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Impact of β-Blockers on Heart Rate and Oxygen Uptake During Exercise and Recovery in Older Patients With Heart Failure With Preserved Ejection Fraction

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Abstract

Purpose: The study aimed to investigate the differences in oxygen uptake ($\dot{V}o_2$) and heart rate (HR) (at rest, submaximal exercise, peak exercise, and recovery) in patients with heart failure with preserved ejection fraction (HFpEF) with β-blockers (BB) or without BB treatment (NBB) and to analyze the relationship between HR reserve (HR_{resv}) and peak $\dot{V}o_2$ ($\dot{V}o_{2peak}$) in BB and NBB.

Methods: A total of 174 HFpEF patients (>65 yr; BB, n = 59; NBB, n = 115) were assessed with a cardiopulmonary exercise test to peak exertion using an incremental protocol. After 5 min of supine rest, HR and $\dot{V}o_2$ (HR_{rest}, $\dot{V}o_{2rest}$) at submaximal exercise (HR_{submax}, $\dot{V}o_{2submax}$), at peak exercise (HR_{peak}, $\dot{V}o_{2peak}$), at 1 min of passive recovery (HR_{rec1}), HR_{resv} ($HR_{peak} - HR_{rest}$), and HR recovery ($HR_{recov} = HR_{peak} - HR_{rec1}$) were evaluated.

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Results: Analysis showed that HR_{rest} (66.0 ± 12.2 vs 69.7 ± 10.6 bpm), HR_{submax} (91.7 ± 16.2 vs 98.6 ± 15.2 bpm), and HR_{rec1} (102.9 ± 18.9 vs 109.4 ± 16.9 bpm) were significantly lower ($P \leq .05$) in BB than in NBB, respectively. However, there were no significant differences ($P \cdot > .05$) ·between the BB and the NBB for HR_{peak}, HR_{resv}, HR_{recov}, $\dot{V}o_{2rest}$, $\dot{V}o_{2submax}$, and $\dot{V}o_{2peak}$. A significant relationship was found between HR_{resv}, and $\dot{V}o_{2peak}$ values in both groups (BB, $r = 0.52$; NBB, $r = 0.49$, $P < .001$).

Conclusions: The nonsignificant differences in HR_{peak}, HR_{resv}, HR_{recov}, or $\dot{V}o_2$ values between BB and NBB HFpEF patients, along with significant correlation between HR_{resv} and $\dot{V}o_{2peak}$, suggest that these measures may have equal utility in prognostic and functional assessment as well as clinical applications, including the prescription of exercise, in elderly HFpEF patients.

Keywords

β-blockers; heart failure; heart rate; oxygen uptake; preserved ejection fraction

Approximately, half of heart failure (HF) patients present a left ventricular ejection fraction (EF) with a normal or preserved EF (HFpEF).[1] Compared with HF patients with reduced EF (HFrEF), those with HFpEF are more likely to be older, female, and obese, and have a greater frequency of hypertension, diabetes mellitus, anemia, chronic kidney disease, and atrial fibrillation.[2,3] Furthermore, exercise intolerance and an impaired heart rate (HR) response to exercise are commonly observed in HFpEF patients.[2,4] While the optimal pharmacological treatment to reduce morbidity or mortality in HFpEF is unclear,[5] combination therapies including mineralocorticoid antagonists, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and β-blockers (BB) are commonly used in these patients.[6] It has been shown that the long-term administration of BB will favorably alter the biological properties of the failing heart and regulate the autonomic system (including HR)[7] compared with non-BB group in HFpEF.[8] Therefore, it has been hypothesized that these changes could be mediated through upregulation of myocardial and sinoatrial β_1-receptors leading to a partially or fully restored chronotropic competence.[9] However, the impact of BB in HFpEF has not been evaluated. Thus, the aims of this investigation were (1) to investigate the differences in HR and oxygen uptake ($\dot{V}o_2$) (at rest, submaximal, peak, and recovery) in elderly HFpEF patients with (BB) or with no (NBB) treatment with BB, and (2) to examine the relationship between HR_{resv} and $\dot{V}o_{2peak}$ in BB and NBB. To our knowledge, this is the first study to specifically examine the impact of BB on HR and its relationship to cardiopulmonary responses in elderly HFpEF patients during exercise and in recovery.

