

Reduced Pulmonary Function Is Associated with Central Arterial Stiffness in Men

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The association of impaired pulmonary function with cardiovascular morbidity and mortality has been reported in several prospective studies. The nature of this association and the mechanisms underlying it are unknown. Both atherosclerosis and central arterial stiffness might be involved. We recently reported, in a 4-yr longitudinal study, that reduced lung function predicts the development of carotid atherosclerotic plaques. In the present study, we report the associations of aortic stiffness with lung function measurements. One hundred and ninety-four men, aged 30 to 70 yr and free of coronary heart disease, who volunteered for a standard health examination were included. FEV₁ and FVC were used to assess lung function. Aortic stiffness was estimated from the carotid-femoral pulse-wave velocity (PWV), which increases proportionally with an increase in aortic stiffness. PWV was significantly and negatively associated with FEV₁ and FVC (partial correlation coefficients adjusted for age and height: -0.27 [$p < 0.001$] and -0.24 [$p < 0.001$], respectively). For every 1 SD increase in PWV (2.5 m/s), FEV₁ decreased by 195.2 ± 50.1 ml ($p < 0.001$) in an age- and height-adjusted analysis. The corresponding decrease in FVC was 190.4 ± 55.0 ml ($p < 0.001$). Further adjustment for cardiovascular risk factors (weight, smoking habits, hypercholesterolemia, diabetes, and hypertension) did not markedly alter these results. In addition, negative associations of PWV with lung function measurements were observed within each category of cardiovascular risk factors. This study suggests that reduced pulmonary function is independently associated with aortic stiffness in men. The interrelations between pulmonary and vascular alterations should be thoroughly investigated.

Keywords: lung function; arterial stiffness; epidemiology

The association of impaired pulmonary function with cardiovascular morbidity and mortality has been reported in several prospective studies (1–3). However, the nature of this association and the mechanisms underlying it are unknown. Vascular alterations, including atherosclerosis and arterial stiffness (a loss of elasticity), might be involved. Atherosclerosis is obviously the main underlying pathology of ischemic cardiovascular diseases. In a recent paper, we reported in a 4-yr longitudinal study of 656 subjects aged 59 to 71 yr, that reduced lung function predicts the development of carotid atherosclerotic plaques (4).

The arterial system serves as a cushion to buffer the pulsatile blood pressure (BP) and flow produced by the heart. The viscoelastic properties of large arterial walls are a major determinant of the speed of propagation of the arterial pressure wave, of the timing of reflection of the wave, and of cardiovascular hemodynamics (5). In fact, arterial stiffness has recently been shown to be a predictor of all-cause and cardiovascular

mortality in hypertensive subjects (6) and in those with end-stage renal disease (7). In addition, a large brachial pulse pressure (an indirect marker of arterial stiffness) was independently associated with morbidity and mortality from cardiovascular and coronary heart disease in both hypertensive and general populations (8–9). Whether central arterial stiffness may contribute to the cardiac events that occur in subjects with reduced lung function is unknown.

In the cross-sectional study described here, of 194 men aged 30 to 70 yr and free of coronary heart diseases, we investigated associations of lung function measurements (FEV₁ and FVC) with carotid-femoral pulse-wave velocity (PWV). It has previously been shown that noninvasive measurement of carotid-femoral PWV is an easy, safe, and reproducible method of assessing aortic arterial stiffness (10).

METHODS

The French National Health Care System provides all working and retired persons with a free medical examination (a standard health check) every 5 yr. The Centre d'Investigations Préventives et Cliniques (the IPC Center) is one of the largest medical centers in France that provides this service for people living in the Paris area. Among those men examined daily, we invited the first who was undergoing antihypertensive drug treatment or had a high systolic BP (≥ 140 mm Hg) or high diastolic BP (≥ 90 mm Hg), and the first normotensive man, aged 30 yr or older, to participate in the study. Ultimately, 202 subjects were included. Eight subjects with a history or clinical evidence of coronary heart disease (myocardial infarction or angina) were excluded from the analysis. The study protocol was approved by the Comité d'Éthique du Centre Hospitalier Universitaire de Cochin, and written informed consent was obtained from all participants.

