Chronic heart failure, chronotropic incompetence and the effects of beta-blockade

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Running title: Heart rate limitation in chronic heart failure

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Abstract: Some patients with chronic heart failure (CHF) have a reduced heart rate rise in response to exercise, termed chronotropic incompetence (CI). The prevalence of CI and how it relates to CHF severity, peak oxygen consumption (pVO₂) and prognosis in CHF patients taking modern medical therapy including β-blockers (βB) is unknown.

Methods: We examined the heart rate response to exercise in 237 patients with CHF in sinus rhythm and compared this to 118 control volunteers. We calculated %maximum age-predicted peak heart rate (%Max-PPHR) and percentage heart rate reserve (%HRR), and used a cut off of <80% as the definition of CI for both. We followed the patients for an average of 2.8 (9) years and looked at mortality related to pVO₂, and the presence or absence of CI.

Results: Percent Max-PPHR <80% identified 103 (43%) and %HRR <80% 170 patients (72%) as having CI. CI was more common in patients on βB than those not taking βB by both methods (80 (49%) v 23 (32%) by %Max-PPHR and 123 (75%) v 47 (64%) by %HRR. Patients with CI by either method had a lower pVO₂ than those without. These differences remained significant both for patients on, or not taking, βB. %HRR, Max-PPHR% and HRR were related to NYHA class and correlated with pVO₂. There was no difference in the slopes relating heart rate to pVO₂ between patients with and without CI (6.1 (1.7) v 5.1 (1.8); p=0.34).

During an average 2.8 year follow up 40 patients (17%) died. In Cox proportional hazard models, peak VO₂ was the most powerful predictor of survival, and neither measure of CI was an independent predictor of outcome.

Conclusions: Peak VO₂ is a powerful marker of prognosis in patients with CHF whether they are taking βB or not. A low heart rate response to exercise in patients with CHF correlates with worse exercise tolerance, but is unlikely to contribute to exercise impairment.
Introduction

Patients with chronic heart failure (CHF) complain of exercise intolerance, usually due to breathlessness and fatigue.[1] This can be objectively assessed as a reduction in peak oxygen consumption (pVO2) and an increase in the ventilatory response to exercise (VE/VCO2 slope) during incremental exercise testing with metabolic gas exchange analysis.[2] The impaired exercise tolerance is likely to be due to an interaction of cardiac and peripheral factors,[3] each under the influence of the chronic sympathetic overactivity seen in CHF.[4][5] This overactivity leads to beta-receptor down-regulation,[6][7] and reduced myocardial sensitivity to beta-agonists,[8] which might in turn lead to a reduction in heart rate response to exercise in patients with heart failure (chronotropic incompetence),[9][10] and thereby contribute to exercise intolerance.

The frequency of a poor heart rate response to exercise in CHF patients increases with increasing severity of the heart failure,[11] and it is also seen in asymptomatic individuals with LV dilatation and reduced LVEF.[12] Some,[13] but not all,[14] studies have suggested that CI might contribute to reduced exercise tolerance.

Little work has been done on chronotropic incompetence and prognosis in heart failure populations but one study has suggested that the prognosis for CHF patients with poor chronotropic reserve is particularly bad.[15] Beta-blockers (βB) reduce resting and peak heart rate but improve prognosis in CHF. These mortality data might therefore not hold true in the modern era of CHF management.

We wanted to establish the prevalence of chronotropic incompetence in a cohort of CHF patients taking modern medical therapy for heart failure, and whether this affected exercise capacity and predicted prognosis.

Methods

We enrolled 237 patients into the study and 118 controls. Chronic heart failure was defined as the presence of symptoms of fatigue or breathlessness on exertion and a left ventricular ejection fraction on echocardiography of less than 40% with no other cause of breathlessness apparent. To be included in the analysis, the condition had to be of at least three months duration prior to the initial visit, with no recent exacerbation or change in medication. We did not include patients with neurological conditions, inducible ischaemia or a history of pulmonary disease, or if their FEV1 was less than 80% of predicted. We also excluded patients with atrial fibrillation. The controls were individuals of a similar age chosen at random from the patient lists of local general practitioners with no history or symptoms of cardiovascular disease.

