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ORIGINAL ARTICLE

Relationship between FEV_1 and arterial stiffness in elderly people with chronic obstructive pulmonary disease

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Abstract
Background Chronic obstructive pulmonary disease (COPD) is highly prevalent in the elderly, and both COPD and age per se are associated with cardiovascular morbidity.
Aims We tested the hypothesis that in elderly COPD patients airflow limitation is associated with arterial stiffness and the relationship, if any, is related to endothelial function and systemic inflammation.
Methods We evaluated lung function, augmentation index (AIx), flow-mediated dilation (FMD), Interleukin-6 (IL-6), and asymmetric dymethilarginine (ADMA) levels in 76 subjects (mean age 73.9 years, SD 6.2) attending a geriatric outpatient clinic.
Results Participants with COPD ($N = 41$) and controls ($N = 35$) did not differ in terms of AIx (30 vs 28.2 %, $P = 0.30$) and FMD (14.2 vs 12.3 %, $P = 0.10$). Similarly, the two groups did not differ with respect to mean concentrations of inflammation markers (IL-6 and C-reactive protein) and ADMA. Among COPD participants there was an inverse correlation between AIx and Forced Expiratory Volume in the first second ($r = -0.349$, $P = 0.02$). This relationship remained significant after correction for potential confounders, including markers of inflammation and ADMA levels ($\beta = -0.194$, $P = 0.001$).
Discussion According to the results of this study, among COPD patients, bronchial patency and AIx are inversely related, and the relationship is explained neither by endothelial function nor by systemic inflammation.
Conclusions In elderly COPD people, increased arterial stiffness is related to reduced pulmonary function and it seems worth testing as a potential marker of higher cardiovascular risk.

Keywords Aged · Arterial stiffness · Augmentation Index · Chronic obstructive pulmonary disease · Pulmonary function tests

Background

The global burden of chronic obstructive pulmonary disease (COPD) is growing parallel to the world's population ageing. It has been reported that the prevalence of the disease in GOLD stage II or higher is around 5 % among individuals aged 40–49 years, but it rises to 19–47 % for men aged 70 years and older [1]. Hence, COPD is predicted to become the third most common cause of death and the fifth cause of disability by the year 2020 [2]. Although it is primarily a respiratory disorder, systemic complications significantly contribute to its morbidity. Particularly, cardiovascular disease is 2–3 fold more common among COPD patients and it accounts for 40–50 % of hospitalizations and deaths [3]. The association between risk of cardiovascular disease and impaired pulmonary function (regardless of the presence of airway obstruction) has been reported in several studies and it is independent of the effects of smoking or other confounding risk factors [4–7].

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The mechanism underlying this relationship remains poorly understood, but it may involve changes in vascular structure and loss of large artery elasticity [8]. Increased arterial stiffness has emerged as a marker of adverse cardiovascular outcomes both in the general population and among high-risk patients [9]. In fact, the loss of large arteries compliance results in greater central aortic systolic pressures, increased left ventricular afterload with decreased diastolic perfusion of the coronary arteries and impaired cardiac performance, as well as in enhanced shear stress and risk of atherosclerosis [9, 10]. Aortic arterial stiffness can be assessed non- invasively by estimation of pulse wave velocity (PWV), a measure of regional arterial stiffness, or by analysis of pulse wave reflections, that is an indirect, more comprehensive expression of large artery elasticity [10].

Higher PWV and Augmentation Index (AIx) have been associated with increased prevalence of COPD and reduced Forced Expiratory Volume in the first second (FEV_1) both in case–control studies [11–14] and in the general population [15, 16].

Among COPD patients, chronic systemic inflammation, as expressed by high levels of interleukin-6 (IL-6) and C-reactive protein (CRP) serum concentrations [17], may contribute or even trigger the remodelling process within the arterial wall leading to degradation of elastic fibres and replacement by collagen deposition [18–20]. In addition, inflammation is associated with endothelial dysfunction, that may lead to functional stiffness of large arteries due to reduced nitric oxide availability [21]. Some observational studies showed that flow-mediated dilation (FMD), a measure of endothelial function which is mediated by nitric oxide, is impaired among COPD patients compared to control subjects [22–24]. It is unknown whether higher serum levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase [25], explain this finding. Indeed, ADMA has emerged as a novel biomarker of endothelial dysfunction and increased cardiovascular risk [26].

