JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 78, NO. 21, 2021

Effect of β-Blocker Withdrawal on Functional Capacity in Heart Failure and Preserved Ejection Fraction

Patricia Palau, MD, PhD,[a,*] Julia Seller, MD,[b,*] Eloy Domínguez, MD, PhD,[c] Clara Sastre, RN,[a] Jose María Ramón, RN,[a] Rafael de La Espriella, MD,[a] Enrique Santas, MD, PhD,[a] Gema Miñana, MD, PhD,[a,d] Vicent Bodí, MD, PhD,[a,d] Juan Sanchis, MD, PhD,[a,d] Alfonso Valle, MD,[b] F. Javier Chorro, MD, PhD,[a,d] Pau Llácer, MD, PhD,[d,e] Antoni Bayés-Genís, MD, PhD,[d,f,g] Julio Núñez, MD, PhD[a,d]

ABSTRACT

BACKGROUND Chronotropic incompetence has shown to be associated with a decrease in exercise capacity in heart failure with preserved ejection fraction (HFpEF), yet β-blockers are commonly used in HFpEF despite the lack of robust evidence.

OBJECTIVES This study aimed to evaluate the effect of β-blocker withdrawal on peak oxygen consumption (peak Vo_2) in patients with HFpEF and chronotropic incompetence.

METHODS This is a multicenter, randomized, investigator-blinded, crossover clinical trial consisting of 2 treatment periods of 2 weeks separated by a washout period of 2 weeks. Patients with stable HFpEF, New York Heart Association functional classes II and III, previous treatment with β-blockers, and chronotropic incompetence were first randomized to withdrawing from (arm A: n = 26) versus continuing (arm B: n = 26) β-blocker treatment and were then crossed over to receive the opposite intervention. Changes in peak Vo_2 and percentage of predicted peak Vo_2 (peak Vo_2%) measured at the end of the trial were the primary outcome measures. To account for the paired-data nature of this crossover trial, linear mixed regression analysis was used.

RESULTS The mean age was 72.6 ± 13.1 years, and most of the patients were women (59.6%) in New York Heart Association functional class II (66.7%). The mean peakVo_2 and peak Vo_2% were 12.4 ± 2.9 mL/kg/min, and 72.4 ± 17.8%, respectively. No significant baseline differences were found across treatment arms. Peak Vo_2 and peak Vo_2% increased significantly after β-blocker withdrawal (14.3 vs 12.2 mL/kg/min [Δ +2.1 mL/kg/min]; $P < 0.001$ and 81.1 vs 69.4% [Δ +11.7%]; $P < 0.001$, respectively).

CONCLUSIONS β-blocker withdrawal improved maximal functional capacity in patients with HFpEF and chronotropic incompetence. β-blocker use in HFpEF deserves profound re-evaluation. (β-blockers Withdrawal in Patients With HFpEF and Chronotropic Incompetence: Effect on Functional Capacity [PRESERVE-HR]; NCT03871803; 2017-005077-39) (J Am Coll Cardiol 2021;78:2042-2056) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on JACC.org.

From the [a]Cardiology Department, Hospital Clínico Universitario, Instituto de Investigación Sanitaria del Hospital Clínico Universitario de Valencia, Universitat de València, Valencia, Spain; [b]Cardiology Department, Hospital de Denia, Alicante, Spain; [c]Fisabio, Universitat Jaume I, Castellón, Spain; [d]Centro de Investigación Biomédica en Red Enfermedades Cardiovascular, Madrid, Spain; [e]Internal Medicine Department, Hospital Ramón y Cajal, Madrid, Spain; [f]Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; and the [g]Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain. *Drs Palau and Seller contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 27, 2021; revised manuscript received August 27, 2021, accepted August 30, 2021.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2021.08.073

The pathophysiology of heart failure with preserved ejection fraction (HFpEF) is complex and multifactorial (1). Compared with control individuals matched for age, sex, and comorbidities, patients with HFpEF have significantly impaired exercise capacity (2). Chronotropic incompetence has emerged as a potential mechanism contributing to exercise functional capacity limitation in HFpEF (1-6).

β-blockers, drugs that blunt the chronotropic response, are frequently prescribed in patients with HFpEF despite no clinical evidence of their benefit (7). Indeed, recent trials in patients with HFpEF (8,9) revealed that more than 75% of patients are receiving β-blockers. Little information is available regarding the role of β-blockers on the pathogenesis of chronotropic incompetence in HFpEF and how β-blocker withdrawal modifies functional capacity in this subset of patients (10). Accordingly, we aimed to evaluate the effect of short-term β-blocker withdrawal on peak oxygen consumption (peak Vo_2) at maximal exercise in patients with HFpEF and chronotropic incompetence.

SEE PAGE 2057

METHODS

STUDY DESIGN. This study was a multicenter, investigator-blinded, randomized, crossover study consisting of 2 treatment periods of 2 weeks each (periods 1 and 2) and a washout period of 2 weeks between them. The study included patients with HFpEF, New York Heart Association (NYHA) functional class II and III/IV, and previous stable treatment with β-blockers. The study design was previously published (11).

The diagnosis of HFpEF was made according to the 2016 European Society of Cardiology Guidelines (7). All patients provided informed consent, and the research ethics committee approved the protocol following the principles of the Declaration of Helsinki and national regulations (Comités de Ética de la Investigación con Medicamentos de l'Hospital Clínic Universitari de València). All analyses were performed by an independent company (MedStat Consulting).

STUDY POPULATION. The eligibility of candidate patients was based on the following inclusion criteria: 1) adult patients aged >18 years with stable symptomatic HF with a NYHA functional class ≥II during the last month; 2) left ventricular ejection fraction (LVEF) >50% by the Simpson method and end-diastolic diameter <60 mm; 3) N-terminal pro-B-type natriuretic peptide (NT-proBNP) >125 pg/mL in the last month; 4) structural heart disease (left ventricle hypertrophy or left atrial enlargement) or diastolic dysfunction estimated by 2-dimensional echocardiography according to the 2016 European Society of Cardiology Guidelines (7); 5) a previous admission for acute HF; 6) previous treatment with stable dosages of β-blockers during the last 3 months; and 7) blunted heart rate (HR) response during a maximal cardiopulmonary exercise testing (CPET), defined as a chronotropic index <0.62 (chronotropic index = $[HR_{peak\ exercise} - HR_{rest}] / [220 - age - HR_{rest}]$) (4). Exclusion criteria were: 1) inability to perform a valid baseline exercise test; 2) significant primary moderate-to-severe valve disease; 3) unstable angina or history of an acute coronary syndrome in the previous 12 months; 4) effort angina or signs of ischemia during CPET; 5) uncontrolled arrhythmias or uncontrolled blood pressure during cardiopulmonary exercise testing; 6) significant primary pulmonary disease, including a history of pulmonary arterial hypertension, chronic thromboembolic pulmonary disease, or chronic obstructive pulmonary disease; 7) chronic treatment with digitalis, calcium channel blockers (verapamil or diltiazem), or ivabradine; 8) HR at rest >75 beats/min; and 9) any other comorbidity with a life expectancy <1 year.

INTERVENTION. Eligibility assessment, randomization, and initial visit. Patients who met the inclusion-exclusion criteria and signed the informed consent form were randomized 1:1 to 2 arms: arm A, for β-blocker withdrawal, or arm B, for β-blocker continuation. At the first visit (visit 1), a comprehensive medical history, physical examination, anthropometry, and examination tests were performed by 2 cardiologists blinded to the patients' allocation groups. The examination tests included an electrocardiogram, 2-dimensional transthoracic echocardiography, CPET, cognitive assessment by Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), quality of life assessment by Minnesota Living with Heart Failure Questionnaire (MLHFQ), continuous electrocardiogram recording during the first 30 days, and blood samples for a panel of baseline biomarkers. Researchers in charge of performing the CPET and the other study procedures, excluding clinical visits, were also blinded to treatment assignment.

