The CLEAR Multicenter Study Concept: Comparing Closed Loop Stimulation and Accelerometer Rate-Adaptive Pacing

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Summary

The Inos^{2+} CLS cardiac pacemaker is a rate-adaptive, dual-chamber device that incorporates the Closed Loop Stimulation (CLS) principle. It continuously monitors the heart's contraction dynamics through unipolar intracardiac impedance. The CLS system is expected to be superior to the accelerometer sensors that regulate the pacing rate during physical stress based on body movement and acceleration. The planned CLEAR multicenter study plans to compare the rate adaption in Inos^{2+} CLS and Philos DR (accelerometer) pacemakers during a treadmill test, daily activities, and a range of control tests. The objective is to assess the function of the autonomic nervous system and of the cardiovascular control loop. Our study hypothesis is that the CLS system will adequately react during all tests and will not be inferior to the accelerometer sensor. A total of 60 patients will be randomized for Inos^{2+} CLS or Philos DR pacemaker implantation. During the first 6 postoperative weeks, the tests will be carried out in the DDD mode to document the patients' restricted performance capability and chronotropic incompetence. Thereafter, all the tests will be repeated in the respective rate-adaptive mode, and the results of CLS and accelerometer rate-adaptive pacing will be compared.

Key Words

Rate-adaptive pacing, Closed Loop Stimulation (CLS), accelerometer sensor, autonomic cardiovascular function

Introduction

Chronotropically incompetent patients will benefit from therapy with rate-adaptive pacemakers depending on their intrinsic rate during peak exercise [1]. The Inos^{2+} CLS rate-adaptive pacemaker (Biotronik, Germany) features Closed Loop Stimulation (CLS) based on unipolar right ventricular impedance monitoring [2-4]. It has been proven that this signal is correlated to the maximum right ventricular pressure gradient, an established parameter for myocardial contractility [5]. It has been shown that CLS is superior to other pacemaker sensors [6,7], yet these observations have not been confirmed in larger, randomized clinical trials.

Study Objectives

The CLS system has not yet been compared to a conventional, rate-adaptive pacemaker system in a randomized clinical study. Accelerometer systems are suited for such a study since they are widely used in clinical practice, and because a multitude of reference data from the literature can be used for sample size calculation and detailed comparison of study results.

The Closed Loop Stimulation: Efficacy Comparison to Accelerometer Rate Adaptive Pacing (CLEAR) multicenter study aims to compare the rate adaption of the Inos^{2+} CLS and Philos DR pacemakers (Biotronik, Germany) during a treadmill test, daily activities (ascending stairs versus descending stairs), and control tests in order to assess the function of the autonomic nervous system and the cardiovascular control loop. The accelerometer sensor in the Philos DR pacemaker reacts to physical stress caused by a change in the acceleration of the upper body. However, it is not sensitive to the differences in types of physical stress that cause the same acceleration effect, and it does not react to loads that have no acceleration effect. We believe that the Inos^{2+} CLS pacemaker will be able to react adequately to all types of stress [6,7] and will be at least equivalent if not superior to the accelerometer pacemaker.

If no significant differences between the two groups can be found for any of the tests, then a comparison between examinations performed in the fixed-rate DDD mode and in the respective rate-adaptive mode should reveal whether the respective rate-adaptive therapy has been of any advantage to the two patient groups. Comparing the examinations done in DDD mode for the Inos^{2+} CLS and the Philos DR patient groups should indicate any differences between the two randomized groups.

Materials and Methods

Pacemakers

The inotropic adaption of the heart to all types of stress leads to a change in the contraction processes, which are detected by the CLS pacemaker and used for rate adaption. Changes in daily routines, administration of cardiovascular drugs, or changes in ventricular contractility, e.g., congestive heart failure (CHF), can cause long-term changes to contraction dynamics. The CLS system compensates for such long-term effects by continuous self-adjustment. Basic rate and maximum sensor rate define the dynamic range of the pacing rates during automatic initialization and continuous adjustment. No parameters other than the basic rate and maximum sensor rate need to be programmed for rate regulation.

The Philos DR accelerometer-based pacemaker has an optional automatic sensor gain feature [8], similar to the continuous adjustment function of Inos^{2+} CLS pacemakers. It also compensates for long-term influences, such as drug modifications, thereby minimizing any possible bias caused by programming the accelerometer sensor parameters.

