The BODE Index, a Multidimensional Grading System, Reflects Impairment of Right Ventricle Functions in Patients with Chronic Obstructive Pulmonary Disease: A Speckle-Tracking Study

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Key Words

BODE index · Chronic obstructive pulmonary disease · Two-dimensional speckle tracking echocardiography · Right ventricular free wall strain

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is not only characterized by chronic airflow limitation, but is also a systemic disease. There is no information about alterations in right ventricle (RV) functions precipitated by systemic manifestations of COPD. **Objectives:** We aimed to evaluate the relationship between the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index that evaluates systemic manifestations of COPD and RV functions by means of 2-dimensional speckle-tracking echocardiography (2D-STE) in COPD patients. **Methods:** The study involved 135 COPD patients and 37 control subjects. All patients underwent 2D-STE, pulmonary function tests and 6-min walk tests, and were divided into quartiles according to their calculated BODE index score. **Results:** COPD patients had im-

paired RV and left-ventricle diastolic functions compared to controls. There was a decreasing trend from quartile 1 (Q₁) to Q₄ in RV functional parameters, i.e. RV free wall strain (RVFW-S, $p < 0.001$), tricuspid annular plane systolic excursion ($p < 0.001$), systolic myocardial velocity ($p < 0.001$), RV fractional area change ($p < 0.001$), RV myocardial performance index ($p < 0.001$) and pulmonary artery systolic pressure ($p < 0.001$). The transmitral Doppler E wave/lateral mitral annular tissue Doppler E wave ratio was similar in the 4 BODE index quartiles ($p = 0.159$). Multivariate analysis was performed to find independent predictors of decreased RVFW-S (≤ 19.06), and the BODE index (in quartiles; OR 4.61 and 95% CI 1.85–11.63) was found to be an independent predictor. In a partial correlation analysis adjusted for forced expiratory volume in 1 s % predicted, RVFW-S was correlated with the 6-min walk distance ($r = 0.498$). **Conclusion:** The BODE index, which can be easily evaluated in office settings, may provide information about reduced RV functions as well as guiding treatment and helping to predict prognosis in COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic airflow limitation that is not fully reversible. It is an important public health problem due to increased morbidity and mortality as well as augmented economic and social loads. It is predicted that it will be the third-most frequent cause of death in the world by 2020 [1, 2]. Therefore, it is very important to identify the predictors of increased morbidity and mortality in patients suffering from this disease. Previous studies demonstrated that some physiological and clinical parameters including forced expiratory volume in 1 s (FEV₁), hypoxemia, increased shortness of breath and a short 6-min walk distance are associated with increased mortality risk in COPD patients [3, 4]. However, these parameters provide limited data about COPD as a systemic disease [5]. Recently, the BODE [body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity] index, a multidimensional grading system, was introduced by Celli et al. [6] to predict the risk of death in patients with COPD. The BODE index evaluates individuals with COPD from multidimensional aspects such as symptoms, nutritional state, degree of airflow limitation and exercise capacity [6, 7]. Recent studies showed that the BODE index can measure disease severity as well as predict survival, annual exacerbation and hospitalization rates [8, 9].

In patients with COPD, cardiovascular-system-related death is the second-most frequent cause of mortality after lung cancer [10, 11]. Previous studies demonstrated that right ventricle (RV) dysfunction is associated with increased cardiovascular events as well as predicting mortality in COPD patients [12, 13]. Therefore, assessment of RV functions in these patients is clinically essential. The evaluation of RV functions with conventional echocardiography is challenging due to the complex geometry of the RV and the lung hyperinflation that occurs in patients with COPD [14, 15]. Two-dimensional speckle-tracking echocardiography (2D-STE) is a novel technique used for the measurement of cardiac mechanics. It assesses myocardial deformation and the myocardial deformation rate by tracking speckles in the myocardium on grayscale (B-mode) images. It can be used to evaluate both global and regional myocardial strain and strain rate without being limited by Doppler beam angle, tethering effect or load dependency [16].

There is no information about the relationship between the BODE index and RV functions. We aimed to evaluate the potential relationship between them, by assessment of 2D-STE-derived strain images in patients with COPD.

Methods

Study Design

This was a single-center, cross-sectional study conducted between August 2011 and April 2013. A total of 135 consecutive COPD patients followed up by the Department of Respiratory Medicine were enrolled. The control group consisted of 37 age- and sex-matched healthy individuals. We excluded patients in whom there was echocardiographic evidence of either regional or global wall motion abnormalities, reduced left ventricle (LV) function, a history of coronary artery disease, angina pectoris, a positive treadmill test or nuclear perfusion stress test, ischemic electrocardiographic findings, chronic renal failure, atrial fibrillation/flutter, 2nd- or 3rd-degree atrioventricular block, RV pacing, moderate-to-severe valvular heart disease, pulmonary embolism, idiopathic pulmonary hypertension, obstructive sleep apnea, pulmonary artery stenosis or RV outflow obstruction, tricuspid structural disease, COPD exacerbation at the time of investigation or poor echocardiographic view. The diagnosis of COPD was based on a history of cigarette smoking of at least 10 pack-years, symptoms and radiographic findings suggestive of COPD and spirometric findings with a postbronchodilator FEV₁/FVC (forced vital capacity) <70% predicted and FEV₁ <80% predicted [1]. At the time of enrollment, all study patients had been free of exacerbations of COPD for at least 6 months.

