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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

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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.

Table 1
Peak gas exchange and ventilatory responses during constant work rate exercise at and above critical power in nine patients with COPD

Variable	Exercise above CP	Exercise at CP	p (two tailed)
FEV_1/FVC (%)	37.6 ± 11.8	37.6 ± 12.2	0.985
Work rate (W)	49.4 ± 6.9	40.6 ± 5.9	0.0006
$\dot{V}O_2$ (L/min)	1.19 ± 0.33	1.05 ± 0.27	0.011
$\dot{V}_E$ (L/min)	44.0 ± 20.9	38.2 ± 13.0	0.090
$\dot{V}_E$/MVV (%)	91.1 ± 19.9	81.9 ± 16.8	0.069
Fb (/min)	31.7 ± 6.6	29.1 ± 5.2	0.100
V_{max} (L/s)	2.22 ± 0.99	1.91 ± 0.57	0.070
V_{max}/PEF (%)	58.4 ± 13.5	52.1 ± 14.8	0.069
T_I/T_{TOT} (%)	39.0 ± 12.6	41.2 ± 0.1	0.389

Data are shown as mean ± standard deviation.
COPD = chronic obstructive pulmonary disease; CP = critical power; Fb = breathing frequency; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MVV = maximal voluntary ventilation (MVV = FEV1 × 40) measured at rest; PEF = peak expiratory flow measured at rest; T_I/T_{TOT} = respiratory duty cycle (inspiratory cycle time/total breathing cycle time); $\dot{V}_E$ = minute ventilation; V_{max} = intrabreath expiratory flow; $\dot{V}O_2$ = oxygen uptake.

3. Results

One of 10 consecutive eligible patients was excluded because of multiple cardiac ventricular premature complexes during exercise. Six men and three women participated. Their mean age and body mass index were 60.2 ± 6.9 years and 27.9 ± 3.0 kg/m^2, respectively. Spirometry done at study entry revealed a forced expiratory volume in 1 second of 1.2 ± 0.5 L; spirometric values obtained shortly before exercise were not significantly different on the two testing occasions. As shown in Table 1, the work rate in the tests above and at CP averaged 49.4 ± 6.9 W and 40.6 ± 5.9 W (77.8% ± 12.6 *vs.* 63.8% ± 15.2 of peak work rate). End-exercise $\dot{V}O_2$ was significantly lower in the CP test. End-exercise minute ventilation, respiratory rate, and peak expiratory flow tended to be lower, and the respiratory duty cycle tended to be higher in the CP test, but these differences did not achieve statistical significance.

Table 2 shows significant differences in the mean heart rate, NN50 count, TINN, normalized units of LF (nuLF) and HF (nuHF), as well as the balance of LF and HF (LF/HF) between rest and either of the two exercise work rates. Compared with exercise at CP, exercise above CP elicited significant differences in the mean heart rate, NN50, RMSSD, and TINN in the time domain analysis, as well as significant differences in the nuLF, nuHF, and LF/HF in the frequency domain measures.

When comparing the ventilatory and HRV parameters during exercise, both LF and HF were negatively correlated with the respiratory rate ($r = -0.76$ and $r = -0.70$, $p < 0.005$) and also the V_{max}/PEF (V_{max}: end-exercise peak intrabreath flow during exercise; PEF: peak expiratory flow) ($r = -0.52$ and $r = -0.49$, $p < 0.05$) (Table 3).

Table 2
Time and frequency domain analysis of heart rate variability indices during constant work rate exercise above and at the CP in nine COPD patients

Variable	Work rate above CP		Work rate at CP		p
	Pre-exercise	Exercise	Pre-exercise	Exercise	
HR (1/min)	88.4 ± 7.8	123.7 ± 15.9*	85.3 ± 7.8	120.3 ± 15.1*	<0.001
RMSSD (ms)	16.2 ± 15.2	9.7 ± 10.7	13.3 ± 6.7	5.2 ± 3.7	<0.001
NN50	31.9 ± 84.5	4.4 ± 11.2*	7.3 ± 9.8	0.1 ± 0.3*	0.184
TINN (ms)	138.3 ± 40.2	85.6 ± 28.6*	139.4 ± 68.1	81.7 ± 48.0*	0.001
nuLF (%)	73.0 ± 20.9	54.2 ± 20.1*	79.7 ± 8.5	70.3 ± 12.8	0.001
nuHF (%)	27.0 ± 20.9	45.8 ± 20.1*	20.3 ± 8.5	29.7 ± 12.8	0.001
LF/HF	4.1 ± 2.3	1.6 ± 1.2*	4.9 ± 2.9	3.1 ± 2.0	0.036

