Application and optimization of the rate response function in dual-chamber pacemakers: Prospective, randomized, cross-over clinical trial study protocol

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INTRODUCTION

Pacemakers are equipped with a function that adjusts the pacing frequency to the patient's current needs ("rate response" function) [1]. However, the impact of this function in dual-chamber pacemakers on the physical performance remains to be fully elucidated [2–3]. Results from previously conducted studies are inconsistent as to the method of optimal programming of the rate response function [4–9]. The European Society of Cardiology guidelines do not contain exhaustive recommendations on how to program, and for which parameters to optimize, the rate response function in patients with cardiological disorders coexisting with chronotropic insufficiency [2–3].

METHODS

Aim

This study aims to assess the impact of rate-responsive pacing on physical performance and to compare benefits and side effects of the rate response function with numerous clinical parameters, with different settings of rate response function used at each stage of the study. The results of the study will reveal which patients benefit the most from pacing with rate response functions.

Study group eligibility criteria

The study group will consist of 100 patients who have had a transvenous dual chamber pacemaker implanted, with more than 50% atrial pacing at study entry. All participants of the study will be at least 18 years of age. Exclusion criteria include the presence of cardiac contraindications, conditions limiting participants' ability to perform an electrocardiographic exercise test or the 6- minute walk test (6MWT), persistent atrial fibrillation, and using a pacing mode other than dual chamber sequential pacing (DDD) for any reason. Patients with conduction system pacing will not be included in the study.

Study endpoints

The primary endpoints of the study are a change in the distance in the 6MWT, a change in the maximum metabolic equivalent of task (MET) achieved during the exercise test, and a change in quality of life assessed by the 36-Item Short Form Survey (SF-36). Secondary endpoints include changes in the percentage of atrial and ventricular pacing, changes in atrial arrhythmia burden, and a change in the New York Heart Association (NYHA) classification when comparing the results of tests performed in DDD and rate-responsive dual chamber sequential pacing (DDDR) modes.

Trial design

At each stage of the trial (visits at 0, 3, and 6 months), patients will have the following tests: 6MWT, International Physical Activity Questionnaire, SF-36 questionnaire, electrocardiographic exercise test (Bruce Protocol), and pacemaker follow-up. The parameters of the rate response function will be set as appropriate to the randomly selected group.

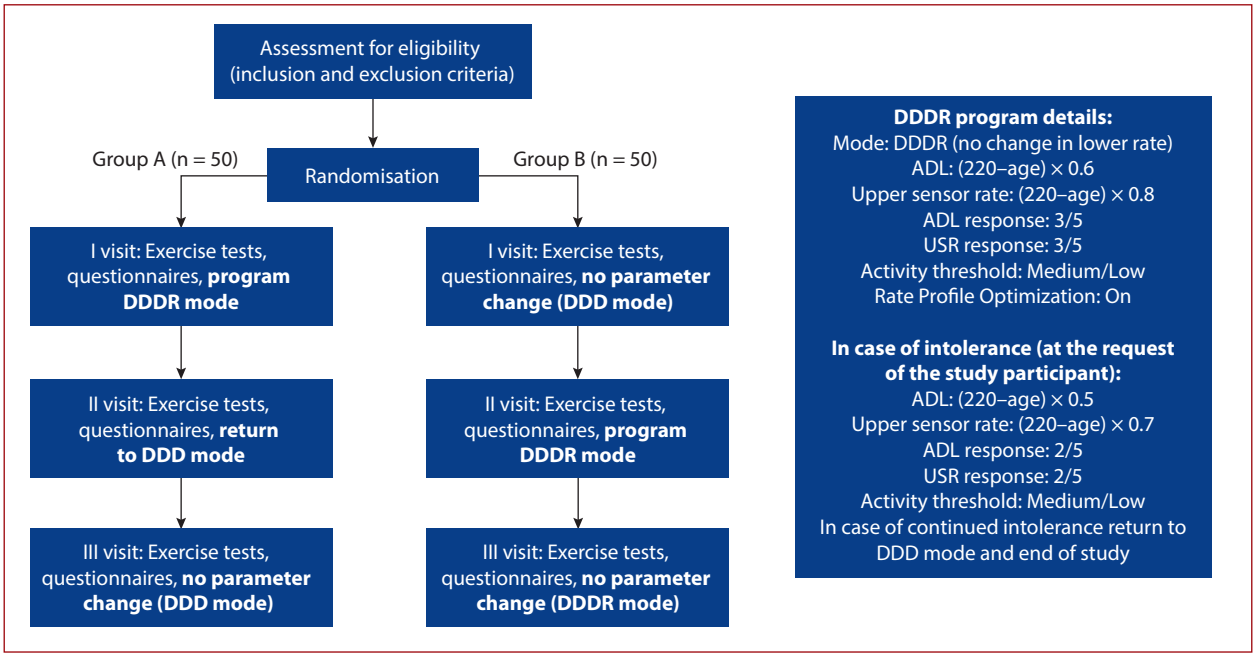

Figure 1. Follow-up and pacemaker programming flowchart

Abbreviations: ADL, Activities of Daily Living Rate; DDD, dual chamber sequential pacing; DDDR, rate-responsive dual chamber sequential pacing; USR, Upper Sensor Rate

