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Left ventricle ejection fraction and strain derived by three-dimensional echocardiography are associated with exercise capacity in the patients with heart failure

Ejekciona frakcija leve srčane komore i miokardna deformacija dobijene trodimenzionalnom ehokardiogrfijom povezane su sa funkcionalnim kapacitetom bolesnika sa srčanom insuficijencijom

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Abstract

Background/Aim. Echocardiography represents the most commonly performed noninvasive cardiac imaging tests for the patients with heart failure (HF). The aim of this study was to assess the relationship between the exercise capacity parameters [peak oxygen consumption (VO_2) and the minute ventilation-carbon dioxide production relationship (VE/VCO_2)] and the three-dimensional speckle-tracking echocardiography (3D-STE) imaging of left ventricular (LV) function in the HF patients with the reduced LV ejection fraction (LVEF). **Methods.** This cross-sectional study included 80 patients with diagnosed ischemic LV systolic dysfunction (LVEF < 45%) divided into subgroups based on the proposed values of analyzed cardiopulmonary exercise testing (CPET) variables: VO_2 peak ≤ 15 mL/kg/min, VO_2 peak > 15 mL/kg/min, VE/VCO_2 slope < 36 and VE/VCO_2 slope ≥ 36. All patients underwent a physical examination, laboratory testing, two-dimensional (2D) and 3DE, and CPET. **Results.** LVEF, global longitudinal, circumferential, radial and area strains were significantly lower in the subgroups of subjects with a peak VO_2 less, or equal to 15 mL O_2/kg per min and with a VE/VCO_2 slope greater, or equal to 36 compared to the subgroups of subjects with a peak VO_2 greater than 15 mL O_2/kg per min and with a VE/VCO_2 slope less than 36. There was a significantly positive correlation between the peak VO_2 values and parameters of 3DE, and a significantly negative correlation between the VE/VCO_2 slope values and parameters of 3DE. **Conclusion.** The results of this study provide further evidence that the LV function can be noninvasively and objectively measured by 3D-STE. A significant correlation between examined parameters suggests that LVEF and strain derived by 3DE are associated with exercise capacity in the patients with HF.

Key words:
heart failure; myocardial contraction; echocardiography; ventricular function, left; exercise test; oxygen consumption.

Apstrakt

Uvod/Cilj. Ehokardiografija predstavlja jedan od najčešće izvođenih neinvazivnih testova analize bolesnika sa srčanom insuficijencijom. Cilj ove studije bio je da se utvrdi odnos između parametara funkcionalnog kapaciteta [maksimalna potrošnja kiseonika (VO_2), ventilatorni ekvivalent za ugljendioksid (VE/VCO_2)] i trodimenzionalne ehokardiografije (3D-STE) leve komore kod bolesnika sa srčanom insuficijencijom i smanjenom ejekcionom frakcijom leve srčane komore (LVEF). **Metode.** Ova studija preseka obuhvatila je 80 bolesnika sa dijagnostikovanom sistolnom disfunkcijom leve srčane komore ishemijske etiologije (LVEF < 45%) podeljene u podgrupe na osnovu predloženih vrednosti analiziranih parametara funkcionalnog kapaciteta: VO_2 ≤ 15 mL/kg/min, VO_2 > 15 mL/kg/min, VE/VCO_2 < 36 i VE/VCO_2 nagib ≥ 36. Svi bolesnici podvrgnuti su fizičkom pregledu, laboratorijskom testiranju, 2DE i 3DE, kao i ispitivanju funkcionalnog kapaciteta. **Rezultati.** Vrednosti LVEF, longitudinalne, cirumferentne, radijalne i površinske miokardne deformacije bile su značajno niže u podgrupama bolesnika sa vrednostima VO_2 ≤ 15 mL O_2/kg po min i VE/VCO_2 ≥ 36 u odnosu na bolesnike podgrupa sa VO_2 > 15 mL O_2/kg po min i VE/VCO_2 < 36. Uočena je značajna pozitivna korelacija između izmerenih vrednosti VO_2 i parametara 3DE, te značajna negativna korelacija između izmerenih vrednosti VE/VCO_2 i parametara 3DE. **Zaključak.** Dobijeni rezultati potvrđuju da se funkcija leve

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komore može neinvazivno i objektivno proceniti primenom 3DE. Uočena značajna korelacija između između ispitivanih parametara ukazuje na to da su LVEF i miokardna deformacija dobijeni 3DE povezani sa funkcionalnim kapacitetom bolesnika sa srčanom insuficijencijom.

