

Title page

Title:

Twitch mouth pressure and disease severity in patients with chronic obstructive pulmonary disease

Author(s): chunrong JU; wei LIU; Rong-chang CHEN

1. Chun-rong JU: Ph D, M.D; E-mail: chunrongju@163.com;

2. Wei LIU: M.D; E-mail: liuwei9921@163.com;

Affiliation: State Key Lab of the Respiratory Disease, Guangzhou Institute of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangdong, China

3. Corresponding author: Rong-chang CHEN, MD, Prof;

E-mail: chenrc_1234@163.com; chenrc@vip.163.com

Affiliation: State Key Lab of the Respiratory Disease, Guangzhou Institute of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangdong, China

Fax: 008620-83062729; Tel: 008620-83062870

The study was performed in the State Key Lab of the Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangdong, China

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The specific contributions of each contributor to the paper:

Dr chunrong JU: contributed to the literature search, acquisition of data, analysis and interpretation of data, and manuscript preparation and submission. *Dr Wei LIU:* contributed to the acquisition of data. *Professor Rongchang Chen:* contributed to conception and design of the study, interpretation of data and critical revision of the article.

Abstract

Introduction: Patients with chronic obstructive pulmonary disease (COPD) have impaired respiratory muscle strength. Twitch mouth pressure (TwPM) in response to magnetic stimulation of the cervical nerve has been suggested to clinically reflect inspiratory muscle strength. However, studies on TwPM values and their relationship with disease severity are limited. Thus, we tested the TwPM values of COPD patients and investigated the relationship of these values with disease severity.

Methods: We recruited 75 COPD patients and 63 age-matched controls. All participants were tested for TwPM, sniff nasal pressure (SNIP), and maximum static inspiratory mouth pressure (P_Imax); the BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index was evaluated for overall severity assessment and the six-minute walk distance (6-MWD) was used to determine the exercise capacity of COPD patients.

Results: COPD patients had markedly lower TwPM values compared with the controls [(10.00±2.17) vs. (13.66±2.20) cmH₂O for males, (8.83±0.89) vs. (11.81±1.98) cmH₂O for female, each with $p < 0.001$]. The TwPM values decreased with increasing COPD severity, and similar trends were observed in the SNIP and P_Imax values. Regression correlation analysis showed that TwPM values were significantly correlated inversely with the BODE index ($R = 0.65$; $p < 0.001$) but positively correlated with 6-MWD ($R = 0.59$; $p < 0.001$) in the COPD group; the SNIP values of COPD patients were also correlated inversely with their BODE index ($R = 0.49$; $p < 0.001$) but positively correlated with their 6-MWD ($R = 0.33$; $p < 0.005$).

Conclusion: TwPM values are 26.8% lower in male COPD patients and 25.3% lower in female COPD patients compared with the controls. The TwPM values of COPD patients decrease with increasing disease severity. TwPM was better correlated with the BODE index and exercise capacity than SNIP and P_Imax, which suggest that TwPM more accurately reflects the overall severity and burden of COPD.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have compromised respiratory muscle function, and inspiratory muscle weakness is an independent predictor of all-cause mortality among COPD patients^[1]. Moreover, hypercapnic respiratory failure caused by inspiratory muscle weakness has been recognized as the leading cause of death among COPD patients^[2]. Determining inspiratory muscle strength is therefore useful in evaluating strategies over preventive and therapeutic approaches for improving respiratory muscle strength. Measuring maximum static inspiratory mouth pressure (P_Imax) is a simple and widely used method for assessing inspiratory muscle strength^[3,4], but this technique is relatively difficult to perform and is subjective^[5]. An alternative method for measuring inspiratory muscle strength involves asking the subject to perform short sniffs at maximal intensity, and sniff nasal inspiratory pressure (SNIP) has been described in COPD patients^[6]. The SNIP maneuver is natural and probably easier to perform than the static effort required by P_Imax; nevertheless, the technique still depends on the cooperation of the subject. Considering the non-volitional technique of twitch transdiaphragmatic pressure in response to phrenic nerve stimulation has been described^[7], the test has been used to determine inspiratory muscle weakness^[8]. This test enables the more accurate assessment of inspiratory muscle contractility^[9], but is invasive because it requires the placement of esophageal and gastric balloon catheters. Thus, another alternative method, mouth pressure in response to magnetic stimulation of the phrenic nerves (TwPM) has been explored, which provides a simple, noninvasive, and objective method for assessing inspiratory muscle strength^[10,11]. However, studies on TwPM values and their relationship with disease severity in COPD are limited. The body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity (BODE) index is a multidimensional COPD index that has been proven superior to forced expiratory volume in the first second (FEV₁) in predicting the risk of death of patients, which can reflect the overall severity of the disease. Therefore, the present study aims to test the TwPM of COPD patients and to investigate the relationship of their BODE indices with their exercise capacity.

