BALNEO RESEARCH Balneo and PRM Research Journal
English Edition
e ISSN 2734 - 8458 p ISSN 2734 - 844X ROMANIAN ASSOCIATION OF BALNEOLOGY

Research article

Optimizing cardiac rehabilitation by pacemaker reprogramming. Can we immediately improve the exercise capacity?

Bogdan Caloian[1,2], Diana Andrada Irimie[1,2,*], Gabriel Nicolae Gusetu[1,2,*], Dan Horatiu Comsa[1,2], Gabriel Laurentiu Cismaru[1,2], Florina Iulia Fringu[1,2], Raluca Tomoaia[1,2], Radu Ovidiu Rosu[1,2], Alexandra Dadarlat-Pop[1,3], Dana Pop[1,2], Dumitru Tudor Zdrenghea[2]

1. Cardiology-Rehabilitation Department, Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania;
2. Clinical Rehabilitation Hospital Cluj-Napoca, Cluj, Romania
3. Heart Institute "Niculae Stancioiu", Cluj-Napoca, Romania;

* Correspondence: D.A. Irimie gurzaudiana@yahoo.com ; G.N. Gusetu gusetu@gmail.com

Citation: Caloian B., Irimie D.A., Gusetu G.N., Comsa D.H., Cismaru G.L., Fringu F.I., Tomoaia R., Rosu R.O., Dadarlat-Pop A., Pop D., Zdrenghea D.T. - Optimizing cardiac rehabilitation by pacemaker reprogramming. Can we immediately improve the exercise capacity? *Balneo and PRM Research Journal* **2023**, *14(3)*: 577

Academic Editor(s):
Constantin Munteanu

Reviewer Officer:
Viorela Bembea

Production Officer:
Camil Filimon

Received: 23.07.2023
Accepted: 15.08.2023
Published: 01.09.2023

Reviewers:
Constantin Munteanu
Mihail Hoteteu

Publisher's Note: Balneo and PRM Research Journal stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Background: Previous studies have demonstrated a direct correlation between pacemaker programming mode and exercise capacity on a long-term follow-up. In the present study we aimed to test whether reprogramming of the pacemaker can produce immediate effects on patients' exercise capacity. Methods: The exercise capacity of 33 patients wearing dual-chamber pacemakers was evaluated by cardiopulmonary exercise test at 24-hour intervals in two programming modes: initially in the single-chamber ventricular pacing mode with a fixed 60bpm rate, and in the second phase in dual chamber pacing mode with exercise adaptable rate, up to 130bpm. Results: The maximum O2 consumption (VO2 max: 12.82±2.70 mL/kg/min vs 14.52±3.25 mL/kg/min, p=0.02), the O2 consumption at the time of the anaerobic threshold (10.76±2.25 mL/kg/min vs 12.30±2.84 mL/kg/min, p=0.008), the duration of exercise (456.76±116.85 seconds vs 510.57±129.56 seconds, p=0.04) and the maximum workload (84.39±17.89W vs 96.36±24.09W, p=0.01) were significantly lower when the pacemakers were programmed in the single chamber ventricular fixed-rate pacing mode compared to the dual chamber rate adaptive pacing mode. Conclusion: Cardiac pacemaker reprogramming is able to exert immediate effects on exercise capacity. Dual chamber pacing with adaptable rate during physical exercise is superior to single chamber fixed rate pacing.
.

Keywords: exercise capacity, pacemaker programming, cardiopulmonary exercise testing.

1. Introduction

Cardiac rehabilitation is an essential method for the social reintegration of patients with cardiovascular diseases. With the aging of the population, an increasing percentage of patients are carriers of implantable cardiac devices used to treat sinus node disease, atrioventricular blocks, ventricular tachyarrhythmias or heart failure with reduced ejection fraction.

These devices influence the exercise capacity and require reprogramming of the parameters in patients included in cardiac rehabilitation programs in order to improve the final result.

In healthy subjects, the adaptation of the cardiovascular system to exertion is done by increasing cardiac output as a result of stimulating the sympathetic vegetative nervous system, with the discharge of adrenaline and noradrenaline, which causes two immediate consequences: increased heart rate (positive chronotropic effect) and increased stroke volume (positive inotropic effect) [1, 2].

By comparison, patients with heart failure with impaired systolic function cannot adequately increase their stroke volume during exertion and partially compensate for it with a much more accelerated chronotropic response from the earliest stages of physical activity [3, 4, 5, 6].

The response of the cardiovascular system to physical exertion is even more complex in pacemaker wearers, whether they associate with heart failure or not. Fixed-rate pacing in patients with chronotropic insufficiency abrogates from the beginning their possibility to increase the cardiac output by increasing the heart rate. On the other hand, in those with effort-adaptive pacing rate (responsive rate), the pacing rate may exceed the intrinsic rate and thus allows an adaptation of the cardiac output to effort much closer to the physiological mechanism [7,8].

Regarding the adjustment of the stroke volume to physical effort in the case of pacemaker wearing patients, several situations are also distinguished. It is well known that the ventricular depolarization generated by the pacemaker does not produce a contraction as effective as in the case of intrinsic ventricular depolarization due to interventricular and intraventricular dyssynchronism [9, 10].

Loss of the physiological contraction sequence in which the atrial systole is followed by the ventricular systole can cause a reduction in the stroke volume by up to 25%. Differences might also occur secondary to the positioning of the pacing lead tip inside the right ventricular cavity (high interventricular septum, low interventricular septum, right ventricular apex) [11].

Previous studies have demonstrated a relation between pacemaker programming mode and exercise capacity[12, 13]. Patients with dual chamber pacemaker had better exercise capacity than those with single chamber pacemakers. Exercise-adaptive pacing rate also proved to be superior to fixed-rate pacing in terms of functional capacity [8].