Treatment intervention and visits. Following screening (visit 0) and randomization (visit 1, day 0)

ABBREVIATIONS AND ACRONYMS

CPET = cardiopulmonary exercise testing

CV = cardiovascular

E/e′ = ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′)

HFpEF = heart failure with preserved ejection fraction

HR = heart rate

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

peak Vo_2 = peak oxygen consumption at maximal exercise

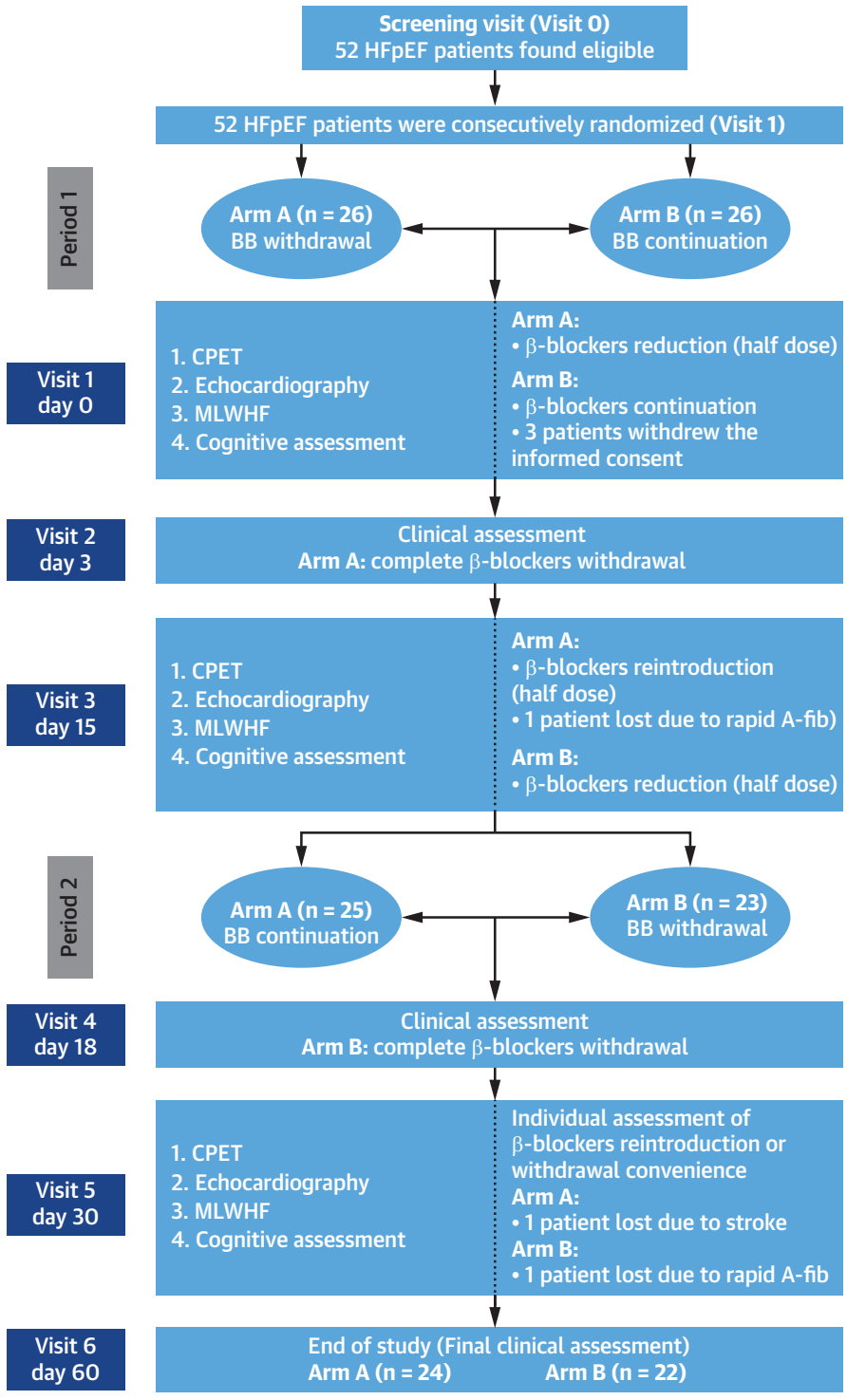
peak Vo_2% = percentage of predicted peak oxygen consumption at maximal exercise

RER = respiratory exchange ratio

VCO_2 = carbon dioxide production

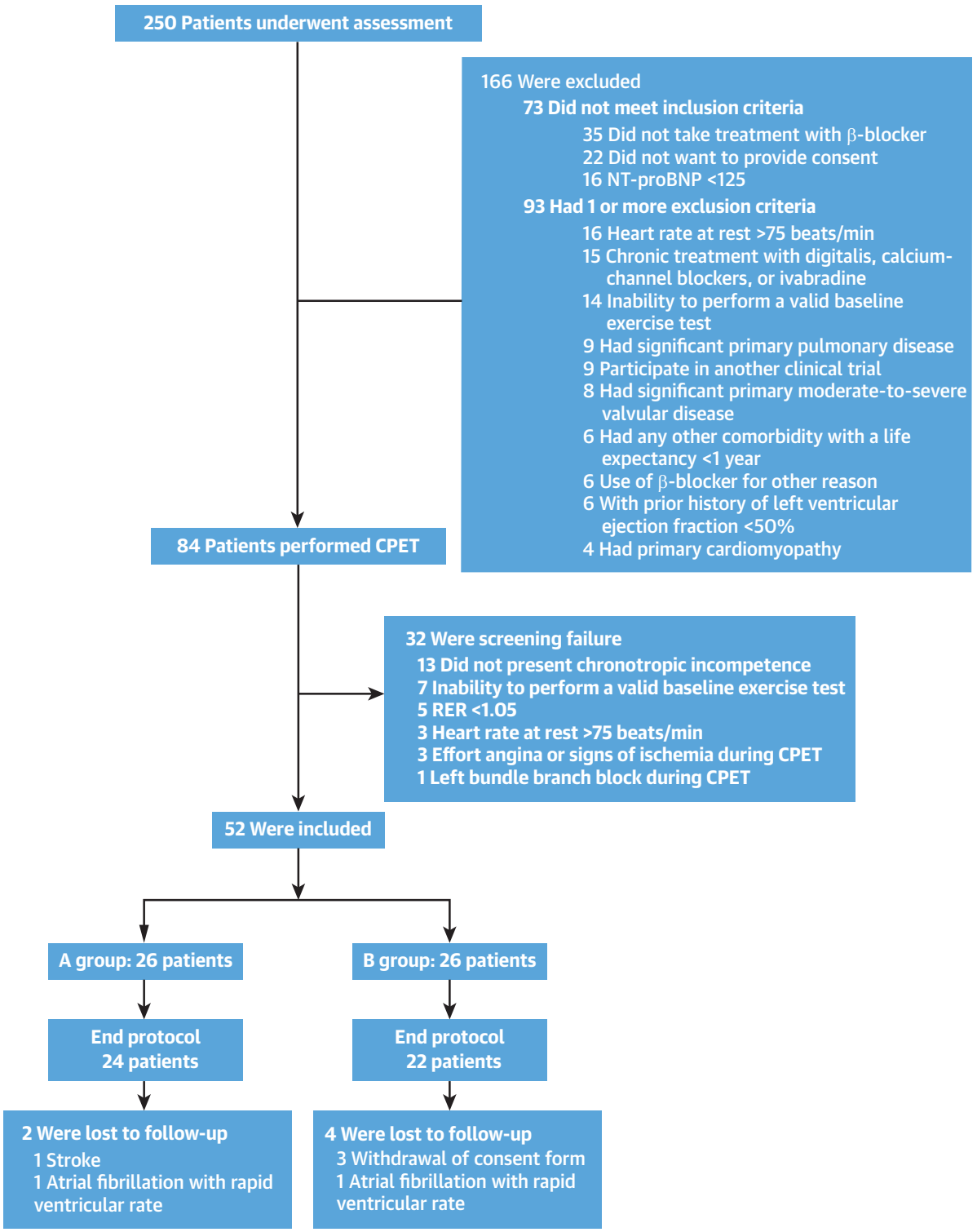
VE = minute ventilation

FIGURE 1 **Flow Diagram of the Study Design**



Flow diagram of treatment intervention and visits of the randomized and crossover study. A-fib = atrial fibrillation; BB = β-blockers; CPET = cardiopulmonary exercise testing; HFpEF = heart failure with preserved ejection fraction; MLWHF = Minnesota Living With Heart Failure Questionnaire.

FIGURE 2 **Flow Diagram of the Study Population**



Flow chart of the total number of patients evaluated and finally included. CPET = cardiopulmonary exercise testing; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RER = respiratory exchange ratio.