We hypothesized that airflow limitation would be associated with increased arterial stiffness measured by AIx and it would be related to systemic inflammation and endothelial dysfunction. We tested this hypothesis in a geriatric COPD population compared to a non-respiratory control group, because, even though COPD and its systemic complications are highly prevalent among the elderly and age per se is associated with increased arterial stiffness, the elderly are seldom enrolled in clinical studies.

Methods

Setting and sample selection

We enrolled in the study patients aged 65 years and older referred to a geriatric outpatient clinic at Campus Bio-Medico University of Rome. COPD patients had stable disease (no recent exacerbations), and were not taking long-term oxygen therapy or regular systemic steroid therapy. Comorbid diseases were ascertained examining past history and medical records. Exclusion criteria were: pulmonary fibrosis, history of lung resection, asthma or a spirometric restrictive pattern; history of ischemic heart disease, heart failure, severe valvular heart disease, cardiomyopathy, arrhythmias; uncontrolled endocrine diseases; inflammatory conditions, such as connective tissue disorders and autoimmune diseases; severe chronic kidney disease (glomerular filtration rate <30 ml/min/1.73 m^2); neoplastic diseases. The study had local Ethics Committee approval and all patients gave written informed consent.

Anthropometry and lung function tests

Anthropometric data were collected for each patient and Body Mass Index (BMI) was determined. Pulmonary function tests were performed using a water-sealed bell spirometer (Biomedin Srl, Padova, Italy). In COPD patients not chronically taking bronchodilator therapy, we assessed the bronchodilator response by administering four separate doses of 100 mcg salbutamol using a spacer; the test was then repeated after a 15-min delay [27]. When available, post-bronchodilator FEV_1 was retained for analysis. For each participant, the best of three technically acceptable maneuvers was selected. We also calculated percent predicted FEV_1 using García-Río spirometric reference equations for European adults aged 65–85 years [28]. Bronchial obstruction was defined as a FEV_1/FVC ratio below the lower limit of normal [27].

Vascular tests

Subjects were studied after an overnight fast and at least 8 h after abstinence from caffeine, tobacco, inhaled short acting beta-2 agonists and vasoactive drugs. Vascular studies were performed in the morning (between 8 and 9 am) in a quiet, temperature controlled room and after resting 10 min in a supine position.

Arterial stiffness was investigated through pulse wave analysis. After peripheral blood pressure was measured, radial artery waveforms were recorded using a

micromanometer (Millar Instruments; Houston, TX) applanation tonometry. Pulse wave analysis (Sphygmocor system; AtCore Medical, Sidney, Australia) was then performed to obtain a central aortic pressure waveform from the radial artery wave via a mathematical transfer function. Therefore, for each patient we calculated augmentation pressure (AP; the difference between the first and second systolic peaks) and augmentation index (AIx; the quotient of AP on pulse pressure expressed as a percentage). In order to avoid interindividual variability secondary to heart rate, AIx was corrected to a heart rate of 75 beats per minute. At least three independent waveforms analyses were obtained from each subjects and the most accurate measurement according to SphygmoCor quality control criteria was retained for analysis.

Under the same conditions we evaluated endothelial function by measuring the change in brachial artery diameter in response to reactive hyperaemia (flow-mediated dilation, FMD). Hyperaemia was induced by deflating a cuff placed around the forearm that had been inflated for 5 min to a 50 mmHg above systolic blood pressure. FMD was expressed as the maximum change in brachial artery diameter after 50, 60 and 70 s of reactive hyperaemia, compared with the diameter of the vessel before cuff inflation. Brachial diameter was therefore obtained as a mean of three measurements. All studies were performed with a high-resolution ultrasound machine (Aplio 80 CV, Toshiba), using a broadband 14-MHz transducer. All ultrasound scans were performed by a single experienced vascular sonographer who was unaware of the subjects' clinical background.

