ORIGINAL ARTICLE

The "right way" to the left chamber in non-severe COPD: Echocardiographic predictors for stress-induced left ventricular diastolic dysfunction

Şiddetli derecede olmayan KOAH'da sol kalp odacıklarına "doğru yol": Stres kaynaklı sol ventriküler diyastolik disfonksiyon için ekokardiyografik prediktörler

Radostina Cherneva, M.D.,[1] Stefan Denchev, M.D.,[2] Zheyna Cherneva, M.D.[2]

[1]Department of Pulmonology, University Hospital for Respiratory Diseases "St. Sophia", Sofia

[2]Department of Cardiology, Medical Institute of the Ministry of Internal Affairs, Sofia

ABSTRACT

Objective: Dyspnea is a major complaint of both chronic obstructive pulmonary disease (COPD) and heart failure with preserved ejection fraction (HFpEF). It often remains underdiagnosed in COPD patients when only echocardiography at rest is performed. The aim of this study was to evaluate the predictive value of cardiopulmonary and echocardiographic parameters at rest for the diagnosis of HFpEF in non-severe COPD patients who complain of exertional dyspnea and have no overt cardiovascular disease.

Methods: A total of 104 COPD patients underwent echocardiography before cardiopulmonary exercise testing (CPET) and 1–2 minutes after peak exercise. The patients were divided into 2 groups based on peak E/e' measurements: patients with masked HFpEF-stress and left ventricular diastolic dysfunction (LVDD; E/e'>15), and patients without masked HFpEF (without stress LVDD). CPET and echocardiographic parameters at rest were measured and the predictive value for stress E/e' was analyzed.

Results: Stress LVDD occurred in 67 of 104 patients (64%). These patients achieved a lower work load, lower 'VO_2 consumption, lower minute ventilation, and higher 'VE/'VCO_2 slope in comparison with patients without stress LVDD. None of the CPET values correlated with stress E/e'. The best independent predictors for stress LVDD were right atrium volume index (RAVI), right ventricle (RV) parasternal diameter, and RV E/A >0.75. The combination of these echocardiographic parameters predicted HFpEF with an accuracy of 91.2%.

Conclusion: There is a high prevalence of stress LVDD in non-severe COPD patients with exertional dyspnea who remain free of overt cardiovascular disease. RAVI, RV parasternal diameter, and RV E/A >0.75 were the only independent predictors of stress LVDD.

ÖZET

Amaç: Dispne, hem kronik obstrüktif akciğer hastalığı (KOAH) hem de ejeksiyon fraksiyonu (HFpEF) korunmuş kalp yetmezliğinde önemli bir yakınmadır. KOAH'ta sadece istirahatte ekokardiyografi çekildiğinde sıklıkla tanısı konamaz. Bu çalışmanın amacı, efor dispnesi yakınması olan ve belirgin kardiyovasküler hastalığı ve şiddetli derecede KOAH'ı olmayan hastalarda HFpEF tanısı için istirahatte saptanan kardiyopulmoner ve ekokardiyografik parametrelerin prediktif değerini değerlendirmekti.

Yöntemler: Toplam 104 KOAH hastasına kardiyopulmoner egzersiz testi (KPET) öncesi ve pik egzersizden 1–2 dakika sonra ekokardiyografi çekildi. Hastalar pik E / e 'ölçümlerine: maskelenmiş HFpEF-stresi ve sol ventrikül diyastolik disfonksiyonu (LVDD; E / e'>15) olan hastalar ve maskelenmiş HfpEF'si olmayan hastalar (stres LVDD'siz) olmak üzere 2 gruba ayrıldı. İstirahatte KPET ve ekokardiyografik parametreler ölçüldü ve E/e 'stresinin prediktif değeri analiz edildi.

Bulgular: Stres LVDD, 104 hastanın 67'sinde (%64) görüldü. Bu hastalarda stres LVDD'si olmayan hastalara kıyasla daha düşük iş yükü, daha düşük 'VO_2 tüketimi, daha düşük dakika ventilasyonu ve daha yüksek' VE/'VCO_2 eğimi saptandı. KPET değerlerinin hiçbiri stres E/e ile ilişkili değildi. Stres LVDD için en iyi bağımsız prediktörler sağ atriyum hacim indeksi (RAVI), sağ ventrikül (RV) parasternal çapı ve RV E/A >0.75 idi. Bu ekokardiyografik parametrelerin kombinasyonu, HFpEF'i %91.2'lik bir doğrulukla öngördü.

Sonuç: Belirgin kardiyovasküler hastalığı olmayan efor dispneli ağır KOAH hastalarında stres LVDD prevalansı yüksektir. RAVI, RV parasternal çapı ve RV E/A >0.75, stres LVDD'nin bağımsız prediktörleriydi.

Received: November 27, 2019 *Accepted:* February 14, 2020

Correspondence: Dr. Zheyna Cherneva. Sofia, Bulgaria, Bul. Gen Skobelev 78 Sofia - Bulgaria.
Tel: 359889569777 e-mail: jenicherneva@yahoo.com

Chronic obstructive pulmonary disease (COPD) remains associated with significant morbidity and mortality.[1] Cardiovascular (CV) complications are among the predominant factors responsible. The early detection of such complications is important for COPD therapeutic control and proper disease management.[2,3] COPD patients have a greater than 4-fold risk of developing coronary artery disease and left ventricle (LV) dysfunction.[4] Magnetic resonance imaging (MRI) studies can establish subclinical LV structural and functional (diastolic) changes even in mild COPD subjects who have no CV risk factors.[5–7] The common symptoms between COPD and LV dysfunction, however, often delay the diagnosis of the CV comorbidity in COPD. Dyspnea and exercise intolerance may be caused by increased diastolic filling pressure, increased pulmonary capillary wedge pressure or ventilation-perfusion/gas exchange abnormalities.

Diastolic filling pressure is often normal at rest, but increases during exercise. Dynamic assessment is a validated approach for the evaluation of effort-induced changes.[8–10] Cardiorespiratory parameters may also be used to discern the cardiac and respiratory nature of the complaints.[11,12]

Performance of stress echocardiography and cardiopulmonary exercise testing together may provide timely detection of LV diastolic dysfunction (LVDD) in COPD patients with exertional dyspnea and no manifest CV disease, and it may facilitate the differential diagnosis of limited physical activity and exertional dyspnea in this patient group.

The performance of these diagnostic approaches, however, is time-consuming and demands special equipment. With this in mind, the objectives set for this study were to 1) detect the frequency of stress LVDD-masked heart failure with preserved ejection fraction (HFpEF) in non-severe COPD patients free of overt CV pathology who complained of exertional dyspnea, and 2) establish whether echocardiographic parameters at rest could be predictors for stress LVDD.

