RESEARCH

Cardiovascular Therapeutics

Chronotropic Incompentence and Functional Capacity in Chronic Heart Failure: No Role of β-Blockers and β-Blocker Dose

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SUMMARY

Aim: To assess the effect of chronotropic incompetence on functional capacity in chronic heart failure (CHF) patients, as evaluated as NYHA and peak oxygen consumption (pVO_2), focusing on the presence and dose of β-blocker treatment. **Methods**: Nine hundred and sixty-seven consecutive CHF patients were evaluated, 328 of whom were discarded because they failed to meet the study criteria. Of the 639 analyzed, 90 were not treated with β-blockers whereas the other 549 were. The latter were further subdivided in high (n = 184) and low (n = 365) β-blockers daily dose group in accordance with an arbitrary cut-off of 25 mg for carvedilol and of 5 mg for bisoprolol. Failure to achieve 80% of the percentage of maximum age predicted peak heart rate (%Max PHR) or of HR reserve (%HRR) constituted chronotropic incompetence. **Results**: No differences were found in NYHA or pVO2 between patients with and without β-blockers and, similarly, between high and low β-blocker dose groups. Twenty and sixty-nine percent of not β-blocked patients showed chronotropic incompetence according to %Max PHR and %HRR, respectively, whereas this prevalence rose to 61% and 84% in those on β-blocker therapy. Patients taking β-blockers without chronotropic incompetence, as inferable from both %Max PHR and %HRR, showed higher NYHA and pVO2 regardless of drug dose, whereas, in not β-blocked patients, only %HRR revealed a difference in functional capacity. At multivariable analysis, HR increase during exercise (ΔHR) was the variable most strongly associated to pVO2 (β: 0.572; SE: 0.008; $P < 0.0001$) and NYHA class (β: −0.499; SE: 0.001; $P < 0.0001$). **Conclusions**: ΔHR is a powerful predictor of CHF severity regardless of the presence of β-blocker therapy and of β-blocker daily dose.

Introduction

Patients with chronic heart failure (CHF) often show reduced exercise capacity, which is usually assessed as reduced peak oxygen consumption (pVO_2) during an incremental exercise test with metabolic gas exchange analysis (CPET) [1–6]. Many factors may be implied in exercise intolerance worsening and, possibly, in the prognosis of CHF patients including chronotropic incompetence [7–9]. However, the precise role of chronotropic incompetence on exercise tolerance is still controversial [10–14]. Indeed, it is well known that chronotropic incompetence shows a progressively higher prevalence with increasing CHF severity [3,14]. Indeed, chronotropic incompetence

in CHF may arise from the reduced myocardial sensitivity to sympathetic modulation together with the β-receptor downregulation interaction, both likely consequences of the sympathetic overactivity observed in CHF [15–17]. Moreover, β-blocker therapy, a medication used worldwide for CHF, reduces rest heart rate (HR) and exercise-induced HR increases. Nevertheless, β-blocker therapy undoubtedly improves symptoms and prognosis in CHF patients [18–21]. Chronotropic incompetence definition and quantification in CHF patients is also *per se* debated, particularly in patients treated with β-blockers [13,22–24]. Usual parameters to assess chronotropic incompetence are peak exercise HR and exercise-induced HR increases. However, because peak exercise HR is strongly correlated with age, it has been suggested considering a patient as chronotropically incompetent when less than 80% of the age-predicted HR is achieved [25]. Unfortunately, peak exercise HR could be heavily influenced by HR at rest, which may be low because of β-blocker therapy and β-blocker dose. Consequently, other approaches have been proposed to evaluate chronotropic incompetence [11,22,26]. One of the proposed options to percentage of maximum age predicted peak HR (%Max PHR) involves the concept of percentage of HR reserve achieved during exercise (%HRR). The HRR is calculated as the difference between Max PHR (220 beats – age) and resting HR. Failure to cover at least 80% of HRR constitutes chronotropic incompetence [11,26].

The aim of this study was to assess, in a large cohort of stable CHF patients, the effect of chronotropic incompetence on functional capacity, as assessed clinically by NYHA class and physiologically by pVO_2. Furthermore, we also focused our attention on possible differences in chronotropic incompetence versus exercise tolerance according to β-blocker treatment and β-blocker dose. To do so, we reanalyzed all cardiopulmonary exercise tests (CPET) done in our laboratory in CHF patients without and with β-blocker therapy, and namely carvedilol or bisoprolol, categorizing the latter in two groups according to daily drug dosage.

