A few more steps lead to improvements in endothelial function in severe and very severe COPD

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Abstract: Introduction: Cardiovascular disease is among the most prevalent concomitant chronic diseases in COPD. Physical activity (PA) modifies endothelial function and is commonly impaired in COPD. However, studies directly investigating the effects of increased PA on endothelial function in COPD are lacking. We investigated the effect of changes in PA on endothelial function in patients with severe to very severe COPD. Furthermore, we determined which variables modify this effect. Materials and methods: This is a secondary outcome analysis from a randomised controlled trial investigating the effects of combined PA counselling and pedometer-based feedback in COPD. We analysed the change in PA based on three visits during one year. We measured PA using a validated triaxial accelerometer, and endothelial function using flow-mediated dilation. Results: Data was analysed from 54 patients, which provided 101 change scores. Multiple regression modelling, including adjustment for baseline step count, showed strong evidence for an association between changes in flow-mediated dilation and changes in PA (p < 0.001). The analysis of several effect modifiers showed no evidence of any influence on the interaction between PA and endothelial function: smoking status (p = 0.766), severity of airflow obstruction (p = 0.838), exacerbation frequency (p = 0.227), lung diffusion capacity of carbon monoxide % pred. (p = 0.735). Conclusion: We found strong evidence that increasing steps per day ameliorates the heavily impaired endothelial function in patients with severe and very severe COPD. Further studies should examine which factors influence this relationship in a positive or negative manner. Keywords: COPD; Cardiovascular disease risk; Endothelial function; Physical activity.

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A few more steps lead to improvements in endothelial function in severe and very severe COPD

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ABSTRACT

Introduction: Cardiovascular disease is among the most prevalent concomitant chronic diseases in COPD. Physical activity (PA) modifies endothelial function and is commonly impaired in COPD. However, studies directly investigating the effects of increased PA on endothelial function in COPD are lacking. We investigated the effect of changes in PA on endothelial function in patients with severe to very severe COPD. Furthermore, we determined which variables modify this effect.

Materials and methods: This is a secondary outcome analysis from a randomised controlled trial investigating the effects of combined PA counselling and pedometer-based feedback in COPD. We analysed the change in PA based on three visits during one year. We measured PA using a validated triaxial accelerometer, and endothelial function using flow-mediated dilation.

Results: Data was analysed from 54 patients, which provided 101 change scores. Multiple regression modelling, including adjustment for baseline step count, showed strong evidence for an association between changes in flow-mediated dilation and changes in PA ($p < 0.001$). The analysis of several effect modifiers showed no evidence of any influence on the interaction between PA and endothelial function: smoking status ($p = 0.766$), severity of airflow obstruction ($p = 0.838$), exacerbation frequency ($p = 0.227$), lung diffusion capacity of carbon monoxide % pred. ($p = 0.735$).

Conclusion: We found strong evidence that increasing steps per day ameliorates the heavily impaired endothelial function in patients with severe and very severe COPD. Further studies should examine which factors influence this relationship in a positive or negative manner.

Clinical Trial Registration: www.ClinicalTrials.gov, NCT03114241.

1. Introduction

Cardiovascular disease (CVD) is among the most prevalent concomitant chronic diseases in patients with chronic obstructive pulmonary disease (COPD) [1], with patients having 2.5 times the risk to develop such when compared to healthy controls [2]. Furthermore, robust evidence from cohort studies is available indicating an increased risk of CVD-related mortality in patients with COPD [3–6]. The severity of airflow obstruction has been shown to be an independent predictor of cardiovascular events, accordingly suggesting higher risk for more severe COPD [7,8].

The endothelium is highly responsive to stimuli such as shear stress, circumferential wall strain, systemic inflammation, and oxidative stress [9,10]. Chronic disease with features such as systemic inflammation and noxious exposure reduce endothelial compliance and lead to dysfunction [11]. Endothelial dysfunction indicates CVD already in early disease stages and is reversible [12]. In patients with COPD, endothelial function has been shown to be remarkably impaired compared to healthy controls [13,14], to decrease significantly over time [15], to be associated with the severity of airflow limitation [16,17], physical...
activity (PA) [18], and exercise capacity [19]. Its function can be assessed in a non-invasive manner and provides predictive information concerning the future occurrence of cardiovascular events [20–23].

Due to the high burden of endothelial dysfunction in COPD, focus should be put on interventions improving endothelial function in these patients. Results from previous studies indicate PA as a modifying factor on endothelial function [17], while PA impairment is common in patients with COPD [24]. However, studies directly investigating the effects of increased PA on endothelial function in COPD are lacking.