METHODS

As we have previously described,[4,10] HFpEF is defined as signs and symptoms of HF according to the National Health and Nutrition Examination Survey HF clinical score of ≥3 and the criteria of Rich et al.[11] Exclusion criteria were preliminary valvular heart disease as the primary etiology of HF, recent stroke or myocardial infarction, uncontrolled hypertension, any other condition that limits the duration of exercise (eg, musculoskeletal or peripheral vascular disease), uncontrolled diabetes mellitus, active treatment for cancer,

anemia (hemoglobin <10 mg·dL^{-1}), renal failure (creatinine >2.5 mg·dL^{-1}), or uncontrolled psychiatric disorders. Eligible patients underwent a physical examination by a cardiologist, electrocardiography at rest and during exercise, echocardiography, and spirometry. Patients who showed significant pulmonary disease or functional impairment by myocardial ischemia were excluded. Participant characteristics and physiological responses to exercise are presented in Tables 1 and 2, respectively.

The Wake Forest University Institutional Review Board approved the study protocol and a written informed consent was obtained from all patients. A total of 174 elderly patients (>65 yr) with HFpEF participated in this research. The number of 174 was obtained from the combined patient enrollment in 2 National Institutes of Health–funded clinical trials (PARIS I and II) that this study was based upon. The participants of this study were divided into those who received BB (n = 59, 34%) and those who did not receive BB (NBB, n = 115). The majority of the BB patients were prescribed selective BB (90%), consisting of atenolol (n = 27), toporol (n = 16), Lopressor (n = 4), metoprolol (n = 3), or bisoprolol (n = 3). The remaining patients were prescribed labetalol (n = 3), propanolol (n = 1), nadolol (n = 1), or carvedilol (n = 1). All participants were on a stable medication regimen and well compensated for 6 mo or more in the New York Heart Association (NYHA) class I-IV.

Participants performed a cardiopulmonary symptom-limited exercise test (CPX) in the upright position on an electronically braked bicycle CPE 2000 (MedGraphics). Initial workload was 12.5 W for 2 min, increased to 25 W for 3 min, and followed thereafter by 25 W increments every 3 min to peak capacity. The CPX was terminated when the participant could no longer continue because of shortness of breath and/or leg fatigue. Respiratory exchange ratio (most achieved >1.1) and a self-reported Borg rating of perceived exertion were also monitored throughout the test to assess fatigue. Breath-by-breath gas exchange data were measured continuously with a CPX-2000 (MedGraphics) during the CPX with the highest values obtained during the final 30 sec used as the peak score. Heart rate was measured continuously during and after exercise by electrocardiographic monitoring. Heart rate and $\dot{V}o_2$ were evaluated after 5 min of supine rest (HR_{rest} and $\dot{V}o_{2rest}$), at submaximal (HR_{submax} and $\dot{V}o_{2submax}$) (ie, after the first stage at 12.5 W), at peak exercise (HR_{peak} and $\dot{V}o_{2peak}$), and at 1 min of passive recovery. Heart rate variables were calculated as follows: heart rate reserve (HR_{resv}), difference between HR_{peak} during exercise and pre-exercise HR_{rest}; HR_{rec1}, HR at 1 min of recovery; and HR_{recov}, difference between HR_{peak} and HR_{rec1}.

Before conducting statistical analysis, all data were analyzed to ensure compliance with the criteria of normality (Kolmogorov-Smirnov test), homoscedasticity (Levene test for homogeneity of variances) and independence (runs test). Comparison between groups was assessed using the Student *t* test. Pearson product moment correlation coefficients were used to assess the relationship between the HR_{resv} and measured $\dot{V}o_{2peak}$ through cardiopulmonary exercise test. Version 22.0 of SPSS was used for statistical analyses. The data are presented as mean ± SD and the level of significance for all the statistical analysis was determined at $P \leq .05$. Since this was a retrospective analysis, a power calculation was

performed using G*Power 3 analysis program.[12] It was determined that an adequate power would be achieved with 115 participants ($\alpha = .05$).

RESULTS

The participants were clinically stable (NYHA class II and class III), nonedematous state, and had no change in medication for more than 60 d. Participants in this investigation demonstrated the typical characteristics of HFpEF, including advanced age (70.8 ± 7.2 yr), female preponderance (79%), obesity (body mass index >30 $kg \cdot m^{-2}$), history of hypertension (83%) (Table 1), and severely reduced $\dot{V}o_{2peak}$ (13.9 ± 2.9 $mL \cdot kg^{-1} \cdot min^{-1}$) (Table 2).[13]

As seen in Table 2, HR_{rest}, $HR_{submax,}$ and HR_{rec1} were significantly lower ($P \leq .05$) in BB than in NBB patients. However, there were no significant or clinically meaningful differences ($P > .05$) in HR_{peak}, HR_{resv}, HR_{recov}, $\dot{V}o_{2rest}$, $\dot{V}o_{2submax}$, and $\dot{V}o_{2peak}$ between the two groups.

