NON INVASIVE DIAGNOSIS AND ASSESSMENT OF THE SEVERITY OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background

Pulmonary hypertension (PH) is a common complication of advanced chronic obstructive pulmonary disease (COPD) and is defined by a mean pulmonary artery pressure (PAP) ≥ 25 mm Hg. Pulmonary vascular remodeling in COPD is the main cause of increase in pulmonary artery pressure and is thought to result from the combined effects of hypoxia, inflammation and loss of capillaries in severe emphysema. There is a paucity of worldwide data on prevalence and incidence of PH in COPD. There are also wide variations in the reported prevalence rates in the few studies that have been carried out. This is largely due to the definition of PH and the method of measurement of PAPs. The diagnosis of PH relies on Doppler echocardiography, and right heart catheterization is needed in a minority of patients.

Objectives

The aim of the study was to determine the prevalence of pulmonary hypertension by echocardiography according to the severity of COPD using GOLD guidelines.

Patients and Methods

This cross-sectional study involved 60 patients with COPD. The entire subjects met certain inclusion and exclusion criteria to exclude other possible contributing factors of pulmonary hypertension. All subjects completed a questionnaire, after clinical examination and investigations, the diagnosis of COPD made by a Specialist Physicians in the hospital and Echocardiography was performed by a cardiologist.

Results

The mean age of included patients was 67.1±11.2 years; males were more than females with male to female ratio as 2.75:1, among study sample (48.4%). COPD patients were current smokers, with mean of 54±29 packs/year, mean Spo2 of COPD patients was 89.7±6 %. The Gold staging of COPD patients was distributed as followings; stage I (25%), stage II (33.3%), stage III (21.7%) and stage IV (20%). Pulmonary hypertension (PH) as diagnosed by echocardiography was present among 66.7% of COPD patients. Prevalence of pulmonary hypertension among COPD patients in our study was 66.7%. Pulmonary hypertension severity was distributed as followings; mild (37.5%), moderate (32.5%) and severe (30%). Right ventricular hypertrophy was present among 31.7% of COPD patients.

Conclusion

High incidence of pulmonary hypertension among patients with chronic obstructive pulmonary Diseases. Pulmonary hypertension severity is related with the severity of chronic obstructive pulmonary diseases and Echocardiography is useful and effective tool for detection of pulmonary hypertension secondary to chronic obstructive pulmonary disease.

Keywords: *Chronic Obstructive Pulmonary Disease, Pulmonary Hypertension, Echocardiography.*

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INTRODUCTION

Chronic obstructive pulmonary disease is (COPD) defined as a disease state characterized by airflow limitation which is not fully reversible [1]. COPD is a major and growing cause of morbidity and mortality worldwide with an increasing prevalence during the past decades [2, 3]. Pulmonary hypertension is defined as a mean pulmonary pressure greater than 25 mmHg at rest or 30 mmHg with exercise as measured by right heart catheterization [4, 5]. COPD is the most common cause of secondary pulmonary hypertension (PH) related to lung diseases [6, 7]. PH secondary to COPD is associated with a worse prognosis of the disease, a low quality of life, as well as with a higher exacerbations frequency, and consequently with an increase in the healthcare cost of COPD patients [8-10]. There is a paucity of worldwide data on prevalence and incidence of PH in COPD, there are also wide variations in the reported prevalence rates in the few studies that have been carried out [11, 12]. The most important mechanisms leading to PH are hypoxic vasoconstriction, pulmonary hyperinflation and endothelial dysfunction [13, 14].

PH should be suspected in COPD patients in the presence of severe dyspnea, decline in lung function, or of severe hypoxemia [15]. A variety of factors may contribute to the development and maintenance of pulmonary hypertension in COPD. The most significant of which are the remodeling of pulmonary vessels and hypoxic pulmonary vasoconstriction [16, 17]. Understanding of the etiopathogenic mechanisms responsible for pulmonary vascular abnormalities in COPD remain incomplete, however, they have been extensively investigated in recent years [18]. Cardiac catheterization is the "gold standard" for the measurement of pulmonary arterial pressures. However, there are significant risks and cost issues associated with the procedure and, in any case, due to the high prevalence of COPD. It would not be feasible to perform cardiac catheterization on every patient with moderate to severe disease [19,20], so echocardiography study is the first method for PH screening in patients with COPD and it should be widely used. It provides a rapid, noninvasive, portable and accurate method to evaluate the right ventricle function, right ventricular filling pressure and tricuspid regurgitation [21,22].

