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Associations of Daily Walking Activity with Biomarkers Related to Cardiac Distress in Patients with Chronic Obstructive Pulmonary Disease

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Key Words
Biomarkers · Accelerometry · Walking intensity · Exercise capacity · Dyspnea

Abstract
Background: The prevalence of cardiovascular mortality is high in Chronic Obstructive Pulmonary Disease (COPD) and the identification of clinical parameters to improve risk stratification is of great interest. ***Objectives:*** This study aims to assess the predictive strength of daily walking activity on expression of cardiac biomarkers in patients with COPD. ***Methods:*** One hundred and five patients with COPD (66.1 ± 8.7 years of age) were prospectively analyzed. Daily walking activity was measured by means of accelerometry. Stepwise multivariate regression analyses were employed with either midregional proatrial natriuretic peptide (MRproANP) or plasma proadrenomedullin (MRproADM) as dependent variables, and age, age-adjusted Charlson score, Modified Medical Research Council Dyspnea Scale (MMRC), Saint Georges Respiratory Questionnaire total score and either total walk, steps per day or fast walk as covariates. ***Results:*** Independent predictors of MRproANP included age ($p = 0.015$) and either total walk or steps per day (both $p < 0.0001$). Total walk or steps per day were the only independent predictors of MRproADM ($p < 0.0001$). There was a significant negative correlation between fast walk and MMRC ($R = -0.70$; $p < 0.001$) and fast walk was only independently predictive of MRproANP but not MRproADM once MMRC was excluded from the list of covariates ($p = 0.023$ and $p = 0.057$, respectively). ***Conclusions:*** Daily walking activity independently predicts levels of circulating MRproANP and MRproADM in stable COPD patients, two prognostic biomarkers of cardiac distress associated with long-term survival upon exacerbation of COPD. Employing activity monitors in the stable state might simplify risk stratification in daily living.

Introduction

The prevalence and incidence of Chronic Obstructive Pulmonary Disease (COPD) is rapidly increasing and evidence suggests it will be the third leading cause of death worldwide within the next decade [1–3]. Exacerbations of COPD are the most common cause of emergency respiratory admissions to hospitals and are a major financial bur-

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den to health services [4]. In addition, COPD is associated with high cardiovascular comorbidity and mortality and the prevalence for cardiovascular-related death remains particularly high in patients suffering acute exacerbations of COPD [5, 6]. Therefore, systemic biomarkers of inflammation and/or cardiac stress have grown in significance regarding their ability to predict clinical prognosis in stable COPD and in the setting of severe acute exacerbations requiring hospital admission [7–10]. Among these are midregional proatrial natriuretic peptide (MRproANP) and plasma proadrenomedullin (MRproADM). Both are markers of cardiac distress and have been shown to be independently predictive of 2-year long-term survival in patients with severe acute exacerbation of COPD [11, 12].

Daily physical activity is another important predictor of mortality in this patient population [10, 13, 14]. The degree of physical impairment significantly correlates with disease severity and markedly impacts the patient's quality of life [15–17]. The usefulness of accelerometers to measure daily activity levels is well documented in patients with COPD [18–22]. They provide an objective measure of daily activity and are found to be more accurate than questionnaires which tend to be subject to bias and typically overestimate the total amount of physical activity [23]. Recent studies have demonstrated accelerometer-based physical activity to be the strongest predictor of all-cause mortality in patients with COPD [10, 14]. Moreover, physical inactivity was shown to be an independent predictor of hospital admission due to severe exacerbation and was positively associated with higher numbers of exacerbations per year further increasing the risk for mortality [14, 24].

Evidence suggests that physical activity attenuates and inactivity augments the occurrence of exacerbations of COPD due to underlying hemodynamic changes and vasoconstriction of the pulmonary vasculature [25–28]. Hence, the purpose of this study is to evaluate the association between accelerometer-based physical activity and prognostic biomarkers in stable COPD patients in order to establish whether ambulatory activity monitoring can simplify risk stratification in daily living.

