

# The BODE index and inspiratory muscle performance in COPD: Clinical findings and implications

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## Abstract

**Objectives:** The Test of Incremental Respiratory Endurance is a novel testing method that provides a unique examination of one's inspiratory muscle strength, work and endurance. Little is known about the relationship between inspiratory muscle performance and mortality risk in obstructive lung disease. We examined the relationship between the Test of Incremental Respiratory Endurance measures and the Body-mass index, airflow Obstruction, Dyspnea and Exercise index in chronic obstructive pulmonary disease.

**Methods:** In all, 70 males with mild-to-very severe chronic obstructive pulmonary disease (mean  $\pm$  standard deviation of  $70.2 \pm 5.9$  years) underwent measurements of body-mass index, spirometry, dyspnea and a 6-min walk test from which the Body-mass index, airflow Obstruction, Dyspnea and Exercise score was calculated. The Test of Incremental Respiratory Endurance provided measures of maximal inspiratory pressure, sustained maximal inspiratory pressure and inspiratory duration.

**Results:** All Test of Incremental Respiratory Endurance parameters inversely correlated with the Body-mass index, airflow Obstruction, Dyspnea and Exercise score: maximal inspiratory pressure ( $r = -0.355$ ,  $p = 0.00$ ), sustained maximal inspiratory pressure ( $r = -0.426$ ,  $p = 0.00$ ) and ID ( $r = -0.278$ ,  $p = 0.02$ ), with sustained maximal inspiratory pressure displaying the highest correlation. Independent significant correlations were also observed between the sustained maximal inspiratory pressure and all Body-mass index, airflow Obstruction, Dyspnea and Exercise score components, except for body-mass index. Finally, sustained maximal inspiratory pressure was significantly different among the Body-mass index, airflow Obstruction, Dyspnea and Exercise index quartiles.

**Discussion:** The significant association between the Body-mass index, airflow Obstruction, Dyspnea and Exercise score and inspiratory muscle performance, in particular sustained maximal inspiratory pressure, suggests that these measures may have a potential prognostic value in the evaluation of chronic obstructive pulmonary disease.

## Keywords

Chronic obstructive pulmonary disease, inspiratory muscle performance, test of incremental respiratory endurance, mortality risk

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## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and incompletely reversible limitation in lung function, usually associated with a constellation of debilitating symptoms and physical impairments.<sup>1</sup> The multi-systemic nature of COPD has prompted a more global evaluation of this condition, other than just relying on the traditional assessment of disease severity and mortality risk based solely on measures of pulmonary function.<sup>2,3</sup> In view of that, composite instruments such as the Body-mass index, airflow Obstruction, Dyspnea and Exercise (BODE) index have been developed.<sup>4</sup> By combining body composition (B), airflow obstruction (O), dyspnea (D) and exercise capacity (E) assessments, the BODE index has been shown to have a superior discriminatory value over other COPD-related parameters as a surrogate marker of mortality risk.<sup>4,5</sup>

As another dimension in the complexity of COPD, measures of respiratory muscle performance are also considered useful parameters for the diagnosis, follow-up and prognosis of this condition.<sup>6–9</sup> Subjects with COPD develop significant deconditioning of the respiratory musculature with particular impairment in inspiratory muscle performance.<sup>10</sup> The inspiratory muscle dysfunction in COPD is attributed to myopathy related to systemic inflammation, changes in chest wall geometry and diaphragm position.<sup>11</sup> In addition, hyperinflation from airway obstruction and loss of lung parenchyma lead to a higher inspiratory load and ventilatory demand which further decreases the pressure-generating capacity of the inspiratory muscles.<sup>12</sup> The clinical implications of weak inspiratory musculature in COPD include impaired exercise capacity, increased dyspnea and poorer quality of life.<sup>9,12,13</sup>

