[Original article]

Heart rate reduction and exercise performance in recent onset heart failure with reduced ejection fraction: arguments for beta-blocker hypo-response

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Objective Beta blockers reduce all-cause mortality and readmissions in heart failure with reduced ejection fraction (HFrEF), which may be explained by their effect on heart rate (HR). This study assessed the impact of HR reduction with beta blockers on exercise capacity in recent onset HFrEF.

Methods and results Fifty consecutive patients with recent onset HFrEF (< 30 days) performed a standardized exercise protocol with respiratory gas analysis at baseline as well as after 6 and 12 months. Patients participated in a quality of care programme aiming to achieve guideline-recommended target doses for beta-blocker therapy. At baseline, 6 and 12 months, 36%, 70% and 62% of patients, respectively, had a resting HR < 70 bpm. Beta-blocker dose after 12 months was comparable in patients with resting HR < 70 versus ≥ 70 bpm (*P* value = 0.631). However, with similar dose uptitration, the former versus the latter had a significantly larger HR reduction (17 ± 22 versus 4 ± 15 bpm; *P* value = 0.027). Peak oxygen consumption (VO_{2max}) was significantly higher when resting HR was < 70 versus ≥ 70 bpm (17.5 ± 5.5 versus 14.4 ± 3.3 mL/min/kg, respectively; *P* value = 0.038). Similar results were observed after 6 months. Patients in whom resting HR decreased at follow-up compared to baseline had a 2.0 ± 3.2 mL/min/kg increase in VO_{2max} compared to a 1.2 ± 7.7 mL/min/kg increase in patients who did not demonstrate a lower resting HR (*P* value = 0.033).

Conclusions In recent onset HFrEF, exercise performance was better when resting HR was controlled < 70 bpm with beta-blocker therapy. However, despite aggressive dose uptitration, many patients did not achieve this target as they had little HR reduction with beta-blocker therapy.

Keywords *Adrenergic beta antagonists – exercise tolerance – heart rate – systolic heart failure.*

INTRODUCTION

Beta blockers are a key component of the medical therapy for chronic heart failure with reduced ejection fraction (HFrEF), as large randomized clinical trials have demonstrated an important reduction in all-cause mortality and readmissions with this treatment[1-4]. Therefore, current heart failure guidelines strongly recommend the use of beta-blocking agents in every HFrEF patient at the same dose used in large clinical trials[5,6]. The underlying pathophysiological rationale is that chronic adrenergic stimulation, mediated by β1-receptor activation, causes changes in myocardial gene expression, resulting in structural damage with a loss of viable cardiomyocytes, depression of myocardial contractility, and progressive ventricular remodelling[7-10]. Another key feature of beta-blocking agents is that they reduce the heart rate. Importantly, a lower resting heart rate is associated with better survival and less morbidity in heart failure[11-13]. Moreover, results from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) suggest that this association may be largely independent from the beta-blocker dose that is taken by the patient[14]. This has fuelled the debate whether beta-blocker dose or resting heart rate is in fact the better treatment target

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in HFrEF, especially because there has been some concern that high beta-blocker doses might impair the maximal heart rate achievable during exercise (i.e., chronotropic incompetence), consequently reducing exercise tolerance and quality of life[15]. However, the link between beta-blocker dose and incidence of chronotropic incompetence has been questioned[16-18]. In the light of this controversy, the aim of this study was to investigate longitudinally the relationship between heart rate control and exercise performance in patients with a new diagnosis of HFrEF, a population that has not been studied extensively before. In addition, the influence of beta-blocker dosing on heart rate control and exercise performance was assessed.

