DESIGN PAPER

Rationale and design of the PACE HFpEF trial: Physiologic accelerated pacing as a holistic treatment of heart failure with preserved ejection fraction

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BACKGROUND In heart failure with preserved ejection fraction (HFpEF), it has been assumed that pharmacologic heart rate suppression should provide clinical benefits through an increase in diastolic filling time. Contrary to this assumption, heart rate lowering in patients with preserved left ventricular ejection fraction and hypertension or coronary artery disease results in adverse outcomes and suggests that the opposite may be beneficial. Namely, shortening the diastolic filling time with a higher heart rate might normalize the elevated filling pressures that are the *sine qua non* of HFpEF. Initial clinical studies that assessed the effects of accelerated heart rates in pacemaker patients with preclinical and overt HFpEF provide support for this latter hypothesis, having shown improvements in quality of life, natriuretic peptide and activity levels, and atrial fibrillation burden.

OBJECTIVE The study sought to determine the effects of continued resting heart rate elevation with and without superimposed nocturnal pacing in HFpEF patients without standard pacing indication.

METHODS The physiologic accelerated pacing as treatment for heart failure with preserved ejection fraction (PACE HFpEF) trial is an investigator-initiated, prospective, patient-blinded multiple crossover pilot study that assesses the impact of accelerated pacing on quality of life, physical activity, N-terminal pro–B-type natriuretic peptide, and echocardiographic measures of cardiac structure and function.

RESULTS Twenty patients were enrolled and underwent dual-chamber pacemaker implantation under U.S. Food and Drug Administration investigational device exemption with both atrial and ventricular physiologic lead placement targeting the Bachmann bundle and the His bundle.

CONCLUSION This manuscript describes the rationale and design of the PACE HFpEF trial, which tests the safety and feasibility of continuous accelerated physiological pacing as a treatment strategy in HFpEF.

KEYWORDS Heart failure with preserved ejection fraction; Accelerated pacing; Conduction system pacing; His bundle; Bachmann bundle; Individualized heart rate; Personalized heart rate; Nocturnal pacing

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is the cause of approximately half of all heart failure (HF) hospitalizations and the therapeutic options in HFpEF are limited. Despite the absence of evidence supporting their use, beta-blockers are often prescribed to treat HFpEF, with the underlying assumption that slowing heart rate helps to increase left ventricular filling by prolonging the diastolic filling time. Contravening this assumption, several studies have found pharmacological heart rate lowering to be detrimental in patients with preserved left ventricular ejection fraction (LVEF) and coronary artery disease or hypertension. In the Losartan Intervention For Endpoint reduction (LIFE) in hypertension trial of atenolol vs losartan, the atenolol arm had a 13% higher accrual rate of adverse cardiovascular endpoints and a 33% higher risk of new onset atrial fibrillation (AF),[1] despite equal blood pressure reductions in both arms. Examining data from hypertensive cohorts at risk for HFpEF and AF, our group demonstrated that beta-blocker use was associated with an excess of HF hospitalization and new-onset AF.[2,3] Similarly, selective heart rate lowering with ivabradine in the Study assessInG the morbidity-mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery

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KEY FINDINGS

- The PACE HFpEF trial is the first study to implement continuous accelerated pacing as a treatment strategy for heart failure with preserved ejection fraction in patients without standard pacing indication (under U.S. Food and Drug Administration investigational device exemption).
- A holistic approach to deliver accelerated pacing safely and effectively is chosen, combining individualized heart rate augmentation with physiologic lead placement that preserves or restores interatrial and interventricular synchrony as well as atrioventricular coupling.
- Imaging assessment of cardiac structure and function in heart failure with preserved ejection fraction patients undergoing continuous accelerated pacing will provide an insight into the remodeling capacity of the cardiac chambers.

disease (SIGNIFY) trial of patients with coronary artery disease without HF at baseline increased the relative risk for HF and AF by 20% and 40%, respectively, when compared with placebo,[4] supporting the notion that selective heart rate suppression is enough to adversely affect patients.