Ključne reči:
srce, insuficijencija; miokard, kontrakcija; ehokardiografija; srce, funkcija leve komore; vežbanje, testovi; kiseonik, potrošnja.

Introduction

Hearth failure (HF) is a complex clinical condition caused by spectrum of various heart diseases. It is a leading cause of morbidity and mortality among people over 65 years of age, with a current prevalence of more than 23 million cases and rising incidence worldwide [1, 2].

Left ventricular ejection fraction (LVEF) is reduced in more than a half of patients with HF [3]. The cardiopulmonary exercise testing (CPET) has an important role in the assessment of HF status [4], especially because the wealth of previous investigations has consistently demonstrated its prognostic values in the HF population [4–8]. The two most frequently assessed variables obtained from CPET are the peak oxygen consumption (VO_2) and the minute ventilation-carbon dioxide production (VE/VCO_2) relationship. VO_2 was the first CPET variable used in clinical practice, and now it is considered to be the diagnostic and prognostic gold standard in HF [9]. Furthermore, previous investigations reported that VE/VCO_2 slope was also significant predictor of survival of patients with HF as the continuous variable and even more prognostically superior to peak VO_2 [6, 10, 11]. These variables, along with LVEF, represent the pivotal predictor of morbidity and mortality in the patients with HF [12, 13]. However, correlation between LVEF and exercise capacity remains unclear, and still needs to be elucidated [14, 15].

Two-dimensional (2D) and three-dimensional (3D) echocardiography represent the most commonly performed noninvasive cardiac imaging tests used to quantitatively assess cardiac volumes, the LVEF, stroke volume, and cardiac output in the patients with HF [16, 17]. 3D speckle-tracking echocardiography (3D-STE) is a new promising method for the quantitative assessment of LV volumes, myocardial strain and strain rate in longitudinal, radial and circumferential dimension [18]. Moreover, 3D-STE overcomes the usual drawbacks of conventional 2D echocardiography, such as the modest interobserver, intraobserver, and the test-retest reproducibility of specific structural and functional parameters [19].

Therefore, this study aimed to explore the relationship between the exercise capacity parameters (VO_2, VE/VCO_2) and 3D-STE imaging of LV function in the HF patients with reduced LVEF.

Methods

This cross-sectional study was conducted at the Department of Cardiology, University Hospital "Dr Dragiša Mišović" Belgrade, Serbia from February 2012 to February 2016. The study was approved by the local Ethics Committee. Informed consent was obtained from all participants after all procedures had been fully explained to them and prior to the clinical and laboratory examinations.

The present study included 80 consecutive patients, with diagnosed ischemic left ventricular systolic dysfunction (LVEF < 45%) and sinus rhythm [3], referred to our clinic due to the condition evaluation. The patients with age over 75 years, severe angina syndrome, atrial fibrillation, severe valvular disease, anemia or chronic obstructive pulmonary disease were excluded from the study.

All patients underwent a physical examination, including anthropometric measures (height, weight), laboratory testing [creatinine, the fasting glucose level, glycated hemoglobin (HbA1c), total cholesterol, high and low density lipoprotein (HDL and LDL) cholesterol, triglycerides, C-reactive protein (CRP), N-terminal *pro* brain natriuretic peptide (NT-*pro* BNP)), echocardiography, and CPET]. Additionally, the body mass index (BMI) was calculated for each patient. Based on the proposed values of analyzed CPET variables (VO_2, VE/VCO_2) [8, 20], all participants were further subdivided into 4 subgroups: VO_2 peak ≤ 15 mL/kg/min, VO_2 peak > 15 mL/kg/min, VE/VCO_2 slope < 36 and VE/VCO_2 slope ≥ 36.

Echocardiography

The echocardiographic examinations were performed by the commercially available Vivid 7 (GE Vingmed, Horten, Norway) ultrasound machine equipped with a 2.5 MHz transducer with harmonic capability. All echocardiographic data were analyzed off-line.

