

# Heart rate response and functional capacity in patients with chronic heart failure with preserved ejection fraction

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## Abstract

**Aims** The mechanisms of exercise intolerance in heart failure with preserved ejection fraction (HFpEF) are not yet elucidated. Chronotropic incompetence has emerged as a potential mechanism. We aimed to evaluate whether heart rate (HR) response to exercise is associated to functional capacity in patients with symptomatic HFpEF.

**Methods and results** We prospectively studied 74 HFpEF patients [35.1% New York Heart Association Class III, 53% female, age (mean  $\pm$  standard deviation)  $72.5 \pm 9.1$  years, and 59.5% atrial fibrillation]. Functional performance was assessed by peak oxygen consumption (peak  $\text{VO}_2$ ). The mean (standard deviation) peak  $\text{VO}_2$  was  $10 \pm 2.8$  mL/min/kg. The following chronotropic parameters were calculated: Delta-HR (HR at peak exercise – HR at rest), chronotropic index (CI) = (HR at peak exercise – resting HR)/[(220 – age) – resting HR], and CI according to the equation developed by Keteyian *et al.* (CIK) (HR at peak exercise – HR at rest)/[119 + (HR at rest/2) – (age/2) – 5 – HR at rest]. In a bivariate setting, peak  $\text{VO}_2$  was positively and significantly correlated with Delta-HR ( $r = 0.35$ ,  $P = 0.003$ ), CI ( $r = 0.27$ ,  $P = 0.022$ ), CIK ( $r = 0.28$ ,  $P = 0.018$ ), and borderline with HR at peak exercise ( $r = 0.22$ ,  $P = 0.055$ ). In a multivariable linear regression analysis that included clinical, analytical, echocardiographic, and functional capacity covariates, the chronotropic parameters were positively associated with peak  $\text{VO}_2$ . We found a linear relationship between Delta-HR and peak  $\text{VO}_2$  ( $\beta$  coefficient of 0.03; 95% confidence interval: 0.004–0.05;  $P = 0.030$ ); conversely, the association among CIs and peak  $\text{VO}_2$  was exponentially shaped.

**Conclusions** In patients with chronic HFpEF, the HR response to exercise was positively associated to patient's functional capacity.

**Keywords** Heart failure with preserved ejection fraction; Functional capacity; Chronotropic response

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## Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) has become the most common form of HF in elderly patients.<sup>1,2</sup> Exercise intolerance and reduced functional capacity are the main clinical manifestations in HFpEF and are associated to decreased quality of life and poor prognosis.<sup>3,4</sup> Despite great efforts, the pathophysiological mechanisms of impaired exercise capacity in these patients are not yet fully elucidated.<sup>5</sup> Although diastolic dysfunction

has been the focus of attention of the researchers, different pathophysiological mechanisms have also been proposed.<sup>6,7</sup> Among them, some evidence endorsed abnormal heart rate (HR) response to exercise as a potential mechanism linked to exercise intolerance in these patients;<sup>8–10</sup> however, the evidence is scarce, and its contribution in patients with chronic HFpEF remains unclear. In this work, we aimed to evaluate the relationship between HR response to exercise and exercise capacity patients with stable chronic HFpEF.

## Methods

### Study population

Between June 2012 and May 2016, we prospectively included 74 outpatients with symptomatic HFpEF followed in the outpatient HF clinic of a single academic centre. The HFpEF diagnosis was performed by trained cardiologists according to the definition proposed by the European Society of Cardiology guidelines.<sup>11</sup> Patients fulfilled all the following inclusion criteria: (a) New York Heart Association (NYHA) Functional Class  $\geq$ II, (b) previous admission for acute HF, (c) clinical stability during the last 3 months, (d) left ventricular ejection fraction  $>50\%$ , and (e) left ventricle hypertrophy and/or left atrial enlargement and/or diastolic dysfunction estimated by two-dimensional echocardiography. Exclusion criteria were (a) inability to perform a valid exercise test; (b) significant primary moderate to severe valve disease; (c) acute coronary syndrome, cardiac surgery, or revascularization within the previous 3 months; and (d) significant primary pulmonary disease, including pulmonary arterial hypertension, chronic thromboembolic pulmonary disease, or chronic obstructive pulmonary disease.

This study was approved by an institutional review committee conforming to the ethical guidelines of the 1975 Declaration of Helsinki, and all patients gave informed consent. Clinical, electrocardiographic, and treatment characteristics were recorded in electronic forms. Patients enrolled underwent cardiopulmonary exercise testing, two-dimensional transthoracic echocardiography, 6 minute walk test, and a blood laboratory test.

