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Personalized accelerated physiologic pacing

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Heart failure with preserved ejection fraction (HFpEF) is increasingly prevalent with a high socioeconomic burden. Pharmacological heart rate lowering was recommended to improve ventricular filling in HFpEF. This article discusses the misperceptions that have resulted in an overprescription of beta-blockers, which in all likelihood have untoward effects on patients with HFpEF, even if they have atrial fibrillation or coronary artery disease as a comorbidity. Directly contradicting the lower heart rate paradigm, faster heart rates provide haemodynamic and structural benefits, amongst which lower cardiac filling pressures and improved ventricular capacitance may be most important. Safe delivery of this therapeutic approach is feasible with atrial and ventricular conduction system pacing that aims to emulate or enhance cardiac excitation to maximize the haemodynamic benefits of accelerated pacing. This conceptual framework was first tested in the myPACE randomized controlled trial of patients with pre-existing pacemakers and preclinical or overt HFpEF. This article provides the background and path towards this treatment approach.

> The real voyage of discovery consists not in seeking new landscapes, but in having new eyes — Marcel Proust (paraphrased from La Prisonnière, 1923)

Introduction

Pharmacological heart rate lowering in patient populations with normal ejection fractions was never proven to be efficacious and may well contribute to both heart failure with preserved ejection fraction (HFpEF) of 50% or higher and atrial fibrillation (AF).[1-3] On the contrary, higher than normal resting heart rates provide haemodynamic and structural benefits. This was the basis for the conceptual framework of heart rate modulation and accelerated pacing as a novel treatment approach for HFpEF and AF. In this article, we will discuss the history of the 'lower heart rate is better paradigm', salutary and adverse effects of beta-blockers, and the effects of heart rate modulation on haemodynamics and the myocardium, which resulted in a programmatic effort to assess the benefits of personalized accelerated physiologic pacing that culminated in the myPACE trial.

Heart rate lowering and diastolic function

There are substantial misperceptions about the effects of heart rate on cardiac function and structure that become clearer in a historical context. The following summarizes a few premises that have led to misunderstandings of pathophysiology and misappropriation of the evidence basis.

Premise #1: heart rate lowering is beneficial

In 1912, the German physiologist Erwin Rhode described that heart rate and blood pressure determine myocardial oxygen consumption.[4] This finding helped physicians realize that lower heart rates and/or blood pressures reduce myocardial ischaemia and effort angina. The advent of propanolol in 1964[5] provided a pharmacological means to

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simultaneously reduce blood pressure and heart rate to lay the foundation for the concept that beta-blockers and heart rate lowering may have cardioprotective effects. In a case series of 21 patients presenting with hypertensive heart failure and preserved systolic function in 1985, Topol *et al.*[6] posited that patients may benefit from pharmacological prolongation of diastole to provide more time for diastolic filling. Despite the absence of randomized controlled trials that confirmed this hypothesis, heart rate suppression with beta-blockers was rapidly adopted and integrated into the heart failure treatment guidelines. The pervasiveness of this paradigm and the ensuing guideline recommendations have contributed to the widespread use of beta-blockers such that they are currently the most prescribed class of medications in HFpEF.[7-9] The modest mortality benefit of beta-blockers in coronary artery disease after myocardial infarction has not been recapitulated in the modern era of reperfusion therapies that aim to preserve ejection fraction.[10,11] This has led to a withdrawal of the beta-blocker recommendation in the 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guidelines for the treatment of coronary artery disease, with exceptions for angina pectoris, recent myocardial infarction, and reduced ejection fraction.[12] It was the evidence from randomized myocardial infarction studies in the modern era of coronary revascularization that led Bangalore *et al.*[11] point out that beta-blocker use increases the risk for heart failure.

Premise #2: beta-blockers are beneficial in heart failure

Controlled randomized trials unequivocally demonstrated that metoprolol, carvedilol, and bisoprolol reduce heart failure–related morbidity and mortality in patients in sinus rhythm and heart failure with reduced ejection fraction (HFrEF).[13] However, patients with AF do *not* derive a morbidity and mortality benefit in the HFrEF trials of beta-blockers.[13,14] Similarly, in two underpowered subgroup analyses of patients with HFpEF, there was no discernible advantage of beta-blockers.[13,15]

Furthermore, in hypertension trials, beta-blockers were found to be inferior when compared with angiotensin receptor blockers, calcium channel blockers, and thiazides, driven by an excess of cardiovascular events such as stroke.[16-18] The guideline-based recommendations for AF rate control favouring beta-blockers have been based on expert opinion predominantly informed by observational analyses without evidence from large randomized trials that compared beta-blockers with placebo or alternative rate control agents.[19]

Premise #3: heart failure with preserved ejection fraction and atrial fibrillation are twin conditions

Both HFpEF and AF are found in above middle-age patients with hypertensive heart disease with progressive diastolic dysfunction that originates from an interdependent deterioration of the atrial and ventricular myocardial substrate. About half of patients with HFpEF have AF and many patients with incident AF will later develop overt HFpEF.[7,20,21] Specific to this context, many clinicians assume that if beta-blockers provide rate control in AF, at a minimum, they should not be harmful in patients with HFpEF and/or AF.

