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Determination of Ventilatory Threshold using Heart Rate Variability in Patients with Heart Failure

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Abstract

Background: The first Ventilatory Threshold (VT₁) has been shown to assess exercise tolerance and help in the exercise rehabilitation prescription of Chronic Heart Failure patients (CHF). However, VT₁ cannot always be detected in CHF by classical methods. Previous investigations revealed that the assessment from Heart Rate Variability (HRV) analysis gives an accurate estimation of VT₁ in trained subjects.

Objectives: This study proposed to examine whether HRV analysis could help in VT₁ determination in CHF.

Methods: 18 CHF patients (12 males and 6 females, age: 62 ± 13 years, weight: 73 ± 17 kg, left ventricular ejection fraction: 0.32 ± 0.7 , VO₂peak: 1.3 ± 0.4 L.min⁻¹) performed a Cycle Incremental Exercise (CPX testing). Beat-to-beat RR interval, Oxygen Uptake (VO₂), carbon production (VCO₂) and minute ventilation (V_E) were collected during the test. VT₁ corresponded to the last point before a first non-linear increase in both V_E and V_E/VO₂. Time (RMSSD) and time-frequency (HFp) domain indices, both extrapolated from the RR time series were calculated.

Results: A marked RMSSD and HFp deflection points were found in the region of VT₁, and were identified as Variability Heart Rate Thresholds (HRVT). No significant difference was found between VT₁ and both HRVT (p<0.05) in terms of VO₂, heart rate values and exercise intensity. Correlations between the different measures ranged from 0.97 to 0.99 providing a strong agreement between all methods (Bland and Altman's method).

Conclusions: These data reveal that HRV analysis using time-frequency indices during CPX testing can provide a useful alternative to the classical VT, determination in CHF patients.

Keywords: First ventilatory threshold; Heart rate variability; Rehabilitation; Chronic heart failure

Introduction

Aging-related cardiac remodeling predisposes elderly patients to heart disease. Significant growth in the elderly population (age \geq 65 years) with Heart Failure (HF) has taken place in developed countries and is occurring in most developing countries [1]. HF is a chronic disease that results in substantial morbidity, mortality and expenditure of health care resources [2]. Current management options for HF included primary [3] and secondary preventions [4]. In the latter, exercise rehabilitation has the potential to increase exercise performance and improve the quality of life of HF patients with or without associated pathologies [5]. However, a multicenter, randomized controlled trial among 2331 HF patients (left ventricular ejection fraction ≤ 0.35) showed a modest significant improvement in self-reported health status with aerobic exercise training compared with usual care without exercise training [6]. Several training programs [7], different exercise modalities (strength, resistance, aerobic endurance exercise performed at constant load intensity or with interval training) and intensity prescription [8-10], but also the difficulty to determine exercise intensity [11] may explain the lack of large improvements in HF with exercise rehabilitation.

Generally, exercise capacity was evaluated during Cardiopulmonary Exercise Testing (CPX) [12]. Peak oxygen uptake (VO₂ peak) [13] but also ventilatory equivalent for carbon dioxide (V_E/VCO_2) slope [14] were the most powerful prognostic parameters obtained in HF patients during CPX testing [12]. First ventilatory threshold (VT₁) was also determined to predict mortality [15] and prescribe aerobic endurance training intensity [16]. VT₁ was classically defined as the point at which the ventilatory equivalent for oxygen (V_E/VO_2) reached the nadir then progressively increased due to relative carbon dioxide production (VCO₂) [17,18]. Although no significant effects of beta-

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blocking agents were found for absolute and relative values of VO₂, power output and Ratings of Perceived Exertion (RPE) at VT [19,20], methods of determination [11], modes of testing [8] or gender [13] may interact on classically VT, identification in HF patients. Opasich et al. [13] reported that VT, was detected in only 28.3% of females (26 of 92 subjects) compared to 64% of males (324 of 505 patients) presented with HF. Kemps et al. [21] also unsuccessfully determined the VT₁ in 9% of 48 patients with HF. Other methods based themselves on the blood lactate concentration or RPE score. In the absence of gas exchange analyzers, VO, at VT can be determined by invasive lactate blood samples [17,18]. In their review, Hansen et al. [22] underlined that VT, and Anaerobic Threshold (AT) are used interchangeably in the literature. They nevertheless reported a wide range (from 58 to 75 % of VO, peak) in AT determination and so a significant difference in heart rate value according to the method used [22]. Zanettini et al. [23] also reported that Self-regulation of exercise intensity based on BORG score was associated to higher heart rate values than VT, workload.