### Cardiopulmonary exercise testing

Maximal functional capacity was evaluated with an incremental and symptom-limited cardiopulmonary exercise testing (CORTEX Metamax 3B) on a bicycle ergometer, beginning with a workload of 10 W and increasing stepwise at 10 W increments every 1 min. During exercise, patients were continuously monitored with 12-lead electrocardiogram and blood pressure measurements every 2 min. Gas exchange data and cardiopulmonary variables were averaged every 10 s values. Peak oxygen consumption (peak  $\text{VO}_2$ ) was considered the highest value of  $\text{VO}_2$  during the last 20 s of exercise. The ventilatory efficiency ( $\text{VE}/\text{VCO}_2$  slope), defined as the slope of the linear relationship between minute ventilation (VE) and carbon dioxide production ( $\text{VCO}_2$ ), was determined by measuring the slope across the entire course of exercise. HR was assessed by continuous electrocardiogram. Resting HR was calculated previous to testing as an average HR during 3 minutes of seated rest; and peak HR was defined as the highest HR achieved during exercise.

### Endpoints

Cardiopulmonary exercise testing results were used to establish the chronotropic response to exercise effort. The primary endpoint was to determine the relationship between Delta-HR and chronotropic index (CI) with peak  $\text{VO}_2$ . Delta-HR was defined as the absolute difference in HR (HR at peak exercise – HR at rest) and CI defined as  $\text{CI} = (\text{HR at peak exercise} - \text{HR at rest}) / [(220 - \text{age}) - \text{HR at rest}]$ .<sup>12,13</sup> We defined chronotropic incompetence based on established criteria<sup>14–16</sup>: CI  $<0.8$  for those not taking beta-blockers and  $<0.62$  for those taking beta-blockers. CI according to the equation developed by Keteyian *et al.*<sup>17</sup> (CIK) defined as  $(\text{HR at peak exercise} - \text{HR at rest}) / [119 + (\text{HR at rest}/2) - (\text{age}/2) - 5 - \text{HR at rest}]$  was selected as a secondary endpoint. The CIK has been considered suitable to predict maximum HR in patients with HF taking beta-blockers.<sup>17,18</sup> In a sensitivity analyses, we explored whether the effect of Delta-HR on peak  $\text{VO}_2$  differed according age ( $>70$  vs.  $\leq 70$  years), gender (male vs. female), rhythm [sinus rhythm (SR) vs. atrial fibrillation (AF)], body mass index ( $>30$  vs.  $\leq 30$   $\text{kg}/\text{m}^2$ ), N-terminal pro-BNP (NT-pro-BNP) ( $>1000$  vs.  $\leq 1000$   $\text{pg}/\text{mL}$ ), and treatment with beta-blockers (yes vs. no).

### Statistical analysis

The bivariate correlations of Delta-HR, CI, and CIK with peak  $\text{VO}_2$  were assessed with Pearson/Spearman correlation coefficient as appropriate. In addition, each of these three exposures was tested as independent predictors of peak  $\text{VO}_2$  using multivariable linear regression analysis. As covariates, most of the variables presented in *Table 1* were initially included in each of the three multivariable models. From there, a reduced model was achieved through a backward selection procedure; for each continuous predictor variable, the linearity assumption with peak  $\text{VO}_2$  tested and the variable transformed to the appropriate fractional polynomial if necessary. To eliminate the potential bias due to ‘regression to the mean’, HR at baseline was included as an additional covariate in the regression models for Delta-HR (analysis of covariance). The discriminative ability of the multivariate models was evaluated with the adjusted  $R^2$ . A two-sided  $P$ -value of  $<0.05$  was considered to be statistically significant for all analyses. All analyses were performed using STATA 14.1.

## Results

The mean (standard deviation) of age was  $72.5 \pm 9.1$ ; 53% of patients were female, 35.1% displayed NYHA III/IV, 59.5% showed AF, and 79.7% were under beta-blocker treatment.

