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Software Development to Standardize the Clinical Diagnosis of Exercise Oscillatory Ventilation in Heart Failure

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Abstract

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

Methods: The software was developed in the "drag-and-drop" G-language using LabVIEW®. Five EOV definitions (Ben-Dov, Corrà, Kremser, Leite, and Sun definitions), two alternative approaches, one smoothing technique, and some basic statistics were incorporated into the interface to visualize four charts of the ventilatory response. EOV identification was based on a set of criteria verified from the interaction between amplitude, cycle length, and oscillation time. Two raters analyzed the datasets. In addition, repeated measurements were verified after six months using about 25% of the initial data. Cohen's kappa coefficient (κ) was used to investigate the reliability.

Results: Overall, 391 tests were analyzed in duplicate (inter-rater reliability) and 100 tests were randomized for new analysis (intra-rater reliability). High inter-rater ($\kappa > 0.80$) and intra-rater ($\kappa > 0.80$) reliability of the five EOV diagnoses were observed.

Conclusion: The present study proposes novel semi-automated software to detect EOV in HF, with high inter and intra-rater agreements. The software project and its tutorial are freely available for download.

Keywords

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

Statements and Declarations

Conflict of Interest: The authors declare that there is no conflict of interest.

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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 ($\dot{V}O_{2.peak}$) and ventilatory efficiency ($VE/\dot{V}CO_2$ slope) [5, 6].

Although the prognostic value is clinically relevant, this marker is not commonly used in clinical practice due to the absence of consensus on the best EOV definition [2, 4, 7], and the lack of standardized data processing techniques. Cornelis et al. [7] highlighted at least nine conceptual variations to identify EOV by the combination of different characteristics of the VE response during CPET: amplitude (h), cycle length (λ), and oscillation time (Δt). Furthermore, the EOV identification depends on the manual data calculation or visual interpretation of the VE response, impacting the diagnosis reliability due to the inter-rater variability [7].

Cornelis et al. [8] developed a graphical interface to automatically detect the ventilatory pattern characteristic of EOV. Different smoothing techniques were applied to remove noise from the breath-by-breath VE signals and the four most common EOV definitions were included in this interface [9-12]. The EOV diagnosis has become faster and less affected by the inter-rater variation. Even though this was a precursor initiative for standardizing EOV identification, it is not clear whether this tool will be made available to manufacturers of all metabolic carts, or if it will be available for a broader application.

To better incorporate the EOV assessment into clinical practice and spread its applicability, we believe that it is necessary to simplify its analysis and improve the inter-rater agreement. Therefore, this study aims to develop a semi-automated tool to standardize the identification of EOV from the CPET exported raw data and test its reliability (intra- and inter-rater). We hypothesize that our tool will be able to support the EOV identification and show a good inter-rater agreement improving the evaluation and follow-up of EOV patients.

Methods

Study design

This cross-sectional study based on retrospective data was approved by the local ethics committee (referee 3.516.801/2019 and 4.558.550/2021). A novel resource was developed to standardize the EOV diagnosis. Data from 500 CPETs performed in a specialized center were selected to initial screening. Only data from HF patients were used to test the tool's reliability (inclusion criteria). Records with exercise time lower than six minutes or resting time lower than 90 seconds were excluded from the analysis for making two EOV definitions unfeasible (exclusion criteria). All CPETs used a personalized ramp protocol on an electronically braked cycle ergometer (Erg 800S; Sensor Medics, Yorba Linda, CA) with breath-by-breath analysis (Vmax 12-3A Series, CareFusion, Yorba Linda, CA).

The experimental design was composed of three phases: 1) Internal consistency: cyclical process between software development and looking for errors in programming. The file was returned to the development phase if any programming conflict was identified during the tool application on selected data. 2) EOV diagnosis: two blinded raters used the developed tool to analyze CPETs from the database; 3) Reliability analysis: inter and intra-rater agreement to EOV-positive and EOV-negative. Figure 1S illustrates the study design (supplementary material). All procedures were done according to current ethical recommendations.

