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Effect of Personalized Accelerated Pacing on Quality of Life, Physical Activity, and Atrial Fibrillation in Patients With Preclinical and Overt Heart Failure With Preserved Ejection Fraction
The myPACE Randomized Clinical Trial

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IMPORTANCE Patients with heart failure with preserved ejection fraction (HFpEF) with a pacemaker may benefit from a higher, more physiologic backup heart rate than the nominal 60 beats per minute (bpm) setting.

OBJECTIVE To assess the effects of a moderately accelerated personalized backup heart rate compared with 60 bpm (usual care) in patients with preexisting pacemaker systems that limit pacemaker-mediated dyssynchrony.

DESIGN, SETTING, AND PARTICIPANTS This blinded randomized clinical trial enrolled patients with stage B and C HFpEF from the University of Vermont Medical Center pacemaker clinic between June 2019 and November 2020. Analysis was modified intention to treat.

INTERVENTIONS Participants were randomly assigned to personalized accelerated pacing or usual care and were followed up for 1 year. The personalized accelerated pacing heart rate was calculated using a resting heart rate algorithm based on height and modified by ejection fraction.

MAIN OUTCOMES AND MEASURES The primary outcome was the serial change in Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. Secondary end points were changes in N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, pacemaker-detected physical activity, atrial fibrillation from baseline, and adverse clinical events.

RESULTS Overall, 107 participants were randomly assigned to the personalized accelerated pacing (n = 50) or usual care (n = 57) groups. The median (IQR) age was 75 (69-81) years, and 48 (48%) were female. Over 1-year follow-up, the median (IQR) pacemaker-detected heart rate was 75 (75-80) bpm in the personalized accelerated pacing arm and 65 (63-68) bpm in usual care. MLHFQ scores improved in the personalized accelerated pacing group (median [IQR] baseline MLHFQ score, 26 [8-45]; at 1 month, 15 [2-25]; at 1 year, 9 [4-21]; $P < .001$) and worsened with usual care (median [IQR] baseline MLHFQ score, 19 [6-42]; at 1 month, 23 [5-39]; at 1 year, 27 [7-52]; $P = .03$). In addition, personalized accelerated pacing led to improved changes in NT-proBNP levels (mean [SD] decrease of 109 [498] pg/dL vs increase of 128 [537] pg/dL with usual care; $P = .02$), activity levels (mean [SD], +47 [67] minutes per day vs −22 [35] minutes per day with usual care; $P < .001$), and device-detected atrial fibrillation (27% relative risk reduction compared with usual care; $P = .04$) over 1-year of follow-up. Adverse clinical events occurred in 4 patients in the personalized accelerated pacing group and 11 patients in usual care.

CONCLUSIONS AND RELEVANCE In this study, among patients with HFpEF and pacemakers, treatment with a moderately accelerated, personalized pacing rate was safe and improved quality of life, NT-proBNP levels, physical activity, and atrial fibrillation compared with the usual 60 bpm setting.

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Visual Abstract

Supplemental content

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Approximately half of patients with heart failure have a preserved ejection fraction (HFpEF) of 50% or higher.[1,2] In addition, 1 in 4 adults has preclinical or American College of Cardiology/American Heart Association stage B HFpEF, defined as structural heart disease without signs or symptoms of heart failure.[1,2] Despite an increasing prevalence and socioeconomic burden, targeted treatments for HFpEF are not yet available.[1,3,4] Pharmacologic heart rate lowering is beneficial for patients with heart failure with reduced ejection fraction.[1,5,6] However, due to neutral or unfavorable results,[5,7-9] β-blockers are no longer recommended for individuals with HFpEF.[4]

Preclinical and exploratory clinical studies suggest that pacing at moderately accelerated rates may convey benefits in individuals with HFpEF.[10-14] Continuous accelerated pacing in a porcine model of concentric left ventricular hypertrophy,[10] hemodynamic assessments in patients with HFpEF,[11,12] and 2 four-week pacing studies in patients with preclinical or overt HFpEF[13,14] suggested improvements in filling pressures and heart failure symptoms. The clinical benefits were most pronounced in patients with conduction system pacing or paced QRS durations shorter than 150 milliseconds.[14]

Here, we present the results of the myPACE trial, in which we tested the novel concept of moderately accelerated pacing in patients with HFpEF over 1 year.

Key Points

Question Among patients with preclinical and overt heart failure with preserved ejection fraction and preexisting pacemakers that limit ventricular dyssynchrony, are moderately accelerated, personalized backup heart rates superior to the nominal setting of 60 beats per minute?

Findings In this randomized clinical trial of 107 participants, moderately accelerated pacing improved health-related quality of life, natriuretic peptide levels, activity levels, and atrial fibrillation compared with the standard 60 beats per minute setting.