At the initial visit each individual had an echocardiographic examination using a Vingmed Vivid 5 scanner (Horten, Norway) using M-mode to determine left ventricular end-diastolic diameter (LVEDD) and the modified Simpson’s rule to calculate left ventricular volumes and ejection fraction (LVEF). Each subject then underwent symptom-limited treadmill-based maximal exercise testing using a
Bruce protocol modified by the addition of a ‘stage 0’ at onset consisting of 3 minutes of exercise at 1.61km/hr (1 mile/hour) with a 5% gradient. Patients were encouraged to exercise to exhaustion. During the tests patients wore a tightly fitted facemask to which was connected a capnograph and a sample tube enabling on-line ventilation and metabolic gas exchange measurements (Jaeger Oxycon Delta, Würtzburg, Germany). A respiratory exchange ratio (RER), (VCO₂/VO₂) of 1.1 was taken to indicate maximal effort. The anaerobic threshold was calculated using the VO₂/VCO₂ slope method.[16] The relationship between ventilation (VE) and carbon dioxide production (VCO₂) (VE/VCO₂ slope) was calculated by simple regression of data collected throughout exercise.[17]

Prior to the exercise test, subjects were seated comfortably and asked not to talk for three minutes. The heart rate over this time was averaged and taken as the resting heart rate. Baseline metabolic gas exchange readings were taken at this time and the monitoring period extended as necessary to achieve 3 minutes of true resting oxygen consumption. Peak heart rate was the averaged heart rate over the final 30 seconds of exercise.

Chronotropic incompetence is defined as an inadequate heart rate response to exercise. Maximal age-predicted heart rate is most commonly calculated by the formula of Astrand (220-age).[18] Chronotropic incompetence can be defined as peak exercise heart rate less than 80-85% of maximal age-predicted peak heart rate (Max-PPHR).[19] As most of the more recent reports have used <80% Max-PPHR, we used this figure in our study. We also calculated %heart rate reserve (%HRR). This is a measure of the change in heart rate from rest to peak exercise as a proportion of the possible maximum change from rest to expected peak heart rate. This might be more useful in a beta-blocked group as it incorporates the resting heart rate as below:

\[
\left( \frac{PHR - RHR}{220 - Age - RHR} \right) \times 100\%
\]

where PHR is peak heart rate and RHR is resting heart rate. We took a %HRR less than 80% as abnormal.

Follow up was censored at 1st July, 2004. We used a computerised local health records database to find if each subject was alive at the censorship date. In subjects on whom there were no data, and in those who were reported as dead, we contacted the general practitioners to confirm the information. We analysed data from patients on βB at the time of the test separately from those not taking βB. Patients were not taking βB at the time of the initial test either because it was their first visit or they had not tolerated them. We also examined the ability of maximal age-predicted peak heart rate and peak heart rate reserve to predict survival during follow-up.

Results are reported as means (SD). We used unpaired Student’s t-test for between group comparisons and paired t-test for within group analyses. A p-value of <0.05 was taken to be significant. We used linear regression analysis to explore the relation between continuous variables and the Chi-squared test (χ²)
to compare between nominal variables. Cox-proportional hazard analyses were used to assess prognostic associations. The hazard ratio (HR) with 95% confidence intervals and p-values by the likelihood-ratio test are given. Hazard ratios for continuous variables apply per unit of the analyzed variable. Kaplan-Meier cumulative survival plots were constructed to illustrate the results (StatView 5.0, Abacus Concepts, Berkeley, USA).