Software development

The software was developed using "drag-and-drop" G-language in the LabVIEW® 2014 (National Instruments Corp®, Texas, US), and was named "EASY-EOV tool". All commands from LabVIEW are freely available for download in the online repository [BLINDED]. The EASY-EOV tool was updated whenever an inconsistency in the simulated tests was observed (see *Internal consistency* section). The major features available are graphic visualization of the ventilatory pattern – at rest and exercise, data smoothing technique, EOV diagnosis in a semi-automated way, alternative approaches to assessing EOV, basic statistics, and data export to further analysis. Figure 2S shows an example of code used in LabView programming.

Ventilatory pattern

Four charts are available in the system: one to view the full VE response (rest, warm-up, exercise, and recovery) and another three to view exercise time, resting period, and the amplitude's borderline of each cycle. Only the main chart (exercise time) allows the ventilatory pattern characteristics to be demarcated as exposed in Figure 1 (nadir-peak-nadir). Figure 1 illustrates a typical EOV pattern, and its main characteristics [2, 3, 7]. The resting period is used to adjust the VE value used in two EOV definitions [12, 14]. The amplitude's borderline chart helps the user to visualize which cycles meet the recommended limit of 15% of VE at rest – red line [12, 14] or 5 $L.min^{-1}$ [10] – green line.

Fig. 1 Minute ventilation (VE) response of an HF EOV-positive patient during the CPET. A, beginning cycle (nadir). B, the peak of the cycle (peak). C, end cycle (nadir). h, amplitude cycle: the difference between the peak of the VE cycle and its baseline (a line between two consecutive nadirs). λ, cycle´s length: distance between two consecutive nadirs (e.g.: A and C). Δt, and oscillation time: total oscillation period during the CPET.

Smoothing technique

Moving average filter (MAF) is a consolidated data pre-processing method to reduce the high-frequency noise influences over the VE data [13], facilitating the cycle identification. The MAF window size can be selected by the user according to guidelines or center expertise (e.g., 5 to 30 breaths).

$$MAF = \left(\dot{V}E_{(i)} + \dot{V}E_{(i+1)} + \cdots + \dot{V}E_{(i+M)}\right) \div M \quad (1)$$

where $\dot{V}E_{(i)}$ is initial data of minute ventilation and M is the number of points in the average. For example, $\dot{V}E_{(i)}$ 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 moving (rolling) average filter was adopted.

EOV identification

The EOV identification was based on a set of criteria verified from the interaction between h, λ and Δt [9-12]. The user must manually mark the beginning, peak, and end of each cycle (nadir-peak-nadir triad) in the exercise chart (EASY-EOV tool demo - supplementary material). After that, the EASY-EOV tool automatically calculates the h, λ and Δt, and the algorithm classifies periodic ventilation following the definition of Corrà [12], Kremser [14], Ben-Dov [9], Leite [10], and Sun [11]. These criteria are summarized in Table 1.

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 ≥ 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 ≥ 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.

Alternative approaches

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

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

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 the second to last exercise interval ($i = \mathrm{N} - 1$).

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

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

Measurement properties

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

Internal consistency

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

Inter-rater agreement

Two independent raters (GSR and LFC) used the software interface and visually labelled the beginning and end of the VE cycles during the CPET. After that, the EASY-EOV tool automatically indicated the EOV presence following the EOV definitions (Table 1), besides calculating the VDI and vVE. Standardized recommendations of how to use the software were given to the CPET-experienced researchers. Both had a training period to standardize the use of the software. All notes were sent to the principal investigator for agreement analysis (positive cases in each definition). The VDI and vVE are automatically calculated from the whole uploaded data set (evaluator independent). Due to this, these indexes were not submitted to an agreement analysis.

Intra-rater agreement

The intra-rater (GSR) agreement was verified after six months of the first screening. An online service (https://www.randomizer.org/) was used to randomize a subset of 100 CPETs previously analyzed [17]. All notes were sent to the principal researcher (MK) to evaluate the agreement.

Results

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

Table 2 Clinical characteristic from the database

Sample size, n	391
Male gender, n (%)	307 (78.5)
Age, years	66.2 ± 11.0
NYHA class III-IV, n (%)	161 (41.2)
Left ventricular eject fraction, %	33.4 ± 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_{2PEAK}, ml.kg.min^{-1}	14.8 ± 5.0
VE/VCO_2 slope	32.2 ± 8.3

Maximal workload, w	74.4 ± 37.5

NYHA, New York Heart Association. VO_{2PEAK}, peak oxygen uptake. VE/VCO_2, minute ventilation-carbon dioxide production.

