Cardiac Contractility Sensor Evaluation in a DDDR System – A Multicenter Study

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Summary

DDDR pacemaker treatment of AV conduction disorders associated with a sick sinus node has motivated the search for an ideal sensor. This study investigated the Inos^{2}DR closed-loop stimulation system which uses the myocardial contractility state as indicator for the rate response. We selected 85 patients from 15 Brazilian implantation centers, presenting various disorders in the cardiac conduction system. The main objective was to evaluate the heart rate response of the pacemaker during ambulatory tests (physical and mental stress) and daily-life activities. The measurements were performed 30 days after implantation. Pacing and sensing thresholds were measured, and the heart rate was monitored during mental stress (mathematical and perception tests) and treadmill tests, using histogram recordings. The heart rate varied from 5 to 160% above basic rate on physical activities and from 3 to 79% on mental stress, with an appropriate attack rate at the beginning of every activity. We conclude that closed-loop stimulation based on cardiac contractility has an excellent performance on heart rate adaptation, comparable to a healthy control group.

Key Words

Artificial cardiac stimulation, closed-loop pacemaker, heart rate response, sinus node disease, AV block

Introduction

While earlier pacemakers reduced patient mortality and alleviated many symptoms, the patients were paced with the same rate under all conditions, a state totally different from that of healthy individuals. Sometimes, this led to remaining symptoms or a low physical capacity. In the last two decades, the objectives of cardiac pacing have expanded. Now, we strive to achieve a total restoration of the functional capacity and of the patient's quality of life. To this end, an adequate heart rate (HR) in response to the load state and AV synchrony are desirable [1-3]. The resulting hemodynamic benefits have become obvious in the newest pacemaker generations.

As a consequence of our grown understanding of cardiac electrophysiology and physiopathology, indications for pacemaker implantation have increased. The resulting, large-scale clinical use of cardiac pacing emphasizes the need for physiologic pacemakers. Rate-responsive pacemakers are of particular benefit to patients suffering from chronotropic incompetence, either due to a sinus dysfunction or to an atrial arrhythmia which prevents the use of the atrial rate as a timer for the ventricular pulses, e.g. frequent atrial fibrillation episodes.

Heart rate variability is of fundamental importance in adjusting the cardiac output (CO) to the metabolic demands in response to physical or mental stress. Under conditions of a metabolic increase, the human organism modifies several parameters besides the HR, such as body movements, ventilation rate, blood pH, temperature, and oxygen saturation, systolic volume, ventricular pressure, QT interval duration, and heart contractility.

Monitoring of one of these parameters, which functions as indicator of the metabolic state, allows the construction of a rate-responsive pacemaker. Efforts in pacemaker development have focused on finding the most suitable biosensors for rate response [4]. Obviously, a parameter that clearly indicates the necessary changes in CO must have the following characteristics: specificity, proportionality, and appropriate response time. Specificity means that the variable should show similar changes than the heart rhythm and not be influenced by unspecific disturbances. Proportionality implies that the selected parameter should change proportionally to the increase or decrease of the load. A good response time is characterized by a quick parameter change at the load onset and a gradual normalization with its termination.

The basic operation principle of a conventional pacemaker is: During exercise, the values of the chosen indicator change; those changes are recorded and quantified by a sensor, processed by an algorithm and translated into a pacing rate change. In consequence, the rate is adapted to the required metabolic demand.

A rate-responsive pacemaker should possess further qualities: durability, reliability, easy implantation and programming, the possibility to remedy complications, and safety even in cases of sensor dysfunction. Other important characteristics are the compatibility with conventional leads and the presence of a circadian rate variation, which is closely related to the patient's state of activity.

Under physiologic conditions, the CO is regulated by medullary centers, meeting the varying hemodynamic demands. All changes in activity, physically or mentally, involve interrelated organic changes, e.g., in the functioning of the lungs, kidneys, heart, vascular and nervous systems. The autonomous nervous system modulates these changes through information received from its receptive system: baroreceptors, volume receptors, and chemoreceptors. Cardiac activity is intimately related to this influence and to the activity of the humoral system. In both, transmitter substances such as catecholamines play a decisive role.