Recently, Cottin et al. [24], Karapetian et al. [25] and Sales et al. [26] proposed a new method for assessing first and second ventilatory

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thresholds from Heart Rate Variability (HRV) analysis. Based on relationship between beat-to-beat R-R intervals, parasympathetic nerve activation and sinus arrhythmia [27], these authors showed a strong agreement between respiratory adjustments and the responses of different index derived from the analysis of R-R time series using a combination of time-frequency [24] or time [25] domains. Generally used for prognosis [28], HRV can be characterized by a series of rhythms including the fundamental frequency and the respiratory sinus arrhythmia (0.12-0.16 Hz). Quantitative measurement of the fundamental frequency and the respiratory sinus arrhythmia can yield important preventative and diagnostic information about the heart, the autonomic nervous system, as well as the ventilatory response to exercise [24-26].

Therefore, the aim of this study was to determine if changes in heart rate variability during cardiopulmonary testing could be used to determine first ventilatory threshold in patients presented with heart failure. We hypothesized that time-frequency or time domain indices on R-R time series could help determine VT₁ in heart failure subjects.

Methods

Subjects

Eighteen patients recently hospitalized for chronic heart failure (CHF, 12 males and 6 females) participated in this study. All presented a Left Ventricular Ejection Fraction (LVEF) equal to 0.32 ± 0.7 . Their physical characteristics (mean \pm SD) were: age 62.0 ± 13.0 years, height 165.0 ± 8.0 cm and mass 73.0 ± 17.0 kg. Each subject was habituated to the experimental procedures prior to the study and did not present any contraindication for exercise rehabilitation. Before participation, subjects were informed of the risks and stresses associated with the protocol and gave their written informed consent in accordance with the ethics guidelines of the University of Picardie Jules Verne and the Principles of Ethical Publishing in the International Journal of Cardiology [29].

Protocol

Two to three hours after a light breakfast, all subjects performed an incremental exercise test in the upright position on an electronically braked ergo meter (ERGOLINE 900, Schiller Medical SAS, Bussy St. Georges, France) in an air-conditioned room (Temperature: 20.3°C, Relative humidity: ~35.0% and Atmospheric pressure: ~762 mmHg). Seat and handlebar heights were set for each subject according to their personal preferences. After 3 minutes at rest and 3-min warm-up at 20 watts, each subject performed a 1-min stage incremental exercise test to volitional exhaustion with 10 watts work increment for total exercise duration not exceeding 20 minutes [30]. The patients were encouraged to exercise to exhaustion, intolerable leg fatigue, or dyspnea. A Respiratory Exchange Ratio (RER) >1.0, the attainment of at least 70% or 85% of predicted maximal values of heart rate and VO₂, respectively, were considered to be an indication of a nearly maximal effort. The subject was stopped if one or several of the following anomalies were detected: drop in systolic blood pressure despite an increase in workload, increasing angina pain, ataxia, dizziness, cyanosis or pallor, serious arrhythmias and ST segment depression [31]. Due to its effects on heart rate - power slope [32] and HRV responses [33], the pedaling frequency was freely chosen by subjects between 60 and 70 revolutions. min⁻¹ and was maintained constant at all times.

Data collection procedures

Breathing Frequency (RF), Tidal Volume (V_T), Ventilation (V_E), Oxygen uptake (VO₂) and carbon dioxide production (VCO₂) were

measured at rest and throughout exercise using a fixed gas analyser (V_{max} sensormedics, Yarba Linda, California, USA) which was calibrated in accordance with the manufacturer instructions. The software of each device was set to automatically eliminate ectopic values and average the data every 5-seconds. The peak oxygen uptake value (VO₂ peak) and the lowest power associated that elicited VO₂ peak (pVO₂ peak) was defined as previously proposed [34]. In addition, Heart Rate (HR) was recorded beat-to-beat continuously (RS800, Polar Electro, Kimpele, Finland) [35]. After the separation of beat-to-beat intervals (RR intervals) by stage, the data were filtered automatically to remove missing or premature beats (Polar ProTrainer 5, Polar electro, Kimpele, Finland). An RR interval was considered as a premature beat if it deviated from the previous qualified interval by >30% [12]. The data were also visually inspected. Finally, HR data were averaged over every breath.