Material and methods

The protocol was approved by the Ethics Committee of Human Investigation of Guangzhou Medical University (Medical ethic number 2011-12). The participants provided their written

informed consent for the study.

Study subjects

The subjects consisted of 75 patients with a clinical diagnosis of COPD according to the GOLD guidelines^[12] and 63 age-matched control subjects (the participants ranged from 50 years to 78 years old). All participants underwent a clinical evaluation and were screened using pulmonary function tests. Patients with COPD were recruited from the outpatient clinics of Guangzhou Institute of Respiratory Disease (State Key Lab of Respiratory Disease), First Affiliated Hospital of Guangzhou Medical University. The inclusion criteria were as follows: spirometry-based diagnosis of COPD, previous smokers who have abstained from smoking for at least 3 years, and in stable condition for at least three months. The exclusion criteria were as follows: 1) Patients with major comorbidities or concomitant diseases that might alter muscle function. These comorbidities included neuromuscular disease, uncontrolled diabetes, thyroid disease, and cancer, etc.; some comorbidities such as osteoporosis and mild to moderate essential hypertension were not excluded from the study because these comorbidities had no effect on respiratory muscle strength. 2) Patients unwilling to participate or sign informed consent. The control group was recruited from the regular check-up department in the same hospital. The criteria for inclusion in control group were as follows: normal spirometry, non-smoker or has abstained from smoking for more than 10 years, and no history of medical illness at the time of the study. In addition, all subjects were assessed by an otorhinolaryngologist to exclude those with nasal septal deviation or rhinitis from the sample. This measure was adopted to ensure that the results of the sniff test were reliable.

The medical treatment of the patients at the time of the study mainly included inhaled bronchodilator therapy in the form of long-acting agonists and/or anti-cholinergic agents. In addition, 85% of the patients were on inhaled corticosteroids (400 µg to 800 µg of budesonide equivalent dose/day). None of the patients was on regular systemic corticosteroids.

Methods

Non-volitional test

Non-volitional test for assessing inspiratory muscle strength was conducted by measuring TwPM in response to magnetic stimulation of the cervical nerve, which was performed based on the method described in a previous study^[11]. The subjects were seated, with the neck flexed at

approximately 60° from the vertical, wearing a noseclip, and breathing gently through a conventional mouthpiece. During all measurements, breathing frequency and airflow were continuously monitored and plotted on a computer screen. The magnetic stimulation was performed manually using a nonresistant occlusion flow device. To prevent glottal closure, magnetic stimulation was performed at the functional residual capacity (FRC) under gentle inspiratory effort against the occluded airway with a small leak, and the inspiratory pressure trigger was approximately -0.5 kPa, according to previous studies^[10,13]. The phrenic nerve roots were stimulated using a cervical magnetic stimulator with a circular 90 mm coil (Magstim 2002; Magstim Inc; Dyfed, Wales, UK). The coil was placed over the spinous process of the C7 vertebra and then moved up and down the cervical spine along the midline until the maximum response was obtained at 80% power output. Thereafter, all stimulations were performed at the same position and at full magnetic output. The stimulations were performed 30 s apart to avoid twitch potentiation. Figure 1 is a photograph of a study participant during magnetic stimulation.

