Preservation of Cardiac Reserve and Cardiorespiratory Fitness in Patients With Acute De Novo Versus Acute on Chronic Heart Failure With Reduced Ejection Fraction

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There is limited understanding on the potential differences in the pathophysiology between de novo heart failure with reduced ejection fraction (HFrEF) and acute on chronic HFrEF. The aim of this study was to assess differences in cardiorespiratory fitness (CRF) parameters between de novo heart failure and acute on chronic HFrEF using cardiopulmonary exercise testing (CPX). We retrospectively analyzed CPX data measured within 2 weeks of discharge following acute hospitalization for HFrEF. Data are reported as median and interquartile range or frequency and percentage (%). We included 102 patients: 32 (31%) women, 81 (79%) black, 57 (51 to 64) years of age, BMI of 34 (29 to 39) Kg/m^2. Of these, 26 (25%) had de novo HFrEF and 76 (75%) had acute on chronic HFrEF. When compared with acute on chronic, patients with de novo HFrEF had a significantly higher peak oxygen consumption (VO_2) (16.5 [12.2 to 19.4] vs 12.8 [10.1 to 15.3] ml·kg^{-1}·min^{-1}, p <0.001), %-predicted peak VO_2 (58% [51 to 75] vs 49% [42 to 59]) p = 0.012), peak heart rate (134 [117 to 147] vs 117 [104 to 136] beats/min, p = 0.004), peak oxygen pulse (12.2 [10.5 to 15.5] vs 9.9 [8.0 to 13.1] ml/beat, p = 0.022) and circulatory power (2,823 [1,973 to 3,299] vs 1,902 [1,372 to 2,512] mm Hg·ml·kg^{-1}·min^{-1}, p = 0.002). No significant difference in resting left ventricular ejection fraction was found between groups. In conclusion, patients with de novo HFrEF have better CRF parameters than those with acute on chronic HFrEF. These differences are not explained by resting left ventricular systolic function but may be related to greater preservation in cardiac reserve during exercise in de novo HFrEF patients. **(Am J Cardiol 2021;00:1−7)**

Acute heart failure (HF) is a life-threatening condition associated with significant morbidity, mortality, and economic burden.[1] Patients who experience an acute HF episode without known underlying heart disease are referred to as having *de novo* HF, distinct from patients with an acute deterioration of a known pre-existing cardiomyopathy referred as having *acute on chronic* HF.[2] Among patients hospitalized for acute HF and reduced ejection fraction (HFrEF), approximately one third of patients have *de novo* HF whereas the others have acute on chronic HFrEF.[3−5] Compared with patients with acute on chronic HFrEF, patients with *de novo* HFrEF are younger, have fewer comorbidities, and a better prognosis.[3,6−8] The reason and pathophysiologic mechanism(s) for such differences are not entirely clear, and not fully explained by differences in demographic or comorbid conditions.[6] Cardiopulmonary exercise testing (CPX) is the gold-standard approach to assessing CRF in patients with HF and appreciates

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limitations that may only be evident during exertion.[9−13] In this context, the aim of the current study was to compare CRF using CPX in patients recently hospitalized for *de novo* versus acute on chronic HFrEF.

Methods

We performed a retrospective review of data from patients who underwent a symptom limited CPX and resting transthoracic echocardiography within 2 weeks of discharge following hospitalization for acute HFrEF at Virginia Commonwealth University Health System (VCUHS) from 2014 to 2020. All patients met criteria for hospitalization for acute decompensated HFrEF were included in the current study. Acute decompensated HFrEF was established as the presentation at admission of dyspnea, respiratory distress, or tachypnea at rest or with minimal exertion, and evidence of elevated cardiac filling pressures or pulmonary congestion (defined as the presence of pulmonary congestion/edema at physical exam or chest radiography, plasma brain natriuretic peptide (BNP) levels ≥200 pg/ml or N-terminal pro-BNP (NTproBNP) ≥600 pg/ml, invasive measurement of left ventricular end-diastolic pressure >18 mm Hg or pulmonary artery occluding pressure >16 mm Hg).[14] All patients had prior documentation of a left ventricular ejection fraction (LVEF) ≤40%. Patients with a primary diagnosis for admission different from decompensated HFrEF (including acute coronary syndromes, hypertensive urgency/emergency, tachy- or bradyarrhythmias) were excluded.