Inclusion Criteria

- Indication for a first implantation or implantation due to an exchange indication of a rate-adaptive DDDR pacemaker
- Existing AV block (AV delay > 200 ms) or ventricular pacing indicated
- Chronotropic incompetence (heart rate at submaximum load < 100 beats/min)
- Programming the maximum pacing rate to 0.8 x [220 – age in years] ppm is not contraindicated
- Age > 30 years, so that the maximum pacing rate of 0.8 x [220 – age in years] ppm is lower than 160 ppm
- Stable medication
- Patients whose medical state is stable
- Patients who are geographically stable and are able and willing to comply with the scheduled follow-ups
- Patients who have been informed about the study by the clinical investigator, who have read and understood the patient information, and who have signed the patient consent form

Exclusion Criteria

- Patients who do not meet the inclusion criteria
- Dual-chamber pacing is contraindicated in cases of atrial flutter/atrial fibrillation
- Rate-adaptive pacing is contraindicated in patients who develop angina or ischemia at higher heart rates
- Patients with NYHA class III, IV
- Patients unable to perform the required tests
- Patients who are currently enrolled in another study

Table 1. Inclusion and exclusion criteria of the CLEAR multicenter study.

Patients

A total of 60 patients with a DDDR indication who are physically able to perform the study tests will be enrolled in the study for a period of 6 months. Inos^{2+} CLS pacemakers require permanent ventricular pacing for rate adaption, limiting their indication mostly to patients with binodal disease. To prevent a potential bias, inclusion and exclusion criteria will be identical for both pacemakers (see Table 1).

Study Design

The CLEAR study is a prospective, randomized study in up to 12 European centers including an Inos^{2+} CLS and a parallel Philos DR group of 30 patients each. Three standard follow-up examinations will be conducted on each patient: prior to hospital discharge after implantation, 6 weeks post-implantation, and 6 months post-implantation (see Figure 1). Inter-individual comparisons of the rate adaption in patients with Inos^{2+} CLS and Philos DR pacemakers will be done during the 6-month follow-up by means of a treadmill test, staircase test, and various control tests. The objective will be to assess the function of the autonomic nervous system and activities of daily life by monitoring with an optional 24-hour Holter ECG. The 6-week follow-up examination, during which the respective clinical tests will be carried out in a fixed-rate DDD pacemaker mode, will serve as the intra-individual control.

Primary Endpoint

The primary endpoint is the maximum load tolerance in metabolic equivalents (1 MET = uptake of 3.5 ml oxygen per time in min and per body weight in kg) during a symptom limited maximum load treadmill test. Treadmill protocols consist of several increasing load stages with differing treadmill speeds and treadmill grades, which are increased in defined time intervals [9,10]. Based on our early experience in exercise testing to evaluate rate-adaptive pacemakers and that of other groups [9-13], a customized treadmill test protocol has been chosen. The common chronotropic assesment exercise protocol (CAEP) [10-13] will be modified by using 1-min intermediate intervals instead of 2-min stages (see Figure 2). The expected oxygen consumption in METs can be found in the literature (reference METs; [11]), or it can be estimated from the treadmill speed and the treadmill grade (estimated METs; [9,11]). For the study patients a maximum load tolerance is estimated approximately by 5 METs [13].