The underlying mechanism by which heart rate lowering in HFpEF is disadvantageous extends from the same reasoning that advocated the benefits of heart rate lowering: prolonged left ventricular filling results in higher filling pressures and wall stress, which are particularly pronounced in stiff hearts. At the beginning of ventricular diastole (= active relaxation), the pressure gradient between the left atrium and left ventricle results in early diastolic filling (= filling by suction). In late diastole, left ventricular filling is largely due to atrial contraction that must overcome the elements of passive ventricular stiffness, the latter being determined by myocardial wall thickness and extracellular matrix composition. In HFpEF, passive stiffness is increased,[5–7] which leads to an exponential steepening of the end-diastolic pressure-volume relationship that is pathognomonic for HFpEF.[8,9] While there is a paucity of direct hemodynamic data examining the acute impact of heart rate lowering on diastolic function, we surmise from the rise in natriuretic peptide levels with beta-blocker use in HFpEF that prolongation of diastole at the steep portion of the end-diastolic pressure-volume relationship only results in a small increase of the end-diastolic volume while filling pressures rise disproportionately. Furthermore, prolongation of diastole increases contractile force by activating the Frank-Starling mechanism, and together with the superposition of the reflected peripheral pulse wave onto systole increases central systolic blood pressure.

With a growing body of evidence for the detrimental effects of heart rate lowering in HFpEF, we have proposed the converse, namely that increasing heart rate may provide a therapeutic benefit. In patients with and without HFpEF, we reported that increasing the heart rate from baseline sinus rhythm in anesthetized patients to 125 beats/min via right atrial pacing acutely lowers left atrial pressures and LV end-diastolic pressure, with the effect being more pronounced in the patients with HFpEF.[10] In the Heart Rate 80 study, we found that a 4-week increase in the lower heart rate setting in pacemaker patients with diastolic dysfunction or HFpEF improved functional capacity, quality of life, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels.[11] Patients with physiologic pacing leads (Bachmann bundle and His bundle leads, respectively) or paced QRS durations of <150 ms derived the largest benefit. Recently, we presented and published the main results from the personalized pacing for diastolic dysfunction and heart failure with preserved ejection fraction (myPACE) trial in which pacemaker patients with physiologic pacing leads or paced QRS duration of <150 ms were randomized either to a personalized accelerated lower rate setting (average recorded heart rate 75 beats/min) or to remain at the nominal lower heart rate setting of 60 beats/min (average recorded heart rate 65 beats/min). Increasing the resting heart rate in the myPACE cohort led to significant improvements in quality of life, physical activity, NT-proBNP levels, and device-detected AF, in both patients with preclinical and overt HFpEF (Figure 1).[12] Preclinical data of moderate heart rate elevations in a porcine model of left ventricular hypertrophy showed beneficial remodeling by improving left ventricular mass-to-volume ratio and diastolic compliance along with the potential to reduce myocardial fibrosis.[13]

The previous data suggest that chronic heart rate augmentation lowers filling pressures and improves hemodynamics in HFpEF patients, leading to the positive clinical outcomes observed in the Heart Rate 80 study and the myPACE trial. Chronic heart rate augmentation may also provide a stimulus toward remodeling with a beneficial reduction in the left ventricular mass-to-volume ratio. In the present study, we advance our investigation to HFpEF patients without pre-existing pacing indication and examine whether a holistic pacing approach—defined as individualized accelerated heart rate via Bachmann and His bundle pacing—results in symptomatic, functional, and ventricular structural improvements.

Methods

Study design

The physiologic accelerated pacing as treatment for heart failure with preserved ejection fraction (PACE HFpEF) trial (NCT04546555) is a single-center, prospective, investigator-initiated, patient-blinded, multiple crossover pilot study to investigate the effects of continued resting heart rate elevation with and without superimposed nocturnal pacing in patients with HFpEF using dual-chamber pacemakers with both atrial and ventricular physiologic leads that target the Bachmann bundle and the His bundle, respectively. This investigational device exemption study is being performed in accordance with the Declaration of Helsinki guidelines and was approved by the U.S. Food and Drug Administration

