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Article:

Chronotropic incompetence does not limit exercise capacity in chronic heart failure

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Abstract

Background: Limited heart rate (HR) rise (HRR) during exercise, known as chronotropic incompetence (CI), is commonly observed in the context of chronic heart failure (CHF). HRR is closely related to workload, the limitation of which is characteristic of CHF. Whether CI is a causal factor for exercise intolerance, or simply an associated feature remains unknown.

Objectives: The aim of this investigation was to clarify the role of the HR on exercise capacity in CHF.

Methods: This series of investigations consisted of a retrospective cohort study and two interventional randomised cross-over studies to assess: 1) the relationship between HRR and exercise capacity in CHF and the effect of 2) increasing HR, and 3) lowering HR on exercise capacity in CHF assessed using symptom limited treadmill exercise testing with metabolic gas exchange to measure peak oxygen consumption (pV_{O2}) in patients with CHF due to left ventricular (LV) systolic dysfunction.

Results: The three key findings of this project are: 1) although exercise capacity is related to HRR in CHF, the association is much weaker in severe CHF as compared to those with normal LV function, 2) increasing HRR using rate-adaptive pacing (versus fixed-rate pacing) in unselected patients with CHF does not improve peak exercise capacity and 3) acutely lowering baseline and peak HR by adjusting

pacemaker variables in conjunction with a single dose of ivabradine (versus placebo) does not adversely affect exercise capacity in unselected CHF patients.

Conclusions: Our data refute the contention that CI contributes to impaired exercise capacity in CHF. This finding has widespread implications for pacemaker programming and the use of heart-rate lowering agents.

Key words: Chronotropic incompetence, exercise capacity, heart failure, heart rate

Abbreviations

CHF	Chronic heart failure
LVSD	Left ventricular systolic dysfunction
CI	Chronotropic incompetence
HR/HRR	Heart rate/Heart rate rise
PHR/RHR	Peak heart rate/Resting heart rate
CPX	Cardiopulmonary exercise test
SR	Sinus rhythm
AF	Atrial fibrillation
pV_{O_2}	Peak oxygen consumption

Introduction

The key feature of chronic heart failure (CHF) due to left ventricular systolic dysfunction (LVSD) is greatly reduced exercise tolerance as a result of fatigue or shortness of breath.[1] A common additional feature is an inability of the heart rate (HR) to increase during exercise, known as chronotropic incompetence (CI), which has been proposed by many to be a major contributor to exercise intolerance.[2][3] CI is defined as either a failure of the peak heart rate (PHR) to reach an arbitrary percentage (usually 80% or 90%) of the age-predicted maximum, or a reduction in the ratio of HR reserve to metabolic reserve (chronotropic index),[4] where a ratio below 0.8 indicates CI, irrespective of age, fitness or functional capacity.[5]

Rate-adaptive cardiac pacing, whereby HR is increased in response to movement or ventilation rate detected by internal device sensors, was developed as an attempt to treat CI.[6][7] In patients receiving standard pacemakers for bradycardia without heart failure, this programming mode is associated with an increase in cardiac output during exercise,[8] and better quality of life,[9][10][11] but inconsistent [12][13] improvements in exercise capacity, compared to fixed rate pacing. On the other hand, rate-adaptive pacing in CHF patients may worsen prognosis and cardiac function.[14][15]

In addition, despite the weight of evidence showing all-cause mortality benefits with pharmacological targeting to reduce the resting HR (RHR),[16][17] many patients do not reach optimal doses of heart rate lowering agents possibly due to a fear of inducing more exercise intolerance, thereby worsening symptoms.[17][18]

Previous studies exploring the relationship between CI and exercise capacity have provided conflicting results, due to the difficulties of adjusting the proposed aetiological factor (HRR) independently of other potential contributing factors, and although there seems to be a strong association, definite causation is unproven. [19][20][21] Therefore, the aim of this investigation was to clarify the role of HR on exercise capacity in patients with LVSD.