Methods

Setting and Study Population

This prospective cohort study evaluates patients with COPD recruited in the 'Predicting Effects and Risk Factors in Exacerbations of Chronic Obstructive Pulmonary Disease' (PROMISE) study [29]. In brief, one of the primary endpoints of the study was to explore predictors that might identify recurrence and poor outcome during and outside exacerbations. One hundred and five patients in the stable condition were consecutively included in this sub-study analysis at the Clinic of Pulmonary Medicine of the University Hospital Basel, Switzerland, between November 2008 and March 2010.

To be eligible for the study, patients had to be diagnosed with COPD on the basis of clinical history such as smoking status or physical examination, and to meet post-bronchodilator spirometric criteria for COPD stage II–IV according to the GOLD guidelines at inclusion. Spirometry was performed by trained lung function technicians according to American Thoracic Guidelines [30]. Once included, assessments included detailed medical history, current medication, duration of disease, comorbidities, physical examination, quality of life (Saint Georges Respiratory Questionnaire; SGRQ) [31], Modified Medical Research Council Dyspnea Scale (MMRC), spirometry, 8-day accelerometry and blood tests to assess MRproANP and MRproADM. Patients enrolled in the PROMISE study had an initial baseline examination followed by a total of four scheduled visits every 6 months. For this subgroup analysis, assessment of daily activity levels and prognostic biomarkers was carried out during a scheduled visit when patients were in a stable condition outside exacerbations. The study was carried out according to the principles of the Declaration of Helsinki and approved by our local ethics committee (Ethic Commission Beider Basel EKBB 295/07). Written informed consent was obtained from all patients.

Measurements of MRproADM and MRproANP

All three biomarkers were assessed in EDTA plasma from all patients using a sandwich immunoassay and documented on paper case report forms. Automated immunoassays are based on sandwich chemiluminescene assays. The following assays were used according to the instructions of the manufacturer: BRAHMS MRproANP KRYPTOR (ThermoFisher Scientific, BRAHMS GmbH, Hennigsdorf, Germany) and BRAHMS MRproADM KRYPTOR (ThermoFisher Scientific). Detailed description of biomarker detection procedures can be read elsewhere [32, 33]. The lower detection limit of the MRproANP assay was 4.3 pmol/l, and its functional sensitivity was 11 pmol/l with an interassay coefficient of variation <20%. The lower detection limit for the MRproADM assay was 0.08 pmol/l and its functional sensitivity was 0.12 pmol/l [11, 12].

Accelerometer Activity Monitoring

Patients were handed the accelerometer (Aipermon® GmbH, Munich, Germany) during a scheduled visit and instructed to wear it continuously during waking hours whilst doing their normal daily routine. The device was attached to the patient's belt and positioned above the left hip. Patients were encouraged to wear the device continuously during normal waking hours for 8 consecutive days. The accelerometer was to be attached upon rising in the morning and only to be taken off for showering, bathing and sleeping. The first and last days when patients received or returned the device were incomplete and thus only 6 consecutive days (24 h) were included in the statistical analysis. All device settings were preprogrammed for each patient to keep patient handling of the accelerometer to a minimum. Patients did not receive any feedback from the device display regarding daily walking time, intensity or steps taken. Upon return, data were copied onto

