Journal of Pulmonary & Respiratory Medicine

Bhattacharyya et al, J Pulm Respir Med 2020, 10:2

Research Open Access

Hemodynamic Endorsement of Post-Exercise Desaturation-Based Decision of Treating COPD-PH: A Pilot Observation

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Received date: October 22, 2019; **Accepted date:** March 13, 2020; **Published date:** March 20, 2020

Abstract

Background: COPD with Pulmonary hypertension (COPD-PH) affects health status and survival adversely; Yet, PH-specific pharmacotherapy has not been recommended for lack of evidence. Recently, post-exercise maximum desaturation ('desat-máx') of ≥ 3% has been considered successfully to identify the responders for PH-specific therapy. It is important to validate the observation hemodynamically.

Method: The 'desat-máx' in 2-chair test was looked for in a cohort of clinico-radio-echocardiographically suggested COPD-PH patients. Their hemodynamic status was elaborated with Right Heart Catheterization (RHC) and those with high (>3%) desat-max were compared to those with low (<3%) desat-max.

Results: Out of 36 patients screened, a total of 15 patients of COPD-PH (all male ex-smokers having mean FEV1 (predicted percentage) as 37.61 ± 15.30) were included. Nine had a 'desat-max' ≥ 3% (mean-6.8 ± 2.6) while 6 had <3% (-1.81 ± 1.3). The higher de-saturators had lower FEV1 percentage (33.11 ± 16.88 *vs.* 44.16 ± 10.64; P=0.17) but had similar systolic pulmonary artery pressure (PAP) (53.2 ± 7.15 *vs.* 51.83 ± 4.87; p=0.33) and universally present left ventricular diastolic dysfunction (LVDD) in echocardiography. At RHC, the higher de-saturators had higher mean-PAP (36.22 ± 7.87 *vs.* 25.5 ± 1.5; p=0.04), pulmonary wedge pressure (22.11 ± 7.06 *vs.* 18.83 ± 3.18; p=0.3), Pulmonary vascular resistance (4.0 ± 2.40 *vs.* 1.72 ± 0.5; p=0.04), transpulmonary gradient (14.11 ± 7.18 *vs.* 6.67 ± 2.42; p=0.03) with slightly lower cardiac output ((3.81 ± 1.22 *vs.* 4.18 ± 1.09; p=0.56).

Conclusion: The higher de-saturators (≥ 3%) in 2CT appear hemodynamically distinct with presence of significantly elevated precapillary PAP to be addressed by PH specific therapy. The issue of presence of concomitant class II PH in them needs further investigation.

Keywords: 2 Chair test; Chronic Obstructive Pulmonary Disease (COPD); Pulmonary hypertension; Desat-max: Maximum Desaturation; Forced expiratory volume in 1 second; Forced vital capacity; Left Ventricular Diastolic Dysfunction; Pulmonary Capillary Wedge Pressure; Pulmonary artery pressure (Systolic); Pulmonary vascular resistance; Transpulmonary gradient; Cardiac output

Introduction

COPD is often complicated by pulmonary hypertension or PH. This is the commonest cause of class III PH been described secondary to hypoxemia and lung diseases [1]. There are two types of situations of PH in COPD as a) PH-COPD (where severe PH associated with mild COPD, and b) COPD-PH (where mild to moderate PH is associated with severe COPD) [2]. The prevalence of PH in COPD found to the tune of 30-70%, [3] and the COPD-PH forms the major bulk of it [3]. The treatment of PH-COPD with pulmonary vasodilators is well established and is supported by a meta-analysis [4]. However, no guideline recommends treatment the patients of COPD-PH with PH-specific medications [1]. Of late, we have looked for the post exercise desaturation of these patients and have demonstrated that those showing a maximum desaturation >3% show improvement to sildenafil. An innovative fixed exercise protocol was introduced with five movements up and down between two chairs (named as 2 chair test). But the observation was not supported by any hemodynamic data. The present manuscript deals with intended hemodynamic endorsement of vasodilator treatment based on post-exercise desaturation-based assessment of COPD-PH [5].

Methods

The study was conducted following the appropriate ethical approval by the independent ethics committee of the Institute of Pulmocare and Research. The candidates for inclusion were selected form the pool of COPD patients been diagnosed and evaluated for pulmonary hypertension.

The Diagnosis of COPD was accomplished through spirometry observing the GOLD guideline [6] following the clinical suspicion of the disease. Radiological evaluations (chest x-ray PA view and HRCT chest, whenever felt necessary) were done to exclude bronchiectasis. All the patients selected for screening were evaluated with Doppler echocardiography when there were:

a)Historical suggestion of PH as out of proportion or apparently unexplained SOB (shortness of breath),

b)Presence of raised JVP and S4 (RV), loud S2with or without pulmonary systolic murmur or parasternal heave,

c)The suggestion of prominent and wide pulmonary arteries at the hila with non-tubular heart and/or suggestion of right ventricular enlargement in chest x-ray, and

d)Evidence of pulmonary artery root dilatation (≥1) compared to aortic root diameter at mediastinum and dilatation of pulmonary arteries compared to corresponding bronchus in 3 or more lobes in HRCT chest.