Meaning This study found that tailoring the pacemaker backup rate to approximate an individual's resting heart rate improved outcomes; heart rate modulation, delivered in a way that maintains or optimizes physiologic conduction, may be a therapeutic target in patients with heart failure with preserved ejection fraction.

Methods

Study Design and Population

This study was a prospective, blinded, parallel-group, randomized clinical trial conducted at the University of Vermont Medical Center. The myPACE heart rate algorithm[15] and study rationale[16] have previously been published, and the trial protocol is detailed in Supplement 1. We consecutively screened adult patients scheduled at the University of Vermont Medical Center pacemaker clinic. Patients with American College of Cardiology/American Heart Association stage B and C HFpEF with an ejection fraction more than 50%, further defined in section 5.1.1 of Supplement 1, were enrolled based on the inclusion and exclusion criteria detailed in eTable 1 in Supplement 2. To minimize offsetting effects of pacemaker-mediated dyssynchrony, we only included patients with predominantly atrial pacing, conduction system pacing, or biventricular pacing. A paced QRS duration of 150 milliseconds or longer was an exclusion criterion. In total, 1523 patients were screened (**Figure 1**) and 199 met the study enrollment criteria. Data on race and ethnicity were not collected. We approached these patients for possible study participation during their routine pacemaker clinic visit and obtained informed written consent from all participants. Individuals were recruited and enrolled from July 2019 to November 2020, with follow-up concluding in December 2021. The trial protocol was approved by the University of Vermont Medical Center institutional review board. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline and was registered at ClinicalTrials.gov.

Intervention and Follow-up

The myPACE algorithm, study flow, and follow-up schedule are provided in section 5.1.4 of Supplement 1. The personalized accelerated heart rate algorithm for myPACE is derived from the averaged resting heart rates of healthy adults according to height[15] and modified by ejection fraction. Enrolled participants completed baseline assessments and were then randomized 1:1 to either a personalized backup heart rate setting (myPACE) or left at the nominal 60 beats per minute (bpm) setting (usual care) for 1 year.

Outcomes

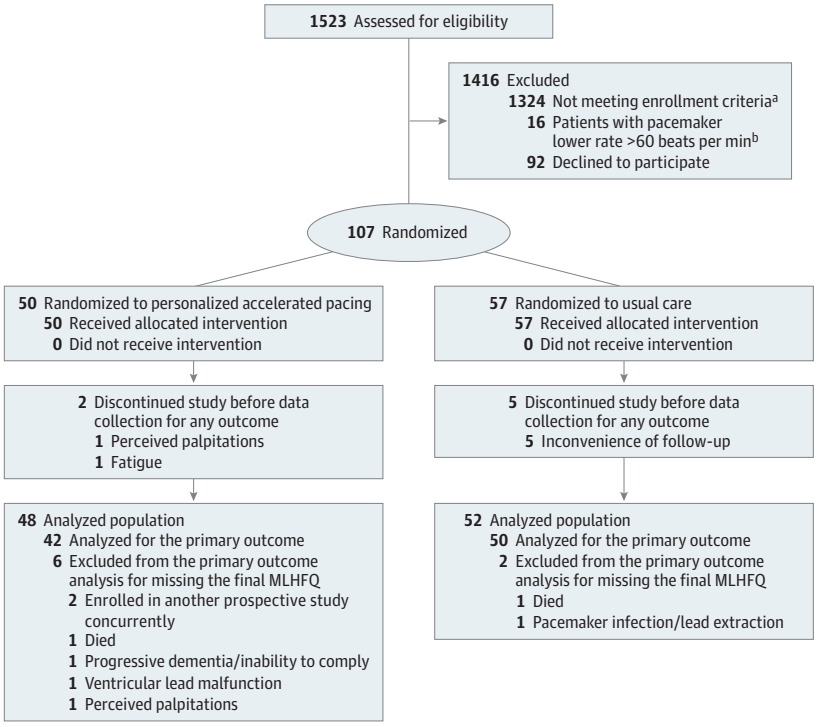
Study end points are outlined in eTable 2 in Supplement 2. The primary outcome of the myPACE study was the change in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score from baseline. Secondary outcomes included changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, pacemaker-detected physical activity, atrial fibrillation (AF), and clinical outcomes. Prespecified clinical outcomes were determined by an independent adjudication committee blinded to patient randomization. Exploratory subgroup analyses of the primary outcome were prespecified.[16] Additional safety measures are detailed in Supplement 1.

Statistical Analysis

Based on a prior pilot study, we estimated that a sample size of 118 individuals (59 per arm) would provide 80% power to detect a clinically significant 5-point change in MLHFQ scores, using a 2-sided type I error rate of 0.05.[16] Due to the COVID-19 pandemic, enrollment was closed in December 2020, as detailed in Supplement 1.

