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ORIGINAL ARTICLE

The Correlations of the Six-minute Walk Test and Respiratory Functions in Chronic Obstructive Pulmonary Disease Patients with Chronic Hypercapnia

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Background: Dyspnea and related disabling symptoms are common in chronic obstructive pulmonary disease (COPD) patients with chronic hypercapnia. Unfortunately, the indicators during the six-minute walk test (6MWT) for prediction of respiratory functions or exercise intolerance in severe COPD has been little investigated. The relationship between parameters during the 6MWT and respiratory functions was therefore assessed in COPD patients with chronic hypercapnia.

Methods: In 2002 and 2003, 37 COPD outpatients with chronic hypercapnia performed the 6MWT, and their respiratory function was measured. Twenty-eight males and nine females with COPD (mean forced expiratory volume in the first second of 26.1% of the predicted value, SD 7.7%) and hypercapnia (mean $PaCO_2$ of 55.5 mmHg, SD 6.4 mmHg) were recruited. All patients were tested to measure pulmonary function, respiratory drive (airway occlusion pressure at 100 ms, $P_{0.1}$), and respiratory muscle strength on the first day. On the second day, arterial blood gas analysis and the 6MWT were performed. Pearson's correlation coefficient and regression analysis were used for data analysis.

Results: The study showed that the six-minute walk distance (6MWD) was weakly correlated with the resting arterial oxygen partial pressure (PaO_2) ($r = 0.349$, $p = 0.034$), expiratory muscle strength (Pemax) ($r = 0.358$, $p = 0.030$), and changes of dyspnea sensation (ΔBorg) ($r = 0.385$, $p = 0.019$); furthermore, ΔBorg was weakly correlated with Pemax ($r = 0.377$, $p = 0.021$). The oxygen saturation measured at the end of the 6MWT ($ExSpO_2$) was significantly correlated with FEV_1/FVC ($r = -0.443$, $p = 0.006$), pH ($r = 0.375$, $p = 0.022$), arterial carbon dioxide partial pressure ($PaCO_2$) ($r = -0.470$, $p = 0.003$), PaO_2 ($r = 0.664$, $p = 0.000$) and $P_{0.1}$ ($r = -0.344$, $p = 0.037$). The results of the multiple linear regression with the 6MWD as the dependent variable revealed that PaO_2, Pemax, and ΔBorg were significant determinants of the 6MWD ($p = 0.018$, adjusted $R^2 = 0.259$).

Conclusion: Measurement of the 6MWT demonstrated that a stronger association of exercise limitation is the value of ΔBorg in COPD patients with chronic hypercapnia. Ventilation constraints, hypoxemia, hypercapnia, and respiratory drive might be associated with oxygen desaturation during the 6MWT in COPD patients with chronic hypercapnia.

1. Introduction

Previous studies showed that hypercapnia in severe COPD patients is always associated with a reduced exercise capacity, and higher morbidity and mortality.[1–3] Recently, the exercise capacity evaluated by the six-minute walk test (6MWT) was shown to be an independent outcome predictor to provide graded severity of this disease in addition to the forced expiratory volume in the first second (FEV_1).[4–7] Furthermore, two prospective studies demonstrated that the six-minute walk distance (6MWD) is a better predictor of mortality than FEV_1 in patients with severe COPD.[8,9]

The 6MWT can be easily performed, and associated parameters during 6MWT could provide important indicators for treatment. Besides walking distance, the degree of dyspnea, oxygen desaturation, and pulse rate, the four variables in the 6MWT, can be used to evaluate integrated responses of the pulmonary, cardiovascular, and muscular systems. It was recently found that the oxygen desaturation profile during walking improves the predictive ability of the 6MWT.[10–12] However, little is known about the correlations of respiratory functions and these parameters during the 6MWT in severe COPD patients with chronic hypercapnia.