Patients were considered: (1) de novo HFrEF if they did not have any prior history of cardiac disease, HF and/or HF hospitalization; or (2) as acute on chronic HFrEF if they had a history of pre-existing cardiomyopathy, HF and/or HF hospitalization at any time.

Patients underwent symptom limited CPX according to American Heart Association guidelines by a clinical exercise physiologist under physician supervision with a metabolic cart connected to a treadmill using a conservative ramping protocol as previously described.[15,16] Patients with a peak respiratory exchange ratio (RER) <1.00 were excluded. Heart rate (HR), blood pressure, and electrocardiography were recorded continuously throughout CPX. Expired gases were collected on a breath-by-breath basis with peak oxygen consumption (VO_2), expressed in $ml{\cdot}kg^{-1}{\cdot}min^{-1}$, defined as the highest 10-second average value during the last 30 seconds of exercise. Percent-predicted peak VO_2 was calculated using the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) equation.[17] Circulatory power, an expression of cardiac reserve, was calculated as product of peak VO_2 and peak systolic blood pressure (BP). Minute ventilation (VE) and carbon dioxide production (VCO_2) were acquired in 10-second interval averages throughout the entire exercise period to calculate the VE/VCO_2 slope via least squares linear regression (y = mx + b, m = slope). The oxygen uptake efficiency slope (OUES) was calculated using the formula VO_2 (l/min) = m ($\log_{10}$ ventilation [VE]) + b, where m=OUES. Peak oxygen (O_2) pulse was calculated by dividing absolute peak VO_2 by the maximum HR during exercise and expressed in ml/beat. Peak VO_2 and O_2 pulse were also corrected by fat-free mass (FFM); $ml/Kg_{FFM}/min$ and $ml/beat/Kg_{FFM}$, respectively).[18−20]

All patients underwent standard transthoracic 2-dimensional Doppler echocardiography using apical 4- and 2-chamber views prior to CPX. LVEF was measured using the modified Simpson method. LV diastolic function was evaluated using trans-mitral diastolic flow tracings assessed with pulsed-wave Doppler from an apical 4-chamber view with early (E)-wave and late (A)-wave velocity measurements, pulsed-wave tissue Doppler early diastolic mitral annular velocity (e') averaged between the lateral and septal annulus, and calculation of the average *E/e'* ratio.[21]

Complete blood count, metabolic panel, and plasma levels of C-reactive protein (CRP) and NTproBNP were analyzed from blood samples collected on the same day immediately prior to CPX.

Single−frequency bioelectrical impedance analysis (RJL System, Inc, Clinton Township, MI) was used in a subgroup of 46 patients to explore changes in body composition between de novo versus acute on chronic HFrEF patients. The patients were placed in a supine position with the superior limbs abducted at 30° and inferior limbs at 45°, and 4 cutaneous electrodes (2 on the foot and 2 on the homolateral hand) were applied. Fat mass (FM), FFM, lean mass (LM), and edema index (ratio of extracellular water by total body water) were calculated.[22]

Descriptive statistics were used to summarize the participants' baseline and clinical characteristics by the de novo HFrEF or acute on chronic HFrEF status. Data are presented as frequency (percentage) or median [interquartile range] for categorical or continuous variables. Categorical data were evaluated using the Chi-Square test or Fisher's exact test as appropriate. Continuous variables were compared using Mann−Whitney *U* test or Spearman's rank test for correlations. All analyses were completed using SPSS, version 24.0 (SPSS; Chicago, IL) with significance set at $\alpha = 0.05$.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Virginia Commonwealth University Institutional Review Board (RAMS-IRB). Informed consent was obtained from all patients.