Methods

Study Sample

We reanalyzed all CPET performed in our Heart Failure Unit Clinic between June 2001 and March 2009 in CHF patients in stable clinical conditions, NYHA classes I–III, with left ventricle ejection fraction (LVEF) $\leq$50%. Treatment was stable and considered optimized by the HF cardiologist in charge of the patient.

We excluded subjects with history and/or clinical documentation of pulmonary embolism or primary valvular heart disease, pericardial disease, severe obstructive lung disease, primary pulmonary hypertension or occupational lung disease, asthma, moderate-severe renal failure (serum creatinine >2 mg/dL), significant peripheral vascular disease, second or higher degree atrio-ventricular block and exercise-induced angina, and/or ST changes. We also excluded from the analysis CHF subjects who did a submaximal effort as evaluable by a <1.05 respiratory exchange ratio (RER) and those whose exercise was interrupted as the result of a medical decision before maximal effort was reached, usually due to severe hypertension or severe arrhythmia, even if RER was >1.05. CHF patients with a non-HR responding pacemaker were excluded. Eventually, we decided to exclude from the analysis all patients on any other β-blockers apart from carvedilol or bisoprolol, and specifically nebivolol and metoprolol, because too few to be assessed. Carvedilol equivalent dose was calculated for bisoprolol treated patients as bisoprolol dose $\times$ 5 [4]. A daily dose of 25 mg of carvedilol and of 5 mg of bisoprolol was arbitrarily fixed as cut-off value to separate high from low β-blocked group.

We analyzed peak HR and HR increase during exercise (ΔHR). However, chronotropic incompetence was defined using the %Max PHR and the %HRR achieved with less than 80% as cut-off value [22,25,26].

Echocardiography examination was performed in our HF unit on each patient within 6 months from CPET. The LVEF was calculated using biplane Simpson's technique [27].

The study and the access to private health information were approved by the local intern review board. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the paper as written.

Cardiopulmonary Exercise Test

A maximal symptom-limited CPET was performed on an electronically braked cycloergometer (Ergometrics-800, SensorMedics, Yorba Linda, CA, USA), with the subject wearing a nose clip and breathing through a mass flow sensor (Vmax29C, SensorMedics) connected to a saliva trap. A personalized ramp exercise protocol was chosen, aiming at a test duration of 10 $\pm$ 2 min [28]. The exercise was preceded by a few minutes of resting breath-by-breath gas exchange monitoring and by a 3-min unloaded warm-up. A 12-lead ECG, blood pressure, and HR were also recorded. CPET was self-terminated by the subjects when they claimed that they had achieved the maximal effort. However, we considered that maximal effort was achieved if the RER (VCO_2/VO_2) was above 1.05. All tests were reevaluated by two expert readers blinded

to β-blocker therapy presence, molecule used, and β-blocker daily dose. The anaerobic threshold (AT) was identified by V-slope analysis of VO_2 and VCO_2 and confirmed by specific behavior of O_2 (VE/VO_2) and CO_2 (VE/VCO_2) ventilatory equivalents and end-tidal pressure of O_2 and CO_2 [29].

Statistical Analysis

Unless otherwise indicated, all data are expressed as mean ± SD. Categorical variables were compared with χ^2 test; a two-sample t-test was used to compare the general characteristics and other continuous data between patient with and without β-blocker therapy. Statistical analysis was also performed by subdividing patients who were taking β-blockers into two groups establishing a cut-off value of 25 mg for carvedilol dose or 5 mg for bisoprolol. We also made a comparison by subdividing the same population under β-blocker treatment into four different subgroups according two different methods of chronotropic incompetence classification (%Max–PHR and %HRR). Because of the normal distribution, a Pearson correlation was used to disclose possible correlations between all the parameters evaluated in each subgroup (entire CHF population, CHF patient with and without β-blocker therapy). Eventually, a multivariable linear regression analysis with stepwise selection of variables (age, LVEF, hemoglobin, peak HR, rest HR, ΔHR, %Max PHR, %HRR, and β-blocker therapy and dose) was used to disclose predictors independently associated with functional capacity as per NYHA classification and pVO_2. A P-value < 0.05 was considered statistically significant. All data were evaluated with the database SPSS-PC+ (SPSS-PC+ Inc., Chicago, IL, USA). All tests were two-sided. A P-value of less than or equal to 0.05 was considered statistically significant.