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A study by Simard et al. demonstrated that patients with deteriorated lung function remained normocapnic at rest by increasing minute ventilation. While those who did not increase their ventilation developed chronic hypercapnia at rest during the 2–4-year follow-up period and were also associated with severe exercise limitations. But the relationships between the arterial carbon dioxide partial pressure ($PaCO_2$), arterial oxygen partial pressure (PaO_2), and forced expiratory volume in first second (FEV_1) are weak.[13] An excessive load on respiratory muscles and a decreased central inspiratory drive were also proposed for those severe patients.[14–16] Thus we hypothesized that those respiratory functions may contribute to strong exercise limitations in severe COPD patients with chronic hypercapnia, and the 6MWT may provide clinically relevant implications with increased predictive ability. Therefore, in this study, we measured respiratory functions and the 6MWT in COPD patients with chronic hypercapnia to: (1) investigate the relationships of four domains of respiratory functions (pulmonary function, arterial blood gas, respiratory muscle strength, and respiratory drive) with walking distance by 6MWT; (2) investigate the relationship of parameters during the 6MWT and respiratory function; and (3) analyze the predictors of walking distance in COPD patients with chronic hypercapnia.

2. Methods

2.1. Design

This study used a cross-sectional, observational design. We followed the principles outlined in the *Helsinki Declaration*. Informed consent was obtained from all participants.

2.2. Participants

Thirty-seven patients with COPD and hypercapnia were recruited from the outpatient clinic of Taipei Medical University–Wan Fang Hospital from January 2002 to December 2003. Enrollment criteria were those with: (1) FEV_1 of <50% of the predicted value; (2) a daytime awake $PaCO_2$ of >45 mmHg,[17] PaO_2 of <80 mmHg , and pH of 7.30–7.45 with room air; (3) medical stability in the preceding 3 months; (4) good motivation to participate in the study; and (5) have not received pulmonary rehabilitation programs. Exclusion criteria were those: (1) who could not perform the 6MWT due to various other diseases (such as orthopedic or neuromuscular problems or other systemic diseases); and (2) who were uncooperative or poorly motivated to participate.

2.3. Measurements

Patients were asked not to use oxygen for 4 h or a bronchodilator for 8 h before the tests. The measured items included a pulmonary function test, arterial blood gas, the 6MWT, respiratory muscle strength, and respiratory drive.

We measured four parameters of the pulmonary function test, including forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) with a portable spirometer (Spiro analyzer ST 250, Fukuda, Sangyo, Japan) according to recommendations of the American Thoracic Society.[18]

During measurements of respiratory drive and muscle strength, the mouthpiece was connected to a pneumotach with an electronically controlled magnetic shutter valve (Erich Jaeger, Hoechberg, Germany). The shutter was activated at end-expiration in irregular intervals during measurement. At the end of expiration, the shutter was automatically set. After 100 ms, we measured the inspiratory mouth pressure ($P_{0.1}$) when the patient attempted to inhale.[19] The mouth occlusion pressure ($P_{0.1}$) was expressed as an absolute value (cmH_2O). The $P_{0.1}$ data were obtained from the mean calculated value of the last 10 breaths. We measured subjects' mouth occlusion pressure at maximum inspiratory (Pimax) and maximum expiration (Pemax) with a spirometer-Master Screen PFT (Erich Jaeger) when the patient was seated. Pimax was measured when the patient maximally inspired from the residual volume, whereas Pemax was recorded as a subject's maximum expiratory effort from the total lung capacity. The shutter was closed and the pressure was measured automatically as soon as the patient began to inhale. Procedures were repeated until three measurements with variability of <5% were acquired. We used the highest value obtained in the data analysis.

On the second day, arterial blood samples were taken at rest while the patients were breathing room air. An arterial blood gas analysis was performed using a gas analyzer (Corning 278 Blood Gas Analyzer, Ciba-Corning Diagnostics, MA, USA). Then the patients completed two 6MWTs per assessment, 1 h apart, following recommendations of the American Thoracic Society Statement.[4] To exclude a learning effect, all subjects were allowed to practice the 6MWT for 1 week before the study.

Patients performed the 6MWT in a 24 m corridor. We encouraged subjects every minute with two phrases: "You are doing well" and "Keep up the good work." They were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt able to continue. Supplemental oxygen was provided to maintain SpO_2 at >90% if needed. We used the higher value of the two walking tests for analysis to minimize training effects.