Data are shown as mean ± SD.
*$p < 0.05$ at end-exercise as compared with rest; p value (right side column) is the comparison of each exercise HRV parameters at and above critical power.
COPD = chronic obstructive pulmonary disease; CP = critical power; HF = high frequency; HR = heart rate; HRV = heart rate variability; LF = low frequency; NN50 count = number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; nu = normalized units; RMSSD = square root of mean sum of squares differences between adjacent NN intervals; TINN = baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals.

Table 3
Correlation between ventilatory parameters and heart rate variability during constant work exercise

Variable	mFb	V_{max}/PEF
LF	−0.76*	−0.52*
HF	−0.70*	−0.49*
LF/HF	−0.12	−0.29

Data are shown as correlation coefficients.
*$p < 0.05$ showed significant difference.
LF = low frequency; HF = high frequency; mFb = average breathing frequency during exercise; PEF = peak expiratory flow; V_{max} = peak flow during exercise.

4. Discussion

In the present study, we demonstrated differences in HRV during constant work rate exercise in COPD patients when comparing exercise above and at CP. In constant work rate exercise above CP, the nuLF and nuHF as well as the LF/HF were significantly lower than in exercise at CP. These changes in HRV suggest that the autonomic balance is shifted towards parasympathetic tone dominance during very heavy exercise compared with exercise at CP (heavy exercise).

In agreement with the results obtained by Bartels et al [9], our results suggest parasympathetic predominance in exercise in COPD patients. In the time domain analysis, the significant increase in RMSSD in heavy work implies a higher vagal stimulus of the sinus node. In work at CP (in which patients did not reach ventilatory limitation), HF was significantly lower and both LF and LF/HF were significantly higher than in work above CP. Our results may indicate that parasympathetic tone is predominant during exercise in which ventilatory limitation is reached. This is in contrast to studies of heavy exercise in healthy participants [19,20] as well as during exercise in COPD patients in which ventilatory limitation is not reached. Additionally, LF/HF, which indicates sympathovagal balance [21], shifted to HF modulation in exercise with ventilatory limitation. This has been observed in exercise below and above the ventilatory threshold in healthy participants [22].

The physiologic explanation for increased parasympathetic cardiac modulation in COPD patients during exercise is not well understood. Two possible mechanisms might contribute to this finding. The first is dynamic hyperinflation that occurs in COPD patients during exercise [23,24], which leads to large intrathoracic pressure swings. The second possible mechanism involves increased respiratory frequency with exercise. An increasing respiratory rate may cause a shift in power out of the LF range and into the HF range [25–27]. In our study, when comparing the ventilatory parameters and HRV during exercise, both LF and HF were negatively correlated with respiratory rate and ventilatory effort as measured by an increased V_{max}/PEF during heavy and very heavy exercise. Inhaled β-agonists can increase sympathetic activity during exercise in healthy participants without parasympathetic (HF) cardiac modulation; however, inhaled cholinergic agents do not affect the HRV in human participants [28].

One limitation in our study is that we did not directly measure sympathetic and parasympathetic tone changes [29] but, instead, used indirect measurements of HRV. Furthermore, we studied a relatively small number of participants without a control group. A larger study population would be desirable to confirm our findings.

In conclusion, the decrease in the nuLF and LF/HF, as well as the decreasing nuHF in heavy and very heavy exercise domains,

suggests that the autonomic balance is shifted toward parasympathetic tone dominance in patients with severe COPD. This correlates with the increasing respiratory rate and V_{max}/PEF during heavy and very heavy exercise in COPD patients.

