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## **BODE index: a new tool to stage and monitor progression of chronic obstructive pulmonary disease**

Wskaźnik BODE: nowe narzędzie do stopniowania ciężkości i śledzenia postępu przewlekłej obturacyjnej choroby płuc

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### **Introduction**

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in adults and currently represents the fourth leading cause of death in the world [1]. It has become a major and growing health problem with a mortality rate that continues to increase [2–5]. COPD is the only leading cause of death showing increases in prevalence worldwide and it is expected that by the year 2020, COPD will become the third leading cause of death in adults [2].

In the United States, the age-adjusted (2005 U.S. Standard Population) mortality rates for COPD has increased from 25.6 per 100 000 in 1979 to 43.5 per 100 000 in 2005 [6].

Although age-adjusted mortality rates in males have slowly declined over the last few years (55.8 per 100 000 in 2000 to 52.3 per 100 000 in 2003), for females the rates have remained unchanged (37.4 per 100 000 in 2000 to 37.8 per 100 000 in 2003) [7], and for the last 3 consecutive years, COPD mortality in women has surpassed that of men, claiming the lives of 63 000 women in contrast to 59 000 men [6].

Although COPD is primarily characterized by the presence of airflow limitation secondary to chronic bronchitis, emphysema or both, the many

systemic manifestations that accompany this disease can effectively signal an increased risk for mortality. Recognizing and quantifying these manifestations provides a more comprehensive assessment of disease severity and helps elucidate prognosis. Several factors, including forced expiratory volume in one second (FEV<sub>1</sub>), airways hyper-responsiveness, severity of dyspnea, gas exchange disturbances, lung hyperinflation, pulmonary hypertension, malnutrition, impaired exercise capacity and health-related quality of life, anemia, and other co-morbidities have been identified as individual variables associated with mortality in COPD. In this monograph, we will review these individual predictors for mortality. We will also discuss the ability of the BODE multidimensional index composed of: the body mass index (B), degree of airflow obstruction (O), level of functional dyspnea (D) and exercise capacity (E) to better stage COPD severity and to monitor and assess its response to therapeutic interventions and to exacerbations.

### **Disease staging**

A stage in medicine relates to a level, a degree, or a period of time in the course of a process. As it relates to COPD, the staging has been arbitrarily

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defined by one single physiological variable, the FEV<sub>1</sub> expressed as a percent of the predicted value which in turn has been derived from the physiological evaluation of normal individuals. Further, the different organizations that have staged COPD, have categorized the patients in different stages without objective evaluation of the FEV<sub>1</sub> thresholds. Fortunately for the field, studies designed for other purposes have validated some of the stages. Thus, pathological, clinical and even pharmacoeconomical studies provide validity to the current staging system.

What has become clear is that the staging based solely on the FEV<sub>1</sub> incompletely describes the complexity of COPD and that it has become desirable to evaluate the patient more comprehensively if we are to impact on outcomes. Further, over the last few years, we have learned that in order for then incorporation of new evaluative tools, they have to be validated. In this monograph, we review the value of variables that have been associated with mortality and thus may have predictive capacity and more specifically, we present the BODE as perhaps the most complete tool to fulfill this need.

### Predictors of mortality in COPD

#### Forced expiratory volume in one second

Spirometry was first introduced in the late 1800's, and with its application to patients with obstructive lung disease, the forced expiratory volume in 1 second (FEV<sub>1</sub>) expressed as a percentage of the forced vital capacity (FVC), has been used as the standard definition of the presence of airflow limitation and its absolute value as percent of the predicted has become the gold standard to stage disease severity in COPD [3]. The landmark study of Fletcher and Peto [8] identified a relationship between airflow obstruction and survival in a study of over 850 of 2700 British men initially tested from 1954 to 1961, and followed for a median of 8 years. The investigators found that in patients with COPD, the risk of death was significantly associated with the initial value of measured FEV<sub>1</sub> [8]. These findings were then expanded by Anthonisen et al. [9], during the Intermittent Positive Pressure Breathing (IPPB) trial which identified both age and FEV<sub>1</sub> as independent and accurate predictors of mortality among 985 patients with COPD, followed over a period of 3 years. A number of studies have since confirmed and further described the relationship between FEV<sub>1</sub>, all cause mortality, and cause-specific mortality [10–13]. Most recently, Mannino et al., described his findings from the National Health and Nutrition

Examination Survey (NHANESI) [14]. The primary outcome in that study was death and the main predictor of interest was baseline lung function. A total of 1301 deaths were found among 5542 adults followed for 22 years in the United States. The authors found a higher risk of death among patients with moderate or severe COPD identified by their baseline spirometry data [15]. These results once again validated the importance of the FEV<sub>1</sub> as a prognostic indicator in COPD and have served the basis to support the current staging system recognized by the different specialty societies.