The Test of Incremental Respiratory Endurance (TIRE) is a novel testing method that provides a unique examination of an individual's inspiratory muscle performance. Besides the traditional measure of maximal inspiratory pressure (MIP), the TIRE provides the sustained maximal inspiratory pressure (SMIP) and inspiratory duration (ID). MIP is related to inspiratory muscle strength and defined as the highest pressure achieved during inspiration measured from residual volume, while SMIP and ID are measured from residual volume to total lung capacity reflecting single-breath work capacity and inspiratory muscle endurance.<sup>14</sup>

The TIRE measures of inspiratory muscle performance have recently been introduced and validated in subjects with obstructive lung disease.<sup>15</sup> However, the relationship between TIRE variables and surrogate markers of mortality risk in COPD is unknown. Therefore, this study investigated the correlations among the TIRE measures, the BODE index and its four components in COPD. We hypothesized that greater inspiratory muscle performance would be associated with lower BODE scores.

## Methods

The study was performed with a convenience sample of 70 subjects with mild to very severe airflow limitation between the ages of 56 and 87 years. Subjects were recruited from the outpatient pulmonary clinics of the Miami Veterans Affairs Healthcare System. We included males over the age of 35 years with a clinical and functional diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria.<sup>1</sup> Subjects had to be clinically stable at the time of data collection (i.e. free from exacerbations for at least 2 months prior to study entry). Exclusion criteria included the presence of other concomitant pulmonary diseases, as well as psychiatric, cognitive, neurological or neuromuscular disorders that may affect performance of the study measures. Written informed consent was obtained from all subjects. The Miami Veterans Affairs Medical Center Institutional Review Board approved all procedures (1251.10).

Subjects underwent measurements of body composition, airflow limitation, shortness of breath and functional exercise capacity from which the BODE index score was calculated. Body composition was assessed using the body mass index (BMI) standard formula of weight in kilograms divided by the square of the height in meters. Spirometry was performed using the Vmax<sup>®</sup> Encore System (Yorba Linda, CA, USA) following American Thoracic Society (ATS) standards,<sup>16</sup> providing post-bronchodilator measures of FEV1 obtained 15–20 min after 400 µg salbutamol was administered via a metered dose inhaler through a spacer. Dyspnea was assessed via the modified Medical Research Council (mMRC) dyspnea scale<sup>17</sup> which ranges from 0 to 4, with higher scores indicating increased breathlessness. Functional exercise capacity was demonstrated by the distance ambulated in meters during the 6-min walk test (6MWT) performed following ATS guidelines.<sup>18</sup>

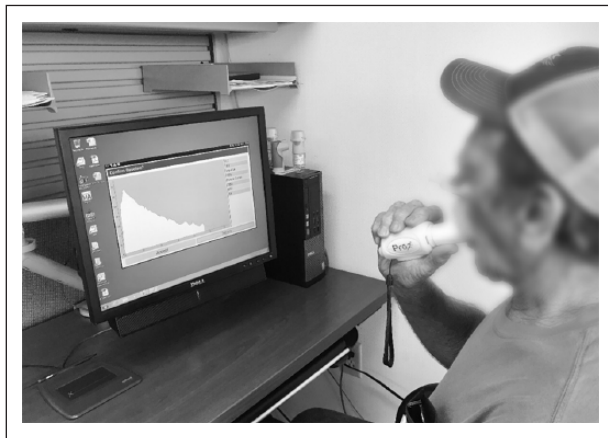
The BODE index combines the above variables by means of a 10-point scale with higher scores indicating higher risk of death. The approximate 4-year survival rates based on the BODE index point system are divided into four quartiles: 80% (0–2 points, quartile I), 67% (3–4 points, quartile II), 57% (5–6 points, quartile III) and 18% (7–10 points, quartile IV).<sup>4</sup>

### TIRE

The TIRE was implemented via the PrO<sub>2</sub> device (Smithfield, RI, USA), which links to a desktop or mobile computer using wireless technology and provides the user with a graphic representation of their inspiratory effort throughout inspiration and real-time biofeedback. This device has a fixed leak via a 2-mm-diameter opening that prevented glottal closure during maximal inspiration. The TIRE maneuver was performed with the subjects seated in

a chair and wearing nose clips following ATS guidelines<sup>19</sup> as shown in Figure 1.

