Reduced lung function in patients with abdominal aortic aneurysm is associated with activation of inflammation and hemostasis, not smoking or cardiovascular disease

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Objective: **Abdominal aortic aneurysms often coexist with reduced lung function and chronic obstructive pulmonary disease (COPD). These conditions are each associated with cigarette smoking, cardiovascular disease, and evidence of increased inflammatory and hemostatic activity. The aim of this study was to determine if these factors accounted for the link between aneurysms and pulmonary disease.**

Methods: **The design was a case-control study comparing patients with an asymptomatic abdominal aortic aneurysm with population-based controls without an aneurysm. Aneurysms were diagnosed by ultrasound scan, and pulmonary function was measured by respiratory questionnaire and spirometry. Activation of inflammation and hemostasis was measured by assay of plasma interleukin-6 (IL-6), fibrinogen, von Willebrand factor (vWF), tissue plasminogen activator (tPA) antigen, fibrin D-dimer, and plasmin antiplasmin complexes.**

Results: **Cases with an abdominal aortic aneurysm (n = 89) had more COPD and worse expiratory lung function as measured by forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) than controls (n = 98) (FEV_1, 1.9 vs 2.2 L, $P < .01$; FEV_1/FVC, 0.67 vs 0.75, $P < .001$) and did not differ in restrictive function (FVC, 2.9 vs 3.0 L, $P = .33$). Cases also had higher levels of lifetime cigarette smoking (30 vs 24 pack-years, $P < 0.01$), cardiovascular disease (35% vs 18%, $P = .01$), plasma fibrinogen (3.5 vs 3.1 g/L, $P = .02$), IL-6 (2.8 vs 1.8, pg/mL, $P < .001$), plasmin antiplasmin complexes (596 vs 384 μg/L, $P = .01$), and D-dimer (442 vs 93 ng/mL, $P < .001$). On multiple logistic regression analysis of lung function and COPD on the risk of aneurysm, both cigarette smoking and cardiovascular disease had little effect on the relationships. For the markers of activated inflammation and hemostasis, plasmin antiplasmin complexes and D-dimer had the most important confounding effect on the odds ratios. All markers combined had a substantial effect: odds ratio of aneurysm for a one standard deviation decrease in FEV_1 fell from 2.3 (95% confidence interval [CI], 1.5 to 3.5) ($P < .01$) to 1.3 (95% CI, 0.55 to 2.4) ($P \geq .05$).**

Conclusion: **The association between reduced respiratory function and abdominal aortic aneurysm was not accounted for by cigarette smoking or cardiovascular disease. We hypothesize that activation of inflammation and hemostasis in response to injury may be an important explanation of the association between aneurysm formation and reduced respiratory function. Further studies are required to test this hypothesis. (J Vasc Surg 2006;43:474-80.)**

Reduced lung function occurs more commonly in patients with abdominal aortic aneurysms (AAAs)[1-5] and is related to an increased risk of rupture.[6-8] Atherosclerotic cardiovascular diseases such as coronary heart disease, peripheral arterial disease, and stroke are also associated with impaired lung function[9-12] and with the occurrence of AAAs.[13] Thus, cardiovascular disease could be a major confounding factor for the association between lung function and aneurysm. Likewise, cigarette smoking is an important risk factor for respiratory disease, cardiovascular disease, and AAA[13] and could have a role in explaining the association between lung function and aneurysm.

Inflammation is an important component of aneurysmal disease as well as chronic respiratory disease and atherosclerosis. In patients with an AAA, proinflammatory cytokines have shown increased expression in aneurysmal aortic tissue[14] and higher circulating levels than in controls without an AAA.[15] Increased cytokine activity may induce degradation of components of the extracellular matrix in the arterial wall leading to aneurysm formation[16] and, furthermore, may enhance coagulation by, for example, upregulation of plasma fibrinogen. The association between reduced lung function and aortic aneurysm could conceivably be mediated or due to a concomitant effect of systemic inflammation and hemostasis.

The aim of this study was to determine whether an association between impaired lung function and AAA was independent or was influenced by the effects of smoking,

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cardiovascular disease, and markers of activated inflammation and hemostasis.

METHODS

The study design was a case-control study comparing cases of asymptomatic AAA with controls without an aneurysm. This investigation was nested partly within the Edinburgh Artery Study, a population cohort study that began in 1988. At baseline, 1592 men and women aged 55 to 74 years were selected randomly from the general population from the age-sex registers of 11 general practices in the City of Edinburgh. Subjects attended a clinic for a comprehensive examination that included measurement of cardiovascular risk factors and disease. Follow-up examinations were conducted at 5 and 12 years and included ultrasound screening for AAAs. Continuous assessment to monitor cardiovascular events took place during the follow-up period. Further details of the design of the Edinburgh Artery Study have been published.[17-19] The study was approved by the Lothian Health Board Ethics Committee.

