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High hsCRP Is Associated With Reduced Lung Function in Structural Firefighters

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Abstract

Background—To assess the association between markers of systemic inflammation and pulmonary function in a population of structural firefighters.

Methods—We studied male career members of a large Midwestern fire department with questionnaires, spirometry, and high-sensitivity C-reactive protein (hsCRP) as a biomarker of systemic inflammation. We examined percent predicted forced expiratory volume in 1s (FEV_1%-predicted) and forced vital capacity (FVC%-predicted).

Results—Complete data were available for 401 firefighters. Higher hsCRP levels were associated with lower lung function values, after adjusting for confounding variables. Specifically, for every twofold increase in log10-hsCRP, FEV_1%-predicted decreased by a mean 1.5% (95% CI: 0.4, 2.6%) and FVC%-predicted decreased by a mean 1.4% (95% CI: 0.4, 2.3%).

Conclusion—hsCRP as a biomarker of systemic inflammation may indicate reduced lung function in structural firefighters.

Keywords

percent predicted forced expiratory volume in 1s (FEV_1%-predicted); percent predicted forced vital capacity (FVC%-predicted); high-sensitivity C-reactive protein (hsCRP)

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the U.S. and a major cause of long-term disability. While cigarette smoking is the probable cause of COPD in the majority of cases, it has been estimated that about 15% of COPD in the overall population may be due to occupational exposures, and a much higher portion of COPD among non-smokers may be due to occupational exposures [Hnizdo et al., 2002]. Firefighters, both municipal (structural) and wildland are known to face respiratory hazards [Musk et al., 1979; Chia et al., 1990; Materna et al., 1992; Scannell and Balmes, 1995; Bergstrom et al., 1997; Burgess et al., 2001; Prezant et al., 2002; Greven et al., 2012]. Researchers have identified particulates and other exposures, heavy physical exertion and cardiovascular strain to be among the chief, nontraumatic health hazards associated with structural firefighting [Guidotti and Clough, 1992; Austin et al., 2001; Fahy, 2005].

Various studies have associated increased serum concentrations of C-reactive protein (CRP), a chemokine, primarily synthesized in the liver but also produced in the respiratory epithelium [Gould and Weiser, 2001], to reduced lung function in healthy populations [Mendall et al., 2000; Cirillo et al., 2002; Mannino et al., 2003; Aronson et al., 2004; Kony et al., 2004; Gan et al., 2005; Walter et al., 2008; Thorleifsson et al., 2009]. Kony and coworkers studied serum CRP levels, forced expiratory volume in 1s (FEV_1), and bronchial hyperresponsivesness (BHR) as measured by methacholine challenge, in 259 adults free of cardiovascular disease or respiratory infection. The authors observed that the mean FEV_1 (adjusted for potential confounders such as age, gender, height and smoking status) was lower in subjects with a high CRP level and BHR was more frequent (41.9% vs. 24.9%) in these individuals than in subjects with lower CRP levels [Kony et al., 2004]. Additionally, Aronson et al. [2004] also observed a strong inverse association between CRP levels and quartiles of FEV_1 as well as forced vital capacity (FVC).

Data collected in the Third National Health and Nutrition Examination Survey (NHANES III) also found associations between increased CRP level and reduced pulmonary function [Cirillo et al., 2002; Mannino et al., 2003; Gan et al., 2005]. Moreover, when Gan et al. [2005] focused on smoking status, the authors observed an additive effect of current smoking on the inverse relationship of CRP, FEV_1 observed previously in this cohort. Similar results were recently observed in a cohort of FDNY World Trade Center disaster first responders [Weiden et al., 2013]. The authors report that individuals with elevated CRP levels obtained within 6 months of 9/11/01 had a significantly increased risk of developing decreased lung function (FEV_1) at their subsequent pulmonary testing, independent of a history of CVD. Two case–control studies of both childhood and adult asthmatics also found increased CRP levels correlated with decreased pulmonary function in steroid-naive participants [Takemura et al., 2006; Deraz et al., 2012]. Takemura and coworkers additionally observed a strong correlation between sputum eosinophils and CRP levels in adult asthmatics, however this was not observed in children [Deraz et al., 2012], possible reflecting the differences in disease etiology.

Genetic studies to date of hsCRP polymorphisms or haplotypes have yielded inconclusive results [Yanbaeva et al., 2009; van Durme et al., 2009; Bolton et al., 2011]. Specifically,

while both Bolton and van Durme observed strong inverse associations between CRP and lung function, neither study was able to identify a CRP polymorphism or haplotype associated with pulmonary dysfunction. Thus, while the association has been described in the literature, the mechanism remains unclear.