Methods

The present manuscript describes the findings of one observational and two interventional studies.

Observational study

Retrospective cohort analysis was performed of consecutive patients referred for metabolic exercise testing (CPX) from the Leeds Outpatient Services between August 2011 and August 2012, all of whom had undergone a transthoracic echocardiogram (TTE) to exclude untreated valvular disease. Inclusion criteria were the ability to perform an exercise test. Exclusion criteria included exertion-limiting angina pectoris, and musculoskeletal limitation. Patients in whom we suspect heart failure with preserved ejection fraction due to abnormalities of diastolic function do not routinely undergo CPX testing and hence were excluded.

We divided patients into groups based upon their resting left ventricular function. The 'no LVSD' group had a normal resting echocardiogram (no evidence of systolic or diastolic dysfunction using BSE criteria and an EF>50%) and no exercise intolerance cause identified. Patients with LVSD (and no other cause of exercise limitation) were

divided into those with 'mild-moderate LVSD' (resting EF >35 but ≤50%) and 'severe LVSD' (resting EF ≤35%).

Interventional Studies

We undertook two randomised cross-over studies in patients with stable CHF and pacemakers or defibrillators. Patients and physicians were blinded to both pacemaker settings and test results. The aim of the first study was to examine whether rate-adaptive pacing in CHF patients increased exercise capacity. The second study aimed to determine whether heart rate limitation using a pure heart rate lowering agent (in patients with sinus rhythm) or pacemaker programming (in patients with atrial fibrillation) impaired exercise capacity.

Inclusion criteria

Patients invited to take part had to have stable CHF due to moderate-severe LVSD (left ventricular ejection fraction ≤45%), persistent symptoms of breathlessness or fatigue on exertion, and a cardiac resynchronisation therapy (CRT) device, with stable lead variables and >95% bi-ventricular pacing, or dual chamber pacemaker/defibrillator with 0% ventricular pacing, implanted for standard indications at least three months previously. Patients also had to be taking optimally tolerated medical therapy with no change in medication or other invasive cardiac procedures for at least three months.

Exclusion criteria

We excluded patients who were dependent on atrial pacing or were unable to give informed consent, along with those that had significant cardiovascular co-morbidities

limiting exercise capacity such as uncontrolled angina, peripheral vascular disease, severe valvular dysfunction, and also non-cardiac conditions such as significant airways disease and musculoskeletal abnormalities that could restrict walking on a treadmill.

Our protocol for heart rate limitation in patients with sinus rhythm included the use of the heart rate lowering agent ivabradine so patients could not currently be taking this medication. Furthermore, patients with contraindications to ivabradine use such as severe hepatic impairment, significant renal impairment (creatinine clearance <15ml.min^{-1}) and long QT syndrome, were also excluded.

Ethical approval was granted by the Health Research Authority (National Research Ethics Service Centre: South Yorkshire REC: 13/YH/0144) and written informed consent was obtained from all participants.

Interventional study 1 – increasing exercise heart rate

Subjects recruited to this study attended on two occasions at the same time of the day one week apart. Prior to each test, their pacemaker was interrogated and then randomly assigned to rate-adaptive pacing (augmented HR rise: rate-response programmed 'on') or fixed rate pacing (intrinsic HR rise: rate response 'off'). Sensor sensitivity was set to maximum and peak paced HR was determined using the '220-age' method.[22]

Interventional study 2 – reducing exercise heart rate

Subjects in this study also attended on two occasions at the same time of the day one week apart. As the peak plasma concentration time after a single oral dose of ivabradine is between 60-120 minutes, patients in sinus rhythm (SR) were randomised to receive either a single 7.5mg dose of ivabradine or matching placebo two hours prior to each CPX test.[23] Patients with AF were randomised by the unblinded cardiac physiologist to either a base rate of 30 bts.min^{-1} or usual settings (base rate of 60 bts.min^{-1}).