METHODS

Study design and population

This retrospective cohort study was designed by the first and last author and carried out in the outpatient cardiology clinic of a single tertiary care centre (Ziekenhuis Oost-Limburg, Genk, Belgium). All patients included in a heart failure quality of care programme at this centre, from May 2009 until January 2013, were screened. A detailed description of the programme has been published before by our group[19]. Briefly, by means of a tag in the patient's electronic medical record, a dedicated heart failure nurse visit was triggered with each hospital readmission (including non-cardiac ward admissions) or outpatient evaluation. Following protocol orders, the nurse decided whether a general cardiology or dedicated heart failure specialist evaluation could potentially improve care. At each contact, general heart failure education was provided and medication adherence assessed. Importantly, a strong emphasis was placed on uptitration of renin-angiotensin system antagonists and beta blockers to guideline-recommended tolerated target doses, although no heart rate target was specified[5,6]. In the current study, patients with a new diagnosis of HFrEF (< 30 days) – confirmed by one of the dedicated heart failure specialists participating in the programme (M.D. & W.M.) – were included. An additional inclusion criterion was performance of a bicycle exercise test with respiratory gas analysis in the outpatient clinic around the time of diagnosis, as well as after 6 (4-8) and 12 (10-14) months, respectively. The study complies with the Declaration of Helsinki. The institutional committee on human research has approved the study protocol and waived the need for informed consent as this was a retrospective observational study. All authors had full access to the data and contributed to the writing of the manuscript. Together, they take responsibility for the integrity of the data and agree to the report as written.

Stratification according to heart rate control

At each time point, patients were stratified according to whether their resting heart rate was < 70 bpm, as recommended by the most recent guidelines of the European Society of Cardiology[5]. Patient characteristics, beta-blocker uptitration, and results of exercise testing were compared between patients with a resting heart rate < 70 versus ≥ 70 bpm at follow-up. Beta-blocker dose was expressed as mg bisoprolol equivalents (1 mg bisoprolol = 1 mg nebivolol = 5 mg carvedilol = 20 mg metoprolol).

Exercise testing

All exercise tests in this study were performed using a standard bicycle protocol in the upright sitting position. Patients were instructed to achieve a constant peddling speed of 55-65 rpm until exhaustion or occurrence of intolerable dyspnoea. Starting resistance was 20 W, with 30 W added after each 2 minutes of exercise. Peak oxygen uptake (VO_{2max}) was defined as the highest mean oxygen uptake for any given period of 30 seconds while exercising or during the 3 minutes of recovery time immediately after exercise. Absolute values were indexed for body weight to account for interindividual differences. Alternatively, peak oxygen pulse was calculated as the ratio of VO_{2max} over heart rate. For each patient, the predicted maximal heart rate [bpm] during exercise was estimated as 220 minus age [years].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, if normally distributed, or otherwise by median (interquartile range). Normality was assessed by the Shapiro-Wilk statistic. The paired student's *t*-test was used to compare repeated measurements. Patient subgroups were compared using the independent-samples student's *t*-test or Mann-Whitney *U* test as applicable. Categorical data were expressed as percentages and compared with Fisher's exact test or the Pearson X^2-test in case of a non-binary response. Statistical significance was always set at a two-tailed probability level of < 0.05. All statistics were performed using IBM® SPSS® (version 22.0 for Windows).

RESULTS

Study population

From May 2009 until January 2013, 800 patients were included in the heart failure quality of care programme at the Ziekenhuis Oost-Limburg of whom 63 had recent

onset HFrEF (diagnosis < 30 days). Fifty patients had exercise data available at baseline, 6 and 12 months of follow-up. Baseline characteristics of these patients, representing the study population, are presented in table 1.

Heart rate control

At baseline, 6 and 12 months of follow-up, resting heart rate was 80 ± 21 bpm, 66 ± 15 bpm and 69 ± 16 bpm, respectively, assessed in stable circumstances at the outpatient clinic. Eighteen versus 32 patients had a baseline resting heart rate < 70 versus ≥ 70 bpm, respectively, with no significant differences in other baseline characteristics between both groups (table 1). After 6 and 12 months, the proportion of patients in whom resting heart rate was controlled < 70 bpm increased from 36% to 70% and 62%, respectively (figure 1). Patients with their resting heart rate controlled < 70 bpm after 1 year more frequently had a diagnosis of ischaemic cardiomyopathy (52% versus 26%) or idiopathic/familial dilated cardiomyopathy (45% versus 42%) instead of a miscellaneous heart failure cause (3% versus 32%; *P* value = 0.014 for the overall difference in diagnosis). Patients with a resting heart rate ≥ 70 bpm after 1 year more often had chronic obstructive pulmonary disease (16% versus 0%; *P* value = 0.049) and tended to have higher heart rates already at baseline (87 ± 19 versus 76 ± 22 bpm; *P* value = 0.075).