We used a pulse oximeter (3301, BCI International, WI, USA) for real data on the pulse rate (PR) and oxygen saturation (SpO_2) measurements per 6 s, and the data were continuously printed with time. The modified Borg scale was evaluated at rest and after the test (expressed as RBorg and ExBorg).[20] The verbal descriptors in the original 10-point Borg scale had been carefully translated into Chinese.[20] Patients were instructed to quantify the intensity of breathlessness at rest and immediately at the end of walking. The RPR and $RSpO_2$ represent PR and SpO_2 after 5 min of complete rest, while ExPR and $ExSpO_2$ represent PR and SpO_2 immediately at the end of the 6MWT. Physiological changes after the 6MWT in the PR (ΔPR), SpO_2 (ΔSpO_2), and Borg scale (ΔBorg) were calculated as "end of exercise" minus resting values.

2.4. Data analysis

The Pearson correlation coefficient and Spearman rank correlation coefficient were calculated to examine the correlation between the 6MWT (distance, ΔBorg scale, ΔSpO_2, ΔPR, ExBorg , $ExSpO_2$ and ExPR) and four domains of respiratory function parameters (pulmonary function, arterial blood gas, respiratory muscle strength, and respiratory drive). Stepwise multiple linear regression analyses were further used to identify variables of respiratory functions that could best predict the walking performance. Respiratory function parameters which were correlated with the 6MWT were included in the stepwise multiple linear regression as independent variables. Statistical significance was accepted at a p value of <0.05.

3. Results

Table 1 summarizes patients' basic data of anthropometrics, pulmonary function, arterial blood gas, respiratory muscle, respiratory drive, and parameters during the six-minute walk test. The mean FEV_1/FVC ratio was 50.9% (SD 12.7%) in COPD patients with a mean FEV_1 of 0.6 L (SD 0.2 L) at 26.1% of the predicted value (SD 7.7%), and daytime hypercapnia with a mean $PaCO_2$ of 55.5 mmHg

Table 1 Patients' basic characteristics, respiratory functions and parameters during the six-minute walk test

Parameter	Mean ± SD ($N = 37$)	Range
Age (y)	64.4 ± 10.9	39–81
Gender M:F	28:9 (76%:24%)	
Weight (kg)	54.6 ± 13.4	32–83
Height (cm)	159.0 ± 8.1	137–173
Body-mass index (kg/m^2)	21.4 ± 4.8	13.30–34.67
Pulmonary function test		
FVC (L)	1.2 ± 0.5	0.5–2.0
FVC % of predicted	41.4 ± 17.1	14–105
FEV$_1$ (L)	0.6 ± 0.2	0.2–1.0
FEV$_1$ % of predicted	26.1 ± 7.7	9.0–48.0
FEV$_1$/FVC (%)	50.9 ± 12.7	31.0–70.6
Arterial blood gas		
pH	7.4 ± 0.04	7.3–7.5
PaCO$_2$ (mmHg)	55.5 ± 6.4	47.2–72.4
PaO$_2$ (mmHg)	52.1 ± 9.5	30.1–70.6
HCO3$^-$ (meq/L)	33.8 ± 3.8	28.0–44.7
BE (meq/L)	7.7 ± 3.5	2.5–17.6
Respiratory muscle strength		
Pimax (cmH$_2$O)	43.8 ± 18.1	15.9–81.5
Pemax (cmH$_2$O)	67.6 ± 23.3	26.9–119.7
Respiratory drive		
P$_{0.1}$(cmH$_2$O)	5.6 ± 2.6	0.4–11.5
Parameters during walk		
6MWD (m)	283.7 ± 113.0	36–456
RBorg	2.8 ± 1.1	1–5
ExBorg	5.8 ± 1.3	4–8
ΔBorg	2.9 ± 1.1	1–5
RSpO$_2$ (%)	86.0 ± 6.5	66–95
ExSpO$_2$ (%)	73.6 ± 10.4	49–92
ΔSpO$_2$ (%)	−12.4 ± 5.8	−29 − −3
RPR (beat/min)	103.8 ± 10.3	88–120
ExPR (beat/min)	129.2 ± 14.1	105–173
ΔPR (beat/min)	25.4 ± 14.7	3–59