Thus, we aimed to investigate the effect of changes in daily PA on endothelial function in patients with severe to very severe COPD and to determine variables modifying this effect.

2. Materials and Methods

2.1. Study subjects

Data was collected between May 2017 and May 2020. This study describes the analysis of the secondary outcome from a randomised controlled trial (RCT) investigating the effects of a combined PA counselling and pedometer-based feedback intervention in severe and very severe COPD [25]. Patients aged 40 years or older with diagnosed severe and very severe COPD (i.e. FEV\(_1\) <50% pred.) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)-guidelines [1] were assessed for eligibility. Patients with diagnosed mental or physical disability precluding informed consent or compliance with the study protocol, experiencing an exacerbation of COPD within the last 6 weeks, attending pulmonary rehabilitation within the last 6 months and pregnant patients were not included. For this analysis, data of patients with at least two consecutive evaluable endothelial function measurements and corresponding PA data out of three study visits were considered.

2.2. Study design

This is a secondary outcome analysis from a single-centre parallel group, randomised controlled trial [25].

The study was conducted in accordance with the declaration of Helsinki and all subjects provided written informed consent. The Ethics Committee of the Canton of Zurich approved the study (EK-ZH-NR: 2016-00151), and the study is registered on www.ClinicalTrials.gov, NCT03114241.

3. Methods

3.1. Experimental design

In the original study, patients were randomised to either a control group receiving usual care or an intervention group receiving PA counselling and pedometer-based feedback in addition to usual care [25]. Overall, three visits took place (i.e. baseline, 3-month, and 12-month visit). During the study period, the intervention group received PA counselling and pedometer-based feedback between the baseline and 3-month visit. Thereafter, an unsupervised period followed, in which the patients were invited to maintain an increased PA. The longitudinal study design allowed us to investigate how the changes in PA affected changes in endothelial function over time.

3.2. Flow-mediated dilation

Endothelial function was assessed via flow-mediated dilation (FMD) of the brachial artery according to published recommendations [22]. Study subjects rested in supine position in a temperature controlled room for 10 min before the measurement. Additionally, patients were asked to abstain from alcohol, tobacco, caffeine, and strenuous exercise for the 24 h before the measurement. The patient’s medication was documented. Longitudinal images of the brachial artery were obtained with a high-frequency (10.0 MHz) ultrasound scanning probe (9L probe on Vivid E9, GE Healthcare, Boston MA, USA) proximal to the antecubital fossa. Two-dimensional images, acquired with ECG gating, were obtained using Doppler ultrasound imaging to assess arterial diameter and flow velocity at baseline. Thereafter, reactive hyperaemia was induced by inflating a pneumatic tourniquet (boso med 1, Bosch + Sohn GmbH und Co. KG, Jungingen, Germany) around the forearm to 200 mmHg and deflating after 5 min. Arterial diameter and flow velocity were repeatedly measured at 45 and 120 s after vascular occlusion. Nitrate-mediated dilation (NMD), was assessed 3 min after a single sublingual dose (0.5 mg) of glyceryl trinitrate (GTN).

All measurements were stored and analysed offline by an assessor who was blinded to group allocation and did not conduct the measurements. Brachial artery diameter was measured automatically at the onset of the R wave using dedicated software (Vascular Research Tools 5; Medical Imaging Applications LLC, Coralville IA, USA). Endothelial-dependent (i.e. FMD) and endothelial-independent vasodilation (i.e. NMD) represent the changes of arterial diameter in percent as related to the baseline diameter. FMD and NMD were derived from the mean values of at least three cardiac cycles at each time point. For analysis, maximum FMD and NMD values were used.

3.3. Daily physical activity

The number of steps per day, an indicator for PA, was measured through a triaxial accelerometer of a multisensory activity monitor (SenseWear Pro™; Bodymedia Inc., Pittsburgh, PA, USA), validated for the use in COPD populations [26]. The device was worn on the upper left arm for seven consecutive days at baseline, three and 12 months of the study. The threshold for valid data was set at 4 days with a minimum of 22.5 h on-body duration per day [24]. Seasonality was considered in the analysis by the season during which the visit took place (i.e., summer, autumn, winter, and spring).

3.4. Respiratory variables

All patients underwent standard pulmonary function testing according to American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines to measure forced expiratory volume in 1 s (FEV\(_1\)), forced vital capacity (FVC), and lung diffusion capacity (TLCO) [27,28]. All reported values were obtained after short-acting bronchodilator application.