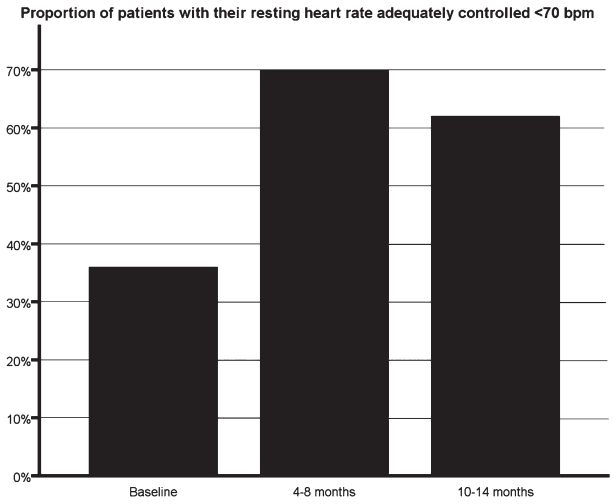

Fig. 1 Heart rate control – Proportion of patients with their resting heart rate adequately controlled < 70 bpm at baseline and follow-up.

Table 1 Baseline characteristics of the study population

	Overall (n = 50)	HR < 70 bpm (n = 18)	HR ≥ 70 bpm (n = 32)	*P* value
Age (years)	65 ± 11	63 ± 11	66 ± 11	0.350
Male gender	68%	78%	63%	0.351
Heart failure cause				0.100
Ischaemic cardiomyopathy	42%	61%	31%	
Idiopathic/familial dilated cardiomyopathy	44%	33%	50%	
Other*	14%	6%	19%	
New York Heart Association functional class				0.101
I	10%	22%	3%	
II	48%	50%	47%	
III	38%	22%	47%	
IV	4%	6%	3%	
Left ventricular ejection fraction (%)	29 ± 10	29 ± 11	28 ± 9	0.710
Heart rate (bpm)	80 ± 21	59 ± 8	92 ± 16	< 0.001
Systolic blood pressure (mmHg)	125 ± 20	122 ± 18	127 ± 20	0.384
Diastolic blood pressure (mmHg)	73 ± 13	71 ± 12	75 ± 13	0.362
Serum haemoglobin (g/dL)	14.3 (12.6-14.6)	14.4 (12.4-14.7)	14.1 (13.0-14.4)	0.558
Serum creatinine (mg/dL)	1.00 (0.84-1.20)	1.03 (0.94-1.20)	0.92 (0.76-1.21)	0.199
History of diabetes	26%	28%	25%	1.000
History of chronic obstructive pulmonary disease	6%	6%	6%	1.000

*Valvular cardiomyopathy (6%), toxic cardiomyopathy (4%), pacemaker-induced heart failure (4%).
HR: heart rate.

Beta-blocker uptitration

In the total population, 44 patients (88%) were prescribed a beta blocker at the moment of their baseline evaluation [dose: 5.0 mg (2.3-5.0 mg) bisoprolol equivalents; figure 2]. This number increased to 46 (92%) after 6 and 12 months [dose: 5.0 mg (5.0-10 mg) bisoprolol equivalents at both time points; figure 2]. At these time points, 41 and 39 patients took a beta-blocker dose of at least 5.0 mg bisoprolol equivalents, respectively. Systolic/diastolic blood pressure was 123 ± 19/70 ± 11 mmHg and 126 ± 22/69 ± 9 mmHg after 6 and 12 months, respectively.

Beta-blocker dose and heart rate response

The beta-blocker dose achieved after 6 months was similar in patients with a resting heart rate < 70 versus ≥ 70 bpm at that moment (*P* value = 0.644). Moreover, the beta-blocker dose increase at 6 months compared to baseline was comparable among both groups (2.1 ± 3.6 mg versus 2.4 ± 3.0 mg bisoprolol equivalents, respectively; *P* value = 0.766). However, patients with their resting heart rate adequately controlled < 70 bpm had a 19 ± 21 bpm decrease compared to baseline, while patients with a resting heart rate still ≥ 70 bpm only had a 4 ± 17 bpm decrease (*P* value = 0.015 for the difference between both groups). Similarly, after 12 months the beta-blocker dose achieved was equivalent in patients with versus without control of their resting heart rate < 70 bpm [5.0 mg (5.0-10 mg) versus 5.0 mg (2.5-10 mg) bisoprolol equivalents, respectively; *P* value = 0.631]. Also, the beta-blocker dose increase at 12 months compared to baseline was comparable among patients with a resting heart rate < 70 versus ≥ 70 bpm (2.0 ± 4.6 mg versus 2.7 ± 2.9 mg bisoprolol equivalents, respectively; *P* value = 0.522). Again, patients with their resting heart rate controlled < 70 bpm had a larger heart rate reduction (17 ± 22 bpm) when compared to patients with a resting heart rate still ≥ 70 bpm (4 ± 15 bpm reduction; *P* value = 0.027 for the difference between both groups). Even in patients (n = 18) who took a beta-blocker dose equal to the guideline-recommended target dose (10 mg bisoprolol equivalents) after 1 year of follow-up, 7 had a resting heart rate ≥ 70 bpm (39%), a proportion comparable to the overall population (38%; figure 1).

