Post Exercise Desaturation Can Help Identifying Treatment Responders of COPD Pulmonary Hypertension in Real World: An Appraisal

Bhattacharyya P[1]*, Sengupta S[1], Bhattacharjee PD[1], Ganguly D[2], Dutta D[2], Mondal S[2], Chowdhury SR[2], Biswas N[2], Roy DG[2] and Haldar I[2]

[1]Institute of Pulmocare and Research, Kolkata, India
[2]Kolkata-Ph group, BM Birla Heart Research Centre, Kolkata, India

Abstract

Background: COPD associated pulmonary hypertension (COPD-PH) leads to desaturation on exercise. It affects the health status and survival adversely.

Objective: To look for the change in pulse rate, arterial oxygen saturation (SpO_2), and the health status on treatment of COPD-PH with sildenafil administered on a desaturation criteria in response to a simple exercise protocol.

Methods: Patients of COPD-PH (diagnosed clinic-radio-echocardiographically) were subjected to a simple and uniform exercise test involving sitting and moving between two chairs (2 chair test). The baseline and post exercise measurement of the pulse rate and SpO_2 at every 10 seconds were recorded for 120 seconds. Patients showing a desaturation ≥ 3% ware prescribed PH-specific pharmacotherapy as sildenafil. Change in resting pulse rate, SpO_2, and COPD assessment test (CAT score) were noted and compared after 90 ± 15 days of observation with or without sildenafil.

Results: Out of 147 COPD patients, 89 (60.5%) had PH of which 62 subject qualified for sildenafil. At the end of follow up 57 and 27 subjects (with or without receiving sildenafil) were available for statistical calculation. Both the group of patients were similar in age, FEV1, FVC, and FEV1/FVC. The treated group showed an improvement in CAT (P<0.0001) and saturation (p=0.0003) while those on COPD therapy alone had mild worsening in arterial oxygen saturation (p=0.03).

Inference: Patients of COPD-PH treated on the basis of exercise desaturation showed significant improvement to PH specific pharmacotherapy. The observation demands attention and validation to define the indication of PH specific pharmacotherapy in COPD-PH.

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; PH: Pulmonary Hypertension; FEV1: Forced Expiratory Volume In 1 Second; FVC: Forced Vital Capacity; SpO_2: Arterial Oxygen Saturation; 2CT: Two Chair Test; 6MWT: 6 Minutes Walk Test; RHC: Right Heart Catheterization.

Introduction

COPD is a common airway disease and is a growing public health problem [1]. By 2020, it is predicted to be the third leading cause of death [2,3]. The sufferers of COPD often develop pulmonary hypertension (PH) that adds to the morbidity and affects the survival adversely [4]. According to recent studies, the prevalence of PH in COPD has been reportedly to be approximately 30%-70% [5]. The majority of this problem is encountered in advanced COPD patients with mild to moderate increase in pulmonary artery pressure (PAP) and is referred to as COPD-PH. However, a small number of patients show high pulmonary arterial pressure (PAP) with relatively mild airflow limitation (expressed as PH-COPD) [6]. While the guidelines are categorically instructive regarding administering PH-specific treatment in PH-COPD patients, they are silent regarding the majority (COPD-PH cases) possibly for lack of high quality evidence to define pharmacotherapy in them. This lack of directives in guidelines might have led to a deterrent effect on decision for PH specific pharmacotherapy by a physician for COPD-PH. Furthermore, for the diagnosis of PH, the situation is often complicated by the demand of right heart catheterization (RHC) which is often not possible in the vast majority of the real world. Thus, a huge number of sufferers of COPD-PH may remain deprived of the benefits of anti PH medications.

In this article, the authors have circumvented the need of RHC by a well-defined clinic-radio-echocardiographic criterion and have tried to count the extent of desaturation following a simple and defined exercise test as an indication of PH pharmacotherapy. They have observed the response to anti-PH based on the change in post exercise desaturation and health status.

Methods

The work had been done at the Institute of Pulmocare and Research based on an ethically approved protocol (approved by Institutional ethics committee of Institute of Pulmocare and Research) (CTRI number-CTRI/2015/07/005962). The subjects were screened and recruited from the out-patient department of the Institute. We formed a "Kolkata PH group" the members of which remained involved in framing the major strategies and the guideline for treatment. The protocol included the following steps:

Diagnosis of COPD

The COPD subjects were diagnosed clinicoradiologically and

confirmed subsequently with spirometry according to the criteria laid by the GOLD guideline [7].