Standard 2D echocardiographic examination

The 2D echocardiographic parameters were obtained as the average value of three consecutive cardiac cycles. The left atrial (LA), left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) diameters, the left ventricular end-systolic (LVESV) and end-diastolic (LVEDV) volumes, the left ventricular posterior wall thickness (PWT), septum thickness, and right ventricle systolic pressure (RVSP) were determined according to the current recommendations [21]. LVEF was estimated by using the biplane method. Transmitral Doppler inflow and tissue pulsed Doppler were obtained in the view of the four chamber apex. The pulsed Doppler measurements included the transmitral early diastolic peak flow velocity (E), late diastolic flow velocity (A), E/A ratio, E velocity deceleration time (DT) and ratio between mitral flow E peak velocity and tissue Doppler derived e' (E/e' ratio) of the septal mitral annulus (MVEes) [22]. The tissue Doppler imaging was used to obtain the left ventricular myocardial velocities in the apical four-chamber view.

2D echocardiography left ventricle strain

The 2D longitudinal strain was performed by Automated Functional Imaging (AFI). The algorithm tracked the wall motion and calculated the percentage of lengthening or shortening in a set of three longitudinal 2D-image planes (apical long, 2-chamber and 4-chamber) and displayed the results for each plane. It then combined the results of all three planes in a single summary, which presented the analysis for each segment along with a global peak strain value for the left ventricle [18]. The frame rate ranged between 50 and 70 Hz.

3D echocardiography examination

A full-volume acquisition of the left ventricle, which required the further analysis, was obtained by harmonic imaging from an apical approach. Six electrocardiogram-gated consecutive beats were acquired during the end-expiratory breath-hold (6–8 s) to generate full volume. The frame rate was higher than 30 frames/s.

All data sets were stored digitally and analyzed off-line by a commercially available software 4D Auto LVQ software (EchoPAC 110.1.2; GE-Healthcare). The software automatically identified in 3D endocardial border of the left ventricular cavity and provided the left ventricular volumes, cardiac output (CO), stroke volume (SV), EF, and left ventricular sphericity index. After that, an automatic trace of the epicardial border was displayed to detect the region of interest required for the 3D assessment of myocardial deformation parameters (speckle tracking). The 3D deformation parameters, global longitudinal strain (GLS), global circumferential strain (GCS), global radial strain (GRS), and global area strain (GAS), were calculated as the weighted averages of the regional values from the 17 myocardial segments at end-systole [23]. If three, or more segments were rejected, the global strain values were not calculated, and these patients were excluded.

Cardiopulmonary exercise testing (CPET)

All patients underwent a maximum symptom-limited (fatigue and/or dyspnea) treadmill exercise test according to the modified Noughton protocol [24]. It consisted of 6 levels lasting for 3 minutes, with constant seed of 3 km/h, and start 0 elevation increasing for 3.5% for each interval. The patients were encouraged to continue with the test as long as their respiratory exchange ratio exceeded 1. The peak oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were assessed with the breath-by-breath gas analysis (CARDIOVIT CS-200 Ergo-Spiro system; Schiller AG, Baar, Switzerland). Spirometry was done in all participants before the cardiopulmonary exercise testing, including forced expiratory volume in the first second (FEV_1) and the measurement of forced vital capacity (FVC), which was computed as a percentage of predicted values, considering age and gender. VO_2 was defined as an average value within the last 20 seconds of exercise and expressed as mL/kg/min and METs (1 MET equals 3.5 mL of oxygen uptake per kilogram of body weight per minute). The ventilatory anaerobic threshold and oxygen uptake at this level, expressed as the percentage of VO_2, was determined in all the participants. The VE/VCO_2 slope, which showed the linear increase of ventilation relative to the carbon dioxide production, was computed automatically by the Schiller computer system.

Statistical analysis

The statistical analyses were performed using the IBM SPSS Statistics for Windows Software (Version 20.0, IBM Corp, Armonk, NY, USA) and R: A Language and Environment for Statistical Computing (Version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria). The results were presented as counts (percentage) or mean ± standard deviation. The group comparisons were performed using the Student's *t*-test or Mann-Whitney U-test. The correlation between two numerical variables was tested using the Pearson correlation analysis. The χ^2 analysis was conducted to assess a statistical significance between categorical data. The receiver operating characteristic (ROC) analysis was performed to determine the best parameter of 3D echocardiography in different subgroups and to calculate the area under the curve, cut-off value, sensitivity, specificity, positive likelihood ratio (LR +), and negative LR (LR-) for the investigated parameters.