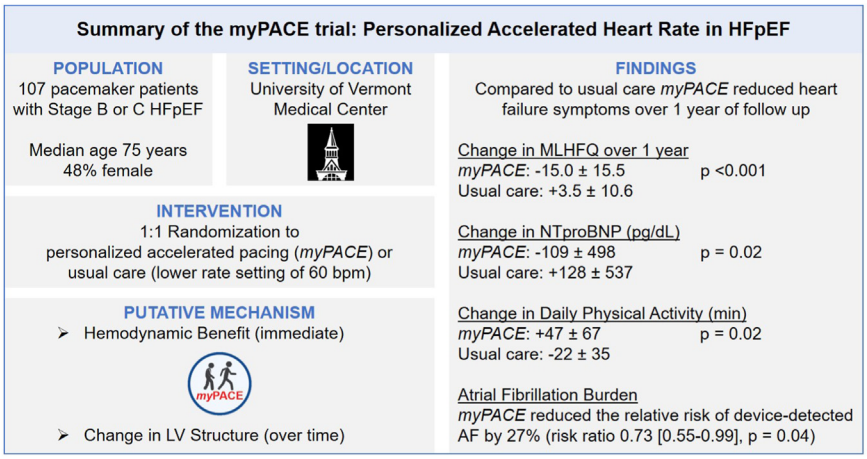

Figure 1 Summary of the myPACE trial of pacemaker patients with preclinical and overt heart failure with preserved ejection fraction (HFpEF) randomized 1:1 to personalized accelerated lower rate setting or nominal lower heart rate setting of 60 beats/min. MLHFQ = Minnesota Living with Heart Failure Questionnaire; NTproBNP = N-terminal pro–B-type natriuretic peptide.

and the Institutional Review Board at the University of Vermont Medical Center. The trial is supported by a grant from Medtronic Inc.

Study participants

After providing written informed consent, eligible HFpEF patients without a standard clinical indication for implantation of a dual-chamber pacemaker were enrolled. Similar to the enrollment criteria of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial[14] and the myPACE trial,[12] patients 18 years of age or older were eligible if they had at least 1 sign and at least 1 symptom of HF, a nondilated left ventricle with a normal LVEF, and controlled blood pressure for at least 30 days prior to enrollment. In addition, eligible patients had to have a history of HF hospitalization within the previous 12 months, or an elevated NT-proBNP >400 pg/mL. Table 1 details the study inclusion and exclusion criteria. The following baseline data are tabulated: (1) demographics, (2) medical history and medication inventory, (3) physical examination, (4) health-related quality-of-life questionnaire (Minnesota Living with Heart Failure Questionnaire [MLHFQ]), (5) 6-minute walk distance, and (6) 24-hour Holter monitor. If a patient is found to have 100% AF burden on 24-hour Holter monitor, a rhythm control strategy is attempted prior to pacemaker implantation. Patients who fail rhythm control are considered a screen failure and do not proceed to pacemaker implantation. Study subjects scheduled for pacemaker implantation also undergo laboratory testing of NT-proBNP, troponin I, and creatinine levels, as well as baseline cardiac imaging (cardiac magnetic resonance imaging and/or transthoracic echocardiogram).

Pacemaker implantation and holistic pacing

All patients undergo dual-chamber pacemaker implantation with a Medtronic Azure S DR magnetic resonance imaging–compatible pacemaker generator, a Medtronic 3830 lead targeting the His bundle, and a Medtronic 3830 lead targeting the Bachmann bundle. At the time of study design and Food and Drug Administration approval, the Medtronic 3830 lead was not yet approved for left bundle branch area pacing. The implantation procedure is carried out by a single experienced high-volume operator (D.L.) at the University of Vermont Medical Center. His bundle lead placement via a precurved or deflectable sheath is guided by (1) intracardiac electrogram recording of a His potential from the lead tip, (2) paced QRS duration and morphology, and (3) fluoroscopy.[15] Bachmann bundle lead placement is facilitated by a deflectable sheath and guided by (1) intracardiac electrogram recording of a split potential as previously reported by us, (2) paced P-wave duration and morphology, and (3) fluoroscopy targeting the high anteroseptal region at the confluence of the superior vena cava and the right atrium.[16]

We refer to holistic pacing as the combination physiologic lead placement (ie Bachmann bundle pacing and His bundle pacing) and an individualized heart rate (iHR) setting. Physiologic lead placement is ideal when implementing accelerated pacing to preserve or restore atrial and ventricular synchrony as well as atrioventricular (AV) coupling. Continuous resting heart rate augmentation is individualized using a height-based algorithm that adjusts to the degree of concentric remodeling (as estimated by LVEF):

$$iHR = 1.1 \times ((height\ \{cm\} \times -0.3744) + 134.82) \times \sqrt{\sqrt{\frac{LVEF}{50}}}$$

The general approach toward a personalized heart rate and derivation of the height–heart rate relationship has been detailed previously.[17] The iHR in the PACE HFpEF trial is intended to be 10% higher than in the myPACE trial to account for the fact that the PACE HFpEF study population has no bradycardia-related pacing indications.