Evaluation

This has been achieved through a defined clinico-radio-echocardiographic protocol been used at the institute and been used for publication before [8,9]. The protocol demands the presence of at least one point from each of the four headings below:

Clinical symptoms of PH: 1) Shortness of Breath (SOB) either unexplained or disproportionate to clinical or radiological (chest X-ray) findings. 2) Demonstration of desaturation at rest or with mild exercise on pulse oximeter. 3) Other symptoms as unexplained fatigue, syncope, etc.

Chest X-ray: 1) Dilated right main pulmonary artery in PA view. 2) Fullness of the retro-sternal space from right ventricular enlargement in lateral view of chest X-ray. 3) Gross PA dilation/fullness of pulmonary bay.

HRCT chest: 1) Pulmonary artery root diameter ≥ aortic root diameter. Pulmonary artery branch diameter ≥ accompanying bronchial diameter in 3 or 4 lobes.

Doppler echocardiography: Estimated pulmonary artery systolic pressure ≥ 40 mm of Hg.

Inclusion of the patients

A COPD patient with age beyond 45 to 75 years and history of exacerbation in the preceding six weeks, having continuing smoking or uncontrolled co-morbidities (viz. chronic heart failure, chronic renal failure, etc.) or any concomitant lung disease (as tuberculosis, malignancy etc. been apparent on evaluation) that can affect the symptoms, optimal evaluation, and treatment regimen were excluded. Any patient not been compliant to uniform COPD pharmacotherapy and the best possible rehabilitation efforts including home oxygen therapy protocol practiced at the institute were also excluded.

Assessment of health status

This was done by the measurement of the CAT score at the beginning of the anti-PH treatment and at the follow up visits. CAT score is regarded as a validated assessment for determining the health status for COPD patients. [10]. It had been collected by the same research staff for all the patients.

Determination of exercise response

This simple exercise test was developed by us at the institute and has been named as 2 Chair Test (2CT) as it includes movement between two chairs.

Two chairs were placed at a distance of 5 feet gap (i.e. end to end) facing each other. A patient is requested to sit on any one of them and rest for a few minutes till his pulse rate and SpO_2 remains stable for 30 seconds. This baseline pulse rate and the SpO_2 was recorded and the patient was then asked to get up and move to the other chair and sit there before getting up and returning to the previous chair. This is recorded as one movement. Thus, the patient was directed to make five movements at his or her pace otherwise continuously with freedom to stop in between if felt necessary for dyspnoea or any physical discomfort. The test has the provision for premature termination; such performance is noted as 3/5 when the patient could move three movements out of five. The reasons for any premature terminations are noted clearly.

The exclusion criteria for the test includes (a) unwillingness to give a written consent, (b) perceived cardiovascular instability clinicoradiologically or gross left ventricular dysfunction in echocardiography, (c) gross musculoskeletal problem as osteoarthritis of knees, (d) vertigo or neurological disorder affecting normal movement, (e) baseline hypoxemia ($SpO_2 \leq 90\%$), and (f) any other systemic problems that can affect the exercise or the performance adversely. Exclusion of Diffused Parenchymal Lung Disease (DPLD) or any other concomitant significant pulmonary disorder were done whenever suspected from clinical examination or chest X-ray through High Resolution Computed Tomography (HRCT) of chest whenever suspected. Similarly, patients with any significant left heart disease on echocardiography were refrained from performing the exercise. After completing the five movements the pulse and saturation were measured immediately and every 10 seconds thereafter for two minutes and the values were recorded. Oxygen supplementation was offered to those who required prolonged time (more than 30 seconds) to recover from de-saturation till the patient turned comfortable.