Laboratory arrangement and exercise protocol

Subjects were exercised using the Bruce protocol, modified by the addition of a 'stage 0' at onset consisting of 3 minutes of exercise at 1.61km.hr^{-1} (1mile.hour^{-1}) with a 5% gradient. Expired air was collected and metabolic gas exchange analysis performed (Vmax 29, Sensormedics, USA) throughout the test. HR (bpm), oxygen uptake (V_{O2}; ml.kg.min^{-1}) and carbon dioxide output (V_{CO2}; ml.kg.min^{-1}) were recorded as 15-second averages. Anaerobic threshold (AT) was calculated using the V_{O2}/V_{CO2} slope method.

The CPX equipment was re-calibrated using manufacturer recommended volume and gas calibration techniques before every exercise test. All test subjects were encouraged to exercise to exhaustion prior to starting the test, and no further motivation or instructions were given. Participants indicated a score for dyspnoea and fatigue from 0 (no symptoms) to 10 (maximal symptoms) using the standardised Borg scoring system, after each stage.[24]

In order to maintain blinding, the continuous 12-lead electrocardiogram (ECG) monitor was obscured throughout the test (and recovery phase) from subjects and the supervising physician. Only the cardiac physiologist was aware of the programming mode or testing arm for the duration of the studies. He monitored the ECG throughout the study and re-programmed the pacemaker to its original settings at the end of every visit.

Sample size calculation

Study 1

We calculated that in order to detect a clinically important pV_{O_2} increase of 1.5 ml.kg.min^{-1} (an increase of 10%) with 80% power, and a two sided alpha of 0.05, we would need a minimum of 22 subjects in the CHF patients with AF, and a minimum of 38 in those with SR. To allow for drop-outs, recruitment targets were 25 with AF and 50 with SR.

Study 2

Post hoc analysis of study 1 demonstrated higher pV_{O_2} values for both SR and AF than expected, thus the predicted group size to demonstrate a clinically important change was revised. A minimum of 12 subjects were needed in the AF group, and a minimum of 20 in SR. To allow for drop-outs, recruitment targets were 15 with AF and 25 with SR.

Statistical Analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS v.21; IBM Corporation, Armonk, NY, USA), *R*: A Language and Environment for

Statistical Computing (v3.2.3; R Development Core Team, Vienna, Austria) and SAS (v9.4; SAS Institute Inc., Cary, NC).

Normality for all continuous variables was tested using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean and standard deviation (mean (SD)) and non-normally distributed continuous variables as median and interquartile range (median ± IQR). Subsequently, associations between groups or interventions and baseline characteristics were assessed using either Analysis of Variance (ANOVA) and the two-sample student t-test for normally distributed values, or the Kruskal-Wallis H test (one-way ANOVA of ranks) for non-normally distributed data. Similar associations with categorical variables were analysed using the Chi-squared test for contingency tables.

The observational study was analysed using a linear mixed model with random intercepts and slope parameters and compared with the model with only random intercepts using the likelihood ratio test. Linear models regressing peak oxygen consumption on heart rate rise were estimated using least squares for inclusion in graphical displays.

Once a familiarization test has been performed, a peak exercise test is not a training stimulus. We have previously performed up to 5 exercise tests in consecutive weeks in patients with CHF and controls, with no longitudinal effects.[25] However to account for any carryover effects, the interventional cross-over studies were analysed using a linear mixed model with a random effect for patient. For each endpoint Y_{ijk} (e.g. pV_{O2}) under consideration in the study:

$$Y_{ijk} = \mu + \tau_i + \pi_j + \lambda_{ij} + \alpha_k + \varepsilon_{ijk}$$

where $\varepsilon_{ijk} \sim N(0,\sigma^2_\varepsilon)$, $\alpha_k \sim N(0,\sigma^2_\alpha)$ and μ is the overall mean, τ is the treatment effect, π is the period effect and λ is the carryover effect (which is mathematically identical to an interaction term between treatment and period). This model was estimated using PROC MIXED in SAS and least squares means estimated for each of these terms and their differences.

