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Personalised Rate-Response Programming Improves Exercise Tolerance after Six Months in People with Cardiac Implantable Electronic Devices and Heart Failure: a phase II study

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Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) is characterised by blunting of the positive relationship between heart rate (HR) and left ventricular (LV) contractility known as the force frequency relationship (FFR). We have previously described that tailoring the rate-response programming of cardiac implantable electronic devices (CIED) in patients with HFrEF based upon individual's non-invasive FFR data acutely improves exercise capacity. We sought to examine whether using FFR data to tailor HR response in HFrEF patients with CIEDs, favourably influences exercise capacity and LV function 6 months later.

Methods: We conducted a single-centre, double-blind, randomized, parallel group trial in patients with stable symptomatic HFrEF, taking optimal guideline-directed medical therapy and with a CIED (cardiac resynchronisation therapy (CRT) or implantable cardioverter defibrillator (ICD)). Participants were randomized on a 1:1 basis between tailored rate-response programming based upon individuals' FFR data, and conventional age-guided rate-response programming. The primary outcome measure was change in walk time on a treadmill walk test. Secondary outcomes included changes in LV systolic function, peak oxygen consumption and quality of life.

Results: We randomized 83 patients with a mean ± SD age 74.6 ± 8.7 years, and mean LV ejection fraction (LVEF) 35.2 ± 10.5. Mean (95%CI) change in exercise time at 6 months was 75.4 (23.4 to 127.5) seconds for FFR-guided rate adaptive pacing and 3.1 (-44.1 to 50.3) seconds for conventional settings (ANCOVA p=0.044 between groups) despite lower peak mean (± SD) heart rates (98.6 ± 19.4 v 112.0 ± 20.3 bts/min). FFR-guided HR settings had no adverse effect on LV structure or function, whilst conventional settings were associated with a reduction in LVEF.

Conclusions: In this phase II study, FFR-guided rate-response programming determined using a reproducible, non-invasive method appears to improve exercise time and limit changes to left ventricular function in people with HFrEF and CIEDs**.** Further work is ongoing to confirm our findings in a multi-centre setting and on longer term clinical outcomes.

Clinical Trial Registration: https://clinicaltrials.gov/ NCT: 02964650

Key words: Force frequency relationship, exercise capacity, heart failure, heart rate

Clinical Perspectives:

1) What is new?

- Rate-adaptive CIED programming taking into account the abnormal force-frequency relationship in patients with HFrEF is associated with improved exercise time,
- Standard age-related rate-adaptive programming might contribute to deteriorating left ventricular function.

2) What are the clinical implications?

- Out-of-the box age-guided rate-adaptive pacing might be a suboptimal choice in patients with heart failure,
- An assessment of the force-frequency relationship might be of clinical benefit in heart failure patients by facilitating personalised rate-adaptive programming.

Non-standard Abbreviations and Acronyms

QoL	Quality of life
HR	Heart rate
CIED	Cardiac implantable electronic device
FFR	Force frequency relationship
CHR	Critical heart rate
CRT	Cardiac resynchronisation therapy
ICD	Implantable cardioverter defibrillator
ESV	End systolic volume
EDV	End diastolic volume
BSA	Body surface area
SBP	Systolic blood pressure
CPX	Cardiopulmonary exercise test
MLWHF	Minnesota living with heart failure

Introduction:

The hallmark of chronic heart failure due to reduced left ventricular ejection fraction (HFrEF) is impaired exercise tolerance: it is the most common presenting symptom, the basis for poor quality of life (QoL),[1] and is related to prognosis.[2,3] Exercise intolerance in HFrEF is commonly thought to be exacerbated by limited heart rate (HR) rise.[4] However, we have previously shown that HR rise programming in people with HFrEF and cardiac implantable electronic devices (CIEDs - cardiac resynchronisation therapy/implantable defibrillators), using standard age-related algorithms does not improve exercise capacity.[5] This is likely to be the result of a decoupling of the usually close relationship between heart rate, left ventricular contractility and stroke volume known as the Force-Frequency Relationship (FFR).[6] In HFrEF, this physiological response is attenuated and characterised by a decline in LV contractility above a certain heart rate (termed the Critical Heart Rate – CHR).[7] We have previously demonstrated that the FFR can reliably be assessed in people with HFrEF and CIEDs using echocardiography.[8] In a randomized, controlled, cross-over study we subsequently showed that personalised HR-programming, guided by these non-invasive FFR data, acutely improves exercise capacity in people with HFrEF, persistent symptoms and a CIED.[8]

The aim of the present study was to explore whether device-based HR rise programming, tailored to an individual's FFR, versus conventional age-guided programming, is associated with improved exercise time in the longer term.