#### Airway hyper-responsiveness

The importance of airways hyper-responsiveness (AHR) in obstructive lung diseases is better defined for asthma than it is for COPD. In the Dutch study from Vlagtwedde et al. [16], histamine challenge airway hyper-responsiveness was evaluated in approximately 2000 patients then followed for over 20 years. In a mortality analysis of this patient cohort, Hosper [17] and collaborators found that increased AHR predicted mortality for COPD after adjusting for gender, age, smoking history and a number of confounders. The number of COPD deaths was very small (21), and more studies are needed to better define the relationship between AHR and mortality in COPD. Results from the lung health study also provide some support to the concept that airways responsiveness may be of importance to predict outcome but the study was not designed to answer this question and the analysis of TORCH and UPLIFT seem to contradict these initial findings.

#### Dyspnea

Dyspnea is the cardinal, most disabling symptom of COPD [18] and the primary reason for patients to seek medical attention [19, 20]. The perception of breathlessness differs from patient to patient, as it responds to the interaction of respiratory mechanics including airflow limitation, and other cognitive and non-volitional neuronal processes. Importantly, the correlation of breathlessness and FEV<sub>1</sub> has been noted to be weak [21]. A number of studies have identified dyspnea as an independent predictor of mortality in this disease. In a prospective, multicenter, 5 year trial, dyspnea was measured by the Medical Research Council Dyspnea Scale (MRC), in a cohort of 227 patients COPD patients [22]. These investigators found that survival was better predicted by dyspnea ( $P < 0.001$ ) than by FEV<sub>1</sub>. These findings were confirmed in a much larger cohort of 625 COPD patients in which dyspnea was also measured with the MMRC and patients followed over time [23]. Thus,

it seems that a relatively simple measurement of a functional dyspnea scale can stratify patients for their chance of dying over time. Based on these observations, the ATS/ERS has suggested that measurement of dyspnea be an integral part of the evaluation of patient with COPD.

### **Hypoxemia**

The presence of hypoxemia ( $\text{PaO}_2 < 55$  mm Hg or  $\text{SaO}_2 < 88\%$ ) while the patient is breathing room air, has long been known to predict mortality in COPD. Conversely, the correction of gas exchange derangement results in better survival. In 1970, Neff and Petty [24] first published a 30–40% reduction in mortality among a group of hypoxic COPD patients given continuous oxygen supplementation. However, the most important evidence supporting its use was derived from 2 large controlled trials evaluating the effect of supplemental oxygen on hypoxemic patients with COPD. The first trial, The British Medical Research Council [25] randomized patients to receive 15 hours of continuous oxygen or room air. The study found a significant reduction in mortality among patients given oxygen supplementation during a follow up period of 5 years. The Nocturnal Oxygen Therapy Trial (NOTT) [26] compared 12 to 24 hours of oxygen supplementation. Mortality among patients given continuous oxygen for 24 hours was half of those given oxygen for only 12 hours. These data show that survival in hypoxemic patients with COPD is proportional to the number of hours of oxygen supplementation. Taken together, these reports confirmed the predictive value of oxygenation on outcome in patients with COPD.

### **Hypercapnia**

Hypercapnia is usually present in patients with advanced COPD and reflects both the severe ventilation-perfusion inequality and the inability of the patient to increase ventilation to maintain an adequate elimination of carbon dioxide. The presence of chronic hypercapnia is usually associated with poor survival in patients with COPD [27–29]. Hypercapnia is commonly associated with hypoxemia and it has been difficult to elucidate which gas exchange derangement carries the most ominous prognosis. A cohort of 4552 hypoxemic patients with COPD patients receiving long-term oxygen therapy (LTOT) in Japan [30] were followed between 1985 and 1993. A total of 1611 patients died during the follow up period (5 year survival 39.5%). The authors found the cumulative survival curves for the hypoxemic, hypercapnic

COPD patients to be quite similar to those of hypoxemic, normocapnic patients. Using Cox proportional hazards analysis the authors identified age, gender,  $\text{PaO}_2$  and %VC as the independent predictor for survival. No statistical significance was found for  $\text{PaCO}_2$ , nor  $\text{FEV}_1/\text{FVC}$ .