Results

The demographic and clinical parameters of the study population are presented in Table 1. The participants were of similar age and gender distribution without significant differences between examined subgroups.

The level of CRP was significantly higher in the subgroup of subjects with a peak VO2 less or equal to 15 mL O2/kg per min compared to the subgroup of subjects with a peak VO2 greater than 15 mL O2/kg per min (p = 0.028) (Table 1). Furthermore, the levels of CPR, NT-pro BNP and creatinine were significantly higher in the subgroup of subjects with a VE/VCO2 slope greater or equal to 36 compared to the subgroup of subjects with a VE/VCO_2 slope less than 36 (p = 0.001; p = 0.002; p = 0.019 respectively) (Table 1). The levels of other analyzed clinical parameters were similar and without significant differences between the investigated subgroups.

The parameters of 2DE in the investigated subgroups are presented in Table 2. RVSP was significantly increased in in the subgroups of subjects with a peak VO_2 less or equal to 15 mL O_2/kg per min compared to the subgroups of subjects with a peak VO_2 greater than 15 mL O_2/kg per min (p = 0.005). Additionally, RVSP was significantly increased (p = 0.003, respectively) while EF biplane, MVEes, and GLS were significantly decreased (p = 0.006; p = 0.036; p = 0.029, respectively) in the subgroups of subjects with a VE/VCO_2 slope greater or equal to 36 compared to the subgroups of subjects with a VE/VCO_2 slope less than 36 (p = 0.019; p = 0.003, respectively) (Table 2).

The 3DE LV strain analysis revealed that the global longitudinal, circumferential, radial and area strains were significantly lower in the subgroups of subjects with a peak VO_2 less or equal to 15 mL O_2/kg per min and with a VE/VCO_2 slope greater or equal to 36 compared to the subgroups of subjects with a peak VO_2 greater than 15 mL O_2/kg per min ($p = 0.014$; $p = 0.037$; $p = 0.003$; $p = 0.010$, respectively) and with a VE/VCO_2 slope less than 36 ($p = 0.005$; $p = 0.038$; $p = 0.009$; $p = 0.009$, respectively). The same trend was observed for the 3D EF (Table 3).

Table 1

Demographic characteristics and clinical parameters of study population

Variables	VO_2 (mL/kg/min)		*p* value	VE/VCO_2 (slope)		*p* value
	≤ 15 (n = 25)	> 15 (n = 55)		< 36 (n = 60)	≥ 36 (n = 20)	
Age (years)	64.9 ± 7.5	63.3 ± 8.9	0.424 [a]	63.4 ± 9.2	64.6 ± 7.7	0.597 [a]
Gender (M/F)	18/7	35/20	0.348 [b]	45/15	13/7	0.466 [b]
BMI (kg/m^2)	27.2 ± 2.9	26.8 ± 3.4	0.577 [a]	27.1±3.2	26.5 ± 3.4	0.490 [a]
NT-pro BNP (pg/mL)	1340.4 ± 1842.7 (311; 186–2073)	1146.8 ± 2775.4 (308; 121–709)	0.352 [c]	789.3 ± 2303 (241; 99–656)	2221.5 ± 2697.2 (777; 300–3723)	0.002 [c]
Creatinine (umol/L)	101.8 ± 50.4	98.3 ± 49.9	0.715 [c]	91.3 ± 40.7	119 ± 63.5	0.019 [c]
Fasting plasma glucose (mmol/L)	7.6 ± 3.3	6.4 ± 2.2	0.080 [a]	6.1 ± 1	7.8 ± 3.5	0.053 [a]
HbA1c (%)	6.6 ± 1.5	6.2 ± 1.1	0.120 [a]	6.1 ± 1	6.8 ± 1.7	0.089 [a]
Cholesterol (mmol/L)	4.8 ± 1.2	5 ± 1.2	0.337 [a]	5.1 ± 1.3	4.5 ± 1	0.120 [a]
LDL (mmol/L)	3 ± 1	3 ± 1.1	0.829 [c]	3.1 ± 1.1	2.7 ± 0.8	0.074 [c]
HDL (mmol/L)	1.2 ± 0.4	1.2 ± 0.4	0.603 [a]	1.2 ± 0.4	1.2 ± 0.4	0.536 [a]
Triglycerides (mmol/L)	1.7 ± 1	1.5 ± 0.8	0.485 [c]	1.7 ± 1	1.4 ± 0.85	0.067 [c]
CRP (mg/L)	4.2 ± 7 (3.3; 1.9–7.9)	6 ± 7 (2.1; 1.4–3.7)	0.028 [c]	3.2 ± 4.3 (2; 1.3–3.7)	8.6 ± 10.2 (3.8; 2.6-8)	0.001 [c]

