Lung Function and Cardiovascular Risk
Relationship With Inflammation-Sensitive Plasma Proteins

G. Engström, MD, PhD; P. Lind, MD; B. Hedblad, MD, PhD; P. Wollmer, MD, PhD; L. Stavenow, MD, PhD; L. Janson, MD, PhD; F. Lindgärde, MD, PhD

Background—The inverse relationship between pulmonary function and incidence of cardiovascular disease remains largely unexplained. This prospective study explored the hypothesis of a relationship with inflammation-sensitive plasma proteins.

Methods and Results—Forced vital capacity (FVC) and plasma levels of fibrinogen, \( \alpha_1 \)-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid were determined in 5064 healthy men aged 28 to 61 years. All-cause mortality, cardiovascular mortality, and incidence of myocardial infarction were monitored over a mean follow-up period of 18.4 years. Low FVC (fourth quartile) was associated with higher protein levels and with increased incidences of myocardial infarction and cardiovascular death. Adjustments for protein levels reduced the age-adjusted relative risks (RRs) for myocardial infarction (from 1.99, 95% CI 1.5 to 2.6, to 1.70, 95% CI 1.3 to 2.2) and cardiovascular death (from 2.71, 95% CI 1.9 to 3.9, to 2.28, 95% CI 1.6 to 3.3) among men with low FVC, corresponding to \( \approx 25\% \) of the excess risk. The risk factor–adjusted RRs were reduced from 1.45 (95% CI 1.1 to 1.9) to 1.38 (95% CI 1.1 to 1.8) and from 1.96 (95% CI 1.4 to 2.8) to 1.85 (95% CI 1.3 to 2.7) for myocardial infarction and cardiovascular death, respectively, corresponding to \( \approx 10\% \) to 15% of the excess risk. Among men with low FVC, the risk factor–adjusted RR for myocardial infarction was 2.5 (95% CI 1.7 to 3.6) for those with high protein levels (\( \geq 2 \) proteins in top quartile) and 1.7 (95% CI 1.1 to 2.4) for those with low protein levels (\( \leq 1 \) protein in top quartile; reference, top quartile of FVC and low protein levels).

Conclusions—FVC is significantly and inversely associated with plasma levels of inflammation-sensitive plasma proteins. This relationship contributes to but cannot fully explain the increased cardiovascular risk among men with low FVC. (Circulation. 2002;106:2555-2560.)

Key Words: forced vital capacity ■ epidemiology ■ inflammation

Reduced pulmonary function, as assessed by forced expiratory volume and forced vital capacity (FVC), is associated with increased incidences of cardiovascular disease and death. The cause for this association, which has been established in both smokers and nonsmokers, is largely unexplained.

Fibrinogen and other inflammation-sensitive plasma proteins (ISPs) are components of the acute phase and the chronic inflammatory response. Inflammation has a role in the development of atherosclerosis, and an increased incidence of myocardial infarction has been reported in individuals with high plasma levels of various ISPs. A low lung function has been associated with increased levels of fibrinogen, C-reactive protein, and white blood cells. However, the relationships between plasma levels of various ISPs and lung function have not been studied extensively in population-based studies.

This study explored whether plasma levels of \( \alpha_1 \)-antitrypsin, ceruloplasmin, fibrinogen, haptoglobin, and orosomucoid are related to FVC and whether these proteins contribute to the increased incidence of myocardial infarction and death among men with reduced FVC.

Methods
Between 1974 and 1983, 22,444 men participated in a screening program for detection of individuals with high risk for cardiovascular diseases. Participation rate was 71%. Determination of plasma proteins was part of the program for 30% of the cohort, selected at random. Complete data on 5 ISPs were available in 6193 men. Men with a history of myocardial infarction, stroke, or cancer (according to questionnaire) and men who reported long-term cough associated with increased mucus production were excluded. Of the remaining 5589 men, information on lung function was available in 5064. Mean age was 46.6 ± 3.9 years (range 28 to 61 years). Baseline characteristics of the study cohort and the relationships between ISP levels and cardiovascular diseases have been presented previously.