Informed consent was obtained from the patients and the local ethics committee approved the study protocol. Baseline clinical and demographic information was obtained from all patients. The medical history of the patients was recorded and a detailed physical examination was performed. Blood analysis was performed after 12 h of fasting. Fasting blood glucose, lipid parameters and creatinine and hemoglobin values were measured. Blood pressure was measured with a sphygmomanometer using an appropriately sized cuff. Values for systolic and diastolic blood pressure were obtained from the average of the second and third measurements. Hypertension was identified on the basis of having to receive anti-hypertensive treatment or when the blood pressure exceeded 140/90 mm Hg in at least 3 measurements. Diabetes was defined as having had to receive oral antidiabetic medication or insulin or having a fasting glucose level of >126 mg/dl. Smoking behavior was defined as 'current' or 'exsmoker' and the number of smoking pack-years was recorded. BMI was calculated and the estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease study equation [17].

All COPD patients were evaluated by spirometry, arterial blood gas analysis, echocardiography and 6-min walk distance, respectively, and all measurements were performed at rest and while breathing room air. The control group underwent echocardiographic assessment only.

Pulmonary Function Tests

Pulmonary function tests were performed, as previously reported [18]. FEV₁ and FVC were measured with a clinical spirometer (ZAN 100, Morgan strumenti scientifici, Italy).

Arterial Blood Gas Analysis

Blood was drawn via the radial or brachial artery. Arterial oxygen pressure, arterial carbon dioxide pressure and arterial oxygen saturation were calculated.

Table 1. Multidimensional components and scoring system for calculation of the BODE index

	FEV ₁ % predicted	mMRC dyspnea score	BMI	6-min walk distance, m
0	≥65	0–1	>21	≥350
1	50–64	2	≤21	250–349
2	36–49	3	–	150–249
3	≤35	4	–	≤149

BODE Index

The BODE index was calculated by a summation of scores obtained from BMI, the modified Medical Research Council (mMRC) dyspnea scale [19], spirometric measurements and 6-min walk distance (table 1). Six-minute walk tests were performed twice at least 30 min apart and the longest walk distance was used for scoring [7]. The BODE index ranged from 0 to 10 points and the patients were divided into quartiles according to their score: quartile 1 (Q₁) = 0–2 points, Q₂ = 3–4 points, Q₃ = 5–6 points and Q₄ = 7–10 points [6].

Conventional Echocardiography

The echocardiographic studies including 2D, M-mode, pulsed-wave Doppler and pulsed tissue Doppler imaging (TDI) examinations were performed from all standard echocardiographic windows using a commercially available echocardiography machine (GE Vivid S5, Vingmed Ultrasound A.S., Horten, Norway) equipped with a 3.6-MHz transducer. LV and RV measurements were performed according to the American Society of Echocardiography guidelines [20, 21]. During the echocardiographic examination, a 1-lead electrocardiogram was recorded continuously. LV dimensions (end-diastolic and end-systolic) and wall thickness (septum and posterior wall) were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the LV. LV volume and ejection fraction were measured using the modified Simpson method from the apical 4-chamber and 2-chamber views. Mitral inflow velocities were evaluated by pulsed-wave Doppler with the sample volume placed at the tip of the mitral leaflets from the apical 4-chamber view. Using the average of three beats, we measured the diastolic early- and late-peak, i.e. the Doppler E wave (E) and Doppler A wave (A) transmitral flow velocity and the E/A ratio. Mitral annulus velocity was measured at the lateral corner of the annulus by TDI using the pulsed-wave Doppler mode. The lateral mitral annular tissue Doppler S wave and E wave (Em) were measured from the apical 4-chamber view with a 2- to 5-mm sample volume. Measurements were recorded with simultaneous electrocardiography at a sweep of 50–100 mm/s. To evaluate LV filling pressures, E/Em ratio was calculated. For RV parameters, TDI recordings were obtained from apical 4-chamber-view-focused RV with the pulsed-wave Doppler sample volume placed on the tricuspid lateral annulus. Peak systolic myocardial velocity (Sm RV) was measured. The sum of RV isovolumic contraction and relaxation time was obtained by subtracting RV ejection time from the interval between the cessation and onset of the tricuspid inflow velocities using pulsed-wave Doppler. The RV myocardial performance index (MPI) was obtained by dividing the sum of both isovolumic

