a personalized ramp protocol on an electronically
9	braked cycle ergometer (Erg 800S; Sensor Medics, Yorba Linda, CA) with breath-by-breath analysis (Vmax 12-
10	3A Series, CareFusion, Yorba Linda, CA).
11	The experimental design was composed of three phases: 1) Internal consistency: cyclical process
12	between software development and looking for errors in programming. The file was returned to the
13	development phase if any programming conflict was identified during the tool application on selected data. 2)
14	EOV diagnosis: two blinded raters used the developed tool to analyze CPETs from the database; 3) Reliability
15	analysis: inter and intra-rater agreement to EOV-positive and EOV-negative. Figure 1S illustrates the study
16	design (supplementary material). All procedures were done according to current ethical recommendations.
17	
18	Software development
19	The software was developed using "drag-and-drop" G-language in the LabVIEW <sup>®</sup> 2014 (National
20	Instruments Corp <sup>®</sup> , Texas, US), and was named "EASY-EOV tool". All commands from LabVIEW are freely
21	available for download in the online repository [BLINDED]. The EASY-EOV tool was updated whenever an
22	inconsistency in the simulated tests was observed (see Internal consistency section). The major features
23	available are graphic visualization of the ventilatory pattern – at rest and exercise, data smoothing technique,
24	EOV diagnosis in a semi-automated way, alternative approaches to assessing EOV, basic statistics, and data
25	export to further analysis. Figure 2S shows an example of code used in LabView programming.
26	

### 1 Ventilatory pattern

3	recovery) and another three to view exercise time, resting period, and the amplitude's borderline of each cycle.
4	Only the main chart (exercise time) allows the ventilatory pattern characteristics to be demarcated as exposed in
5	Figure 1 (nadir-peak-nadir). Figure 1 illustrates a typical EOV pattern, and its main characteristics [2, 3, 7]. The
6	resting period is used to adjust the VE value used in two EOV definitions [12, 14]. The amplitude's borderline
7	chart helps the user to visualize which cycles meet the recommended limit of 15% of VE at rest – red line [12,
8	14] or 5 L.min <sup>-1</sup> [10] – green line.
9	
10	Fig. 1 Minute ventilation (VE) response of an HF EOV-positive patient during the CPET. A, beginning cycle
11	(nadir). B, the peak of the cycle (peak). C, end cycle (nadir). h, amplitude cycle: the difference between the peak
12	of the VE cycle and its baseline (a line between two consecutive nadirs). $\lambda$ , cycle's length: distance between two
13	consecutive nadirs (e.g.: A and C). $\Delta t$ , and oscillation time: total oscillation period during the CPET.
14	
15	Smoothing technique
16	Moving average filter (MAF) is a consolidated data pre-processing method to reduce the high-
17	frequency noise influences over the VE data [13], facilitating the cycle identification. The MAF window size
18	can be selected by the user according to guidelines or center expertise (e.g., 5 to 30 breaths).
19	
20	$MAF = \left( \dot{V}E_{(i)} + \dot{V}E_{(i+1)} + \dots + \dot{V}E_{(i+M)} \right) \div M $ (1)
21	
22	where $\dot{V}E_{(i)}$ is initial data of minute ventilation and M is the number of points in the average. For example,
23	$\dot{V}E_{(i)}$ is the first VE's registered data, $\dot{V}E_{(i+1)}$ is the second one, and so successively. In this study, a 7-breaths
24	moving (rolling) average filter was adopted.
25	
26	EOV identification
07	

Four charts are available in the system: one to view the full VE response (rest, warm-up, exercise, and

27 The EOV identification was based on a set of criteria verified from the interaction between h,  $\lambda$  and  $\Delta t$ 28 [9-12]. The user must manually mark the beginning, peak, and end of each cycle (nadir-peak-nadir triad) in the 1 exercise chart (EASY-EOV tool demo - supplementary material). After that, the EASY-EOV tool automatically

2 calculates the h,  $\lambda$  and  $\Delta t$ , and the algorithm classifies periodic ventilation following the definition of Corrà [12],

- 3 Kremser [14], Ben-Dov [9], Leite [10], and Sun [11]. These criteria are summarized in Table 1.
- 4