The software project in National Instruments proprietary format and the tutorial are freely available for download from the Mendeley Data repository under Creative Commons licenses (CC BY-NC-SA 4.0). Repository number: [BLINDED]. The main functions available in the EASY-EOV tool are described in Table 3.

Table 3 Available features in the EASY-EOV tool

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 $L.min^{-1}$ vs 600 sec).
Change the unit	Button to change the main chart unit ($L.min^{-1}$ or $mL.min^{-1}$).
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).
Results	

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.

The software requires a spreadsheet with CPET raw data: time, workload, and minute-ventilation (VE). Other parameters such as oxygen uptake (VO_2), carbon dioxide production (VCO_2), ventilatory equivalents for oxygen (VE/VO_2) and for carbon dioxide (VE/VCO_2), and end-tidal carbon dioxide tension ($P_{ET}CO_2$) can be available according to CPET routine. The preferred format to input data is breath-by-breath, with CPET time in seconds, and VE in $L.min^{-1}$.

Briefly, the raw data must be imported (.txt file tab-separated) and the input channels adjusted to select the VE and workload channels accordingly to the .txt file columns. Afterward, the user must select the MAF window size, and the CPET main data window (incremental exercise). Data processing methods were implemented to identify the EOV features. Figure 2 illustrates the software interface.

Fig. 2 EASY-EOV tool interface.

Reliability

From the full database, 443 files were selected according to our inclusion criteria (HF patients). Of them, 51 records did not present values at resting making the application of two definitions unfeasible, and one test fail to register the VE response. Therefore, 391 tests were analyzed in duplicate (inter-rater reliability) and 100 tests were randomized for new analysis (intra-rater reliability). Table 4 presents the inter and intra-rater reliability measures for each EOV definition.

Table 4 Reliability measure for the exercise oscillatory ventilation identification

Definition	Inter-rater (κ) n = 391	Intra-rater (κ) n = 100

	EOV prevalence			EOV prevalence		
	Reviewer 1	Reviewer 2	Reliability	Reviewer 1a	Reviewer 1b	Reliability
Ben-Dov et al. [8]	59 (15.1)	59 (15.1)	0.92 ± 0.03	17 (17.0)	14 (14.0)	0.87 ± 0.07
Corrà et al. [11]	58 (14.8)	48 (12.3)	0.83 ± 0.04	17 (17.0)	16 (16.0)	0.89 ± 0.06
Kremser et al. [14]	45 (11.5)	36 (9.2)	0.85 ± 0.05	13 (13.0)	13 (13.0)	0.82 ± 0.09
Leite et al. [9]	29 (7.4)	26 (6.6)	0.86 ± 0.05	7 (7.0)	5 (5.0)	0.82 ± 0.12
Sun et al. [10]	18 (4.6)	17 (4.3)	0.97 ± 0.03	6 (6.0)	5 (5.0)	0.90 ± 0.10

Cohen's kappa coefficient (κ). Values expressed as n (%) or mean ± standard-deviation.

Discussion

This is the first study that developed a freely available semi-automated tool to standardize the clinical diagnosis of EOV in HF. The EASY-EOV tool automatically calculates the h, λ, and Δt, besides indicates the EOV presence after users manually marks the beginning, peak, and end of each cycle. Our data indicate high inter-rater and intra-rater agreement for EOV diagnosis. This offers new resources and possibilities for professionals to use this prognostic marker in clinical practice.

To automate EOV analysis, Cornelis et al. [8] developed a graphical interface that can be incorporated exclusively into software from a research partner company. The premise was that only visual inspection could cause a strong diagnostic bias, so the authors observed that the wavelet transformation smoothed the signal without any data loss, incorporating it into the interface with the four most usual EOV definitions [9-12]. They concluded that their approach could make the EOV diagnosis faster and more rater-independent.

Although this resource appears to be robust, the authors [8] pointed out that it is still necessary to test its validity and reliability. In addition, Cornelis' interface seems to be for the exclusive use of the software of a metabolic cart (manufacturer-dependent). This fact prevents its use in other equipment to aid in the EOV diagnosis, restricting its applicability in the clinical practice of a few doctors or CPET experts who may buy that application.