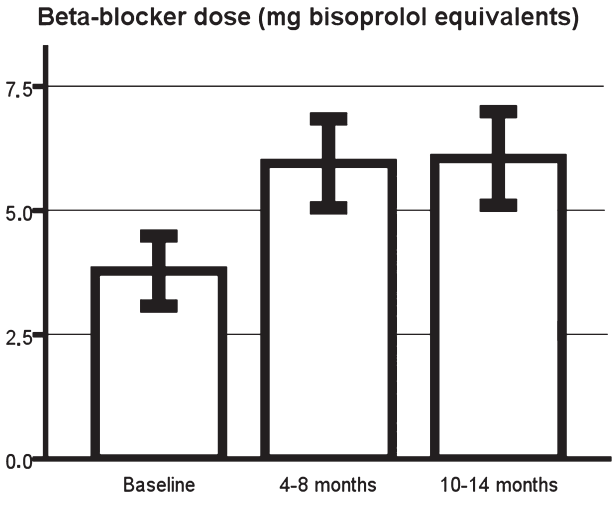

Fig. 2 Beta-blocker dose – Achieved beta-blocker dose in patients at first evaluation, after 6 and 12 months of follow-up. Bars indicate mean with 95% confidence intervals.

Exercise performance

VO_{2max} was 14.3 ± 4.4 mL/min/kg at baseline, increasing significantly to 16.2 ± 6.2 mL/min/kg after 6 months (*P* value = 0.007) and 16.3 ± 4.9 mL/min/kg after 12 months (*P* value = 0.004; figure 3; table 2). The peak oxygen pulse and maximal heart rate during exercise did not change significantly over time (table 2). Overall, the respiratory quotient at peak exercise was 1.15 ± 0.14, indicating that the majority of patients reached their anaerobic threshold.

Exercise performance in patients with versus without adequate heart rate control

Both after 6 months of follow-up (17.6 ± 6.6 versus 13.4 ± 4.1 mL/min/kg; *P* value = 0.031) and after 12 months (17.5 ± 5.5 versus 14.4 ± 3.3 mL/min/kg; *P* value = 0.038), patients with a resting heart rate < 70 versus ≥ 70 bpm, respectively, had significantly higher VO_{2max} values (figure 4). At any follow-up time, former versus latter patients also had a non-significantly higher peak oxygen pulse (12.6 ± 3.5 mL/beat versus 11.1 ± 3.2 mL/beat; *P* value = 0.070) and a similar maximal heart rate during exercise (112 ± 20 bpm versus 114 ± 23 bpm; *P* value = 0.616). Patients in whom resting heart rate decreased at follow-up compared to baseline had a 2.0 ± 3.2 mL/min/kg increase in VO_{2max} compared to a 1.2 ± 7.7 mL/min/kg increase in patients who did not demonstrate a lower resting heart rate (*P* value = 0.033).

DISCUSSION

This study assessed heart rate reduction through beta-blocker therapy and its relationship with exercise tolerance in patients with recent onset HFrEF, a population that has not been studied extensively before. Major findings were: (1) one third of patients failed to achieve

