Reduced Lung Function, C-Reactive Protein, and Increased Risk of Cardiovascular Mortality
Kyoung-bok Min, PhD; Jin-young Min, PhD

Background: We explored whether reduced lung function is a predictor of mortality due to cardiovascular or coronary artery disease (CVD or CAD), and, if this hypothesis is correct, whether C-reactive protein (CRP), a systemic inflammatory marker, is responsible for this association in a general population-based cohort.

Methods and Results: We used the Third Nutrition and Health Examination Survey (NHANES III) database and the NHANES III Linked Mortality File. A total of 13,310 participants ≥20 years of age who completed a spirometric test at baseline examination were included. On comparison of the participants in the lowest forced vital capacity percent predicted (FVC% pred) quartile with those in the highest quartile, the hazard ratio (HR) was 2.1 (95% CI: 1.7–2.6) for cardiovascular mortality and 2.2 (95% CI: 1.6–3.2) for coronary mortality. A similar association was observed for forced expiratory volume in 1 s percent predicted (FEV1% pred). When the participants with the highest FVC% pred or FEV1% pred (Q4) and low CRP (≤0.22 mg/dl) were defined as the reference group, the adjusted HR for cardiovascular mortality was significantly increased in the individuals with the lowest spirometric volume (Q1), and the risk was prominent in individuals with high CRP (>0.22 mg/dl).

Conclusions: There is a significant association between lung function parameters and death from CVD and CAD in the general population. (Circ J 2014; 78: 2309–2316)

Key Words: Coronary artery disease; Inflammation; Lung

Lung function decline is a significant predictor of adverse cardiovascular events. Many epidemiologic studies have demonstrated that poor lung function, as indicated by a low forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC), is associated with an increased risk of coronary artery disease (CAD), stroke, and cardiovascular death. This risk is independent of cigarette smoking, which is a shared risk factor for lung function and cardiovascular disease (CVD). Moreover, lung function parameters are a powerful predictor of cardiovascular mortality compared with socioeconomic position, cardiovascular risk factors (ie, serum cholesterol and blood pressure), and Framingham risk score alone.

The exact mechanisms responsible for the association between lung function and cardiovascular risk remain unclear. Low-grade systemic inflammation, however, has been identified as a plausible mechanistic pathway. Subjects with a reduced FEV1 or FVC have elevated levels of circulating inflammatory markers, such as C-reactive protein (CRP) and fibrinogen, compared with individuals with normal lung function. The cardiovascular risk of subjects with low spirometric parameters significantly differs based on systemic inflammation level, suggesting an interplay of systemic inflammation with reduced lung function in the development of cardiovascular events.

Although several studies have evaluated the association between lung function and cardiovascular events, evidence of a link between lung function, systemic inflammation, and cardiovascular mortality is still limited. In this study, we explored whether decline in lung function, as measured by FVC percent predicted (FVC% pred) and FEV1 percent predicted (FEV1% pred), is a predictor of mortality due to CVD or CAD, and, if this hypothesis is correct, whether CRP, a systemic inflammatory marker, is responsible for this association in a general population-based cohort.

Methods

We used the Third Nutrition and Health Examination Survey (NHANES III) database and the NHANES III Linked Mortality File. A total of 13,310 participants ≥20 years of age who completed a spirometric test at baseline examination were included. On comparison of the participants in the lowest forced vital capacity percent predicted (FVC% pred) quartile with those in the highest quartile, the hazard ratio (HR) was 2.1 (95% CI: 1.7–2.6) for cardiovascular mortality and 2.2 (95% CI: 1.6–3.2) for coronary mortality. A similar association was observed for forced expiratory volume in 1 s percent predicted (FEV1% pred). When the participants with the highest FVC% pred or FEV1% pred (Q4) and low CRP (≤0.22 mg/dl) were defined as the reference group, the adjusted HR for cardiovascular mortality was significantly increased in the individuals with the lowest spirometric volume (Q1), and the risk was prominent in individuals with high CRP (>0.22 mg/dl).