In the present study we aimed to test the hypothesis that reprogramming the pacemaker can produce immediate effects on patients' exercise capacity.

2. Results

In this study, 33 patients with a mean age of 69.64±4.03 years were enrolled. Of these, 10 (30.3%) were female and 23 (69.7%) were male.

At the analysis of the whole group, an increase of VO2 max was observed after changing the pacing mode from VVI to DDDR, by 13.26%: 12.82±2.70mL/kg/min compared to 14.52±3.25mL/kg/min (figure 1A).

The same observation was made about oxygen consumption (VO2) when reaching the anaerobic threshold, where the increase was 14.42%: 10.76±2.25mL/kg/min in VVI programming mode compared to 12.30±2.84 in DDDR mode (figure 1B).

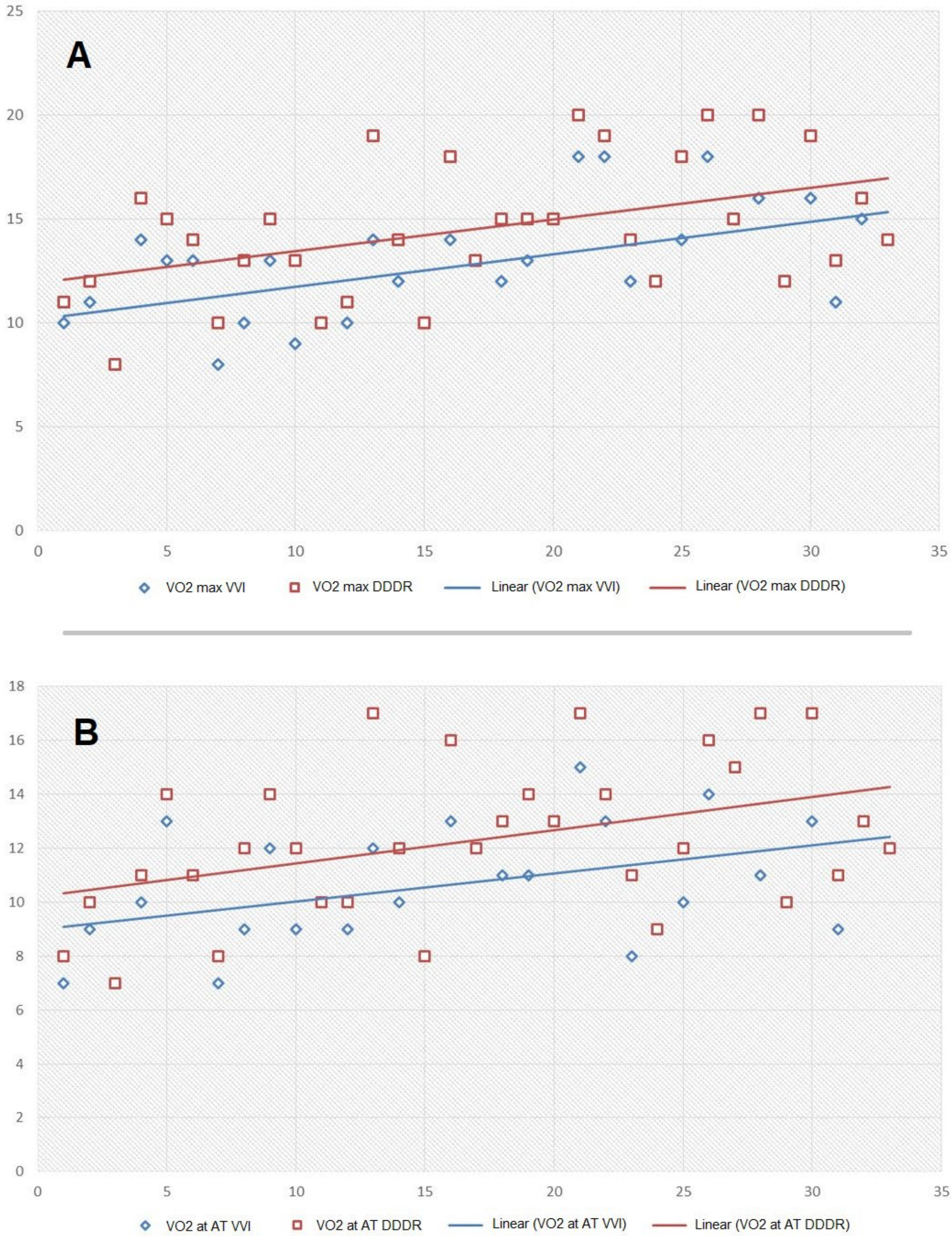
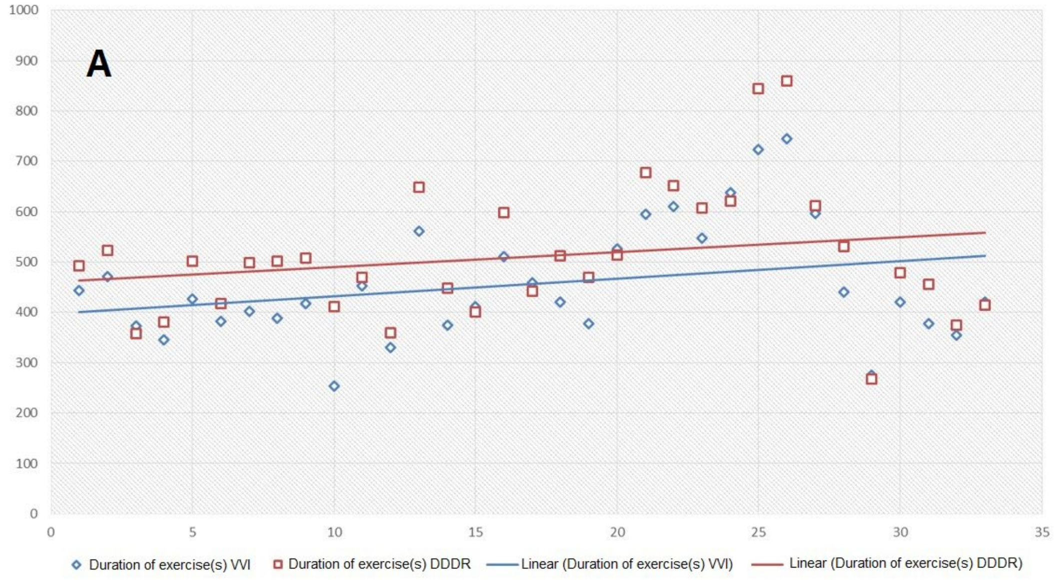


