Original Study

Long-term non-invasive mechanical ventilation improves six minutes walk distance in patients with chronic respiratory failure*

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SUMMARY. AIM: To investigate the effect of long-term non-invasive mechanical ventilation (LTMV) on exercise performance measured by the 6-minute walk test (6MWT) in patients with chronic respiratory failure (CRF). **MATERIALS AND METHOD:** A prospective study was conducted in a tertiary referral hospital between January 2007 and April 2008 on 21 consecutive patients with a diagnosis of CRF and indications for non-invasive mechanical ventilation (NIV) at home. The patients were evaluated using the 6MWT on two occasions; before the LTMV therapy and in the 6th month of therapy. Dyspnoea and fatigue were evaluated by a modified Borg scale at the beginning and at the end of the 6MWT. Other factors evaluated included the type of NIV device, inspiratory and expiratory pressures, arterial blood gasses (ABG), pulmonary function tests (PFT) and the findings on transthoracic echocardiography (TTE). **RESULTS:** Of the 21 patients, 14 were male, 14 (66.7% had chronic obstructive pulmonary disease (COPD), 2 (9.5%) had kyphoscoliosis, 2 (9.5%) had obstructive sleep apnoea syndrome (OSAS), 2 (9.5%) had tuberculosis sequelae, and one (4.8%) had obesity hypoventilation syndrome (OHS). The mean 6MWT distance was found to have increased from 237.71 m to 295.14 m with the use of LTMV for 6 months. Improvement was detected in the mean PaO_2/FiO_2 ratio, from 259 mmHg to 269.57 mmHg. No change was observed in the resting dyspnoea scores and fatigue scores with the use of LTMV at the beginning of 6MWT, but the dyspnoea scores at the end of 6MWT showed significant improvement with treatment. Blood gas analysis after LTMV use revealed no change in pH values, SaO_2 % or PaO_2/FiO_2 ratio. A borderline significant decrease was found in $PaCO_2$ ($p= 0.057$). Among PFT values, statistically significant increase was observed only in forced expiratory volume in one second (FEV1). **CONCLUSION:** LTMV use in patients with CRF results in significant improvement in exercise capacity. 6MWT can be a useful tool for the objective evaluation of functional exercise capacity in patients with CRF. ***Pneumon 2014, 27(3):220-225.***

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INTRODUCTION

Long-term noninvasive mechanical ventilation (LTMV) is widely used for the treatment of chronic respiratory failure (CRF), because of its beneficial effects on morbidity and mortality, particularly in CRF due to chest wall and neuromuscular diseases. The use of LTMV results in improvement in gas exchange, ventilation and cardiac function, decreases mortality and hospitalization due to respiratory diseases, and improves quality of life (QoL) and sleep[1]. Chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (OHS) are the most common indications for LTMV.

Among the goals of treatment in the patients with CRF, studies highlight the importance of preserving and improving the functional capacity of the patients[1,2]. This study aimed to demonstrate the change in exercise capacity with the use of LTMV, and the efficacy of the 6-minute walk test (6MWT), an objective measurement, in monitoring LTMV therapy.

MATERIALS AND METHOD

This was a prospective cross-sectional study conducted in an intensive care unit (ICU) of a tertiary referral hospital. The study group consisted of 21 consecutive patients with the diagnosis of CRF, who had indications for the application of non-invasive ventilation (NIV) at home between January 2007 and April 2008. The patients were evaluated using 6MWT twice by the same trained physiotherapist; once before the start of LTMV therapy and once at follow-up at the end of the 6th month of treatment. Fatigue and dyspnoea were evaluated by a modified Borg scale at the beginning and at the end of the 6MWT. Clinical characteristics, complaints and physical examination findings of the patients, the type of NIV device, inspiratory and expiratory pressures, laboratory results, arterial blood gases (ABG), pulmonary function tests (PFT) and transthoracic echocardiography (TTE) data were recorded on the occasion of each 6MWT. The study was approved by the local Ethical Committee and informed consent was obtained from all the participants.

The blood sample for ABG analysis was taken according to the Allen test from the radial artery with an injector washed with at least 0.1 ml heparin and inserted at a right angle, with the patient in a sitting position. ABG analysis was performed in the ICU by Bayer Rapidlab 348 (Germany) brand ABG measuring device, measuring the parameters pH, $PaCO_2$, PaO_2, HCO_3, and SaO_2. All the patients included in the study had hypercapnic respiratory insufficiency, with $PaCO_2$ >45 mmHg.