The echo-cardiography for each candidate was performed following a fixed protocol where a single expert had done the test using a fixed machine in the morning hours. The left and right ventricular global motion with systolic or diastolic left ventricular dysfunctions were noticed along with determination of systolic pulmonary artery pressure. All the patients underwent a modified exercise protocol of 2 chair test (2CT) as a part of institutional innovative protocol [7]. The test includes:

a)Five up-and down movements (sit-get up and move to the other chair to sit- get up and return) between two chairs been kept face to face at five feet apart and

b)The post-exercise measurement of pulse rate and arterial oxygen saturation (SpO_2) at every 10 seconds for 2 minutes immediately following the exercise. The criteria for selection was same as been used earlier by us and was endorsed by the Kolkata PH group [5].

The selection of the subjects for right heart catheterization was done from willing patients following proper written informed consent. Any patients having:

a)Exacerbation in the preceding 6-weeks,

b)Any known valvular or ischemic, cardiovascular morbidity,

c)Arrhythmia,

d)Concomitant any other pulmonary morbidity,

e)Any other significant systemic disease (hepatic, renal, neurological, gastrointestinal, hematological, metabolic etc.) was excluded.

RHC was done through cannulation of either femoral or internal jugular vein [8,9]. We used a Swan Ganj balloon tipped catheter and measured the PCWP (pulmonary capillary wedge pressure), systolic PAP (pulmonary artery pressure), right ventricular pressure and right atrial pressure following standard procedural methods. We measured oxygen saturation from PA (pulmonary artery), RV (right ventricle), RA (right atrium), SVC (superior vena cava), IVC (inferior vena cava) and aorta. We calculated oxygen saturation by Dehmer's formula using the formula VO_2 (oxygen consumption) equal to 125 × BSA (body surface area). The measurement of BSA was done by putting body weight (Kg) and height (cm) in the calculation [10]. The cardiac output was measured using Fick's principle.

In our study, we looked for the trans-pulmonary gradient (TPG) and the pulmonary vascular resistance (PVR). The transpulmonary gradient was calculated by subtracting the PCWP from the mean-PA pressure and a TPG value >12 mmHg is considered significant for diagnosis of "out of proportion right sided heart failure", without a left sided component [11]. The pulmonary vascular resistance (PVR) is subsequently determined by dividing the TPG with cardiac output.

Pulmonary hypertension was defined with mean-PAP >25 mmHg and PCWP as <15 mmHg. A mean PAP >25 mmHg with the PCWP >15 mm without reduction in left ventricular (LV) ejection fraction made the diagnosis of class-II PH and when such a situation was admixed with increased PVR and TPG, the condition was marked as mixed class III and class II PH.

Statistical Calculation

The spirometric, echocardiographic, and hemodynamic parameters were tabulated under the status of saturation as <3% and ≥ 3% and unpaired the Students' test' was applied to compare the difference in any of the parameters selected. A p-value<0.05 was taken as significant.

Results

Out of 36 COPD patients been screened, written informed consent for RHC was obtained from 22 subjects. Of them, 21 patients performed the 2-chair test and 20 underwent right heart catheterization that diagnosed PH 15 of them. The hemodynamic data of these patients were arranged into two groups as per their desat-max status as >3% or <3% as was done earlier by us in our published strategy of treating COPD-PH (5). The desat-max was found significantly different between the two groups (-6.66 ± 2.69 *vs.* -1.5 ± 1.29; p=0.004).

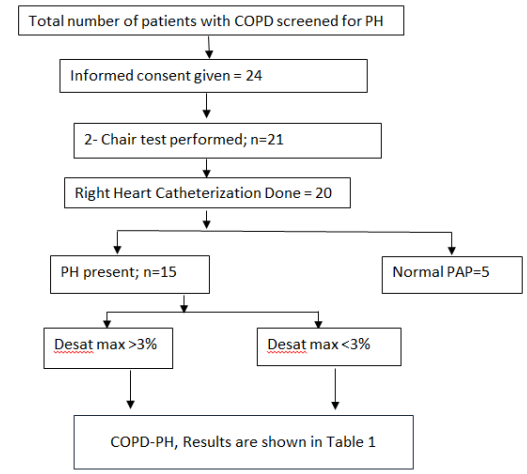

Figure 1: Flowchart showing the total number of patients with COPD that are screened for PH.