Figure 1. A. Maximum effort capacity estimated by the higher max VO2 value in the case of DDDR programming mode compared to VVI mode. **B.** Reaching the anaerobic threshold at a higher value of VO2 in the case of DDDR compared to VVI. AT = anaerobic threshold.

Regarding the duration of effort, the difference between the two programming modes was on average 53 seconds (11.78%) in favor of DDDR, with averages of 456.76±116.85 seconds in ventricular unicameral pacing mode and 510.57±129.56 seconds in bicameral (Figure 2A).

The maximum workload followed the same trend, with an average value of 84.39±17.89W in VVI mode and 96.36±24.09W in DDDR mode (Figure 2B).



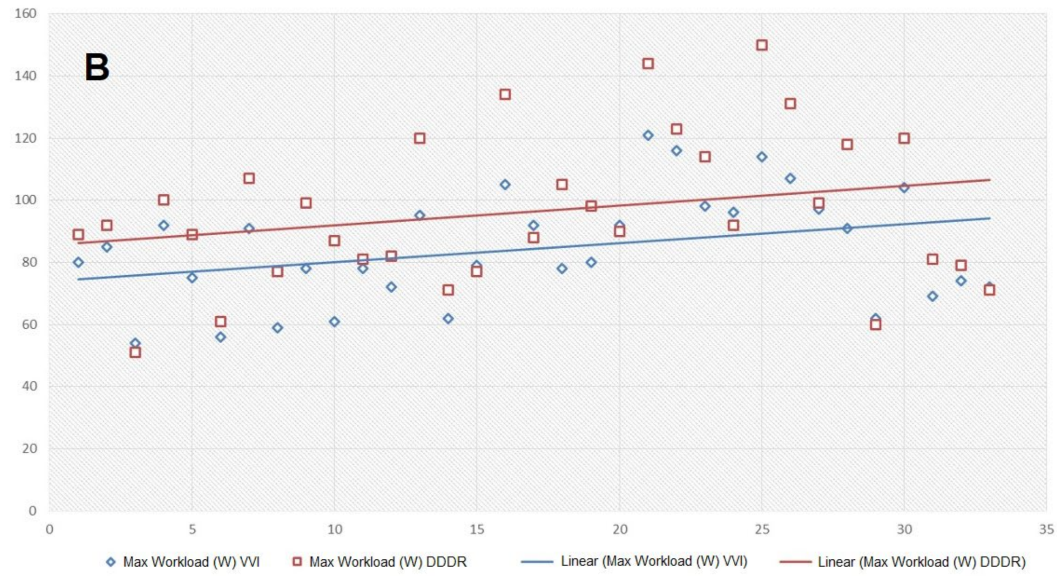


Figure 2. A. The duration of the exercise test was longer in DDDR programming mode. **B.** The maximum workload was higher in the case of DDDR programming mode compared to VVI mode.

The maximum heart rate reached during exercise was also higher when the test was performed with patients programmed in dual chamber mode, with the rate response function activated, with an average of 98.42±16.16 beats/minute in VVI mode and 111.56±15.0 beats/minute in DDDR mode.

The two programming modes recorded similar values of VO2/HR (VVI: 10.55±2.46 vs. DDDR: 10.93±2.80) and VE/VCO2 (VVI: 36.67±8.26 vs. DDDR: 35.19±7.44) ratios, as well as peripheral saturation of O2 at the maximum effort threshold (VVI: 96.49±2.0% vs DDDR: 96.67±1.83%).

The statistical significance of the comparisons presented above is shown in Table 1.

Table 1. Comparative analysis of the parameters obtained by cardiopulmonary exercise testing in the two programming modes of pacemakers, VVI and DDDR. VO2 = volume of oxygen, AT = anaerobic threshold, HR = heart rate, VE = minute volume, VCO2 = volume of carbon dioxide, SpO2 = peripheral oxygen saturation, SD = standard deviation.

Parameter	**VVI**	**DDDR**	**p**
VO_2max (mL/kg/min)	12.82	14.52	**0.024388**
SD	2.70	3.25	
Duration of effort (s)	456.76	510.58	**0.04057**
SD	116.85	129.55	
Max Workload (W)	84.39	96.36	**0.012628**
SD	17.89	24.09	
VO_2 at AT (mL/kg/min)	10.76	12.30	**0.008569**
SD	2.25	2.84	
VO2/HR	10.55	10.93	0.279322
SD	2.46	2.80	
HR max (beats/min)	98.42	111.55	**0.000551**
SD	16.16	15.00	
VE/VCO2	36.67	35.19	0.223734
SD	8.26	7.44	
SpO_2 (%)	96.48	96.67	0.350776
SD	2.00	1.83	

Depending on the heart rate during the exercise test, we defined two groups: group R - patients in whom the rate response function was activated automatically at exercise in DDDR mode and group I - patients who maintained their intrinsic heart rate throughout the test effort with the pacemaker programmed in DDDR mode.