Figure 1 shows that the CO depends on two variables: HR and stroke volume (SV). Both are regulated by the medullary centers in two ways: chronotropically and inotropically. The control centers receive constant feedback from the variations of mean arterial blood pressure (MABP) and total peripheral resistance (TPR), which are in turn influenced by the CO. Thus, a closed control loop is created.

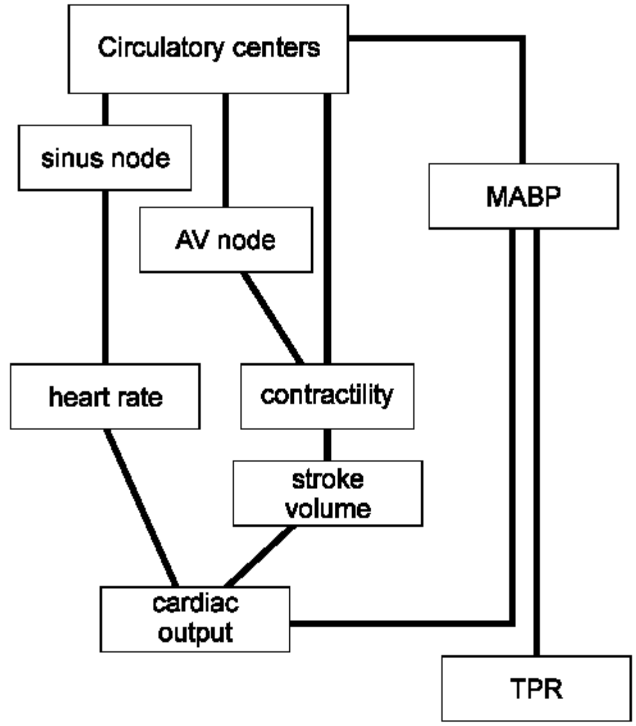

Figure 1. Cardiac output control by the medullary centers through HR (chronotropy) and SV (inotropy).

Physiologic closed-loop control

Diseases of the cardiac conduction system affect the chronotropic regulation. The loss or limitation of the pulse generation in the sinus node and/or the loss or limitation of AV conduction restricts CO regulation to changes of the venous return flow and the myocardial contractility (inotropic adaptation). While these factors are important, CO increase is quantitatively and temporally quite limited. However, the cardiac contractility state continues to reflect the influence of the medullary centers directly. Its monitoring therefore yields an outstanding parameter for the artificial re-establishment of the closed loop control of CO.

The concept of the Closed-Loop Stimulation pacemaker

Cardiac contractility, mainly in the isovolumetric contraction phase, is reflected in the myocardial impedance, the monitoring of which constitutes an excellent load change indicator. It allows the re-establishment not only of a physiologically adaptive HR but of the intrinsic closed-loop control. Contractility values can be obtained by recording the unipolar impedance between the electrode tip in the right ventricle and the pacemaker housing [5]. The impedance variations obtained in this configuration are caused mainly by

changes of the conductivity around the distal electrode. Due to the changing contractility and ratio of the blood and myocardium volume in the vicinity of the electrode tip during isovolumetric contraction and ejection, the conductivity varies, reflecting the tone and geometric changes of the myocardium. Therefore, the impedance signals reflect the contractile state directly and immediately.
Implantation of a closed-loop pacemaker based on the contractile status of the myocardium re-establishes the influence of the medullary centers on the HR (figure 2) [6]. Since the impedance is measured by the same electrode that paces the ventricle, conventional leads can be used — another advantage of this concept. In cases of pacemaker exchange, already implanted leads can remain and continue to be used.

