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Heart Rate Recovery After 6-min Walking Test Predicts Acute Exacerbation in COPD

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Abstract

Introduction Abnormalities of autonomic function have been reported in patients with chronic obstructive pulmonary disease (COPD). Our objectives were to identify determinants of abnormal heart rate recovery at 1 min (HRR_1) following completion of the 6-min walk test (6MWT) in COPD and to establish whether abnormal HRR_1 predicts acute exacerbations (AECOPD).

Methods Hundred one COPD patients (FEV_1 (SD) 53 (19) % predicted) were prospectively recruited in a multi-center study. HRR_1 after the 6MWT was evaluated as the difference between heart rate at the end of the test and 1 min into the recovery (HRR_1). Linear and logistic regression was used to identify predictors of HRR_1 and AECOPD, respectively. The best HRR_1 cut-off point to predict AECOPD was selected using the receiver operating characteristics (ROC) curves. The follow-up period was 12 months.

Results Distance covered during the 6MWT (m) and DLco (% predicted) were independently associated with HRR_1 ($r^2 = 0.51$, $p = 0.001$). Among several potential covariates, HRR_1 emerged as the most significant predictor of AECOPD (Odds ratio [OR], 0.91 per beat of recovery; 95% confidence interval [CI], 0.85–0.97; $p = 0.02$). The ROC analysis indicated that subjects with HRR_1 less than 14 beats (AUC, 0.71 [CI] 0.60–0.80; $p = 0.0001$) were more likely to suffer an exacerbation during the follow-up period (for HRR_1, $p = 0.004$ [log-rank test]).

Conclusions HRR_1 after the 6MWT is an independent predictor factor for AECOPD. Further studies are warranted to examine the physiological mechanisms associating a delayed HRR and acute exacerbations in COPD patients.

Keywords COPD · Exercise · Biomarker

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Introduction

There is increase evidence that abnormal heart rate recovery (HRR) after the 6-min walking test (6MWT) is associated with morbidity and mortality in various respiratory diseases [1–3]. However, the literature is scarce regarding the relationship between HRR after the 6MWT and prognosis in patients with chronic obstructive

pulmonary disease (COPD) [4, 5]. In chronic respiratory entities, abnormal autonomic cardiac response could be consequence of a lower parasympathetic activation and/or increased sympathetic tone, being widely accepted that parasympathetic activations plays a protective role [6]. Consequently, it is possible that numerous factors present in COPD patients namely hypoxemia, dynamic hyperinflation, systemic inflammation, and medication could affect the autonomic cardiac response to exercise with adverse consequence in diseases prognosis [7].

The two main objectives of our study were to identify the determinants of heart rate recovery at 1 min (HRR_1) after completion of a 6MWT and to establish whether abnormal HRR_1 predicts acute exacerbations (AECOPD).

Methods

We performed a prospective multicentre study that included the follow sites: Discipline of Physiotherapy, Faculty of Health Sciences, University of Sydney; Fundación Neumológica Colombiana, Bogotá; ELEGI/Colt laboratory, University of Edinburgh; Centre for Inflammation Research, The Queen's Medical Research Institute; 1st Department of Respiratory Medicine, National and Kapodistrian University of Athens; and Hospital Clinic in Barcelona. The protocol was accepted by the local ethics committees at each study site.

The main inclusion criterion were: (1) COPD patients with stable disease (2 months without exacerbations) and, (2) optimized medication according to GOLD guidelines [8]. Patients were excluded if they had an unstable cardiovascular disease, such as heart failure or coronary artery disease. Patients with pace maker, using medication that affect heart rate recovery (i.e., B-Blockers, calcium antagonist, etc.), or cardiac arrhythmia (i.e., atrial fibrilation) were also excluded. Active participation in a Pulmonary Rehabilitation program during the last 12 months was another exclusion criterion.

Patients were followed up for 12 months after the execution of the 6MWT. An investigator recorded the patients' vital status and the frequency of AECOPD (with or without hospital admission). *AECOPD was defined according to the GOLD definition* as acute events characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leaded to a change in medication [8].

The 6MWT was performed according to American Thoracic Society [9]; however, the test was modified by recording heart rate at the end of the 6MWT and at 1 min after completion of the test with the patient seated.

