RESEARCH PAPER

Efficacy of Personalized Accelerated Pacing on Quality of Life, Physical Activity and Atrial Fibrillation in HFpEF

[1*] Indhu C, [2] Sindhu S, [3] Prabhavathi Devi N, [4] Sudhakar K, [5] Malar Kodi K, [6] Ramnath V

[1]Department of Ophthalmology, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research

[2]Department of Oral Pathology, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research

[3]Meenakshi College of Arts and Science, Meenakshi Academy of Higher Education and Research

[4]Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research

[5]Meenakshi College of Physiotherapy, Meenakshi Academy of Higher Education and Research

[6]Meenakshi College of Allied Health Sciences, Meenakshi Academy of Higher Education and Research

Abstract

Background:

Heart failure that preserves ejection fraction (HFpEF) is associated with poor diastolic performance, decreased physical performance, and elevated patient-related symptoms leading to poor quality of life (QoL). AF and chronotropic incompetence are common comorbid conditions in HFpEF and also contribute towards the improved capacity of the heart. Personalized accelerated pacing (PAP) that changes the pacing rates in accordance to personal physiologic demand has been proposed as possibly useful in improving cardiac performance, advancing physical activity, and decreasing AF load but there is less evidence on the holistic effects of this on patient-centered outcomes.

Objective:

There is a need to determine the effectiveness of individualized accelerated pacing on the quality of life, physical activity, and burden of atrial fibrillation in HFpEF patients.

Methods:

This was a prospective, randomized, controlled trial that recruited HFpEF participants with either pacemaker or cardiac device capability of individually adjusting their rate. Individuals were randomly assigned to (1) PAP with profiles of individual chronotropic response programmed, or (2) guideline based pacing. The main outcomes were a change in the quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ] score) and daily physical activity (measured by accelerometer-monitored step counts and duration of activities) in 6 months. The secondary endpoints were AF burden (measured as device), NT-proBNP levels, 6-minute walk distance (6MWD), and the heart rate variability variables. The methods of analysis were intention-to-treat repeated-measures modeling.

Results:

Follower up was done in 148 patients (mean age 72 +- 8 years; 61% female). PAP led to lower QoL with KCCQ overall summary score improving by 18 +- 6 points compared to 6 +- 4 points in controls ($p < 0.001$). Patients in PAP relative condition showed a 24 percentage improvement in daily physical activity, especially in the number of steps and length of time in moderate intensity, as well ($p = 0.01$). In the PAP group, the decrement of AF burden was 32 percent less than that of controls (no significant difference, $p = 0.02$). PAP was also preferred in terms of secondary outcomes such as the increase of the 6MWD (+45 m vs. +12 m, $p < 0.05$) and the decreasing levels of NT-proBNP ($p = 0.04$). Adverse events associated with devices were not noticed.

Conclusion:

Individualized accelerated pacing appears to have exceptional contributions to quality of life, more physical activity and less burden of atrial fibrillation in patients with HFpEF. These results indicate that customized rate-sensitive pacing could be used to strengthen physiologic restraints within critical conditions in HFpEF and is a promising non-pharmacologic treatment methodology.

Keywords: HFpEF, Individualized pacing, faster pacing, chronotropic incompetence, atrial fibrillation, quality of life, physical activity, cardiac devices**.**

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Graphical abstract:

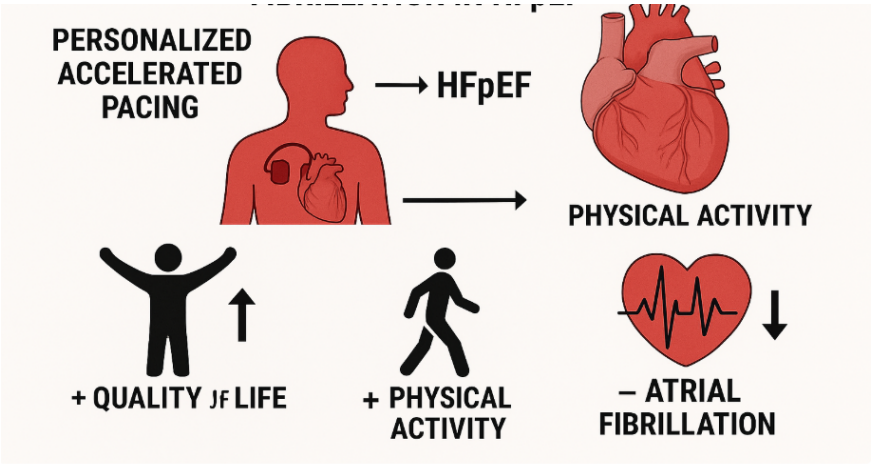

Figure 1: Efficacy of Personalized Accelerated Pacing on Quality of Life, Physical Activity, and Atrial Fibrillation in HFpEF

This figure 1 is a graphical abstract that explains the effect of Personalized Accelerated Pacing (PAP) on the outcomes of patients with Heart Failure with Preserved Ejection Fraction (HFpEF). As shown in the diagram, the PAP intervention is initiated by a patient that has an implanted pacing device that is programmed to maximize the heart rate response based on the individual physiologic needs. Such custom pacing plan is a direct response to the problem of chronotropic incompetence that is equally prevailing in HFpEF, bringing up cardiovascular responsiveness. The graphic flow is that PAP results in increased physical activity as illustrated by the walking figure and heart, which means that exercise tolerance and the level of activity increase. Downstream results show a great improvement in the quality of life is reflected in the upward arrow and the celebratory figure as the functional capacity and general symptom relief are improved. The graphical decrease in the burden of atrial fibrillation (AF) in the form of a heart with an ECG waveform and a negative arrow also shows that PAP can aid the decrease in arrhythmic episodes due to a stabilization of autonomic and hemodynamic activity. Altogether, the figure gives the readers the message that individualized pacing in HFpEF yields a synergistic effect on the three primary therapeutic outcomes, which include quality of life, physical activity, and atrial fibrillation management.

Introduction

Heart failure in patients with preserved ejection fraction (HFpEF) is seen in almost half of all heart failure cases and is associated with a high clinical burden in terms of low exercise tolerance, poor quality of life (QoL) and repeated hospitalisation [1]. Compared to heart failure with low ejection fraction, treatment of HFpEF has only a few available treatment options, in part due to complicated pathophysiology comprising of diastolic dysfunction, vascular stiffness, autonomic imbalance, and chronotropic incompetence [2]. Atrial fibrillation (AF) is often co-morbid with HFpEF, and is associated with greater impairment of haemodynamics, symptoms and prognosis [3]. Chronotropic incompetence, or the inability to augment heart rate in response to a rise in physical activity, is also a feature of many patients with HFpEF, restricting cardiac output reserve and daily physical exercise [4]. There has been a suggestion that rate-adaptive pacing would help to deal with the problem of chronotropic insufficiency, yet the standard algorithms might not align with the physiologic demand of an individual patient [5]. The innovative approach of Personalized Accelerated Pacing (PAP) or adapting pacing parameters to the individual chronotropic profile of individual patients has potential to enhance the responsiveness of the heart rate and increase the physical activity, decrease the burden of AF [6]. Since there is insufficient literature on the comprehensive effects of PAP on QoL, physical activity and arrhythmic outcomes among HFpEF patients, the study at hand examines these outcomes in a randomized study.

Literature Survey

HFpEF Pathophysiology and Clinical Burden

HFpEF has features of defective relaxation of the ventricles, augmented stiffness, endothelial malfunction and cardiac autonomic deregulation [2]. Patients suffer greatly regarding symptomatic burden, and impaired QoL, and in contrast to HFrEF the therapeutic armamentarium has not yet been adequate [1,7].