Table 1 PACE HFpEFtrial inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ≥18 y	Cardiac pacemaker or defibrillator in situ
Echocardiogram within the past 24 mo that reported an LVEF ≥55% * AND left ventricular end-diastolic volume index <80 mL/m^2	Life expectancy is <12 mo
Heart failure hospitalization in the past 12 mo OR echocardiogram within the past 24 mo that reported left ventricular hypertrophy AND an NT-proBNP >400 pg/mL	Uncontrolled hypertension (average blood pressure of >140/90 mm Hg on office visits in the last 30 d or on home blood pressure log or actively undergoing uptitration of antihypertensive medication)
At least 1 symptom of heart failure in the past 12 mo (dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea)	More than moderate valvular disease
At least 1 sign of heart failure in the past 12 mo (pulmonary edema or pleural effusion on chest radiography, lower extremity edema, jugular venous distention, rales)	Chronic hypoxic respiratory failure requiring supplemental oxygen
Controlled blood pressure, defined as average blood pressure <130/80 mm Hg on office visits in the last 30 d or on home blood pressure log or patient has completed uptitration of antihypertensive medications	Long-standing persistent atrial fibrillation
	Baseline ECG with non–left bundle branch block morphology AND QRS duration >150 ms
	Subject is unable or unwilling to perform the 6-min walk test or Minnesota Living with Heart Failure Questionnaire
	Subject is currently enrolled or planning to enroll in a potentially confounding trial during the course of the study

ECG = electrocardiography; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PACE HFpEF = physiologic accelerated pacing as treatment for heart failure with preserved ejection fraction.
*Initial inclusion criteria allowed LVEF ≥50%. This was modified to ≥55% following an unanticipated adverse event of hospitalization for ventricular tachycardia during exposure of nocturnal accelerated pacing at 110 beats/min.

Nocturnal pacing to explore remodeling and the upper boundary of pacing benefit

In one of the phases of the study, nocturnal pacing at a HR of 110 beats/min for 10 hours between 8 PM and 6 AM in addition to continuous resting HR elevation is programmed, with the goal to maximize the hemodynamic benefit at night (ie to improve sleep) and induce eccentric left ventricular remodeling akin to the structural changes seen with accelerated pacing in a porcine model of left ventricular hypertrophy.[13] To deliver nocturnal pacing at an accelerated heart rate, the sleep function of the pacemaker is inverted (ie the lower rate limit is programmed to 110 beats/min and with the sleep function enabled the resting heart rate will gradually drop to the iHR at 6 AM and return to the higher rate of 110 beats/min at 8 PM). Rate profile optimization is turned off to ensure that accelerated pacing of 110 beats/min is limited to the nighttime hours.

While our previous observations demonstrate that an acute heart rate elevation to 125 beats/min in subjects with and without HFpEF consistently resulted in lower left atrial pressures,[10] we reasoned that a prolonged exposure to 110 beats/min would be the upper boundary of what might be considered clinically acceptable yet would be sufficient to demonstrate beneficial remodeling. Akin to our previous investigation of safety and feasibility of nocturnal heart rate elevation, we limited the exposure to 110 beats/min to 4 weeks.[18]

Study protocol

After the pacemaker implantation, each patient is randomly assigned to different pacing settings in a multiple crossover design, as illustrated in Figure 2. During the first 3 months (phase I) the following pacing modalities were randomly assigned for 1 month each: atrial pacing at iHR, dual-chamber pacing at iHR (DDDR iHR), and rate-adaptive pacing only (atrial pacing at iHR 40). In phase 2, following the exposure to the initial 3 pacing modalities, patients are assigned DDDR iHR+ (superimposed nocturnal pacing at 110 beats/min between 8 PM and 6 AM) and DDDR iHR in a random fashion.

