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SHORT COMMUNICATION

Feasibility of physiological pacing rate in cardiac resynchronization therapy

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Abstract

Aims Although cardiac resynchronization therapy (CRT) improves functional capacity in heart failure patients, a blunted heart rate (HR) response remains after treatment. So we aimed to evaluate the feasibility of the physiological pacing rate (PPR) in CRT patients.

Methods A cohort of 30 clinical mildly symptomatic CRT patients underwent the six-minute walk test (6MWT). During the 6MWT, HR, blood pressure, and maximum walking distance were assessed. The measurements were obtained in a pre to post manner, with CRT at nominal settings and with the physiological phase (CRT PPR), in which HR was increased by 10% above the maximum HR achieved previously. The CRT cohort also comprised a matched control group (CRT CG). In the CRT CG, the 6MWT was repeated after the standard evaluation with no PPR. The evaluations were blinded for patients and for the 6MWT evaluator.

Results During the 6MWT, CRT PPR led to an increase in walking distance of 40.5 m (9.2%; $P < 0.0001$) when compared with baseline trial. Additionally, CRT PPR increased the maximum walking distance compared with CRT CG 479.3 ± 68.9 m vs. 420.3 ± 44.8 m, respectively, $P = 0.001$. In the CRT CG, CRT PPR increased the variation in walking distance, compared with baseline trials, respectively 2.40 ± 3.8% vs. 9.25 ± 7.0%, $P = 0.007$.

Conclusions In mildly symptomatic CRT patients PPR is feasible, leading to improvements in functional capacity. In this regard, the efficacy of PPR must be confirmed by controlled randomized trials.

Keywords Cardiac resynchronization therapy; Heart failure; Heart rate

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Introduction

Heart failure is an independent predictor of a blunted heart rate (HR) response during exercise, as well as a blunted HR that results in death.[1] Cardiac resynchronization therapy (CRT) can enhance functional capacity.[2] However, blunted HR remains and is detected in up to 70% of heart failure patients.[3] On the other hand, a complex set of adrenergic activation sequences that is imbalanced in heart failure patients is partially rebalanced by CRT.[2]

However, this effect is not fully achieved with current treatment options. Our previous study suggests that, during moderate levels of exercise intensity, muscle adrenergic nerve activity, and HR increment do not perform equally.[2]

Therefore, this study aimed to evaluate the impact of using the physiological pacing rate (PPR) on functional capacity in mildly symptomatic idiopathic CRT patients.

Methods

Study population

This translational and acute interventional feasibility study enrolled a cohort of 30 mildly symptomatic CRT patients, especially those with idiopathic cardiomyopathy. Patients were excluded if they had undergone CRT implantation within

6 months, had a previous diagnosis of sinus node dysfunction or pacemaker rate-response sensor activation, had a recent acute coronary or cerebrovascular event, had uncontrolled diabetes mellitus, had atrial tachyarrhythmia, exhibited an inability to walk, were pregnant, were younger than 18, or had a reduced life expectancy.

Study protocol

Eighteen enrolled CRT patients constituted the interventional group (CRT PPR), and 12 patients were selected as a matched control group (CRT CG). The patients were randomly assigned to the groups; however, some treatment choice was permitted, mainly for matching the groups' baseline characteristics. The six-minute walk test (6MWT) was performed during baseline and PPR and was performed according to the recommendations of the American Thoracic Society.[4] HR, systolic and diastolic blood pressure (SBP and DBP), and maximum walking distance were assessed.

Cardiac resynchronization therapy physiological pacing rate group procedures

The baseline attempt of the 6MWT was performed under basic CRT HR programming. In this phase, the maximum HR reached was recorded. After the exercise protocol was repeated, reprogramming the lower CRT rate up to 10% above the maximum HR reached during exercise. The CRT CG underwent the same 6MWT protocol without reprogramming the basic CRT rates (no PPR). The paced atrioventricular intervals were kept physiological throughout all the procedures, maintaining ventricular resynchronization. The evaluations were kept blinded to patients and for the 6MWT evaluator. All the CRT devices were programmed in DDD mode, with a lower rate of 60 b.p.m. and an upper rate of 130 b.p.m.

Statistical analysis

All data were evaluated for normality using the Kolmogorov–Smirnov test. Sample variability is described by means and standard deviations or medians and interquartile ranges (IQRs). Continuous variables were evaluated by the *t*-test, and the dichotomic by Fisher's exact test. A two-tailed *P* value of <0.05 was chosen as significant.

Results

The mean characteristics of the groups are shown in *Table 1*.

