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Original Article

Relationship between coronary artery disease and pulmonary arterial pressure in patients with chronic obstructive pulmonary disease

Muntecep Asker[1], Selvi Asker[2], Ugur Kucuk[3], Hilal Olgun Kucuk[1], Bulent Ozbay[4]

Departments of [1]Cardiology, [2]Chest Disease, Van Training and Research Hospital, Van, Turkey; [3]Department of Cardiology, Van Military Hospital, Van, Turkey; [4]Department of Chest Disease, Sıtkı Kocman University, Faculty of Medicine, Mugla, Turkey

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Abstract: The aim of the present study was to determine whether there is a relationship between coronary artery disease and pulmonary hypertension and whether pulmonary hypertension is an additional risk factor for the presence and extent of coronary artery disease in patients with chronic obstructive pulmonary disease. Patients diagnosed with chronic obstructive pulmonary disease and pulmonary hypertension, and undergone diagnostic coronary angiography for evaluation of suspected coronary artery disease constituted the study group. Patients were divided into two groups according to the presence or absence of coronary artery disease and compared for age, gender, accompanying chronic disease, and pulmonary function tests. A total of 95 patients were recruited in the study. Comparison of the groups revealed that two groups were significantly different on gender (p=0.029), presence of hypertension (p=0.027), and biomass (p=0.040). Correlation analysis of variables revealed that male gender (rs=0.224, p=0.029), hypertension (rs=0.227, p=0.07) were positively correlated with the presence of coronary artery disease. FEV_1/FVC ratio (rs=-0.253, p=0.013) and sPAP (rs=-0.215, p=0.037) were negatively correlated with the presence of coronary artery disease. High prevalence of coronary artery disease in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease was found. However, no correlation between the presence and severity of coronary artery disease and pulmonary hypertension was detected.

Keywords: Coronary artery disease, hypertension, pulmonary, pulmonary disease, chronic obstructive

Introduction

Many studies have shown that comorbidity with regard to chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) exists at different rates; and that especially, they share a common risk factor, namely, cigarette smoking [1]. COPD and CAD comorbidity affects quality of life and increases mortality [2]. The incidence and prevalence of CAD are increasing in the developing world [3]. This is caused by the rapid socioeconomic growth in developing countries, increasing exposure to risk factors for CAD, such as diabetes, hypercholesterolemia, hypertension and smoking. In the developed world, COPD affects more than 1 in 20 of the adult population; and over the next few years, COPD is projected to be the third leading cause of death [3].

The presence of pulmonary hypertension (PH) in COPD is well recognized as an independent prognostic indicator [4]. In addition to increased mortality, PH in COPD is associated with increased hospitalization rates and decreased exercise capacity [5, 6]. Mechanisms for the development of pulmonary hypertension in COPD include both lung parenchymal and vascular pathologies [7].

In the present study, we aimed to determine whether there is a relationship between CAD and PH and whether PH is an additional risk factor for the presence and extent of CAD in patients with COPD.

Material and methods

Study population

This study was approved by the local Institutional Review Board (2013-3). Written informed consent was obtained from all subjects. Patients diagnosed with COPD and PH, and undergone

Table 1. Demographic and clinical characteristics of the study group

Age (years ± SD)	63.6±8.85
Gender; male, female (n, %)	52 (54.7%), 43 (45.3%)
Hypertension (n, %)	34 (35.8%)
Diabetes mellitus (n, %)	22 (23.2%)
Smoking (n, %, pack years ± SD)	59 (62.1%), 43±20.6
Biomass (n, %)	68 (71.6%)
Coronary artery disease (n, %)	68 (71.6%)
FEV_1 (mean ± SD)	46.4±18.2
FVC (mean ± SD)	42.6±16.9
FEV_1/FVC (mean ± SD)	75±4.71
sPAP (mmHg) (mean ± SD)	59.9±11.7
dPAP (mmHg) (mean ± SD)	25.1±6.39
mPAP (mmHg) (mean ± SD)	35.9±8.53

FEV_1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; mPAP=Mean pulmonary artery pressure; sPAP=Systolic pulmonary artery pressure; dPAP=Diastolic pulmonary artery pressure.

diagnostic coronary angiography for evaluation of suspected coronary artery disease from May 2009 to September 2012 constituted the study group.

Patients with chronic kidney disorder; severe liver disease, malignity, moderate to severe valvular heart disease, an ejection fraction < 50% and those acute COPD exacerbation were excluded from the study.

