

HEART RATE RECOVERY AFTER 6-MINUTE WALKING TEST PREDICTS ACUTE EXACERBATION IN COPD

Diego A. Rodríguez¹; Eleni A. Kortianou² Jennifer A. Alison³ Alejandro Casas⁴;
Santiago Giavedoni⁵; Anael Barberan-Garcia⁶; Ane Arbillaga⁷; Jordi Vilaró⁸;
Elena Gimeno-Santos⁶⁻⁷; Ioannis Vogiatzis⁹; Roberto Rabinovich⁵
and Josep Roca⁶

¹Pulmonology Department, Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Universitat Pompeu Fabra (UPF), CIBERES, (ISCiii), Barcelona, Spain.

²Technological Educational Institution of Central Greece, Pulmonary Rehabilitation Unit, Sotiria Hospital, Athens, Greece.

³Faculty of Health Sciences, The University of Sydney, Australia.

⁴Fundación Neumológica Colombiana, Bogotá, Colombia.

⁵ELEGI/Colt laboratory, UoE/MRC Centre for Inflammation Research, The Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, UK.

⁶Pulmonology Department (ICT), Hospital Clínic, IDIBAPS, CIBERES (ISCiii), Barcelona, Spain.

⁷Centre for Research in Environmental Epidemiology (CREAL) Barcelona, Spain.

⁸FCS Blanquerna, Universitat Ramon Llull, Barcelona.

⁹ First Department of Respiratory Medicine, National and Kapodistrian, University of Athens, Greece. Faculty of Health and Life Sciences, Northumbria University Newcastle, UK

Corresponding author: Diego A. Rodríguez. Servei de Pneumologia, Hospital del Mar, Passeig Maritim 25 08003 Barcelona, Spain. Tel: 34-93-2483548, Fax: 34-93-2483425, E-mail: darodriguez@parcdesalutmar.cat

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 (HRR₁) following completion of the 6-min walk test (6MWT) in COPD and to establish whether abnormal HRR₁ predicts acute exacerbations (AECOPD).

Methods: 101 COPD patients (FEV₁ (SD) 53 (19) % predicted) were prospectively recruited in a multi-centre study. HRR₁ after the 6MWT was evaluated as the difference between heart rate at the end of the test and one minute into the recovery (HRR₁). Linear and logistic regression was used to identify predictors of HRR₁ and AECOPD, respectively. The best HRR₁ 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 (meters) and DLco (% predicted) were independently associated with HRR₁ ($r^2=0.51$, $p=0.001$). Among several potential covariates, HRR₁ emerged as the most significant predictor of AECOPD (Odds Ratio [OR], 0.91 per beat of recovery; 95% confidence interval [CI], 0.85 to 0.97; $p=0.02$). The ROC analysis indicated that subjects with HRR₁ less than 14 beats (AUC, 0.71 [CI] 0.60 to 0.80; $p=0.0001$) were more likely to suffer an exacerbation during the follow-up period (for HRR₁, $p=0.004$ [log-rank test]).

Conclusions: HRR₁ 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.

INTRODUCTION

There is increase evidence that abnormal heart rate recovery (HRR) after the six minute walking test (6MWT) is associated with morbidity and mortality in various respiratory diseases (1-3). However, the literature is scares 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 be 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 following 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 criteria 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 a pacemaker, used medication that affected heart rate recovery (ie. B-Blockers, calcium antagonist, etc) or cardiac arrhythmia (ie. atrial fibrillation) 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 were 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 led 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 minute 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 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 HRR₁ after 6MWT (Table 2A). In table 2B, univariate and multivariate regression analyses showed that HRR₁ remained an independent predictor of the frequency for AECOPD over the follow-up period. In ROC analysis, HRR₁ presented an area under the curve (AUC) of 0.703 (95% CI 0.604 to 0.801) for the prediction of AECOPD. An HRR₁ 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 HRR₁ values are presented in figure 1. Patients with low HRR₁ presented increased risk of AECOPD at 12 months post-6MWT assessment compared to those patients with a high HRR₁ response ($p=0.004$, log-rank test). Accordingly, patients with low HRR₁ showed a mean exacerbations 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 six-minute 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 were 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 COPD, are associated with autonomic dysfunction and sympathetic over activation (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 HRR₁ 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, HRR₁ 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.

Legend Figure 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)

Compliance with Ethical Standards:

Funding: This study was not funded

Conflict of Interest:

Author DAR declares that he has no conflict of interest

Author EK declares that she has no conflict of interest

Author JAA declares that she has no conflict of interest

Author AC declares that he has no conflict of interest

Author SG declares that he has no conflict of interest

Author ABG declares that he has no conflict of interest

Author AA declares that she has no conflict of interest

Author JV declares that he has no conflict of interest

Author EGS declares that she has no conflict of interest

Author IV declares that he has no conflict of interest

Author RR declares that he has no conflict of interest

Author JR declares that he has 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.