Demographics and health-related variables were tabulated at baseline. Continuous variables are expressed as mean (SD) or median (IQR), and categorical variables are expressed as number (%). The primary analysis was a modified intention-to-treat complete case analysis of participants with completed data for at least 1 efficacy end point (ie, baseline and full follow-up for MLHFQ scores, NT-proBNP, and physical activity). A secondary intention-to-treat analysis included all randomized participants with at least baseline measures, carry-

Figure 1. CONSORT Flow Diagram of myPACE Study Participants Leading to the Analyzed Population



MLHFQ indicates Minnesota Living with Heart Failure Questionnaire.

[a] Reasons for patient exclusion are detailed in eMethods in Supplement 2.

[b] Sixteen patients with lower rates >60 beats per minute were enrolled as an exploratory cohort and are not included in this analysis, as detailed in Supplement 1.

ing forward prior measurements for any missing follow-up measures (eMethods in Supplement 2). Both approaches analyzed participants by their original assigned group.

Continuous variables were compared within and between groups using repeated measures analysis of variance analyses. Because of non-normality, the analysis of variance used square root-transformed MLHFQ scores and patient activity levels and log-transformed NT-proBNP. Change in MLHFQ scores, NT-proBNP (as a percent change), and physical activity from baseline to each follow-up time approximated the normal distribution and did not require transformation. The raw values of these measures were not square root or log transformed.

The AF analysis evaluates the change in any device-detected AF from baseline to 1-year follow-up between groups to provide a risk ratio of any AF as a binary outcome. Mixed-effects generalized linear models with Poisson family, log link, and robust variance estimation estimated the proportion with any AF throughout follow-up. Cox proportional hazards models estimated hazard ratios for a cumulative outcome of the time to the first clinical event. Multilevel linear mixed effects estimated the difference in MLHFQ score at each time point for each stratified subgroup. Stata 17.0 (StataCorp) was used. Two-sided *P* values were statistically significant at less than .05.

Results

Patient Characteristics and Randomization

Overall, 107 patients with a baseline pacemaker lower rate of 60 bpm were enrolled, completed baseline studies, randomly assigned, and started their assigned intervention (Figure 1). Seven individuals were lost to follow-up or dropped out before any subsequent data collection (5 in usual care, 2 in the personalized accelerated pacing group), leaving 52 participants in usual care and 48 in the personalized accelerated pacing group. Reasons for individual patient drop-out are detailed in eTable 3 in Supplement 2. Patient characteristics were well balanced between arms (**Table 1**). The median (IQR) age was 75 (69-81) years, 48 (48%) were female, and the median (IQR) H_2FPEF score was 6 (5-8). H_2FPEF scores stratified by patients with stage B and C HFpEF and by New York Heart Association functional class 1 and 2 or more symptoms are shown in eTables 4 and 5 in Supplement 2. At baseline, the median (IQR) pacemaker-recorded heart rate over the prior 6 months was 65 (65-70) bpm for usual care and 65 (61-70) bpm for personalized accelerated pacing. The median (IQR) programmed rate was 60 (60-60) bpm with usual care and 75 (70-75) bpm with personalized accelerated pacing, and the resultant median (IQR) pacemaker-recorded heart rate over a 2-year follow-up was 65 (63-68) bpm with usual care and 75 (75-80) bpm with personalized accelerated pacing.

Primary Outcome

Of 100 participants with follow-up data, 92 (50 in usual care, 42 in the personalized accelerated pacing group) completed all MLHFQ surveys and were included in the primary outcome analysis with a mean (SD) follow-up duration of 378 (83) days. MLHFQ scores from baseline to follow-up differed between the personalized accelerated pacing and usual care groups (**Figure 2**A). Compared with baseline, mean (SD) MLHFQ scores decreased by 0.6 (9.1) points at 1 month and increased