Laboratory analysis

Fasting blood samples were collected for determination of glucose, cholesterol, serum creatinine and C-reactive protein levels. Arterial blood gases were measured at rest. Blood was sampled at the time of baseline, centrifuged and serum stored at −80 °C for subsequent analysis. Using high-sensitivity quantitative ELISA kits (Quantikine® HS Human IL-6 Immunoassay) we measured IL-6 levels in 64 subjects (34 obstructed, 30 non-obstructed). ADMA concentrations were determined in 66 participants (34 obstructed, 32 non-obstructed) using high-performance liquid chromatography.

Analytic approach

We compared people with COPD with control subjects, defined as participants with normal spirometry, no history of respiratory symptoms and no signs of lung impairment on physical examination. Comparisons between groups were made using unpaired *t* test for continuous variables and Chi squared test for categorical data. To estimate the correlation between demographic and clinical characteristics and AIx and FMD we used the Pearson's correlation coefficient. We then used a multivariable linear regression model in order to analyse the degree of correlation between AIx and lung function taking into account potential confounders. Model selection was based on the theoretical factors able to influence both vascular compliance and lung function. We did not use a strategy based on statistical significance because in a study with a relatively small sample size it could lead to the exclusion from the adjusted analysis of potentially important confounders. All the analyses were performed on the total sample and in the two study groups separately using R for Windows (V.2.15.1).

Results

The study included 76 participants (mean age 73.9 years, SD 6.2 years), 41 COPD patients and 35 controls. The two groups had similar age, sex, BMI, lipid profile, diabetes prevalence and average serum glycaemia (Table 1), with the exception of smoke exposure, that was higher in the COPD group (average pack-years of 34.9 vs 15). There were no differences between groups with respect to concentrations of CRP (mean 2.42 mg/dL, SD 2.08 vs 2.23 mg/dL, SD 1.8 in COPD and non-COPD participants, respectively), IL6 (4.03 pg/mL, SD 4.65 vs 3.92 pg/mL, SD 4.82) and ADMA (3.19 μmol/L, SD 2.87 vs 3.18 μmol/L, SD 3.89).

Regarding vascular tests, FMD was available for 37 COPD patients and 30 controls. As it is showed in Table 2, mean systolic blood pressure and consequently pulse pressure were slightly but not significantly higher in the COPD group than in the control group (mean systolic blood pressure: 136 mmHg, SD 17 vs 131 mmHg, SD 16, mean pulse pressure 55 mmHg, SD 13 vs 51 mmHg, SD 12). We found no significant differences between groups in terms of AIx (30 %, SD 6.4 vs 28.2 %, SD 9.8) and FMD (14.2 %, SD 8 vs 12.3 %, SD 6.8) (Table 2). While in the total population there was no significant correlation between percent predicted FEV_1 and vascular parameters ($r = -0.01$, $P = 0.42$ for AIx, $r = -0.17$, $P = 0.17$ for FMD), in the subgroup of patients with COPD an inverse correlation between AIx and percent predicted FEV_1 was observed ($r = -0.349$, $P = 0.02$) (Table 3; Fig. 1). This relationship remained significant after correction for age, gender, smoking exposure, diabetes mellitus, renal function, use of cardiovascular drugs, inflammatory markers and ADMA levels ($\beta = -0.194$, $P = 0.001$) (Table 4).

