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Airflow obstruction was associated with elevation of brachial-ankle pulse wave velocity but not ankle-brachial index in aged patients with chronic obstructive pulmonary disease

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ABSTRACT

Objective: Both brachial-ankle pulse wave velocity (baPWV) and ankle-brachial index (ABI) are important predictors for cardiovascular disease (CVD). Patients with chronic obstructive pulmonary disease (COPD) are at high risk of CVD. But the association between airflow obstruction and baPWV or ABI was still unclear. The study was aimed to investigate the influencing factors on arterial stiffness in aged COPD patients.

Methods: 67 aged patients with COPD and 67 age- and sex-matched controls without COPD were enrolled in this study. COPD patients were grouped into four groups according to the Global Initiative for Chronic Obstructive Lung Disease Guidelines (GOLD). Both baPWV and ABI were evaluated. Spirometry indices, blood pressure, smoking history and related laboratory parameters were also collected.

Results: Comparing with controls, all COPD patients had significantly higher baPWV (1933 ± 355 cm/s versus 1515 ± 256 cm/s, $P < 0.001$) but not ABI ($P = 0.196$). And baPWV values were significantly highest at GOLD stage 4. Forced expiratory volume in 1 s (FEV_1) was the most significant factor influencing baPWV, after adjusting for age, systolic blood pressure and other traditional cardiovascular risk factors ($\beta = -0.463$, $P = 0.014$).

Conclusion: Arterial stiffness was serious in aged patients with COPD. Spirometry index FEV_1 was a possible important predictor for the severity of arterial stiffness of COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a severe public health problem. According to World Health Organization estimation, 65 million people suffer from moderate to severe COPD worldwide. In 2013, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) predicted that COPD might become the third cause of death by 2020 following cancer, cardiovascular disease (CVD) [1].

Aged people are the majority of patients with COPD and at high risk of CVD. Notably, CVD is the major comorbidity as well as the leading cause of hospitalization and death in COPD patients [2]. In addition, COPD is also supposed to be an increased risk factor of CVD [3]. Though a close association was found between COPD and CVD, the possible link between them still needed to be elucidated. Arterial thrombosis was supposed to be one of possible links but no consistent results were found on the association between thrombosis and COPD [4,5]. Similarly, arterial calcification was one type of arterial dysfunction related to higher risk of CVD, which was common in both aged and COPD patients [6,7]. However, there has been limited information about the association between COPD and arterial calcification. In addition, the association between arterial calcification and airflow obstruction remained controversial [4,5,8,9]. Besides, patients with COPD tended to suffer severe arterial stiffness, another important risk factor of CVD [2,10,11]. Studies showed that PWV was higher in COPD patients [11–15]. Moreover, as GOLD was a widely used standard to classify the severity of COPD patients, the relationship between GOLD stages

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and arterial stiffness also remained uncertain [10,12,16–18]. Though the correlation of arterial stiffness and COPD had been reported before, the possible influencing factors were not clear yet.

Therefore, we conducted a cross-sectional study to investigate the relationship between airflow obstruction and arterial dysfunction. And we also investigated the possible influencing factors on arterial stiffness in COPD patients and looked for possible strategies.

2. Methods

2.1. Study population and data collection

Between January 2013 and August 2014, a total of 148 participants from the outpatient clinic department of Sun Yat-sen Memorial Hospital of Sun Yat-sen University were recruited in this study. 8 patients who did not meet our inclusion criteria or met the exclusion criteria were excluded. And we also excluded 6 patients who refused to conduct brachial-ankle pulse wave velocity (baPWV) or ankle-brachial index (ABI) measurement. At last, 67 were patients with COPD, and 67 were age- and sex-matched controls without COPD. The study flow chart of this study was show in Figure Supplementary. Data collection included demographic data, smoking history, medical history, diagnosis and treatment of comorbidities, anthropometric measures. Inclusion criteria of participants were (1) at the age over 60 years old; (2) presenting airway obstruction as reflected by post-bronchodilator force expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <70% by spirometry and diagnosed as COPD according to the GOLD guidelines [1]. Especially, all participants meeting the following criteria were excluded: (1) serious cardiovascular disease (uncontrolled congestive heart failure, unstable angina pectoris or recent myocardial infarction); (2) uncontrolled hypertension (systolic blood pressure (SBP) $\geq$ 160 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg); (3) dyskinesia of the lower limbs; (4) history of post-exercise syncope; (5) malignancy; (6) severe renal dysfunction or hepatic diseases; (7) disability to complete lung function measurement.

