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Age and cigarette smoking modulate the relationship between pulmonary function and arterial stiffness in heart failure patients

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Abstract

The aim of this study was to assess the relationship between arterial stiffness and pulmonary function in chronic heart failure (CHF).

Outpatients previously diagnosed as CHF were enrolled between April 2008 and March 2010, and submitted to arterial stiffness measurement and lung function assessment. Spirometry was performed by measuring forced vital capacity (FVC), the fraction of predicted FVC, forced expiratory volume in 1 second (FEV_1), the percentage of predicted FEV1 in 1 second, FEV_1 to FVC ratio, and the percentage of predicted FEV_1/FVC. Cardio-ankle vascular index (CAVI) was considered for the estimation of arterial stiffness.

The 354 patients assessed included 315 nonsmokers, and were 68.2±7.2 years' old. Unadjusted correlation analyses demonstrated CAVI was positively related to age ($r=0.3664$, $P<0.0001$), and negatively related to body mass index (BMI, $r=-0.2040$, $P=0.0001$), E/A ratio ($r=-0.1759$, $P=0.0010$), and FEV_1 ($r=-0.2987$, $P<0.0001$). Stepwise multivariate regression analyses showed age ($r^2=0.2391$, $P<0.0001$), BMI ($r^2=-0.2139$, $P<0.0001$), smoking ($r^2=0.1211$, $P=0.0130$), E/A ratio ($r^2=-0.1082$, $P=0.0386$), and FEV_1 ($r^2=-0.2550$, $P<0.0001$) were independent determinants of CAVI. In addition, there is a significant interaction between CAVI and forced expiratory volume in 1 second (FEV_1) in relation to age ($P_{int}<0.0001$) and smoking ($P_{int}=0.0001$). Meanwhile, pulmonary function was not associated with BMI or E/A ratio.

These findings demonstrated that reduced pulmonary function is associated with the increased CAVI, and had an interactive effect with age and smoking on CAVI in patients with CHF.

Abbreviations: Aix = augmentation index, BMI = body mass index, CAVI = cardio-ankle vascular index, CFPWV = carotid-femoral pulse wave velocity, CHF = chronic heart failure, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, hs-CRP = high-sensitivity C-reactive protein, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, RV = residual volume.

Keywords: arterial stiffness, chronic heart failure, pulmonary function

1. Introduction

Accumulating evidences demonstrate that arterial stiffness is significantly involved in heart failure.[1,2] Fluid dynamic of blood flow, altered activities of endothelial relaxing factors, and adipokine and neurohumoral factor dysregulation result in increased arterial stiffness in heart failure.[3] Progression of arteriosclerosis related to atherosclerosis promotes anatomical changes of the vessels, which cause increased arterial tree stiffness. Increased arterial stiffness imposes a disproportionate load on the heart, which causes forward flow reduction and untimely discontinuation of ventricular ejection. In addition, diastolic function and ventricular relaxation are directly damaged by arterial stiffness, negatively impacting heart function and complicating heart failure.[1,2] Consequently, arterial stiffness is considered a critical factor in heart failure control and prevention.

Arterial stiffness can easily be measured; cardio-ankle vascular index (CAVI), a novel parameter not dependent on blood pressure, was proposed for arterial stiffness assessment.[4,5] Its significance for lifestyle-related diseases and cardiac ailments, such as diabetes mellitus,[6] carotid arteriosclerosis,[7,8] hypertension,[9] and kidney abnormalities, is well-known, indicating CAVI is increased in arteriosclerosis.[10] CAVI is high in heart failure patients both with low and intact left ventricular ejection fraction (LVEF).[1,2,10–13] However, the factors contributing to elevated CAVI in heart failure remain unclear.

Impaired pulmonary function in chronic heart failure (CHF) is well-known. A study assessing 20 stable ambulatory individuals with cardiomyopathy-induced heart failure indicated that tidal expiratory flow limitation is common.[14] Individuals presenting stable mitral valve disease show decreased FEV1, forced vital capacity (FVC), and diffusing capacity of the lung for carbon monoxide, alongside enhanced residual volume (RV), which

Editor: Jinxian Xu.