**Results**

Table 1 shows control and patient characteristics split by therapy. The groups were similar for height, age, and sex. There was no difference between the patient groups in terms of aetiology, LV function and diameters, exercise time, RER, and predicted peak heart rate (PHR) or spirometry (FEV₁ or FVC)(table1). Patients taking βB had a lower resting heart rate and achieved a lower PHR, lower %maximal age-predicted peak heart rate (%Max-PPHR) and a lower %heart rate reserve (%HRR) than patients not taking βB but there was no difference between these two groups for pVO₂, VE/VCO₂ slope or the ratio between pVO₂ and PHR. Patients on βB exercised for longer than those not taking βB. Figures 1a and 1b show the relationships between PHR and ∆HR and pVO₂ for patients on and off βB and controls.

Table 1: Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients with beta-blocker (n=164)</th>
<th>Patients without beta-blocker (n=73)</th>
<th>Controls (n=118)</th>
<th>p value between patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (10)</td>
<td>68 (11)</td>
<td>65 (12)</td>
<td>0.11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (8)</td>
<td>168 (11)</td>
<td>169 (10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.5 (15.9)</td>
<td>76.0 (17.3)</td>
<td>74.2 (12.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>123/41</td>
<td>55/18</td>
<td>62/56</td>
<td></td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.5 (0.9)</td>
<td>6.3 (1.2)</td>
<td>4.9 (0.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32.0 (7.0)</td>
<td>33.3 (9.8)</td>
<td>59.3 (8.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Aetiology (n)</td>
<td>DCM 29, BP 10, IHD 121</td>
<td>DCM 21, BP 2, IHD 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes type I/II (%)</td>
<td>4/12</td>
<td>4/10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>38</td>
<td>21</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide (mg)¹</td>
<td>68 (46)</td>
<td>72 (38)</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>ACEi/AIIA ² (%)</td>
<td>84</td>
<td>78</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Amiodarone (currently / last 6months)(%)</td>
<td>5/2</td>
<td>7/0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>7</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aspirin/Warfarin (%)</td>
<td>70/29</td>
<td>68/33</td>
<td>7/0</td>
<td></td>
</tr>
<tr>
<td>New York Heart Association I, II, III (%)</td>
<td>6, 74, 19</td>
<td>5, 72, 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate rest (/min)</td>
<td>72 (15)</td>
<td>80 (17)</td>
<td>71 (11)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Heart rate peak (/min)</td>
<td>123 (25)</td>
<td>133 (26)</td>
<td>157 (21)</td>
<td>0.0045</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>First group</th>
<th>Second group</th>
<th>Third group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted peak HR</td>
<td>154 (9.6)</td>
<td>153 (10.8)</td>
<td>155 (12)</td>
<td>0.23</td>
</tr>
<tr>
<td>%Max-PPHR</td>
<td>80 (15)</td>
<td>87 (17)</td>
<td>102 (11)§</td>
<td>0.0005</td>
</tr>
<tr>
<td>HRR</td>
<td>31 (23)</td>
<td>19 (25)</td>
<td>-3 (17)§</td>
<td>0.0004</td>
</tr>
<tr>
<td>% HRR</td>
<td>63 (26)</td>
<td>73 (32)</td>
<td>104 (21)§</td>
<td>0.017</td>
</tr>
<tr>
<td>pVO2 (ml/kg/min)</td>
<td>20.4 (5.7)</td>
<td>19.5 (5.3)</td>
<td>34.4 (9.4)§</td>
<td>0.35</td>
</tr>
<tr>
<td>Ve/VCO2 slope</td>
<td>36.0 (8.2)</td>
<td>36.6 (6.7)</td>
<td>28.3 (3.9)§</td>
<td>0.55</td>
</tr>
<tr>
<td>Exercise time (s)</td>
<td>498 (198)</td>
<td>435 (218)</td>
<td>788 (290)§</td>
<td>0.02</td>
</tr>
<tr>
<td>RER</td>
<td>1.02 (0.1)</td>
<td>1.02 (0.1)</td>
<td>1.02 (0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>pVO2/peak HR ratio</td>
<td>0.13 (0.03)</td>
<td>0.13 (0.03)</td>
<td>0.22 (0.05)§</td>
<td>0.34</td>
</tr>
<tr>
<td>Follow-up (days alive)</td>
<td>1032 (337)</td>
<td>898 (410)</td>
<td>909 (326)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Values are means (SD).