Selection of patients with COPD-PH for anti-PH treatment

Any patients having COPD-PH been diagnosed according to the protocol ('a' and 'b' as above) were included. All of them had similar COPD pharmacotherapy as inhaled corticosteroid with long acting β2 agonist plus short acting anti- muscarinic agents according to the protocol. They were then subjected to 2 chair test (2 CT). The patients showing at least ≥ 3% drop in SpO_2 in 2-CT (on the basis of an existing protocol practised by the Institute [9]) were chosen for anti-PH therapy as per the endorsement by the consensus group. The drug prescribed was sildenafil (10 mg thrice a day to start with and build up to 20 mg thrice daily after a week). Patients with history of intolerance to sildenafil or been on nitrate were excluded. The adverse reactions of the medicine was discussed at the time of prescription (especially of the possibility of increase in dyspnoea, dizziness, blindness, pedal swelling, headache, and uneasiness) and all the patients were requested to stop the drug and report the investigator at the earliest on development of any significant known or suspected adverse reactions. Blanket home oxygen therapy was not prescribed, but all were warned about the chance of emergency demand of oxygen supplementation after the initiation of the anti-PH therapy and arrange oxygen accordingly.

The follow up protocol

The follow up was fixed following 90 (± 15) days of initiation and whenever felt necessary by the patient with a mandatory reporting after 7 days of starting medication. At the follow up visits, details of clinical examination with assessment of CAT score and 2-Chair Test were repeated. A repeat echocardiography was also suggested at the follow up visit but it was not made mandatory.

The statistical analysis

Statistical analysis was done using graph pad prism 7 software. Statistical significance between the two different categories (treatment group and non-treatment group) was analysed using t-test (Wilcoxon t-test). The mean and standard deviation among the two groups were also calculated using the same software.

Results

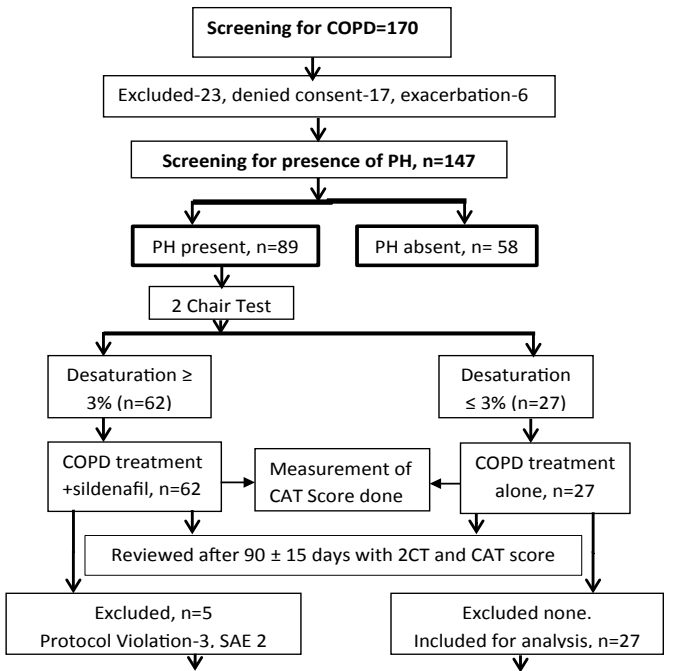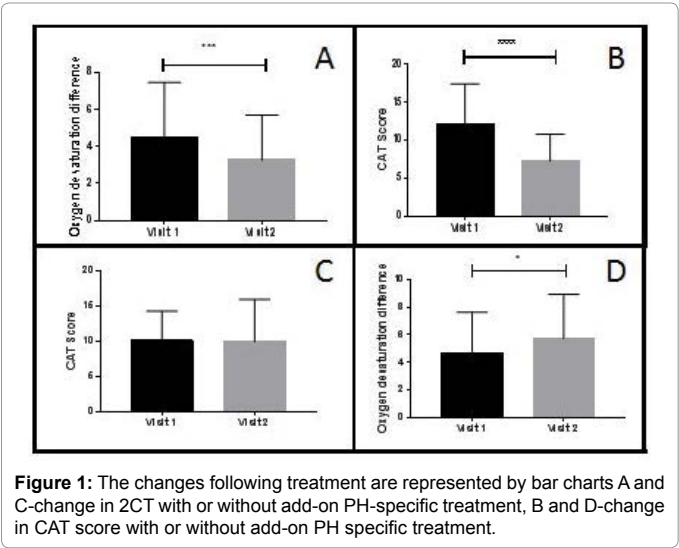A total 147 patients were screened and 89 (60.5%) patients were selected with the presence of PH. On subjecting the patients to 2-CT, 27 patients showed ≤ 3% and 62 had ≥ 3% desaturation of SpO_2 qualifying the latter group for the anti-PH therapy. 12 patients from the treatment group and 8 patients from non-treatment were prescribed oxygen supplementation. The details of both these group of patient from