Methods:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design

The study was a double-blind, single centre, randomized, controlled, parallel-group phase II trial comparing FFR-guided rate-adaptive programming with standard age-related rate-adaptive programming in patients with HFrEF taking optimal guideline-directed medical therapy, and already having a CIED, (cardiac resynchronisation therapy (CRT) or implantable cardioverter defibrillator (ICD)) according to international guidelines. The primary outcome of this study was change in treadmill exercise walk time at 6 months from baseline, with key secondary outcomes of change in peak oxygen consumption, cardiac function and QoL. Patients were eligible if they had stable (>3 months) symptomatic HFrEF, were willing and able to provide written consent and walk on a treadmill, and prepared to fill in quality of life questionnaires. Patients were ineligible if they had significant cognitive impairment, a life expectancy of less than 6 months, angina pectoris limiting exercise tolerance or were taking calcium channel blockers.

Baseline study procedures

Echocardiography

This has been described previously,[8] but briefly, from 22nd June 2017 all participants were invited to the Cardiovascular Clinical Research Facility at Leeds Teaching Hospitals NHS Trust, Leeds, UK and underwent full baseline echocardiography with two-dimensional grey-scale and tissue Doppler images recorded in two and four chamber views at resting heart rates and at each 15 beats/minute increase during an incremental pacing protocol. Images were

stored in the ‘Echopac’ digital imaging system and analysed offline (GE, Milwaukee, WI, USA). This analysis included a calculation of left ventricular (LV) end diastolic and end systolic volumes using the biplane discs (modified Simpson’s) method.[9] A mean of three measurements was used in the final analysis. The frame at the R-wave was taken as end diastole, and the frame with the smallest LV cavity, as end systole. The LV end-systolic volume (ESV) index (ESVi) was calculated at each stage as ESV/body surface area (BSA), where BSA was calculated using the Mosteller equation.[10]

Blood pressure measurement

Calculation of the end-systolic pressure-volume relation requires measurement of the LV pressure at end-systole.[11] Systolic blood pressure (SBP) measured using a manual blood pressure cuff was used as a surrogate for end-systolic LV pressure. Blood pressure recordings were made using a sphygmomanometer and a standard stethoscope to coincide with echocardiographic images at each heart rate stage. SBP was recorded at the point where the first tapping sound (phase 1 Korotkoff) occurred for 2 consecutive beats.[12]

Pacing protocol

Echocardiographic images were collected at rest with intrinsic atrial rhythm or a base rate of 40bts/min, following which atrial pacing was initiated in the DDD-mode (or VVI in those with atrial fibrillation (AF)) for CRT patients and AAI-mode (or DDD with long AV delays to avoid RV pacing, or VVI for those in (AF)) for subjects without CRT, at the lowest multiple of 10 above baseline. After four minutes, a further set of echocardiographic images were recorded, and subsequently the pacing rate increased in stepwise 15-bts/min intervals

with images recorded after every four minutes. This was repeated until the maximum predicted heart rate predicted by Åstrand (220-age) was reached. At this point peak data were collected and pacing was returned to baseline settings. For safety, subjects were asked to remain in the research facility for a further 30 minutes.

Force frequency calculation

Dividing the systolic pressure by the LVESVi (SBP/LVESVi) gives a surrogate of contractility,[13,14,15] which has been validated against invasive methods.[13,15] Our protocol allowed us to plot the FFR for each participant. We defined the heart rate at which, in a biphasic pattern, the SBP/LVESVi reached maximum value or that at which beyond the SBP/LVESVi declined by 5% as the 'critical heart rate'. In a negative FFR, (in cases where there was no increase in contractility with increments in heart rate) baseline heart rate was deemed the critical heart rate.[16]

