Restoration of Circadian Variation and Physiologic Rate Behaviour through Closed Loop Stimulation: RAPID Study Findings

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Summary

In conventional open-loop rate-adaptive pacing systems, the physician tailors pacemaker response during physical exercise by carefully programming several rate-adaptive parameters for each individual. Conversely, Closed Loop Stimulation (CLS) systems modulate the pacing rate automatically based on the inotropic drive, and allow the physician to program only the basic and maximum pacing rate. These systems continually adjust their internal non-programmable rate-responsive parameters to changing patient conditions. The goal of this multicenter study, which included 16 centers from three European countries, was to evaluate the appropriateness of CLS rate profiles during daily activities as well as the long-term stability of the CLS rate response. 102 patients (mean age 71.4 ± 8.4 years, 38 % female) who had been implanted with dual-chamber Inos pacemakers participated in the RAPID study (Rate Behavior of the Pacing System Inos² CLS during Daily Life). The pacemaker clearly differentiated activities such as walking along a level corridor, climbing stairs, and descending stairs, with the corresponding maximum CLS rates of 89 ± 12 beats/min, 106 ± 18 beats/min, and 95 ± 15 beats/min, respectively (P < 0.05 for any pair of activities). A 24-hour heart rate trends retrieved from the pacemaker memory at 3, 6, and 12 months after implantation revealed appropriate heart rates in all the patients except for two whose pacing rates during the night were faster than desired. Mean incidence of atrial pacing in the total population during the entire study was 81 ± 17 %, with daily mean rates at the three different follow-ups ranging from 75.2 – 76.8 beats/min (P = ns) and nightly mean rates ranging from 67.6 – 69.2 beats/min (P = ns). The small variation in the mean daily and mean nightly rates implies long-term stability of the CLS rate adaptation. The 6.9 – 9.0 beats/min difference in the mean heart rate between day and night (P < 0.05) as well as a clear distinction between stair climbing versus descending indicates excellent sensitivity of CLS systems to real physiologic demands.

Key Words

Rate adaptive pacing, contraction dynamics, Closed Loop Stimulation

Introduction

The latest generation of rate-adaptive systems based on impedance cardiography (Inos pacemaker family, Biotronik, Germany) offers a fully automatic rate response, where only basic rate and maximum closed loop rate are programmable by the physician. Such systems are also termed Closed Loop Stimulation (CLS), since the pacemaker is incorporated into, and the pacing rate is continuously guided by, the natural cardiovascular control loop [1-8].

The multicenter RAPID study (Rate Behavior of the Pacing System Inos² CLS during Daily Life) was begun in 1998 to evaluate the appropriateness of CLS rate profiles during daily activities, as well as the long-term stability of the CLS rate response. The investiga-

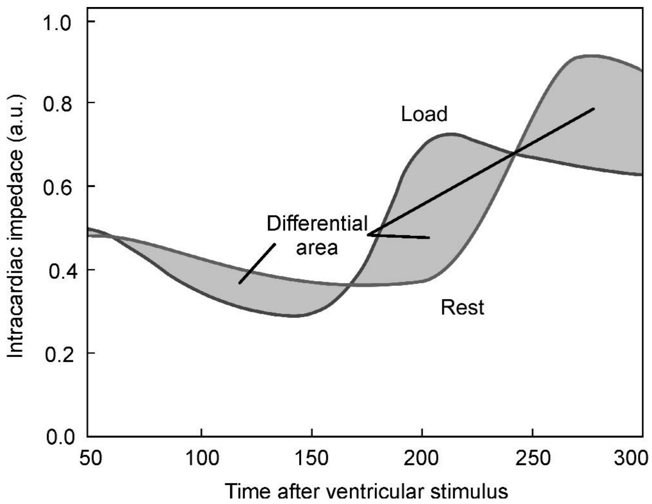

Figure 1. The intracardiac impedance curve is determined for the period between 50 and 300 ms after a ventricular stimulus, which involves isovolumetric contraction and the beginning of the ejection phase. The surface area below the current curve (load) is compared with the area below the slowly updated reference curve (rest). The "differential area" in between the curves (shown in grey) is multiplied by a self-adjustable internal rate-responsive factor to determine the pacing rate.