Conclusions: There is a significant association between lung function parameters and death from CVD and CAD in the general population. (Circ J 2014; 78: 2309–2316)

Key Words: Coronary artery disease; Inflammation; Lung
NHANES III is based on a complex multistage probability sampling design. Appropriate sampling weights are needed to estimate prevalence, means, medians, and other statistics. The sampling weights are used to produce correct population estimates because each sampled person does not have an equal probability of selection. The sampling weights incorporate the differential probabilities of selection and include adjustments for non-coverage and non-response.14

We initially included 14,994 study participants who were aged ≥20 years and who successfully completed a spirometric test at the time of examination. From this sample, 665 participants were excluded because they had a history of heart attack or cerebrovascular disease. We also excluded 1,019 participants who had missing variables for cardiovascular risk factors. The cohort analysis in the present study was thus based on 13,310 NHANES III participants.

NHANES is a publicly released dataset, so we did not need informed consent to use this dataset. This study was exempt from the Institutional Review Board approval of Ajou University Hospital.

**Baseline Data Collection**

The participants were interviewed in NHANES III to obtain information on age (20–29, 30–39, 40–49, 50–59, 60–69, or ≥70 years), gender (male or female), race/ethnicity (white, black, Hispanic, or other), education (less than high school, high school graduate, or college or more), and smoking status (current, former, or never). Regarding disease history, hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg, anti-hypertensive drug use, or prior physician diagnosis of hypertension. Hyper-cholesterolemia was defined as serum total cholesterol level ≥6.19 mmol/L, current medication use, or self-reported diagnosis by a physician.

### Table 1. Baseline Characteristics vs. FVC% Pred and FEV1% Pred

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Q1 (78.49)</th>
<th>Q2 (89.50–98.86)</th>
<th>Q3 (98.87–108.00)</th>
<th>Q4 (≥108.01)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>507±16.9</td>
<td>856±28.6</td>
<td>874±29.2</td>
<td>758±25.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30–39</td>
<td>483±17.4</td>
<td>752±26.8</td>
<td>811±28.9</td>
<td>757±27.0</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>506±23.2</td>
<td>564±25.9</td>
<td>593±27.2</td>
<td>517±23.7</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>484±32.3</td>
<td>386±25.7</td>
<td>334±22.3</td>
<td>297±19.8</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>594±33.5</td>
<td>408±23.0</td>
<td>343±19.4</td>
<td>426±24.1</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>635±30.7</td>
<td>385±18.6</td>
<td>417±20.2</td>
<td>632±30.6</td>
<td></td>
</tr>
</tbody>
</table>

**Gender**

- **Male**: 1,442 (23.4) 1,659 (26.9) 1,539 (24.9) 1,536 (24.9) 0.0004
- **Female**: 1,772 (24.8) 1,692 (23.7) 1,833 (25.6) 1,851 (25.9)

**Race/Ethnicity**

- **White**: 1,524 (26.6) 1,448 (25.3) 1,442 (25.2) 1,318 (23.0) <0.0001
- **Black**: 892 (23.8) 870 (23.2) 912 (24.3) 1077 (28.7)
- **Hispanic**: 798 (20.8) 1,033 (26.9) 1,018 (26.5) 992 (25.8)

**Education**

- **Less than high school**: 864 (29.0) 658 (22.1) 648 (21.7) 812 (27.2) <0.0001
- **High school**: 1,575 (24.5) 1,650 (25.7) 1,671 (26.0) 1,523 (23.7)
- **College or more**: 775 (19.8) 1,043 (26.6) 1,053 (26.8) 1,052 (26.8)

**Cigarette smoking**

- **Current smoker**: 902 (25.6) 933 (26.5) 907 (25.7) 782 (22.2) <0.0001
- **Former smoker**: 855 (26.5) 720 (22.4) 783 (24.3) 863 (26.8)
- **Never smoker**: 1,457 (22.2) 1,698 (25.8) 1,682 (25.6) 1,742 (26.5)

**History of disease**

- **Hypertension**: 1,288 (33.4) 872 (22.6) 828 (21.5) 870 (22.6) <0.0001
- **Dyslipidemia**: 1,070 (27.3) 964 (24.6) 921 (23.5) 959 (24.5) <0.0001
- **Diabetes**: 542 (40.3) 330 (24.6) 257 (19.1) 215 (16.0) <0.0001
- **Asthma**: 283 (32.5) 205 (23.5) 190 (21.8) 194 (22.3) <0.0001
- **COPD**: 340 (40.1) 190 (22.4) 169 (19.9) 150 (17.7) <0.0001