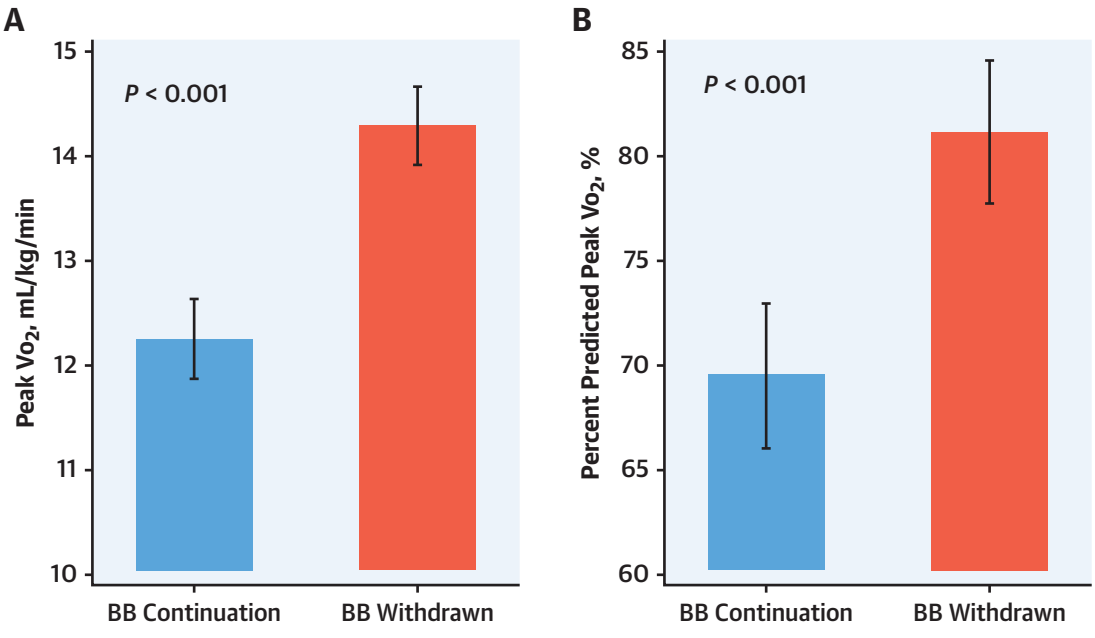
TABLE 1 Baseline Characteristics of the Patients Stratified by Randomization Arm

	All Patients (N = 52, 100%)	Arm A (n = 26, 50%)	Arm B (n = 26, 50%)	*P* Value
Demographic and medical history				
Age, y	74.5 (68.5-79.5)	73 (68-77)	76.5 (72-80)	0.101
Women	31 (59.6)	14 (53.9)	17 (65.4)	0.572
BMI, kg/m^2	31.1 ± 4.7	30.9 ± 5.3	31.3 ± 4.0	0.741
Caucasian	52 (100.0)	26 (100.0)	26 (100.0)	1.000
Previous admission for AHF	52 (100.0)	26 (100.0)	26 (100.0)	1.000
Hypertension	46 (88.5)	22 (84.6)	24 (92.3)	0.668
Diabetes mellitus	21 (40.4)	9 (34.6)	12 (46.2)	0.572
Dyslipidemia	37 (71.2)	16 (61.5)	21 (80.8)	0.132
Current smoker	4 (7.7)	4 (15.4)	0 (0.0)	0.110
Prior smoker	12 (23.1)	6 (23.1)	6 (23.1)	1.000
Prior history of IHD	12 (23.1)	7 (26.9)	5 (19.2)	0.743
Prior history of stroke	1 (1.9)	1 (3.9)	0 (0.0)	1.000
Prior history of atrial fibrillation	20 (38.5)	11(42.3)	9 (34.6)	0.776
Prior history of COPD	6 (11.5)	5 (19.2)	1 (3.9)	0.191
NYHA functional class III/IV	18 (34.6)	8 (30.8)	10 (38.5)	0.771
Vital signs at rest				
Heart rate, beats/min	64.8 ± 8.8	64.9 ± 10.8	64.8 ± 8.8	0.531
Systolic blood pressure, mm Hg	123.4 ± 16.8	124.5 ± 14.2	122.4 ± 16.8	0.637
Diastolic blood pressure, mm Hg	65.6 ± 8.4	64.2 ± 8.0	67.1 ± 8.7	0.225
Echocardiographic and electrocardiographic parameters				
Left ventricular ejection fraction	64.7 ± 7.1	63.8 ± 7.1	65.7 ± 7.0	0.338
Left atrial volume index, mL/m^2	39.8 ± 13.7	42.5 ± 16.3	37.1 ± 10.2	0.164
Left ventricular mass index, g/m^2	108.0 ± 31.6	108.1 ± 31.1	107.9 ± 32.7	0.984
Septal E/e′ ratio	14.6 (12.3-19.1)	14.3 (11.6-19.1)	15.2 (13.4-18.5)	0.486
Left bundle branch block	5 (9.6)	2 (7.7)	3 (11.5)	0.638
Atrial fibrillation at inclusion	10 (19.2)	7 (26.9)	3 (11.5)	0.291
Laboratory values				
Hemoglobin, g/dL	13.3 ± 1.4	13.4 ± 1.7	13.1 ± 1.1	0.459
eGFR, mL/min/1.73 m^2	64.7 ± 21.2	67.2 ± 23.5	62.2 ± 18.8	0.399
Serum sodium, mEq/L	140.9 ± 3.1	140.5 ± 2.9	141.3 ± 3.3	0.304
NT-proBNP, pg/mL	400.5 (205.5-1,039.5)	424 (234-1,294)	344.5 (204-662)	0.341
CA125, U/mL	10 (7-14.5)	10 (7.7-15)	10 (7-14)	0.653
Cardiopulmonary exercise testing variables				
Peak Vo_2, mL/kg/min	12.4 ± 2.9	12.2 ± 2.9	12.5 ± 2.9	0.687
Peak Vo_2%	72.4 ± 17.8	67.6 ± 17.9	77.2 ± 16.6	0.051
VE/VCO_2 slope	33.7 ± 5.4	34.1 ± 5.7	33.4 ± 5.1	0.644
Respiratory exchange ratio	1.2 (1.1-1.3)	1.1 (1.1-1.3)	1.2 (1.1-1.3)	0.581
Chronotropic index	0.41 ± 0.14	0.40 ± 0.13	0.41 ± 0.16	0.842
Heart rate at exercise peak, beats/min	97.2 ± 14.7	97.1 ± 15.8	97.3 ± 13.9	0.956
Quality of life and cognitive function variables				
MLHFQ	26 (11-40)	25 (13-35)	27 (11-40)	0.869
MoCA score	20.7 ± 4.6	21.5 ± 4.0	19.8 ± 5.2	0.219
MMSE score	27.5 ± 2.3	28.0 ± 1.7	27.1 ± 2.7	0.173
Medical treatment				
ACE inhibitor or ARB	39 (75)	19 (73.1)	20 (76.9)	0.755
Loop diuretics	44 (84.6)	21 (80.8)	23 (88.5)	0.781
MRA	6 (11.5)	2 (7.7)	4 (15.4)	0.668
Statins	35 (67.3)	18 (69.3)	17 (65.4)	1.000

Values are median (interquartile range), n (%), or mean ± SD.

ACE = angiotensin-converting enzyme; AHF = acute heart failure; ARB = angiotensin receptor blocker; BMI = body mass index; CA125 = serum carbohydrate antigen 125; COPD = chronic obstructive pulmonary disease; E/e′ = ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′); eGFR = estimated glomerular filtration rate; IHD = ischemic heart disease; MLHFQ = Minnesota Living With Heart Failure Questionnaire; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association functional class; NT-proBNP = N-terminal pro B-type natriuretic peptide; peak Vo_2 = peak oxygen consumption; peak Vo2% = percentage of predicted peak oxygen consumption; VCO_2 = carbon dioxide production; VE = minute ventilation; VE/VCO_2 slope = ventilatory efficiency.