Table 1. Baseline Characteristics of the Study Population by Pacing Group

Characteristic	No. (%)	
	Usual care (n = 52)	Personalized accelerated pacing (n = 48)
Age, median (IQR), y	75 (69-80)	76 (70-86)
Female	27 (52)	21 (44)
Male	25 (48)	27 (56)
BMI, mean (SD)	31.1 (7.1)	30.4 (7.1)
Height, mean (SD), cm	168 (13)	170 (12)
Heart rate, median (IQR), beats/min[a]	65 (61-70)	65 (65-70)
H_2FPEF score, median (IQR)	6.0 (5.0-8.0)	6.0 (5.5-7.0)
HFpEF stage B	14 (27)	10 (21)
HFpEF stage C	38 (73)	38 (79)
NYHA functional class		
I	28 (54)	23 (48)
II	13 (25)	14 (29)
III	7 (13)	7 (15)
IV	4 (8)	4 (8)
Hypertension	43 (83)	40 (83)
Paroxysmal atrial fibrillation	26 (50)	23 (48)
Persistent atrial fibrillation	7 (13)	4 (8)
Coronary artery disease	17 (33)	18 (38)
Diabetes	15 (29)	15 (31)
Obstructive sleep apnea	16 (31)	13 (27)
BP, mean (SD), mm Hg[b]		
Systolic	134 (17)	131 (20)
Diastolic	72 (10)	74 (10)
Echocardiography		
Ejection fraction, mean (SD), %	59 (6)	60 (4)
LA diameter, mean (SD), mm[c]	40 (8)	40 (6)
LA volume, mean (SD), mL/m^2[d]	36 (15)	40 (16)
LV septal wall, mean (SD), mm[e]	12 (2)	11 (2)
LV posterior wall, mean (SD), mm[f]	11 (2)	11 (2)
Average E/e', mean (SD)[g]	13 (6)	14 (7)
Primary pacing indication		
Sick sinus syndrome	28 (54)	28 (60)
Atrioventricular block	23 (45)	16 (34)
Chambers paced		
Atrial pacing[h]	20 (38)	21 (44)
Mix of atrial and ventricular pacing	27 (52)	24 (50)
Ventricular pacing only	5 (10)	3 (6)
Atrial lead type[i]		
Bachmann bundle area lead	19 (37)	17 (35)
Right atrial appendage lead	33 (63)	30 (63)
Ventricular lead type[j]		
Right ventricular lead[k]	24 (46)	22 (48)
His bundle or left bundle branch lead, %	16 (31)	15 (32)
Biventricular system	6 (12)	3 (6)
Percentage of time pacing by lead type[l]		
Atrial pacing, median (IQR), %	57 (13-86)	47 (5-86)
Right ventricular septal pacing, median (IQR), %	0.1 (0.0-1.0)	0.4 (0.0-7.3)
His bundle or left bundle branch, median (IQR), %	96 (37-100)	100 (34-100)
Biventricular pacing, median (IQR), %	100 (100)	100 (100)
Electrocardiogram parameters, median (IQR), ms		
Intrinsic P-wave	120 (104-130)	119 (102-130)
Paced P-wave	130 (110-150)	120 (98-142)
Intrinsic QRS	115 (97-135)	118 (105-130)
Paced QRS	120 (110-130)	115 (105-127)
Medications		
β-Blocker	22 (42)	21 (44)
ACEI	12 (23)	9 (19)
ARB	14 (27)	13 (27)
Dihydropyridine CCB	17 (33)	11 (23)
Nondihydropyridine CCB	6 (12)	4 (8)
Antiarrhythmic drug	11 (22)	12 (25)
Loop diuretic	14 (27)	17 (35)
Laboratory values		
Creatinine, median (IQR), mg/dL[b]	0.9 (0.8-1.1)	1.0 (0.8-1.1)
NT-proBNP, median (IQR), pg/mL	302 (169-672)	413 (154-1265)
Heart failure score		
MLHFQ score, median (IQR)	18.5 (5.5-41.0)	25.5 (8.0-42.5)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CCB, calcium channel blocker; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricular; MLHFQ, Minnesota Living with Heart Failure Questionnaire Score; NT-proBNP, N-terminal brain natriuretic peptide; NYHA, New York Heart Association.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] Pacemaker-recorded mean heart rate over 6 months prior to enrollment.

[b] Usual care: n = 51; personalized accelerated pacing: n = 47.

[c] Usual care: n = 46; personalized accelerated pacing: n = 44.

[d] Usual care: n = 38; personalized accelerated pacing: n = 36.

[e] Usual care: n = 44; personalized accelerated pacing: n = 39.

[f] Usual care: n = 43; personalized accelerated pacing: n = 39.

[g] Usual care: n = 33; personalized accelerated pacing: n = 24.

[h] Either atrial lead alone or a dual chamber system with <0.1% right ventricular pacing.

[i] Usual care: n = 52; personalized accelerated pacing: n = 47.