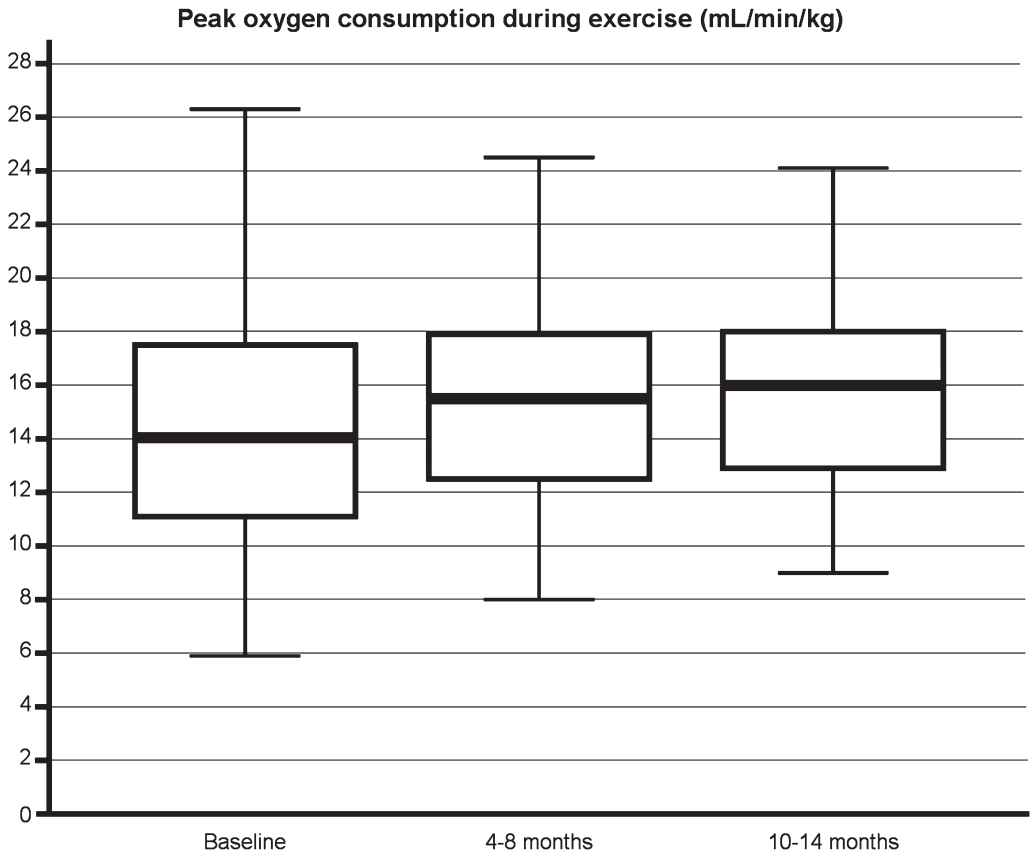

Fig. 3 Exercise performance – Evolution of the peak oxygen consumption during exercise over time.

adequately controlled resting heart rates <70 bpm, despite aggressive beta-blocker uptitration in the context of a quality of care programme with particular emphasis on this part of treatment; (2) beta-blocker uptitration was similar in patients with versus without adequately controlled heart rate, but the latter group had little heart rate reduction, arguing for a phenotype of beta-blocker hypo-responders; (3) patients with their resting heart rate controlled <70 bpm showed an improved exercise capacity compared to patients with a higher resting heart rate. Our results support pursuing an adequate control of resting heart rates already early after the diagnosis of HFrEF, which might improve exercise performance and presumably quality of life.

Beta-blocking agents are a cornerstone in the treatment of chronic HFrEF, as they reduce both all-cause mortality and readmissions[1-4]. There is good evidence that at least a major part of these effects is explained by a reduction in resting heart rate. In a recent meta-analysis of beta-blocker trials, including 19,537 chronic HFrEF patients, heart rate reduction accounted for 41% of the decrease in all-cause mortality with beta-blocker

Table 2 Evolution of exercise parameters over time

	Baseline (n = 50)	6 months (n = 50)	*P* value*	12 months (n = 50)	*P* value*
Peak oxygen consumption (mL/min/kg)	14.3 ± 4.4	16.2 ± 6.2	0.007	16.3 ± 4.9	0.004
Peak oxygen pulse (mL/beat)	11.0 ± 4.3	12.0 ± 3.6	0.059	12.1 ± 3.4	0.248
Maximal heart rate (bpm)	111 ± 22	110 ± 21	0.453	115 ± 21	0.334
Percentage of predicted maximal heart rate achieved	72 ± 15	71 ± 13	0.365	74 ± 13	0.268
Respiratory quotient	1.10 ± 0.13	1.17 ± 0.13	0.017	1.18 ± 0.15	0.070

*Compared to baseline.