Results

We studied 102 patients, 32 (31%) females, 81 (79%) black, 57 [51 to 64] years of age with a BMI of 34 (29 to 39) Kg/m^2. The LVEF was 30% (23 to 36) and the peak VO_2 was 13.3 (10.4 to 16.6) $ml{\cdot}kg^{-1}{\cdot}min^{-1}$, corresponding to 51 (44 to 61) % of predicted.

Of these patients, 26 (25%) had de novo HFrEF and 76 (75%) had acute on chronic HFrEF. Baseline characteristics of the 2 groups are summarized in Table 1. When compared with patients with acute on chronic HFrEF, patients with de novo HFrEF were significantly younger (50 [42 to 57] vs 60 [54 to 67] years p <0.01) and had a significantly lower prevalence of coronary artery disease (CAD) (4 [15%] vs 31 [41%], p = 0.014) and atrial fibrillation (0 [0%] vs 24 [32%], p <0.001).

Table 1
Baseline characteristics between de novo versus acute on chronic heart failure with reduced ejection fraction

	De novo (n=26)	Acute on chronic (n=76)	p value
Variables			
Women	9 (35%)	23 (30%)	0.680
Age (years)	50 [42-57]	59 [53-67]	**<0.001**
White	5 (19.2%)	16 (21.1%)	0.843
Black	21 (80.8%)	60 (78.9%)	0.843
Body mass index (kg/m^2)	35.1 [29.4-38.7]	32.0 [28.5-39.5]	0.390
Hypertension	23 (88%)	67 (88%)	1
Diabetes mellitus	10 (38%)	37 (49%)	0.367
Dyslipidemia[†]	14 (54%)	48 (63%)	0.401
Coronary artery disease	4 (15%)	31 (41%)	**0.030**
Atrial fibrillation	0 (0%)	24 (32%)	**<0.001**
Current smoker	12 (46%)	26 (34%)	0.277
Laboratory			
Hemoglobin (g/dl)	14 [12.2-15.7]	13.2 [11.7-14.3]	0.102
Hematocrit (%)	43.5 [38.6-47.6]	41.1 [37.9-44.5]	0.089
White blood cell (10^9/l)	6.2 [5.5-7.7]	6.4 [5.1-7.6]	0.817
Total bilirubin (mg/dl)	0.55 [0.40-0.70]	0.70 [0.50-1.00]	**0.017**
Creatinine (mg/dl)	1.1 [0.89-1.4]	1.3 [1.1-1.7]	**0.017**
NTproBNP (pg/ml)	681 [259-1342]	1307 [691-3083]	**0.005**
high sensitivity-C-Reactive-Protein (mg/l)	5.11 [2.79-9.04]	5.23 [2.47-11.57]	0.925
Echocardiography			
LV ejection fraction (%)	30 [24-37]	30 [23-36]	0.654
LV end-diastolic volume (ml)	177 [147-215]	182 [145.5-225.6]	0.659
LV end-systolic volume (ml)	123 [86-146]	133 [98-170]	0.361
Tricuspid annular plane systolic excursion (cm)	1.9 [1.6-2.2]	1.8 [1.5-2.1]	0.128
E/e' ratio	16.2 [10.6-18.3]	17.9 [13.2-24.4]	**0.029**
e' (cm/s)	6 [5.01-7.64]	5.85 [4.28-7.05]	0.310
Cardiovascular Medications			
ACEi/ARB	23 (88%)	65 (85%)	1
Beta-blockers	24 (92%)	71 (93%)	1
Beta-blocker dose (mg)[*]	50 [25-100]	50 [25-100]	0.332
Mineralocorticoid receptor antagonist	15 (58%)	25 (33%)	**0.025**
SGLT2i	2 (8%)	4 (5%)	0.621
Loop diuretic	23 (88%)	70 (92%)	0.690
Nitrates	6 (23%)	20 (26%)	0.744
Hydralazine	5 (19%)	22 (29%)	0.332

ACEi = angiotensin-converting enzyme inhibitors; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; NTproBNP = N-terminal-pro hormone-B-type natriuretic peptide; SGLT2i = sodium-glucose co-transporter-2 inhibitors.