**Table 1** Baseline characteristics of study population

Variables	Included patients (n = 74)
<b>Demographic, medical history and vital signs</b>	
Age, years	72.5 ± 9.1
Female, n (%)	39 (53)
Weight, kg	82 ± 15.1
Body surface area, m <sup>2</sup>	1.9 ± 0.2
Body mass index, kg/m <sup>2</sup>	31.2 (28.2–35)
Hypertension, n (%)	67 (90.5)
Dyslipidaemia, n (%)	61 (81)
Diabetes mellitus, n (%)	37 (50)
Ischaemic heart disease, n (%)	27 (36.5)
Baseline NYHA Class III/IV, n (%)	26 (35.1)
Previous smoker, n (%)	26 (35.1)
Atrial fibrillation, n (%)	44 (59.5)
Systolic blood pressure, mmHg	129 ± 16
HR, b.p.m.	69 ± 14
HR at peak exercise, b.p.m.	99 ± 21
Delta-HR, b.p.m.	30 ± 16
CI	0.39 ± 0.22
CIK	0.70 ± 0.38
<b>Laboratory</b>	
Haemoglobin, g/dL	12.8 ± 1.5
Ferritin, ng/mL	91 (48–175)
GFR, mL/min/m <sup>2</sup>	58.4 ± 24.3
NT-pro-BNP, pg/mL	1021 (363–2109)
<b>Echocardiography</b>	
LVEF, %	68.4 ± 9.8
TAPSE, mm	21.8 ± 4.2
LAVI, mL/m <sup>2</sup>	46 (39–58)
LVMI g/m <sup>2</sup>	125 (104–125)
E/e' ratio	16.9 (13.4–23.4)
PASP, <sup>a</sup> mmHg	46 (39–53)
<b>Exercise performance</b>	
Peak VO <sub>2</sub> , mL/min/kg	10 ± 2.8
VE/VCO <sub>2</sub> slope	35 ± 7.6
RER	1.04 ± 0.1
METs	2.4 ± 0.9
6-MWT, m	262 (198–350)
<b>Treatment</b>	
Beta-blockers, %	59 (79.7)
ACEI, %	14 (18.9)
ARB, %	36 (48.6)
Anti-aldosterone, %	21 (28.3)
Loop diuretics, %	58 (78.4)
Thiazides, %	22 (29.7)
Digoxin, %	5 (6.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; CI, chronotropic index based on the Astrand formula (220 – age); CIK, chronotropic index according to the equation of Keteyian *et al.*; Delta-HR, absolute difference between heart rate at peak exercise and heart rate at baseline; GFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; HR, heart rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; METs, metabolic equivalents; NT-pro-BNP, NT-pro-BNP; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; peak VO<sub>2</sub>, peak oxygen consumption; RER, respiratory exchange ratio; 6-MWT, distance walked in 6 minutes; TAPSE, tricuspid annular plane systolic excursion; TSAT, transferrin saturation index; VE/VCO<sub>2</sub> slope, relationship between minute ventilation and the rate of CO<sub>2</sub> elimination. Continuous variables are presented as mean ± standard deviation or median (interquartile range) as appropriate; categorical variables as percentages.

<sup>a</sup>Data available in 59 patients.

The means (standard deviation) of resting HR and systolic blood pressures were 69 ± 14 b.p.m. and 129 ± 16 mmHg, respectively. The mean peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, respiratory exchange ratio (RER), and peak HR were 10 ± 2.8 mL/min/kg, 35 ± 7.6, 1.04 ± 0.1, and 99 ± 21 b.p.m., respectively. Following the criteria of chronotropic incompetence defined above, we found that 66 patients (89.2%) displayed chronotropic incompetence. Baseline characteristics of the study population are summarized in *Table 1*.

There were no differences in the medians (interquartile range) of Delta-HR across age (>70 vs. ≤70 years), gender (male vs. female), rhythm (SR vs. AF), body mass index (>30 vs. ≤30 kg/m<sup>2</sup>), NT-pro-BNP (>1000 vs. ≤1000 pg/mL), and treatment with beta-blockers (yes vs. no) as shown in *Figure 1*.

In a bivariate setting, peak VO<sub>2</sub> was negatively correlated with age ( $r = -0.39$ ,  $P = 0.001$ ), NT-pro-BNP ( $r = -0.26$ ,  $P = 0.028$ ), E/e' septal ( $r = -0.26$ ,  $P = 0.029$ ), and pulmonary artery systolic pressure ( $r = -0.32$ ,  $P = 0.015$ ) while positively correlated with haemoglobin ( $r = 0.41$ ,  $P < 0.001$ ), transferrin saturation index ( $r = 0.39$ ,  $P = 0.001$ ), serum ferritin ( $r = 0.28$ ,  $P = 0.022$ ), Delta-HR ( $r = 0.35$ ,  $P = 0.003$ ), CI ( $r = 0.27$ ,  $P = 0.022$ ), CIK ( $r = 0.28$ ,  $P = 0.018$ ), and RER ( $r = 0.53$ ,  $P < 0.001$ ). HR at peak exercise ( $r = 0.22$ ,  $P = 0.055$ ) and right ventricular function (tricuspid annular plane systolic excursion:  $r = 0.20$ ,  $P = 0.088$ ) were borderline correlated. Left atrial volume index ( $r = -0.16$ ,  $P = 0.179$ ), glomerular filtration rate (GFR:  $r = 0.15$ ,  $P = 0.210$ ), and HR at rest ( $r = -0.06$ ,  $P = 0.633$ ) were not correlated with peak VO<sub>2</sub>.

