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# Relation between Cor Pulmonale Status and Metrics of Six Minute Walk Test in Patients with Chronic Obstructive Pulmonary Disease: A Cross Sectional Study

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## Abstract

**Background:** Cor pulmonale is a complication of chronic obstructive pulmonary disease (COPD). The use of the six minute walk test (6MWT) to discriminate between COPD patients with and without cor pulmonale remains unclear.

**Objectives:** To study whether the existence of cor pulmonale in COPD is related to characteristic findings in distance and desaturation in 6MWT.

**Material and Methods:** Patients with confirmed COPD who were referred to rehabilitation unit of Masih Daneshvari hospital were studied. Subjects were categorized into cor pulmonale and non cor pulmonale according to physical examination and echocardiography findings. Standard 6MWT was performed according to published statements. The covered distance and the amount of oxygen desaturation were recorded. Comparisons between the two groups were conducted in two-tailed using Mann-Whitney tests.

**Result:** A total of 101 patients were evaluated (78 male and 23 female). There were 49 cor pulmonale (48.5%) and 52 non cor pulmonale (51.5%) with a mean age of  $59.98 \pm 15.92$  and  $51.88 \pm 19.04$  ( $p > 0.05$ ), respectively. The mean of 6MWT distance in patients with and without cor pulmonale were  $264.85 \pm 114.1$  meters and  $344.13 \pm 84.19$  meters, respectively ( $p < 0.05$ ). Oxygen desaturation in cor pulmonale and non-cor pulmonale patients were  $8.71 \pm 6.41\%$  and  $7.90 \pm 6.80\%$ , respectively ( $p > 0.05$ ).

**Conclusion:** The distance covered by cor pulmonale subjects in 6MWT is significantly less than non cor pulmonale. However, despite the oxygen desaturation in both groups, there is no significant difference between two groups.

**Keywords:** Chronic obstructive pulmonary disease; Six minute walk test; Cor pulmonale

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important reasons for disability and death in patients with moderate to severe airways obstruction. The disease has been known as the third-most common cause of death in the worldwide [1]. It has shown that the prevalence of COPD in Iran is about 5.57% and it is on the rise [2]. Cor pulmonale refers to pulmonary hypertension (PHtn) response and is a consequence of hypoxic respiratory diseases and generally. Functional or structural abnormalities of the heart that are secondary to dysfunction of the endothelial of pulmonary vessels as well as proliferation of smooth muscle can lead to Cor pulmonale [3,4]. The exact prevalence of cor pulmonale in COPD is unknown but a wide range between 20-91% has been estimated based on the severity of COPD [5,6]. Besides, the cor pulmonale, which is routinely a consequence of COPD, has been reported to be a cause of 10 to 30% of heart failure admissions in the United States [7]. It has been shown that Cor pulmonale reduces the survival rate of affected subjects significantly. The mean survival of COPD patients with and without clinical signs and symptoms of Cor pulmonale is estimated to be seven and 13.5 years, respectively [8-11]. Hence, early detection of Cor pulmonale is essential and the involved patients need more diagnostic evaluation as well as special attention.

Some investigations including echocardiography, arterial blood gas measurement, lung biopsy, right heart catheterization and exercise stress test are the important items that have been involved in the diagnosis and evaluation of Cor pulmonale [4]. Various laboratory-based exercise stress tests are developed to investigate the impact of the disease on the patient's functional capacity (FC) and disability. Despite of the quite accuracy of laboratory-based exercise tests, their cost is very high that consequently limits the application of such tests. Field exercise tests are considered as the alternatives to laboratory-based exercise tests. They have some advantages since they are cheaper than laboratory-based exercise tests and can be carried out using easily accessible instruments. It has been widely accepted that the FC estimated by using the field tests, is same as the measured FC using a laboratory-based exercise test [4].