LL carried out the studies, participated in collecting data, and drafted the manuscript. BH performed the statistical analysis and participated in its design. SG, YY, and JY helped to collect data. All authors read and approved the final manuscript.

None of the authors have a conflict of interest with regard to the data presented in this article.

This study was financially supported by grants from the National Natural Science Foundation of China (No. 81401580), Zhejiang Province Natural Science Foundation (No. LY14H150006), and the Health and Family Planning Commission of Zhejiang Province (No. 2013KYA002).

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Medicine (2017) 96:10(e6262)

Received: 12 October 2016 / Received in final form: 25 January 2017 / Accepted: 6 February 2017

http://dx.doi.org/10.1097/MD.0000000000006262

were correlated to valvular disease severity.[12] In addition, the cardiothoracic ratio is inversely correlated to total lung capacity and vital capacity.[15] Overall, patients with CHF present with restrictive lung diseases with altered diffusion ability. Recently, studies indicated that impaired pulmonary function is correlated to enhanced arterial stiffness in healthy individuals as well as other subpopulations such as children[16] and patients with hypertension,[17] diabetes, kidney ailments, and chronic obstructive pulmonary disease.[18] However, the association of pulmonary function with arterial stiffness in CHF patients remains unknown.

This study assessed association of pulmonary function and arterial stiffness assessed by CAVI, in 354 CHF patients.

2. Methods

2.1. Patients

Three hundred and fifty-four consecutive outpatients with stable CHF were enrolled at the Heart Failure Clinic of Zhejiang hospital from April 2008 to March 2010. Eligibility criteria included: diagnosis of heart failure determined in accordance with the European Society of Cardiology and the American Heart Association/the American College of Cardiology recommendations and age >18 years. Exclusion criteria were acute myocardial infarction or ischemic stroke within 3 months, dementia, severe chronic pulmonary disease, end-stage kidney disease, lung cancer and emphysema (diagnosed by computerized tomography), and other severe diseases. This study had approval from the ethics committee of Zhejiang Hospital. Each patient provided written informed consent.

2.2. Patient characteristics and biochemical measurements

Medical history and physical examination were recorded. The following clinical data and information were collected: age, sex, smoking and drinking statuses, concurrent diseases, medication use, and medical history. Habitual smoking was defined as current smoking >1 cigarette/day for over 1 year. Habitual drinking was considered for alcohol consumption >10 year and alcohol intake >5 g/day. The same doctor with experience assessed brachial blood pressure 3 consecutive times with a routine protocol, for each participant.

Venous blood samples were taken after overnight fasting for the measurement of plasma glucose concentration and for measurements of serum concentration of total cholesterol and triglycerides. Serum creatinine, high-sensitivity C-reactive protein (hs-CRP), and hemoglobin A1c were detected by standard methods.[19,20] Plasma BNP concentration was measured using the Triage Meter system (Biosite, San Diego, CA) to detect a fluorescent signal that reflects the amount of BNP in the sample. Detection limits of the Triage BNP test was from 5 to 2000 pg/mL. The interassay coefficient of variation in our study was 2.9%. All biochemical measurements were performed at the central laboratory of Zhejiang Hospital (Hangzhou, China).

2.3. Echocardiography

Left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) were assessed by M-mode echocardiography on an ultrasound system (Hewlett Packard, Andover, MA). LVEF was evaluated by the Simpson's method. LV diastolic function was determined by Doppler echocardiography. Transmitral flow velocity was obtained from the apical transducer with sample volume between the mitral leaflet tips. Then, peaks of early (E velocity) and late (A velocity) transmitral flow velocities were obtained, and their ratios (E/A) derived.