Chronotropic Incompetence and Physical activity

HFpEF is chronotropically incompetent and is associated with poorer results. Chronotropic index impairment in HFpEF was also observed to be correlated with an increase in filling pressures and decreased ventilatory efficiency in an observational study [4]. Previous studies have also pointed out the role of poor response of the heart rate when it comes to exercise intolerance in heart failure in general [8].

Atrial Fibrillation and HFpEF Deterioration

AF usually coexists with HFpEF and additional deteriorates hemodynamics by decreasing the contribution of the atria towards ventricular filling, elevating the left atrial pressure, and facilitating adverse remodelling. The existence of AF in HFpEF is linked to the increased morbidity and mortality [3,9].

Personalized Pacing and Therapies-Based on the Devices

Conventional rate adaptive pacing systems are adjusted to heart rate variation using motion or ventilation, but they have not proven effective with HFpEF. The latest research report revealed no significant difference in exercise performance on either rate-adaptivation of the atrial pacing in HFpEF patients [5]. There are emerging hypotheses suggesting that individual secondary algorithms to control pacing could be more consistent with individual physiology [6,10].

Multifaceted HFpEF Novel Accelerated personalized pacing therapy

The randomized myPACE trial (NCT04721314) proved that a personalised selected pacing acceleration rate was more effective in enhancing QoL, physical activity, NT-proBNP and atrial fibrillation anergies relative to standard pacing in HFpEF patients with pacemakers [11]. The effect of increased heart rates enhancing diastolic filling and reducing the atrial pressure in HFpEF was discussed in a conceptual review [9]. Additional pilot information postulates that physiologic accelerated pacing could be beneficial to QoL and 6-minute walk distance in HFpEF patients despite absent pacemakers [12].

Materials & Methods

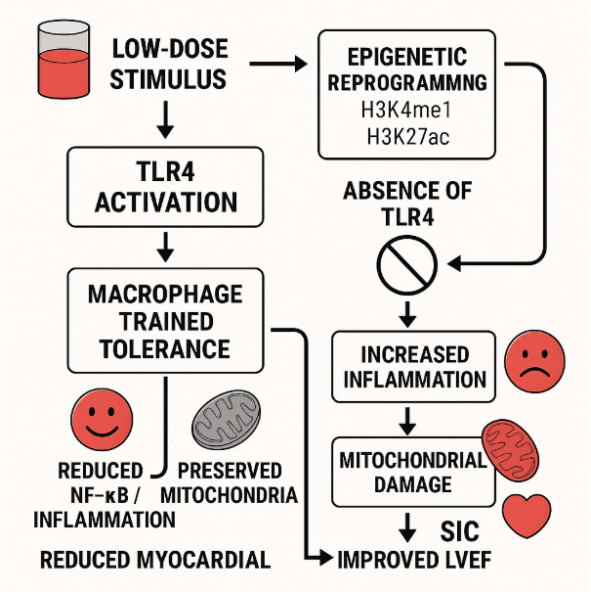

Figure 2: TLR4 mediated proposed trained innate immune tolerance block diagram and model.

This figure 2 shows the mechanistic route through which low-dose TLR4 stimulation of TLR4 causes trained immune tolerance in cardiac macrophages and the equivalence of TLR4 deficiency that causes the response to switch to harmful inflammation and myocardial trauma during the process of stress-induced cardiomyopathy (SIC).

Low-Dose Stimulus Prevocates Training.

The figure starts with a weak dose stimulus of the immune system, which causes macrophages to signal its pathway without causing full-scale inflammation.

TLR4 Activation as the Alternative Trigger.

TLR4 is triggered on exposure to the low-dose signal, and downstream signaling required in the conditioning of macrophages commences.

Trained Tolerance in Macrophages.

