Echocardiographic predictors of exercise intolerance in patients with heart failure with severely reduced ejection fraction

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Abstract
Decreased exercise capacity (EC) is an established predictor of cardiac and all-cause mortality in patients with chronic heart failure (HF). No correlation has been found between EC and left ventricular (LV) ejection fraction. Moreover, data about the effect of right ventricular (RV) function on EC in HF with severe LV dysfunction are limited and contradictory. In this study, we aimed to investigate the relationship between EC and myocardial mechanics in patients with HF with reduced ejection fraction.

Consecutive patients with symptomatic HF and LV ejection fraction ≤35% were prospectively assessed. All patients were evaluated with enhanced echocardiography. A symptom-limited treadmill cardiopulmonary exercise test (CPX) was performed within 24-hour interval. Patients were stratified into 4 groups according to their EC defined by Weber’s classification. Prognosis of EC, expressed as oxygen uptake at peak exercise (peak VO₂), was evaluated in multivariate linear regression analysis model.

Sixty-seven patients with New York Heart Association classes II to III and a mean LV ejection fraction of 26 ± 7% were enrolled. A wide range of peak VO₂ was observed in CPX with patient exercise performance distributed to all classes according to Weber’s classification. Significant differences were found in RV systolic and diastolic functions between groups with different classes of EC: RV peak systolic myocardial velocity (S’) (P < .001), tricuspid annular plane systolic excursion (TAPSE) (P = .003), RV E’ (P = .003). In patients with functional decline, systolic pulmonary artery pressure (PASP) was higher (P = .029) and TAPSE/PASP ratio was lower (P = .006). No significant differences were found in LV diameter, systolic and diastolic function, and degree of mitral regurgitation.

Thirty three patients with RV systolic dysfunction showed lower peak VO₂ and oxygen uptake at anaerobic threshold (P = .008, P = .006, respectively), shorter exercise time (P = .003), and lower systolic blood pressure (P = .01) than in patients with normal RV systolic function. Logistic multivariate linear regression analysis with stepwise inclusion and exclusion revealed that gender, RV S’, and RV free wall strain were independent predictors of peak VO₂.

RV function, assessed as S’ and free wall strain, was independently related to EC, measured using CPX, in patients with HF and severe LV systolic dysfunction.

Abbreviations: CPX = cardiopulmonary exercise test, E’ = early diastolic myocardial velocity, E/E’ = ratio of early diastolic transmural velocity to early diastolic myocardial velocity, EC = exercise capacity, EF = ejection fraction, FAC = fractional area change, GLS = global longitudinal strain, HF = heart failure, LV = left ventricular, NT-proBNP = plasma N-terminal pro B-type natriuretic peptide, PASP = pulmonary artery systolic pressure, Peak VO₂ = oxygen uptake at peak exercise, RV = right ventricular, S’ = peak systolic myocardial velocity, TAPSE = tricuspid annular plane systolic excitation, VO₂-AT = oxygen uptake at anaerobic threshold.

Keywords: cardiopulmonary exercise testing, echocardiography, exercise capacity, heart failure, right ventricular dysfunction

1. Introduction
Decreased exercise capacity (EC) is an established predictor of cardiac and all-cause mortality in both the general population and patients with chronic heart failure (HF).[1,2] Cardiopulmonary exercise test (CPX) is an objective and quantitative method for measuring EC parameters. Despite the importance of CPX results, it is still performed rarely.[3] Left ventricular (LV) systolic function is a strong prognostic marker in HF, but previous studies failed to find a correlation between EC and ejection fraction (EF), an established LV systolic parameter.[4,5] In patients with HF with reduced EF, peak oxygen uptake was neither correlated with EF nor with global longitudinal strain (GLS). GLS is a novel and accurate systolic function parameter derived from speckle tracking echocardiography.[4] A wide spectrum of exercise ability and functional impairment is presented among patients with severe LV systolic dysfunction. We hypothesized that EC is more closely related to the right ventricular (RV) function than to the degree of LV dysfunction in these patients. The role of the
right ventricle in HF has been overlooked for many years. However, several recent studies performed in various populations of patients with HF have reported that poor outcomes are correlated with RV dysfunction, independent of the degree of LV dysfunction.\textsuperscript{[7–9]} Limited and contradictory data about the impact of RV function on EC in advanced HF with severe LV dysfunction have been published.\textsuperscript{[13,14]}

