Both moderate and severe exacerbations accelerate physical activity decline in COPD patients

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Take home message: Exacerbations have a negative impact on long-term daily physical activity of COPD patients.

Keywords: COPD, physical activity, exacerbations, prospective study.

Text Word count: 1198

Figures: 1

To the editor

Physical activity (PA) is a relevant outcome measure in COPD. Low PA is prevalent and drives prognosis [1]. Unfortunately, the determinants of PA and its change over time are poorly understood [1]. The fact that the PA progressively declines over time along with worsening of lung function and health status [2], suggests that the PA decline could be due to the progression of the disease and specifically to acute exacerbations [3]. An acute reduction in PA at the onset has been reported both in severe exacerbations requiring a hospitalization [4] and in ambulatory treated exacerbations [5,6]. A sustained PA reduction has been shown one month after hospital discharge [4] whereas PA almost returns to stable levels after community treated exacerbations [6]. One study found faster PA decline in patients with a history of ≥2 exacerbations in the 12 months prior to the study [5]. This analysis did not adjust for confounders of the association (*e.g.* airflow obstruction, symptom burden) or external variables influencing PA (*e.g.* climate). It could also be argued that the greater decline in PA was due to lower health status at baseline. Although PA is an important outcome for COPD patients, little is known about the role of exacerbations on patients' experience of PA. Importantly, both the amount of activity and difficulties experienced during activity are integral to the concept of PA limitation [7]. The aim of the present analysis was to assess the association between the number and severity of exacerbations and changes in PA and PA experience.

As part of the IMI-JU PROactive study [7,8], patients with COPD from mixed healthcare settings (tertiary hospitals, rehabilitation centres and primary care) in 5 European centres [Athens (Greece), Edinburgh and London (UK), Leuven (Belgium) and Groningen (The Netherlands)] were studied at baseline and at 12 months follow-up. Patients followed and those lost to follow-up were comparable. Objective PA was measured using the Dynaport Movemonitor accelerometer (McRoberts BV, The Hague, The Netherlands). The main PA outcome analysed was the change (difference between baseline and one year) in daily step count, the secondary outcome was the change in intensity during locomotion. Patient experience of PA was assessed with the Clinical visit PROactive Physical Activity in COPD (C-PPAC) instrument [7], which consists of a total score and amount and difficulty scores. The number and severity of COPD exacerbations during the 12-month follow-up was retrieved [8]. We defined exacerbations as moderate (treated in an ambulatory setting with systemic antibiotics and/or systemic glucocorticosteroids) or severe (requiring hospital admission), following the GOLD initiative guidelines [9]. In addition to the number of exacerbations, we generated a variable combining the number and the severity of exacerbations. The association between exacerbation variables and PA change was analysed using regression analysis adjusted for

baseline PA values. To remove the effect of potential confounders (see footnote Figure 1) we built a multivariable linear model for each PA outcome. Sensitivity analyses were performed excluding patients (i) with a COPD admission in the year before recruitment, (ii) with extreme PA values ($\leq 5^{th}$ or $\geq 95^{th}$ percentiles) and (iii) with a COPD admission 2 months prior to the final measurement to exclude an acute effect. As post hoc explanatory analyses we tested the (bivariate) association between exacerbation variables and change in FEV_1, 6MWD and mMRC, adjusted for baseline. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

The present analysis is based on 141 patients with valid data at baseline and follow-up (75% male, with a mean (SD) of 67 (8) years, 27 (5) $kg.m^{-2}$ BMI, 59 (21) % predicted FEV_1) of whom eighty-one (57%) experienced at least one exacerbation during follow-up. In the whole group there was a small, non-significant decline in step count [5209 (3050) $steps.day^{-1}$ at baseline *vs* 5019 (3099) $steps.day^{-1}$ at follow-up]; while movement intensity [1.82 (0.26) $m.s^{-2}$ at baseline *vs* 1.80 (0.28) $m.s^{-2}$ at follow-up], exercise capacity [452 (119) m at baseline *vs* 450 (123) m at follow-up] and FEV_1 [1.62 (0.69) l at baseline *vs* 1.63 (0.69) l at follow-up] did not change. Patients had a baseline mean C-PPAC total score of 69 (13), with domain scores for amount and difficulty 64 (16) and 74 (15), respectively.

The number of exacerbations was related to the decline in $steps.day^{-1}$. In the multivariable model, a mean (SE) change of 251 (207), -144 (262) and -797 (244) $steps.day^{-1}$ was observed in patients who had presented no, one, or two or more exacerbations during follow-up respectively (Figure 1A). Patients experiencing two or more moderate exacerbations (-753 $steps.day^{-1}$) and those experiencing at least one severe exacerbation (-705 $steps.day^{-1}$), showed a larger decline in PA than those with no exacerbations (Figure 1B). There was no association between exacerbations during follow-up and changes in PA intensity ($m.s^{-2}$). In relation to patient experience of PA, Figure 1 (C,E) shows that patients with 2 or more exacerbations suffered more deterioration in C-PPAC amount (-4.2 points) and difficulty (-1.9 points) scores compared to patients having no or only one exacerbation. Patients experiencing two or more moderate exacerbations or at least one severe exacerbation showed a larger decline in C-PPAC amount and difficulty scores than those with no exacerbations, however some of these associations were not statistically significant (Figure 1 D,F). All sensitivity analyses yielded comparable results. Having exacerbations was related to a significant ($p<0.01$) larger increase in mMRC score but not to changes in 6MWD or FEV_1.