Table 1. Patient demographics and clinical parameters

GOLD	II	III	IV	p value
Patients	29	42	34	
Male/female	21/8	32/10	22/12	0.55
Age, years	64.4 ± 7.9	65.1 ± 8.8	68.8 ± 8.8	0.090
BMI	27.8 ± 5.9	27.3 ± 6.4	23.8 ± 4.4	0.010*
Current or former smoker	29	42	34	0.99
SpO_2 saturation	95.3 ± 2.0	94.6 ± 2.4	94.0 ± 2.7	0.085
FEV_1%	59.9 ± 5.9	42.0 ± 7.0	28.8 ± 10.7	<0.0001*
SGRQ total score	33.2 ± 20.8	37.6 ± 15.3	46.1 ± 16.0	0.013*
MMRC	2.3 ± 0.77	2.6 ± 0.86	3.2 ± 0.84	<0.0001*
Age-adjusted Charlson score	4.5 ± 2.5	4.4 ± 2.9	4.7 ± 2.5	0.94
Depression	3 (6.5)	4 (10)	7 (21)	0.18
MRproANP, pmol/l	67.2 (51–115)	95.4 (51–188)	115 (66–178)	0.10
MRproADM, pmol/l	0.575 (0.50–0.67)	0.670 (0.53–0.97)	0.700 (0.58–0.1.1)	0.033*
Total walk, min/day	64.1 ± 34.5	50.7 ± 23.2	42.6 ± 29.2	0.014*
Steps per day	5,156 ± 2,830	4,463 ± 2,151	3,308 ± 2,367	0.011*
Fast walk, min/day	4.2 ± 8.1	2.9 ± 5.4	0.47 ± 1.0	0.024*
Medication				
Long AC	20 (69)	35 (83)	28 (82)	0.21
ICS/LABA	21 (72)	33 (83)	27 (79)	0.18
LTOT	0	0	20 (80)	<0.0001*
β-Blocker	7 (25)	15 (36)	17 (50)	0.58
ACE inhibitor	9 (32)	17 (40)	10 (29)	0.61

Data are presented as mean ± SD and median (IQR) for biomarkers proANP and proADM, or n (%). Overall group comparison across different GOLD stages was done using one-way ANOVA; post hoc group differences were tested by t test. Long AC = Long-acting anticholinergic; ICS/LABA = fixed combination of ICS/LABA; LTOT = oxygen therapy. * Statistical significance was set at $p \leq 0.05$.

a PC and their content was viewed via ActiCoach MPAT2Viewer, (Aipermon). Wearing time included minutes per day spent passively (i.e. sitting), actively (i.e. movement, but not walking), walking (0–5 km/h or 0–80 m/min), fast walking (>5 km/h or 81–115 m/min) and steps per day. Data was analyzed according to total walking time (min/day), walking intensity (fast walk >5 km/h) and steps per day. Total walk was computed from adding the parameters walk + fast walk together. The device used was a three-dimensional accelerometer measuring movement continuously in three axes (x, y, z). Data output is provided in 60-second intervals for each consecutive day (24 h) with the exact time and date for each epoch. Activity modes and accelerometer detection accuracy were extensively validated and detailed results are reported elsewhere [34, 35]. In summary, the device was able to accurately detect steps to 99% at walking speeds ranging as low as 20 m/min onwards. The device was originally designed for use in a large multi-center study investigating the feasibility of remote telemedical patient monitoring [36–38].

Data Analysis

Statistical analysis was done using SPSS software (version 19.0, SPSS Inc., Chicago, Ill., USA). Data were descriptively analyzed reporting mean ± standard deviation (SD) for quantitative measurements and percentages for frequencies. Data for quantitative biomarker values were described as median interquartile range (IQR). Statistical comparisons of measurements across different GOLD stage categories were done using one-way ANOVA. Post hoc group differences were tested by unpaired Student's t test and statistical significance was set at $p \leq 0.05$. Bivariate correlations were investigated using Pearson's correlation coefficient (R). Correlations were two tailed and statistically significant at the level of $p \leq 0.01$. Multivariate linear regression analyses were performed to assess the influence of age, age-adjusted Charlson score, MMRC Dyspnea Scale, SRGO total score and either total walking time, steps per day or fast walking, respectively, on circulating levels of MRproANP and MRproADM as dependent variables.

Results

Patient Characteristics

A total of 105 patients (GOLD II, n = 29; GOLD III, n = 42; GOLD IV, n = 34) were included in the study. Demographics and clinical characteristics of the study population are depicted in table 1. The mean age of the patient population was 66.1 ± 8.7 years and 71% were men. Most patients were taking a long-acting anticholinergic agent (85%) and a combination of ICS/LABA 82 (84%).