We hypothesized that hsCRP as a biomarker of systemic inflammation may indicate reduced lung function in structural firefighters.

MATERIALS AND METHODS

Subjects

We studied male career members of a large Midwestern municipal fire department with spirometry, blood, exercise tolerance, and questionnaire data from 2007 to 2009. The study was approved by the Harvard School of Public Health Human Subjects Committee and the local institutional review board. Informed consent was obtained in writing from each participant prior to data collection. Information on firefighters who chose not to consent or participate was not available.

Venous Blood Samples

Whole non-fasting blood samples were collected by venous phlebotomy in EDTA tubes, and buffy coat were extracted and stored in cell lyses solution at −20°C for analyses. High sensitivity CRP concentration was determined by immunochemiluminometric assay on a Roche COBAS Integra® (detection limit of 0.1mg/L). These analyses were performed by LabCorp (Burlington, NC).

Questionnaire

Participants were administered a health, lifestyle, and occupational history questionnaire while undergoing their fire department's standard medical examination [Durand et al., 2011]. For the purposes of this analysis, we examined responses to history of pulmonary disease including asthma, COPD, diabetes, heart disease, or hypertension.

Spirometry

FEV_1 and FVC were obtained from participants in the standing position by trained technicians following ATS guidelines [Miller et al., 2005] using a Welch Allyn® PC-Based Spirometer Model SP (Welch Allyn, Inc., Skaneateles Falls, NY). Predicted values were derived from Knudson's 1983 tables [Knudson et al., 1983]. All measurements were taken pre-bronchodilator.

Cardiorespiratory Fitness

Cardiorespiratory fitness was determined from a symptom limited maximal treadmill exercise testing with electrocardiogram monitoring and estimation of oxygen consumption (METS) following the Bruce protocol. The participants were encouraged to continue exercise until volitional exhaustion, even after exceeding 85% of their maximum predicted heart rate defined as (220-age). The cohort achieved an average of 98.9% (SD 5.9) of maximal age-predicted heart rate on these tests. During the exercise test, total treadmill time

in seconds (ETTT) and maximum METS (maxMETS) achieved were recorded. The details of this analysis in this cohort have been previously reported [Baur et al., 2011].

Statistical Methods

Descriptive statistics were calculated for demographic and clinical variables. Ordinary least squares regression techniques were used to examine associations between percent predicted values of FEV_1 (FEV_1%-predicted), predicted values of FVC (FVC%-predicted), as well as the ratio of FEV_1 to FVC using the following predictor variables: current smoker, history of pulmonary disease, body mass index (BMI) which was calculated by dividing the weight (kg) by height (cm squared), maxMETs, resting systolic and diastolic blood pressures, current hypertension (resting systolic blood pressure ≥140mmHg or resting diastolic blood pressure ≥90mmHg). We also examined hsCRP levels and weight (kg), which were not normally distributed and were $\log_{10}$-transformed to achieve an approximate normal distribution. HsCRP was additionally categorized and examined based on distributional quartiles. Specifically, ≤0.57mg/L (n = 103) (referent category), >0.57 to ≤1.08 (n = 101) (Q2), >1.08 to ≤2.48mg/L (n = 102) (Q3), and >2.48mg/L (n = 97) (Q4). Multivariable models were chosen based on an initial evaluation using stepwise selection techniques. Variables that were retained were significant with $P < 0.05$. Overall goodness of fit of the models was assessed using the likelihood ratio test, a statistical tool that compares the fit of the null and alternative models.

Airways obstruction on spirometry was defined according to the Global Initiative for Chronic Obstructive Lung Disease criteria for COPD using the FEV_1, FVC, and FEV_1/FVC. Severe COPD (FEV_1/FVC <0.70 and FEV_1 <50% predicted), moderate COPD (FEV_1/FVC <0.70 and FEV_1 ≥50% to <80% predicted), and mild COPD (FEV_1/ FVC<0.70 and FEV_1=80%). Restriction was defined as an FEV_1≥70% and FVC<80% predicted [Pauwels et al., 2001]. All analyses were performed using SAS statistical software (version 9.3).

RESULTS

Characteristics of the population are summarized in Table I. Complete data were available for 401 individuals. Participants had a median age of 36 years. Sixteen (4%) reported a history of pulmonary disease (e.g., asthma and or chronic bronchitis) and 16 (4%) reported active pulmonary disease. One participant reported a history of heart disease. We did not record information on race/ethnicity; however, we know that fire departments where our subjects work are 85–90% White, as previously documented [Poston et al., 2011].