In this study, we aimed to investigate the relationship between EC and myocardial mechanics expressed as echocardiographic parameters, particularly RV geometry and function assessment, in patients with HF with reduced ejection fraction.

2. Methods
2.1. Study population and design
Consecutive patients with symptomatic HF of New York Heart Association (NYHA) classes II and III and severe LV systolic dysfunction (LV EF ≤ 35%) referred to our cardiology department for consideration of cardiac resynchronization therapy were screened between January 2013 and December 2015. All patients remained on optimal medical therapy with no further options for myocardial revascularization or other etiologic HF treatment. Patients with hemodynamic instability, severe organic valvular disease, chronic lung diseases, and inability to perform an exercise treadmill test were excluded. A total of 67 patients were enrolled in this observational study and were prospectively assessed. All patients were evaluated with echocardiography and CPX within 24-hour interval. Routine laboratory testing and measurement of plasma N-terminal pro B-type natriuretic peptide (NT-pro BNP) were performed.

The study met the requirements of the Declaration of Helsinki. The protocol was approved by the Postgraduate Medical School Ethics Committee. All participants provided their written informed consent.

2.2. Echocardiographic assessment
Echocardiographic examinations were performed with the Vivid E9 ultrasound machine (GE Healthcare, Horten, Norway). Echocardiograms were blinded to clinical, electrocardiographic, and angiographic parameters. All measurements were performed according to the recommendations of the American Society of Echocardiography and the guidelines for echocardiographic assessment of the right heart.\textsuperscript{[13,14]} LV EF was calculated according to the modified Simpson’s rule. dP/dt was calculated from mitral regurgitant curve obtained using continuous wave Doppler. Diastolic LV function was assessed in patients with sinus rhythm using an integrative approach based on recent recommendations by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.\textsuperscript{[15]} Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LV EF was used, based on mitral inflow velocities (E wave and A wave), E/E’ ratio, tricuspid regurgitation velocity, and left atrial maximum volume index. Mitral inflow velocities were assessed using spectral pulsed wave Doppler with the sample volume positioned at the tips of the mitral valve leaflets during a brief apnea. The E/E’ ratio was calculated from the transmitial E wave and mean lateral and septal segments E’ wave velocities derived from tissue Doppler. Peak velocity of tricuspid regurgitation jet was measured with continuous wave Doppler, obtained from multiple views. The left atrial maximum volume was calculated from the apical 4- and 2-chamber views using biplane area-length method. The left atrial maximum volume index was defined as left atrial maximum volume divided by the body surface area. Diastolic dysfunction was determined as grade 1 with impaired relaxation and normal filling pressure, grade 2 with increased left atrial pressure and grade 3 with increased left atrial pressure and restrictive filling pattern. Mitral regurgitation was graded as small, moderate, or severe (secondary) using an integrative approach based on the following quantitative parameters derived from Doppler examination: effective regurgitant orifice area, regurgitant volume, and supportive data (vena contracta measurements, pattern of pulmonary flow, and left atrial size). Examination of the right ventricle was performed from a modified apical 4-chamber view focused on the right ventricle. Measurements of fractional area change (FAC) of RV and tricuspid annular plane systolic excursion (TAPSE), and assessment of RV wall motion abnormalities were carried out. TAPSE was measured with M-mode echocardiography as the maximum displacement of the lateral tricuspid annulus. RV FAC was calculated as follows: RV (end diastolic area – end systolic area) × 100% divided by RV end diastolic area. Systolic pulmonary artery pressure (PASP) was estimated by calculating the systolic pressure gradient between the right ventricle and right atrium with the maximum velocity of the tricuspid regurgitant jet using the modified Bernoulli equation. Subsequently, estimated right atrial pressure based on the diameter of the inferior vena cava and its respiratory variations was then added to this gradient. TAPSE/PASP ratio was taken as a noninvasive index of RV to pulmonary circulation coupling.