Laboratory arrangement and exercise protocol

Subjects were exercised using the ramping treadmill protocol.[17] Expired air was collected and metabolic gas exchange analysis performed (Ultima CardO2, Medgraphics, St Paul MN, USA) throughout the test. Heart rate (HR (beats/min)), oxygen uptake (V_{O_2}; mL/kg/min) and carbon dioxide output (V_{CO_2}; mL/kg/min) were recorded as 15-second averages. Anaerobic threshold (AT) was calculated using the V-slope method. Stroke volume can be estimated during cardiopulmonary exercise testing (CPX) through the calculation of an exercise 'oxygen pulse' (O_2/HR; dividing O_2 by HR (units = mL O_2 per beat)).[18]

The CPX equipment was re-calibrated using manufacturer recommended volume and gas calibration techniques before each test. All test subjects were encouraged to exercise to exhaustion and no further motivation or instructions were given. The arrangement of the laboratory to ensure double-blinding has been described previously.[5,8] 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 unblinded cardiac physiologist was aware of the programming mode or testing arm. They monitored the ECG throughout the study, and only communicated with the other team members if there were safety concerns. The effective delivery of biventricular stimulation in patients with CRT was confirmed from electrocardiographic traces at peak exercise at both time points by the absence or fusion or other QRS morphology changes.

Quality of life

At baseline and 6 month follow-up, participants were asked to complete three quality of life assessments; the Minnesota Living with Heart Failure (MLWHF) questionnaire, the EuroQoL5D (EQ5D) score and a visual analogue scale of overall quality of life.[19]

Randomisation

Following baseline testing, patients were randomly allocated, using random number generation, to one of two groups, and their device was programmed by the unblinded cardiac physiologist to either conventional age-related rate-adaptive pacing,[20] or rate adaptive pacing guided by their FFR assessment, specifically limiting the ‘upper sensor rate’ to the ‘critical heart rate’. Atrio-ventricular (AV) delay programming was optimised in order to avoid fusion

and maintain consistent biventricular stimulation at higher heart rates in those with CRT devices, and device-specific pacing avoidance algorithms were activated in those patients in SR without CRT devices. VVIR programming was the default for those patients in AF. Patients were blinded to their allocation.

Follow-up

Patients were telephoned at one week to assess safety and were invited back at 6 months for repeat cardiopulmonary exercise test, transthoracic echocardiography and quality of life assessment.

Primary outcome measure

Treadmill walk time was our primary outcome. Exercise capacity is the key driver of impaired quality of life in HF,[1,21] and treadmill walk time is therefore a patient-oriented outcome of direct clinical relevance and can easily be converted to distance. In a previous randomized clinical trial we observed significant variability in 6-minute corridor walk testing,[22] and therefore elected to use treadmill walk time as our primary outcome measure for the present study.

Sample size

The trial was designed as a single centre phase II trial since there was an absence of data describing variability in outcomes to be able to robustly design a definitive trial. The aim of this trial was to make initial unbiased comparison of groups and inform variability in outcomes in the target population of patients. As such, the target sample size was based on achieving a sample size appropriate to estimate the variability in the 6 month

primary outcome measure, according to published guidance for phase II trials.[23] We aimed to have outcome data at 6 months for a minimum of 70 patients and the recruitment target was inflated to 85 patients for anticipated drop out.

Statistical analyses

Analyses followed a predefined plan as set out in the trial protocol (NCT: 02964650). As a phase II trial, the aim was to describe outcomes, and variability in outcomes, descriptively. Normality for continuous variables was visually explored by distribution plots, tested using the Shapiro-Wilk test and skewness and kurtosis levels were confirmed at <1 for all key variables. After testing for normality, continuous baseline characteristics were reported as mean and standard deviation (mean (SD)). Analysis of co-variance (ANCOVA) was used to assess inter-group differences in outcome variables. All across treatment group comparisons were two-sided and presented as mean change (95% confidence interval). Exploratory post-hoc univariable analyses of candidate variables against the primary endpoint as predictors of change were undertaken with the aim of adding all variables with a p-value <0.10 to a multivariable model. Data were analysed using the Statistical Package for the Social Sciences (SPSS v.23; IBM Corporation).

Funding and ethical considerations

Funding for the trial was through an NIHR Post-Doctoral Fellowship Award (JG) and a Leeds Trustees Fellowship Award (JEL). Following ethical review by East Midlands-Derby Research Ethics Committee, the trial was approved by the Health Research Authority of the United Kingdom, (17/EM/0004).