Medical information, obtained through a standardized questionnaire, included each subject's demographic background, medical history, drug use, and personal habits, such as cigarette consumption. The smoking habit section of the questionnaire included detailed information on whether the subject had ever smoked cigarettes, duration of cigarette smoking, average daily number of cigarettes smoked, and age at which smoking ceased (if applicable). Subjects were classified as never smokers, ex-smokers, or current smokers. For ever-smokers, cigarette pack-years were also calculated, by multiplying the number of years of smoking by the average number of cigarettes smoked per day and dividing by 20. Three independent measurements of systolic and diastolic BP were taken in the right arm, using a manual sphygmomanometer after a 10-min rest, and the average of the last two measurements was used for the statistical analyses. Subjects with a systolic BP ≥ 160 mm Hg and/or a diastolic BP ≥ 95 mm Hg and/or subjects who were using antihypertensive drugs were considered to be hypertensive. Hypercholesterolemia was defined as a total cholesterol level ≥ 6.2 mmol/L (2.40 g/L) or the use of lipid-lowering drugs. Subjects who reported a medical history of diabetes or use of antidiabetic drugs, or who had a fasting plasma glucose level ≥ 7.0 mmol/L (1.26 g/L), were considered diabetics. Each subject's body mass index (BMI) was computed as weight (in kilograms) divided by height (in meters) squared.

Lung Function Measurements

Pulmonary function tests were performed with a Spyro Analyzer spirometer (Model ST-200; Fukuda Sangyo). The tests were performed

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TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	Men (n = 194)	
	Mean ± SD or Number (%)	Number (%)
Age, yr	57.3 ± 10.5	
Height, cm	173.6 ± 7.5	
Weight, kg	82.6 ± 13.8	
BMI, kg/m ²	27.2 ± 3.9	
Smoking habit		
Never smoker	54 (27.8%)	
Ex-smoker	70 (36.1%)	
Smoker	70 (36.1%)	
Smoking among ever smokers, pack-years	15.7 ± 13.8	
Total cholesterol, mg/dl	223.9 ± 36.2	
Hypercholesterolemia	75 (38.7%)	
Glucose, mg/dl	101.2 ± 16.1	
Diabetes	19 (9.8%)	
Systolic BP, mm Hg	140.4 ± 19.4	
Diastolic BP, mm Hg	88.0 ± 11.7	
Hypertension	98 (50.5%)	
FEV ₁ , ml	3,293 ± 737	
FVC, ml	4,006 ± 838	
FEV ₁ /FVC ratio, %	82.2 ± 8.5	
Pulse wave velocity, m/s	11.7 ± 2.5	

Definition of abbreviations: BMI = body mass index; BP = blood pressure.

with the subject in a sitting position and with noseclips in place. Each subject performed at least three spirometric tests (with at least two reproducible and acceptable maneuvers). Reproducibility was considered as present when the second highest values of FEV₁ and FVC were within 5% of the highest values. The highest measured value of FEV₁ and the corresponding measured value of FVC were coded for computer analysis. The correlation coefficient between FEV₁ and FVC was 0.88 (p < 0.001). The ratio of FEV₁ to FVC (FEV₁/FVC) was also calculated.

PWV

Carotid-femoral PWV was evaluated by a single physician (who did not perform lung function examinations), using two pressure probes. The method used, which involves an automatic device (Complior; Colson, Paris, France) has been extensively analyzed (11). Briefly, two pressure waves were recorded transcutaneously at the base of the neck for the right common carotid artery and over the right femoral artery. PWV was determined as the foot-to-foot velocity of each wave. The foot of the pressure wave was identified as the beginning

point of the sharp systolic upstroke. Pulse transit time was determined as the average of 10 consecutive beats. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites. Aortic PWV was calculated as the ratio of distance to transit time. The validation of this automatic method, and its reproducibility, have been previously reported, with an intraobserver repeatability coefficient of 0.93 and an interobserver reproducibility coefficient of 0.89 (11).

Data Analysis

Standard procedures of the Statistical Analysis System (SAS, Inc., Cary, NC) were used for univariate and multivariate analyses. The associations of PWV with cardiovascular risk factors were assessed through the use of correlation coefficients, t tests, and analysis of variance. The associations of FEV₁ and FVC (as dependent variables) with each cardiovascular risk factor and with PWV (as independent variables) were first assessed with partial correlation coefficients, analysis of covariance (ANCOVA), or linear regression models adjusted for age and height. Multiple linear regression models and ANCOVA with simultaneous inclusion of age, height, cardiovascular risk factors, and PWV were subsequently used.

RESULTS

The main characteristics and measurements of the study population are presented in Table 1. The age of the 194 men in the study was 57.3 ± 10.5 (mean ± SD) yr. Seventy subjects (36.1%) were current smokers, 98 (50.5%) were hypertensive, and 19 (9.8%) were diabetic.