Activation of the rate response function during exercise testing after activation of DDDR mode was observed in 11 (33.33%) of the 33 patients.

Patients whose rate response function was not automatically activated during exercise in DDDR mode (group I) reached a maximum effort heart rate in VVI mode by 19.8% higher (mean ± standard deviation: 104.18 ± 13.9 vs 86.91 ± 14.54 beats)/min). In DDDR mode, however, the maximum heart rate was higher in those in whom the responsive rate function was activated automatically (group R) compared to those in whom it was not activated (116.45 ± 12.55 vs. 109.09 ± 15.78 beats/minute).

Evaluating comparatively the two groups in terms of parameters obtained in the cardiopulmonary exercise test, we observed that the values of VO2 max, VO2 at the time of the anaerobic threshold, as well as the maximum effort threshold reached had a statistically significant increase only in group R, no and in group I. The increase in effort duration, although observed in absolute value in both groups, did not reach the threshold of statistical significance (Table 2).

Table 2. Comparison between patients in whom in DDDR mode the rate response function was activated automatically during exercise (group R) and those who maintained their intrinsic heart rate throughout the exercise test (group I). VO2 = volume of oxygen, AT = anaerobic threshold, SD = standard deviation.

The rate response function automatically activated in DDDR							
YES				NO			
Parameter	**Mean**	**SD**	**p**	**Parameter**	**Mean**	**SD**	**p**
VO_2max VVI	12.27	3.07	**0.027**	**VO_2max VVI**	13.09	2.52	0.104
VO_2max DDDR	15.18	3.57		**VO_2max DDDR**	14.18	3.11	
Duration of effort VVI (s)	471.09	148.42	0.070	**Duration of effort VVI (s)**	449.59	100.77	0.161
Duration of effort DDDR (s)	569.00	151.11		**Duration of effort DDDR (s)**	481.36	109.63	
Max Workload VVI (W)	83.64	17.77	**0.013**	**Max Workload VVI (W)**	84.77	18.36	0.131
Max Workload DDDR (W)	104.91	23.01		**Max Workload DDDR (W)**	92.09	23.98	
VO2 at AT VVI	10.18	2.27	**0.021**	**VO2 at AT VVI**	11.05	2.24	0.087
VO2 at AT DDDR	12.73	3.13		**VO2 at AT DDDR**	12.09	2.74	

Another comparative analysis was performed according to the sex of the patients, observing significant differences in terms of maximum oxygen consumption, oxygen consumption at the time of the anaerobic threshold and the maximum workload achieved by changing the type of pacing from VVI to DDDR among men, but not of women. Significantly higher maximum effort heart rates were achieved in both the female and male groups in the bicameral pacing mode with the rate response function activated. For the other parameters followed, no statistically significant differences were noted (Table 3).

Table 3. Comparison between the two sexes of the parameters obtained by cardiopulmonary exercise testing in the two programming modes of pacemakers, VVI and DDDR. VO2 = volume of oxygen, AT = anaerobic threshold, HR = heart rate, VE = minute volume, VCO2 = volume of carbon dioxide, SpO2 = peripheral oxygen saturation, SD = standard deviation.

Influence of changes in pacing mode on the parameters of the cardiopulmonary test in both sexes						
	Women			**Men**		
Parameter	**Mean**	**SD**	**p**	**Mean**	**SD**	**p**
Age (years)	70.50	2.92		69.26	4.43	
VO_2max VVI (mL/kg/min)	12.10	2.18		13.13	2.88	
VO_2max DDDR	13.70	2.41	0.068	14.87	3.55	**0.037**
Duration of effort VVI (s)	398.80	78.90		481.96	122.98	
Duration of effort DDDR	447.90	93.08	0.110	537.83	135.30	0.075
Max Workload VVI (W)	80.70	16.08		86.00	18.73	
Max Workload DDDR	90.70	20.77	0.122	98.83	25.44	**0.029**
VO_2 at AT VVI(mL/kg/min)	10.40	1.90		10.91	2.41	
VO_2 at AT DDDR	11.80	2.25	0.075	12.52	3.09	**0.028**
VO_2/HR VVI	9.50	2.07		11.00	2.52	
VO_2/HR DDDR	9.70	2.11	0.416	11.46	2.93	0.285
HR max VVI (beats/min)	103.60	14.89		96.17	16.49	
HR max DDDR	114.50	10.60	**0.038**	110.26	16.61	**0.003**
RER	1.19	0.11		1.12	0.12	
VE/VCO_2 VVI	34.47	6.62		37.63	8.84	
VE/VCO_2 DDDR	34.04	6.16	0.441	35.69	8.01	0.220
SpO_2 VVI (%)	96.80	0.92		96.35	2.33	
SpO_2 DDDR	96.90	0.74	0.396	96.57	2.15	0.372

3. Discussion

In the present study, we tested the hypothesis according to which the reprogramming of the pacemaker can significantly influence in the short term the patient's exercise capacity by using one of the most accurate and comprehensive evaluation methods, the cardiopulmonary exercise test.

Pair samples were made, comparing the most relevant parameters for exercise capacity, initially in the single chamber ventricular fixed-rate pacing mode (VVI) and later in the dual chamber, atrio-ventricular mode, with activated rate response function (DDDR).

A statistically significant increase in maximum oxygen consumption (VO2 max), oxygen consumption at the time of the anaerobic threshold (VO-AT), maximum reached workload and duration of exercise when patient pacemakers were programmed in DDDR mode.

Reporting the results obtained in the present study to the existing data in the literature is difficult due to the fact that studies in this field are few, most of them being case reports or original research on small series of cases, but their results are encouraging.