Written informed consent was obtained from all participants. The trial was prospectively registered at clinicaltrials.gov (NCT: 02964650).

Results:

A total of 83 patients were recruited between 2nd November 2017 and 16th January 2019: 38 randomized to FFR-guided rate adaptive programming and 45 to conventional age-guided programming (Figure 1). The two randomized groups were balanced for important baseline variables including FFR variables: critical heart rate (bts/min), peak contractility and exercise testing variables: resting HR (65.9 ± 9.4 v 66.4 ± 9.1) and peak exercise HR (116.2 ± 21.8 v 120.4 ± 19.5) (Table 1).

Of the 83 patients enrolled, 38 were allocated FFR-guided HR rise programming and 45 to conventional age-guided programming. There were 3 patients in each group who did not tolerate the intervention. These patients were reprogrammed to their original settings and remained in the intention to treat analysis (Figure 1).**Error! Bookmark not defined.** Six-month follow-up data were available on 69 patients. Of the 14 patients not reassessed, one had died and 13 declined to attend or were lost to follow-up. Of those that attended, 3 declined to undergo a cardiopulmonary stress test.

Device interrogation at follow-up confirmed high mean (SD) rates of biventricular pacing in both groups at baseline (98.12 ± 2.07 v 98.26 ± 1.73%) and follow-up (97.80 ± 2.17 v 98.13 ± 2.18%), with no difference in change between mean (95%CI) baseline and follow-up between the FFR-guided group (0.37 (-0.58 to 0.26) and the age-guided group (-0.31 (-0.34 to 0.71). Patients allocated FFR-guided rate-adaptive programming had lower mean

(SD) peak heart rates during the follow-up exercise test (98.6 ± 19.4 v 112.0 ± 20.3 bpm).

Review of the baseline and follow-up exercise ECG traces confirmed that effective CRT was delivered without fusion in those with CRT devices. Moreover, in those without CRT devices, the percentage of right ventricular pacing was not different between the two groups at baseline or follow-up, and there was no across randomized group mean (95% CI) change in right ventricular pacing percentage between baseline and follow-up within the FFR-guided (1.36 (-3.3 to 6.1) and standard age-guided groups (-1.81 (-8.4 to 4.8)).

Primary outcome measure

At 6 months, patients allocated FFR-guided programming experienced a greater improvement in mean (±SD) treadmill walk time, compared with patients randomized to conventional age-guided programming. Changes in the FFR-guided arm versus conventional arm from baseline to six months were as follows: 376 (± 172) to 468 (± 252) seconds vs 414 (± 197) to 423 (± 217) seconds respectively (Figure 2). The mean difference between groups on 2-sample ANCOVA was 72.3 seconds (95% CI: 2.0 to 142.7 seconds; p=0.044, test statistic=4) in favour of FFR-guided programming (Table 2), an increase of 20% (or around 54 meters) from baseline. In the post hoc univariable analysis of predictors of change, no baseline variable reached a p-value of <0.10 (data not shown).

Secondary outcome measures

Six months of FFR-guided rate-adaptive pacing was not associated with a change in mean (±SD) LV ejection fraction (LVEF) (35.3% (±10.6) at baseline to 35.9% (±10.6) at follow-up). However, patients allocated conventional programming experienced a reduction in LVEF from 35.1 (±10.6) to 32.1% (±11.7) with a mean difference between groups of 3.7% (95% CI: 0.9 to 6.4; p=0.009) in favour of FFR-guided programming (Table 2, Figure 3). Mean difference between randomized groups on 2-sample ANCOVA was 3.5% (95% CI: 0.6 to 6.3)%) in favour of FFR-guided programming (Table 2, Figure 3). There was no significant change in LVEDV in either randomized group with changes from baseline of: 3.2mL (95% CI: -7.5 to 14.0 mL) and 5.5 mL (95% CI: -4.5 to 14.0 mL) (Table 2) in the FFR-guided and conventional groups respectively. There was also no significant change in LVESV from baseline to follow-up, in the FFR-guided group: 1.8 mL (95% CI: -6.2 to 9.7 mL), or the conventional group 10.0 mL (95% CI: 2.6 to 17.5 mL) (Table 2, Figures 4a and 4b).