First ventilatory threshold and cardiac thresholds determination

First Ventilatory Threshold (VT,) was determined from the time course curves of V_E/VO₂, V_E/VCO₂ and end-tidal PCO₂ (PETCO₂). VT, corresponded to the last point before a first non-linear increase in V_F/VO₂ whereas V_F/VCO₂ and PETCO₂ remained relatively constant [17,18]. Heart rate variability was analyzed using time domain (RMSSD, the root mean square of the successive differences between adjacent RR intervals) and frequency domain (high frequency energy, HF, frequency range: 0.15 - 0.5 Hz) indices. These approaches were chosen because they used the same type of visual technique used to determine first ventilatory threshold [24-26]. Firstly, to determine the cardiac threshold, the RMSSD and the HF power (HFp) of RR intervals for each stage of exercise were graphically plotted against work rate. A marked RR interval turn point was identified as the Heart Rate Variability Threshold (HRVT) [25]. The evaluation was based on a time-frequency analysis method. This method allows observation of the evolution of the HFp and RMSSD over time, using the freeware Kubios software (Analysis Software 2.0, Kuopio, Finland). VT, and cardiac thresholds were graphically determined by three independent, experienced researchers in blind conditions [36]. If all investigators agreed (VO₂ results within 100 mL.min⁻¹), simple averaging was done [16]. If they disagreed, they discussed their results and compared to the results with the automatic VT₁ detection based on computed V-slope method during the graded exercise test [17]. Finally, there were no indeterminate VT₁.

Statistical methods

Descriptive statistics were expressed as means and Standard Deviations (SD). Measures of Skweness, Kurtosis and the Fisher-Snedecor test were used to verify the normality and homogeneity of the data. Two-way analysis of variance was used to compare the heart rate in the VT₁ and the heart rate in HRVT (VT₁ vs. HRVT-RMSSD, VT₁ vs. HRVT-HFp and HRVT-RMSSD vs. HRVT-HFp). Furthermore, the relationships between power, VO₂ and heart rate values at the VT₁ and both cardiac thresholds were assessed using a spreadsheet [37]. Briefly the spreadsheet used linear regression to assess the agreement for both raw and log transformed data and provided measures of bias and its 95% confidence limits. The spreadsheet also provided the Pearson's correlation coefficient (r) and coefficient of determination (r²) for measured variables. Limits of agreement were used to assess the agreement between threshold determination methods [38]. The statistical significance (alpha) level was set at p<0.05.

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Page 3 of 6

Results

The maximal heart rate and VO₂ values in the graded exercise test were 120 ± 23 beat.min⁻¹ and 1327 ± 400 mL.min⁻¹ (69.5 ± 21.4 % of predicted peak of VO₂) occurring at a maximum power output of 85 \pm 23 W. VT, in the graded exercise test occurred at a power output of 40.3 \pm 15.0 W, i.e. 59.9 \pm 14.5% of VO, peak. VO, and HR values associated at VT, were 782 \pm 288 mL.min⁻¹ and 97.0 \pm 18.0 beats.min⁻¹ ¹ (i.e. 80.8 \pm 20.0% of HR_{max}), respectively. No significant differences were found in power, VO, and HR values between VT, HRVT-RMSSD and HRVT-HFp methods (Table 1) [39]. Pearson correlation analysis indicated significant relationships between VT₁ and HRVT-RMSSD; power (r=0.97, p<0.01), VO₂ (r=0.99, p<0.01) and HR (r=0.99, p<0.01). Residual analysis, illustrated in figures 1A and 2A, indicates a strong agreement between VT1 and HRVT-RMSSD methods in terms of power, VO₂ and HR values (Table 1). Mean bias between VT₁ and HRVT-RMSSD was -3.5% for power (ranged from -5.4 to 0.8 watts), -2.9% for VO, (ranged from -8.0 to 1.0 mL.min⁻¹) and -1.2% for HR (ranged from -4.8 to 0.8 beat.min⁻¹). High correlations were also found between VT₁ and HRVT-HFp in power (r=0.92, p<0.01), VO₂ (r=0.98, p<0.01) and HR (r=0.98, p<0.01) (Table 1). The correlation for power, VO2 and HR values associated at VT1 and HRVT-HFp showed a strong agreement, which was confirmed by Bland-Altman analysis (Figures 1B and 2B). Mean bias between $\mathrm{VT_1}$ and HRVT-HFp was equal to 1.1% of power (ranged from -0.2 to -0.1 watts), -2.3% of VO₂ (ranged from -3.0 to -1.0 mL.min⁻¹) and -0.4% of HR (ranged from -2.2 to 3.1 beat. min⁻¹), respectively (Table 2).

