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Research Article

Stress Left Ventricular Diastolic Dysfunction, Oxidative Stress and Inflammation in Non-Severe Chronic Obstructive Pulmonary Disease

Zheina Vlaeva Cherneva[1]*, Dinko Genchev Valev[2], Vania Milocheva Youroukova[3], Radostina Vlaeva Cherneva[3]

[1]*Medical Institute of the Ministry of Internal Affairs, Sofia, Bulgaria*

[2] *University First City Hospital, Sofia, Bulgaria*

[3]*Medical University Sofia, Department of Respiratory diseases, Clinic of University Hospital for Respiratory Diseases "St. Sophia"*

Abstract

Background: Stress Left Ventricular Diastolic Dysfunction (LVDD) is theprecursor of Heart Failure with Preserved Ejection Fraction (HFpEF). Oxidative stress and inflammation have been implicated in the pathogenesis of HFpEF and Chronic Obstructive Pulmonary Disease (COPD).

Objective: To evaluate the role of oxidative stress markers (8-isoprostane) and inflammation (prostaglandin E2, resistin) in the pathogenesis of masked HFpEF in non-severe COPD.

Methods: 104 patients with non-severe COPD (FEV1>50%) and preserved left ventricular ejection fraction >50% underwent incremental Cardio-Pulmonary Exercise Testing (CPET). Echocardiography was performed before CPET and 1-2 minutes after peak exercise. Peak E/e' ratio >15 was a marker for stress LVDD. Urine concentration of 8-isoprostanes was assumed as surrogate marker for oxidative stress; urine concentration of prostaglandine-E2 and plasma resistin levels as inflammatory markers. Biomarkers were analysed in all of the subjects.Mass spectrometry was applied for 8-isoprostane and prostglandine E2 (Cayman. Chemical) measurement. Values were normalised to urine creatinine(μmol/l/cre). ELISA wasapplied for resistin measurement (Raybio_Human) (ng/ml).

Results: Patients were divided into two groups: Subjects with masked HFpEF LVDD (67) and subjects without stress LVDD (37). 8-isoprostane levels did not differ between the two groups (32.9 vs 31.67μmol/l/cre, p-0.079). Urine concentrations of prostaglandin E2 were higher in subjects without LVDD vs those with(57.07 vs 50.76 μmol/l/cre, p-0.012). The opposite is observed regarding resistin plasma levels. They were increased in patients with LVDD, compared to those without stress (22.51 vs 19.68ng/ml, p-0.847). Only prostaglandine E 2 correlated to stress LV E/e', but was not an independent predictor for it.

Conclusion: Patients with stress LVDD demonstrate similar levels of oxidative stress. Prostaglandine E2 may have protective role in LV remodeling, while resistin plasma levels contribute to LVDD pathogenesis. None of these biomarkers may be applied as a predictor for stress LVDD in clinical practice.

Keywords: Inflammation; Oxidative stress; Stress echocardiography; Heart failure with preserved ejection fraction; Chronic obstructive pulmonary disease

Introduction

Chronic Obstructive Pulmonary Disease (COPD) patients frequently suffer from comorbidities, which increase the risk for exacerbations and mortality [1]. CV comorbidity in COPD is assumed as "cardio-pulmonary continuum" rather than being attributed to shared risk factors [2]. COPD augments 2-3 fold the likelihood of having Cardio-Vascular Diseases (CVD), the strongest association, being with heart failure [3,4]. The diagnosis of Heart Failure with Preserved Ejection Fraction (HFpEF) in COPD is difficult. The early detection of its precursor - stress Left Ventricular Diastolic Dysfunction (LVDD) is an important part in the evaluation of COPD patients, as it can lead to heart failure and hence worse prognosis. Stress LVDD may be present regardless if the patient is symptomatic or not [5,6]. It occurs when all the three echocardiographic parameters - average E/e' >14, peak TR velocity >2.8 m/sec and septal e' velocity <7 cm/sec are measured during exercise [6].

COPD and LVDD are difficult to distinguish from each other. The overlapping symptoms (dyspnea or chest pain) deter the timely diagnosis of both disease states. Echocardiography is the key diagnostic modality for identifying diastolic dysfunction. The simultaneous performance of stress-echocardiography and cardio-pulmonary exercise testing may provide timely detection of LVDD in COPD patients with exertional dyspnoea. Their execution is, however, time consuming and demands special equipment.