Data are expressed as n (%) or median [interquartile range].

[*] Beta-blocker dose (mg) expressed as metoprolol equivalent dose.

[†#] Dyslipidemia was defined as elevated total or low-density lipoprotein cholesterol levels (total cholesterol above 200 mg/dL or low-density lipoprotein cholesterol levels above 130 mg/dl) or use of cholesterol-lowering drugs.

There were no statistically significant differences between the groups in terms of pharmacological treatment, except for a higher use of mineralocorticoid receptor antagonists in patients with de novo HFrEF. Of note, there was no difference regarding the dose of beta-adrenergic receptor blockers, expressed as metoprolol equivalent dose, between the 2 groups (Table 1).

Patients with de novo HFrEF had significantly lower NTproBNP values (681 [259 to 1,342] vs 1307 [691 to 3,083] pg/ml, p = 0.005) and creatinine levels (1.1 [0.9 to 1.4] vs 1.3 [1.1 to 1.7] mg/dl, p = 0.017). No significant differences were noted comparing the 2 groups in terms of hemoglobin, hematocrit, or CRP values (Table 1).

Patients with de novo HFrEF had a significantly lower E/e' ratio (16.2 [10.6 to 18.3] vs 17.9 [13.2 to 24.4], p = 0.029) but without any significant differences in LVEF or left ventricle end-diastolic and end-systolic volumes (Figure 1, Table 1).

There were no significant differences between the 2 groups in the resting blood pressure, HR, or peak RER. The peak HR with exercise was significantly higher in de novo versus chronic HFrEF patients (134 [117 to 147] vs 117 [104 to 136] beats/min, p = 0.004), whereas peak systolic and diastolic blood pressure was not significantly different.

When compared with patients with acute on chronic HFrEF, patients with de novo HFrEF had a significantly higher peak VO_2 (16.5 [12.2 to 19.4] vs 12.8 [10.1 to 15.3] ml·kg^{-1}·min^{-1}, p = 0.001), and peak VO_2 expressed as percent-predicted according to the FRIEND equation (58% [41 to 75] vs 49% [42 to 59], p = 0.024) (Figure 1, Table 2). Patients with de novo HFrEF also had a significantly higher peak O_2 pulse (12.2 [10.5 to 15.5] vs 9.9 [8.0 to 13.1] ml/