PATIENTS AND METHODS

This cross-sectional study was conducted at the Shar and Shahid Dr. Hemn teaching Hospitals and medical outpatient departments in Sulaimani Governorate, from January 2016 – January 2017. The study included sixty patients with chronic obstructive pulmonary diseases, with mean age of 67.1±11.2 years; 35% of them were in age group 70-79 years. Males to female ratio (2.75:1), patients diagnosed as COPD who's clinically stable were included in the study. However, Patients with the following conditions were excluded: respiratory co-morbidities like restrictive lung disease, and asthma, left heart diseases (systolic LV failure, diastolic LV failure, aortic valve stenosis or regurgitation, mitral valve stenosis or regurgitation), congenital heart disease, patients with poor echo window and patients who were unable to perform spirometry.

Data were collected via full medical history and complete clinical examination, and all patients were subjected to verbal agreement and the data were recorded in a pre-constructed data sheet which included information about: age, gender and occupation, Smoking history, clinical co-morbidities (Diabetes Mellitus and Hyper tension), Oxygen Saturation (SPO_2) level, Gold staging, Electrocardiography (ECG) and Echocardiographic findings.

After clinical examination and investigations, the diagnosis of COPD made by a Specialist Physicians in the hospital and Echocardiography was performed by a cardiologist. Echocardiography device was Philips X50 Cx cart, GE vivdEq, ECG done by 12 lead electrocardiography.

All patients were investigated by spirometry they were diagnosed and classified according to GOLD guidelines (FEV_1 /forced vital capacity (FVC) ratio < 70% predicted), mild ($FEV_1 \geq 80\%$ of predicted), moderate ($50\% \leq FEV_1 < 80\%$ predicted), severe ($30\% \leq FEV_1 < 50\%$ predicted), and very severe ($FEV_1 <$ 30% predicted), respectively [23].

Resting two-dimension transthoracic Doppler echocardiography were performed for all the patients. Pulmonary hypertension (PH) is defined in this study as systolic pulmonary artery pressure (sPAP) ≥ 30 mmHg [23]. This value was chosen according to the definition of pulmonary hypertension. PH is classified into mild, moderate, and severe category as (sPAP) 30–50, 50–70 and >70 mmHg respectively (using Chemla formula, mean pulmonary arterial pressure (MPAP) =0.61 sPAP + 2 mmHg and putting value of 25–35, 35–45, and>45 mmHg of MPAP for mild, moderate, and severe pulmonary hypertension, respectively [24]. Tricuspid regurgitation was identified by color flow

Doppler technique and the maximum jet velocity was measured by continuous wave Doppler without the use of intravenous contrast, right ventricle dimension was measured by M-Mode echo and right ventricular dilation or corpulmonale was said to be present when it exceeded the normal range of 0.9-2.6 cm [24].

All patients gave their informed consent; the study has been approved by Ethical Committee of College of Medicine.

RESULTS

This study includes 60 patients with COPD, with mean age of 67.1±11.2 years; 35% of them were in age group 70-79 years. Males were more than females with male to female ratio as 2.75:1, Table 1.

The distribution of mean smoking history among COPD patients was 54±29 packs/year; 56.4% of them had <50 packs/year. Mean duration of smoking was 37.7±13.5 years; 78.2% of them had duration of ≥30 years. All these findings were shown in Table 2.

Mean Spo2 of COPD patients was 89.7±6 %. The Gold staging of COPD patients was distributed as followings; stage I (25%), stage II (33.3%), stage III (21.7%) and stage IV (20%). All these findings were shown in Table 3.

More than two thirds (78.3%) of COPD patients had tricuspid regurgitation which is diagnosed by echocardiography; 63.8% of them had mild type, 25.5% had moderate type and 10.7% of them had severe type of tricuspid regurgitation. All these findings were shown in table 4.

Pulmonary hypertension (PH) as diagnosed by echocardiography was present among 66.7% of COPD patients. The PH severity was distributed as followings; mild PH (37.5%), moderate PH (32.5%) and severe PH (30%). Right ventricular hypertrophy was present among 31.7% of COPD patients. All these findings were shown in Table 5.

There was a significant association between increased age of COPD patients and PH (p=0.01). Moreover significant association was observed between retired COPD patients and PH (p=0.03). All these findings were shown in Table 6.

Current study showed significant association between increased smoking packs/year of COPD patients and PH (P=0.009). All these findings were shown in Table 7.

There was a highly significant association between tricuspid regurgitation in COPD patients and PH (P<0.001), Moreover there was a significant association between patients with severe tricuspid regurgitations and PH (P=0.02). A highly significant association was observed between RVH in COPD patients and PH (p<0.001). All these findings were shown in Table 8.

As shown in Table 9, a highly significant association was observed between COPD patients with severe PH and lower mean of SpO_2 (P=0.02), while no significant association was observed with other variables.

Table 1. Sociodemographic characteristics of COPD patients.

