MINI-FOCUS ISSUE: EXERCISE PERFORMANCE AND CARDIAC REHABILITATION

Rate-Response Programming Tailored to the Force-Frequency Relationship Improves Exercise Tolerance in Chronic Heart Failure

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ABSTRACT

OBJECTIVES This study sought to examine whether the heart rate (HR) at which the force-frequency relationship (FFR) slope peaks (critical HR) could be used to tailor HR response in chronic heart failure (CHF) patients with cardiac pacemakers and whether this favorably influences exercise capacity.

BACKGROUND CHF secondary to left ventricular (LV) systolic dysfunction is characterized by blunting of the positive relationship between HR and LV contractility known as the FFR.

METHODS This observational study was carried out in patients with CHF and healthy subjects with pacemaker devices. The study assessed the 3 important features of the FFR (critical HR, peak contractility, and the FFR slope), and their reproducibility was measured noninvasively using echocardiography. The investigators then undertook a double-blind, randomized, controlled crossover study comparing the effects of tailored pacemaker rate-response programming on the basis of the FFR with conventional rate-response programming on exercise time and maximal oxygen consumption.

RESULTS The study enrolled 90 patients with CHF into the observational cohort study: mean age, 73.6 ± 8.9 years; mean left ventricular ejection fraction (LVEF), $33.5 \pm 10.9\%$. The study investigated 15 control subjects with normal LV function (LVEF, $55.6 \pm 5.3\%$). The critical HR (103 ± 22 beats/min vs. 126 ± 15 beats/min; $p = 0.0002$), peak contractility (3.8 ± 3.7 SBP/LVESVI vs. 9.8 ± 4.1 SBP/LVESVI; $p = 0.0001$), and the slope of the FFR ($p < 10^{-15}$) were lower in patients with CHF than in control subjects. A total of 52 patients, with a mean LVEF of $32 \pm 11\%$ on optimal therapy, took part in the crossover study. Rate-response settings limiting HR rise to below the critical HR led to greater exercise time (475 ± 189 s vs. 425 ± 196 s; $p = 0.003$) and higher peak oxygen consumption (17.3 ± 4.6 ml/kg/min vs. 16.6 ± 4.7 ml/kg/min; $p = 0.01$).

CONCLUSIONS A personalized approach to rate-response programming, determined using a reproducible noninvasive method for assessing the FFR, improves exercise time in patients with CHF and pacemaker devices. (Bowditch Revisited: Defining the Optimum Heart Rate Range in Chronic Heart Failure; NCT02563873) (J Am Coll Cardiol HF 2018;6:105–13) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**ABBREVIATIONS
AND ACRONYMS**

CHF = chronic heart failure

CRT = cardiac
resynchronization therapy

FFR = force-frequency
relationship

HR = heart rate

LV = left ventricular

LVESV = left ventricular
end-systolic volume

LVESVI = left ventricular
end-systolic volume index

LVSD = left ventricular systolic
dysfunction

SBP = systolic blood pressure

Characterized by reduced exercise tolerance, chronic heart failure (CHF) secondary to left ventricular (LV) systolic dysfunction (LVSD) has a deleterious impact on quality of life in millions of individuals worldwide (1). Advances in our understanding of the pathophysiology of CHF have informed the development of drugs and devices, including cardiac resynchronization therapy (CRT), that have substantially improved life expectancy (2-5). Nonetheless, many patients with CHF and CRT remain significantly limited (6).

An important determinant of exercise performance is thought to be LV contractility, which in 1871 was shown to be positively coupled to increments in heart rate (HF) (7). As HR increases in healthy humans, LV contractility and stroke volume increase simultaneously (8). Using invasive measurements, we and other investigators have shown that this critical physiological response, described as the force-frequency relationship (FFR), becomes flattened in patients with CHF, with a decline in LV contractility occurring above a certain HR (9,10). We hypothesized that by defining an individual's FFR noninvasively (and in particular the peak of this response before the decline in contractility characteristic in CHF), it may be possible to tailor individual pacing algorithms to exploit a patient's unique physiology. Here we show that it is possible to use a noninvasive, reproducible approach to define the peak of the force-frequency curve of patients with CHF with CRT devices in situ and use this information to improve exercise capacity.