METHODS

Patients and study protocol

This was a prospective study performed with 224 clinically stable outpatients who had been diagnosed with COPD at the University Hospital for Respiratory Diseases "St. Sophia," in Sofia, Bulgaria. A total of 163 met the eligibility criteria and demonstrated non-severe COPD with forced expiratory volume in 1 second (FEV_1) >50%. All of the subjects had exertional dyspnea and were free of overt CV disease. In all, 104 patients (64 men, 40 women; mean age of 62.9±7.5 years) were considered eligible and enrolled after applying the exclusion criteria. The study was approved by the Ethical Committee of the Medical University, Sofia (no: 5/12.03.2018). All of the patients provided written, informed consent before participation in the study. They were acquainted with the aim of the study, its scientific value, and the potential presentation of data at different forums.

Abbreviations:

AT	*Anaerobic threshold*
CI	*Confidence interval*
COPD	*Chronic obstructive pulmonary disease*
CPET	*Cardiopulmonary exercise testing*
CV	*Cardiovascular*
DT	*Deceleration time*
FEV_1	*Forced expiratory volume in 1 second*
FVC	*Forced vital capacity*
HF	*Heart failure*
HFpEF	*Heart failure with preserved ejection fraction*
HFrEF	*Heart failure with reduced ejection fraction*
LA	*Left atrium*
LV	*Left ventricle*
LVDD	*Left ventricular diastolic dysfunction*
MRI	*Magnetic resonance imaging*
OR	*Odds ratio*
RA	*Right atrium*
RAVI	*Right atrium volume index*
RER	*Respiratory exchange ratio*
ROC	*Receiver operating characteristic*
RV	*Right ventricle*
RVWT	*RV wall thickness*
TR	*Tricuspid regurgitation*

The following exclusion criteria were used: 1) LV ejection fraction <50%, 2) LVDD at rest that was classified as greater than grade I, 3) echocardiographic signs of systolic pulmonary arterial hypertension, 4) valvular heart disease, 5) documented cardiomyopathy, 6) severe uncontrolled hypertension (systolic blood pressure >180 mmHg and diastolic blood pressure >90 mmHg), 7) atrial fibrillation or malignant ventricular arrhythmia, 8) known ischemic heart disease, 9) anemia, 10) diabetes mellitus, 11) cancer, 12) chronic kidney disease, 13) recent chest or abdominal surgery, 14) recent exacerbation (during the previous 3 months), or 15) recent change in medical therapy (during the previous 3 months).

Procedures

Pulmonary function testing

All of the participants underwent a preliminary clinical examination, which included a chest X-ray and

spirometry, electrocardiogram, and echocardiography evaluations. Those eligible for the study performed additional spirometry and exercise stress tests. Both tests were performed using a Vyntus device (Vyaire Medical Inc., Chicago, IL, USA) according to the guidelines. Spirometry was performed after a bronchodilation test with the application of (400 μkg) of salbutamol. Following the European Respiratory Society guidelines, a post-bronchodilation ratio of FEV_1/forced vital capacity (FVC) <70% was used for the diagnosis of COPD.[13] Only patients with mild/moderate airway obstruction (FEV_1 >50%) were selected. The severity of COPD was staged according to the Global Initiative for Chronic Obstructive Lung Disease criteria.[14]

Stress test protocol – cardiopulmonary exercise testing

All of the patients underwent a symptom-limited incremental exercise stress test according to the guidelines.[15] The test was performed on a bicycle after the clinical examination and spirometry testing. Gas and flow sensors were calibrated before each test. Clinical monitoring of the patients included standard electrocardiography throughout the whole exercise test with manual blood pressure measurements and heart rate recordings at the end of every stage.

A continuous ramp protocol was applied. After 2 minutes of unloaded pedaling (rest phase- 0W), a 3-minute warm-up phase (20W) followed. The test phase included 20W/2min load increments. Patients were instructed to pedal with 60 rotations per minute.

A breath-by-breath analysis was used to evaluate expiratory gases. Peak values of oxygen consumption, carbon dioxide production, and ventilatory slope ('VE/'VCO_2) were determined using the highest 30-second average value obtained during the last stage of the exercise test. The peak respiratory exchange ratio (RER) was estimated on the basis of these values. An RER >1.1 was used to define maximal effort. Since the study group consisted of COPD patients, a dual approach to the measurement of the anaerobic threshold (AT) was applied. Both V-slope method and the ventilatory equivalents method for 'VO_2 and 'VCO_2 were used. The modified Borg Scale was used to evaluate peak dyspnea.

Good quality echocardiographic images could be acquired in all of our patients with mild and moderate (non-severe) COPD. The echocardiography included the generally applied approaches of M-mode, 2-dimensional, and Doppler echocardiography. Routine structural and hemodynamic indices of both chambers were measured according to the guidelines.[16] LV systolic function was defined using the modified Simpson's rule. The diastolic function of both ventricles was evaluated using the E/A ratio at rest.[16] As a more precise approach for diastolic dysfunction detection, tissue Doppler analysis was used. The e' value was used as the average of medial and the lateral measurements for the mitral annulus. The recommended variables for identifying diastolic dysfunction at rest and their abnormal cut-off values are the annular e' velocity, septal e' <7 cm/sec, and lateral e' <10 cm/sec; average E/e' ratio >14; left atrium (LA) volume index >34 mL/m^2; and a peak tricuspid regurgitation (TR) velocity >2.8 m/sec. LVDD is determined to be present if more than half of the available parameters meet these cut-off values. Grade I diastolic dysfunction is defined as E/A<1, deceleration time (DT) >200 msec, and an average E/e'<8. The Grade II classification parameters are 1>E/A<2, 160 >DT<200 msec, and an average 8>E/e'<15. Grade III is assumed if the E/A >2, DT<160 msec, and the average E/e'>15.

Stress echocardiography was performed 1-2 minutes after peak exercise. It was considered positive when all of the following conditions are met during exercise: average E/e' >14 or septal E/e' ratio >15, peak TR velocity >2.8 m/sec, and septal e' velocity <7 cm/sec.

The dimensions of the right ventricle (RV) were assessed from the long-axis parasternal and apical 4-chamber views.[17] Tricuspid annular plane systolic excursion and S peak velocity were analyzed for RV systolic function evaluation. RV wall thickness (RVWT) was measured in end-diastole. Systolic pulmonary arterial pressure was calculated using the Bernoulli equation and the anaerobic threshold (AT).[18,19] Right atrium volume index (RAVI) was measured at RV end-systole according to Simpson's modified rule.