### **Static hyperinflation**

The presence of lung hyperinflation is a frequent occurrence in patients with COPD and one that is easily recognized on the physical exam by the presence of barrel-shaped chest. Hyperinflation results from the destruction of lung parenchyma, loss of lung elastic recoil. The resting inspiratory capacity (IC) performed during pulmonary function testing mirrors the end-expiratory lung volume and its decrease is taken to represent increased end-expiratory lung volume. Schols et al. [31], reviewed data from 603 patients and used IC expressed as a percentage of normal, as an index of hyperinflation. The authors did not find IC to predict mortality in this cohort. However, in another prospective study [22], hyperinflation expressed as the residual volume to total lung capacity ratio or  $\text{RV}/\text{TLC}$  proved to be a powerful predictor of mortality in patients with COPD. A recent study examined the predictive value of the ratio of inspiratory to total lung capacity or  $\text{IC}/\text{TLC}$  as a measurement of functional reserve and predictor of survival. In this study of 689 patients (95% males) with COPD,  $\text{IC}/\text{TLC}$  was found to be an important independent predictor of increased mortality after 34 months of follow-up. The increase in mortality became critical at an  $\text{IC}/\text{TLC}$  threshold below 25% (critical hyperinflation) [32]. The authors termed this ratio the “inspiratory fraction” and interpreted it to be analogous to the ejection fraction so popular in the evaluation of patients with heart failure.

### **Pulmonary hypertension**

Pulmonary hypertension (PH) is defined as a mean pulmonary artery mean pressure (Ppa) at rest, equal or greater than 20 mm Hg. Although it is generally recognized that PH is common in COPD, when present, it is usually mild to moderate in severity [33, 34]. In a recent retrospective study of 998 patients undergoing right heart catheterization between 1990 and 2002, only 11 patients were identified as having severe PH as the result of COPD [35]. Some reports have reported an increased mortality rate among these patients when compared to patients with similar degree of airflow limitation but no evidence of severe PH. It is generally accepted that the presence of PH in COPD correlates with the presence of chronic hypoxemia

[36–38]. Conversely, studies have shown that treatment with LTOT slows the progression of PH in a high percentage of hypoxemic COPD patients although complete normalization is infrequently seen [36]. In earlier studies by Weitzenblum and colleagues, 3 consecutive measurements of pulmonary artery pressure (Ppa) by right heart catheterizations in a small group of COPD patients affected by hypoxemia (mean PaO<sub>2</sub> 50 ± 6.6 mm Hg). From the baseline measurement T0 to T1 (47 ± 28 months), hypoxemia worsened from 59 ± 9 to 50 ± 6 and Ppa worsened from 23 ± 6 to 28 ± 7 mm Hg in patients not receiving LTOT. Patients were then prescribed O<sub>2</sub> for 15 to 18 hours/day and a third measurement was obtained after 31 ± 18 months. The investigators observed a significant decrease in Ppa in 12 out of 16 patients (28 ± 7 to 23.9 ± 6 mm Hg ( $p < 0.005$ )) which suggested modulation of PH after the correction of hypoxemia. However, not all hypoxemic patients showed this beneficial effect. In a study by Ashutosh and co-investigators [37], the response of the Ppa to the administration of 28% oxygen for 24h was measured in 28 patients with COPD. Of these patients, 17 responded with a decrease of > 5 mm Hg and 11 did not. More importantly, the investigators found an 88%, 2 year survival among responders versus 22% among non responders. These findings suggest that LTOT attenuates the development of more severe PH overtime and by doing so decrease mortality in COPD. The natural history of PH in COPD was studied by Kessler et al. [38] in 131 COPD patients with mild to moderate hypoxemia not meeting criteria for LTOT. The patients were followed for 6.8 ± 2.9 years with 2 right heart catheterizations. During the first measurement (T0), all patients had normal Ppa (< 20 mm Hg). The patients underwent a steady-state 40 watts exercise test and Ppa post exercise was also measured, and 76 (group 2) were noted to developed exercise induced PH (Ppa > 30 mm Hg). On average, these patients had higher resting Ppa than the 55 patients (group 1) that did not have PH during exercise (16 ± 3 vs. 14 ± 2 mm Hg,  $p = 0.001$ ). During the second catheterization Ppa had changed to 19 ± 7 and 16 ± 5 respectively ( $p = 0.01$ ). 33 patients developed resting Ppa, 9 from group 1 and 24 from group 2. These patients had significantly higher Ppa at rest and with exercise at T0 as well as lower resting and exercise PaO<sub>2</sub> when compared to those who did not develop PH. The authors suggested that higher resting and exercise Ppa at baseline predicted the development of PH over a 6 year period. The development of PH is rather slow in patients with mild to moderate hypoxemic COPD not meeting criteria for LTOT and

