

Comparison of Long Term Oxygen-Therapy (LTOT) and LTOT Combined with Sildenafil and Simvastatin in the Treatment of Severe Chronic Obstructive Pulmonary (COPD) with Hypoxia at Rest and Severe Pulmonary Arterial Hypertension

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Abstract

Background: Pulmonary arterial hypertension is frequent in patients with severe chronic obstructive pulmonary disease (COPD). It increases the morbidity and mortality of patients with advanced stage of COPD. The use of long-term oxygen therapy (LTOT) and some other vasodilators seems necessary to prevent pulmonary arterial hypertension (PAH) and right heart failure in these patients.

Objective: This study was planned to compare the effect of LTOT alone and LTOT combined with sildenafil (PDE-5 inhibitor) and simvastatin (HMG CoA reductase inhibitor) on pulmonary arterial pressure of patients with severe COPD having hypoxia at rest.

Methods: It was a cross-sectional and comparative study. All patients with severe COPD having hypoxia at rest ($SpO_2 < 88\%$) had been classified in three groups: Group 1 (treated with LTOT), Group 2 (treated with LTOT+sildenafil), and Group 3 (treated with LTOT+sildenafil+simvastatin). All study patients had been treated with conventional therapy (long-acting beta2-agonists+inhaled corticosteroids+long-acting muscarinic antagonists) and followed up during 6 months with one visit every three months. The mean systolic pulmonary arterial pressures (PAP) had been measured by transthoracic echocardiography (TTE).

Results: Ninety-eight patients with severe COPD and hypoxia at rest were included in this study (Group 1:32 patients, Group 2:35 patients, and Group 3:31 patients). The systolic PAPs and diffusing capacity of the lungs for carbon monoxide (DLCO) were significantly ameliorated after 3 to 6 months. The mean systolic PAP in patients from Group 2 and Group 3 were significantly lower than that in Group 1 at 3 months (41 ± 9 mmHg and 39 ± 7 mmHg vs. 46 ± 10 mmHg; $P < 0.05$ and $P < 0.05$; respectively). After 6 months, oxygen consumption (VO_2 max) and 6 minutes walking distances were significantly increased in patients from Group 2 and Group 3 ($P < 0.05$ and $P < 0.05$; respectively).

Conclusion: LTOT is an efficacy treatment for severe COPD patients with hypoxia at rest and PAH. Sildenafil and simvastatin have some additional effect on the reduction of PAP and physical exercise capacity.

Keywords: COPD; Hypoxia; Pulmonary hypertension; Sildenafil; Simvastatin

Introduction

COPD is a leading cause of morbidity and mortality worldwide that provides a strong economic and social burden for all countries [1,2]. The prevalence and mortality of COPD vary across different populations and countries. In emergent countries, the prevalence of COPD is mainly related to tobacco smoking, although indoor air pollution from exposing the burning of biomass fuels are also the risk of COPD [3-5].

One of the main important complications of patients with COPD is pulmonary arterial hypertension (PAH). PAH appears usually in advanced stage of COPD where the airflow obstruction becomes more severe. Although new pathophysiological mechanisms of PAH in subjects with COPD have been proposed recently, which related to chronic alveolar hypoxia-induced vasoconstriction and vascular remodeling are still the main mechanism [6]. Previous studies showed that there was the correlation between increased pulmonary arterial pressure (PAP) and survival prognostic in patients with severe COPD

[7]. In severe COPD patients, the PAP might be measured preferably by non-invasive method with the use of transthoracic echocardiography (TTE).

The existence of PAH in subjects with COPD is one of the criteria for prescribing long-term oxygen therapy (LTOT). LTOT may prevent a worsening progression of increased PAP and its repercussion on right ventricular function. Currently, LTOT is easily to access for

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patients with COPD in advanced stage and even though for those who are living in developing countries. However, the new insights into the pathophysiology of PAH related to COPD suggest some potential target therapies that aim to stabilize the pulmonary hemodynamic and vascular remodelling in these patients [8]. Among them, the effect of type 5 phosphodiesterase (PDE-5) inhibitors and non-selective RhoA/Rho-kinase inhibitors such as statins has been demonstrated recently [9,10]. Statins, the 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, reduce RhoA activation by preventing post-translational isoprenylation of the protein and its translocation to the plasma membrane [11]. This effect reduces pulmonary vasoconstriction in different causes of hypoxia-induced PAH.