Results

We identified 967 CHF patients with CPET suitable for our primary analysis. The diagram of study sample, according to the selection criteria, is reported in Figure 1. From the 967 tests, we firstly excluded 263 because maximal effort was not achieved (RQ < 1.05 or interrupted for medical reasons). We also excluded 33 tests because of pacemaker-related chronotropic incompetence and, eventually, another 32 tests because subjects were treated with metoprolol or nebivolol.

Of the 639 effectively analyzed CHF patients, 90 (14%) did not receive β-blockers whereas 549 (86%) did, being 325 under carvedilol treatment and 224 under bisoprolol treatment. Patients with and without β-blocker therapy were well matched with respect to age, gender distribution, LVEF, RER, and functional capacity assessed either in terms of NYHA class or as pVO_2 (Table 1). Moreover, atrial fibrillation prevalence was slightly but significantly lower in patients with β-blockers than those without (12% vs. 20%, $P = 0.041$) while no difference between these two groups was found with respect to ischemic etiology (53% vs. 55%, P = ns) and diabetes prevalence (19% vs. 17%, P = ns). Patients taking β-blocker therapy had an average carvedilol or carvedilol equivalent dose for bisoprolol-treated subjects of 18 ± 12 mg. Treatment with digoxin and amiodarone showed

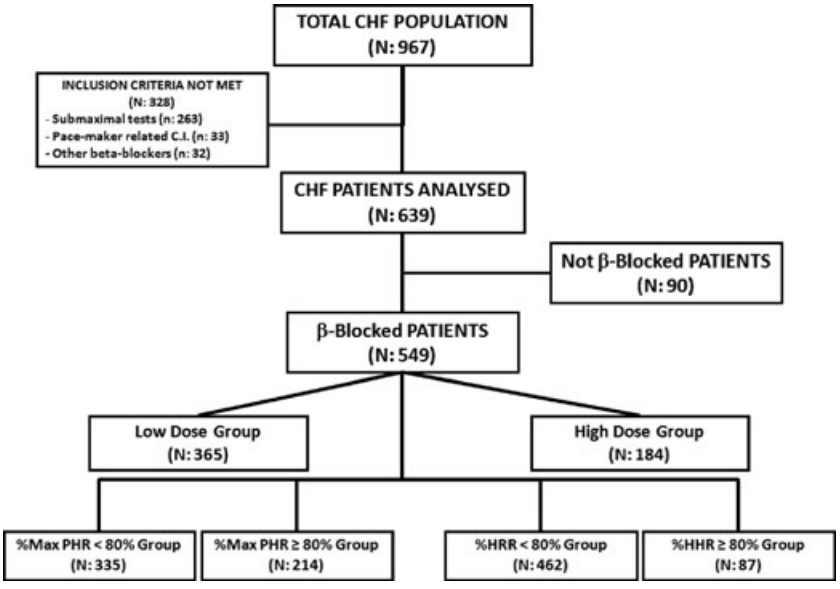

Figure 1 Diagram showing the step-by-step screening procedures of the population studied. C.I., chronotropic incompetence. Low dose group: chronic heart failure patients taking a daily dose of below 25 mg of carvedilol or below 5 mg of bisoprolol. High dose group: chronic heart failure patients taking a daily dose equal to or above than 25 mg of carvedilol or equal to or above 5 mg of bisoprolol.

Table 1 Clinical and CPET data of the study sample according β-blocker therapy

Variables	CHF with β-blocker therapy (N = 549)	CHF without β-blocker therapy (N = 90)	*P*-values
Age (years)	62 ± 11	64 ± 12	ns
Male, n (%)	451(82)	68(76)	ns
NYHA class	2.3 ± 0.7	2.2 ± 0.7	ns
LVEF (%)	35 ± 8	38 ± 9	ns
Hb (mg/dL)	13.7 ± 1.5	13.6 ± 1.5	ns
Rest HR (bpm/min)	73 ± 14	80 ± 16	0.000
Peak HR (bpm/min)	122 ± 24	130 ± 27	0.002
%Max PHR	77 ± 14	84 ± 15	0.000
%HHR	60 ± 31	71 ± 46	0.003
ΔHR (bpm/min)	49 ± 19	50 ± 22	ns
Peak VO_2 (mL/kg/min)	15.6 ± 4.5	15.7 ± 5.2	ns
RER	1.15 ± 0.1	1.13 ± 0.1	ns
β-Blocker dose (mg)	18 ± 12	–	–
ACE-I/ARBs (%)	96	85	0.001
Nitroderivates (%)	15	22	ns
Diuretics (%)	75	75	ns
Spironolacton (%)	49	51	ns
Amiodarone (%)	4	16	0.000
Digoxin (%)	2	8	0.005

Data are expressed as mean ± SD. LVEF, left ventricular ejection fraction; Hb, hemoglobin; HR, heart rate; ΔHR, [peak HR − rest HR]; %Max PHR, percentage of maximum age predicted peak heart rate; %HRR, percentage of HR reserve; VO_2, oxygen uptake; RER, respiratory exchange ratio. β-Blocker dose, carvedilol dose equivalent.

