Higher prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm

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Background and aim: **The risk factors of aortic aneurysm (AA) are comparable with those described for chronic obstructive pulmonary disease. This study was performed to determine whether patients with AA have a higher than average prevalence of obstructive airway disease.**
Methods: **We performed pulmonary function tests in 240 consecutive patients (182 men and 58 women; age, 70 ± 10 years) with thoracic or abdominal AA. The results were compared with those in individuals without obvious cardiovascular disease (control) and in patients with coronary artery disease who were matched for age, gender, smoking status, and other atherosclerotic risk factors.**
Results: **Patients in the AA group had a lower forced expiratory volume in 1 second/forced vital capacity (%) and carbon monoxide diffusing capacity (%/predicted value) than did the control group ($P < .01$). The proportion of patients with airway obstruction, defined as forced expiratory volume in 1 second/forced vital capacity of 70% or less, was higher in the AA group (100/240; 42%) than in the control (51/223; 23%) and coronary artery disease (43/238; 18%) groups. Multiple logistic regression analysis results revealed that the presence of an AA and male gender were associated with a higher risk of airway obstruction (odds ratio, 2.928; 95% CI, 1.722 to 4.979; and odds ratio, 1.622; 95% CI, 1.055 to 2.493, respectively).**
Conclusion: **These data suggest that AA may be a risk factor indicative of the presence of chronic obstructive pulmonary disease. A higher prevalence of depressed pulmonary function should be suspected as a preoperative risk in presence of thoracic or abdominal AA as compared with other types of cardiovascular disorders. (J Vasc Surg 2002;36:35-40.)**

The quality of pulmonary function is inversely related to the incidence of cardiac disease, including coronary artery disease (CAD) and congestive heart failure.[1,2] The association between reduced pulmonary function and risk of heart disease is thought to reflect similar characteristics, such as poor physical fitness, obesity, unfavorable lipid profiles, and tobacco abuse.[3]

The risk factors associated with thoracic or abdominal aneurysms, and other cardiovascular disease, are comparable with those associated with chronic obstructive pulmonary disease (COPD), including age and cigarette smoking, and the frequent presence of pulmonary emphysema complicating aortic aneurysmal disease has been noted.[4,5] A high prevalence of aortic dissection or abdominal aortic aneurysm (AAA) and an accelerated rate of aneurysm expansion have been observed in a few studies of patients with severe COPD.[6,7] In one large recent study, a weak though significant association was found between AAA and COPD among patients whose aneurysm was 4 cm or more in diameter.[8] Controversy, however, persists with regard to the actual prevalence of obstructive airway disease, including COPD, in patients with AAA, particularly among Asian populations.

The results of pulmonary function tests performed in 240 patients with thoracic or abdominal aneurysm were compared with those of control individuals and of patients with CAD matched with respect to age, gender distribution, and daily cigarette consumption. The objective of this study was to determine whether Japanese patients with aortic aneurysms (AAs) in either the abdomen or the thorax have a significantly higher prevalence of obstructive airway disease than patients with other cardiovascular disorders.

STUDY POPULATIONS AND METHODS

Patients with aortic aneurysms. The index population consisted of 240 consecutive Japanese patients with AA referred to the pulmonary function testing laboratory of the National Cardiovascular Center, Osaka, Japan, from February 1997 to September 1999 (AA group). The diagnosis of AA was established with the presence of a more than 40 mm-diameter aorta on contrast-enhanced computed tomography of the chest or abdomen.[9,10] Computed tomographic films were interpreted by two physicians experts in vascular medicine or surgery. The AA group consisted of 118 patients with AAA, 100 with thoracic AA (TAA), and 22 with both AAA and TAA. A history of CAD, in absence of recent symptoms or electrocardiographic

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Table I. Numbers of patients referred, excluded for major criteria, and ultimately enrolled in each study group

	Control	*CAD*	*AA*
Overall numbers of referred patients	287	312	320
Numbers of excluded patients	64	74	80
Dissecting aneurysm	0	0	16
Secondary aneurysm*	0	0	4
Unstable angina	0	5	2
Unstable heart failure	0	4	1
History of asthma	12	17	18
Current wheezing	8	8	9
Smoking within 3 months	34	28	21
Use of bronchodilators†	7	9	8
Steroid use‡	3	3	1
Numbers of enrolled patients	223	238	240

*As a result of aortoaortic syndrome or Marfan syndrome.
†Theophylline, β-stimulating or anticholinergic agents.
‡Oral predonisolone or inhaled beclomethasone dipropionate.

changes as the result of myocardial ischemia within 1 year before the study, was present in 51 patients with AA. Exclusion criteria included dissecting AA, saccular aneurysm, aneurysm as the result of aortoarteritis syndrome or Marfan syndrome, unstable angina, unstable heart failure, history of bronchial asthma, current wheezing, tobacco smoking within 3 months before pulmonary function testing, and the use of theophylline, β-adrenergic agonists, anticholinergic agents, and oral or inhaled corticosteroids.