Statistical analysis

Descriptive statistics were used to present the demographic and clinical data. The Kolmogorov-Smirnov test was used to assess the normality of distribution. Continuous variables were expressed as median and interquartile range when the data were not normally distributed and with mean±SD if normal distribution

was observed. Categorical variables were presented as proportions. Data were compared between patients with and without stress LVDD. An unpaired Student's t-test was performed for normally distributed continuous variables, and the Mann-Whitney U test was used in other cases. Categorical variables were compared with a chi-square test or the Fisher exact test. The Spearman's rank correlation test was performed to analyze the association between clinical parameters and stress LV E/e'. Receiver operating curve (ROC) analysis was performed to test LV echocardiographic parameters at rest that may best accurately distinguish between stress LV E/e' >15 or <15. The cut-off values with the best sensitivity and specificity were selected. Univariable regression analysis was also performed to evaluate which cardiopulmonary and echocardiographic parameters were associated with stress LV E/e' >15. Multivariable logistic regression analysis using a forward stepwise approach detected the significant independent predictor of stress LV E/e' >15. Regression analysis was applied with the echocardiographic parameters as qualitative parameters, using their cut-off values. Predictive models were constructed. In all cases, a p value of <0.05 determined using SPSS for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA) statistical software was considered significant.

RESULTS

Demographic and clinical data

Subjects enrolled in the study were Caucasians with a mean age of 62.50±8.5 years and a body mass index of 27.26±6.92 kg/m^2. They were divided into 2 groups: subjects with stress LVDD (64%, 67/104) and those without (36%, 37/104). There was no significant difference in the demographic or respiratory parameters. The 2 groups differed, however, in the CPET parameters. Patients without stress LVDD performed better. They stopped exercise at higher load and they also had a lower 'VE/'VCO2 slope, which may be indicative of lower pulmonary-venous pressure and a better ventilation/perfusion ratio (Table 1).

In all, 16 (15%) patients had mild COPD while 88 (85%) were grouped as having moderate COPD. Seven (44%) of the patients with mild COPD showed stress LVDD and 9 (56%) did not demonstrate stress LVDD. Of the patients with moderate COPD, 72 (82%) had stress LVDD, while 16 (18%) did not (Table 1).

According to the objective American Thoracic Society/American College of Chest Physicians criteria, exercise was considered maximal in all patients. The majority of the patients, 78 (75%), stopped exercise due to dyspnea; leg fatigue was the reason for exercise cessation in 26 (25%) patients. The patients differed significantly in terms of exercise cessation factors (Table 1). In patients with stress LVDD, dyspnea was the predominant limiting factor, seen in 65 (97%), while it was reported as a reason for stopping the exercise test in only 13 (35%) of the patients without stress LVDD. Leg fatigue was reported by 2 (3%) of the patients with stress LVDD, and in the group of those without stress LVDD it was the reason for exercise cessation in 24 (65%) (Table 1). The ventilatory and CV response parameters during exercise in the 2 groups are presented in Table 1. Most of the patients without stress LVDD, 24 (65%), stopped exercise due to leg fatigue and only 13 (35%) reported dyspnea. These subjects achieved higher load, and demonstrated a higher minute ventilation at peak load, a higher oxygen pulse, higher peak 'VO_2, and a higher 'VO_2 at AT in comparison with the stress LVDD group.

LV parameters

The patients had normal LV dimensions and preserved LV systolic function (Table 2). The median LV wall thickness was 12 mm (min-max: 11–13 mm); 62% of the subjects demonstrated evidence of LV hypertrophy. The LA and LV dimensions were within normal limits. The median LAVI in the group without stress-induced LVDD was lower, 28.34 mL/m^2 (min-max: 26.58–31.29 mL/m^2), in comparison with the group with LVDD, where there was a median of 29.18 mL/m^2 (min-max: 27.61–32.83 mL/m^2).

Only 30% of the patients had LV grade I diastolic dysfunction at rest (average E/e'<8); the remaining 70% had normal LV diastolic function at rest. A total of 67% of all of the patients had LVDD during exercise (E/e'>15). No significant difference was found in either structural or functional parameters of the LV at rest between the patients with and without stress LVDD (Table 2).

RV parameters

There was no significant difference between the 2 groups in terms of the functional (systolic and diastolic) parameters of the RV at rest. In contrast, the

Table 1. Anthropometric, clinical, and cardiopulmonary characteristics of the patients with and without stress LVDD

	Patients without stress LVDD (37)	Patients with stress LVDD (67)	*p*
Demographic data			
Age, years	60.00±7.00	64.00±7.00	0.143*
Male: female gender, n	21:16	44:23	0.298‡
Current smokers, n (%)	23 (62)	39 (58)	0.176‡
Former smokers, n (%)	4 (11)	17 (25)	0.981‡
Non-smokers, n (%)	10 (27)	11 (17)	0.375‡
Pack years	27.21 (23.87–31.76)	33.79 (30.51–37.87)	0.491†
Body mass index (kg/m^2)	27.00 (24.75–31.00)	27.96 (22.75–30.75)	0.207†
Respiratory function			
FVC (l/min)	2.06 (1.76–3.09)	2.34 (1.77–3.09)	0.213†
FEV_1, (l/min)	1.31 (0.94–1.53)	1.36 (1.14–1.75)	0.408†
FEV_1/FVC %	60.5 (46.91–67.47)	53.30 (45.76–66.55)	0.764†
mMRC	1.55±0.49	1.70±0.79	0.891†
Acid-base balance			
pO_2 (mmHg)	68.60 (63.4–71.8)	71.35 (64.7–74)	0.298†
pCO_2 (mmHg)	32.30 (30.1–35.37)	37.65 (32.5–40)	0.275†
Saturation (%)	94.9 (94.4–95.25)	95.00 (94.02–95.67)	0.763†
CPET parameters			
Peak load, W	82.75 (69.8–89.1)	76.05 (68.4–92.1)	0.041†
Peak ’VE, 1/min	40 (34–52.5)	38.50 (32–48)	0.148†
Peak ’VO_2, mL/kg/min	14.30 (12.6–16.15)	13.90 (12.67–15.7)	0.794†
Peak RER	1.06 (0.98–1.19)	1.09 (1.00–1.28)	0.808†
Peak O_2 pulse mL/kg/min	9.80 (9.5–12.2)	7.90 (6.15–9.32)	0.751†
VE/VCO_2 slope	34.08 (33.98–36.72)	36.93 (34.19–38.74)	0.032†
Exercise cessation factors, n (%)			
Dyspnea	13 (35)	65 (97)	0.023‡
Leg fatigue	24 (65)	2 (3)	0.038‡
GOLD stages, n (%)			
GOLD I	9 (56)	7 (44)	0.701‡
GOLD II	16 (18)	72 (82)	0.435‡