Table 1 Subjects demographics, clinical and laboratory characteristics

	Total population	COPD	Non-COPD	*P* value[†]
N	76	41	35	
Age, years	73.9 (6.2)	74 (5.8)	73.8 (6.6)	0.917
Male gender, %	51	56	46	0.501
Body mass index, kg/m^2	27 (4)	26.6 (4.6)	27.6 (3.7)	0.303
Pack-years smoking	26 (32)	34.9 (37)	15 (19.8)	0.004
Diabetes (*n*, %)	6 (8)	2 (5)	4 (11)	0.529
Fasting glucose, mg/dL	100 (16)	101.1 (14.4)	98.7 (18)	0.537
Serum creatinine, mg/dL	0.86 (0.24)	0.86 (0.23)	0.85 (0.24)	0.839
GFR, mL/min/1.73 m^2	81.3 (18.8)	82.1 (20)	81.1 (18.7)	0.837
Total cholesterol, mg/dL	194 (34)	193 (32)	195 (36)	0.835
LDL-cholesterol, mg/dL	118 (25)	115 (27)	121 (22)	0.254
CRP, mg/L	2.34 (1.95)	2.42 (2.08)	2.23 (1.8)	0.700
IL-6, pg/mL	3.98 (4.68)	4.03 (4.65)	3.92 (4.82)	0.931
ADMA, μmol/L	3.19 (3.09)	3.19 (2.87)	3.18 (3.39)	0.984
Statins (*n*, %)	14 (18)	8 (20)	6 (17)	1
Ace-inhibitors (*n*, %)	43 (57)	22 (54)	21 (60)	0.746
Beta-blockers (*n*, %)	10 (13)	6 (15)	4 (11)	0.943
LABA, ICS/LABA combination (*n*, %)	28 (37)	28 (68)	0	<0.001
Anticholinergic (*n*, %)	18 (24)	18 (44)	0	<0.001

Values are expressed as mean ± SD

COPD chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume in the first second, *GFR* glomerular filtration rate (modification of diet in renal disease equation), *CRP* C-reactive protein, *IL-6* Interleukin-6, *ADMA* asymmetric dimethylarginine, *LABA* long-acting β agonist, *ICS/LABA* inhaled corticosteroid/long-acting β agonist

[†] Comparison between COPD and non-COPD group

Table 2 Subjects hemodynamic data and pulmonary function

	Total population	COPD	Non-COPD	*P* value
FEV_1, L	1.9 (0.7)	1.5 (0.5)	2.3 (0.7)	<0.001
FEV_1 pp	77.8 (23.6)	61.9 (16.6)	96.4 (15.4)	<0.001
FEV_1:FVC ratio	65.3 (13.2)	55.7 (9.7)	76.6 (5.9)	<0.001
Peripheral systolic blood pressure, mmHg	134 (16)	136 (17)	131 (16)	0.510
Peripheral diastolic blood pressure, mmHg	81 (10)	81 (11)	80 (9)	0.887
Peripheral pulse pressure, mmHg	52 (13)	55 (13)	51 (12)	0.483
Heart rate, bpm	67 (10)	68 (11)	66 (10)	0.340
Augmentation Index-75, %	29 (8.1)	30 (6.4)	28.2 (9.8)	0.302
Flow-mediated dilation, %	13.3 (7.5)	14.2 (8)	12.3 (6.8)	0.104

COPD chronic obstructive pulmonary disease, *FEV_1 pp* percent predicted forced expiratory volume in the first second, *FVC* forced vital capacity

Discussion

Our study showed that in a geriatric cohort of COPD patients, there is a significant correlation between lung function measured using FEV_1 and arterial stiffness measured using AIx. This finding was independent of age, sex, systemic inflammation, cardiovascular risk factors, cumulative lifelong smoke exposure and use of cardiovascular drugs. Zureik et al. [29] firstly described an independent relationship between reduced lung function and increased arterial stiffness measured through PWV. Some case–control studies demonstrated that COPD patients have decreased vascular compliance compared to control subjects [11–14, 16]. Our data expand this current knowledge by investigating the relationship between arterial stiffness and bronchial obstruction in a geriatric population.