Insert figure 1

Mouth pressure was assessed using a differential water pressure transducer (range: ± 150 cmH₂O; China). The output signals of mouth pressure and the surface electromyograph of the respiratory muscles were recorded using a Powerlab 8/16SP analogue–digital instrument (National Instruments, Austin, TX, USA) and a personal computer (Apple Computer Inc., Cupertino, CA, USA) running Chart 5.1 software. The measurements were repeated at least five times, and the pressure tracings were visible to the operator until three satisfactory stimulations were obtained. The mean TwPM of three attempts were chosen for data analysis.

Volitional tests

Volitional tests consisting of P_Imax and SNIP assessments were performed on seated based on standard methods^[14]. The P_Imax was measured as the lowest pressure sustained for 1 s during a maximum inspiratory effort from residual volume^[14,15]. The subjects were instructed to breathe through the mouthpiece while wearing a noseclip. During the maneuver, the computer screen was visible to both the subject and monitor, and the subject was encouraged verbally with simultaneous visual feedback on the monitor. Every subject performed each measure at least five times until three acceptable and reproducible results were obtained, that is, with no leakage and with a less than 10% difference between measurements^[16].

The SNIP test was performed by placing a nasal plug in one of the nostrils (no preference for right or left) while keeping the contralateral nostril patent^[17,18]. The subjects were instructed to perform short sharp sniffs with a closed mouth, starting from FRC after a quiet breath. They were asked to breathe normally with a closed mouth and to perform 10 maximal, short, and sharp sniffs 30 s intervals. The FRC was not controlled but was identified as the end of expiration during quiet breathing. Similarly, the monitor was visible to the subjects, and the sniffs were recorded until no further increase in pressure could be obtained; the highest value was used for analysis^[16–18]. TwPM, SNIP, and PImax were all expressed as positive values even though they were negative with respect to the atmosphere.

Spirometric function

Spirometry was performed by experienced certified technicians at the lung function laboratory in the Key Laboratory. The lung function equipment met the criteria of the European Respiratory Society (ERS)^[19]. The height and weight of the subjects were recorded, with the subjects barefooted and wearing indoor clothing. Spirometry was performed on each seated subject using a MICROLAB 3300 spirometer (Micro Medical, Kent, UK), according to ERS standards. The best value of three recordings was used. The FEV₁ and FVC values are expressed as percentages of the predicted values, adjusted for age, gender, and height. The predicted values were those of the European Community of Coal and Steel approved by the ERS^[20]. For patients with COPD, irreversible airflow obstruction was confirmed using a post-bronchodilator (400 µg of salbutamol) FEV₁/FVC < 70%. The severity of airflow obstruction was classified according to the GOLD guidelines^[12].

Calculation of BODE index

The BODE index was calculated in COPD patients using the score proposed by Celli et al^[21]. Dyspnea was assessed according to the modified Medical Research Council scale^[22]. Exercise capacity was evaluated using the 6 min walk distance, based on the guidelines of the American Thoracic Society^[23]. The BODE index was calculated for each patient using variables obtained within 4 weeks of enrolment, and the total value for each patient ranged from 0 to 10, with higher scores indicating more severe disease.

Statistical analysis

Statistical analysis was performed using SPSS 12.0 package for Windows (SPSS Inc,

Chicago, IL, USA) and Graphpad Prism v. 5 (Graphpad Software Inc., San Diego, CA, USA). Normally distributed data are expressed as means \pm standard deviation (SD). Non-normally distributed data are expressed as medians (range). The level of statistical significance was set at $p < 0.05$. Two independent-sample t-tests and Chi-Square test were used for univariate testing between the COPD group and the control group. The differences among the multiple groups (controls and COPD patients at different GOLD stages) were tested by ANOVA, with the least significant difference test for post hoc pairwise comparison. The Pearson correlation coefficient was used to correlate the independent variables (age, weight, height, BMI, and history of smoking) with the dependent variables (TwPM, SNIP, and PImax, respectively) in the COPD group. Multiple regression modeling was developed stepwise to determine the dependent relationship of inspiratory muscle strength (TwPM, SNIP, and PImax values) with the BODE index, FEV₁%pred, and 6-MWD in COPD patients. The values were adjusted for confounding factors, including age, weight, height, BMI, and history of smoking.