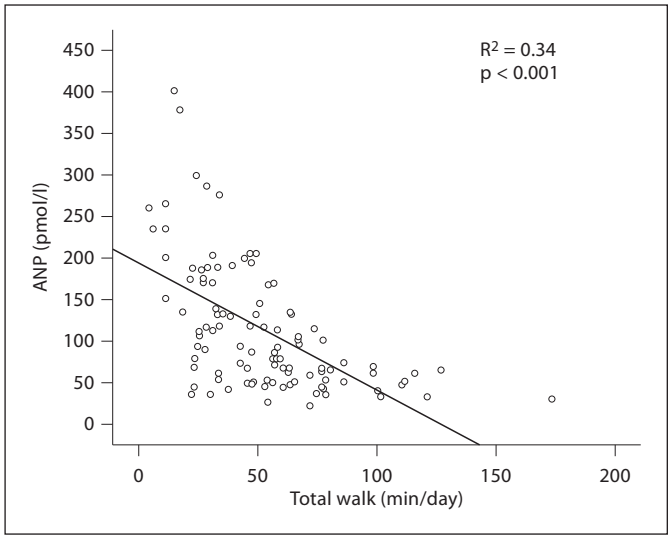

Fig. 1. Scatter plot of total walk (min/day) and MRproANP (pmol/l).

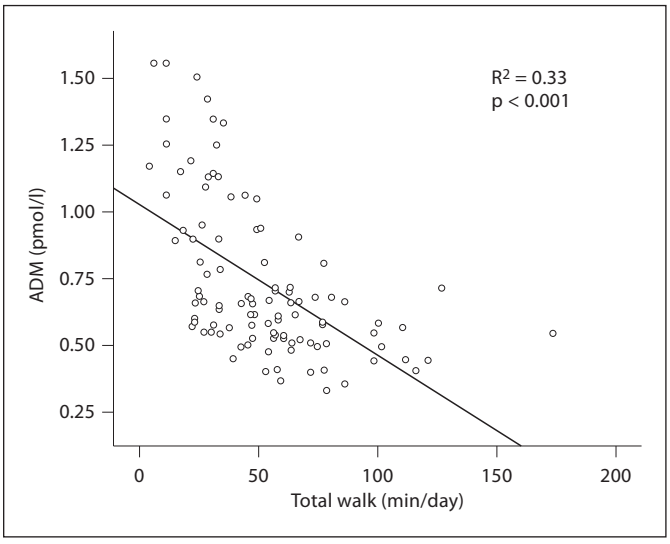

Fig. 2. Scatter plot of total walk (min/day) and MRproADM (pmol/l).

Activity Data

The overall mean wearing time of the accelerometer was 10.7 ± 2.9 h/day. There was a statistical difference ($p < 0.05$) in minutes per day in total walking time, fast walking and steps per day between GOLD II, III and IV.

Bivariate Correlations

Significant correlations ($p \leq 0.01$) with both MRproANP and MRproADM are listed in table 2 and include age, age-adjusted Charlson score, MMRC, total walk, fast walk, and steps per day. SGRQ total score showed a significant correlation with MRproADM ($p = 0.01$) but not MRproANP ($p = 0.046$). FEV_1 (% predicted), SpO_2, depression, BMI and smoking status showed no significant correlation with either biomarker. There was a significant negative correlation between total walk and MRproANP with regression index ($R^2 = 0.34$; $p < 0.001$) and an estimated regression equation of: MRproANP = –1.53 – 7.25 × total walk (fig. 1). Likewise, there was a significant negative correlation between total walk and MRproADM with regression index ($R^2 = 0.33$; $p < 0.001$) and an estimated regression equation of: MRproADM = –0.006 – 7.08 × total walk (fig. 2). There was also a significant negative correlation found between fast walk and MMRC ($R = –0.70$; $p < 0.001$).