**Height (cm)**

- 166.1±0.3 167.5±0.3 166.7±0.3 166.2±0.3 <0.0001

**BMI (kg/m²)**

- 28.1±0.2 27.2±0.2 26.8±0.2 26.6±0.2 <0.0001

**TC (mg/dl)**

- 209.6±1.6 203.6±1.5 203.8±1.5 204.3±1.5 <0.0001

**CRP (mg/dl)**

- 0.6±0.0 0.5±0.0 0.4±0.0 0.4±0.0 <0.0001

**Serum ferritin (ng/ml)**

- 146.5±5.5 136.1±5.3 124.4±4.5 124.9±4.5 <0.0001

(Table 1 continued the next page.)
Diabetes was defined as fasting plasma glucose ≥6.99 mmol/L, non-fasting plasma glucose ≥11.1 mmol/L, current insulin use, or prior physician diagnosis of diabetes. History of respiratory disease included asthma or chronic obstructive pulmonary disease (COPD) based on prior physician diagnosis. Anthropometric variables included height in centimeters and body mass index (BMI), which was calculated by dividing weight in kilograms by height in meters squared. Total cholesterol (mg/dl), CRP (mg/dl), and ferritin were included as biomarkers of mortality risk and were treated as continuous variables.

In addition, because most participants (56%) had CRP below the lowest detectable level of 0.22 mg/dl, CRP was categorized into 2 subgroups: low CRP (≤0.22 mg/dl) and high CRP (>0.22 mg/dl).

Mortality Follow-up
The International Classification of Diseases, 9th Revision (ICD-9) was used for deaths occurring from 1988 through 1998, and International Classification of Diseases, 10th Revision (ICD-10) was used for deaths occurring from 1999 through 2000. The underlying causes of death were grouped according to the coding system of the National Center for Health Statistics. All deaths from 1988–1998 that were coded under the ICD-9 Clinical Modification guidelines were replaced by the ICD-10 underlying causes of death.

In addition to all-cause mortality, we studied the following specific causes of death: CVD (ICD-10 code I00–I99) and CAD (ICD-10 code I20–I25).

Lung Function Test
Lung function testing (spirometry) was performed according to the 1987 American Thoracic Society recommendations. A more detailed description is available in the Hankinson et al study. Briefly, using screening questions, participants who had undergone chest or abdominal surgery within 3 weeks or had experienced heart problems (myocardial infarction or heart attack, angina or chest pain, or congestive heart failure) were excluded from testing. Body measurements were taken, in-
Table 2. Mortality According to FVC% Pred and FEV1% Pred

<table>
<thead>
<tr>
<th></th>
<th>Standardized mortality (%)(^1)</th>
<th>CVD mortality</th>
<th>Model I</th>
<th>Adjusted HR (95% CI)</th>
<th>CAD mortality</th>
<th>Model I</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC% pred</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (≤86.84)</td>
<td>10.4 (9.5–11.3)</td>
<td>2.2 (1.8–2.6)</td>
<td>1.7 (1.4–2.1)</td>
<td>5.6 (5.0–6.3)</td>
<td>2.2 (1.7–3.0)</td>
<td>1.8 (1.4–2.4)</td>
<td></td>
</tr>
<tr>
<td>Q2 (86.85–97.16)</td>
<td>7.6 (6.6–8.5)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.2 (0.9–1.6)</td>
<td>4.3 (3.6–5.0)</td>
<td>1.5 (1.1–2.1)</td>
<td>1.4 (1.0–2.0)</td>
<td></td>
</tr>
<tr>
<td>Q3 (97.17–106.74)</td>
<td>7.3 (6.4–8.2)</td>
<td>1.3 (1.0–1.6)</td>
<td>1.2 (1.0–1.5)</td>
<td>4.1 (3.4–4.7)</td>
<td>1.3 (0.9–1.9)</td>
<td>1.3 (0.9–1.9)</td>
<td></td>
</tr>
<tr>
<td>Q4 (≥106.75)</td>
<td>6.6 (5.9–7.3)</td>
<td>Reference</td>
<td>Reference</td>
<td>3.8 (3.3–4.3)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>P-trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0023</td>
<td></td>
</tr>
</tbody>
</table>