intervals by the ejection time. From the modified apical 4-chamber view including the RV apex, the RV end-diastolic and end-systolic areas were calculated. RV fractional area change (FAC) was calculated as the percentage value of difference between RV end-diastolic and end-systolic areas divided by the RV end-diastolic area. To determine the motion and excursion of the annulus, the M-mode cursor was oriented to the junction of the tricuspid valve plane with the RV free wall, using images in the apical 4-chamber view. Maximal tricuspid annular plane systolic excursion (TAPSE) was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the peak descent during ventricle systole. Pulmonary artery systolic pressure (PAPs) was estimated using the approach of calculating the systolic pressure gradient between the RV and right atrium by the maximum velocity of the tricuspid regurgitant jet, using the modified Bernoulli equation and then adding an estimated right atrial pressure to this value, based on both the size of the inferior vena cava and the change in caliber of this vessel with respiration.

Two-Dimensional Speckle-Tracking Analysis

2D-STE images of the RV were acquired at end-diastole in the RV from the RV-focused view. Second harmonic imaging was used to improve endocardial border detection (1.7–2.0 MHz). Three consecutive cardiac cycles were recorded at end expiration. The frame rate was kept between 70–100 frames/s. Using commercially available 2D strain software (EchoPAC 108.1.12, General Electric Medical Systems, Horten, Norway), the endocardial border in the end-systolic frame was manually traced from the RV-focused view, and a region of interest was traced with a point-and-click approach on the endocardium at end-diastole in the RV from the RV-focused view. A second, larger region of interest was then generated and manually adjusted near the epicardium. Special care was taken to fine-tune the region of interest, using visual assessment during cine-loop playback to ensure that segments were tracked appropriately. Segments that failed to track were manually adjusted by the operator. Any view in which 2 or more segments could not be tracked was not included in the analysis. Finally, segments were tracked on a frame-by-frame basis using the sum of absolute difference algorithm. The RV was divided into 6 standard segments (at the basal, middle and apical levels), and 6 corresponding time-strain curves were generated. RV free wall (RVFW-S) and RV septal wall strain were separately calculated by averaging each of the 3 regional peak systolic strains along the entire RV free and septal walls, respectively. All measurements were performed by one experienced cardiologist blinded to data about the clinical status of the patients.

Statistical Analysis

SPSS 17.0 statistical software (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis. Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are expressed as percentages. The Kolmogorov-Smirnov test was used to test the normality of distribution of continuous variables. Group means for continuous variables were compared with the use of the Student t test, the Mann-Whitney U test, ANOVA or the Kruskal-Wallis test, as appropriate. Categorical variables were compared with the χ^2 test. The Tukey honestly significant difference test was used for post hoc analysis. The Pearson or Spearman correlation analysis was used for assessing the correlation between RVFW-S and continuous variables depending on Gaussian distributions.

The COPD patients were divided into 2 groups according to the median value of RVFW-S (>19.06 and ≤ 19.06). Two multivariate logistic regression analyses were performed to find independent associates of impaired RVFW-S (≤ 19.06). In model 1, age, TAPSE, RV FAC, BODE index, RV MPI, PAPs and Sm RV were entered into the model as independent variables. BODE index components including BMI, mMRC dyspnea score, FEV₁ % predicted and 6-min walk distance were entered into model 2 as independent variables. The partial correlation analysis was used for assessing the correlation between RVFW-S and 6-min walk distance after adjustment for FEV₁ % predicted. Interobserver agreement of echocardiographic parameters obtained from 2D-STE data was calculated by means of the Bland-Altman analysis and the intra-class correlation coefficient was used to assess intraobserver agreement. Receiver-operating characteristic curve analysis was performed to detect the cut-off value of FEV₁ % predicted and 6-min walk distance for the prediction of RVFW-S (≤ 19.06). Area under the curve (AUC) comparison was performed with the MedCalc software program, release 7.3.0.1 (MedCalc Software, Belgium). A two-tailed $p < 0.05$ was considered statistically significant.

Results

The study population consisted of 135 COPD patients and 37 control subjects. The baseline characteristics of patients and controls are shown in table 2. Laboratory parameters did not differ between the 2 groups. With regard to clinical features, only 2 variables differed between the groups: the incidence of current and previous smoking was significantly higher in the COPD group ($p < 0.001$ and $p < 0.001$, respectively). The patients with COPD had decreased RV functional parameters including RVFW-S ($p < 0.001$), TAPSE ($p < 0.001$), Sm RV ($p < 0.001$), RV FAC ($p < 0.001$) and increased RV MPI ($p < 0.001$) and PAPs ($p < 0.001$) compared to the control group. Of the LV diastolic parameters, the E/A ratio was significantly decreased ($p < 0.001$) and the E/Em ratio was significantly higher in the COPD group than in the control group ($p = 0.003$). The other measurements of LV were similar in the 2 groups. When patients were classified with respect to the BODE index, 28.1% ($n = 38$) were BODE 1 (Q_1), 26.7% ($n = 36$) were BODE 2 (Q_2), 22.2% ($n = 30$) were BODE 3 (Q_3) and 23.0% ($n = 31$) were BODE 4 (Q_4). Multiple comparisons were performed between the BODE index quartiles and the control group. The control group had a smoking history of a lower number of pack-years than the BODE index quartiles (which did not differ across quartiles, $p < 0.001$). Other clinic and laboratory parameters of the BODE index quartiles and the control group were similar. Although the E/Em ratio showed a decreasing trend from Q_1 to Q_4 , there was no significant difference between the BODE index quartiles ($p = 0.159$).