REFERENCES

1. Swigris JJ, Swick J, Wamboldt FS, Sprunger D, du Bois R, Fischer A, Cosgrove GP, Frankel SK, Fernandez-Perez ER, Kervitsky D, Brown KK. Heart rate recovery after 6-min walk test predicts survival in patients with idiopathic pulmonary fibrosis. *Chest*. 2009 Sep;136(3):841-8.
2. Minai OA, Nguyen Q, Mummadi S, Walker E, McCarthy K, Dweik RA. Heart rate recovery is an important predictor of outcomes in patients with connective tissue disease-associated pulmonary hypertension. *Pulm Circ*. 2015 Sep;5(3):565-76.
3. Swigris JJ, Olson AL, Shlobin OA, Ahmad S, Brown KK, Nathan SD. Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respirology*. 2011 Apr;16(3):439-45.
4. Van Gestel AJ, Kohler M, Steier J, Sommerwerck U, Teschler S, Russi EW, Teschler H. Cardiac autonomic function and cardiovascular response to exercise in patients with chronic obstructive pulmonary disease. *COPD*. 2012 Apr;9(2):160-5.
5. Shiroishi R, Kitagawa C, Miyamoto N, Kakuno N, Koyanagi H, Rikitomi N, Senjyu H. Heart rate recovery after the 6-min walk test is related to 6-min walk distance and percutaneous oxygen saturation recovery in patients with COPD. *Respirology*. 2015 May;20(4):671-3.
6. Seshadri N, Gildea TR, McCarthy K, Pothier C, Kavuru MS, Lauer MS. Association of an abnormal exercise heart rate recovery with pulmonary function abnormalities. *Chest*. 2004 Apr;125(4):1286-91.

7. Nasis I, Kortianou E, Vasilopoulou M, Spetsioti S, Louvaris Z, Kaltsakas G, Davos CH, Zakynthinos S, Koulouris NG, Vogiatzis I. Hemodynamic effects of high intensity interval training in COPD patients exhibiting exercise-induced dynamic hyperinflation. *Respir Physiol Neurobiol*. 2015 Oct; 217:8-16
8. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from:<http://goldcopd.org> [accessed 27.12.16].
9. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
10. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 143: 29-36.
11. Lacasse M, Maltais F, Poirier P, Lacasse Y, Marquis K, Jobin J, LeBlanc P. Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. *Respir. Med.* 2005; 99: 877–86.
12. Cahalin LP, Arena R, Labate V, Bandera F, Lavie CJ, Guazzi M. Heart rate recovery after the 6 min walk test rather than distance ambulated is a powerful prognostic indicator in heart failure with reduced and preserved ejection fraction: a comparison with cardiopulmonary exercise testing. *Eur J Heart Fail*. 2013 May;15(5):519-27.
13. Iturriaga R, Del Rio R, Idiaquez J, Somers VK. Carotid body chemoreceptors, sympathetic neural activation, and cardiometabolic disease. *Biol Res*. 2016 Feb 26;49:13.

14. Wang X, Jiang Z, Chen B, Zhou L, Kong Z, Zuo S, Liu H, Yin S. Cardiac autonomic function in patients with acute exacerbation of chronic obstructive pulmonary disease with and without ventricular tachycardia. *BMC Pulm Med.* 2016 Aug 20;16(1):124
15. Goulart CD, Cabiddu R, Schneiders PB, Antunes San Martin E, Trimer R, Borghi-Silva A, da Silva AL. Is cardiac autonomic modulation during upper limb isometric contraction and Valsalva maneuver impaired in COPD patients? *Int J Chron Obstruct Pulmon Dis.* 2017 Mar 13;12:849-857.
16. Rodríguez DA, Arbillaga A, Barberan-Garcia A, Ramirez-Sarmiento A, Torralba Y, Vilaró J, Gimeno-Santos E, Gea J, Orozco-Levi M, Roca J, Marco E. Effects of interval and continuous exercise training on autonomic cardiac function in COPD patients. *Clin Respir J.* 2016 Jan;10(1):83-9.
17. Camillo CA, Laburu Vde M, Gonçalves NS, Cavalheri V, Tomasi FP, Hernandes NA, Ramos D, Marquez Vanderlei LC, Cipulo Ramos EM, Probst VS, Pitta F. Improvement of heart rate variability after exercise training and its predictors in COPD. *Respir Med.* 2011 Jul;105(7):1054-62.

Table1 Anthropometric and functional characteristics of the COPD patients

Variables	Total Patients (n = 101)
General characteristics	
Sex, M/F (n,)	82/19
Age (yr)	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-Minute 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 (meters)	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).
 Definition of abbreviation: mMRC = modified Medical Research Council;
 LTOT = Long Term Oxygen Therapy; BMI = body mass index;
 FFMI = fat free mass index; FEV₁ = forced expiratory volume in one second.
 IC/TLC = Inspiratory to Total Lung Capacity ratio. SGRQ = Saint George
 Respiratory Questionnaire.

Table 2

A. Univariate and multivariate linear regression analysis evaluating the determinants of HRR₁

Variable	Heart Rate Recovery ₁ after 6MWT			
	Univariate Analysis		Multivariate Analysis	
	r	p-value	β-value (95%CI)	p-value
Age (yrs)	-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 (meters)	0.512	0.001	0.31 (0.01 to 0.61)	0.045
Adjusted r ²				0.51

B. Univariate and multivariate binary logistic regression analysis evaluating the effect of HRR₁ 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 to 2.89)	0.007		
Charlson score	2.16 (0.80 to 5.83)	0.048		
6MWD (meters)	0.98 (0.98 to 0.99)	0.0001	0.99 (0.98 to 0.99)	0.03
Previous exacerbation (last year)	4.89 (1.02 to 23.53)	0.047		
HRR ₁ (beats)	0.93 (0.88 to 0.98)	0.0001	0.91 (0.85 to 0.97)	0.02
FEV ₁ (%predicted)	0.97 (0.95 to 1.00)	0.050		

6MWT = 6-min walk test. FEV₁ = forced expiratory volume in one second. DLco = diffusing capacity of the lung for carbon monoxide. 6MWD = 6-min walk distance. PaO₂ = partial pressure of oxygen in arterial blood gases. mMRC = modified Medical Research Council. AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease. HRR₁ = heart rate recovery at 1 min after completion of the 6-min walk test.