5 Table 1 Criteria adopted in the five main definitions to diagnose exercise oscillatory ventilation

Author	Criteria
Ben-Dov et al. [9]	Two or more consecutive cycles with the VE average $\geq 25\%$ cycle and 30 to 60s of length.
Corrà et al. [12]	At least 60% oscillation in total CPET time with amplitude > 15% of VE at rest.
Kremser et al. [14]	At least 66% of total exercise time with amplitude $> 15\%$ of the VE at rest.
Leite et al. [10]	Three or more regular oscillations with SD length < 20% of cycle average and amplitude above 5 L.min-1.
Sun et al. [11]	Three or more consecutive cycles with the VE average $\geq$ 30% cycle and 40 to 140s of length. Positive oscillations in at least three other CPET variables.

VE, minute ventilation. CPET, cardiopulmonary exercise test. SD, standard deviation.

6

### 7 Alternative approaches

8 In an alternative way to the binary analysis (EOV-positive or negative), the Ventilation Dispersion 9 Index (VDI) and the VE variability (vVE) were implemented in the system. The VDI combines the cycle's h 10 with the oscillation frequency during the CPET [15], whereas the vVE analyses the VE response through time-11 domain linear methods, as the standard deviation of VE (SDNN) and its relativized form (SDNN/n) to reduce 12 the influence of the number of observations registered [16].

13

14 
$$VDI = \sum_{i=0}^{N-1} \frac{dVE_{(i)} + dVE_{(i+1)}}{2} \times [T_{(i+1)} - T_{(i)}]$$
 (2)

15

where VDI is Ventilation Dispersion Index, dVE is the absolute difference between the VE and the mean VE every 30s, T is the exercise time in seconds, and "i" is the data interval starting at 70s of exercise (i = 0) through

18 the second to last exercise interval (i = N - 1).

1

2 
$$vVE = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n - 1}} \div number of cycles$$
 (3)

3

4 where vVE is the minute ventilation variability,  $x_i$  is VE standard deviation, x is the mean standard deviation of 5 VE, n is the total of standard deviations. The vVE is calculated using data from the entire exercise period (main 6 chart). For example, zero to 480 seconds.

7

#### 8 Measurement properties

9 According to the COSMIN taxonomy, the principal domains that determine the quality of an instrument 10 are reliability, validity, and responsiveness [17]. The reliability of the measures (inter-rater and intra-rater 11 agreement) was assessed by Cohen's kappa coefficient ( $\kappa$ ) for the positive cases in each definition, adopting k  $\geq$ 12 0.80 as an adequate measure [18]. The internal consistency (a reliability domain) was assessed using the CPET 13 data from a diagnosed EOV patient to test algorithm software.

14

#### 15 Internal consistency

16 Throughout the development phase, the software version was updated whenever a rater identified some 17 programming conflict in the statistic routine, export data, VE characteristics interaction, and EOV identification 18 (e.g., not exporting the data correctly or not signaling the EOV presence when all the recommended criteria 19 were fulfilled). In these cases, the software was sent to the development sector (Figure 1S). Some CPETs raw 20 data were used to stress the software algorithms (virtual codes) during the development phase to test its internal 21 consistency. No programming conflict was observed after the last update (on May 15th, 2021). 22

#### 23 Inter-rater agreement

24 Two independent raters (GSR and LFC) used the software interface and visually labelled the beginning 25 and end of the VE cycles during the CPET. After that, the EASY-EOV tool automatically indicated the EOV 26 presence following the EOV definitions (Table 1), besides calculating the VDI and vVE. Standardized

1	recommendations of how to use the software were given to the CPET-experienced researchers. Both had a
2	training period to standardize the use of the software. All notes were sent to the principal investigator for
3	agreement analysis (positive cases in each definition). The VDI and vVE are automatically calculated from the
4	whole uploaded data set (evaluator independent). Due to this, these indexes were not submitted to an agreement
5	analysis.
6	
7	Intra-rater agreement
8	The intra-rater (GSR) agreement was verified after six months of the first screening. An online service
9	( <u>https://www.randomizer.org/</u> ) was used to randomize a subset of 100 CPETs previously analyzed [17]. All
10	notes were sent to the principal researcher (MK) to evaluate the agreement.
11	