Received June 18, 2002; revision received August 23, 2002; accepted August 24, 2002.
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© 2002 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000037220.00065.0D

2555
An electroimmunoassay method was used to assess plasma levels of Inflammation-Sensitive Plasma Proteins (ISP) in a reference population of white nonsmokers. Residual FVC was measured with a Spirotron apparatus. FVC was negatively associated with all ISPs in both smokers and nonsmokers. Recent respiratory infection was recorded if it had occurred within 3 weeks before the examination. Two categories were used for the presence of diabetes. Subjects with a fasting whole blood glucose ≥6.7 mmol/L and ≥2 ISPs in top quartile were considered to have diabetes.

**Baseline Examinations**

FVC was measured with a Spirotron apparatus (Drägerwerk AG) with the subjects in a standing position without nose clips. Specially trained nurses performed the tests. One acceptable maneuver with respect to the subject’s performance and cooperation was required. The volumes were standardized for age and height by use of an equation from a reference population of white nonsmokers. The sample was therefore categorized according to the subjects in a standing position without nose clips. Specially trained nurses performed the tests. One acceptable maneuver with respect to the subject’s performance and cooperation was required.

**Statistical Analysis**

Cox’s proportional hazard model was used to analyze mortality and cardiac event rates in categories of lung function and to adjust for potential confounders. A general linear model, with linear contrast, was used to compare mean values of FVC or ISP and to calculate adjusted means. Survival plots of different categories of risk factors were used to compare mean values of FVC or ISP and to calculate adjusted means.

**Follow-Up**

All cases were followed up from the baseline examination until death or December 31, 1997. Information on cause of death was retrieved from the Swedish Causes of Deaths register. Cause of death was based on autopsy in ~40% of cases. A cardiac event was defined as fatal or nonfatal myocardial infarction (International Classification of Diseases, 9th Revision [ICD-9] code 410) or death due to chronic ischemic heart disease (ICD-9 codes 412 to 414). Only the first events were counted. Cases of nonfatal myocardial infarction were retrieved from the Malmö Myocardial Infarction Register and the Swedish hospital discharge register.

**Results**

**Study Cohort**

Mean age was 46.7 ± 3.9 years for nonsmokers (n = 2733) and 46.5 ± 3.9 years for smokers (n = 2331). Mean residual FVC (ie, observed minus predicted FVC) was −0.10 L (±0.75 L) in nonsmokers and −0.36 L (±0.77 L) in smokers. Residual FVC among smokers with a consumption of more than 20 cigarettes per day (n = 570) was −0.53 ± 0.74 L.

**FVC in Relation to ISP**

FVC was negatively associated with all ISPs in both smokers and nonsmokers. This relationship was independent of other risk factors (Table 1).

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**TABLE 1. ISPs (g/L) in Relation to Quartile of Residual FVC in Nonsmokers and Smokers**

<table>
<thead>
<tr>
<th>ISP</th>
<th>FVC Quartile</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (Highest)</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>Nonsmokers, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.27 ± 0.73</td>
<td>3.32 ± 0.71</td>
<td>3.41 ± 0.77</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>1.11 ± 0.54</td>
<td>1.17 ± 0.57</td>
<td>1.22 ± 0.58</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>0.296 ± 0.06</td>
<td>0.303 ± 0.06</td>
<td>0.308 ± 0.06</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>0.74 ± 0.19</td>
<td>0.76 ± 0.18</td>
<td>0.79 ± 0.19</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td>1.17 ± 0.25</td>
<td>1.20 ± 0.24</td>
<td>1.21 ± 0.25</td>
</tr>
</tbody>
</table>

| Smokers, n   |             |     |     |     |     |     |
| Fibrinogen   | 3.60 ± 0.83 | 3.67 ± 0.75 | 3.70 ± 0.75 | 3.76 ± 0.86 | 0.001 | 0.02 |
| Haptoglobin  | 1.56 ± 0.67 | 1.61 ± 0.67 | 1.67 ± 0.68 | 1.74 ± 0.76 | <0.001 | <0.001 |
| Ceruloplasmin| 0.322 ± 0.07 | 0.328 ± 0.07 | 0.331 ± 0.07 | 0.339 ± 0.07 | <0.001 | 0.002 |
| Orosomucoid  | 0.85 ± 0.20 | 0.86 ± 0.20 | 0.87 ± 0.21 | 0.89 ± 0.22 | 0.001 | 0.02 |
| α1-Antitrypsin| 1.32 ± 0.28  | 1.35 ± 0.26 | 1.34 ± 0.28 | 1.37 ± 0.28 | 0.007 | 0.05 |