Subjects were instructed to perform a maximal and sustained inspiratory effort following a full expiration. They were encouraged to inspire deeply generating as much pressure as possible within 1–2 s of inspiration and continue to inspire maximally for as long as possible. All measurements were obtained from 3–5 consecutive trials with 60 s rest intervals between efforts. Visual feedback and strong encouragement were given throughout testing. For each successful effort, MIP was recorded in centimeters of water (cmH<sub>2</sub>O) and SMIP documented in pressure time units (PTU), representing the area under the curve generated from the start to the end of inspiration. The ID was recorded in seconds and characterized the total duration of inspiration during each sustained maximal inspiratory effort. Figure 2 presents an example of a TIRE graph obtained via the PrO<sub>2</sub> device.



**Figure 1.** The Test of Incremental Respiratory Endurance (TIRE) procedure. Subjects received standardized instructions and encouragement to facilitate maximal performance.

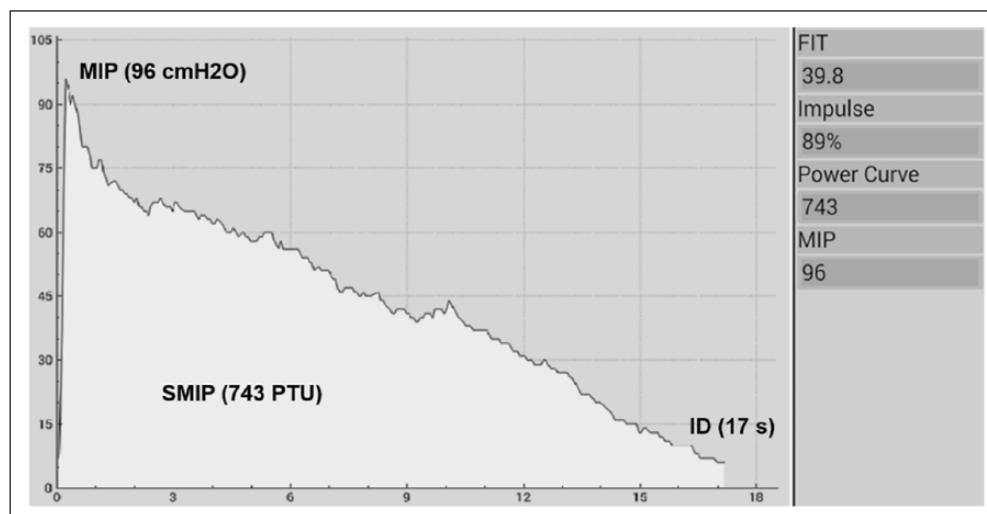
## Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 24 (Armonk, NY, USA) and included descriptive statistics, Shapiro–Wilk normality tests and bivariate correlation (Pearson’s) analyses to investigate relationships among all variables used in this study. We also performed a two-tailed Kruskal–Wallis test followed by pairwise comparisons to analyze the inspiratory muscle function of subjects in different BODE index quartiles. Two-tailed independent-samples t-tests were used to assess whether differences in respiratory muscle function existed between subjects classified as having normal weight (BMI < 25) and those who were overweight/obese (BMI > 25). Multivariate analyses were performed to determine whether there were differences in MIP, SMIP, ID and the BODE score based on age, height or weight of the subjects. Statistical significance was set at an alpha level of 0.05. Finally, a post hoc power analysis was conducted using G\*Power version 3.1.9.2 (Universität Kiel, Kiel, Germany).

## Results

The mean  $\pm$  standard deviation (SD) age, height and weight of the subjects were  $70.2 \pm 5.9$  years,  $176.2 \pm 7.4$  cm and  $81.1 \pm 17.9$  kg, respectively. Participants were 10.3% GOLD I, 25% GOLD II, 14.7% GOLD III and 50% GOLD IV. The mean  $\pm$  SD BODE index score was  $4.2 \pm 2.3$ . The BODE index and measures of inspiratory muscle performance were found to be normally distributed. Table 1 summarizes descriptive statistics of outcome measures included in the study across BODE scores. Figure 3 shows box plots for each TIRE measure in different BODE quartiles.

