PERSPECTIVES IN CONTRAST

Accelerated physiologic pacing in patients with heart failure with preserved ejection fraction: An argument in support of therapeutic heart rate modulation

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Early and contemporary therapies for heart failure with preserved ejection fraction

In the earliest heart failure guidelines, the primary therapeutic goal for patients with diastolic heart failure was "to reduce symptoms by lowering the elevated filling pressures without significantly reducing cardiac output."[1] Ten years earlier, a case series described a new clinical syndrome in elderly hypertensive patients with concentric hypertrophy, a small left ventricular (LV) cavity, and a supranormal left ventricular ejection fraction (LVEF) ≥65% who presented with dyspnea or chest discomfort.[2] Nine of the 21 patients received a beta-blocker or a calcium channel blocker and experienced symptomatic improvement. The authors likened this to the favorable response patients with hypertrophic cardiomyopathy experienced with these medications, thought to be due to "improvements in relaxation time and filling rate, a decrease in heart rate and thus prolongation of diastole, and an increase in end-systolic volume because of negative inotropic action."[2] The initial heart failure guidelines recommended beta-blockers and non–dihydropyridine calcium channel blockers to improve LV diastolic filling, relaxation, and compliance in patients with heart failure with preserved ejection fraction (HFpEF) while acknowledging that limited data supported this therapeutic strategy.[1,3,4]

Over the past 2 decades, clinical trials evaluating pharmacologic heart rate suppression in patients with HFpEF (now defined as LVEF ≥50%) have been neutral.[5,6] Moreover, these medications negatively affect exercise tolerance.[7,8] Therefore, despite being a part of the HFpEF treatment pathway in guidelines from 1995 to 2021,[1,3,4,9] negative chronotropic agents such as beta-blockers are no longer recommended except in the setting of concomitant atrial tachyarrhythmias.[10] Before recent trials showed that sodium glucose cotransporter-2 (SGLT-2) inhibitors reduce heart failure events and hospitalizations in patients with HFpEF,[11,12] effective therapies remained elusive. The pathophysiology of HFpEF is heterogeneous, with abnormalities at the cellular, organ, and system levels. However, the final common pathway of congestive symptoms, which affect quality of life, morbidity, and mortality, is the elevation of LV filling pressures at rest and with exercise.[13,14]

KEY FINDINGS

- The longstanding belief that slow heart rates benefit patients with heart failure with preserved ejection fraction (HFpEF) must be reconsidered.
- An important mechanism by which continuous, moderately accelerated physiologic pacing alleviates symptoms in patients with HFpEF *at rest* is by reducing cardiac filling pressures.
- With fully physiologic pacing (combining Bachmann bundle area atrial pacing with His-bundle or left bundle branch ventricular pacing), moderately accelerated pacing could be tailored to the individual patient without the offsetting effects of pacemaker-mediated dyssynchrony.
- Just as HFpEF and atrial fibrillation increase sharply with age, the prevalence of bradyarrhythmias due to cardiac conduction disease are projected to increase as the global population ages. Pacing is the only way to selectively increase the heart rate in patients with bradyarrhythmias at that occur at baseline or result from use of atrioventricular nodal blocking agents needed for another indication.
- Continuous accelerated physiologic pacing is a promising potential therapy for patients with HFpEF based on physiologic principles and hemodynamic pacing studies. Further multicenter, randomized studies are needed to prove and validate these hypotheses and findings.

KEYWORDS Heart failure with preserved ejection fraction; Heart rate modulation; Accelerated pacing; Conduction system pacing; Hemodynamics; Resting heart rate (Heart Rhythm O^2 2024;5:327–333)

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Targeting a persistent reduction in cardiac filling pressures

A pulmonary artery pressure–guided strategy to proactively reduce hemodynamic congestion was one of the first interventions to improve outcomes in patients with HFpEF.[15] Compared with usual care, heart failure hospitalizations were 46% lower in the treatment group in which diuretic therapy was adjusted based on an implantable continuous hemodynamic monitor.[15] This trial demonstrated that small but chronic filling pressure reduction significantly benefited these patients. A common thread among the handful of HFpEF clinical trials meeting their primary efficacy endpoint—pulmonary artery pressure–guided medical management,[15] therapeutic weight loss,[16] the glucagonlike peptide-1 receptor agonist semaglutide,[17] SGLT-2 inhibitors,[11,12] and moderately accelerated physiologic pacing[18]—is that these medications or therapeutic strategies result in a persistent reduction of cardiac filling pressures.[15,17–23] One of the proposed benefits of SGLT-2 inhibitors in HFpEF is a resetting of the internal volume setpoint to optimize volume status, facilitating diuresis during periods of hypervolemia while maintaining protective counterregulatory mechanisms to prevent hypovolemia, kidney injury, and neurohormonal activation during periods of euvolemia.[23,24] Obesity is a risk factor for HFpEF through various mechanisms, one of which involves hemodynamic derangements related to an increase in total blood volume and abnormal blood volume distribution.[13,21,22] Among the pleiotropic effects of weight loss in obese patients with HFpEF are the significant improvements in biventricular and atrial filling pressures.[17,22]