Control population. Two additional age-matched groups of patients were studied. The first was a control group consisting of 223 consecutive Japanese patients without apparent cardiovascular disorders. The control group comprised 223 consecutive Japanese individuals without apparent cardiovascular disorders referred to our laboratory by an attending physician from our ambulatory care department or hospital for screening cardiopulmonary function tests. This group included 166 patients with hypertension, 19 patients with diabetes, and 67 patients with hyperlipidemia.

Coronary artery disease population. The CAD group consisted of 238 Japanese patients, including 105 patients with stable exercise-induced angina pectoris and 133 patients with old myocardial infarctions, in absence of recent symptoms or of electrocardiographic changes as the result of myocardial ischemia within 1 month of pulmonary function testing. The CAD group was studied as the second control group. To create a group age-matched with the AA group, consecutive patients 45 years of age or older were selected from the control and the CAD groups because all patients in the AA group were between the ages of 45 and 87 years. The overall number of referred patients, the number of excluded patients for each of the major exclusion criteria, and the number of patients ultimately enrolled in this study are shown in Table I.

A detailed history of cigarette consumption and of prior illnesses was obtained from all study participants, and blood samples were collected for measurements of fasting serum cholesterol. *Hypertension* was defined as a history of systolic blood pressure more than 160 mm Hg and diastolic pressure more than 100 mm Hg before treatment, according to the guideline of the Joint National Committee VI.[11] *Hypercholesterolemia* was defined as a serum cholesterol level more than 240 mg/dL and low density lipocholesterol more than 130 mg/dL before treatment, according to the guideline of National Cholesterol Education Program/Adult Treatment Panel III.[12] All study participants were explained the purpose of the study and granted informed consent. Important baseline clinical characteristics of the three study populations are shown in Table II.

Pulmonary function testing. Diagnostic spirometry, including carbon monoxide diffusing capacity (DLCO) with single-breath technique, was performed in all study participants with standardized equipment (FUDAC-70; Fukuda-denshi, Tokyo, Japan) in our pulmonary function laboratory.[13] All measurements were performed in triplicate before the prescription of a bronchodilator to allow a choice of the best of three sets of data. *Obstructive airway disease* was defined as a measured forced expiratory volume in 1 second/forced vital capacity (FEV1.0/FVC) × 100 of 70% or less. Other indices of pulmonary function, including vital capacity (VC), VC/predicted value (%VC), FEV1.0, FEV1.0/predicted value (%), forced expiratory flow rate at 50% of the VC, and DLCO also were compared among the three groups.[14]

Statistical analysis. The study participant characteristics, including gender, age, smoking history, level of cigarette consumption (in pack-years), body height and weight, systemic blood pressure, blood glucose and cholesterol levels, and pulmonary function testing measurements were systematically recorded and analyzed with computer software for statistical analysis (Stat View 5.0; Abacus Concepts, Inc, Berkeley, Calif). The association between *obstructive airway disease*, defined as FEV1/FVC of 70% or less, and hypertension or hypercholesterolemia among the three groups was examined with multiple comparisons rank sum test.[15]

Measurements of age, cigarette consumption (pack-years), and results of pulmonary function tests are presented as mean ± standard deviation. Differences among

Table II. Baseline characteristics of three study groups

	Control	*CAD*	*AA*
No. of patients (male/Female)	223 (162/61)	238 (195/43)	240 (182/58)
Age, years; range	68.8 ± 9.2 (47-87)	68.5 ± 6.5 (48-89)	69.9 ± 9.3 (45-87)
Body height (cm*)	161 ± 8	161 ± 7	162 ± 9
Body weight (kg*)	60.3 ± 10.9	60.3 ± 10.6	58.9 ± 10.3
Cigarette smoking history			
Current smokers	87 (39%)	104 (44%)	91 (38%)
Former smokers	71 (32%)	83 (35%)	76 (32%)
Never smokers	65 (29%)	51 (21%)	73 (30%)
No. of pack-years*	48.5 ± 33.0	52.5 ± 43.7	49.2 ± 35.3
Presence of hypertension	159 (71%)	146 (61%)	155 (65%)
Presence of hypercholesterolemia	56 (%)	83 (%)†	68 (%)
History of CAD	0	238 (100%)	51 (21%)

*Mean ± SD. †$P < .01$ versus control and AA.
Current smokers = patients who had smoked within 5 years and quit smoking for 3 months before pulmonary function testing; former smokers were patients who had quit smoking for more than 5 years.

