Personalized Pacing for Diastolic Dysfunction and HFpEF - Design and Rationale for the myPACE Randomized Controlled Trial

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Short title: MyPACE study Rationale

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ABSTRACT

**Background:** Patients with pacemakers and heart failure with preserved ejection fraction (HFP EF) or isolated diastolic dysfunction (DD) may benefit from a higher backup heart rate (HR) setting compared with the standard setting of 60 beats-per-minute (bpm).

**Objective:** Assess the effects of a personalized backup HR setting (myPACE group) compared with 60bpm (control group).

**Methods:** In this prospective blinded randomized controlled study, pacemaker patients with DD or HFP EF and atrial pacing with intrinsic ventricular conduction or conduction system or biventricular pacing are randomized to the myPACE group or control group for 1 year. The primary outcome is the change in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores. Secondary endpoints include changes in N-terminal pro-brain natriuretic peptide levels, physical and emotional MLHFQ subscores, pacemaker-detected atrial arrhythmia burden, patient activity levels, and thoracic impedance, hospitalization for heart failure, atrial fibrillation, cerebrovascular accident, or myocardial infarction, and loop diuretic or anti-arrhythmic medication initiation or up-titration. A sample size of 118 subjects is expected to allow detection of a 5-point change in MLHFQ score in an intention-to-treat analysis and allow initial assessment of clinical outcomes and subgroup analyses.

**Results:** Enrollment began in July 2019. As of November 2020, 107 subjects have been enrolled. It is projected that the 1-year follow-up will be completed by December 2021.

**Conclusions:** Atrial pacing with intrinsic ventricular conduction or advanced ventricular pacing at a higher, personalized backup HR may be a therapeutic target for patients with isolated DD or HFP EF. The myPACE trial is designed to test this hypothesis.
KEYWORDS: diastolic dysfunction, heart failure with preserved ejection fraction, heart rate, pacing
INTRODUCTION

Half of the patients with heart failure (HF) have a preserved ejection fraction (HFpEF) and more than one in four adults have diastolic dysfunction (DD).\textsuperscript{1,2} Despite an increasing prevalence and socioeconomic burden, targeted treatments for patients with HFpEF are lacking.\textsuperscript{1,3}

Clinical trials have demonstrated benefit of pharmacological heart rate (HR) lowering with select beta-blockers and ivabradine in HF with a reduced ejection fraction (HFrEF).\textsuperscript{1,4} Without an evidence-basis it is often assumed that lower HRs also provide a benefit to patients with DD and HFpEF by prolonging relaxation to allow for better ventricular filling.\textsuperscript{1,5} The relationship of elevated HR with adverse outcomes lends further associative support to the notion that lower HR could be beneficial.\textsuperscript{6}

However, HRs themselves may not cause adverse outcomes and there are studies that suggest that intentionally increasing resting HR in HFpEF may have therapeutic value.\textsuperscript{7}

In the following, we present the rationale for the myPACE study, which hypothesizes that a personalized pacing intervention providing moderately higher resting HRs to pacemaker patients with HFpEF or isolated DD may convey therapeutic benefits.