## 12 **Results**

- 13 The clinical characteristic from the database used to test the software development (internal consistency
- 14 and reliability) is presented in table 2. Our sample was predominantly composed by data from male elderly
- 15 patients with low cardiorespiratory capacity.
- 16

17	Table 2         Clinical characteristic from the database	
	Sample size, n	391
	Male gender, n (%)	307 (78.5)
	Age, years	$66.2 \pm 11.0$
	NYHA class III-IV, n (%)	161 (41.2)
	Left ventricular eject fraction, %	$33.4 \pm 9.0$
	β-blockers, n (%)	347 (88.7)
	Angiotensin-converting enzyme type-I, n (%)	243 (62.1)
	Calcium antagonist, n (%)	155 (39.6)
	Diuretics, n (%)	309 (79.0)
	VO <sub>2PEAK</sub> , ml.kg.min <sup>-1</sup>	$14.8 \pm 5.0$
	VE/VCO <sub>2</sub> slope	$32.2 \pm 8.3$

Maximal workload, w

### $74.4\pm37.5$

NYHA, New York Heart Association. VO<sub>2PEAK</sub>, peak oxygen uptake. VE/VCO<sub>2</sub>, minute ventilation-carbon dioxide production.

- 1
- 2
- The software project in National Instruments proprietary format and the tutorial are freely available for
- 3 download from the Mendeley Data repository under Creative Commons licenses ( CC BY-NC-SA 4.0).

4 Repository number: [BLINDED]. The main functions available in the EASY-EOV tool are described in Table 3.

5

6

Function	Description				
Controls					
Open file	Path indicating the file to be imported (txt file accepted).				
Channel selection	Field to change the data input according to the original data source.				
Channel descriptions	File heather. Available data for analysis and reference channels to use.				
Export data Button to copy/export data (basic stats, vVE, and cycle markers).					
Clear data Button to clear all insert data of the oscillatory cycles (nadir-peak-nadir)					
Legends Caption for the chart markings (main window and VE peak limit).					
Chart					
Full data	Top left chart for visualization of all available data.				
Exercise time	Main chart for the VE response visualization during exercise.				
Resting data	Top chart for the VE response visualization at rest.				
Standard unit	Button to fix the graph's scale (80 L.min <sup>-1</sup> vs 600 sec).				
Change the unit	Button to change the main chart unit (L.min <sup>-1</sup> or mL.min <sup>-1</sup> ).				
Adjust rest data	Field to adjust the beginning and end of the resting period (top window).				
Adjust exercise data	Field to adjust the beginning and end of the exercise (main window).				
VE peak limit	Chart displaying the amplitude boundaries used to identify EOV.				
Smoothing					
MAF	Button to activate the MAF function.				
MAF window	Field to select the MAF length (e.g., 7-cycles or other).				

EOV definition	Indicates the EOV presence according to each definition.
vVE	Calculates the minute-ventilation variability value according to original equation.
VDI	Calculates the Ventilation Dispersion Index according to original equation.

CPET, cardiopulmonary exercise test. EOV, exercise oscillatory ventilation. MAF, moving average filter. VE, minute ventilation. vVE, minute ventilation variability. SD, standard deviation. VDI, ventilation dispersion index.