Presence of > 20% stenosis in coronary circulation was defined as CAD and its severity was evaluated via Gensini score. Right heart catheterization was performed in all patients and those with a mean pulmonary artery pressure > 25 mmHg were recruited in the study. PH was diagnosed with Doppler transthoracic echocardiography using an estimated pulmonary artery pressure greater than 40 mmHg. Mean pulmonary artery pressure (mPAP), systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP) were recorded. Forced expiratory volume in 1 second (FEV_1); forced vital capacity (FVC) and FEV_1/FVC ratio were measured with MIR Spirolab spirometer (Via Del Maggiolino, Rome, Italy), in accordance with the American Thoracic Society recommendations [8]. The best value of three recordings was used. Diabetes mellitus patient was defined as someone who was clinically diagnosed with diabetes or was taking diabetic medications. Hypertension was defined as resting systolic or diastolic blood pressure > 140 mmHg or > 90 mmHg, respectively, at two different clinic visits or the prescription of antihypertensive medication. COPD disease severity was classified according to The Global Initiative for Obstructive Lung Disease (GOLD) guidelines [9]. GOLD stages were defined as follows:

Stage I (mild): FEV_1/forced vital capacity (FVC) < 70% and $FEV_1 \geq 80\%$ predicted. With or without chronic symptoms (cough, sputum production).

Stage II (moderate): FEV_1/FVC < 70% and FEV_1 < 80% predicted and ≥ 50% predicted. With or without chronic symptoms (cough, sputum production).

Stage III (severe): FEV_1/FVC < 70% and FEV_1 < 50% predicted and ≥ 30% predicted. With or without chronic symptoms (cough, sputum production).

Stage IV (very severe): FEV_1/FVC < 70% and FEV_1 < 30% predicted or FEV_1 < 50% predicted plus chronic respiratory failure (PaO_2 < 8.0 kPa with or without $PaCO_2$ > 6.7 kPa while breathing air at sea level).

Statistical analyses

Data were analyzed using the Statistical Package for Social Sciences 17.0 for Windows (SPSS Inc., Chicago, IL). Parametric tests were applied to data of normal distribution and nonparametric tests were applied to data of questionably normal distribution. Comparisons between the groups were carried out using Student's *t*-test and the chi-square test. The correlations between variables were evaluated with the Spearman correlation test. The strength of association between PAP and severity of CAD were measured in terms of an odds ratio in the 95% confidence interval by using multivariate logistic regression analysis. Data are expressed as mean ± SD. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

A total of 95 patients (52 male; 43 female; mean age 63±8 years) were recruited in the study. Demographic and clinical characteristics of the study group are summarized in **Table 1**. Patients have a mild to moderate COPD with a mean FEV_1/FVC of 75±4.71. mPAB was 35.9±

Table 2. Comparison of demographic and clinical characteristics between two study groups

	CAD (-)	CAD (+)	*P* Value
Age (years ± SD)	61.9±9.76	64.3±8.43	0.150
Gender; male, female (n, %)	10 (37%), 17 (63%)	42 (61.8%), 26 (38.2%)	0.029
Hypertension (n, %)	5 (18.5%)	29 (42.6%)	0.027
Diabetes mellitus (n, %)	6 (22.2%)	16 (23.5%)	0.892
Smoking (n, %, pack years ± SD)	15 (55.5%), 38.3±19.7	44 (64%), 45.6±20.7	0.801
Biomass exposure (n, %)	16 (59.3%)	19 (27.9%)	0.040
Gensini score (median ± SD)	N/A	33.6±23.6	N/A
FEV_1	43.2±18.9	47.7±17.9	0.567
FVC	39.5±16.3	43.9±17.1	0.786
FEV_1/FVC	76±16.3	74.6±5.42	0.227
sPAP (mmHg)	62.9±12.1	58.7±11.4	0.701
dPAP (mmHg)	26±6.73	24.7±6.25	0.684
mPAP (mmHg)	37.3±8.21	35.3±8.64	0.841

CAD=Coronary artery disease; FEV_1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; mPAP=Mean pulmonary artery pressure; sPAP=Systolic pulmonary artery pressure; dPAP=Diastolic pulmonary artery pressure.