BE = base excess; ExBorg = Borg score at the end of the 6MWT; ExPR = heart rate measured at the end of the 6MWT. ExSpO2 = oxygen saturation measured at the end of the 6MWT; FEV$_1$ = forced expiratory volume in the first second; FVC = forced vital capacity; HCO_3^- = arterial bicarbonate; P$_{0.1}$ = airway occlusion pressure at 100 ms; PaCO$_2$ = arterial carbon dioxide partial pressure; PaO$_2$ = arterial oxygen partial pressure; Pemax = maximum expiratory pressure; Pimax = maximum inspiratory pressure; RBorg = resting Borg score; RPR = resting heart rate; RSpO$_2$ = resting oxygen saturation. Changes after exercise of Borg scale, SpO$_2$, and PR are, respectively, represented by ΔBorg, ΔSpO$_2$, and ΔPR.

Table 2 Correlations of the six-min walk distance (6MWD) with respiratory functions and parameters during the six-minute walk test

	6MWD
Pulmonary function test	
FVC (L)	0.157
FEV1 (L)	0.175
FEV$_1$/FVC (%)	−0.092
Gas exchange	
pH	−0.018
PaCO$_2$ (mmHg)	−0.210
PaO$_2$ (mmHg)	0.349*
HCO3$^-$ (meq/L)	−0.194
BE (meq/L)	−0.145
Respiratory muscle strength	
Pimax (cmH$_2$O)	0.275
Pemax (cmH$_2$O)	0.358*
Respiratory drive	
P$_{0.1}$	−0.222
Parameters during walking	
ΔBorg	0.385*
ΔSpO$_2$	0.118
ΔPR	0.254
ExBorg	0.014
ExSpO$_2$	0.263
ExPR	0.104

BE = base excess; ExBorg = Borg score at the end of the 6MWT; ExPR = heart rate measured at the end of the 6MWT; ExSpO$_2$ = oxygen saturation measured at the end of 6MWT; FEV$_1$ = forced expiratory volume in the first second; FVC = forced vital capacity; HCO_3^- = arterial bicarbonate; P$_{0.1}$ = airway occlusion pressure at 100 ms; PaCO$_2$ = arterial carbon dioxide partial pressure; PaO$_2$ = arterial oxygen partial pressure; Pemax = maximum expiratory pressure; Pimax = maximum inspiratory pressure.
Changes after exercise in the Borg scale, SpO$_2$, and PR are, respectively, represented by ΔBorg, ΔSpO$_2$, and ΔPR.
* $p < 0.05$.

Table 3 Correlations between parameters during the six-minute walk test and respiratory function

	ΔBorg	ΔSpO$_2$	ΔPR	ExBorg	ExSpO$_2$	ExPR
Pulmonary function test						
FVC (L)	0.220	0.168	0.007	−0.115	0.263	−0.031
FEV$_1$ (L)	0.239	−0.087	0.120	−0.194	−0.052	−0.040
FEV$_1$/FVC (%)	−0.080	−0.358*	0.080	−0.106	−0.443*	0.003
Gas exchange						
pH	0.140	0.184	−0.087	−0.056	0.375*	−0.087
PaCO$_2$ (mmHg)	−0.17	0.186	−0.240	0.243	−0.470*	−0.178
PaO$_2$ (mmHg)	0.122	0.509*	0.129	−0.147	0.664*	0.024
HCO3$^-$ (meq/L)	−0.054	−0.133	−0.225	0.193	−0.256	−0.137
BE (meq/L)	0.072	−0.061	−0.185	0.253	−0.127	−0.098
Respiratory muscle strength						
Pimax (cmH$_2$O)	0.264	−0.099	0.196	0.090	0.079	0.139
Pemax (cmH$_2$O)	0.377*	−0.060	0.069	0.192	0.053	0.061
Respiratory drive						
P$_{0.1}$	0.105	−0.095	−0.319	0.280	−0.344*	−0.253

BE = base excess; ExBorg = Borg score at the end of the 6MWT; ExPR = heart rate measured at the end of the 6MWT; ExSpO$_2$ = oxygen saturation measured at the end of 6MWT; FEV$_1$ = forced expiratory volume in the first second; FVC = forced vital capacity; HCO_3^- = arterial bicarbonate; P$_{0.1}$ = airway occlusion pressure at 100 ms; PaCO$_2$ = arterial carbon dioxide partial pressure; PaO$_2$ = arterial oxygen partial pressure; Pemax = maximum expiratory pressure; Pimax = maximum inspiratory pressure.
Change after exercise in the Borg scale, SpO$_2$ and PR are, respectively, represented by ΔBorg, ΔSpO$_2$, and ΔPR.
* $p < 0.05$.