Tissue Doppler was recorded during shallow respiration or end-expiratory apnea. Guided by a 2-dimensional (2D) 4-chamber view, a sample volume was placed 1 cm above the tricuspid annulus at the RV free wall. Peak systolic myocardial velocity (S’) and peak early (E’) and late diastolic velocities for the RV were obtained (Fig. 1). Guided by a 2D 4- and 2-chamber views, a sample volume was placed at basal segments septal, lateral, inferior and anterior LV wall, where S’ and E’ were obtained. The average of these 4 basal systolic velocities was used to calculate LV S’. The average of septal and lateral early diastolic velocities was used to calculate LV E’.

2D speckle tracking echocardiography was performed for LV and RV deformation analysis. The images were acquired with frame rates of 70 to 90 frames/s and stored for 3 cycles. These images were analyzed offline using computer software (Echopac 09; GE Healthcare, Horten, Norway). LV GLS was determined by 2D speckle tracking from apical 3-, 4- and 2-chamber views based on the American Society of Echocardiography’s 17-segment LV model. Three sampling points were manually placed on the endocardial border of 2 basal points of the mitral annulus and at the apex. The region of interest was automatically generated and manually edited for border tracing optimization. LV GLS was calculated as the arithmetical mean of regional strains.

An apical 4-chamber view focused on the right ventricle was used for RV deformation analysis. RV systolic longitudinal strain was evaluated by gray-scale imaging through the septum and RV free wall. RV free wall strain was calculated as the average of 3 regional strains comprising the lateral wall (Fig. 2A and B).

All measurements were performed on a minimum of 3 cardiac cycles for patients without atrial fibrillation and 6 cardiac cycles for patients with atrial fibrillation, and the mean values were recorded.
RV systolic dysfunction was defined as RV $S' < 9.5 \text{ cm/s}$ derived from tissue Doppler.\textsuperscript{[13]}

2.3. Exercise capacity

A symptom-limited treadmill CPX with a Schiller Cardiovit CS-200 (Schiller, Baar, Switzerland) and an Ergo Spiro adapter (Ganshorn, Niederlaufer, Germany) was performed by each patient at the same time of day (between 11 AM and 1 PM). The Naughton or modified Bruce protocol was used depending on the patient functional status. Cardiopulmonary exercise tests were performed once. All patients were carefully instructed to achieve maximal effort and all of them were familiar with 10-point Borg fatigue scale. Oxygen consumption, carbon dioxide production, and ventilation during exercise were analyzed breath by breath.

Oxygen uptake at peak exercise (peak VO\textsubscript{2}) and at anaerobic threshold (VO\textsubscript{2}-AT) was used as EC parameters. Weber’s classification was used to categorize patient EC based on peak VO\textsubscript{2}: class A ($> 20.0 \text{ mL/kg/min}$), class B ($16.0–20.0 \text{ mL/kg/min}$), class C ($10.0–15.9 \text{ mL/kg/min}$), and class D ($< 10.0 \text{ mL/kg/min}$).\textsuperscript{[16]} Maximal predicted oxygen uptake values were calculated according to the Wasserman/Hansen equations.\textsuperscript{[17]}

Anaerobic threshold was assessed using the V-slope method. Other analyzed exercise parameters were minute ventilation, ventilatory reserve at peak exercise, minute ventilation-carbon dioxide production slope, exercise duration, heart rate exercise acceleration, heart rate at peak exercise, and blood pressure at peak exercise. All CPX were performed according to the American Thoracic Society/American College of Chest Physicians Guidelines.\textsuperscript{[18]}

2.4. Statistical analysis

Categorical variables are presented as frequency and percentage. Continuous variables are presented as mean ± standard deviation (SD) or as median as appropriate. Continuous variables were compared with the Student’s $t$-test or the Mann–Whitney $U$ test for nonparametric data. A $P$-value < .05 was considered statistically significant.