Bolsin published in 2014 the case of a patient with a bicameral pacemaker in whom an immediate improvement in functional capacity was achieved by adjusting the pacing algorithm (raising the minimum pacing rate from 60 to 80/min and accelerating the response to increase the pacing rate on exertion). Maximum oxygen consumption, oxygen consumption at the time of the anaerobic threshold, duration of effort and maximum load reached increased by 15-25%, results comparable to those found in our study [14].

Another study published by Capucci reports the improvement in exercise capacity measured by cardiopulmonary exercise test (increased VO2 max, VO2 at anaerobic threshold, effort duration by 20-25%) for 8 patients after switching from DDD programming mode to DDDR mode. The authors explain the results by the increase in maximum heart rate during exercise [15].

Jutzy also observed an increase in exercise capacity and cardiac output by programming pacemakers in DDDR compared to VVIR and DDD in 14 patients evaluated by cardiopulmonary exercise test and cardiac ultrasound [16]. Other small clinical trials report similar results.

Another important observation of our study is related to the behavior of the heart rate during physical exertion.

Depending on the heart rate response during exercise testing with the pacemaker programmed in DDDR mode, we identified two categories of patients: group I - those who maintained their intrinsic heart rate throughout the exercise test (patients with normal chronotropic function) and group R, in which the rate response function was activated automatically during exertion (patients with chronotropic dysfunction).

In other words, in group R, the rate of increase in the rate of depolarizations generated by the sinus node was lower compared to that set for the pacemaker, which is why intrinsic atrial depolarizations (and sometimes intrinsic ventricular depolarizations) were replaced with those generated by the pacemaker. Activation of this exercise adaptive function was found in one third of the patients enrolled in the study.

Patients in group R achieved a significantly lower maximum heart rate of effort compared to group I in the VVI programming mode, which is why their maximum oxygen consumption was also lower in this pacemaker programming mode.

After activating the rate response function, the patients in group R had an increase of approximately 20% of the maximum heart rate, even exceeding in absolute value the average maximum heart rate of effort of patients in group I, a difference that was not statistically significant.

What did significantly differ in this group of patients was the maximum oxygen consumption (VO2 max), 25% higher in DDDR mode compared to VVI mode, the oxygen consumption at the time of the anaerobic threshold and the maximum workload, which cannot be stated about the patients in group I in whom the difference between the two modes of pacing was not statistically significant.

It should be noted that the division of patients into groups with chronotropic incompetence (group R) and without chronotropic incompetence (group I) was practically performed by the pacemaker algorithm and was not based on a clinical diagnosis of chronotropic incompetence.

For this research, the rate response function was activated with the standard settings made by the manufacturer, but the reprogramming of the maximum heart rate and the speed with which it is reached during exercise can be customized for each patient, and the effects of adjusting this function on capacity may be the subject of further studies.

Gierula recommends a model of individualization of the pacing algorithm with rate response function that takes into account the relationship rate - contraction force in patients with heart failure and biventricular pacemakers (cardiac resynchronization therapy) or cardiac defibrillators, a model that was validated in a randomized, dou-ble-blind clinical trial [17].

Analyzing the whole group of patients, we found that, although the maximum heart rate of effort was higher in DDDR mode than VVI, no significant differences were noted in the VO2/HR ratio (indicator of heart rate of the left ventricle). This indicates that the two variables had a directly proportional evolution after activating the bicameral pacing mode with the effort-adaptive pacing rate.

It is well known that heart rate depends on two elements: heart rate and heart rate. In the case of pacemaker wearers, both components can be influenced by how the pacemaker is programmed.

By switching from VVI pacing mode to DDD mode, the beat volume can be increased during exertion by bringing the contribution of atrial contraction to ventricular filling as a result of restoring atrioventricular synchronism in patients in sinus rhythm.

However, this is only valid if the ventricular rate is paced during exercise, as is the case with those with a severe form of sinus node disease, “pacemaker-dependent” or those with atrioventricular conduction disorders that persist during effort or are triggered by effort.

A large proportion of implanted pacemakers for sinus node disease, as in the case of patients enrolled in the present study, show an increase in heart rate during exercise beyond the minimum pacing rate (usually 60 pacing / minute).

However, the question arises whether this increase in heart rate is adequate for a good adaptation of cardiac output to exercise or whether this category of patients is affected by a chronotropic incompetence that significantly limits their functional capacity.

To answer this question, we refer to the results of a study published in 2009 in the journal PACE by Passman [18]. They compare the exercise capacity of 11 patients with bicameral cardiac defibrillator, without indication for pacing (with adequate chronotropic function) programmed in the AAIR and VVI pacing modes, respectively.

For these patients there were no significant differences in maximum VO2, anaerobic threshold or duration of exercise because in both pacing modes, in the absence of chronotropic incompetence, the heart rate increased adequately during exercise and in the VVI setting mode pacing of cardiac defibrillators - which could have influenced cardiac output by causing atrioventricular or interventricular dyssynchrony - remained inactive.

Considering that in none of the patients in our study did the pacemaker function in AS-VP mode (atrial sensed - ventricular paced, ie own atrial depolarization followed by pacemaker-induced ventricular depolarization due to a delay in atrioventricular conduction), we can equate the AAIR pacing mode in the study presented above to the DDDR mode in our study.

In other words, the increase in maximum oxygen consumption and, implicitly, in cardiac output is explained in the case of patients enrolled in our study based on the increase in heart rate and not of the ventricular stroke volume.

From the moment of automatic activation of the rate response function, the pacemakers from group R worked during the exercise tests either in atrial paced - ventricular sensed mode (in 6 of the 11 patients), ie stimulated atrial depolarization followed by intrinsic atrioventricular conduction, physiologically, or in the atrial paced mode - ventricular paced (in the other 5 patients), with both atrial and ventricular depolarization triggered by the pacemaker).