| FEV1% pred       |                                   |               |                |                      |               |                |                      |
| Q1 (≤89.49)      | 11.2 (10.2–12.1)                  | 2.6 (2.1–3.2) | 2.1 (1.7–2.6)  | 6.0 (5.3–6.7)        | 2.8 (2.0–3.8) | 2.2 (1.6–3.2)  |
| Q2 (89.50–98.86) | 7.6 (6.7–8.6)                     | 1.6 (1.3–2.0) | 1.6 (1.3–1.9)  | 4.6 (3.9–5.3)        | 1.9 (1.4–2.7) | 1.8 (1.2–2.5)  |
| Q3 (98.87–108.00)| 6.9 (6.1–7.8)                     | 1.5 (1.2–1.9) | 1.4 (1.2–1.8)  | 4.0 (3.4–4.7)        | 1.5 (1.0–2.1) | 1.4 (1.0–2.1)  |
| Q4 (≥108.01)     | 6.2 (5.5–6.6)                     | Reference     | Reference      | 3.3 (2.8–3.8)        | Reference     | Reference      |
| P-trend          | <0.0001                           | <0.0001       | <0.0001        | 0.0001               | 0.0001        | 0.0001         |

\(^1\) Age- and gender-standardized mortality from CVD and CAD. Model I was adjusted for age, sex, race/ethnicity, and education. Model II was further adjusted for smoking, history of disease (hypertension, dyslipidemia, diabetes, asthma, or chronic obstructive pulmonary disease), height, BMI, TC, CRP, and ferritin.

To further assess whether CRP contributed to the association between lung function and mortality, we divided CRP into 2 subgroups, low CRP (≤0.22 mg/dl) and high CRP (>0.22 mg/dl), based on the detection limit. HR was calculated for the extreme quartiles (Q1) of each FVC% pred and FEV1% pred in relation to CRP level, by classifying participants with the highest spirometric parameters (Q4) and low CRP as the reference group. The model was adjusted for age, gender, race/ethnicity, education, smoking, history of CVD or respiratory disease, height, BMI, and total cholesterol.

Results

Table 1 lists the frequency (%) and mean±SE for FVC% pred and FEV1% pred, grouped by subject baseline characteristics. Significant trends in all characteristics were observed for both quartiles of FVC% pred and FEV1% pred (P<0.05 for trend). Specifically, participants with the lowest FVC% pred or FEV1% pred were more likely to be older, female, white, and have less than high school education. These participants had also a history of disease (ie, hypertension, dyslipidemia, diabetes, asthma, and COPD) and elevated BMI, total cholesterol, CRP, and serum ferritin. In this sample, the overall prevalence was 9.2% (n=1,224) for CVD mortality and 4.9% (n=657) for CAD mortality. The subject baseline characteristics with and without CVD or CAD mortality are provided in Table S1.

Table 2 lists age- and gender-standardized mortality and the HR (95% CI) for mortality from CVD and CAD based on the quartile of the spirometric volume at baseline. CVD and CAD mortality was the highest in the lowest quartile (Q1), and the mortality rate gradually decreased as the quartiles increased. On comparison of the participants in the lowest FVC% pred quartile with the individuals in the highest quartile, the adjusted HR was 2.1 (95% CI: 1.7–2.6) for cardiovascular mortality and 2.2 (95% CI: 1.6–3.2) for coronary mortality, after adjusting for CVD risk factors, including smoking, CVD history (ie, hypertension, dyslipidemia, and diabetes), BMI, total cholesterol, CRP, and ferritin level. The risk significantly increased, even in response to a small reduction (ie, Q2 and Q3) in FVC% pred. For FEV1% pred, the corresponding HR were
Lung Function, CRP, and CV Mortality