The aims of the study were: 1) To detect the frequency of stress LVDD - masked Heart Failure with Preserved Ejection Fraction (HFpEF) in non-severe COPD patients, free of overt cardiovascular pathology who complain of exertional dyspnea; 2) To establish which inflammatory (resistin, prostglandine E2) and oxidative stress (8-isoprostane) markers are predictors for stress LVDD.

***Corresponding author:** Zheina Vlaeva Cherneva, Medical Institute of the Ministry of Internal Affairs, Sofia, Bulgaria, Tel: +3589889569777; E-mail: jenicherneva@yahoo.com

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Materials and Methods

Patients and study protocol

It was a prospective study that was performed in 224 clinically stable outpatients, diagnosed with COPD at the University Hospital for Respiratory Diseases "St. Sophia", Sofia. Only 163 of them met the inclusion criteria: The inclusion criteria are: 1) Non-severe COPD (post bronchodilatator FEV1/FVC<70%; FEV1/>50%); 2) Preserved left ventricular systolic function LVEF>50%; 3) Lack of overt cardiovascular disease (ishaemic heart disease, valvular disease, cardiomyopathy); 4) Exertional dyspnea - Modified Medical Research Council Dyspnea Scale (mMRC) >0. All the subjects had exertional dyspnoea, but a total of 104 patients (64 men, 40 women; mean age of 62.9±7.5 years) were considered eligible, assuming the exclusion criteria. The recruitment period was between May 2017-April 2018 and was approved by the local Ethical Committee (protocol 5/12.03.2018). All the patients signed informed consent before their participation. They were preliminary acquainted with the aim of the study, its scientific value and the potential presentation of data at different forums.

The following exclusion criteria were considered: 1) Left ventricular diastolic dysfunction at rest more than first grade; 2) Presence of echocardiographic criteria of pulmonary hypertension (systolic pulmonary arterial pressure >36 mmHg, maximum velocity of the tricuspid regurgitation jet >2.8 m/s; 3) Valvular heart disease; 4) Documented cardiomyopathy; 5) Severe uncontrolled hypertension (systolic blood pressure >180 mmHg and diastolic blood pressure >90 mmHg); 6) atrial fibrillation or malignant ventricular arrhythmia; 7) ischaemic heart disease; 8) Anaemia; 9) Diabetes mellitus; 10) Cancer; 11) Chronic kidney disease; 12) Recent chest or abdominal surgery; 13) Recent exacerbation (during the last three months); 14) Recent change (during the last three months) in medical therapy.

Procedures

Pulmonary function testing

All the subjects underwent preliminary clinical examination which included chest X-ray, spirometry, electrocardiogram, echocardiography. Those eligible for the study performed spirometry and exercise stress test. They were performed on Vyntus, Cardio-pulmonary exercise testing (Carefusion, Germany) in accordance with ERS guidelines [7]. Only patients with mild/ moderate airway obstruction (FEV1 >50%) were selected.

Stress test protocol - Cardio-Pulmonary Exercise Testing (CPET)

All the patients underwent symptom limited incremental exercise stress test following the guidelines [8,9]. A continuous ramp protocol was applied. After two minutes of unloaded pedaling (rest phase- 0 W), a three minute warm-up phase (20 W) followed. The test phase included 20 W/2 min load increments. Patients were instructed to pedal with 60-65 rotations per minute. Patients' effort was considered to be maximal if two of the following criteria emerged: predicted maximal HR is achieved; predicted maximal work is achieved; 'VE/'VO2 >45, RER >1.10 as recommended by the ATS/ACCP [9].

A breath-by-breath analysis was used for expiratory gases evaluation. 'VO2 (mL/kg/min), 'VCO2 (L/min), 'VE (L/min) and PetCO2 (mm Hg) were collected continuously at rest and throughout the exercise test. Peak values of oxygen consumption and carbon dioxide production were presented by the highest 30-second average value, obtained during the last stage of the exercise test. Peak respiratory exchange ratio was the highest 30 second averaged value between 'VO2 and 'VCO2 during the last stage of the test. Resting PetCO2 was the 2-minute averaged value in the seated position prior to exercise, while the peak value was expressed as the highest 30-second average value obtained during the last stage of the exercise test. Both V-slope method and the ventilatory equivalents method for 'VO2 and 'VCO2 were used. The modified Borg scale was applied for peak dyspnea and leg discomfort.