In the group randomized to FFR-guided rate adaptation there was a trend to favourable changes in CPX variables from baseline, compared with the conventional programming group with a mean difference between groups of 1.14mL/kg/min (95% CI: -0.1 to 2.4 mL/kg/min). Peak O_2 pulse increased in the FFR-guided group with a mean difference between the groups of 2.02mL/beat (95% CI: 0.5 to 3.5 mL/beat) (Table 2).

There was no difference in change in QoL observed over the follow-up period between the randomized groups. Mean change from baseline for EQ5D was: -0.02 (95% CI: -0.07 to 0.04) and -0.06 (95% CI: -1.11 to -0.01) for FFR-guided and conventional groups respectively. The mean change in EQ-VAS from

baseline was: -1.16 (95% CI: -6.72 to 4.40) and -3.35 (95% CI: -8.56 to 1.86) for FFR-guided versus conventionally programmed groups and mean change in baseline in the MLWHF questionnaire was -0.04 (95% CI: -4.33 to 4.26) for the FFR-guided group and -0.63 (95% CI: -4.65 to 3.40) for the conventionally programmed group.(Table 2).

Discussion

Although disease modifying treatments have substantially improved life expectancy in HFrEF,[24] they have had much less impact on exercise capacity – the main driver of QoL and a key target for patients.[1,21] Consequently, millions of patients with HFrEF worldwide suffer a persistently poor QoL and are unable to undertake activities of daily living. We have previously shown an acute improvement in exercise time with FFR-guided rate-adaptive pacing, and the aim of the present study was therefore to explore whether long-term tailored HR programming could improve exercise time in patients with HFrEF receiving guideline-directed optimal medical and device therapy.

The key results of the present trial are that in people with HFrEF receiving optimal guideline-directed medical and device therapy, six months of tailored FFR-guided HR-programming leads to improved exercise time and prevents the decline in left ventricular ejection fraction seen in patients randomized to conventional age-related programming.

Heart rate rise and exercise capacity

Cardiac output is a function of HR and stroke volume. Thereby, poor HR rise during exercise could, by adversely affecting cardiac output, contribute to exercise intolerance. However, the relationship between HR rise, cardiac

output and exercise capacity, and how their interaction changes with age, sex, fitness and disease is poorly understood. For example, despite >80 years of research there is no clear 'target' HR in healthy adults.[25,26,27] Datasets are small and of limited generalizability.[28] The most frequently quoted 'Åstrand formula' (220-age), is the benchmark by which a diagnosis of 'poor HR rise' (chronotropic incompetence) is made.

Heart rate rise and device therapy in HFrEF

CIEDs all have a programming option which can detect movement or increased ventilation and increase HR accordingly, known as rate-adaptive pacing. In patients without HF, compared with fixed rate programming (rate-adaptive option deactivated), rate-adaptive programming increases cardiac output during exercise,[29] improves QoL,[30,31] but inconsistently improves exercise capacity.[32]

The situation is unclear in HFrEF where HR limitation is a cornerstone of therapy. Even without beta-blockers, patients with HFrEF frequently fail to achieve their age-predicted maximal HR during exercise.[3,33,34] This is commonly perceived to contribute to reduced exercise tolerance.[35,36] This paradox, where HR limitation using beta-blockers reduces hospitalisation and mortality,[37,38] yet is proposed to exacerbate exercise intolerance possibly contributes to poorly defined HR targets in guidelines,[39] and low rates of achievement of optimal beta-blocker doses,[40,41] even when a CIED could provide HR support,[42] despite overwhelming data of their dose-related prognostic benefit.[43]

Treatment for 30-40% of people with HFrEF includes a CIED. Rate-adaptive pacing during exercise through an age-related algorithm in HFrEF unreliably improves exercise capacity.[44] In fact, our previous work and that of others suggest that higher heart rates due to imprecise rate-adaptive pacing could be disadvantageous.[45,46] Despite this, the proven benefits of HR limitation, and a limited evidence base to guide when rate-adaptive pacing should be used, the standard age-related rate-adaptive algorithm is active in >68% of 210,000 CRT devices in the USA.[47]

Cardiac contractility during exercise

HR contributes to cardiac output, a key determinant of exercise capacity.[48] In health, cardiac output is positively coupled to LV contractility (the power of contraction) by the force frequency relationship (FFR).[7] The FFR ensures that LV contractility and thereby stroke volume increase with HR to compensate for reduced filling time. We and others have shown that this critical physiological response is flattened in patients with HFrEF with a decline in LV contractility above a certain HR.[8,15] In HFrEF therefore, the close relationship between HR and stroke volume is perturbed such that ‘maximal’ HR is not synonymous with ‘optimal’ HR.