However, the role of LTOT in association with PDE-5 and statin, a non-selective RhoA/Rho-kinase inhibitor, in the treatment of PAH for subjects with severe COPD has not been clarified. This study was planned to demonstrate the effect of LTOT vs. LTOT combined with sildenafil, a PDE-5 inhibitor, or statin in patients with severe COPD having hypoxia at rest and PAH.

Patients and Methods

Patients

COPD patients with PAH diagnosed by TTE (transthoracic echocardiography) were included in the present study after signing an Institutional Review Board (IRB) approved consent and meeting the inclusion and exclusion criteria. The present study had been approved by LMC (Lam Dong Medical College) Institutional Review Board.

Exclusion criteria: Study subjects having one of the following criteria were excluded from the study: acute or sub-acute myocardial infarction; decompensated heart failure or uncontrolled high blood pressure; COPD with severe exacerbations due to low airway infection requiring management in the Intensive Care Unit; current treatment with LTOT, PDE-5 inhibitors or statins; severe disorders of liver function; unable to perform the functional or biological testing required by study protocol.

Inclusion criteria: Stable and severe COPD with PAH, diagnosed by TTE, having severe resting hypoxemia ($SpO_2 < 88\%$) were included in the present study. They were randomly divided into three groups based on PAH treatment: Group 1: treated with conventional therapy (CT) recommended by GOLD combined with LTOT; Group 2: treated with CT combined with LTOT and sildenafil; Group 3: treated with CT combined with sildenafil and simvastatin.

Methods

Study design: It was a cross-sectional, descriptive, and comparative study. All data on medical history, clinical examination, and laboratory tests were collected for statistical analyses. The study subjects were followed up during six months. The conventional treatment was included LABA (long-acting β_2 -agonists) associated with ICS (inhaled corticosteroids), LAMA (long-acting muscarinic antagonists), and SABA (short-acting β_2 -agonists) as needed. LTOT was prescribed for patients who had severe resting hypoxemia ($SpO_2 < 88\%$) to assure $90\% < SpO_2 < 95\%$ with the use of LTOT > 15 hours/day (during sleep and in day time or whole day) [12,13]. Sildenafil 50 mg twice a day was prescribed for patients from Group 2 and Group 3 in combined with conventional treatment (CT). Simvastatin 20 mg one a day was prescribed to patients of Group 3.

Laboratory techniques

Pulmonary function test: Lung function testing was done by Body Box 500 (Medisoft, Sorinnes, Belgium) for whole-body plethysmography. The reversibility of FEV₁ (forced expiratory volume in one second) was evaluated after 15 min post-BD with 400 μ g of salbutamol. The airflow limitation was considered reversible when the increase of FEV₁ $\geq 12\%$ and 200 mL. The measure of diffusing capacity of the lungs for carbon monoxide (DLCO) was performed by standard recommended guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [14,15].

Six-Minute walking test (6MWT): All study subjects performed the 6MWT and VO₂ max test at inclusion and after 3 months and 6 months of follow up. The 6MWT was accomplished as recommended by ATS [16]. The 6-minute walk distance (6MWD) and the change of oxygen desaturation were collected for analyses.

Maximal oxygen consumption test (VO₂ max): VO₂ max was performed by using an Ergo Card (Medisoft). It was based on the symptom-limited physical exercise test with ventilatory expired gas analysis using a cycle ergometer. The workload from 5 Watts to 10 Watts or 15 Watts/minute protocol had been adapted for each study subject to obtain at least 8 min (with 2 min of warming up for the first step) of exercise duration as recommended previously [17]. The peak of oxygen consumption uptake (VO₂ max) was used for comparing the exercise capacity of study patients at inclusion and after 3 and 6 months.