With each monthly visit the following measures are obtained: (1) physical examination; (2) MLHFQ; (3) 6-minute walk distance (6MWD); (4) blood draw for the assessment of NT-proBNP, troponin I, and creatinine; (5) 12-lead electrocardiography; (6) device interrogation; and (7) adverse event assessment. The transthoracic echocardiogram is repeated at 3 months (at the time of completion of phase I) and at 5 months (at the time of completion of phase 2). Cardiac magnetic resonance imaging is repeated at 5 months (after completion of phase 2).

Primary and secondary study endpoints and safety endpoints are summarized in Table 2 and are defined on ClinicalTrials.gov (NCT04546555).

Statistical analysis

In a secondary analysis of over 1200 hospitalized patients with HF, the clinically important difference in total MLHFQ score from baseline to 6 months was 8.20 points (95% confidence interval 1.79–20.58 points), with a baseline MLHFQ score of 55.8 ± 22.6, corresponding to a 15% improvement.[19] Assuming an effect size of 30% difference in MLHFQ score with an estimated baseline mean of 55.8 ± 22.6, the sample size required to provide 80% power and 5% significance level (2-sided type I error) is 16 patients. To account for an estimated 20% attrition rate, the total number of patients required for this trial is 20.

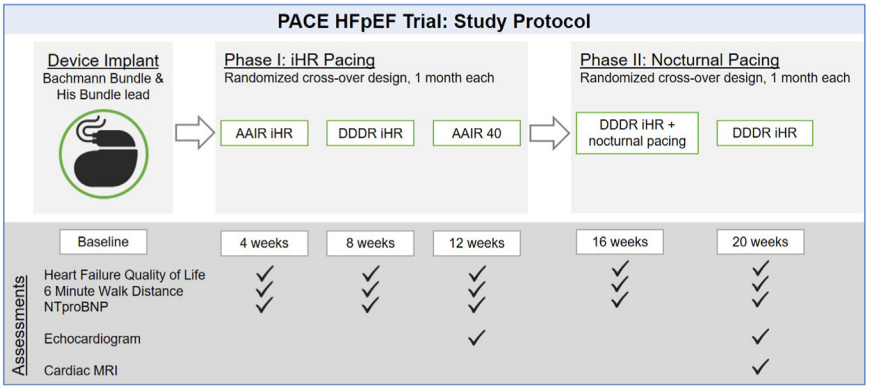

Figure 2 Schematic of the PACE HFpEF study protocol. AAIR = atrial pacing at individualized heart rate; DDDR = dual-chamber pacing at individualized heart rate; HFpEF = heart failure with preserved ejection fraction; iHR = individualized heart rate; MRI = magnetic resonance imaging; NTproBNP = N-terminal pro–B-type natriuretic peptide; PACE HFpEF = physiologic accelerated pacing as treatment for heart failure with preserved ejection fraction.

Current status

Enrollment started in February 2021 and was completed in November 2022. All study participants underwent successful dual-chamber pacemaker implantation and completed outcome measures in June 2023.

Discussion

The PACE HFpEF trial is the first study to assess the safety, feasibility, and efficacy of moderately accelerated pacing as a treatment for HFpEF patients who do not have a bradycardia-related pacing indication. This investigation combines holistic pacing that comprises individualized resting heart rate augmentation delivered via atrial and ventricular physiologic pacing leads and nocturnal heart rate elevation with the goal to optimize left-sided filling pressures and promote eccentric left ventricular remodeling, thereby improving symptoms and physical function.

