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Systemic inflammation and lung function: A longitudinal analysis

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ABSTRACT

Background: Systemic inflammation is associated with impaired lung function in healthy adults as well as in patients with lung disease. The mechanism for this association is unknown and it is unclear if systemic inflammation leads to impaired lung function or if poor lung function leads to inflammation. We explored the temporal associations between blood C-reactive protein (CRP), fibrinogen, and white blood cells, and lung function in young adults.

Methods: Spirometry, plethysmography, and diffusion capacity were measured in a population-based cohort at ages 32 and 38 years. High-sensitivity CRP, fibrinogen, and white blood cells were measured at the same ages.

Results: Higher levels of CRP and, to a lesser extent, fibrinogen were associated with lower lung volumes in cross-sectional analyses at both ages 32 and 38 years. Higher CRP and fibrinogen at age 32 were associated with higher FEV_1 and FEV_1/FVC at age 38, but not other measures of lung function. Lower lung volumes (total lung capacity, functional residual capacity, and residual volume) but not airflow obstruction (FEV_1/FVC) at age 32 were associated with higher CRP at age 38. Associations between age 32 lung function and fibrinogen at follow-up were weaker, but consistent. There were no longitudinal associations between white blood cells and lung function.

Conclusions: We found no evidence that systemic inflammation causes a decline in lung function. However, lower lung volumes were associated with higher CRP and fibrinogen at follow-up indicating that pulmonary restriction may be a risk factor for systemic inflammation. The mechanism for this association remains unclear.

1. Introduction

There is a poorly understood association between systemic inflammation and reduced lung volumes [1–6]. This association is not only present among patients with chronic lung disease, but is also found in apparently healthy young adults. The mechanism(s) behind this association are unknown but may be important for a number of reasons. It is possible that chronic systemic inflammation from a non-respiratory cause leads to an accelerated decline in lung function. Conversely, unrecognised lung disease may result in systemic inflammation with deleterious effects on other aspects of health. Finally, confounding factors, such as obesity, may impact on both lung function and systemic inflammation [7,8]. Since systemic inflammation is implicated in the pathogenesis of cardiovascular diseases, the association may also help to explanation the association between low lung function and cardiovascular mortality [9].

Most studies of lung function and systemic inflammation have been cross-sectional and it remains uncertain which comes first. Two studies found that higher levels of C-reactive protein (CRP) and fibrinogen in young adulthood were associated with a subsequent decline in lung volumes [5,10], but this was not found in other longitudinal studies [2,6,11]. One study found that high CRP levels were associated with subsequent lung function decline only in men [12]. Another suggested that the association between lung function and inflammation may be confounded by adiposity [13]. A recent study confirmed cross-sectional associations between CRP and spirometric lung function, and also found associations between changes in CRP and changes in lung function over 13 years of follow-up. However, baseline CRP levels did not predict lung function decline, nor did baseline lung function predict changes in CRP leaving the temporal sequence between CRP and lung function undetermined [14].

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A large Mendelian randomisation study found that, although high levels of CRP were associated with COPD, participants with genetically elevated levels of CRP were not more likely to develop COPD or experience a greater decline in FEV_1 during follow-up [15]. This suggests that CRP does not directly mediate a decline in lung function, but it remains possible that CRP levels are an indirect marker of another inflammatory process that impacts on the lungs. A smaller (all male) cohort found an association between baseline CRP levels and FEV_1 decline, but this was not predicted by CRP genotype leading the authors to speculate that the association between CRP and lung function could be due to reverse causality – the possibility that impaired lung function causes elevation of CRP [16].

Although there has been considerable research interest in systemic inflammation and obstructive airways disease [17], studies of healthy populations suggest that the association between inflammation and lung function is equally strong for the FVC as the FEV_1 and appear to indicate lung restriction rather than airflow obstruction [2,11,14]. One study found an association between systemic inflammation and static lung volumes, but not with airflow obstruction [3]. Most studies have reported spirometry only and we are not aware of any follow-up studies using a broad range of lung function tests.

We previously reported an association between blood CRP levels and reduced spirometric lung volumes in young adults [2]. We now report a 6-year follow-up of this cohort with pulmonary function tests of spirometry, static lung volumes, airways conductance, and gas transfer. Our primary aim is to assess whether CRP levels predict a subsequent decline in lung function or whether poor lung function predicts higher CRP at follow-up. We further aim to assess whether inflammation is associated with a restrictive or obstructive physiological impairment. We also considered blood fibrinogen [10,13,18] and white blood cell counts [19] as alternative measures of systemic inflammation that have also been associated with lung function.