Table III. Results of pulmonary function tests in three study groups

	Control	*CAD*	*AA*
Vital capacity (L)	2.9 ± 2.7	3.3 ± 5.8	3.0 ± 4.1
FEV1.0 (L)	2.0 ± 0.6	2.1 ± 0.6	1.9 ± 0.6
FEV1.0 % predicted	88.0 ± 23.6	89.2 ± 20.7	84.6 ± 24.0
FEV1.0/FVC ratio (%)	74.1 ± 12.7	75.6 ± 10.3	70.9 ± 12.3*
Never smokers	78.1 ± 8.1	78.9 ± 7.8	72.1 ± 10.8
Former smokers	73.3 ± 14.0#	75.9 ± 10.4	71.9 ± 11.2
Current smokers	70.4 ± 13.6##	73.9 ± 10.8#	68.4 ± 14.8#
FEF50% /% predicted	52.4 ± 26.9	58.5 ± 30.0	44.9 ± 25.1*
DLCO (mL/min/Torr)	16.8 ± 5.1	16.6 ± 5.2	15.1 ± 5.1*
DLCO/% predicted	106 ± 23	100 ± 27*	95 ± 24*
DLCO/VA (% predicted)	92 ± 30	86 ± 28	82 ± 27*

FEV1.0 in men (in women*) = 3.44 (2.67*) × body height (m) − 0.033 (0.027*)× age (year) − 1.00 (0.54*).
Predicted values: FEF50% in men (in women*) = (0.00024 [0.00017*] × [age]^2 − 0.0577 [0.0487*] × age + 4.438 [4.086*]) × body height.
DLCO in men (in women*) = (10.9 [7.1*] × body height − 0.067 [0.054*] × age − 5.89 [0.89*]) × 2.97 (2.99*).
Values are means ± SD; *$P < .05$ versus control group; # $P < .05$ versus never smokers; ## $P < .05$ versus former smokers.
FEF50%, Forced expiratory flow at 50% of forced vital capacity; *VA,* alveolar ventilatory volume.

the three groups were tested with one-way analysis of variance with multiple comparisons. Differences were considered significant when P was less than .05 with Scheffé test.

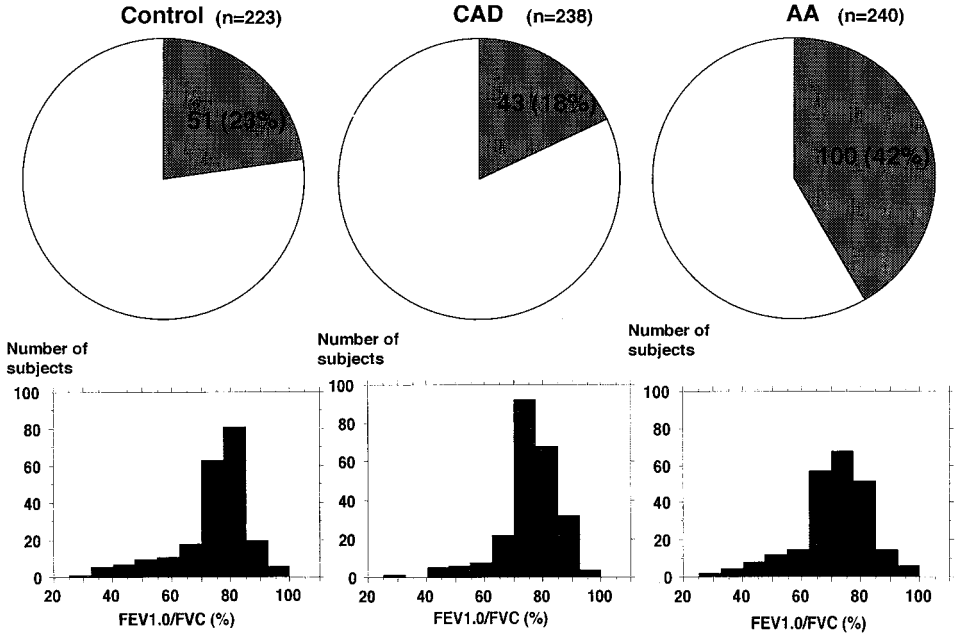
Correlations between age, body height, or body weight and pulmonary function expressed as FEV1/FVC were tested with multiple regression analysis in each group. Multiple logistic regression analysis was performed to ascertain whether the presence of an AA was independently associated with obstructive airway disease, compared with gender, history of cigarette smoking, presence of hypertension, or CAD.