The recruitment target was 100 cases and 100 controls, especially to ensure a reasonably representative sample of asymptomatic aneurysms. The intention was to select most cases from the Edinburgh Artery Study, but owing to the low numbers identified, most cases were selected consecutively from the elective surgical waiting list at the Royal Infirmary of Edinburgh.Cases were included if they had an anteroposterior aortic diameter of at least 3 cm confirmed at the study clinic. The aortic diameter was measured by ultrasound scan using a 3 MHz transducer and an ATL UM9 HDI (Bothell, Wash) system, and the maximum of three readings was taken as the diameter. The few cases derived from the Edinburgh Artery Study were identified at the 12-year examination. An Aloka 500 portable scanner (Tokyo, Japan) was used in the homes of a few subjects who were unable to attend the clinic.

Controls were all selected from within the Edinburgh Artery Study population. Potential controls were stratified into 5-year age and sex groups, and matched controls were randomly selected from these strata by using random number tables. They were oversampled to allow for nonattendance at the clinic. Ultrasound screening at the 12-year examination confirmed the absence of aortic aneurysm.

Cases and controls also completed a questionnaire on smoking the World Health Organization (WHO) questionnaire inquiring about angina, intermittent claudication, and previous myocardial infarction[20]; and the Medical Research Council questionnaire was used for respiratory symptoms.[21] Height was measured without shoes to the nearest 5 mm by using a stadiometer, weight was measured without outer clothing to the nearest 100 g using a digital scale (Soehnle, Murrhardt, Germany). Respiratory function, determined by forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR), was measured three times by using a hand-held spirometer (Vitalograph Ltd, Buckingham, United Kingdom). Systolic and diastolic blood pressure was measured in the right arm by using a Hawksley random zero sphygmomanometer (Sussex, United Kingdom) and systolic pressures in the right and left ankles with the aid of a Doppler ultrasound probe (Sonicaid, Sussex, United Kingdom). A 12-lead electrocardiogram (ECG) was recorded. A 20-mL venous blood sample was taken without tourniquet, centrifuged, and aliquots of citrated plasma were stored at −40°C. These measures were included in the Edinburgh Artery Study 12-year examination with the exception of the respiratory symptoms and lung function tests, which were assessed only for this case-control study.

In the laboratory, the following markers of activated inflammation and hemostasis were measured: plasma interleukin-6 (IL-6) by high sensitivity enzyme-linked immunoabsorbent assay (ELISA) (R & D Systems, Minneapolis, Minn), fibrinogen (Clauss assay), von Willebrand factor (vWF) (ELISA, DAKO, Glostrup, Denmark), tissue plasminogen activator (tPA) antigen, fibrin D-dimer, and plasmin-antiplasmin complexes (ELISAs, Biopool, Ventura, Calif). The selection of factors was dependent on assays conducted at the 12-year follow-up examination in the Edinburgh Artery Study. C-reactive protein (CRP) was assayed only at baseline 12 years earlier and was therefore not included in the current analysis; assays were not available for serum proteases including matrix metalloproteinases.

Measures of respiratory function consisted of PEFR, FEV_1, FVC, and the FEV_1/FVC ratio as well as the percentage of subjects with values derived from a healthy reference population of known age, sex, height, and ethnic group.[22] The maximum value of the three repeat respiratory tests was used in the analyses. A history of respiratory symptoms suggestive of chronic bronchitis was considered to be present if a positive response was given to questions on the usual occurrence of cough or phlegm first thing in the morning in winter or of wheeze (attacks of wheezing or whistling in the chest).[21]

A modification of the Global Initiatives for Chronic Obstructive Lung Disease (GOLD) definitional criteria[23] was used to classify subjects into the mutually exclusive categories of severe COPD (FEV_1/FVC <0.7 and FEV_1 $<50\%$ predicted), moderate COPD (FEV_1/FVC <0.7 and FEV_1 50% to $<80\%$ predicted), mild COPD (FEV_1/FVC <0.7 and FEV_1 $\geq 80\%$ predicted), symptoms only (presence of symptoms in absence of lung function abnormality), restrictive lung disease (FEV_1 ≥ 0.7 and FVC $<80\%$ predicted), or no lung disease (none of the above).

Cigarette-smoking status was defined by the three categories of current, ex, and never. Lifetime cigarette consumption was analyzed by pack-years (number of years smoked × average number of packs smoked per day). The distribution was skewed with a few heavy smokers, and so a square root transformation was used. Body mass index (BMI) was calculated as kg/m^2. The ankle brachial index (ABI) was calculated for each leg by dividing ankle pressure by arm systolic pressure and the lower of the left and right indices was used in the analysis. The presence of cardiovascular disease was defined as any one of the following: myocardial infarction (any two of positive WHO question-

naire, or subject remembering that a doctor had diagnosed myocardial infarction, or ECG evidence), angina (positive WHO questionnaire plus either ECG evidence of ischemia or subject remembering that a doctor had diagnosed angina), or intermittent claudication (positive WHO questionnaire). Diabetes mellitus was not specified in the analysis because of very small numbers in the study sample.

