HYPOTHESIS

Does physical inactivity cause chronic obstructive pulmonary disease?

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ABSTRACT

COPD (chronic obstructive pulmonary disease) is the most common pulmonary disease and is the only common cause of death in which mortality is presently rising. It is caused by the inhalation of smoke, which leads to oxidative stress and inflammation both in the lungs and systemically. Reduced physical activity is a well-recognized consequence of the condition, but we argue here that inactivity is itself an early cause of lung function decline and symptoms. This hypothesis is supported by data from population studies that link activity levels to decline in spirometric indices, both in smokers and non-smokers. In addition, smokers with low physical activity levels are more likely to be diagnosed subsequently with COPD. Physical exercise reduces oxidative stress, has an anti-inflammatory effect and reduces the frequency of upper respiratory tract infections, providing a number of mechanisms by which it could attenuate the harmful effects of smoking. There is sufficient evidence to justify population trials of lifestyle interventions aimed at improving physical activity levels and reducing lung function decline in people diagnosed with early COPD through spirometry screening.

INTRODUCTION

COPD (chronic obstructive pulmonary disease) is caused by the inhalation of noxious material, particularly smoke from tobacco or from the burning of biomass for cooking and heating [1]. It is a major and growing public health problem affecting approx. 10% of people over the age of 40 worldwide [2]. It is predicted to become the third largest cause of death and the fifth biggest contributor to disability adjusted life years by 2020 [3]. In the classic disease model, inhaled smoke causes inflammation and oxidative stress which leads to airway disease – chronic bronchitis, and the destruction of the lung parenchyma – emphysema. These pathological processes combine to produce expiratory airflow limitation. This reduced ventilatory capacity, combined with pulmonary vascular abnormalities and cardiac impairment, produces breathlessness and exercise limitation.

In addition, COPD is recognized to have significant systemic consequences and to be associated with a range of common co-morbidities. The distinction between the two is difficult and depends on whether the systemic features are considered to represent an 'overspill' of inflammatory mediators from the lung, or rather if COPD is considered to be one manifestation of an underlying systemic disorder or common susceptibility (reviewed in [4,5]).

COPD is insidious and progressive, with many patients not presenting until they have relatively advanced disease. For this reason, lung function screening has been advocated to identify early disease in at risk groups; usually defined as people with respiratory symptoms, including cough and sputum production, who are or have been smokers. Since smoking cessation is known to influence decline in lung function [6–9] and mortality [10] in COPD, and a diagnosis of COPD also increases the chance of quitting [11,12], it will clearly remain the cornerstone of health intervention at this point. Evidence that increasing physical activity levels in people with early COPD could reduce disease progression would

Key words: co-morbidity, chronic obstructive pulmonary disease (COPD), exercise, lung function, oxidative stress, smoking.
Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; IL, interleukin; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α.
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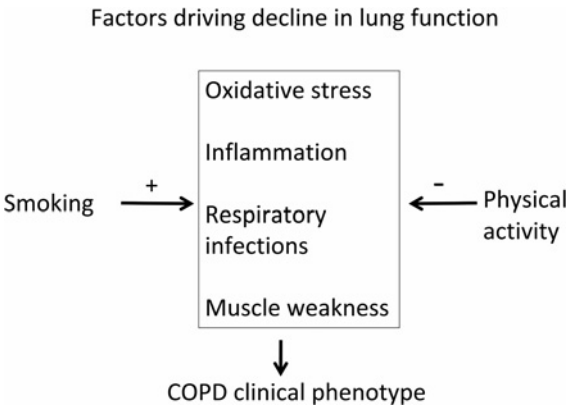

Figure 1 Mechanisms by which physical activity might reduce the impact of smoking on the lungs

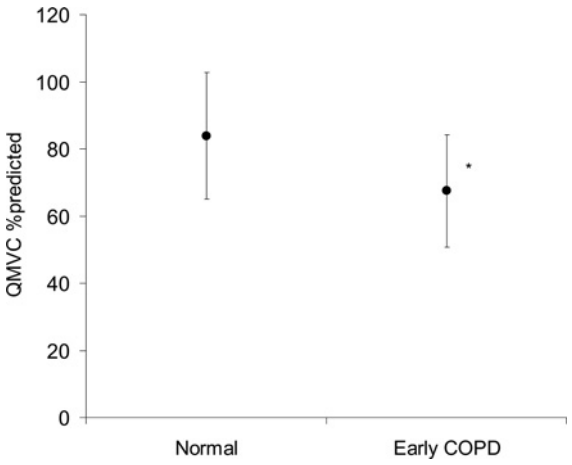

Figure 2 Quadriceps strength was reduced in COPD patients with early COPD (GOLD grades I and II) compared with age-matched controls

In COPD patients with early COPD, quadiceps strength was 67.5 (16.8) % predicted compared with 83.9 (18.8) % predicted (*$P = 0.0003$). Re-analysis of data from [95].

open the possibility of an additional useful intervention in this context, further strengthening the case for a robust screening programme.