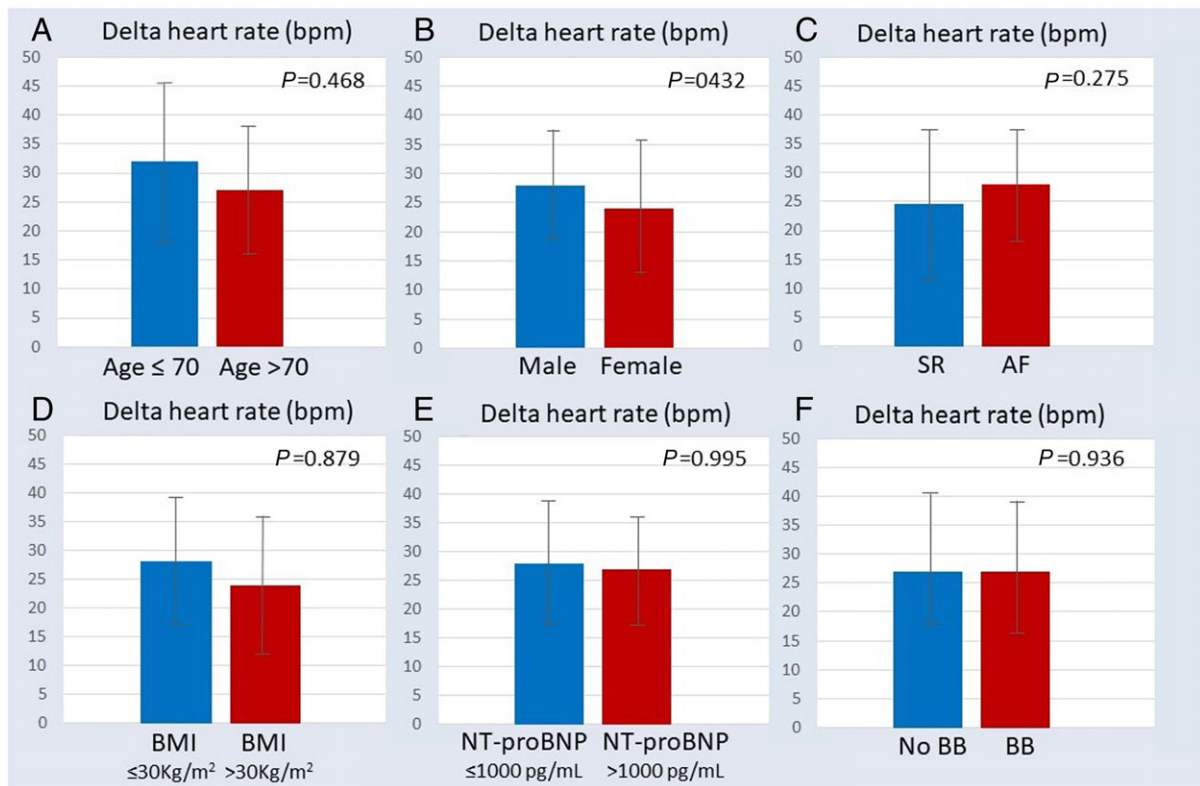
We performed multivariable linear regression analyses for each of the three exposures; Delta-HR (Model 1), CI (Model 2), and CIK (Model 3) included the following covariates: age, gender, body surface area, AF rhythm, NYHA ≥3, GFR, haemoglobin, NT-pro-BNP, E/e' septal, and RER. HR at baseline was included as additional covariate in the regression models for Delta-HR. The variables treatment with digoxin and beta-blockers did not achieve statistical significance, and thus, they were excluded. Each of the three exposures was positively associated with peak VO<sub>2</sub>.