Results

Characteristics of the subjects

No exclusions were imposed for all participants who submitted to the assessments. The characteristics of the controls and patients are detailed in Table 1. The gender constituent ratio significantly differed between the two groups. The two groups were matched in terms of age and height, but differences were observed for weight, BMI, inspiratory muscle strength, and history of smoking. The median number of pack years for previous smokers was [0 (0–7) pack-years] for the controls and [20 (0–35) pack-years] for the COPD patients.

Insert table 1

The spirometric function test showed that COPD patients exhibited severely obstructed airflow, as defined by the GOLD criteria, with FEV₁ less than 50% predicted. The patients were stratified for the disease severity based on GOLD guidelines as follows: stage II, 16 (14M and 2F); stage III, 32 (26 M and 6 F), and stage IV, 27 (23 M and 4 F) patients.

Muscle strength

Figure 2 shows a typical example of the TwPM recordings during magnetic stimulation of the cervical nerves in the healthy controls. The mean TwPM was significantly lower in COPD patients

than the controls [(10.00 \pm 2.17) vs. (13.66 \pm 2.20) cmH₂O for males (p < 0.001), (8.83 \pm 0.89) vs. (11.81 \pm 1.98) cmH₂O for females (p < 0.001). When stratified for disease severity based on the GOLD guidelines, TwPM decreased with increasing COPD severity, and the SNIP and PImax values exhibited similar trends (Table 2). Figure 3A shows the differences in TwPM between the COPD patients and the controls when stratified for gender. Figure 3B shows the differences in TwPM among the four subgroups (male controls, male COPD patients at GOLD stages II, III, and IV).

Insert figure 2

Insert table 2

Insert figure 3A and 3B

BODE index

Table 3 shows the results of the variables used to compute the BODE index of COPD patients, with stratification for the severity distribution based on the GOLD guidelines.

Insert table 3

Correlations

The Pearson correlation analysis showed that the TwPM values of COPD patients were significantly correlated with age (r = -0.24, p = 0.04) and BMI (r = 0.26, p = 0.02), but not with height (r = 0.17, p = 0.16), weight (r = 0.12, p = 0.29), or history of smoking (r = -0.14, p = 0.22). SNIP was slightly correlated with BMI (r = 0.228, p = 0.049), but not with age (r = -0.11, p = 0.34), height (r = 0.23, p = 0.05), or weight (r = 0.228, p = 0.049). None of the parameters was significantly correlated with the PImax of the COPD patients, each with p > 0.05.

Adjusting for the confounding factors, the multiple regression analysis showed that TwPM was moderately correlated inversely with the BODE index (R^2 =0.461, P <0.001) (Table 4), but positively correlated with 6-MWD and FEV₁%pred (each p < 0.05). The similar results were also observed for SNIP, but with lower R (Table 5). The PImax values were slightly correlated with the variables, with R values significantly lower than those for SNIP. Table 5 shows the correlation coefficients of inspiratory muscle strength (TwPM, SNIP, and PImax) with the clinical parameters of COPD.

Insert table 4

Insert table 5

Discussion

The present cross-sectional study investigated the differences in inspiratory muscle strength between COPD patients and age-matched controls using both volitional (SNIP and P_Imax) and non-volitional (TwPM) techniques. To our knowledge, this is the first study to describe separately the TwPM of male and female COPD patients and the relationship of TwPM with the BODE index in COPD. The principal findings are summarized as follows: (1) TwPM markedly decreased with increasing disease severity among patients with moderate to very severe COPD, similar to SNIP and P_Imax. (2) TwPM was better correlated with the BODE index and exercise capacity than SNIP and P_Imax, which suggests that TwPM more accurately reflects the overall severity of COPD than SNIP and P_Imax.