All statistical tests were two-sided and any p-value less than 0.05 was called as statistically significant.

Results

Observational study

During the prospective data collection period, 214 patients underwent outpatient clinical assessment, 12 lead ECG, CPX testing and echocardiography. Of these, 19 were excluded because of significant co-morbidities (n=12) and poor quality tests (n=7) leaving 195 patients. There were 48 participants in the 'no LVSD' group, 57 in the 'mild-moderate LVSD' group and 90 in the 'severe LVSD' group. Baseline characteristics are shown in Table 1.

Whereas in subjects with 'no LVSD' there was a strong correlation between HRR and pV_{O_2} (linear regression, $r^2=0.420$, ANOVA F value <0.01) this relationship was much less obvious in patients with CHF ($r^2=0.366$, ANOVA F value <0.01 for mild-moderate LVSD and $r^2=0.179$, ANOVA F value <0.01 for severe LVSD). These associations are further demonstrated by the differing slope terms in linear models for each group (Figure 1). A linear mixed model with random intercepts and slopes

for each group compared with a mixed model with only random intercepts was shown to fit the observational study data better (likelihood ratio test $\chi^2_2 = 19.0$, $p < 10^{-4}$). This indicates that there is evidence that the slope varies between the groups suggesting distinctions in this relationship even within the CHF cohort, with a less steep slope in those with severe LVSD as compared to mild-moderate LVSD and no LVSD (Figure 1).

CI (defined as chronotropic index <0.8) was present in 107 of the heart failure cohort. Patients with CI had lower exercise time (477 95%CI [425, 539] vs. 382 95%CI [342, 422] s; p<0.001), pVO$_2$ (16.3 95%CI [14.9, 17.7] vs. 15.9 95%CI [14.8, 17.0] ml.kg.min^{-1}; p<0.001) and AT (13.7 95%CI [13.0, 14.3] vs. 12.1 95%CI [11.5, 12.7] ml.kg.min^{-1}; p<0.001), despite similar EF, co-morbidities and medications (Figure 2).

Interventional study 1 – increasing exercise heart rate

A total of 79 patients were enrolled in this study; 53 with SR and 26 with AF. Baseline characteristics are shown in Table 2 and analysis for the primary endpoint and all secondary endpoints are shown in Supplementary Table 1 (SR) and Supplementary Table 2 (AF).

In subjects with SR, rate-adaptive pacing led to higher HR at submaximal (p=0.003) and maximal exercise (p<0.001) (Figure 3), but no changes in any CPX variables including pVO$_2$ (17.0 95%CI [15.6, 18.5] vs. 16.6 95%CI [15.2, 18.1] ml.kg.min^{-1}; (p=0.350), exercise time (459 95%CI [390, 526] vs. 464 95%CI [397, 533] s; p=0.644), AT (12.8 95%CI [11.8, 13.8] vs. 12.2 95%CI [11.2, 13.2] ml.kg.min^{-1}, p=0.075), VE/VCO$_2$ slope (to peak: 35.7 95%CI [32.8, 38.5] vs. 36.3 95%CI [33.4, 39.1]; p=0.533; to AT: 30.4 95%CI [28.1, 32.9] vs. 31.5 95%CI [29.1, 33.9]; p=0.353),

respiratory exchange ratio (RER; 1.09 95%CI [1.05, 1.12] vs. 1.09 95%CI [1.06, 1.12]; p=0.806), oxygen pulse (12.4 (3.5) vs. 11.7 (3.5), p=0.605), end-tidal oxygen tension (PET$_{O_2}$; 111 95%CI [107.9, 114.0] vs. 112 95%CI [109.0, 115.2] mmHg; p=0.287), or perceived exertion level (Borg) scores (for shortness of breath; 4.2 95%CI [3.8, 4.6] vs. 4.1 95%CI [3.6, 4.5], p=0.458; and leg weakness; 4.6 95%CI [4.0, 5.3] vs. 4.8 95%CI [4.2, 5.5]; p=0.494).