inclusion till the final follow up are presented in Figure 1 and Table 1; it also elaborates the changes in CAT score and 2CT (pulse rate and saturation) statistically between the two groups. Both the groups had similar age, lung function status and mean systolic pulmonary artery pressures. The patients receiving treatment, showed a reduction in desaturation (i.e. from 4.48 ± 2.9 to 3.28 ± 2.4, p-value ≤ 0.0003) and a CAT score (12 ± 5.3 to 7.2 ± 3.5, p-value ≤ 0.0001) and improvement on the baseline resting saturation was (95.91 ± 2.8 to 96.25 ± .5, p-value=0.2). When the changes at each 10 seconds were added to see the 'cumulative' value, there has been no difference in the cumulative change of the pulse rate before and after treatment for both the groups. However, while the cumulative change in SpO_2 is seen to have reduced in the treated patients significantly (from 4.48 ± 2.9 to 3.28 ± 2.4; p=0.0003), the same has worsened for the untreated group (from 4.66 ± 2.9 to 5.7 ± 3.10; p=0.03) for the change. In the treatment group 1 patient and in the non-treatment 2 patients were reported to be on long term oxygen therapy (LTOT). These changes are displayed by bar chart in Figure 1. The adverse events noted are listed in Table 1.

Discussion

The results (Table 1) indicate that the baseline pulse rate has dropped in the treated patients with sildenafil while it has increased in the untreated group after 3 months of follow up. However, in the cumulative change in the pulse rate remained nearly unchanged. The impact was best perceived in reduction of desaturation in the treated group (p=0.0003) and the reverse in the untreated group (p=0.03). Concomitant to that, the CAT score improved significantly (i.e. reduced) in the treated patients again with the PH specific agent (p=0.0001) suggesting an overall positive effect on the health status. The experience further suggests that the drug sildenafil has been well tolerated in our patients.

PH develops mostly in the advanced COPD and reasons implicated are hypoxemia, polycythaemia, loss of pulmonary vascular bed from destruction of lung, and hyperinflation [11,12]. Hypoxic pulmonary vasoconstriction is considered as a major contributor for the development of PH in COPD and Intestinal lung diseases [13,14]. The development of PH in COPD affects the quality of life and the survival prospect adversely [15]. Hence, the condition needs to be addressed. Incidentally, the PH guidelines are not clearly instructive about pharmacotherapy of this condition allowing confusion in therapeutic decision making to prevails in this domain [16].

Figure 1: The changes following treatment are represented by bar charts A and C-change in 2CT with or without add-on PH-specific treatment, B and D-change in CAT score with or without add-on PH specific treatment.

Parameters	Treatment Group (n=57)		P-Values	Non-Treatment Group (n=27)		P-Values
	Initial	After 3 months		Initial	After 3 months	
M:F ratio	51:06:00			26:01:00		
Mean Age	66.4 ± 6.6			66 ± 6.9		
Mean (%) FVC	59.35 ± 18.7			58.63 ± 13.9		
Mean (%) FEV1	43.4 ± 18.9			41 ± 16.01		
Mean FEV1/FVC	51.19 ± 17.1	No significant difference observed		P 52.7 ± 11.16	No significant difference observed	
Mean (%) FEF25-75	18.6 ± 13.03			14.77 ± 11.04		
Mean PAP (Systolic)	46.7 ± 8.6			45.9 ± 15.1		
Mean CAT	12 ± 5.3	7.2 ± 3.5	<0.0001	10.07 ± 4.15	9.92 ± 5.94	0.8
Pulse rate at baseline	86.48 ± 15.8	83.5 ± 12.9	0.13	84.66 ± 17.08	86 ± 13.23	0.3
SaO_2 at baseline	95.91 ± 2.8	96.25 ± 2.5	0.2	95.25 ± 2.1	94.9 ± 2.7	0.6
Maximum change in PR	20.3 ± 9.3	20.9 ± 9.5	NS	23.14 ± 11.6	23.78 ± 9.8	0.8
Maximum change in SaO_2	4.48 ± 2.9	3.28 ± 2.4	0.0003	4.66 ± 2.9	5.7 ± 3.1	0.03
SAE	Reported hospitalization-2					
Adverse reaction	Increased shortness of breath-4 (7.01%), pedal edema-4 (7.01%), and dizziness-2 (3.5%), and muscle spasm-2 (3.5%)					

Table 1: The flow chart elaborates the details of the patients from screening to final follow up. The table elaborates the baseline characteristics as age, spirometric lung functions of the patients qualifying or not qualifying for anti PH treatment along with the changes in CAT score and parameters in 2CT (pulse rate and saturation). SAE: Serious Adverse Event.