The present analyses show that the acute drop in PA after an exacerbation [4,5,6] has an important and lasting effect that cannot be attributed to confounders or baseline PA. A higher exacerbation

frequency was, as expected, associated with a more pronounced PA decline. Patients with frequent exacerbations constitute a specific disease phenotype with a worse prognosis, specifically a faster loss in lung function [10], a greater worsening of health status [11] and a substantial reduction in the amount of PA (-797 steps.day^{-1}) as indicated by our findings. An unexpected finding from this study is that two or more moderate events result in a long-term decline that is clinically relevant [12] and equivalent to that of a severe event, confirming the importance of prevention and early management of exacerbations regardless of the severity [9].

The fact that exacerbations result in a decrease in the amount of PA can be interpreted as part of the multiple systemic consequences [9]. First, we could hypothesize that the decline is a consequence of a loss in exercise capacity. Against this hypothesis, our data fail to show an association between exacerbations during follow-up and changes in exercise capacity. Second, the PA decline could potentially be explained based on a worsening of symptoms during an exacerbation leading to more inactivity, bringing patients in a vicious cycle of symptoms and inactivity [13]. Based on our explanatory analysis showing an association between exacerbations and an increase in dyspnoea, the latter hypothesis would be a plausible mechanism.

The present results have important implications for daily clinical practice and underscore the importance of identifying frequent exacerbators, as supported by the combined GOLD classification [9]. Our results support the promotion of interventions to increase PA, such as coaching programs in the less [14] or pulmonary rehabilitation in the more severe patients [15] after an exacerbation.

ACKNOWLEDGEMENTS

The PROactive Consortium members are as follows. Nathalie Ivanoff: Almirall, Barcelona, Spain; Niklas Karlsson and Solange Corriol-Rohou: AstraZeneca AB, Gothenburg, Sweden; Ian Jarrod: British Lung Foundation, London, UK; Damijen Erzen: Boehringer Ingelheim, Nieder-Ingelheim, Germany; Mario Scuri and Roberta Montacchini: Chiesi Farmaceutici S.A. Parma, Italy; Paul McBride: Choice Healthcare Solutions, Hitchin, UK; Nadia Kamel: European Respiratory Society, Lausanne, Switzerland; Maggie Tabberer: GlaxoSmithKline, Uxbridge, UK; Thierry Troosters, Wim Janssens, Heleen Demeyer and Fabienne Dobbels: Katholieke Universiteit Leuven, Leuven, Belgium; Judith Garcia-Aymerich: ISGlobal, Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; Pim de Boer: Netherlands Lung Foundation, Amersfoort, The Netherlands; Karoly Kulich Novartis, Basel, Switzerland; Michael I. Polkey and Nick S. Hopkinson: Royal Brompton and Harefield NHS Foundation Trust, London, UK; Ioannis Vogiatzis: Thorax Research Foundation, Athens, Greece; Enkeleida Nikai: UCB, Brussels, Belgium; Thys van der Molen and Corina De Jong: University Medical Center, Groningen, The Netherlands; Roberto A. Rabinovich and Bill MacNee: University of Edinburgh, Edinburgh, UK; Milo A. Puhan and Anja Frei: University of Zurich, Zurich, Switzerland.

We are grateful for the input from the PROactive project ethics board, advisory board and patient input platform.

FINANCIAL SUPPORT STATEMENT

The PROactive project is funded by the Innovative Medicines Initiative Joint Undertaking (IMU JU) #115011. This work was supported by the Flemish Research Foundation (grant # G.0871.13). HD is the recipient of a joint ERS/SEPAR Fellowship (LTRF 2015) and is a post-doctoral research fellow of the FWO-Flanders. ZL is the recipient of an ERS fellowship (LTRF 2016). ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya.

POTENTIAL CONFLICTS OF INTEREST

Thierry Troosters has served on advisory boards and his institution received speaker fees from BI, AZ, Novartis. Judith Garcia-Aymerich has received speaker fees from Esteve and her institution has received speaker fees from AZ, outside the submitted work. Michael Polkey has served on advisory boards for BI.

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FIGURES

Figure 1. Decline in steps.day^{-1} (A-B) and C-PPAC instrument (D-F) according to COPD exacerbations in the 12-m follow-up (multivariable linear regression).

Data presented as estimated marginal means (Least squares means) and SEM. Final models are adjusted for baseline physical activity and total CAT score. Other potential confounders (age, gender, smoking habit, BMI, any COPD admissions in previous 12 months, FEV_1 % predicted, FVC % predicted, FEV_1/FVC ratio, ATS/ERS stage, 6MWD, mMRC and HADS anxiety and depression scores) were tested and finally not included because they were not independently related to both the exposure and the outcome, nor modified (>10% change) the estimates for the remaining variables. * Patients without severe exacerbations. ** Irrespective of the number of moderate exacerbations.