

Brief Report

Safety and Feasibility of a Nocturnal Heart Rate Elevation—Exploration of a Novel Treatment Concept

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ABSTRACT

Background: Diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) are associated with myocardial fibrosis and concentric left ventricular hypertrophy (LVH). In a preclinical model of LVH, we demonstrated that a moderate increase in heart rate can reduce interstitial fibrosis and improve LV compliance. We therefore hypothesized that moderately elevated heart rates can be used to beneficially modify the myocardial substrate in patients with diastolic dysfunction and HFpEF. As a preliminary step to test this hypothesis, we evaluated if patients can tolerate this novel pacemaker-based treatment approach without adverse effects.

Methods and Results: A pacemaker-mediated increase in heart rate to 100 beats/min for 5 hours at night was tested over 4 weeks in 10 patients with diastolic dysfunction. The patients underwent a physical examination, biomarker collection, 6-minute walk test, heart failure questionnaire, and echocardiography before and after the pacing intervention. None of the patients reported any symptoms at night. No arrhythmias were induced. Eight patients completed the protocol. Three patients experienced unanticipated daytime pacing from an interfering pacemaker function. There were no detrimental changes in biomarkers or LV systolic function.

Conclusions: Nocturnal pacing at a rate of 100 beats/min appears to be safe and well tolerated in this small exploratory patient cohort. (*J Cardiac Fail* 2019;25:67–71)

Keywords: Heart Failure, Preserved Ejection Fraction, Heart Rate, Pacemaker, Night Pacing.

Heart failure with preserved ejection fraction (HFpEF) affects about one-half of the patients with heart failure.¹ Despite the high prevalence and economic burden of this disease, treatment options are limited.

At a structural level, HFpEF is commonly associated with left ventricular (LV) concentric remodeling, myocardial fibrosis, and an increased LV mass-volume

ratio.^{2–5} An increase in the resting heart rate can induce eccentric remodeling and LV wall thinning through an innate myocardial adaptation that effectively lowers the mass-volume ratio.^{6,7} This may improve LV compliance and decrease interstitial fibrosis without neurohumoral activation or heart failure, as demonstrated in preclinical models.^{7,8}

In this first safety and feasibility study, we tested the hypothesis that electronic pacing at 100 beats/min at night can be tolerated by patients with diastolic dysfunction and HFpEF.

Methods

Patient Population

We prospectively enrolled patients in the pacemaker clinic of the University of Vermont Medical Center. The following inclusion criteria were used: adults ≥ 18 years of age with dyspnea on exertion, a Medtronic dual-chamber pacemaker, echocardiographic evidence of LVH and left atrial dilation on a previous

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Table 1. Patient Characteristics and Pacing Outcomes

Patient	Age	Sex	Comorbidities	NYHA	Outcomes
1	64	F	HTN, TAVR, CAD, IDDM, end stage renal disease on hemodialysis, hypothyroidism	II	No symptoms with night pacing. Very limited physical activity at baseline.
2	72	F	HTN, IDDM, CKD III, hypothyroidism	II	No symptoms with night pacing.
3	86	M	HTN, severe osteoarthritis, HLD, AF, SND	I	No symptoms with night pacing.
4	65	M	HTN, IDDM, osteoarthritis, paroxysmal AF, OSA, SND	III	No symptoms with night pacing.
5	76	M	HFpEF, HTN, IDDM, COPD, lung cancer, paroxysmal AF	II	No symptoms with night pacing but developed daytime palpitations and shortness of breath on day 2 after enrollment. Study withdrawal on day 5. Symptoms resolved with reprogramming.
6	61	F	HFpEF, HTN, IDDM, hypothyroidism, OSA, paroxysmal AF	II	No symptoms with night pacing.
7	82	M	HTN, CAD, stage III CKD, osteoarthritis, hypoparathyroidism, OSA, SND	I	No symptoms with night pacing.
8	82	F	HFpEF, HTN, hypothyroidism, OSA	IV	No symptoms with night pacing. In wheelchair: no 6MWT.
9	85	F	HTN, osteoarthritis, paroxysmal AF, SND	I	No symptoms with night pacing, daytime palpitations. Study withdrawal on day 3. Symptoms resolved with reprogramming. Declined postintervention 6MWT.
10	73	M	HFpEF, HTN, paroxysmal AF, SND	III	No symptoms with night pacing, but patient noticed elevated daytime heart rates of 110 beats/min 3 weeks after enrollment. Rate-response feature was disabled with resolution of symptoms. Patient completed study without other issues.

AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HLD, hyperlipidemia; HTN, hypertension; IDDM, insulin-dependent diabetes mellitus; OSA, obstructive sleep apnea; SND, sinus node dysfunction; TAVR, transcatheter aortic valve replacement.

echocardiogram, and an ejection fraction $\geq 50\%$. Exclusion criteria were as follows: greater than moderate valve disease, angina pectoris, oxygen-dependent chronic obstructive pulmonary disease, and pulmonary arterial systolic pressures >50 mm Hg. The Institutional Review Board at the University of Vermont approved this protocol. All patients provided written consents. Clinical vignettes for all patients are provided in [Table 1](#).

Study Protocol

As outlined in [Fig. 1](#), enrolled patients underwent a baseline physical examination, blood sample collection, 6-minute walk test (6MWT), Minnesota Living With Heart Failure Questionnaire (MLHFQ), and transthoracic echocardiography. The pacemaker was then programmed to preferentially deliver atrial pacing in DDD(R) mode at a rate of 100 beats/min from midnight to 5 AM without changing the daytime rate. Previous pacemaker settings were restored after 4 weeks or at the time of withdrawal from the study. All clinical assessments

performed at baseline were then repeated. Telephone calls to assess symptoms were made to the patients on days 3 and 14 as well as 2 weeks after the final clinic visit.

Pacemaker Programming

The pacemakers were programmed to deliver 5 hours of DDD(R) pacing with a lower rate limit of 100 beats/min from midnight to 5:00 AM. At present, no pacemaker function can provide selective higher rate pacing at night. This obstacle was overcome by an inversion of the “sleep function.” The purpose of the sleep function is to allow for a lower rate limit during sleep with the intention of preventing unnecessary pacing. With this feature activated, the “bedtime” window was set from 5 AM to midnight. This created 2 distinct pacing windows: 1) a 5-hour window from midnight to 5 AM during which the device was set to pace at 100 beats/min; and 2) a 19-hour period from 5 AM to midnight during which the sleep function was activated and set to pace at the prestudy daytime lower rate limit (typically 60 beats/min).

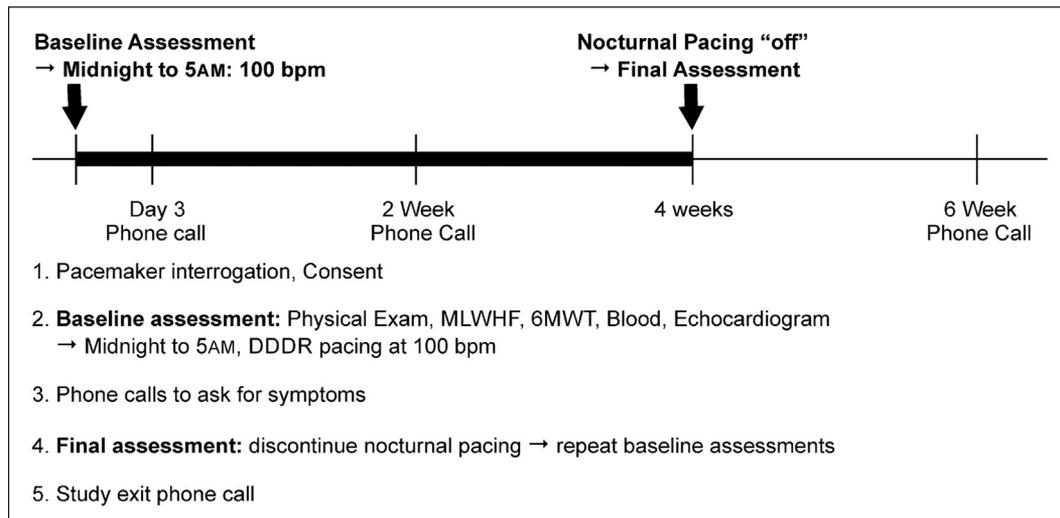


Fig. 1. Schematic of the experimental protocol. MLWHF, Minnesota Living With Heart Failure Questionnaire; 6MWT, 6-minute walking test.

Biomarkers

Serum samples were sent to the clinical laboratory of the University of Vermont Medical Center for determination of creatinine, troponin I, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Additional markers of cardiac fibrosis and remodeling were evaluated at baseline and after the intervention.