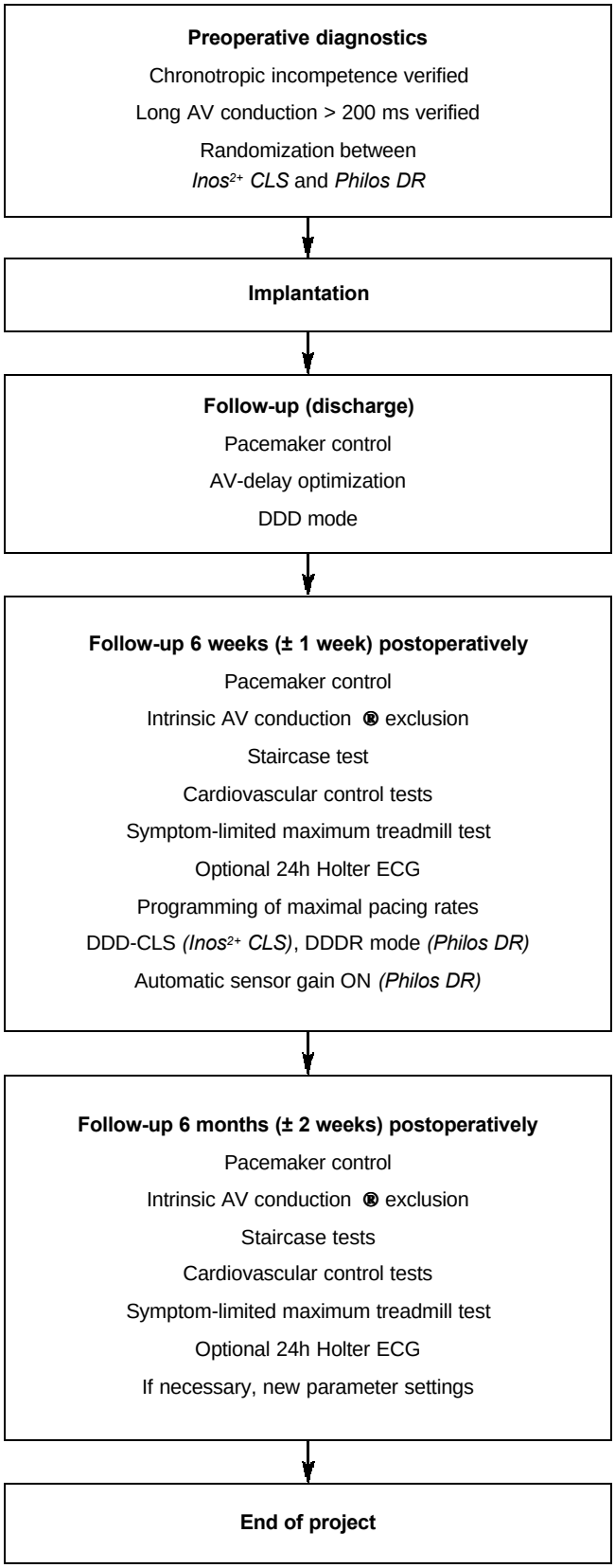

Figure 1. Flow chart of the CLEAR multicenter study.

The superiority of CLS may be small for our study patients, which will have a medium load tolerance to perform the treadmill test in DDD and DDDR mode without risk. To avoid a large sample size, it will be shown that the new therapy is better, or, in the worst case, not significantly worse than the reference therapy [14], i.e. $Inos^{2+}$ CLS group will exceed the maximum load tolerance of the Philos DR group minus an equivalence limit of $\delta = 1$ MET. Given a significance level of $\alpha = 5\%$, a power of 80%, and a sufficient safety margin based on the implemented according-to-protocol method, 60 patients will be included in the study.

Secondary Endpoints

The secondary endpoints will result from heart rate and blood pressure measurements during the following tests.

The treadmill test causes an increase in heart rate. The CAEP treadmill test was developed to establish a linear relationship between the individual load stages and the expected heart rate [15].

The staircase test was designed to simulate a daily-life sub-maximum load and to test the specificity of the respective sensor. A physiologic adaption of the sensor rate requires a higher pacing rate when ascending than when descending stairs, which has already been observed in patients with CLS pacemakers [6,16].

The Valsalva maneuver consists of a short expiration against the closed glottis (pressure breathing), leading to a rise in intrathoracic pressure, which in turn influences cardiovascular regulation. As soon as expiration is no longer blocked, further characteristic adaption mechanisms of the cardiovascular system with physiologic vacillations of the blood pressure and the heart rate result [17,18]. This non-invasive test of the autonomic function of the cardiovascular system is easily done and is conclusive, i.e., much comparison data to the Valsalva ratio already exists which is determined by the longest RR interval from the surface ECG after the maneuver and the shortest RR interval (RR_{min}) during the maneuver. The Valsalva ratio is a marker of the function of the autonomic control mechanisms and should be above 1.4 in healthy persons [18]. It has already been qualitatively proven that CLS can at least partially restore this cardiovascular reflex [19]. In contrast, an accelerometer sensor is not capable of reacting to a Valsalva maneuver.

The active orthostasis test is performed by having the patient remain in an initial resting phase in the supine position and then abruptly changing position from the supine to the upright position [17,18]. To counter the drop in blood pressure due to the change in the amount of venous blood and in order to avoid syncope, the physiologic rate increase should be in the range of 5 to