2.4. Measurement of CAVI

CAVI was assessed as reported previously.[21] Briefly, cuffs were wrapped around the 4 extremities, then a microphone detecting heart sounds was positioned on the sterna angle for phonocardiography, and electrocardiographic electrodes were placed on both wrists with the patient lying supine. Cuff pressure was maintained at 30 to 50 mmHg to ensure minimal effects on hemodynamics. Next, blood pressure was recorded. CAVI was determined as: $CAVI = a([2\rho/\Delta P] \times \ln[Ps/Pd]PWV^2) + b$. Ps and Pd are systolic and diastolic pressures, respectively; ΔP is Ps-Pd, and ρ blood density; a and b are constants. Right and left CAVI values were averaged.

2.5. Spirometry

Spirometry was carried out following the American Thoracic Society guidelines without administration of a bronchodilator on a computerized spirometer (Yaeger, MS-PET, Germany).[22,23] FEV_1 is percentage of predicted values (FEV_1%predicted) for each patient according to Crapo equations. Percentages of predicted FVC and FEV_1 were calculated. FEV_1/FVC and percentage of predicted FEV_1/FVC were also calculated.

2.6. Statistical analysis

Continuous variables were assessed by Student *t* test; categorical variables were evaluated by χ^2 or Fisher exact test. Variables with statistical significance in univariate regression ($P < 0.1$) were further assessed by multivariate linear regression, to identify independent predictive factors for CAVI. $P < 0.05$ was considered statistically significant. SAS version 9.13 (SAS Institute, Cary, NC) was employed for statistical analysis.

3. Results

3.1. Patient features

In the present study, 363 individuals presenting with diastolic heart failure were enrolled. Nine of them were excluded because of refusal to perform pulmonary function assays and without satisfactory carotid waveforms. Therefore, a total of 354 patients were included in the final analysis.

The participants were further divided according to current smoking status, and patient features are shown in Table 1. Among smokers, 33 subjects were male, whereas 135 males were identified as nonsmokers. Smokers and nonsmokers were similar in age, systolic and diastolic blood pressure, heart rate, serum creatinine, history of hypertension, diabetes mellitus, treatment drug, LAD, LVEDD, FVC, %FVC, %FEV1, and FEV to FVC ratio ($P > 0.05$). Compared with nonsmokers, smokers had higher percentage of alcohol intake, serum triglycerides, LVESD, E-A ratio, FEV_1, CVAI, and lower body mass index (BMI), total cholesterol, history of coronary heart disease, and LVEF (all $P < 0.05$). Less women had smoking habits ($P < 0.001$). The patients included 168 men and 186 women. Men and women had similar age, blood pressure, total cholesterol, E/A ratio, and atrial fibrillation ($P > 0.05$). However, men had higher BMI, hs-CRP, serum triglycerides, creatinine, LVEDD, LVESD, FVC, FEV_1,

Table 1

Characteristics of the smokers and nonsmokers patients.