In line with this, we showed that programming CIEDs to increase the HR to the standard age-related ‘maximal-HR’ does not improve exercise time.[5] We hypothesised that this was because conventional rate-adaptive algorithms do not take into account the altered FFR in HFrEF, and that there might be a HR beyond which there is lower contractility, and therefore reduced cardiac output. We subsequently confirmed, using echocardiography, an abnormal FFR with impaired contractility across the entire HR range in HFrEF with a

lower slope in response to HR increases, lower peak contractility and a lower HR for peak contractility, termed the critical HR, above which contractility worsens.[8] We were able to determine an ideal range of HR over which contractility increased in all patients.

In an unselected group of patients with HFrEF, we then carried out a randomized, double-blind, cross-over study of acute programming of the rate-adaptive algorithm based upon individual's FFR (limiting HR rise to below the critical HR), versus standard settings (increasing to age-predicted maximum). We found an acute improvement in mean exercise time despite a much lower peak HR. FFR-guided programming was also associated with greater exercise time than fixed-rate pacing (rate-adaptive algorithm programmed off).[8] This cross-over study informed the design of the current study.

Limitations

This was designed as a single centre phase II trial and the data should be interpreted in light of this. However, participants were approached consecutively, with no selection bias in terms of response to CRT. For example, it is possible that so-called 'responders' to CRT may have less to gain from tailored rate-adaptive programming, but our selection criteria were deliberately inclusive, requiring ongoing symptomatic heart failure. The trial was randomized and undertaken in a double blind fashion to reduce bias as previously described.[5,8] In addition, our approach was informed by results from our randomized, placebo-controlled cross-over study in 52 patients showing a favourable effect of FFR-guided HR rise programming on exercise capacity.[8]

Whilst the changes we observed in LVEF are smaller than the published patient-level measurement error of echocardiography, it is possible to confidently detect smaller margins by studying groups of people. Scans were analysed offline by an experienced operator blinded to treatment and time point. Moreover, any systematic error in measurement will have been accounted for by our randomized design. The difference in change in LVEF was statistically significant by our predefined criteria. If persistent, a reduction in LVEF in the standard-care arm of this magnitude is likely to be associated with an adverse outcome.[49]

Based upon our previous work, we a priori chose exercise time as our primary outcome as one of direct patient relevance. Our study was not powered to detect differences in measures of quality of life and we did not measure concentrations of B-type natriuretic peptide at baseline or follow-up. Future mechanistic work could include changes in neurohormones and sympathetic activation, and the effects of higher heart rates on stroke volume and left ventricular perfusion.

Fewer than half of the patients in this study had previously participated in a double-blind cross-over study of FFR-guided heart rate programming versus standard adaptive rate response programming.[8] During that study, patient's CIEDs were programmed according to their FFR or using standard age-related settings only for the duration of the visit in random order. Between the two study visits, which were a week apart, the device was programmed to usual care. These two exercise tests are unlikely to stimulate a training effect and the last patient in the acute cross-over study completed follow-up 7 months before the first patient was enrolled into the present study. Moreover,

patients in the current study were randomly allocated to the intervention and the primary outcome of the study is change in exercise time. There is therefore no potential for a carry-over or training effect that could influence the present results.

Finally, our approach to establish the FFR in patients with CIEDs requires skills in echocardiography and CIED programming and is likely to add time to echocardiographic-based optimisation of CRT devices.

Conclusions

In a novel, single centre, randomized, double-blind, controlled trial we have shown for the first time that CIED HR rise programming guided by non-invasive FFR data appears to be associated with improved exercise time and reduced progressive deterioration in LV function. Future work is planned to explore the mechanisms of our finding, to determine whether the greater increase in exercise time than peak oxygen consumption represents greater efficiency, to determine if the CHR can be predicted from clinical variables and also to confirm our findings in a multi-centre setting and on longer term clinical outcomes including hospitalisation. Furthermore, future research will need to explore whether patients with less severe left LV systolic dysfunction and also those with persistent symptoms but no existing indication for a CIED might also benefit from this approach.