Arterial oxygenation independent of the change in FiO_2 was evaluated using the parameter PaO_2/FiO_2[3].

PFTs were performed in the hospital Pulmonary Function Test Laboratory using a ZAN 300 (Germany) spirometry device with the patient in the 90° seated position and the nose closed; the best result of at least three forced expiration maneouvres was used. Body mass index (BMI) was calculated from the height (cm) and body weight (kg) of each subject for the spirometric measurements and percentages of the estimated and measured values were calculated. Measurements were performed in accordance with the recommendations of the American Thoracic Society (ATS)[4]. Spirometric measurement recording included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, and the volume between 25% and 75% of forced expiratory flow (FEF 25 - 75).

The patients performed the 6MWT according to the ATS 2002 consensus[5]. They were asked to walk for 6 minutes on a 50m corridor marked at 3 m intervals, as rapidly as possible with their own tempo. The test was supervised by a single observer. The patients were informed of the method prior to the test and were told that they could slow down if they were feeling shortness of breath and take a rest whenever they wanted, and that they would be allowed to start the test again and to continue. During the test the patients were encouraged with the standard words as defined in the test guidelines. Blood pressure, heart rate and saturation values were recorded before and at the end of test. The degrees of dyspnoea and fatigue were assessed by modified a Borg Scale at the beginning and at the end of test, categorized between 0 and 10.

Patients who had been receiving oxygen therapy for a long time and those with SO_2 <88%, measured by pulse oximetry before the 6MWT, walked under oxygen support. The distance walked in 6 minutes was measured at the end of the test.

The heart rate achieved during 6MWT was evaluated according to the maximum heart rate, calculated using the formula 220 - age[6].

All patients underwent detailed transthoracic echocardiographic examination (Vivid 5 GE Healthcare, USA). Left ventricular systolic function was calculated by the ejection fraction (volumetric, biplane Simpson method). Valvular pathology, wall movement defects, congenital anomalies and hypertrophic changes were recorded.

Right ventricular systolic pressure was obtained by peak systolic velocity obtained from tricuspid insufficiency

flow and $P= 4v^2$ formula. Pulmonary arterial pressure (PAP) was calculated by adding the right atrial pressure value to the above measurement.

Systolic PAP was calculated using the Bernoulli equation:Systolic PAP= [4 x (tricuspid insufficiency flow rate)^2] + right atrial pressure.

Right atrial pressure was estimated from the subcostal image according to the diameter of the inferior vena cava and variability of the vein during respiration (inspiratory collapse).

Statistical analysis

Statistical analysis was performed with NCSS 2007&PASS 2008 Statistical Software (Utah, USA). Categorical variables were presented as number of cases (percentage), continuous variables as mean ± standard deviation), and as median, range. The paired Student's *t*-test (when normally distributed) or Wilcoxon test (when non-normally distributed) were used to test for differences within groups. Correlations between parameters were assessed by Spearman's correlation analysis. $p<0.05$ was considered statistically significant.

RESULTS

Baseline demographic characteristics of the 21 participants with CRF are demonstrated in Table 1. Of the 21 patients, 7 (33.3%) were female and 14 (66.7%) were male, and the mean age was 61.71±12.07 years; 14 (66.7% had chronic obstructive pulmonary disease (COPD), 2 (9.5%) had kyphoscoliosis, 2 (9.5%) had obstructive sleep apnoea syndrome (OSAS), 2 (9.5%) had tuberculosis sequelae, and one (4.8%) had obesity hypoventilation syndrome (OHS). The mean time since diagnosis was 9.71±7.96 months. There were 10 patients who had quit smoking, for a mean of 12.1±7.01 years. The mean smoking rate was 40 [75-0] pack-years.

6-MWT was evaluated before and after 6 months of NIV treatment. The treatment resulted in no significant change in dyspnoea scores obtained before the test (1, [7-0]; 0, [3-0]; p= 0.277), but the dyspnoea scores at the end of 6MWT showed significant increment with treatment (1, [6-0]; 3, [8-0]; p= 0.008).

NIV treatment produced no change in fatigue scores either at the beginning or at the end of 6MWT ([0 [9-0]; 2 [10-0]; p= 0.497] and [0 [10-0]; 0 [10-0]; p= 0.832] respectively).