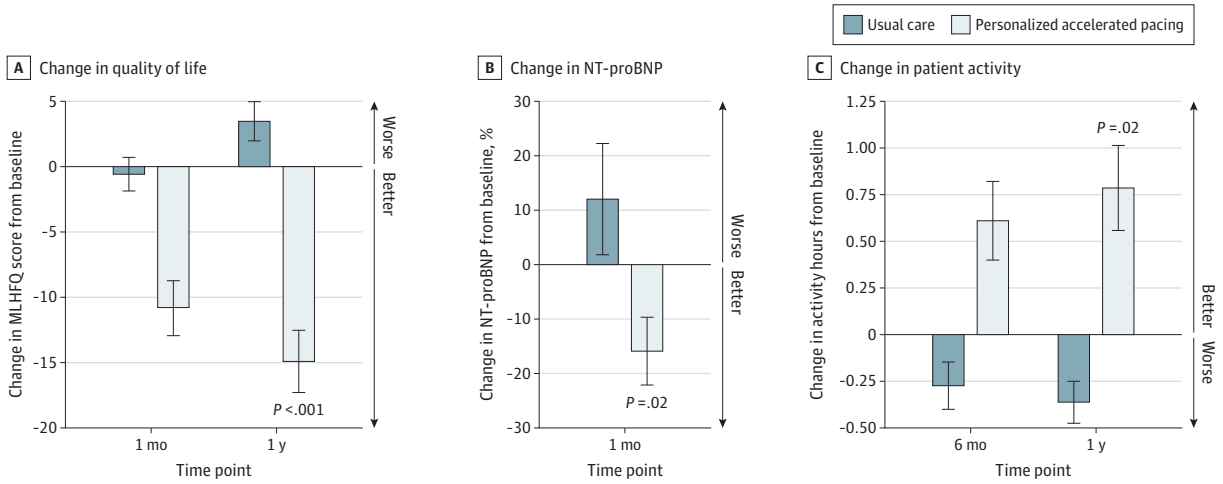
[j] Usual care: n = 46; personalized accelerated pacing: n = 40.

[k] Presence of a right ventricular septal lead but with minimal ventricular pacing and paced QRS <150 milliseconds.

[l] Percentage pacing refers to the amount of time that pacing is delivered from a lead site, among patients with that lead type (ie, among patients with atrial leads in the usual care group, they are paced from their atrial lead 57% of the time at baseline).

(worsened) by 3.5 (10.6) points at 1 year for usual care. MLHFQ scores improved by a mean (SD) of 10.9 (13.7) and 15.0 (15.5) points for the personalized accelerated pacing group at 1 month and 1 year, respectively. Between-group pairwise comparisons demonstrated similar MLHFQ scores at baseline and better MLHFQ scores in the personalized accelerated pacing group at 1-month and 1-year follow-up compared with usual care. Waterfall plots and box and whisker plots are provided in eFigures 1 and 2 in Supplement 2, respectively.

Figure 2. The Change in Minnesota Living with Heart Failure Questionnaire (MLHFQ) Quality-of-Life Scores, N-Terminal Pro–Brain Natriuretic Peptide (NT-proBNP), and Pacemaker-Detected Physical Activity Levels Between Groups



A, Between-group difference in the change in MLHFQ scores from baseline to 1-month to 1-year follow-up between personalized accelerated pacing and usual care groups ($P < .001$). Change in scores from baseline are shown as mean (SE).
B, Relative percent change in NT-proBNP from baseline to 1-month follow-up between groups ($P = .02$). The data are presented as mean (SE).
C, Between-group difference in the change in pacemaker-detected physical activity level (by accelerometer) from baseline to 6-month and 1-year follow-up ($P < .001$). The data are presented as mean (SE).

Compared with usual care, square root–normalized physical, emotional, and social domain scores significantly improved in the personalized accelerated pacing group (eTable 6 in Supplement 2).

Secondary Outcomes

NT-proBNP Levels

Baseline and follow-up NT-proBNP levels were available in 91 patients (50 in usual care, 41 in the personalized accelerated pacing group). Between-group pairwise comparisons of log-transformed NT-proBNP levels confirmed similar NT-proBNP levels at baseline and lower NT-proBNP levels with personalized accelerated pacing at follow-up compared with usual care. The change in log-transformed NT-proBNP levels from baseline to follow-up differed between groups, as shown in Figure 2B.

Pacemaker-Detected Activity Levels

Pacemaker-detected activity levels were available for the 50 patients who had pacemaker models with activity sensors (24 in usual care, 26 in the personalized accelerated pacing group). Median (IQR) pacemaker-detected daily activity levels at baseline were 2.5 (2.1-3.9) hours for usual care and 2.6 (1.5-3.1) hours for personalized accelerated pacing. The change in activity levels from baseline to follow-up differed between groups over follow-up, as shown in Figure 2C. Compared with baseline, mean (SD) daily activity decreased by 22 (35) minutes at 1 year with usual care and improved by 36 (62) minutes at 6 months and 47 (67) minutes at 1 year with personalized accelerated pacing. At 1-year follow-up, daily activity levels were greater with personalized accelerated pacing (median [IQR], 3.1 [2.0-4.3] hours) than with usual care (median [IQR], 2.9 [1.7-4.0] hours) ($P = .003$).