FIGURE 3 Primary Endpoint: Change in Mean Peak VO_2 and Peak VO_2%



(A) The change in peak oxygen consumption (peak Vo_2) after β-blocker (BB) withdrawal was +2.1 ± 1.29 ($P < 0.001$). **(B)** The increase in the percentage of predicted peak oxygen consumption (peak Vo_2%) was +11.74 ± 2.32 ($P < 0.001$).

visits, the procedures across treatment arms were the following:

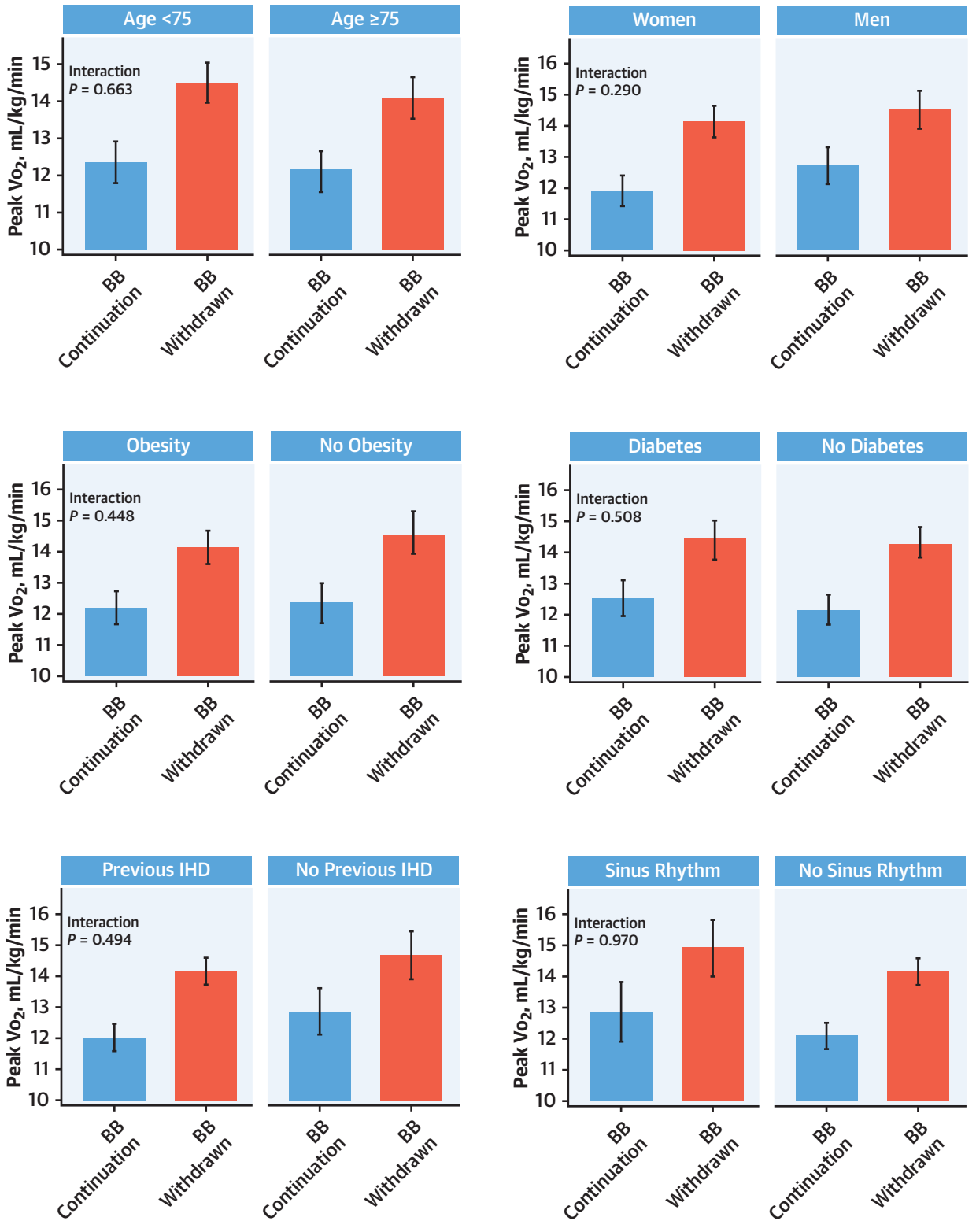
1. Arm A: Patients allocated to this arm were instructed to reduce by half their dose of β-blocker (Figure 1). The patients were advised of potential adverse effects and instructed to contact outpatient HF clinics if any adverse effect occurred. Patients were checked at 3 days (visit 2, day 3) by a cardiologist. If clinically stable, the patients were told to withdraw the β-blocker. All the procedures of the study were repeated at 15 days (visit 3, day 15). After visit 3, the patients initiated the previous half dose of β-blocker until the third day (visit 4, day 18). If clinically stable, the patient increased the β-blocker dosage to the prior dosage and repeated all the examination tests at 30 days (visit 5, day 30).

2. Arm B: Patients allocated to this arm continued with their treatment unchanged and were evaluated 3 days later (visit 2, day 3) and continued treatment with β-blocker (Figure 1). All of the study procedures were repeated at 15 days (visit 3, day 15); the patients were then instructed to reduce the dose of β-blocker by half. Likewise, the patients were advised of potential adverse effects and to contact an outpatient HF clinic if any adverse effect occurred. Patients were revisited in 3 days (visit 4, day 18), and if clinically stable, the patient withdrew the β-blocker and repeated all the examination tests at 30 days (visit 5, day 30).

At visit 5, the responsible cardiologist assessed all the examination tests and individually decided the appropriateness of β-blocker reintroduction or withdrawal in both arms. A cardiologist of the HF unit clinically evaluated all patients at 60 days after randomization (visit 6, day 60). Additional visits were permitted according to the patient's clinical status and were registered.

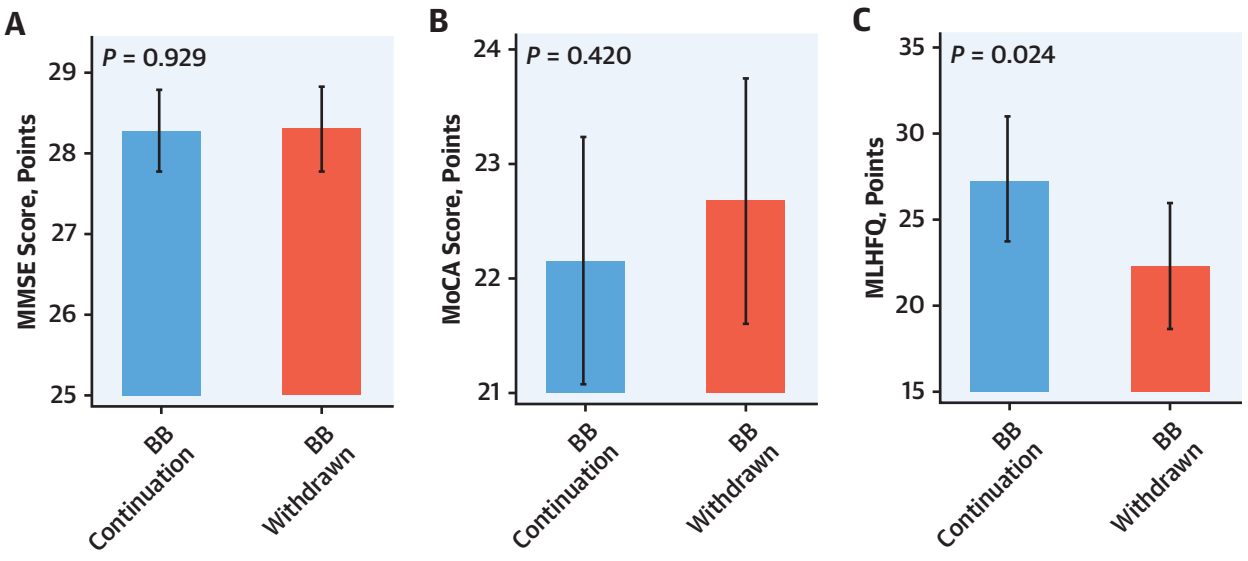
CPET. Maximal functional capacity was evaluated using incremental and symptom-limited CPET (CORTEX Metamax 3B) on a bicycle ergometer, beginning with a workload of 10 W and increasing gradually in a ramp protocol at 10-W increments every 1 minute. We define maximal functional capacity as the point when the patient stops pedaling because of symptoms, and the respiratory exchange ratio (RER) is ≥1.05. During exercise, patients were monitored with 12-lead electrocardiogram and blood pressure measurements every 2 minutes. Gas exchange data and cardiopulmonary variables are averages of values taken every 10 seconds. Peak Vo_2 was defined as the highest value of Vo_2 during the last 20 seconds of exercise. Once peak Vo_2 was obtained, we calculated its percentage of predicted peak Vo_2 (peak Vo_2%), defined as the

FIGURE 4 Change in Mean Peak Vo_2 and Peak Vo_2% Across the Subgroups



No differential effect of the treatment strategy across subgroups was found for peak Vo_2. IHD = ischemic heart disease; other abbreviations as in Figures 1 and 3.

FIGURE 5 Secondary Endpoints: Change in Mean Cognitive and Quality-of-Life Scores



(A and B) No differences were found in cognitive scores between treatment strategies. **(C)** A significant decrease in Minnesota Living With Heart Failure Questionnaire (MLWHF) was found when β-blockers (BB) were withdrawn (22.3 vs 27.4; $P = 0.024$). MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment.

percentage of predicted peakVo2 adjusted for sex, age, exercise protocol, weight, and height according to Wasserman/Hansen standard prediction equation. The ventilatory efficiency was determined by measuring the slope of the linear relationship between minute ventilation (VE) and carbon dioxide production (VCO_2) across the entire course of exercise (VE/VCO_2 slope). Each subject underwent 3 tests (at baseline, 15 days, and 30 days).