Premise #4: sub-specialization and reliance on expert opinion

Cardiology is an increasingly complex field, which has led to sub-specialization that increases practitioner's reliance on expert opinion. The lack of crosstalk between sub-specialities' creates vulnerabilities, wherein important findings in one area may not change practice in another; hence, the slow speed with which the evidence of inferiority of beta-blockers as an antihypertensive agent, or the lack of benefit in HFrEF with AF, has altered their use as first-line therapy in AF.

Beta-blockers and heart rate lowering: experience, evidence, and concerns

The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS ischaemic heart disease guidelines poignantly summarize the unfavourable effects of beta-blockers as follows: 'the principle adverse effects of beta-blockers are fatigue, exercise intolerance, lethargy, insomnia, nightmares, and impotence'.[22] Applying the basic principle of clinical practice, *primum non nocere*, to the use of beta-blockers, the mortality and morbidity advantages should be marked and unequivocal to outweigh the substantial number of undesirable effects. As discussed above, the only condition with an unambiguous evidence basis is HFrEF with sinus rhythm, but not other conditions where beta-blockers are commonly prescribed. The National Health and Nutrition Examination Survey determined in 2015 that ~11% of the adult US population receive beta-blockers,[23] while only ~1% of the population has HFrEF.[24]

As stated, without any evidence from clinical trials, it is a long-standing dogma that prolongation of diastole by slowing the heart rate is beneficial in HFpEF, which has contributed to beta-blocker prescription rates between 80 and 86% in contemporary HFpEF cohorts and trials.[7-9] To further study the proposed benefits of lower heart rates, ivabradine, a sinus node-specific inhibitor, was evaluated in a trial of 179 HFpEF patients with resting heart rates of 70 b.p.m. or higher.[25] The findings were neutral and did not reveal any benefit. More recently, it was documented that beta-blocker discontinuation in patients with HFpEF can improve natriuretic peptide levels and exercise capacity.[26,27] This may have contributed to a 2022 AHA/ACC/HFSA heart failure guideline committee decision to rescind the previous recommendation for beta-blockers in HFpEF, which had been in place since 1995.[24] In a recent article from our group, we discussed that the evidence basis for beta-blockers for rate control for AF is similarly weak and pointed to randomized studies and analyses which indicate that beta-blockers may be inferior to other rate-control medications such as digoxin and non-dihydropyridine calcium channel blockers.[3]

But is there really any high-quality evidence that links pharmacological heart rate lowering to adverse clinical outcomes? The 2006 guideline-influencing RACE II AF trial, which compared strict and lenient rate control, provided an early glimpse into the potential adverse effects of heart rate suppression.[28] Compared with a

heart rate goal of 80 b.p.m. or lower, there was a numerical signal towards fewer adverse outcomes in the group of patients with rates up to 110 b.p.m. In the year prior, a large randomized hypertension trial that compared atenolol and losartan[16] revealed that the relative risk of developing AF was ~30% higher with atenolol.[29]

Adverse effects of heart rate lowering were obvious in a 19 102 patient outcomes trial of ivabradine in coronary artery disease without heart failure at baseline. The highly selective suppression of sinus node activity by ivabradine reduced heart rates by ~10 b.p.m., which improved angina pectoris, similar to beta-blockers.[30] However, amongst the group of patients with activity-limiting angina, the relative risk of death and myocardial infarction increased by 18% with ivabradine, indicating that antianginal heart rate lowering may have untoward effects on clinical outcomes in this high-risk subgroup. Even more startling, the relative risk for new-onset heart failure and AF increased by 20 and 40%, respectively. Following these lines of evidence, we conducted secondary analyses of the TOPCAT HFpEF trial of spironolactone and the SPRINT hypertension trial that confirmed that beta-blocker use was associated with an excess risk of heart failure and AF, likely driven by lower heart rates as the culprit.[31–33] These data support our contention that beta-blocker use generally, and heart rate lowering specifically, are associated with an increased risk for incident heart failure and AF. The question that arises is: how is it that heart rate suppression can lead to adverse clinical outcomes?

Lower than normal heart rates impair diastolic filling

Heart rates are optimized to the physical properties of the heart and body size. Case in point is the heart rate distribution amongst mammals, i.e. mice have rates in excess of 500 b.p.m., whereas blue whales have heart rates as low as 2 b.p.m.[34,35] The relationship of body size and heart rate is recapitulated across human growth to explain why newborns commonly have pulse rates above 120 b.p.m.[36] Thereafter, heart rates fall with age while the principal association of body size and resting heart rate is maintained.[37] The roughly 5 b.p.m. difference in the average resting heart rate between women and men can be explained by the height difference. On first sight, such differences appear of little relevance but in the following, we will argue that changes below or above individual set points have meaningful haemodynamic and structural consequences.

