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HEART RATE RECOVERY AFTER 6-MINUTE WALKING TEST

PREDICTS ACUTE EXACERBATION IN COPD

Diego A. Rodríguez[1]; Eleni A. Kortianou[2] Jennifer A. Alison[3] Alejandro Casas[4];
Santiago Giavedoni[5]; Anael Barberan-Garcia[6]; Ane Arbillaga[7]; Jordi Vilaró [8];
Elena Gimeno-Santos[6-7]; Ioannis Vogiatzis[9]; Roberto Rabinovich[5]
and Josep Roca[6]

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

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

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

[4]Fundación Neumológica Colombiana, Bogotá, Colombia.

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

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

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

[8]FCS 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 (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: 101 COPD patients (FEV_1 (SD) 53 (19) % predicted) were prospectively recruited in a multi-centre study. HRR_1 after the 6MWT was evaluated as the difference between heart rate at the end of the test and one minute 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 (meters) 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 to 0.97; p=0.02). The ROC analysis indicated that subjects with HRR_1 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 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.

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 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 side

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 had an unstable cardiovascular disease, such as heart failure or coronary artery disease. Patients with pace maker, use medication that affect 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 criteria.

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 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 minute after completion of the test with the patient seated.

4

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 HRR_1 after 6MWT (Table 2A). In table 2B, 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 to 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 figure 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 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.

DISCUSION

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 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.

Legend Figure 1

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

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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