Forced expiratory volume in one second can predict SYNTAX score in patients with chronic obstructive pulmonary disease

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Abstract

Background: The SYNTAX score is an angiographic score that predicts coronary artery disease (CAD) complexity. It has been shown to be useful for decision making about percutaneous coronary intervention or coronary artery bypass grafting among patients with CAD. Higher SYNTAX scores are indicative of more complex disease. Chronic obstructive pulmonary disease (COPD) is characterised by limitation of airflow. Measurement of forced expiratory volume in one second (FEV1) in spirometry is used for diagnosis and to determine the severity of the disease.

Aim: To evaluate the relationship between FEV1 and SYNTAX score in patients with COPD.

Methods: Seventy-eight patients with a previous diagnosis of COPD and 48 patients without COPD were enrolled. Spirometry and coronary angiography were performed in all patients. SYNTAX score was calculated and compared between the two groups. The correlation between FEV1 and SYNTAX score was analysed.

Results: SYNTAX score was higher in patients with COPD than in patients without COPD (23.22 ± 12.10 vs. 17.92 ± 11.21, respectively; p = 0.013). Multivariate analysis demonstrated that COPD was independently predictive for intermediate and high SYNTAX score (odds ratio 4.833; 95% confidence interval 2.228–10.485; p < 0.001). Mean FEV1 (% predicted) was 64.7 ± 11.4 and negatively correlated with SYNTAX score in COPD group (r = –0.266 and p = 0.018). The receiver operating characteristic analysis yielded a cutoff value of 65.5 for the FEV1 to predict SYNTAX score ≥ 23, with sensitivity and specificity being 78.6% and 70%, respectively.

Conclusions: COPD is a predictor of higher SYNTAX scores. FEV1 is associated with more severe and complex CAD.

Key words: SYNTAX score, chronic obstructive pulmonary disease, forced expiratory volume in one second

INTRODUCTION

The SYNTAX score is a visual angiographic score that represents coronary artery disease (CAD) complexity by taking into account the number of lesions and their functional and anatomic components, including location, presence of bifurcations, tortuosity, total occlusions, collaterals, thrombus, and calcification. It has been shown to be useful for decision making about optimal revascularisation strategy: percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) among patients with CAD. Higher SYNTAX scores are indicative of more complex disease and are related to a troublesome therapeutic challenge. Patients with high SYNTAX score have increased rate of major adverse cardiac or cerebrovascular events [1].

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality worldwide [2]. Its prevalence...

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in the adult population is in the 4% to 10% range [3]. It is characterised by limitation of airflow. Spirometry is used for diagnosis and determining the severity of the disease. Forced expiratory volume in one second (FEV1) is used to grade the severity of the airway obstruction.

Chronic obstructive pulmonary disease is associated with increased mortality in patients with CAD undergoing PCI or CABG [4, 5]. It has also been reported that COPD is strongly associated with the risk of incident heart failure [6]. In this study we hypothesised that the severity of COPD may be associated with the complexity of the CAD. Thus, we studied the relationship between FEV1 and SYNTAX score.

METHODS
This is a prospective clinical trial including 108 patients with COPD and 76 patients without COPD. All patients underwent coronary angiography because of having stable angina pectoris or ischaemia in non-invasive tests. History of diabetes mellitus, hypertension, dyslipidaemia, smoking status, echocardiographic, and laboratory measurements were recorded. Two patients without previous history of COPD were excluded from the non-COPD cohort based on their spirometry results: FEV1/forced vital capacity (FVC) < 70%. Because the SYNTAX score could not be calculated, 30 patients with noncritical CAD or normal coronary arteries in the COPD group and 26 patients with noncritical coronary disease or normal coronary arteries in the non-COPD group were excluded from the study after the coronary angiography was performed (Fig. 1). The other exclusion criteria were as follows: chronic lung disease other than COPD, previous coronary revascularisation, acute coronary syndrome, severe valvular heart disease, history of malignancy or inflammatory disease, and hepatic or renal insufficiency. This study protocol was approved by the Local Ethics Committee, and written informed consent was obtained from all patients.