Although it is clear that patients with advanced COPD have reduced activity levels because of their condition, here we advance the hypothesis that a low level of physical activity, while being a consequence of advanced COPD is itself a factor driving disease progression. Certainly, as only a proportion of smokers develop COPD, and smokers with and without COPD both have airway inflammation, there must be other modifying factors, both genetic and environmental, that determine individual susceptibility [13]. That physical activity could be making a significant contribution to this, is based first on epidemiological observations and secondly on the known effects of exercise on factors thought to be driving the progression of lung disease in COPD, including systemic inflammation, oxidative stress and infection.

Our hypothesis is based on the following arguments (Figure 1): (i) reduced physical activity and muscle strength are features of early COPD; (ii) patients with low levels of physical activity have a more rapid decline in lung function; and (iii) plausible biological pathways exist to explain how inactivity might contribute to oxidative stress and inflammation, with deleterious consequences for both lung and skeletal muscle.

REDUCED PHYSICAL ACTIVITY IN COPD

Since daily activities cause undue breathlessness in COPD patients, it is understandable that they should either choose to, or be forced to, reduce their activity levels to avoid this sensation. Indeed the inability to perform daily activities because of physical limitation is the most common symptomatic complaint in COPD patients [14]. Reduced physical activity has been observed in all stages of COPD [15–18] and confers a poor prognosis. Patients with low physical activity levels are more likely to be admitted to hospital with acute exacerbations of their disease [19]. Exacerbations themselves lead to a dramatic reduction in physical activity [20] and health status [21], which can be prolonged, reflected in reduced time spent outdoors [22]. Activity limitation is also associated with a greater likelihood of relapse after discharge following emergency department attendance [23], and patients who remain inactive after a severe exacerbation have a greater risk of readmission [20,24].

The systemic consequences of COPD are well recognized, and loss of muscle bulk is a frequent finding in COPD [25], is most pronounced in locomotor muscles [26,27] and is associated with excess mortality [28,29] and impaired quality of life [30]. Exercise limitation in COPD is directly related to skeletal muscle weakness [31–33], and quadriceps strength is associated with survival in COPD [34]. An acute fall in strength has been noted in patients admitted with acute exacerbations of COPD [35–37]. Quadriceps strength is reduced in patients with early COPD (Figure 2), i.e. before they would be expected to have limiting breathlessness and, compared with lifelong never smokers, in individuals with normal spirometry and a past or current history of smoking [38].

EFFECTS OF PHYSICAL ACTIVITY

A number of studies have confirmed an association between low physical activity levels and adverse health outcomes including cardiovascular risk [39] and total mortality [40,41]. It has also been demonstrated that increasing the level of physical activity in mid life can significantly reduce mortality rates [42].

Table 1 Studies linking lung function to a decline in physical activity

Author	Study population at baseline	Follow-up	Outcome
Garcia-Aymerich et al. [49,50] (Copenhagen City Heart Study)	Danish smokers without COPD: mean age 52 (12) years at baseline	10 years	High physical activity group had less rapid decline in FEV_1 and were less likely to develop COPD
Jakes et al. [51] (EPIC study)	Men and women without COPD aged 45–74 years	3.7 years	FEV_1 decline was less rapid in those reporting greater leisure time activity and more stair climbing
Pelkonen et al. [52]	Men aged 40–59 years in rural Finland	25 years	FEV_1 decline was less rapid in highest PA tertile
Twisk et al. [53] (Amsterdam Growth and Health Study)	Adolescents mean age 13 years	14 years	Increases in physical activity were associated with an increase in vital capacity
Canoy et al. [54] (North Finland Birth Cohort Study)	Infancy	31 years	Sedentarism associated with lower FEV_1
Cheng et al. [55]	Healthy subjects aged between 25 and 55 years	Up to 5 years	FEV_1 increased in those with a sustained high activity level and fell in sedentary individuals
Sandvik et al. [56]	1393 healthy Norwegians aged 40–59 years	7.2 years	FEV_1 declined more rapidly in smokers independent of physical activity levels

Further evidence for the importance of physical activity in COPD comes from the response to pulmonary rehabilitation. This is an exercise training programme to increase physical activity and is a well-established therapeutic strategy for out-patients with COPD, improving exercise capacity and quality of life as well as reducing hospital admissions and health care costs [43–46]. Pulmonary rehabilitation has an impact upon a number of aspects of the BODE (body mass index, dyspnoea and exercise) score [47], but evidence that it actually improves mortality is so far lacking. Of note, pulmonary rehabilitation given soon after an exacerbation reduces subsequent attendance at the emergency department [48].