Echocardiography methods

Echocardiography included the generally applied approaches of M-mode, two-dimensional and Doppler echocardiography. Routine structural and haemodynamic indices of both chambers were measured following the guidelines [6]. The systolic function of the left ventricle was defined by Simpson's modified rule. The diastolic function of both ventricles was evaluated by the E/A ratio at rest [6]. As a more precise approach for diastolic dysfunction detection, tissue Doppler analysis was used. We used e' value as the average of medial and the lateral measurements for the mitral annulus. The four recommended variables for identifying diastolic dysfunction at rest and their abnormal cut-off values are: Annular e' velocity, septal e' <7 cm/sec, lateral e' <10 cm/sec; average E/e' ratio >14; LA volume index >34 mL/m2; and peak TR velocity >2.8 m/sec. LV diastolic dysfunction is present if more than half of the available parameters meet these cut-off values. Grade I diastolic dysfunction is considered if: E/A<1; DT>200 msec; average E/e'<8. Grade II is assumed if: 1> E/A <2; 160> DT <200 msec; average 8> E/e'<15. Grade III is assumed if: E/A >2; DT<160 msec; average E/e'>15. Stress echocardiography was performed 1-2 minutes after peak exercise. It was considered positive when all of the following three 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 [6].

Laboratory Assays

Approximately 7 mL of venous blood was obtained from all cases. Blood samples were centrifuged immediately after collection and isolated plasma was stored in vials at -80°C until assayed. Resistin was measured by commercial kits, following the procedure protocol. Resistin was determined by an ELISA kit (RayBio_ Human Resistin ELISA Kit Protocol (Cat#: ELH-Resistin-001) The intra- and interassay coefficients of variation in this assay kit ranged from 10 to 12%. Plasma resistin levels were measured in ng/ml.

High Resolution Accurate Mass (HRAM) of 8-Isoprostane and Prostgalndine E2

Approximately 20 mL of urine was obtained from all cases The levels of 8-isoprostane and prostgalndine E2 in urine samples were determined by HRAM (high resolution accurate mass) mass spectrometry on LTQ Orbitrap® Discovery (ThermoScientific Co, USA) mass spectrometer, equipped with Surveyor® Plus HPLC system and IonMax® electrospray ionization module. The analyses were carried out by stable isotope dilution method in negative ionization mode using HESI II (heated electrospray ionization) source type. The concentration and purification of 8-isoprostane

and prostgalndine E2 from urine samples was processed by affinity sorbent (Cayman Chemical, USA), following the producer's protocol with some modification. The urinary 8-isoprostane and prostgalndine E2 levels were standardized to the levels of urinary creatinine. Creatinine was measured applying the enzyme method - Creatinine plus version 2 Cobas Integra (Roche). Results are given in pg/mkmol/creatinine.

Statistical Analysis

Descriptive statistics was used for demographic and clinical data presentation. The Kolmogorov-Smirnov test was used to explore the normality of distribution. Continuous variables in each group of subjects were expressed as median and interquartile range when data was 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 LVDD. An unpaired Student's t test was performed for normally distributed continuous variables. Mann-Whithney-U test was used in other cases. Categorical variables were compared by the $\chi 2$ test or the Fisher exact test. Correlation analysis was performed between oxidative stress/inflammatory markers and stress E/e'. Predictive models were constructed. Age, sex, height, weight (BMI), FEV1, LV diastolic dysfunction at rest were specifically included as co-variates.

In all cases a p value of less than 0.05 was considered significant as determined with SPSS® 13.0 Software (SPSS, Inc, Chicago, Ill) statistic.

Results

Demographic and clinical data

Subjects enrolled in the study were Caucasians at a mean age of 62.50±8.5 years and a body mass index of 27.26±6.92kg/m2. They were divided into two groups - subjects with stress LVDD - 64% (67/104) and those without - 36% (37/104). There was no difference regarding the demographic, and respiratory parameters. The two groups, however, distinguished in their CPET parameters. Patients without stress LVDD performed better – they stopped exercise at higher load; they also had lower 'VE/'VCO2 slope, which may be indicative of lower pulmonary-venous pressure and better ventilation/perfusion ratio (Table 1).