although predictive of outcome, is not easy to determine with accuracy.

### Malnutrition

Nutritional depletion is a frequent finding among patients with COPD, in particular those with advanced disease. The prevalence of weight loss in stable COPD is in the range of 20% and it increases to 35% among those patients who are hospitalized [39, 40]. Several studies have found that the body mass index (BMI) is an independent risk factor for COPD mortality [41–43]. Landbo et al. [42], found BMI to be an independent predictor of all-cause and respiratory mortality among COPD patients with and FEV<sub>1</sub> < 50% predicted in the Copenhagen City study. The impact of malnutrition on survival in COPD was also examined retrospectively by Schols [31] et al., in 400 COPD patients who participated in a pulmonary rehabilitation program. A low BMI (< 25 kg/m<sup>2</sup>) was associated with a significant increase in the risk for mortality ( $p < 0.001$ ). In an analysis of 203 COPD patients who received nutritional support, weight gain (> 2 kg/8 wks) was a significant predictor of survival [44]. Studies using more complex tests to evaluate nutrition, such as mid-thigh [45] and mid-arm [46] muscle cross-sectional area obtained by computerized tomography, have also shown significant association between malnutrition and mortality in COPD, with a predictive value that is superior to that of BMI. Taken together, the evidence suggests that weight loss and malnutrition represent an independent risk factor for mortality in patients with COPD. Although the measurement of fat free mass is more accurate than the BMI to determine the degree of muscle mass loss, the simplicity and of the BMI make it an attractive marker for use in clinical practice.

### Exercise capacity

Exercise intolerance is seen in many patients with COPD and is likely multi-factorial in origin. Limitations in exercise capacity reflect the respiratory and non-respiratory expressions of the disease and the integrated activities of the pulmonary and cardiovascular systems. The peak oxygen uptake (Peak VO<sub>2</sub>) determined during a cardiopulmonary exercise test (CPX), has been shown to predict survival in COPD patients undergoing lung resection [47, 48], and to be a better predictor of survival than FEV<sub>1</sub> and health status [49]. In a study by Epstein et al. [50], COPD patients who were unable to perform an evaluative CPX were 11 times more likely to die following lung resection than those able to complete the test. The 6-minute

walk distance (6MWD) is a simple field test which has also been correlated with mortality in COPD patients in a variety of settings, including post-pulmonary rehabilitation [51], and lung-volume reduction surgery (LVRS) [52, 53]. Gerardi [51] and colleagues reported on predictors of survival in a group of severe COPD patients graduating from a pulmonary rehabilitation program. In this rather homogeneous group of patients with a uniformly low FEV<sub>1</sub>, the 6MWD was a better predictor of survival than the FEV<sub>1</sub>. In another study by Pinto-Plata [54] and colleagues, exercise capacity was tested with the 6MWD in 198 patients with severe COPD followed for 2 years. In this patient cohort, survival increased progressively with increases in the 6MWD, when distances were divided into discrete 100-meter increments. Those patients unable to walk 100 meters had a mortality rate approaching 90% at 1 year. On the other hand, COPD patients with similar degree of airflow limitation who were able to walk > 400 meters had significantly higher survival ( $p < 0.0001$ ). The investigators also found that the 6MWD test was a better predictor of mortality than FEV<sub>1</sub> and BMI. In this study, the decline in 6MWD occurred independently of changes in FEV<sub>1</sub>, indicating that both tests measure different domains of the disease and could be considered complementary. More recently, our group has shown that the 6MWD distance is most useful in those patients with COPD who have an FEV<sub>1</sub> lower than 50% predicted. In this group, the FEV<sub>1</sub> ceases to change significantly over time whereas the 6MWD accelerates its rate of decline, maintaining its predictive value. This makes the 6MWD particularly useful in these patients.