The correlation analysis between the HR_{reserv} and $\dot{V}o_{2peak}$ values indicated that these variables were significantly related ($P < .001$) in both groups (BB, $r = 0.52$; NBB, $r = 0.49$).

DISCUSSION

This study examined the impact of BB on HR response in elderly HFpEF patients during exercise and in recovery and to explore the relationship between HR and $\dot{V}o_2$ in these patients. This investigation determined that there were no significant differences for BB versus NBB regarding HR_{peak}, HR_{resv}, HR_{recov}, and $\dot{V}o_2$ values (rest, submaximal, and peak). Furthermore, significant and similar correlations observed between HR_{resv} and $\dot{V}o_{2peak}$ suggest that BB treatment does not impact the relationship of these measures.

Traditionally, the BB treatment for HFpEF has been recommended since the negative chronotropic effect of the medication increases diastolic filling period[14] and lowers HR_{rest}. This effect has been associated with a reduced mortality and morbidity of newly diagnosed HFpEF patients.[15] However, in real-world hospitalized older HFpEF patients, there was no evidence that BB therapy had any independent associations with long-term outcomes, regardless of the class or daily dosage of the BB used.[16] Thus, studies have shown that chronotropic incompetence is highly prevalent in HFpEF and the use of BB, in the absence of tachycardia, may decrease exercise capacity,[17] but not the risk of hospitalization[18] or result in an improvement in exercise capacity or symptoms.[19] Because chronic BB therapy attenuates plasma norepinephrine levels,[20] diminished exercise-induced increases in catecholamines may contribute to chronotropic incompetence in BB-treated HFpEF patients, mainly due to exercise HR_{peak} influenced by a lower HR_{rest}. In this study, although HR_{rest}, was significantly lower (Table 2) in BB than in NBB patients, the minimal difference (~3 bpm) is not a clinically meaningful value. In contrast, results from this study suggest that BB chronic therapy does not affect $\dot{V}o_{2peak}$, HR_{resv}, or HR_{peak} between BB and NBB participants. Thus, we may be observing a BB paradox, given the similar chronotropic

response in BB and NBB. It is possible that chronic BB therapy may have decreased neurohormone levels and/or increased β-receptor sensitivity, resulting in an increase in cardiac contractility.[9,21] Alternatively, several drugs, including BB, have been shown to lose their effectiveness over time.[21] In any case, data from this investigation suggest that BB does not appear to have a major impact on HR response to exercise in HFpEF patients. Subsequently, the use of different CPX-termination criteria or chronotropic incompetence criteria would not be necessary for these patients.[22]

These observations are reinforced with the lack of significant difference in HR_{recov} between NBB and BB (Table 2). The NBB and BB had a similar decline in HR_{recov}, which is indicative of a normal autonomic balance between sympathetic and parasympathetic tone during the acute phase of exercise recovery. While there are a number of methods available to evaluate HR_{recov}, the most widely used threshold for increased risk of all-cause mortality has been a decrease in HR from peak exercise to 1 min of passive supine recovery of <18 bpm.[22] In this study, both groups exceeded the criteria HR_{recov} (BB = 20.3 ± 12.3 and NBB =19.6 ± 11.0 bpm). These results along with previous studies in HFrEF population[23] appear to confirm that chronic BB treatment has no meaningful effect on the HR_{recov} in patients with HFpEF.

In line with previous studies in HFrEF population,[24] we found significant relationship between functional capacity ($\dot{V}o_{2peak}$) and HR_{resv} regardless of the presence or absence of BB treatment. The HR is widely used for prescribing and designing exercise intensity on the basis that a linear relationship between HR and both $\dot{V}o_2$ and work rate increase during incremental exercise is known to exist.[25] Consequently, these data suggest that HFpEF patients on chronic BB therapy can use the same HR ranges as recommended to other patients.[25] The study by Carvalho et al[26] also demonstrated a significant positive relationship between $\%HR_{resv}$ and $\% \dot{V}o_{2resv}$ in older HFrEF patients but only in patients on optimized BB therapy but not in nonoptimized HFpEF patients.

Several limitations of the study should be considered. First, data for this investigation were collected at a time when BB therapy was not widely used in HFpEF; thus, only 34% of patients in this investigation were taking this medication and since then, the target dosing recommendation has increased. Second, since patients were not randomized to BB versus NBB therapy, there may have been a selection bias with less well-controlled HF patients that may affect these results. Third, taking into account that this is a retrospective study, we recognize some potential biases, such as data from a single center and the subsequent lack of generalizability. Finally, without invasive hemodynamics testing (both at resting supine and during exercise), we can only speculate about potential alterations in autonomic nervous system function. This study can serve as an initial evaluation of the effects of low-dose BB on HR and $\dot{V}o_2$ in an HFpEF population. Future studies will be needed to examine the effects of BB prescribed at target doses for HFpEF patients according to the most recent standards.