Chronotropic Interventions in Preserved-EF Populations

The “lower HR is better” paradigm has not been confirmed in patients with preserved ejection fraction (EF) with or without clinical HF.\textsuperscript{5} Several reports in related patient-populations with normal or preserved EFs suggest that pharmacological HR-lowering with beta-blockers or ivabradine is either not beneficial or associated with adverse outcomes (Supplement Table 1).\textsuperscript{4,8-10} A patient-level meta-analysis of 11 randomized controlled trials investigating beta-blockers in HF found no evidence of a benefit in the subgroup of patients with EF $\geq 50\%$.\textsuperscript{4} In fact, among patients with preserved EF with and without clinical HF, studies have revealed signals of harm associated with HR-lowering therapies. In the large SIGNIFY trial comprised of patients with stable coronary disease without HF, selective HR-lowering with ivabradine (from a mean HR of 70 beats-per-minute [bpm] to 60bpm) did not improve outcomes.\textsuperscript{8} In fact, there was a 20% relative increase in HF hospitalizations and a 40% relative increase in atrial fibrillation.
(AF) in the ivabradine group. Two large hypertension trials that compared beta-blockers to other antihypertensive agents also suggested an increase in cardiovascular events in the beta-blocker arm despite a similar level of blood pressure lowering between groups. A few mechanisms have been proposed to explain these counterintuitive outcomes. Lower HRs have been shown to generate peripherally reflected systemic pressure waves that superimpose onto systole and lead to increased central blood pressure and afterload. In addition, prolonged ventricular filling results in a larger ventricular load and higher filling pressures that combine to increase ventricular wall stress. These mechanisms explain why patients on HR-lowering medications have higher natriuretic peptide levels, which in turn is a predictor of incident AF and HF. With these mechanisms at play, higher HRs with a shortened ventricular filling time should have the opposite effect. This was demonstrated in hemodynamic studies involving HFpEF patients, where atrial pacing reduced left ventricular (LV) end-diastolic pressures by up to 50%. Aside from the immediate hemodynamic effects, prolonged exposure to moderately elevated HRs may induce beneficial changes in the ventricular structure and substrate that improve diastolic distensibility by reducing fibrosis or improving the LV volume-to-mass ratio.

For these reasons, we hypothesized that patients with HFpEF or isolated DD may derive a benefit from moderately higher resting HRs. In two prospective pilot studies, we explored this concept in pacemaker patients with isolated DD or HFpEF. In the first study we raised the backup pacing rate to 100bpm at night for 4 weeks. In the second study we set the lower rate to 80bpm for 4 weeks. The moderate HR elevation significantly improved quality of life (QoL), functional capacity, and N-terminal pro-brain natriuretic peptide (NTproBNP) levels among patients with paced QRS durations <150ms. When the HR setting was returned to the standard backup rate of 60bpm, QoL and NTproBNP worsened, further supporting a beneficial effect of a higher resting HR in this population. Studies that assess effects of higher HRs in this population are summarized in Supplement Table 2. Next, we discuss the pacing modalities best suited to deliver accelerated pacing in patients with isolated DD and HFpEF.
Electrophysiological Abnormalities in HFpEF and Advanced Pacing Modalities

Patients with HFpEF have a propensity towards sinus node dysfunction (SND), including chronotropic incompetence, which explains why over 20% of patients with HFpEF have a permanent pacemaker.\textsuperscript{20,21} While atrial pacing addresses SND without the associated detrimental effects of dyssynchronous right ventricular (RV) pacing, co-existing atrioventricular nodal (AVN) conduction disease and an intrinsic AV delay at higher atrial rates may result in more ventricular pacing. Current pacing guidelines favor the use of pacing algorithms permissive of non-physiologic programmed AV delays in dual chamber devices to minimize the percentage of RV pacing, ideally to less than 20%.\textsuperscript{22} A simple way to limit RV pacing is to use a slower backup pacing rate. Hence in clinical practice, the pacemaker backup rate is typically left unchanged from the nominal setting of 60bpm.\textsuperscript{23}

Since we are proposing to use pacing to increase resting HR, the potential therapeutic value cannot come at the expense of abnormal electrical activation, and neither non-physiologic AV-adaptive pacing nor reliance on atrial pacing alone will allow us to achieve that objective in most patients. With the advent of physiologic pacing targets–such as His bundle pacing (HBP) and left bundle branch area pacing (LBBAP)–as well as optimized biventricular pacing, the pacemaker backup rate can be customized to higher HRs without the offsetting effects of pacemaker-mediated dyssynchrony. The synergy of restored chronotropy and preserved atrio-ventricular and inter-ventricular synchrony may increase the potential benefits of this novel treatment approach for patients with isolated DD and HFpEF (Figure 1).