Relationship between resting heart rate and cardiac filling pressures in HFpEF

A hallmark of diastolic dysfunction in HFpEF is an exponential rise in the end-diastolic pressure–volume relationship (Figure 1).[25] With the prolongation of diastole that occurs with low heart rates, slight increases in left ventricular end-diastolic volume (LVEDV) and stroke volume come at the expense of exponential increases in left ventricular end-diastolic pressure (LVEDP) (Figure 1).[19,26–30] This translates to elevation in left atrial and upstream pressures with resultant atrial remodeling and secondary pulmonary hypertension, predisposing patients to atrial fibrillation (AF) and right ventricular dysfunction in the long term as well as pulmonary congestion in the near term.[19,31–33] An important mechanism by which physiologic accelerated pacing alleviates symptoms in patients with HFpEF *at rest* is by reducing cardiac filling pressures through heart rate modulation. Studies over the past 3 decades (Tables 1 and 2) consistently demonstrate that pacing at moderately higher heart rates moves the end-diastolic pressure–volume relationship curve down and to the left (Figure 1), reducing left-sided cardiac pressures.[19,26–30]

Heart rate has been a known determinant of myocardial performance since the 1870s, when physiologist Henry Bowditch observed that cardiac inotropy increases with faster heart rates (the force–frequency relationship). A positive lusitropic effect also occurs with faster heart rates (frequency-dependent acceleration of relaxation). In studies of patients with HFpEF *at rest,* diastolic function parameters do not deteriorate with faster pacing rates and, in some cases, significantly improve compared with baseline values during heart

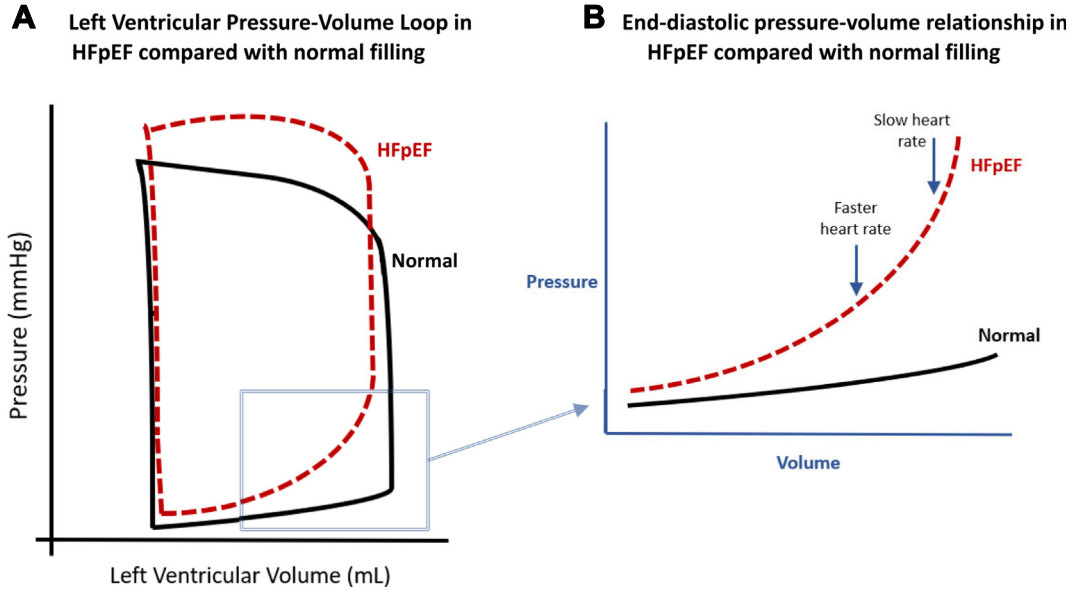

Figure 1 Left ventricular pressure–volume loops and end-diastolic pressure–volume relationship in heart failure with preserved ejection fraction (HFpEF) compared with healthy controls. **A:** In patients with HFpEF, passive stiffness increases the end-diastolic pressure-volume relationship (EDPVR) exponentially compared with normal diastolic filling. **B:** Prolongation of diastole at the steep portion of the diastolic pressure–volume line results in a slight increase in end-diastolic volume at the expense of exponential elevations in left ventricular end-diastolic filling pressure. At faster heart rates, left ventricular filling at end-diastole is shifted down and leftward on the diastolic pressure–volume line from the exponential to the more linear portion of the EDPVR in patients with HFpEF.