Discussion

The aim of this study was to determine if changes in Heart Rate Variability (HRV) during cardiopulmonary testing could help determine first ventilatory threshold (VT,) in patients presented with Heart Failure (HF). Our main result showed a good agreement between VT, and both cardiac thresholds (i.e HRVT-RMSSD and HRVT-HFp) in terms of power, VO, and HR values. The Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation Committee for Science Guidelines recommend a minimum of 30 min per session of moderate intensity aerobic activity, on most days of the week, or at least three to four times per week [4]. Generally, maximal graded tests are performed to measure aerobic capacity and prescribe exercise intensity [18]. In addition, VO, peak and VT, are usually considered as non-invasive indices of exercise training. Classically, detecting the VT₁ is based itself on gas exchange analysis [17,18]. Gaskill et al. [40] demonstrated that combined ventilatory equivalencies, excess CO, production and the modified V-slope method were valid and reliable for VT, determination in 185 males with different training status (from sedentary to aerobic endurance athletes). However, specific metabolic responses to exercise [14] but also the variety of methods used [16] may explain the greater difficulty to determine VT1 in HF patients compare to normal subjects [11]. Furthermore, exercise testing mode (cycling vs. treadmill) could impact on oxygen uptake and heart rate responses to exercise and consequently on VT, [8]. Beckers et al. [8] showed a higher VO, and HR values at VT, during treadmill event compared to bicycle testing.

	Maximal Values	1st Ventilatory threshold (VT,)	HRVT-RMSSD threshold	HRVT-HFp threshold
Power Watts	85 ± 23	40.3 ± 15.0	43.0 ± 18.0	40.0 ± 15.0
% PMT		59.9 ± 14.5	50.6 ± 21.2	47.1 ± 20.0
Oxygen uptake				
mL.min ⁻¹	1327 ± 400	782 ± 288ª	820 ± 310 ª	790 ± 290 ª
% of maximal value	69.5 ± 21.4*	58.9 ± 21.7	61.8 ± 23.4	59.5 ± 21.8
Heart rate				
Beat.min ⁻¹	120 ± 23	97 ± 18	98 ± 20	97 ± 17
% of maximal value	75.9 ± 14.6*	80.8 ± 15.0	81.7 ± 16.7	80.8 ± 14.2

^ap<0.05: significant difference between maximal physiological values measured during incremental exercise. ^bp<0.05: significant difference between values associated at the first ventilatory threshold determined by gas exchange (VT₁) and cardiac thresholds determined in time (HRVT-RMSSD) or time-frequency (HRVT-HFp) domains. *Maximal measured data expressed in percentage of aged-predicted peak oxygen uptake and heart rate values according to Arena et al. [39]

Table 1: Mechanical power, oxygen uptake and heart rate values associated at the peak value, first ventilatory and both cardiac thresholds measured during graded test.

	Pearson correlation	Mean bias value	Lower and Upper bias values
VT₁ vs. HRVT-RMSSI)	· · · · ·	
Power watts	r=0.97	- 3.5 %	(-5.4, 0.8) watts
	(p<0.01)		
VO ₂ mL.min ⁻¹	r=0.99	-2.9 %	(-8.0, 1.0) mL.min ⁻¹
	(p<0.01)		
Heart rate			
Beat.min ⁻¹	r=0.99	-1.2 %	(-4.8, 0.8) Beat.min ⁻¹
	(p<0.01)		
VT, vs. HRVT-HFp			
Power watts	r=0.92	1.1 %	(-0.2, -0.1) watts
	(p<0.01)		
VO ₂ mL.min ⁻¹	r=0.98	-2.3 %	(-3.0, -1.0) mL.min ⁻¹
	(p<0.01)		
Heart rate			
Beat.min ⁻¹	r=0.98	-0.4 %	(-2.2, 3.1) Beat.min ⁻¹
	(p<0.01)		

Table 2: Correlations, mean bias and limits of agreement between first ventilatory threshold determined by gas exchange (VT₁) and cardiac thresholds determined in time (HRVT-RMSSD) or time-frequency (HRVT-HFp) domains.