Table 3. Lung Function Pattern and Mortality

<table>
<thead>
<tr>
<th>Lung function</th>
<th>CVD mortality</th>
<th>CAD mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. events (%)</td>
<td>Adjusted HR† (95% CI)</td>
</tr>
<tr>
<td>Normal FVC and FEV₁ (FVC% pred ≥80, FEV₁% pred ≥80)</td>
<td>825 (7.4)</td>
<td>Reference</td>
</tr>
<tr>
<td>Normal FVC and low FEV₁ (FVC% pred ≥80, FEV₁% pred &lt;80)</td>
<td>119 (15.0)</td>
<td>1.4 (0.9–2.0)</td>
</tr>
<tr>
<td>Low FVC and normal FEV₁ (FVC% pred &lt;80, FEV₁% pred ≥80)</td>
<td>55 (18.8)</td>
<td>2.8 (1.5–5.2)</td>
</tr>
<tr>
<td>Low FVC and low FEV₁ (FVC% pred &lt;80, FEV₁% pred &lt;80)</td>
<td>225 (21.5)</td>
<td>2.1 (1.5–2.8)</td>
</tr>
</tbody>
</table>

†Adjusted for age, sex, race/ethnicity, smoking, education, the history of disease, height, BMI, TC, CRP, and ferritin. Abbreviations as in Tables 1, 2.

Figure. Cumulative (A,C) cardiovascular and (B,D) coronary artery disease mortality for extreme forced vital capacity percent predicted (FVC% pred) or forced expiratory volume in 1 s percent predicted (FEV₁% pred) quartiles and C-reactive protein (CRP). (●) High CRP (>0.22 mg/dl); (○) low CRP (<0.22 mg/dl).

1.7 (95% CI: 1.4–2.1) for cardiovascular mortality and 1.8 (95% CI: 1.4–2.4) for coronary mortality. Significant overall trends in risk were observed for both FVC% pred and FEV₁% pred (P<0.05 for trend). In addition, subgroup analyses were conducted based on ever smoking (former and current smokers), age (<65 years or ≥65 years) and sex (Tables S2–S4). Except for the FEV₁% pred related to CVD and CAD mortality among adults (<65 years), there was an overall significant association between lung function and mortality from CVD and CAD.

Table 3 lists the distribution of CVD and CAD mortality by combination of FVC% pred and FEV₁% pred. Lung function was categorized into 4 groups: normal FVC and normal FEV₁ (FVC% pred ≥80, FEV₁% pred ≥80); normal FVC and low FEV₁ (FVC% pred ≥80, FEV₁% pred <80); low FVC and normal FEV₁ (FVC% pred <80, FEV₁% pred ≥80); and low FVC and low FEV₁ (FVC% pred <80, FEV₁% pred <80). As
expected, participants with normal lung function had the lowest prevalence of mortality. Regarding the mortality from CVD and CAD, the participants with low FVC and low FEV1 had the highest prevalence of mortality (21.5% and 11.6%, respectively), followed by those with low FVC and normal FEV1 (18.8% and 10.6%, respectively). Adjusted HR for CVD and CAD mortality were significantly increased in individuals with the lowest FVC% pred or FEV1% pred (Q4) and low CRP were defined as the potential risk factors. When participants with the highest spirometric volumes (Q4), participants in the lowest quartile (Q1) had an increased risk of CVD (HR, 2.1; 95% CI: 1.7–2.6) and CAD (HR, 3.8; 95% CI: 1.9–7.8) or who had low FVC and normal FEV1 (CVD: HR, 2.1; 95% CI: 1.5–2.8; CAD: HR, 2.1; 95% CI: 1.3–3.2) compared with those with normal lung function. Subjects with normal FVC and low FEV1, however, were not associated with that mortality risk.

We further investigated the association between lung function and cardiovascular mortality by assessing CRP level. Figure presents the cumulative mortality from CVD and CAD in the extreme quartiles of FVC% pred and FEV1% pred, by classifying individuals based on whether they had high (>0.22 mg/dl) or low (≤0.22 mg/dl) CRP. Participants with the lowest spirometric volume and high CRP had the highest cumulative risk, and the risk was nearly 15% and 7–8% for CVD and CAD, respectively.

Table 4 lists the HR for mortality in the extreme quartiles of lung volume in relation to CRP level, after adjusting for potential risk factors. When participants with the highest spirometric parameters (Q4) and low CRP were defined as the reference group, the adjusted HR for cardiovascular mortality significantly increased in individuals with the lowest FVC% pred or FEV1% pred (Q1), and the risk was prominent in subjects with high CRP. A similar pattern was observed for CAD mortality. Individuals who had the lowest spirometric parameters (Q1) and >0.22 mg/dl CRP simultaneously had the highest HR for FVC% pred and for FEV1% pred: HR, 2.4 (95% CI: 1.5–3.7), and HR, 2.3 (95% CI: 1.6–3.3), respectively.