Variables	No.	%
Age, mean±SD (67.1±11.2) years		
<60	15	25.0
60-69	15	25.0
70-79	21	35.0
≥80	9	15.0
Total	60	100.0
Gender		
Male	44	73.3
Female	16	26.7
Total	60	100.0

Table 2. Smoking history of COPD patients.

Variables	No.	%
Smoking		
Non-smoker	3	5.0
Current smoker	29	48.4
Passive smoker	2	3.3
Ex-smoker	26	43.3
Total	60	100.0
Packs/year mean±SD (54±29 packs/year)		
<50 packs/year	31	56.4
≥50 packs/year	24	43.6
Total	55	100.0
Duration of smoking mean±SD (37.7±13.5 years)		
<30 years	12	21.8
≥30 years	43	78.2
Total	55	100.0

Table 3. Spo2 and GOLD staging of COPD patients.

Variables	No.	%
Spo2 mean±SD (89.7±6 %)		
Gold staging		
Stage I	15	25.0
Stage II	20	33.3
Stage III	13	21.7
Stage IV	12	20.0
Total	60	100.0

Table 4. Echocardiography findings for COPD patients.

Variables	No.	%
Tricuspid regurgitation		
Yes	47	78.3
No	13	21.7
Total	60	100.0
Tricuspid regurgitation severity		
Mild	30	63.8
Moderate	12	25.5
Severe	5	10.7
Total	47	100.0

Table 5. Echocardiography findings for COPD patients.

Variables	No.	%
Pulmonary hypertension		
Yes	40	66.7
No	20	33.3
Total	60	100.0
Pulmonary hypertension severity		
Mild	15	37.5
Moderate	13	32.5
Severe	12	30.0
Total	40	100.0
Right ventricular hypertrophy		
Yes	19	31.7
No	41	68.3
Total	60	100.0

Table 6. Distribution of sociodemographic characteristics of COPD patients according to PH.

Variables	PH		No PH		χ^2	P
	No.	%	No.	%		
Age (year)						
<60	6	15.0	9	45.0		
60-69	9	22.5	6	30.0	10.4*	0.01
70-79	16	40.0	5	25.0		
≥80	9	22.5	0	-		
Gender						
Male	30	75.0	14	70.0	01	0.68
Female	10	25.0	6	30.0		
Occupation						
Housewife	5	12.5	5	25.0		
Public servant	2	5.0	3	15.0	8.7*	0.03
Self employed	7	17.5	7	35.0		
Retired	26	65.0	5	25.0		

Table 7. Distribution of smoking history of COPD patients according to PH.

Variables	PH		No PH		χ^2	P
	No.	%	No.	%		
Smoking						
Non-smoker	1	2.5	2	10.0		
Current smoker	17	42.5	12	60.0	4.9*	0.1
Passive smoker	1	2.5	1	5.0		
Ex-smoker	21	52.5	5	25.0		
Packs/year						
<50 packs/year	17	44.7	14	82.4	6.7	0.009
≥50 packs/year	21	55.3	3	17.6		
Duration of smoking						
<30 years	6	15.8	6	35.3	2.6*	0.1
≥30 years	32	84.2	11	64.7		

Table 8. Distribution of echocardiography findings of COPD patients according to PH.

Variables	PH		No PH		χ^2	P
	No.	%	No.	%		
Tricuspid regurgitation						
Yes	39	97.5	8	40.0	25.9*	<0.001
No	1	2.5	12	60.0		
Tricuspid regurgitation severity						
Mild	22	56.4	10	100.0	7.2*	0.02
Moderate	12	30.8	0	-		
Severe	5	12.8	0	-		
Right ventricular hypertrophy						
Yes	19	47.5	0	-	13.9	<0.001
No	21	52.5	20	100.0		

Table 9. Distribution of age, packs, duration of smoking and means Spo2 according to PH severity.

PH severity	Age	Packs/year	Duration	Spo2
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Mild	70.8±10.7	44.6±31.1	34.6±16.6	91.8±2.3
Moderate	66.6±12.5	64.6±23.7	43.9±11	89.2±4.8
Severe	74.1±6.7	68±30	46.1±13.7	81.8±5.4
ANOVA (P value)	0.2	0.09	0.06	<0.001

DISCUSSION

Chronic obstructive pulmonary disease is a significant health care burden worldwide [25].

The mean age of the patients was 67.1±11 years, which is in agreement to that reported by Ozben et al [26] in which the mean age of the patients was (64.2 ± 10.9), while it was not consistent with that reported by Soliman et al [27] in which the mean age was 59±9.16 years and also not similar to that done by Forfia et al [28] when the mean age was 55±15.