METHODS

This paper describes the findings of 1 observational and 1 interventional study.

OBSERVATIONAL STUDY. Subjects. Patients with CHF secondary to LVSD (LV ejection fraction ≤50%) with persistent symptoms on exertion and a CRT device, implantable cardioverter-defibrillator, or standard pacemaker for at least 3 months were recruited (Leeds NIHR Cardiovascular Clinical Research Facility, Leeds Teaching Hospitals NHS trust, Leeds, United Kingdom). Patients also had to be taking optimally tolerated medical therapy with no change in medication or other invasive cardiac procedures for at least 3 months. We also enrolled an unselected consecutive group of patients with a standard pacemaker, normal atrioventricular conduction, no evidence of heart failure, and normal echocardiographic findings as a control group.

Information was collected on comorbidities, past medical history, medication, pacemaker settings, and New York Heart Association functional class. All patients gave written informed consent, and the study was approved by the local ethics committee and registered on clinicaltrials.gov (Bowditch Revisited: Defining the Optimum Heart Rate Range in Chronic Heart Failure; NCT02563873).

Echocardiographic techniques. Full baseline echocardiography was carried out with gray-scale and tissue Doppler images recorded in 2- and 4-chamber views by using harmonics to improve border definition if necessary (GE Vivid E95, GE Healthcare, Milwaukee, Wisconsin). Further images were recorded at each 15-beat frequency increase during the incremental pacing protocol. Images were stored in the EchoPAC digital imaging system (GE Healthcare) and analyzed off-line. This analysis included a calculation of LV end-diastolic volume and LV end-systolic volume (LVESV) that used the biplane disks (modified Simpson) method by tracing the endocardial border, excluding the papillary muscles (11). An average of 3 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 was considered to represent end-systole. The LVESV index (LVESVI) was calculated at each stage as LVESV/body surface area, where body surface area was calculated using the Mosteller equation (12).

Blood pressure measurement. Calculation of the end-systolic pressure-volume relationship requires measurement of the LV pressure at end-systole (13,14). Systolic blood pressure (SBP) measured with 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 coinciding with echocardiographic images at each HR stage. SBP was recorded at the point where the first tapping sound (phase 1 Korotkoff) occurred for 2 consecutive beats (15).

Pacing protocol. Echocardiographic images were collected at rest, after which atrial pacing was initiated in the DDD-mode (or VVI in patients with atrial fibrillation) for CRT-treated patients and in the AAI-mode (or DDD with long atrioventricular delays to avoid right ventricular pacing, or VVI for patients in atrial fibrillation) for subjects without CRT, at the lowest multiple of 10 above baseline. After 4 min, a further set of echocardiographic images was recorded, and subsequently the pacing rate increased in stepwise 15-beat intervals with images recorded after every 4 min. This was repeated until the maximum predicted HR 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 min.

Force-frequency calculation. Dividing the SBP by the LVESVI (SBP/LVESVI) gives a surrogate of contractility (16-20), which has been validated against invasive methods (15,19). In our protocol, we repeated these measures at a series of HR stages (induced by pacing) to allow us to plot the FFR. The slope of this relationship was then calculated as the ratio between SBP/LVESVI change from baseline and HR increase from baseline. We defined the HR at which, in a biphasic pattern, the SBP/LVESVI reached maximum value or that beyond the SBP/LVESVI declined by 5% as the "critical HR." In a negative FFR (in cases where there was no increase in contractility with increments in HR), baseline HR was deemed the critical HR (21).

Reproducibility. Each image set was anonymized and reported by a second echocardiographer for interoperator reproducibility. For intraoperator reproducibility, each image set was also reported a second time by the initial reporter. For each dataset, we documented the HR at which peak contractility was reached (the critical HR), peak contractility itself, and the slope of the FFR as described earlier.

RANDOMIZED CONTROLLED TRIAL. Patients with CHF who were included in the observational phase of the study were subsequently invited to participate in a double-blind, randomized, crossover treadmill-based study comparing exercise time under conventional rate-response settings with rate-response settings taking into account the data from the FFR assessment. An unselected subgroup was invited to attend a third (blinded) exercise test with fixed-rate pacing.