Statistical Analysis

Biomarker, echocardiographic parameters, 6MWT duration, and MLHFQ comparisons were made by means of paired *t* tests and confirmed with the use of Wilcoxon rank sum tests. A *P* value of $\leq .05$ was used to indicate statistical significance. The data are presented in the figures as individual data points and medians with interquartile range at baseline and after the 4-week intervention.

Results

Patients

A total of 195 patients presenting for routine pacemaker clinic visits were screened, and 10 patients were enrolled. Mean age was 75 ± 9 years. Six patients were female. Four patients had a clinical diagnosis of HFpEF. Mean ejection fraction at enrollment was $58 \pm 5\%$.

Feasibility, Tolerability, and Unanticipated Daytime Pacing

The pacing protocol was successfully initiated in all enrolled patients. None of the patients described symptoms during the 5-hour nocturnal pacing window in the telephone interviews and at the clinic visit. A total of 8 patients completed the 4-week study. Two patients withdrew early after experiencing daytime palpitations and elevated pulse rates of 100–130 beats/min. A third patient also experienced

palpitations and elevated pulse rates during the day, which resolved after disabling the rate-responsive pacing feature.

Outcome Measures

Two patients did not participate in the postintervention 6MWT. As shown in Fig. 2, the 6MWT distance increased by an average of $23 \pm 19\%$, from 258 ± 55 meters to 322 ± 99 meters ($P = .01$). NT-proBNP and troponin did not significantly change with the intervention. Echocardiography did not reveal any changes in ejection fraction (baseline $58 \pm 5\%$, postintervention $56 \pm 6\%$; $P = .33$), LV outflow tract velocity time integral, and LV volumes. The biomarkers also did not exhibit any significant changes (Supplemental Fig. 1).

Safety

The participants did not report any symptoms aside from those described above that occurred with unintended pacing outside of the treatment window. No arrhythmias were induced during the study as determined via device interrogation.

Discussion

In this exploratory study, we found that nocturnal pacing at a moderately increased heart rate of 100 beats/min is feasible, generally well tolerated, and safe. None of the patients demonstrated worsening heart failure. However, 3 patients experienced elevated heart rates outside of the experimental pacing window owing to an unanticipated conflict with an ancillary pacemaker function.

Rationale for Exploring Higher Heart Rates

The proposition of using elevated resting heart rates as a treatment for heart failure may, at first glance, appear to be ill advised. Typical concerns are that high resting heart rates