The results of those tests will be analyzed in groups with comparable age, sex, body mass index, NYHA class, Canadian Cardiovascular Society class left ventricular ejection fraction, diseases (myocardial infarction, coronary artery disease, hypertension, heart failure, valvular diseases, cardiomyopathies, congenital heart diseases), pharmacotherapy, indications for pacemaker implantation, percentage of pacing, and atrial arrhythmias burden. The study is a single-blinded cross-over trial. Each participant of the study will have repeated diagnostic tests included in the scheme, both in the DDD and DDDR stimulation modes, to objectify the results of exercise tests and questionnaires. The A and B arms of the study groups differ in the order of introducing the same modification of the pacing mode from DDD to DDDR and vice versa. Details of rate response pacing parameters and the order of parameter changes in both groups are provided in Figure 1.

At the end of participation in the study, the decision to leave the pacemaker in DDD or DDDR mode will be made by the patient with support and consultation of a cardiologist, taking into account the results of all diagnostic tests performed during their participation.

Follow-up and pacemaker parameters

At each visit, the following data will be retrieved from the pacemaker device: pacing mode, lower rate, atrioventricular delay after pacing and sensing, percentage of atrial and ventricular pacing, heart rate histograms, and the number of recorded arrhythmias in the device's memory (duration/percentage of episodes). Apart from the rate response function settings, no other parameters are expected to be standardized. Any changes to other parameters, if necessary, will be recorded and considered for any possible impact on the test results. The effect of native or paced rhythm during exercise tests will be considered for impact on the test results. This study includes pacemaker models with accelerometric sensors. Due to technological differences in the algorithms and functioning of pacemakers from different companies, the study will be conducted only on Medtronic and Vitatron pacemakers. Parameters selected for use in this study are partly in line with those described in previous original studies in this area and with the programming recommendations described in review papers [1, 10, 11].

Statistical analysis

Assuming a 350 (127) m standardized mean difference in the 6MWT and 6.0 (1.5) MET standardized mean difference in the exercise test, with a significance level of 5%, a power of 80%, and a drop-out rate of 10%, 100 patients are needed in both groups. Initial statistical analysis of results will consist of validation of the appropriateness of the randomization method and analysis of the distribution of continuous data. Randomization will be carried out using the functionality of the statistical program (R version 4.0.3), with the matching of variables for the purpose of this study. Patients will be randomly assigned to groups A or B, maintaining similarity of the compared arms in terms of the number, age, and sex. Continuous data will be represented as arithmetic means and standard deviation or as medians and interquartile ranges. The distribution of data will be assessed for normality using the Shapiro-Wilk test. Comparison of continuous data between the groups will be based on Student's t-test or the Mann-Whitney U test,

as determined by normality of distribution. Ordinal data will be evaluated by the Kruskal-Wallis H test. An analysis of variance for repeated measures will be performed to compare the groups (either the non-parametric equivalent of the Friedman test or the aligned rank analysis of variance). For multiple comparisons, Bonferroni or Holm-Bonferroni correction will be applied.

Registration and ethics

This study will be performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee Medical University of Warsaw No. KB/173/2021.

Expected results

Our hypothesis assumes an improvement in physical capacity (expressed as an improvement of maximum MET achieved in an electrocardiographic exercise test) with rate-responsive pacing, in comparison with DDD mode pacing with constant base rate.

RESULT AND DISCUSSION

The current state of knowledge on the use and optimization of the function of frequency adaptation in pacemakers is insufficient due to the small number of studies available and the contradictory results that have been recorded [4–9]. Furthermore, specific recommendations in the guidelines of the European Society of Cardiology on cardiac pacing and cardiac resynchronization therapy are limited [2, 3]. Many studies rely on the electrocardiographic treadmill exercise test as an objective method of assessment of physical performance and progress in cardiac rehabilitation or for optimization of settings of implantable devices and cardiac [7, 12, 13]. Therefore, this study will deepen the research on the impact of the rate response function on physical performance in a homogeneous group of patients and will reveal which patients would benefit the most from rate-adapted pacing.

Article information

Conflict of interest: None declared.

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