-	
2	The software requires a spreadsheet with CPET raw data: time, workload, and minute-ventilation (VE).
3	Other parameters such as oxygen uptake (VO <sub>2</sub> ), carbon dioxide production (VCO <sub>2</sub> ), ventilatory equivalents for
4	oxygen (VE/VO <sub>2</sub> ) and for carbon dioxide (VE/VCO <sub>2</sub> ), and end-tidal carbon dioxide tension (PETCO <sub>2</sub> ) can be
5	available according to CPET routine. The preferred format to input data is breath-by-breath, with CPET time in
6	seconds, and VE in L.min <sup>-1</sup> .
7	Briefly, the raw data must be imported (.txt file tab-separated) and the input channels adjusted to select
8	the VE and workload channels accordingly to the .txt file columns. Afterward, the user must select the MAF
9	window size, and the CPET main data window (incremental exercise). Data processing methods were
10	implemented to identify the EOV features. Figure 2 illustrates the software interface.
11	
12 13	Fig. 2 EASY-EOV tool interface.
14	Reliability
15	From the full database, 443 files were selected according to our inclusion criteria (HF patients). Of
16	them, 51 records did not present values at resting making the application of two definitions unfeasible, and one
17	test fail to register the VE response. Therefore, 391 tests were analyzed in duplicate (inter-rater reliability) and
18	100 tests were randomized for new analysis (intra-rater reliability). Table 4 presents the inter and intra-rater
19	reliability measures for each EOV definition.
20	
21	Table 4         Reliability measure for the exercise oscillatory ventilation identification
	Definition Inter-rater ( $\kappa$ ) Intra-rater ( $\kappa$ )
	n = 391 $n = 100$

	EOV prevale	ence		EOV prevalence		
	Reviewer 1	Reviewer 2	Reliability	Reviewer 1a	Reviewer 1b	Reliability
Ben-Dov et al. [8]	<mark>59 (15.1)</mark>	<mark>59 (15.1)</mark>	$0.92\pm0.03$	17 (17.0)	14 (14.0)	$0.87\pm0.07$
Corrà et al. [11]	58 (14.8)	48 (12.3)	$0.83\pm0.04$	17 (17.0)	<mark>16 (16.0)</mark>	$0.89\pm0.06$
Kremser et al. [14]	45 (11.5)	36 (9.2)	$0.85\pm0.05$	13 (13.0)	13 (13.0)	$0.82\pm0.09$
Leite et al. [9]	29 (7.4)	<mark>26 (6.6)</mark>	$0.86\pm0.05$	7 (7.0)	<mark>5 (5.0)</mark>	$0.82\pm0.12$
Sun et al. [10]	18 (4.6)	17 (4.3)	$0.97\pm0.03$	<mark>6 (6.0)</mark>	<mark>5 (5.0)</mark>	$0.90\pm0.10$

Cohen's kappa coefficient ( $\kappa$ ). Values expressed as n (%) or mean  $\pm$  standard-deviation.

1

## 2 **Discussion**

3 This is the first study that developed a freely available semi-automated tool to standardize the clinical 4 diagnosis of EOV in HF. The EASY-EOV tool automatically calculates the h,  $\lambda$ , and  $\Delta t$ , besides indicates the 5 EOV presence after users manually marks the beginning, peak, and end of each cycle. Our data indicate high 6 inter-rater and intra-rater agreement for EOV diagnosis. This offers new resources and possibilities for 7 professionals to use this prognostic marker in clinical practice. 8 To automate EOV analysis, Cornelis et al. [8] developed a graphical interface that can be incorporated 9 exclusively into software from a research partner company. The premise was that only visual inspection could 10 cause a strong diagnostic bias, so the authors observed that the wavelet transformation smoothed the signal 11 without any data loss, incorporating it into the interface with the four most usual EOV definitions [9-12]. They 12 concluded that their approach could make the EOV diagnosis faster and more rater-independent. 13 Although this resource appears to be robust, the authors [8] pointed out that it is still necessary to test 14 its validity and reliability. In addition, Cornelis' interface seems to be for the exclusive use of the software of a 15 metabolic cart (manufacturer-dependent). This fact prevents its use in other equipment to aid in the EOV 16 diagnosis, restricting its applicability in the clinical practice of a few doctors or CPET experts who may buy that 17 application. 18 Our software does not have this specificity. It can be used with data extracted from any manufacturer's 19 system. This feature makes its use universal. In addition to allowing the export of oscillatory period data (e.g., 20 amplitude, cycle duration and total duration), the EASY-EOV tool allows the application of two approaches that