Before LTMV, the median distance walked by the patients during the 6MWT was 250m, range 0-440m. After 6 months of LTMV, the median distance walked by the patients during the 6MWT was 300m, range 150-500m, and the mean distance was 295.14±94.31m. The increase in

TABLE 1. Baseline demographic characteristics of 21 patients with chronic respitatory failure.

Age	34-77 years	Mean	61.71±12.07 years
Gender	Female	n: 7	33.3%
	Male	n: 14	66.6%
Duration of diagnosis	0-30 months	Mean	9.71±7.96 months
Smoking	0-75 pack-years	Mean	(33.0±25.71 years)
Diagnoses	Kyphoscoliosis	2	9.5%
	COPD	n: 14	66.7%
	OHS	n: 1	4.8%
	OSAS	n: 2	9.5%
	TB sequelae	n: 2	9.5%
Ventilator type	BIPAP	n: 4	19%
	BIPAP/S	n: 8	38%
	BIPAP/ST	n: 9	43%
Ventilator pressure		**Min-Max (cm H20)**	**Mean±SD (cm H20)**
	IPAP	10-28	19.38±5.40
	EPAP	5-10	6.19±1.20

COPD: Chronic obstructive pulmonary disease, OHS: Obesity hypoventilation, OSAS: Obstructive Sleep Apnoea, TB: Tuberculosis, IPAP: Inspiratory positive airway pressure, EPAP: Expiratory positive airway pressure.

TABLE 2. Change in SO_2 (%) and pulse rate during 6-minute walk test (6MWT) in 21 patients with chronic respiratory failure before and after long-term non-invasive mechanical ventilation (LTMV)

		Min-Max	Mean±SD	P
Before LTMV	Difference in SO_2 (%)	-29.0 - 5.0	-6.55±8.84	0.629
	Difference in pulse rate	0-56	17.72±16.23	0.685
After LTMV	Difference in SO_2 (%)	0-27	8.90±7.35	0.938
	Difference in pulse rate	1-56	18.0±12.26	0.919

SO_2%= oxygen saturation.

the distance walked before and after LTMV was statistically significant (p= 0.002). There was no correlation between the distance walked and the changes in desaturation ratio and pulse during the 6MWT after LTMV (p >0.05) (Table 2). Moderate positive correlation was detected between the distance walked and PaO_2/FiO_2 after LTMV (r: 0.523, p= 0.015) (Figure 1).

Of the PFT measurements, only FEV1 showed a statistically significant change (p= 0.031) after LTMV. In ABG gas analysis, the pH value the SO_2 (%) ratio average and PaO_2/FiO_2 ratio showed no change, while the $PaCO_2$ pressure decreased slightly after LTMV (p= 0.057) (Table 3).

TABLE 3. Arterial blood gases and respiratory function tests before and after 6 months of long-term non-invasive mechanical ventilation (LTMV) in 21 patients with chronic respiratory failure.

	Before LTMV	**After LTMV**	P value
pH	7.41±0.05	7.41±0.03	0.890
PaO_2/FiO_2	259.0±32.84	269.57±50.13	0.337
PCO_2	55.30±7.70	50.28±9.82	0.057
SO_2 (%)	88.3±5.83	88.72±5.68	0.790
FEV_1 (Lt)	0.83±0.40	0.89±0.44	0.031
FVC (Lt)	1.21±0.53	1.35±0.64	0.142
FEV_1/FVC (%)	69.96±20.81	70.38±18.94	0.874

PaO_2/FiO_2: partial arterial oxygen gas pressure/Fraction of inspired oxygen, PCO_2: partial arterial carbon-dioxide pressure, SO_2%: oxygen saturation, FEV_1: Forced Expiratory Volume at 1st second, FVC: Forced Vital Capacity.

DISCUSSION

The present study corroborated the documented benefit of LTMV, and showing a statistically significant increase in the 6MWT distance with long term NIV use (6 months) in a series of patients with CRF from various causes (COPD, kyphoscoliosis, OSAS, tuberculosis sequelae and OHS).