As for the RV functional parameters, RVFW-S, TAPSE, Sm RV and RV FAC showed a decreasing trend from the control group to the Q_4 patients, while for RV MPI and PAPs there was an increasing trend (table 3). The BODE index components, i.e. BMI (26.4 ± 4.0 , 25.8 ± 4.9 , 25.4 ± 4.6 , 23.1 ± 5.1), mMRC dyspnea score (1.0 ± 0.5 , 1.7 ± 0.5 , 2.6 ± 0.5 , 3.3 ± 0.4), FEV₁ % predicted (65.4 ± 10.8 , 48.9 ± 11.2 , 38.7 ± 7.5 , 31.4 ± 6.8) and 6-min walk distance (423.6 ± 98.2 , 315.1 ± 58.1 , 231.0 ± 62.3 , 101.7 ± 39.7), were measured in Q_1 – Q_4 .

Univariate correlation analysis of COPD patients revealed that RVFW-S was positively correlated with TAPSE ($r = 0.462$, $p < 0.001$), Sm RV ($r = 0.384$, $p < 0.001$) and RV FAC ($r = 0.501$, $p < 0.001$). RV MPI and PAPs were negatively correlated with RVFW-S ($r = -0.372$, $p < 0.001$ vs. $r = -0.414$, $p < 0.001$, respectively). For the COPD patients, a correlation analysis between the echocardiographic parameters (both conventional echocardiography and 2D-STE) of RV, FEV₁ % predicted and 6-min walk distance was performed (table 4).

Predictors of Decreased RVFW-S

Patients with COPD were divided into 2 groups according to the RVFW-S value (>19.06 and ≤ 19.06) which was the median value of RVFW-S in COPD subjects. To find independent predictors of decreased RVFW-S (≤ 19.06), two multivariate logistic regression analyses were performed. In model 1, independent variables such as BODE index quartiles, age, TAPSE, RV FAC, RV MPI, PAPs and Sm RV were entered into the model. The R^2 of logistic regression was 0.491 and the BODE index quartiles were found to be independent predictors of decreased RVFW-S (table 5). Table 6 shows the characteristics of COPD patients according to the RVFW-S value. RVFW-S was compared with the nominal components of the BODE index. Patients with an mMRC score of 3–4 had significantly lower RVFW-S values than those with a score of 0–2 (17.5 ± 1.4 vs. 20.2 ± 2.0 , $p < 0.001$). Regarding the BMI, RVFW-S was significantly lower in patients with BMI ≤ 21 than in those with BMI > 21 (18.4 ± 2.1 vs. 19.5 ± 2.2 , $p = 0.014$) (fig. 1). To establish which BODE index parameter is the most important for predicting RVFW-S (≤ 19.06), BMI, mMRC dyspnea score, FEV₁ % predicted and 6-min walk distance were entered into model 2 as independent variables. Age (OR 1.05, 95% CI 1.00–1.09, $p = 0.039$), FEV₁ % predicted (OR 0.97, 95% CI 1.00–0.94, $p = 0.037$) and 6-min walk distance (OR 0.99, 95% CI 1.00–0.98, $p = 0.001$) were independently associated with RVFW-S (≤ 19.06). Receiver-operating characteristic curve analysis was performed to detect the cut-off