Haemodynamic effects of below normal heart rates

The main mechanism whereby below normal heart rates are detrimental involves the abnormal prolongation of left ventricular filling. The added ventricular blood volume in end-diastole produced by atrial contraction is countered by an exponential rise in resistance from the ventricular myocardium due to passive stiffness.[2] This is not much of a problem in healthy hearts with compliant myocardium. However, with ageing and in patients with hypertensive remodelling, blood volume expansion and lower than normal heart rates lead to a disproportionate rise in filling pressures that increase wall stress in both atria and ventricles, as shown in *Figure 1*. Resultant elevations in left atrial pressure are the cardinal source of dyspnoea and contribute to atrial myopathy and AF.[21] Low heart rates also slow myocardial relaxation kinetics and increase central blood pressures by activation of the Frank–Starling mechanism and reflected peripheral pressure waves superimposed onto late systole, which may provide an added stimulus for concentric remodelling.[38] It was proposed that this increase in central blood pressure contributes to the higher risk of stroke with beta-blockers in the aforementioned hypertension trials.[39]

It is important to acknowledge that a well-established age-dependent left ventricular volume loss and increasing wall thickness, which starts in midlife, plays a concomitant role in the reduction of myocardial compliance.[40] Consequently, stroke volumes fall and cardiac output is only maintained if the heart rate increases. However, the available population data suggest that resting heart rates remain stable from adulthood into senescence,[36,41] leaving many older adults in a relative state of sinus bradycardia. In other words, resting heart rates between 60 and 70 b.p.m. are likely too low for the majority of concentrically remodelled hearts that—based on the altered physical properties described—would function more optimally at higher rates. This pathological mechanism also links sinus node dysfunction, atrial myopathy, and atrial arrhythmias.[42]

Myocardial remodelling by heart rate modulation

Heart rates both above and below an ideal range will not only effect haemodynamics, they will also lead to structural changes due to remodelling of the myocardium. Generally, below normal heart rates induce concentric remodelling with reduction of ventricular volumes, whereas above normal heart rates result in eccentric remodelling and dilation. Hence, sinus rate lowering with beta-blockers or ivabradine reduces left ventricular size in HFrEF, which improves systolic function,[24,43] while prolonged exposure to high heart rates, i.e. AF with rapid ventricular conduction, drives eccentric remodelling and left ventricular dilation. Reestablishing a lower heart rate by restoring sinus rhythm is sufficient to return the heart to normal dimensions and function in the case of tachycardia-induced cardiomyopathy.

Despite the importance of myocardial plasticity in health and disease, i.e. athletics and heart failure, the mechanisms that govern heart rate-induced remodelling have not been characterized. Such profound changes in cardiac structure and function are only possible with an orchestrated and tightly synchronized change in gene expression that not only affects the shape and function of cardiac myocytes but also necessitates the inclusion of cells that define the extracellular matrix, conduction system, and cardiac vasculature. Analogous to the regulation of the plasticity of skeletal muscle, it is likely that myokines, which are frequently mistaken as inflammation factors, play key roles.[44] How the heart is

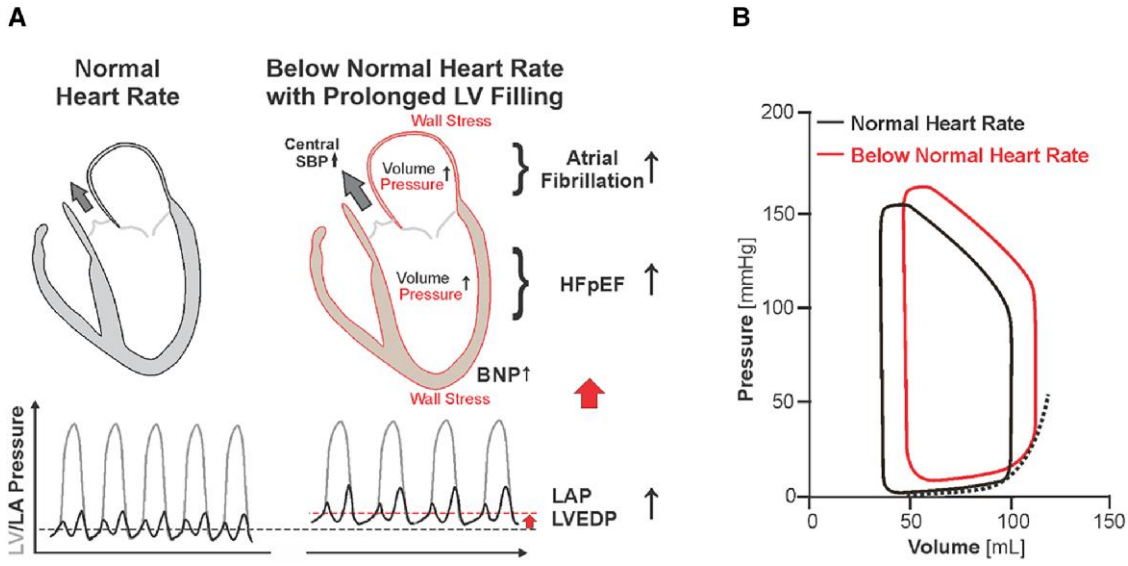

Figure 1 Effects of below normal heart rates on intracardiac haemodynamics. (*A*) Below normal heart rates lead to intracardiac congestion due to prolonged diastolic filling. The added blood volume is encountering opposing forces from the increasingly less compliant left ventricular myocardium, an effect that is disproportionally pronounced in hypertensive heart disease and heart failure with preserved ejection fraction. This increases both atrial and ventricular filling pressures and wall stress, which raises the risk for incident heart failure with preserved ejection fraction and atrial fibrillation. (*B*) Rightward shift of the pressure–volume loop with prolonged ventricular filling (rightloop). Left ventricular end-diastolic pressure (right lower corner of the loop) rises while following the end-diastolic pressure–volume relationship that is exponential in heart failure with preserved ejection fraction (dotted line). LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure.