*Unpaired t test; †Mann-Whitney U test; ‡Chi-square test. CPET: Cardiopulmonary exercise testing; FEV_1: Forced expiratory volume in 1second; FVC: Forced vital capacity; GOLD: Global Initiative on Obstructive Lung Disease; LVDD: Left ventricular diastolic dysfunction; mMRC: Modified Medical Research Council; O_2 pulse: Oxygen pulse; pCO_2: Partial pressure of carbon dioxide; RER: Respiratory exchange ratio; ’VE: Ventilation;’VO_2: Oxygen consumption.

geometry of the right atrium (RA) was distinctive. RAVI, RV parasternal diameter, and RVWT revealed significant differences between the groups with and without LVDD. The median RAVI value in the group without stress-induced LVDD was lower 17.57 (min-max: 16.07–19.97 mL/m^2) in comparison with the group with LVDD, in which there was a median of 22.66 (min-max: 21.31–24.13 mL/m^2). The same was observed with the mean RVWT of 5.00 mm (min-max: 4.5–6.5 mm) vs 6.50 mm (min-max: 6–7 mm) and RV parasternal diameter 23 mm (min-max: 21–25 mm) vs 28 mm (min-max: 26–31 mm) (Table 2).

Ventilatory, cardiopulmonary, and echocardiographic parameters and stress LVDD

Spearman’s rank correlation analysis showed that none of the ventilatory and cardiopulmonary exercise testing parameters correlated with stress LV E/e’. In contrast, some of the echocardiographic pa-

Table 2. Echocardiographic parameters of the patients with and without stress LVDD

	Patients w/o stress LVDD (37)	Patients with stress LVDD (67)	*p*
LV structural parameters			
LAVI (mL/m^2)	28.34 (26.58–31.29)	29.18 (27.61–32.83)	0.286*
TDD (mm)	50 (47.5–53)	52 (48–55)	0.506*
TSD (mm)	32 (28–35)	34 (30–37)	0.463*
TDV (mL)	120 (110–130)	122.5 (115–142)	0.626*
TSV (mL)	39 (37–43)	42 (39–44)	0.461*
LVEF, (%) Simpson	63.50 (60–66)	60.00 (57–65)	0.673*
Septum (mm)	12.00 (11–13)	12.00 (11–13)	0.897*
PW (mm)	12.00 (11.75–12)	12.00 (11–13)	0.981*
LV functional parameters at rest			
E/A ratio	0.79 (0.75–0.85)	0.85 (0.76–1.20)	0.420*
E/e' aver ratio	6.66 (6.25–8.33)	6.97 (5.76–8.15)	0.736*
LV functional parameters after exercise stress test			
E/A ratio	1.25 (0.8–1.5)	1.73 (1.55–2.00)	0.042*
E/e' average	8.07 (6.7–9.6)	17.33 (15.71–8.46)	0.038*
RV structural parameters			
RAVI (mL/m^2)	17.57 (16.07–19.97)	22.66 (21.31–24.13)	0.037*
RVWT (mm)	5.00 (4.5–6.5)	6.50 (6–7)	0.046*
RV diameter parasternal (mm)	23 (21–25)	28 (26–31)	0.048*
RV diameter basal (mm)	35 (32–36)	37 (35.5–38)	0.136*
RV diameter medial, (mm)	24 (22–26.75)	26 (24.5–29)	0.625*
RV functional parameters at rest			
E/A ratio	0.83 (0.75–0.95)	0.69 (0.62–0.75)	0.761*
E/e' average	5.47 (4.56–5.69)	4.16 (3.33–5.00)	0.764*
TAPSE (mm)	23.00 (22.00–26.00)	22.00 (21.00–23.00)	0.985*
TR jet velocity (m/s)	2.16 (1.98–2.31)	2.34 (2.04–2.42)	0.618*
AT (msec)	170 (163.75–180)	170 (160–180)	0.737*
sPAP (mmHg)	26.00 (25–28)	28.00 (25–30)	0.839*

*Mann-Whitney U test. AT: Anaerobic threshold; LAVI: Left atrium volume index; LVDD: Left ventricular diastolic dysfunction; LVEF: Left ventricle ejection fraction; PW: Posterior wall; RAVI: Right atrium volume index; RV: Right ventricle; RVWT: Right ventricle wall thickness; sPAP: Systolic pulmonary artery pressure; TAPSE: Tricuspid annular plane systolic excursion; TDD: Telediastolic dimension; TDV: Telediastolic volume; TR: Tricuspid regurgitation; TSD: Telesystolic diameter; TSV: Telesystolic diameter.

rameters (LV E/A ratio at rest, RAVI, RVWT, RV parasternal diameter, RV E/A ratio at rest) demonstrated a statistically significant association with stress-induced LVDD (E/e'>15) (Table 3). ROC curves were constructed to find the best cut-off values for these parameters (Table 4). The only functional parameter of the LV with clinical importance was the E/A ratio at rest (cut-off: 0.86), which detected stress LVDD with a sensitivity of 56.06% and a specificity of 77.78%. Of the right heart structural parameters, RAVI, RVWT, and the RV parasternal diameter were the echocardiographic indicators with good sensitivity and specificity for stress-induced LVDD. A cut-off value of 19.67 mL/m^2 for RAVI identified the patients with stress LVDD (sensitivity: 84.79%, specificity: 82.37%) (Fig. 1), a cut-off value of 5.07 mm for RVWT (sensitivity: 78.34%, specificity: 58.36%), a cut-off value of 25.5 mm for the RV parasternal diameter (sensitivity: 83.33%, specificity 72.22%), and a cut-off value of 0.75 for

Table 3. Correlation analysis between ventilatory, cardiopulmonary and echocardiographic parameters with stress LV E/e' ratio