Pulmonary Function

Pulmonary function tests results are summarized in Table II. The median FEV_1%-predicted was 95% (10th, 90th percentiles: 80%, 115%), the median FVC%-predicted was 99% (10th, 90th percentiles: 84%, 117%) and the median ratio was 81% (10th, 90th percentiles: 73%, 86%). Twenty-four participants (6%) had airways obstruction on spirometry (10 moderate, 14 mild) and four other participants' spirometry indicated a restrictive pattern. There were no subjects with mixed disease.

Systemic Inflammation

The median hsCRP concentration level was 1.06mg/L (10th, 90th percentiles: 0.31mg/L, 4.85mg/L). High hsCRP values, defined as greater than 3mg/L [Pearson et al., 2003], were observed in 83 participants (21%). There were no hsCRP values below the limit of detection.

Pulmonary Function and Systemic Inflammation

Figure 1 shows mean FEV_1%-predicted and FVC %-predicted values by hsCRP quartiles. Higher mean hsCRP levels were associated with lower mean lung function values. The mean FEV_1 for participants in the highest hsCRP quartile (93.3%), was significantly lower than for individuals in the lowest quartile (99.4%; $P<0.01$). This difference was even more pronounced for FVC%-predicted. Specifically, the mean FVC%-predicted for participants in the highest hsCRP quartile (94.8%) was significantly lower than the lowest quartile (104%) ($P < 0.001$), as well as values in the second (99.7%; $P < 0.05$) and third quartiles (100%) ($P < 0.05$).

In multivariable analysis, higher hsCRP levels were associated with lower lung function values and are detailed in Tables III and IV. Specifically, for every 1 $\log_{10}$mg/L increase $\log_{10}$ hsCRP, mean FEV_1%-predicted decreased by 5.3% (95% CI: 1.6, 8.9%) after adjusting for BMI, resting systolic blood pressure, and achieved MaxMETs. This corresponds to an adjusted mean reduction of 1.6% (95% CI: 0.5, 2.7%) for each twofold increase in hsCRP. Current smoker, history of pulmonary disease, current hypertension, $\log_{10}$ weight and resting diastolic blood pressure were not associated with FEV_1%-predicted in this cohort. Moreover, for every twofold increase in hsCRP, FVC%-predicted decreased by a mean 1.4% (95% CI: 0.4, 2.4%) (regression estimate for $\log_{10}$ hsCRP: −04.7 (95% CI: −7.9, −1.5)) after adjusting for $\log_{10}$ weight. Current smoker, history of pulmonary disease, current hypertension, achieved MaxMETs, resting systolic blood pressure, resting diastolic blood pressure and BMI were not associated FVC%-predicted in this cohort.

DISCUSSION

Lung function declines, specifically FEV_1, are established risk factors for CVD, rivaling that of cholesterol [Sin et al., 2005]. Similar to other studies, we observed an inverse relationship between higher hsCRP and lung function as measured by FEV_1%-predicted and FVC%-predicted, after adjusting for established potential confounders. Unlike Gan et al. we did not observe an additive effect of current smoking onFEV_1%-predicted in our cohort. However, given the limited number of subjects currently smoking, we may not have had sufficient statistical power to observe such a difference.

While numerous studies have found a negative association between lung function reduction and increasing CRP, the mechanism remains unclear. Genetic studies to date of hsCRP polymorphisms or haplotypes have not helped elucidate the mechanism [Yanbaeva et al., 2009; van Durme et al., 2009; Bolton et al., 2011]. In the absence of definitive genetic studies some researchers have suggested reverse causality [Bolton et al., 2011] or an undefined mediator between lung function and CRP may be driving the association between the two outcomes. CRP has also been linked to the development of ischemic heart disease

and stroke, the two primary causes of death in individuals with COPD. Higher levels of systemic inflammation may simply represent spill over from inflammation in the airways. Concurrent examination of systemic inflammation, eosinophilic and neutrophilic, from induced sputum, in this population may assist in answering this question.