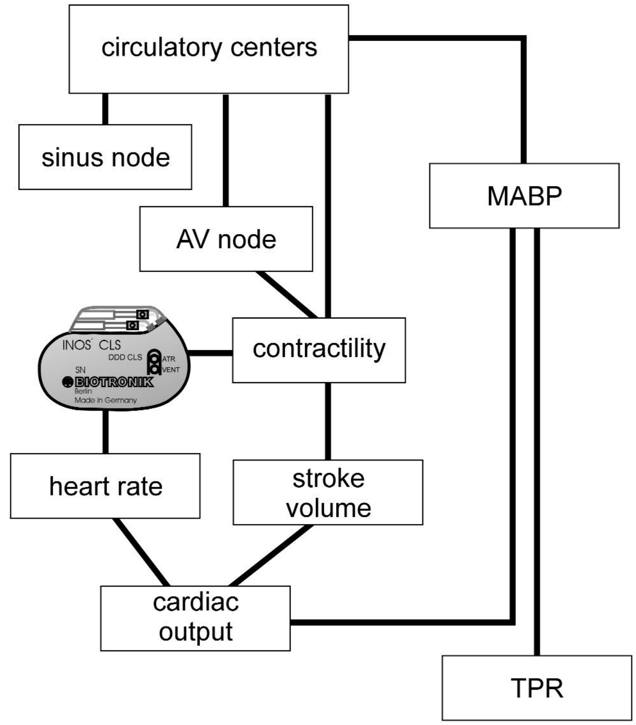

Figure 2. Artificial re-establishment of HR variation by the pacemaker in cases of chronotropic incompetence, using cardiac inotropy.

Objective

This study aimed to evaluate the rate response of the Closed-Loop Stimulation (CLS) pacemaker in situations of physical and mental stress, both during ambulatory tests and daily activities of pacemaker patients.

Materials and Methods

This multicenter study summarizes the experience of 15 Brazilian implant centers with the INOS^{2}DR (BIOTRONIK, Germany), a closed-loop pacemaker system based on the contractile status of the myocardium. The total number of patients was 85, 43 of them male and 42 female. The mean age was 55.7 years (range 13 to 92). Pacemaker implantation was indicated due to sinus node disease in 19 patients, first-degree AV block in 48, and binodal disease (sinus node disease and block) in 18 patients.
The measurements were performed 30 days after implantation to secure an appropriate maturation of the heart-electrode interface. At that time, the atrial and ventricular pacing and sensing thresholds were measured, as well as the atrial and ventricular lead impedance. All pacemakers were programmed in DDD CLS mode, i.e., dual-chamber pacing with rate response.
The pacemaker possesses a recording system that can monitor the HR over 24 h. During examination, the patients were instructed to fill in a diary detailing their activities, daily-life stress situations, and possible symptoms. On the second day after initialization and programming, the patients' 24-h histograms were analyzed. The patients then underwent mental and physical stress tests. For evaluation of the pacing rate variation during mental stress, they were submitted to 2 standard tests:

a) Mathematical tests — The patients were asked to accomplish simple mathematical operations, but in great amount and in a short period of time (4 min).
b) Test of visual perception — The patients had to select one among several ideograms on a page in a short period of time (40 s). This test was particularly used for illiterate patients who had difficulties to accomplish mathematical operations.

For evaluating the rate variation during physical exercise, an ergometric test was programmed. Besides walking, the patients ascended and descended stairs to analyze the rate response to that activity.
During all tests, the patients were monitored with dynamic electrocardiography (24-h Holter recording) and asked for the appropriate completion of their diaries, in addition to rate variation documentation by the stored histograms and the telemetrically interrogated pacemaker data.