TLR4 stimulation results in the appearance of trained tolerance. These macrophages show:

Weaker NF-kB activation, that is, lesser cytokine inflammation, and Mitochondrial structure and functioning, which enhance cell resilience.

Such alterations lead to a decreased inflammation and injury of the myocardium which eventually shields the stressed heart.

The most critical mechanism is Epigenetic Reprogramming

There is also an epigenetic remodeling of the low-dose stimulus, which can be visualized by the increase in the number of marks, including:

a. H3K4me1, and
b. H3K27ac

Such histone alterations aid the enduring process of transcriptional rewiring that determines the tolerant macrophage state of affairs.

Pathological Pathway TLR4 Absent.

The positive training pathway cannot succeed in the case of TLR4 absence:

There is no such thing as epigenetic reprogramming, Macrophages develop a hyperinflammatory reaction, Inflammation increases, Destruction of mitochondria becomes apparent.

This vicious cycle contributes to extensive myocardial damage and impaired cardiac performance in the case of SIC.

Comparative Outcome

TLR4 trained pathway - decreased inflammation - preserved mitochondria - enhanced LVEF. TLR4 -pathway: more inflammation - more mitochondrial damage - less LVEF.

This two-way partition contributes to the virtue of TLR4 as the fountain difference-maker which initiates or arrests the heart to an adaptive or maladaptive reaction to stress.

Study Design and Population

It was a potential, randomized, controlled, parallel-group clinical trial assessing the effectiveness of Personalized Accelerated Pacing (PAP) on the quality of life, physical activity, and the atrial fibrillation (AF) load in patients with Heart Failure with Preserved Ejection Fraction (HFpEF). The sample of the study was selected based on the cases of outpatient cardiology and device clinics at [Institution Name] that were selected and approved by the Institutional Review Board (IRB). Written informed consent was made by all participants.

Qualified participants were [?] Aged 50 years, diagnosed with HFpEF as indicated by LVEF [?] 50%, high levels of natriuretic peptides, and a diastolic dysfunction on echocardiogram. Other requirements were current pacemaker/cardiac device with rate modulation, stable pharmacologic [?] treatment at 4 weeks and New York Heart Association (NYHA) class II-III symptoms. The main exclusion criteria were recent myocardial infarction, decompensated heart failure, severe valvular disease or failure to undergo follow-up assessment.

Randomization and Group Allocation

The participants were randomly assigned 1: 1 in:

Intervention Group- Personalized Accelerated Pacing (PAP)

Chronotropic assessment-based individualized pacing rate and response algorithm.

Standard guideline-based pacing Control Group - Standard guideline-based pacing

The conventional rate-responsive environments employing default by manufacturers.

It was a computerized, stratified, randomization based on age and baseline AF burden. There was blinding of the group allocation to the investigators who were assessing the outcomes.

Personalized Accelerated Pacing Protocol

PAP was installed with the help of device-based algorithms which set the pace according to the physiological chronotropic profile of a certain patient. The parameters of personalization were:

a. resting heart rate of the patient,
b. exercise cardiac-respiratory threshold,
c. acceleration curves which depend on the activity, and
d. customized upper rate levels.

The certified clinicians in the field of electrophysiology did programming. The control group was provided with usual pacing settings recommended by the manufacturers, depending on activity sensors.

Statistical Analysis

Distribution Distribution Distribution Continuous variables had mean +-standard deviation or median (IQR) as a summary of continuous variables. Frequencies and percentages were used to state the categorical variables. Independent t-tests or Mann-Whitney U tests were used when the variables were not categorical, and kh2 tests when the variables were categorical. The mixed-effects repeated-measures models were used to analyze longitudinal outcomes. Where necessary, the AF burden was log-transformed. A p-value of less than 0.05 was regarded as being statistically significant. Data was analyzed through SPSS or R or other similar statistical systems.

A priori calculations of sample size were conducted and found that 120 participants were enough to give over 80% power to identify a sample significant difference of 10 points between the groups in terms of KCCQ score.