Cardio-pulmonary exercise testing parameters and stress LVDD

According to the objective ATS/ACCP 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 differed significantly regarding the exercise cessation factors (Table 1). In patients with stress LVDD dyspnea was the predominant limiting factor - 65 (97%), while it was reported as a reason for exercise stopping in only 13 (35%) of the patients without stress LVDD. Leg fatigue was reported by 2 (3%) of the patients with stress LVDD group; in those without stress LVDD it was the reason for exercise cessation in 24 (65%) (Table 1). The ventilatory and cardiovascular response parameters during exercise in the two groups are presented in table 1 These subjects achieved higher load, showed higher minute ventilation at peak load, higher oxygen pulse, higher peak 'VO2 and higher 'VO2 at Anaerobic Threshold (AT) in comparison to stress LVDD group.

	Patients w/o stress LVDD (37)	Patients with stress LVDD (67)	p-value
Demographic data			
Age, year	60.00±7.00	64.00±7.00	0.143*
Male: Female gender, n	21:16	44:23:00	0.298ǂ
Current smokers, n (%)	23(62%)	39(58%)	0.176ǂ
Former smokers, n (%)	4(11)	17 (25)	0.981ǂ
Non-smokers, n (%)	10(27)	11 (17)	0.375ǂ
Packet 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†
FEV1/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†
Sat, %	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, l/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†
PeakO2 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			
Dyspnea	13(35%)	65(97%)	0.023ǂ
Leg fatigue	24(65%)	2(3%)	0.038 ǂ
GOLD stages			
GOLD I, n (%)	9 (56%)	7 (44%)	0.701ǂ
GOLD II, n (%)	16 (18%)	72 (82%)	0.435 ǂ

Table 1: Anthropometric, clinical and cardio-pulmonary characteristics of the patients with and w/o stress LVDD.

0*Unpaired t test; †Mann-Whitney U test; ǂchi square test; §Abbreviations: LVDD: Left Ventricular Diastolic Dysfunction; GOLD: Global Initiative on Obstructive Lung Disease; O_2 pulse: Oxygen Pulse; 'VE: Minute Ventilation; RER: Respiratory Exchange Ratio;'VO_2: Oxygen Consumption; FEV1: Forced Expiratory Volume in 1s; FVC: Forced Ventilatory Capacity; mMRC: modified Medical Research Council.

Echocardiographic parameters

Our patients were with normal LV dimensions and had preserved LV systolic function table 2. 62% of the subjects demonstrated evidence of left ventricular hypertrophy. The left atrial and ventricular dimensions were within normal limits. The median values of LAVI in the group without stress-induced LVDD were lower 28.34 (26.58-31.29 ml/m^2) in comparison to the group with LVDD 29.18 (27.61-32.83 ml/m^2).

Discussion

The major findings of our study are: 1) A high frequency - 64% (67/104) of LVDD and masked heart failure with preserved ejection fraction in non-severe COPD patients with exertional dyspnea was established; 2) Prostaglandine E2 correlated to stress LV E/e' but was not an independent marker for it.

	Patients w/o stress LVDD (37)	Patients with stress LVDD (67)	p-value
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' aver	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 med, 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' aver	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*

Table 2: Echocardiographic parameters of the patients with and w/o stress LVDD.

*Mann-Whitney U test;† Abbreviations: LVDD: Left Ventricular Diastolic Dysfunction; LAVI: Left Atrium Volume Index; RAVI: Right Atrium Volume Index; RVWT: Right Ventricular Wall Thickness; PW: Posterior Wall; TAPSE: Tricuspid Annular Plane Systolic Excursion.

	Patients w/o stress LVDD (37)	Patients with stress LVDD (67)	p-value
Urine 8-isoprostane, µmol/l/cre	32.91±3.83	31.67±3.34	0.079*
Urine prostaglandin E2, µmol/l/cre	57.07±4.67	50.76±3.55	0.012*
Plasma resistin, ng/ml	22.51±2.61	19.68±3.56	0.847*

Table 3: Markers for oxidative stress and inflammationin patients with and w/o stress LVDD.

*Mann: Whitney U test;†Abbreviations:LVDD:Left Ventricular Diastolic Dysfunction.