The fact that some patients switched to atrial paced - ventricular paced mode after activation of the function of adapting the rate of pacing to exertion indicates that in their case there isn’t an isolated damage to the sinus node, but a dysfunction of the overall excito-conductive system, unmasked by the way the pacemaker works during exercise.

In healthy individuals, pacing of the sympathetic nervous system during exertion, by releasing adrenaline and noradrenaline, causes a positive dromotropic response, increasing the speed of conduction through the atrioventricular node. In patients with latent conduction disorders, however, the effort may have the opposite effect of inducing or aggravating atrioventricular block [19, 20].

The mean age of the patients enrolled in our study was relatively low for a cohort of pacemaker wearers, just under 70 years of age. The explanation comes from the way in which the patients were selected, namely carriers of bicameral pacemaker, without comorbidities that would significantly limit the capacity for effort.

There is a tendency in our country, but also in other states, based mainly on economic reasons, to implant mainly bicameral pacemakers to young patients, in sinus rhythm, physically active. A retrospective analysis conducted in the USA on 259 pacemaker implant procedures confirms that patients under the age of 65 received a bicameral pacemaker more frequently [21].

Another comparative analysis we performed in the present study was that between men and women. If in men, reprogramming of the pacemaker from VVI mode to DDDR significantly increased the maximum oxygen consumption, oxygen consumption at the time of the anaerobic threshold and the maximum workload, in women the difference in the above parameters was only in absolute value, but was not statistically significant. This could be explained by the small number of female patients enrolled in the study, twice as small as that of men.

One of the most relevant clinical studies in the field of sinus node disease that followed over 20,000 patients over an average period of 17 years reports a similar incidence in both sexes, but noting that, for the Caucasian population, in the age range 65-74 years, the incidence is 0.73 ‰ for women and 1.05 ‰ for men [22]. This could be one of the explanations why the group of female patients wearing a pacemaker is smaller compared to the male gender.

Another possible explanation would be that men in this age group are often perceived as more physically active than women, which is why a dual chamber pacemaker is more frequently implanted. Our assumption is proven by the authors of a multicenter, retrospective study conducted in Germany which, analyzing over 17,000 cardiac pacing procedures, found that dual chamber pacemakers were implanted more frequently in men than in women [23].

A large, observational, retrospective clinical study conducted in the US and published by Varma et al. in 2017 [24] showed that there are no significant differences between men and women in terms of long-term survival after implantation of a pacemaker. Although there is clear evidence in the literature that supports a close, directly proportional relationship between exercise capacity and overall survival [25], such an analogy for pacemaker patients can only propose a hypothesis that needs to be tested by clinical studies.

Among the limitations of the study, we want to mention the relatively small number of enrolled patients, given that most pacemaker patients are elderly, with limited exercise capacity due to the presence of comorbidities, and the total number of bicameral pacemakers implanted for sinus node disease is low.

Also, the consequences of intraventricular and interventricular asynchrony secondary to ventricular pacing during exercise on the cardiac output was not evaluated. Complementing the data obtained by cardiopulmonary exercise test with concomitant evaluation by exercise ultrasound, would certainly allow a much better understanding of the clinical significance of all pathophysiological mechanisms involved in cardiac pacing during exercise.

Another limitation is that the study was not double-blind, both the programming of pacemakers and the interpretation of cardiopulmonary exercise tests being performed by the same investigator.

In terms of clinical implications, our study shows that simple reprogramming of pacemakers can achieve a significant immediate improvement in exercise capacity and that the effects of reprogramming can be assessed exactly by cardiopulmonary exercise testing.

The way in which the pacing rate is adapted during exercise significantly influences the patient's functional capacity and should not be easily overlooked by the interventional cardiologist or treating cardiologist, especially since some pacemakers have this function disabled in the default programming mode.

Also, the reaction speed of the rate response function can be individualized for each patient, a simple adjustment of the maximum rate depending on age is sometimes not enough to obtain optimal results.

Given the complexity and wide variety of settings of the pacing algorithm available to modern devices, our study did not aim to identify an ideal way of programming, but, starting from a simple model, to draw attention to the fact that pacemaker programming must be individualized and that the cardiopulmonary exercise test is an effective way to get immediate feedback on the consequences of the implemented changes.

4. Materials and Methods

The study was conducted in the Cardiology department of the Clinical Rehabilitation Hospital in Cluj-Napoca between January 2019 and December 2019.

We enrolled consecutive patients with permanent dual chamber pacemaker implanted for symptomatic sick sinus syndrome at least 6 months before who presented themselves for the routine control of the device.

Sick sinus syndrome was defined according to the ESC Guidelines on cardiac pacing and cardiac resynchronization therapy and included one of the following conditions: sinus bradycardia (sinus rate < 60 beats/minute), sinus pause for at least 2 seconds or bradycardia-tachycardia syndrome (alternating paroxysms of regular or irregular atrial tachyarrhythmias and slow atrial and ventricular rates).

Patients with atrial fibrillation at the time of initial assessment, those with a history of significant structural heart disease (dilated cardiomyopathy with moderate or severe impaired systolic function, severe symptomatic ischemic heart disease, severe pulmonary hypertension) and those with extracardiac comorbidities that could have significantly limited exercise capacity, such as respiratory (chronic obstructive pulmonary disease, severe asthma), neurological (stroke), musculoskeletal or vascular disease(chronic obliterative arteriopathy of the lower limbs) were excluded.

Initially, the pacemaker was interrogated, with the determination of the atrial and ventricular pacing threshold, the amplitude of the P and R waves, the impedance of the two probes and battery voltage to exclude malfunctions. At the end of the query, the pacemaker was programmed in single chamber ventricular pacing mode (VVI), with a fixed pacing rate of 60/minute, the responsive rate function being deactivated, and the rest of the parameters were kept at standard values.