The analysis was carried out according to a predetermined statistical plan by using SPSS version 12 (SPSS, Chicago, Ill) for Windows (Microsoft, Redmond, Wash) and consisted of a comparison of clinical and blood assay data between cases and controls. Logistic regression was used to assess univariate differences in risk factors between cases and controls. The distributions of plasma fibrinogen, tPA and vWF were skewed, and so square root transformations were used. A natural log transformation was used for D-dimer, IL-6, and plasmin anti-plasmin complexes. Logistic regression was used to calculate age, sex, and height-adjusted odds ratios for aneurysm according to lung function and severity of COPD. Those with restrictive lung disease were excluded from this analysis because it is a type of disease different from COPD. Odds ratios were further adjusted for inflammatory and hemostatic factors, smoking, and cardiovascular disease. Throughout all analyses, a two-sided $P < .05$ was used to denote statistical significance. A variable was considered to have a possible confounding effect if the odds ratio changed by ≥20%.

RESULTS

The study sample comprised 89 cases of asymptomatic AAA, of which 81 were selected from the waiting list for elective aneurysm repair in the Royal Infirmary of Edinburgh and eight were identified by ultrasound scanning in the Edinburgh Artery Study. Of the 139 controls selected, 98 attended for examination. No controls were subsequently found to have an aneurysm. The median aneurysm diameter (interquartile range) of cases was 4.5 cm (3.9 to 5.1 cm) and controls, 2.0 cm (1.8 to 2.3 cm).

The demographic, risk factor, and cardiovascular status of the cases and controls is shown in Table I. The mean age of all subjects was 73.5 years, and 72% were men. As expected from the matching scheme, no significant differences in age or sex were found between cases and controls. BMI was lower in cases than controls ($P = .03$), whereas systolic blood pressure and a history of cigarette smoking were significantly higher in cases ($P = .01$). Indicators of cardiovascular disease were also more common in cases ($P = .01$). About one third of cases had evidence of previous myocardial infarction, angina, or claudication. The mean ABI was significantly lower in cases than in controls ($P < .001$).

Plasma levels of fibrinogen, IL-6, plasmin antiplasmin complexes, and D-dimer were significantly higher in aneurysm cases than controls (Table II). The differences in median levels of IL-6 ($P < .001$), plasmin antiplasmin complexes ($P = .01$), and D-dimer ($P < .001$) were substantial. Table III shows that lung function was worse in aneurysm cases than in controls. FVC was slightly but nonsignificantly reduced, whereas the measures of expiratory flow (FEV_1 and PEFR) were significantly reduced ($P < .01$), resulting in a lower FEV_1/FVC ratio in cases than in controls (0.67 vs 0.75, $P < .001$). Similar differences were found for the predicted results according to age, sex, and height. The frequency of COPD was also found to differ between cases and controls ($P < .001$), with more cases having severe, moderate, or mild COPD relative to no lung disease compared with controls.

The extent to which the difference in lung function tests between cases and controls was independent of markers of activated inflammation and hemostasis, cigarette smoking, and the presence of cardiovascular disease is demonstrated in the logistic regression models shown in Table IV. The odds ratios for aneurysm (95% confidence intervals [CI]) for a one standard deviation decrease in FEV_1, PEFR, and FEV_1/ FVC, adjusting for age, sex, and height, were each >2 ($P < .01$). Adjusting for cardiovascular disease or cigarette smoking had no important effect on the odds ratios. Adjusting for each of the inflammatory and hemostatic markers, only plasmin antiplasmin complexes and D-dimer had a confounding effect, reducing odds ratios by ≥20%. The most notable effect was for D-dimer. Adjusting for all the inflammatory and hemostatic markers also had a substantial effect, reducing the odds ratios to nonsignificant levels. Further adjustment for smoking, cardiovascular disease, and ABI had little effect.