sensing changes in heart rate to initiate differential gene expression is unknown but an area of particular interest in our group. Our analysis of gene expression signatures of left ventricular biopsies obtained from HFpEF patients with and without AF is providing first insights into the dysregulation of key regulatory proteins that contribute to concentric remodelling in HFpEF.[45]

Higher than normal heart rates improve diastolic filling

The advent of cardiac pacing led to the finding that accelerated atrial pacing resulted in marked reductions in filling pressures in patients.[46] This basic observation was overshadowed by subsequent haemodynamic studies in patients with hypertrophic cardiomyopathy and myocardial ischaemia where pacing resulted in higher end-diastolic pressures, which was confirmed *in silico*.[47-49] The finding that filling pressures disproportionately increase in HFpEF with exercise strengthened the belief that diastolic pressures would rise in response to higher heart rates.[50] However, the results by Westermann *et al.*[51] and Wachter *et al.*[52] clearly demonstrated that left-sided filling pressure decreased when HFpEF patients were paced from the atrium at rates up to 120 b.p.m. When compared with the resting heart rate, left ventricular end-diastolic pressure strikingly normalized (from 17 to 8 mmHg) at 120 b.p.m. while end-diastolic, end-systolic, and stroke volumes declined. In left atrial pressure recordings, we confirmed that HFpEF patients derive a marked haemodynamic benefit from pacing that results in lower atrial and ventricular filling pressures.[53] These findings suggested that accelerated pacing may present a treatment opportunity aimed at preventing incident AF and HFpEF, by intracardiac decongestion.[54]

In addition, *ex vivo* pacing experiments in myocardial strip preparations obtained from HFpEF patients during open heart surgery revealed that cytosolic calcium levels and diastolic tone increased disproportionately in HFpEF myocardium in response to pacing at sequentially higher rates.[55-57] This provided a mechanism for the observed improvements in filling pressures described above.[54] Nevertheless, the sarcoplasmatic reticulum-mediated acceleration of relaxation kinetics at higher rates, a key component of the force–frequency relationship,[58,59] was principally preserved, providing some reassurance that contraction amplitudes would not be adversely affected at higher heart rates.[60]

Steps towards a clinical trial

As discussed, elevated left atrial pressures are a central source of dyspnoea in HFpEF. This is especially true at night, when patient alleviate their symptoms by raising their chest position to reduce filling pressures, for example, with pillows, giving us the clinical symptom of orthopnoea. Affected patients tend to have interrupted sleep patterns that can result in paroxysmal nocturnal dyspnoea. We reasoned that patients may benefit most from filling pressure reductions at night, when heart rates are the lowest and filling pressures are predictably higher. We also surmised that improvements in sleep might lead to secondary gains in heart failure-related quality of life, which may positively affect activities of daily living. This symptom-focused approach differs substantially from most treatment interventions tested in HFpEF that focus on demonstrating improvements in

exercise tolerance. Nevertheless, it is our clinical impression that the majority of HFpEF patients are more interested in a better quality of life than improving peak exercise. We therefore decided to first test the concept of accelerated pacing at night.

The nocturnal heart rate 100 study

To first explore this approach, we screened for 10 patients with pacemakers and evidence of diastolic dysfunction. Pacemakers were programmed to preferentially deliver atrial pacing in the DDD(R) mode at a rate of 100 b.p.m. from midnight to 5 a.m. over 1 month without changing the lower rate.[61] To deliver such rate windows in an automated fashion, we inverted the pacemaker's 'sleep function' to be active between 5 a.m. to midnight to provide the lower pacing rate during the day. This pilot study revealed that accelerated pacing at night was tolerated without adverse signals. Some patients reported improvements in symptoms and demonstrated an increase in their 6 min walk distance.

The lower rate 80 study

After the encouraging results with nocturnal pacing, we tested if a permanent rise in the lower rate setting to 80 b.p.m. for 1 month would provide sustained haemodynamic benefits. Patients were assessed at baseline and at 1 month of lower rate pacing at 80 b.p.m., and 2 weeks after returning the lower pacing rate to 60 b.p.m. The key finding of this 20 participant study was that patients with atrial pacing from Bachmann's bundle and ventricular conduction system pacing had a 46% reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of myocardial wall stress at 80 b.p.m., when compared with a 4 and 13% change with pacing from the right atrial appendage and right ventricular apical septum (interaction P-value $= 0.04$). Conversely, patients with a paced QRS duration of >150 ms—most often due to the presence of a right ventricular lead—appeared to benefit the least.