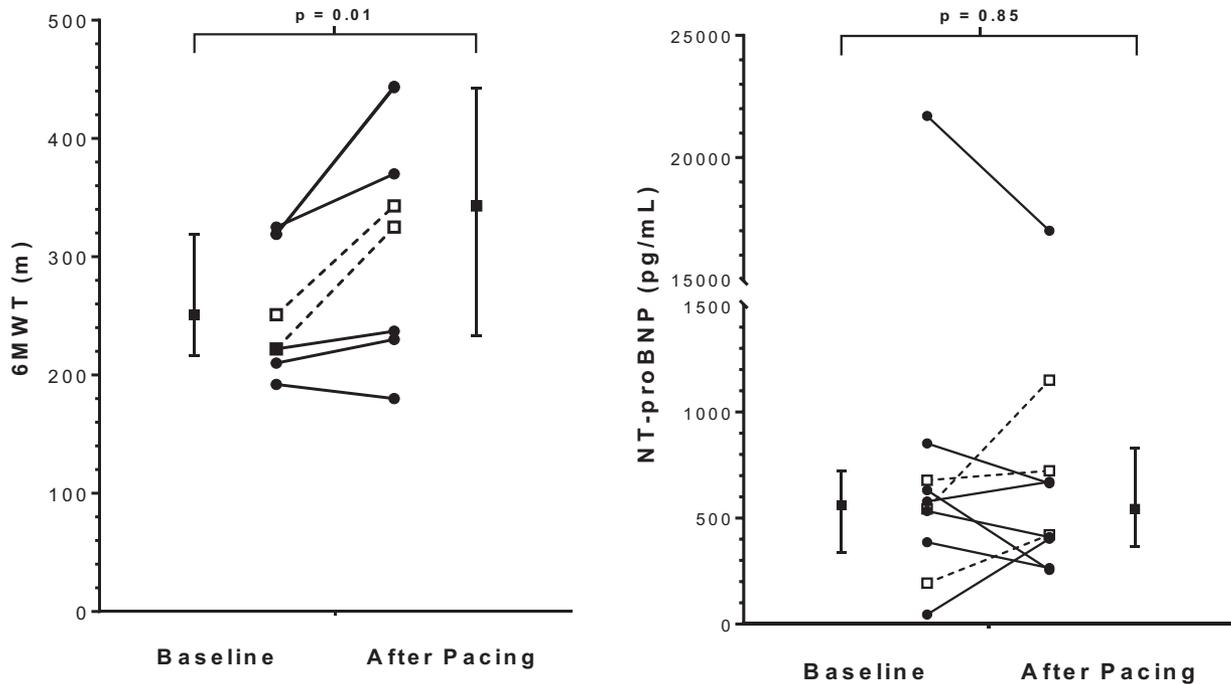


Fig. 2. Individual 6-minute walk test (6MWT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) data displayed with median \pm interquartile ranges. Open squares connected by dashed lines represent the patients on night pacing protocol who experienced inappropriate daytime pacing. Assessments and blood collection were made just prior (Baseline) and immediately after (After Pacing) programming.

have been associated with a poor prognosis, impaired coronary flow, and tachycardia-induced cardiomyopathy. Furthermore, pharmacologic heart rate lowering provides a marked mortality reduction in patients with HF_rEF. For these reasons, it has been widely assumed that the benefits of lower heart rates can be generalized to patients with HF_pEF. However, a review of the literature in patient populations with HF_pEF suggests detrimental effects of lower heart rates and reveal potentially beneficial effects of higher heart rates.⁹

To first evaluate this concept, we studied the effects of moderate heart rate elevations in a porcine model of concentric LVH and fibrosis.⁷ We observed that a pacemaker-mediated increase in heart rate by \sim 40% increased the end-diastolic volume by approximately one-third and reduced wall thickness by \sim 10% without changing LV mass or ejection fraction. We also found that these effects of heart rate could be readily titrated and did not result in neurohumoral activation or heart failure if the rate remained within the physiologic range. This study also confirmed previous studies that suggested that pacing-induced eccentric remodeling can reduce interstitial fibrosis.⁸

First Experience in Human Subjects

The primary focus of this exploratory study was to determine whether pacing at 100 beats/min during sleep would be tolerated and safe. This pacing rate was chosen because it is at the upper end of the physiologic resting range and has been reported to be safe in patients with atrial fibrillation.¹⁰ None of the study patients developed symptoms

during nocturnal pacing, nor did any develop symptoms or signs of heart failure, left ventricular dysfunction, or arrhythmias. Because the total amount of pacing was limited in both time and intensity, we did not expect to find any changes to LV function and geometry. Unexpectedly, the 6MWT improved after the pacing intervention in all but 1 subject. Although promising, these results must be viewed with caution because all patients were aware that they were receiving an experimental treatment that “exercises” the heart. It was also reassuring that the biomarker levels were unchanged.

Study Limitations

As discussed, the intervention was limited in time and intensity by the technologic constraints of the pacemaker features. The cause of the unintended and symptomatic accelerated daytime pacing outside of the therapeutic window was due to an interaction between our programming and pacemaker features that depend on heart rate and activity information collected throughout the day to automatically optimize the rate-adaptive pacing. We think that this limitation can be overcome by a dedicated algorithm that is inhibited by the activity response.

Future Studies

With the experience gained from this study, a multicenter, prospective, single-blinded trial (REVAMP, NCT03210402) will evaluate the safety and feasibility of a moderate heart rate elevation in a larger group of patients.

Conclusion and Outlook

Nocturnal pacing at a rate of 100 beats/min was well tolerated, and most patients demonstrated an improvement in 6MWT. There were no signals to suggest worsening heart failure, arrhythmias, or ischemia. Future evaluations of this approach will require a dedicated pacemaker function that allows for adjustments of treatment duration and intensity and conceivably patient feedback.

Disclosures

Medtronic supported this research project. The University of Vermont has filed for intellectual property protection for the use of pacemakers to prevent and treat HFpEF.

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Supplementary Data

Supplementary data related to this article can be found at [doi:10.1016/j.cardfail.2018.06.009](https://doi.org/10.1016/j.cardfail.2018.06.009).

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