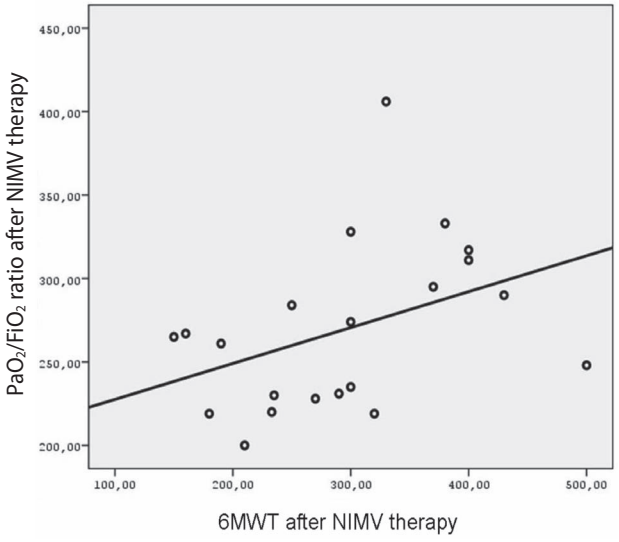

FIGURE 1. The relation between 6-minute walk test (6MWT) distance and PaO_2/FiO_2 after non-invasive mechanical ventilation (NIMV) therapy in 21 patients with chronic respiratory failure (r: 0.52, p<0.015) Spearman's correlation coefficient).

The use of long term oxygen support and/or LTMV in CRF is based on evaluation during a stable period. LTMV has been reported to result in improvement in gas exchange, ventilation, and cardiac function, decrease in the rate of mortality and hospitalization due to respiratory disease and improvement in QoL and sleep[1]. COPD and OHS are the most common indications for NIMV and both show gradually increasing prevalence.

The measurement of walk distance is a quick, cheap method for the evaluation of physical endurance and it reflects the capacity of daily activity. It has been reported that the results of 6MWT provide a better marker for mortality, independent of FEV_1 and BMI, and a short walk distance has been associated with increased mortality rate[7,8]. Cote and colleagues reported that a 6MWT distance of less than 350m is a poor prognostic factor in patients

with COPD[9]. One study followed patients with COPD for 5 years and demonstrated that the higher the decrease of 6MWTthe shorter the survival rate[10], and that an annual decrease in walk distance of 54m was an indication of poor prognosis. Despite the documented contribution of LTMV to improvement in QoL and laboratory parameters, the number of reports on its contribution to exercise capacity has been limited. In the present study, LTMV was demonstrated to increase the exercise capacity of patients with CRF as assessed by 6MWT.

Specifically, this study demonstrated that after receiving LTMV therapy for 6 months there was no change in the fatigue scores of patients according to modified Borg scale before and after 6MWT, but an increment in the dyspnoea score. These scores are subjective because they are defined by the perception of the patients. Although after using LTMV for 6 months, the patients defined themselves as more dyspnoeic at the end of the 6MWT, they achieved longer walking distances. In one study on patients with COPD a significant correlation was found between the perception of dyspnoea and walking distance; increased dyspnoea perception was related to decreased walking distance[10], and Carter and colleagues also reported that the 6MWT distances were correlated with changes in symptoms[11]. In the present study, it was found that although the dyspnoea perception increased, walking distance also increased. This increased perception of dyspnoea in patients under LTMV therapy, accompanying their increase in performance, may be due to their emotional status; it may also be an indicator of their increased respiratory dysfunction at the time when they were not having LTMV therapy.

Cochrane meta-analysis of the effects of LTMV in hypercapnic patients with COPD revealed that nocturnal LTMV use for at least 3 months has neither clinical nor statistically significant effect on PFT, gas exchange, respiratory muscle strength or exercise tolerance; however, small studies have stressed the significant effects of LTMV on these parameters[12]. The present study identified an increase only in FEV_1 when PFT before LTMV was compared with PFT after LTMV. Absence of a significant change in the other parameters of PFT might be due to low number of study participants.

Although many studies have found LTMV use controversial in patients with COPD and CRF, various improvements with its use have been documented: in QoL measured in the third month; a decrease in $PaCO_2$ values detected in the first month, and an increase in PaO_2 values and decrease in duration of hospital stay detected in the 6th month of LTMV use[2]. Among the ABG parameters also used in monitoring LTMV therapy, pH and saturation (%) values and calculated PaO_2/FiO_2 rates were found unchanged in the present patient group. A slight increase was noted in $PaCO_2$ values. Despite improvement, particularly in the PaO_2/FiO_2 ratio, its remaining under hypoxia level (PaO_2/FiO_2 <300) was attributed to the high grade of disease in the study group.