Transthoracic echocardiography (TTE): Transthoracic echocardiography provided pulmonary arterial pressure (PAP) in all study patients. The estimation of PAP was based on the peak velocity of the jet of tricuspid regurgitation by using the simplified Bernoulli equation [18]. The PA systolic pressure (sys PAP) > 50 mmHg measured by TTE was used to diagnose PAH in COPD subjects [19].

Statistical analyses: All collected data were analyzed by SPSS 22.0 software (Chicago; USA). Categorical variables were expressed as numbers or percentages. Continuous variables were presented as mean \pm SD. The pair-comparison of mean using Mann-Whitney U test and more than two groups with Kruskal-Wallis test. The P value < 0.05 was considered as significant.

Results

Clinical and functional characteristics of study subjects at inclusion

From January 2016 to Mars 2017, 98 patients with severe COPD were included in the present study. They had been randomly classified in three different groups as described previously:

Group 1: Patients had been planned to be treated with conventional therapy recommended by GOLD [20], combined with long-term oxygen therapy (LTOT);

Group 2: Patients had been selected for treating with conventional therapy combined with LTOT and sildenafil 50 mg twice per day;

Group 3: Patients had been randomized for treating with conventional therapy combined with LTOT, sildenafil 50 mg twice per day, and simvastatin 20 mg one per day.

In the present study, there were no significant differences between 3 groups for age, male/female percentage, and BMI (Table 1). The tobacco consumption was not significantly different between 3 groups

(Table 1). There was any patient with mMRC (Modified British Medical Research Council) at grade 0-2 in 3 groups. The score of mMRC and the times of previous hospitalization were not significantly different between study groups (Table 1).

The mean systolic pulmonary arterial pressures (PAP) had been measured by transthoracic echocardiography (TTE) confirming pulmonary arterial hypertension (PAH). They were not significantly different between study groups (58 ± 8 mmHg vs. 60 ± 9 mmHg and 59 ± 7 mmHg; $P > 0.05$, $P > 0.05$, and $P > 0.05$; respectively; Table 1). All the patients had severe airway obstruction with $30\% < FEV_1 < 50\%$ and FEV_1/FVC ratio $< 70\%$. They also had the moderate decrease of DLCO ($44 \pm 13\%$, $43 \pm 12\%$, and $42 \pm 14\%$; respectively; Table 1). There were no significant differences between 3 groups for maximal oxygen consumption (VO_2 max: $34 \pm 8\%$ vs. $32 \pm 10\%$ and $36 \pm 9\%$; $P > 0.05$, $P > 0.05$, and $P > 0.05$; respectively; Table 1) and 6 minutes walking distances (6MWD: 212 ± 86 m vs. 224 ± 74 m and 217 ± 95 m; $P > 0.05$, $P > 0.05$, and $P > 0.05$; respectively; Table 1).

Effect of sildenafil combined with simvastatin and LTOT in association with conventional treatment after 3 months

The results showed that patients treated with conventional therapy combined with LTOT, sildenafil 100 mg, and simvastatin 20 mg (Group 3) had the percentage of mMRC grade 3 was significant higher and mMRC grade 4 was significant lower than two other groups (62.7% vs. 53.6% and 55.4%; 37.3% vs. 46.4% and 44.6%; $P < 0.05$ and $P < 0.05$; respectively; Table 2); while there was no significant difference between Group 2 (treated with conventional therapy combined with LTOT and

Parameters	Group 1 N=32	Group 2 N=35	Group 3 N=31	P
Treatment				
Conventional treatment, %	100	100	100	NC
Long-term oxygen therapy, %	100	100	100	NC
Sildenafil, %	0	100	100	NC
Sildenafil+Simvastatin, %	0	0	100	NC
Dyspnea Status, mMRC				
Grade 0-2, %	0	0	0	NC
Grade 3, %	53.6	55.4	62.7	NS*, <0.05**, ***
Grade 4, %	46.4	44.6	37.3	NS*, <0.05**, ***
Hospitalization During 3 Months, %	9.3	8.5	9.6	NS**, ***, ***
Transthoracic Echocardiography				
Systolic PAP, mmHg	46 ± 10	41 ± 9	39 ± 7	<0.05*, **, NS***
Lung Function Testing				
FEV ₁ , %	46 ± 12	45 ± 13	49 ± 11	NS**, **, ***
DLCO, %	56 ± 13	64 ± 11	63 ± 12	<0.05*, **, NS***
Cardiopulmonary Exercise Testing				
Oxygen consumption, %VO ₂ max	36 ± 7	34 ± 9	37 ± 8	NS**, **, ***
6 Minutes' Walk Test				
6MWD, meters	217 ± 92	229 ± 82	225 ± 91	NS**, **, ***