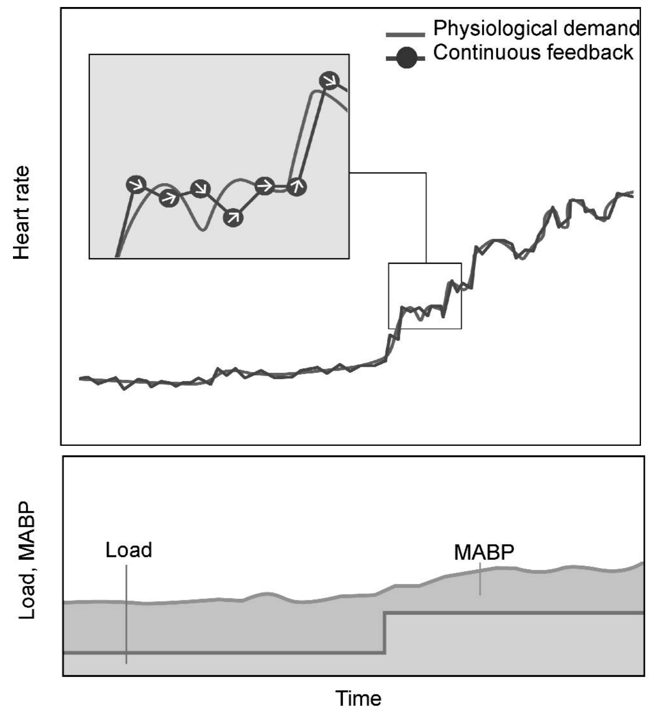

Figure 2. A continuous feedback loop established in Closed Loop Stimulation systems ensures that the pacing rate closely follows cardiovascular demands. MABP = mean arterial blood pressure.

tion comprised 16 clinics from three European countries (see Clinical Investigators list).

Materials and Methods

102 patients were enrolled in the RAPID study from January 1998 to December 1999. The mean age of the participating patients was 71.4 ± 8.4 years; 38 % were female and 62 % male. Indications for pacing were sick sinus syndrome in 50 patients (49 %), atrioventricular block in 25 (24 %), binodal disease in 22 (21 %), and other indications in five patients (5 %).

Inos^2 DR, Inos^2 CLS, and Inos^{2+} CLS pacemakers were implanted together with conventional tined or screw-in pacemaker leads from three different manufacturers (Biotronik, Germany; Medtronic, USA; and Guidant, USA). All pulse generators were dual-chamber devices using the same algorithm to translate changes in the contraction dynamics into pacing rate variation.

Pacemaker Description

In addition to pacing pulses, Inos pacemakers deliver biphasic subthreshold pulses (31.25 µs in deviation, with a rate of 32 Hz) to monitor contraction dynamics. Thereby, current is injected and corresponding voltage is measured between the tip of the ventricular lead and the pacemaker housing. The morphology of the measured impedance curve is illustrated in Figure 1. The curve reflects local changes in myocardial contraction dynamics in the area surrounding the lead tip [9]. By regulating the pacing rate according to changes in contraction dynamics, the pacemaker is effectively incorporated into the natural cardiovascular control loop. Since contractility and the heart rate interact with each other, a pacing rate that is too slow will cause an increase in contractility due to the baroreceptor reflex (triggered by a suboptimal systemic blood pressure), thereby indicating to the pacemaker that a faster heart rate is necessary. The reverse occurs for a pacing rate that is too fast. In theory, this interaction establishes a negative feedback loop that continuously guides the pacing rate towards an optimal value that matches current hemodynamic demands (Figure 2). The CLS principle of this particular type represents an artificial sinus node controlled by the baroreceptor reflex, where only the basic and maximum closed loop rates can be programmed by the physician. Other rate-responsive parameters are continuously self-adjusted to changing patient conditions and cannot be regulated externally. In their present technical form, CLS pacemakers require ventricular pacing in all heart cycles to ensure stable morphology of the sensed intracardiac signal. Dynamic atrioventricular (AV) delay should be programmed to slightly overdrive spontaneous AV conduction during rest and exercise. Intrinsically conducted ventricular beats are not taken into account and can cause a gradual decrease of the pacing rate toward the basic rate. Upon resumption of ventricular pacing, the pacing rate gradually increases to the CLS-indicated rate. The atrium may be paced, sensed, or both.

Study Protocol

After pacemaker implantation, the DDD-CLS mode (i.e., CLS) was enabled and other pacemaker parameters were programmed under physicians' discretion except for the dynamic AV-delay, which had to be about 30 ms shorter than the intrinsic AV conduction interval.