Table 1 Summary of atrial pacing hemodynamic studies in patients with HFpEF at rest

Study	Study population	Baseline heart rate in sinus rhythm* (bpm)	Atrial pacing rates (BPM)	Findings in HFpEF patients at faster heart rates compared with baseline
Liu et al[26] 1993	Adults with HFpEF (n = 10) and controls without heart failure (n = 8)	HFpEF: 80 ± 14 Control: 71 ± 9	100, 120, and 150	• ↓ in left ventricular end-diastolic pressure at faster rates • Stroke volumes ↓ to a similar extent between HFpEF patients and controls; cardiac output did not decrease • Improvement in parameters of active relaxation at faster rates
Yamanaka et al[27] 2006	Adults with HFpEF (n = 18) and HFrEF (n = 11)	HFpEF: 80 ± 11 HFrEF: 77 ±18	+20 and +40 above baseline	• ↓ in left ventricular end-diastolic pressure at faster rates
Sohn et al[28] 2007	Adults with diastolic dysfunction (n = 11) and controls (n = 8)	Not reported	80 and 120	• ↓ in left ventricular end-diastolic and left ventricular mean pressure at faster rates
Westermann et al[29] 2008	Adults with HFpEF (n = 70) and controls (n = 20)	HFpEF: 71 [65–82] Control: 76 [65–85]	120	• ↓ in left ventricular end-diastolic pressure (from median 16 mm Hg to 8 mm Hg) • Improvement in parameters of active relaxation • Stroke volumes ↓ but cardiac output ↑ compared with baseline (from median 6.8 to 8.2 L/min)
Wachter et al[30] 2009	Adults with HFpEF (n = 17) and controls (n = 7)	HFpEF: 66 [60–68] Control: 72 [67–90]	100 and 120	• ↓ in left ventricular end-diastolic pressure (from median 17 mm Hg to 8 mm Hg) • Improvement in parameters of active relaxation at faster rates • Cardiac index ↑ compared with baseline (but not statistically significant)
Silverman et al[19] 2020	Adults with HFpEF (n = 10) and controls presenting for AF ablation (n = 12)	HFpEF: 70 ± 9 Control: 65 ± 7	95 and 125	• ↓ in left ventricular end-diastolic pressure (from mean 17 mm Hg to 9 mm Hg) • ↓ in mean left atrial pressure (from mean 17 mm Hg to 12 mm Hg) • Systemic blood pressure did not change at faster rates

AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.
*Values are given as mean ± SD or median [interquartile range]

rates in the range of 60–70 bpm.[29,30] Importantly, the expected reduction in LVEDV and stroke volume with increased heart rate neither reduces cardiac output[29,30] nor affects systemic blood pressure.[19] In studies assessing cardiac output, it increases with accelerated pacing compared with baseline.[29,30] Finally, the decrease in LV end-systolic volume that occurs with moderately accelerated pacing is accompanied by a diastolic "suction" effect, which enhances early diastolic filling.[34,35]

Among patients with preclinical and overt HFpEF, lower resting heart rates are associated with higher natriuretic peptide levels and worsened diastolic function by echocardiographic parameters.[18,31,33] Lower heart rates increase central blood pressures[36,37] and LVEDP,[26–30] which contribute to increased wall stress, neurohormonal activation, and, over time, further ventricular stiffening and hypertrophy.[38,39] In clinical trials, targeting a lower heart rate in older patients with preserved LVEF ≥50% with or without clinical heart failure failed to show benefit and may be detrimental, with increased risk of incident AF and heart failure hospitalizations.[18,33,40–43]

Notably, the hemodynamic studies outlined in Tables 1 and 2 were conducted in patients with HFpEF who were paced at increasing rates while *at rest*. We cannot extrapolate these results to the complex interplay of physiologic and hemodynamic changes in this population during exercise. The recent RAPID-HF (Rate-Adaptive Atrial Pacing in Diastolic Heart Failure) study highlights this point. RAPID-HF was a

Table 2 Cardiac hemodynamics during atrial pacing in patients with heart failure with preserved ejection fraction at rest