	Total (n = 354)	Nonsmokers (n = 315)	Smokers (n = 39)	*P*
Sex/male, n (%)	168 (47.5)	135 (42.9)	33 (84.6)	<0.0001
Age, y	68.2 ± 7.2	68.3 ± 7.1	67.1 ± 8.2	0.1936
Body mass index, kg/m^2	25.99 ± 3.20	26.01 ± 3.31	25.81 ± 2.33	0.0102
Systolic BP, mmHg	130.7 ± 7.0	130.4 ± 7.1	132.9 ± 6.0	0.2068
Diastolic BP, mmHg	79.2 ± 7.3	79.0 ± 7.3	81.1 ± 7.4	0.8123
Heart rate, beats/min	73.5 ± 9.7	73.7 ± 9.7	72.2 ± 9.4	0.8170
Alcohol intake, n (%)	63 (17.8%)	45 (14.3%)	18 (46.2%)	<0.0001
BNP, pg/mL	138 (96 to 152)	136 (104 to 150)	144 (92 to 154)	0.2365
hs-CRP, mmol/L	2.08 ± 2.41	2.16 ± 2.21	1.99 ± 2.61	0.1450
Biochemical parameters				
Fasting glucose, mmol/L	5.81 ± 1.49	5.80 ± 1.44	5.88 ± 1.04	0.0154
Triglyceride, mmol/L	1.89 ± 1.10	1.81 ± 0.94	2.53 ± 1.86	<0.0001
Total cholesterol, mmol/L	5.21 ± 0.99	5.22 ± 1.02	5.12 ± 0.67	0.0025
Serum Creatinine (μmol/L)	74.3 ± 18.3	72.6 ± 17.7	87.6 ± 17.4	0.9207
Related disorders				
Hypertension, n (%)	255 (72.0)	230 (73.0)	25 (64.6)	0.1533
Diabetes mellitus, n (%)	81 (22.0)	75 (23.8)	6 (15.4)	0.2374
Atrial fibrillation, n (%)	30 (8.5)	28 (8.9)	2 (5.1)	0.0854
Coronary heart disease, n (%)	132 (37.3)	131 (41.6)	1 (2.6)	0.0087
Treatment drugs				
ACEI/ARB, n (%)	180 (50.8)	156 (49.6)	24 (61.6)	0.7562
Beta-blockers, n (%)	135 (38.1)	117 (37.2)	18 (46.2)	0.5953
Diuretics, n (%)	165 (46.6)	105 (62.5)	60 (32.5)	0.7106
Aspirin, n (%)	138 (39.0)	120 (38.0)	18 (46.2)	0.5490
Statin, n (%)	54 (15.3)	48 (15.2)	6 (15.4)	0.9870
Echocardiography parameters				
LAD, mm	32.9 ± 4.0	32.7 ± 6.4	34.0 ± 3.5	0.2323
LVEDD, mm	48.1 ± 4.9	47.8 ± 4.8	50.7 ± 4.9	0.7513
LVESD, mm	30.7 ± 4.9	30.4 ± 4.2	32.8 ± 6.4	<0.0001
Ejection fraction, %	55.3 ± 7.5	55.7 ± 7.2	54.5 ± 9.8	0.0054
E/A ratio	0.74 ± 0.18	0.73 ± 0.18	0.79 ± 0.11	0.0006
Pulmonary function				
FVC, L	2.68 ± 0.63	2.66 ± 0.61	2.89 ± 0.74	0.0974
Percentage of predicted FVC (%)	88.1 ± 16.4	88.8 ± 16.5	82.3 ± 14.2	0.2646
FEV_1, L	2.15 ± 0.54	2.13 ± 0.52	2.30 ± 0.65	0.0461
Percentage of predicted FEV_1 (%)	93.5 ± 19.1	94.6 ± 19.1	85.4 ± 17.3	0.4664
FEV_1/FVC ratio	80.1 ± 6.6	80.2 ± 6.6	79.4 ± 6.7	0.8494
Percentage of predicted FEV_1/FVC (%)	103.8 ± 8.7	103.9 ± 8.6	103.1 ± 9.1	0.6133
CAVI	8.57 ± 1.10	8.55 ± 1.03	8.78 ± 1.53	0.0002

Values were mean ± SD, geometric mean (95% CI), or number of subjects (percentage of the column total). ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = B-type natriuretic peptide, BP = blood pressure, CAVI = cardio ankle vascular index, E/A ratio = ratio of early transmitral flow velocity to atrial flow velocity, FEV_1 = forced expiratory volume in 1s, FVC = forced volume capacity, hs-CRP = high-sensitivity C-reactive protein, LAD = left atrial diameter, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter.

BNP, fasting glucose, percentage of predicted FVC, FEV_1, and FEV_1/FVC, CAVI, and AIx compared with women (all $P < 0.05$) (data no shown).

3.2. Associations of arterial stiffness indexes with clinical parameters

Linear regression was carried out to assess associations of CAVI indexes with various clinical parameters (Table 2). Interestingly, CAVI was positively associated with age ($r = 0.3664$, $P < 0.0001$), and negatively with BMI ($r = -0.2040$, $P = 0.0001$), E/A ratio (r = −0.1759. $p = 0.0010$), and FEV_1 ($r = -0.2987$, $p < 0.0001$).