**Nonparametric trend:** *P* for trend adjusted for age, body mass index, cholesterol, systolic blood pressure, recent respiratory infection, diabetes, tobacco consumption (smokers only), physical inactivity, and angina pectoris in a general linear model.

†† for trend adjusted for age, body mass index, cholesterol, systolic blood pressure, recent respiratory infection, diabetes, tobacco consumption (smokers only), physical inactivity, and angina pectoris in a general linear model.
An increasing number of ISPs in the top quartile was associated with reduced residual FVC. The inverse trend between FVC and number of proteins in the top quartile remained significant among both smokers and nonsmokers after adjustments for age, body mass index, cholesterol, systolic blood pressure, diabetes, recent respiratory infection, physical activity, angina pectoris, and smoking.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Q4 (vs Q1–3)</th>
<th>Age Adjusted</th>
<th>Risk Factors*</th>
<th>CVD Mortality</th>
<th>Age Adjusted</th>
<th>Risk Factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>2.0 (1.7–2.4)</td>
<td>1.5 (1.3–1.9)</td>
<td>2.1 (1.6–2.6)</td>
<td>1.6 (1.2–2.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>1.7 (1.4–2.0)</td>
<td>1.3 (1.04–1.5)</td>
<td>1.6 (1.3–2.1)</td>
<td>1.2 (0.95–1.6)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>1.6 (1.3–2.0)</td>
<td>1.3 (1.1–1.6)</td>
<td>1.7 (1.3–2.2)</td>
<td>1.4 (1.1–1.8)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>1.6 (1.3–2.3)</td>
<td>1.5 (1.2–1.8)</td>
<td>2.2 (1.8–2.8)</td>
<td>1.7 (1.3–2.2)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td>1.7 (1.4–2.0)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.9 (1.5–2.4)</td>
<td>1.6 (1.2–2.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Q4 indicates fourth quartile. Values are relative risk (95% CI).
*Adjusted for age, body mass index, cholesterol, systolic blood pressure, recent respiratory infection, diabetes, smoking, tobacco consumption, physical inactivity, and angina pectoris.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Q1 (Highest)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>3.0 (2.0–4.6)</td>
<td>2.1 (1.3–3.2)</td>
<td>4.4 (2.6–7.3)</td>
<td>3.3 (2.0–5.6)</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>2.8 (2.1–3.7)</td>
<td>1.9 (1.4–2.5)</td>
<td>3.5 (2.4–5.1)</td>
<td>2.5 (1.6–3.7)</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>3.6 (2.6–4.9)</td>
<td>2.1 (1.5–3.0)</td>
<td>3.5 (2.2–5.4)</td>
<td>2.1 (1.3–3.4)</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>2.5 (2.4–3.5)</td>
<td>1.8 (1.2–2.6)</td>
<td>3.5 (2.6–3.9)</td>
<td>2.2 (1.4–2.8)</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td>1.7 (1.4–2.0)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.9 (1.5–2.4)</td>
<td>1.6 (1.2–2.0)</td>
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<table>
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<tr>
<th>Protein</th>
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<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>3.0 (2.0–4.6)</td>
<td>2.1 (1.3–3.2)</td>
<td>4.4 (2.6–7.3)</td>
<td>3.3 (2.0–5.6)</td>
</tr>
<tr>
<td>Haptoglobin</td>
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<td>1.9 (1.4–2.5)</td>
<td>3.5 (2.4–5.1)</td>
<td>2.5 (1.6–3.7)</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>3.6 (2.1–3.7)</td>
<td>2.1 (1.5–2.5)</td>
<td>3.5 (2.2–5.4)</td>
<td>2.1 (1.3–3.4)</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>2.5 (2.4–3.5)</td>
<td>1.8 (1.2–2.6)</td>
<td>3.5 (2.6–3.9)</td>
<td>2.2 (1.4–2.8)</td>
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<td>1.4 (1.1–1.7)</td>
<td>1.9 (1.5–2.4)</td>
<td>1.6 (1.2–2.0)</td>
</tr>
</tbody>
</table>