ENDPOINTS. The study's primary endpoint was defined as the average change from baseline in mean peak Vo_2. We also evaluated the average change from baseline in peak Vo_2% as a coprimary endpoint. The secondary endpoints were: 1) absolute changes in cognitive function assessed by MMSE and MoCA; 2) absolute changes in echocardiogram parameters (ratio of mitral peak velocity of early filling [E] to early diastolic mitral annular velocity [e′] [E/e′] ratio and left atrial volume index); 3) absolute changes in quality of life assessed by MLHFQ; and 4) absolute changes in the biomarkers NT-proBNP and serum carbohydrate antigen 125. Exploratory endpoints included changes in LVEF, circulatory power (peak Vo_2 × peak systolic blood pressure), VE/VCO_2 slope, and RER.

Safety endpoints included the composite event of the total number of episodes of cardiovascular (CV) admissions or all-cause mortality at 6 months after the intervention.

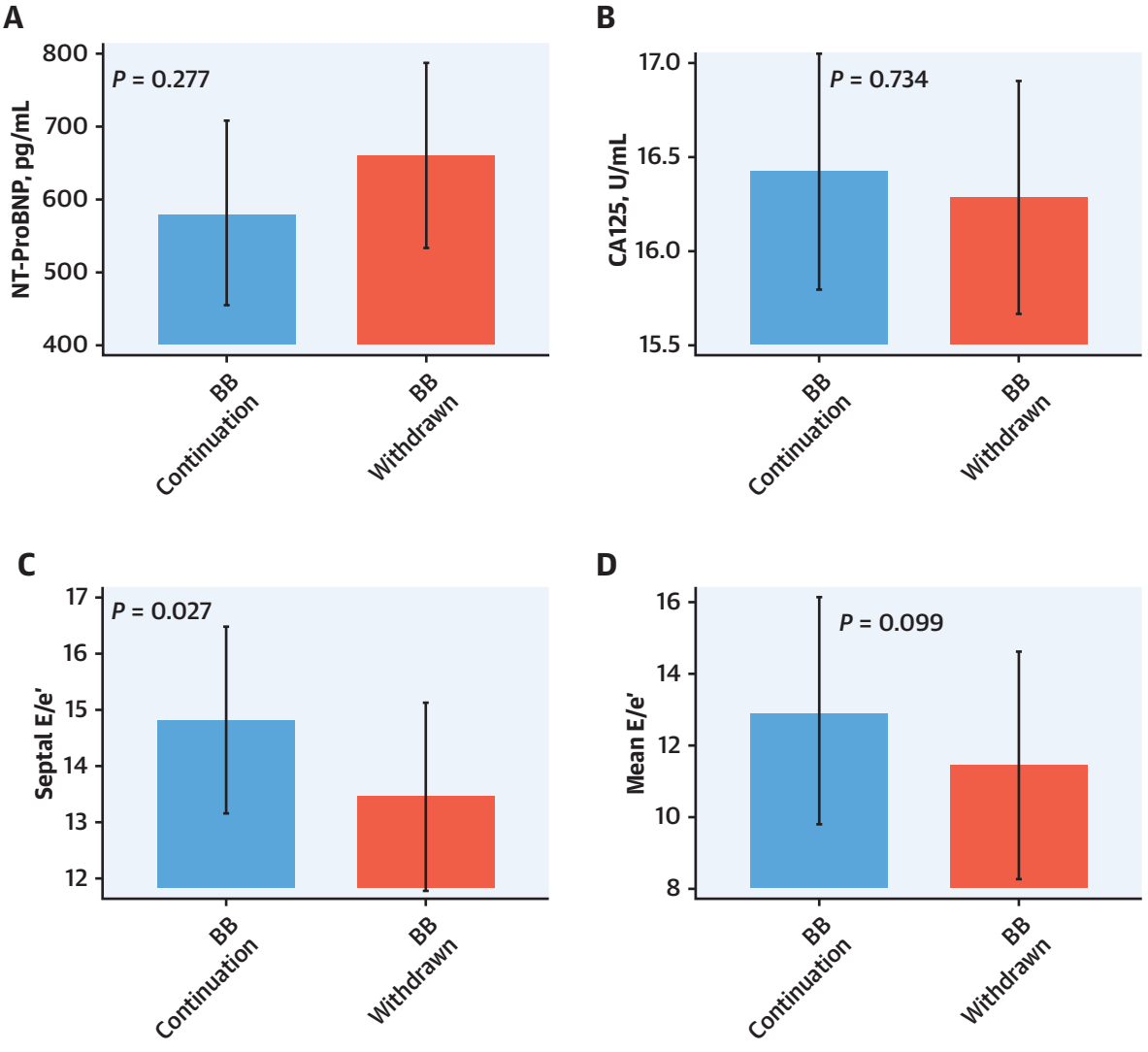
STATISTICAL ANALYSIS. All statistical comparisons were made under a modified intention-to-treat principle.

DESCRIPTIVE ANALYSIS. Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]), and discrete variables as percentages. At baseline, the comparisons of means, medians, and frequencies among treatment groups were carried out using Student's *t*-test, Wilcoxon test, and chi-square test, respectively.

SAMPLE SIZE. The null hypothesis of the primary efficacy endpoint stated no differences in the mean peak Vo_2 and peak Vo_2% among patients in arm A and patients in arm B when averaged for the 2 periods (β-blocker withdrawal vs β-blocker continuation). Thus, in the absence of a period effect, the between-arm comparison (β-blocker withdrawal vs β-blocker continuation) averaged for the 2 periods defined the success of the treatment strategy. Based on a prior study of our group in HFpEF, we assumed eligible patients had a mean peak Vo_2 of 10 ± 2.8 mL/kg/min (5). Similarly, based on prior studies about the adverse effects of HR slowing in patients with HFpEF (12), we speculated that β-blocker withdrawal would increase peak Vo_2, by 1.2 mL/kg/min and a common SD of 2.0 (11).

Assuming an allocation ratio of 1:1, a total of 42 patients (21 patients per group) would provide 90%

FIGURE 6 Secondary Endpoints: Change in Mean Biomarker Levels and Echocardiographic Parameters



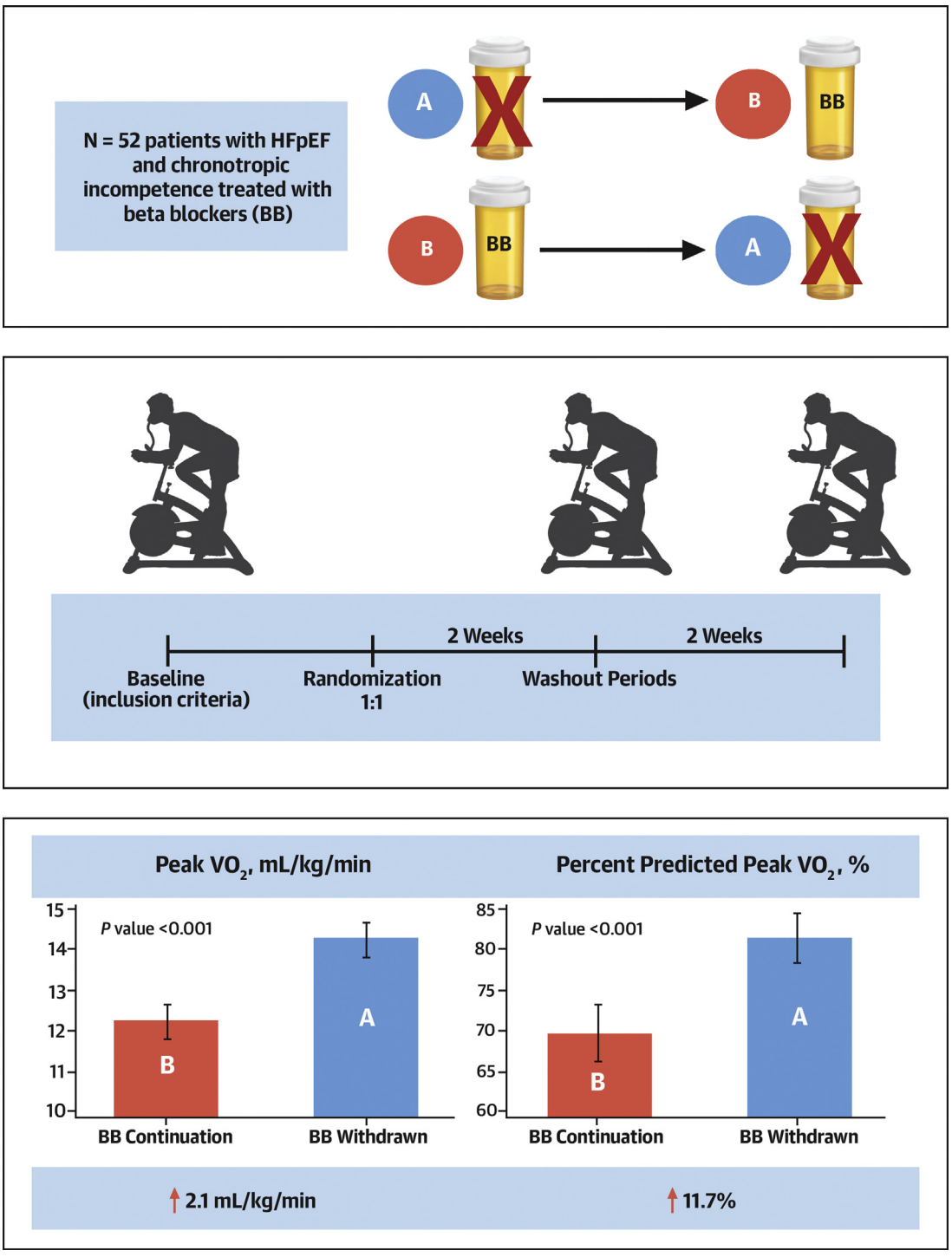
No significant changes were found in mean biomarker levels **(A and B)** or in mean E/e′ ratio **(D).** The septal E/e′ ratio decreased significantly when BBs were withdrawn **(C)**. CA125, serum carbohydrate antigen 125; E/e′, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′); other abbreviations as in Figures 1 and 2.