Hemodynamic measures assessed	Hemodynamic values by paced heart rates	
Sohn et al[36] 2007	**Paced at 80 bpm**	**Paced at 120 bpm**
Stroke volume (mL)	51 ± 13	30 ± 7*
LV end-diastolic dimension (mm)	44 ± 3	39 ± 3
LV mean diastolic pressure (mm Hg)	~8 ± 3	~5 ± 3.5*
Westermann et al[37] 2008	**Sinus 71 [65–82] bpm**	**Paced at 120 bpm**
LVEDP (mm Hg)	16 [12–22]	8 [5–13]*
Stroke volume (mL)	94 [80–111]	72 [51–85]*
Cardiac output (L/min)	6.8 [5.5–8.0]	8.2 [5.9–10.8]*
LVEDV (mL)	151 [118–170]	109 [90–128]*
LVESV (mL)	59 [36–66]	52 [35–61]*
Wachter et al[38] 2009	**Sinus 66 [60–68] bpm**	**Paced at 120 bpm**
LVEDP (mm Hg)	16.8 [13.1–20.2]	8.3 [5.6–17.7]*
Silverman et al[22] 2020	**Sinus 70 ± 9 bpm**	**Paced at 125 bpm**
Mean left atrial pressure (mm Hg)	17 ± 6	12 ± 3*
LVEDP (mm Hg)	17 ± 5	9 ± 3*
LVEDV/body surface area (mL/m^2)	37 ± 9	25 ± 8*
LVESV/body surface area (mL/m^2)	14 ± 5	10 ± 5*

Values are given as mean ± SD or median [interquartile range].

LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

*Significantly different compared with baseline.

single-center, double-blind, randomized crossover trial that evaluated rate-adaptive atrial pacing during exercise specifically, *without alteration of resting heart rate*, in 29 patients with HFpEF and chronotropic incompetence.[44] Rate-adaptive pacing did not improve oxygen consumption at anaerobic threshold, quality of life, or N-terminal pro–brain natriuretic peptide (NT-proBNP). Similar to these findings, a prespecified subgroup analysis of the *my*PACE study found no incremental benefit of rate-adaptive pacing in addition to resting heart rate modulation in HFpEF patients.[18] Activity levels among patients with HFpEF are notoriously low; in the *my*PACE study, patients were active for just 10% of the day before randomization, based on device-detected activity levels.[18]

Building on these hemodynamic studies in patients with HFpEF at rest (Tables 1 and 2) and previous HFpEF trials showing the benefits of persistent cardiac decongestion, a robust treatment response is more likely with a pacing intervention that provides continuous resting heart rate modulation than with rate-adaptive pacing, which is active only during the limited periods of physical exertion.

Resting heart rate modulation: A therapeutic target in HFpEF

In a pilot crossover study in patients with HFpEF and preexisting pacemakers, investigators of the Heart Rate-80 study increased the pacemaker backup rate from the nominal 60 bpm (baseline) to 80 bpm for 4 weeks in 20 patients with preclinical or overt HFpEF.[45] After 4 weeks at the higher rate, investigators turned the programmed lower rate back to 60 bpm. The temporary 20-bpm increase significantly improved quality-of-life scores and 6-minute walk distance. Outcomes worsened when pacing returned to the nominal setting. Patients with Bachmann bundle area and His-bundle leads benefited the most, highlighting the importance of the pacing approach. Based on these results, the single-center *my*PACE blinded, randomized controlled trial included only stage B and C HFpEF patients with pre-existing pacing systems that would not induce dyssynchronous right ventricular pacing at higher rates (ie, only patients with atrial ± conduction system or biventricular pacing were included). In the *my*PACE trial, an accelerated personalized pacing rate that resulted in a 10-bpm average increase in heart rate over 1 year (*my*PACE group: median heart rate 75bpm) improved quality of life, NT-proBNP levels, physical activity, and AF burden compared with the standard lower rate setting of 60 bpm (usual care: median heart rate 65 bpm).[18]

The decrease in hemodynamic congestion and myocardial wall stress with continuous accelerated pacing is reflected in the reduction in NT-proBNP.[18,46] Accumulating secondary effects of chronic decongestion (less orthopnea, better sleep, increased energy, and physical activity levels) may potentiate benefits over time.[18,43,46] Moderately accelerated pacing improved functional capacity in the Heart Rate-80 study and improved activity levels by 30% in the *my*PACE study,[18,46] which has important downstream health benefits.[46–48] Patients with a relatively low burden of AF benefited the most in *my*PACE,[18] suggesting that accelerated pacing prevented or slowed detrimental atrial structural and electrical remodeling, likely due to left atrial unloading.[49] In a preliminary 3-year follow-up analysis of the *my*PACE study, there was a significant reduction in the primary clinical event composite outcome in the *my*PACE group compared with usual care, predominantly driven by fewer heart failure events.[43]