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Disclosures

There are no conflicts of interest for any of the authors with respect to the current work.

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Figure legends

Figure 1: Consort diagram demonstrating patient enrolment, randomisation and disposition during the study.

Figure 2: Change in treadmill walk time following six months of conventional versus force-frequency-guided rate-adaptive pacing programming presented as mean (95% CI).

Figure 3: Change in left ventricular ejection fraction following six months of conventional versus force-frequency-guided rate-adaptive pacing programming presented as mean (95% CI).

Figure 4 a and b: Change in left ventricular end systolic volumes (a) and left ventricular diastolic volumes (b), following six months of conventional versus force-frequency-guided rate-adaptive pacing programming presented as mean (95% CI).

Table 1: Patient demographics and baseline at randomisation - intention-to-treat population

	Total (n=83)	Tailored (n=38)	Conventional (n=45)
Male sex No. (%)	58 (71)	27 (73)	31 (69)
Age, years	74.6 ± 8.7	73.7 ± 10.6	75.4 ± 6.8
Ischaemic heart disease No. (%)	52 (63)	26 (68)	26 (58)
Atrial Fibrillation No. (%)	30 (36)	13 (34)	17 (38)
Hypertension No. (%)	39 (47)	16 (42)	23 (51)
NYHA class No.(%)			
II	58 (70)	27 (71)	31 (69)
III	25 (30)	11 (29)	14 (31)
Creatinine (imol/L)	108.3 ± 37.2	107.7 ± 27.5	108.9 ± 45.5
Medication No. (%)			
Beta blockers	80 (96)	38 (100)	42 (93)
Bisoprolol equivalent dose (mg/day)*	7.4 (3.8)	7.7 (3.2)	7.0 (4.2)
ACEi/ARB	78 (94)	34 (90)	37 (82)
Ramipril equivalent dose (mg)*	6.2 (3.5)	6.3 (3.3)	6.2 (3.6)
Loop diuretic	50 (60)	24 (63)	26 (58)
Statin	69 (83)	30 (79)	39 (87)
Device allocation No. (%)			
CRT-D	35 (42)	13 (34)	22 (49)
CRT-P	23 (28)	9 (24)	14 (31)
DR-ICD	25 (30)	16 (42)	9 (20)
Resting haemodynamics			
Resting heart rate (bpm)	66.1 ± 9.2	65.9 ± 9.4	66.4 ± 9.1
Systolic blood pressure (mmHg)	123.8 ± 20.5	122.0 ± 21.4	125.2 ± 19.9
Echocardiography and FFR data			
LVEF (%)	35.2 ± 10.5	35.3 ± 10.6	35.1 ± 10.6
LVEDV (mL)	142.7 ± 62.5	141.2 ± 73.0	144.0 ± 52.8
LVESV (mL)	95.9 ± 62.5	95.7 ± 60.7	96.1 ± 45.1
Peak contractility	4.4 ± 2.8	4.6 ± 3.1	4.2 ± 2.5
Critical heart rate (bpm)	104.6 ± 17.8	106.7 ± 18.0	102.8 ± 17.7
Exercise test results			
Treadmill walk time (seconds)	397.1 ± 185.9	376.4 ± 172.1	414.9 ± 197.2
Peak oxygen consumption (ml/kg/min)	15.5 ± 5.6	15.1 ± 6.4	15.9 ± 4.9
V_E/VCO_2 slope	32.7 ± 9.6	32.3 ± 9.4	33.2 ± 9.8
Peak exercise heart rate (bpm)	118.5 ± 20.6	116.2 ± 21.8	120.4 ± 19.5
O_2 pulse (mL/beat)	10.89 ± 3.69	10.46 ± 3.67	11.28 ± 3.71
Quality of life scores at baseline			
EQ5D-5L	0.72 ± 0.17	0.71 ± 0.14	0.72 ± 0.19
Visual analogues scale	66.4 ± 16.2	64.7 ± 17.2	67.8 ± 15.1
MLWHFQ	31.1 ± 19.7	32.8 ± 18.7	29.7 ± 20.5