Conventional treatment: LABA (long-acting beta2-agonists)+ICS (inhaled corticosteroids) [Seretide® (Salmeterol/Fluticasone)]+LAMA (long-acting muscarinic antagonists) [Spiriva® (Tiotropium)], and SABA as needed [Ventoline® (Albuterol)]; mMRC: modified British Medical Research Council (mMRC) Questionnaire; PAP: pulmonary arterial pressure; FEV₁: forced expiratory in one second; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWD: 6 minutes walking distance.

*Group 1 vs. Group 2; **Group 1 vs. Group 3; ***Group 2 vs. Group 3.

NC: Non comparison; NS: No significantly difference with $P > 0.05$.

Table 2: Clinical and functional characteristics of study subjects after 3 months with treatment.

sildenafil 100 mg) and Group 1 (treated with conventional therapy combined with LTOT alone; Table 2).

The mean systolic PAPs in patients from Group 2 and Group 3 were significantly lower than that in Group 1 after 3 months of treatment (41 ± 9 mmHg and 39 ± 7 mmHg vs. 46 ± 10 mmHg; $P < 0.05$ and $P < 0.05$; respectively; Table 2). There was no significant difference between Group 2 and Group 3 ($P > 0.05$; Table 2). Although after 3 months, the mean value of FEV₁ was not significantly different between three groups, the mean values of DLCO in patients from Group 2 and Group 3 were significantly higher than that in Group 1 ($64 \pm 11\%$ and $63 \pm 12\%$ vs. $56 \pm 13\%$; $P < 0.05$ and $P < 0.05$; respectively; Table 2). There were no significant differences between 3 groups for VO_2 max and 6MWD (Table 2).

Effect of sildenafil combined with simvastatin and LTOT in association with conventional treatment at 6 months

The present study showed that patients from Group 2 and Group 3 had the percentage of mMRC grade 3 was significant higher and mMRC grade 4 was significant lower than Group 1 (62.7% and 66.5% vs. 56.3%; $P < 0.05$ and $P < 0.05$; respectively; 37.3% and 33.5% vs. 43.7%; $P < 0.05$ and $P < 0.05$; respectively; Table 3), while there was no significant difference between Group 2 and Group 3 (Table 3).

After 6 months, the mean systolic PAP in patients of Group 2 and Group 3 were significantly lower than that in Group 1 (40 ± 7 mmHg and 38 ± 9 mmHg vs. 45 ± 8 mmHg; $P < 0.05$ and $P < 0.05$; respectively; Table 3). However, there were no significant differences between Group 2 and Group 3 ($P > 0.05$; Table 3). The mean values of FEV₁ and DLCO were not significantly different between 3 groups after 6