Six-minute walk test (6MWT) is one of the well-established field tests and is a simple, objective, reproducible and clinically relevant test. It has been developed to evaluate the patients' FC and its utilization has been validated in different clinical conditions such as cardio respiratory diseases [12]. In the recent years, 6MWT has been also used to evaluate and follow up patients with primary and secondary PHtn after their treatment [13,14]. In this test, a subject walks back and forth in a corridor as far as possible in six minutes. The distance covered by the patient is a primary measurement and is correlated with the patients FC. In various studies, this test has been accepted as an index to grade the severity of the disease in COPD patients as well as candidates for the lung transplantation [12]. For many years, the importance of the oxygen desaturation during 6MWT was unknown. Therefore, in a statement proposed by American Thoracic Society (ATS) in 2002, oxygen saturation (SPO<sub>2</sub>) monitoring during 6MWT was not stated as a standard procedure [15-17]. More recent trials have shown that there is a tendency between levels of the oxygen desaturation during the 6MWT and the degree of the heart and respiratory performance [18,19]. Accordingly, European Respiratory Society (ERS) and ATS proposed the continue monitoring of the oxygen as a standard procedure during the 6MWT in the official field test [20,21].

Despite of a high prevalence of COPD in Iran, few studies have focused on the results of 6MWT in these patients. In this study, it was attempt to investigate the impact of cor pulmonale in COPD patients by checking both SPO<sub>2</sub> and distance during 6MWT.

## Material and methods

### Study population

This study is a cross sectional study that was carried out between November 2015 and September 2016. Patients with confirmed COPD who were referred to the pulmonary rehabilitation unit of Masih Daneshvari hospital, were involved in the study. Masih Daneshvari hospital is a tertiary center for respiratory diseases in Tehran, Iran. The non-Cor pulmonale group contained the subjects with COPD that had not a physical examination and/or echocardiography evidence of PHtn. Written informed consent was obtained from each patient prior to the participation. The exclusion criteria of the study included those with (1) previous lower extremity trauma, (2) preliminary metabolic diseases such as hypothyroidism and diabetes mellitus (DM), (3) renal impairments and (4) previous ischemic heart disease (IHD).

### Physical and history questionnaire

Documents including medical history, physical examination, pulmonary function test and echocardiography were obtained and participants were accordingly categorized into Cor pulmonale and non-Cor pulmonale groups.

The physical examination findings evaluated in the study include ankle edema and prominent jugular vein. The echocardiography findings include the dilated right ventricle,

tricuspid valve regurgitation and elevated pulmonary artery pressure. The Participants that showed one of these criteria were grouped as Cor pulmonale.

Here, in order to avoid errors and forms of misclassification bias, the authors utilized the data of the physical exams that were collected by others. This may be a form of bias that includes misclassification.

### Walking measurement

The standard 6MWT was performed for all subjects according to the ATS statement [15]. Patients were excluded from the 6MWT if they had unstable angina or myocardial infarction in a previous month, resting heart rate  $\geq 120$ , systolic blood pressure  $\geq 180$  mmHg, diastolic blood pressure  $\geq 100$  mmHg and superficial oxygen saturation (SpO<sub>2</sub>)  $\leq 88\%$ . The test was done along a flat and straight corridor (length: 30 meter). Prior to the test, each patient sat on a chair located close to the start line and was relaxed for at least 20 min. Then, a well-trained technician explained the process of 6MWT to the patients. The patients were asked to walk as far as possible for six minutes. The lap counter was set to zero and the timer was set to six minutes. The number of laps was recorded. The total distance walked was calculated rounding to the nearest meter, and recorded on the worksheet. In the case of intolerable shortness of breath or fatigue, subjects were allowed to rest while the timer was not stopped. If the participants felt chest pain, severe dyspnea, severe fatigue, staggering or severs calf pain at any time the test was terminated. At the end of the six minutes, the covered distance (in meter) and patients' heart rate were measured.

### Oxygen saturation measures

Patients' heart rate, blood pressure, and SPO<sub>2</sub> were measured with a pulse oxymeter probe (OXYCOUNT Mini-Weinmann-Germany) from their right index finger. During the test, SPO<sub>2</sub> was automatically recorded every 30 seconds. SPO<sub>2</sub> was recorded as the percentage of the oxygen saturation. To calculate the differences of the SPO<sub>2</sub>, the SPO<sub>2</sub> that was recorded before the test was compared to the SPO<sub>2</sub> measured at the end of the test. The SPO<sub>2</sub> difference was also reported in percentage.

For statistical analysis, SPSS 11 software was used. Results were expressed as a mean  $\pm$  standard deviation (SD). Comparisons between two groups were conducted in two-tailed using Mann-Whitney tests. Value of P less than 0.05 was considered significant.