The higher de-saturating group had significantly worse degree of airflow limitation (FEV1/FVC= 0.41 ± 0.10 *vs.* 0.57 ± 0.15; p=0.0001 and predicted percentage of FEV1 as 33.11 ± 16.88 *vs.* 44.16 ± 10.64; p=0.17) (Table 1). However, in echocardiographic measurements, there was no difference in the LVEF, PAP, and tricuspid regurgitation jet velocity values between the two groups (p>0.05); and both the groups had LV diastolic dysfunction The RHC revealed an universally high PCWP in all the patents but there were significantly higher mPAP (36.22 ± 7.87 *vs.* 25.5 ± 1.51 mm of Hg; p=0.006), TPG (14.11 ± 7.18 *vs.* 6.67 ± 2.42; p=0.03), and PVR (4.0 ± 2.4 *vs.* 1.72 ± 0..5; p=0.04) in the patients with higher desat-max. (>3%) (Figure 1 and Table 1).

COPD-PH			
	Desaturation >3% (n=9)	**Desaturation <3% (n=6)**	**p-value**
2 chair test 'desat-max'			
Mean maximum desaturation (desaturation Maximum- 'desat-max'): -4.9 ± 3.28			
Desat-max	-6.66 ± 2.69	-1.5 ± 1.29	**0.004**
Spirometry			
FVC	60.66 ± 13.40	60.16 ± 9.06	0.93
FEV1 (% predicted)	33.11 ± 16.88	44.16 ± 10.64	0.17
FEV1/FVC	0.41 ± 0.1	0.57 ± 0.15	**<0.0001**
FEF25-75	11.88 ± 11.42	19 ± 15.79	0.32
Echocardiography			
LVEF	59.11 ± 6.97	61.33 ± 8.11	0.29
RWMA	none		
PAP (systolic)	53.2 ± 7.15	51.83 ± 4.87	0.33
TR jet velocity (m/sec)	3.31 ± 0.26	3.17 ± 0.25	0.18
Right heart catheterization			
PCWP	22.11 ± 7.06	18.83 ± 3.18	0.3
PVR (Wood's unit)	4.0 ± 2.40	1.72 ± 0.5	**0.04**
CO	3.81 ± 1.22	4.18 ± 1.09	0.56
TPG	14.11 ± 7.18	6.67 ± 2.42	**0.03**
mPAP	36.22 ± 7.87	25.5 ± 1.51	**0.006**

Table 1: Consort for patients screened and characteristic parameters included in study.

Discussion

There are several interesting revelations from the results (Table 1). The two groups had significant difference in the desat-max (6.66 ± 2.69 *vs.* 1.5 ± 1.29; p=0.00023). The striking features of the higher (>3%) de-saturators were a) more severe airflow obstruction and b) worse hemodynamic status as far as the RHC measured parameters as PAP, TPG, PVR, and CO are concerned (Table 1).

As per the lung function is concerned, the significantly low FEV1/FVC ratio in patients with higher de-saturators suggests more severe airflow obstruction and possibly more remodeling since this ratio has also been regarded as a surrogate marker of remodeling in similar obstructive airway disease as asthma [12].

The indirect hemodynamic data reveals no left ventricular systolic dysfunction (marked by ejection fraction and wall motion abnormality) in any of the groups but universally present left ventricular diastolic dysfunction (LVDD). The information obtained from RHC data is clearly indicative of a) presence of selective and significant pre-capillary contribution in PH for patients with higher (>3%) desat-max in 2-chair test, and b) an universally raised PCWP across the groups suggesting cardiac contribution in the development of PH (class II PH) in these patients. Thus, the raised pulmonary vascular resistance (PVR) and the trans-pulmonary gradient (>12 mmHg) makes the group with high desat-max indicated for pulmonary vasodilator therapy. Hence, our results ratify the decision of post-exercise maximum desaturation-based decision of treatment of COPD-PH with sildenafil and documentation of improvement earlier [5].

The management of COPD-PH has been marred in controversy and no good evidence is available to suggest that treatment of these patients with pulmonary vasodilator is beneficial. Most of the trials have been done with extrapolations of knowledge from treating PAH. They are mostly small having no uniformity in the patient selection and choice of the end points for analysis [13-19]. The confusion was such that an international authority has recommended a definite 'no' to sildenafil to treat COPD-PH [20]. In this scenario, we tried the job a little differently and decided to treat COPH-PH based on post exercise recovery response of SpO_2 in 2-chair test [5]. This decision was made through the argument and collective wisdom of the PH group that endorses the concept of post exercise desaturation reflecting the circulatory compromise from class III PH in COPD. Further, our previous work with decision of slowly building up the dose of sildenafil

was possibly correct as the chance of worsening of the ventilation-perfusion mismatch remains a matter of concern in these patients [5]. Hence, based on our hemodynamic endorsement of the past experience, one may think to shift from an emphatic 'no' to a cautious 'yes' to the treatment of COPD-PH with sildenafil.