Therefore, target heart rates and workloads used to prescribe tailored exercise training in patients with chronic heart failure based on VT, were often open to debate with the result that VO₂ peak became the preferred criterion for aerobic capacity compared to VT, in HF patients [11,13,30]. Kemps et al. [21] showed that Oxygen Uptake Efficiency Slope (OUES) and the time constant of VO₂ kinetics during recovery from sub maximal constant-load exercise (tau-rec) were determined successfully in all patients in contrast with VT, which could not be determined in 9% of their patients. Therefore, they concluded that OUES and tau-rec are useful in clinical practice for the assessment of training effects in HF patients, especially in cases of poor subject effort during symptom-limited exercise testing or when patients are unable to reach a maximal exercise level [21]. However, exhaustive exercise needs to be performed in order to reach peak oxygen uptake, which is dependent on muscular de conditioning, patient motivation and exercise testing mode [8]. Despite good agreement of VO, peak between bicycling and treadmill testing modalities, Beckers et al. [8] also reported a significant difference in absolute value without a modification of V_r/VCO₂ slope. Initially gases exchange analysis was proposed by Beaver et al. [17] to none-invasively determinate the onset of lactate excess during incremental exercise. Excess CO_2 is generated when lactate is increased during exercise because Hydronium buffering by bicarbonate. However, some factor such skeletal muscle glycogen stores, diet, site and type of blood sampling could influence the lactate levels [22]. Method could also interact on threshold determination based on blood lactate responses. Though there was agood correlation between three different methods, Dickstein et al. [41] reported a threshold determination at different percentage of VO₂ peak (from 58 to 75%) according to the method. Finally, self-regulation of exercise training intensity based on the RPE score associated at VT₁ could promote overtraining. For similar increase in aerobic capacity, Zanettini et al. [23] showed exercise prescription based on RPE induced higher mean values of training workloads and heart rate compared to exercise based on VT, determination.

In the last decade, Cottin et al. [24] and Karapetian et al. [25] have proposed to assess the ventilatory thresholds from Heart Rate Variability (HRV) analysis in athletes and healthy adults. Based on beat-to-beat R-R time series, they used RMSSD, a time domain index [25], or the high frequency peak, a cardiac index derived from



Figure 2: Bland-Altman plots of heart rate measured at the first ventilatory threshold (VT1) and cardiac threshold in time (HRVT-RMSSD, A) and time-frenquency (HRVT-HFp, B) domains. Short dash line are mean difference and dotted lines indicate upper and lower 95% limits of agreement.

Page 5 of 6

time frequency analysis [24], to determine cardiac threshold. They all observed a good correlation between VT, and cardiac threshold whatever the mathematical method or exercise modalities used (kayak, cycling, running) [24,25,42]. In the present study, we did not show a significant difference between cardiac thresholds and VT₁. We also observed a good agreement between workload and heart rate values at VT, and workload and heart rate induced cardiac thresholds. Anosov et al. [42] already observed significant changes in the behavior of the instantaneous frequency of high frequency in the region of the VT,. They suggested a mechanical effect of breathing rate to the sinus node around VT₁ [42]. It has been reported controversial effects of drug therapies on ventilatory efficiency but they are unknown on HRV responses to exercise. Hence unselective beta-blocker administration (Carvedilol) induced a lower Vr/VCO2 slope compared to selective beta1-blocker (Bisoprolol) or no treatment management [43-45]. At rest, De Vecchis et al. [45] reported an adverse effect of scopolamine compared to Carvedilol, which provoked a decrease in low frequency power with no surge of total and high frequency powers. Lurje et al. [46] observed an increase in HRV in 28 patients on betablockers (Atenolol or Metoprolol). It has also been reported a positive effect of Propranolol administration on High-Frequency (HF) and Low-Frequency (LF) bands in HF patients. Acanfora et al. [47] reported that propranolol significantly reduced LF power and increased HF power, with respect to placebo. Then Propranolol reduced premature ventricular beats in patients with coronary artery disease and severe ventricular arrhythmias possibly through an improvement of cardiac autonomic regulation. Like V_v/VCO₂ slope, drug therapies induced controversial effects on main spectral indexes of HR, but our current observation and the results of recent studies [26,48,39] were in agreement with the results in healthy subjects which concluded that heart rate variability was a none invasive method to estimate VT, in individuals with metabolic or cardiac disease.

Conclusion

Based on beat-to-beat R-R intervals, our results showed a good agreement between classical VT₁ determination based on gas exchanges and cardiac thresholds. Therefore, spectral and temporal R-R time series analysis could help to determine an accurate first ventilatory threshold. Other studies will be necessary to investigate the sensitivity of the VT₁ determination from the cardiac thresholds in relation to the exercise mode (walking, swimming and cycling) and verify whether this method is transferable among HF patient whom VT₁ determination was not reliable.

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Page 6 of 6

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