All TIRE measures significantly and inversely correlated with the BODE score: MIP ( $r = -0.355$ ,  $p = 0.00$ ), SMIP ( $r = -0.426$ ,  $p = 0.00$ ) and ID ( $r = -0.278$ ,  $p = 0.02$ ). Figure 4



**Figure 2.** Inspiratory muscle strength and endurance assessment template obtained via the PrO<sub>2</sub> device.

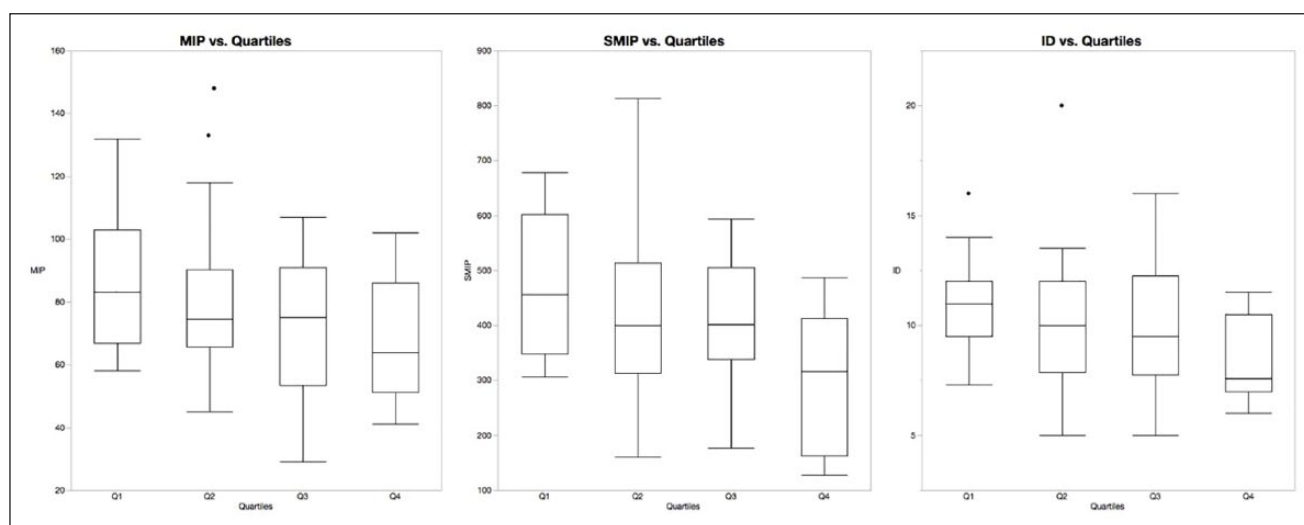
**Table 1.** Descriptive statistics of the study population by BODE index quartiles.

	General group	Quartile I (0–2 points)	Quartile II (3–4 points)	Quartile III (5–6 points)	Quartile IV (7–10 points)	p value*
N (% of total)	70 (100%)	15 (21.4%)	26 (37.1%)	17 (24.3%)	12 (17.1%)	
Age (years)	70.2 ± 5.9	69.5 ± 4.8	69.7 ± 6.1	71.1 ± 5.3	70.5 ± 8.0	0.83
<b>BODE variables</b>						
BMI (kg/m <sup>2</sup> )	25.7 ± 5.3	27.3 ± 4.6	25.9 ± 5.6	23.2 ± 4.0	26.8 ± 7.1	0.11
Post-BD FEV1 (L)	1.5 ± 0.6	2.1 ± 0.4	1.6 ± 0.5	1.4 ± 0.6	0.9 ± 0.2	0.00
Post-BD FEV1 (% predicted)	45.3 ± 17.0	63.5 ± 11.3	46.4 ± 14.2	39.2 ± 15.3	28.7 ± 7.2	0.00
mMRC (0–4)	1.9 ± 1.2	0.9 ± 0.7	1.8 ± 1.0	2.2 ± 1.3	3.4 ± 0.5	0.00
6MWD (m)	298.2 ± 108.2	387.3 ± 58.9	318.4 ± 79.7	276.7 ± 104.1	159.9 ± 81.3	0.00
<b>TIRE outcomes</b>						
MIP (cmH <sub>2</sub> O)	77.8 ± 23.6	86.9 ± 23.5	80.9 ± 24.7	72.5 ± 22.5	67.4 ± 19.5	0.18
SMIP (PTU)	405.3 ± 140.0	469.7 ± 124.0	415.2 ± 148.1	409.7 ± 115.8	297.2 ± 124.3	0.02
ID (s)	10.0 ± 2.8	11.1 ± 2.2	10.1 ± 3.1	10.0 ± 3.0	8.4 ± 2.0	0.05