Pacemaker-Detected AF

Pacemaker-detected AF data were available for 85 patients who had pacemaker models with AF detection capabilities (46 in usual care, 39 in the personalized accelerated pacing group). As shown in **Figure 3**, the proportion of patients with device-detected AF at baseline (17 of 46 [37%]) and 1-year follow-up (18 of 46 [39%]) remained the same with usual care. Treatment with personalized accelerated pacing reduced the proportion of patients with device-detected AF from 31% (12 of 39) at baseline to 18% (7 of 39) at 1 year. Compared with usual care, treatment with personalized accelerated pacing reduced the relative risk of device-detected AF by 27% (risk ratio, 0.73 [95% CI, 0.55-0.99]); $P = .04$).

Clinical Events/Safety

The overall number of adverse events was low. For personalized accelerated pacing, 4 participants had 4 adverse events; with usual care, 11 participants had 17 adverse events (**Table 2**). A cumulative incidence plot is provided in eFigure 3 in Supplement 2.

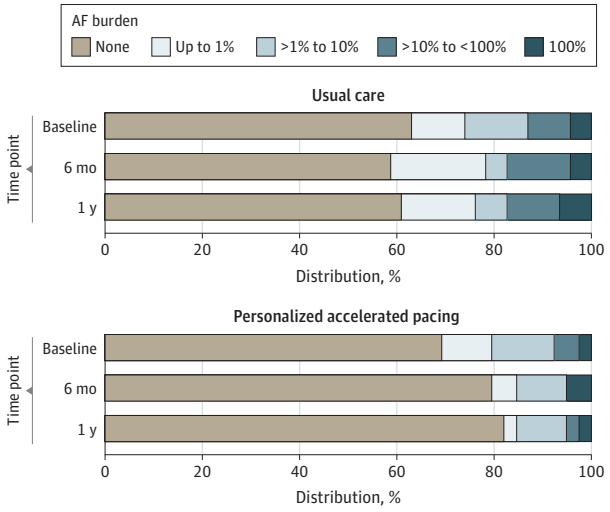
Secondary Analysis of MLHFQ, NT-proBNP, and Physical Activity Measures, Carrying Forward the Last Value for Missing Follow-up Values

As is shown in eFigure 4 in Supplement 2, including all 107 participants with at least baseline measures yielded similar results to the primary analysis.

Subgroup Analyses, Pacemaker-Detected Intrathoracic Impedance, and Blinding Assessment

All subgroups had symptomatic benefits from personalized accelerated pacing, as shown in eFigures 5 and 6 in Supplement 2. Women and patients with overt HFpEF appeared to benefit more. Less than a quarter of the enrolled patient had

Figure 3. Relative Distribution of Pacemaker-Detected Atrial Fibrillation (AF) Burden at Baseline, 6-Month, and 1-Year Follow-up With Personalized Accelerated Pacing and Usual Care



In the personalized accelerated pacing group, AF was detected in 31% of patients at baseline and 18% at 1-year follow-up, whereas the proportion of patients with AF did not change with usual care.

pacemakers with thoracic impedance recording capabilities. We did not detect between-group differences in thoracic impedance in this underpowered sample (eTable 7 in Supplement 2). Blinding was assessed by asking participants if they believed that their heart rate setting had been changed at the 1-month and 1-year follow-up visits. The number of incorrect vs correct answers remained balanced between groups (eFigure 7 in Supplement 2).

Discussion

In patients with pacemakers who had preclinical and overt HFpEF, treatment with a personalized accelerated pacing rate (myPACE) resulted in significant improvements in health-related quality of life as measured by the MLHFQ instrument compared with the standard lower rate setting of 60 bpm (usual care). NT-proBNP levels, physical activity levels, and device-detected AF also improved in the personalized accelerated pacing group compared with usual care.

Personalized Accelerated Pacing Approach

The mean adult resting heart rate is between 71 and 79 bpm.[15] However, in patients with pacemakers, the nominal lower rate setting of 60 bpm is commonly used to limit dyssynchronous right ventricular pacing.[17,18] With the increasing adoption of conduction system pacing from the His bundle or left bundle branch area, more physiologic and personalized pacemaker backup rates can be used without the offsetting effects of pacing-induced dyssynchrony. As previously described,[15,16] the myPACE rate is based on height and modified by ejection fraction to provide a personalized resting heart rate within the normal range.

Although chronotropic incompetence is common among patients with HFpEF,[19] it was not the focus of the myPACE study. However, rate-adaptive pacing was active in most patients to treat chronotropic incompetence (eFigure 5 in Supplement 2).