Exclusion criteria. For this part of the investigation, we invited patients who had participated in the first study and who did not have peripheral vascular disease or noncardiac conditions such as significant airway disease and musculoskeletal abnormalities that could restrict walking on a treadmill.

Laboratory arrangement and exercise protocol. Subjects recruited to this randomized crossover study were present on 2 (or 3) consecutive occasions at the same time of day 1 week apart. Before each test, the pacemaker was interrogated, and patients were then randomly assigned to the following: rate-adaptive pacing with conventional age-determined settings (22); optimized settings on the basis of the results of their FFR assessment; specifically limiting the rate-response algorithm to the critical HR; or, for patients agreeing to do a third test, fixed-rate pacing with rate-response settings to "off."

Subjects were exercised using the ramping treadmill protocol (23). Expired air was collected, and metabolic gas exchange analysis was performed (Ultimo CardO2, Medical Graphics, St. Paul, Minnesota) throughout the test. HR (beats/min), oxygen uptake (Vo_2) (ml/kg/min), and carbon dioxide output (Vco_2) (ml/kg/min) were recorded as 15-s averages. Anaerobic threshold was calculated using the V-slope method.

The cardiopulmonary exercise test equipment was recalibrated 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 (24). To maintain blinding, the continuous 12-lead electrocardiogram 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. The unblinded cardiac physiologist monitored the electrocardiogram throughout the study, communicated only with the other team members unless there were safety concerns, and reprogrammed the pacemaker to its original settings at the end of every visit.

SAMPLE SIZE CALCULATION. Observational study. Previous studies exploring contractility in patients with heart failure were able to demonstrate significance using heart failure cohorts of 11 ± 4 subjects and control cohorts of 8 ± 3 subjects (25). Hence we aimed to recruit at least 12 subjects as our "control" population.

Randomized controlled trial. The primary endpoint of this study was change in exercise time,

TABLE 1 Subject Demographics at Baseline Visit

	Non-HF (n = 15)	HF Patients (n = 90)	p Value*
Male	14 (93)	79 (88)	0.53
Age, yrs	71.1 ± 16.0	73.5 ± 8.9	0.39
Ischemic heart disease	2 (13)	54 (60)	0.0008
Diabetes mellitus	4 (27)	28 (31)	0.73
BSA, m^2	1.9 ± 0.1	2.0 ± 0.2	0.07
NYHA functional class			0.0001
I	15 (100)	1 (1)	
II	n/a	70 (78)	
III	n/a	19 (21)	
Beta-blockers	3 (20)	82 (91)	0.0001
ACE inhibitor/ARB	3 (20)	77 (86)	0.0001
Furosemide dose, mg/day	0	47 (26)	
Digoxin	0 (0)	15 (17)	0.084
AA	0 (0)	38 (42)	0.001
Device (PPM/ICD/CRT)	n/a	14/9/67 (16/10/74)	
Atrial fibrillation	3 (20)	25 (28)	0.51
LVEF, %	55.6 ± 5.3	33.3 ± 10.8	0.0001
Critical heart rate, beats/min	126 ± 15	103 ± 22	0.0002
Peak contractility, SBP/LVESVI	9.8 ± 4.1	3.8 ± 3.7	0.0001
Force-frequency relationship†	0.054 ± 0.042	0.011 ± 0.028	<0.0001

Values are n (%) or mean ± SD. *p values are from unpaired Student *t* tests or chi-squared tests as appropriate. †From likelihood ratio test in linear mixed model.

AA = aldosterone antagonist; ACE = angiotensin-converting enzyme; ARB = aldosterone receptor blocker; BSA = body surface area; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; LVESVI = left ventricular systolic volume index; n/a = not applicable; NYHA = New York Heart Association functional class; PPM = permanent pacemaker; SBP = systolic blood pressure.

with a secondary endpoint of peak oxygen consumption. On the basis of guidelines for pilot studies (26,27), and accounting for a dropout rate of 20%, we aimed to recruit 28 patients to achieve 20 participants with complete data.