Data are presented as mean ± standard deviation or number of participants; for parameters NT-pro BNP and CRP median, 25 and 75 percentile were also presented.
M – male; F – female; BMI – body mass index; NT-pro BNP – N-terminal pro brain-type natriuretic peptide; LDL – low-density lipoprotein; HDL – high-density lipoprotein; CRP – C reactive protein; VO2 – peak oxygen consumption; VE/VCO2 – ventilation/carbon dioxide production relationship. [a]Student's *t*-test; [b]χ^2 test; [c]Mann-Whitney U-test.

Table 2

Two-dimensional echocardiography parameters in the investigated group

Variables	VO_2 (mL/kg/min)		*p* value	VE/VCO_2 (slope)		*p* value
	≤ 15 n = 25	> 15 n = 55		< 36 n = 60	≥ 36 n = 20	
LA (mm)	45.2 ± 6.5	43.7 ± 6.3	0.343 [a]	43.5 ± 6	46 ± 7.2	0.119 [a]
LVEDD (mm)	58.9 ± 8.5	55.7 ± 7.5	0.114 [a]	55.7 ± 7.8	58.9 ± 7.8	0.107 [a]
LVESD (mm)	48.1 ± 7.9	45.8 ± 7.9	0.214 [a]	45.7 ± 8	48.4 ± 7.6	0.171 [a]
LVEDV/BSA (mL/m^2)	78 ± 22	77.1 ± 26.5	0.884 [a]	74.6 ± 26.2	84.4 ± 20.9	0.115 [a]
LVESV/BSA (mL/m^2)	51.5 ± 20.1	49.3 ± 23.1	0.678 [a]	47.4 ± 23.1	56.5 ± 18.3	0.097 [a]
EF biplane (%)	34.1 ± 8.1	37.2 ± 6.3	0.200 [b]	37.6 ± 6.6	32.3 ± 7.1	0.006 [b]
RVSP (mmHg)	41.4 ± 19.9	30.6 ± 10.1	0.005 [a]	31.2 ± 12.4	40.9 ± 13.8	0.003 [a]
MVEes	0.047 ± 0.013	0.050 ± 0.015	0.492 [a]	0.051 ± 0.015	0.044 ± 0.011	0.036 [a]
GLS (%)	10.7 ± 3.7	12.2 ± 3.3	0.084 [b]	12.3 ± 3.2	10.4 ± 3.8	0.029 [b]

Data are presented as mean ± standard deviation.
LA – left atrium; LVEDD – left ventricular end diastolic diameter; LVED – left ventricular end systolic diameter; LVEDV – left ventricular end diastolic volume; LVESV – left ventricular end systolic volume; EF biplane-two-dimensional ejection fraction; BSA – body surface area; RVSP – right ventricle systolic pressure; MVEes-ratio between mitral flow E peak velocity and tissue Doppler derived e' of the septal mitral annulus; GLS – global longitudinal strain; VO_2 – peak oxygen consumption; VE/VCO_2 – ventilation/carbon dioxide production relationship.
[a]Student's *t*-test; [b]Mann-Whitney U-test.