Parameters	Group 1 N=32	Group 2 N=35	Group 3 N=31	P
Age, years	61 ± 8	63 ± 7	62 ± 9	NS*, **, ***
Male/Female, %	90.7	91.5	93.6	NS*, **, ***
BMI, kg/m ²	22.4 ± 4.3	21.7 ± 3.7	22.6 ± 3.4	NS**, **, ***
Tobacco consumption, pack-year	39 ± 7	37 ± 9	40 ± 8	NS*, **, ***
Dyspnea status, mMRC				
Grade 0-2, %	0	0	0	-
Grade 3, %	37.5	34.2	32.2	NS*, **, ***
Grade 4, %	62.5	65.8	67.8	NS**, **, ***
Hospitalization, times/previous year	2.5 ± 1.5	2.2 ± 1.3	2.7 ± 1.8	NS*, **, ***
Transthoracic Echocardiography				
Systolic PAP, mmHg	58 ± 8	60 ± 9	59 ± 7	NS*, **, ***
Lung Function Testing				
FEV ₁ , %	42 ± 7	39 ± 9	41 ± 8	NS*, **, ***
FEV ₁ /FVC, %	54 ± 8	52 ± 6	53 ± 5	NS*, **, ***
TLC, %	114 ± 14	113 ± 22	117 ± 16	NS*, **, ***
RV, %	177 ± 16	175 ± 21	178 ± 19	NS*, **, ***
FRC, %	162 ± 18	166 ± 21	165 ± 22	NS*, **, ***
DLCO, %	44 ± 13	43 ± 12	42 ± 14	NS*, **, ***
Cardiopulmonary Exercise Testing				
Oxygen consumption, %VO ₂ max	34 ± 8	32 ± 10	36 ± 9	NS*, **, ***
6 Minutes' Walk Test				
6MWD, meters	212 ± 86	224 ± 74	217 ± 95	NS*, **, ***

BMI: Body Mass Index; mMRC: modified British Medical Research Council; PAP: Pulmonary Arterial Pressure; FEV₁: Forced Expiratory in One Second; FVC: Forced Vital Capacity; TLC: Total Lung Function; RV: Residual Volume; FRC: Functional Residual Capacity; DLCO: Diffusing Capacity of the Lung for Carbon Monoxide; 6MWD: 6 Minutes Walking Distance.

*Group 1 vs. Group 2; **Group 1 vs. Group 3; ***Group 2 vs. Group 3.

NS: No significantly difference with $P > 0.05$.

Table 1: Clinical and functional characteristics of study subjects at inclusion.

months (Table 3). The oxygen consumption (VO₂ max) and 6MWD in patients from Group 3 were significantly higher than that in patients with Group 1 and 2 (41 ± 7% vs 37 ± 9% and 36 ± 8%; P<0.05 and P<0.05; respectively; 275 ± 74 m vs. 223 ± 87 and 231 ± 92%; P<0.05 and P<0.05; respectively; Table 3).

Effect of treatment on systolic PAP, DLCO, and VO₂ max after 3 months and 6 months in patients from three groups

The results of present study showed that, in Group 1 (treated with conventional therapy combined with LTOT), systolic PAP were significantly decreased after 3 month and 6 months (46 ± 10 mmHg and 45 ± 8 mmHg vs 58 ± 8 mmHg; P<0.01 and P<0.01; respectively; Figure 1A), but there was no significant difference between 3 months and 6 months (46 ± 10 mmHg vs 45 ± 8 mmHg; P>0.05; Figure 1A). The mean DLCO were significantly increased after 3 months and 6 months in this group (56 ± 13% and 61 ± 6% vs 44 ± 13%; P<0.05 and P<0.01; respectively; Figure 1A). There was no significant difference of DLCO after 3 months and 6 months (P>0.05). The mean VO₂ max was not significant differences at inclusion and after 3 to 6 months (Figure 1A).

In Group 2 (treated with conventional therapy, LTOT, and sildenafil), the mean systolic PAP were significantly decreased after 3 month and 6 months (41 ± 9 mmHg and 40 ± 7 mmHg vs 60 ± 9 mmHg; P<0.05 and P<0.01; respectively; Figure 1B). That was not significantly different between 3 and 6 months (41 ± 9 mmHg vs 40 ± 7 mmHg; P>0.05; Figure 1B). The mean DLCO were significantly increased after 3 and 6 months in Group 2 (64 ± 11% and 65 ± 9% vs 43 ± 12%; P<0.01 and P<0.01; respectively; Figure 1B). There was no significant difference of the mean DLCO after 3 months and 6 months (P>0.05; Figure 1B). The mean VO₂ max was not significant differences