Because physical activity levels are reported to be low among HFpEF patients,\textsuperscript{24,25} this study focuses on pacemaker lower rate adjustments rather than rate-adaptive pacing. Increasing the pacemaker backup rate exposes the patient to the pacing intervention for longer periods of time, which allows us to evaluate chronic effects of moderately higher HRs. Chronotropic incompetence is common among HFpEF patients\textsuperscript{21} and the ongoing RAPID-HF trial is evaluating the efficacy of rate-adaptive pacing in this population (NCT02145351). While rate-adaptive pacing is not the focus of myPACE, potential
benefits will be evaluated in a subgroup analysis. The decision to program rate-adaptive pacing in myPACE is left to the discretion of the patient’s cardiologist based on individual patient characteristics.

**Rationale for myPACE**

The pacemaker backup rate is typically left at or near the factory setting of 60bpm. This one-size-fits-all approach does not consider that the average adult resting HR is between 71 to 79bpm or that 60bpm may not be the optimal resting HR for pacemaker-reliant patients with isolated DD or HFpEF. The primary aim of myPACE is to evaluate the effects of a higher, individualized pacemaker backup rate in patients with isolated DD or HFpEF on changes in symptoms and QoL compared with the standard rate of 60bpm. This will be assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Secondary aims are to study NTproBNP, which is a surrogate marker for myocardial wall stress and a predictor of HF, and relevant clinical and pacemaker-recorded outcomes over 1 year.

**METHODS AND ANALYSIS**

**Study population**

Pacemaker clinic patients at the University of Vermont Medical Center (UVMMC) are consecutively screened and approached for possible study participation during their standard-of-care pacemaker clinic visit. Table 1 outlines study inclusion and exclusion criteria. Definitions of HFpEF and isolated DD are detailed in the Supplement. To reduce dyssynchronous RV pacing that could occur with a higher backup rate, we limit myPACE enrollment to patients with either (1) atrial pacing with intact AVN conduction or minimal RV septal pacing with paced QRS duration <150ms, or (2) HBP, LBBAP, or biventricular pacing with paced QRS duration <150ms.

**Personalized heart rate algorithm**

For myPACE we developed a personalized HR algorithm based on physiologic resting HRs in healthy individuals to provide a customized lower rate setting for pacemaker patients. The rationale and
validation of the underlying height-HR relationship has been previously described\textsuperscript{26} and additional details about the HR algorithm are available in the Supplement. The myPACE personalized HR algorithm (Figure 2) is:

\[
\text{Personalized HR [bpm]} = (\text{Height [cm]} \times -0.3744 + 134.82) \times \sqrt{\frac{\text{Ejection Fraction [%]}}{50}}.
\]

**Study design**

This is a single center, prospective, blinded, randomized controlled study conducted at UVMMC. Patients are randomized 1:1 to either a personalized backup HR setting (myPACE group) or to the standard 60bpm setting (control group) for 1 year. A summary of the study is outlined in Figure 3 and blinding is detailed in the Supplement.

Enrolled subjects complete the following baseline measurements prior to randomization:

- MLHFQ, NTproBNP, and a pacemaker interrogation. The validated MLHFQ survey instrument was chosen as a primary outcome because it is an independent predictor of cardiovascular events, death, and future hospitalizations that is highly correlated with NYHA stage and is a measure of treatment efficacy.\textsuperscript{27,28} Baseline characteristics (Supplement) are tabulated after enrollment.

**Outcomes**

Primary and secondary study endpoints are summarized in Table 2. Pacemaker-detected endpoints are collected over the 1-year study period. Recorded and adjudicated clinical outcomes (Table 2) are presented individually and as a composite outcome without censoring. Clinical outcomes are monitored throughout the study period, will be assessed by chart review and by patient interview at the 1-year follow-up visit, and final adjudication will be determined by an independent committee blinded to patient randomization.

At the exit visit, after study data has been collected, the group assignment will be assessed and disclosed to the patient. Participants randomized to the myPACE group are offered, in consultation with
their primary cardiologist, to have their pacemaker programmed back to the standard 60bpm or to remain at the personalized HR. This information will be tabulated. Exploratory subgroup analyses are detailed in the Supplement.