Age, hypertension, and diabetes were positively associated with PWV. The correlation coefficient of PWV with age was 0.44 (p < 0.001). Hypertensive subjects had higher mean values of PWV than nonhypertensive subjects (12.8 ± 2.4 versus 10.7 ± 1.7 m/s, p < 0.001). The mean values of PWV in diabetic and nondiabetic men were, respectively, 13.1 ± 2.3 and 11.6 ± 2.2 m/s (p < 0.02). In contrast, the other risk factors (height, weight, BMI, smoking habit, and hypercholesterolemia) were not significantly related to PWV. The mean value of PWV in never smokers, ex-smokers, and current smokers were, respectively, 12.0 ± 2.6 m/s, 11.3 ± 2.1 m/s, and 12.1 ± 2.8 m/s (p = 0.75).

The associations of FEV₁ with cardiovascular risk factors and PWV are presented in Table 2. As expected, smoking habit was associated with FEV₁ in both age- and height-adjusted analysis and in full multivariate analysis. PWV was signifi-

TABLE 2. ASSOCIATIONS OF FEV₁ WITH CARDIOVASCULAR RISK FACTORS AND PULSE-WAVE VELOCITY IN LINEAR REGRESSION MODELS

	FEV ₁				
	Age- and Height- Adjusted Regression Coefficients* (ml)		Multivariate Regression Coefficient† (ml)		Multivariate R ² (%)
	Mean ± SD	p Value	Mean ± SD	p Value	
Age, per 10.5-yr increase‡	-267.7 (51.0)	< 0.001	-211.7 (56.1)	< 0.001	7.4
Height, per 7.5 cm increase‡	249.4 (46.8)	< 0.001	259.6 (51.9)	< 0.001	12.0
Weight, per 13.8 kg increase‡	-43.0 (52.0)	0.41	-23.3 (52.6)	0.66	—
Smoking habit					
Ex-smokers versus never smokers	-51.8 (116.3)	0.65	-48.5 (116.6)	0.68	—
Smokers versus never smokers	-312.1 (117.7)	< 0.008	-339.5 (117.1)	< 0.001	5.3
Hypercholesterolemia, yes versus no	-26.3 (93.7)	0.78	23.5 (91.8)	0.79	—
Diabetes, yes versus no	8.0 (155.4)	0.96	31.5 (150.0)	0.83	—
Hypertension, yes versus no	-147.7 (98.4)	0.14	-78.4 (107.4)	0.47	—
PWV, per 2.5 m/s increase‡	-195.2 (50.1)	< 0.001	-193.1 (52.7)	< 0.001	6.8

Definition of abbreviation: PWV = pulse-wave velocity.

* For each variable, the regression coefficient was calculated from a linear regression model including this variable plus age and height. For age and height, regression coefficients were calculated from a linear regression model simultaneously including these two variables.

† All variables were simultaneously included in the model.

‡ Approximately one standard deviation.

TABLE 3. ASSOCIATIONS OF FORCED VITAL CAPACITY WITH CARDIOVASCULAR RISK FACTORS AND PULSE WAVE VELOCITY IN LINEAR REGRESSION MODELS

	FVC				
	Age- and Height-Adjusted Regression Coefficients* (ml)		Multivariate Regression Coefficient† (ml)		Multivariate R ² (%)
	Mean ± SD	p Value	Mean ± SD	p Value	
Age, per 10.5-yr increase‡	-230.9 (56.4)	< 0.001	-181.8 (60.8)	< 0.003	5.2
Height, per 7.5 cm increase‡	389.2 (51.0)	< 0.001	430.7 (56.4)	< 0.001	22.7
Weight, per 13.8 kg increase‡	-124.1 (55.9)	0.03	-88.0 (56.7)	0.13	—
Smoking habit					
Ex-smokers versus never smokers	-168.2 (126.0)	0.18	-138.5 (125.6)	0.27	—
Smokers versus never smokers	-360.7 (125.5)	< 0.005	-438.6 (127.2)	< 0.001	6.1
Hypercholesterolemia, yes versus no	-52.0 (101.8)	0.61	41.9 (99.0)	0.67	—
Diabetes, yes versus no	-70.6 (168.4)	0.68	-59.3 (161.7)	0.71	—
Hypertension, yes versus no	-243.3 (106.2)	0.02	-158.2 (115.8)	0.17	—
PWV, per 2.5 m/s increase‡	-190.4 (55.0)	< 0.001	-158.1 (57.3)	< 0.006	5.0

Definition of abbreviation: PWV = pulse-wave velocity.

* For each variable, regression coefficient was calculated from a linear regression model including this variable plus age and height. For age and height, regression coefficients were calculated from a linear regression model simultaneously including these two variables.

† All variables were simultaneously included in the model.