### Discussion

In this prospective cohort study of a representative sample of the US population, we found that reduced lung function was significantly associated with cardiovascular mortality in adults. The participants with the lowest FVC% pred or FEV1% pred (Q1) at baseline had a nearly 2-fold increased risk of CVD and CAD mortality compared with individuals with the highest baseline FVC% pred or FEV1% pred (Q4). After adjusting for cardiovascular risk factors (ie, smoking, hypertension, diabetes, and systemic inflammatory markers), the HR remained significant and was dose responsive (P<0.05 for trend; Table 4). Subgroup analyses based on ever smoking (former and current smokers), age (<65 years and ≥65 years), and sex also indicated a robust association between lung function and mortality risk. In addition, the cardiovascular risk differed when the CRP was stratified as low (≤0.22 mg/dl) or high (>0.22 mg/dl). CRP level increased cardiovascular mortality risk, and the risk increases were prominent among the subjects with the lowest spirometric data.

The present findings reinforce existing evidence of an association between lung function and cardiovascular mortality. Many studies, from epidemiologic studies to systematic reviews, have shown that reduced lung function, even a relatively modest reduction, significantly predicts cardiovascular mortality over short- and long-term follow-up periods. The current study also showed significant trends of increasing risk with diminishing spirometric volumes. Compared with the highest spirometric volumes (Q4), participants in the lowest quartile (Q1) had an increased risk of CVD (HR, 2.1; 95% CI: 1.7–2.6) for FVC% pred; HR, 1.7, 95% CI: 1.4–2.1 for FEV1% pred). The increased risks were present not only in the participants with the worst spirometric parameters but also in those individuals with a moderate reduction. A significant increase in CAD mortality was of particular interest. Few studies have focused on reduced lung function as a predictor of CAD or death. From a longitudinal study of the Renfrew and Paisley survey, Hole et al found that subjects with the lowest FEV1% pred had a nearly 2-fold increased risk of ischemic heart disease mortality. Schünemann et al examined whether lung function remained a significant predictor of mortality over 25 years using data from the Buffalo Health Study. For the entire follow-up period, the adjusted HR for ischemic heart disease were 2.11 (95% CI: 1.20–3.71) for men and 1.96 (95% CI: 0.99–3.88) for women. These observations were similar to...
the present risk estimate, with an approximately 2-fold increased risk, and suggested that the increased risk was apparent even for a slight reduction of FEV1% pred. In the Atherosclerosis Risk in Communities study, Schroeder et al found a strong association between lung function and the incidence of CAD among women but a weaker association among men, both in the full cohort and among never smokers. More interestingly, a recent study showed that the addition of FVC to Framingham risk score, which is a global risk algorithm for estimating cardiovascular event risk, provided a significant benefit in predicting mortality (area under the curve, 0.64 vs. 0.56; P<0.05) in intermediate-risk individuals. Although lung function effectively predicts CVD and CAD mortality, the mechanism underlying this association is still unclear. Several potential explanations for the association have been proposed. First, smoking may be responsible for this relationship because smoking affects both lung function and CVD and death. This association, however, is independent of smoking status and is present in never smokers. Sabia et al found that the contribution of smoking history (current smoking, recent ex-smoker, long-term ex-smoker, and never smoker) to lung function and cardiovascular risk association might not be very large, implying that smoking is not the only explanation for this phenomenon. Second, lung function could be an indicator of general health, thus associating poor lung function with mortality risk in general. Third, the lung is a primary defense organ against external toxic agents, such as air pollution and diesel exhaust fumes, and could result in increased tolerance to toxic substances, which then leads to disease and death. In addition, a potential central player in the association is low-grade systemic inflammation. Systemic inflammatory markers have been inversely associated with spirometric indices and have been suspected of being involved in lung function-related cardiovascular events. Recent data emphasized the importance of inflammatory markers, which explain more of the association between lung function and mortality than other variables, including socioeconomic position, health behaviors, cardiovascular risk factors, and disease.