COPD patients were grouped into four grades of severity of airflow obstruction based on the GOLD spirometric classification: GOLD 1, $FEV_1 \geq 80\%$ predicted; GOLD 2, $50\% \leq FEV_1 < 80\%$ predicted; GOLD 3, $30\% \leq FEV_1 < 50\%$ predicted; GOLD 4, $FEV_1 < 30\%$ predicted [1].

2.2. Collection of laboratory parameters and life quality

Laboratory parameters including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and high-sensitivity C-reactive protein (hsCRP) were measured using venous serum samples. Each COPD patient should fast overnight for at least 10 h before venipuncture. All venous serum samples were measured by a standardized and certified program using an automatic biochemical analyzer (AU5800, BECKMAN COULTER, U.S.A.) in the Sun Yat-sen Memorial Hospital. Blood oxygen saturation (SaO_2) at rest was measured before the test through a fingertip pulse oximeter (Prince-100c, HEAL FORCE, China). Patient's life quality was evaluated by the Chinese version of St-George Respiratory Questionnaire (SGRQ) [19]. The total score of the questionnaire was marked.

2.3. Spirometry

FEV_1 and FVC were measured by a spirometer (CHESTGRAPH HI-101, TOKYO, Japan) when patients were asked to exhale with their maximal effort after maximal inhalation. The normal predicted value of FEV_1, based on age, sex, height, weight and other factors, was calculated using reference equations [20]. The machine calculated and output the ratio of FEV_1 and FVC (FEV_1/FVC), as well as the ratio of FEV_1 and its predicted value which was used to grade the severity of airflow obstruction according to GOLD standard. The measurement did again after 20 min since 0.4 mg inhalational salbutamol was given to the patients. Post-bronchodilator spirometry indices were collected in this study.

2.4. Measurement of baPWV

baPWV was assessed by a non-invasive vascular screening device (VP-1000, OMRON, Japan) through the method provided by the manufacturer. Participants rested for 10 min in supine position before a well-trained examiner performed the assessment. A plethysmographic sensor connected to the cuffs, which wrapped around the brachia and ankles, to record simultaneously the pulse volume waveforms. The time interval (ΔT) between the wave fronts of the brachial and ankle waveforms was determined. The length from brachium to ankle (ΔL) was calculated based on the participant's height [21]. Then by using the formula: baPWV = $\Delta L/\Delta T$ (cm/s), baPWV was calculated for each side. The average of left and right baPWV was used for subsequent analyses. The unit of baPWV in this study was cm/s. The higher values of PWV indicated stiffer arteries [12].

2.5. Measurement of ABI

ABI was measured by a non-invasive vascular screening device (VP-1000, OMRON, Japan) according to the method reported before [22]. After a 10-min-rest, SBP was measured in the brachial artery of both arms and in the posterior tibial and dorsal pedal arteries of both legs. The ABI for each leg was defined by the ratio between the highest lower limb SBP value and the highest upper limb SBP value. Participants with ABI value between 0.9 and 1.4 detected in each side were defined as normal and those with ABI value over 1.4 in either side were defined as having high ABI, indicating suspicious arterial calcification [23]. Participants were excluded once they had one leg with low ABI while the other leg with high ABI.

2.6. Statistical analysis

Data were reported as mean values with standard deviation (SD) for continuous variables, and frequencies for categorical variables. The following data were compared between COPD patients and controls with the methods of the Student's t-test, Mann–Whitney U test and Pearson chi-square when appropriate. The group differences among GOLD stages were assessed by analysis of variance (ANOVA) or Pearson chi-square according to the data types. Multiple linear regression analysis was used to explore the factors affecting baPWV in COPD patients. All statistical analyses were performed using the software SPSS 22.0. For all statistical tests, two-tailed $P = 0.05$ was chosen to be the threshold of the statistical significance.

3. Results

3.1. Comparison of demography and arterial functions between the patients with COPD and controls

The demographic and arterial functional data of the patients with COPD and controls were shown in Table 1. COPD group tended to have significantly higher baPWV values in the comparison to controls (1933 ± 355 cm/s versus 1515 ± 256 cm/s, $P < 0.001$). Interestingly, the results showed no statistical significance between