power at an αsignificance level of <0.05. Assuming 20% of the participants would withdraw or be lost to follow-up, a total of 26 patients per arm (52 patients) was estimated to be required. The software used for the sample size calculation was "xsampsi" from Stata 15.1 (StataCorp).

INFERENTIAL ANALYSES. A linear mixed regression model was used to analyze the primary and secondary continuous endpoints. Because of hierarchical levels of nesting (treatment sequence within patient ID and the latter among study centers), the model included study center and patient ID as random effects. All analyses included the baseline value of the endpoint as a covariate (mixed model within the framework of analysis of covariance). The period effect was tested by modeling the interaction between the treatment group and the period. The linear mixed regression model results are presented as least square means with 95% CIs and *P* values. Stata 15.1 was used for the analyses.

CORRELATION ANALYSIS. We performed a Pearson correlation analysis between the differences in Δpeak

CENTRAL ILLUSTRATION β-Blocker Withdrawal Improved Maximal Functional Capacity in Patients With Heart Failure With Preserved Ejection Fraction



Palau, P. et al. J Am Coll Cardiol. 2021;78(21):2042-2056.

Randomized and crossover study evaluating the effect of β-blocker (BB) withdrawal on maximal functional capacity in patients with heart failure with preserved ejection fraction (HFpEF) and chronotropic incompetence. β-blocker withdrawal resulted in a short-term improvement of peak oxygen consumption (peak Vo_2).

Vo_2 (peak $Vo_{2\ \beta\text{-blocker withdrawal}}$ − peak $Vo_{2\ \beta\text{-blocker continuation}}$) against the differences in HR at peak exercise −ΔHRpeak $_{\text{exercise}}$ − ($HR_{\text{peak exercise }\beta\text{-blockers withdrawal}}$ − HRpeak $_{\text{exercise }\beta\text{-blockers continuation}}$). Results are shown for the sample as a whole and stratified by sequence.

MEDIATION ANALYSIS. We suspected that $HR_{\text{peak exercise}}$ might act as a mediator variable for the effect of the treatment intervention on peak Vo_2, meaning that it sits in the causal pathway between the treatment and the outcome, as shown in Supplemental Figure 1. Because of the hierarchical nature of the data, we used the Krull and MacKinnon approach for this mediation analysis (13). Here, the mediation model mimics the mixed regression analysis using patient ID and study center as random effects and the baseline value of peak Vo_2, sequence, and period as covariates. Normal-based 95% CIs and *P* values were estimated through bootstrapping (1,000 replications).

RESULTS

From October 1, 2018, to December 31, 2020, 82 patients with HFpEF underwent CPET assessment, and 52 of them met eligibility criteria and were finally randomized. A detailed flowchart is presented in Figure 2. Among patients who performed the CPET, the most frequent causes of screening failure were not meeting a chronotropic incompetence criterion, inability to perform a valid exercise stress test, and RER <1.05 (Figure 2).

BASELINE CHARACTERISTICS. Patient characteristics are presented in Table 1. At baseline, the mean age was 72.6 ± 13.1 years, 59.6% were women, 88.5% had a history of hypertension, 80.8% were in sinus rhythm, 66.7% were in stable NYHA functional class II, and all had a prior admission for decompensated HF. The mean LVEF, LV mass index, and left atrial volume index were 64.7 ± 7.1%, 108.0 ± 31.6 g/m^2, and 39.8 ± 13.7 mL/m^2, respectively. The median NT-proBNP was 401 pg/mL (IQR: 206-1,040). There were no significant differences in clinical, echocardiographic, or laboratory data across treatment arms. Likewise, there were no differences in pharmacological treatment across both groups (Table 1).

β-BLOCKER TREATMENT. All the patients were receiving stable doses of β-blockers (>12 weeks). The most frequently prescribed β-blocker was bisoprolol (46 patients, 88.5%) with a median dose of 2.5 mg/daily (IQR: 2.5-5.0).

RESPONSE TO EXERCISE. The mean HR_{rest}, $HR_{\text{peak exercise}}$, and chronotropic incompetence were 64.8 ± 8.8 beats/min, 97.2 ± 14.7 beats/min, and 0.41 ± 0.14, respectively. The mean peak Vo_2, peak Vo_2%, and VE/VCO_2 slope were 12.4 ± 2.9 mL/min/m^2, 72.4 ± 17.8, and 33.7 ± 5.4, respectively. RER was ≥1.05 in all patients. There were no significant differences in baseline CPET parameters between treatment arms (Table 1).

PRIMARY ENDPOINT. The mean of peak Vo_2 for β-blocker withdrawal and β-blocker continuation for sequence A were 14.06 ± 3.35 and 12.26 ± 3.24 mL/kg/min, respectively (Δ+1.87 ± 1.28; $P < 0.001$). Likewise, estimates for sequence B were 14.48 ± 3.79 and 12.24 ± 3.05 mL/kg/min for β-blocker withdrawal and β-blocker maintenance, respectively (Δ+2.21 ± 1.32; $P < 0.001$). The overall peak Vo_2 efficacy estimate between the 2 sequences (β-blocker withdrawal vs β-blocker continuation) was determined to be +2.04 ± 1.29 ($P < 0.001$). In a mixed regression analysis, the least square means for peak Vo_2 were 14.29 (95% CI: 13.91-14.67) and 12.24 (95% CI: 11.86-12.61) mL/kg/min for β-blocker withdrawal and β-blocker continuation, respectively, and the difference was estimated as +2.05 (95% CI: 1.68-2.42; $P < 0.001$) (Figure 3A). The interaction of treatment with period was not significant, corroborating the absence of a period effect ($P = 0.928$).

Similar findings were found when peak Vo_2% was analyzed. Peak Vo_2% for β-blocker withdrawal and β-blocker continuation in arm A were 78.06 ± 21.53 and 74.26 ± 12.17, respectively (Δ+13.12 ± 13.76; $P < 0.001$). Likewise, estimates for sequence B were 84.51 ± 23.32 and 64.94 ± 22.37 for β-blocker withdrawal and β-blocker continuation, respectively (Δ+10.25 ± 18.48; $P = 0.0143$). The overall increase in peak Vo_2% when β-blockers were withdrawn was 11.74 ± 2.32% ($P < 0.001$). In a mixed regression analysis, the least-square means for peak Vo_2% were 81.12 (95% CI: 77.67-84.57) and 69.43 (95% CI: 65.99-72.88) for β-blocker withdrawal and β-blocker continuation, respectively, and the difference was estimated as 11.68 (95% CI: 7.10-16.27; $P < 0.001$) (Figure 3B). The interaction of treatment with period was also not significant ($P = 0.796$).

