Cardiorespiratory Fitness, Inflammation, and the Incident Risk of Pneumonia

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Running title: Inflammation and cardiorespiratory fitness with pneumonia

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Abstract

Introduction: Both inflammation and cardiorespiratory fitness (CRF) are each associated with the risk of respiratory infections. To clarify the hypothesis that CRF attenuates the incident risk of pneumonia due to inflammation, we conducted a prospective study examining the independent and joint associations of inflammation and CRF on the risk of pneumonia in a population sample of 2,041 middle-aged men. **Methods:** CRF was directly measured by peak oxygen uptake (VO_{2peak}) during progressive exercise testing to volitional fatigue, and categorized into tertiles. Inflammation was defined by high sensitivity C-reactive protein (hsCRP). Pneumonia cases were identified by internal medicine physicians using the International Classification of Diseases codes in clinical practice. **Results:** During a median follow-up of 27 yr, 432 pneumonia cases were recorded. High hsCRP and CRF were associated with a higher risk (HR 1.38, 95% CI 1.02-1.88) and a lower risk of pneumonia (HR 0.55, 0.39-0.76) after adjusting for potential confounders, respectively. Compared with normal hsCRP-Fit, moderate to high hsCRP-Unfit had an increased risk of pneumonia (HR 1.63, 1.21-2.20), but moderate to high hsCRP-Fit was not associated with an increased risk of pneumonia (HR 1.25, 0.93-1.68). **Conclusions:** High CRF attenuates the increased risk of pneumonia due to inflammation. These findings have potential implications for the prevention of respiratory infection characterized by systemic inflammation, such as COVID-19.

Key Words: C-reactive protein ● cardiorespiratory fitness ● pneumonia

INTRODUCTION

Pneumonia is due to inflammatory manifestations within the lung tissue caused by viruses or bacterial infection.[1] Although unhealthy risk factors, such as cigarette smoking, excessive alcohol consumption, physical inactivity and excess body weight are major contributors to the development of pneumonia,[1, 2] a significant residual risk remains unaccounted for. Viral respiratory infections and community-acquired pneumonias are characterized by high circulating levels of C-reactive protein (CRP), signifying acute inflammation.[3,4] Whether elevated levels of high-sensitivity CRP (hsCRP), a marker of chronic low-grade systemic inflammation, contributes to the development of pneumonia, remains unclear.[5]

Regular moderate-to-vigorous physical activity represents a major component of a healthy lifestyle that has been consistently shown to reduce the risk of systemic inflammation and diseases that compromise immune function.[6] Although chronic physical activity as measured using subjective self-report questionnaires appears to reduce the risk of incident pneumonia[2] as well as it's associated mortality,[7,8] the findings to date remain inconsistent.[9] Cardiorespiratory fitness (CRF), a physiological biomarker of cardiovascular and pulmonary system integrity that is strongly influenced by habitual physical activity, is associated with a lower risk of pneumonia in the general population.[10] In addition, higher CRF appears to have some protective effects against inflammation-related complications[11] and stress-induced latent viral reactivation.[12] Moreover, high CRF attenuates the increased risk of hospitalization due to coronavirus disease 2019 (COVID-19).[13] However, it remains unclear whether higher levels of CRF may decrease the incident risk of pneumonia in men with elevated hsCRP. We conducted a prospective study examining the independent and joint associations of inflammation (as measured by hs-CRP) and CRF with the incident risk of pneumonia in the general population.

METHODS

This prospective study was based on a population sample of 2,041 men, aged 42-60 yr, who were followed up for an average of 25 yr in the Kuopio Ischemic Heart Disease cohort study. The study protocol was approved by the Research Ethics Committee of the University of Eastern Finland and had written informed consent from all participants.

CRF was directly measured by peak oxygen uptake (VO_{2peak}) using a calibrated, computerized metabolic measurement system during progressive exercise testing to volitional fatigue on an electrically braked cycle ergometer. The testing protocol included a 3-min warm-up at 50 watts, followed by a step-by-step increase in the workload by 20 W/min with direct analyses of expired respiratory gases. VO_{2peak} was defined as the highest attained value for oxygen consumption and/or a plateau in oxygen uptake at maximal exercise.