All of the subjects tolerated both the volitional (SNIP and P_Imax) and non-involitional (TwPM) techniques. TwPM, SNIP, and P_Imax were all significantly decreased among patients relative to controls. The result shows that all three techniques are suitable for clinically assessing inspiratory muscle strength in patients with moderate to very severe COPD. However, P_Imax was more difficult for subjects than TwPM and SNIP. When we analyzed the P_Imax values, we should consider the difficulty of subjects in performing maximal effort because this test is highly dependent on both their effort and instructions of individual technologists^[24]. Moreover, achieving the quality goal does not necessarily mean that the subject exerted maximal effort^[25]. SNIP was easier to performed and less unpleasant for each subject than the P_Imax test, which is consistent with previous studies^[26,27]. This finding confirms that SNIP could be used as an alternative or as a complement for P_Imax measurement^[28]. Nevertheless, SNIP also depends on volitional muscle contraction.

In contrast to the volitional tests P_Imax and SNIP, TwPM is an objective measurement independent of the instructions of the technologists and the learning curves and cooperation of subjects. Moreover, cervical magnetic stimulation was well tolerated by the subjects, and it facilitated the repeated measurement of inspiratory muscle contractility. These findings are consistent with those of previous studies^[10,11,29]. In addition, TwPM values are reportedly reproducible^[14] and highly correlated with the twitch transdiaphragmatic pressures under the same stimulation conditions^[11, 29,30], which indicates that TwPM values accurately reflect inspiratory

muscle strength. Nonetheless, TwPM test is non-invasive unlike twitch transdiaphragmatic pressure. These points suggest that the TwPM test is sufficiently valid and more suitable than the other tests for clinically assessing inspiratory muscle strength. Moreover, magnetic stimulation of cervical nerve is simple and easy to apply, and the instrumentation is relatively easy for technologists and for the subjects. The advantages of the TwPM test over volitional tests suggest that TwPM is a potential routine test for all hospital departments, especially intensive care units. For example, the TwPM test is ideal for evaluating the inspiratory muscle strength of COPD patients to be weaned from mechanical ventilation support. Moreover, the TwPM test could be better than volitional tests for evaluating the inspiratory muscle strength of patients with muscular disease or those dependent on mechanical ventilation.

The mean TwPM values were 26.8% lower in male COPD patients and 25.3% lower in female COPD patients compared with the controls. The mean TwPM was similar to that reported by Kabitz et al for German COPD patients^[31], although they only described the TwPM values of male patients. Our data suggest that inspiratory muscle strength of COPD patients is substantially impaired, regardless of gender. Expiratory flow obstruction and a concomitant increase in inspiratory work cause respiratory muscle weakness among COPD patients^[32]. Consistently, the present data show that TwPM values were markedly decreased in patients with moderate to very severe COPD, which indicates that impaired inspiratory muscle strength of COPD is associated with airflow limitation. A variety of factors can compromise inspiratory muscle function in COPD. These factors may be classified into local mechanical changes and systemic pathophysiologic changes. The diaphragm always works in an unfavorable position under airflow limitation and hyperinflation, which decreases the inspiratory muscle capacity and compromises inspiratory muscle function through overloading of the intrinsic positive end expiratory pressure and hyperinflation^[33,34]. Consistent with these studies, our TwPM values were significantly correlated with the FEV₁%pred of COPD patients, which was also reported by Kabitz et al^[31]. Thus, decreased inspiratory muscle strength is at least partly attributed to the airflow limitation of COPD. However, airflow limitation and hyperinflation does not fully explain the impairment of inspiratory muscle strength, as systemic pathophysiologic changes also serve important functions in respiratory muscle dysfunction. These systemic changes include systemic inflammation^[35],

hypoxemia and the related oxidative stress and myopathy^[36,37], undernutrition^[38], endocrine disturbances^[39], and remodeling of respiratory muscles^[40].