All patients enrolled in this study had peak exertional heart rates less than 90% peak predicted heart rate. There was no heterogeneity in change in exercise response between those patients with significant CI at baseline (chronotropic index <0.8; n=66) versus those without (n=13).

In subjects with AF, rate-adaptive pacing led to higher HR at AT (p=0.035) and peak exercise (p<0.001) (Figure 3), but although this was associated with a small increase in pV$_{O_2}$ (15.3 95%CI [13.8, 16.7] vs. 14.2 95%CI [12.7, 15.8] ml.kg.min^{-1}; p=0.058), there was no change in the exercise time (417 95%CI [323, 511] vs. 401 95%CI [307, 495] s; p=0.396), V$_E$/V$_{CO_2}$ slope (to peak: 37.3 95%CI [33.3, 41.2] vs. 39.2 95%CI [35.3, 43.2], p=0.152; to AT: 31.3 95%CI [27.2, 35.4] vs. 33.1 95%CI [29.0, 37.2] ml.kg.min^{-1}; p=0.092), RER (1.15 95%CI [1.08, 1.21] vs. 1.13 95%CI [1.06, 1.19]; p=0.568), oxygen pulse (12.9 95%CI [11.2, 14.6] vs. 14.9 95%CI [13.2, 16.6]; p=0.012), PET$_{O_2}$ (114 95%CI [110, 117] vs. 117 95%CI [113, 120] mmHg; p=0.060) or perceived exertion level (Borg) scores (for shortness of breath; 4.9 95%CI [4.1, 5.7] vs. 4.4 95%CI [3.6, 5.1]; p=0.0636; and leg weakness; 5.2 95%CI [4.5, 6.0] vs. 4.9 95%CI [4.1, 5.6]; p=0.327).

Interventional study 2 – lowering exercise heart rate

A total of 40 patients were enrolled in this study; 26 with SR and 14 with AF. Baseline characteristics are shown in Table 3 and analysis for the primary endpoint and all secondary endpoints are shown in Supplementary Table 3 (SR) and Supplementary Table 4 (AF).

In patients with SR, the use of the sinus node blocker (ivabradine) resulted in a HR reduction at rest (p<0.001), submaximal exercise (p=0.035) and at peak (p<0.001)(Figure 4), with no effect on HRR (48 95%CI [38, 58] vs. 49 95%CI [41, 59] bpm; p=0.588). There was no change in the overall exercise time (534 95%CI [431, 639] vs. 554 95%CI [450, 658] s; p=0.396), oxygen pulse (14.4 95%CI [12.7, 16.0] vs. 13.9 95%CI [12.2, 15.5]; p=0.286), $PETO_2$ (110 95%CI [107, 113] vs. 111 95%CI [109, 115] mmHg; p=0.560), oxygen consumption at AT (p=0.700) and at peak (p=0.588) (Figure 4). The symptom score profiles and all other measured CPX variables were similar in both tests.

In CHF patients with AF, reducing the pacemaker base rate resulted in significant differences in resting HR (p=0.002) and HRR (p=0.030) with no change in the chronotropic index (0.61 95%CI [0.46, 0.76] vs. 0.66 95%CI [0.48, 0.84]; p=0.6). When randomised to a lower resting HR, patients achieved a longer exercise time (434 95%CI [308, 561] vs. 482 95%CI [356, 609] s; p=0.042) with no change in pVO_2 (p=0.207) or $PETO_2$ (113 65%CI [110, 117] vs. 114 95%CI [111, 117] mmHg; p=0.061) (Figure 4). Symptoms score profiles and other measured CPX variables were not significantly different across the two tests.