Chronic obstructive pulmonary disease
In all patients in the COPD group a pulmonary specialist made a previous diagnosis of COPD according to clinical examination (chronic and progressive dyspnoea, chronic cough and sputum, history of risk factors) and spirometry results (FEV1/FVC < 70%), and they were receiving bronchodilator therapy. They had to be clinically stable for at least four weeks prior to entry to be enrolled. Spirometry was performed to all patients in the study according to the American Thoracic Society guidelines within three days before coronary angiography [7]. Post-bronchodilator measurement of FEV1/FVC ratio was < 70% in all COPD patients and ≥ 70% in all patients without COPD. None of the patients in the study exhibited bronchodilator reversibility (based on post-bronchodilator FEV1 improvement > 12% and > 200 mL). COPD was evaluated and excluded by a pulmonary specialist in the non-COPD cohort. FEV1 was used as the main measurement of the severity of the airflow limitation for this study. COPD grade was determined according to GOLD classification as FEV1 ≥ 80% grade 1, 80% > FEV1 ≥ 50% grade 2, 50% > FEV1 ≥ 30% grade 3, and 30% < FEV1 grade 4 [8]. There was no need for hospitalisation or therapy modification in the last three months in patients with COPD.

SYNTAX score and angiographic analysis
Baseline diagnostic angiograms of the patients were assessed independently by two experienced interventional cardiologists who were blinded to the spirometry results. SYNTAX score for each patient was calculated by scoring all coronary lesions producing ≥ 50% diameter stenosis in vessels ≥ 1.5 mm, using the SYNTAX score algorithm which was available on the SYNTAX website. In cases of disagreement regarding the SYNTAX score, an additional observer was consulted and the final decision was made by consensus. A low SYNTAX score was defined as ≤ 22, an intermediate score as 23–32, and a high score as ≥ 33 [1].

Figure 1. Study profile; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; FEV1 — forced expiratory volume in one second; FVC — forced vital capacity
Statistical analysis
Kolmogorov-Smirnov test was used to evaluate normal distribution. Continuous variables were expressed as mean ± standard deviation, and categorical variables were defined as number and percentage. Student’s t test was used to compare continuous variables. Differences in the distribution of categorical variables were assessed by $\chi^2$ analysis. Univariate analysis was performed to assess the impact of coronary risk factors and COPD on the SYNTAX score. Any variable that had a univariate test p value < 0.25 was accepted as a candidate for multivariate logistic regression analysis. The degree of association between SYNTAX scores and FEV1 was evaluated by Spearman’s rank correlation analyses. The receiver operating characteristic (ROC) was used to demonstrate FEV1 cutoff value for predicting SYNTAX score $\geq 23$. Results were considered significant when the p value was $< 0.05$. SPSS version 20 was used for the analysis.