RESULTS

Important characteristics, including age, gender ratio, body height and weight, cigarette smoking profile, and prevalence of hypertension, did not differ among the control, CAD, and AA groups (Table II). Hypercholesterolemia was significantly more prevalent in the CAD group than in the control and AA groups ($P < .01$).

The main results of the pulmonary function tests in the three study groups are presented in Table III. The indices of airway obstruction, FEV1.0/FVC ratio (%), and forced expiratory flow rate at 50% of the VC were significantly lower in the AA group than in the control and CAD groups ($P < .01$). Furthermore, DLCO and the DLCO-alveolar ventilatory volume ratio were significantly lower in the AA group than in the control and CAD groups ($P < .05$). No significant difference was seen in VC, VC/predicted value (%VC), FEV1.0, and FEV1.0/predicted value (%) among the three groups. In all three groups, FEV1.0/FVC ratio (%) of current smokers was lower than in former or never smokers.

The percentages of patients with obstructive airway disease (FEV1/FVC ≥70%) in each group is shown in the Fig. With multiple comparison rank sum test, patients with AA had a significantly higher prevalence rate of airway obstruction (100/240; 42%) than control subjects (51/223; 23%) and patients with CAD (43/238; 18%). Furthermore, patients with AA had a higher prevalence rate of more severe *airflow obstruction*, defined as a FEV1/FVC of less than 55% (AA group: 27/240; 11.3%; control group: 20/223; 9.0%; CAD group: 11/238; 5.0%). No significant correlation was found between size of the aneurysm and



Pie graphs show higher proportion of airway obstructive disease, defined as FEV1.0/FVC(%) 70 or less, in AA group (100/240; 42%) than in control (51/223; 23%) or CAD (43/238; 18%) groups. Histograms show distribution of FEV1/FVC(%) in each group.

Table IV. Results of multiple logistic regression analysis

Variable	*RR estimate*	*95% CI*	P *value*
Male gender	1.622	1.055-2.493	.0276
Presence of hypertension	0.967	0.562-1.664	.9023
Presence of hypercholesterolemia	0.634	0.369-1.090	.0993
History of CAD	1.159	0.800-1.680	.4341
Presence of AA	2.928	1.722-4.979	<.0001

RR = risk ratio.

FEV1/FVC (%) or any other measurement of pulmonary function.

Multiple logistic regression analysis results revealed that presence of an AA and male gender were independently related to obstructive airway disease, in contrast to presence of hypertension and hypercholesterolemia (Table IV). In multiple regression analysis, FEV1/FVC correlated negatively with patient age in the overall study population, in the control group, and in the CAD group, and no correlation was found between FEV1/FVC and other clinical variables in the AA group. Correlation coefficients and *P* values in each group are shown in Table V.

DISCUSSION

This study confirmed that Japanese patients with TAA or AAA have a high prevalence rate of obstructive airway disease and that pulmonary function indices of airway obstruction in patients with AA are lower than in a control population and in patients with CAD. Patients with AA not only were more likely to have an FEV1/FVC of less than 70%, as shown in the Fig, but also to have a higher prevalence rate of FEV1/FVC of less than 55%, which is consistent with unequivocal airway obstruction. We also showed that DLCO and DLCO-alveolar ventilatory volume ratio were lower in patients with AA than in the control and CAD groups. With respect to DLCO, the association between AAs and airway obstructive disease is likely the result of an association with pulmonary emphysema rather than with chronic bronchitis, in which DLCO is known to be preserved.