Multivariate Regression Analyses

We ran stepwise multivariate regression analyses with either MRproANP or MRproADM as dependent variables (table 3). The first model included age, age-adjusted Charlson score, MMRC, SRGO total score and total walk as covariates. The only independent predictors of MRproANP in this model were age and total walk ($p = 0.015$ and $p < 0.0001$, respectively) and the only independent predictor of MRproADM was total walk ($p < 0.0001$). In the second model we exchanged total walk with steps per day in the list of covariates and outcome remained similar. Here too, age and steps per day were the only independent predictors of MRproANP ($p = 0.045$ and $p < 0.0001$, respectively) and steps per day only was independently predictive of MRproADM ($p < 0.0001$). Finally, we added fast walk as a covariate instead of either total walk or steps per day. In this model, none of the abovementioned covariates were independently predictive of MRproANP and the only independent predictor of MRproADM was MMRC ($p = 0.006$). Fast walk was only independently predictive of MRproANP but not MRproADM once MMRC was excluded from the list of covariates ($p = 0.023$ and $p = 0.057$, respectively).

Discussion

Our results indicate that daily walking activity is an independent predictor of MRproANP and MRproADM in stable COPD patients, two prognostic biomarkers markedly elevated upon exacerbation of COPD and predictive of increased mortality risk. The daily amount of

Table 2. Significant correlations with MRproADM and MRproANP

	MRproADM (R)	p value	MRproANP (R)	p value
Age, years	0.32	0.001*	0.39	<0.0001*
FEV_1 (% predicted)	–0.16	0.11	–0.12	0.24
SpO_2	–0.22	0.025	–0.20	0.040
Age-adjusted Charlson score	0.35	<0.0001*	0.39	<0.0001*
Depression	–0.012	0.90	0.003	0.977
Smoking	0.089	0.369	0.17	0.077
BMI	0.232	0.019	–0.04	0.70
MMRC dyspnea scale	0.54	<0.0001*	0.43	<0.0001*
SGRQ total score	0.33	0.01*	0.20	0.046
Total walk, min/day	–0.57	<0.0001*	–0.58	<0.0001*
Fast walk, min/day	–0.33	<0.0001*	–0.37	<0.0001*
Steps per day	–0.49	<0.0001*	–0.50	<0.0001*

Bivariate correlations of nonparametric variables using Pearson's correlation coefficient R. SpO_2 = Resting SpO_2 saturation. * Statistical significance was set at $p \leq 0.01$.

Table 3. Multivariate regression analysis with total walk or steps per day as covariates

Dependent variable	Model covariates	Regression coefficient B (95% CI)	p value
Model 1			
MRproANP	Constant	48.2 (–68.0; 164)	0.41
	Age, years	2.20 (0.43; 4.0)	0.015*
	Age-adjusted Charlson score	–1.24 (–7.09; 4.6)	0.67
	MMRC dyspnea scale	–4.7 (–27.9; 18.4)	0.69
	SGRQ total score	0.41 (–0.53; 1.34)	0.39
	Total walk, min/day	–1.5 (–2.0; –0.93)	<0.0001*
MRproADM	Constant	0.55 (–0.11; 0.98)	0.014
	Age, years	0.003 (–0.004; 0.009)	0.39
	Age-adjusted Charlson score	0.006 (–0.016; 0.027)	0.60
	MMRC dyspnea scale	0.03 (–0.05; 0.12)	0.43
	SGRQ total score	0.003 (–0.002; 0.006)	0.12
	Total walk, min/day	–0.004 (–0.007; –0.002)	<0.0001*
Model 2			
MRproANP	Constant	14.3 (–108; 137)	0.82
	Age, years	1.9 (0.03; 3.8)	0.045*
	Age-adjusted Charlson score	–0.45 (–6.7; 5.8)	0.89
	MMRC Dyspnea scale	5.7 (–18.3; 29.7)	0.64
	SGRQ total score	0.37 (–0.62; 1.37)	0.46
	Steps per day	–0.013 (–0.019; –0.006)	<0.0001*
MRproADM	Constant	0.44 (–0.01; 0.89)	0.055
	Age, years	0.002 (–0.005; 0.009)	0.56
	Age-adjusted Charlson score	0.008 (–0.015; 0.031)	0.48
	MMRC dyspnea scale	0.067 (–0.021; 0.15)	0.13
	SGRQ total score	0.003 (–0.001; 0.006)	0.15
	Steps per day	–0.0004 (–0.0006; –0.0001)	<0.0001*