RESULTS
Data of the 48 patients with CAD and 78 patients with both COPD and CAD were analysed. Patients characteristics are shown in Table 1. The patients in the two groups were well balanced with regard to age, gender, body mass index, any smoking history, diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein levels. As expected, patients with COPD had lower FEV1 (64.7 ± 11.4 vs. 81.6 ± 3.0, respectively; p < 0.001). The SYNTAX score was higher in patients with COPD than in those without COPD (23.22 ± 12.10 vs. 17.92 ± 11.21, respectively; p = 0.013). COPD was predictive for intermediate and high SYNTAX score in multivariate analysis (odds ratio 4.833; 95% confidence interval [CI] 2.228–10.485; p < 0.001). Left ventricular ejection fraction was similar in both groups. Patients with COPD had higher systolic pulmonary artery pressure (SPAP) and lower tricuspid annular plane systolic excursion (TAPSE) than patients without COPD (p < 0.001 and p < 0.001, respectively). White blood count and haematocrit levels were higher in patients with COPD (p < 0.001; p = 0.03). In COPD patients, the SYNTAX score was negatively correlated with FEV1 (r = –0.266; p = 0.018). There was no correlation between FEV1 and SYNTAX score in patients without COPD. Ejection fraction, SPAP, and TAPSE were also correlated with SYNTAX score in patients with COPD. FEV1 and ejection fraction were independently correlated with SYNTAX score in multivariate analysis (Table 2). The cutoff value of FEV1 to predict SYNTAX score $\geq 23$ was 65.5 identified by ROC. The area under the ROC curve with FEV1 being used to detect SYNTAX score $\geq 23$ was 0.749 (95% CI 0.639–0.858; p < 0.001).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No COPD (n = 48)</th>
<th>COPD (n = 78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>64.2 ± 8.1</td>
<td>66.6 ± 9.4</td>
<td>0.165</td>
</tr>
<tr>
<td>Gender (men)</td>
<td>38 (79.2%)</td>
<td>58 (74.4%)</td>
<td>0.807</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>26.9 ± 3.9</td>
<td>27.5 ± 4.0</td>
<td>0.426</td>
</tr>
<tr>
<td>Any smoking history</td>
<td>41 (85.4%)</td>
<td>67 (85.9%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (31.2%)</td>
<td>34 (43.6%)</td>
<td>0.170</td>
</tr>
<tr>
<td>Systolic blood pressure [mm Hg]</td>
<td>131.5 ± 15.2</td>
<td>130.8 ± 16.2</td>
<td>0.803</td>
</tr>
<tr>
<td>Diastolic blood pressure [mm Hg]</td>
<td>85.2 ± 7.5</td>
<td>85.0 ± 8.8</td>
<td>0.882</td>
</tr>
<tr>
<td>Low density lipoprotein [mg/dL]</td>
<td>117.6 ± 30.6</td>
<td>116.6 ± 29.9</td>
<td>0.854</td>
</tr>
<tr>
<td>High density lipoprotein [mg/dL]</td>
<td>40.1 ± 10.8</td>
<td>42.0 ± 11.8</td>
<td>0.356</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 s (% predicted)</td>
<td>81.6 ± 3.0</td>
<td>64.7 ± 11.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>17.92 ± 11.21</td>
<td>23.22 ± 12.10</td>
<td>0.013</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.8 ± 10.9</td>
<td>52.7 ± 10.7</td>
<td>0.170</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure [mm Hg]</td>
<td>20 ± 3.2</td>
<td>44 ± 8.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tricuspid annular plane systolic excursion</td>
<td>2.3 ± 0.23</td>
<td>1.9 ± 0.38</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Haemoglobin [g/L]</td>
<td>14.13 ± 1.35</td>
<td>14.51 ± 1.3</td>
<td>0.133</td>
</tr>
<tr>
<td>Haematocrit [%]</td>
<td>41.72 ± 3.4</td>
<td>43.25 ± 4.01</td>
<td>0.032</td>
</tr>
<tr>
<td>White blood cell [10³/µL]</td>
<td>5.7 ± 2.03</td>
<td>7.1 ± 2.16</td>
<td>0.001</td>
</tr>
<tr>
<td>$\beta$ agonist [%]</td>
<td>–</td>
<td>70 (89%)</td>
<td>–</td>
</tr>
<tr>
<td>Anticholinergic agents [%]</td>
<td>–</td>
<td>44 (56%)</td>
<td>–</td>
</tr>
<tr>
<td>Inhaled steroids [%]</td>
<td>–</td>
<td>53 (67%)</td>
<td>–</td>
</tr>
</tbody>
</table>

Continuous data are shown as mean ± standard deviation, categorical variables are shown as n (%); COPD — chronic obstructive pulmonary disease
An FEV1 value of 65.5 had a sensitivity of 78.6% and specificity of 70%. In subgroup analysis according to FEV1 in patients with COPD, there were 55 GOLD grade 2 and 23 GOLD grade 3 COPD patients. The SYNTAX score was higher in the grade 3 COPD patients than in the grade 2 COPD patients (28.5 ± 5.8 vs. 21.0 ± 12.5; p = 0.047, respectively).

DISCUSSION

In the present study we found that SYNTAX score was higher in patients with COPD than in those without COPD, and FEV1 was negatively correlated with SYNTAX score in COPD patients.

Coronary artery disease and COPD are common in the adult population. When these two diseases co-exist, diagnosis and treatment may become complicated. Many studies have demonstrated that COPD is an independent risk factor for cardiovascular disease and is associated with increased cardiovascular mortality [9]. In a recent meta-analysis drawn from 25 studies, it was reported that patients with COPD had a two- to five-fold increased cardiovascular risk compared with age- and sex-matched controls without COPD [10]. The contribution of COPD and its severity to the atherosclerotic process remains largely unknown. Only a few studies have evaluated the characteristics of coronary atherosclerotic lesions in COPD.