Parameters	LVDD	
	Spearman rho	*p*
Cardiopulmonary parameters		
Peak load, W	0.029	0.843
Peak 'VE, (l/min)	0.024	0.852
Peak 'VO_2 (mL/kg/min)	0.128	0.567
RER	0.063	0.743
Peak O_2 pulse (mL/kg/min)	0.104	0.602
VE/VCO_2 slope	0.354	0.079
Ventilatory parameters		
FVC, (l/min)	0.281	0.113
FEV_1, (l/min)	0.017	0.958
LV structural parameters		
LAVI (mL/m^2)	0.487	0.079
LVEF, (%) Simpson	0.392	0.563
Septum (mm)	0.083	0.681
PW (mm)	0.059	0.924
LV functional parameters at rest		
E/A ratio	0.326	0.042
E/e' aver ratio	0.437	0.052
RV structural parameters		
RAVI (mL/m^2)	0.601	0.039
RVWT (mm)	0.150	0.047
RV diameter parasternal (mm)	0.283	0.042
RV diameter basal (mm)	0.093	0.068
RV diameter med (mm)	0.031	0.092
RV functional parameters at rest		
E/A ratio	0.261	0.044
E/e' average	0.038	0.714
TR jet velocity (m/s)	0.049	0.634
AT (msec)	0.542	0.821
sPAP (mmHg)	0.227	0.284
TAPSE (mm)	0.156	0.076

AT: Anaerobic threshold; LAVI: Left atrium volume index; LVDD: Left ventricular diastolic dysfunction; LVEF: Left ventricle ejection fraction; O_2 pulse: Oxygen pulse; pCO_2: Partial pressure of carbon dioxide; PW: Posterior wall; RAVI: Right atrium volume index; RER: Respiratory exchange ratio; RV: Right ventricle; RVWT: Right ventricle wall thickness; sPAP: Systolic pulmonary artery pressure; TAPSE: Tricuspid annular plane systolic excursion; TDD: Telediastolic dimension; TDV: Telediastolic volume; TR: Tricuspid regurgitation; TSD: Telesystolic diameter; TSV: Telesystolic diameter; 'VE: Ventilation; 'VO_2: Oxygen consumption.

RV E/A ratio at rest (sensitivity: 75.76%, specificity: 83.33%) (Fig. 2, 3).

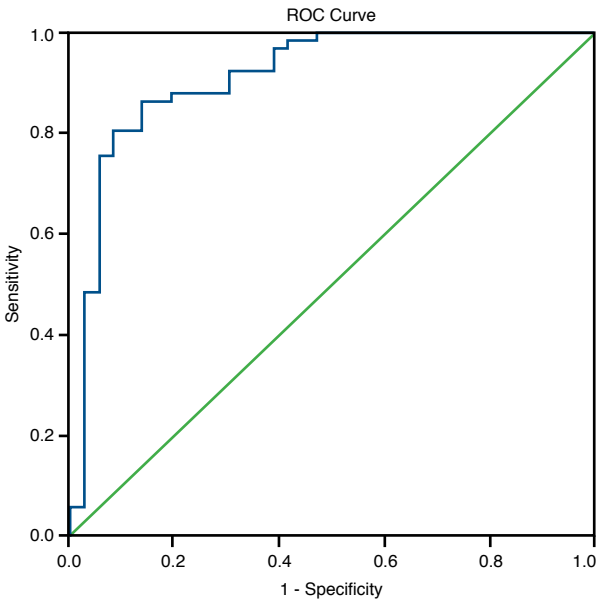

Figure 1. ROC analysis of RAVI. A receiver operating characteristic (ROC) curve analysis cut-off value of 19.67 mL/m^2 for right atrium volume index (RAVI) discriminated the patients with stress left ventricular diastolic dysfunction (sensitivity: 84.79%; specificity: 82.37%).

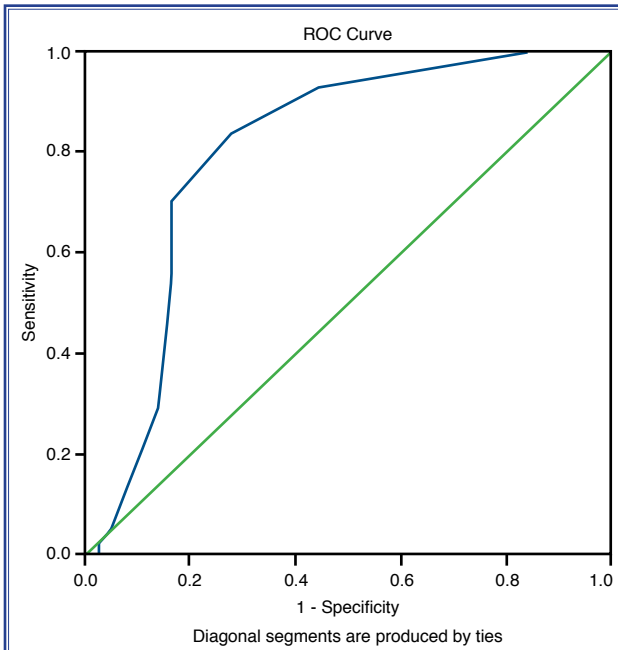

Figure 2. ROC analysis of the right ventricular parasternal diameter. A receiver operating characteristic (ROC) curve analysis cut-off of 25.5 mm for the right ventricular parasternal diameter identified the patients with stress left ventricular diastolic dysfunction (sensitivity: 83.33%, specificity: 72.22%).

Table 4. Receiver operating characteristic curve analysis using cut-off values of the echocardiographic parameters

	Area under the curve	95% CI	Cut-off value	Sensitivity	Specificity
LV E/A ratio at rest	0.62	0.51–0.73	0.86	56.06%	77.78%
RV parasternal diameter (mm)	0.79	0.69–0.90	25.5	83.33%	72.22%
RVWT (mm)	0.57	0.48–0.76	5.07	78.34%	58.36%
RAVI (mL/m^2)	0.88	0.82–0.93	19.67	84.79%	82.37%
RV E/A ratio at rest	0.80	0.71–0.89	0.75	75.76%	83.33%

CI: Confidence interval; LV: Left ventricle; RAVI: Right atrium volume index; RV: Right ventricle; RVWT: Right ventricle wall thickness.

Univariate regression analysis was performed with the selected cut-off values. The data are presented in Table 5. A RAVI value >19.67 mL/m^2 showed the highest odds ratio (OR) of 19.26 (95% confidence interval [CI]: 12.096–27.465), followed by the RV parasternal diameter (OR 13.00, 95% CI 4.903–34.471), RV E/A ratio (OR: 9.37, 95% CI: 3.657–24.031), and RVWT (OR: 4.732, 95% CI: 2.518–8.892). In multivariable logistic regression analysis with a forward step approach using the covariates of age, body mass index, and FEV_1, the RAVI, RV parasternal diameter, and RV E/A remained the independent predictors for stress LVDD. The combination of these 3 echocardiographic parameters predicted stress LVDD with an accuracy of 91.2%.