In Model 1, Delta-HR was linear and positively associated with peak VO<sub>2</sub> [ $\beta$  coefficient of 0.03; 95% confidence interval (0.004–0.05);  $P = 0.030$ ]. *Figure 2A* depicts this association, after centring Delta-HR at its median value (27 b.p.m.). The  $R^2$  estimated for this model was 0.68.

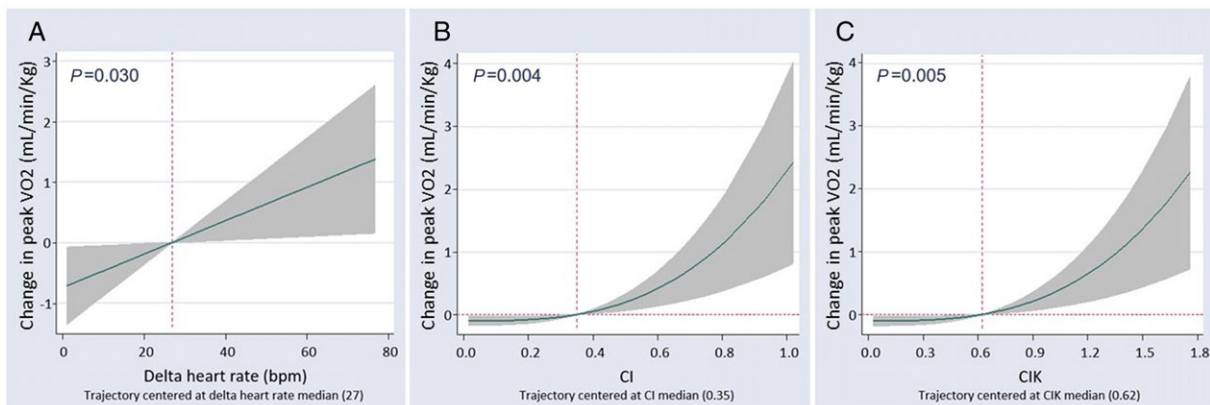
In Model 2, CI showed a positive and exponential association with peak VO<sub>2</sub> as depicted in *Figure 2B*. For instance, using as a reference point the median of CI (0.35) when CI is 0.41, 0.6, 0.81, and 1.02, the predicted mean change in peak VO<sub>2</sub> is 0.06, 0.41, 1.16, and 2.41 mL/min/kg, respectively. The  $R^2$  estimated for this model was 0.70.

Likewise, in Model 3, the adjusted association of CIK with peak VO<sub>2</sub> was also significant, positive, and exponentially shaped as shown in *Figure 2C*. For instance, using as reference point the median of CI (0.62) when CIK is 0.91, 1.24, 1.5, and 1.76, the predicted mean change in peak VO<sub>2</sub> is

**Figure 1** Delta heart rate across subgroups of age, gender, type of rhythm, body mass index, NT-pro-BNP, and beta-blocker treatment. AF, atrial fibrillation; BB, beta-blocker treatment; BMI, body mass index; NT-pro-BNP, N-terminal pro-BNP; SR, sinus rhythm.



**Figure 2** Functional form of the adjusted association among different chronotropic indexes and predicted change in peak  $\text{VO}_2$ . Variables modelled with fractional polynomials. CI, chronotropic index, a measure of chronotropic response based on the Astrand formula; CIK, chronotropic index according to the equation of Keteyian *et al.*; Delta heart rate, absolute difference between heart rate at peak exercise and heart rate at baseline; peak  $\text{VO}_2$ , peak oxygen consumption.



0.22, 0.72, 1.35, and 2.25 mL/min/kg, respectively. The  $R^2$  estimated for this model was 0.70.

In a sensitivity analyses, we found that the effect of Delta-HR on peak  $\text{VO}_2$  did not significantly differ according the pre-specified subgroups: age (>70 vs. ≤70 years:  $P$ -value for the interaction = 0.672), gender (male vs. female:  $P$ -value

for the interaction = 0.606), rhythm (SR vs. AF:  $P$ -value for the interaction = 0.160), body mass index (>30 vs. ≤30 kg/m<sup>2</sup>:  $P$ -value for the interaction = 0.631), NT-pro-BNP (>1000 vs. ≤1000 pg/mL:  $P$ -value for the interaction = 0.268), and treatment with beta-blockers (yes vs. no:  $P$ -value for the interaction = 0.986).

## Discussion

In this study, we found that patients with symptomatic HFpEF displayed a high prevalence of blunted HR response to exercise and it was independently associated to patient's functional capacity impairment evaluated by peak  $\text{VO}_2$ .