FIGURE 1 Force-Frequency Relationship in Patients and Controls
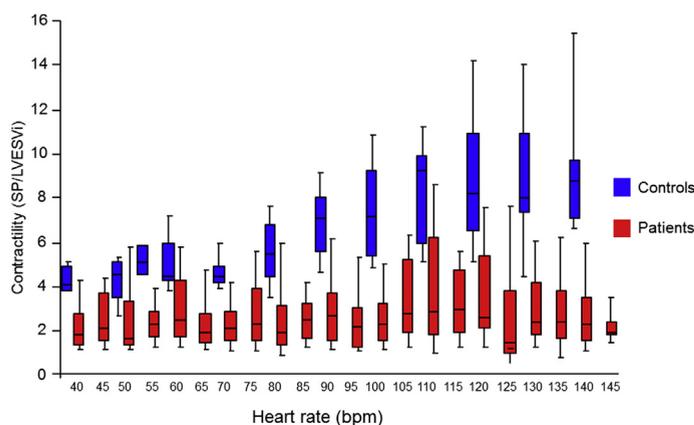
The impaired contractile response (as described by the ratio of systolic blood pressure [SP] to left ventricular end-systolic volume index [LVESVI]) to heart rate rise in patients with chronic heart failure compared with control subjects. Values are mean (95% confidence interval).

Statistical analysis. Data were analyzed using the Statistical Package for the Social Sciences SPSS version 21 (IBM Corp., Armonk, New York), *R*: A Language and Environment for Statistical Computing version 3.2.3 (R Development Core Team, Vienna, Austria), and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Normality for all continuous variables was tested using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean and mean ± SD, and non-normally distributed continuous variables were reported as median (interquartile range). Subsequently, associations between groups or interventions and baseline characteristics were assessed using either analysis of variance and the 2-sample Student *t* test for normally distributed values or the Kruskal-Wallis *H* test (1-way analysis of variance of ranks) for non-normally distributed data. Similar associations with categorical variables were analyzed using the chi-squared test for contingency tables.

Once a familiarization test has been performed, a peak exercise test is not a training stimulus. We previously performed up to 5 exercise tests in consecutive weeks in patients with CHF and controls, with no longitudinal effects (28). However, to account for any carryover effects, the interventional crossover study was analyzed using a linear mixed model with a random effect for subject. For each endpoint Y_{ak} (e.g., exercise time) under consideration in the study:

$$Y_{ak} = \mu + d_i + \pi_j + i_n + \alpha_k + i_{nk}$$

where $i_{nk} \sim N(0, \sigma^2_\varepsilon)$, $\alpha_k \sim N(0, \sigma^2_\alpha)$ 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 were estimated for each of these terms and their differences.

All statistical tests were 2-sided, and any p value <0.05 was called statistically significant.

Ethical approval for both phases of the investigation was granted by the Health Research Authority (National Research Ethics Service Centre: Yorkshire and the Humber REC: 12/YH/0097). Written informed consent was obtained from all participants. The crossover study was registered on clinicaltrials.gov (NCT02563873) before any patient enrollment.

RESULTS

OBSERVATIONAL STUDY. We enrolled 90 patients with CHF and 15 control subjects with normal LV

function into the first phase of the study. Baseline clinical, echocardiographic, and pacemaker variables are shown in **Table 1**. We were able to establish the 3 key variables of peak contractility, critical HR, and the slope of the relationship between HR and contractility in all patients.

Patients with CHF had lower mean peak contractility, lower mean critical HR, and a lower slope of the relationship between HR and contractility below the critical HR (the FFR) than control subjects (**Table 1, Figure 1**).
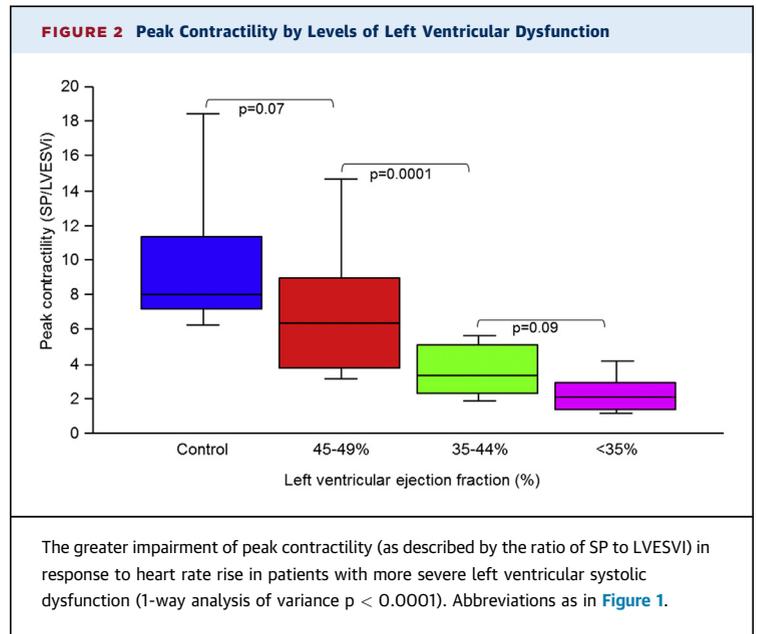
Separate models were required for each group, as compared with considering the data overall. This was confirmed by a likelihood ratio test for a saturated model compared with a simple additive model for HR, HR^2, and patient group (chi-square test $= 214.63$; $p < 10^{-15}$). Further examining the relationship in linear mixed effects models showed that there was little evidence of a quadratic relationship in each group of patients:

- Controls: $0.2915604 + 0.0844503 \times HR - -0.00017 \times HR^2$
- CHF: $1.971 + 7.170e^{-03} + 2.510e^{-05} \times HR^2$

In the controls, the linear term was significant ($p < 0.05$), and the quadratic term showed weak evidence of being required ($p = 0.15$). However, for CHF the linear term was not significant ($p = 0.334$), and the quadratic term was not significant ($p = 0.525$). Considering the linear terms, in controls, for every 10 beats/min increase in HR there was a 0.8-unit increase in contractility. For the patients with CHF, this relationship was significantly less, at <0.02.

The Strand formula calculated a higher peak HR than the calculated critical HR for all except 1 CHF patient (mean HR 146 ± 9.0 vs. 103 ± 22; $p < 0.0001$), and all but 3 control subjects (149 ± 16 vs. 126 ± 15; $p = 0.002$). The inaccuracy of the Strand formula in beats per minute was greater in patients than in control subjects (43 ± 24 vs. 23 ± 24; $p = 0.0039$). Age was unrelated to any of the measures of cardiac function including contractility, and there was no relationship between critical HR and resting LV function in either group. However, in patients with CHF, there was a strong correlation between peak contractility and baseline ejection fraction (0.50; 95% confidence interval: 0.33 to 0.64; $p < 0.0001$) (**Figure 2**).

Reproducibility. The linear mixed effects models allowed direct assessment of the reproducibility of the reading of the echocardiograms by different operators through components of variance. The percentage of variation in the models for controls and CHF attributed to the contractility measurement by

FIGURE 2 Peak Contractility by Levels of Left Ventricular Dysfunction

The greater impairment of peak contractility (as described by the ratio of SP to LVESVI) in response to heart rate rise in patients with more severe left ventricular systolic dysfunction (1-way analysis of variance $p < 0.0001$). Abbreviations as in **Figure 1**.

different operator or repeated assessment by the same operators was <1% of variance.

INTERVENTIONAL STUDY. A total of 52 patients were enrolled in this study (**Table 2**). Baseline clinical and echocardiographic variables of this subgroup were not different from those of patients enrolled in the

TABLE 2 Baseline Variables of Patients Enrolled in the Randomized, Controlled, Crossover Trial (N = 52)

Male	44 (85)
Age, yrs	73.8 ± 9.6
Etiology	
Ischemic heart disease	33 (63)
Diabetes mellitus	15 (29)
BSA, m^2	2.0 ± 0.2
NYHA functional class	
I	0 (0)
II	43 (83)
III	9 (17)
Beta-blockers	47 (90)
ACE inhibitor/ARB	47 (90)
Furosemide dose, mg/day	43 ± 24
Digoxin	6 (12)
AA	21 (40)
Device (CRT/ICD)	50/2 (96/4)
Atrial fibrillation	15 (29)
LVEF, %	32 ± 11
Critical heart rate, beats/min	101 ± 19
Peak contractility, SBP/LVESVI	3.4 ± 2.0

Values are n (%) or mean ± SD.
Abbreviations as in **Table 1**.