In a study by Liang et al. [11] it was found that patients with COPD were more likely to have multi-vessel disease than patients without COPD. Topsakal et al. [12] demonstrated that COPD was an independent predictor of higher Gensini and Extent scores, and that patients with COPD had atherosclerotic lesions with worse morphologic properties. It has been reported that patients with COPD undergoing PCI had a significantly higher incidence of cardiac mortality and myocardial infarction than patients without COPD [4]. It was also reported that the severity of COPD was associated with increased mortality after PCI [4]. In the current study, we found that higher SYNTAX scores were related to the presence and the severity of COPD. Having more complex coronary lesions in COPD may play a role in the increased mortality and adverse events after PCI.

Forced vital capacity is used to classify COPD patients into stages: the lower the FEV1, the more severe the disease. There are many studies that investigate the relationship between severity of COPD and cardiovascular diseases. It was demonstrated that FEV1 was associated with early mortality following CABG [5]. In a large population-based study over an average follow-up of 14.9 years, low FEV1 was found to be associated with incident heart failure [6]. In a study by Schroeder et al. [13], carotid intima–media thickness (cIMT) and ankle-brachial index (ABI) were used to evaluate subclinical atherosclerosis, and a significant relationship was found between FEV1 and both cIMT and ABI [13]. It has been reported that epicardial adipose tissue (EAT) volume is a predictor of future incident coronary heart disease [14]. Zagaceta et al. [15] observed an association between EAT volume and FEV1. We found a negative correlation between SYNTAX score and FEV1. This association may contribute to the increased cardiovascular risk in COPD patients. Patients with low FEV1 and unknown CAD may need aggressive risk factor modification, and with known CAD may need aggressive secondary prevention. Spirometry is a simple, non-invasive tool, and it can provide information to predict lesion complexity and may facilitate deciding treatment strategy (invasive vs. conservative) or

Table 2. Univariate and multivariate regression analysis between SYNTAX score and variables

<table>
<thead>
<tr>
<th>SYNTAX</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure</td>
<td>0.206</td>
<td>0.021</td>
</tr>
<tr>
<td>Tricuspid annular plane systolic excursion</td>
<td>-0.259</td>
<td>0.003</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 s</td>
<td>-0.248</td>
<td>0.005</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.335</td>
<td>0.007</td>
</tr>
</tbody>
</table>
selecting optimal revascularisation modality in patients with both COPD and CAD.

Coronary artery disease and COPD share common risk factors such as age, sedentary lifestyle, and smoking. But the exact mechanism explaining the relation between COPD and atherosclerosis is not fully understood. Several mechanisms have been suggested to link COPD and atherosclerosis. It was suggested that some shared genetics may play a role in airway obstruction and cardiovascular risk. Sabater-Lieal et al. [16] reported that single nucleotide polymorphisms associated with lung function are related with cIMT and susceptibility to CAD. Atherosclerosis is accepted as an inflammatory disease, and COPD shows the characteristics of chronic low-grade systemic inflammation [17, 18]. In our study, we found that patients with both COPD and CAD had higher white blood counts than patients with only CAD. Many studies have established that systemic inflammatory markers are elevated in patients with COPD [19, 20]. Inflammation not only initiates atheroma but also contributes to progression of lesions and thrombus formation [17]. Ongoing and/or potential exaggerated inflammation in COPD may be the possible cause for the progression of atherosclerosis and complex lesions. Multiple factors take part in the pathogenesis of atherosclerosis. In addition to inflammation, endothelial dysfunction, oxidative stress, and oxidised LDL are responsible for atheroma formation [17, 21]. Overproduction of reactive oxygen species and impaired antioxidant capacity were found to be associated with COPD [22]. Also, oxidised LDL was found to be higher in patients with COPD compared with healthy controls [23]. Oxidative stress and inflammation can lead to endothelial dysfunction. Impaired endothelial function assessed by flow mediated dilatation was observed in COPD [24]. COPD may negatively alter atherosclerotic process through these mechanisms.

Pulmonary hypertension is associated with reduced survival in COPD. Worsening airflow obstruction is associated with increasing mean pulmonary artery pressure [25]. Hypoxia, oxidative stress, endothelial dysfunction, and inflammation take part in both COPD and CAD and may affect pulmonary and coronary vasculature simultaneously.

In the present study, SYNTAX score was correlated with SPAP as well as FEV1 in univariate analysis in COPD patients.