Table 2. Baseline characteristics of patients with COPD and controls

Variables	Controls (n = 37)	Patients with COPD (n = 135)	p value
Age, years	67.7±3.9	69.6±10.6	0.100
Male	32 (86.5)	125 (92.6)	0.244
Hypertension	13 (35.1)	54 (40)	0.591
Diabetes mellitus	4 (10.8)	19 (14.1)	0.605
Current smoker	9 (24.3)	58 (43)	0.039
Exsmoker	4 (10.8)	73 (54.1)	<0.001
Pack-years of smoking	15.0±21.4	56.2±25.4	<0.001
BMI	24.4±1.3	25.3±4.7	0.278
eGFR ≥60 ml/min/1.73 m ²	35 (94.6)	117 (86.7)	0.183
SBP, mm Hg	133.1±12.8	136.7±18.2	0.266
DBP, mm Hg	79.9±14.3	82.9±11.4	0.175
FEV ₁ % predicted	–	47.3±17.6	–
FEV ₁ /FVC, %	–	61.1±9.9	–
FVC % predicted	–	83.6±7.4	–
LDL-cholesterol, mg/dl	123.5±14.7	119.6±26.2	0.243
HDL-cholesterol, mg/dl	43.0±6.5	40.5±10.3	0.081
Triglycerides, mg/dl	145.4±23.8	135.1±49.9	0.078
Total cholesterol, mg/dl	185.4±15.3	177.9±34.3	0.200
Hemoglobin, mg/dl	12.8±0.7	13.3±1.6	0.060
Fasting plasma glucose, mg/dl	97.5±17.1	103.3±18.1	0.081
Calcium-channel blockers	7 (18.9)	19 (14.1)	0.466
Beta-blockers	3 (8.1)	5 (3.7)	0.260
ACE inhibitors or ARB	9 (24.3)	35 (25.9)	0.843
Statins	7 (18.9)	25 (18.5)	0.956
Oral antidiabetics	3 (8.1)	14 (10.4)	0.683
Insulin	3 (8.1)	5 (3.7)	0.260
LV end-diastolic volume, ml/m ²	94.6±15.8	87.7±23.4	0.091
LV end-systolic volume, ml/m ²	37.2±7.7	36.6±10.2	0.697
LV end-diastolic dimension, mm	47.0±4.0	46.0±4.0	0.456
LV end-systolic dimension, mm	28.0±4.0	29.0±3.0	0.318
LV ejection fraction, %	60.6±4.6	59.1±5.4	0.097
Septal wall thickness, mm	11.1±1.0	11.1±1.7	0.975
Posterior wall thickness, mm	10.3±0.9	10.6±1.5	0.172
E/A ratio	1.01±0.20	0.85±0.20	<0.001
Sm, systolic tissue velocity, cm/s	11.2±2.0	10.6±2.1	0.175
E/Em ratio	7.6±1.2	8.4±1.9	0.003
RVFW-S, %	–25.4±2.6	–19.3±2.2	<0.001
RVSWS-S, %	–20.2±1.1	–19.9±0.8	0.142
TAPSE, cm	2.4±0.2	2.0±0.2	<0.001
Sm RV, m/s	15.9±2.2	11.8±3.3	<0.001
RV FAC, %	52.5±5.9	44.2±6.7	<0.001
RV MPI	0.24±0.05	0.41±0.08	<0.001
PAPs, mm Hg	21.5±4.9	32.2±7.5	<0.001

Figures denote mean ± SD or n (%). ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RVSW-S = RV septal wall strain; SBP = systolic blood pressure; Sm = lateral mitral annular tissue Doppler S wave.

Table 3. Comparison of RV functional parameters between the control group and the BODE index quartiles

Variables	Control group (n = 37)	Q ₁ (n = 38)	Q ₂ (n = 36)	Q ₃ (n = 30)	Q ₄ (n = 31)	p value
RVFW-S, %	-25.5±2.6	-21.3±1.9	-19.9±1.6 ^a	-18.4±1.2	-17.1±1.3	<0.001
TAPSE, cm	2.36±0.17	2.18±0.18	2.05±0.16	1.97±0.17	1.77±0.16	<0.001
Sm RV, m/s	15.9±2.2	14.2±3.1	12.5±3.1	10.7±2.0	8.9±2.1	<0.001
RV FAC, %	52.5±5.9	48.6±3.6 ^b	47.9±4.3	41.4±5.8	37.0±5.4	<0.001
RV MPI	0.24±0.05	0.35±0.06	0.40±0.08	0.43±0.06	0.48±0.06	<0.001
PAPs, mm Hg	21.5±4.9	28.0±4.8 ^c	29.3±5.2	35.4±6.5 ^d	37.6±8.8	<0.001

^a Nonsignificance between Q₂ and Q₃. ^b Nonsignificance between Q₁ and Q₂. ^c Nonsignificance between Q₁ and Q₂. ^d Nonsignificance between Q₃ and Q₄.

Table 4. Correlation analysis of 6-min walk distance and FEV₁ with RV echocardiographic parameters in patients with COPD

Variables	6-min walk distance, m	FEV ₁ % predicted
RVFW-S (%)	0.644*	0.543*
TAPSE (cm)	0.622*	0.415*
Sm RV (m/s)	0.533*	0.468*
RV FAC (%)	0.588*	0.487*
RV MPI	-0.491*	-0.372*

* p < 0.001.