3.5. Exacerbations

Acute exacerbations of COPD (AECOPD) were defined as increases in COPD specific symptoms such as dyspnoea, cough and/or sputum production leading to a prescription of antibiotics and/or corticosteroids. Severe acute exacerbations of COPD (SAECOPD) were defined as AECOPD that required hospital admission. AECOPD and SAECOPD count was observed through patient’s medical history and confirmed through medical documentation of the patient’s general practitioner, pulmonologist, and hospital. Patients were categorized into infrequent exacerbators (0–1 annual AECOPD or SAECOPD), and frequent exacerbators (≥2 annual AECOPD or SAECOPD).

3.6. Analysis

All results are shown as mean (SD) or median (25th, 75th percentile) unless otherwise stated. Normal distribution of the variables was determined visually using quantile-quantile plots. A two-sided p-value of <0.05 was considered to be statistically significant.

The primary outcome of the study was change in daily step count, an indicator for PA, from baseline to 12 months after inclusion. Sample size calculation was performed to detect a difference in daily step count of 725 (1000) steps per day between the groups at study end and is based
on data from our previous cohort [29]. Calculation determined 37 patients per group to be sufficient, yielding at a power of 80%, setting α to 0.05 and accounting for a dropout rate of 15%.

For the analysis of the secondary outcome FMD, a multiple regression model containing the changes in FMD between subsequent follow-up visits as the dependent variable and the change in daily step count (expressed as 100 steps per unit) as the independent variable was fitted. A random intercept for each subject and random slopes for changes in PA were assumed out of the graphical interpretation of the raw data. The model was adjusted for baseline step count and measurement time point. This model was tested against various models including single variables possibly modifying the effect (i.e. smoking status, GOLD classification, exacerbation frequency, inhalation (long-acting beta-agonists (LABA), glucocorticosteroids (GC)), lung diffusion capacity).

Statistical analysis was performed using STATA Version 16 (StataCorp. 2019, Texas, TX, USA).

4. Results

Of the 74 patients included in the original study, 57 (29 out of the intervention, and 28 out of the control group) attended at least two follow-up visits with evaluable FMD measurements and were included for analysis. For details see Fig. 1. Overall, 100 change scores were available for analysis from these patients. In 44 out of 57 patients, change scores from baseline to follow-up 1 and follow-up 1 to follow-up 2 were analysed, in 10 patients only from baseline to follow-up 1 and in the remaining 3 patients from follow-up 1 to follow-up 2.

The sample had a mean age of 65 (9) years, was mainly male (67%), and had a FEV1 of 3.45 (9.1) % pred. Administered drugs with known effects on endothelial function were antihypertensive drugs in 29 (51%), β-blockers in 13 (23%), cholesterol-lowering drugs in 14 (25%), and LABA + GC in 32 (56%) of the participants. Complete baseline characteristics are shown in Table 1. The analysis sample did not differ from the sample in the original study in terms of baseline characteristics.

Baseline FMD was 2.8 (1.4) %, changed by −0.56 (1.64) % in the intervals with stable or declining PA, and increased by 0.99 (1.67) % in the phases with enhanced PA. Baseline NMD was 15.5 (7.8) %, changed by −2.1 (−4.5/2.7) % in the phases with stable or declining PA, and by −1.2 (−8.7/1.4) % in the phases with enhanced PA. Baseline PA was 2451.6 (1151.7, 4315.9) steps per day, changed by −390 (−1411, −101) steps per day in the phases with stable or declining PA, and increased by 1102 (503, 1718) steps per day in the phases with PA improvement. Additional change scores are displayed in Table 2.

Multiple regression modelling, including adjustment for baseline step count and time point of measurement, showed strong evidence for an association between changes in FMD and changes in daily step count (B = 0.07, 95% CI = 0.04/0.10, p < 0.001). See Fig. 2 for a graphical display of the association between changes in FMD and PA. The analysis of effect modifications showed no evidence for an influence of smoking status (B = 0.10, 95% CI = −0.54/0.74, p = 0.766), severity of airflow obstruction (B = 0.06, 95% CI = −0.48/0.59, p = 0.838), exacerbation frequency (B = 0.36, 95% CI = −0.22/0.93, p = 0.227), LABA + GC (B = −0.10, 95% CI = −0.23/0.04, p = 0.155), and TLCO % pred. (B = 0.00, 95% CI = −0.14/0.02, p = 0.735). There was no evidence for an association between change in NMD and change in daily step count (B = −0.00, 95% CI = −0.00/0.00, p = 0.261).

5. Discussion

This is the first study to investigate the impact of intended changes in PA on endothelial function in patients with severe and very severe COPD. We found strong evidence that alterations in PA are independently related to endothelial function. Furthermore, there is no evidence that this effect is influenced by smoking status, severity of airflow obstruction, exacerbation frequency, and lung diffusion capacity.

