

# STUDY ON PULMONARY INVOLVEMENT IS THE LEADING CAUSE OF SYSTEMIC SCLEROSIS

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## ABSTRACT

*The pulmonary rehabilitation center of a university hospital. Thirty-eight patients with mild to very severe COPD were evaluated. Pulmonary function and baseline dyspnea index (BDI) were assessed, handgrip strength, maximal inspiratory pressure (Pimax), and 6MWD were measured, and the one-repetition maximum (1RM) was determined for each of four exercises (bench press, lat pull down, leg extension, and leg press) performed on gymnasium equipment. Quality of life was assessed using the St. George Respiratory Questionnaire (SGRQ). We found statistically significant positive correlations between 6MWD and body weight ( $r = 0.32$ ;  $p < 0.05$ ), BDI ( $r = 0.50$ ;  $p < 0.01$ ), FEV(1) ( $r = 0.33$ ;  $p < 0.05$ ), Pimax ( $r = 0.53$ ;  $p < 0.01$ ), and all values of 1RM. A statistically significant negative correlation was observed between 6MWD and dyspnea at the end of the 6-min walk test ( $r = -0.29$ ;  $p < 0.05$ ), as well as between 6MWD and the SGRQ activity domain ( $r = -0.45$ ;  $p < 0.01$ ) and impact domain ( $r = -0.34$ ;  $p < 0.05$ ) and total score ( $r = -0.40$ ;  $p < 0.01$ ). Multiple regression analysis selected body weight, BDI, Pimax, and lat pull down 1RM as predictive factors for 6MWD ( $R(2) = 0.589$ ). The results of this study showed the importance of the skeletal musculature of the thorax and upper limbs in submaximal exercise tolerance and could open new perspectives for training programs designed to improve functional activity in COPD patients*

*Key words: rehabilitation, dyspnea, determined, gymnasium equipment, predictive.*

## INTRODUCTION

Pulmonary involvement is the leading cause of systemic sclerosis (SSc)-related deaths. A simple test to evaluate exercise capacity is the 6-min walk test (6MWT), and the walk distance is used as a primary outcome in clinical trials. Hemoglobin desaturation during a 6MWT is predictive of mortality in patients with primary pulmonary hypertension. To evaluate the walk distance and resting oxygen saturation - oxygen saturation after the 6-min period (DeltaSat) during the 6MWT in patients with SSc, and to establish correlations between the 6MWT results and other clinical variables 110 SSc patients were analysed. DeltaSat was defined as a fall of end-of-test saturation  $\geq 4\%$ . Clinical and demographic data were collected. All the patients were submitted to chest radiographs and high-resolution CT (HRCT) and underwent pulmonary function testing and echocardiography, and the presence of autoantibodies was determined. The variables associated with a walk distance  $< 400$  m ( $p < 0.05$ ) were age, dyspnea index, fibrosis on radiography,

pulmonary arterial systolic pressure (PASP)  $\geq 30$  mm Hg, and desaturation. The variables associated with DeltaSat ( $p < 0.05$ ) were age, positive anti-Scl-70 autoantibody, dyspnea index, fibrosis on radiography, FVC  $< 80\%$  of predicted, PASP  $\geq 30$  mm Hg, and ground-glass or reticular opacities on HRCT. In the multivariate logistic regression analysis, three variables were significant when tested with walk distance: age, race, and dyspnea index; four variables were significant when tested with DeltaSat: age, dyspnea index, positive anti-Scl-70 autoantibody, and FVC  $< 80\%$  of predicted. Desaturation during a 6MWT provides additional information regarding severity of disease in scleroderma patients with pulmonary manifestations.<sup>177</sup>