Table 2 Outcome measures of the PACE HFpEF trial

Primary outcome measures
Change in composite MLHFQ at 1, 2, 3, 4, and 5 mo compared with baseline
Relative change in NT-proBNP from baseline to 1, 2, 3, 4, and 5 mo
Secondary outcome measures
Change in 6-min walk distance
Incident atrial fibrillation
Burden of atrial fibrillation
Hemodynamic changes assessed by transthoracic echocardiogram
Change in left ventricular mass/volume ratio by cardiac magnetic resonance imaging
Safety outcomes
Risk assessment associated with pacemaker implantation (pocket hematoma, infection, phrenic or diaphragmatic stimulation, lead endocarditis, lead dysfunction/dislocation, pneumothorax, hemopericardium, death)
Doubling in baseline troponin
Doubling in NT-proBNP
25% or greater increase in systolic blood pressure

MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

The clinical management of HFpEF remains challenging and despite recent advances many patients continue to experience fatigue and dyspnea with tasks of daily living despite adequate treatment of volume status and comorbidities. In this context, it is noteworthy that although sodium-glucose cotransporter-2 (SGLT-2) inhibitors in 2 landmark studies (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction [EMPEROR-Preserved]) and Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction [DELIVER]) provided an approximate 20% reduction in HF events, quality of life and NT-proBNP were little affected.[20,21]

The compromise in quality of life and exertional restrictions may be more relevant to patients than overall survival.[22] Acknowledging the importance of physical function and quality of life for HF patients, a 2019 statement from the U.S. Food and Drug Administration emphasized that symptom improvement and enhanced physical function are important and valid endpoints.

Pharmacological treatment of HFpEF

Until recently, pharmacologic treatments for HFpEF have only yielded neutral results, and typically the trials included HF patients with an LVEF between 40% and 49%, which is now considered a mildly reduced ejection fraction by the 2022 HF guidelines. A summary of relevant clinical trials is provided in Table 3. Current guidelines recommend SGLT-2 inhibitors, mineralocorticoid receptor antagonists and combination angiotensin receptor-neprolysin inhibitors; however, as summarized in Table 3, the clinical outcomes even where statistically significant do not demonstrate a robust clinical response. The Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) trial of sacubitril-valsartan showed a trend toward improvement in the composite primary endpoint, which was driven by HF events, but the subgroup analysis revealed that only patients with a median LVEF of 57% or lower derived this benefit.[23,24] Treatment with sacubitril-valsartan as compared

Table 3 Recent HFpEF clinical trials and impact on quality of life, NT-proBNP, and physical function

Clinical trial	LVEF inclusion	Primary endpoint	QoL	ΔBNP or NT-proBNP	Physical function
TOPCAT (2014)[14]; spironolactone vs placebo	≥45%	Nonsignificant: composite of CV death, aborted cardiac arrest, HF hospitalization	Mean KCCQ 64.4 vs 63.1 (ns)	N/A	N/A
PARAGON (2019)[23,24]; valsartan vs LCZ696	≥45%	Nonsignificant: composite of CV death, HF hospitalization	Δ KCCQ −2.5 vs −1.5 (ns)	↓ 19% in geometric mean NT-proBNP with LCZ696	N/A
EMPEROR-Preserved (2021)[20]; empagliflozin vs placebo	>40%	Hazard ratio for composite of CV death and HF hospitalization: 0.79 (95% confidence interval 0.69–0.90)	N/A	↓ median NT-proBNP by 29 pg/mL vs 9 pg/mL	N/A
PRESERVED-HF (2021)[25]; dapagliflozin vs placebo	≥45%	Improvement in KCCQ at 12 wk	Mean KCCQ 68.6 vs 62.8 (*P* value = .001)	Mean NT-proBNP 733 pg/mL vs 739 pg/mL	6MWD 262 m vs 242 m (baseline 244 m)
DELIVER (2022)[21]; dapagliflozin vs placebo	>40%	Hazard ratio for composite of CV death and HF event: 0.82 (95% confidence interval 0.73–0.92)	Mean KCCQ placebo corrected Δ −2.4	N/A	N/A

6MWD = 6-min walk distance; BNP = B-type natriuretic peptide; CV = cardiovascular; DELIVER = Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction; EMPEROR-Preserved = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas Cit Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; N/A = not applicable; ns = not significant; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PARAGON = Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; PRESERVED-HF = Dapagliflozin in PRESERVED Ejection Fraction Heart Failure; QoL = quality of life; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

with valsartan alone did not provide patients with an improvement in quality of life.