Discussion

The results of our series of investigations provide a number of important and novel outcomes. Firstly, we have shown that CI is very common in patients with CHF and the prevalence is related to the severity of the left ventricular systolic dysfunction. Secondly, we have shown that increasing heart rate in unselected patients with CHF does not improve exercise tolerance or improve symptoms and thirdly, that lowering heart rate does not worsen exercise tolerance or exercise-related symptoms.

In our prospectively collected dataset of unselected patients with CHF due to left ventricular systolic dysfunction (LVSD), we found a prevalence of CI of 73%, higher in patients with more severe disease as described by cardiac function. However, although our observational data demonstrate a strong positive correlation between HRR and peak oxygen consumption in patients without CHF, this relationship is much weaker in the CHF cohort, and flat in those with the most severe disease suggesting that correcting the CI might not lead to improved exercise tolerance particularly in these, most limited patients.

Previous studies examining this have provided conflicting results. Although Al-Najjar et al and Jorde et al reported a relationship between exercise capacity on CPX testing and the presence of CI in stable CHF patients,[2][26] this association was not seen by Roche et al and Clark et al who reported no significant difference in important exercise variables between CHF subjects with and without CI.[27][19] We have also previously described a poor correlation between peak heart rate and exercise capacity in CHF patients (r=0.003; p=0.98), in contrast to the strong relationship seen in control subjects (r=0.85, p<0.001).[28]

The findings from our observational data stimulated the hypotheses for the subsequent intervention studies; that CI is not a contributor to exercise intolerance in unselected patients with CHF.

The first of these demonstrated that overall, increasing PHR to 'correct' CI does not result in any improvement in oxygen consumption, exercise time or symptoms in CHF. The situation was different in the presence of AF, where we found pVO_2 to be a little higher but without change in exercise time or AT. Hence, CI seems to be a bystander rather than a contributor to exercise intolerance in patients with CHF. Unlike the situation described by Tse et al in 20 patients with CRT, where rate-adaptive pacing led to an incremental benefit only in those with severe CI, but a worsening of exercise capacity in a those with less severe CI,[29] our data do not allude to a heterogeneity of response to rate adaptive pacing across degrees of CI. Whether increasing heart rate through rate adaptive pacing in an effort to correct the CI leads to worse metabolic efficiency as hinted at in our AF patients is worthy of further exploration.

In our second interventional study, we found that reducing RHR did not result in any worsening of exercise capacity in either the sinus or AF cohorts. In fact, starting at a lower resting HR in AF resulted in higher HRR and longer exercise time, with similar pVO_2, thus implying an increase in overall metabolic efficiency, and achieving greater workload for a similar oxygen consumption.

Our findings are consistent with those reported in the study by Sarullo et al in a randomised placebo-controlled trial of 60 CHF patients with LVSD, where heart rate reduction with ivabradine resulted in dramatic increases in both endurance exercise time during a constant workload test (14.8 vs. 28.2 minutes; $p < 0.05$) and pVO$_2$ on a graded maximal exercise test (13.5 vs. 17.9 mL/kg/min; p<0.05).[30] The CARVIVA trial using ivabradine alone or in combination with a beta-blocker also described greater walk distance in 6 minutes in CHF patients.[31]

Patients with CHF have impaired biomechanical efficiency compared to controls.[32] Thus reducing the resting HR may reduce the oxygen requirement per unit of work, by reducing myocardial oxygen demand thereby increasing overall metabolic efficiency.[33] This may also be one way in which heart rate reduction improves outcomes in patients with CHF.[34][35]

The mechanical dysfunction and loss of metabolic capability that is characteristic of CHF is closely linked to the degree of abnormal myocardial calcium handling.[36] Calcium cycling is a major determinant of cardiac contractility, and abnormalities thereof lead to a reduction in the force-frequency relationship, and impairment of the Bowditch effect.[37][38] Calcium cycling is both dependent on, and a determinant of, the heart rate.[39] Thus there may be an optimal heart rate range in CHF beyond which the limit for effective calcium handling is exceeded. A lower heart rate range could restore calcium homeostasis and improve myocardial energetics,[40] and may be the mechanistic basis for our findings.