Prognosis of EC was tested in multivariate linear regression analysis model. Multivariate model was developed with stepwise inclusion and exclusion at a significance level of 0.1. The fit of the model and the number of parameters used were evaluated according to Akaike’s Information Criterion. Age, sex, atrial fibrillation, RV function parameters (RV $S'$, TAPSE, RV FAC, RV free wall strain, and TAPSE/PASP), and LV function parameters (EF, end systolic volume, degree of mitral regurgitation, and $E/E'$ ratio) were tested. The analyses were carried out using the STATISTICA software (version 7; StatSoft, Inc., Poland) and R Core Team (2018) software (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

3. Results

Baseline demographic and clinical characteristics of patients are presented in Table 1. The mean age of the study population was 67 ± 9 years, and the majority of the patients were male (81%). Patients were distributed between NYHA classes II (40%) and III (60%). Ischemic etiology of HF was found in 75% of the patients. All patients received optimal medical treatment. CPX was performed safely in all patients. All tests were performed until patient exhaustion or exertion > 8 points in the modified Borg scale. None of the patients had exercise limiting factors other than dyspnea and/or fatigue. Pulmonary limitations of exercise were not noted, and the mean respiratory exchange ratio in the entire group was 1.05 ± 0.1.

The mean peak VO\textsubscript{2} for the entire group was 13.9 ± 5.0 mL/kg/min. Patients were stratified into 4 groups according to their EC defined by Weber’s classification. We observed a wide range of peak VO\textsubscript{2} with minimum at 4.3 mL/kg/min and maximum at 27.8 mL/kg/min. The exercise performance of patients was distributed to all classes according to Weber’s classification: class A in 10 patients (15%), class B in 7 patients (10%), class C in 37 patients (55%), and class D in 13 patients (19%).
NT-pro BNP was elevated in all patients, with the highest level in the class D group \((P = .045)\). The groups did not differ in other demographic and clinical baseline characteristic parameters.

Echocardiographic parameters are presented in Table 2. In the total study population, LV systolic function was severely reduced. No significant differences were found in EF, \(dP/dt\), LV diameter, LV \(S'\), LV GLS and degree of mitral regurgitation between groups according to EC classes. Grade of LV diastolic dysfunction was assessed in 59 patients with sinus rhythm. All of them presented diastolic dysfunction—grade 1 in 28 (48%) patients, grade 2 in 13 (19%), and grade 3 in 18 (27%) patients but no significant differences were revealed regarding grading in relation to functional classes. Significant differences were found in RV systolic and diastolic functions expressed as RV \(S'\) \((P < .001)\), TAPSE \((P = .003)\), and RV \(E'\) \((P = .003)\) between groups with different levels of EC. Differences in RV FAC, RV 2D strain, and RV free wall strain did not reach statistical significance. Systolic pulmonary artery pressure was higher \((P = .029)\) and TAPSE/PASP ratio as a noninvasive index of RV to pulmonary circulation coupling was lower \((P = .006)\) in patients with functional decline. No differences were found for RV diameters. A significant correlation was found between RV \(S'\) and the EC parameters: peak VO\(_2\) \((r = 0.52, P < .001)\) and percent of maximal predicted values \((r = 0.44, P < .001)\). We compared CPX

![Figure 2. Example of RV 2D strain assessment. (A) 6—segments model of RV free wall and interventricular septum. (B) 3—segments model of RV free wall.](image)
parameters between 34 patients with normal RV systolic function and 33 patients with RV systolic dysfunction (Table 3).