Reprogramming was followed by a symptom-limited cardiopulmonary exercise test during which the following variables were recorded:

• resting heart rate, maximum heart rate during exercise, recovery time (the time required for the heart rate to return to the initial value)

• blood pressure every 2 minutes

• peripheral O2 saturation at rest and during effort

• continuous monitoring of the electrocardiogram

• effort duration (sec) and maximum reached effort threshold (W)

• respiratory exchange ratio (RER)

• O2 consumption at anaerobic threshold (VO2-AT) and during maximum effort (VO2 max);

• VE/VCO2 and VE/VO2 slopes, VO2/HR ratio.

After completion of the cardiopulmonary exercise test, the pacemaker was reprogrammed in dual chamber mode, and the responsive rate function was reactivated, thus switching to DDDR pacing mode. No other changes in pacing parameters were made.

At 24 hours after the first test, patients underwent a second cardiopulmonary exercise test, following the same variables.

Cardiopulmonary exercise testing methodology

A CORTEX MetaLyzer® system with General Electric cycle ergometer and MetaSoft Studio® software (Cortex Biophysik GmbH, Leipzig, Germany) was used for cardiopulmonary exercise testing.

At the beginning of each stress test, the flow sensor was calibrated using the test system piston cylinder and the O2 and CO2 pressure sensor by placing it in a neutral space with constant gas pressure. atmospheric.

The exercise test was preceded by the measurement of resting blood pressure, peripheral O2 saturation and resting spirometry, the patient being instructed that after 5 cycles the normal respirations to perform a forced inhale, followed by a prolonged forced exhalation while wearing a mask with the flow sensor connected. The fan curves were validated by the test system software.

Types of pacemakers and ways of programming

Pacing parameters were not changed during the study, the patients being evaluated with the settings made by the treating cardiologist.

Pacemakers used in subjects included in the study were bicameral: Medtronic Sensia SEDR01 DR or St. Jude Medical Sustain XL DR.

The programmers recommended by the manufacturers were used to interrogate the devices, respectively Medtronic Pacemaker and ICD Programmer model 2090 (Medtronic) and St. Jude Medical Merlin Patient Care System (St. Jude Medical).

Statistical analysis

The following software was used for statistical data analysis and graphical representation: IBM SPSS Statistics Software version 26 (International Business Machines Corporation, Armonk, North Castle, New York, NY, USA) and Microsoft Office 2013 Excel Data Analysis module (Microsoft Corp., Redmond, WA, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania (Approval Code number 448/ 19.12.2018). Informed consent was obtained from all subjects involved in the study.

5. Conclusions

Cardiac pacemaker reprogramming is able to exert immediate effects on exercise capacity especially by maintaining contraction synchronism between the atria and ventricles and by adapting the heart rate during exercise in patients with chronotropic incompetence. By optimizing the pacemaker parameters we can increase the chances of a favorable response of the patient to the cardiac rehabilitation program.