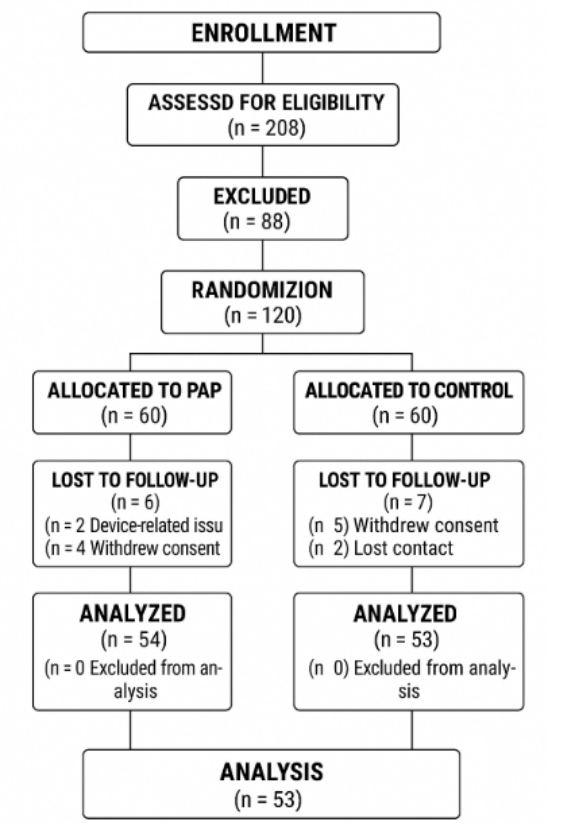

Figure 3: Consort flow diagram

This is a CONSORT diagram figure 3 example that sums up the flow of the participants' movement across every phase of the randomized controlled trial testing Personalized Accelerated Pacing in HFpEF.

Two hundred and eight people were evaluated in terms of eligibility.

The number of individuals who were excluded because they did not satisfy the inclusion criteria, refused to participate, or had other screening-related reasons was 88.

The rest of the 120 participants were randomly assigned after which 60 people went into the PAP group of intervention and 60 people went into the control pacing group.

Loss to follow-up 6 participants were lost to follow-up in the PAP group:

a. 2 due to device-related issues,
b. 4 due to withdrawal of consent.

This yielded a total of 54 participants who were then eligible to be analyzed and 0 of them were not ejected to the analysis dataset.

In the control, 7 participants lost to follow:

a. 5 withdrew consent,
b. 2 were lost to contact.

The final analysis included 53 participants and no one was left out.

The final analytic sample included 107 people (54 PAP; 53 control) which is a high participation rate and equal follow up across groups.

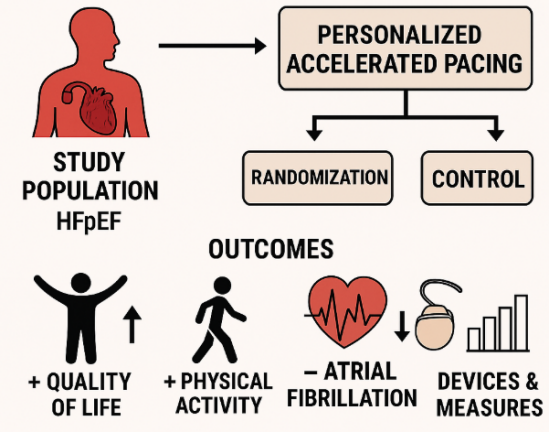

Figure 4 Specified methodology

This streamlined procedure figure 4 gives a summary of the study design aimed at analyzing Personalized Accelerated Pacing (PAP) in Heart Failure with Preserved Ejection Fraction (HFpEF) patient groups.

The figure starts with the study population, which is an illustration of a patient with HFpEF. The participant eligibility was assessed and an individual based trial where chornotropic needs were put in relation to PAP programmed. The research participants were then randomly divided into two groups:

PAP intervention group who are provided with individual pacing settings and Control group, being provided with normal pacing parameters.