GOLD: the Global Initiative for Chronic Obstructive Lung Disease classification; BMI: body mass index; post-BD FEV1: post-bronchodilator forced expiratory volume in the first second; mMRC: modified Medical Research Council dyspnea scale; 6MWD: 6-min walk distance; TIRE: Test of Incremental Respiratory Endurance; MIP: maximal inspiratory pressure; SMIP: sustained maximal inspiratory pressure; ID: inspiratory duration.

Values are expressed as mean ± standard deviation.

\*p values reflect Kruskal–Wallis comparisons across groups (Quartile I vs II vs III vs IV).

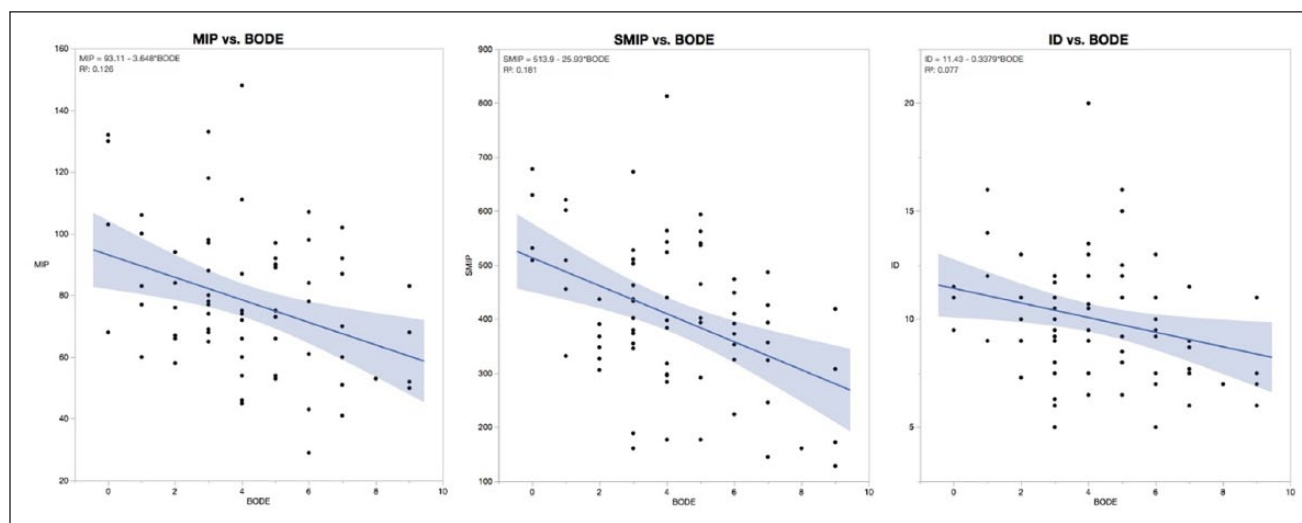
**Figure 3.** Distribution of MIP, SMIP and ID values across BODE quartiles.

shows the relationship between the BODE score and all TIRE measures. Based on Cohen's<sup>20</sup> guideline to interpreting effect size, the strength of the above associations ranged from low (i.e. ID) to moderate (i.e. MIP and SMIP), with SMIP displaying the highest correlation among the inspiratory measures. As a comparison, variables used to calculate the BODE index itself (i.e. FEV1, 6MWT and dyspnea) displayed correlation coefficients of  $\pm 0.6$ , a value not too far from the one found for SMIP.