While finding a significant correlation between FEV_1 and AIx among COPD patients, we did not find higher AIx values

Table 3 Correlation between demographic clinical and laboratory variables and indices of arterial stiffness of endothelial function

	AIx			FMD		
	COPD	Non-COPD	Total	COPD	Non-COPD	Total
FEV_1 pp†	−0.349*	0.258	−0.095	−0.140	−0.052	−0.168
Age†	−0.094	0.162	0.059	−0.047	0.236	0.085
Cholesterol†	0.209	0.170	0.182	0.142	0.006	0.079
Pack years†	−0.095	−0.023	−0.013	0.020	−0.400*	−0.055
CRP†	0.152	0.284	0.215	0.024	−0.038	0.006
IL-6†	−0.041	0.304	0.119	−0.176	−0.162	−0.162
ADMA†	−0.080	−0.107	−0.090	−0.025	0.056	0.006
GFR†	0.250	0.164	0.197	0.295	-0.089	0.147
Sex§	13.095**	2.222	9.388*	0.805	0.028	0.497
Diabetes mellitus§	0.476	1.862	3.114	1.183	6.827*	0.671
Statin use§	0.021	0.356	0.287	0.894	1.071	0.035
ACE-inhibitors use§	0.241	0.117	0.005	0.133	1.780	1.181
Beta-blockers use§	0.281	0.588	0.927	0.307	1.325	0.060

COPD chronic obstructive pulmonary disease, *FEV_1 pp* percent predicted forced expiratory volume in the first second, *CRP* C-reactive protein, *IL-6* Interleukin-6, *ADMA* asymmetric dimethylarginine, *GFR* glomerular filtration rate (modification of diet in renal disease equation)

† Pearson's *r*, § *F* value, * $P < 0.05$, ** $P < 0.001$

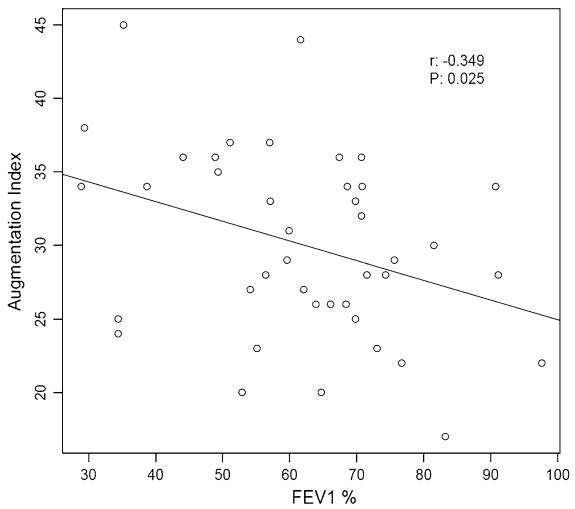

Fig. 1 Correlation between forced expiratory volume in the first second (FEV_1) and Augmentation Index in participants with FEV_1 below lower limit of normal

Table 4 Multiple regression analysis of subjects with FEV_1 below lower limit of normal with Augmentation Index as the dependent variable

	β	*P*
FEV_1pp	−0.1942	0.001
Age	0.4418	0.019
Cholesterol	−0.0164	0.668
Pack years	−0.0069	0.829
CRP	0.0796	0.831
IL-6	0.3339	0.128
ADMA	−0.4416	0.189
GFR	0.0070	0.891
Sex	−9.1532	<0.001
Diabetes mellitus	1.8905	0.573
Statin use	−8.9957	0.003
ACE-inhibitors use	−6.4412	0.004
Beta-blockers use	4.1043	0.073

FEV_1 pp percent predicted forced expiratory volume in the first second, *CRP* C-reactive protein, *IL-6* Interleukin-6, *ADMA* asymmetric dimethylarginine, *GFR* glomerular filtration rate (modification of diet in renal disease equation)

in the COPD group than in the control group. This finding seems to be in contrast with previous reports. Actually, all the published studies found a significant relationship between bronchial obstruction and increasing PWV [12–15, 30–33], but the influence of airflow limitation on AIx is still a matter of debate. Two studies [11, 12] described that COPD patients have greater AIx, but Janner et al. [16] found an independent significant association between COPD and AIx only in men younger than 60 years of age when mild COPD were excluded. More recently, Sievi and colleagues [34] found no association between FEV_1 and AIx. We performed our study in a geriatric cohort (in contrast with the abovementioned studies) but we did not measure PWV. It is worth remembering that AIx is a composite measure of arterial stiffness which increases linearly up to the age of 50 years, then reaches a plateau and minimally increases after the age of 65 years

[35]. Thus, as aging itself may decrease arterial compliance, it could be difficult to find significant differences between groups of elderly subjects who have both stiffer arteries per se and a relatively homogeneous distribution of AIx. Therefore, either the older age of our sample and the technique used to measure arterial stiffness may explain some of the findings that are at odds with previous reports.

