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Original Article

Heart rate variability during constant work rate exercise at and above the critical power in patients with severe chronic obstructive pulmonary disease

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ABSTRACT

Objective: Heart rate variability is useful in evaluating cardiac autonomic balance. We investigated cardiac autonomic modulation in patients with severe chronic obstructive pulmonary disease (COPD) during heavy and very heavy exercise at and above the critical power (CP).
Materials and Methods: Nine nonhypoxemic patients with COPD (mean forced expiratory volume in 1 second: 1.2 ± 0.5 L; forced expiratory volume in 1 second/forced vital capacity: $37.6 \pm 12\%$) completed an initial incremental exercise test on a cycle ergometer followed by four constant work rate tests to define their CP. In addition, patients underwent a test at their calculated CP for a target of 20 minutes. The CP test plus a test above CP of sufficient duration to allow heart rate variability analysis were studied further. In these tests, R-R interval data were analyzed for variability in the frequency domain before and during exercise.
Results: Compared with rest, the power of the normalized low-frequency component (nuLF) decreased (73.0 ± 20.9 *vs.* 54.2 ± 20.1; $p = 0.01$) and the power of normalized high-frequency component (nuHF) increased (27.0 ± 20.9 *vs.* 45.8 ± 20.1; $p = 0.01$) during exercise, resulting in a decrease in LF/HF (4.1 ± 2.3 *vs.* 1.6 ± 1.2; $p = 0.01$) suggesting a relative increase in parasympathetic tone during exercise. When compared with exercise at CP, exercise above CP featured significantly higher values for the square root of the mean squared differences of the successive R-R intervals, the baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all N-N intervals and the nuHF, as well as significantly lower values for the nuLF and LF/HF. During exercise above and at the CP, both LF and HF negatively correlated with the respiratory rate ($r = -0.76$ and $r = -0.70$, $p < 0.005$) and the V_{max}/PEF (ratio of end-exercise peak expiratory flow and peak expiratory flow during a forced maneuver at rest) ($r = -0.52$ and $r = -0.49$, $p < 0.05$).
Conclusion: The decrease in nuLF and LF/HF with increasing nuHF in very heavy exercise domains suggests that the autonomic balance is shifted toward parasympathetic tone dominance in patients with severe COPD. This correlates with increasing respiratory rate and ventilatory effort (V_{max}/PEF) during heavy and very heavy exercise in COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a complex condition with a number of comorbidities, and cardiovascular function is commonly impacted [1]. Cardiac death is the leading cause of mortality in patients with COPD [2], and it has been postulated that autonomic dysfunction increases the risk of cardiovascular death [3]. Characterizing autonomic balance might be helpful in understanding the pathophysiology of cardiac problems in COPD patients [1].

Heart rate variability (HRV) is a noninvasive method for assessing autonomic function that has been used in the clinical setting [4]. Patients with COPD appear to have impaired autonomic regulation at rest, as well as during exercise [5–9]. Spectral analysis of HRV is the most commonly used descriptive methodology. COPD patients have been found to have reduced HRV as well as increased high-frequency (HF) modulation at rest. During exercise, a decrease in the low frequency (LF)/HF ratio in COPD patients compared with

healthy participants has been described. These findings suggest that, during exercise, cardiac parasympathetic modulation is increased and the balance of cardiac modulation shifts toward parasympathetic predominance in COPD patients [9]. However, performing this analysis in COPD patients during exercise is often difficult. Many patients cannot achieve a steady state of HRV during high intensity constant work rate exercise (this requires at least a 5 minute period of steady-state exercise) because of dyspnea [9].

The diminished exercise tolerance in COPD has been physiologically characterized by reduced peak oxygen uptake ($\dot{V}O_{2peak}$), maximum work rate, and lactate threshold in incremental maximal exercise tests, and by slowed gas exchange ($\dot{V}O_2$, $\dot{V}CO_2$) and ventilatory ($\dot{V}_E$) kinetics and limited endurance in constant work rate exercise tests [10–13]. During these high-intensity exercise bouts, however, the most powerful factor limiting exercise is ventilatory limitation. It has been shown that, during high intensity constant work rate exercise bouts, minute ventilation reaches about the same level as that is attained at the limit of tolerance in an incremental exercise test [14]. This is in sharp contrast with healthy participants' responses, where minute ventilation virtually never reaches its physiological limits. The relationship between the work rate at which the exercise is limited and the corresponding endurance time follows a hyperbolic relationship, the power-duration curve. The horizontal asymptote of the hyperbola is the critical power (CP). Exercise at the CP can be maintained for a virtually infinite time (i.e., 20 minutes or more), whereas the physiological responses ($\dot{V}O_2$, $\dot{V}_E$) approach, but do not reach their upper limit.