CHANGES IN PEAK Vo_2 AND HR AT PEAK EXERCISE. HR at peak exercise significantly increased when β-blockers were withdrawn (least-square means of 127 vs 97 beats/min; $P < 0.001$). We found a significant and positive correlation between Δpeak Vo_2 (peak $Vo_{2\ \beta\text{-blocker withdrawal}}$ − peak $Vo_{2\ \beta\text{-blockers continuation}}$) and the $\Delta HR_{\text{peak exercise}}$ ($HRpeak\ exercise_{\beta\text{-blockers withdrawal}}$ − $HRpeak\ exercise_{\beta\text{-blockers continuation}}$), with a Pearson correlation coefficient of 0.357 ($P = 0.015$). Because of the significant correlation between Δpeak Vo_2 and

$\Delta HR_{peak\ exercise}$, we performed a mediation analysis to disentangle how much of the treatment effect on peak Vo_2 was caused by an indirect effect mediated by the concomitant increase in HR at peak exercise. The mediation analysis showed that simultaneous changes in $HR_{peak\ exercise}$ accounted for 36% of the peak Vo_2 response to treatment strategy ($P = 0.006$).

SUBGROUP ANALYSIS. We found no differential effect of the treatment strategy across the prespecified subgroups (age [<75 vs ≥75 years], sex, obesity, diabetes mellitus, ischemic etiology, and sinus rhythm) for peak Vo_2 (**Figure 4**).

SECONDARY ENDPOINTS. No significant differences were found among periods for any of the secondary endpoints.

MMSE and MoCA scores. No differences were found in MMSE and MoCA scores between treatment strategies (**Figures 5A and 5B**).

MLHFQ. A significant decrease in MLHFQ was found when β-blockers were withdrawn (22.3 vs 27.4; $P = 0.024$) (**Figure 5C**). β-blockers withdrawal resulted in a nonsignificant improvement of the physical dimension (Δ−1.8; 95% CI: −4.0 to 0.4; $P = 0.106$) and a significant change in the emotional dimension (Δ−2.4; 95% CI: −4.7 to −0.1; $P = 0.043$).

Biomarkers. NT-proBNP and serum carbohydrate antigen 125 did not differ between the treatment groups (**Figures 6A and 6B**).

Echocardiographic parameters. The septal E/e′ ratio significantly decreased when β-blockers were withdrawn. No significant changes were found for the mean E/e′ ratio and left atrial volume index (**Figures 6C and 6D**, respectively).

EXPLORATORY ENDPOINTS. LVEF. No significant differences were found among treatment groups (Supplemental Figure 1).

Circulatory power. There was an increase in circulatory power for the β-blockers withdrawn group (Supplemental Figure 1).

VE/VCO_2 slope. No significant differences were found among treatment groups (Supplemental Figure 1).

RER. There were no differences across treatment arms (Supplemental Figure 1).

SAFETY ENDPOINTS. No deaths were recorded at the 6-month follow-up. At 1 month, we identified a total of 3 CV hospitalizations in 3 patients (2 in arm A, and 1 in arm B). At 6 months, we recorded a total of 4 CV hospitalizations in 3 patients (2 in arm A, and 1 in arm B). Of these 4 CV admissions, 3 occurred in the sequence A randomization (median: 58 days; IQR: 32-350 days) and 1 in sequence B (17 days; this patient withdrew their informed consent at visit 2). No admissions were registered during the 15-day β-blocker withdrawal period in either arm. During this period, 2 episodes of atrial fibrillation were recorded (both successfully cardioverted).

At visit 5, β-blockers were finally withdrawn in 27 patients, and the dosage was reduced by at least one-half in 19 patients.

DISCUSSION

In patients with HFpEF and chronotropic incompetence, β-blocker withdrawal resulted in substantial short-term improvement in peak Vo_2 (**Central Illustration**). Furthermore, we found significant improvement in surrogates of quality of life and left ventricular end-diastolic pressures. However, no significant changes were found for natriuretic peptides, other echocardiographic markers, or cognitive parameters. To our knowledge, the PRESERVE-HR (β-blockers Withdrawal in Patients With HFpEF and Chronotropic Incompetence: Effect on Functional Capacity) study is the first trial to evaluate, in a short time frame, the effect of β-blocker withdrawal on maximal functional capacity in a subset of patients with HFpEF and chronotropic incompetence. Overall, our results highlight the role of chronotropic incompetence as a crucial pathophysiological mechanism in HFpEF and consequently open new therapeutic avenues in these patients.

HFpEF: A NEED FOR PRECISION MEDICINE. The failure of multiple therapeutic strategies in demonstrating a robust clinical benefit in HFpEF likely reflects incomplete knowledge about the complex and heterogeneous pathophysiology of the syndrome (1,8,9,14). Indeed, the concept of HFpEF as a disorder of LV diastolic function has been recently revisited. Other significant pathophysiological contributors have been suggested to play a relevant role; these include impairment in ventricular-arterial coupling, systolic dysfunction beyond LVEF, low skeletal muscle O_2 extraction, pulmonary hypertension right-sided HF, inflammation, and chronotropic incompetence (1-4,14). Thus, traditional criteria are insufficient for an accurate diagnosis to identify the diverse underlying pathophysiological phenotype (7). Indeed, new widely available clinical tools aiming to identify different HFpEF phenotypes are the first and necessary step for individualizing the management of this complex syndrome.

CHRONOTROPIC INCOMPETENCE IN HFpEF. Chronotropic incompetence is defined as the inability of the heart to increase its rate appropriately with increased activity or demand. Chronotropic incompetence is a common finding in patients with HF

(3-6). In HF with reduced EF, chronotropic incompetence leads to exercise intolerance, impairs quality of life, and is associated with adverse CV events (3,4). In HFpEF, chronotropic incompetence is common in recent studies and associated with a limited functional capacity (3-6,15). The mechanism of chronotropic incompetence in HFpEF remains elusive, but several have been proposed. There is an open debate about whether a blunted increase in HR is the cause of the reduced exercise capacity or is secondary to premature cessation of exercise because of high filling pressures or early muscle fatigue (3,4,16). Peripheral muscle dysfunction, autonomic nervous imbalance, sinus node remodeling causing a reduction in sinus node reserve, and impairment of cardiac β-receptor responsiveness have been proposed as causal mechanisms behind the chronotropic incompetence in HF (3,4,16).

β-BLOCKER TREATMENT IN HFpEF. The evidence endorsing the utility of β-blockers in HFpEF is inconclusive. A Japanese open-label trial that enrolled 245 patients with HF and LVEF >40% showed a neutral effect of carvedilol versus placebo on the composite of CV death or unplanned HF hospitalization (17). Likewise, a recent patient-based meta-analysis of 11 randomized HF trials did not demonstrate any benefit of β-blocker for patients with HFpEF (18). Despite the lack of evidence of their benefit, the use of β-blockers in HFpEF is highly prevalent (8,9). For instance, in the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial, 79.5% of patients were on β-blocker treatment at baseline (9). This lack of consensus about the benefit of β-blocker in HFpEF may be attributed to the phenotypic heterogeneity of this syndrome. These patients were treated with β-blockers with no consideration of their HFpEF phenotype and essential factors that may determine the adequacy of such treatment, such as age, sex, presence of stable angina, type of rhythm, baseline HR, HR reserve, and chronotropic incompetence, among others.

MECHANISMS BEHIND THESE FINDINGS. Recently investigators have questioned traditional beliefs supporting the benefit of lowering HR in HFpEF by prolonging the time for ventricular filling (10). HR is a crucial determinant of cardiac output. At maximal exercise in healthy control subjects, Vo_2 increases about 4-fold, with a 2.2-fold increase in HR (3,19). Experimental studies have shown that, within a physiological range, higher HRs are associated with a reduction in LV end-diastolic pressure caused by accelerated myocardial contraction and relaxation (20). In HFpEF, these beneficial effects have also been suggested by documenting a reduction in NT-proBNP, an established surrogate of LV end-diastolic pressures (21). In agreement with these findings, we found a significant and positive association between $\Delta HR_{peak\ exercise}$ and Δpeak Vo_2 similar to that previously described by other investigators (3,4,22).

Furthermore, clinical results from HR-lowering strategies in HFpEF have been discouraging. For instance, in the ELANDD (Effects of the Long-term Administration of Nebivolol on the Clinical Symptoms, Exercise Capacity, and Left Ventricular Function of Patients With Diastolic Dysfunction) trial, carvedilol versus placebo failed to improve the 6-minute walking distance test in 116 patients with HF and LVEF >45% (23). A recent secondary analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial showed that β-blocker use was associated with an increased risk of HF hospitalizations in patients with LVEF ≥50% (8). In a crossover randomized clinical trial that included 22 patients who were symptomatic for HFpEF with predicted peak Vo_2 <80%, 15-day treatment with ivabradine resulted in a mean HR reduction of 20 beats/min together with a decreased peak Vo_2 compared with placebo (−2.1 vs 0.9 mL/kg/min; $P = 0.003$) (12). The EDIFY (Preserved Left Ventricular Ejection Fraction Chronic Heart Failure With Ivabradine Study) randomized clinical trial, which enrolled 179 patients with HFpEF and HR >70 beats/min, failed to improve the E/e′ ratio, walking distance, or NT-proBNP levels (24). Beyond the negative chronotropic effects of β-blockers, some investigators have also suggested that HR-lowering drugs may have harmful effects on exercise-dependent lusitropy by prolonging diastolic filling, increasing ventricular volumes and pressures, and increasing central pressures (25,26).