1	were recently proposals (vVE and VDI) to assess this ventilatory phenomenon – all in a single tool.
2	Furthermore, we expect to may provide free access to the tool, with an open library for possible updates.
3	Brawner et al. [15] investigated the clinical reliability of the EOV diagnosis. The authors sent
4	worksheets from 243 CPET data to six CPET experts to diagnose EOV according to three definitions [10, 14,
5	19]. They had to answer whether the tests were positive, negative, or inconclusive for EOV. Agreement between
6	raters was low ( $\kappa < 0.47$ ). In contrast, Ingle et al. [20], applying the Corrà and Leite definitions in 240 CPETs of
7	HF patients and found an intraclass correlation of 0.86 (0.82-0.89) and 0.78 (0.73-0.83), respectively. Studies
8	evaluating the intra-rater reliability were not identified. Our study demonstrated similar and superior reliability
9	data to those mentioned above and analyzed for the first time the intra-rater reliability.
10	The lack of a gold standard definition to aid in the diagnosis of this phenomenon contributes to high
11	intra- and inter-rater variability since each specialized center applies a protocol according to local expertise
12	producing numerous conceptual variations [7]. Nevertheless, our study showed high intra- and inter-rater
13	reliability using a semi-automated system. The EASY-EOV tool also mitigates methodological bias and
14	standardizes assessment protocols. In addition, this tool allows analyzing the data of any test and analyzer,
15	regardless of the system that was obtained. Our perspective is that it can be improved over the years and,
16	through new guidelines and software improvements, contribute to the implementation of this important
17	prognostic marker in clinical practice.
18	In the $\beta$ version, we provide five classic definitions to identify the EOV cases [9-12, 14], two
19	alternative techniques to quantify the fluctuations in the ventilatory pattern [15, 16], as well as other resources
20	that allow to automatically calculate different parameters and to export the report to a database. Even so, the
21	software has some limitations, such as the need for raters' training to identify the cycles, spreadsheets
22	dependency to enter the correct data into the system, the CPET time conversion may be needed (e.g., conversion
23	from standard format (hours/minutes/seconds or similar) to seconds, as well as the LabVIEW® license is
24	required.
25	

# 26 Conclusion

We describe the development of semi-automated software to standardize the clinical diagnosis of EOV,
showing high inter-and intra-rater agreement. This user-friendly interface allows greater use of this prognostic
marker in clinical practice, improving EOV detection and follow-up. As it is an open-source resource it is

- 1 possible to incorporate new features into the tool, besides automating the entire process of detecting oscillatory
- 2 cycles. These improvements can be developed by several users, benefiting all health professionals.

3

## 4 References

- 5 1. Agostoni P, Salvioni E (2019) Exertional periodic breathing in heart failure: mechanisms and clinical
- 6 implications. Clin Chest Med 40(2):449-457. http://doi.org/10.1016/j.ccm.2019.02.016
- 7 2. Ribeiro GS, Deresz LF, Salvioni E, Hansen D, Agostoni P, Karsten M (2022) Sensitivity and specificity of
- 8 different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in
- 9 chronic heart failure patients. Int J Cardiol. http://doi.org/10.1016/j.ijcard.2022.05.041
- 10 3. Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M (2022) Exercise training effects on
- 11 metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic
- 12 review and meta-analysis. Eur J Prev Cardiol 29(6):e233-e236. http://doi.org/10.1093/eurjpc/zwab195
- 13 4. Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D (2015) Prognostic respiratory parameters in
- 14 heart failure patients with and without exercise oscillatory ventilation a systematic review and descriptive
- 15 meta-analysis. Int J Cardiol 182:476-486. http://doi.org/10.1016/j.ijcard.2015.01.029
- 16 5. Guazzi M, Myers J, Peberdy M, Bensimhon D, Chase P, Arena R (2008) Exercise oscillatory breathing in
- 17 diastolic heart failure: prevalence and prognostic insights. Eur Heart J 29(22):2751-2759.
- 18 http://doi.org/10.1093/eurheartj/ehn437
- 19 6. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga, et al (2007) Exercise oscillatory
- 20 ventilation may predict sudden cardiac death in heart failure patients. J Am Coll Cardiol 50(4):299-308.
- 21 http://doi.org/10.1016/j.jacc.2007.03.042
- 22 7. Cornelis J, Beckers P, Vanroy C, Volckaerts T, Vrints C, Vissers D (2015) An overview of the applied
- 23 definitions and diagnostic methods to assess exercise oscillatory ventilation a systematic review. Int J Cardiol
- 24 190:161-169. http://doi.org/10.1016/j.ijcard.2015.04.111
- 8. Cornelis J, Denis T, Beckers P, Vrints C, Vissers D, Goossens M (2017) Development of a clinical applicable
- 26 graphical user interface to automatically detect exercise oscillatory ventilation: The VOdEX-tool. Int J Cardiol
- 27 240:291-296. http://doi.org/10.1016/j.ijcard.2016.12.159
- 28 9. Ben-Dov I, Sietsema K, Casaburi R, Wasserman K (1992) Evidence that circulatory oscillations accompany
- ventilatory oscillations during exercise in patients with heart failure. Am Rev Resp Dis 145(4):776-781.
- 30 http://doi.org/10.1164/ajrccm/145.4\_pt\_1.776
- 31 10. Leite J, Mansur A, Freitas H, Chizola P, Bocchi E, Terra-Filho, et al (2003) Periodic breathing during
- 32 incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac
- 33 transplantation. J Am Coll Cardiol 41(12):2175-2181. http://doi.org/10.1016/S0735-1097(03)00460-1
- 34 11. Sun X, Hansen J, Beshai J, Wasserman K (2010) Oscillatory breathing and exercise gas exchange
- abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol 55(17):1814-1823.
- 36 http://doi.org/10.1016/j.jacc.2009.10.075