As mentioned previously, the use of SGLT-2 inhibitors in the EMPEROR-Preserved and DELIVER trials showed a reduction in the combined risk for HF hospitalization and cardiovascular death over placebo. With the use of empagliflozin, this effect appeared to be attenuated with higher LVEF. Unfortunately, most drugs including empagliflozin have failed to show any relevant functional improvement, which is commonly assessed in the 6MWD.[26] With empagliflozin the median increase in walk distance was 4 m vs a 4-m decline with placebo (*P* = ns), sacubitril-valsartan (mean increase of 9.7 m vs 13.2 m for the comparator group),[27] and spironolactone (median decline of 6 m in the effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction (Aldo-DHF) trial; no change in peak oxygen uptake).[28,29]

The notable exception is dapagliflozin, which improved quality of life, measured by the Kansas City Cardiomyopathy Questionnaire by 5.8 points at 12 weeks and increased 6MWD by 18 meters in the Dapagliflozin in PRESERVED Ejection Fraction Heart Failure (PRESERVED HF) trial.[25] The subsequent DELIVER trial demonstrated a reduction in the composite of cardiovascular death and HF events with dapagliflozin as compared with placebo, yet with only a mean quality of life improvement over placebo of 2.4 points.

Device-based treatment of HFpEF

Various device-based therapies are currently under evaluation for HFpEF. A subgroup analysis of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial found that HF medication adjustment (predominantly diuretic therapy) guided by wireless pulmonary artery pressure monitoring effectively reduced congestive HF hospitalizations for patients with New York Heart Association functional class III symptoms.[30] Investigations of intra-arterial shunt devices to reduce elevated pulmonary capillary wedge pressure have yielded mixed results. Early feasibility studies appear promising,[31] yet the only sham-controlled study[32] to date was neutral, with a signal for harm in patients with latent pulmonary vascular disease, raising the questions whether intra-atrial shunt devices might improve left ventricular filling pressures at the cost of worsening right ventricular function.[33]

Other strategies being evaluated involve neuromodulation: sympathetic stimulation increases preload by recruiting blood from the splanchnic venous circulation, which results in a

rapid rise in left ventricular end-diastolic pressure in patients with HFpEF. Ablation of the right-sided greater splanchnic nerve can inhibit excessive splanchnic stimulation: a recent 11-patient feasibility study showed significant improvements in quality of life and exercise capacity.[34] A larger, randomized, sham-controlled Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF (Rebalance-HF) trial (NCT04592445) is completed and reported overall neutral results (publication pending). Similarly, neuromodulation via baroreflex activation therapy aims at inhibiting sympathetic stimulation to the heart, kidney, and peripheral vasculature, resulting in lower blood pressure. Baroreflex activation therapy is approved for the treatment of HF with reduced ejection fraction to improve HF symptoms, while the application in HFpEF is an active area of investigation.

Exercise and weight loss for HFpEF

Using a 2 × 2 factorial design, the Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction (SECRET) trial demonstrated that caloric restriction and supervised exercise over 20 weeks improved peak oxygen consumption in obese patients with HFpEF but did not improve quality of life.[35] In a subgroup analysis of the positive Physical Rehabilitation for Older Patients Hospitalized for Heart Failure (REHAB-HF) trial, HFpEF patients with recent acute decompensated HF appear to have a larger gain from a multidomain physical rehabilitation intervention as compared with patients with HF and reduced ejection fraction.[36] Undoubtedly, enhancing patients' fitness is desirable, but access and adherence to a supervised exercise program pose practical challenges. Patients with HFpEF are commonly sedentary, and symptom burden can limit even activities of daily living to such a degree that starting and adhering to an exercise program is practically unattainable. Facilitating the individual's ability to increase their physical activity to the level that they can pursue daily activities without being limited by shortness of breath is often a necessary step to have the patients' buy-in to become an active participant of an exercise program.

The Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (STEP-HFpEF) trial provided some early evidence that weight loss with a glucagon-like peptide 1 agonist in obese HFpEF patients provides benefits on quality of life measured with the Kansas City Cardiomyopathy Questionnaire clinical summary score (estimated difference, 7.8 points; 95% confidence interval 4.8–10.9; $P < .001$) and 6MWD (estimated difference, 20.3 m; 95% confidence interval 8.6–32.1 m; $P < .001$), but it remains to be seen if these benefits are sustainable and lead to improvements in clinical outcomes.[37]

Heart rate modulation as a treatment for HFpEF

Continuous resting heart rate augmentation may serve as a stepping stone to allow HFpEF patients regain physical function in their daily activities. Increasing heart rate acutely lowers left atrial and left ventricular filling pressures to provide targeted cardiac decongestion. Resting heart rate augmentation for 4 weeks improved physical function in the Heart Rate 80 study, and patients receiving accelerated pacing in the myPACE trial had a 30% increase in device detected activity levels.