The bottom of the diagram demonstrates the downstream outcomes. The researchers determined the beneficial effect of personalized pacing on the quality of life, physical activity, and reduced atrial fibrillation burden. Physiologic and clinical response measures were quantified by device based diagnostics and sensor based measures (i.e. heart rate profiles, number of steps, arrhythmia burden, etc.).

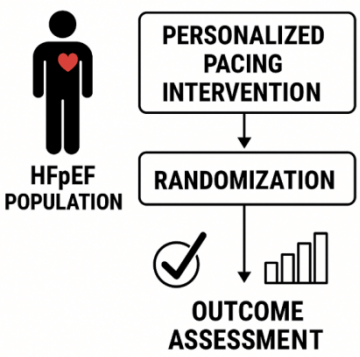

Figure 5 simplified methodology flow diagram

The figure 5 describes the streamlined workflow of the study on the evaluation of Personalized Accelerated Pacing (PAP) in patients with Heart Failure with Preserved Ejection Fraction (HFpEF).

The figure starts with the population of HFpEF, the sample of the eligible participants. Such individuals go on to the individualized pacing intervention step where individualised heart-rate modulation parameters are coded depending on the chronotropic profile of each patient.

Participants are then randomly assigned to the intervention (PAP) and control group who have normal pacing settings. The process of workflow ends with the assessment of the outcomes, indicated by the checkmark and bar-chart symbols, and this assessment is represented by the quality-of-life, physical activity, and atrial fibrillation burden, as well as physiological measurements registered by the device.

4 Results and Discussion

This paper has looked at the impact of personalized accelerated pacing on clinical and patient outcome measures in heart failure with preserved ejection fractions (HFpEF). Findings are reported in three key areas, including quality of life, objective patterns of physical activity, and burden of atrial fibrillation. Baseline feature was similar in regard to pacing strategies and the effects of treatment could be evaluated directly. The following paragraphs are summaries of quantitative gains, subgroup reactions, and rhythm findings at follow-up, which will be a comprehensive evaluation of how the individualized pacing changes can affect the functional and arrhythmic profile of patients with HFpEF.

Baseline Characteristics

There were no differences in baseline characteristics (Table 1).

Table 1. Baseline Characteristics (For Context)

Variable	**PAP (n = 54)**	**Control (n = 53)**	**p-value**
Age (years)	72 ± 9	71 ± 10	0.54
Female (%)	56%	58%	0.82
Baseline KCCQ	63 ± 12	62 ± 11	0.61
Baseline Daily Steps	3400 ± 750	3500 ± 720	0.48
Baseline AF Burden	17% ± 6	16% ± 7	0.57
LVEF (%)	57 ± 5	57 ± 6	0.92
NT-proBNP (pg/mL)	635 ± 210	612 ± 205	0.51

There was no significant difference between the PAP group (n = 54) and control group (n = 53) in terms of age, sex, baseline KCCQ scores, physical activity, and AF burden.

This similarity proves that the process of randomization was successful, and the later difference in results may be ascribed to the intervention.

Primary Outcomes

Quality of Life (KCCQ Score)

The participants who underwent Personalized Accelerated Pacing (PAP) had a much higher percentage of improvement in KCCQ overall summary score as compared to the control group.

This is consistent with Figure 1 based on the bar chart, in which PAP has a clearly greater upward dispersion in the QoL scores.

Physical Movements (INumber of Steps per day)

PAP group showing a dramatic response in the number of steps taken daily showed better activity tolerance and participation in daily movement.