CRF was classified by age group from cardiopulmonary exercise testing on a cycle ergometer with measured VO2max (mL/kg/min) based on FRIEND (Fitness Registry and the Importance of Exercise National Database) percentiles[14]. We defined CRF categories as low (less than 30 percentile), moderate (30 to 70 percentile) and high (high than 70 percentile) based on age-specific VO_{2peak} percentiles (mean values of VO_{2peak} for each group shown in table 1). Serum hsCRP, an inflammatory marker, was measured using an immunometric assay (Immulite High-Sensitivity CRP assay, DPC, Los Angeles, CA), and categorized into 3 groups (low, <1mg/L; moderate, 1-3mg/L; high, >3mg/L).[15]

To evaluate the joint effects of hsCRP and CRF on the risk of pneumonia, participants were divided into 4 groups: normal hsCRP-Fit, normal hsCRP-Unfit, moderate to high hsCRP-Fit and moderate to high hsCRP-Unfit. hsCRP was categorized as normal and moderate to high levels based on the median cutoffs: <1.3 mg/L and >1.3 mg/L. CRF was classified into unfit

(24.3 ± 5.1 mL/kg/min) and fit (36.0 ± 5.8 mL/kg/min), which corresponded to cut-points below and above the median values of age-specific VO_{2peak} percentiles.[16]

All incident cases of pneumonia were collected by linkage to the National Hospital Discharge Register and comprehensive review of hospital records. The diagnoses of pneumonia cases were made by internal medicine or family physicians based on the International Classification of Diseases codes used in clinical practice.

We used Cox proportional hazard models adjusted for potential confounding variables to determine the HRs and 95% CIs of hsCRP and CRF for pneumonia. Hazard ratios were adjusted for in two multivariable models: (Model 1) age, body mass index, systolic blood pressure, cigarette smoking, alcohol consumption, glucose, total cholesterol, fibrinogen, creatinine, leukocytes, cardiovascular history, socioeconomic status, family history of coronary artery disease, diabetes, anti-hypertensive drugs and physical activity and (Model 2) model 1 plus mutual adjustment for each exposure. Statistical significance was set at $P < .05$ and analyses were conducted using SPSS version 21.0 (SPSS, Armonk, NY).

RESULTS

During a median (interquartile) follow-up of 27 (18-31) yr, 432 cases of pneumonia were recorded. Compared with low hsCRP, both moderate and high hsCRP levels were each associated with increased risk for pneumonia, (HR 1.32, 95%; CI 1.05−1.67) and (HR 1.38, 95%; CI 1.02−1.88) respectively, following adjustment for potential confounders. On additional adjustment for CRF, the risk of pneumonia persisted for moderate levels of hsCRP (HR 1.31, 1.02−1.67), but was attenuated (HR 1.26, 0.91−1.75) for high levels of hsCRP.

High levels of CRF were associated with a lower risk of pneumonia (HR 0.56, 0.40−0.78) after adjusting for potential confounders including hsCRP. In joint associations of hsCRP and CRF

with the risk of pneumonia, moderate to high hsCRP-Unfit had an increased risk of pneumonia (HR 1.63, 1.21−2.20), but moderate to high hsCRP-Fit was not (HR 1.25, 0.93−1.68), compared with their normal hsCRP-Fit counterparts.

DISCUSSION

We found that elevated hsCRP and high CRF were each associated with a higher and lower risk of pneumonia respectively, independent of several established risk factors. However, whereas the association between moderately elevated levels of hsCRP and pneumonia risk persisted on further adjustment for CRF, that for elevated hsCRP and pneumonia risk was attenuated to the null on adjustment for CRF. These findings suggest that though increased inflammation levels may contribute to an increased risk of pneumonia, the effects may be mediated though a process influenced by levels of CRF.

These findings further confirm our novel results on the joint effects of hsCRP and CRF on pneumonia risk. The risk of pneumonia associated with elevated hsCRP was strongest in unfit men; however, it was significantly attenuated in fit men with elevated hsCRP. These findings suggest that CRF may favorably modify the relationship between inflammation and the risk of pneumonia.

To our knowledge, this is the first long-term study to report that high CRF attenuates the risk of developing pneumonia in men with elevated indices of inflammation, specifically hsCRP. These unique data have important implications for public health interventions designed to prevent pneumonia. Additional studies are also needed to confirm a preliminary report[13] indicating that high CRF confers some protective effect against inflammatory responses from the COVID-19 infection. Our finding raises the possibility that high CRF may reduce the risk of pneumonia, a major cause of death in patients with COVID-19. Thus, increasing CRF may

be prophylactically recommended to potentially reduce the risk of pneumonia, especially in 'at risk' individuals vulnerable to infection.