As previously noted, CVD events are the leading cause of morbidity and mortality in structural firefighters affecting 1 in 1,000 structural firefighters annually [Fahy, 2005; Soteriades et al., 2011]. Higher BMI and lower cardiorespiratory fitness, as measured by achieved MaxMETs are among the factors associated with an elevated CVD risk profile in firefighters [Baur et al., 2011]. We observed a borderline significant association between higher cardiorespiratory fitness, as measured by achieved MaxMETs and higher FEV_1%-predicted values but not vital capacity. We observed an association between higher FEV_1%-predicted and higher BMI and an inverse relationship between higher FEV_1%predicted and resting systolic blood pressure after adjusting for hsCRP and MaxMETS.

There is evidence that particulate matter (PM) produced by fires may be more toxic than PM from ambient air due to chemical components found in the smoke [Wegesser et al., 2009]. Leonard et al. [2007] examined six sets of aerodynamically size-selected aerosol samples at a large fire. The authors found smoke particles in all size fractions, with highest overall mass fraction on filters in the fine range. Ultrafine particles (<0.1μm diameter) may produce greater inflammation than larger particles, simply due to a much larger total surface area to volume ratio of the former. Ultrafine particles may escape phagocytosis by alveolar macrophages, easily gaining access to the pulmonary interstitium. The severity of airways inflammation due to particulate exposures is correlated with particle surface area [Brown et al., 2001; Oberdorster, 2001].

Additionally, smoke particulate may be associated with adverse respiratory health outcomes as a result of the generation of toxic free radicals [Bankson et al., 1993; Jankovic et al., 1993; Leonard et al., 2000]. Leonard et al. [2007] used electron spin resonance to measure carbon-centered as well as hydroxyl radicals produced by a Fenton-like reaction with smoke. The authors observed that OH radical precursors were more prevalent (per unit mass) in the ultrafine-sized particles and caused a significant increase in cellular H_2O_2 production, DNA strand breaks, and reactive oxygen species (ROS)-induced lipid peroxidation as measured by malondialdehyde (MDA). Thus, exposure to chemicals and fine particulates routinely encountered during structural firefighters overhaul operations, where respiratory protection is generally not donned [Burgess et al., 2001] could generate ROS, potentially leading to oxidative damage and inflammation and may explain the increased risk of lower lung dysfunction in this healthy worker population comprising primarily non-current smokers. Moreover, Weiden et al., observed a significant inverse association between CRP and FEV_1 in firefighters exposed to PM generated by the World Trade Center Disaster [Weiden et al., 2013]. The authors hypothesized that the increased systemic CRP levels could reflect pulmonary vessel damage. It is of note, that some of the mean predicted values for lung function we observed were lower than the referent population. However, our study lacked a means to quantify this type of exposure Further research is needed to examine how our findings might relate to exposure.

We examined hsCRP which minimizes the biological variation in the samples. Only obtaining one measure of hsCRP, which varies by season [Sung, 2006], could have affected our results. However, the testing took place over the course of a few years year so any potential misclassification would be non-differential.

We did not observe a difference among individuals with a history of pulmonary or cardiovascular disease. However, given the small number of individuals with these outcomes, 16 and one respectively, we may have lacked sufficient statistical power to observe one if it did exist.

Our study has a number of limitations. We examined only one biomarker of inflammation. Future studies should examine sputum biomarkers of neutrophilic inflammation, such as myeloperoxidase, which has been linked to occupationally-related airways obstruction [Jung and Park, 1999]. We do not have exposure data on participants which limited our ability to examine dose–response relationships. Moreover, we lack lower respiratory symptom data such as wheeze and shortness of breath, which limits the interpretation of our objective findings as they relate to overall well-being and function. Finally, our study population (n = 401) with complete data that was analyzed constituted 98% of the male members of the fire department who consented to participate. While the possibility of selection bias does exist, we do know that our consented population has a very similar age, BMI, and expected ethnic composition to that found in a randomly sampled, population-based study of career firefighters [Poston et al., 2011].

hsCRP, a biomarker of systemic inflammation potentially generated from lifestyle and occupational exposures including smoke particulate, is associated with diminished exercise tolerance and oxidative stress. Damage reflected in elevated HsCRP may result in reduced lung function in structural firefighters. Our results corroborate the findings of an inverse relationship between CRP and lung function observed in both occupational settings and the general population. The long-term significance of these findings to the cardiopulmonary health of structural firefighters, including the relationship to exposure, should be investigated further.