FEV₁, forced expiratory volume in the first second; FVC, forced ventilatory capacity; LVEDD, left ventricular end diastolic dimension form M-mode echocardiography; LVEF, left ventricular ejection fraction (%); DCM, dilated cardiomyopathy; IHD, ischaemic heart disease; BP, hypertensive heart failure; †, the mean daily dose of frusemide (or frusemide equivalent) is given; ACEi, angiotensin converting enzyme inhibitor; AIIA, angiotensin II inhibitor; %Max-PPHR%, percent maximal age-predicted peak heart rate; HRR, heart rate reserve; %HRR, percent heart rate reserve; pVO₂, peak oxygen consumption; Ve/VCO₂ slope, slope relating ventilation to carbon dioxide production; RER, respiratory exchange ratio (VCO₂/VO₂); HR/VO₂ slope, slope relating heart rate to oxygen consumption; †, p<0.05 for difference between all patients and controls; #, p<0.0001 for difference between all patients and controls.

PREVALENCE OF CHRONOTROPIC INCOMPETENCE AND THE EFFECT OF BETA-BLOCKERS

We used two definitions for chronotropic incompetence (CI). Using %Max-PPHR <80%, 103 (43%) of patients had CI (ΔHR 37 (17) v 60 (19)/min; p<0.001)

Patients with CI had a lower pVO₂ than those without 18.6 (5.3) v 21.2 (5.5); p=0.0007, and a steeper Ve/VCO₂ slope (37.9 (9.0) v 35.0 (6.4); p=0.005).

Patients on βB were more likely to have CI than those not taking βB (80 (49%) v 23 (32%);χ²p=0.015).

When we used %HRR <80%, to define CI, 170 patients (72%) were identified as having a poor rise in heart rate on exercise (ΔHR 41 (16) v 71 (18)/min; p<0.0001). Patients with CI had a lower pVO₂ than those without (17.8 (4.8) v 22.4 (4.8); p=0.0002) and a steeper Ve/VCO₂ slope (34.3 (7.0) v 37.0 (8.0); p=0.02). Beta-blocked patients were more likely to have CI than those not on βB (123 (75%) v 47 (64%);χ²p=0.04).

Figures 2a and b show the % Max-PPHR and % HRR in heart failure patients and the relation to NYHA class split by beta-blocker use. PeakVO₂ correlated with %HRR, and Max-PPHR% both in patients taking and those not taking β-blocker (figures 3a and b).

Patients taking βB identified as having CI by either method had a lower pVO₂ (%Max-PPHR; 18.9 (5.3) v 21.7 (5.6); p=0.002 and %HRR; (19.2 (5.3) v 24.0 (5.3); p<0.0001), and a steeper Ve/VCO₂ slope (37.5 (9.7) v 34.8 (6.3); p=0.03 and 36.8 (8.7) v 34.0 (6.3); p=0.03) than those taking βB but without CI. Patients not taking βB but having CI by either method also had a lower pVO₂ (%Max-PPHR; 17.9 (5.6) v 20.0 (5.0); p<0.05 and %HRR; 17.8 (4.9) v 22.4 (4.8);
p=0.0002) and steeper VE/VCO₂ slope (39.1 (6.1) v 35.5 (6.8); p=0.03 and 39.1 (6.1) v 35.6 (6.8); p=0.03 than those not on βB without CI.

**SURVIVAL RESULTS**
During an average follow up period of 2.8 years (0.9), 40 patients died of whom 19 were taking βB at the time of the initial exercise test. Many of the patients not on βB at the time of the test eventually were started on them, (n=48, 66% of those not taking βB at baseline) and absolute mortality at follow-up was lower for those that did eventually start βB than for those who did not (8 of 48, (17%) v 10 of 27 (37%), p=0.05). Overall, patients dead at follow-up had a lower baseline pVO₂, (17.5 (4.0) v 20.6 (5.7); p=0.0015) and steeper VE/VCO₂ slope (40.3 (7.0) v 35.5 (7.7); p=0.0004) than those surviving.