**Additional Safety Outcomes**

The following safety outcomes are reported separately: 1) patient-reported symptoms of palpitations or chest discomfort thought to be pacing-related, 2) worsening fatigue, or 3) worsening HF symptoms following randomization. Safety monitoring is detailed in the Supplement.

**Statistical plan**

The null hypothesis is that there will be no difference in MLHFQ scores between the myPACE and control arms. The alternative hypothesis is superiority of one over the other backup rate. Based on prior pilot study data in a similar population of patients, with an anticipated mean ± standard deviation baseline MLHFQ score of 31±15 we will need to enroll 59 patients in each group to provide 80% power to detect a clinically relevant >5-point change in the composite MLHFQ score (2-sided test).\(^{19,29,30}\) We set a goal to enroll 130 patients assuming attrition rates similar to our previous pilot studies to anticipate patient drop-out.

Baseline characteristics will be presented as mean ± standard deviation or median (interquartile range). Continuous variables will be compared using unpaired Student t tests, Wilcoxon matched pairs tests, and analysis of variance. Categorical variables will be compared using contingency table analysis. The cumulative number of individual and composite adjudicated endpoint events (total number of endpoints for each subject) over time will be analyzed by the Anderson and Gill Cox regression model.

The primary analysis is intention-to-treat. A per-protocol analysis including all patients who remained in their randomized group for at least 1 month with last observation carried forward will be
performed secondarily. MLHFQ scores and NTproBNP are analyzed as per-individual changes within groups and between-groups without correction for multiple comparisons (MLHFQ).

**Trial management and status**

The UVM Institutional Review Board (IRB) approved this study and myPACE will adhere to the Declaration of Helsinki guidelines. Informed written consent is obtained from all trial participants prior to enrollment and randomization. Oversight will be provided by a Trial Steering and Adjudication Committee and an independent member of the IRB. The protocol is registered at ClinicalTrials.gov (NCT04721314). Patients started enrolling in July 2019. As of November 15, 2020, 107 patients had been enrolled. Due to the COVID-19 pandemic, and to comply with an IRB request, a 1-month interim analysis was performed to exclude futility defined as a worsening of the average MLHFQ as a reason to end the study. As there was a signal of benefit enrollment was closed. The preliminary and updated 1-month MLHFQ and NTproBNP data was reported virtually at the 2021 ACC meeting. The study is projected to complete 1-year follow-up of all patients by December 2021. The research findings will be submitted for publication to peer-reviewed journals and trial participants will be informed of study results.

**DISCUSSION**

The rationale for myPACE is derived from two complementary clinical observations. Over the last two decades evidence has accrued suggesting that the effects of pharmacological HR-lowering in patient populations with preserved EFs are either neutral or associated with signals of harm, including HF, AF, and stroke (Supplement Table 1). Additional studies suggest that modest increases in HR using pacemakers may benefit patients with HFpEF or isolated DD (Supplement Table 2). Pacing studies in a porcine model of hypertensive heart disease, clinical hemodynamic assessments in patients with HFpEF, and two exploratory patient studies in patients with pacemakers and isolated DD or HFpEF collectively suggest a benefit of moderately elevated HRs in concentric LV hypertrophy,
isolated DD or HFpEF. Neither pilot study raised safety concerns such as tachycardia-mediated cardiomyopathy.\textsuperscript{18,19}

\textit{myPACE} is the first randomized, blinded trial to assess median term effects of pacing-mediated moderate HR acceleration on QoL, natriuretic peptide levels, and clinical outcomes. The algorithm utilized in \textit{myPACE} provides study participants with an individualized HR that is determined by height and modified by baseline EF. Enrollment and follow-up are facilitated by a single referral center and a cardiac electrophysiology group that emphasizes physiologic pacing in all patients.\textsuperscript{32}