(SD 6.4 mmHg). Patients could walk an average of 283.7 m (SD 113.0 m).

Table 2 shows that the 6MWD was weakly correlated with resting: PaO$_2$ ($r = 0.349$, $p = 0.034$), the maximum expiratory pressure ($r = 0.358$, $p = 0.030$) and ΔBorg ($r = 0.385$, $p = 0.019$) in COPD patients with hypercapnia. As shown in Table 3, ΔBorg was weakly correlated with Pemax ($r = 0.377$, $p = 0.021$), and ΔSpO$_2$ was correlated with FEV$_1$/FVC ($r = -0.358$, $p = 0.030$) and PaO$_2$ ($r = 0.509$, $p = 0.001$). ExSpO$_2$ was significantly correlated with FEV$_1$/FVC ($r = -0.443$, $p = 0.006$), pH ($r = 0.375$, $p = 0.022$), PaCO$_2$ ($r = -0.470$, $p = 0.003$), PaO$_2$ ($r = 0.664$, $p = 0.000$), and P$_{0.1}$ ($r = -0.344$, $p = 0.037$).

The three significant variables, PaO$_2$, Pemax, and ΔBorg were included in the stepwise multiple linear regressions with the 6MWD (Table 4). PaO$_2$, Pemax, and ΔBorg were significant determinants of the 6MWD ($p = 0.018$, adjusted $R^2 = 0.259$). This explained 25.9% of the variance in the 6MWD.

4. Discussion

The average 6MWD in our patients with hypercapnic COPD was 283.7 m. We found that the ΔBorg score during the 6MWT was positively correlated with both the 6MWD and Pemax. This

Table 4 Stepwise multiple regression for the six-minute walk distance (6MWD)

Variable	Standardized β	t	p value	Adjusted R^2
Model 1			0.025*	0.136
ΔBorg	0.369	2.347	0.025*	
Model 2			0.011*	0.234
ΔBorg	0.336	2.228	0.033*	
PaO_2	0.314	2.083	0.045*	
Model 3			0.018*	0.259
ΔBorg	0.289	1.840	0.075	
PaO_2	0.254	1.582	0.123	
Pemax	0.179	1.068	0.293	

ΔBorg = change after exercise in the Borg scale; PaO_2 = arterial oxygen partial pressure; Pemax = maximum expiratory pressure.
* $p < 0.05$.

indicates that the CO_2 retention group reached almost severe dyspnic sensations (a Borg score of about 6 at the end of exercise) while walking, which makes it difficult to continue, so it seems that they recruited more expiratory muscles to reduce dynamic hyperinflation.[21] Furthermore, a longer walking distance would also indicate a higher tolerance level of dyspnea change. In previous studies, strong correlations were found among dynamic hyperinflation, neuromechanical dissociation, and the Borg score during a symptom-limited incremental cycle ergometric test in patients with COPD.[22] O'Donnell's study showed that the Δ end expiratory lung volume, Δ tidal volume, and Δ respiratory rate accounted for 61% of the variance in ΔBorg.[23] We therefore assumed that patients with stronger expiratory muscles would be able to relieve dynamic hyperinflation (a limiting factor of exercise) thus being able to walk a longer distance, so a greater dyspnea sensation change would also be present.[21–23]