Table I. Subject characteristics and cardiovascular disease in cases of abdominal aortic aneurysm and controls

	Cases (n = 89)	*Controls (n = 98)*	P*
Age (years)	73.5 ± 0.5	73.5 ± 0.5	.95
Sex (% male)	64 (71.9)	70 (71.4)	.94
Height (cm)	166.9 ± 1.0	166.6 ± 0.9	.81
Weight (kg)	70.0 ± 1.4	73.0 ± 1.4	.12
Body mass index (kg/m^2)	25.0 ± 0.4	26.3 ± 0.4	.03
Blood pressure (mm Hg)			
Systolic	153.9 ± 2.4	145.7 ± 2.1	.01
Diastolic	80.1 ± 1.6	78.2 ± 1.2	.32
Cigarette Smoking			
Current smoker	28 (31.5)	12 (12.2)	.01
Ex-smoker	51 (57.3)	55 (56.1)	.01
Never smoker	8 (9.0)	31 (31.7)	.01
Pack-years†	30.1 ± 0.1	23.8 ± 0.1	<.01
Cardiovascular disease			
Myocardial infarction	10 (11.2)	10 (6.1)	.22
Angina	11 (12.4)	6 (10.2)	.64
Intermittent claudication	19 (21.3)	8 (8.2)	.01
All cardiovascular‡	31 (34.8)	18 (18.4)	.01
Ankle brachial index	0.81 ± 0.03	1.01 ± 0.02	<.001

Data are mean ± SE or number (%). Totals may not correspond to all cases and controls due to missing data and/or duplication.
*Calculated using logistic regression.
†Means derived from square root distributions and back transformed. Only current and ex-smokers included.
‡Myocardial infarction and/or angina and/or intermittent claudication.

Table II. Median (interquartile range) of plasma inflammatory and hemostatic factors in cases of abdominal aortic aneurysm and controls

	Cases (n = 89)	*Controls (n = 98)*	P*
Fibrinogen (g/L)	3.5 (2.9-4.1)	3.1 (2.7-3.6)	.02
Interleukin-6 (pg/mL)	2.8 (2.0-4.2)	1.8 (1.3-2.7)	<.001
Plasmin antiplasmin (μg/L)	596.0 (432.0-877.8)	383.5 (273.8-485.5)	.01
vWF (IU/dL)	122.5 (98.0-150.2)	123.0 (101.0-152.0)	.55
tPA antigen (ng/mL)	7.9 (6.0-11.1)	8.6 (6.8-11.5)	.64
D-dimer (ng/mL)	441.5 (198.8-771.0)	93.0 (57.8-158.8)	<.001

vWF, von Willebrand factor; *tPA*, tissue plasminogen activator.
Medians are not all based on total numbers of cases and controls due to few missing assays.
*Calculated for logistic regression models for aneurysm with each inflammatory and hemostatic factor entered as continuous variable.

Table III. Measures of lung function and chronic obstructive pulmonary disease in cases of abdominal aortic aneurysm and controls

	Cases n = 89	*Controls n = 98*	*OR (95% CI) of aneurysm*	P*
FVC (L)	2.9 ± 0.1	3.0 ± 0.1	1.15 (0.86, 1.55)	.33
FVC (% predicted)	81.5 ± 2.0	86.6 ± 1.8	1.32 (0.98, 1.79)	.07
FEV_1 (L)	1.9 ± 0.1	2.2 ± 0.1	1.60 (1.17, 2.19)	<.01
FEV_1 (% predicted)	74.4 ± 2.5	88.9 ± 2.2	1.98 (1.41, 2.78)	<.001
FEV_1/FVC	0.67 ± 0.02	0.75 ± 0.01	1.99 (1.41, 2.81)	<.001
FEV_1/FVC (% predicted)	90.8 ± 2.1	102.2 ± 1.5	2.09 (1.46, 2.99)	<.001
PEFR (L/min)	278.0 ± 14.0	340.1 ± 14.5	1.60 (1.17, 2.19)	<.01
PEFR (% predicted)	41.6 ± 2.1	51.6 ± 1.9	1.81 (1.28, 2.56)	<.001
COPD† (%)	(n = 87)	(n = 94)		
Severe COPD	13 (14.9)	4 (4.3)	13.00 (3.10, 54.54)	<.001‡
Moderate COPD	20 (23.0)	11 (11.7)	7.27 (2.28, 23.16)	<.001‡
Mild COPD	15 (17.2)	7 (7.4)	8.57 (2.41, 30.43)	<.001‡ <.001§
Restrictive lung disease	19 (21.8)	23 (24.5)	3.30 (1.12, 9.74)	.03‡
Symptoms only	14 (16.1)	25 (26.6)	2.24 (0.74, 6.78)	.15‡
No lung disease	6 (6.9)	24 (25.5)		

OR, Odds ratio; *CI*, confidence interval; *FVC*, forced vital capacity; *FEV_1*, forced expiratory volume in 1 second; *PEFR*, peak expiratory flow rate; *COPD*, chronic obstructive pulmonary disease.
Figures are mean ± SE or number (%) except for % predicted, which is % of result in healthy persons of same age, sex and height ± SD.
Odds ratios for the lung function measures are unadjusted and are per 1SD decrease standardized. COPD is fitted as categoric variable and the odds ratios are comparing each category to no lung disease.
*Calculated by using logistic regression.
†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), mild COPD (FEV_1/FVC <0.70 and FEV_1 ≥80% predicted), restrictive lung disease (FEV_1 ≥0.70 and FVC <80% predicted) symptoms only (presence of respiratory symptoms in the absence of any lung function abnormality) and no lung disease.
‡Represents significance of odds ratio in each COPD group compared with no lung disease.
§Represents significance of difference in COPD overall between cases and controls.