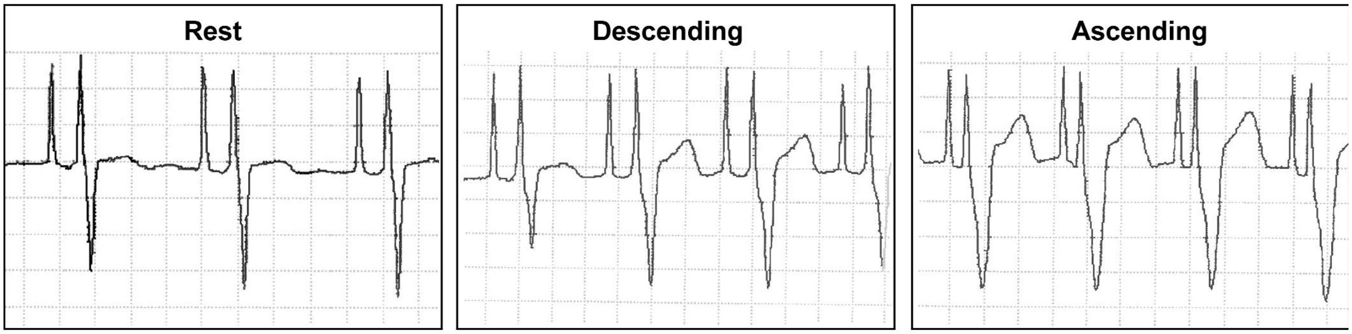

Figure 3. Dynamic ECG recordings documenting the pacing rate modification during stair-climbing exercise (total of 20 steps).

Statistical analysis

The test used to compare the mean values was the Student's t-test. For comparison of variables, variance analysis of repeated data was applied. Values of $P<0.05$ were defined as statistically significant.

Results and Discussion

The mean pacing thresholds at implantation were 0.76 ± 0.40 V for the atrium and 0.52 ± 0.35 V for the ventricle in the unipolar configuration, and the mean sensing thresholds were 2.59 ± 1.49 mV for the atrium and 11.79 ± 4.92 mV for the ventricle in the bipolar configuration.

During pacemaker initialization 30 days after implantation, the mean pacing thresholds were 1.34 ± 0.64 V (atrial) and 1.10 ± 0.57 V (ventricular), and the sensing thresholds were 2.82 ± 1.79 (atrial) and 6.62 ± 1.36 mV (ventricular).

The intraoperative results are congruent with previous experiences, given that conventional endocardial leads were used. The chronic thresholds measured 30 days after implantation show an elevation of the pacing thresholds by about 100% and a reduction of the ventricular sensitivity by around 50%, revealing that the heart-electrode interface had not yet reached a stable, chronic state.

Physical Activity

An HR increase was observed soon after the beginning of exercise. The rates reached an increase of 5% to 160% above the basic pacemaker rate. It is important to point out that the MABP showed comparable variations which were similar to that of healthy individuals.

The stair-climbing exercise (20 steps) demonstrated that the rise in HR is significantly larger when ascending (28 ± 14 bpm) than when descending stairs (18 ± 10 bpm) (figure 3). The fact reflects the larger metabolic demand during ascending and demonstrates the correct rate response of the pacemaker.

The results of the Holter recordings and the histograms show significant rate variations during daily activities (figure 4).

Mental Activity

The mental stress tests (figure 5) and the 24-h Holter analysis reveal that the pacemaker rate varied from 3 to 79% above the basic rate.

The heart, as central organ of the cardiovascular system, responds almost immediately to the demands transmitted by the central and autonomous nervous system. The medullary centers exert their influence through two mechanisms: chronotropy and inotropy, i.e., through the HR and the myocardial tone. Although rate changes are more pronounced under load than contractility changes, both are important in the adjusting the CO, and they are closely related [7][8]. This accounts for the great advantage of the contractility based closed-loop concept: by monitoring the changing myocardial tone, it adapts the pacing rate under conditions of physical as well as mental stress (with rate increases to 160 and 79% above basic rate, respectively).

It has already been demonstrated that these rate variations are similar to those of a healthy control group [9]. Clinical pre- and postoperative evaluation of this patient group reveals a significant improvement of the functional NYHA class (figure 6), demonstrating the

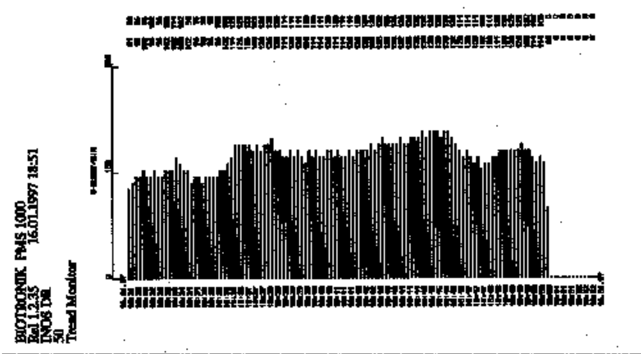

Figure 4. Rate histogram obtained by pacemaker telemetry. Patient HVAP, female, 61 years.