## Results

In this study, 180 patients participated in the pulmonary rehabilitation program were included. The 79 patients were excluded from the study. The exclusion criteria were included past medical history of DM (n=56), previous documented IHD (n=61) and clinical evidence of chronic renal failure (n=13) and finally, 101 patients were evaluated (78 male and 23 female). Mean ages of the participants were 59.98  $\pm$  15.92 and 51.88  $\pm$

19.04 in the Cor pulmonale and non-Cor pulmonale groups, respectively. There were no significant differences in the gender and age between two groups ( $P>0.05$ ). Mean BMIs of the patients with Cor pulmonale and without Cor pulmonale were  $19.14 \pm 3.6$  and  $21.08 \pm 2.54$ , respectively and difference between two groups was significant ( $p<0.05$ ).

The characteristics of each group (mean  $\pm$  SD) as well as statistical differences between two groups are shown in **Table 1**. In the echocardiography study, mean Systolic Pulmonary Arterial Pressure (SPAP) in the Cor pulmonale and non-cor pulmonale groups were  $48.64 \pm 10.42$  mmHg and  $32.24 \pm 4.10$  mmHg, respectively and SPAP difference between two groups was significant ( $p<0.05$ ). In the spirometry study, mean FEV<sub>1</sub>/FVC in the patients with and without cor pulmonale were  $49.1 \pm 4.3$  and  $61.34 \pm 7.8$ , respectively. Besides, mean of FEV<sub>1</sub> in percent in the subjects with and without cor pulmonale were predicted

to be  $37.22 \pm 4$  and  $41.4 \pm 11.2$ , respectively. Considering to both FEV<sub>1</sub>/FVC and FEV<sub>1</sub> measurements, the difference between two groups was significant ( $p<0.05$ ). It should be noted that the spirometry data may include bias that includes poor patient effort in the maneuver required for the measurement of lung function. Anthropometric data might also reduce confounding in the investigating relation.

Results of the 6MWT in the mentioned groups are shown in the **Table 1**. The mean of the traveled distances (in meter) during the test were  $264.85 \pm 114.1$  and  $344.13 \pm 84.19$  in the cor pulmonale and non-cor pulmonale groups, respectively. The difference between the groups was significant ( $p<0.001$ ). Oxygen desaturation (in percent) in the cor pulmonale and non-cor pulmonale patients were  $8.71 \pm 6.41$  and  $7.90 \pm 6.80$ , respectively. The differences between the groups was not significant ( $P=0.351$ ).

**Table 1:** The characteristics of the patients in cor pulmonale and non-cor pulmonale group.

Variables	Total	Cor-pulmonale	Non-corpormonale	p-value
Number of patients	101	49(48.5%)	52(51.5%)	-
Sex				
Male	78(77.2%)	40(81.6%)	38(73.1%)	-
Female	23(22.8%)	9(18.4%)	14(26.9%)	
Age	$55.81 \pm 17.97$	$59.98 \pm 15.92$	$51.88 \pm 19.04$	0.061
BMI	-	$19.14 \pm 3.6$	$21.08 \pm 2.54$	0.001*
Echocardiography SPAP (mmHg)	-	$48.64 \pm 10.42$	$32.24 \pm 4.10$	0.001*
Spirometry				
FEV <sub>1</sub> /FVC	-	$49.1 \pm 4.3$	$61.34 \pm 7.8$	0.001*
FEV <sub>1</sub>	-	$37.22 \pm 4$	$41.4 \pm 11.2$	0.021*
6MWT				
Distance (m)	$305.67 \pm 107$	$264.85 \pm 114.1$	$344.13 \pm 84.19$	<0.001*
Desaturation (%)	$8.30 \pm 6.59$	$8.71 \pm 6.41$	$7.90 \pm 6.8$	0.351

\*=Significant difference.

## Discussion

The purpose of the current report was to study the differences in the FC and amount of the oxygen desaturation during 6MWT on the COPD participants with and without evidence of cor pulmonale. The results showed that there were significant differences in the BMI, pulmonary function test and pulmonary artery pressure estimated by echocardiography between the cor pulmonale and non-cor pulmonale groups. Furthermore, the distances travelled by the cor pulmonale subjects during 6MWT are significantly less than the non cor pulmonale. However, the decrease in SPO<sub>2</sub> was seen in both groups, but there was no significant difference in the amount of the oxygen desaturation between two groups.