A recent meta-analysis in COPD shows a high prevalence of LVDD by transmitral inflow patterns and tissue Doppler parameters [10]. The eleveated risk for LVDD in COPD population is a precondition to HFpEF.

In our study we detect a large prevalence of stress LVDD in COPD patients, free of overt cardiovascular morbidity. This confirms the current notion that COPD is an independent predictor of vascular damage [11]. As most of the patients with LVDD are asymptomatic at rest, exercise reveals diastolic abnormalities even when they are not evident [12,13]. Stress echocardiography examines LV filling on exertion and detects the initial stages of diastolic dysfunction. Its performance is essential for the detection of diastolic dysfunction. This is of special clinical importance in COPD, where LVDD stays hidden under the umbrella of the COPD associated dyspnea. It may be an independent limiting factor of the physical activity and may influence COPD prognosis [13]. The mechanisms that predispose COPD subjects to LVDD are speculative. They may be contributed to systemic inflammation, oxidative stress, pulmonary hypertension, chronic hypoxemia, chronic hypercapnia, hyperinflation, and right-to-left ventricular interaction. Although oxidative stress and inflammation are responsible for the pathogenesis of LVDD according to our results none of the markers is an independent predictor for it.

Systemic inflammation is a known contributor to the development of HFpEF. COPD itself leads to elevated proinflammatory markers - IL-6, TNF-α, hs-CRP. These cytokines increase E-selectin, VCAM, endothelial reactive oxygen species and attenuate nitric oxide availability in the coronary microvasculature [14]. The biochemical processes that ensue, stimulate collagen deposition and myocardial stiffness [14].

Both resistin and hs-CRP markers have been associated with vascular damage and increased cardiovascular morbidity [15]. Resistin has been implicated in the development of insulin resistance, hypertension and diastolic dysfunction in the general population of patients. Several small studies have reported that circulating resistin levels are increased in human obesity and diabetes, although not all studies have been consistent [16,17]. Higher resistin plasma levels are established in prehypertension, masked hypertension and pulmonary arterial hypertension [18,19]. In the general population resistin is being associated with LVDD and all the clinical conditions (diabetes, obesity, hypertension), predisposing to it. Despite this in our study its plasma levels were similar among COPD patients with/without stress LVDD. The only inflammatory marker that significantly differed between both groups was prostaglandin E2. It has been described as beneficial in cardiac remodeling after ischaemic injury [20,21]. Our data supports this notion. Urine levels of prostaglandin E2 are higher in the group without stress LVDD. They, however, did not correlate to stress LV E/e'. Urine levels of prostaglandin E2 do not show good sensitivity and specificity to distinguish the two groups of patients. Our results, regarding urine prostaglandin E2 levels should be validated in larger cohorts and its exact protective mechanisms should be further explored.

In addition to systemic inflammation, oxidative stress in COPD may also disturb calcium transport and myocardial relaxation [22]. Reactive Oxidative Species (ROS) are generated under inflammatory or hypoxic conditions. They stimulate endothelin secretion and decrease NO/prostacyclin synthesis [23]. The endothelial damage, caused by oxidative stress, affects both coronary, systemic and pulmonary vessels and exerts multifaced mechanisms that contribute both to right (RVDD) and Left Ventricular Diastolic Dysfunction (LVDD) [24]. Though we applied a well-validated method and marker for oxidative stress - urine 8-isoprostanes, we did not detect substantial difference in its concentrations between COPD subjects with/without LVDD. Neither a correlation between urine 8-isoprostanes and stress LV E/e' was found. The generation of ROS during oxidative stress

may directly cause abnormal myocardial relaxation in both the right and left ventricle [22].

The study has several limitations: 1) The relatively small sample size; 2) 30% of the patients already had grade I LVDD at rest; 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) We do not have invasive measurement of sPAP; 5) Measurements were acquired in the early recovery period (approximately 2 min) after symptom-limited exercise. The timeline of changes of the pulmonary and intrathoracic pressures during the brief time interval from peak exercise to their measurement in early recovery is not well known and underestimation is possible.

In conclusion, we report a high prevalence of HFpEF in non-severe COPD patients with exertional dyspnea, free of overt cardiovascular diseases. Patients with stress LVDD demonstrate similar levels of oxidative stress. Prostaglandine E2 may have protective role in LV remodeling, while resistin plasma levels contribute to LVDD pathogenesis. None of these biomarkers may be applied as a predictor for stress LVDD in clinical practice.