DOES PHYSICAL ACTIVITY INFLUENCE LUNG FUNCTION DECLINE?

The definitive study, which would be a randomized controlled trial to evaluate the effect of a sustained increase in physical activity on lung function, has not yet been performed. However, several prospective cohort studies have found associations between physical activity level and change in lung function over time (Table 1).

The Copenhagen City Heart Study [49,50] recruited a general population cohort of adults who were subject to repeat examination every 5 to 10 years. In a landmark study, spirometry obtained at a mean age of 52 years (1981–1983) was compared with results 10 years later. Patients with COPD at baseline were excluded for this analysis. Smokers with a low level of self-reported physical activity had a more rapid decline in lung function and were more likely to develop COPD (odds ratio high to moderate physical activity compared with low physical activity; 0.76, CI 0.62–0.93) than those who were physically active [49]. This relationship was confirmed in an analysis using a marginal structural model to deal with the potential effects of time-dependent confounding [50].

In the European Prospective Investigation into Cancer (EPIC) study [51] which recruited people aged 45–74 years, FEV_1 (forced expiratory volume in 1 s) decline was less rapid over a mean of 3.7 years follow up in subjects who reported climbing more stairs or participation in vigorous leisure time activities.

In a rural Finnish cohort of men recruited between the ages of 40 and 59 spirometry was recorded over 25 years [52]. Decline in a slightly different lung function measure, the $FEV_{0.75}$, was 9.8 ml/year more rapid in those in the lowest tertile of physical activity compared to the highest over the first 10 years. Because of attrition, the numbers available for follow up declined over time, but a significant difference persisted after 25 years follow up. Lung function declined more rapidly in continued smokers, but the effect of physical activity on lung function decline was independent of smoking status.

Changes in physical activity were positively correlated with changes in vital capacity between the ages of 13 and 27 years in the Amsterdam Growth and Health Study [53], and a sedentary lifestyle was associated with a lower FEV_1 at the age of 31 in the North Finland Birth Cohort Study [54]. Cheng et al. [55] reported data on healthy subjects aged between 25 and 55 studied on two occasions up to 5 years apart. In those who reported a sustained high activity level over follow up, mean FEV_1 actually increased by 50 ml at the second measurement, whereas it fell by 40 ml in those who remained sedentary [55].

A study from Norway of 1393 middle-aged apparently healthy subjects found that physical activity levels were lower in smokers. Smokers had a more rapid decline in FEV_1, but reported physical activity levels did not influence change in lung function independently of this [56].

A feature of all the studies cited above is that they have been based on self-reported physical activity levels rather than on direct measurements of activity, and this imprecision may in fact be underestimating the effect size. Relevant to this, a major joint initiative between the European Union and a consortium of pharmaceutical companies started in September 2009 to develop a patient-reported outcome for physical activity in COPD (www.PROactiveCOPD.com). An element of this will be the use of physical activity monitors to provide objective data, which would be of use in any intervention study in this area.

A second issue is the potential for reverse causality; it could be argued that reduced physical activity is a consequence of early disease rather than a cause, though this seems improbable in studies in relatively young and ostensibly healthy populations. Moreover, Watz et al. [15] have shown that physical activity is reduced even in COPD patients with mild disease, who would be expected to have ventilatory limitation only at high levels of physical activity. In that study, although exercise capacity (6-min walk distance) was very similar in patients with GOLD grade I COPD and patients with chronic bronchitis but without airflow obstruction, physical activity level was lower in the COPD patients. It was also lower in patients with airflow obstruction who reported no breathlessness (MRC dyspnoea score of 1 out of 5), suggesting that it is behaviour rather than capacity that is important at this stage.

BIOLOGICAL MECHANISMS EXIST TO LINK PHYSICAL ACTIVITY AND OXIDATIVE STRESS

The inhalation of tobacco smoke causes the generation of ROS (reactive oxygen species) [57] which, if they exceed the capacity of antioxidant systems, leads to oxidative stress, which can have an adverse impact upon the structure and function of lipids, protein and nucleic acids. Oxidative stress has been identified both in smokers [58–60] and in the lungs, circulation and muscles of patients with COPD [61,62] and oxidative capacity has been proposed as a lung protective factor [63]. Oxidative stress occurs in muscle as a consequence of inactivity [64], an effect more pronounced with age in animal models [65]. Current smokers with normal spirometry have evidence of oxidative stress in the quadriceps [66]. Interestingly, we have also recently observed evidence of oxidative stress in the quadriceps of patients with profound respiratory impairment and reduced physical activity due to an extrapulmonary disorder, scoliosis, in which lung parenchymal disease does not occur [67]. Conversely, antioxidant activity is enhanced by exercise [68] and increases in response to endurance training [69,70]. Smoking causes impaired lipid and glucose metabolism, and this, combined with the increased ROS produced by smoke exposure, can lead to postprandial oxidative stress, particularly if a diet high in processed carbohydrates and saturated fat is consumed [71]. Moderate physical activity has been shown to reduce this postprandial oxidative stress, probably due to an increase in antioxidant capacity and improved glucose and triglyceride clearance [72], and may therefore protect against the adverse effects of smoking. Interestingly, there is evidence that pulmonary rehabilitation reduces the oxidative stress response to exercise that occurs in COPD patients [73].