The only relation between CI and outcome in Kaplan Meier analysis that we found was between the presence or absence of CI using the %HRR definition in that group of patients not taking βB at baseline (figure 4). Univariate predictors of survival relating to heart rate during exercise are given in table 2. In a model including resting and peak heart rate only, increasing resting heart rate was an adverse predictor (hazard ratio 1.03 (1.01 – 1.05; P=0.003) and increasing peak rate was a predictor of better outcome (HR 0.98 (0.97 – 0.99; P=0.008). Peak oxygen consumption was the most powerful single predictor of outcome. In a multivariate model constructed with age, beta-blocker use, peak oxygen consumption and chronotropic incompetence, peak oxygen consumption is the most powerful predictor of outcome (table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HR</td>
<td>1.02</td>
<td>1.00 – 1.04</td>
<td>0.07</td>
<td>3.3</td>
</tr>
<tr>
<td>Peak HR</td>
<td>0.99</td>
<td>0.98 – 1.00</td>
<td>0.14</td>
<td>2.3</td>
</tr>
<tr>
<td>Delta HR</td>
<td>0.98</td>
<td>0.96 – 0.99</td>
<td>0.003</td>
<td>9.2</td>
</tr>
<tr>
<td>%max PPHR</td>
<td>1.0</td>
<td>0.98 – 1.01</td>
<td>0.76</td>
<td>0.1</td>
</tr>
<tr>
<td>%HR reserve</td>
<td>0.99</td>
<td>0.98 – 1.00</td>
<td>0.20</td>
<td>1.7</td>
</tr>
<tr>
<td>CI (%max PPHR)</td>
<td>1.13</td>
<td>0.62 – 2.08</td>
<td>0.69</td>
<td>0.2</td>
</tr>
<tr>
<td>CI (%HR reserve)</td>
<td>0.87</td>
<td>0.45 – 1.68</td>
<td>0.67</td>
<td>0.2</td>
</tr>
<tr>
<td>Beta blocker use</td>
<td>0.52</td>
<td>0.29 – 0.95</td>
<td>0.03</td>
<td>4.3</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.02 – 1.10</td>
<td>0.0004</td>
<td>13.9</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>1.05</td>
<td>1.05 – 1.08</td>
<td>&lt;0.0001</td>
<td>13.1</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td>0.88</td>
<td>0.82 – 0.93</td>
<td>&lt;0.0001</td>
<td>18.6</td>
</tr>
</tbody>
</table>

Hazard ratios for continuous variables apply per unit of the analyzed variable.
CI; Chronotropic incompetence, other abbreviations as for table 1.
Table 3: Cox-proportional survival analyses according to measures of chronotropic incompetence (multivariate analysis excluding Ve/VCO2 slope). Combined $\chi^2$ 26.4 (P<0.0001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00 – 1.07</td>
<td>0.07</td>
<td>3.4</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>0.89</td>
<td>0.83 – 0.96</td>
<td>0.002</td>
<td>9.6</td>
</tr>
<tr>
<td>Beta blocker use</td>
<td>0.69</td>
<td>0.37 – 1.30</td>
<td>0.19</td>
<td>1.7</td>
</tr>
<tr>
<td>CI (%max HR)</td>
<td>1.22</td>
<td>0.63 – 2.38</td>
<td>0.55</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Hazard ratios for continuous variables apply per unit of the analyzed variable.

CI; Chronotropic incompetence, other abbreviations as for table 1.