Author Contributions: Conceptualization, Bogdan Caloian, Dumitru Zdrenghea and Dana Pop; Data curation, Dan Comsa; Formal analysis, Gabriel Nicolae Gusetu and Gabriel Cismaru; Investigation, Gabriel Cismaru; Methodology, Bogdan Caloian; Project administration, Bogdan Caloian; Resources, Bogdan Caloian, Gabriel Nicolae Gusetu, Gabriel Cismaru and Radu Rosu; Software, Diana Irimie, Florina Fringu and Alexandra Dadarlat-Pop; Supervision, Dumitru Zdrenghea and Dana Pop; Validation, Diana Irimie, Raluca Tomoaia and Alexandra Dadarlat-Pop; Visualization, Radu Rosu; Writing – review & editing, Dumitru Zdrenghea and Dana Pop. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania (Approval Code number 448/ 19.12.2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Nystoriak MA and Bhatnagar A: Cardiovascular Effects and Benefits of Exercise. Front Cardiovasc Med. 2018 Sep 28;5:135. doi: 10.3389/fcvm.2018.00135.
2. Ikäheimo TM: Cardiovascular diseases, cold exposure and exercise. Temperature (Austin). 2018 Feb 1;5(2):123-146. doi: 10.1080/23328940.2017.1414014.
3. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN and Sullivan MJ: American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation. 2003 Mar 4;107(8):1210-25. doi: 10.1161/01.cir.0000055013.92097.40.
4. Alvarez P, Hannawi B and Guha A: Exercise And Heart Failure: Advancing Knowledge And Improving Care. Methodist Debakey Cardiovasc J. 2016 Apr-Jun;12(2):110-5. doi: 10.14797/mdcj-12-2-110.
5. Vega RB, Konhilas JP, Kelly DP and Leinwand LA: Molecular Mechanisms Underlying Cardiac Adaptation to Exercise. Cell Metab. 2017 May 2;25(5):1012-1026. doi: 10.1016/j.cmet.2017.04.025.
6. Mezzani A, Corrà U and Giannuzzi P: Central adaptations to exercise training in patients with chronic heart failure. Heart Fail Rev. 2008;13(1):13-20. doi: 10.1007/s10741-007-9053-y.
7. Palmisano P, Aspromonte V, Ammendola E, Dell'era G, Ziacchi M, Guerra F, Aquilani S, Maglia G, Del Giorno G, Giubertoni A, Boriani G, Capucci A, Pietro Ricci R and Accogli M: Italian Association of Arrhythmology and Cardiac Pacing (AIAC). Effect of fixed-rate vs. rate-RESPONSIve pacing on exercise capacity in patients with permanent, refractory atrial fibrillation and left ventricular dysfunction treated with atrioventricular junction aBLation and bivEntricular pacing (RESPONSIBLE): a prospective, multicentre, randomized, single-blind study. Europace. 2017 Mar 1;19(3):414-420. doi: 10.1093/europace/euw035.
8. Caloian B, Sitar-Taut AV, Gusetu GN, Pop D and Zdrenghea DT. The Influence of Cardiac Pacemaker Programming Modes on Exercise Capacity. In Vivo. 2018 Mar-Apr;32(2):419-424. doi: 10.21873/invivo.11256.
9. Tops LF, Schalij MJ and Bax JJ: The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. Journal of the American College of Cardiology. 2009 Aug;54(9):764-776. https://doi.org/10.1016/j.jacc.2009.06.006.
10. Tops LF, Suffoletto MS, Bleeker GB, Boersma E, van der Wall EE, Gorcsan J 3rd, Schalij MJ and Bax JJ: Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. J Am Coll Cardiol. 2007 Sep 18;50(12):1180-8. doi: 10.1016/j.jacc.2007.06.011.
11. Simantirakis EN, Vardakis KE, Kochiadakis GE, Manios EG, Igoumenidis NE, Brignole M and Vardas PE: Left ventricular mechanics during right ventricular apical or left ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation. J Am Coll Cardiol. 2004 Mar 17;43(6):1013-8. doi: 10.1016/j.jacc.2003.10.038.
12. Gierula J, Paton MF, Lowry JE, Jamil HA, Byrom R, Drozd M, Garnham JO, Cubbon RM, Cairns DA, Kearney MT, Witte KK. Rate-Response Programming Tailored to the Force-Frequency Relationship Improves Exercise Tolerance in Chronic Heart Failure. JACC Heart Fail. 2018 Feb;6(2):105-113. doi: 10.1016/j.jchf.2017.09.018.
13. Prech M, Grygier M, Mitkowski P, Stanek K, Skorupski W, Moszyñska B, Zerbe F, Cieśliński A. Effect of restoration of AV synchrony on stroke volume, exercise capacity, and quality-of-life: can we predict the beneficial effect of a pacemaker upgrade? Pacing Clin Electrophysiol. 2001 Mar;24(3):302-7. doi: 10.1046/j.1460-9592.2001.t01-1-00302.x. PMID: 11310298.
14. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R and Vardas PE: 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013 Aug;15(8):1070-118. doi: 10.1093/europace/eut206.
15. Bolsin S, Colson M, Ridley D and Ward C: Improved performance on cardiopulmonary exercise testing following DDDR pacemaker adjustment: a case report. Br J Anaesth. 2014;112(6):1065-1066. doi: 10.1093/bja/aet587.
16. Capucci A, Boriani G, Specchia S, Marinelli M, Santarelli A and Magnani B: Evaluation by cardiopulmonary exercise test of DDDR versus DDD pacing. Pacing Clin Electrophysiol. 1992;15(11 Pt 2):1908-1913. doi: 10.1111/j.1540-8159.1992.tb02992.x.

17. Jutzy RV, Florio J, Isaeff DM, Marsa RJ, Bansal RC, Jutzy KR, Levine PA and Feenstra L: Comparative evaluation of rate modulated dual chamber and VVIR pacing. Pacing Clin Electrophysiol. 1990 Dec;13(12 Pt 2):1838-46. doi: 10.1111/j.1540-8159.1990.tb06900.x.
18. Gierula J, Lowry JE, Paton MF, Cole CA, Byrom R, Koshy AO, Chumun H, Kearney LC, Straw S, Bowen TS, Cubbon RM, Keenan AM, Stocken DD, Kearney MT and Witte KK: Personalized Rate-Response Programming Improves Exercise Tolerance After 6 Months in People With Cardiac Implantable Electronic Devices and Heart Failure: A Phase II Study. Circulation. 2020 May 26;141(21):1693-1703. doi: 10.1161/CIRCULATIONAHA.119.045066.
19. Passman R, Banthia S, Galvez D, Sheldon T and Kadish A. The effects of rate-adaptive atrial pacing versus ventricular backup pacing on exercise capacity in patients with left ventricular dysfunction. Pacing Clin Electrophysiol. 2009 Jan;32(1):1-6. doi: 10.1111/j.1540-8159.2009.02169.x.
20. Danon A, Militianu A and Schliamser J: The outcome of exercise-induced atrioventricular block, EP Europace. 2017;19(3):201–202.
21. Park MY, Shin WS, Shim BJ, Lee SJ, Park JH, Koh YS and Lee JM: Exercise-induced intranodal atrioventricular block. Korean Circ J. 2012 Oct;42(10):698-701. doi: 10.4070/kcj.2012.42.10.698.
22. Jensen PN, Gronroos NN, Chen LY, Folsom AR, deFilippi C, Heckbert SR and Alonso A: Incidence of and risk factors for sick sinus syndrome in the general population. J Am Coll Cardiol. 2014 Aug 12;64(6):531-8. doi: 10.1016/j.jacc.2014.03.056.
23. Veerareddy S, Arora N, Caldito G and Reddy PC: Gender differences in selection of pacemakers: a single-center study. Gend Med. 2007;4(4):367-373. doi:10.1016/s1550-8579(07)80066-0.
24. Varma N, Mittal S, Prillinger JB, Snell J, Dalal N and Piccini JP: Survival in Women Versus Men Following Implantation of Pacemakers, Defibrillators, and Cardiac Resynchronization Therapy Devices in a Large, Nationwide Cohort. J Am Heart Assoc. 2017;6(5):e005031. doi:10.1161/JAHA.116.005031.
25. Nowak B and Misselwitz B: Expert committee 'Pacemaker', Institute of Quality Assurance Hessen, et al. Do gender differences exist in pacemaker implantation? Results of an obligatory external quality control program. Europace. 2010;12(2):210-215. doi: 10.1093/europace/eup312.