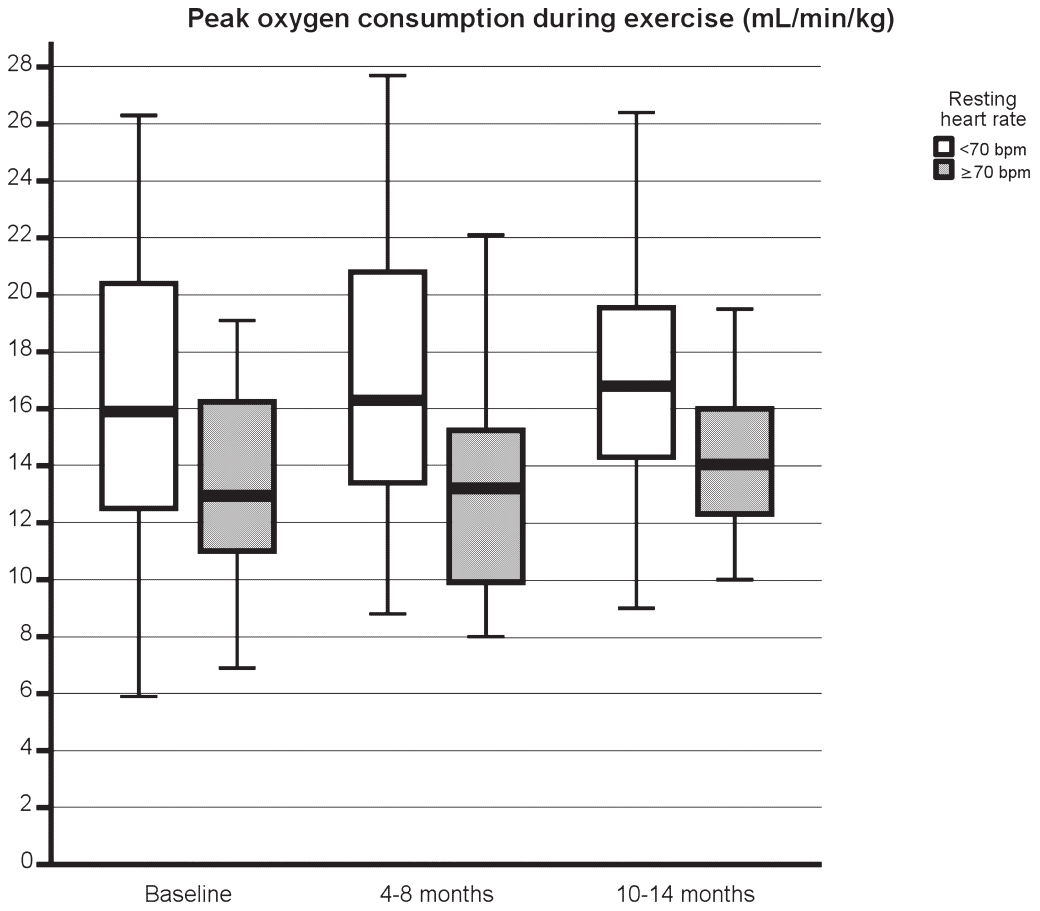

Fig. 4 Heart rate control and exercise performance – Comparison of the peak oxygen consumption during exercise according to resting heart rate control (< 70 bpm versus ≥ 70 bpm).

therapy[20]. Furthermore, in a similar analysis, the survival benefit of beta blockers was significantly associated with heart rate reduction, but not with beta-blocker dose[21]. However, the strongest evidence in favour of an independent effect of heart rate reduction on clinical outcome in heart failure patients is the SHIFT[13]. In this trial, 6,505 chronic HFrEF patients with a resting heart rate ≥ 75 bpm were randomized to treatment with either ivabradine 7.5 mg BID or matching placebo on top of conventional therapy. Treatment with ivabradine, a "funny current" inhibitor which decreases heart rate by reducing sinus node automaticity, resulted in significantly lower heart failure mortality, less readmissions, and better quality of life[22]. A post-hoc analysis of SHIFT revealed that 26.5% of patients received a medium to high beta-blocker dose, while 23% received the guideline-recommended target or a higher dose[14]. Despite these differences in beta-blocker dosing, resting heart rate was similar in both groups at 79 bpm. This suggests that the inclusion criteria of SHIFT may have selected patients with a heart rate relatively unresponsive to beta-blocker therapy.