**Discussion**

Patients with CHF have a reduced heart rate rise on exercise (chronotropic incompetence (CI)). Different methods of defining CI lead to different estimates of its prevalence. Previous data using %Max-PPHR had suggested that less than 30% of patients with CHF had chronotropic incompetence.[14] Our data suggest that 32% of patients not yet on $\beta$B have CI when defined by <80%Max-PPHR and 64% if a definition of <80%HRR is used. In beta-blocked patients the figures are higher; 49% with %Max-PPHR and 75% with %HRR.

Chronotropic incompetence (CI) was related to the severity of the heart failure as measured by symptom assessment (NYHA class) and peak oxygen consumption (pVO2). In patients with CI the pVO2 was lower and the Ve/VCO2 slope was steeper. We found a close relationship between pVO2 and %HRR, %Max-PPHR and HRR in both beta-blocked patients and those not taking $\beta$B. These results support previous data that the CI is linked to the severity of heart failure. It was thought that CI might be an important cause of the reduction in exercise capacity in CHF patients, but previous work [20] and the present study does not support this view. Patients with CI did have reduced exercise capacity, but the slope relating heart rate to pVO2 was the same for those with and without CI. This suggests that at matched work loads, the heart rates were similar and that reduced heart rates might merely reflect work being performed, or in incremental tests, the duration of exercise. Subjects taking $\beta$B had significantly lower peak heart rates and more CI than those not taking $\beta$B with no overall difference in pVO2 despite a greater exercise time. Longitudinal studies examining the effects of acute and long-term beta-blockade on patients with heart failure have not shown a reduction of pVO2 despite reductions in peak heart rate with beta-blocker therapy.[20][21]

Poor chronotropic response to exercise predicts a poor outcome in patients having stress myocardial perfusion scans.[22][23][24][25] independent of severity of coronary disease and left ventricular function.[26][27] In heart failure patients chronotropic incompetence is associated with poor heart rate variability [28] and disturbed cardiac autonomic status.[29]

Percent heart rate reserve, perhaps because it includes the resting heart rate might be useful in populations on heart-rate limiting agents. It is possibly a more
reliable marker of prognosis in patients undergoing myocardial perfusion scanning than percentage maximal predicted heart rate,[30] and might therefore also be more useful in the modern heart failure population, many of whom will be taking βB, than measures using percentage of predicted. The present study is the first to use this calculation in a large heart failure population taking contemporary therapy.

Assessing chronotropic response in CHF patients might not only be important as a simple way to further stratify patients at higher risk of cardiac death, but there are data suggesting that chronotropic incompetence can be improved with physical training. The identification of these patients might allow further targeting of medical and device therapy and exercise training to those who will most benefit from it.[31]

Previous data have suggested that the presence of chronotropic incompetence might be a more powerful predictor of mortality than pVO₂ and VE/VCO₂ slope.[15] It has also been suggested in a review of 127 patients with CHF that in individuals tolerating beta-blocker therapy, pVO₂ is not useful for predicting mortality.[32] In our study, pVO₂ was a stronger predictor of mortality than %HRR and %MAX-PPHR, and patients dead at follow-up had lower pVO₂ and steeper VE/VCO₂ slopes than those surviving whether they were taking βB at baseline or not.

The heart rate slowing effects of beta-blockade are important in improving prognosis, patients with greater heart rate reductions gain additional prognostic benefits.[33][34] There are no published data examining the influence of heart rate reductions during exercise and outlook in CHF patients. However, higher sympathetic hormone levels during exercise are associated with a worse outcome.[35] Recent small non-randomised studies have suggested that target doses and heart rate lowering might be less important and that any dose of beta-blocker might be sufficient to improve outlook.[36][37] In our study, in patients not taking βB at the time of the test, chronotropic incompetence, or a poor heart rate response to exercise was associated with increased mortality over the subsequent three years. In contrast, patients on βB with a poor heart rate response to exercise did not have a higher mortality. Patients on βB with a lower heart rate response to exercise, implying more aggressively beta-blockade did not have a worse outcome, even though the pVO₂ was lower in patients with %HRR<80%. Pure heart rate-limiting agents without some of the potential side effects or contraindications of βB are currently under investigation and may be useful in individuals unable to tolerate beta-blockade.[38] Our data support the concept that chronotropy is not a major factor in determining exercise capacity in patients with CHF and patients taking βB chronotropic limitation might be an important goal. It is therefore not surprising that pVO₂ remains an important predictor of mortality in patients treated with βB.
Conclusions
Chronotropic incompetence is common in patients with chronic heart failure, and its prevalence is greater in patients taking beta-blockers. Patients with more severe symptoms of chronic heart failure and greater reductions in exercise tolerance have a greater reduction in heart rate response to exercise and a higher mortality. Peak oxygen consumption was the most powerful and consistent predictor of mortality in all subgroups of patients including patients taking beta-blockers. Patients with chronotropic incompetence off beta-blockade have an increased mortality than those without. Chronotropic incompetence due to aggressive beta-blocker therapy does not predict mortality.
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Legends