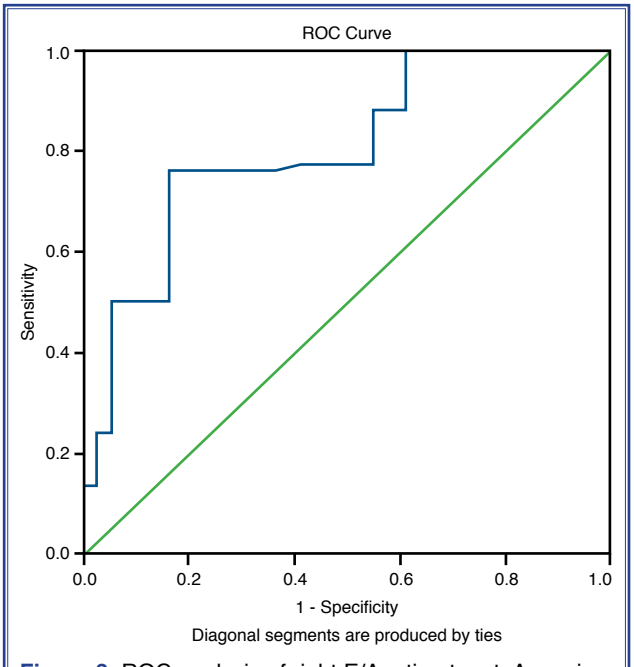

Figure 3. ROC analysis of right E/A ratio at rest. A receiver operating characteristic (ROC) curve analysis cut-off of 0.75 for the right E/A ratio at rest distinguished stress LVDD (sensitivity: 75.76%, specificity: 83.33%).

DISCUSSION

The major findings of our study are 1) a high frequency (64%, 67/104) of stress LVDD in non-severe COPD patients with exertional dyspnea was established; 2) cardiopulmonary exercise testing parameters were distinctive between the patients with and without stress LVDD, but none correlated with stress E/e'; 3) the combination of 3 echocardiographic parameters: RAVI >19.67 mL/m^2, RV parasternal parameter >25.5 mm and RV E/A ratio >0.75, discriminated patients with stress LVDD from those without stress LVDD with an accuracy of 91.2%.

To the best of our knowledge, this is the first study of combined exercise stress echocardiography in non-severe COPD patients with exertional dyspnea and no overt CV disease. As most authors report on the incidence of diastolic dysfunction at rest, we cannot compare our data with other studies of non-severe COPD patients.[20–22] The increase of E/e'>15 at peak exercise during cardiopulmonary testing was the cut-off point for stress LVDD and was considered a marker of masked HFpEF in our patients. It was present in 67% of the group. Our results are much different from those seen in a non-COPD population. Nedeljkovic et al.[23] performed exercise stress echocardiography in 87 hypertensive patients with exertional dyspnea and normal LV function. They reported a lower prevalence (9.2%) of masked HFpEF. Kaiser et al.[24] investigated a general population of 87 patients with exertional dyspnea and reported that 9% had an E/A <0.75.

The higher prevalence of masked HFpEF in our COPD patients confirms the current thought that COPD is an independent predictor of vascular damage.[25,26] It is associated with increased levels of arterial stiffness and myocardial fibrosis even when no manifest CV disease is observed.[27,28] The link between

Table 5. Logistic regression analysis between the cut-off values of the echocardiographic parameters and stress LV E/e' ratio

	p	OR	95% CI
Univariable regression analysis			
Left ventricle E/A ratio rest	0.023	2.917	1.159–7.342
Right ventricular parasternal diameter (mm)	0.000	13.000	4.903–34.471
Right ventricle wall thickness (mm)	0.000	4.732	2.518–8.892
Right atrium volume index (mL/m^2)	0.000	19.267	12.096–27.465
Right ventricle E/A ratio rest	0.000	9.375	3.657–24.031
Multivariable logistic regression analysis			
Right ventricular parasternal diameter (mm)	0.001	19.567	3.131–22.290
Right atrium volume index (mL/m^2)	0.000	24.061	4.485–29.100
Right ventricle E/A ratio	0.007	10.853	1.913–21.564

CI: Confidence interval; LV: Left ventricle; OR: Odds ratio.

LVDD and COPD is complex and probably evolves as a result of various mechanisms, such as mechanical/functional (deterioration in FEV_1, emphysema, hyperinflation),[29] biological (systemic inflammation, hypoxemia, endothelial dysfunction),[30,31] and neurohumoral (excess sympathetic nerve activity) factors.[32]

The pathophysiological mechanisms of diastolic dysfunction refer to abnormalities of LV diastolic distensibility and relaxation. Diastolic dysfunction may limit LV filling and the aerobic capacity, regardless of LV function.[33] As most patients with HFpEF are asymptomatic at rest, exercise reveals diastolic abnormalities even when they are not evident.[10,34] Stress echocardiography examines LV filling on exertion and detects the initial stages of diastolic dysfunction and performance is important for the detection of diastolic dysfunction. This is of special clinical importance in COPD, where HFpEF can stay hidden under the umbrella of COPD-associated dyspnea. It may be an independent limiting factor of the physical activity and may influence COPD prognosis.

Indeed, the COPD patients with HFpEF in our study achieved a lower load during testing and performed with lower peak 'VO_2, lower oxygen pulse, and higher '$VE/'VCO_2$ slope. Our data are consistent with previous findings in the general HFpEF population. Nedeljkovic et al.[23] also detected a lower load, lower oxygen consumption, and higher ventilator slope in hypertensive patients with exertional dyspnea and stress LVDD. Kaiser et al.[24] described increased heart rate reserve and reduced oxygen pulse in a general population of patients with exertional dyspnea. Guazzi et al.[35] also established an association between diastolic dysfunction, peak oxygen consumption, ventilatory efficiency, and heart rate recovery.

The pathophysiological mechanisms explaining the link between CPET variables and the stress E/e' ratio are multifactorial. An abnormal increase in the '$VE/'VCO_2$ slope is a consequence of ventilation-perfusion abnormalities.[36–38] Diminished $PetCO_2$, peak VO_2 values, and a high ventilatory slope have all been previously linked to increasing pressure in the pulmonary vasculature, a condition that can be precipitated by LVDD.[39,40] An elevation in pulmonary pressure leads to ventilation-perfusion abnormalities and negatively impacts gas-exchange response during exercise.[41] It may be even more exaggerated in COPD patients with HFpEF and may accentuate the sensation of dyspnea. Although it is not possible to determine rank contributions to each pathophysiological process, autonomic dysfunction, elevated pulmonary pressure, dynamic hyperinflation and COPD-related gas-exchange abnormalities serve as plausible factors for the link between diastolic dysfunction and abnormal CPET response in patients with COPD and HFpEF. The predominant factor may be different in each patient, depending on disease severity and clinical phenotype. This may be the reason for the absence of a distinctive CPET factor correlating with stress LVDD in our study. The pathophysiological mechanisms seem to be more complex, which explains the echocardiographic predictors of stress LVDD. According to our data, the echocardiographic parameters

with the best predictive value for stress LVDD were RAVI, the RV parasternal diameter, and an RV E/A ratio >0.75.