We found that the EC parameters assessed as peak VO$_2$ and VO$_2$-AT were significantly lower in patients with RV systolic dysfunction. Peak VO$_2$ expressed as a percent of maximal predicted values was also lower in this group. Exercise time was shorter and peak systolic blood pressure was lower in the RV systolic dysfunction group. No differences were found in percent of predicted maximal HR achieved at peak exercise, which proves the absence of differences in chronotropic response between groups. Investigated groups did not differ in ventilatory response to exercise assessed in VE/VCO$_2$ slope. In all patients, no pulmonary limitations of exercise were noted. Ventilatory reserve at peak exercise was preserved in both groups.

Logistic multivariate linear regression analysis with stepwise inclusion and exclusion revealed that gender, RV S', and RV free wall strain were independent predictors of peak VO$_2$. Inclusion E/E' ratio as an LV filling parameter improved the model but showed no statistical significance (P = .069) (Table 4).

4. Discussion

In this study, consecutive patients with HF with severely reduced EF were investigated. Despite advanced LV systolic dysfunction, we found a wide spectrum of EC. In addition, gender, RV S', and RV free wall strain were independent predictors of peak VO$_2$. As a result, the end model of EC prognosis enclosed echocardiographic parameters of RV long axis function and LV filling pressure.

We found that the presence of RV systolic dysfunction in patients with LV failure was independently related to a lower EC both expressed in absolute values and as a percent of maximal predicted values when compared with patients without RV systolic dysfunction. Exercise testing in chronic HF can provide information about patient functional capacity, which is an important factor to assess functional class, evaluate therapy, and estimate risk, as well as to reach therapeutic decisions with regard to time of cardiac transplantation. In patients with chronic HF, exercise intolerance...
is a strong predictor of survival and HF progression.\textsuperscript{[16,19]} According to HF guidelines and scientific statements, CPX is recommended to assess the EC of a population of patients with HF.\textsuperscript{[3,13–22]}

The origin of RV systolic dysfunction in patients with chronic HF can be primary, caused by ischemia or cardiomyopathy, or secondary to LV dysfunction as a consequence of elevated pulmonary vascular resistance. As the right ventricle is functionally coupled to the pulmonary circulation, the importance of arterio-ventricular interaction and arterial load on cardiac performance is recognized, particularly in patients with pulmonary hypertension.\textsuperscript{[23]} Although patients with primary pulmonary hypertension were not represented in our study group, higher systolic pulmonary artery pressure was found among patients with exercise intolerance. Elevated LV filling pressure and mitral regurgitation can aggravate RV afterload, and therefore impaired RV-arterial coupling can be observed. Since RV dysfunction was rather secondary to LV impairment in our study group, its function had to be considered in the interaction with LV function. Nevertheless, RV dysfunction could also affect LV function due to ventricular interdependence. A lower LV preload could be caused by lower RV contractility with lower RV stroke volume. An enlarged right ventricle could compress the LV and disturb relaxation and filling of the chamber. These abnormalities could be present at rest and aggravate during exercise or appear only during exercise.

The role of RV in determining EC is being vigorously investigated. The detailed assessment of RV dysfunction was a particular feature of our study. Assessment of RV longitudinal systolic contractility could be used as a parameter of RV function because of the predominance of RV longitudinal fibers and their role in stroke volume generation.\textsuperscript{[124]} We used RV S′ as the main indicator of RV function in our analysis of CPX results, which was in accordance with current recommendations.\textsuperscript{[11] This simple and reproducible method to assess RV longitudinal function could be used in clinical settings because it is less time consuming and widely available in many echocardiographic laboratories. RV free wall strain derived from speckle tracking echocardiography was included in multivariate analysis as a novel, angle-independent, quantitative parameter of deformation. This parameter is free of LV tethering influence.