It has been shown that the incidence of PHtn increases as the COPD worsens [22,23]. Vascular remodeling secondary to chronic hypoxemia, inflammation and loss of the vascular bed in

emphysematous state are the main causes for increasing the pulmonary artery pressure in the COPD patients [24]. Unfortunately, studies about the impact of cor pulmonale on FC in COPD patients are really limited. Most of studies are based on CPET, which is a sensitive test that could explain the pattern of expired gas in different cardiopulmonary diseases [25]. In a study based on the 6MWT, it was shown that the distance covered during six minutes was significantly lower in the cor pulmonale subjects compared to non-cor pulmonale COPD patients [24]. In some studies, the average distance traveled in patients suffering from COPD is reported to be between 283 to 388 meters and vary depending on the severity of the disease [26,27]. However, different variables such as ethnicity, height, weight, BMI and muscle mass, level of education and the presence of underlying disease influence the results of 6MWT [28]. The results of the current study showed that distance traveled by the patients without evidence of cor pulmonale is

considerably more than the subjects without any evidence of cor pulmonale. This difference may be due to the differences between the BMIs of two groups. Agrawal et al studied the demographic characteristics (such as BMIs) of COPD patients that were in different stages of the disease [29]. In their study, there was a significantly reverse correlation between the severity of COPD and BMI. The lower BMI in the cor pulmonale group could explain the lower distance travelled during the 6MWT. Measuring the oxygen saturation during the 6MWT was not been accepted as a standardized procedure [15] until Takigawa et al. discussed the importance of the oxygen saturation monitoring during 6MWT for the first time [17].

Casanova et al showed the role of the distance travelled and oxygen desaturation during 6MWT on survival of COPD patients [16]. Travelled distances lower than 340 meters and oxygen drop more than 6% in COPD patients were demonstrated to be associated with the worst prognosis. As far as we know, to date, the impact of cor pulmonale on oxygen desaturation during the 6MWT has not been studied. Oxygen desaturation is a common phenomenon in COPD patients during exercise. The main cause of hypoxemia in COPD is ventilation/perfusion (V/Q) mismatch secondary to progressive airflow obstruction and destruction of the pulmonary vessels which increased by diseases progression [30,31]. Holverda et al studied the result of utilizing of CPET on COPD patients with and without evidence of secondary PHtn [25]. Oxygen desaturation was observed in both groups, and the oxygen loss in the group with increased pulmonary pressure was significantly more than another group. The findings of Holverda et al. were in contrast to the results of the current study. This controversy may be related to the difference in the quality of tests that were used in two studies. The exercise test in the current research was self-paced and not sensitive and accurate as CPET. The differences in the results of two studies could be explained by the fact that oxygen desaturation in COPD patients is multifactorial.

There are other factors and variables that might explain our findings that include asthma history, tobacco use, gender effect, air pollution, indoor cooking practices, occupational exposures that effect the respiratory system, and genetic or host factors that predispose a study subject to developing COPD and cor pulmonale.

One of limitations of the current study was the employing of traditional and old device to measure oxygen saturation during the 6MWT. Nowadays, utilizing the portable CPET devices during the 6MWT is on the rise. Such devices have a low weight and give a lot of information about the underling mechanism of hypoxemia during 6MWT.

Another limitation of this study was the using of BMI instead of subjects muscle mass variable. In order to the weight changes that results from peripheral edema in cor pulmonal subjectse, using the BMI does not seem logical. The use of muscle mass variable, which could be obtained by special instruments, can eliminate such errors and give useful information about the muscle fibers.

## Conclusion

Considering the results of this study, there is significant difference in BMI, pulmonary function test and pulmonary artery pressure estimated by echocardiography between the cor pulmonale and non-cor pulmonale groups. Moreover, the distance travelled by the cor pulmonale subjects during the test was significantly less than non-cor pulmonale patients. However, despite of the decreasing in the oxygen saturation in both groups, no significant difference was seen in the amount of desaturation between two groups.

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