Physical activity and inflammation

Oxidative stress is one of the drivers of inflammation and is also thought to promote corticosteroid resistance by reducing the activity of histone deacetylases, thus prolonging the transcription of inflammatory mediators by NF-κB (nuclear factor κB). Prospective data from the Framingham study have confirmed a link between systemic inflammation and decline in lung function [74], and high physical activity levels were associated with reduced levels of CRP (C-reactive protein) [75].

During exercise in healthy subjects, cytokines are produced, principally IL (interleukin)-6, which stimulates the production of anti-inflammatory cytokines including IL-1ra (IL-1 receptor antagonist) and IL-10 [76,77]. IL-6 production occurs in the absence of muscle damage and is related to the intensity, duration and muscle mass recruited during exercise [78]. Transcription of IL-6 mRNA is increased in response to exercise [79]. IL-6 inhibits the production of TNF-α (tumour necrosis factor-α) [80] a key pro-inflammatory cytokine implicated in the pathogenesis of COPD. IL-6 also enhances lipolysis [81–83] and enhances insulin sensitivity [83] which has an impact upon oxidative stress as described above [71].

Physical activity and infections

Moderate physical activity is associated with reduced susceptibility to upper respiratory tract infections [84,85]. Interestingly, Garcia-Aymerich et al. [86] demonstrated an inverse relationship between the amount of vigorous activity COPD patients undertook and bacterial colonization; colonization was present in 43 % of samples from those in the lowest quartile of physical activity, but in only 22 % of those in the highest quartile, which could be a protective mechanism in COPD progression, as both bacterial [87] and viral [88] colonization are associated with more rapid decline in lung function.

Physical activity and pulmonary vascular disease

Pulmonary vascular disease is also a feature of COPD though its aetiology is poorly understood. Exercise is known to enhance the formation of prostacyclin

and reduces that of thromboxane A2, which leads to vasodilatation and reduced platelet aggregation [89]. An imbalance in these factors has been implicated in both primary and secondary pulmonary hypertension [90] and may therefore be relevant in the progression of COPD.

BEHAVIOURAL FACTORS

A possible confounder to the relationship between physical activity and COPD progression might arise because smoking is associated with other risk behaviours apart from reduced physical activity, including alcohol consumption and poor nutrition. There is limited evidence of clustering of adverse health behaviours [91,92], but it may be the case that individuals with a higher physical activity level might adopt other healthier lifestyle choices (perhaps as yet of unrecognized benefit), which protect against lung diseases. We also speculate that individuals with low physical activities may be more likely to accept symptoms of breathlessness as a 'normal' part of aging, which could lead to a delay in seeking medical attention and a worse clinical outcome.

Many of the co-morbidities associated with COPD including coronary artery disease, peripheral vascular disease, glucose intolerance and osteoporosis are associated with inactivity [5]. For a given lung function impairment, inactive COPD patients have more co-morbidity, with a higher systemic inflammation, higher brain natriuretic peptide levels and more frequent left ventricular impairment [93]. Low physical activity levels in patients prior to their first hospital admission were associated with reduced gas transfer, walking capacity and greater levels of systemic inflammation (CRP and TNF-α) [86]. These data suggest that physical inactivity drives both the progression of COPD and its common co-morbidities. Although these are not the main focus of this article, their amelioration would improve the overall health experience of COPD patients [5].

SUMMARY AND FUTURE WORK

A reduction in physical activity is a feature of COPD. Sedentary lifestyles are associated with more rapid decline in lung function, and exercise is likely to attenuate the harmful effects of smoking, including oxidative stress, systemic inflammation and respiratory infections. Prospective intervention data to confirm that physical inactivity promotes the development of COPD is needed in order to guide intervention strategies.

The proliferation of spirometry screening may offer an opportunity to test this hypothesis, as large numbers of people with early disease are being identified. Patients with grade I or II COPD or even apparently healthy smokers could be randomized to intensive lifestyle interventions to improve activity, perhaps utilizing mobile technology and the impact on lung function decline assessed. There is evidence that exercise interventions can enhance smoking cessation [94], so the possibility of differential smoking cessation would need to be factored into sample size calculations.

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