Table V shows similar effects of the markers of activated inflammation and hemostasis, smoking, and cardiovascular disease on the relationships between increasing severity of COPD on the risks of aneurysm. Lifetime smoking and cardiovascular disease had little influence on the magnitude of the odds ratio. Plasmin antiplasmin complexes and D-dimer were the only markers that had a specified confounding effect in reducing the odds of aneurysm for increasing severity of COPD. The combined effect of all the inflammatory and hemostatic markers was comparable. Further adjustment for smoking, cardiovascular disease, and ABI had little effect.

Finally, in logistic regressions on aortic aneurysm, which included one measure of lung function in each model and all inflammatory and hemostatic factors, smoking, cardiovascular disease, and ABI, D-dimer was found to be strongly and independently related to aneurysm in each model. The odds ratio (95% CI) for one SD increase in D-dimer in each model was 5.9 (2.7, 12.6) with FEV_1, 5.1 (2.5, 10.6) with PEFR; 4.6 (2.3, 9.5) with FEV_1/FVC, and 5.0 (2.4, 10.3) with COPD (all $P < .001$).

DISCUSSION

The principal findings of this study were that individuals with an AAA had worse lung function and more COPD than controls without AAAs. The lung function affected was primarily obstructive (reduced expiration) and not restrictive (reduced vital capacity). Aneurysm cases had higher levels of cigarette smoking, cardiovascular disease, and plasma levels of markers of inflammation and hemostasis. The associations between lung function, COPD, and aneurysms were only marginally affected by smoking and cardio-

Table IV. Logistic regressions of FEV_1, PEFR and FEV_1/FVC on abdominal aortic aneurysm adjusting for smoking, cardiovascular disease, and inflammatory and hemostatic factors

	Odds ratio of aneurysm (95% confidence interval)		
Adjusted for age, sex, and height plus:	*FEV_1 1 SD decrease (0.70L)*	*PEFR 1 SD decrease (139.78L/min)*	*FEV_1/FVC ratio 1 SD decrease (0.12)*
—	2.3 (1.5, 3.5)*	2.0 (1.4, 3.0)*	2.2 (1.5, 3.1)*
Smoking (pack-years)	2.1 (1.4, 3.3)*	1.9 (1.3, 2.8)*	2.0 (1.4, 3.0)*
Cardiovascular disease‡	2.2 (1.4, 3.3)*	1.9 (1.3, 2.9)*	2.1 (1.5, 3.1)*
Fibrinogen (g/L)	2.0 (1.3, 3.2)*	1.9 (1.2, 2.8)†	2.1 (1.4, 3.1)*
Interleukin-6 (pg/mL)	1.9 (1.2, 3.1)*	1.8 (1.2, 2.7)*	1.9 (1.3, 2.8)*
Plasmin antiplasmin (μg/L)	1.5 (1.0, 2.5)	1.5 (1.0, 2.2)	1.8 (1.2, 2.8)*
vWF (IU/dL)	2.5 (1.6, 3.9)*	2.1 (1.4, 3.3)*	2.6 (1.7, 4.0)*
tPA antigen (ng/mL)	2.3 (1.5, 3.6)*	2.0 (1.3, 3.0)*	2.3 (1.5, 3.4)*
D-dimer (ng/mL)	1.2 (0.7, 2.0)	1.2 (0.7, 1.8)	1.5 (0.9, 2.4)
All inflammatory and hemostatic factors§	1.3 (0.7, 2.4)	1.2 (0.7, 2.0)	1.6 (0.9, 2.9)
All inflammatory and hemostatic factors§, smoking, cardiovascular disease, ABI	1.0 (0.5, 2.0)	1.1 (0.7, 1.9)	1.5 (0.8, 2.7)

FEV_1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity; *PEFR,* peak expiratory flow rate; *vWF,* von Willebrand factor; *tPA,* tissue plasminogen activator; *ABI,* ankle brachial index.
*$P < .01$.
†$P < .05$ (*P* values derived from the logistic regressions).
‡Cardiovascular disease: myocardial infarction and/or angina and/or intermittent claudication.
§Fibrinogen, interleukin-6, plasmin antiplasmin, vWF, tPA, D-dimer.