The present study showed that pulmonary hypertension is more in patients with advanced age an observation in line with Gartman et al [29] study in USA, and Fayngersh et al [30], however they asked either this association is attributable to age alone, or other comorbidities contributing to pulmonary hyper tension in the elderly.

Current study showed that (73.3%) of the patients are male and this might be directly related to COPD prevalence where it is more common in males than females due to smoking habits, and this is consistent with GOLD 2013 [31], as it showed male predominance of COPD. The current study showed that elderly aged COPD patients were significantly at higher risk of PH (P=0.01). This is similar to results of Berra et al [32] study in Switzerland. The effects of ageing on the respiratory system have been well studied; in particular, a progressive decline in lung function seen with normal ageing, which is largely associated with an alteration of the system mechanics of the lung– thorax and shows a decrease in static elastic recoil of the lung, an increase of chest-wall stiffness and a decrease in the respiratory muscles strength. Loss of the total capillary lung volume has also been demonstrated. All these factors may lead to or facilitate increase in peripheral vascular resistance and subsequent development of PH even in the absence of clear associated disease [32].

prevalence of pulmonary hypertension (PH) among COPD patients in our study was 66.7%. This rate is higher than that reported by Gologanu et al [33] study in Romania as 38.7% and Mahishale et al [34] study in India as 41.9%. This is related to the fact that prevalence of PH in stable COPD varies from 20 to 91% depending on the definition of PH mean pulmonary artery pressure(mPAP) >20 versus >25 mmHg, the severity of COPD (forced expiratory volume in the first second: FEV1), and the method of measuring the pulmonary artery pressure (echocardiography versus right heart catheterization) [35].

The severity of PH in present study was distributed as followings; mild PH (37.5%), moderate PH (32.5%) and severe PH (30%). These findings are in agreement to that reported by zoliman et al [36] study in Egypt which found lower proportion of COPD patients with severe PH.

Current study showed that 31.7% of COPD patients had right ventricular hypertrophy and RVH was significantly associated with PH, an observation consistent with that reported by Scharf et al [37], as they showed that in patients with severe emphysema evaluated for lung volume reduction surgery, 61.4% of patients had a mean pulmonary artery pressure greater than 20 mm Hg. As this value represents the upper limit of normal resting mean PAP [38].

In our study, 78.3% of COPD patients had tricuspid regurgitations in which 63.8% of them was mild, Moreover there was significant association between

incidence of tricuspid regurgitation, its severity among COPD and PH which is in agreement with Kessler et al [39]. Pulmonary hypertension, frequently seen in COPD patients is responsible for the low quality of echocardiography [40] thus the likelihood of estimating systolic pulmonary artery pressure (sPAP) is lower in patients with marked pulmonary hypertension. The quality of the tricuspid regurgitation was adequate in our study for the estimation of sPAP in all patients with tricuspid regurgitation which is not always Possible. One study estimated sPAP in only two thirds of the patients with tricuspid regurgitation [41]. This is of great value, as the absence of an echocardiographic high sPAP excludes important PH and further unnecessary invasive evaluation due to its high negative predictive value (87%) [42].

The recent study showed significant association between smoking duration, increased packs and pulmonary hypertension, this finding coincides with results of Elwing et al [14]. Tobacco smoke is not only toxic to the airways and lung parenchyma but also has an effect on the pulmonary vasculature and may play a significant role in the development of PH, The small pulmonary arteries of smokers develop intimal thickening due to elastin deposition, increased collagen production, and smooth muscle proliferation regardless of the development of obstructive lung disease [43].

COPD patients at stage IV in our study were significantly at higher risk of developing PH. This is similar to results of Chaouat et al [44] which stated that severity of COPD is a significant risk factor for PH.

Current study showed that Spo2 level of COPD patients was significantly lower among patients with severe COPD ($P<0.001$). This finding is consistent with results of Gupta et al [45] which stated that SPO2 is decreasing progressively with increased severity of COPD. Our study showed a significant association between COPD patients with Gold stage IV and severe PH ($P=0.001$). This finding revealed a significant association between severity of COPD and severity of PH. These findings are in accordance to that of Khther et al [46] study in Erbil and Jamaati et al [47] study in Iran which reported that severity of PH is significantly correlated with severity of COPD. Essentially, COPD severity has direct effect on prognosis, and it is one of the major determinants of mortality, and exacerbation. On the other hand, severity of COPD has a major effect on response to treatment [47].

Current study conclude that prevalence of pulmonary hypertension among patients with chronic obstructive pulmonary diseases is higher than international normal range. The pulmonary hypertension severity is more likely to be related with the severity of chronic obstructive pulmonary diseases. We recommend regular screening programs for pulmonary hypertension in patients with chronic obstructive pulmonary diseases, additional large sized studies regarding pulmonary hypertension among patients with chronic obstructive pulmonary diseases.

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