Limitations of the study
Our study has some limitations. First, this is a cross-sectional study, and therefore the associations can be interpreted as either a cause or a consequence. Longitudinal studies should confirm the relationship between severity of COPD and progression and complexity of CAD. Second, the small sample size of the present study generates the need to validate the results in a larger patient cohort. Third, because the patient characteristics are limited by the randomisation criteria, our results may not apply to COPD patients in general. Fourth, white blood cell count was used as a marker of inflammation, but studying C-reactive protein would strengthen the role of inflammation in pathogenesis and the prognosis of both diseases. Lower limit of normal (LLN) for FEV1/FVC rather than fixed ratio of FEV1/FVC can be used as a cutoff for diagnosis and exclusion of COPD to prevent overdiagnosis in the elderly and underdiagnosis in young adults. Because lower limit of normal values have not been validated for our country we could not use these data. Nevertheless, this is the first study investing the impact of COPD severity on the complexity of CAD. Although multiple mechanisms may play a role in the association between COPD and CAD, our findings may open new perspectives in understanding increased mortality of the two common complex diseases and managing these two diseases in daily practice.

CONCLUSIONS
To the best of our knowledge, this study is the first to evaluate the relationship between FEV1 and SYNTAX score. We observe that COPD is a risk factor for complex CAD, and FEV1 is negatively correlated with SYNTAX score. This association may contribute to the increased cardiovascular mortality in patients with COPD. Therapeutic strategies that adequately manage COPD may slow down atherosclerosis and prevent formation of complex lesions in COPD patients.

Conflict of interest: none declared

References


Natężona pierwszosekundowa objętość wydechowa jako czynnik predykcyjny wyniku w skali SYNTAX u pacjentów z przewlekłą obturacyjną chorobą płuc

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Streszczenie

Wstęp: Skala SYNTAX opiera się na wynikach badania angiograficznego i służy do oceny złożoności choroby wieńcowej (CAD). Jest ona pomocna w podejmowaniu decyzji dotyczącej tego, która metoda leczenia jest bardziej odpowiednia u danego pacjenta z CAD — przekształcona interwencja wieńcowa czy pomostowanie aortalno-wieńcowe. Wyższa punktacja w skali SYNTAX oznacza bardziej zaawansowane zmiany w naczyniach wieńcowych. Przewlekła obturacyjna choroba płuc (COPD) powoduje ograniczenie przepływu powietrza w drogach oddechowych. Pomiar natężonej pierwszosekundowej objętości wydechowej (FEV1) w ramach badania spirometrycznego stosuje się w celu ustalenia rozpoznania i określenia zaawansowania choroby.

Cel: Badanie przeprowadzono w celu oceny zależności między FEV1 a wynikiem w skali SYNTAX u pacjentów z COPD.

Metody: Do badania włączone 78 pacjentów z rozpoznaną wcześniej COPD i 48 osób niechorujących na COPD. U wszystkich uczestników badania wykonano spirometrię i koronarografię. Ustalono punktację w skali SYNTAX i porównano wyniki między grupami. Analizowano korelację między wartościami FEV1 i wynikiem w skali SYNTAX.

Wyniki: Punktacja w skali SYNTAX była wyższa u pacjentów z COPD niż u osób niechorujących na COPD (odpowiednio 23,22 ± 12,10 vs. 17,92 ± 11,21; p = 0,013). W analizie wieloczynnikowej wykazano, że COPD była niezależnym czynnikiem predykcyjnym pośredniej i wysokiej liczby punktów w skali SYNTAX (iloraz szans 4,833; 95% przedział ufności 2,228–10,485; p < 0,001). Średnia FEV1 (% wartości należnej) wynosiła 64,7 ± 11,4 i była ujemnie skorelowana z punktacją w skali SYNTAX w grupie pacjentów z COPD (r = –0,266; p = 0,018). Na podstawie analizy krzywych ROC ustalono wartość progową FEV1 wynoszącą 65,5, która pozwala prognozować wynik w skali SYNTAX wynoszący ≥ 23 z czułością 78,6% i swoistością 70%.

Wnioski: Przewlekła obturacyjna choroba płuc jest czynnikiem predykcyjnym wysokiej punktacji w skali SYNTAX. Niski wskaźnik FEV1 wiąże się z cięższą i bardziej złożoną postacią CAD.

Słowa kluczowe: skala SYNTAX, przewlekła obturacyjna choroba płuc, natężona pierwszosekundowa objętość wydechowa

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