Table 5. The predictors of RVFW-S (≤19.06) in the logistic regression analysis

	Multivariate p value	Multivariate OR (95% CI)
Age (years)	0.052	1.05 (1.00–1.09)
BODE index (quartiles)	0.001	4.61 (1.85–11.63)
TAPSE (cm)	0.223	0.19 (0.01–2.73)
RV FAC	0.633	0.98 (0.89–1.07)
RV MPI	0.307	29.41 (0.06–98.03)
PAPs (mm Hg)	0.414	0.04 (0.01–1.06)
Sm RV (m/s)	0.714	4.29 (1.97–9.32)

value of FEV₁ % predicted and 6-min walk distance in predicting RVFW-S (≤19.06). FEV₁ % predicted identified patients with RVFW-S (≤19.06) with a specificity of 80.6%, a sensitivity of 60.3% with a cut-off value of 49% (AUC 0.760, 95% CI 0.679–0.829). In addition, the optimal cut-off value for the 6-min walk distance was 260, yielding a specificity of 66.7% and a sensitivity of 87.3% (AUC 0.810, 95% CI 0.733–0.872). In order to identify

Fig. 1. The mean values of RVFW-S according to mMRC dyspnea scores 0–2 versus 3–4 and BMI >21 versus ≤21.

which parameters were the most accurate, we compared the AUC of both receiver-operating characteristic curves and there was no significant difference (p = 0.241). The partial correlation analysis was performed for assessing the correlation between RVFW-S and 6-min walk distance after adjustment for FEV₁ % predicted. Figure 2 shows the partial correlation of 6-min walk distance (r = 0.498 vs. p < 0.001) with RVFW-S.

Reproducibility

Intra- and interobserver variability were assessed from echocardiographic data obtained from a subgroup of 20 subjects. To assess interobserver variability, the second operator (who was unaware of the previous measurements) analyzed RV functions with 2D-STE. One month

Table 6. The characteristics of patients according to the two categories of RVFW-S

Variables	RVFW-S >19.06 (n = 63)	RVFW-S ≤19.06 (n = 72)	p value
Age, years	69.4±10.7	69.7±10.7	0.897
Male	61 (96.8)	64 (88.9)	0.079
Hypertension	24 (38.1)	30 (41.7)	0.673
Diabetes mellitus	10 (15.9)	9 (12.5)	0.574
Current smoker	28 (44.4)	30 (41.7)	0.745
Exsmoker	34 (54.0)	39 (54.2)	0.982
Pack-years of smoking	53.4±22.8	58.7±23.3	0.233
BMI ≤21	7 (11.1)	19 (26.4)	0.025
eGFR ≥60 ml/min/1.73 m ²	52 (82.5)	65 (90.3)	0.187
SBP, mm Hg	136.9±20.8	136.4±15.7	0.881
DBP, mm Hg	81.7±12.1	84.0±10.7	0.246
FEV ₁ % predicted	55.5±17.3	40.1±14.6	<0.001
FEV ₁ /FVC, %	65.4±8.5	57.9±10.5	<0.001
FVC % predicted	86.0±7.6	81.5±6.7	<0.001
PaO ₂	78.5±11.2	65.3±9.4	<0.001
PaCO ₂	38.0±3.5	43.0±6.9	<0.001
SO ₂	95.5±2.4	91.4±4.0	<0.001
LDL-cholesterol, mg/dl	121.1±26.6	118.3±25.9	0.528
HDL-cholesterol, mg/dl	40.2±8.5	40.8±11.7	0.728
Triglycerides, mg/dl	134.9±46.9	135.2±52.7	0.972
Total cholesterol, mg/dl	181.8±33.1	174.5±35.2	0.216
Hemoglobin, mg/dl	13.1±1.4	13.4±1.7	0.378
Fasting plasma glucose, mg/dl	104.6±19.0	102.2±17.4	0.449
LV end-diastolic volume, ml/m ²	88.5±22.7	87.0±24.1	0.713
LV end-systolic volume, ml/m ²	36.4±11.4	36.8±9.1	0.844
LV end-diastolic dimension, mm	46.4±3.6	45.6±4.4	0.252
LV end-systolic dimension, mm	28.6±2.4	28.8±3.1	0.711
LV ejection fraction, %	59.1±5.9	59.1±4.9	0.980
Septal wall thickness, mm	11.1±1.6	11.1±1.8	0.913
Posterior wall thickness, mm	10.6±1.4	10.6±1.6	0.982
E/A ratio	0.83±0.17	0.86±0.15	0.199
E/Em ratio	8.7±1.7	8.1±2.0	0.103
TAPSE, cm	2.1±0.2	1.9±0.2	<0.001
Sm RV, m/s	13.0±3.4	10.7±2.8	<0.001
RV FAC, %	47.2±5.1	41.5±6.9	<0.001
RV MPI	0.38±0.08	0.44±0.08	<0.001
PAPs, mm Hg	29.5±5.4	34.6±8.3	<0.001
mMRC dyspnea score 3–4	6 (9.5)	37 (51.4)	<0.001
Six-minute walk distance, m	354.7±117.7	210.8±116.5	<0.001