Table V. Logistic regressions of chronic obstructive pulmonary disease on abdominal aortic aneurysm adjusting for smoking, cardiovascular disease and inflammatory and hemostatic factors

Adjusted for age, sex, and height, plus:	*Odds ratio (95% CI) of aneurysm for an increase in one category of COPD severity**
—	1.7 (1.3, 2.1)†
Smoking (pack-years)	1.6 (1.3, 2.1)†
Cardiovascular disease	1.6 (1.3, 2.0)†
Fibrinogen (g/L)	1.5 (1.2, 1.9)†
Interleukin-6 (pg/mL)	1.5 (1.2, 1.9)‡
Plasmin antiplasmin (μg/L)	1.3 (1.1, 1.7)‡
vWF (IU/dL)	1.7 (1.3, 2.1)†
tPA antigen (ng/mL)	1.6 (1.3, 2.0)†
D-dimer (ng/mL)	1.3 (1.0, 1.7)
All inflammatory and hemostatic factors§	1.4 (1.0, 1.9)
All inflammatory and hemostatic factors,§ smoking, cardiovascular disease, ABI	1.3 (0.9, 1.9)

COPD, Chronic obstructive pulmonary disease; *vWF,* von Willebrand factor; *tPA,* tissue plasminogen activator; *ABI,* ankle brachial index.
*Categories of severity of COPD: severe (FEV_1/FVC <0.7 and FEV_1 < 50% predicted), moderate (FEV_1/FVC <0.7 and FEV_1 <80% predicted), mild (FEV_1/FVC <0.7 and FEV_1 50 to ≥80% predicted), symptoms only (presence of symptoms in absence of lung function abnormality), no disease (none of the above and no restrictive lung disease (FEV_1 ≥0.7 and FVC <80% predicted). These categories were fitted as ordinal variables.
†$P < .01$.
‡$P < .05$ (*P* derived from logistic regressions).
§Fibrinogen, interleukin-6, plasmin antiplasmin, vWF, tPA, D-dimer.

vascular disease but were substantially changed and became nonsignificant on adjusting for the markers of inflammation and hemostasis.

Our results confirm the findings of other clinical[1,2] and community studies[3-5] showing an association between COPD and AAAs. In veterans screened in the United States,[3] men born in 1914 in Malmo,[4] and in a population cross-sectional study in Denmark,[5] evidence of COPD was related to an increased risk of aneurysm. Impaired lung function was found in a case-control study in Japan[1] to be more common in cases of thoracic and abdominal aneurysms than in coronary heart disease patients and healthy controls.

The degree of respiratory impairment may be important; in a consecutive group of emphysema patients, those with the lowest FEV_1/FVC had a higher prevalence of aneurysms than those with a moderate reduction.[2] Chronic pulmonary disease has also been related to the risk of aneurysm rupture in autopsy series[6] and in the follow-up of aneurysm patients,[7,8] although, surprisingly, reduced aneurysm growth was found in one study.[5] However, the overall evidence indicates that an association does exist between impaired lung function and the presence of AAAs.

AAAs occur frequently in the presence of atherosclerosis[13] and its clinical manifestations.[9-12] Reduced expiratory flow has been associated longitudinally with a higher incidence of fatal and nonfatal coronary heart disease and stroke.[9-11] Furthermore, impaired lung function has been associated with subclinical cerebral infarction and white matter lesions[24] as well as carotid stenosis and a low ABI.[12] We have shown, however, that the association between both reduced expiratory flow (FEV_1 and PEFR) and COPD with the risk of aortic aneurysm was independent of concomitant cardiovascular disease. The Aneurysm Detection And Management (ADAM) study[3] in the United States also found the association to be independent of atherosclerotic diseases; in a Danish study, the association

became nonsignificant on adjustment for cardiovascular diseases, but this may have been due to the small numbers involved.[5]

Cigarette smoking is a strong risk factor for AAA. The risk is greater than, and independent of, the effect of smoking on coronary heart disease.[13,25] Smoking is a common cause of COPD and therefore may be a confounding factor for the association between impaired lung function and aneurysm. We found, however, that the relationship between lung function (FEV_1, PEFR, and FEV_1/FVC) and COPD with risk of aneurysm was independent of lifetime cigarette smoking. An effect independent of a history of smoking regularly was also found in the ADAM study.[3] The association of impaired pulmonary function with aneurysm rupture has also been shown to be independent of smoking.[7,8] This independence does not, of course, rule out some effect of smoking on both lung function and aneurysm contributing to the association, perhaps mediated by a common pathway such as inflammation.

Inflammation and activation of hemostasis (resulting in a laminated luminal thrombosis) are important characteristics of AAAs. An inflammatory infiltrate, including lymphocytes and macrophages, is present in the aneurysm adventitia and media and is associated with increased breakdown of the extracellular matrix.[16] Aneurysms have also been shown to contain/secrete excess inflammatory cytokines, including IL-6,[14] which may enhance proteolysis in the aneurysm wall.[26] These cytokines increase the expression of matrix metalloproteinase (MMP-9) in macrophages, which are the primary source of this elastolytic proteinase[16] and are becoming recognized as having an important role in the pathobiology of aneurysms.[27] Circulating levels of cytokines, including IL-1β, IL-6, and tumor necrosis factor-α, have also been found to be higher in patients with aneurysms than in those with coronary heart disease or healthy controls.[15] Inflammatory cytokines are associated with increased production of acute phase proteins such as C-reactive protein and fibrinogen that are elevated in the plasma of aneurysm patients.[28,29] The extent to which systemic activation of inflammation and hemostasis is a cause or consequence (or both) of aneurysm formation is unclear, however.