Design of the myPACE trial

The results from the observational pilot studies allowed for power calculations for a pragmatic randomized clinical trial in patients with pre-existing pacemakers with a focus on the changes in heart failure-related quality-of-life scores as a main outcome using a validated instrument—the 21-item Minnesota living with heart failure questionnaire (MLHFQ). Secondary efficacy endpoints were NT-proBNP levels, pacemaker-detected physical activity, and AF burden with a 1-year follow-up.[62,63]

The cohort of pacemaker patients at the University of Vermont Medical Center was particularly well suited because it is a large referral centre and all implanters emphasize physiologic pacing in an attempt to maintain or optimize physiologic atrial and ventricular conduction.[64,65] The goal of only enrolling patients with pacemaker systems emulating normal excitation was to maximize the haemodynamic benefit of accelerated pacing while mitigating opposing negative effect from dyssynchrony. In addition, allowing enrolment of patients with preclinical HFpEF with echocardiographic features of hypertensive heart disease without overt heart failure might demonstrate that accelerated pacing could benefit an even larger population as a *preventative* strategy, especially when compared with pacing systems programmed to the current nominal lower rate setting of 60 b.p.m.

The question remained what an optimal heart rate should be? Based on our results that left atrial pressures improve with rates up to 125 b.p.m., the results of the RACE II AF trial suggesting that ventricular rates as high as 110 b.p.m. may be safe, and our nocturnal pacing data indicating that night heart rates of 100 b.p.m. were tolerated, heart rate elevations up to 125 b.p.m. could be considered. However, the results in our preclinical hypertensive heart disease porcine model (Stage B HFpEF) clearly demonstrated that even moderate heart rate elevations induced eccentric remodelling with concomitant reductions in ejection fraction. Raising the heart rate by a factor of 1.6 in micro-swine (from 93 ± 6 to 150 b.p.m.) increased left ventricular end-diastolic volumes by $54 \pm 3\%$ ($P < 0.01$), whereas ejection fractions fell from 58 ± 1 to $45 \pm 1\%$ ($P < 0.05$).[60] After pacing rates were lowered from 150 to 125 b.p.m., left ventricular dilation reverted to about half while ejection fractions rose to the lower limits of normal. In this heart rate range, blood levels of B-type natriuretic peptide (BNP), noradrenaline, and galectin-3, all biomarkers of heart failure, remained within normal limits and none of the animals developed signs or symptoms of heart failure even when paced for extended periods.[60] These results suggested that pacing remodelling at moderately elevated rates was physiologic and that the drop in ejection fraction was more comparable to the changes seen in extreme endurance athletes than being pathologic.[66,67] We therefore anticipated that with accelerated pacing, some patients with ejection fractions at the lower limits of normal, i.e. 50–55%, would experience a reduction in ejection fraction below 50% as part of the pacing remodelling. As this would raise concerns for a transition towards HFrEF, we aimed to provide patients with an ejection fraction of 50% with a 'normal' resting heart rate, knowing that this would still exceed their sleep heart rate by ~10 b.p.m. to provide a nocturnal haemodynamic benefit.[68]

The allometric heart rate–height relation of humans between ages five and adulthood obtained from national registry data—revealed a linear relationship that could be used to provide personalized heart rates, as shown in *Figure 2*.[37] As previously mentioned, heart rate differences between adult males and females are largely accounted for by the difference in height. As supranormal ejection fractions, i.e. 65% and higher, are typically a reflection of a small chambers size with concentric remodelling, we developed an algorithm that would use an ejection fraction of 50% as a pivot. Patients with ejection fractions above 50% would receive incrementally higher heart rates that would produce more eccentric remodelling to recoup some of the left ventricular volume losses that are part of normal ageing and an independent predictor of heart failure.[40,69] The equation was fitted across the ejection fraction spectrum so that patients with reduced ejection fractions would have heart rates found to be efficacious in HFrEF trials of beta-blockers and ivabradine.[24,70] The reduced ejection fraction side of the equation may be