As the cut-off value in FMD discriminating for increased risk for developing CVD is drawn at 7.1% [36], and the cut-off value in FMD discriminating for severe endothelial dysfunction is drawn at 4.1% [31], the patients in our sample presented a severely impaired FMD of 2.8 (1.4)%. Translating our results, the observed median increase of PA in our analysis was 1102 steps per day, associated with a mean increase in FMD of approximately 1%, leading to a reduction in risk for cardiovascular events of 8–13% [22]. Future studies might investigate if PA enhancement would further accentuate the decrease in CVD risk achieved through medication.

Treatment of CVD and endothelial dysfunction in COPD should be carried out according to established guidelines [1], including beta-blockers [32] and statins [33]. Our findings suggest the addition of PA increasing interventions to the management of patients with COPD and endothelial dysfunction.

In comparison to the available evidence, our findings support the positive association between PA and FMD in various stages of COPD presented in previous cross-sectional studies [13,17], by adding strong evidence that endothelial dysfunction in severe to very severe COPD is
modifiable through PA increasing actions. However, available evidence on the most effective interventions in promoting PA in COPD is inconclusive [34] and the results out of our RCT suggest that some patients with COPD are more prone to respond positively to PA enhancement interventions than others. Therefore, future studies should focus on phenotyping patients with COPD according to their ability to respond to PA enhancement programmes.

Interestingly, the previously suggested association of airflow obstruction with endothelial dysfunction could not be confirmed as an effect modifier influencing the impact of PA on FMD in our study [17], which might be due to our sample consisting exclusively of patients with severe to very severe COPD. With respect to the other modifying variables investigated, our findings are in line with a previous study from our department, stating that smoking status and exacerbation frequency may not modify the impact of increased PA on FMD in severe to very severe COPD [17]. However, only few patients in our sample were current smokers (14%).

Our finding of a non-significant change in NMD confirms that increased PA targets the endothelium directly, independent from vascular smooth muscle cell function.

Future investigations on the topic are needed and are suggested to identify the FMD response of different phenotypes of COPD patients to PA enhancing interventions.

This study has some limitations. As it was a secondary analysis, the findings may be influenced by insufficient power. However, the lack of power does not affect the strong evidence towards a positive impact of increased PA on endothelial function in COPD. Secondly, the rate of patients not attending at least two subsequent follow-up visits with FMD measurements was 23%. However, the patients not being considered for the analysis were not different in terms of baseline characteristics – especially disease severity - as compared to the current study sample. To test for generalizability of our findings, a further study with more participants including milder COPD stages would be needed.

6. Conclusion

In conclusion, we found strong evidence that an enhancement of PA ameliorates the heavily impaired endothelial function in patients with severe and very severe COPD. Targeted PA enhancing interventions are therefore encouraged for clinical practice. However, the most effective means for this are still a matter of research. Factors influencing the relationship between PA and endothelial function in a positive or negative manner remain to be studied.

Summary conflict of interest statements

M. Kohler reports personal fees from Bayer, Astra Zeneca, Boehringer Ingelheim, Novartis, Roche, CSL Behring, Mundipharma outside the submitted work. M. Kohler is member of the board of the Deep Breath Initiative (DBI). A company that provides services in the field of breath analysis.

C.F. Clarenbach reports personal fees from Roche, Novartis, Boehringer Ingelheim, GSK, Astra Zeneca, Sanofi, Vifor, Mundipharma outside the submitted work.

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Author contributions

NAS and CFC designed the study. DK and NAS collected study data. DK analyzed the data and wrote the first draft of the manuscript. NAS, ST, MR, MK, and CFC contributed to data interpretation and revised the study.

Table 2
Change scores stratified according to the course of PA.

| Total | Baseline to follow-up 1 | Follow-up 1 to follow-up 2 |
|-------|-------------------------|---------------------------|
|       | N          | FMD, %     | Step count, N | N          | FMD, %     | Step count, N | N          | FMD, %     | Step count, N |
| Declining or stable PA | 63 | -0.56 (1.64) | -390 (-1411, -101) | 31 | -0.11 (1.34) | -250 (-512/-37) | 32 | -1.01 (1.79) | -685 (-2312/-238) |
| Increasing PA            | 38 | 0.99 (1.67)  | 1102 (503, 1718) | 23 | 1.37 (1.72)  | 1512 (1040/3072) | 15 | 0.41 (1.45)  | 584 (133/870)      |

Data are median (25th, 75th percentile), mean (SD) or N. PA: physical activity; FMD: flow-mediated dilation.
manuscript critically. CFC was the primary investigator.

Role of the sponsors

The funder did not contribute to any part of the study.

Other contributions

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Data availability statement

The data supporting the findings of this study are available upon reasonable request to the corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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