### Health status

Health Related Quality of Life (HRQoL) is an important patient-reported health outcome in COPD. HRQoL has been defined as: „The extents to which one’s usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment” [55]. To this effect, COPD is a disease that has a profound impact on patients’ HRQoL, even among patients with relatively modest airflow limitation [56]. Importantly, a weak association between HRQoL and the FEV<sub>1</sub>, has long been described. This poor correlation reflects the marked heterogeneity and complexity of COPD. Domingo-Salvany [57] and colleagues were the first to describe an association between measurements of HRQoL and mortality in COPD. In their study, 321 male patients were tested with both generic and disease specific HRQoL instruments. The patients were followed for a mean

4.8 years and mortality was documented. The investigators found that survival was shorter among patients with worse quality of life scores. The predictive value of HRQoL has been confirmed in subsequent studies [58, 59]. Using univariate analysis, HRQoL was also identified as a predictor of mortality in a study of 609 patients with severe emphysema enrolled in the National Emphysema Treatment Trial (NETT) [59]. However, the administration of health status questionnaires takes time and may be difficult to score.

### Anemia

Anemia is a common co-morbidity in many chronic diseases and its importance in COPD is now receiving attention. Recent reports suggests that anemia in COPD patients may be more prevalent than expected and could be associated with increased mortality [60–62]. The reported prevalence of anemia in COPD ranges from 10% to 15% in patients suffering from severe forms of the disease. In a study of 2524 COPD patients who were prescribed long-term oxygen therapy, 12.6% of males and 8.2% of females were identified as anemic [61]. Recently, in a retrospective analysis of prospectively collected data from a cohort of 683 COPD patients [23, 62], Cote et al. observed anemia in 17% of the cohort in contrast to polycythemia which was present in only 6% of the patients (and when present carried no clinical relevance). Anemic patients had significantly higher dyspnea, lower 6MWD, and shorter median survival (49 vs. 74 months) when compared to non-anemic COPD patients. These differences remained significant when controlling for the relevant demographic, physiologic, and disease covariates in regression analyses, where anemia was an independent predictor of the above outcomes. The relationship between anemia and mortality in COPD, and the possible effect that its correction may have on survival, need to be confirmed by prospective and controlled clinical trials.

### Comorbidities

Tobacco use is without doubt the most important etiologic factor behind the development of COPD [63]. Cigarette smoking induces a state of systemic inflammation characterized by the intense interaction and accumulation of cells capable of inducing a marked oxidant-anti-oxidant imbalance that results in cellular injury [64]. Miller et al. [65] reported that the numbers of circulating CD8+ T-cells were increased and CD4+ T-cells decreased in heavy smokers. This abnormality was

reversible upon discontinuation of smoking. A low CD4+/CD8+ ratio is a characteristic of the inflammation seen in COPD and it is genetically controlled [66]. It is possible then, that in genetically predisposed smokers tobacco initiates a state of generalized, chronic inflammation. A comorbidity is defined as a disease that coexists with the primary disease of interest. Because the toxic effects of tobacco extend to other organ systems, it is no surprise that the most common comorbid conditions associated with COPD are cardiovascular disease and cancer [67]. In a study by Soriano [68] et al., from the UK General Practice Research Database, 2699 patients with COPD were identified. Compared with controls, COPD patients had a significantly higher comorbidity burden, in particular cardiovascular diseases, osteoporosis and cataracts. The association with mortality was described by Almagro [69] et al., in a study of hospitalized COPD patients who had their comorbidities measured by the Charlson index [70]. The authors found that a higher score in the Charlson index was an independent predictor of mortality among these patients ( $p < 0.001$ ). This independent predictive value of comorbidities in COPD has also been demonstrated by others [23–32].

### Multidimensional mortality risk assessment in COPD

Since the early studies of Fletcher and Peto [8], FEV<sub>1</sub> has been used to define the severity of the disease and its prognosis. For many years now, FEV<sub>1</sub> and age have been considered as the most important prognostic indicators in this disease. Unfortunately, both of them are, for the most part, irreversible. Paradoxically, most studies designed to evaluate the effectiveness of therapies in COPD have focused on the change in FEV<sub>1</sub> over time as the outcome of interest and the failure of most therapies to significantly increase or delay the rate of decline of FEV<sub>1</sub> has led to an unjustified nihilism. As presented in this monograph, multiple factors other than FEV<sub>1</sub> are also associated with mortality in COPD and actually predict outcome better than the FEV<sub>1</sub>. Some of these factors reflect the systemic involvement of COPD, and many of them are amenable to treatment [59, 71–76]. As such, sole reliance on FEV<sub>1</sub> in the evaluation of a patient with COPD, would lead to an incomplete assessment of disease severity. It seemed reasonable to us that a composite index that incorporated the most important predictors of mortality, reflecting not only impairment in lung function, but also systemic consequences of the disease, could provide a more comprehensively way to evaluate COPD.