Parameters	Group 1 N=32	Group 2 N=35	Group 3 N=31	P
Treatment				
Conventional treatment, %	100	100	100	NC
Long-term oxygen therapy, %	100	100	100	NC
Sildenafil, %	0	100	100	NC
Sildenafil+Simvastatin, %	0	0	100	NC
Dyspnea status, mMRC				
Grade 0-2, %	0	0	0	NC
Grade 3, %	56.3	62.7	66.5	<0.05**, NS***
Grade 4, %	43.7	37.3	33.5	<0.05**, NS***
Hospitalization, %	6.2	5.7	6.4	NS**, ***, ***
Transthoracic Echocardiography				
Systolic PAP, mmHg	45 ± 8	40 ± 7	38 ± 9	<0.05**, ***, NS***
Lung Function Testing				
FEV ₁ , %	48 ± 8	50 ± 9	49 ± 10	NS*, ***, ****
DLCO, %	61 ± 6	65 ± 9	64 ± 8	NS*, **, ****
Cardiopulmonary Exercise Testing				
Oxygen consumption, %VO ₂ max	37 ± 9	36 ± 8	41 ± 7	NS*, <0.05**, ***
6 Minutes' Walk Test				
6MWD, meters	223 ± 87	231 ± 92	275 ± 74	NS*, <0.05**, ***

Conventional treatment: LABA (long-acting beta₂-agonists)+ICS (inhaled corticosteroids) [Seretide® (Salmeterol/Fluticasone)] + LAMA (long-acting muscarinic antagonists) [Spiriva® (Tiotropium)], and SABA as needed [Ventoline® (Albuterol)]; mMRC: modified British Medical Research Council (mMRC) Questionnaire; PAP: pulmonary arterial pressure; FEV₁: forced expiratory in one second; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWD: 6 minutes walking distance.

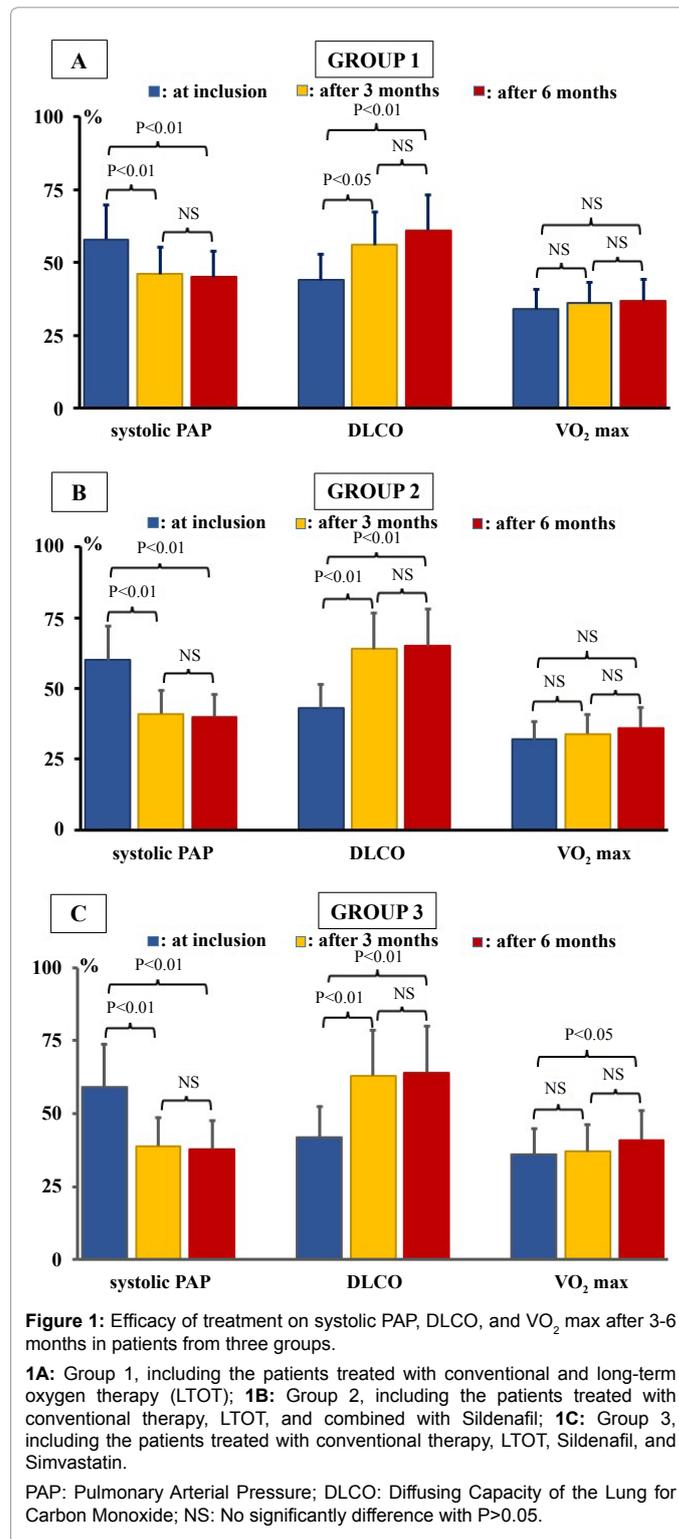
*Group 1 vs. Group 2; **Group 1 vs. Group 3; ***Group 2 vs. Group 3.