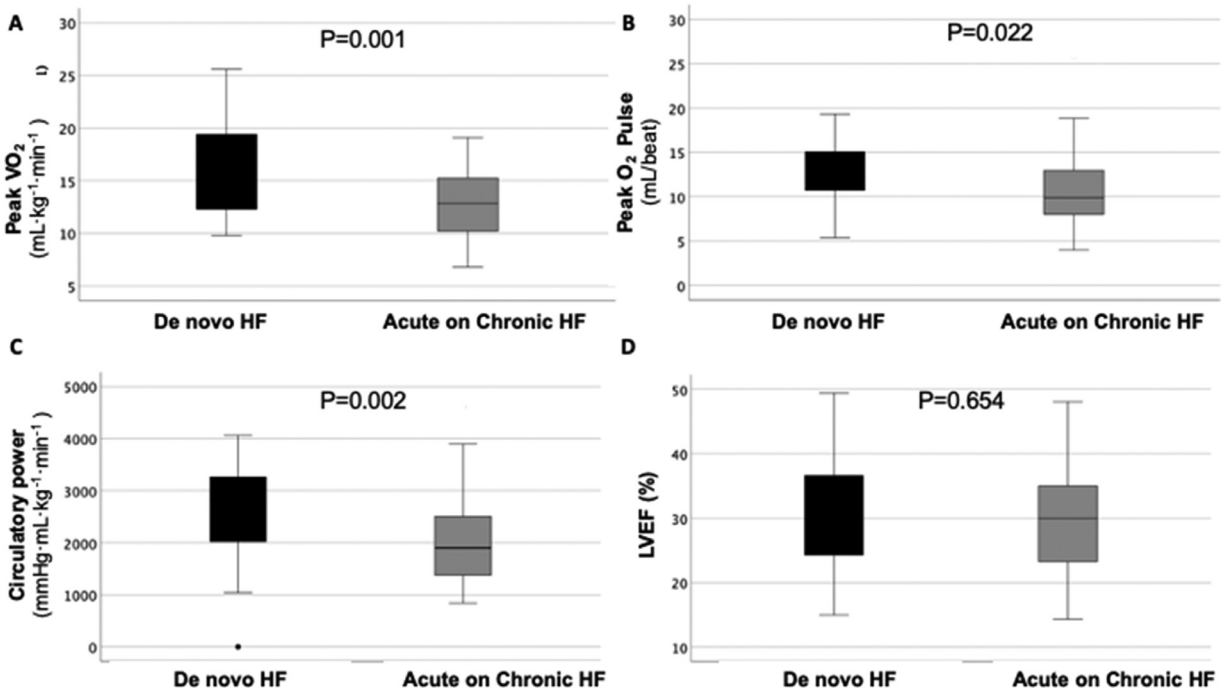

Figure 1. Differences between *de novo* and acute on chronic heart failure with reduced ejection fraction.
Legend: Box-Whisker plot of peak VO_2 (*Panel A*), peak oxygen pulse (*B*), circulatory power (*C*), and left-ventricular ejection fraction (*D*) between *de novo* versus acute on chronic heart failure with reduced ejection fraction. HF = heart failure; LVEF = left-ventricular ejection fraction; VO_2 = oxygen consumption.

beat, p = 0.022) and circulatory power (2,823 [1,973 to 3,299] vs 1,902 [1,372 to 2,512] mm Hg·ml·kg^{-1}·min^{-1}, p = 0.002) compared with acute on chronic HFrEF. Moreover, patients with de novo HFrEF had significantly longer exercise times (9.0 [6.0 to 11.2] vs 6.4 [4.4 to 8.3] minutes, p = 0.002) compared with those patients with acute on chronic HFrEF (Table 2). A significant correlation was observed between peak HR and peak VO_2 (R = +0.320, p <0.001), and between ΔHR (difference between peak HR minus resting HR) and peak VO_2 (R = +0.348, p < 0.001). There was no correlation between the dose of beta blockers and peak VO_2 (R = +0.006, p = 0.953).

Body composition was assessed in 46 (45%) individuals. There were no differences in fat mass, fat-free mass, fat mass index, fat-free mass index, or total body water between the 2 groups (all p >0.05) (Table 3).

Discussion

Patients with acute HFrEF represent a heterogeneous group. Approximately one-fourth of patients with a recent hospitalization for acute HFrEF present de novo, without a prior diagnosis of HF, whereas the remaining three-fourths present with acute on chronic HF. Our results are in line

Table 2
Cardiopulmonary exercise test results between de novo and acute on chronic heart failure with reduced ejection fraction