Figures denote mean ± SD or n (%). DBP = Diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PaCO₂ = arterial carbon dioxide pressure; PaO₂ = arterial oxygen pressure; SBP = systolic blood pressure; SO₂ = arterial oxygen saturation.

later, the first operator repeated the analysis to assess the intraobserver variability. Agreement analysis of inter- and intraobserver variability for RVFW-S measurements revealed high agreement, i.e. a mean difference of 0.09 (95% limit of agreement −0.99, 1.16) and an intraclass

correlation coefficient of 0.993 (95% CI 0.983–0.997), respectively. Agreement analysis of interobserver variability for RVSW-S was a mean difference of −0.05 (95% limit of agreement −0.71, 0.61) and the intraclass correlation coefficient for RVSW-S was 0.972 (95% CI 0.931–0.989).

Fig. 2. The partial correlation of FEV₁ % predicted and 6-min walk distance with RVFW-S after adjusted for parameters of blood gas analysis, i.e. FEV₁ % predicted.

Discussion

This study demonstrated that increased BODE index parameters were associated with progressive impairment of RV systolic functions in COPD patients, assessed by 2D-STE-derived RVFW strain. Six-minute walk distance was found to be positively correlated with RVFW-S after adjustment for FEV₁ % predicted. To the best of our knowledge, this study is also the first to show the independent association between BODE index quartiles and RV dysfunction in subjects with COPD.

There is growing evidence that COPD is not only characterized by a chronic airflow limitation, but is also a systemic disease. Some extrapulmonary disorders such as cardiovascular disease, peripheral skeletal muscle dysfunction, diabetes and chronic kidney disease, are frequently seen in individuals with COPD. It has thus been proposed that COPD is in fact part of a chronic systemic inflammatory disease [22]. COPD is defined functionally according to FEV₁ in the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. In previous reports, FEV₁ was found to be independently associated with prognosis and the exacerbation of COPD [9]. However, evaluating FEV₁ only is insufficient to describe the mortality and clinical conditions of COPD, which is complex and involves more than airflow obstruction [22]. Celli et al. [6] introduced a new multidimensional grading system, the BODE index, incorporat-

ing the systemic (i.e. BMI and exercise capacity) and functional (airflow obstruction and dyspnea) components of COPD. The BODE index was found to be a better predictor of death from any cause and from respiratory causes than the FEV₁ value.

Cardiovascular disease is one of the leading causes of mortality in patients with COPD. The RV is a conduit between the systemic and pulmonary circulation that is affected by the vascular remodeling induced by the systemic and local effects of COPD. In other words, COPD mainly affects the structure and functions of the RV. The evaluation of RV functions in COPD patients is crucial because of the relationship between RV dysfunction and increased mortality [15, 23]. Although both RV functions and BODE index predict increased mortality in COPD patients, the relationship between them has not been studied up to now (except for the individual components of BODE index). RV dysfunction occurs in the early phase of lung involvement in COPD patients, but clinical signs are occult unless signs of systemic congestion are present (these develop in the later stages of the disease). Therefore, the evaluation of RV function by noninvasive methods has gained importance. In clinical practice, 2D echocardiography is the most frequently used noninvasive method for this evaluation. It is accompanied by important limitations, however, including the complex geometry of the RV, the predominantly longitudinal orientation of its myofibrils and poor echogenicity in COPD patients [15, 23]. 2D-STE is a new technique which permits the differentiation of active motion from passive motion, independent of the Doppler angle of incidence, tethering effect and load dependency. This differentiation represents a part of the stress-strain relationships that define myocardial contractility. Thus, strain can be decreased even in the setting of normal contractility if regional or global stress, e.g. afterload, is elevated. This is even more pronounced in the setting of RV circulation, which is especially sensitive to afterload elevation and may be useful for evaluating subtle changes when compared with other conventional echocardiographic techniques [24, 25].

In previous studies, 6-min walk distance and BMI, which reflect the systemic manifestation of COPD, were found to be associated with increased mortality [26, 27]. Other studies evaluated the impact of exercise capacity and BMI on RV functions. In contrast to our results, Cuttica et al. [28] reported that structural changes in the RV, including RV wall thickness and right atrial area, were associated with a decrement in 6-min walk distance in nonsevere COPD patients, independent of lung function. They did not find an association between exercise capac-

ity and RV functions as assessed by TAPSE or RV FAC. Their study included patients with nonsevere COPD, classified according to GOLD criteria, and the study population consisted of different races such as Hispanic, Asian, black and white, with Caucasians being predominant. The clinical characteristics of patients, such as blood pressure, smoking history and fasting plasma glucose levels were not defined. The impact on RV functions and exercise capacity of COPD severity, racial variations and clinical characteristics could explain why the results of their study were not compatible with ours. In another study, Schoos et al. [29] investigated the echocardiographic predictors of exercise capacity in COPD patients. They reported that tricuspid regurgitation was the only independent predictor of exercise tolerance among RV functional parameters including RVFW-S. There may be several explanations for their conflicting results. The study population was enrolled according to the GOLD classification and 84% had GOLD class II–III COPD. There was no detailed information about past medical history or the latest exacerbations of COPD. Inclusion and exclusion criteria were also not explained clearly; for instance, factors like obstructive sleep apnea could have affected RV function and interfered with the interpretation of the findings.