The characteristics of dyspnoea in idiopathic pulmonary fibrosis (IPF) during a 6-min walk test are not clear. This study was designed to evaluate dyspnoea and desaturation during the 6-min walk test in IPF in comparison with that in chronic obstructive pulmonary disease (COPD), which is one of the most studied chronic lung diseases. The 41 consecutive patients with IPF included in this study were assessed by a 6-min walk test and concurrent measures of disease severity. Forty-one age-matched and resting PaO<sub>2</sub> value-matched COPD patients who had undertaken the test during the same period were selected as the control. Only O<sub>2</sub> saturation at the end of the test was an independent predictor of dyspnoea in IPF ( $r(2)=0.27$ ,  $P=0.0005$ ), whereas forced expiratory volume in 1s (FEV<sub>1</sub>) was the only predictor in COPD ( $r(2)=0.16$ ,  $P=0.0096$ ). Desaturation was significantly more severe in IPF ( $83.6\pm 9.1\%$  in IPF versus  $88.0\pm 5.9\%$  in COPD,  $P<0.001$ ). In contrast, dyspnoea assessed with the Borg scale was significantly more severe in COPD ( $3.6\pm 2.1$  in IPF versus  $4.6\pm 1.9$  in COPD,  $P<0.05$ ). O<sub>2</sub> saturation is an independent predictor of dyspnoea at the end of a 6-min walk test in IPF. In comparison with COPD, desaturation is more severe, although dyspnoea is milder.

## REVIEW OF LITERATURE

Functional studies may be useful to predict survival in idiopathic pulmonary fibrosis (IPF). Various cutoffs of 6-min-walk distance (6MWD) have been suggested to identify patients at a high risk of death. To examine the association between 6MWD and survival in patients with IPF listed for lung transplantation, and to identify sensitive and specific cutoffs for predicting death at 6 mo. A retrospective cohort study was performed on 454 patients classified as having IPF listed for lung transplantation with the United Network for Organ Sharing between June 30, 2004 and July 22, 2005. Lower 6MWD was associated with an increased mortality rate ( $p$  value for linear trend  $< 0.0001$ ). Patients with a walk distance less than 207 m had a more than fourfold greater mortality rate than those with a walk distance of 207 m or more, despite adjustment for demographics, anthropometrics, FVC % predicted, pulmonary hypertension, and medical comorbidities (adjusted rate ratio, 4.7; 95% confidence interval, 2.5-8.9;  $p < 0.0001$ ). 6MWD was a significantly better predictor of 6-mo mortality than was FVC % predicted (c-statistic = 0.73 vs. 0.59, respectively;  $p = 0.02$ ). Lower 6MWD was strongly and independently associated

with an increased mortality rate for wait-listed patients classified as having IPF. 6MWD was a better predictor of death at 6 mo than was FVC % predicted.

## MATERIAL AND METHOD

This study was developed to investigate the influence of thoracic and upper-limb muscle function on 6-min walk distance (6MWD) in patients with COPD. A prospective, cross-sectional study. The pulmonary rehabilitation center of a university hospital. Thirty-eight patients with mild to very severe COPD were evaluated. Pulmonary function and baseline dyspnea index (BDI) were assessed, handgrip strength, maximal inspiratory pressure (Pimax), and 6MWD were measured, and the one-repetition maximum (1RM) was determined for each of four exercises (bench press, lat pull down, leg extension, and leg press) performed on gymnasium equipment. Quality of life was assessed using the St. George Respiratory Questionnaire (SGRQ). We found statistically significant positive correlations between 6MWD and body weight ( $r = 0.32$ ;  $p < 0.05$ ), BDI ( $r = 0.50$ ;  $p < 0.01$ ), FEV(1) ( $r = 0.33$ ;  $p < 0.05$ ), Pimax ( $r = 0.53$ ;  $p < 0.01$ ), and all values of 1RM. A statistically significant negative correlation was observed between 6MWD and dyspnea at the end of the 6-min walk test ( $r = -0.29$ ;  $p < 0.05$ ), as well as between 6MWD and the SGRQ activity domain ( $r = -0.45$ ;  $p < 0.01$ ) and impact domain ( $r = -0.34$ ;  $p < 0.05$ ) and total score ( $r = -0.40$ ;  $p < 0.01$ ). Multiple regression analysis selected body weight, BDI, Pimax, and lat pull down 1RM as predictive factors for 6MWD ( $R(2) = 0.589$ ). The results of this study showed the importance of the skeletal musculature of the thorax and upper limbs in submaximal exercise tolerance and could open new perspectives for training programs designed to improve functional activity in COPD patients.<sup>180</sup>