Table 2 Clinical and CPET data of CHF patients therapy as per β-blocker dose level (high daily dose = carvedilol ≥ 25 mg and bisoprolol ≥ 5 mg)

Variables	CHF low dose group (N = 365)	CHF high dose group (N = 184)	*P*-values
Age (years)	63 ± 11	60 ± 11	0.003
Male, n (%)	297(81)	154(84)	ns
NYHA class	2.3 ± 0.7	2.2 ± 0.7	ns
LVEF (%)	35 ± 8	36 ± 8	0.027
Hb (mg/dl)	13.6 ± 1.6	13.9 ± 1.5	0.036
Rest HR (bpm/min)	73 ± 14	72 ± 13	ns
Peak HR (bpm/min)	122 ± 25	120 ± 22	ns
%Max PHR	78 ± 15	75 ± 13	ns
%HHR	61 ± 30	58 ± 33	ns
ΔHR (bpm/min)	49 ± 19	49 ± 17	ns
pVO_2 (mL/kg/min)	15.4 ± 4.6	15.9 ± 4.1	ns
β-Blocker dose (mg)	11 ± 4	32 ± 10	0.000
RER	1.15 ± 0.1	1.15 ± 0.1	ns
ACE-I/ARBs (%)	95	97	ns
Nitroderivates (%)	17	10	0.010
Diuretics (%)	76	73	ns
Spironolacton (%)	49	48	ns
Amiodarone (%)	5	3	ns
Lanoxin (%)	1	4	0.024

Data are expressed as mean ± SD. LVEF, left ventricular ejection fraction; Hb, hemoglobin; HR, heart rate; ΔHR, [peak HR − rest HR]; %Max PHR, percentage of maximum age predicted peak heart rate; %HRR, percentage of HR reserve; pVO_2, peak oxygen uptake; RER, respiratory exchange ratio. β-Blocker dose, carvedilol dose equivalent.

a slightly lower prevalence in CHF patients treated with β-blockers (Table 1). CHF patients treated with β-blockers showed a lower rest and peak HR whereas no difference was found in ΔHR (Table 1).

The arbitrarily defined drug daily dose cut-off value of 25 mg for carvedilol and 5 mg for bisoprolol allowed us to separate a low (66%) from high (34%) β-blocker dose group (Figure 1). The latter group showed a lower age and slightly higher values of LVEF and hemoglobin (Hb) than the low dose group and a higher prevalence of digoxin treatment (Table 2). Nevertheless, no difference was found with respect to functional capacity and chronotropic response parameters.

Of the 90 CHF patients not on β-blocker treatment, 22 (24%) and 62 (69%) were classified as chronotropically incompetent according to the cut-off value of 80% of %Max PHR and %HRR, respectively. Differences between groups, according to the presence or to the absence of chronotropic incompetence, are shown in Table 3. Only patients without chronotropic incompetence defined according to the cut-off value of 80% for %HRR were characterized by higher functional capacity according to NYHA class and pVO_2 than those with chronotropic incompetence (Table 3). Moreover, %HRR ≥ 80% group showed higher values of HR derived variable and significantly better functional parameters (Table 3).

Of the 549 CHF patients on β-blocker treatment, 335 (61%) and 462 (84%) were classified as chronotropically incompetent according to the cut-off value of 80% of %Max PHR and %HRR, respectively. Differences between groups according to the presence or not of chronotropic incompetence are shown in Table 4. Notably, patients without chronotropic incompetence, regardless of its definition, were characterized by functional capacity parameters (NYHA class and pVO_2) better than those with chronotropic incompetence (Table 4). Furthermore, differently from patients not on β-blocker treatment, although %HRR ≥80% group showed higher values of HR-derived data, no differences were found with respect to NYHA, LVEF and pVO_2 (Table 4).

Univariate analysis between functional capacity parameters (NYHA class and pVO_2) and chronotropic response to the exercise in each group are shown in Table 4. Although a significant relationship was found for all HR derived data, the best coefficient values were those obtained between functional capacity parameters and ΔHR (Table 5, Figure 2).