2. Methods

Study members were born in Dunedin, New Zealand between April 1972 and March 1973 [20,21]. 1037 children participated in the first follow-up assessment at age 3 years, constituting the base sample of the study. This analysis examines the associations between CRP and lung function at ages 32 and 38 years. At each age, over 95% of living Study members were assessed (972/1015 at age 32 and 961/1007 at age 38), although not all consented to both blood and lung function tests. Study members are mostly of New Zealand/European ethnicity with 7.5% identifying as Māori at age 26 years. Few Study members identified with other ethnicities [22]. The Otago Ethics Committee approved the study. Written informed consent was obtained at each assessment.

Information about respiratory health was obtained at each age using questions from the American Thoracic Society and the European Community Respiratory Health Survey questionnaires [23,24]. Current smokers were defined as those who reported having smoked at least one cigarette a day for at least one month during the previous year. Former smokers were those who had smoked in the past but not within the previous year.

Cumulative smoking was calculated as the pack-years of cigarettes smoked up to each age (20 cigarettes/day for 1 year = 1 pack-year).

Height and weight were measured in light clothing without shoes to calculate Body Mass Index (BMI) in kg/m^2. Spirometry (FEV_1 and FVC), static lung volumes (total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV)), specific airways conductance (sG_{aw}), single-breath diffusing capacity for carbon monoxide (DL_{CO}), and alveolar volume by methane dilution (V_A) were measured to European Respiratory Society/American Thoracic Society standards [25–30] using a body plethysmograph (CareFusion, Yorba Linda, CA). Spirometry was repeated after 200mcg salbutamol via large volume spacer. Participants were asked to avoid using their usual inhalers on the day of the test.

CRP was measured using a high-sensitivity immunoturbidimetric assay (Roche Diagnostics, Germany). Fibrinogen was measured using an automated coagulation analyser (Sysmex; Mahberg, Germany). Haemoglobin and white blood cell counts were measured on an automated analyser (Sysmex Corporation, Japan). Exhaled carbon monoxide was measured twice using a Micro CO monitor, (Micromedical, UK) and the mean value was recorded.

2.1. Statistical methods

Previous analyses of this cohort suggest that associations between CRP and lung function may differ between men and women [2]. Interactions with sex were therefore investigated for all models. Pregnant women were excluded from all analyses. Because corticosteroids may suppress systemic inflammation and also influence lung function, participants using either oral or inhaled corticosteroids were also excluded.

Linear regression was used to examine cross-sectional associations between inflammation and lung function at ages 32 and 38 using all data available at each age. Analyses were stratified by sex and adjusted for height, BMI, and pack-years of smoking up to that age. Analyses of DL_{CO} and DL_{CO}/V_A also adjusted for exhaled carbon monoxide and haemoglobin.

For longitudinal analyses, linear regression was first used to assess associations between CRP at age 32 and changes in lung function at follow-up by using age 38 lung function values as the outcome while adjusting for the same measure at age 32. There was no evidence that sex was an effect modifier in these analyses, so analyses used the combined data set including sex as a covariate. Other covariates were height, changes in BMI, and the pack-years of cigarettes smoked between these assessments. Changes in exhaled carbon monoxide and haemoglobin were included when the outcome was DL_{CO} or DL_{CO}/V_A. Interactions between sex and each of baseline CRP, change in pack-years, change in BMI, and (for DL_{CO} and DL_{CO}/V_A) change in haemoglobin were investigated and retained where statistically significant.

Next, the direction of the association was reversed and a second set of linear regression models used lung function at 32 to predict CRP levels at age 38 adjusting for age 32 CRP values using the same approach and covariates described above.

CRP was log-transformed for all analyses. Lung function values were also log transformed where this improved the normality and/or homoscedasticity of the residuals. In such cases, ratios of geometric means are reported rather than differences in arithmetic means.

The analyses were repeated using blood fibrinogen [10,13,18] and white blood cell counts. Both were log-transformed for all analyses.

Stata 13.1 (College Station TX) was used with statistical significance determined by two-sided $p < 0.05$. No adjustments were made for multiple comparisons and interpretation of results focuses on patterns rather than isolated instances of statistical significance.

3. Results

Participant characteristics are shown in Table 1.