Our data show that COPD patients have markedly decreased 6-MWD relative to the controls, which is reportedly associated with dyspnea and/or lower limb muscle fatigue. Our data is consistent with a study that associated impaired skeletal muscle endurance with the physical inactivity and altered lung function of COPD patients^[41]. COPD patients often experience a downward spiral of symptom-induced inactivity that leads to peripheral muscle weakness, especially of lower limb muscles^[42,43]. Consistent these study results, our study shows that decreased 6-MWD is significantly correlated with the TwPM values in COPD. 6-MWD, a global marker for functional capacity in the cardiorespiratory domain integrates diverse physiologic components^[44]. Moreover, 6-MWD is suitable for predicting the survival of COPD patients^[45]. Collectively, our results suggest that decreased TwPM indicate impaired inspiratory muscle strength, as well as decreased exercise capacity in COPD.

TwPM values were significantly correlated inversely with the BODE index of COPD, which indicates that these COPD indices have complex interactions. Kabitz et al.^[31] found that TwPM values are correlated with both FEV₁%pred and 6-MWD in COPD, but they did not investigate the relationship between TwPM values and the BODE index. The BODE index is an important multidimensional index for the severity of COPD that incorporates four independent predictors of survival^[46]; 6-MWD and FEV₁%pred are two of the four clinically functional parameters. Considering COPD is multidimensional, the BODE classification scheme, which incorporates more parameters, is likely to predict more accurate outcomes^[47]. The BODE index has been proven to correspond to important differences in the health status of COPD patients^[48]. Therefore, the inverse correlation between TwPM values and the BODE index suggests that decreased inspiratory muscle function imposes a substantial burden on COPD patients and reflects their poor health status.

The current study has several limitations. First, no preference for the occluded nostril was considered in our study. Thus, although patients with nasal septal deviation and rhinitis were excluded, we are uncertain whether the methodology influenced the standardization of the procedure. Second, few female patients with COPD were included in the study; thus, the conclusion should be confirmed using further studies with more female patients, although the

limited female population in this study is sufficient for understanding the inspiratory muscle strength of COPD patients. Third, the predicted values for spirometric function were calculated based on the ERS; using a specific reference value based on the regression of a large sample population of healthy Chinese would be more helpful.

In conclusion, TwPM values are 26.8% lower in male COPD patients and 25.3% lower in female COPD patients compared with the controls. The TwPM values of COPD patients decrease with increasing disease severity. The better correlations of TwPM values with the BODE index and exercise capacity compared with those of SNIP and P_{Imax} suggest that TwPM more accurately reflects the overall severity and burden of COPD.

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Figure legends

Fig. 1. Photograph of non-volitional tests for assessing inspiratory muscle strength; the subject was seated, with the neck flexed at approximately 60° from the vertical when the magnetic stimulation of the cervical nerve was performed.

Fig. 2. Simultaneous force and surface electromyography recordings during twitch mouth pressure (TwPM) tests: the lines on the top channel represent three consecutive TwPM values; surface electromyography signals from respiratory muscles are shown on channels 2, 3 and 4. The mean TwPM was approximately 17.5 cmH₂O in this normal male subject.

Fig. 3. Analysis (mean ± SD) of the TwPM values shows that (A) COPD patients had significantly lower TwPM values compared with the controls among both males and females; (B) COPD patients had lower TwPM values than the control and they decreased with increasing GOLD stage among male patients.