	De novo (n=26)	Acute on chronic (n=76)	p value
Variables			
Peak VO_2 (mL·kg^{-1}·min^{-1})	16.5 [12.2-19.4]	12.8 [10.1-15.3]	**0.001**
%-Predicted VO_2 (%)	58 [50-75]	49 [41-59]	**0.024**
VE/VCO_2 slope	33 [28.3-37.7]	34.5 [31.2-40.4]	0.147
Oxygen uptake efficiency slope	2.01 [1.49-2.43]	1.43 [1.17-1.89]	**0.002**
Circulatory Power (mm Hg·ml·kg^{-1}·min^{-1})	2823 [1973-3299]	1902 [1372-2512]	**0.002**
Peak O_2 pulse (ml/beat)	12.2 [10.5 -15.5]	9.9 [8.0-13.1]	**0.022**
Peak respiratory exchange ratio	1.11 [1.04-1.17]	1.11 [1.05-1.18]	0.461
Exercise time (min)	9.0 [6.0-11.0]	6.4 [4.4-8.3]	**0.002**
Rest heart rate (beats/min)	81 [74-97]	79 [67-89]	0.131
Maximal heart rate (beats/min)	134 [117-147]	117 [104-136]	**0.004**
Rest systolic blood pressure (mm Hg)	113 [104-134]	118 [105-130]	0.887
Maximal systolic blood pressure (mm Hg)	166 [144-182]	144 [124-172]	0.070
Rest diastolic blood pressure (mm Hg)	76 [66-85]	74 [65-81]	0.557
Maximal diastolic blood pressure (mm Hg)	80 [73-91]	77 [64-84]	0.095

O2 = oxygen; VE/VCO_2 = ventilation/carbon dioxide production; VO_2 = oxygen consumption.
Data are expressed as median [interquartile range].

Table 3
Body composition between de novo versus acute on chronic heart failure with reduced ejection fraction

	De novo (n=12)	Acute on chronic (n=34)	p value
Fat mass (kg)	38 [30.5-48]	34 [21.9-44.6]	0.260
Fat-free mass (kg)	60 [49.3-72.3]	61.7 [51.3-73.5]	0.617
Lean mass (kg)	16.3 [12.9-18.9]	15.8 [13.1-19.4]	0.698
Fat mass index (kg/m^2)	12.4 [9.2-18.4]	11.8 [7.9-14.6]	0.582
Fat-free mass index (kg/m^2)	20.2 [17.4-22]	22.1 [18.9-24.4]	0.074
Fat mass (% total body weight)	35.7 [32-48.7]	34 [26-41]	0.250
Fat-free mass (% total body weight)	64.3 [51.3-67.9]	65.9 [51.3-73.5]	0.250
Fat-free mass/Fat mass ratio	1.80 [1.05-2.12]	1.93 [1.40-2.84]	0.240
Lean mass/Fat mass ratio	0.46 [0.27-0.56]	0.52 [0.35-0.80]	0.271
Skeletal muscle mass (% total body weight)	30.3 [22.4-35.3]	29.7 [21.8-33]	0.635
Total body water (% total weight)	47.7 [38-50]	46 [38.8-54.5]	0.276
Intracellular water (% total body water)	55.3 [49.7-57.5]	54.2 [48.6-56.5]	0.484
Extracellular water (% total body water)	43.7 [42.2-50.2]	45.5 [43.4-51.4]	0.460
Peak VO_2 (ml/Kg_{FFM}/min)	28.5 [22.7-32.8]	18.1 [15.2-21.1]	**<0.001**
Peak O_2 pulse (ml/beat/Kg_{FFM})	0.21 [0.19-0.23]	0.16 [0.13-0.18]	**<0.001**

FFM = fat free mass; O_2 = oxygen; VO_2 = oxygen consumption.
Data are expressed as median [interquartile range].

with a recent large-scale study including 2,328 patients hospitalized with HF, with a diagnosis of either de novo (n = 721, 31%) or acute on chronic HF (n = 1,607, 69%), whereas those with acute on chronic HF were older, and had a higher prevalence of comorbidities (e.g., CAD, hypertension, chronic lung disease, cerebrovascular disease). Echocardiography data were available for two-thirds of patients with acute on chronic HF having a lower LVEF. Of note, patients with acute on chronic HF had higher mortality rates at both 1- and 10-years of follow-up compared with de novo HF patients, which persisted following adjustment for age, co-morbidities, and established risk factors for HF, suggesting that other features inherent to this group of patients underlie the increased mortality observed.[6]