Table 3

Three – dimensional ejection fraction and variables

Variables	VO_2 (mL/kg/min)		*p*-value	VE/VCO_2 (slope)		*p*-value
	≤ 15 (n = 25)	> 15 (n = 55)		< 36 (n = 60)	≥ 36 (n = 20)	
3D EF (%)	33.1 ± 8.9	37.7 ± 6.7	0.011 [a]	38.2 ± 6.6	31.6 ± 8.4	0.001 [a]
Longitudinal strain (%)	8.1 ± 3.3	10.3 ± 3.8	0.014 [a]	10.4 ± 3.5	7.8 ± 3.7	0.005 [a]
Circumferential strain (%)	7.7 ± 3	9.6 ± 3.9	0.037 [a]	9.5 ± 3.7	7.7 ± 3.3	0.038 [a]
Radial strain (%)	18.4 ± 7.9	24.9 ± 10.3	0.003 [a]	24.7 ± 9.8	18.3 ± 9.3	0.009 [a]
Area strain (%)	14.1 ± 5.2	18 ± 6.3	0.010 [a]	17.9 ± 6	13.9 ± 6	0.009 [a]

Data are presented as mean ± standard deviation; 3D EF – three-dimensional ejection fraction; VO_2 – peak oxygen consumption; VE/VCO_2 – ventilation/carbon dioxide production relationship; [a] Student's *t*-test.

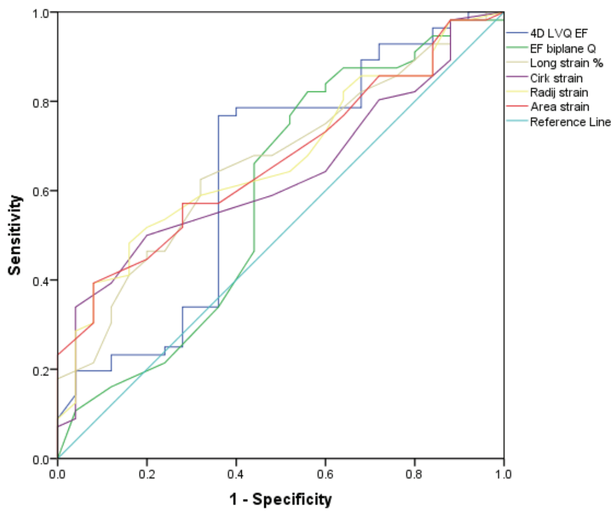

Fig. 1 – Receiving operating characteristic (ROC) curve of the investigated parameters in relation to a peak oxygen consumption (VO_2) values.

An impact of a peak VO_2 and VE/VCO_2 slope values on the 3DE parameters was further investigated by the ROC analysis. The ROC curve areas for the 3DE parameters in relation to a peak VO_2 values were presented in Figure 1 and Table 4. The highest area under the ROC curve was observed for the radial strain 0.67 [95% confidence interval (CI) 0.55–0.79] (p = 0.015). When considering the highest level of sensitivity, the cut-off value for radial strain was 24.5 %; with the sensitivity of 84 % and specificity of 48 %, while the positive and negative likelihood ratios (LR+, LR-) were 1.62 and 0.33, respectively.

The ROC curve areas for the 3DE parameters in relation to the VE/VCO_2 slope values were presented in Figure 2 and Table 5.

The highest area under the ROC curve was observed for the 3D EF 0.73 [95% confidence interval (CI) 0.60–0.86] (p = 0.001). When considering the highest level of sensitivity the cut-off value for 3D EF was 36.04 %; with the sensitivity of 78.3 % and specificity of 75.9 %, while LR+, LR- were 3.24 and 0.29, respectively.

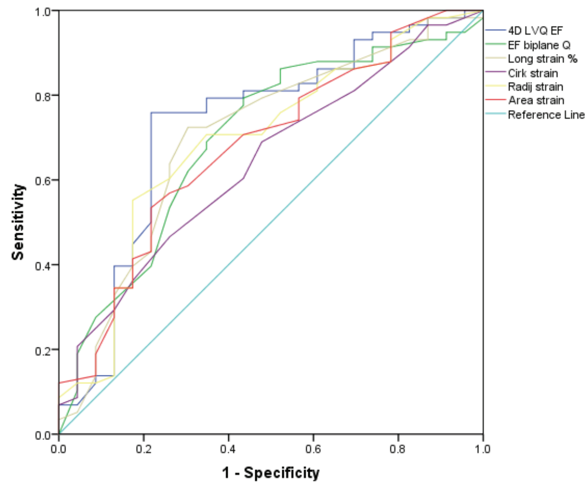

Fig. 2 – Receiving operating characteristic (ROC) curve of the investigated parameters in relation to a ventilation/carbon dioxide production relationship (VE/VCO_2) slope values.

We observed a significantly positive correlation between the peak VO_2 values and parameters of 3DE (Table 6). On the other hand, there was also a significantly negative correlation between the VE/VCO_2 slope values and parameters of 3DE (Table 6).