Our software does not have this specificity. It can be used with data extracted from any manufacturer's system. This feature makes its use universal. In addition to allowing the export of oscillatory period data (e.g., amplitude, cycle duration and total duration), the EASY-EOV tool allows the application of two approaches that were recently proposals (vVE and VDI) to assess this ventilatory phenomenon – all in a single tool. Furthermore, we expect to may provide free access to the tool, with an open library for possible updates.

Brawner et al. [15] investigated the clinical reliability of the EOV diagnosis. The authors sent worksheets from 243 CPET data to six CPET experts to diagnose EOV according to three definitions [10, 14, 19]. They had to answer whether the tests were positive, negative, or inconclusive for EOV. Agreement between raters was low (κ <0.47). In contrast, Ingle et al. [20], applying the Corrà and Leite definitions in 240 CPETs of HF patients and found an intraclass correlation of 0.86 (0.82-0.89) and 0.78 (0.73-0.83), respectively. Studies evaluating the intra-rater reliability were not identified. Our study demonstrated similar and superior reliability data to those mentioned above and analyzed for the first time the intra-rater reliability.

The lack of a gold standard definition to aid in the diagnosis of this phenomenon contributes to high intra- and inter-rater variability since each specialized center applies a protocol according to local expertise producing numerous conceptual variations [7]. Nevertheless, our study showed high intra- and inter-rater reliability using a semi-automated system. The EASY-EOV tool also mitigates methodological bias and standardizes assessment protocols. In addition, this tool allows analyzing the data of any test and analyzer, regardless of the system that was obtained. Our perspective is that it can be improved over the years and, through new guidelines and software improvements, contribute to the implementation of this important prognostic marker in clinical practice.

In the β version, we provide five classic definitions to identify the EOV cases [9-12, 14], two alternative techniques to quantify the fluctuations in the ventilatory pattern [15, 16], as well as other resources that allow to automatically calculate different parameters and to export the report to a database. Even so, the software has some limitations, such as the need for raters' training to identify the cycles, spreadsheets dependency to enter the correct data into the system, the CPET time conversion may be needed (e.g., conversion from standard format (hours/minutes/seconds or similar) to seconds, as well as the LabVIEW® license is required.

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

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Figure 1S

Experimental design

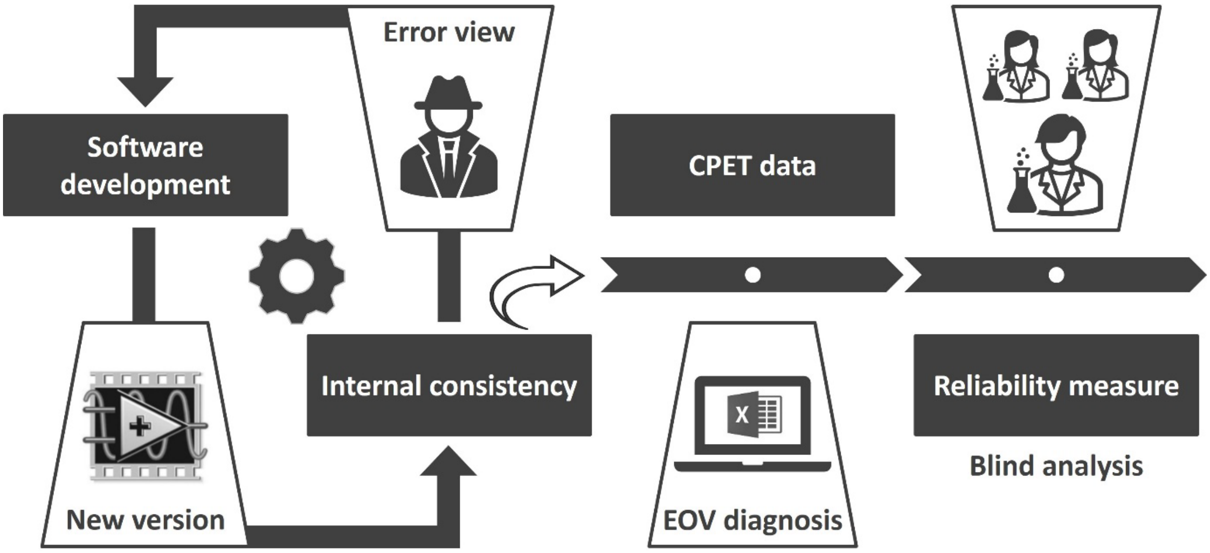


Figure 1S. Experimental design. Phase 1 (internal consistency): cyclical process between software development and looking for errors in programming; when any programming conflict was identified, the file was sent to the development phase. Phase 2 (EOV diagnosis): two blinded raters used the developed 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