Multivariate regression analysis with MRproANP and MRproADM as dependent variables and either total walk (model 1) or steps per day (model 2) included in the lists of covariates. * Statistical significance was set at $p \leq 0.05$.

physical activity was inversely proportional to levels of circulating MRproADM across increasing GOLD stages, meaning that GOLD IV patients presented with lowest levels of daily walking activity and highest levels of circulating MRproADM. This linear trend between activity and biomarker expression was not observed for MRproANP. Although our data suggests a meaningful association between physical activity and both biomarkers associated with cardiac distress in stable COPD patients, this association seems significantly more pronounced with MRproADM, a more novel biomarker known for its diagnostic capabilities in the presence of acute heart failure [39]. MRproADM is considered a surrogate marker of overall cardiopulmonary distress including the development of transient myocardial dysfunction due to its counter regulatory properties in response to bronchoconstriction, pulmonary arterial hypertension, airway inflammation and/or infection during exacerbation of COPD [12].

The development of underlying cardiovascular disease, in particular heart failure, is a common cause for mortality in COPD. The recent TORCH study was able to show that 30% of deaths in COPD patients were related to cardiovascular morbidity and 40% were due to COPD [40]. Stolz et al. [12] were able to demonstrate the importance of systemic biomarkers of cardiac distress in patients with COPD by suggesting that MRproANP and MRproADM, both well recognized in terms of clinical prognosis in cardiovascular disease and/or heart failure, also show prognostic significance in COPD in terms of hospitalization due to exacerbation and long-term survival [11, 41]. Moreover, Watz et al. [42] were able to demonstrate higher values of systemic inflammation markers and concomitant cardiovascular comorbidities such as left ventricular dysfunction in physically inactive patients with COPD compared to those that showed moderate activity levels.

A recent study by Garcia-Rio et al. [14] was able to show a linear dose-response relationship between accelerometer-derived physical activity levels and mortality or hospital admission due to severe acute exacerbations of COPD. The authors suggest that physical inactivity augments exacerbation of COPD, rather than vice versa, leading to more frequent hospital admission due to exacerbation compared with patients who showed moderate to high levels of physical activity [14]. In addition, it has been shown that patients who were markedly inactive following hospital discharge after exacerbation of COPD were more likely to be readmitted if activity levels remained low [43]. Similar results have been reported using self-reported physical activity levels and health status questionnaires [13, 25]. Our data adds to this existing pool of evidence by linking physical activity to two novel cardiac biomarkers known for their clinical significance in predicting outcome in COPD patients. Therefore, we hypothesize that the use of daily activity monitoring might prove useful in order to simplify risk stratification of COPD patients in daily living and thus facilitate early recognition of patients at risk.

Previous investigators have shown only weak correlations with lung parameters, particularly the degree of airway obstruction and physical activity levels [14, 22, 44]. Nevertheless, walking intensity is attenuated by disease severity and markedly reduced in patients with higher GOLD stages [18–22, 45, 46]. In our study population the level of exertional dyspnea was found to be a significant confounder in regards to the predictive strength of walking intensity but not walking volume on circulating levels of prognostic biomarkers. Seemingly, exertional dyspnea arises from airflow limitation due to vasoconstriction of the pulmonary vasculature, thus limiting movement intensity. However, caution should be taken when solely using absolute activity volume (min/day) irrespective of intensity, as patients with COPD tend to show intermittent activity spurts instead of continuous movement allowing for total activity to possibly be overestimated [18–22].

In conclusion, we could show an independent and significant association between walking activity assessed by accelerometry and two prognostic biomarkers of cardiac distress in patients with COPD. Employing activity monitors in stable COPD patients enables continuous patient monitoring in a real-life setting and might simplify risk stratification by enabling early recognition of patients at risk for exacerbation of COPD. Subsequent future studies are needed, however, to evaluate whether continuous activity monitoring can ascertain exacerbation of COPD in patients at risk and if changes in daily physical activity can be directly associated to changes in circulating biomarkers of cardiac distress.

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