As in previous studies, more expiratory muscle recruitment was found when the intensity of the dyspnic sensation rose to an intolerable level as greater dynamic hyperinflation occurred.[24] When ventilation increased during exercise, the functional residual capacity increased in COPD patients, in contrast to normal subjects who had increased inspiratory muscle activity. Consequently, this imposed an even-greater tonic load on inspiratory muscles, so a higher neural drive will necessitate the generation of lower tidal volumes. At the same time, the load on expiratory muscles disproportionately increased when ventilation increased. When this disproportionate increase in muscle load occurs, it can be a relevant factor in the sensation of dypnea. Severely hypercapnic COPD patients might blunt their response to CO_2 stimulation[17]; therefore, length-tension inappropriateness of respiratory muscles seems to override chemical inputs for dyspnea.[25] We therefore consider that more expiratory muscles were recruited, rather than inspiratory muscles, when a sense of higher breathlessness occurred during the 6MWT, to override the increasing mechanical load of hyperinflation. In addition, other studies have shown that CO_2 retention in stable hypercapnic COPD patients is mainly due to an inability of the lungs to increase ventilation, and not due to respiratory muscle dysfunction.[26]

We found oxygen desaturation of 73.6% at the end of the 6MWT ($ExSpO_2$) in our study. Furthermore, the $ExSpO_2$ also showed correlations with FEV_1/FVC, pH, $PaCO_2$, PaO_2, and $P_{0.1}$, which suggested that patients with greater restrictive constraints, more acidosis, higher $PaCO_2$, lower PaO_2, and a higher respiratory drive were more responsive to greater oxygen desaturation during the walking test. Previous studies reported that arterial hypoxemia during exercise occurs in severe COPD as a result of a fall in mixed venous tension on low ventilation-perfusion lung units and shunting. The ability to increase lung perfusion and to distribute inspired ventilation during exercise is also compromised.[27] High physiological dead space in the setting of a blunted tidal volume response to exercise in hyperinflated COPD further compromises CO_2 elimination and inspired ventilation. The derangements of blood gas, such as lower pH, higher $PaCO_2$, and less PaO_2, beyond critical levels will excessively stimulate ventilation, aggravate dynamic hyperinflation, and cause early ventilatory limitations to exercise.

It must be emphasized that, in this study, the chemical factors of pH, $PaCO_2$, and PaO_2, and the mechanical fators of FEV_1/FVC and $P_{0.1}$, contributed the $ExSpO_2$ during the walking test. The greater CO_2 retention of severe COPD patients, they would walk with more oxygen desaturation, an additional chemical stimulus, which might determine the sensation of dyspnea during the walking task, which in turn would induce exercise intolerance. Furthermore, during the 6MWT, the patients could self-adjust the walking speed, and the severe COPD patients usually took several breaks during the walking task. Therefore, the parameters of $ExSpO_2$, and not ΔSpO_2, during the walking task might be more predictable for baseline arterial blood gas of severe COPD patients, as shown by the significant correlation of $ExSpO_2$ with $PaCO_2$, PaO_2, and pH. We therefore agree that the 6MWT is sensitive for detecting oxygen desaturation in patients with COPD,[28] and that the 6MWT could provide clinicians a method of prediction of the baseline hypoxemia or hypercapnia level both noninvasively and safely.

In the present study, according to the stepwise multiple linear regression analyses, the PaO_2, Pemax, and ΔBorg accounted for only 25.9% of the variance in the 6MWD. Due to the multifactorial aspect of exercise intolerance in severe COPD patients, there was weak prediction of exercise capacity by PaO_2, Pemax and ΔBorg in our results; therefore, we suggest that other substantial factors in determining the exercise capacity of severe COPD patients with hypercapnia be further investigated.

This study had some limitations. First, the small sample size may have affected the power of the calculations. Second, this study lacked a control group for comparison. Third, COPD, a systemic disease, has severe impacts on physical function; therefore, skeletal muscle strength needs to be investigated further. Fourth, we did not measure the change of magnitude of hyperinflation after 6MWT, which is thought to be a stimulus of the dypnea sensation.

5. Conclusion

The resting PaO_2, expiratory muscle strength, and change in the dyspnea sensation during the 6MWT accounted for 25.9% of the variance in the 6MWD. Not only the FEV_1/FVC and $P_{0.1}$ but also the hypoxemia and hypercapnia in severe COPD patients with chronic hypercapnia might be attributable to exercise-induced oxygen desaturation during the 6MWT.

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