Table 3. Correlation analysis of variables correlated with the presence of coronary artery disease

	r	*P* Value
Age (years)	0.113	0.276
Gender	0.224	0.029
Hypertension (mmHg)	0.227	0.027
Diabetes mellitus	0.014	0.893
Smoking	0.146	0.270
Biomass exposure	-0.293	0.040
FEV_1	0.063	0.547
FVC	0.078	0.450
FEV_1/FVC	-0.253	0.013
sPAP (mmHg)	-0.215	0.037
dPAP (mmHg)	-0.148	0.155
mPAP (mmHg)	-0.145	0.163

FEV_1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; mPAP=Mean pulmonary artery pressure; sPAP=Systolic pulmonary artery pressure; dPAP=Diastolic pulmonary artery pressu.

8.53 mmHg. A total of 68% of the participants had CAD. Median Gensini Score was 14.

Comparison of variables between groups were shown in **Table 2**. Comparison of the groups revealed that two groups were significantly different on gender (p=0.029), presence of hypertension (p=0.027), and biomass (p=0.040).

The results of correlations between CAD and continuous variables are shown in **Table 3**. Correlation analysis of variables revealed that male gender (rs=0.224, p=0.029), hypertension (rs=0.227, p=0.07) were positively correlated with the presence of CAD. FEV_1/FVC ratio (rs=-0.253, p=0.013) and sPAP (rs=-0.215, p=0.037) were negatively correlated with the presence of CAD.

Discussion

Both COPD and CAD are highly prevalent worldwide, and rates are sure to increase with the ageing of the population. It is believed that, by 2030, COPD will be the direct underlying cause of 7.8% of all deaths and 27% of deaths related to smoking- only surpassed by 33% for cancer and 29% for cardiovascular disease [10]. The impact of COPD and CAD on health is therefore huge, and, given the relative frequency of the two diseases and their common causal factors, most notably smoking, the possibility that they are associated in the same patient is very high. COPD is a major cause of morbidity and mortality worldwide, with an increasing prevalence in recent years [11]. One well-known complication of COPD is PH. The pulmonary vasculature of patients with COPD associated PH is markedly abnormal and shows increased intimal and medial thickening that cause luminal narrowing and vascular obstruction of the small pulmonary arteries [11]. These vascular changes lead to an increase in pulmonary vascular resistance and elevation of pulmonary artery pressures. In most cases, PH associated with COPD develops slowly over time and the pressure increases approximately 0.4 mmHg yearly [12].

Moderately severe COPD is associated with PH in 10%-35% of patients [13].

Chaouat *et al*. showed the role for interleukin-6 (IL-6), a systemic inflammatory marker, in the development of PH in patients with COPD [14]. IL-6 was also found to be associated with the presence and severity of thoracic aortic calcification [15]. In another study, the severity of aortic calcification was shown to be significantly correlated to decrease in the cross-sectional area of small pulmonary vessels as a result of loss of vasodilation ability due to endothelial dysfunction [16]. However, in the present study, mPAP values of patients with and without CAD was similar, possibly pointing out the co-operating different pathophysiological mechanisms including hypoxic vasoconstriction, mechanical stress of hyperinflated lungs and capillary loss.

In PH, lungs are a source of vasoconstrictor mediators as well as a target. One of the characteristics of PH is an imbalance in tissue and circulating levels of these vasoactive mediators as a result of endothelial dysfunction [17]. Mediators important in pulmonary artery vasodilation, including nitric oxide synthase and prostacyclin synthase, are deficient in the COPD pulmonary vascular bed [18, 19]. Endothelin-1, a potent pulmonary artery vasoconstrictor, occurs in higher concentrations in the tissue and serum of patients with COPD compared with normal subjects [20]. Vascular endothelial growth factor is increased in COPD lung tissue, and its level correlates with the degree of intimal thickening [21]. These mediators are also implicated in CAD pathophysiology; yet PH can worsen coexisting atherosclerotic process. Data evaluating patients with COPD who have undergone right heart catheterization have consistently shown an inverse relationship between pulmonary artery pressure and survival [4]. Advanced atherosclerosis can be the cause of increased mortality in this group but our study did not define a correlation between PH and the presence and severity of CAD. Although prevalence of CAD in study population is high (68%), despite relatively low presence of atherosclerosis risk factors, Gensini score of the participants were low designating less severe disease. Worsening hemodynamics is possibly the major cause of increased cardiovascular events rather than atherosclerosis.

In conclusion, we found a high prevalence of CAD in patients with PH secondary to COPD. However, despite similar operating pathophysiological mechanisms and resultant inflammatory cascade, no correlation between the presence and severity of CAD and PH was detected.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Muntecep Asker, Department of Cardiology, Van Yuzuncu Yil University Medical Faculty, Van 65100, Turkey. Tel: +9050-52514705; Fax: +904322121954; E-mail: muntecepasker@gmail.com

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