RAVI is a reproducible and easy-to-measure echocardiographic parameter that has garnered increased interest during the last decade.[42–44] MRI and echocardiographic studies emphasize that RA geometry and RAVI are independent prognostic markers of heart failure with reduced ejection fraction (HFrEF).[45,46] RAVI adds independent prognostic value to multifaceted scores in which cardio-pulmonary parameters are components.[47,48] Sallach et al.[45] and Darahim[46] described modest correlation between RAVI and RV E/A ratio in HFrEF; however, no correlation was found with the E/e' ratio. This confirms a poor correlation of RA volume with RV filling pressure.[49] Sallach et al. reported that RAVI was significantly associated with LV diastolic dysfunction. It is plausible that LVDD exacerbates pulmonary congestion and additionally increases pulmonary capillary wedge pressure in patients with HFrEF. Both the pulmonary capillary and pulmonary venous pressure elevation are retrograde transmissions and manifest as RV overload and RA enlargement. The pathophysiology of RA remodeling that we present in our patients may be very similar. In COPD patients with HFpEF, transthoracic pressure gradients may accelerate RA/right chamber remodeling and they may become apparent even more early stages of LVDD than in the general population. This is confirmed by the fact that COPD patients with stress LVDD have RA geometry that is normal, but significantly different in comparison with those without stress LVDD. Bearing in mind that both LVDD and pulmonary hypertension are associated with an increased number of exacerbations, accelerated decline of ventilatory function, and higher mortality, timely detection is of clinical importance.[50] Whether left-sided dysfunction precedes or follows right-sided dysfunction in HFrEF is, however, elusive. The data regarding RAVI in COPD patients are described under the conditions of pulmonary hypertension and chronic respiratory failure. The pathophysiology of elevated RAVI in COPD patients is unresolved. The same issue applies regarding RAVI in HF. Given the prognostic role and easy measurement of RAVI, catheterization studies are warranted to determine the precise pathophysiological role in impaired LV cardiac function and hemodynamics.

Study limitations

The main limitations of this study are 1) the relatively small sample size; 2) the presence of coronary artery disease cannot be excluded, as neither invasive (coronary angiography) nor sophisticated imaging modalities (exercise single photon emission computed tomography, myocardial perfusion imaging) were performed; 3) COPD patients experience enhanced pressure swings during the respiratory cycle and measurements were performed at the end of expiration, which may influence the results; 4) there is no invasive measurement of systolic pulmonary artery pressure; and 5) measurements were acquired in the early recovery period (approximately 2 min) after symptom-limited exercise. The timeline of the changes of pulmonary and intrathoracic pressure during the brief time interval from peak exercise to measurement in early recovery is not well known, and underestimation is possible.

Conclusion

We report a high prevalence of stress LVDD in non-severe COPD patients with exertional dyspnea who were free of overt CV disease. The combination of RAVI, RV parasternal diameter, RV E/A >0.75 predicted stress LVDD in these patients with 91% accuracy; however our data need validation in larger cohort studies.

Acknowledgements

We would like to acknowledge Professor Vukov, who performed the statistical analysis.

Ethical statement: Ethics approval for the study protocol was received from the Ethics Committee of the Medical University, Sofia protocol 5/12.03.2018.

Funding statement: There were no external funding sources for this study.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: R.C., Z.C.; Design: R.C., Z.C.; Supervison: S.D.; Materials: R.C., Z.C.; Data: R.C., Z.C.; Analysis: R.C., Z.C.; Literature search: R.C., Z.C.; Writing: R.C., Z.C.; Critical revision: R.C., Z.C.

REFERENCES

1. Ford ES, Murphy LB, Khavjou O, Giles WH, Holt JB, Croft JB. Total and state-specific medical and absenteeism costs of

COPD among adults aged ≥ 18 years in the United States for 2010 and projections through 2020. Chest 2015;147:31–45.
2. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Ann Epidemiol 2006;16:63–70. [CrossRef]
3. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005;26:1887–94. [CrossRef]
4. Onishi K. Total management of chronic obstructive pulmonary disease (COPD) as an independent risk factor for cardiovascular disease. J Cardiol 2017;70:128–34. [CrossRef]
5. Sabit R, Bolton CE, Fraser AG, Edwards JM, Edwards PH, Ionescu AA, et al. Sub-clinical left and right ventricular dysfunction in patients with COPD. Respir Med 2010;104:1171–8. [CrossRef]
6. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263–71. [CrossRef]
7. Fu M, Zhou J, Thunström E, Almgren T, Grote L, Bollano E, et al. Optimizing the Management of Heart Failure With Preserved Ejection Fraction in the Elderly by Targeting Comorbidities (OPTIMIZE-HFPEF). J Card Fail 2016;22:539–44.
8. Oh JK, Park SJ, Nagueh SF. Established and novel clinical applications of diastolic function assessment by echocardiography. Circ Cardiovasc Imaging 2011;4:444–55. [CrossRef]
9. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006;47:1891–900. [CrossRef]
10. Ha JW, Oh JK, Pellikka PA, Ommen SR, Stussy VL, Bailey KR, et al. Diastolic stress echocardiography: a novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise Doppler echocardiography. J Am Soc Echocardiogr 2005;18:63–8. [CrossRef]
11. O'Donnell DE, Elbehairy AF, Faisal A, Webb KA, Neder JA, Mahler DA. Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing [published correction appears in Eur Respir Rev. 2016 Dec;25(142):513]. Eur Respir Rev 2016;25:333–47. [CrossRef]
12. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure-normal ejection fraction. J Cardiopulm Rehabil Prev 2010;30:165–72. [CrossRef]
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38. [CrossRef]
14. GOLD strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease. Executive summary update (2018). Available at: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf. Accessed Mar 9, 2020.
15. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. Circulation 2016;133:e694–e711. [CrossRef]
16. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321–60. [CrossRef]
17. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32. [CrossRef]
18. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
19. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119. [CrossRef]
20. Huang YS, Feng YC, Zhang J, Bai L, Huang W, Li M, et al. Impact of chronic obstructive pulmonary diseases on left ventricular diastolic function in hospitalized elderly patients. Clin Interv Aging 2014;10:81–7. [CrossRef]
21. Kubota Y, Asai K, Murai K, Tsukada YT, Hayashi H, Saito Y, et al. COPD advances in left ventricular diastolic dysfunction. Int J Chron Obstruct Pulmon Dis 2016;11:649–55. [CrossRef]
22. Caram LM, Ferrari R, Naves CR, Tanni SE, Coelho LS, Zanati SG, et al. Association between left ventricular diastolic dysfunction and severity of chronic obstructive pulmonary disease. Clinics (Sao Paulo) 2013;68:772–6. [CrossRef]
23. Nedeljkovic I, Banovic M, Stepanovic J, Giga V, Djordjevic-Dikic A, Trifunovic D, et al. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. Eur J Prev Cardiol 2016;23:71–7. [CrossRef]
24. Kaiser T, Debapriya D. Can Diastolic Dysfunction Be