Laboratory parameters such as $PaCO_2$, PO_2, and SO_2 are used in the diagnosis, follow up and management of patients with CRF. According to these parameters, attempts are made to provide the optimum level of oxygen to maintain vital functions and to eliminate CO_2. Many studies have shown that desaturation during daily life activities cannot be adjusted with respect to the resting arterial gas profile only[13,14]. One study comparing the desaturation levels during daily life and during 6MWT showed that 6MWT helps in indicating the levels of daily desaturation and also provides information on the oxygen flow required to correct exercise-related desaturation[15]. The same study reported that pulse oximetry monitoring with 6MWT is better than daily routine pulse oximetry for detecting exercise-related desaturation.

The authors suggest that 6MWT, which is simple, cost effective and does not require sophisticated equipment, is more beneficial and objective in monitoring patients with CRF and in evaluating their exercise tolerance and the effects of LTMV on these patients, than the subjective scores (Borg scales) and laboratory tests (PFT, ABG). The present study has some important limitations. It included hypercapnic patients who (>45 mmHg). There are no established evidence-based criteria for the indications for long term use of NIMV, so the authors had to use empirical selection. There are no data available on compliance to NIV therapy. The methodological approach on the selection of ventilator type was based on traditional criteria, such as the presence of apnoea, accompanying sleep disorders, etc. The selection algorithm should have been established more precisely. The other limitations are related to the lack of a control group and the very small sample size, and finally, the study group was very heterogeneous.

CONCLUSION

In conclusion, the 6MWT is an effective tool in the patients who have CRF to evaluate the effectiveness of LTMV. On the other hand, the LTMV may increase the exercise capacity of the patients with CRF.

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Conflicts of interest

The authors have no conflict of interest.

REFERENCES

1. Leger P, Bedicam JM, Cornette A, et al. Nasal intermittent positive pressure ventilation: Long-term follow-p in patients with severe chronic respiratory insufficiency. Chest 1994; 105:100-5.
2. Tsolaki V, Pastaka C, Karetsi E, et al. One-year non-invasive ventilation in chronic hyperkapnic COPD: Effect on quality of life. Respiratory Meedicine 2008; 102:904-11.
3. Modell JH, Graves SA, Ketover A. Clinical course of 91 consecutive near-drowning victims. Chest 1976; 70:231-8
4. American Thoracic Society. Standardization of spirometry. 1987 update. Statement of the American Thoracic Society. Am Rev Respir Dis 1987; 136:1285-98.
5. Casaburi R, Coates AL, Enright PL, et al. ATS Statement: Guidelines for the Six-Minute Walk Test. American Journal of Respiratory and Critical Care Medicine. 2002; 166:111-7.
6. Fox EL, Bowers RW, Foss ML. The physiological basis of physical education and athletics. Dubuque: Wm C Brown Publishers 1989; 435.
7. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 2004; 23:28-33.
8. Szekely LA, Oelberg DA, Wright C, et al. Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. Chest 1997; 111:550-8.
9. Cote CG, Casanova C, Marin JM, et al. Validation and comparison of reference equations for the 6-min walk distance test. Eur Respir J 2008; 31:571-8.
10. Casanova C, Cote CG, Marin JM, et al. The 6-min walking distance: long-term follow up in patients with COPD Eur Respir J 2007; 29:535-40.
11. Carter R, Holiday DB, Nwasubura C, Stocks J, Grouthues C, Tiep B. 6-minute walk work for assessment of functional capacity in patients with COPD. Chest 2003; 123:1408-15
12. Wijkstra PPJ, Lacasse Y, Guyatt GH, Goldstein R, Struik F. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. Cochrane Library 2009, Issue 3.
13. Morante F, Güell R, Mayos M. Efficacy of the 6-Minute Walk Test in Evaluating Ambulatory Oxygen Therapy. Archivos de Bronconeumologia 2005; 41:596-600.
14. Morrison D, Skwarski KM, MacNee W. The adequacy of oxygenation in patients with hypoxic chronic obstructive pulmonary disease treated with long-term domiciliary oxygen. Respir Med 1997; 91:287-91.
15. Pilling J, Cutaia M. Ambulatory oximetry monitoring in patients with severe COPD: a preliminary study. Chest1999; 116:314-21.