Several clinical studies have described associations between AA and aging, male gender, cigarette smoking, and hypertension.[7,16] Except for hypertension, these factors have often also been found to be associated with COPD. Indeed, several studies have reported a univariate association between AAA and COPD.[17,18] Other studies have observed comparable abnormalities in elastase activity in both AA and COPD.[19] This study supports such findings in Asian or Japanese populations. Because our study only addressed issues of disease prevalence, common factors that

Table V. Results of correlation analyses

Variable	*Age*	*Body height*	*Body weight*	*Cigarette smoking history (pack-years)*
Overall population correlation coefficient	−0.222	−0.137	0.048	−0.072
P value	<.0001	.0131	.3838	.1403
Control group correlation coefficient	−0.23	0.043	−0.029	−0.155
P value	.0157*	.6604	.7626	.0962
CAD group correlation coefficient	−0.3	−0.155	0.125	−0.09
P value	.0003	.0718	0.1518	.2397
AA group correlation coefficient	−0.092	−0.218	0.025	−0.024
P value	.3788	.0524	.8156	.8006

may exist between AA and COPD could not be identified. One may, however, hypothesize that the high prevalence of obstructive airway disease in patients with AA is related to common inflammatory mechanisms or that it may be the result of a genetic susceptibility to common risk factors, such as aging and cigarette smoking, different from other cardiovascular disorders.[20-22]

On the other hand, one large study from Denmark found no statistically significant association between AAA and COPD after adjustment for smoking history.[23] Furthermore, in a recent report from the large Aneurysm Detection and Management cohort study, COPD was not independently associated with 3.0 cm-diameter to 3.9 cm-diameter AAAs (odds ratio, 1.06; 95% CI, 0.97 to 1.17). In the group with AAAs 4.0 cm or more in diameter, although the odds ratio was significant, its value was low (1.21; 95% CI, 1.06 to 1.38), and this association was lost after adjustment for the number of years of smoking.[8] From these results, a history of cigarette smoking seems to be a predominant factor in the association between AA and COPD. In consideration of the association of these two conditions, smoking behavior appears to be the common denominator underlying the susceptibility to both AA and COPD. Indeed, the FEV1.0/FVC ratio (%) of current smokers was lower than that of never smokers, including in the AA group (Table II).

Several explanations may exist for the differences between our results and those of other large cohort studies, which may be interpreted as limitations of our study. First, because our population was Japanese, whether our results can be extrapolated to other ethnic groups is not known. Second, a diagnosis of airway obstruction, instead of COPD, was used in our study because pulmonary function tests were performed only once. However, patients with histories of bronchial asthma, current wheezing, or use of theophylline or β-adrenergic agonists were excluded to avoid the inclusion of patients who had reversible bronchial constriction or who were in a phase of acute exacerbation. Third, this study was performed at a single center, where a high percentage of referred patients are at high surgical risk. Therefore, our study population may have had more serious preoperative disorders, including more advanced pulmonary disease, than at average medical institutions. In addition, the number of patients studied may have been relatively small compared with previous studies,[8,23] and the absence of a correlation between presence of airway obstruction and cigarette smoking may have been the result of a statistical type 2 error.

In this study, a higher prevalence rate of depressed pulmonary function was found among patients with AA than among patients with CAD matched for multiple clinical characteristics, although hypercholesterolemia was more prevalent in the CAD group than in the AA group. Several reports have indicated that pulmonary emphysema also is associated with AA and is a preoperative risk factor. A prospective study of respiratory failure after surgery for TAA and AAA revealed that COPD was an independent predictor of severe postoperative complications, along with smoking history and cardiac and renal disease.[24] Smith and coworkers[25] reported that appropriate preoperative care, with a detailed respiratory assessment and careful attention to pulmonary function in the postoperative period, was associated with a favorable postoperative course and no operative mortality. To our knowledge, however, a higher prevalence rate of depressed pulmonary function in patients with AA, compared with other atherosclerotic disorders, had not been clearly shown, although one study found that patients with severe COPD and a FEV1.0/VC decreased to less than 55% had a significantly higher prevalence rate of aortic dilatation or AAA compared with patients with less severe COPD.[6] Our data point to the importance of testing pulmonary function and assessing the results in detail before undertaking surgical treatment of AA as compared with other cardiovascular disease, including CAD.

In summary, patients with TAA or AAA had a high prevalence rate of airway obstruction on pulmonary function testing, and the presence of an AA was related to the presence of obstructive airway disease, expressed as a lower FEV1/FVC (%) than in control subjects or patients with CAD, who were matched for age, gender, smoking history, and cardiovascular risk factors. One may hypothesize that smoking is the common underlying cause of aneurysms and obstructive airway disease in biologically susceptible patients. Further studies are needed to identify common inflammatory or genetic mechanisms that may coexist in obstructive airway disease and in aneurysmal vascular disease.

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