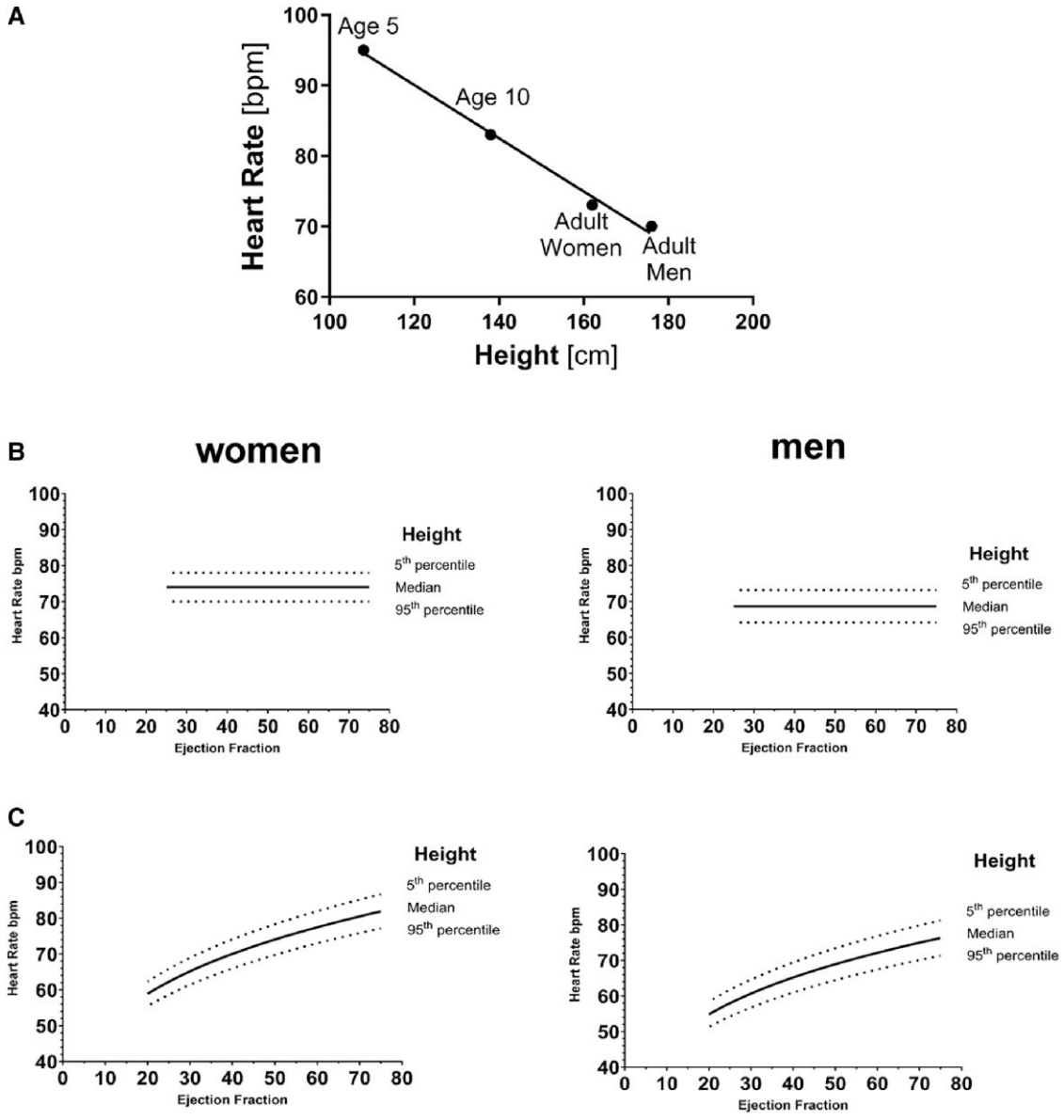

Figure 2 Height–heart rate relationship. (*A*) The human height and resting heart rate relationship. Linear regression of height and resting heart rate obtained from group medians of national survey and growth chart data. (*B*) Ranges of personalized heart rates (5th percentile, median, and 95th percentile) without consideration of ejection fraction in both women and men. (*C*) The modified personalized heart rate algorithm used in myPACE with an ejection fraction 50% pivot. (Personalized HR (b.p.m.) = (height [cm] × -0.3744) + 134.82) × $\sqrt{\sqrt{}}$ (ejection fraction [%]/50). A patient with an ejection fraction of 50% will be treated with a normal resting heart rate for their height to minimize the risk of ejection fraction reductions. At higher ejection fractions (>50%), patients are treated with incrementally higher heart rates to produce eccentric remodelling.

useful in the future to optimize pacemaker settings for patients with a dilated cardiomyopathy to support reverse remodelling towards normal left ventricular dimensions and function.

The myPACE trial started to enrol patients in the summer of 2019. The basic design and timeline is provided in *Figure 3*.[71]

Key findings of the myPACE trial

The main findings of the myPACE trial have been reported.[72] Briefly, in patients with clinically indicated pacemakers who had subclinical or overt HFpEF, treatment with a personalized accelerated pacing rate (myPACE) that increased mean heart rates from 65 to 75 b.p.m. resulted in substantial improvements in health-related quality of life measured by the MLHFQ instrument when compared with the standard lower rate setting of 60 b.p.m. (usual care), as shown in *Figure 4*. With personalized accelerated pacing, the median (interquartile range) MLHFQ score improved from 26 (8-45) to 9 (4-21) ($P < 0.001$) and worsened with usual care from 19 (6-42) to 27 (7-52) ($P = 0.03$). N-terminal pro-brain natriuretic peptide levels, physical activity, and device-detected AF also improved in the