Considerable attention has been focused on CRP in relation to the association between lung function and cardiovascular mortality. CRP level has been used as a consistent measure of underlying low-grade systemic inflammation and as an important marker linked to the development of cardiovascular events. Circulating CRP level is associated with increased mortality in both the general population and COPD patients. Although an association between lung function, inflammation, and CVD and death has been suggested, few studies have evaluated the potential relationship. Engstrom et al investigated whether FVC was associated with high inflammation-sensitive plasma proteins (ISP) including 1-antitrypsin, ceruloplasmin, fibrinogen, haptoglobin, and orosomucoid, and whether inflammatory markers contributed to increased cardiovascular events among men with reduced FVC. They found that low FVC was associated with high ISP and with an increased risk of myocardial infarction and cardiovascular death. Notably, among men with low FVC, the relative risk of myocardial infarction was 2.5 (95% CI: 1.7–3.6) for individuals with high protein levels and 1.7 (95% CI: 1.1–2.4) for men with low protein levels. Sin and Man reported that subjects with moderate and severe airflow obstruction had an increased risk of ischemic changes on electrocardiogram. In particular, individuals with elevated CRP (>0.22 mg/dl) had a nearly 2-fold (relative odds, 2.2; 95% CI: 1.5–3.3) increased risk of cardiac injury. The present observations are similar to these results. We found that cumulative mortality from CVD and CAD increased as lung function decreased and that CRP was elevated. High CRP significantly increased HR among subjects with the lowest FVC% pred or FEV1% pred (Table 4). These findings suggest an important role for systemic inflammation in the link between poor lung function and cardiovascular risk.

Establishing whether reduced lung function elicits systemic inflammation or whether increased systemic inflammation leads to a decline in lung function is difficult. The present results suggest that reduced lung function is responsible for systemic inflammation. An experimental study by Suwa et al provided evidence supporting this hypothesis. The inhalation of fine particulate matter in hyperlipidemic rabbits provoked a low-grade pulmonary inflammatory response, a release of potentially harmful cytokines, and changes in blood coagulability. That study suggested that particle-induced airway inflammation leads to the propagation of systemic inflammation, which may in turn increase the risk of acute cardiovascular events and the potential for accelerated atherosclerosis and CVD. Future studies are needed to clarify the mechanistic pathways related to systemic inflammation in the association between lung function and cardiovascular risk.

The lung function test is a non-invasive method used in clinical settings to provide additional prognostic information on CVD that may help to better predict the risk for future cardiovascular events. In addition, previous studies suggested that there are associations between impaired lung function and inflammation markers as well as prospective cardiovascular events. Clinicians who manage patients with possible respiratory inflammation, such as an occupational history or exposure to dust and particles, could evaluate both the cardiovascular and respiratory systems. By exploring emerging data that indicate a link between lung function, inflammation and CVD, new management strategies to produce better outcomes in patients who have impaired lung function and CVD may be discovered.

The limitations of this study included the use of a single spirometric measurement at baseline and a long interval between measurement and follow-up. We acknowledge that lung function certainly changed over the follow-up period, and that the influence of changes in lung function on the risk of death was not addressed. In addition, because spirometric testing is effort-dependent, a degree of measurement error in the ascertainment of lung function can exist, despite a standardized protocol and strict quality control. The NHANES III Linked Mortality File ascertained mortality from death certificates, but this approach may overestimate the burden of cardiovascular events as the cause of death, especially at older ages. Future studies may in turn increase the risk of acute cardiovascular events and the potential for accelerated atherosclerosis and CVD.

Conclusions

Lung function decline is associated with an increased mortality risk from CVD and CAD in the general population. We have also provided evidence of the significant association between spirometric lung volume, CRP, and cardiovascular mortality. The present study confirms the findings of previous reports and indicates that the association between reduced lung function and cardiovascular risk is mediated by low-grade systemic inflammation. This suggests that lung function measures are beneficial for targeting individuals who are at high risk.
risk of cardiovascular mortality.

Acknowledgments

This study has no conflict of interest to declare. This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (grant number, 2012R1A1A0104318, 2012R1A1A3017058).

Disclosures

All authors have no conflict of interest to declare.

References