Our data suggest that the improved exercise capacity seen as a result of rate adaptive pacing in patients without heart failure,[41] cannot be extrapolated into patients with heart failure in whom there are strong prognostic benefits of heart rate limitation.[42][43]

Limitations

Our observational study has biases that are common in studies of this type. There is a degree of patient selection in that those who are too unwell with advanced HF symptoms, or have other co-morbidities that may preclude a treadmill based exercise test may not be referred for a CPX test by the clinician responsible for their care. Our non-CHF group was younger than our CHF group; a common problem with comparisons of this type is finding enough 'normal' older people.

Resting ventricular function was used to divide cohorts into no LVSD, mild-moderate LVSD and severe LVSD. EF has been shown to correlate poorly with exercise capacity and as such a better way to discriminate LVSD severity may have been to use questionnaires that assess the activities of daily living, 6-minute walk tests, NYHA status or dose of diuretics required to control the LVSD symptoms. Nonetheless, LVSD treatment guidelines rely on echocardiographic EF measurements to stratify LVSD severity and to guide treatment decisions. Hence, EF was chosen as the measure with which to separate the cohorts, as this information was readily available.

The groups in our observational study were not matched for height, weight, age or level of training; all of which can affect peak V_{O2}. Although we cannot exclude the

possibility of systematic differences in the level of motivation or encouragement from the technicians running the tests between subject groups, we feel that this is unlikely and was not borne out in the metabolic gas data, where the respiratory exchange ratio (RER) was greater than 0.99 in all three groups.

We sought to address some of these issues in the interventional studies, yet we only included those patients with pacemaker devices, who may exhibit a different chronotropic response to those without any indications for pacing.

The totality of our data are also limited by the bias around inviting patients to participate that have previously completed a good quality exercise test. However, the observational data were collected in consecutive patients. Our use of a modified version of the Bruce protocol was dictated by a desire to use a consistent protocol for all patients, to allow us to compare exercise times rather than just metabolic gas analysis data, and the fact that treadmill-based activity is associated with greater upper body movement required for activation of the rate-response algorithms in pacemakers. We acknowledge that this exercise modality and protocol might not have been ideal for all of our patients but on balance we feel the protocol choice did not materially alter our results. The early, low workload stage allowed even those patients with the greatest limitation in exercise capacity to complete at least the first stage, reducing the bias towards less limited patients.

Finally, small increases in heart rate were seen in all tests, and we are unable to comment whether our observations would have been the same had there been no heart rate increases at all.

Conclusion

We have demonstrated that <mark>the degree of</mark> heart rate rise during exercise in patients with heart failure due to left ventricular systolic dysfunction may not be important in determining exercise capacity. These findings have clinical implications for pharmacological and device treatment strategies. Although CI and exercise tolerance are related, correcting this in CHF patients is unnecessary and might have adverse metabolic effects. Physicians and their patients should be reassured that optimal doses of heart-rate-lowering agents with the aim of achieving the best prognostic outcomes is unlikely to objectively worsen exercise capacity.

Perspectives:

Competency in Medical Knowledge: Chronotropic incompetence (CI) has previously been considered a causal factor for functional limitation in CHF. This investigation demonstrates that despite the presence of an association, no strong causal link exists between CI and exercise intolerance.

Competency in Patient Care: Patients with moderate/severe CHF can be reassured that optimal doses of HR lowering medications for prognostic benefits, will not impact their functional capacity.

Translational Outlook: This investigation shows that limiting exercise-related heart rate rise in patients with CHF is well tolerated and does not reduce exercise capacity. Further work is needed to determine the optimal heart rate range for individual patients based on the cardiac force-frequency relationship, and whether exercise tolerance can be improved by tailoring the heart rate response with a combination of medications and pacemaker settings.

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