The aim of the present study was to noninvasively investigate cardiac autonomic modulation in patients with severe COPD during heavy and very heavy exercise at and above the CP. Our hypothesis was that COPD patients would show a dominance of parasympathetic tone in their autonomic balance during heavy and very heavy exercise. We also sought to determine whether measures of HRV were related to the approach of ventilatory limitation during exercise.

2. Material and methods

2.1. Patients

COPD patients were prospectively recruited at the Los Angeles Biomedical Research Institute in 2009. Patients gave written informed consent for their participation. Inclusion criteria included classification of COPD as Global Initiative for Chronic Obstructive Lung Disease [15] Stage III or IV based on screening spirometry while taking prescribed bronchodilator therapy. None of the patients received short acting bronchodilators 30 minutes before exercise. Patients were also required to manifest ventilatory limitation during the initial incremental exercise test (defined as a maximal minute ventilation/maximal voluntary ventilation > 0.9) and to reach a peak work rate of at least 40 W. Patients who manifested arterial saturation, as assessed by pulse oximetry, of less than 88% during exercise were excluded. Those with an unstable cardiovascular condition (recent acute coronary syndrome or frequent arrhythmias before or during exercise), those with exercise-limiting musculoskeletal abnormalities, and those in the active phase of pulmonary rehabilitation were also excluded.

2.2. Determination of the CP

Exercise was performed on an electronically braked cycle ergometer. Patients breathed through a mouthpiece with a nose clip in place, and ventilation and gas exchange were recorded breath-by-breath by a computerized system (V_{max} Spectra, Viasys,

Yorba Linda, CA, USA). Each patient performed an incremental test, with work rate increased at 5–10 W/min to establish the peak work rate. On two different days (with at least 2 days between testing days with 2 hours between tests on a given day), four constant work rate tests were performed, with work rates ranging above and below the determined peak work rate for the patient. The four pairs of work rate-endurance time points were then graphed as work rate versus 1/(endurance time): the CP was determined as the Y-intercept of the regression of these data [16].

2.3. Calculation of HRV

Two constant work rate tests were chosen for HRV analysis. One was the highest constant work rate above CP, which was at least 7 minutes long, a duration considered adequate for HRV analysis. The other was an additional test performed at the CP. HRV analysis was performed both at rest and during constant work rate exercise in each test. HRV analysis was performed on R-R interval data extracted from electrocardiogram recordings (Polar RS800CX, Polar Electro Oy, Kempele, Finland) [17]. Patients with technically inadequate electrocardiogram tracings or those showing cardiac arrhythmias with significant frequency were excluded from analysis. The HRV was determined from (1) a pre-exercise resting period for 512 beats and (2) a period encompassing at least 512 heartbeats after 3 minutes of unloaded pedaling and 2 minutes of loaded exercise. HRV was analyzed in both the time and frequency domains. The time domain analysis was obtained from the standard deviation of the R-R intervals (an estimate of overall HRV) and the square root of the mean squared differences of the successive R-R intervals (RMSSD, an estimate of short-term HRV). Additionally, the NN50 count (number of pairs of adjacent NN intervals differing by more than 50 milliseconds in the entire recording), TINN (baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals), and R-R triangular index were calculated. Fast Fourier transformation was used for the frequency domain (power spectral) analysis. The powers of the very LF (VLF) band (<0.04 Hz), LF band ($0.04-0.15$ Hz) and HF band ($>0.15-0.4$ Hz) were calculated as the area under the portion of the curve related to each component [18]. The powers of the HF, LF, and LF/HF ratio were considered representative of parasympathetic activity, sympathetic activity with parasympathetic components, and sympathovagal balance, respectively. VLF data were not collected because of poor accuracy of VLF measures from 512 heartbeats. HF and LF were analyzed in absolute and normalized units. Normalized units of LF and HF were obtained as:

$$P/(TP - VLF) \times 100$$

where P is the power of LF or HF, and TP is the total power of the spectral density and VLF is the power of the VLF [4].

2.4. Statistical analysis

Numerical data were entered into Excel (Microsoft, Seattle, WA, USA) spreadsheets for each patient. Analysis was performed using SPSS statistical software for Windows version 10.0 (SPSS, Chicago, IL, USA). Descriptive statistics (mean $\pm$ standard deviation) were calculated for each variable. Resting and exercise HRV parameters were compared between the two constant work rate exercise sessions by two-way repeated measures analysis of variance. Correlations between HRV parameters and continuous variables from patient data were derived by Pearson's correlation. The Bonferroni correction to optimize the error was performed. Statistically significant differences were defined as a p value less than 0.05.