Figure 1a  Relation between peak heart rate and peak oxygen consumption in patients on beta-blockers (grey circles)\((r=0.45; \ p<0.001)) and not on beta-blockers (unfilled circles)\((r=0.49; \ p<0.001)) and controls (black circles)\((r=0.44; \ p<0.001))

Figure 1b  Relation between peak heart rate and peak oxygen consumption in patients on beta-blockers (grey circles)\((r=0.56; \ p<0.001)) and not on beta-blockers (unfilled circles)\((r=0.60; \ p<0.001)) and controls (black circles)\((r=0.53; \ P<0.001))

Figure 2a  Percent maximal peak heart rate (%Max-PPHR) in patients taking (black bars) and not taking beta-blockers (grey bars) and the relation to NYHA class.

Figure 2b  Percent heart rate reserve (%HRR) in patients taking beta-blockers (black bars) and not taking beta-blockers (grey bars) and the relation to NYHA class.

Figure 3a  Relationship between pV\(\text{O}_2\) and percent maximal peak heart rate (%Max-PPHR) in patients taking beta-blockers (filled circles and solid trendline)( \(r=0.39, \ p<0.0001\)), and not taking beta-blockers (unfilled circles and dashed trendline)(\(r=0.31, \ p<0.0001\)).

Figure 3b  Relationship between pV\(\text{O}_2\) and percent heart rate reserve (%HRR) in patients taking beta-blockers, (filled circles and solid trendline)\((r=0.38, \ p<0.0001)) and not taking beta-blockers (unfilled circles and dashed trendline)\((r=0.31, \ p<0.0001))

Figure 4  Survival grouped by chronotropic incompetence based on %HR reserve in patients not on a betablocker

Competing interests: None
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Figure 2a

The bar chart illustrates the %Max PPHR across different NYHA classes.

- **Controls**: 100% Max PPHR
- **NYHA class 1**: 100% Max PPHR

Significant differences are indicated by p-values:
- Controls vs. NYHA class 1: p<0.0001
- Controls vs. NYHA class 2: p<0.01
- Controls vs. NYHA class 3: p<0.02
Figure 2b

The graph shows the percentage of heart rate reduction (%HRR) across different NYHA classes (Control, 1, 2, 3) with statistical significance indicated for each class:

- Controls: p<0.0001
- NYHA class 1: p<0.01
- NYHA class 2: p<0.002
- NYHA class 3: p<0.01
Figure 3a

The graph shows the relationship between PVO2 (ml/kg/min) and %Max peak predicted heart rate. The correlation coefficients are given as follows:

- $r = 0.39$, $p < 0.0001$
- $r = 0.31$, $p < 0.0001$
Figure 3b

$P\dot{V}O_2$ (ml/kg/min) vs. %Heart rate reserve

- $r=0.44$, $p<0.0001$
- $r=0.42$, $p<0.0001$
Figure 4

Cumulative survival over time (days) for two groups: No CI (N=27) and CI (N=47). The logrank test shows a significant difference between the two groups with a p-value of 0.03.

P (logrank) = 0.03