- 1 12. Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats A, et al (2002) Oscillatory ventilation
- 2 during exercise in patients with chronic heart failure: Clinical correlates and prognostic implications. Chest
- 3 121(5):1572-1580. http://doi.org/10.1378/chest.121.5.1572
- 4 13. Smith S (2003) Digital signal processing. A practical guide for engineers and scientists. Burlington,
- 5 Newnes Elsevier.
- 6 14. Kremser C, O'Toole M, Leff A (1987) Oscillatory hyperventilation in severe congestive heart failure
- 7 secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. Am J Cardiol 59(8):900-905.
- 8 15. Brawner C, Ehrman J, Myers J, Chase P, Vainshelboim B, Farha S, et al (2018) Exercise oscillatory
- 9 ventilation: interreviewer agreement and a novel determination. Med Sci Sports Exerc 50(2):369-374.
- 10 http://doi.org/10.1249/mss.00000000001423
- 11 16. Castro R, Lima S, Sales A, Nobrega A (2017) Minute-ventilation variability during cardiopulmonary
- 12 exercise test is higher in sedentary men than in athletes. Arq Bras Cardiol 109(3):185-190.
- 13 http://doi.org/10.5935/abc.20170104
- 14 17. Mokkink L, Prinsen C, Bouter L, Cecilia A, Bouter L, Vet H, Terwee C (2016) The COnsensus-based
- 15 Standards for the selection of health Measurement INstruments (COSMIN) and how to select an outcome
- 16 measurement instrument. Braz J Phys Ther 20:105-113. http://doi.org/10.1590/bjpt-rbf.2014.0143
- 17 18. McHugh M. Interrater reliability: the kappa statistic (2012) Biochem Med 22(3):276-282.
- 18 19. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, et al (2012) Clinical recommendations
- 19 for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 126(18):2261-
- 20 2274. http://doi.org/10.1161/CIR.0b013e31826fb946
- 20. Ingle L, Isted A, Witte KK, Cleland J, Clark A (2009) Impact of different diagnostic criteria on the
- 22 prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure.
- 23 Eur J Cardiovasc Prev Rehabil 16(4):451-456. http://doi.org/10.1097/HJR.0b013e32832a4f54

## Figure 1S

### **Experimental design**



**Figure 1S.** Experimental design. Phase 1 (internal consistency): cyclical process between software development and looking for errors in programming; when any programming conflict was identified, the file was sent to the development phase. Phase 2 (EOV diagnosis): two blinded raters used the developed tool to analyze CPETs from the database. Phase 3 (reliability analysis): inter and intra-rater agreement to EOV-positive and EOV-negative. CPET, cardiopulmonary exercise test. EOV, exercise oscillatory ventilation.

# Figure 2S

## LabView programming code



Figure 2S. Code sample used for Ben-Dov definition on the LabView.