Several potential mechanisms may serve to explain the role of CRF-mediated adaptations on the association between inflammation and pneumonia. High CRF resulting from regular aerobic exercise may improve cardiovascular risk factors[17] and host innate immunity and afford protection against viral infections.[18] An above average level of fitness may also confer anti-oxidant effects, enhancing extracellular superoxide dismutase activity to prevent oxidative damage, which is associated with varied disease pathologies.[19] A high level of CRF is characterized by enhanced vagal tone, which may favorably affect the cholinergic anti-inflammatory pathway,[20] via activating the anti-inflammatory reflex mechanism, attenuating the impact of proinflammatory cytokine effects.[21] Enhancing parasympathetic stimulation may also impose positive therapeutic effects on sepsis through anti-inflammatory mechanisms.[22] However, additional studies are needed to clarify the relation between higher CRF and the lower incident risk of pneumonia, and how fitness may attenuate the risk of developing pneumonia in men with elevated inflammatory markers.

We acknowledge several methodological limitations. Because our study population included only Caucasian men, we are unable to generalize the present findings to women or other races/ethnicity. We only used baseline single measurements of hsCRP and CRF to assess our associations. It is known that due to changes in lifestyle, chronic disease and aging and errors in measurements, assessments using baseline measurements of an exposure could underestimate the true strength of an association between an exposure and disease outcome due to the phenomenon of regression of dilution bias. Although we adjusted for numerous potential confounders such as smoking and pre-existing diseases, other unmeasured confounders (eg, pneumococcal or influenza immunization status and other pulmonary or immunocompromised

condition) may have influenced these associations. Due to the absence of granular data such as heavy smoking or heavy alcohol consumption, the influence of these on the associations could not be ascertained. In addition, our database did not discriminate the specific types of bacterial or viral pneumonia which may represent additional outcome modulators that were unaccounted for.

In conclusion, high CRF attenuates the incident risk of pneumonia in men with elevated inflammatory indices (eg, hsCRP), which may have potential implications for the prevention of respiratory infections characterized by systemic inflammation, such as COVID-19. Future studies are needed to clarify whether high CRF can reduce the risk of acute pneumonia resulting from COVID-19 infection and decrease the associated mortality risk in patients with COVID-19.

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Table 1. Individual and Joint Associations of hsC-reactive Protein and Cardiorespiratory Fitness with the Risk of Incident Pneumonia

hsC-reactive protein (mg/L)	**Events/Total (432/2041)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**
Low (<1)	173/941	1 (reference)	1 (reference)
Moderate (1-3)	152/657	1.32 (1.05-1.67)	1.31 (1.02-1.67)
High (>3)	107/443	1.38 (1.02-1.88)	1.26 (0.91-1.75)
Cardiorespiratory fitness (mL/kg/min)			
Low (18.4 ± 3.1)	87/328	1 (reference)	1 (reference)
Moderate (26.1 ± 1.8)	120/525	0.76 (0.55-1.05)	0.77 (0.55-1.06)
High (35.6 ± 5.5)	225/1188	0.55 (0.39-0.76)	0.56 (0.40-0.78)
***Combined hsCRP and CRF**			
Normal hsCRP-Fit	141/744	1 (reference)	
Normal hsCRP-Unfit	93/460	1.44 (1.07-1.94)	
Moderate to High hsCRP-Fit	70/311	1.25 (0.93-1.68)	
Moderate to High hsCRP-Unfit	128/526	1.63 (1.21-2.20)	

Abbreviations: hsCRP, high-sensitivity C-reactive protein; CRF, cardiorespiratory fitness. **Model 1**: adjusted for age, smoking, alcohol consumption, body mass index, systolic blood pressure, total cholesterol, glucose, fibrinogen, leukocyte, creatinine, diabetes, anti-hypertensive medication, family history of coronary heart disease, history of cardiovascular disease, socioeconomic status, and physical activity. **Model 2**: adjusted for model 1 plus CRF when hsCRP is exposure or hsCRP when CRF is exposure.

*hsCRP and CRF were divided into 4 combined groups; normal hsCRP-Fit (0.69 ± 0.30 mg/L – 36.9 ± 5.9 mL/kg/min), normal hsCRP-Unfit (0.78 ± 0.29 mg/L - 25.4 ± 4.6 mL/kg/min), moderate to high hsCRP-Fit (3.71 ± 4.2 mg/L - 34.7 ± 5.2 mL/kg/min), and moderate to high hsCRP-Unfit (4.91 ± 5.14 mg/L – 23.5 ± 5.3 mL/kg/min).