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 time of diagnosis or in the early clinical course.[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 remodeling.[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 If 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.

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 doses after 12 months were comparable for patients with resting HR < 70 bpm (14 ± 10 mg/day) versus ≥ 70 bpm (14 ± 10 mg/day) (P=0.79). However, with similar dose uptitration, the former versus the latter had a significantly larger HR reduction (17 ± 22 bpm versus 4 ± 15 bpm; P=0.027). Peak oxygen consumption (VO2max) was significantly higher when resting HR was < 70 bpm versus ≥ 70 bpm (17.5 ± 5.5 mL/min/kg versus 14.4 ± 3.3 mL/min/kg, respectively; P=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 VO2max compared to a 1.2 ± 7.7 mL/min/kg increase in patients who did not demonstrate a lower resting HR (P=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.
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., that beta-blockers might impair chronotropic incompetence), consequently reducing maximal heart rate achievable during exercise (i.e., that beta-blockers might impair chronotropic incompetence, but this relationship between beta-blocker heart rate and maintenance of chronotropic incompetence has been questioned). At the time of this retrospective analysis, the aim of this study was to investigate the relationship between heart rate control and exercise performance to patients with a new diagnosis of HFrEF, a population that has not been studied extensively before. In addition, the influence of beta-blockers 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 center (Ziekenhuis Oost-Limburg, Genk, Belgium). All patients included in this study had received the same protocol treatment and analysis from May 2009 until January 2013, were screened. A detailed description of the program has been published by one of the authors. Briefly, by means of a tag in the patient’s electronic medical record, enrolled patients were invited to participate in the program. The inclusion criteria were confirmed by one of the dedicated heart failure specialists. Inclusion was always set at a two-tailed probability level of < 0.05. Statistical significance was estimated as 220 minus age [years]. Statistical analysis

Continuous variables were expressed as means ± standard deviation, if normally distributed, or otherwise by median (interquartile range). Normally was assessed by the Shapiro-Wilk statistic. The p value for the test was considered statistically significant if p < 0.05. Differences were compared using the independent-samples t test or the Mann-Whitney U test as appropriate. Categorical data were expressed as percentages and compared with Fisher’s exact test or the Pearson’s χ² test in case of a non-binary response. Statistical significance was estimated at a two-tailed probability level of < 0.05. All statistics were performed using IBM SPSS (version 22.0 for Windows).

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 pedaling speed of 60 rpm and substituting or no assistance (i.e., no resistance). The duration 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 individual differences. Alternatively, peak oxygen pulse was calculated as the ratio of VO₂max to heart rate. For each prediction, the peak oxygen uptake was estimated as 220 minus age [years].

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 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 at 1 (± 1) and 12 (± 2) months, respectively. The study complied with the Declaration of Helsinki. The institutional committee on research ethics waived the need for informed consent, as the data were retrospectively observational study. All medical chart data in the database contributed to the writing of the manuscript. Together, they had responsibility for the integrity of the data and agree to the report as written.
Heart rate & exercise performance in second heart failure

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).

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. Eighty versus 52 patients had a baseline resting heart rate ≥ 70 bpm, respectively, and tended to have higher heart rates already at baseline (87 ± 19 versus 76 ± 22 bpm; P value = 0.075). After 6 and 12 months, the proportion of patients whose resting heart rate was controlled < 70 bpm increased from 88% to 70% and 62%, respectively (figure 1). Patients with a resting heart rate controlled < 70 bpm after 1 year more frequently had a diagnosis of ischemic 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 (18% versus 5%; P value < 0.001) and tended to have higher heart rates already at baseline (87 ± 19 versus 76 ± 22 bpm; P value = 0.075).

Table 1: Baseline characteristics of the study population

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

HR: heart rate.

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

**Exercise performance**

VO\(_2\text{max}\) 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\(_2\text{max}\) 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\(_2\text{max}\) 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 been studied extensively before. More findings were (1) one third of patients failed to achieve...
Heart rate & exercise performance in recent heart failure

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. 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 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 the part of treatment. (1) Beta-blocker uptitration was either in patients with systole without adequately controlled heart rate, but the latter group had little heart rate reduction, arguing for a phenotype of beta-blocker hypo-responders; (2) 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 rate already early after the diagnosis of HFrEF, which brought progressive exercise performance and sustainable quality of life.

![Fig. 3](image)

**Table 2** Evolution of exercise parameters over time

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

*Compared to baseline.
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 despite already aggressive 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

Treatment of heart failure with beta-blockers is controversial. It has been suggested 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 despite already aggressive 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

For instance, in a similar analysis, the survival benefit of beta-blockers was significantly associated with heart rate reduction, but not with beta-blocker dose. However, the strongest evidence in favor of an independent effect of heart rate reduction on clinical outcomes in heart failure patients is the SHIFT. 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 sinoauricular automaticity, resulted in significantly lower heart failure mortality, less decompensation, and better quality of life. A post-hoc analysis of SHIFT revealed that 26.5% of patients received a medium to high beta-blocker dose, while 32.5% received the guideline-recommended target or higher dose. Despite these differences in beta-blocker dosing, resting heart rate was similar in both groups at 79 bpm, suggesting 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-responsiveness, 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.
the beta-blocker dosing schedule. 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 comorbid conditions. Based on our limited sample size, there was no compelling argument 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 adequate beta-blocker uptitration, only 24% of patients had at least 50% of the guideline-recommended target doses 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 ibutilide) should be considered early after the diagnosis of HFrEF, especially when the patient is already actively being treated 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 recommendation can be made.

STUDY LIMITATIONS

Some limitations should be acknowledged when interpreting the study results. First, the cross-sectional nature, retrospective study with limited sample size. Therefore, our results should be considered exploratory and hypothesis generating. Second, although, 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. Fourth, our study was underpowered to assess potential differences between different beta-blocker agents, which might demonstrate different beta-adrenergic responsiveness. However, all patients took a beta-blocker agent specified by current heart failure guidelines (50% bisoprolol, 9% carvedilol, and 41% nebivolol).

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 bpm versus ≥ 70 bpm had a similar beta-blocker dose utilization but low heart rate reductions, 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.

ACKNOWLEDGEMENTS

Frederik Verbrugge is supported by a doctoral fellowship of the Research Foundation – Flanders (FWO, 11L8214N). Frederik Verbrugge, Lars Grieten, and Woutfried Mullens are researchers for the Limburg Clinical Research Program (LCRP UHasselt-ZOL-Jessa), supported by the foundation Limburg Sterk Merk (LSM), Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital. Special thanks to the nursing team of the outpatient clinic of the Cardiology Department of Ziekenhuis Oost-Limburg for their help in performing the exercise tests.

CONFLICT OF INTEREST: none.
REFERENCES