### Prevalence and pathophysiology of chronotropic incompetence

The prevalence of chronotropic incompetence reported among previous studies is widely variable, ranging from 20% to 75%.<sup>8–10,19–21</sup> The criteria used to define chronotropic incompetence, as well as patient characteristics (age, disease severity, heart rhythm, and drug therapy), could explain these differences. In the present study, we postulate that the greater severity and the proportion of beta-blocker treatment (79.7%) of the patients may explain the higher prevalence of chronotropic incompetence here reported.

An appropriate increase in peak  $\text{VO}_2$  during exercise depends on adequate HR response according to the Fick equation<sup>22</sup>:  $\text{VO}_2 = [\text{HR} \times \text{stroke volume}] \times [\text{arterial-venous oxygen content difference}]$ . In this way, chronotropic incompetence, defined as the inability of the heart to increase adequately during physical exertion, has been proposed as one of the key mechanisms linked to exercise intolerance in HFpEF in some studies.<sup>8–10,19</sup> The pathophysiology of impaired HR response is complex and has been associated to autonomic imbalances such as (a) the decrease in beta-receptor density;<sup>23</sup> (b) the desensitization of beta-receptors despite the presence of increased circulating catecholamine levels;<sup>24–26</sup> and (c) the remodelling of sinus node function.<sup>27</sup> However, the causative role of chronotropic incompetence in the pathophysiology of this syndrome is difficult to establish. Blunted HR response may just be a consequence of decreased exercise capacity in which other mechanisms such as premature cessation of exercise due to dyspnoea or muscle fatigue might be playing a pivotal role.<sup>6,28,29</sup> However, the high prevalence of chronotropic incompetence in the presence of adequate effort and the robust multivariate associations found in this study lead us to speculate abnormal HR response to exercise may play a causative role.

### Clinical implications

Lack of effective medical treatments for patients with HFpEF has driven an empiric medical management.<sup>30</sup> In agreement with present findings, previous studies exploring the effect of medical therapies such as beta-blockers<sup>31–35</sup> to reduce HR response have shown neutral or negative results on functional capacity<sup>35</sup> and adverse clinical endpoints<sup>33</sup> in patients with HFpEF. In this regard, studies of the effect of ivabradine treatment in terms of improvement of functional capacity in

HFpEF patients have shown contradictory results.<sup>36,37</sup> The main reasons underlying these controversial findings are unclear but may reflect several differences in the study designs, patient's characteristics, and the doses of ivabradine. Overall, we believe these inconsistent results reflect the complex and heterogeneous pathophysiology and different clinical phenotypes of this syndrome. In light of these findings, we postulate that the more advanced the disease, especially in elderly patients, the greater the importance of chronotropic incompetence as a crucial pathophysiological mechanism in patients with HFpEF.

Conversely, in the setting of HF with reduced ejection fraction (HFrEF), recently, Jamil *et al.*<sup>38</sup> examined the relationship between exercise HR rise and exercise capacity in patients with clinical stability and previous pacemaker implantation. The negative results obtained in this study contribute to our understanding of the role of HR response in patients with HFrEF, but the controversy in patients with HFpEF remains alive.

In our opinion, this line of research has important therapeutic implications. For instance, and based on this and other results, we may envision a potential clinical benefit of HR-lowering drug withdrawal in patients with HFpEF and chronotropic incompetence. Along this line, the RAPID-HF trial (NCT02145351) is currently testing the hypothesis that improved HR responsiveness via rate-adaptive atrial pacing will improve exercise capacity in patients with HFpEF. In addition, despite current evidence not strongly supporting beta-blocker therapy in HFpEF, these agents are frequently prescribed in daily clinical practice.<sup>39</sup> The results of this study called into question the use of beta-blockers in patients with HFpEF and chronotropic incompetence.

### Study limitations

There are some limitations that need to be acknowledged. First, the main limitations of this study are the lack of a control group of meaningful similarities and differences and the limited potential for generalizing our results to other populations with HF due to the small sample size. Second, although we did not find any differential effect of chronotropic parameters across the type of rhythm, we cannot exclude a Type II error. Further larger studies evaluating separately patients with SR and AF are warranted. Finally, with the present data, we cannot unravel the pathophysiological mechanism endorsing this association.

## Conclusions

In patients with chronic HFpEF, the HR response to exercise is positively associated to patient's functional capacity evaluated by peak  $\text{VO}_2$ . Further studies are warranted to

explore the pathophysiological role of chronotropic incompetence in HFpEF.

## Conflict of interest

None declared.

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