Chronic heart rate augmentation may also stimulate LV eccentric remodeling in HFpEF, as demonstrated in a

preclinical study[50] and a secondary analysis of echocardiograms of *my*PACE participants.[51] Normal aging results in a 15%–20% reduction in LVEDVs and an unfavorable increase in the ventricular mass-to-volume ratio.[49,52,53] Continuous accelerated pacing may partially restore LV volumes and improve mass-to-volume ratios and distensibility over time.[51,52] Patients with preclinical HFpEF also responded to accelerated pacing in the *my*PACE and Heart Rate-80 studies,[18,46] suggesting that a greater number of patients in the early stages of HFpEF may benefit from higher heart rates when the disease progression is still modifiable. The PACE HFpEF (Physiologic Accelerated Pacing as a Treatment in Patients With Heart Failure With Preserved Ejection Fraction) study will quantify the degree of cardiac remodeling induced by accelerated pacing with serial cardiac MRIs.[54]

Moderately accelerated pacing implementation: As physiologic as possible

Based on the known harmful effects of dyssynchronous right ventricular[55] and perhaps right atrial appendage pacing,[56,57] the optimal way to institute heart rate modulation via pacing is to recapitulate physiologic cardiac activation as closely as possible.[58,59] In the *my*PACE study, one-third of patients had Bachmann bundle area atrial leads,[58,60] and right ventricular septal pacing occurred <0.5% of the time over the 1-year study period in both the *my*PACE and control groups. Because ventricular pacing was primarily via His-bundle or left bundle branch area pacing (n = 31), this may have provided synergistic benefits by improving synchronous activation and relaxation in patients with HFpEF and conduction abnormalities.[61,62] Systolic and diastolic mechanical dyssynchrony is common among patients with HFpEF, the extent of which correlates with the magnitude of diastolic dysfunction, LV hypertrophy, and aerobic limitations.[63] Because diastole represents approximately two-thirds of the cardiac cycle at resting heart rates, restoring synchronous relaxation may be an important untapped therapeutic target in this population.[62–64] Combining Bachmann bundle area atrial pacing with His-bundle or left bundle branch ventricular pacing can maintain or restore normal, physiologic interatrial, atrioventricular, and interventricular activation during accelerated pacing.[55,58,59,61]

Withdrawal of heart rate–lowering medications, such as beta-blockers, in patients without a clear indication is the simplest way to liberalize the heart rate in patients with HFpEF. However, physiologic pacing is the most effective way to institute accelerated heart rate modulation for patients with indications for such medications (ie, AF) or bradyarrhythmias due to conduction system disease. Among patients with HFpEF, the prevalence of AF is between 40% and 60%,[64] which partially explains why over two-thirds of patients with HFpEF are treated with beta-blockers in contemporary studies.[41,42,65] In addition, just as HFpEF and AF increase sharply with age, the incidence of cardiac conduction disease requiring permanent pacing is projected to increase as the global population ages.[66,67] The prevalence of bradyarrhythmias requiring pacemaker implantation occurred in 1 in 5 HFpEF patients in a recent registry study.[68] The number of patients with preclinical (stage B) HFpEF and pacing indications likely is higher. Pacing is the only way to selectively increase heart rate in patients with bradycardia or those with concomitant use of atrioventricular nodal blocking agents used for another indication. Additional advantages of pacemakers are that the heart rate can be titrated to individual response, and patient compliance is not an issue.

Conclusion

As our understanding of HFpEF has evolved, so have the guideline recommendations for its management. The pathophysiology of HFpEF is complex, and the patients affected are heterogeneous. However, a primary treatment goal for HFpEF remains "to reduce symptoms by lowering the elevated filling pressures without significantly reducing cardiac output."[1] Accelerated physiologic pacing may provide an effective, individualized, and titratable strategy to achieve this goal, particularly as the number of patients with preclinical or overt HFpEF, conduction system disease, and AF continues to increase with the aging global population. To date, this concept has only been tested in patients with standard pacing indications and specialized pacing systems. If accelerated physiologic pacing also induces beneficial cardiac remodeling, this could expand the therapeutic indication in patients with HFpEF. Continuous accelerated physiologic pacing is a promising potential therapy for patients with HFpEF based on physiologic principles and hemodynamic pacing studies. Further multicenter, randomized studies are needed to prove and validate these hypotheses and findings.

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