In conclusion, the results of this study indicate that chronic treatment with BB may favorably alter the biological properties of the cardiac autonomic system regulation in

elderly patients with HFpEF, such that there are no meaningful differences in HR_{peak}, HR_{resv}, HR_{recov}, and functional capacity ($\dot{V}o_{2peak}$) between those with or without BB therapy. The significant correlation between HR_{resv} and $\dot{V}o_{2peak}$ suggests that these measures may have equal utility in prognostic and functional assessment as well as clinical applications, including the prescription of exercise, in elderly HFpEF patients.

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Table 1

Participant Characteristics[a]

Variable	BB n = 59	NBB n = 115	AP n = 174	*P* value BB Versus NBB
Age, yr	70.7 ± 6.8	70.9 ± 7.4	70.8 ± 7.2	.892
Sex				
Female, %	70.3	82.4	78.6	
Race				
White, %	85.9	75.4	78.6	
Other, %	14.1	24.6	21.4	
Body mass, kg	83.9 ± 16.1	81.8 ± 17.4	82.5 ± 17	.457
BMI, kg/m^2	30.9 ± 4.7	30.6 ± 5.8	30.7 ± 5.4	.637
NYHA class, %				
I	0	0.7	0.5	
II	67.2	69.7	68.9	
III	32.8	29.6	30.6	
HTN, %				
Yes	92.2	78.2	82.5	
DM, %				
Yes	18.8	15.5	16.5	
Blood pressure, mm Hg				
Systolic	147 ± 19.7	142.0 ± 17	143.9 ± 18.1	.058
Diastolic	81.8 ± 9.7	81.5 ± 10.1	81.6 ± 10.0	.846
Medications, %				
Diuretics	55.3	64.5	62.8	
ARB	15.8	9.5	10.6	
ACE	44.7	51.5	50.2	
CCB	31.6	29.0	29.5	
Nitrates	21.1	20.1	20.3	
Aspirin	44.7	37.9	39.1	
Digoxin	23.7	32.5	30.9	

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; AP, all participants; ARB, angiotensin receptor blocker; BB, participants with β-blocker therapy; BMI, body mass index; CCB, calcium-channel blockers; DM, diabetes mellitus; HTN, hypertension; NBB, participants with no β-blocker therapy; NYHA, New York Heart Association.

[a] Values are mean ± SD or n (%).

Table 2

Exercise Testing Values of the Study Population[a]

Variable	BB n = 59	NBB n = 115)	*P* Value BB Versus NBB
HR_{rest}, bpm	66 ± 12.2	70 ± 10.6	.038[b]
HR_{submax}, bpm	92 ± 16.2	99 ± 15.2	.007[b]
HR_{peak}, bpm	123 ± 19.8	129 ± 20.1	.073
HR_{reserv}, bpm	57 ± 17.1	59 ± 17.4	.464
HR_{rec1}, bpm	103 ± 18.9	109 ± 16.9	.023[b]
HR_{recov}, bpm	20 ± 12.3	20 ± 11.0	.699
Peak blood pressure, mm Hg			
Systolic	190 ± 26.2	183 ± 24.2	.093
Diastolic	86 ± 11.4	86 ± 11.3	.962
$\dot{V}o_{2rest}$, $mL \cdot kg^{-1} \cdot min^{-1}$	3.4 ± 0.6	3.4 ± 0.5	.711
$\dot{V}o_{2submax}$, $mL \cdot kg^{-1} \cdot min^{-1}$	8.6 ± 1.4	8.5 ± 1.5	.586
$\dot{V}o_{2peak}$, $mL \cdot kg^{-1} \cdot min^{-1}$	14.1 ± 3	13.8 ± 2.9	.479
RER_{peak}	1.1 ± 0.1	1.1 ± 0.1	.863

Abbreviations: BB, participants with β-blocker therapy; HR_{peak}, peak HR; HR_{rec1}, heart rate at 1-min recovery; HR_{recov}, heart rate recovery = (HR_{peak}− HR_{rec1}); HR_{reserv}, heart rate Reserve = (HR_{peak}− HR_{rest}); HR_{rest}, resting HR; HR_{submax}, HR at submaximal load; NBB, participants with no β-blocker therapy; RERpeak, peak respiratory exchange ratio; $\dot{V}o_{2peak}$, peak oxygen uptake; $\dot{V}o_{2rest}$, resting oxygen uptake; $\dot{V}o_{2submax}$, submaximal oxygen uptake.

[a]Values are means ± SD.

[b]Significantly different from BB ($P < .05$).