Stepwise multivariate regression was performed for the identification of parameters independently correlated to CAVI. We found that age ($r^2 = 0.2391$, $P < 0.0001$), BMI ($r^2 = -0.2139$, $P < 0.0001$), smoking ($r^2 = 0.1211$, $p = 0.0130$), E to A ratio ($r^2 = -0.1082$, $P = 0.0386$), and FEV_1 ($r^2 = -0.2550$, $P < 0.0001$) were independent determinants of CAVI, of which FEV_1 was the most powerful predictor for CAVI ($R^2 = -0.2807$, $P < 0.0001$) after adjustment for age, smoking, alcohol intake, sex, BMI, systolic and diastolic blood pressure, LVEF, E/A ratio, and FEV_1. The analysis was repeated adjusting for medication, history of hypertension, and coronary heart disease, and results were not altered (data not shown).

3.3. Interaction between age, smoking, and FEV_1 on arterial stiffness

Next, combined effects of age, smoking, and FEV_1 on arterial stiffness were assessed. We found a significant age- and smoking-FEV_1 interaction on CAVI ($P_{int} < 0.0001$, $P_{int} = 0.0001$). In patients with $FEV_1 \leq 2.38$ L/s, CAVI was significantly greater in individuals aged >69 years than in those aged ≤69 years (9.24 ± 0.13 vs. 8.27 ± 0.14; $P = 0.0008$), whereas among patients with $FEV_1 > 2.38$ L/s, CAVI values were similar across different age subgroups ($P = 0.86$) (Fig. 1). Furthermore, when $FEV_1 \leq 2.38$ L/s, CAVI was significantly greater in smokers than nonsmokers

Table 2

Univariate and multivariate analyses for CAVI.

	Univariate		Multivariate	
	r	*P*	β	*P*
Age, y	0.3664	<0.0001	0.2391	<0.0001
Sex/male	0.0866	0.1039	—	—
BMI	−0.2040	0.0001	−0.2139	<0.0001
Smoking	0.0653	0.2200	0.1211	0.0130
LVEF	−0.0056	0.9170	—	—
E/A ratio	−0.1759	0.0010	−0.1082	0.0386
FEV_1	−0.2987	<0.0001	−0.2550	<0.0001

BMI = body mass index, CAVI = cardio-ankle vascular index, FEV_1 = forced expiratory volume in 1 second, LVEF = left ventricular ejection fraction.

(11.24 ± 0.79 vs. 8.63 ± 0.09; $P = 0.0029$), whereas at FEV_1 >2.38 L/s, similar CAVI values were obtained between smoker and nonsmoker subgroups ($P = 0.27$) (Fig. 2). In addition, neither BMI nor E/A ratio-FEV_1 interaction on CAVI was observed (data not shown).

4. Discussion

The present study demonstrated that lung function is independently correlated to changes in arterial stiffness in patients with CHF with adjustment for potential confounders. In addition, we firstly demonstrated interactions between age and pulmonary function, smoking and pulmonary function in arterial stiffness, as determined using CAVI. These results suggest that impaired pulmonary function leads to a higher cardiovascular risk in this population of patients.

The association of pulmonary functions with arterial stiffness has been studied widely over the last few years. A negative correlation was reported between FEV_1 and arterial stiffness reflected by carotid-femoral pulse wave velocity (CFPWV).[24] Meanwhile, an inverse correlation between FEV_1 and CFPWV in pediatric patients with mild-to-moderate asthma was demonstrated.[25] Patients with chronic obstructive pulmonary disease also have significantly higher CFPWV values.[24] Interestingly, decreased FEV_1 was shown to be significantly associated with enhanced arterial stiffness, as assessed by peripheral pulse pressure in the general population.[26] In Masugata et al's[27] study of 45 hypertensive outpatients, another measure of arterial stiffness, CAVI, was shown to be independently associated with FEV_1/FVC ratio. However, discrepant findings have been reported. The Seattle Nikkei Health Study did not support the previously reported association of abnormal pulmonary function with aortic PWV.[28] Different clinical characteristics of participants may account for the differences in results from various reports. This study indicated for the first time that in CHF patients, CAVI was significantly correlated to FEV_1 after adjusting for confounders, supporting the notion of an association of pulmonary function with arterial stiffness.