Table 4

Receiving operating characteristics (ROC) curve of the investigated parameters in relation to a peak oxygen consumption (VO_2) values

Variables	Area	SE	95% CI lower bound	95% CI upper bound	p value
EF biplane (%)	0.589	0.071	0.444	0.735	0.201
3D EF (%)	0.641	0.071	0.502	0.781	0.043
Longitudinal strain (%)	0.667	0.062	0.545	0.789	0.017
Circumferential strain (%)	0.634	0.063	0.511	0.757	0.055
Radial strain (%)	0.670	0.061	0.550	0.790	0.015
Area strain (%)	0.667	0.061	0.548	0.786	0.017

EF – ejection fraction; 3D EF – three dimensional EF; SE – standard error; CI – confidence interval.

Table 5

Receiving operating characteristics (ROC) curve of the investigated parameters in relation to a VE/VCO_2 slope values

Variables	Area	SE	95% CI lower bound	95% CI upper bound	p value
EF biplane (%)	0.698	0.066	0.569	0.827	0.006
3D EF (%)	0.729	0.067	0.598	0.861	0.001
Longitudinal strain (%)	0.702	0.067	0.571	0.833	0.005
Circumferential strain (%)	0.640	0.066	0.510	0.770	0.050
Radial strain (%)	0.692	0.067	0.562	0.822	0.007
Area strain (%)	0.680	0.066	0.551	0.809	0.012

EF – ejection fraction; 3D EF – three dimensional EF; VE/VCO_2 – ventilation/carbon dioxide production relationship. SE – standard error; CI – confidence interval.

Table 6
Correlation between the parameters of cardiopulmonary exercise testing and three-dimensional echocardiography parameters

Variables	VO_2 (mL/kg/min)	VE/VCO_2 (slope)
3D EF (%)	0.258 *	-0.358 **
Longitudinal strain (%)	0.368 **	-0.343 **
Circular strain (%)	0.317 **	-0.316 **
Radial strain (%)	0.376 **	-0.366 **
Area strain (%)	0.373 **	-0.339 **

EF – ejection fraction; 3D EF – three dimensional EF; VE/VCO_2 – ventilation/carbon dioxide production relationship; VO_2 – peak oxygen consumption.
$^{*}p < 0.05$; $^{**}p < 0.001$.

Discussion

HF prevalence ranges between 2% and 3% in the general population [25], including the Serbian population [26], with increasing trend due to the population ageing. LVEF is an established predictor of adverse cardiovascular outcomes in the HF patients [3]. However, several studies suggested that its prognostic utility of HF was limited due to the poor sensitivity in detecting early myocardial dysfunction [27, 28]. Echocardiography remains the most commonly performed noninvasive cardiac imaging test for the patients with HF in routine clinical practice [16, 17]. Its capacity to quantify the complex cardiac structures and provide insights into the myocardial functions and mechanics has dramatically improved with development of 3D-STE, as the novel method for the quantitative assessment of LV volumes, myocardial strain and strain rate in longitudinal, radial and circumferential dimension [18].

A recent meta-analysis conducted by Ma et al. [17] investigated clinical utility of 3D-STE for the LV function in the patients with chronic HF. The authors included 7 case-control studies with a total of 375 patients with HF and 181 healthy control participants in the final review. The meta-analysis results showed that the LVEF in the HF patients was significantly lower than in the controls. Furthermore, global longitudinal, circumferential and radial strain were also impaired in the HF patients compared to the controls. Based on the provided results they concluded that the LV function in the patients with HF can be noninvasively and objectively measured by 3D-STE [17] which is in agreement with our results. Several previous studies, not included in this meta-analysis, also investigated the utility of different strain and strain rates assessed by 3D-STE in the HF patients [29, 30]. Kleijn et al. [29] stated that the area strain represented the echocardiographic standard for the quantitative assessment of global and regional LV function. On the other hand, Zhang et al. [30] reported that the longitudinal, circumferential and radial strains were significantly associated with a prognosis in chronic systolic HF which was in accordance with our results. We demonstrated the significantly lower values of analyzed strains and 3D EF in both subgroups with the poor prognosis of HF (VO_2 peak ≤ 15 mL/kg/min, VE/VCO_2 slope ≥ 36). Furthermore, we demonstrated that the highest areas under the ROC curves were for radial strain in relation to a peak VO_2 values and 3D EF in relation to a VE/VCO_2 slope values. Our results are also in agreement with the study of Cho et al. [31] who proposed a multicriteria echocardiographic analysis and stated that the clinical approach needed to be multiparametric, as the sum of different positive parameters permitted an improved patient risk diagnosis. Additionally, our results of 2DE are in accordance with the previously reported results related to the patients with HF [32].