References

[1] Chhabra SK, De S. Cardiovascular autonomic neuropathy in chronic obstructive pulmonary disease. Respir Med 2005;99:126–33.
[2] Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. JAMA 2005;294:1255–9.
[3] Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141:122–31.
[4] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93: 1043–65.
[5] Stewart AG, Waterhouse JC, Howard P. Cardiovascular autonomic nerve function in patients with hypoxaemic chronic obstructive pulmonary disease. Eur Respir J 1991;4:1207–14.
[6] Volterrani M, Scalvini S, Mazzuero G, Lanfranchi P, Colombo R, Clark AL, et al. Decreased heart rate variability in patients with chronic obstructive pulmonary disease. Chest 1994;106:1432–7.
[7] Stein PK, Nelson P, Rottman JN, Howard D, Ward SM, Kleiger AE, et al. Heart rate variability reflects severity of COPD in PiZ alpha1-antitrypsin deficiency. Chest 1998;113:327–33.
[8] Scalvini S, Porta R, Zanelli E, Volterrani M, Vitacca M, Pagani M, et al. Effects of oxygen on autonomic nervous system dysfunction in patients with chronic obstructive pulmonary disease. Eur Respir J 1999;13:119–24.
[9] Bartels MN, Jelic S, Ngai P, Basner RC, DeMeersman RE. High-frequency modulation of heart rate variability during exercise in patients with COPD. Chest 2003;124:863–9.
[10] Cooper CB. Exercise in chronic pulmonary disease: aerobic exercise prescription. Med Sci Sports Exerc 2001;33(7 Suppl):S671–9.
[11] Diaz O, Villafranca C, Ghezzo H, Borzone G, Leiva A, Milij-Emilij J, et al. Breathing pattern and gas exchange at peak exercise in COPD patients with and without tidal flow limitation at rest. Eur Respir J 2001;17:1120–7.
[12] Nery LE, Wasserman K, Andrews JD, Huntsman DJ, Hansen JE, Whipp BJ. Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. J Appl Physiol 1982;53:1594–602.
[13] Palange P, Galassetti P, Mannix ET, Farber MO, Manfredi F, Serra P, et al. Oxygen effect on O2 deficit and VO2 kinetics during exercise in obstructive pulmonary disease. J Appl Physiol 1995;78:2228–34.
[14] Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power-duration relationship. Am J Respir Crit Care Med 2000;162(2 Pt 1):497–504.
[15] Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007 Sep 15;176(6):532–55.
[16] Malaguti C, Nery LE, Dal Corso S, De Fuccio MB, Lerario MC, Cendon S, et al. Alternative strategies for exercise critical power estimation in patients with COPD. Eur J Appl Physiol 2006;96:59–65.
[17] Niskanen JP, Tarvainen MP, Ranta-Aho PO, Karjalainen PA. Software for advanced HRV analysis. Comput Methods Programs Biomed 2004;76:73–81.
[18] Ori Z, Monir G, Weiss J, Sayhouni X, Singer DH. Heart rate variability. Frequency domain analysis. Cardiol Clin 1992;10:499–537.
[19] Robinson BF, Epstein SE, Beiser GD, Braunwald E. Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. Circ Res 1966;19:400–11.
[20] Orizio C, Perini R, Comande A, Castellano M, Beschi M, Veicsteinas A. Plasma catecholamines and heart rate at the beginning of muscular exercise in man. Eur J Appl Physiol Occup Physiol 1988;57:644–51.
[21] Pagani MLF, Guzzetti S, Rimoldi O, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178–93.
[22] Cottin F, Medigue C, Lepretre PM, Papelier Y, Koralsztein JP, Billat V. Heart rate variability during exercise performed below and above ventilatory threshold. Med Sci Sports Exerc 2004;36:594–600.
[23] O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:770–7.
[24] Ma S, Hecht A, Varga J, Rambod M, Morford S, Goto S, et al. Breath-by-breath quantification of progressive airflow limitation during exercise in COPD: a new method. Respir Med 2010;104:389–96.
[25] Nakamura Y, Yamamoto Y, Muraoka I. Autonomic control of heart rate during physical exercise and fractal dimension of heart rate variability. J Appl Physiol 1993;74:875–81.
[26] Casadei B, Moon J, Johnston J, Caiazza A, Sleight P. Is respiratory sinus arrhythmia a good index of cardiac vagal tone in exercise? J Appl Physiol 1996;81:556–64.
[27] Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R-R interval power spectra is largely ignored. J Appl Physiol 1993; 75:2310–7.
[28] Dragone AJ, Parlow JL. Effects of inhaled albuterol and ipratropium bromide on autonomic control of the cardiovascular system. Chest 1997;111:1514–8.
[29] Narkiewicz K, van de Borne P, Montano N, Hering D, Kara T, Somers VK. Sympathetic neural outflow and chemoreflex sensitivity are related to spontaneous breathing rate in normal men. Hypertension 2006;47:51–5.