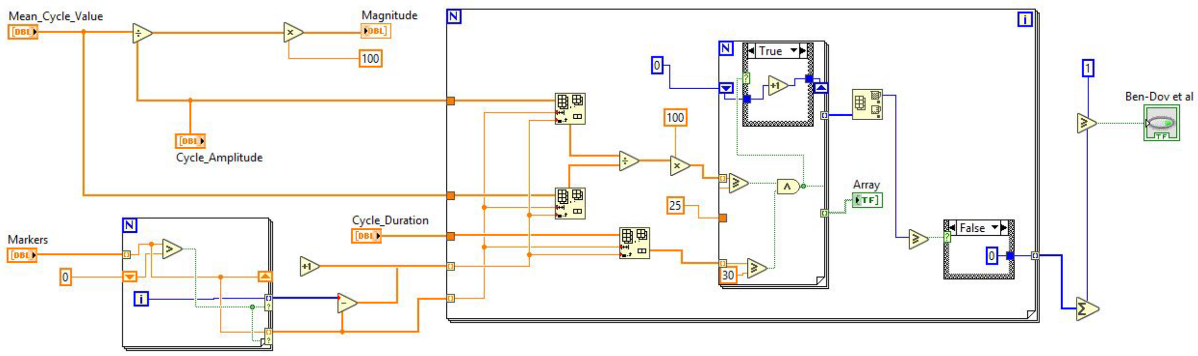
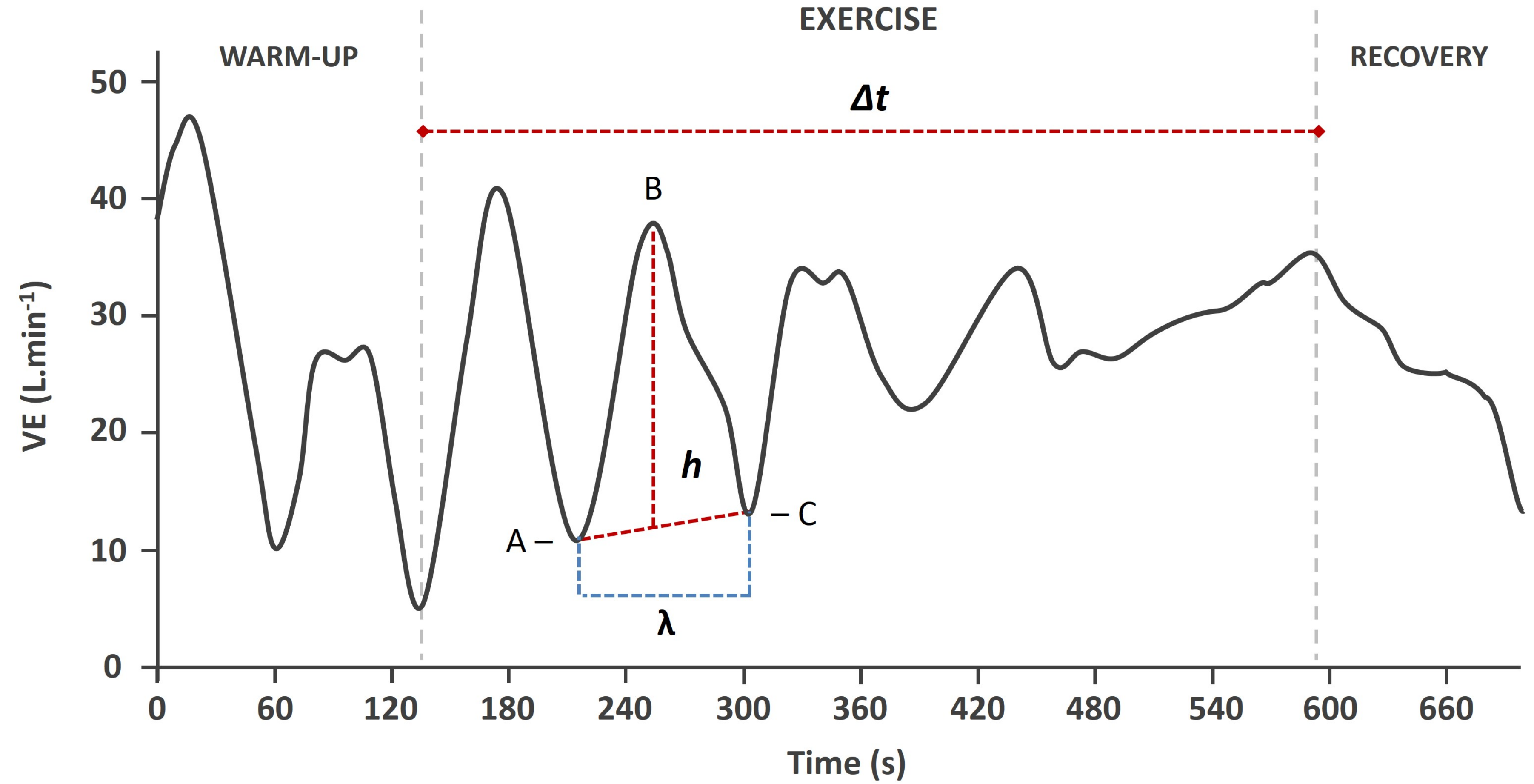
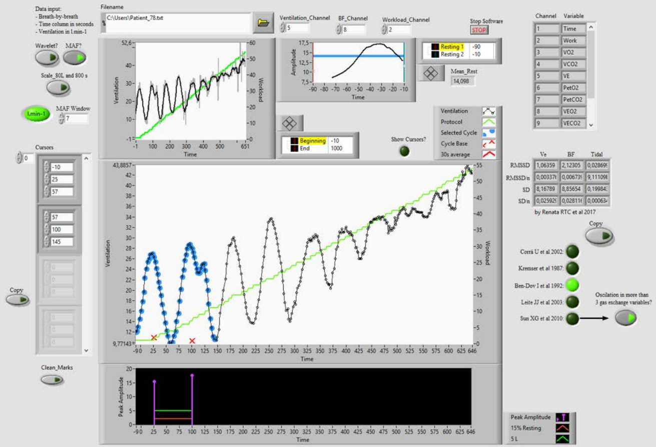