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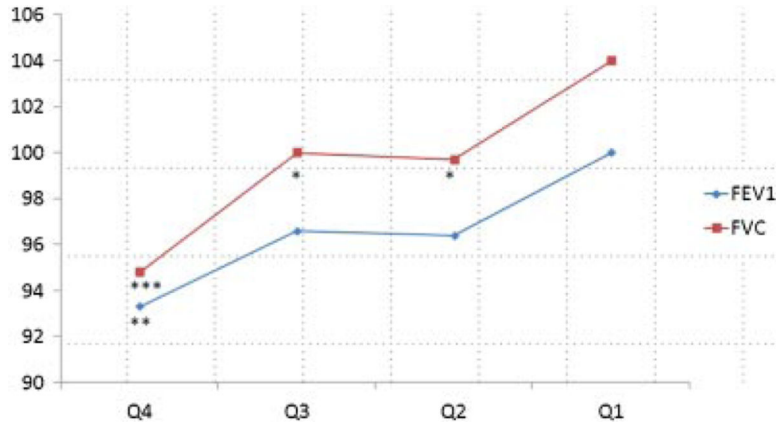

FIGURE1.

Mean $FEV_1$and FVC%-predicted values by hsCRP category. ***Significant from Q1 (referent) at <0.001. **Significant from Q1 (referent) at <0.01. *Significant from Q1 (referent) at <0.05.

TABLE I.

Subject Characteristics at Examination

Variable	N = 401
Age (years)	36(27,47)[a]
Male gender, n (%)	401 (100)
Body mass index (kg /m^2)	29(24,36)[a]
Weight (kg)	91.6 (74.4,113)[a]
Resting diastolic blood pressure (mm Hg)	80 (70,90)[a]
Resting systolic blood pressure (mm Hg)	120 (108,138)[a]
MaxMETs achieved during ETT[b]	10.1 (7.9,13.2)[a]
Current smoker, n (%)	34(8.5)
Former smoker, n (%)	55(14)
Pulmonary disease (ever), n (%)[c]	16(4)
Current hypertension, n (%)[d]	73 (18)
History of heart disease, n (%)[e]	1 (0.2)
High sensitivity C-reactive protein (μg/ml)	1.06 (0.3,4.9)[a]

[a]Median and10th, 90th percentiles.

[b]Maximum metabolic equivalent (MET) achieved during exercise tolerance test (ETT).

[c]History of pulmonary disease including asthma and COPD.

[d]Resting systolic blood pressure ≥140 mm Hg or resting diastolic blood pressure ≥90 mm Hg.

[e]History of heart disease includes diabetes, heart disease, or hypertension.

TABLE II.

Pulmonary FunctionTest Results

Variable	N = 401
Percent predicted forced expiratory volume in 1s (FEV_1%-predicted)	95(80,115)[a]
Percent predicted forced vital capacity (FVC%-pred icted)	99 (84,117)[a]
FEV_1/FVC(%)	81 (73,86)[a]
Moderate COPD, n (%)	10(3)
Mild COPD, n (%)	14(4)
Restrictive lung disease, n (%)	4 (1)

[a]Median and10th, 90th percentiles.

TABLE III.

Predictors of FEV_1%-Predicted,OLS Estimates and 95% CIS

Variable[a]	Unadjusted	Adjusted[b]
HsCRP(per1 $\log_{10}$ mg/L higher)	−4.2(−7.3, −1.0)	−5.3(−8.9,−1.6)
Body mass index (per1 kg/m^2 higher)	0.1 (−0.3,0.4)	0.6 (0.2,1.0)
Resting systolic blood pressure (per10 mm Hg higher)	−1.4 (−2.6,−0.1)	−1.7 (−2.9,−0.4)
Achieved maxMETs (per1 MET higher)	0.6 (−0.1,1.3)	0.8 (−0.0,1.7)

OLS, Ordinary least squares.

[a] Current smoker, history of pulmonary disease, current hypertension, $\log_{10}$ weight and resting diastolic blood pressure were not associated with FEV_1%-predicted in this cohort and so were not included in the regression model.

[b] Estimates from the regression model that included all four variables shown.

TABLE IV.

Predictors of FVC%-Predicted,OLS Estimates and 95% CIS

Variable[a]	Unadjusted	Adjusted[b]
HsCRP(per1 $\log_{10}$mg/L)	−5.9(−8.8, −3.0)	−4.7 (−7.9, −1.5)
Weight (per1 $\log_{10}$ lb higher).	−30.6(−48.8, −12.5)	−19.6 (−39.1,−0.05)

OLS, ordinary least squares.

[a]Current smoker, history of pulmonary disease, current hypertension, achieved maxMETs, resting systolic blood pressure, resting diastolic blood pressure and BMI were not associated FVC%-predicted in this cohort and so were not included in the model.

[b]Estimate from the regression model that included both variables shown.