Identified on cardiopulmonary Exercise Testing. Chest 2017;152:976. [CrossRef]
25. Fisk M, McEniery CM, Gale N, Mäki-Petäjä K, Forman JR, Munnery M, et al. Surrogate Markers of Cardiovascular Risk and Chronic Obstructive Pulmonary Disease: A Large Case-Controlled Study. Hypertension 2018;71:499–506.
26. Neilan TG, Bakker JP, Sharma B, Owens RL, Farhad H, Shah RV, et al. T1 measurements for detection of expansion of the myocardial extracellular volume in chronic obstructive pulmonary disease. Can J Cardiol 2014;30:1668–75. [CrossRef]
27. Anderson WJ, Lipworth BJ, Rekhraj S, Struthers AD, George J. Left ventricular hypertrophy in COPD without hypoxemia: the elephant in the room?. Chest 2013;143:91–7. [CrossRef]
28. Schoos MM, Dalsgaard M, Kjærgaard J, Moesby D, Jensen SG, Steffensen I, et al. Echocardiographic predictors of exercise capacity and mortality in chronic obstructive pulmonary disease. BMC Cardiovasc Disord 2013;13:84. [CrossRef]
29. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med 2010;362:217–27. [CrossRef]
30. Maclay JD, McAllister DA, Johnston S, Raftis J, McGuinnes C, Deans A, et al. Increased platelet activation in patients with stable and acute exacerbation of COPD. Thorax 2011;66:769–74.
31. Mills NL, Miller JJ, Anand A, Robinson SD, Frazer GA, Anderson D, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax 2008;63:306–11. [CrossRef]
32. Andreas S, Anker SD, Scanlon PD, Somers VK. Neurohumoral activation as a link to systemic manifestations of chronic lung disease. Chest 2005;128:3618–24. [CrossRef]
33. Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. N Engl J Med 2004;351:1097–105. [CrossRef]
34. Gibby C, Wiktor DM, Burgess M, Kusunose K, Marwick TH. Quantitation of the diastolic stress test: filling pressure vs. diastolic reserve. Eur Heart J Cardiovasc Imaging 2013;14:223–7.
35. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. J Am Coll Cardiol 2005;46:1883–90. [CrossRef]
36. Banning AP, Lewis NP, Northridge DB, Elborn JS, Hendersen AH. Perfusion/ventilation mismatch during exercise in chronic heart failure: an investigation of circulatory determinants. Br Heart J 1995;74:27–33. [CrossRef]
37. Wada O, Asanoi H, Miyagi K, Ishizaka S, Kameyama T, Seto H, et al. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. Am Heart J 1993;125:790–8. [CrossRef]
38. Reindl I, Wernecke KD, Opitz C, Wensel R, König D, Dengler T, et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. Am Heart J.1998;136:778–85. [CrossRef]
39. Arques S, Roux E, Luccioni R. Current clinical applications of spectral tissue Doppler echocardiography (E/E' ratio) as a noninvasive surrogate for left ventricular diastolic pressures in the diagnosis of heart failure with preserved left ventricular systolic function. Cardiovasc Ultrasound 2007;5:16. [CrossRef]
40. Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. Chest 2005;127:1637–46. [CrossRef]
41. Straburzyńska-Migaj E, Szyszka A, Trojnarska O, Cieśliński A. Restrictive filling pattern predicts pulmonary hypertension and is associated with increased BNP levels and impaired exercise capacity in patients with heart failure. Kardiol Pol 2007;65:1049–57.
42. Moneghetti KJ, Giraldeau G, Wheeler MT, Kobayashi Y, Vrtovec B, Boulate D, et al. Incremental value of right heart metrics and exercise performance to well-validated risk scores in dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging 2018;19:916–25. [CrossRef]
43. Ivanov A, Mohamed A, Asfour A, Ho J, Khan SA, Chen O, et al. Right atrial volume by cardiovascular magnetic resonance predicts mortality in patients with heart failure with reduced ejection fraction. PLoS One 2017;12:e0173245. [CrossRef]
44. Luong C, Thompson DJ, Bennett M, Gin K, Jue J, Barnes ME, et al. Right atrial volume is superior to left atrial volume for prediction of atrial fibrillation recurrence after direct current cardioversion. Can J Cardiol 2015;31:29–35. [CrossRef]
45. Sallach JA, Tang WH, Borowski AG, Tong W, Porter T, Martin MG, et al. Right atrial volume index in chronic systolic heart failure and prognosis. JACC Cardiovasc Imaging 2009;2:527–34. [CrossRef]
46. Darahim K. Usefulness of right atrial volume index in predicting outcome in chronic systolic heart failure. J Saudi Heart Assoc 2014;26:73–9. [CrossRef]
47. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34:1404–13. [CrossRef]
48. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424–33.
49. Nagueh SF, Zoghbi WA. Evaluation of right ventricular diastolic function. Klein AL, Garcia MJ, editors. Diastology: Clinical Approach to Diastolic Heart Failure. 1st ed. New York, NY: Saunders; 2008. p. 171–80. [CrossRef]
50. Abusaid GH, Barbagelata A, Tuero E, Mahmood A, Sharma G. Diastolic dysfunction and COPD exacerbation. Postgrad Med 2009;121:76–81. [CrossRef]

Keywords: Cardiopulmonary exercise testing; chronic obstructive pulmonary disease; heart failure with preserved ejection fraction; stress echocardiography.

Anahtar sözcükler: Kardiyopulmoner egzersiz testi; kronik obstrüktif akciğer hastalığı; ejeksiyon fraksiyonu korunmuş kalp yetersizliği; stres ekokardiyografisi.