Interestingly, a recent EuroHeart Failure survey showed that 85% of patients suffering from HF underwent the echocardiography testing, while only 4.4% underwent the cardiopulmonary exercise test (CPET) [33]. However, in our clinical center, the CPET is widely used in the clinical assessment of patients with HF and the main objective of this study was to explore the relationship between the exercise capacity parameters (VO_2, VE/VCO_2) and 3D-STE imaging of LV function in the HF patients with reduced LVEF. We observed a significantly positive correlation between the peak VO_2 values and parameters of 3DE, and a significantly negative correlation between the VE/VCO_2 slope values and the parameters of 3DE which is in agreement with the previously reported results [34, 35]. Namely, Peterson et al. [34] stated that the 3D-STE measures had a strong linear association with estimates of functional capacity. Additionally, Donal et al. [35] reported a moderate correlation between 3D-STE and the functional capacity parameters.

The prognostic value of exercise testing is well-established in the assessment of HF status [4]. A peak VO_2 and VE/VCO_2 slope are the most frequently assessed variables obtained from CPET and previous studies confirmed their utility in the assessment of patients with HF [4-8]. However, it is important to emphasize that it was reported that VE/VCO_2 slope may be a better predictor of outcome than peak VO_2 in the HF population [5, 6]. There are two possible reasons for the differences between the prognostic value of the VE/VCO_2 slope and peak VO_2. Potential weaknesses of peak VO_2 are its dependence on the subject effort and the influence of peripheral metabolism. On the other hand, unlike peak VO_2, the VE/VCO_2 slope is generally linear and remains relatively constant throughout a progressive exercise test that makes it independent of subject effort. Therefore, in the event of submaximal effort, the VE/VCO_2 slope would theoretically maintain the diagnostic and prognostic significance [5, 6].

The analysis of clinical parameters revealed that the levels of CRP were significantly increased in the HF patients in the subgroups with a peak VO2 less or equal to 15 mL O2/kg per min and with a VE/VCO2 slope greater or equal to 36. These results suggest that the patient with a poor prognosis of HF are characterized with the increased inflammation. It was stated that the increased CRP levels in the patients with HF may be a consequence of an ischemic necrosis that initiate this potent inflammatory stimulus [36]. Our results are in accordance with the study of Liu et al. [37] that reported a positive correlation between the increased CRP level and the increased level of serum complement factors C3, C4, C5b9 in the HF patients.

Furthermore, we observed the significantly higher values of creatinine in the HF patients with a peak VO_2 less or equal to 15 mL O_2/kg per min and with a VE/VCO_2 slope greater or equal to 36 compared to the HF patients with a peak VO_2 greater than 15 mL O_2/kg per min and with a VE/VCO_2 slope less than 36. These results imply worsening of renal function in the patients with HF. There is increasing evidence that persistent increase in creatinine is correlated with a poor prognosis of patients with HF [38–42], which is in agreement with our results.

HF is characterized by the dysfunctional natriuretic peptide system. Tsutamoto et al. [43] were the first to demonstrate that a single BNP measurement was predictable of mortality in HF. Moreover, Koglin et al. [44] reported that the patients with chronic HF and high BNP levels had a higher probability of deterioration of their functional status or death than those with only moderate increased BNP levels. In our study, the levels of NT-pro BNP were significantly higher in the HF patients with poor prognosis. A wealth of previous studies also reported that the plasma concentrations of NT-pro BNP are increased in the patients with HF and accurately predict LVEF as well as morbidity and mortality in these patients [45–47] which is in line with our results.

Conclusion

The results of this study provide further evidence that LV function can be noninvasively and objectively measured by 3D-STE. The observed significant correlation between examined parameters suggests that LVEF and strain derived by 3D echocardiography are associated with exercise capacity in the patients with HF.

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