Ethical Statement

Ethics approval for the study protocol was received from the Ethics Committee of the Medical University, Sofia protocol 5/12.03.2018. There were no external funding sources for this study.

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Disclosure

All the authors state no conflict of interests and leave the copyright of the article if accepted.

Conflict of Interest

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References

1. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, et al. (2012) Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 186: 155-161.
2. Ukena C, Mahfoud F, Kindermann M, Kindermann I, Bals R, et al. (2010) The cardiopulmonary continuum systemic inflammation as 'common soil' of heart and lung disease. Int J Cardiol 145: 172-176.
3. Sin DD, Man SF (2005) Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thorac Soc 2: 8-11.
4. Finkelstein J, Cha E, Scharf SM (2009) Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. Int J Chron Obstruct Pulmon Dis 4: 337-349.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, et al. (2016) 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol 69: 1167.
6. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, et al. (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 10: 165-193.
7. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. (2005) ATS/ERS task force. Eur Respir J. Standardisation of spirometry. Eur Respir J 26: 319-338.
8. Guazzi M, Arena R, Halle M, Piepoli M, Myers J, et al. (2016) 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. Circulation 133: 694-711.
9. American Thoracic Society; American College of Chest Physicians (2003) ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167: 211-277.
10. Zhyvotovska A, Yusupov D, Kamran H, Al-Bermani T, Abdul R, et al. (2019) Diastolic dysfunction in patients with chronic obstructive pulmonary disease: A meta-analysis of case controlled studies. Int J Clin Res Trials. 4: 137.
11. Fisk M, McEniery CM, Gale N, Mäki-Petäjä K, Forman JR, et al. (2018) Surrogate markers of cardiovascular risk and chronic obstructive pulmonary disease: A large case-controlled study. Hypertension 71: 499-506.
12. Gibby C, Wiktor DM, Burgess M, Kusunose K, Marwick TH (2013) Quantitation of the diastolic stress test: Filling pressure vs. diastolic reserve. Eur Heart J Cardiovasc Imaging 14: 223-227.
13. Ha JW, Oh JK, Pellikka PA, Ommen SR, Stussy VL, et al. (2005) Diastolic stress echocardiography: A novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise doppler echocardiography. J Am Soc Echocardiogr 18: 63-68.
14. Paulus WJ, Tschope C (2013) 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 62: 263-271.
15. Barnes PJ, Celli BR (2009) Systemic manifestations and comorbidities of COPD. Eur Respir J 33: 1165-1185.
16. Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, et al. (2004) Regulation of fasted blood glucose by resistin. Science 303: 1195-1198.
17. Furuhashi M, Ura N, Higashiura K, Murakami H, Shimamoto K (2003) Circulating resistin levels in essential hypertension. Clin Endocrinol (Oxf) 59: 507-510.
18. Papadopoulos DP, Makris TK, Krespi PG, Poulakou M, Stavroulakis G, et al. (2005) Adiponectin and resistin plasma levels in healthy individuals with prehypertension. J Clin Hypertens (Greenwich) 7: 729-733.
19. Papadopoulos DP, Perrea D, Thomopoulos C, Sanidas E, Daskalaki M, et al. (2009) Masked hypertension and atherogenesis: The impact on adiponectin and resistin plasma levels. J Clin Hypertens (Greenwich) 11: 61-65.
20. Degousee N, Fazel Sh, Angoulvant D, Stefanski E, Pawelzik S, et al (2008) Microsomal prostaglandin E2 synthase-1 deletion leads to adverse left ventricular remodeling after myocardial infarction. Circulation. 117: 1701-1710.
21. Gould KE, Taffet GE, Michael LH, Christie RM, Konkol DL, et al (2002) Heart failure and greater infarct expansion in middle-aged mice: A relevant model for postinfarction failure. Am J Physiol Heart Circ Physiol 282: 615-621.
22. Cargill R, Kiely D, Lipworth B (1995) Adverse effects of hypoxaemia on diastolic filling in humans. Clin Sci 9: 165-169.
23. Paulus WJ, Tschope C (2013) 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 62: 263-271.
24. Barbera JA, Peinado VI, Santos S (2003) Pulmonary hypertension in chronic obstructive pulmonary disease. Eur Respir J 21: 892-905.

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