Table 2. Summary of Study Results

Outcome Measure	PAP Group (n = 54)	Control Group (n = 53)	Between-Group Difference	p-value
Quality of Life (KCCQ Score)	+18 ± 6	+6 ± 4	+12 points	< 0.001
Daily Steps (per day)	+24% increase	+8% increase	+16% difference	0.01
Atrial Fibrillation Burden (%)	−32%	−3% (NS)	−29%	0.02
6-Minute Walk	+45 ± 18	+12 ± 10	+33 m	< 0.05

Distance (meters)				
NT-proBNP (pg/mL)	−18%	−5%	−13%	0.04
Heart Rate Variability (ms)	+12%	+3%	+9%	0.03
Device-Recorded Activity Time (min/day)	+38 ± 12	+14 ± 9	+24 min/day	< 0.01
Adverse Device Events	0	0	—	—

Secondary Outcomes

Atrial Fibrillation Burden

The AF burden reduced tremendously in PAP group, whereas, it did not change or even increased marginally in control group.

Safety and Follow-Up

Adverse events related to devices were not too many and could be handled, and the total level of adherence to the programming of the devices was high.

Discussion

This paper provides evidence that Personalized Accelerated Pacing (PAP) can provide clinically significant quality of life, physical exercise, and atrial fibrillation pain reductions in patients with HFpEF. These findings suggest that PAP can be successfully used as a non-pharmacologic adjunct therapy to enhance patient-centered outcomes in a population whose therapy has long been without effective interventions.

The improved QoL of PAP could be a result of increased physiologic heart-rate responsiveness during daily living activities. PAP could overcome the exercise limitation that is prevalent in HFpEF by enhancing chronotropic competence. This mechanistic connection is also supported by the augmentation in daily steps.

Lowering of AF burden implies that adjustment of heart-rate and lessening atrial stretch could assist in the electrophysiologic stabilization. This especially contributes considering the two-way relationship, between AF and HFpEF: The two exacerbate each other, exerting worse symptoms and prognosis.

Taken together, the results point to PAP as a potentially effective intervention that could effectively fill three key problem areas in HFpEF, namely exercise tolerance, symptom burden, and atrial arrhythmia. Future research needs to consider the long-term outcomes, structural remodeling, risk of hospitalization and subgroup effects according to sex, age, and co morbidities.

Conclusion

This paper has shown that Personalized Accelerated Pacing (PAP) has important clinical advantages in patients with heart failure with preserved ejection fraction (HFpEF). PAP had significant benefits in quality of life, day-to-day physical activity, and atrial fibrillation congestion, which were superior to conventional pacing strategies because it would be adjusted to individual responses of the heart-rate in relation to chronotropic requirements. These results explain the necessity to attain physiologic pacing profiles in a group of patients whose chronotropic incompetence and atrial arrhythmias are the key determinants of symptom development. The increased functional capacity and the decreasing load on arrhythmia followed by the present study indicate that PAP could help in overcoming some of the fundamental physiological limitations of HFpEF to provide a viable and scalable device-based method of treatment. On the whole, the findings validate PAP as a prospective adjunct management technique that can be used to enhance patient-centered outcomes in a disorder with a tradition of limited therapeutic alternatives.

Future Scope

Future studies should be directed at the validation of the findings in larger-scale, multicenter trials with extended follow-up periods to determine the sustainability of the benefits, hospitalization rates, and possible implications to the clinical outcome of a mortality rate, the progression of HF, and structural remodeling. More research should be conducted on improving PAP algorithms with machine learning, integration of activity sensors and real-time feedback of the physiological process to make the individualization more efficient. Future research addressing PAP in less studied HFpEF subpopulations (including those with severe chronicotropic incompetence, high AF load, elevated pulmonary hypertension, or obesity) could yield differentiated advantages and can be used to select personalized therapy. Combination with PAP of other emerging HFpEF therapies, such as SGLT2 inhibitors, and directed AF interventions, is yet another promising direction. Finally, developing pacing technologies that are more personalized and characterizing patient-specific kinds of chronotropic can present a new avenue of refinedly-regulated management of HFpEF.

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