Table 3 Clinical and CPET data of CHF patient without β-blocker therapy as per chronotropic incompetence

Variables	%Max PHR < 80% group (N = 22)	%Max PHR ≥ 80% group (N = 68)	*P*-values	%HRR < 80% group (N = 62)	%HRR ≥ 80% group (N = 28)	*P*-values
Age (years)	64 ± 12	64 ± 12	ns	65 ± 11	62 ± 13	ns
Male, n (%)	18(82)	50(74)	ns	47(76)	21(75)	ns
NYHA class	2.3 ± 0.8	2.2 ± 0.7	ns	2.4 ± 0.7	1.8 ± 0.7*	0.000
LVEF (%)	37 ± 8	38 ± 9	ns	37 ± 9	38 ± 8	0.044
Hb (mg/dL)	13.0 ± 1.7	13.8 ± 1.4	0.04	13.3 ± 1.6	14.2 ± 1.3	ns
Rest HR (bpm/min)	69 ± 10	83 ± 15	0.000	76 ± 12	89 ± 16*	0.000
Peak HR (bpm/min)	106 ± 20	138 ± 24	0.002	117 ± 18	159 ± 17*	0.000
%Max PHR	68 ± 9	89 ± 14	0.000	76 ± 10	101 ± 10*	0.000
%HHR	41 ± 18	81 ± 29	0.000	52 ± 18	103 ± 27*	0.000
ΔHR (bpm/min)	37 ± 21	55 ± 20	0.002	41 ± 18	71 ± 15*	0.000
pVO_2 (mL/kg/min)	14.6 ± 4.4	16.0 ± 5.4	ns	14.2 ± 4.2	19.2 ± 5.8*	0.000
RER	1.13 ± 0.1	1.12 ± 0.1	ns	1.15 ± 0.1	1.16 ± 0.1*	ns
ACE-I/ARBs (%)	92	80	ns	89	63	ns
Nitroderivates (%)	23	22	ns	27	11	ns
Diuretics (%)	74	76	ns	80	71	ns
Spironolacton (%)	46	55	ns	50	46	ns
Amiodarone (%)	20	14	ns	13	20	ns
Digoxin (%)	5	10	ns	5	11	ns

Data are expressed as mean ± SD. *$P < 0.000$%HRR ≥ 80% group vs. %Max PHR ≥ 80% group. LVEF, left ventricular ejection fraction; Hb, hemoglobin; HR, heart rate; ΔHR, [peak HR − rest HR]; %Max PHR, percentage of maximum age predicted peak heart rate; %HRR, percentage of HR reserve; pVO_2, peak oxygen uptake; RER, respiratory exchange ratio.

Table 4 Clinical and CPET data of CHF patient on β-blocker therapy as per chronotropic incompetence

Variables	%Max PHR < 80% group (N = 335)	%Max PHR ≥ 80% group (N = 214)	*P*-values	%HRR < 80% group (N = 462)	%HRR ≥ 80% group (N = 87)	*P*-values
Age (years)	62 ± 11	62 ± 11	ns	62 ± 11	62 ± 10	ns
Male, n (%)	283(84)	168(79)	ns	382(82)	69(79)	ns
NYHA class	2.4 ± 0.6	2.0 ± 0.7	0.000	2.3 ± 0.7	1.9 ± 0.7	0.000
LVEF (%)	35 ± 9	36 ± 8	ns	35 ± 9	36 ± 8	0.044
Hb (mg/dL)	13.6 ± 1.6	13.8 ± 1.5	ns	13.6 ± 1.5	14 ± 1.6	ns
Rest HR (bpm/min)	68 ± 11	80 ± 14	0.000	71 ± 12	85 ± 16*	0.000
Peak HR (bpm/min)	108 ± 16	143 ± 18	0.002	115 ± 17	159 ± 18*	0.000
%Max PHR	68 ± 8	90 ± 11	0.000	73 ± 10	100 ± 11*	0.000
%HHR	44 ± 13	84 ± 35	0.000	51 ± 16	108 ± 31*	0.000
ΔHR (bpm/min)	39 ± 14	63 ± 16	0.000	44 ± 16	74 ± 13*	0.000
pVO_2 (ml/kg/min)	14.4 ± 3.8	17.4 ± 4.8	0.000	15.1 ± 4.2	18.2 ± 5.1	0.000
β-Blocker dose (mg)	19 ± 12	17 ± 11	0.048	18 ± 12	16 ± 11	ns
RER	1.15 ± 0.1	1.15 ± 0.1	ns	1.15 ± 0.1	1.16 ± 0.1	ns
ACE-I/ARBs (%)	95	96	ns	96	96	ns
Nitroderivates (%)	16	13	ns	15	15	ns
Diuretics (%)	80	67	0.001	78	65	0.021
Spironolacton (%)	49	49	ns	50	45	ns
Amiodarone (%)	4	4	ns	4	3	ns
Lanoxin (%)	1	3	0.041	1	6	0.012