NC: Non comparison; NS: No significantly difference with P>0.05.

Table 3: Clinical and functional characteristics of study subjects after 6 months with treatment.

at inclusion and after 3 to 6 months in patients from this group (Figure 1B).

The present study showed that in Group 3 (treated with conventional therapy, LTOT, sildenafil, and simvastatin), the mean systolic PAP were significantly decreased after 3 month and 6 months (39 ± 7 mmHg and 38 ± 9 mmHg vs 59 ± 7 mmHg; P<0.01 and



$P < 0.01$; respectively; Figure 1C). In this group, the mean DLCO were significantly increased after 3 and 6 months ($P < 0.01$ and $P < 0.01$; respectively; Figure 1C). There was no significant difference between after 3 months and 6 months ($P > 0.05$; Figure 1C). However, the mean VO_2 max was significantly increased between 6 months and at inclusion in patients from Group 3 (Figure 1C).

Discussion

The results of present study showed that in patients with severe COPD having hypoxia at rest, the treatment with sildenafil alone (Group 2) and sildenafil associated with simvastatin (Group 3) in combined with conventional and long-term oxygen therapy (LTOT) was better than that by using only conventional therapy and LTOT (Group 1) to ameliorate a dyspnea status after 6 months of follow-up (Tables 2 and 3). Especially, the patients from Group 3 had the significant amelioration of dyspnea status after 3 months confirming by the decrease of percentage of patients with mMRC grade 4 and the increase of mMRC grade 3 (Table 2). However, after 6 months, the patients from Group 2 and Group 3 had no significant differences of dyspnea status. It suggests that the effect of sildenafil or sildenafil combined with simvastatin was similar after 6 months follow up. Sildenafil associated with LTOT was better sildenafil alone in ameliorating dyspnea status might be due to its effect on vascular modulation by reducing pre- and post-load for right heart in severe COPD patients with hypoxia at rest.

Until now, the exact mechanism of sildenafil or other phosphodiesterase-5 (PDE-5) inhibitors on dyspnea status of patients with COPD has not been well demonstrated [21,22]. However, its role in amelioration of dyspnea status in patients with other cardio-respiratory diseases has been described by previous studies [23,24]. Sildenafil might decrease dyspnea by its effect on pulmonary arterial vasodilation via increasing cyclic guanosine monophosphate (cGMP) produced by nitric oxide (NO) [25,26]. Although the effect of simvastatin in severe COPD has been demonstrated previously [27], the combination of sildenafil and simvastatin in reducing dyspnea status in these patients has not been clarified. It might be due to the effect of this combined treatment on pulmonary arterial pressure (PAP).