Independent significant correlations were also observed between SMIP and all the individual measures used to calculate the BODE index, except for BMI. SMIP positively correlated with post-bronchodilator FEV1 percent predicted ( $r=0.353$ ,  $p=0.00$ ) and 6-minute walk distance ( $r=0.427$ ,

$p=0.00$ ) and negatively correlated with dyspnea severity ( $r=-0.369$ ,  $p=0.00$ ). Both MIP ( $r=0.292$ ,  $p=0.01$ ) and ID ( $r=0.367$ ,  $p=0.00$ ) were also positively related to distance walked. Finally, a significant and positive correlation was found between MIP and post-bronchodilator FEV1 percent predicted ( $r=0.308$ ,  $p=0.01$ ), while ID was negatively related to dyspnea scores ( $r=-0.381$ ,  $p=0.00$ ). There were no further correlations between either MIP or ID and other BODE variables.

A Kruskal–Wallis test revealed a statistically significant difference in SMIP values among BODE index quartiles,  $\chi^2(3)=9.174$ ,  $p=0.02$ , with a mean rank SMIP of 44.0 for Quartile I, 36.3 for Quartile II, 37.2 for Quartile III and 20.7 for Quartile IV. Pairwise comparisons indicated that SMIP



**Figure 4.** Scatterplots with lines of best fit on the relationships of MIP (left), SMIP (middle) and ID (right) with the BODE score in the study population.

was significantly lower in Quartile IV compared to the first three quartiles. A near-significant difference was also found in ID among quartiles, while no significant difference was found in MIP values. Furthermore, significant quartile differences were observed in all variables used to calculate the BODE score, except for BMI (Table 1). When assessing whether body composition influenced respiratory muscle performance in this study, our analyses revealed no significant differences in MIP, SMIP or ID between subjects of different BMI. Furthermore, our analyses revealed no statistically significant effect of age on MIP, SMIP, ID and the BODE index in the study sample. No significant effect on the above dependent variables was found either when height or weight was used as fixed factors.

A priori sample size estimation could not be undertaken as there were no published SMIP data upon which to base the calculation. Sample size was also limited due to resource and time constraints. However, a post hoc power analysis based on the main correlation investigated in this study (SMIP versus the BODE index,  $R^2=0.181$ ) and using a two-tail test at an alpha-level of 0.05 revealed that the sample used ( $n=70$ ) has a power of 0.96 (96%) for the proposed aim.

## Discussion

To the best of our knowledge, this is the first study to examine the relationship between the TIRE measures and the BODE index in subjects with COPD. Our findings confirmed that MIP, SMIP and ID are significantly associated with the BODE index, with SMIP displaying the greatest correlation and being the only TIRE measure able to discriminate among BODE quartiles.

Our study subjects had moderate to severe airflow obstruction, moderate to severe dyspnea and reduced functional exercise capacity (i.e. 6-min walk distance less than

350 meters).<sup>21</sup> Poor inspiratory muscle performance was also noted in the sample based upon previous work demonstrating the TIRE normative reference values.<sup>22</sup>

MIP has been the traditional measure of inspiratory muscle strength in COPD. We found no significant differences in MIP among BODE quartiles, in contrast with findings from a study performed by Anami et al.<sup>23</sup> However, we observed that MIP values tended to decrease gradually as BODE scores increased. Moreover, and again in contrast to the findings from Anami, our study showed a significant and inverse correlation between MIP and the BODE index. Donaria et al.<sup>24</sup> also found a significant inverse correlation between sniff nasal inspiratory pressure (SNIP) and the BODE index as well as a significant difference between BODE quartiles 1–2 versus 3–4. These findings are in keeping with ours and highlight the importance of inspiratory performance in COPD.