Proposed Mechanisms of Action

The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) was the first study to confirm that heart rate is a therapeutic target in heart failure.[6] While heart rate–lowering benefits individuals with heart failure with reduced ejection fraction,[6] the clinical outcomes in patients with normal ejection fractions are less favorable[20] and may be deleterious. Pharmacologic heart rate–lowering in these patients has been associated with reduced functional capacity,[7,8] increased rates of AF[21] and heart failure hospitalizations,[9,22] cardiovascular mortality, myocardial infarction, and stroke.[5,23,24] In addition, heart rate–lowering increases central arterial systolic and left ventricular diastolic pressures, which combine to increase atrial and ventricular wall stress.[25,26]

Conversely, moderately higher heart rates enhance myocardial contractility and accelerate relaxation kinetics by augmentation of cellular calcium handling reflected in the myocardial force-frequency and relaxation-frequency relationships. This was evident in atrial pacing studies of patients with preserved ejection fraction with and without HFpEF.[11,12,27,28] Up to rates of 125 bpm, relaxation kinetics accelerate and diastolic pressures decrease to normal levels in patients with HFpEF. The reduction in filling pressures at higher heart rates in patients with HFpEF can be explained by a leftward and downward shift of the pressure-volume relationship toward smaller left ventricular volumes and pressures. This reduces exposure to the exponential rise in myocardial stiffness, which is pathognomonic in HFpEF, and promotes early diastolic filling by suction, thereby reducing atrial pressures.[11,29,30] These effects may explain the reduction in NT-proBNP and AF with personalized accelerated pacing. Another potential advantage of moderately accelerated pacing in this population is a modest increase in cardiac output.[12,31,32]

The hemodynamic benefits of moderately higher heart rates in patients with HFpEF are immediate. Accumulating secondary effects (less orthopnea, better sleep, increased energy, and physical activity levels) could potentiate benefits over time. However, these secondary effects are unlikely to fully explain the continued improvements over 1 year, which are most pronounced in activity levels and the physical MLHFQ domain scores.

Although several potential mechanisms may explain the continued improvements in the personalized accelerated pacing group, cardiac remodeling likely plays a role. Even moderate increases in heart rate will inevitably induce some eccentric remodeling over time. This was evident in a porcine stage B HFpEF pacing model where moderate increases in heart rate led to beneficial remodeling. Heart rate–dependent remodeling resulted in a reduction in ventricular wall thickness and a more favorable left ventricular mass-to-volume ratio, which improved ventricular compliance.[10] Normal aging results in a 15% to 20% reduction in left ventricular end dia-

Table 2. Clinical Events

	No.			
	Usual care (n = 52)		Personalized accelerated pacing (n = 48)	
Event	Events	Patients	Events	Patients
All events	17	11	4	4
Death	1	1	1	1
Myocardial infarction	0	0	0	0
Heart failure hospitalizations	1	1	0	0
Heart failure urgent visit	3	3	0	0
Stroke	0	0	1	1
Atrial fibrillation hospitalization	2	2	0	0
Atrial fibrillation urgent visit	1	1	0	0
Loop diuretic drug[a]	6	6	2	2
Anti-arrhythmic drug[b]	3	3	0	0

[a] Initiation or dose doubling.

[b] Initiation.

stolic volumes and an unfavorable increase in the ventricular mass-to-volume ratio.[31,32] Prolonged accelerated pacing may partially restore normal left ventricular volumes, mass-to-volume ratios, and left ventricular distensibility over time,[10] which may improve cardiac output reserve.[31-33] The ongoing PACE HFpEF study will quantify the degree of remodeling induced by accelerated pacing with serial cardiac magnetic resonance imaging (NCT04546555). The finding that patients with preclinical HFpEF also benefited (eFigure 5 in Supplement 2) suggests that an even larger number of patients in the early stages of HFpEF may benefit from higher heart rates when the disease progression can still be modified as a preventive measure.

Associated Benefits for Activity Levels and AF Burden

The finding that activity levels increased over 1 year in the personalized accelerated pacing group parallels the quality-of-life improvements. The effect size at 1 year is comparable with the increase in activity levels achieved with cardiac resynchronization therapy: each 10-minute increase in daily activity was associated with a 4% risk reduction in heart failure hospitalization or death.[34] It was also determined that every 5-point change in MLHFQ score alters the relative risk for heart failure by about 8%.[35,36]

NT-proBNP levels predict not only HFpEF but also AF.[37,38] Because filling pressures and wall stress likely improve in personalized accelerated pacing, reflected in lower NT-proBNP levels, we reasoned that atrial unloading might be another benefit. This may explain the reduction in pacemaker-detected AF in the personalized accelerated pacing cohort. Although we did not study heart rate lowering, our results support the conceptual framework that lower heart rates may predispose patients with preserved ejection fractions to AF and HFpEF, as evident in large outcome studies of ivabradine and β-blockers and our secondary analysis of the TOPCAT trial.[5,9,21-26]

In summary, this study suggests that treatment with a moderately accelerated rate (myPACE) is safe and beneficial in an older patient population with preclinical and overt HFpEF and indications for cardiac pacing. Demonstrating that shortened diastolic filling benefits patients with HFpEF contradicts canonical thinking and may help reduce the overprescription of β-blockers to allow higher heart rates in this population.[8,9,29] In addition to symptomatic relief, moderately accelerated pacing may result in lower health care utilization, as signaled in the clinical outcomes (Table 2) and present a valuable approach for many patients with pacing indications if properly administered.