Table 1 Participant characteristics

	CRT (n = 18)	CRT CG (n = 12)
Age (years)	54.4 ± 9.1	54.2 ± 14.9
BMI (kg/m^2)	25.3 ± 3.0	25.3 ± 4.2
Sex, *n* (%)		
Male	11 (61)	7 (59)
Female	7 (39)	5 (42)
Echocardiogram		
LVEF (%)	35.7 ± 9.6	35.3 ± 7.0
LVESV (mL)	122.6 ± 53.1	127.9 ± 27.1
LVEDV (mL)	197.4 ± 67.5	192.1 ± 29.7
E/E′	8.48 ± 3.19	8.85 ± 3.59
Functional class, *n* (%)		
NYHA-II	18 (100)	12 (100)
NT-pro BNP (pg/mL)	158.6 ± 171.4	166.0 ± 168.9
HF aetiology, *n* (%)		
Idiopathic	18 (100)	12 (100)
Medications, *n* (%)		
Beta-blocker	18 (100)	12 (100)
ACEI or ARB	17 (96)	12 (100)
Spironolactone	14 (77)	10 (83)

The values are presented as the mean ± SD/median and interquartile range.
6MWT, six-minute walk test; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CG, control group; CRT, cardiac resynchronization therapy; HF, heart failure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

Table 2 Pre- to post-analysis

	CRT (n = 18)	CRT PPR (n = 18)
Walking distance (m)	438.8 ± 57.5	479.3 ± 68.9*
HR (b.p.m.)	74.5 ± 11.7	83.4 ± 12.4*
SBP (mmHg)	125.0 ± 16.7	122.6 ± 18.0
DBP (mmHg)	70 [68–82]	74 [70–78]
sO_2 (%)	96 [95–97]	96 [95–97]

Values in mean ± SD/median and interquartile range.
CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; HR, heart rate; PPR, physiological pacing rate; SBP, systolic blood pressure; sO_2, oxygen saturation.
*CRT vs. CRT PPR: $P < 0.05$.

Physiological pacing rate results during the six-minute walk test

HR following the walk was 74.5 ± 11.7 b.p.m. at nominal settings and increased to 83.4 ± 12.4 b.p.m. with PPR, $P = 0.009$ (*Table 2*). HR was also higher in the CRT during PPR than in the CRT CG with no PPR 83.4 ± 12.4 b.p.m. vs. 73.4 ± 8.0 b.p.m., respectively, $P = 0.002$. There was no difference between the groups in SBP or DBP (*Table 2*).

PPR was associated with a 40.5 m (9.2%) improvement in walking distance: CRT during PPR 479.3 ± 68.9 m vs. CRT at baseline trial 438.8 ± 57.5 m, $P < 0.0001$ (*Table 2*). Furthermore, the CRT group during PPR walked farther distances

than the CRT CG with no PPR: 479.3 ± 68.9 m vs. 420.3 ± 44.8 m, respectively, P = 0.001. Indeed, there was no significant difference between the CRT PPR group and CRT CG at baseline trials 438.8 ± 57.5 m vs. 411 ± 33.2 m, respectively, P = 0.15. In this regard, the increment in the walking distance compared with the baseline trials between the CRT during PPR and CRT CG with no PPR was 9.25 ± 7.0% vs. 2.40 ± 3.8%, respectively, P = 0.006.

Conclusions

In this study, PPR was well tolerated and feasible, and by inducing a 10% increase in HR with CRT, we obtained haemodynamic improvement and functional capacity enhancement.

Overall, HR is blunted in heart failure with reduced ejection fraction, even after CRT. It is well known that a blunted HR in cardiopulmonary exercise testing is a reason for not responding to CRT. Adrenergic hyperactivity is related to this behaviour.[3] In our study of muscle sympathetic nerve activity, the inappropriate augmentation in blood flow during exercise was remarkable.[2]

In this regard, programmed PPR with CRT improves walking distance during the 6MWT, which is clinically relevant.[5] Accordingly, PPR can be easily programmed within pacemaker-responsive sensors since almost all pacemakers allow programming HR thresholds for moderate levels of exercise. And this approach also carries little or no extra cost, with minimal resource consumption.

The limitations of our study are due to its exploratory character and possible training effects, especially during the 6MWT. To maximize the PPR effects, we only included patients with idiopathic cardiomyopathy, despite ischaemic cardiomyopathy being the most frequent indication of CRT. Indeed, the evaluation with cardiopulmonary exercise testing could help to clarify the benefit of such approach.

In conclusion, in mildly symptomatic CRT patients PPR is feasible, leading to improvements in functional capacity. In this regard, the efficacy of PPR must be confirmed by controlled randomized trials.

Conflict of interest

None declared.

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