TABLE 3   Exercise Variables in 52 Patients With Heart Failure During Conventional and Optimized Heart Rate Programming

	Programming	Mean	95% Confidence Interval	Mean Difference	95% Confidence Interval	p Value
Exercise time, s	Tailored	474.74	(420.69 to 528.79)	49.85	(18.41 to 81.29)	0.0025
	Not tailored	424.89	(370.84 to 478.94)			
Peak Vo_2, ml/kg/min	Tailored	17.31	(16.00 to 18.62)	0.75	(0.16 to 1.34)	0.0134
	Not tailored	16.56	(15.25 to 17.87)			
O_2 pulse	Tailored	13.39	(12.33 to 14.45)	3.21	(2.33 to 4.08)	<0.0001
	Not tailored	10.19	(9.13 to 11.25)			
$Ve Vco_2$ slope	Tailored	31.80	(29.81 to 33.78)	−1.89	(−3.38 to −0.40)	0.0139
	Not tailored	33.69	(31.70 to 35.67)			
Peak RER	Tailored	1.01	(0.99 to 1.04)	−0.00	(−0.03 to 0.02)	0.7456
	Not tailored	1.02	(0.99 to 1.05)			
Peak heart rate, beats/min	Tailored	109.11	(106.01 to 112.21)	−28.88	(−32.83 to −24.93)	<0.0001
	Not tailored	137.99	(108.87 to 167.12)			

O_2 = oxygen; RER = respiratory exchange ratio; Ve/Vco_2 slope = relationship between ventilation and carbon dioxide output; Vo_2 = oxygen consumption.

FIGURE 3   Results of the Randomized, Placebo-Controlled Double-Blind Crossover Study of Tailored Versus Standard Rate-Response Programming

(A) Greater exercise time with tailored programming. **(B)** Higher peak oxygen consumption with tailored programming. **(C)** Greater oxygen pulse with tailored programming. **(D)** Lower heart rate with tailored rate-response programming. All values are mean (95% confidence interval). HR = heart rate; O_2 = oxygen.

observational study. Of these 52 patients, 12 underwent a third test with fixed-rate pacing.

Table 3 and Online Table 1 show the exercise variables for conventional and optimized HR rise tests. Optimized settings were associated with improved exercise time, peak oxygen consumption, oxygen pulse, and lower V_{ET}/V_{CO_2} slope, whereas HR was lower and respiratory exchange ratio was the same despite a small period effect (Figures 3A to 3D).

Fixed-rate pacing in 12 unselected patients led to similar exercise times as Strand-guided conventional rate-response pacing (Online Figures 1A to 1C). Furthermore, there was no heterogeneity in the benefits of tailored programming between patients with and without diabetes mellitus, those with and without atrial fibrillation, and those with and without ischemic heart disease (Online Tables 2 to 4).

DISCUSSION

Our study demonstrates that patients with CHF have an impaired force-frequency curve compared with controls that can easily be assessed using a noninvasive, reproducible echocardiographic method and that peak contractility is related to the baseline cardiac function. We have also shown that using the data from the force-frequency curve in patients with CHF allows us to tailor pacing algorithms targeting the critical HR and leads to a significant improvement in exercise time and peak oxygen consumption.

Rate-adaptive cardiac pacing, whereby HR is increased in response to movement or ventilation detected by internal device sensors, was developed as an attempt to treat exercise intolerance thought to result from chronotropic incompetence (29,30). The settings are broadly based on a series of experiments to describe maximal HR and age in healthy adults (31-33). Although there are numerous published datasets describing maximal HR changes with aging (34-37), the "Strand formula" (220 – age), which in itself is an extrapolation of data from various sources, remains the most frequently used. However, all datasets are taken from healthy individuals exercising to physiological maximum. In patients without CHF who are receiving standard pacemakers for bradycardia, rate-adaptive programming on the basis of a simple, age-related algorithm is associated with an increase in cardiac output during exercise (38), and better quality of life (39-41), but inconsistent improvements in exercise capacity (42,43), compared with fixed-rate pacing.

We have demonstrated that chronotropic incompetence as determined by the standard equation

seems not to be a limiting factor in maximal performance in patients with CHF (17,44,45), because *conventional* rate-adaptive pacing in patients with CHF does not improve exercise capacity compared with fixed-rate pacing (17). Furthermore, we and other investigators have shown that rate-adaptive pacing may worsen prognosis and cardiac function (46,47).