Potential Risks

Possible disadvantages of pacing at a moderately increased rate include the initial reductions of left ventricular volume reserve and an impaired Frank-Starling mechanism due to underfilling, which could lead to hypotension and orthostatic intolerance. In acute hemodynamic studies, stroke volumes were reduced in patients with HFpEF at atrial pacing rates of 120 bpm[11,12,28] but not at 80 bpm,[39] suggesting that there may be a therapeutic window that optimizes filling pressures and lusitropic effects without compromising cardiac output.[11,12,28,39] Like in our prior hemodynamic and clinical pilot studies,[11,13,14] moderately accelerated pacing did not appear to be associated with untoward effects.

As discussed, standard right ventricular pacing could offset the benefits of higher pacing rates by causing pacing-induced cardiomyopathy, as reported in patients with more than 40% right ventricular pacing.[40] We mitigated this risk in personalized accelerated pacing by enrolling patients with pacing systems that maintain or optimize physiologic ventricular conduction,[41-43] such as those with predominantly atrial pacing, conduction system pacing, or biventricular pacing (eTable 8 in Supplement 2), as shown in Table 1. Patients with dual-chamber pacemakers with a right ventricular septal lead had minimal pacing from this site: median (IQR), 0.2% (0%-1.8%) right ventricular pacing. It is therefore important not to extrapolate the myPACE findings to patients with a high burden of dyssynchronous right ventricular pacing. Our enrollment and follow-up were facilitated by a single referral center and an electrophysiology group that emphasizes physiologic atrial and ventricular pacing.[43-45] Other potential risks are discussed in the eMethods in Supplement 2. Nonetheless, the fa-

vorable safety profile over 1 year suggests that potential risks were outweighed by the benefits in most patients.

Limitations

Substantial efforts were made to maintain blinding and minimize biases in data collection. Although participant blinding appeared satisfactory (eFigure 7 in Supplement 2), some participants or caregivers may have been able to determine the assignment. More than half of the patients had sick sinus syndrome as the primary pacing indication, which likely increases the effect size of the personalized accelerated pacing intervention. In contrast to other contemporary HFpEF trials, we included some patients without a diagnosis of HFpEF. Despite this widened enrollment, we maintained a median H_2FPEF score of 6, which has a more than 90% HFpEF probability[46] and suggests that HFpEF was underdiagnosed in our population. The primary analysis was a modified intention-to-treat complete case analysis, which can result in biased estimates of treatment effects. However, our last observation carried forward intention-to-treat analysis, including all 107 randomized patients (eFigure 4 in Supplement 2) yielded similar results. Finally, although the MLHFQ and NT-proBNP levels were not significantly different, values were nominally higher in the personalized accelerated pacing group compared with usual care. Thus, there is a potential for regression to the mean as a potential contributor to the results. Finally, due to the COVID-19 pandemic, enrollment closed early.

Conclusions

In this randomized, blinded trial in patients with stage B and C HFpEF and preexisting pacemaker systems that limit ventricular dyssynchrony, treatment with a moderately accelerated personalized backup pacing rate (myPACE) resulted in significant improvements in health-related quality of life compared with the standard lower rate setting of 60 bpm (usual care). Pacing at a moderately accelerated personalized backup rate in this population also improved natriuretic peptide levels, activity levels, and AF compared with usual care. The myPACE study supports the concept of heart rate modulation as a therapeutic intervention in HFpEF and provides additional evidence that moderately higher, and not lower, heart rates are beneficial in this complex patient population with an unmet need for therapies addressing underlying hemodynamic and cardiac structural abnormalities. Considering that this is a single-center trial, additional trials in larger populations of symptomatic patients with HFpEF are needed to confirm these findings.

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Concept and design: Infeld, Wahlberg, Silverman, LeWinter, Lustgarten, Meyer.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Infeld, Wahlberg, Cicero, Plante, MuthuKrishnan, Lustgarten, Meyer.
Critical revision of the manuscript for important intellectual content: Infeld, Wahlberg, Meagher, Novelli, Habel, Silverman, LeWinter, Lustgarten, Meyer.
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