\textbf{Other Benefits of Pacing}

Besides the reduction in filling pressures and wall stress, higher HRs have additional effects. The force-frequency relationship or Treppe phenomenon enhances intrinsic myocardial contractility that is preserved in HFpEF.\textsuperscript{33,34} The HR-mediated rise in contractility is associated with faster relaxation kinetics that largely depend on the acceleration of intracellular calcium sequestration mediated by the sarcoplasmic reticulum.\textsuperscript{35} An increase in the stimulation rate of isolated contracting human myocardium from 60bpm to 90bpm shortens the time to half maximal relaxation (RT50) by 11%.\textsuperscript{36} The calciotropic effect of pacing and increase in relaxation velocity also lower filling pressures by suction and shift the pressure-volume loop leftwards (Figure 4) from larger to smaller LV volumes, which are less exposed to the exponential portion of the end-diastolic pressure-volume relationship.\textsuperscript{5,7}

Chronic reduction in filling pressures and wall stress may lead to beneficial remodeling over time. In an experimental model we have shown that even modest HR elevations can lead to a physiological eccentric remodeling with an associated reduction in ventricular wall thickness, a lower mass-to-volume ratio and improved compliance without leading to tachycardia-induced cardiomyopathy.\textsuperscript{17} While the underlying molecular mechanisms of HR-induced eccentric remodeling are unknown there is a linear HR dose-dependence to suggest that even minor increases in HR are associated with sub-clinical remodeling.\textsuperscript{17}
In addition, as cardiac output is the product of HR and stroke volume, higher HRs may modestly improve cardiac output, which in addition to lowering left sided filling pressures, may contribute to a better quality of life. The personalized HRs in myPACE will exceed sleep HRs by at least 10bpm, which could provide an additional remodeling stimulus while also decreasing nocturnal filling pressures that may reduce orthopnea, improve the quality of sleep and well-being, and perhaps in turn facilitate increased daytime physical activity.

Potential Hazards of Pacing

Higher HRs increase myocardial oxygen consumption proportionally.\textsuperscript{37,38} It is therefore possible that higher-rate pacing increases the risk for demand ischemia, whereas HR-lowering generally reduces this risk. However, in the SIGNIFY trial, which investigated the effects of ivabradine among patients with stable coronary disease without clinical HF, selective HR-lowering by 10bpm did not improve outcomes. On the contrary, among the sub-group of patients with activity-limiting angina the primary composite endpoint of death from cardiovascular causes or nonfatal myocardial infarction was significantly greater in the ivabradine group.\textsuperscript{8}

The potential benefit of an increased HR in patients with isolated DD or HFpEF using standard RV pacing could be offset by a pacing-induced cardiomyopathy, as reported in patients with more than 40% RV pacing.\textsuperscript{39} As discussed, pacing-induced cardiomyopathy is mitigated with biventricular pacing and likely to an even greater extent by HBP.\textsuperscript{40,41} An increase in backup HR is also expected to reduce vagally-mediated HR variability. This may not be directly harmful, however, as HR variability - like low resting HR - has been shown to be a marker rather than a conveyor of good health.\textsuperscript{42} Furthermore, based on prior data\textsuperscript{17,18,19} the proposed pacing rates in this study are unlikely to induce clinically relevant eccentric remodeling and tachycardia-mediated cardiomyopathy, however, this is an important safety endpoint that we will track. Based on the studies in our pre-clinical model we expect that the increase in LV end-diastolic volume will remain below 10%.
Other Limitations

It could be argued that effective blinding of study participants for the myPACE HR intervention cannot be accomplished. However, the same argument can be made for HR-lowering medications such as beta-blockers or ivabradine. To assess this potential source of bias we have introduced a question to assess patient blinding at the 1-month and 1-year follow-up. Another limitation of the myPACE study design is that sample size estimates for clinical outcomes could not be made for a lack of comparator data.