The knowledge of treatment of any pulmonary hypertension has been borrowed from the treatment of PAH (pulmonary artery hypertension) [15,16]. Physiologically, the PAH and COPD-PH have essential differences. While in COPD-PH there has been a preceding and concomitant compromise of the respiratory reserve there is an isolated reduction in the circulatory reserve in PAH [17,18].

The dearth of recommendations for pharmacotherapy of COPD-PH, though unfortunate, keeps a space for independent thinking and development. The condition has been addressed with controlled trials [19-24], but the lack of uniformity in selection criteria, choice of the agent, methodology, and the end point selection of the different efforts remains a major concern [19-22,24-26]. Thus, the results have been somewhat conflicting to frame a recommendation for treatment [27]. However, despite that at least two recent meta-analysis have been in favour of treating overt PH at rest in COPD subjects [13,28].

Understanding the status of accessible or exhausted pulmonary and pulmonary vascular reserves appears important to decide an intervention in PH. Since all of our patients belonged to severe COPD (GOLD stage-3 and 4), the chance of improvement of the respiratory reserve was virtually missing in them. Therefore, the very post-exercise desaturation in our 2-Chair test protocol reflects significant exhaustion of the pulmonary vascular reserve. Here, the cardiac output fails to commensurate with the increased oxygen demand from the exercise even though it was a much less rigorous protocol than six minutes' walk test (6MWT). The 3% fall was empirical and was kept in a way to explain the physiological jeopardy. This understanding had made the PH group members to contemplate trying pulmonary vasodilatation with sildenafil in a desperate effort to prevent desaturation. Taking into consideration the chance of ventilation-perfusion mismatch, the group decided to build up the dose slowly. The presence of mild increase in dyspnoea as a common side effect suggests that the apprehension was justified and the strategy building up the dose of sildenafil was correct as the dyspnoea could be accommodated without discontinuation of sildenafil. The consensus also decided to observe the patients with less than 3% desaturation and analyse their trend in 2-CT and CAT score without imposing anti-PH therapy after 3 months. Incidentally, these patients showed a significant worsening in desaturation despite no change in CAT score (p=0.03). Although the 3% mark on exercise (2CT) is a reasonable cut-off value to predict the perceptible impact on health status with sildenafil in our COPD-PH patients, it is possible, that some of the patients in the untreated group could have improved had they been given sildenafil. One needs to evolve a more precise medication-strategy in future for these patients. The 2CT can measure improvement in pulse rate and saturation and, unlike the 6MWT it does not provide any idea about the exercise capacity. Efforts to establish the role of 2CT in sick PH patients as a substitute of six minute walk test may be worthwhile. A better and elaborate measurement of desaturation along with hemodynamic studies may be worthwhile to assess the vascular reserve in patients with ventilatory capacity. We had used a fixed dose of phosphodiesterase-5 inhibitor sildenafil [29]; it will be interesting to see both the acute and the dose response effects of the agent in future. Other anti-PH drugs too may be tested in the similar fashion in COPD-PH patients. That PH specific instrument as EmPhasis could have been better for the assessment of the health status [30]; incidentally, we had observed that CAT and EmPhasis correlate well in these patients [31]. The greatest criticism of the work may come from the fact of not looking at the hemodynamic criteria which was difficult to procure in our real world. Similarly lack of the repeat peak pulmonary artery pressure measurement at follow up also remains a serious weakness. Despite them, the improvement in health status (CAT score) parallel to the improvement in desaturation indicate towards the positive impact of our strategy of subject selection and pharmoco-intervention.

Conclusion

Exercise desaturation guided graded administration of anti-PH medication in COPD-PH patients appears worthwhile. Validation of the exercise test (2CT) and the decision algorithm with hemodynamic data and exercise capacity may prove extremely useful in future to recommend PH specific therapy in COPD-PH.

Declaration of Interest

It is declared that none of the authors involved in the work has or had any kind of conflict of interest relating to the research authorities.

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