Data are expressed as mean ± SD. *$P < 0.000$%HRR ≥ 80% group vs. %Max PHR ≥ 80% group. LVEF, left ventricular ejection fraction; Hb, hemoglobin; HR, heart rate; ΔHR, [peak HR − rest HR]; %Max PHR, percentage of maximum age predicted peak heart rate; %HRR: percentage of HR reserve; pVO_2, peak oxygen uptake; RER, respiratory exchange ratio. β-Blocker dose, carvedilol dose equivalent.

The multivariable linear regression analysis confirmed that ΔHR was the variable more strongly independently associated with pVO_2 (β: 0.572; standard error: 0.008; $P < 0.0001$). However, also LVEF (β: 0.212; standard error: 0.018; $P < 0.0001$) and age (β: −0.205; standard error: 0.015; $P < 0.0001$) remained independently linked to pVO_2. Similarly, when NYHA class was the dependent factor at multivariate analysis, again ΔHR was the best

Table 5 Pearson correlation between main clinical and CPET data in study groups

Variables	Peak HR	ΔHR	%Max PHR	%HRR
Total population (n = 639)				
NYHA	−0.43	**−0.51**	−0.33	−0.30
pVO_2	+0.49	**+0.58**	+0.37	+0.35
Not β-blocked patients (n = 90)				
NYHA	−0.47	**−0.61**	−0.33	−0.26
pVO_2	+0.52	**+0.63**	+0.36	+0.30
β-Blocked patients (n = 539)				
NYHA	−0.43	**−0.50**	−0.33	−0.33
pVO_2	+0.49	**+0.57**	+0.38	+0.39

Correlation coefficients (r) reported are only those with significant *P*-value < 0.001. HR, heart rate; ΔHR, [peak HR − rest HR]; %Max PHR, percentage of maximum age predicted peak heart rate; %HRR, percentage of HR reserve; pVO_2, peak oxygen uptake. Note that the best r value between functional capacity and chronotropic response to exercise is for the relationship with ΔHR in each subgroup (bold values).

variable independently associated with (β: −0.499; standard error: 0.001; $P < 0.0001$) followed by age (β: 0.218; standard error: 0.002; $P < 0.0001$) and LVEF (β: 0.185; standard error: 0.003; $P < 0.0001$).

Discussion

In this study, conducted in a large, single-center, cohort of stable CHF patients, we confirmed the influence of chronotropic incompetence on functional capacity either as evaluated in terms of NYHA classes or from pVO_2. We also provide an analysis of the impact of β-blocker treatment on exercise tolerance and chronotropic response in CHF patients, showing that, although chronotropic incompetence is most often observed in patients treated with β-blockers, either β-blocker therapy *per se* or β-blocker dose does not affect pVO_2 and ΔHR. Eventually, we showed that both the two methods most commonly used to evaluate chronotropic incompetence, namely %Max PHR and %HRR, identify the patients under β-blocker therapy with the most severe CHF, whereas only the %HRR method does it in those not taking β-blockers.

First, we must admit that, because of the retrospective nature of the current study, we performed a reanalysis of previously done CPETs and, accordingly, we do not know why CHF patients were treated or not with β-blockers or why carvedilol or bisoprolol had been chosen. However, we know that the cardiologist in charge of the patient considered the β-blocker dose used the highest possible for each individual. We also know that patients were reported stable as regards both clinical conditions and therapeutic regimen.

Patients with CHF typically have a blunted HR response to exercise and this phenomenon has been attributed to sympathetic overactivity with a consequent reduced myocardial sensitivity to sympathetic modulation together with a β-receptor downregulation [15–17,30]. Differences in prevalence of chronotropic incompetence are reported in CHF patients either on β-blocker therapy or not [10]. A previous study by Witte *et al.* [13], conducted on a total of 237 CHF patients, evaluated chronotropic incompetence using the same two methods we adopted in the current report. In not β-blocked patients, Witte *et al.* [13] showed a 32% and 64% prevalence of chronotropic incompetence according to the %Max PHR and %HRR, respectively, whereas in patients on β-blocker therapy these percentages were 49% and 75%. Our data, obtained in a much larger population, are in line with those of Witte, although we found a considerably higher prevalence of chronotropic incompetence in β-blocked patients, 64% and 84%, using the two abovementioned methods.