The present study showed that while the mean PAPs were significantly reduced in patients from three groups after 3 months and 6 months within treatment (Figures 1A-1C; Tables 1-3), the patients from Group 2 and Group 3 had the level of systolic PAP decreasing more significant than that in Group 1. This result suggest that LTOT (long-term oxygen therapy) alone or in combination with sildenafil or sildenafil associated with simvastatin may be also effective in treatment of PAP in patients with severe COPD and pulmonary arterial hypertension (PAH) and it may be more efficacy with combined treatment. Although the use of LTOT has been recommended strongly in patients with severe COPD having hypoxia at rest or for those with severe PAH, especially for severe COPD with PAH [20,28,29], the effect of LTOT combined with sildenafil or sildenafil associated with simvastatin has not been clearly demonstrated.

In patients with COPD, LTOT has been prescribed when oxygen saturation at rest less than 88% or 90% for those with congestive heart failure [20,28]. In patients with severe COPD, LTOT prevents not only the progression to right heart failure but also the survival free of acute exacerbation [29]. Moreover, in patients with cigarette smoking-induced COPD having hypoxia at rest, even though in acting smoking with normal lung function, LTOT might prevent hypoxia-related endothelial dysfunction and pulmonary vasoconstriction with the evolution toward pulmonary vascular remodelling and PAP [30,31].

The result of our study showed that in Group 1, the mean systolic PAP was significantly reduced after 3 months treated with conventional therapy (bronchodilators and inhaled corticosteroids) associated with LTOT and it was similar to LTOT combined with sildenafil or with sildenafil plus simvastatin (Tables 2 and 3; Figures 1A-1C). However, the combined treatment of LTOT with sildenafil or sildenafil associated with simvastatin was more efficacy in the reduction of PAP measured by transthoracic echocardiography (EET) (Tables 2 and 3). The role of sildenafil in treatment of PAH has been described previously but its role in COPD patients with PAH has not been well demonstrated [22,24]. In general, PDE-5 inhibitors could reduce PAP by the effect on vasodilation. Recently, the role of simvastatin (HMG CoA reductase inhibitor) in PAH has been studied. Statin is ubiquitous drug and also non-selective RhoA/Rho-kinase inhibitor. Although the effect of statin in amelioration of lung function in patients with COPD has been described recently, its role in the treatment of PAH has been still discussed. Simvastatin might inhibit the hypoxia-induced vasoconstriction mediated by RhoA/Rho-kinase [32]. Recent study realized by our group showed the activity of RhoA/Rho-kinase signaling pathway had been increased in smokers and in smokers with COPD [30]. It suggests that statin might be a potential additional treatment in severe COPD with hypoxia at rest.

Interestingly, the present study showed that LTOT alone or combined with sildenafil or sildenafil plus simvastatin in all COPD patients treated with conventional therapy (long-acting β_2 -agonists+inhaled corticosteroids+long-acting muscarinic antagonists) also ameliorated the decrease of DLCO after 3 months and 6 months (Figures 1A-1C). This effect was more significantly in patients treated with LTOT combined with sildenafil and simvastatin (Tables 2 and 3). This result suggests that in COPD patients with hypoxia at rest, the use of LTOT might correct a ventilation - perfusion imbalance frequently presented in COPD, due to hypoventilation or hypoperfusion [33]. However, the results of present study showed that oxygen consumption (VO_2 max) and 6 minutes walking distances were significantly increased only in COPD patients treated with LTOT combined with sildenafil or sildenafil associated with simvastatin (Tables 2 and 3). It suggests that the use of these drugs might protect patients with severe COPD having PAH from physical exercise. With a small number of patients and short-term follow-up, the use of transthoracic echocardiography as an only criteria for diagnosis of PAH, and the lack of right heart catheterization to confirm the diagnosis of PAH, the present study had some limitations to advise the routine use of sildenafil and simvastatin in patients with severe COPD having hypoxia at rest. With the short-term follow-up, the other additional limitation of the present study was related to the pharmacokinetic interactions among the prescribed drugs and the complications of these drugs for long-term treatment.

Conclusion

Pulmonary arterial hypertension is a frequent comorbidity in patients with severe COPD. Long-term oxygen therapy in association with conventional therapy as recommended by GOLD is still the best choice for patients with hypoxia at rest. The role of other additional drugs such as PDE-5 inhibitors and HMG CoA reductase inhibitors should be evaluated by more studies.

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Disclosure

The authors report no conflicts of interest in this study.

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