The 6-min walk test (6MWT) is commonly used to evaluate exercise capacity in patients with pulmonary arterial hypertension (PAH). However, little is known about the corresponding metabolic stress as measured by cardiopulmonary exercise testing. PAH trials traditionally use 6MW as the primary endpoint. Concerns regarding a "ceiling effect" masking efficacy have led to exclusion of patients with milder disease from most trials (BL 6MW > 450 m). STRIDE I evaluated the selective endothelin A receptor antagonist, sitaxsentan (SITAX), in a 12-week randomized, double-blind, trial (178 patients) employing placebo (PBO), 100 mg or 300 mg SITAX orally once daily in PAH and included patients with NYHA class II, congenital heart disease and a BL 6MW > 450 m, groups often excluded from previous trials. We analyzed 6MW effects For All Pts (intention-to treat) and those meeting Traditional enrollment criteria, defined as patients with NYHA class III or IV and 6MW < or = 450 m at BL with idiopathic PAH or PAH related to connective tissue disease. The 100 mg and 300 mg SITAX arms are pooled based on similar treatment effects on 6MW. Existence of a "ceiling effect" is supported by these data. The magnitude of the treatment effect and statistical power when using 6MW as the endpoint. Comparisons between PAH trials that do not adjust for the effects of differing enrollment criteria require caution.<sup>182</sup>

To describe the results of the 6-min walking test performed on admission to an intensive rehabilitation program after cardiac surgery and to develop, through an algorithm based on a few clinical indicators, reference tables in order to apply distance walked values more efficiently in the individual patient at his/her entry into a cardiac rehabilitation program. A total of 2,555 consecutive patients admitted between January 2001 and December 2002 to the Cardiac Rehabilitation Department of the S. Maugeri Foundation early after cardiac surgery performed a 6-min walking test within the fourth day of hospital admission. The mean walked distance was 296 +/- 111 m (+/- SD). At multiple regression analysis, age, sex, and comorbidity were independent predictors of walking test performance. The left ventricular ejection fraction only influenced the walked distance in men. Starting from these variables, we propose an algorithm and specific reference tables. Reference values for gender-, age-, comorbidity-, and systolic function-related test performance in patients after cardiac surgery at the beginning of the rehabilitative phase are provided. Once a new patient has been categorized through simple parameters, the actual distance walked could be compared with the matched reference value, thus making the interpretation of the result more efficient. The walked distance might be used to define different levels of disability and to personalize therapeutic exercise prescriptions.<sup>183</sup>

The study was designed to evaluate the prognostic value of the 6-min walk test (6MWT) in patients with mild to moderate congestive heart failure (CHF). Two hundred and fourteen patients (119 men and 95 women, mean age 64 years) were followed for a mean period of 34 months to assess event-free survival (death, heart transplantation). Sixty-six patients (34%) died (63 cardiovascular causes, 2 cancer and 1 stroke) and five patients underwent heart transplantation. For patients who walked <300 m during the 6MWT, survival was 62% compared with 82% in patients who walked 300-450 m or >450 m. With univariate analysis, NYHA class was the strongest predictor of death. LVEF ( $P < 0.0001$ ), aetiology of heart failure ( $P < 0.001$ ), LV filling pattern ( $P = 0.002$ ) and 6MWT distance ( $P < 0.01$ ) were all significantly related to survival. No significant relationship was found between survival, peak oxygen consumption or anaerobic threshold. Multivariate analysis using the Cox-stepwise regression model showed that LV fractional shortening ( $P < 0.009$ ) and 6MWT distance ( $P < 0.0005$ ) were the strongest prognostic markers.

## CONCLUSION

The present study, therefore, measured ventilatory variables and heart rate during the 6MWT and symptom-limited incremental maximal exercise testing in 20 patients with PAH. The distance walked in 6 min was 450 +/- 22 m (mean +/- se). During the 6MWT, ventilation, O<sub>2</sub> consumption, CO<sub>2</sub> production and heart rate increased during the first 3-4 min, and then remained stable. As compared with the maximum values measured during the cardiopulmonary exercise test, O<sub>2</sub> consumption tended to be higher (14.2 +/- 0.6 versus 12.9 +/- 0.7 mL.kg<sup>-1</sup>.min<sup>-1</sup>), while maximum ventilation (46 +/- 3 versus 57 +/- 4 L.min<sup>-1</sup>), respiratory quotient (0.90 +/- 0.02 versus 1.15 +/- 0.02)

and heart rate (119+/-4 versus 135+/-4 beats.min-1) remained lower. In conclusion, patients with pulmonary arterial hypertension exercise at higher aerobic capacity and lower metabolic stress during the 6MWT than during a cardiopulmonary exercise test

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