The role of systemic activation of inflammation and hemostasis in explaining the increased risk of coronary heart disease in those with COPD was investigated in the Third National Health and Nutrition Examination Survey (NHANES) in the United States.[30] A reduced FEV_1 was associated with higher plasma fibrinogen and C-reactive protein levels, confirming that activated inflammation and hemostasis in COPD had both a low-grade systemic and local effect. COPD and C-reactive protein were found to have an additive effect in predicting risk of cardiac injury. Higher levels of inflammatory proteins associated with impaired lung function have been shown to occur independently of smoking, and it has been suggested that genetic polymorphisms predisposing to exaggerated inflammatory responses may also be relevant.[31] Nevertheless, the increased risk of atherosclerotic cardiovascular disease in those with COPD may be only partly related to inflammation. Other factors, such as high blood pressure and diabetes mellitus, which also occur more commonly in those with COPD, may be important.[32,33]

The inflammatory and hemostatic factor that had the largest effect in reducing the association between impaired lung function and aortic aneurysm was D-dimer, an indicator of fibrin formation and degradation. We have shown in earlier analyses of the Edinburgh Artery Study population that D-dimer levels were higher in aneurysm cases than controls,[29] and this has been confirmed in subsequent studies in Japan.[34,35] Plasmin antiplasmin complexes, an indicator of fibrinolytic activation, also had a considerable confounding effect on the associations between lung function and aneurysms. Plasmin is a common activator of proteolytic systems in aneurysmal degradation of the aortic wall, and plasmin antiplasmin complexes have been shown to be predictive of the rate of aneurysm growth.[36] To our knowledge, plasmin antiplasmin complex levels have not been reported in relation to COPD, but given that most inflammatory processes disturb the balance in coagulation and fibrinolysis, it would not be surprising if plasmin antiplasmin complex levels were elevated, as has been shown in patients with bronchial asthma.[37]

CONCLUSION

The association of reduced respiratory function in aneurysm cases in this study was not explained by either cigarette smoking or cardiovascular disease but became nonsignificant on adjusting for markers of inflammation and hemostasis. We hypothesize that response to injury (activation of inflammation and hemostasis) may be an explanation of the association. We suggest further studies (eg, of genotypes influencing inflammatory responses) to test this hypothesis. The influence of inflammatory and hemostatic factors on the association could, however, simply reflect an epiphenomenon in which these factors are a marker for unknown biologic effects leading to formation of aneurysm and lung disease.