Results are presented as the mean and standard deviation (SD) for normally distributed variables or median and percentile 25–75 (P25-75) for skewed numerical variables. Univariate and multivariate linear and logistic regression analyses were performed in order to evaluate the determinants of abnormal heart rate recovery and the factors associated with AECOPD, respectively. Receiver Operating Characteristic (ROC) analysis was performed

Table 1 Anthropometric and functional characteristics of the COPD patients

Variables	Total patients ($n = 101$)
General characteristics	
Sex, M/F (n)	82/19
Age (year)	66 (8)
Current smokers (%)	16
mMRC dyspnea scale	1(1–1.7)
Frequent exacerbator (%)	10
LTOT (%)	22
C-reactive protein (mg/dl)	0.8 (0.2)
Body composition	
BMI (m/kg^2)	26.9 (4)
FFMI (m/kg^2)	18.0 (5)
Comorbidities condition	
Diabetes (%)	17
Chronic heart failure (%)	9
Hypercholesterolemia (%)	23
Hypertension (%)	45
Obesity (%)	19
Charlson index	2 (2–2.8)
Pulmonary function	
FEV_1 (% predicted)	53 (19)
DL_{CO} (% predicted)	58 (17)
IC/TLC ratio	0.33(0.1)
PaO_2 (mmHg)	74 (17)
SGRQ (Total)	44 (20)
6-min walk test	
Heart basal (beats/min)	85 (12)
Heart final (beats/min)	112 (16)
SpO_2 basal (%)	95 (2)
SpO_2 Final (%)	91 (5)
Borg scale (dyspnea) basal	0.7 (0.6–1.4)
Borg scale (dyspnea) final	4 (3.4–4.7)
Borg scale (legs) basal	0.7 (0.6–1.4)
Borg scale (legs) final	3 (2.3–3.5)
Distance (m)	427 (108)
Heart rate recovery (HRR_1) (beats)	17 (13–19)

Results are expressed as mean (SD) or median and percentile 25–75 (P25–75)

mMRC modified Medical Research Council, *LTOT* long-term oxygen therapy, *BMI* body mass index, *FFMI* fat-free mass index, *FEV_1* forced expiratory volume in one second, *IC/TLC* inspiratory-to-total lung capacity ratio, *SGRQ* Saint George Respiratory Questionnaire

for the evaluation of the performance of HRR_1 in the prediction of AECOPD and in order to determine the best cut-off point for HRR_1 to predict AECOPD [10]. Afterwards, Kaplan–Meier analysis was used to assess the differences in the times to first AECOPD during follow-up period among subjects according to dichotomous classification of HRR_1 (above or below the best cut-off point). The log-rank test determined statistical significance. Calculations were done with SPSS/PC (version 22, SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered significant.

Results

A total of 101 COPD patients were evaluated. Subject characteristics are listed in Table 1. After univariate and multivariate lineal regression analyses, 6MWT and DLco were the only independent determinants of HRR_1 after 6MWT (Table 2). In Table 3, univariate and multivariate regression analyses showed that HRR_1 remained an independent predictor of the frequency for AECOPD over the follow-up period. In ROC analysis, HRR_1 presented an area under the curve (AUC) of 0.703 (95% CI 0.604–0.801) for the prediction of AECOPD. An HRR_1 equal or less than 14 beats appears as the best cut-off point to predict AECOPD. Kaplan–Meier curves evaluating the time to first AECOPD according to HRR_1 values are presented in Fig. 1. Patients with low HRR_1 presented increased risk of AECOPD at 12 months post-6MWT assessment compared to those patients with a high HRR_1 response ($p = 0.004$, log-rank test). Accordingly, patients with low HRR_1 showed a mean exacerbation of 1.5 (1.7) at 12 months. In contrast, patients with HRR > 14 beats had a 0.5 (1) exacerbations during the same follow-up period.

Discussion

The current study demonstrates that HRR_1 is a clinical biomarker with a significant predictive capacity for AECOPD. To our knowledge, this is the first study aimed at identifying whether the abnormal HR response after the 6MWT predicts main outcomes in COPD. We also found that the 6-min walking distance and the diffusion capacity for carbon monoxide are the main determinants of HRR_1 [1, 7].

Previous studies examining the prognostic value of the HRR_1 after the 6MWT in respiratory patients showed that a HRR_1 below 13 or 16 beats was associated with poorer survival in patients with pulmonary fibrosis and pulmonary hypertension, respectively [1, 2]. Our study shows that patients with HRR_1 greater than 14 beats had a very low likelihood of AECOPD over the follow-up period.

In regards to the autonomic abnormal cardiac response in COPD, more than ten years ago Laccase et al. [11] demonstrated an association between HRR_1 after a maximal exercise test and mortality. However, HRR_1 after the 6MWT in COPD as a prognostic factor has never been reported. This is a tangible clinical finding given that the 6MWT is a widely used, simple test to apply into the clinical scenario [12].