Conclusion

myPACE is a prospective, randomized, and blinded trial designed to evaluate the effects of higher HRs in pacemaker patients with isolated DD or HFpEF in whom potentially adverse effects of pacing will be mitigated by ventricular pacing that facilitates synchronous interventricular activation. myPACE is testing the paradigm-changing hypothesis that moderately higher HRs, and not lower HRs, might provide important benefits for this complex patient population with an unmet need for evidence-based targeted therapies.

Funding Sources
This research was supported by grant R01 HL-122744 (Dr. Meyer) and the HRS Research Fellowship Award and the Cardiovascular Research Institute of Vermont’s Martin M. LeWinter Young Investigator and Early Career Research Awards (Dr. Infeld).

Disclosures
Dr. Meyer and the University of Vermont have licensed patents for the use of pacemakers for the prevention and treatment of heart failure with preserved ejection fraction. Dr. Lustgarten and Dr. Meyer have received research funding from Medtronic. Other authors report no competing interests.

Authorship
All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent
Informed written consent is obtained from all trial participants prior to enrollment and randomization.

Ethics Statement
The UVM Institutional Review Board (IRB) approved this study and myPACE will adhere to the Declaration of Helsinki guidelines.
### Table 1. *myPACE* Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Adults &gt;18 years old with a pacemaker</td>
<td>Paced QRS duration &gt;150ms</td>
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<tr>
<td>Pacemaker lower rate set to 60 bpm at baseline</td>
<td>Infiltrative cardiomyopathy</td>
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<tr>
<td>Left ventricular ejection fraction &gt;50% assessed by Simpson’s biplane method</td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>DD or HFpEF (defined in Supplement)</td>
<td>More than moderate valvular stenosis or regurgitation</td>
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<tr>
<td>SND with intact AVN conduction or minimal right ventricular pacing (&lt;2%) and paced QRS &lt;150ms OR impaired AVN conduction with His bundle or left bundle branch area pacing or biventricular pacing and paced QRS &lt;150ms</td>
<td>Aortic valve replacement in the past 1 year</td>
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<tr>
<td>Subject is expected to remain available for follow-up visits</td>
<td>Significant primary pulmonary disease on home oxygen</td>
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<tr>
<td>Life expectancy &gt; 1 year</td>
<td>Uncontrolled hypertension defined by BP &gt;160/100 mmHg on two measurements ≥15 minutes apart</td>
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<td></td>
<td>Creatinine &gt;2.5 or hemoglobin &lt;8g/dL</td>
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<tr>
<td></td>
<td>Pregnancy</td>
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<td></td>
<td>Patient participating in another clinical trial</td>
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Abbreviations: AVN=atrioventricular nodal, bpm=beats-per-minute, DD=diastolic dysfunction, HFpEF=heart failure with preserved ejection fraction, NTproBNP=N-terminal pro-brain natriuretic peptide, SND=sinus node dysfunction

Above inclusion and exclusion criteria adapted from Heart Rate 80 study,\(^9\) the ongoing REVAMP trial (NCT03210402), and the clinical judgement of investigators.
### Table 2. myPACE Study Endpoints