Despite a small number of recruitments in the study, the concept of looking at the desat-max in 2-chair test in endorsing treatment decision for COPD-PH highlights the 2-chair test. It is already been established as a highly reproducible one and comparable to 6-minute-walk-test (6MWT). Being a submaximal exercise test, it is qualitatively similar to 6MWT but the measurement variables are changes in pulse rate and SpO_2 measured at every 10 seconds post-exercise. This uniformly applied test ratified our presumption that post exercise recovery pattern in pulse rate and SpO_2 is indicative of relatively selective recovery response of the cardiopulmonary system. Moreover, we picked up the desaturation-max as a measurement of the jeopardy of the circulatory reserve in the patients with COPD-PH. The respiratory reserve of these subjects with advanced COPD was already compromised and since they have been optimally treated, the room for improvement in ventilation was supposed to be limited. In such a state, it is likely that the reduced circulatory reserve from PH determines the post-exercise desaturation [5] and, thus, it was presumed that cautious use of induced pulmonary vasodilatation can, to some extent, be helpful in these subjects with predominantly hypoxemia induced PH.

The revelation of uniformly raised PCWP in these patients without any valvular heart disease or LV systolic dysfunction or pericardial disease or restrictive cardiomyopathy is indicative of the presence of HFpEF. The only plausible explanation of such raised PCWP is the presence of LV diastolic dysfunction (LVDD) apparent universally on echocardiography. We have already seen a high prevalence of LVDD in patients of advanced COPD with or without co-presence of other known risk factors for LVDD as diabetes, hypertension, and hypothyroidism [21]. Several causes that have been implicated for such LVDD in COPD include a) hindering normal LV filling of left ventricle from right ventricular dilation and interventricular septal displacement towards left ventricular lumen [22-24], (b) hypoxia [25], (c) prolonged use of beta 2 agonist [26] and d) restriction and impedance on pericardium from by hyper-inflated lungs [27]. The individual contribution needs to be looked for since some of them may be amenable to treatment. We have seen that the majority (roughly 60% of them) have significant myocardial ischemia in stress myocardial scintigraphy [28].

Higher than normal wedged pressure (PCWP) has been observed in many COPD studies lately. In the National Emphysema Treatment Trial, the PCWP was found higher than the upper limit of normal (12 mmHg) in 61% of the patients [27]. From a retrospective record of mixed population of COPD (including all spirometric stages), the prevalence of PH was 18% on hemodynamic studies with slightly higher prevalence in advanced (GOLD III and IV) disease. The mean FEV1 predicted was 41 ± 16% with mean pulmonary artery pressure as 20 ± 8 and the mean PCWP being 6 ± 4 mm of Hg at rest [29]. Interestingly, in our observation, we had the mean PCWP around 20 mm of Hg in both the groups which is far higher. It may have been influenced by selection bias to some extent as we have chosen subset of mostly advanced and symptomatic COPD population and allowed them to choose or deject RHC. It is possible that relatively sick patients opted to get investigated further with the hope of relief.

Incidentally the mean-PAP in the higher de-saturators is significantly high (36.22 *vs.* 25.5 mm Hg; p=0.006) with the airflow obstruction (FEV1/FVC) been significantly low compared to less de-saturators. It suggests that possibly beyond a critical level of airflow obstruction, the hypoxemia induced PH turns overt. Hence, it will be interesting to learn when and how the pre and post capillary contribution start picking up at the severity scale of COPD and which of them remains predominant at which stage of the disease on the time scale of suffering and how the co-morbidities play into it. Therefore, the issue of COPD PH needs to be looked at with a far inclusive outlook than just COPD derived hypoxemia.

The most important weakness of the study is the small number of subjects for RHC and the possible selection bias (only advanced cases) as discussed above. A robust hemodynamic study is now required to validate recommend our experience in clinical practice. The other weaknesses are the omissions of the assessment of the impact of co-morbidities and placing an in-depth echocardiographic assessment especially for LVDD. We had to depend on some formulae for some of the important RHC derived standards. One such is the cardiac output been calculated from the estimated VO_2 that is known to vary from VO_2 derived from using Douglous bag [30]. In resting state, the standard calculations for Cardiac output should be accurate as long as the BSA is calculated and VO_2 is measured accurately.

Conclusion

It may be interesting to look for the exercise related changes in COPD-PH and to follow these patients longitudinally in a randomized fashion to unveil the natural history and the effects of intervention in them. This appears important again in view of the latest revelation of the importance of the presence of borderline pulmonary hypertension to affect the survival prospect adversely in COPD-PH. Therefore, the inclusion of the patients with PA pressure between 18 and 25 mm of Hg (borderline pulmonary hypertension) also demands elaborate research.

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