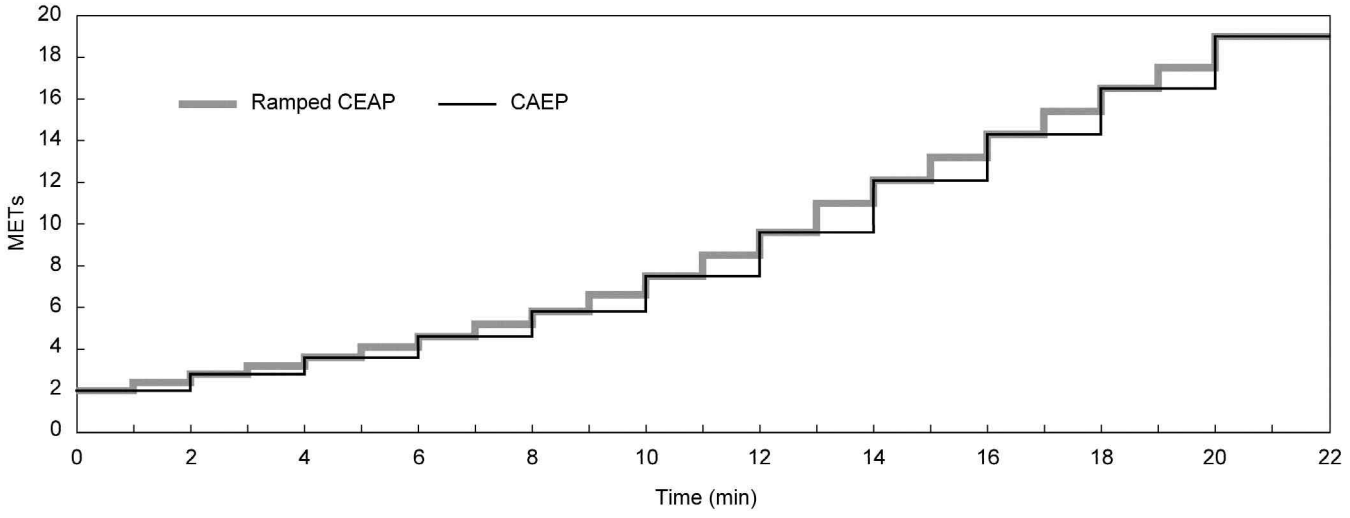

Figure 2. Linear relation between load in metabolic equivalents (METs) and duration of the "ramped" CAEP treadmill test with 1-min intermediate steps and the CAEP treadmill test with 2-min intermediate steps [10]. The expected METs can be estimated from the treadmill speed and treadmill grade [11,12]:
VO_2 (ml/kg/min) = 3.5 + 0.1 x speed (m/min) + 1.8 x grade(%/100) x speed (m/min) : walking up to and including stage 7
VO_2 (ml/kg/min) = 3.5 + 0.2 x speed (m/min) +0.9 x grade (%/100) x speed (m/min) :running

20 bpm [19]. The CLS-system can react to the changed contraction dynamics. An accelerometer sensor can principally detect the change in movement connected with the orthostasis test, but the programming of the sensor threshold and the rate slope could prevent an adequate increase in pacing rate.

The mental stress test is performed by an arithmetic test during which the number 17 must be serially subtracted from 1000 as fast as possible [18,21]. This test checks the sympathetic regulation of the cardiovascular system. Pacemakers with an accelerometer sensor or other sensors that do not capture a cardiovascular parameter cannot react to such tests by adapting the pacing rate. However, a restoration of rate dynamics and cerebral perfusion during mental stress should have a particularly positive effect in physically inactive elderly patients. An adequate reaction of CLS to mental stress has already been documented [6]. However, the previous study results were not significant due to the small number of patients involved in the study. Since there was no randomization during the pacemaker implantation and no reference measurement in the non rate-adaptive DDD pacemaker mode, a possible bias caused by the intrinsic rhythm cannot be verified.

The handgrip test is an isometric physical load where a fist force of 30% of the individual maximum force development must be exerted [18]. The test checks the sympathetic regulation of the cardiovascular system. Pacemakers with an accelerometer sensor cannot react to such tests by adaptating the pacing rate. A restoration of rate dynamics as with CLS [7] can provide chronotropically incompetent patients with a higher performance capability even during static physical loads.

A 24-hour Holter ECG may be performed in a subgroup of patients with noticeable/atypical autonomic function, which will be analyzed by means of heart rate variability (HRV) [22] in order to classify this group of patients. Additionally, circadian heart rate variation will be analyzed. In contrast to CLS, pacemakers with an accelerometer sensor are not able to restore the heart rate variation without programming an artificial night program.

Discussion

The advantage of CLS systems has already been proven in several unicenter studies. Nevertheless, the results were not statistically significant owing to the small number of patients who participated in the studies or due to the lack of common reference measurements. Thus, the CLEAR randomized multicenter study has been designed to verify the benefit of CLS in comparison to established accelerometer rate-adaptive pacing by means of defined and standardized clinical tests. The study has already started with five centers and is planned to conclude by the end of 2003.

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