RR indicates relative risk.
*Adjusted for age and number of ISPs in top quartile (categorical variable).
†Adjusted for age, body mass index, cholesterol, systolic blood pressure, recent respiratory infection, diabetes, physical inactivity, angina pectoris, smoking, and tobacco consumption.
‡Adjusted for age, ISP, and risk factors.
Survival and Cardiac Events in Relation to FVC and ISP

A total of 675 men died and 474 suffered a fatal or nonfatal cardiac event during the follow-up. All ISPs were associated with an increased cardiovascular risk. The risk increased with the number of proteins in the top quartile (Table 2).

The age-adjusted risk of death and cardiac events was significantly increased for men with low FVC (fourth quartile; Table 3). Adjustments for number of ISPs in the top quartile significantly increased for men with low FVC (fourth quartile). The risk increased with ISP and other cardiovascular risk factors.

The risk factor-adjusted excess risk was reduced by about 25% for all end points. The risk factor—adjusted excess risk was reduced by about 10% when ISP levels were added to the model (Table 3). These relationships were consistent in smokers and nonsmokers. The increased risk for men with FVC in the third quartile was similarly reduced by adjustments for ISP.

Table 4 presents an analysis of the extreme quartiles of FVC in relation to ISPs. The 5 ISPs were reduced in a principal component analysis into 3 factors, accounting for 80% of the variance. The results in Table 3 were very similar when the factors were used in the analysis instead of the number of elevated ISPs: the relative risks for men with FVC in the fourth quartile were further reduced by ≈0.01 with this model. The results were also almost identical when the 5 ISPs were entered as continuous variables.

**Additional Analyses**

The 5 ISPs were reduced in a principal component analysis into 3 factors, accounting for 80% of the variance. The results in Table 3 were very similar when the factors were used in the analysis instead of the number of elevated ISPs: the relative risks for men with FVC in the fourth quartile were further reduced by ≈0.01 with this model. The results were also almost identical when the 5 ISPs were entered as continuous variables.

**Discussion**

Even though the inverse relationship between lung function and incidence of cardiovascular diseases has been known for many years, the cause of this relationship remains largely unexplained. Lung function was inversely related to plasma levels of ISP in this population-based cohort. The cardiovascular risk among men with low FVC showed significant differences between those with high and low ISP levels. Adjustments for ISP levels reduced the relative risks for men with low FVC. It can be concluded that relationships with ISP levels contribute to the increased risk among men with low FVC. However, the increased risk was not fully explained by ISP and other cardiovascular risk factors.
Cardiac event rates among men with FVC in highest (Q1) and lowest (Q4) quartile and with 0 to 1 (ISP−) or 2 to 5 (ISP+) ISPs in top quartile. Survival curves are unadjusted. Presented relative risks (95% CIs) are risk factor adjusted (see footnote, Table 4). RR indicates relative risk.

The 5 proteins in the present study can be regarded as different markers of inflammation and the actions of proinflammatory cytokines. Because the ISP has shown nonlinear relationships with incidence of cardiac events, the top quartile was used as a cutoff, and the number of elevated ISPs was used in the analysis. The cardiovascular risk increased, and FVC decreased with the number of elevated ISPs. This measure also had an acceptable reliability in terms of internal consistency, ie, the correlation between each ISP and the remaining sum score was fully adequate (α=0.64). The results suggest that a composite measure of inflammation is preferable to individual ISPs in studies of cardiovascular disease and in assessment of risk.