possibility of improving the patients' quality of life. In some patients, that improvement was truly surprising, as in the case of DCM (female, 64 years) suffering from accentuated cardiomegaly (+++ / ++++), class IV, and using drugs for ICC treatment. After receiving the pacemaker implant, she was upgraded to class I, re-established her habitual activities, and showed an oxygen consumption curve pattern identical to that of a healthy individual during non-strenuous physical activity in the ergometric test.

A great number of pacemaker implants in Brazil is performed in carriers of Chagas' disease. Since changes of the pacing rate are related to cardiac contractility, a possible advantage of CLS pacing consists of maintaining an appropriate rate in those patients. The CLS system does not share a common drawback of other sensors, namely to pace with an elevated rate in order to make up for a low ejection fraction. Attempting to increase the CO in such a way would worsen the myocardial dysfunction in Chagas' patients. On the contrary, the closed-loop pacemaker will answer the decreased myocardial tone with a lower pacing rate.

Commonly, due to clinical needs, pacing rates are changed by programming and initialization. However, in the absence of the necessary technical or skill prerequisites, the CLS pacemaker can modify its rate in response to the administration of contractility-influencing drugs. Transvenous injection of metoprolol, which has negative inotropic effects, or of digoxin, which affects inotropy positively, reduces or increases the pacing rate correspondingly [10]. This "medication programmability" is another yet unstudied option that should be clinically explored.

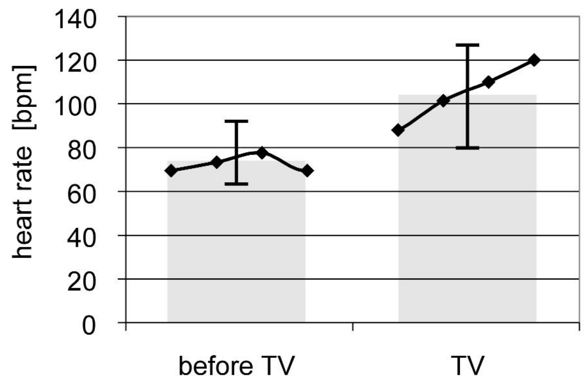

Figure 5. Significant pacing rate change observed with patient DCN, 64 years, while watching a TV soap opera, without any physical activity.

Conclusion

The closed-loop concept enables the pacemaker to accomplish appropriate heart rates, during physical as well as mental activities.

The rate response is fast, almost immediate, and very similar to that of normal individuals, giving testimony to the excellent performance of the CLS pacemaker.

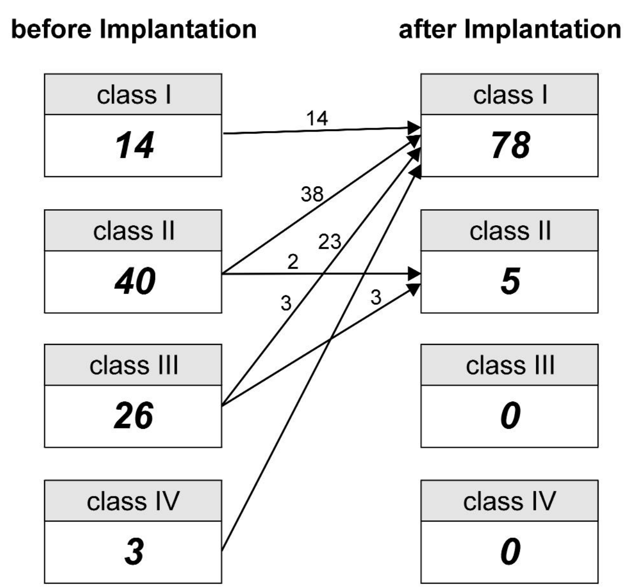

Figure 6: Functional NYHA classification before and after Inos²DR implantation.

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