Contrasting with our results, the Rate-Adaptive Atrial Pacing for Heart Failure With Preserved Ejection Fraction (RAPID-HF) trial tested rate-adaptive atrial pacing alone using legacy lead placement (right atrial appendage, right ventricle) without alteration of resting heart rate in HFpEF patients with chronotropic incompetence and found that augmentation of exercise heart rate did not improve exercise capacity or quality of life.[38]

It is our supposition that heart rate modulation for the treatment of HFpEF requires a permanent resting heart rate augmentation to achieve cardiac decongestion. The implementation of this strategy requires a holistic approach: individualized meaning an approximation to not only restore a normal heart rate, but also counteract the hemodynamic impairment from concentric remodeling. Continuous resting heart rate augmentation is individualized using an advanced height-based ejection fraction–modified algorithm. Pacing to augment resting rest heart and institute accelerated nocturnal pacing requires preservation and/or restoration of intrinsic atrial and ventricular conduction as well as AV electromechanical coupling. Lead placement in the Bachmann bundle and His bundle or left bundle branch area are critical to achieving this goal.

Knowledge gaps

The optimal range of heart rates for any given HFpEF patient is unknown, although we surmise that patients with higher left ventricular mass-to-volume ratio benefit more from a relative higher individualized pacing rate than patients with more normal left ventricular chamber size and wall thickness. The formula used to determine iHRs accounts for LVEF, which depends on left ventricular chamber size and mass-to-volume ratio.

It is unclear if it is necessary to modify the pacemaker's rate settings in the long run, or whether accelerated pacing provides a new set point for cardiac function. Similarly, optimal duration and individualization of the nocturnal heart rate setting remain to be determined.

The optimal range and means of tailoring sensed and programmed AV delay are not well defined in HFpEF. AV delays were individualized based on electrical data, including intrinsic PR interval, and atrial stimulus to P-wave onset with the goal to avoid AV dyssynchrony, generally in the range of 130 to 180 ms. Nominal AV hysteresis programming was typically used to prevent rate acceleration pseudo-pacemaker syndrome and approximate AV shortening that should occur with an increased adrenergic input.

Limitations

This trial examines the impact of moderate continuous accelerated pacing with and without nocturnal heart rate

augmentation on quality of life and functional status as well as the impact on imaging parameters from transthoracic echocardiography and cardiac magnetic resonance imaging. While it is reasonable to assume that changes in those measures are mediated by acute and/or chronic hemodynamic changes, no direct hemodynamic measures are assessed.

It is important to acknowledge that all patients undergo pacemaker implantation, which in itself may convey a perceived benefit, regardless of pacing intervention. The magnitude of this placebo effect from the device may vary. Notably, no placebo effect was seen in the RAPID-HF trial, which assessed the efficacy of rate adaptive pacing in HFpEF patients with chronotropic incompetence.

The height-based algorithm to determine the individualized resting heart rate is adjusted for the degree of concentric remodeling by including LVEF. This approach is practical but does not account for other determinants of resting heart rate, such as sex, weight, or level of physical training (although physical activity levels are generally low in patients with HFpEF). Further investigations are needed to determine whether the current height-based algorithm approximates a resting heart rate that optimizes electromechanical function in HFpEF patients.

Conclusion

The PACE HFpEF trial is designed to determine the safety and feasibility of continuous accelerated physiological pacing with and without superimposed nocturnal higher rate pacing in HFpEF patients without a standard pacemaker indication. This trial optimizes the delivery of this novel intervention—accelerated pacing—via Bachmann bundle and His bundle lead placement and will help refine the treatment requirements for a pivotal study.

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Patient Consent: Written informed consent is provided by all participants.

Ethics Statement: This investigational device exemption study is being performed in accordance with the Declaration of Helsinki guidelines and was approved by the U.S. Food and Drug Administration and the Institutional Review Board at the University of Vermont Medical Center.

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