Our study in patients with recent onset HFrEF further supports the phenotype of beta-blocker hypo-responders, arguing that it is already present early on and not the result of chronic treatment. Importantly, we observed that beta-blocker dosing and uptitration were actually very similar in patients with a heart rate < 70 bpm versus ≥ 70 bpm after 6 and 12 months. However, the absolute degree of heart rate reduction with similar beta-blocker uptitration was much larger in patients who reached the target of control. Moreover, even in patients who took the full guideline-recommended dose of beta blockers, the proportion of patients with a resting heart rate ≥ 70 bpm was similar to the overall population.

It is intriguing to speculate what might be the reason for beta-blocker hypo-responsiveness. First, it could be that such patients represent a population with a higher baseline adrenergic tone, who consequently require higher beta-blocker doses to adequately suppress the sympathetic system. However, as patients with insufficient control of their resting heart rate demonstrated only a negligible heart rate reduction of 4 bpm despite already aggressive beta-blocker uptitration, it seems unlikely that a further dose increase would have resulted in adequate resting heart rate control < 70 bpm. Interestingly, genetic polymorphisms have been described that might influence beta-blocker responsiveness and would explain the variable heart rate response observed, independent of

the beta-blocker dosing schedule[23]. Alternatively, patients with a higher resting heart rate despite adequate beta-blocker uptitration might just represent a population that is sicker, with more advanced HFrEF or co-morbid conditions. Based on our limited sample size, there were no compelling arguments that patients with a heart rate ≥ 70 bpm had more advanced cardiac disease as their ejection fraction and blood pressure were very similar to patients with a resting heart rate < 70 bpm. However, the former group did have a higher incidence of chronic obstructive pulmonary disease.

CLINICAL IMPLICATIONS

Because of limitations inherent to our retrospective study design, the question whether further reducing resting heart rate with non-beta-blocking agents in HFrEF patients with inadequate control would have resulted in improved exercise capacity, cannot be fully addressed. However, our results demonstrate that even with aggressive beta-blocker uptitration (> 75% of patients took at least 50% of the guideline-recommended target dose after 6 months), heart rate is inadequately controlled in about one third of patients with recent onset HFrEF and such patients have a lower exercise capacity. The results of the present study may therefore suggest that non-beta-blocking agents which reduce the heart rate (i.e., digoxin or ivabradine) should be considered early after the diagnosis of HFrEF, especially in patients who demonstrate little resting heart rate reduction with beta-blocker therapy. Such a combination therapy instead of aggressively pursuing higher beta-blocker doses might potentially improve exercise capacity and hence quality of life. However, this hypothesis should be tested further in adequately powered randomized clinical trials before any firm recommendation can be made.

STUDY LIMITATIONS

Some limitations should be acknowledged when interpreting the study results. First, this was a single-centre, retrospective study with limited sample size. Therefore, our results should be considered exploratory and hypothesis-generating. Second, as explained, one should be careful to draw conclusions regarding causality between heart rate control and exercise performance because of the retrospective study design. On the other hand, patients were followed longitudinally with no drop-out during one year. Third, the cut-off of 70 bpm for adequate heart rate control is somewhat arbitrary and largely based on the results of only one randomized clinical trial (SHIFT). However, this target is also used by recent heart failure guidelines[5]. Fourth, our study was underpowered to assess potential differences between different beta-blocker agents, which might demonstrate different beta-adrenergic responsiveness[24,25]. However, all patients took a beta-blocker agent specified by current heart failure guidelines (70% bisoprolol; 9% carvedilol, and 21% nebivolol) [5].

CONCLUSION

Patients with recent onset HFrEF demonstrated improved exercise performance when their resting heart rate was controlled < 70 bpm through beta-blocker therapy. However, despite aggressive uptitration to guideline-recommended target doses, many patients may not achieve this target. Importantly, in our population, patients with a resting heart rate < 70 versus ≥ 70 bpm had a similar beta-blocker dose uptitration but less heart rate reduction, arguing against inertia to uptitrate as the major reason for inadequate heart rate control and suggesting that some patients might respond less well to beta-blocker therapy.

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CONFLICT OF INTEREST: none.

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