Continuous variables are mean ± SD unless otherwise stated, categorical variables are n (%) as indicated. Mean doses (*) are calculated as described previously.[31]
NYHA; New York Heart Association, NT-pro-BNP; N-terminal pro B-type natriuretic peptide, ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blocker, ARNi; Angiotensin Receptor-Neprilysin Inhibitors, CRT-D; Cardiac Resynchronization Therapy with Defibrillator, CRT-P; Cardiac Resynchronization Therapy Pacemaker, DR-ICD; Dual chamber Implantable Cardioverter Defibrillator, FFR; force-frequency relationship, LVEF; left ventricular ejection fraction, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end systolic volume, VE/VCO_2 slope; slope relating ventilation and carbon dioxide output, bpm; beats per minute, EQ5D-5L; Euro-quality of life score -5 questions, MLWHF; Minnesota Living with Heart Failure Questionnaire.

Table 2: Change in primary and secondary outcome variables in patients following 6 months of tailored v conventional pacemaker heart rate rise programming, intention-to-treat population

Endpoint	Randomised treatment	Final mean value [95% CI]	Mean change after 6 months [95% CI]	ANCOVA difference in mean change [95% CI]
Primary outcome				
Treadmill walk time (s)	Tailored	483.15 [431.10, 535.20]	75.40 [23.35, 127.45]	**72.31 [1.94, 142.67]***
	Conventional	401.84 [363.62, 458.07]	3.09 [-44.14, 50.31]	
Secondary outcomes				
LVEF (%)	Tailored	35.79 [33.80, 37.78]	-0.23 [-2.31,1.84]	**3.46 [0.61, 6.30]**
	Conventional	32.13 [30.28, 33.00]	-3.69 [-5.62, -1.76]	
LVEDV (mL)	Tailored	146.63 [135.87, 157.39]	3.24 [7.52, 14.00]	-2.29 [-16.99, 12.42]
	Conventional	148.92 [138.91, 158.92]	5.52 [-4.48, 15.53]	
LVESV (mL)	Tailored	97.36 [89.36, 105.35]	1.78 [-6.22, 9.77]	-8.26 [-19.18, 2.67]
	Conventional	105.61 [98.18, 113.05]	10.03 [2.60, 17.47]	
pVO_2 (ml/kg/min)	Tailored	16.72 [15.81, 17.64]	0.84 [-0.07, 1.75]	1.14 [-0.10, 2.38]
	Conventional	15.59 [14.75, 16.43]	-0.30 [-1.14, 0.54]	
Peak O_2 Pulse (mL/beat)	Tailored	13.84 [12.75, 14.94]	2.74 [1.64, 3.83]	**2.02 [0.53, 3.51]**
	Conventional	11.82 [10.82, 12.83]	0.72 [-0.29, 1.73]	
VE/VCO_2 slope	Tailored	32.81 [30.30, 35.32]	-0.73 [-3.24, 1.78]	0.50 [-2.91, 3.91]
	Conventional	32.31 [30.00, 34.62]	-1.23 [-3.54, 1.08]	
EQ5D	Tailored	0.73 [0.68, 0.78]	-0.02 [-0.07, 0.04]	0.04 [-0.04, 0.12]
	Conventional	0.66 [0.62, 0.71]	-0.06 [-1.11, -0.01]	
EQ-VAS	Tailored	67.13 [62.18, 72.07]	-1.16 [-6.72, 4.40]	2.19 [-5.44, 9.82]
	Conventional	62.84 [58.28, 67.41]	-3.35 [-8.56, 1.86]	
MLWHFQ	Tailored	31.68 [27.45, 35.91]	-0.04 [-4.33, 4.26]	0.59 [-5.32, 6.49]
	Conventional	30.25 [26.34, 34.15]	-0.63 [-4.65, 3.40]	

Values are mean change [95% confidence intervals]; 95% significance shown in bold
LVEF; left ventricular ejection fraction, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end systolic volume, pVO_2; peak oxygen consumption, VE/VCO_2 slope; slope relating ventilation and carbon dioxide output, EQ5D-5L; Euro-quality of life score -5 questions, VAS; visual analogue scale, MLWHF; Minnesota Living with Heart Failure Questionnaire, * denotes $p<0.04$