The mechanisms responsible for the associations of pulmonary function and arterial stiffness in CHF patients remain essentially ununderstood. It is most likely that neurohumoral factors are activated in these patients. The rennin-angiotensin-aldosterone system plays a central role in myocardial remodeling, and also contributes to vascular fibrosis, including pulmonary artery.[29] Inflammatory reactions involved in increased vascular stiffness and impaired pulmonary function may also explain our findings.

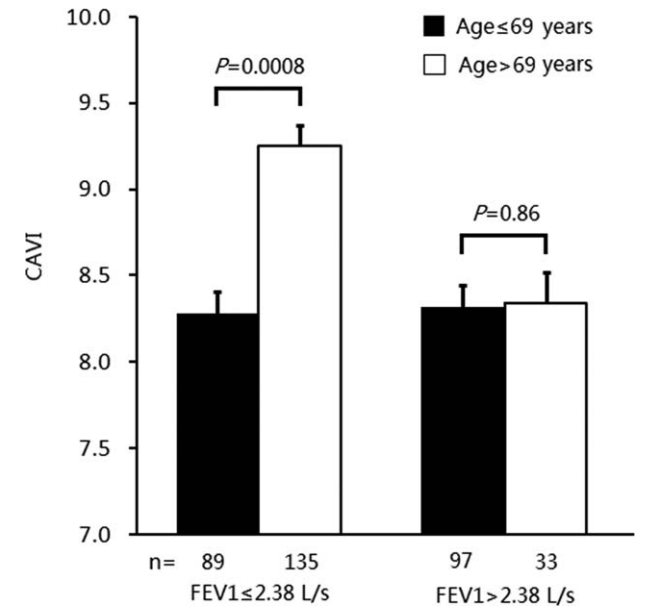

Figure 1. Interaction of age and FEV_1 on CAVI. Error bars represent the SD. CAVI = cardio ankle vascular index, FEV_1 = forced expiratory volume in 1 second, SD = standard deviation.

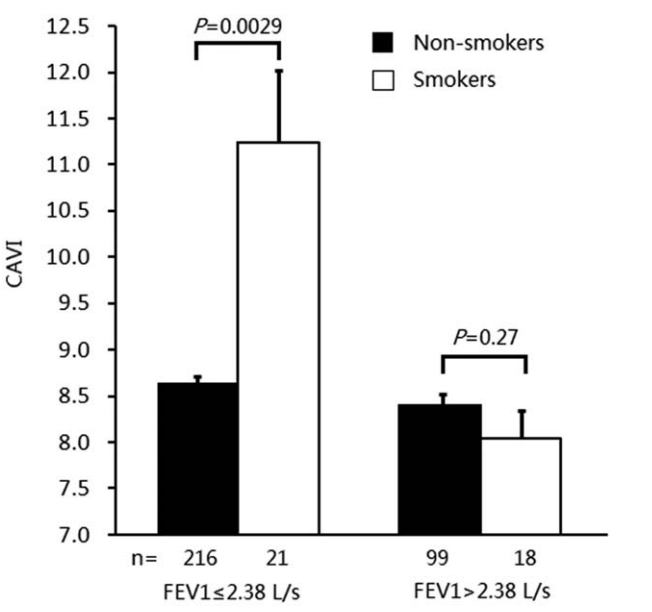

Figure 2. Interaction of cigarette smoking and FEV_1 on CAVI. Error bars represent the SD. CAVI = cardio ankle vascular index, FEV_1 = forced expiratory volume in 1 second, SD = standard deviation.