‡ Approximately one standard deviation.

cantly and negatively associated with FEV₁ (partial correlation coefficient adjusted for age and height: -0.207, $p < 0.001$). For every 1 SD increase in PWV (2.5 m/s), FEV₁ decreased by 195.2 ml ($p < 0.001$) in age- and height-adjusted analysis (Table 2). Further adjustment, for cardiovascular risk factors, did not alter these results (Table 2). In the multivariate linear regression model, the variance of FEV₁ explained (as R²) by PWV was 6.8% (Table 2).

The associations of FVC with cardiovascular risk factors and PWV are presented in Table 3. Smoking habit, hypertension, and increased weight were related to decreased FVC in age- and height-adjusted analysis. The two latter associations (for hypertension and weight) did not reach significance in the multivariate analysis (Table 3). A negative association was observed between PWV and FVC (partial correlation coefficient adjusted for age and height: -0.24, $p < 0.001$). For every 1 SD increase in PWV, FVC decreased by 190.4 ml ($p < 0.001$) in age- and height-adjusted analysis, and by 158.1 ml ($p < 0.01$) in the multivariate adjusted analysis (R² = 5.0%) (Table 3).

Subjects taking beta-blocker medications ($n = 24$) had a lower age- and height-adjusted FVC than did those who did not take these medications ($3,692.6 \pm 144.4$ [mean \pm SD] ml versus $4,050 \pm 52.3$ ml, $p < 0.03$). They also tended to have a lower FEV₁, but the difference did not reach significance ($3,125.6 \pm 133.5$ ml versus $3,316.1 \pm 48.3$ ml, $p = 0.19$). The use of other antihypertensive medications (diuretics, renin-angiotensin system inhibitors, or calcium channel blockers) was not related to measured values of lung function. In the multivariate linear regression models (for both FEV₁ and FVC), the substitution of systolic BP and use of beta-blockers for hypertension did not markedly modify the results. In these models, every 1 SD increase in PWV was associated with a 192.3-ml decrease in FEV₁ ($p < 0.001$), and 156.3 ml decrease in FVC ($p < 0.01$). In the latter model, use of beta-blockers remained negatively and significantly associated with FVC (regression coefficient: -349.7 ml, SD = 151.9 ml, $p < 0.03$, R² = 2.8%).

When FEV₁ and FVC were used as categorical variables (divided into tertiles), similar patterns of results were observed (Figure 1). Negative associations of PWV with FEV₁ and FVC were also observed within each category of cardiovascular risk factors (Table 4). Although the correlation coefficients were somewhat stronger in hypertensive subjects, the interaction terms were not statistically significant ($p > 0.35$ for all).

The FEV₁/FVC ratio was also, but to a lesser extent, negatively related to PWV. The age- and height-adjusted and multivariate-adjusted correlation coefficients were -0.16 and -0.15, respectively ($p < 0.05$ for each).

DISCUSSION

The study reported here, involving a relatively large sample of men free of coronary heart disease, demonstrated that reduced pulmonary function was strongly associated with aortic stiffness, even after adjustment for conventional cardiovascular risk factors. The magnitude of the associations and the consistency of the results observed in a number of important subgroups are noteworthy. To our knowledge, this is the first reported study of the relationship between reduced lung function and central arterial stiffness. FEV₁ and FVC, and to a lesser extent the FEV₁/FVC ratio were all related to PWV, suggesting that both pulmonary obstructive and restrictive disorders may be implicated in these associations.

The nature of these associations is largely unknown. The most plausible explanation is that alterations in respiratory and arterial function stem at least in part from the same pathologic processes. If true, this would lead to the observa-

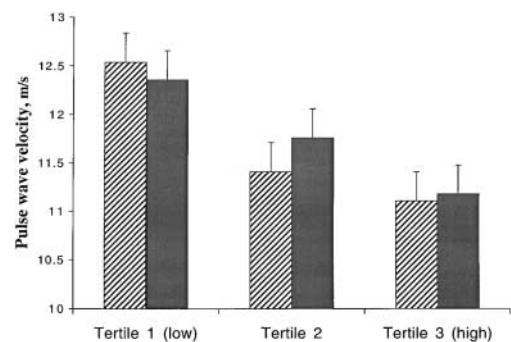


Figure 1. Mean \pm SEM of pulse wave velocity, adjusted for age, height, weight, smoking habit, hypercholesterolemia, diabetes, and hypertension by tertiles of FEV₁ and FVC. Range for tertiles: FEV₁ (ml) = 1,530 to 3,010, 3,020 to 3,640, and 3,650 to 5,190; FVC (ml) = 2,060 to 3,650, 3,660 to 4,380, and 4,390 to 6,270. ▨, FEV₁ ($p < 0.05$ for linear trend); ■, FVC ($p < 0.05$ for linear trend).

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