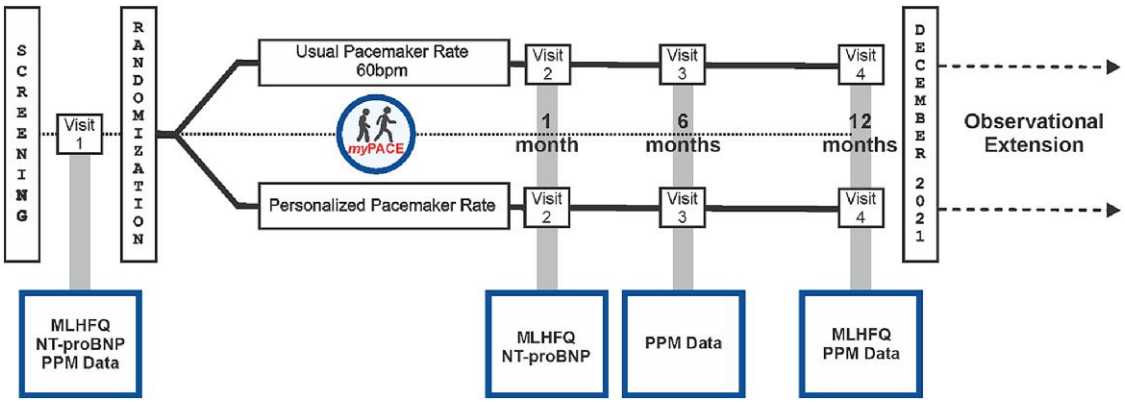

Figure 3 myPACE study design and flow. Pacemaker clinic patients at the University of Vermont Medical Center were consecutively screened. Those enrolled completed a Minnesota Living With Heart Failure Questionnaire, N-terminal pro-brain natriuretic peptide level, and a pacemaker interrogation. Patients were then randomized to a personalized pacemaker rate (myPACE) or remained at the nominal rate of 60 b.p.m. (Usual care) for 1 year. N-terminal pro-brain natriuretic peptide levels were repeated at 1 month and the Minnesota living with heart failure questionnaire was repeated at 1 month and 1 year. Pacemaker data and clinical outcomes were monitored continuously over the course of 1 year. NT-proBNP, N-terminal pro-brain natriuretic peptide.

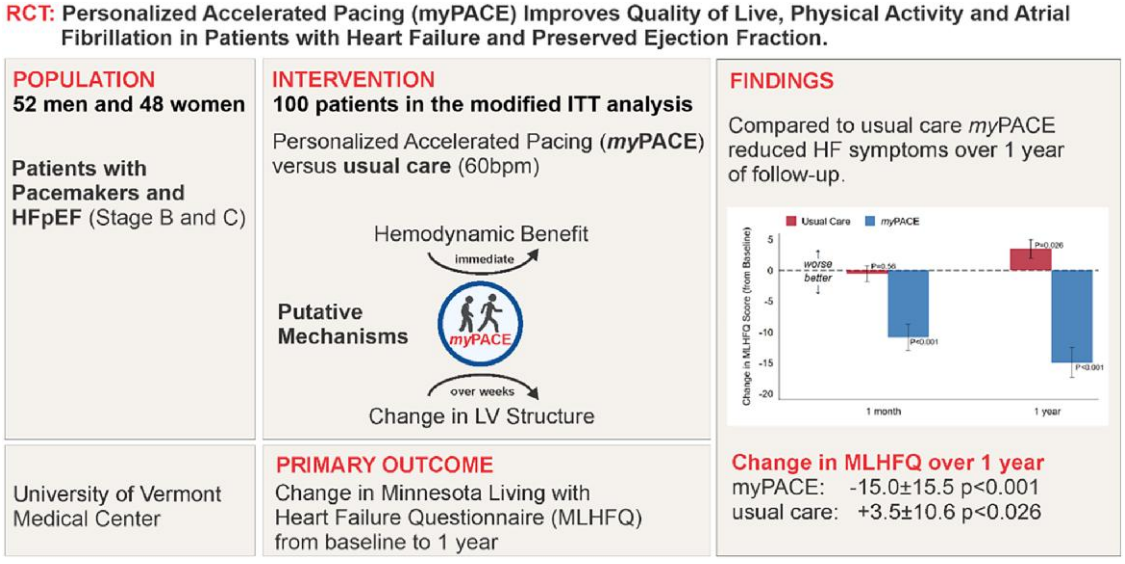

Figure 4 Primary outcome of the myPACE randomized controlled trial.

personalized accelerated pacing cohort. But how do the findings from this small study compare to the much larger outcomes studies of sodium–glucose cotransporter-2 (SGLT-2) inhibitors, the only clearly efficacious treatment of HFpEF? The primary composite of heart failure events and cardiovascular death was reduced by ~20%, with empagliflozin and dapagliflozin, which was primarily driven by the reduction in heart failure events.[8,9] Only dapagliflozin marginally improved the related KCCQ quality-of-life score when compared with placebo [2.4 points; 95% confidence interval (CI), 1.5–3.4], while empagliflozin did not (1.3 points; 95% CI, 0.5–2.2). In addition, NT-proBNP levels did not improve. Hence, there remains an unmet need for HFpEF treatments that provide more substantial symptom relief, ideally by reducing cardiac filling pressures and atrial and ventricular wall stress, which is what physiologic accelerated pacing may achieve.

The accelerated pacing intervention appeared safe with a low number of adverse clinical events. In the accelerated pacing arm, four participants had a single adverse clinical event. With a lower rate setting of 60 b.p.m., 11 patients had 17 adverse events, most of them heart failure and AF-related. Since most participants elected to remain on their respective treatment allocation, clinical outcome analyses are feasible and an assessment of cardiac structure and function that provide early confirmation of the predicted changes is forthcoming. It is important to reiterate that any relative bradycardia, i.e. the current nominal pacemaker lower rate setting of 60 b.p.m., will worsen diastolic function. This helped myPACE to be a positive trial and should lead to a reconsideration of the lower rate standard once conduction system pacing is more widespread. In retrospect, since every patient already had an implanted device, it became obvious that the