CLINICAL IMPLICATIONS AND FUTURE LINES OF RESEARCH. Under the premise that our findings are further validated with subsequent trials, we propose the withdrawn of β-blockers in patients with HFpEF and documented chronotropic incompetence as a therapeutic strategy to improve short-term functional capacity. Knowing that chronotropic incompetence is highly prevalent in many patients with HFpEF treated with β-blockers (3,4,8,9), we speculate that a non-negligible proportion of patients with HFpEF in daily clinical practice may benefit from such

withdrawal. In this study, we carefully selected a population with stable HFpEF, baseline HR <65 beats/min, and established chronotropic incompetence after a CPET. It is essential to underline that we evaluated a subset of patients with HFpEF, and thus, our results should not be extrapolated to the entire spectrum of patients with HFpEF.

Because there are so many uncertainties in the diagnosis and management of HFpEF, future studies in this field should look into: 1) a better understanding of the pathophysiology of chronotropic incompetence; and 2) defining the clinical utility of β-blockers according to age, sex, LVEF, right ventricular parameters, functional capacity, comorbidities, type of electrocardiogram rhythm, HR, and chronotropic incompetence. We believe that some of these clinical characteristics may significantly modify the effect of β-blockers in patients with HFpEF. We also need more robust evidence about the long-term efficacy and safety of β-blocker cessation. It is worth noting that current trials are evaluating the impact of rate-adaptive atrial pacing on exercise capacity in patients with HFpEF (RAPID-HF [Efficacy Study of Pacemakers to Treat Slow Heart Rate in Patients With Heart Failure]; NCT02145351).

Finally, this study emphasizes the role of exercise tests in evaluating patients with HFpEF. More specifically, CPET emerges as a useful clinical tool for identifying a chronotropic incompetence-HFpEF phenotype and consequently for tailoring the treatment with β-blockers. It is a small step into phenotyping and personalizing management in these patients.

STUDY LIMITATIONS. First, the current findings applied only to patients with stable HFpEF and established chronotropic incompetence, predominantly in sinus rhythm. They cannot be extrapolated to other clinical scenarios, prevalent subgroups, or milder forms of the syndrome. Second, low statistical power may explain the neutral effect of the intervention on some secondary endpoints. Third, oxygen pulse and perceived exertion tests for addressing changes in HF-related symptoms were not evaluated. Finally, the study was not designed to evaluate the mid- to long-term functional and clinical effects of β-blocker withdrawal.

CONCLUSIONS

In this multicenter, randomized, crossover study, short-term β-blocker withdrawal resulted in a short-term improvement of maximal functional capacity in patients with HFpEF and chronotropic incompetence. Further studies are needed to confirm these results, elucidate the underlying pathophysiological mechanisms behind these findings, and explore adverse clinical outcomes.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by grants from the Spanish Ministry of Economy and Competitiveness through the Carlos III Health Institute: Fondos de Investigación Sanitaria (PI17/01426), and cofunded with European Regional Development Fund and Centro de Investigación Biomédica en Red Enfermedades Cardiovascular funds (16/11/00420 and 16/11/00403). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Julio Núñez, Servicio de Cardiología, Hospital Clínico Universitario, Instituto de Investigación Sanitaria, Universitat de Valencia, Valencia-Spain, Avenida de Blasco Ibáñez, 17, 46010 Valencia, Spain. E-mail: yulnunez@gmail.com. Twitter: @yulnunezvill. OR Dr Eloy Domínguez, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Universitat Jaume I, Castellón-Spain, Avinguda de Vicent Sos Baynat, s/n, 12071 Castellón, Spain. E-mail: edominguezmafe@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Chronotropic incompetence impairs exercise capacity in patients with HFpEF. Withdrawing β-blocker medications, which blunt the chronotropic response, can improve short-term functional capacity in patients with HFpEF and chronotropic incompetence.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the long-term efficacy and safety of β-blocker withdrawal and to clarify the pathophysiological mechanisms involved.

REFERENCES

1. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014;11(9):507–515.

2. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56(11):845–854.

3. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123(8):1010–1020.

4. Zweerink A, van der Lingen ACJ, Handoko ML, van Rossum AC, Allaart CP. Chronotropic incompetence in chronic heart failure. *Circ Heart Fail*. 2018;11(8):e004969.

5. Domínguez E, Palau P, Núñez E, et al. Heart rate response and functional capacity in patients with chronic heart failure with preserved ejection fraction. *ESC Heart Fail*. 2018;5(4):579–585.

6. Wolsk E, Kaye DM, Komtebedde J, et al. Determinants and consequences of heart rate and stroke volume response to exercise in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2021;23(5):754–764. https://doi.org/10.1002/ejhf.2146

7. Ponikowski P, Voors AA, Anker SD, et al, Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18(8):891–975.

8. Silverman DN, Plante TB, Infeld M, et al. Association of β-blocker use with heart failure hospitalizations and cardiovascular disease mortality among patients with heart failure with a preserved ejection fraction: a secondary analysis of the TOPCAT trial. *JAMA Netw Open*. 2019;2(12):e1916598.

9. Solomon SD, McMurray JJV, Anand IS, et al, PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609–1620.

10. Meyer M, LeWinter MM. Heart rate and heart failure with preserved ejection fraction: Time to slow β-blocker use? *Circ Heart Fail*. 2019;12(8):e006213.

11. Palau P, Seller J, Domínguez E, et al. Beta-blockers withdrawal in patients with heart failure with preserved ejection fraction and chronotropic incompetence: effect on functional capacity rationale and study design of a prospective, randomized, controlled trial (the Preserve-HR trial). *Clin Cardiol*. 2020;43(5):423–429.

12. Pal N, Sivaswamy N, Mahmod M, et al. Effect of selective heart rate slowing in heart failure with preserved ejection fraction. *Circulation*. 2015;132(18):1719–1725.

13. Krull JL, MacKinnon DP. Multilevel modeling of individual and group level mediated effects. *Multivariate Behav Res*. 2001;36(2):249–277.

14. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*. 2016;134(1):73–90.

15. Palau P, Domínguez E, Seller J, Sastre C, Bayés-Genís A, Núñez J. Chronotropic incompetence predicts distance walked in six-minute walk test in heart failure with preserved ejection fraction. *J Card Fail*. 2020;26(11):1024–1025.

16. Sarma S, Stoller D, Hendrix J, et al. Mechanisms of chronotropic incompetence in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2020;13(3):e006331.

17. Yamamoto K, Origasa H, Hori M, J-DHF Investigators. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). *Eur J Heart Fail*. 2013;15(1):110–118.

18. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39(1):26–35.

19. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res*. 1986;58(2):281–291.

20. Karliner JS, LeWinter MM, Mahler F, Engler R, O'Rourke RA. Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. *J Clin Invest*. 1977;60(3):511–521.

21. Nambiar L, Silverman D, Vanburen P, LeWinter M, Meyer M. Beta-blocker cessation in stable outpatients with heart failure with a preserved ejection fraction. *J Card Fail*. 2020;26(3):281–282.

22. Magrì D, Palermo P, Cauti FM, et al. Chronotropic incompetence and functional capacity in chronic heart failure: no role of β-blockers and β-blocker dose. *Cardiovasc Ther*. 2012;30(2):100–108.

23. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. *Eur J Heart Fail*. 2012;14(2):219–225.

24. Komajda M, Isnard R, Cohen-Solal A, et al, EDIFY Investigators. Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial. *Eur J Heart Fail*. 2017;19(11):1495–1503.

25. Cheng CP, Igarashi Y, Little WC. Mechanism of augmented rate of left ventricular filling during exercise. *Circ Res*. 1992;70(1):9–19.

26. Messerli FH, Rimoldi SF, Bangalore S, Bavishi C, Laurent S. When an increase in central systolic pressure overrides the benefits of heart rate lowering. *J Am Coll Cardiol*. 2016;68(7):754–762.

KEY WORDS β-blockers, chronotropic incompetence, crossover trial, heart rate, HFpEF, peak Vo_2, percentage of predicted peakVo_2

APPENDIX For a supplemental figure, please see the online version of this paper.