The health examination program was begun several years before the now commonly used guidelines for standardization of spirometry were published. The equipment and procedure of the lung function test were not quite in accordance with these guidelines. For example, no nose clips were used, and only 1 acceptable test was required. However, despite this limitation, the associations between FVC, cardiovascular risk factors, and cardiovascular mortality were similar to the results reported from other studies. Although inferior precision may have influenced the validity, it is likely that splitting the cohort into quartiles of FVC reduced the degree of misclassification.

One question is whether the degree of atherosclerosis differed between the groups at baseline and whether elevated ISP levels are merely a marker of preexisting atherosclerosis. Several cardiovascular risk factors, eg, smoking, hypertension, cholesterol, and diabetes, are associated with increased ISP levels. These risk factors have also been associated with reduced lung function. Men with a history of myocardial infarction and stroke were excluded from the analysis. Angina pectoris and the major cardiovascular risk factors were taken into account in the analysis. We cannot rule out, however, that asymptomatic atherosclerosis at baseline was more prevalent among men with low FVC and high ISP levels.

The reason men with reduced lung function have higher ISP levels is unclear. Various cytokines, such as interleukin-6, are produced by inflammatory cells at multiple sites and induce the synthesis of proteins in the liver. Inflammatory processes often play key roles in the pathogenesis of different forms of pulmonary diseases. Furthermore, smoking and other environmental agents could induce inflammation, and the ISP levels could reflect the effects of these agents on the lungs. Smokers had higher ISP levels than nonsmokers. Studies of apparently healthy smokers have shown that a reduced ventilatory capacity is associated with increased pulmonary clearance, ie, inhaled substances are rapidly absorbed in the blood. A study of healthy smokers reported increased blood levels of nicotine and cotinine and increased ISP levels in men whose lung function was reduced. Differences in lung clearance and exposure to substances that cause atherosclerosis could contribute to the relationships between reduced FVC, high ISP levels, and atherosclerosis among smokers.

The relationship between reduced FVC and high ISP levels, however, was similar among nonsmokers. Another possible cause for the relationships between FVC, ISPs, and cardiovascular disease is genetic polymorphisms related to inflammatory mediators and a predisposition to exaggerated inflammatory responses. Much of the variation in plasma fibrinogen concentrations appears to be hereditary. Although results are conflicting, polymorphisms in the promoter gene of the inflammatory mediator tumor necrosis factor-α have been related to chronic obstructive pulmonary disease. However, the study cohort was from the general population, and genetic determinants for moderately reduced lung function may be different from those of clinical disease.

Although associations with increased ISP levels contributed to the increased cardiovascular risk among men with low FVC, ISP levels and other cardiovascular risk factors could not completely account for the increased risk for men with low FVC. The full explanation for this relationship remains to be explored. Longitudinal studies have shown that reduced lung function is associated with future increase in blood pressure and the development of diabetes. Associations between reduced FVC and an increased incidence of other cardiovascular risk factors during the long follow-up could thus contribute to the increased risk in this group. For methodological reasons, it is difficult to take this into account in a prospective study. Ventricular arrhythmia is another risk factor that has been associated with reduced lung function. Even though the present cohort was relatively young, relationships with subclinical cardiac diseases could contribute to the increased risk among individuals with low FVC.

Local and national registers were used for case retrieval. A validation study from the National Hospital Discharge Register showed that the diagnosis "myocardial infarction" was false in only 5% of the cases. Until 1992, cause of death was based on autopsy for almost all out-of-hospital deaths in the city. There is no reason to suspect any bias with respect to case retrieval in the different categories of FVC and ISP. Change of exposure is another cause of bias in prospective
studies. Men with high blood pressure and high lipid levels were referred for further evaluation and treatment. Smokers were advised to quit smoking but were not offered any help to do so. Because these risk factors were more common among men with high ISP levels, they would benefit most from the interventions.

A low FVC was associated with higher levels of ISPs. This association contributes to the increased cardiovascular risk in men with a low FVC. However, ISP and traditional cardiovascular risk factors cannot fully explain the increased risk in men with low FVC.

Acknowledgments

This study was supported by grants from the Swedish Council for Social Research and the Åke Wiberg Foundation.

References


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Circulation. 2002;106:2555-2560
doi: 10.1161/01.CIR.0000037220.00065.0D
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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