In line with the previous studies of Witte *et al.* [13] and Jorde *et al.* [31], we found a significant relationship between functional capacity and HR-derived parameters with the strongest correlation found between pVO_2 and ΔHR, regardless of the presence or absence of β-blocker treatment. It should be noticed, however, that we analyzed only the correlation between functional capacity and chronotropic incompetence and that this should not be considered a cause/effect relationship. Indeed, Witte *et al.* [32] proposed that chronotropic incompetence is the consequence and not the cause of CHF. Similarly, Huang *et al.* [33] showed that chronotropic incompetence was correlated with a variety of other variables known to be associated with increasing severity of CHF, again suggesting that chronotropic incompetence as the consequence rather than the cause of impaired functional capacity in CHF.

Another interesting and original finding of this study regarded the power of the two methods for chronotropic incompetence analysis with respect to the presence or the absence of β-blocker therapy. In fact, both %Max PHR and %HRR methods, when applied to the β-blocked group, revealed CHF patients with similar functional status, exercise capacity and, therefore, likely, with similar prognosis. Instead, in not β-blocked population, the %HRR ≥80% group showed better functional capacity parameters than %Max PHR ≥80% group. Therefore, our hypothesis, supported also by univariate analysis results, is that the HR increase during exercise might be greater in not β-blocked CHF patients and that %HRR is a more precise method than %Max PHR in chronotropic