In this study, we found no difference between COPD and controls in terms of CRP and IL-6; moreover, adding these inflammatory markers to the multiple regression analysis did not alter the relationship between FEV_1 and AIx in the subset of COPD patients. Arterial stiffness measured by PWV is positively associated with CRP in apparently healthy middle-aged adults [19] and in older adults [36]. Higher levels of inflammatory mediators were described in COPD patients compared with controls [13, 37, 38]. Moreover, chronic elevation of CRP and other systemic inflammatory markers has been reported to be a predictor of cardiovascular risk and mortality for all causes both in healthy subjects and in COPD patients [37, 39, 40]. Nevertheless, studies investigating systemic inflammation as a predictor of arterial stiffness in COPD led to constrasting results. Sabit et al. [13] found that serum IL-6 and Tumor Necrosis Factor α soluble receptor 1 and 2 were greater in COPD patients than control subjects and that AIx was significantly related to these inflammatory markers in patients, but not in control subjects. Instead, consistent with our results, two recent studies found no correlation between PWV [31] and AIx [34] and markers of inflammation in COPD patients. It is worth remembering that, while the finding of elevated inflammation markers is common, persistent systemic inflammation affects only a minority of COPD patients [41]: studying this specific subgroup of patients may help clarifying if a correlation between inflammatory markers and increased arterial stiffness exists.

Our results did not support the hypothesis that the relationship between FEV_1 and AIx could be related to endothelial function, in contrast with previously reported data that showed an impaired FMD in patients with COPD as opposed to normal subjects [22–24]. However, the above mentioned studies differ for mean age of the study population and for the method used to assess endothelial function. In addition, it should be considered that FMD is an echografic, operator-dependent procedure, which makes results from different studies difficult to compare.

Further negating the hypothesis that endothelial dysfunction is related to bronchial obstruction, in our sample COPD and non-COPD subjects did not differ with respect to ADMA levels. Increased ADMA concentrations have been associated with endothelial dysfunction and cardiovascular risk factors [26] and have been recognised as predictors of mortality in patients with established coronary artery disease [42]. No previous studies specifically investigated concentrations of ADMA in patients with COPD. However, as aging itself is associated with endothelial dysfunction [43] it is possible that in our population the effects of aging may be dominant over any effect of COPD on endothelial activity.

In the interpretation of the results, some limitations of this study should be taken into account. First, our sample was relatively small and we cannot exclude the lack of significant difference between groups is due to low statistical power. Second, as we do not have data on younger patients our results are not directly comparable with those of previous publications. Third, no endothelium-independent vasodilator (e.g. nitroglycerine) was used as a control in order to assess vasomotor function. Fourth, in our cohort we did not measure PWV, the gold standard of measurements of arterial stiffness, but we only had data on AIx, an indirect measure of vascular compliance that is dependent on heart rate and on left ventricular performance. Nevertheless, we reported AIx as a normalised index for a heart rate of 75 beats per minute and we included in the study patients without history of cardiac disease and no signs of ventricular impairment. Even though pulse wave analysis should be coupled to PWV to exhaustively assess arterial stiffness, this would not alter the relationship between AIx and FEV_1 we described, as AIx and PWV are independent and complementary measures of vascular compliance. Finally, given the cross-sectional design of the study, we cannot infer causal mechanism linking bronchial obstruction and arterial stiffness.

In conclusion, in our cohort of elderly people, we found no difference in terms of AIx between COPD subjects and age- and sex-matched controls. Among COPD patients, there was an independent relationship between lung function and arterial stiffness, which was not explained by endothelial function nor by systemic inflammation. The correlation between poor lung function and decreased vascular compliance may represent a mechanism of increased cardiovascular mortality in COPD.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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