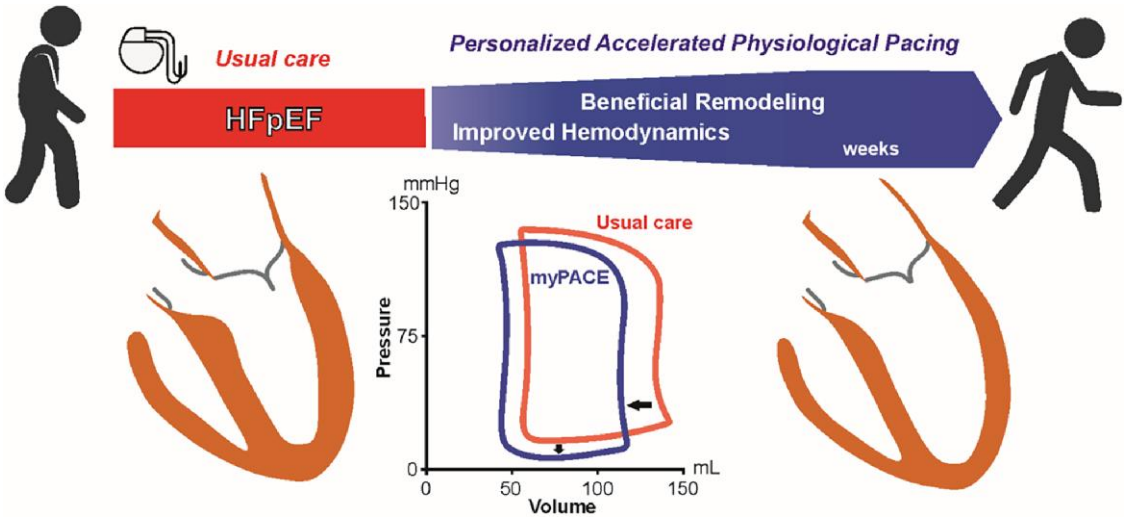

Figure 5 Illustration of the main effects of personalized accelerated physiological pacing. The immediate haemodynamic benefits are followed by eccentric remodelling with a reduction in wall thickness and increased capacitance that improves left ventricular compliance and reserve capacity.

study also benefited from a lack of a placebo effect, which is a substantial confounder in heart failure trials that involve device implantations.[73–75]

The overall results confirmed that quality of life is a viable treatment goal in this large group of patients, whereas a primary focus on exercise capacity, i.e. by restoring chronotropic incompetence with rate adaptive pacing, may not be beneficial (*Figure 5*).[76]

As discussed, we only allowed pacing systems that preserved or shortened intrinsic conduction to synchronize both contraction and relaxation. In the atrium, Bachmann bundle leads were present in more than one-third of patients.[65] Minimizing or eliminating both atrial and ventricular dyssynchrony allowed us to permanently raise the lower rate setting without offsetting effects from mechanical dyssynchrony.

Knowledge gaps and outlook

The myPACE trial was a single-centre study amongst patients with pre-existing pacemaker systems with optimized lead positions. As mean resting heart rates in HFpEF populations are typically ~72 b.p.m., a modified treatment algorithm will be necessary to provide a meaningful haemodynamic benefit. At least initially, pacing at higher rates will require integration of efficacy and safety evaluations by close clinical follow-up to optimize the dosing of heart rate. Prolonged exposure to a single accelerated pacing rate will predictably silence physiological remodelling with a risk of terminal structural arrest, i.e. by irreversible crosslinking of extracellular matrix collagen, which is common in end-stage HFrEF.[77] This is preventable by pacing rate variations that add therapeutic efficacy, which is examined in the PACE-HFpEF trial (NCT04546555), our first cohort of HFpEF patients *without* standard pacemaker indications. PACE-HFpEF is primarily comparing pacing modes using an upgraded algorithm.

If the benefits are confirmed, it is conceivable that next-generation devices will integrate haemodynamic and clinical data into the treatment algorithms to auto-adjust dosing and thereby minimize the risk from ‘guesstimate’ interventions that may adversely affect safety and efficacy. Besides its potential to reduce incident HFpEF and AF in the elderly and in hypertensive heart disease, it is conceivable that personalized accelerated pacing may also benefit patients with non-obstructive hypertrophic cardiomyopathy or other conditions with a restrictive cardiac physiology. Current treatment recommendations for these conditions embrace the same ‘slower heart rate—better filling’ rationale that was effectively refuted by the myPACE trial.[78]

Until our findings are confirmed and safeguards are implemented, it is our contention that the current evidence supports the notion that pharmacological heart rate lowering is not beneficial and may be even harmful in many patients with hypertensive heart disease. We therefore discontinue or replace beta-blockers in most patients with HFpEF and AF. Given the high prevalence of both conditions in an ageing population, it is predictable that the residual risk will remain high, even after widespread beta-blocker de-prescription and adoption of pharmacological advances that include SGLT-2 inhibitors and glucagon-like peptide 1 agonists for weight loss. Changing demographics combined with a high prevalence of hypertension will require the development of targeted treatments that address the progression of diastolic dysfunction and the underlying structural abnormalities. In this regard, personalized accelerated physiological pacing may present a unique opportunity with the added benefit that it does not depend on adherence.

Conclusions

The synergy of atrial and ventricular conduction system pacing and accelerated personalized heart rate modulation is a holistic approach that aspires to optimize atrial and ventricular electromechanical function and myocardial substrate to improve quality of life and reduce adverse clinical outcomes in the elderly and in patients with hypertensive heart disease.

The early clinical evidence suggests that this therapeutic modality may find use in the prevention and treatment of HFpEF and AF.

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Data availability

No new data were generated or analysed in support of this research.

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