Follow-up examinations took place at 1.5 to 3 months (1^{st} follow-up), 6 months (2^{nd} follow-up), and 12 months (3^{rd} follow-up) after pacemaker implantation. At the beginning of each follow-up examination, the rolling 24-hour heart rate trend and counters showing the percent of paced and sensed events in the atrium and ventricle in the period between the previous and current follow-up points, were interrogated from the pacemaker memory. Patients provided a diary of activities corresponding to the retrieved 24-hour trend. An in-clinic activity test was performed at the 1^{st} follow-up examination. This test included stair climbing for 3 minutes followed by 2 minutes of rest, stair descending for 3 minutes followed by 2 minutes of rest, and 3 minutes of walking along a level corridor. A short-term pacemaker rate trend was obtained in conjunction with the in-clinic testing.

Data Analysis

A 24-hour heart rate trend consisted of 45 points, each representing the mean heart rate during a 32-minute period. The individual 24-hour trends were pooled at each follow-up examination among all patients for whom pacemaker interrogation was performed accurately. Mean daily and nightly rates in each individual were then obtained from the 24-hour trends for each follow-up examination. The "day" was considered to begin with getting up in the morning and to end with going to bed in the evening, as recorded in the patient diary. Heart rates during the initial period of rest, as well as the maximum rates during stair climbing, stair descending, and walking, were extracted from the short-term pacemaker trends obtained during in-clinic testing. Pooled 24-hour heart rate trends are presented as mean values ± standard errors of the mean, and other data are given as mean values ± standard deviations. Two-tailed t-tests were used in the statistical evaluations, with P-values < 0.05 considered significant.

Results

The mean programmed basic rate was 60 ± 3 beats/min, the maximum closed loop rate was 121 ± 9 beats/min, and the paced AV-delay was 166 ± 12 ms at the basic rate and 108 ± 16 ms at 130 beats/min (point of maximum AV-delay shortening). Ventricular pacing was achieved in 99.2 % of heart cycles during the entire study, implying nearly continuous CLS rate adaptation. Atrial pacing (CLS guided rate) was present in 82 ± 17 % of the heart cycles in the period between pacemaker implantation and the 1st follow-up examination, in 80 ± 17 % of the heart cycles between 1^{st} and 2^{nd} follow-up examination, and in 82 ± 16 % of heart cycles between 2^{nd} and 3^{rd} follow-up examination. The differences in the percentages of atrial pacing over time were not statistically significant.

Pooled 24-hour heart rate trends are shown in Figure 3. The difference between the three trend lines was insignificant at all sample points, with the exception of the heart rate around 6:00 that was significantly different for the 3-month versus the 12-month follow-up (P = 0.044). The individual 24-hour heart rate trends appeared appropriate in all cases, except for two patients in whom pacing rates during night were faster than desired. This was resolved by decreasing the maximum closed loop rate to 80 beats/min or by reprogramming the pacemaker to the DDD mode.

Mean heart rates during day and night and the related statistical evaluations are shown in Tables 1 and 2. The in-clinic test results and statistical values are summarised in Tables 3 and 4, with more details on stair climbing versus stair descending provided in Figure 4.

Conclusion

Pooled data in 102 patients who took part in the multicenter RAPID study indicated the ability of the studied