We herein confirm that patients with de novo HFrEF are younger (by approximately 10 years) and have significantly less cardiac comorbidities than those with acute on chronic HFrEF. Despite these differences in clinical characteristics, we failed to find any differences in cardiac systolic function (i.e., LVEF) between the 2 groups, and differences in diastolic function were rather minimal. We found, however, that acute de novo HFrEF patients have significantly better CRF compared with those with acute on chronic HFrEF. Peak VO_2 is a primary measure of CRF and an independent predictor of cardiac and all-cause mortality.[23] In patients with systolic HF who complete a maximal exercise test, as in this study, peak VO_2 is largely a measure of cardiac output with exercise and hence of cardiac reserve.[24,25] Circulatory power, another measure that integrates peak VO_2 with blood pressure has been shown to better reflect cardiac function and improve prognostic assessment.[11] The significantly lower values for peak VO_2 and circulatory power in patients with acute on chronic HFrEF may reflect a decline of cardiac reserve over time.[26] While peak VO_2 declines with age, the reduction observed in those with acute on chronic HFrEF is beyond that expected with the differences in age alone. We show that patients with acute on chronic HFrEF have reduced peak O_2 pulse, a surrogate measure of exercise stroke volume, compared with de novo HFrEF. Moreover, in patients with advanced HFrEF, the ability to increase stroke volume is limited and cardiac output is largely dependent on HR response.[10] We herein show that acute on chronic HFrEF patients also have significantly lower peak HR with exercise. An impaired chronotropic response is a known contributor of reduced CRF in patients with HFrEF. Chronic sympathetic overactivation may lead to downregulation and desensitization of cardiac β-receptors, which is thought to be the main mechanism of chronotropic incompetence in patients with long-standing HF.[27,28] β-adrenergic desensitization is a hallmark of advanced chronic HFrEF and is mediated by a reduction in the expression of the β1-adrenergic receptors as well as changes in the signaling downstream of the G-protein coupled receptor.[29] β-adrenergic receptor blockers used for the treatment of HFrEF may worsen chronotropic response.[30] However, we found no correlation between the doses of β-adrenergic blockers and peak VO_2, nor a difference in doses of β-adrenergic blockers between the 2 groups thus making it an unlikely contributor to the impaired peak HR response and reduced peak VO_2 in those with acute on chronic HFrEF.

The poorer exercise capacity in patients with acute on chronic HFrEF may account for the unfavorable outcomes observed in this subpopulation.[23] VE/VCO_2 slope, an index of ventilator response to exercise, has emerged as an outcome indicator even more powerful than peak VO_2, however despite the steeper VE/VO_2 slope in patients with acute on chronic HFrEE, no significant difference between the 2 groups was observed.[31] This may be due to the small sample size or by the differences in physical conditioning/muscle between the 2 groups affecting peak VO_2 more than VE/VCO_2 slope.

Altogether these findings show the progressive nature of HFrEF and highlight the importance of CPX measures in reflecting cardiac reserve early following hospitalization for acute decompensated HF to illustrate different pathophysiologic mechanisms between these groups not apparent with resting left ventricular systolic function (i.e., LVEF).

This study has several limitations including the retrospective nature of this observation leading to potential for

selection or data collection biases and the small number of cases limiting the power to detect significant differences paired with an imbalance between groups in the number of several key characteristics. Furthermore, despite incorporating bioelectrical impedance analysis estimates of body composition, we did not adequately address peripheral determinants (i.e., peripheral oxygen extraction) of CRF in the 2 groups.

In conclusion, patients with acute de novo HFrEF patients have better CRF fitness as compared with patients with acute on chronic HFrEF patients. The difference in CRF is not explained by differences in resting hemodynamic parameters or left ventricular systolic function but rather related to greater preservation in cardiac reserve with exercise in de novo HFrEF patients.

Disclosures

The authors have no conflicts of interest to disclose.

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