Our recent study has demonstrated that RV dysfunction in patients without LV failure could diminish EC.\textsuperscript{[23]} However, previous data about the influence of RV systolic dysfunction on EC in patients with HF were ambiguous. The positive correlation between RV function and exercise in patients with chronic HF caused by coronary artery disease or idiopathic dilated cardiomyopathy. They found a positive correlation between RV ejection fraction and peak VO₂. Furthermore, Di Salvo et al.\textsuperscript{[24]} demonstrated a positive correlation among RV function, EC, and prognosis in cardiac transplantation candidates.

In contrast to our results, Gadsboll et al.\textsuperscript{[27]} found no correlation between maximal exercise parameters and RV systolic function, assessed as ejection fraction in radionuclide ventriculography. Although their patients showed a wide range of LV function and size, more than half of the patients had

| Table 2 |
| --- |
| **Echocardiographic measurements in patients with different levels of exercise capacity.** |

| Variables | All patients n = 67 | A n = 10 | B n = 7 | C n = 37 | D n = 13 | P-value |
| --- | --- | --- | --- | --- | --- | --- |
| RV outflow diameter, cm | 3.2 ± 0.6 | 3.0 ± 0.5 | 3.1 ± 0.5 | 3.1 ± 0.5 | 3.4 ± 0.7 | .29 |
| RV inflow diameter, cm | 4.0 ± 0.7 | 4.0 ± 0.5 | 3.7 ± 0.4 | 4.0 ± 0.7 | 4.3 ± 0.7 | .25 |
| RV S′, cm/s | 10 ± 3 | 14 ± 2 | 10 ± 3 | 9 ± 2 | 10 ± 2 | <.001 |
| RV E′, cm/s | 8 ± 4 | 11 ± 3 | 7 ± 3 | 7 ± 3 | 9 ± 5 | .003 |
| TAPSE, mm | 24 ± 5 | 20 ± 5 | 20 ± 5 | 18 ± 4 | 19 ± 4 | .003 |
| RV fraction area change, (%) | 38 ± 13 | 42 ± 11 | 40 ± 11 | 40 ± 13 | 32 ± 14 | .17 |
| RV 2D strain (%) | −13 ± 6 | −17 ± 5 | −15 ± 5 | −12 ± 4 | −9 ± 7 | .08 |
| RV free wall 2D strain (%) | −16 ± 8 | −23 ± 7 | −18 ± 8 | −16 ± 6 | −13 ± 10 | .13 |
| TAPSE/PASP | 0.7 ± 0.4 | 1.0 ± 0.4 | 0.9 ± 0.3 | 0.6 ± 0.3 | 0.5 ± 0.3 | .006 |
| LV end diastolic volume, mL | 206 ± 39 | 218 ± 39 | 185 ± 39 | 210 ± 68 | 205 ± 66 | .68 |
| LV end systolic volume, mL | 156 ± 58 | 156 ± 55 | 135 ± 48 | 162 ± 62 | 154 ± 49 | .68 |
| d/dt, mm Hg/s | 540 ± 103 | 619 ± 155 | 533 ± 103 | 540 ± 144 | 522 ± 130 | .37 |
| LV S′, cm/s | 4 ± 1 | 5 ± 2 | 5 ± 2 | 4 ± 1 | 4 ± 1 | .14 |
| LV GLS (%) | −7 ± 3 | −8 ± 5 | −9 ± 3 | −7 ± 2 | −6 ± 5 | .10 |
| Mitral regurgitation, n (%) | .08 |
| Mild | 35 (52) | 6 (60) | 5 (71) | 20 (64) | 4 (31) | |
| Moderate | 21 (31) | 2 (20) | 2 (29) | 14 (36) | 3 (23) | |
| Severe | 9 (13) | 1 (10) | 0 (0) | 3 (8) | 5 (18) | |
| LV E′ | 16 ± 8 ± 7.4 | 15 ± 5 ± 5.8 | 15.7 ± 7.8 | 17.3 ± 8.0 | 17.5 ± 7.2 | .77 |
| PASP, mm Hg | 35 ± 18 | 29 ± 14 | 23 ± 6 | 35 ± 17 | 47 ± 21 | .029 |
| LV diastolic dysfunction, n (%) | .19 |
| Grade 1 | 28 (42) | 6 (21) | 5 (18) | 14 (50) | 3 (11) | |
| Grade 2 | 13 (19) | 1 (8) | 1 (8) | 10 (77) | 1 (8) | |
| Grade 3 | 18 (27) | 3 (17) | 1 (6) | 8 (44) | 6 (33) | |