Although the relationship between autonomic cardiac dysfunction and COPD is not fully clarified, our findings provide evidence that chronic complex diseases, such as

Table 2 Univariate and multivariate linear regression analysis evaluating the determinants of HRR_1

Variable	Heart rate recovery$_1$ after 6MWT			
	Univariate analysis		Multivariate analysis	
	r	p value	β value (95%CI)	p value
Age (years)	−0.203	0.030	−0.93 (−0.21 to 0.39)	0.542
Gender (male)	0.352	0.001	4.89 (−1.73 to 11.5)	0.143
FEV_1 (% predicted)	0.440	0.001	0.11 (−0.59 to 0.28)	0.190
DLco (% predicted)	0.375	0.010	0.15 (0.04 to 0.29)	0.048
PaO_2 (mmHg)	0.297	0.014	0.01 (−0.20 to 0.22)	0.918
mMRC scale	−0.402	0.001	−1.00 (−3.41 to 1.41)	0.407
Heart rate (basal)	−0.256	0.006	−0.10 (−0.30 to 0.08)	0.265
6MWD (m)	0.512	0.001	0.31 (0.01 to 0.61)	0.045
Adjusted r^2			0.51	

6MWT 6-min walk test, *FEV_1* forced expiratory volume in one second, *DLco* diffusing capacity of the lung for carbon monoxide, *6MWD* 6-min walk distance, *PaO_2* partial pressure of oxygen in arterial blood gases, *mMRC* modified Medical Research Council, *HRR_1* heart rate recovery at 1 min after completion of the 6-min walk test

Table 3 Univariate and multivariate binary logistic regression analysis evaluating the effect of HRR_1 and significant confounders on AECOPD during 12-months follow-up

Variable	AECOPD during 12-months follow-up			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
mMRC scale	1.82 (1.17–2.89)	0.007		
Charlson score	2.16 (0.80–5.83)	0.048		
6MWD (m)	0.98 (0.98–0.99)	0.0001	0.99 (0.98–0.99)	0.03
Previous exacerbation (last year)	4.89 (1.02–23.53)	0.047		
HRR_1 (beats)	0.93 (0.88–0.98)	0.0001	0.91 (0.85–0.97)	0.02
FEV_1 (% predicted)	0.97 (0.95–1.00)	0.050		

FEV_1 forced expiratory volume in one second, *6MWD* 6-min walk distance, *PaO_2* partial pressure of oxygen in arterial blood gases, *mMRC* modified Medical Research Council, *AECOPD* acute exacerbation of chronic obstructive pulmonary disease, *HRR_1* heart rate recovery at 1 min after completion of the 6-min walk test

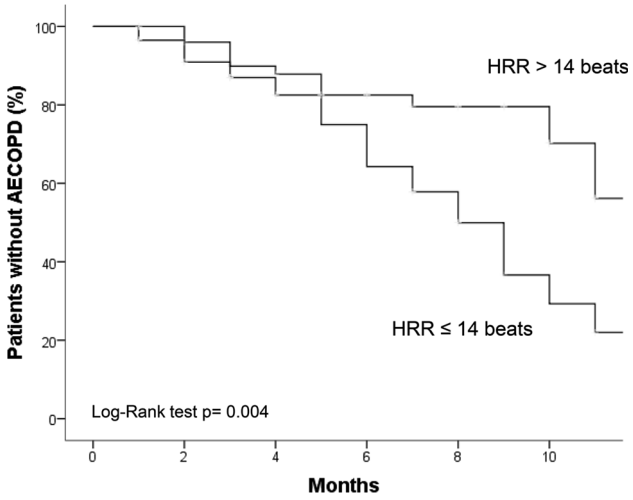

Fig. 1 The Kaplan–Meier analysis showed that HRR1 $\leq$ 14 beats is associated with significantly shorter time to first AECOPD than HRR1 $>$ 14 ($p = 0.004$ by the log-rank test)

COPD, are associated with autonomic dysfunction and sympathetic overactivation [13]. Moreover, a recent published study indicates that heart rate variability (HRV) at rest (as expression of autonomic imbalance) during AECOPD might increase the risk of sudden death [14]. However, although the relationship between HRV and HRR_1 has been partially explored in COPD [15], these markers of autonomic function could be potentially modulated as consequence of physical exercise training into pulmonary rehabilitation programs [16, 17].

In conclusion, HRR_1 after the 6MWT could be a potential predictor of AECOPD in COPD patients. Research is needed to examine the physiological mechanisms linking the delayed HRR and frequency of AECOPD in COPD patients.

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Compliance with Ethical Standards

Conflict of interest Authors DAR, EK, JAA, AC, SG, ABG, AA, JV, EGS, IV, RR, JR declares that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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