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REFERENCES

1. Sakamaki F, Oya H, Nagaya N, Kyotani S, Satoh T, Nakanishi N. High prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm. J Vasc Surg 2002;36:35-40.
2. Laarhoven CJHM, Borstlap ACW, Henegouwen DPvB, Palmen FMLHG, Verpalen MCPJ, Shoemaker MC. Chronic obstructive pulmonary disease and abdominal aortic aneurysms. Eur J Vasc Surg 1993;7:386-90.
3. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hy RJ, Makaroun MS, et al. The Aneurysm Detection And Management study screening program. Validation cohort and final results. Arch Intern Med 2000; 160:1425-30.
4. Bengtsson H, Bergqvist D, Ekberg O, Janzon L. A population based screening of abdominal aortic aneurysms (AAA). Eur J Vasc Surg 1999;5:53-7.
5. Lindholt JS, Heickendorft L, Antonsen S, Fasting H, Henneberg EW. Natural history of abdominal aortic aneurysm with and without coexisting chronic distributive pulmonary disease. J Vasc Surg 1998;28: 226-33.
6. Sterpetti AV, Cavallaro A, Cavallari N, Allegrucci P, Tamburelli A, Agosta F, et al. Factors influencing the rupture of abdominal aortic aneurysms. Surg Gynecol Obstet 1991;173:175-8.
7. Cronenwett JL, Murphy TF, Zelenock GB, Whitehouse WM, Lindenauer SM, Graham LM, et al. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. Surgery 1985;98: 472-83.
8. Brown LB, Powell JT; the UK Small Aneurysm Trial Participants. Risk factors for aneurysm rupture in patients kept under surveillance. Ann Surg 1999;230:289-97.
9. Hole DJ, Watt GCM, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. Br Med J 1996;313:711-5.
10. Truelson T, Prescott E, Lange P, Schnohr P, Boysen G. Lung function and risk of fatal and non fatal stroke. The Copenhagen City Heart Study. Int J Epidemiol 2001;30:145-51.
11. Friedman GD, Klatsky AL, Siegelaulb AB. Lung function and risk of myocardial infarction and sudden cardiac death. N Engl J Med 1976; 294:1071-5.
12. Engström G, Hedblad B, Valind S, Janzon L. Asymptomatic leg and carotid atherosclerosis in smokers is related to degree of ventilatory capacity. Longitudinal and cross-sectional results from "Men born in 1914", Sweden. Atherosclerosis 2001;155:237-43.
13. Lee AJ, Fowkes FGR, Carson MN, Leng GC, Allan P L. Smoking, atherosclerosis and risk of abdominal aortic aneurysm. Eur Heart J 1997;18:671-6.
14. Reilly JM, Miralles M, Wester WN, Sicard G A. Differential expression of prostaglandin E2 and interleukin-6 in occlusive and aneurysmal aortic disease. Surgery 1999;126:624-7.
15. Juvonen J, Surcel H-M, Satta J, Teppo A-M, Bloigu A, Syrjala H, et al. Elevated circulating levels of inflammatory cytokines in patients with abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 1997;17: 2843-7.
16. Shah PK. Inflammation, metalloproteinases, and increased proteolysis. An emerging pathophysiological paradigm in aortic aneurysm. Circulation 1997;96:2115-7.
17. Fowkes FGR, Housley E, Riemersma RA, Macintyre CCA, Cawood EHH, Prescott RJ, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared to ischaemic heart disease in the Edinburgh Artery Study. Am J Epidemiol 1992;135:331-40.
18. Leng GC, Lee AJ, Fowkes FGR, Whiteman M, Dunbar J, Housley E, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol 1996;25:1172-81.
19. Smith FB, Lee AJ, Price JF, van Wijk MC, Fowkes FGR. Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population. Journal of Vascular Surgery 2003;38:1323-30.
20. Rose GA. The diagnosis of ischaemic pain and intermittent claudication in field surveys. Bull WHO 1962;27:645-58.
21. MRC Committee on Research into Chronic Bronchitis. Questionnaire on respiratory symptoms. London: Medical Research Council, 1996.
22. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 1999;159:179-87.
23. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/ WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care 2001;163:1256-76.
24. Liao D, Higgins M, Bryan NR, Eigenbrodt ML, Chambless LE, Lamar V, et al. Lower pulmonary function and cerebral subclinical abnormalities detected by MRI. Chest 1999;116:150-6.
25. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk from aortic aneurysm compared with other smoking – related diseases: a systematic review. J Vasc Surg 2003;38:329-34.
26. Thompson RW, Parks WC. Role of matrix metalloproteinases in abdominal aortic aneurysms. Ann N Y Acad 1996;800:157-74.
27. Tilson MD. The polymorphonuclear leukocyte and the abdominal aortic aneurysm: a neglected cell type and a neglected disease. Circulation 2005;112:154-6.
28. Powell JT, Muller BR, Greenhalgh RM. Acute phase proteins in patients with abdominal aortic aneurysms. J Cardiovasc Surg 1987;28: 528-30.
29. Lee AJ, Fowkes FGR, Lowe GDO, Rumley A. Haemostatic factors, atherosclerosis and risk of abdominal aortic aneurysm. Blood Coagul Fibrinolysis 1996;7:695-701.
30. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003;107:1514-9.
31. Engström G, Lind P, Hedblad B, Wollmer P, Stavenow L, Janzon L, et al. Lung function and cardiovascular risk. Relationship with inflammation-sensitive plasma proteins. Circulation 2002;106:2555-60.
32. Engström G, Wollmer P, Vallind S, Hedblad B, Janzon L. Blood pressure increase between 55 and 68 years of age is inversely related to lung function: longitudinal results from the cohort study "Men born in 1914". J Hypertens 2001;19:1203-8.
33. Engström G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population based cohort study. Diabetic Med 2002;19:167-70.
34. Yamazumi K, Ojiro M, Okumura H, Aikou T. An activated state of blood coagulation and fibrinolysis in patients with abdominal aortic aneurysms. Am J Surg 1998;175:297-301.
35. Nomura F, Ihara A, Yoshitatsu M, Tamura K, Katayama A, Ihara K. Relationship between coagulation cascade, cytokine, adhesion molecule and aortic aneurysm. Eur J Cardiothorac Surg 2003;1034-9.
36. Lindholt JS, Jorgensen B, Fasting H, Henneberg EW. Plasma levels of plasmin anti-plasmin complexes are predictive for small abdominal aortic aneurysms expanding to operation - recommendable sizes. J Vasc Surg 2001;34:611-5.
37. Banach-Wawrzenczyk E, Dziedziczko A, Rox D. Fibrinolysis system in patients with bronchial asthma. Med Sci Monit 2000;6:103-7.

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