When investigating the relationship between inspiratory muscle strength and the BODE components independently, we observed that greater MIP values were significantly related to attenuated airflow obstruction, consistent with findings by Tudorache et al.<sup>8</sup> in a study of 121 subjects with mild to severe COPD, but in contrast to the work published by Khalil et al.<sup>25</sup> on 40 COPD subjects with moderate to severe disease. Differences in disease severity and sample sizes used in the above studies might explain these discrepancies. In view of the above results, further investigation on the relationship of MIP and FEV1 appears warranted. We also found that MIP is independently associated with functional exercise capacity, in agreement with findings from several studies indicating that inspiratory muscle strength was positively related to the 6MWT.<sup>7–9</sup>

Several investigators have associated MIP to mortality risk in COPD but not specifically to BODE scores.<sup>26–30</sup> Hodgev and Kostianev<sup>27</sup> found that MIP was an independent



predictor of mortality in 63 subjects followed up over a period of 5 years. Liu et al.<sup>26</sup> also assessed MIP as a predictor of longitudinal mortality in 114 subjects with COPD and found a significant relationship between these two outcomes, even though MIP did not independently predict mortality in the cohort.

The SMIP, represented as the area under the curve in the pressure–time graph generated during the TIRE maneuver (Figure 2), displayed the greatest correlation with the BODE index among the other TIRE measures. We observed that greater SMIP values were independently and significantly related to reduced airflow limitation, less dyspnea, longer distance walked in the 6MWT and thus lower BODE scores in the entire group of subjects. Furthermore, SMIP values significantly differed among BODE quartiles, highlighting its value in identifying severity of COPD.

The association between SMIP and the BODE index has not been previously examined. Our findings highlight the associative and higher discriminatory value SMIP appears to have over more traditional measures of inspiratory muscle performance (i.e. MIP) in capturing differences in COPD-related symptoms and physiological measurements.

Like SMIP, ID also appears to have substantial value in assessing the inspiratory muscle performance of subjects with COPD as it relates to the BODE index. Our findings suggest that subjects able to achieve a longer total duration of inspiration during a sustained maximal inspiratory effort displayed lower BODE scores. Although not statistically different ( $p=0.05$ ), subjects with more severe levels of COPD were found to have a shorter ID compared to ones with less disease severity. In addition, a longer ID was significantly related to a greater distance walked in the 6MWT and reduced dyspnea in our study population. These findings may be due to impaired inspiratory muscle mechanics.

There is no previous literature examining the relationship between either SMIP or ID and the BODE index in COPD, but our analyses suggest these are likely better markers of inspiratory muscle performance than MIP and may provide greater associative and discriminatory abilities in identifying outcomes associated with mortality risk in this population. Further investigation of the TIRE as a prognostic tool in COPD appears plausible.

Our study is subject to some limitations. First, the study population was composed only by males recruited from a single medical center, limiting the generalization of the results. Second, all analyses were cross-sectional. Also, we advise readers that the non-significant difference in MIP and ID across BODE quartiles must be interpreted with caution due to the likelihood of a Type II error. Further investigation in a sample of both males and females with COPD via the TIRE in a longitudinal manner is likely to provide a greater comprehension of the relationship between MIP, SMIP and ID and survival in obstructive lung disease. Despite these limitations, the results of this study provide a step forward toward the understanding of inspiratory muscle performance

in COPD and how it relates to the BODE index, laying the groundwork for future research.

## Conclusion

Single-breath inspiratory work capacity and endurance rather than inspiratory muscle strength seems to have a greater degree of association with pulmonary, perceptive and functional outcomes in COPD. The relationship between TIRE measures of inspiratory muscle work and endurance and the BODE index components have not been previously examined, but our findings reveal that greater SMIP was significantly associated with lower BODE scores, which may provide another method by which mortality risk in COPD can be assessed. Improvements in SMIP via the TIRE training method may facilitate greater survival in this population by facilitating a favorable cascade of physiological events on the disability associated with COPD.

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## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval for this study was obtained from The Miami Veterans Affairs Medical Center Institutional Review Board (1251.10).

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## Informed consent

Written informed consent was obtained from all subjects before the study.

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