Values are expressed as mean±SD and (%) and range or number. $E′/E =$ ratio of early diastolic transmitral velocity to peak early diastolic myocardial velocity, $S′ =$ early diastolic myocardial velocity, GLS = global longitudinal strain, LV = left ventricular, PASP = systolic pulmonary artery pressure, RV = right ventricular, $S =$ systolic myocardial velocity, TAPSE = tricuspid annular plane systolic excursion. LV diastolic dysfunction assessment was done for patients in sinus rhythm.
Table 3
Cardiopulmonary exercise test parameters in patients with and without right ventricular dysfunction.

| Variables | All patients n = 67 | Right ventricular dysfunction |
|-----------|---------------------|-------------------------------|
|           | No n = 34 | Yes n = 33 | P-value |
| Exercise time, min | 5.8 ± 3.7 | 7.6 ± 4.3 | 4.3 ± 2.5 | .003 |
| Heart rate at rest, beats/min | 77 ± 14 | 74 ± 13 | 80 ± 14 | .21 |
| Heart rate at peak exercise, beats/min | 106 ± 19 | 109 ± 18 | 13 ± 18 | .48 |
| Heart rate at peak exercise/maximal predicted (>100%) (%) | 77 ± 15 | 78 ± 12 | 77 ± 15 | .72 |
| Systolic blood pressure at peak exercise, mm Hg | 136 ± 24 | 144 ± 26 | 128 ± 21 | .010 |
| Diastolic blood pressure at peak exercise, mm Hg | 72 ± 9 | 71 ± 11 | 72 ± 8 | .91 |
| Respiratory exchange ratio at peak exercise | 1.05 ± 0.10 | 1.08 ± 0.09 | 1.02 ± 0.10 | .13 |
| Oxygen uptake at peak exercise, mL/kg/min | 13.9 ± 5.0 | 18.1 ± 6.1 | 12.0 ± 2.9 | .008 |
| Oxygen uptake at peak exercise/maximal predicted, mL/kg/min (%) | 54 ± 22 | 63 ± 24 | 47 ± 18 | .009 |
| Oxygen uptake at anaerobic threshold, mL/kg/min | 12.4 ± 3.9 | 13.9 ± 4.2 | 11.0 ± 3.2 | .006 |
| VE/VCO2 slope | 31.1 ± 7.1 | 28.8 ± 7.6 | 33.2 ± 6.4 | .17 |
| Breath reserve at peak exercise (%) | 43 ± 19 | 38 ± 18 | 47 ± 18 | .07 |

Values are expressed as mean ± SD and (%) and range or number.

4.2. Limitations
This study has several limitations. First, our study group was relatively small. The examined population was homogenous with similar symptom score, disease stage, and severe LV dysfunction. Therefore, the obtained findings should be confirmed in larger populations. Second, the results could not be extrapolated to patients with the most severe HF and classified as NYHA class IV because we excluded patients with inability to perform the exercise treadmill test. Third, CPX was performed only once for each patient and accidental lower exercise performance might happen. However, we made every effort to properly instruct the patient and perform CPX in the stable conditions. At last we did not relate our findings to clinical outcomes. Follow-up studies are required to analyze the relationship among echocardiographic parameters, exercise intolerance, and clinical events.

5. Conclusions
We have demonstrated that RV function, assessed as $S'$ and free wall strain, was independently related to EC, measured using CPX in patients with HF and severe LV systolic dysfunction.

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