### BODE as a staging tool

In the initial study by our group [23], 207 patients with COPD were prospectively enrolled and the predictive value of a number of variables was evaluated. These variables included: age, gender, smoking history in pack per year, forced vital capacity, FEV<sub>1</sub>, dyspnea measured with the MMRC, BMI, functional residual capacity, inspiratory capacity, hematocrit, and albumin level. The independent association with mortality at one year was evaluated with stepwise forward logistic-regression analysis. The authors identified 4 variables that predicted an elevated risk for death: BMI (B), degree of airflow obstruction (O) as measured by FEV<sub>1</sub>, dyspnea as measured by the MRC dyspnea scale (D), and exercise capacity (E) as measured by the 6MWD test. These variables were incorporated into a multidimensional scale, the BODE index, that ranged from 0 (least risk) to 10 (highest risk) (see Table 1). The BODE index was then prospectively validated in a separate cohort of 625 predominantly male patients with COPD who were evaluated every 6 months for at least 2 years, or until death. The authors found that each quartile increase in the BODE Index score yielded an increase in the risk for mortality. Those patients with a BODE index in the quartile 4 (BODE Index score of 7 to 10) had a mortality rate of 80% at 52 months. The results of this study indicated that the BODE index was a much better predictor of mortality than any of the individual variables alone.

The predictive value of BODE has been tested by other investigators [77–79]. In a study by Ong et al. [77], 127 COPD patients were recruited and tested with the BODE index. The patients were followed for up to 2 years and the number of hospital admissions and mortality were documented. The investigators found the median BODE score to be

**Table 1. Calculation of the BODE index. Points from each variable are added according to the threshold value measured for each one. The value ranges from 0 to a maximum of 10**

BODE Score				
Variable	0	1	2	3
FEV <sub>1</sub> , % predicted	≥ 65	50–65	35–49	≤ 35
Dyspnea: MRC	0–1	2	3	4
6MWD, meters	≥ 350	250–349	150–249	≤ 149
BMI	> 21	≤ 21		

FEV<sub>1</sub> = forced expiratory volume in 1 second; MRC = Medical Research Council; 6MWD = 6-minute walk distance test; BMI = body mass index

lower among survivors than among non survivors (4 vs. 6, respectively,  $p = 0.003$  and a significant effect of the BODE scores on mortality (HR, 1.30; 95% CI, 1.08 to 1.56;  $p = 0.006$ ). The investigators used Poisson regression analysis to evaluate the effect of BODE scores on hospitalizations and found BODE to also be a predictor of this outcome.

### **BODE as a surrogate marker of disease modification**

In addition to its predictive capacity BODE has also been found to be a very good surrogate marker of ulterior outcome. In a retrospective clinical study of 186 patients with severe emphysema, Imfeld [78] and colleagues tested the predictive value of the change in BODE following LVRS. The investigators found that the post-operative change in BODE at 6 months, but not the pre-operative BODE predicted survival. Most patients undergoing LVRS showed an improvement in BODE index following the intervention from 7.2 (quartile 4), to 4.0 (quartile 2)  $p < 0.001$ . Those patients having the most improvement in BODE had the best 5 year survival (HR, 0.497, 95% CI, 0.375 to 0.659;  $p < 0.001$ ). The investigators found that the ability of the BODE index was able to predict the risk of death (0.74), better than the FEV<sub>1</sub> (0.63). The authors of the NETT trial had the unique opportunity to explore this concept in a cohort submitted to a randomized trial. Martinez and co-workers have just reported those results. Constructing a modified BODE index where the dyspnea was evaluated using the San Diego dyspnea scale instead of the original modified MRC one, the authors explored the predictive value of the magnitude of change of BODE at 6 months post-randomization on ulterior mortality. The results showed that the change in BODE at 3, 6 and 12 months predicted long-term mortality in the whole cohort. Further, the BODE was a better predictor than any of its individual components.