Figure 2S. Code sample used for Ben-Dov definition on the LabView.


EXERCISE
WARM-UP
RECOVERY
Δt
B
h
A
C
λ
VE (L.min-1)
0
10
20
30
40
50
0
60
120
180
240
300
360
420
480
540
600
660
Time (s)



Data input:
- Breath-by-breath
- Time column in seconds
- Ventilation in l.min-1
Filename
C:\Users\Patient_78.txt
Ventilation_Channel
5
BF_Channel
8
Workload_Channel
2
Stop Software
STOP
Channel
Variable
1 Time
2 Work
3 VO2
4 VCO2
5 VE
6 PetO2
7 PetCO2
8 VEO2
9 VECO2
Wavelet?
MAF?
Scale_80L and 800 s
l.min-1
MAF Window
7
Ventilation
Workload
Time
Amplitude
Resting 1 -90
Resting 2 -10
Mean_Rest
14,098
Beginning -10
End 1000
Show Cursors?
Ventilation
Protocol
Selected Cycle
Cycle Base
30s average
Cursors
0
-10
25
57
57
100
145
Copy
Ve
BF
Tidal
RMSSD 1,06359 2,12305 0,02869
RMSSD/n 0,00337 0,00673 9,11109
SD 8,16789 8,85654 0,19984
SD/n 0,02592 0,02811 0,00063
by Renata RTC et al 2017
Copy
Corrà U et al 2002:
Kremser et al 1987:
Ben-Dov I et al 1992:
Leite JJ et al 2003:
Sun XG et al 2010:
Oscilation in more than 3 gas exchange variables?
Clean_Marks
Peak Amplitude
Time
Peak Amplitude
15% Resting
5 L