The reason for the failure of increments in HR to increase exercise capacity in patients with CHF may be that conventional rate-adaptive pacing algorithms do not take into account the altered cardiac contractile function in CHF.

Increased contractility during exercise is thought to be important to maintain stroke volume in the presence of impaired filling during higher HRs. The FFR is abnormal in CHF such that contractility does not rise normally with increases in HR. In agreement with this, in our cohort of unselected, optimally managed patients with CHF secondary to LVSD, we demonstrated a consistent and reproducible impairment of the FFR with a lower critical HR, lower peak contractility, and a lower FFR slope than in subjects without CHF.

We hypothesized that noninvasive assessment of the FFR could provide a physiologically relevant descriptor of the optimal HR range and peak HR that could be used to optimize rate-response programming patients with CHF. To examine this we performed a randomized, double-blind, placebo-controlled crossover study of optimized rate-response programming versus conventional rate-response programming in patients with CHF to examine this concept. Our study showed that this precision-approach rate-adaptive programming can acutely improve treadmill exercise time and peak oxygen consumption. This approach represents a paradigm in rate-responsive pacing for patients with CHF in which the pacemaker rate-response settings are personalized to work in synergy with and take advantage of intrinsic cardiac physiology.

STUDY LIMITATIONS. Our observational study has biases that are common in studies of this type. There is a degree of patient selection in that those patients who are too unwell with advanced CHF or who have other comorbidities may be less keen to participate in clinical research.

The age of our non-CHF group was similar to that of our CHF group, and some patients were taking angiotensin-converting enzyme inhibitors and beta-adrenoceptor antagonists for hypertension. We do not believe that this materially altered our findings. Our methodology restricted us to patients with pacemaker devices, who may exhibit a different

contractile response to increased HRs than patients without a pacemaker device.

We cannot exclude the possibility of systematic differences in the level of motivation or encouragement from the technicians running the tests at different time points. However, we believe that the randomization and double-blind study design will have removed any significant bias. Our blinding procedure has worked well in previous reports (24). Although we defined a pre-specified significance level for rejecting hypotheses for the primary endpoint, no multiple testing control was applied to the secondary endpoints. Therefore all results determined on the basis of secondary endpoints should be considered as hypothesis generating.

We used the ramping treadmill protocol to be consistent for all patients, to allow us to compare exercise times rather than just metabolic gas analysis data, and because 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 may not have been ideal for all of our patients, but on balance we doubt that the protocol choice materially altered 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, thereby reducing the bias toward less limited patients.

Our FFR data were collected with patients in the supine position, and the exercise testing on the treadmill was upright. This positioning has the potential to alter loading conditions, which could have an effect on the critical HR. However, upright echocardiography has an adverse effect on image quality and patient comfort (48,49). Furthermore, the Bowditch phenomenon as originally described and its mechanism are purported to be loading independent.

Finally, our data were collected immediately following pacemaker reprogramming during 2 (3) visits to the NIHR Leeds Cardiovascular Clinical Research Facility at Leeds Teaching Hospitals NHS Trust, and pacing was reset to nominal values for each patient at the end of the visit. Whether longer-term rate-response optimization tailored for the FFR data is safe and has beneficial effects on exercise capacity remains to be proven.

CONCLUSIONS

We have demonstrated that a reproducible, noninvasive assessment of the FFR is possible in patients with a pacemaker and that using these data to personalize the rate-response settings of the pacemaker can improve exercise time in patients with CHF and LVSD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Noninvasive assessment of contractility is reproducible and identifies a physiological HR range target to which to program a pacemaker. This precision programming improves exercise time in patients with CHF. Optimizing pacemaker settings on the basis of a simple and reproducible noninvasive assessment of the FFR in patients with heart failure can improve exercise capacity.

TRANSLATIONAL OUTLOOK: This investigation shows that carefully assessing patients' physiological response to increased HRs can be directly translated into clinical benefits while also providing a potential mechanism for the lack of benefit of conventional rate-response programming in patients with CHF.

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KEY WORDS exercise capacity, force-frequency relationship, heart failure, heart rate

APPENDIX For supplemental tables and a figure, please see the online version of this paper.