In our study, RVFW-S was positively correlated with 6-min walk distance after adjustment for FEV₁ % predicted. RV systolic function, which is especially sensitive to afterload elevation, is even more pronounced in the setting of COPD [24, 25]. Fluctuations of pulmonary artery pressure and an increase in venous blood return into the RV during exercise may explain the relationship between exercise capacity and RV deformation. Patients in our study with a BMI ≤ 21 had a lower RVFW-S value than those with a BMI >21 . Reduced muscle mass and cachexia are associated with increased mortality in COPD [26]. The mechanism involved in the loss of muscle mass and in skeletal muscle atrophy seems to be related to systemic inflammation and oxidative stress through reducing protein synthesis and accelerating protein catabolism. Furthermore, cardiac myocytes, i.e. protein-rich tissue, may be affected by similar proteolytic processes [15, 30, 31]. RV myocardium and functions might be affected through this pathophysiological mechanism in COPD patients with a low BMI.

FEV₁ reflects the degree of pulmonary impairment and is a well-known predictor of mortality in COPD. A link between RV functions and FEV₁ representing COPD severity has been evaluated. In line with our findings, Vitarelli et al. [32] reported that strain-rate imaging param-

eters are correlated with respiratory function tests in COPD patients. In our study, RVFW-S was positively correlated with FEV₁ % predicted. In a previous report, FEV₁ % predicted was associated with systemic inflammation [33]. Impaired respiratory functions and subsequent hypoxemia usually have a negative impact on RV functions, which could be further affected by the increased systemic inflammatory process. In our study, patients with an mMRC dyspnea score of 3–4 had a lower RVFW-S value than those with a score of 0–2. The mMRC dyspnea scale reflects the perception by patients of symptoms related to skeletal muscle atrophy and loss of muscle mass as a consequence of the systemic manifestation of COPD [6, 30]. A higher mMRC dyspnea score and a lower RVFW-S may contribute to common presentations that reflect increased systemic inflammation. Our findings about diastolic functions are in line with previous studies. Individuals with COPD had an increased E/Em ratio compared to the control group and this gradually decreased with increasing BODE index parameters. A reduction in LV filling pressure due to reduced preload and hyperinflation is probably the potential mechanism responsible for LV diastolic dysfunction in patients with COPD [34, 35]. In our study, increased BODE index scores were associated with decreased RVFW-S, which could not be detected by conventional parameters that evaluate RV functions. In a similar manner, Giusca et al. [36] stated that RV functions could be better described with deformation imaging rather than conventional parameters, due to changes in apical transverse motion when RV dysfunction occurs.

The definition of COPD has evolved from a disease limited to the lungs to a multisystem disorder comprising pulmonary and systemic inflammation. This disease should thus be evaluated by multidimensional methods and managed with a multidisciplinary approach [22]. Multidimensional evaluation should include RV functions that can be directly influenced by the negative pulmonary and systemic effects of COPD. Although assessment of RV function could provide useful data for pulmonologist in terms of planning treatment and predicting prognosis, it is not easily obtained in pulmonary clinics. The BODE index is a multidimensional grading system and can be evaluated easily in office settings, but its relation to RV functions was not studied before now. This study provides essential information about the clinical implications of the relationship between the BODE index and RV functions.

Limitations

The main limitation of this study was its relatively small sample size. Second, RV strain was assessed by 2D-STE software which was mainly developed for LV strain; however, previous studies did demonstrate acceptable feasibility and reproducibility for the RV strain. Third, the estimation of the PAPs was based only on tricuspid regurgitation measurements and an invasive pressure measurement was not used. However, this widely used Doppler-derived pressure estimation is well recognized and has been documented as having good correlation with simultaneously obtained catheter-derived measurements. BODE index quartiles can vary in the course of time. Our study did not inform about the impact of BODE index quartile interchange on RV functions, necessitating further studies. Finally, we did not perform

measurements of the diffusing capacity of carbon monoxide, but these are not strictly necessary for the diagnosis of COPD.

Conclusion

The BODE index is an easily calculated multidimensional grading system for evaluating COPD patients in pulmonary clinics. It not only provides information about the pulmonary aspects of the disease such as airflow limitation, it also evaluates the systemic clinical manifestations. Our study revealed that assessment of the BODE index provides information about RV functions and that as the BODE index parameters increase, there is a decrement in RVFW-S as a sign of RV dysfunction.

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