<table>
<thead>
<tr>
<th><strong>Primary outcomes</strong></th>
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<tr>
<td>Change in MLHFQ total scores at baseline, 1 month, and 1 year [categorical, relative, and absolute changes]</td>
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<tr>
<th><strong>Secondary outcomes</strong></th>
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<tr>
<td>• NTproBNP levels from baseline to 1 month after enrollment [categorical, absolute, and relative changes]</td>
</tr>
<tr>
<td>• MLHFQ emotional score and physical score [categorical, absolute, and relative changes]</td>
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<tr>
<td>• Pacemaker-monitored data over 1-year study period:</td>
</tr>
<tr>
<td>o atrial fibrillation/tachycardia burden</td>
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<tr>
<td>o pacemaker-detected activity levels by accelerometer</td>
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<tr>
<td>o thoracic impedance (surrogate marker for volume overload)</td>
</tr>
<tr>
<td>• Clinical endpoints over 1-year study period (composite and individual):</td>
</tr>
<tr>
<td>o heart failure hospitalization or invasive outpatient intervention (intravenous loop diuretic)</td>
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<tr>
<td>o loop diuretic initiation or up-titration</td>
</tr>
<tr>
<td>o atrial fibrillation hospitalization or invasive outpatient intervention (emergency department visit for symptomatic or rapid atrial fibrillation or cardioversion)</td>
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<tr>
<td>o antiarrhythmic medication initiation or up-titration</td>
</tr>
<tr>
<td>o stroke or transient ischemic attack</td>
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<tr>
<td>o myocardial infarction</td>
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<tr>
<td>• Blinding efficacy assessment at 1 month and 1 year</td>
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<table>
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<tr>
<th><strong>Adverse outcomes</strong></th>
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<tr>
<td>• patient reported symptoms of palpitations or discomforts thought to be related to pacing</td>
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<tr>
<td>• worsening fatigue</td>
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<tr>
<td>• worsening heart failure symptoms</td>
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Abbreviations: MLHFQ=Minnesota Living with Heart Failure Questionnaire
**Figure 1.** Pacing at moderately higher HRs improves myocardial relaxation and decreases filling pressures in patients with heart failure with preserved ejection fraction or isolated diastolic dysfunction. Conduction system or biventricular pacing that optimizes ventricular synchrony avoids deleterious effects that could be seen with a high burden of right ventricular pacing. *Abbreviations: HR=heart rate*  

**Figure 2.** Personalized Heart Rate Algorithm in myPACE. We developed a HR algorithm based on physiologic resting HRs in healthy adults to provide a customized backup HR to pacemaker patients based on height (5th percentile, median and 95th percentile) in both women and men, shown above, and modified by ejection fraction. *Abbreviations: HR=heart rate*  

**Figure 3.** myPACE Study Flowchart. Patients scheduled in our pacemaker clinic are consecutively screened. Those enrolled complete a baseline MLHFQ quality of life score, NTproBNP, and a pacemaker interrogation. Patients are randomized to either the myPACE or the control group. NTproBNP was repeated at 1-month and MLHFQ was repeated at 1-month and 1-year. Pacemaker-detected data and clinical outcomes are monitored during the 1-year study period. *Abbreviations: MLHFQ=Minnesota Living with Heart Failure Questionnaire, NTproBNP=N-terminal pro-brain natriuretic peptide*  

**Figure 4.** Figure Pressure Volume (PV) loop. Schematic left ventricular PV loops derived from hemodynamic studies in patients with HFpEF. Effects of a HR increase from the pacemaker backup rate of 60bpm to normal HRs is shown. Higher HRs lower left ventricular end-diastolic volume and pressure by a shortened left ventricular filling time and leftward shift of the PV loop.
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Normal Resting Heart Rate

Higher Resting Heart Rate

Advanced Pacing

Standard RV Pacing

LV Pressure

Chronotropy

Optimized Conduction

ECG

LOWER FILLING Pressures
CONTRACTILE SYNCHRONY
KEY FINDINGS

- The myPACE study is the first randomized controlled study testing the hypothesis that atrial pacing at moderately higher heart rates might provide important benefits for pacemaker patients with heart failure and preserved ejection fraction (HFpEF) or isolated diastolic dysfunction compared with the standard backup setting of 60 beats-per-minute. With increasing adoption of physiologic pacing techniques, the pacemaker backup rate can be customized to higher rates without the offsetting effects of pacemaker-mediated dyssynchrony.
- The study uses a novel personalized heart rate algorithm to provide a customized lower rate setting for pacemaker patients.
- The findings from myPACE will help address knowledge gaps related to tailoring the pacemaker lower rate setting in pacemaker patients with HFpEF or isolated diastolic dysfunction.
- The myPACE study tests the paradigm-changing hypothesis that moderately higher heart rates, and not lower heart rates, might be a therapeutic target for patients with HFpEF, a complex patient population with an unmet need for evidence-based therapies.