The capacity of patients to significantly modify their BODE index post LVRS suggests that the BODE index can be used not only as a staging tool but also one to evaluate disease modification. To this effect, other interventions have also proven to be able to modify BODE. Pulmonary rehabilitation (PR) is known to improve several of the surrogate markers for mortality in COPD, namely dyspnea, health status and exercise capacity. Based on this observation, it was hypothesized that PR would be able to modify the severity of COPD and the risk for mortality, as measured by the BODE Index [79]. In this study, of the 246 patients who qualified for and were offered rehabilitation, 116 accepted and

completed the 8-week, 3-times weekly rehabilitation program; 130 declined participation. The change in BODE scores at 3 months were compared between rehabilitated patients and non PR participants. The patients had severe COPD both by FEV<sub>1</sub> and by the BODE Index scores. 75% of patients belonging to the 3rd and 4th quartiles. Patients were followed for more than 2 years or until death. A total of 30% of the patients who graduated from PR joined a maintenance program and exercised 3 times weekly for the entire 2-year period. Following PR, 71% of the participating patients improved their BODE Index scores by at least 1 point, of these 25% improved by 2 points. After graduation from PR, the BODE Index decreased significantly from 5.07 to 4.18. This resulted in a "shift" from the 3rd to the 2nd BODE quartile, and their initially predicted mortality of 20% to 30% changed to an observed mortality of 11.2%. Patients who declined-PR had a worse BODE index at entry of 6.94 (approaching BODE 4th quartile), and in this group there was almost a 20% worsening of BODE over time. This group of patients had the highest mortality rate (50%). For patients who responded to PR, defined as an improvement in the BODE Index score of at least 1 point, the BODE index improved by 25% at 3 months, compared with the patients who did not respond to rehabilitation. This improvement in BODE score was maintained for a full 2 years after the start of pulmonary rehabilitation, while patients who did not participate in pulmonary rehabilitation had an 18% deterioration in BODE. These results support the concept that the BODE Index can be a useful tool to assess disease modification.

### **BODE as a tool to reflect disease progression**

Patients with advanced COPD experience frequent exacerbations (E) and hospitalizations which are usually associated with poor outcomes and with worsening of the FEV<sub>1</sub> [80].

In a study assessing the impact of exacerbations on several patient-centered outcomes [81] and BODE, this multidimensional index proved to be a more sensitive tool than FEV<sub>1</sub> alone to reflect progression of disease over a 2 year follow up period. In this study, 205 patients were recruited and evaluated with the BODE index at baseline while stable, during the exacerbation episode and every six months thereafter. The authors presented data on the impact of exacerbations on FEV<sub>1</sub>, 6MWD, MMRC, BMI and BODE. 130 patients experienced exacerbations and 75 patients remained exacerba-

tion free for the duration of the study. Exacerbators showed a worsening of BODE index of 1.38 points during the E event and although there was a partial improvement, the BODE index at 24 months remained 1.09 points above baseline. On the contrary, non exacerbators showed a negligible increase in BODE at 2 years (0.07 points) which differed significantly from that of the exacerbators ( $p < 0.001$ ). Interestingly, the BODE components that had the greatest impact during and after the exacerbation were the 6MWD and the MMRC dyspnea. Actually, the 6MWD did not return to its original value after the episode.

In summary, the response of the BODE to exacerbations, LVRS and PR indicate that the BODE index, not only reflects disease severity and is therefore an excellent tool to stage patients with COPD, but also, that its changes reflect ulterior outcome, suggesting that the BODE Index can be used as both surrogate marker for mortality and as a tool to assess disease modification.

### Conclusions

Although FEV<sub>1</sub> remains the diagnostic defining tool in COPD and its most important physiologic indicator of severity of airflow obstruction, its predictive value is weak above 50% [8] of its predicted value. Once patients reach very low values of FEV<sub>1</sub>, other markers of mortality in COPD become more accurate. Chief among these predictors of mortality are dyspnea, exercise capacity, and BMI. Evidence also exists for markers such as health status, anemia, hypoxemia, comorbidities and hyperinflation, among others. Simple to use, the validated multidimensional BODE Index encompasses the predictive validity of the best of these potential surrogates into a single measure of disease severity and survival. The BODE index that captures the multidimensional manifestations of COPD is a valuable tool not only in the assessment of severity (staging) and progression of disease, but also in evaluating the response to medical interventions.

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