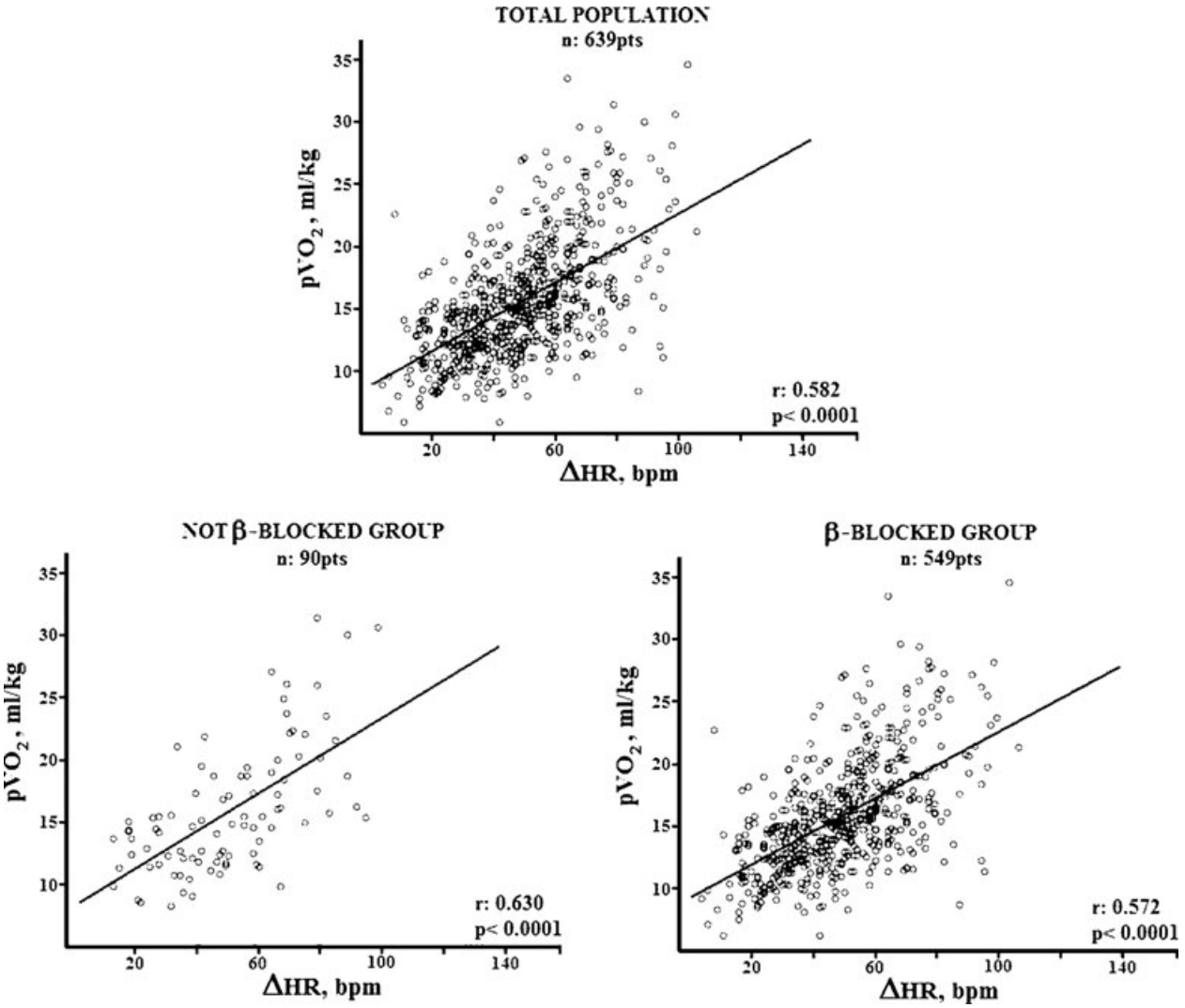

Figure 2 Relationship between heart rate exercise induced increase (ΔHR) and peak oxygen consumption (pVO_2) in the whole chronic heart failure population (upper panel), in not β-blocked patients (bottom panel on the left), and in those on β-blocker therapy. "r" values are for Spearman analysis.

incompetence quantification in such CHF population. Indeed, it is well-known that β-blocker therapy improves functional status regardless of its HR related effect making %HRR and %Max PHR methods equivalent for chronotropic identification [15–21].

Some trials recommend a daily dose of at least 50 mg/day of carvedilol, and consequently of 10 mg for bisoprolol considering a 5-to-1 ratio [4], as the target dose to be reached for an optimal β-blocker treatment in CHF patients [20,21]. Nevertheless, it is well known that during up-titration of β-blockers difficulties may arise which involve too low blood pressure or HR [18,19]. A previous study by Carvalho *et al.* [24] analyzed the effect on exercise tolerance of an optimized β-blocker treatment with carvedilol defined as a 50 mg daily dose and a rest HR ranging from 50 to 60 beats/min. This elegant study, conducted on a small number of patients, showed that optimized therapy did not lead to better exercise performance. The actual study has been done on a real life population with stable β-blocker treatment. Indeed, we arbitrarily decided to categorize patients receiving β-blocker treatment in two groups according to a cut-off daily dosage of 25 mg for carvedilol and 5 mg for bisoprolol. As in Carvalho's paper [24], we found no differences in functional class and capacity between low and high dose. Supporting this datum is the lack of this difference in chronotropic incompetence with respect to β-blocker dose.

Study Limitations

This study design did not allow us to make any conclusion about the cause-effect relationship between chronotropic incompetence and reduced exercise capacity in CHF patients. Another limitation, strictly linked to this type of retrospective analysis, consists in a lack of exact degree of physical detraining in our study sample. Indeed, we cannot speculate if a blunted HR response induced by β-blocker therapy could represent an adjunctive disadvantage in patients less trained. Eventually, we are strongly convinced that further investigations are needed not only with respect to the influence of β-blockers but also to the role of each of the main drug classes that are part of the standard therapy of CHF, including ACE-I and vasodilators.

Finally, we fixed a cut-off value to define chronotropic incompetence and we prefer to adopt one in line with a previous similar study by Witte *et al.* [13]. We recognize that this type of approach and, more in general, the use of any cut-off value for any continuous variable, is arbitrary and could be criticable but it is undoubtedly useful from a clinical point of view.

Conclusions

In conclusion, the most simple analysis of chronotropic incompetence, namely ΔHR, is a strong predictor of CHF severity as assessed by NYHA and pVO_2 regardless of β-blocker therapy and dose. The %HRR method seems to be more appropriate for evaluating CHF severity in patients not taking β-blocker whereas both %HRR and %Max PHR could be considered equivalent in assessing clinical status of those CHF patients treated with β-blockers.

Author Contribution

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- Pietro Palermo, MD: concept/design and drafting article
- Filippo Cauti, MD: data analysis/interpretation, statistics
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- Alessandra Magini, MD: data analysis/interpretation, statistics
- Carlo Vignati, MD: data collection and data interpretation
- Marina Alimento, MD: data collection and data interpretation
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Conflict of Interest

The authors declare no conflict of interests.

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