In this study, CRP concentrations were positively associated with CAVI, suggesting an interaction of abnormal inflammatory responses with arterial injury. These results were consistent with previous findings that serum CRP is associated with arterial stiffness parameters in healthy individuals[30] and in individuals with hypertension[31] or type 2 diabetes mellitus.[32] In addition, oxidative stress and endothelium dysfunction could pathogenetically contribute to a negative association of pulmonary function with arterial stiffness in CHF. The intrinsic relationship between pulmonary function and arterial stiffness in CHF patients merits further study.

The associations of arterial stiffness with age and smoking have been studied widely in the past. Aging is a potent determinant of atherosclerosis. One of the most important mechanisms behind the association of smoking and arterial stiffness is concurrently increased circulating and local catecholamine levels, which causes endothelial dysfunction.

The current study demonstrated that age and smoking modulated the association of pulmonary function with arterial stiffness in individuals suffering from heart failure. Studies assessing how age and smoking affect the relationship between arterial stiffness and pulmonary function are very limited. A nationwide study in the United States involving 13,090 adults indicated that the association of peripheral pulse pressure with FEV_1 varies with age:[26] it is positive in patients between age 20 and 39 years, and negative in patients older than 40 years; the strongest negative association was obtained for individuals older than 60 years.[26] Bolton et al[33] assessed 827 men aged 47 to 67 years, and found a weaker correlation between lung function and PWV in individuals that have never smoked compared with the remaining population. Recently, a study of school-age children born extremely preterm indicated that augmentation index (AIx) (reflecting arterial stiffness and global wave reflection) increases by 2.7% per z score reduction in FEV_1 and by 4.9% in individuals whose mothers smoked during pregnancy.[34] These data, taken together, suggested that age and smoking may interact with pulmonary function on arterial stiffness. Our study showed for the first time age– and smoking–pulmonary function interaction on arterial stiffness in patients with CHF. In FEV_1 $\leq$2.38 L/s subjects, CAVI was significantly higher in individuals aged >69 years than in those aged $\leq$69 years, and in smokers than nonsmokers; meanwhile, age or smoking alone did not alter CAVI in CHF subjects with FEV_1 $\leq$2.38 L/s.

The exact mechanisms underlying age– and smoking–-pulmonary function interactions on arterial stiffness remain to be elucidated.[35] Indeed, age, smoking, and pulmonary function in combination have synergistic detrimental effects on arterial stiffness. Our data may be interpreted by that neither stimulus exhausts vessel elasticity during damage, with possibility of subsequent deterioration in the presence of another harmful hit.[36–38] The interactive effects described above deserve further attention. Of note, many pathophysiologic mechanisms, responsible for the cross-sectional association of impaired pulmonary function and increased arterial stiffness, are caused by aging and cigarette exposure: aging and smoking cause injury to the vascular endothelium, produce superoxides, increase the production and release of endothelin, cause endothelial dysfunction, and result in proinflammatory cytokine and adipokine alterations.[29,39–42] Certainly, the mechanisms behind age- and smoking- pulmonary function interactions in arterial stiffness need further studies.

This study had several limitations. First, no distinction was made between heart failure patients with preserved and reduced left ventricular EF. Diastolic function was assessed without tissue Doppler imaging. In addition, all assessed subjects were stable, and could perform pulmonary function assays; therefore, these findings might not be applicable to individuals with severe heart failure. Some biases could be present because of the differences in clinical parameters caused by smoking. Nevertheless, these differences are intrinsic to smoking and one of the aims of the present study was to examine the effect of smoking on arterial stiffness and clinical parameters in this population of patients. In addition, the associations revealed by the multivariate analysis were relatively weak. The sample size was relatively small and the clinical manifestations of the patient covered a relatively wide range, introducing variability in the study; large sample studies are warranted to confirm these findings and control for these biases. Finally, nonsmoker and smoker groups were quite equilibrated in size, which could impact the statistical power. However, the interaction between smoking, age, and CAVI is a novel finding.

In conclusion, pulmonary function, FEV_1, was associated with arterial stiffness, and had an interactive influence with age and smoking on arterial stiffness in CHF. These results suggest that impaired pulmonary function leads to a higher cardiovascular risk in this population of patients. The underlying mechanisms deserve further assessment.

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