Tables

Table 1. General characteristics of study participants

Characteristic	Controls (n = 63)	COPD (n = 75)	Statistics	P value
Sex, M (%)	40 (63%)	63 (84%)	21.05*	<0.01
Age (year)	64.01 ± 7.01	64.43 ± 7.91	0.73	0.47
Height (m)	160.2 ± 6.24	162.85 ± 6.3	0.15	0.88
Weight (kg)	63.34 ± 9.33	53.29 ± 8.53	6.55	<0.001
BMI (kg/m ²)	23.79 ± 2.90	20.08 ± 2.89	7.49	<0.001
FEV ₁ %pred (%)	96.13 ± 9.78	38.99 ± 14.01	27.25	<0.001
FEV ₁ /FVC (%)	82.36 ± 8.15	42.97 ± 11.79	22.40	<0.001
FVC%pred (%)	95.20 ± 12.07	72.04 ± 16.76	9.27	<0.001
Ex-smokers (%)	12 (19%)	57 (76%)	44.42*	<0.001

*: chi-square value; the other values in the column represent *t* values;

BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume at 1st second; %pred = percent of predicted value; FVC = forced vital capacity. Values are mean ± SD or percentage.

Table 2. Inspiratory muscle function (mean ± SD)

Variables	Sex	Control	COPD (stage II)	COPD (stage III)	COPD (stage IV)	P value
Number (M/F)		63 (40/23)	16 (12/2)	32 (26/6)	27 (23/4)	<0.01
TwPM (cmH ₂ O)	male	13.66 ± 2.20	11.89 ± 2.41	10.51 ± 1.61	8.18 ± 1.14	<0.001
	female	11.81 ± 1.98	9.86 ± 0.76	8.88 ± 0.74	8.24 ± 0.51	<0.001
SNIP (cmH ₂ O)	male	103.17 ± 14.62	99.78 ± 14.14	85.78 ± 10.48	78.47 ± 7.29	<0.001
	female	89.45 ± 11.48	76.81 ± 3.90	70.01 ± 4.08	63.61 ± 3.44	<0.001
PImax(cmH ₂ O)	male	97.03 ± 15.51	76.26 ± 8.16	71.56 ± 8.68	65.64 ± 8.20	<0.001
	female	83.10 ± 8.25	65.80 ± 4.82	64.06 ± 6.45	63.72 ± 6.76	<0.001

TwPM = twitch mouth pressure; SNIP = sniff pressure; PImax = maximum inspiratory mouth pressure

Table 3. BODE index and functional parameters of COPD patients

	Stage II	Stage III	Stage IV
Number (%)	16 (21%)	32 (43%)	27 (36%)
BMI (kg/m ²)	20.18 ± 3.14	20.90 ± 2.91	19.05 ± 2.49
FEV ₁ %pred (%)	59.67 ± 5.69	41.23 ± 6.33	24.49 ± 4.45
MMRC dyspnea scale (score)	1.00 ± 0.63	1.87 ± 0.75	3.22 ± 0.75
6-MWD (meter)	401.88 ± 70.15	355.63 ± 49.01	264.81 ± 64.20
BODE index (score)	2.25 ± 1.29	4.51 ± 1.67	7.74 ± 1.43

BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, exercise capacity; MMRC = modified Medical Research Council; 6-MWD = six minute walk distance. Values are mean ± SD or percentage.

Table 4. Correlation of BODE index with TwPM value with adjustment for confounding factor

	Unstandardized B	Standard Beta	Error	P value
Constant	16.494		1.564	<0.001
BODE index	-0.517	-0.647	0.068	<0.001
Age	-0.063	-0.225	0.024	0.01

BODE = body mass index, airflow obstruction, dyspnea, exercise capacity

Table 5. Correlation coefficients (R values) of inspiratory muscle strength with clinical parameters

	TwPM correlation	P Value	SNIP correlation	P Value	PImax correlation	P Value
FEV ₁ %pred	0.629	<0.001	0.35	0.002	0.253	0.029
6-MWD	0.593	<0.001	0.33	0.003	0.277	0.016
BODE index	0.652	<0.001	0.49	<0.00	0.265	0.022

TwPM = twitch mouth pressure; SNIP = sniff pressure; PImax = maximum inspiratory mouth pressure

BODE = body mass index, airflow obstruction, dyspnea, exercise capacity; FEV₁ = forced expiratory volume at 1st second; %pred = percent of predicted value; 6-MWT = six minute walk test.