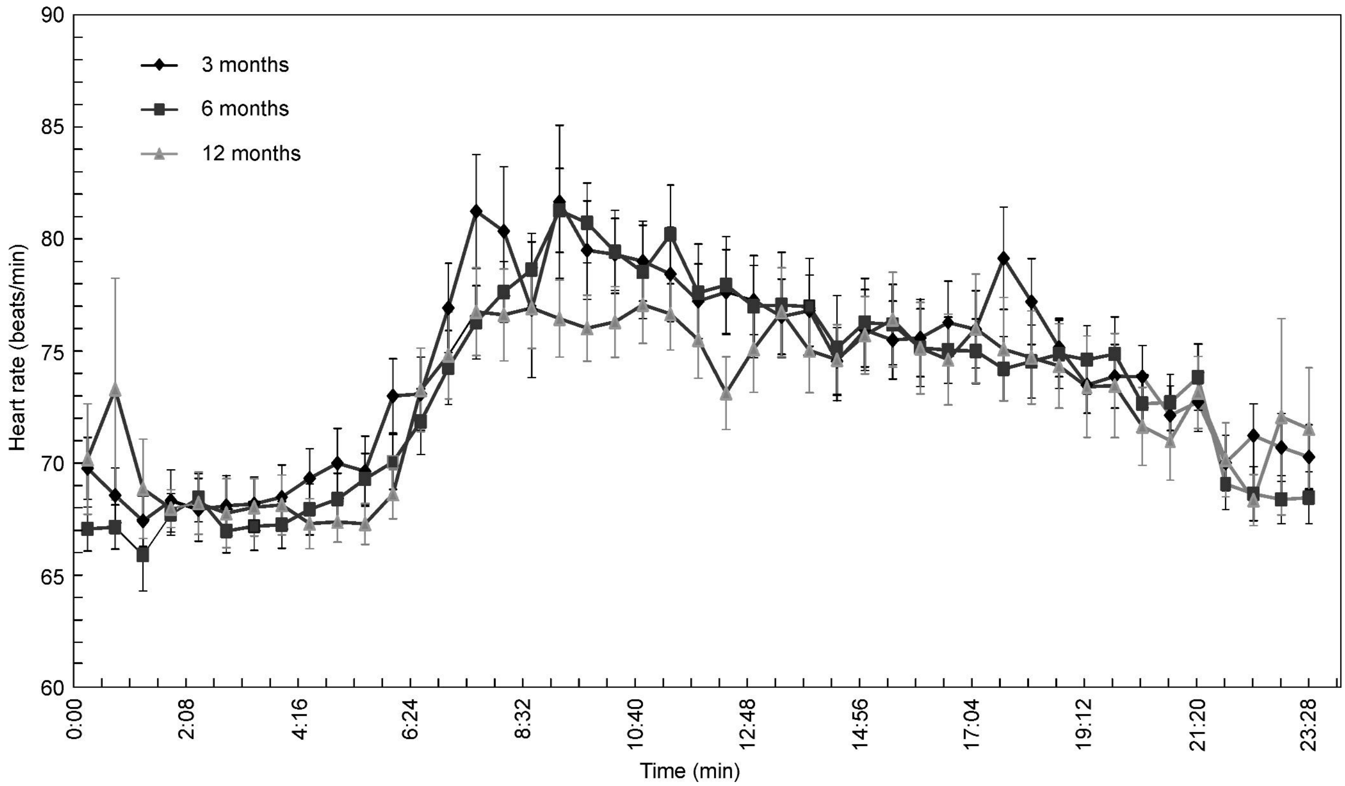

Figure 3. Heart rates (mean ± standard error of the mean) recorded in the pacemaker memory over 24 hours in conjunction with the 3, 6, and 12-month follow-ups. Pacemaker counters indicated a mean incidence of atrial pacing ³ 80 % in the time periods between follow-up examinations.

CLS pacemakers to clearly distinguish between activities that reflect different circulatory demands, such as walking along a level corridor, stair climbing, and stair descending. The 24-hour heart rate trends exhibited a typical diurnal pattern and were appropriate in the vast majority of the patients, with the exception of two patients who experienced faster-than-desired heart rates during the night. The long-term stability of the CLS rate adaptation has been suggested by the insignificant differences between 24-hour heart rate trends taken at 3, 6, and 12 months after pacemaker implantation, and by negligible variations in the daily and nightly mean rates over time. Therefore, automatic CLS rate adaptation provided appropriate heart rate trends despite the minimum requirements for pacemaker programming, which are now reduced to selecting the basic and maximum pacing rates.

Follow-up Control		Mean heart rate (beats/min)
3 months:	day	76.8 ± 8.3
	night	69.2 ± 7.6
6 months:	day	76.6 ± 8.6
	night	67.6 ± 6.4
12 months:	day	75.2 ± 7.6
	night	68.3 ± 6.0

Table 1. Mean heart rates during day and night at different follow-up examinations.

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Comparison	P-value
3 months: day vs. night	< 0.05
6 months: day vs. night	< 0.05
12 months: day vs. night	< 0.05
Day: 3 months vs. 6 months	0.90
Day: 3 months vs. 12 months	0.45
Day: 6 months vs. 12 months	0.38
Night: 3 months vs. 6 months	0.33
Night: 3 months vs. 12 months	0.59
Night: 6 months vs. 12 months	0.68

Table 2. Significance of the differences between mean heart rates during day and night.

Activity	Maximum heart rate (beats/min)
Stair climbing	106 ± 18
Stair descending	95 ± 15
Walking	89 ± 12
Resting	70 ± 9

Table 3. Heart rate during in-clinic activities.

Comparison	P-value
Stair climbing vs. descending	< 0.05
Stair climbing vs. walking	< 0.05
Stair climbing vs. resting	< 0.05
Stair descending vs. walking	< 0.05
Stair descending vs. resting	< 0.05
Walking vs. resting	< 0.05

Table 4. Significance of the differences between maximum pacing rates during in-clinic activities.

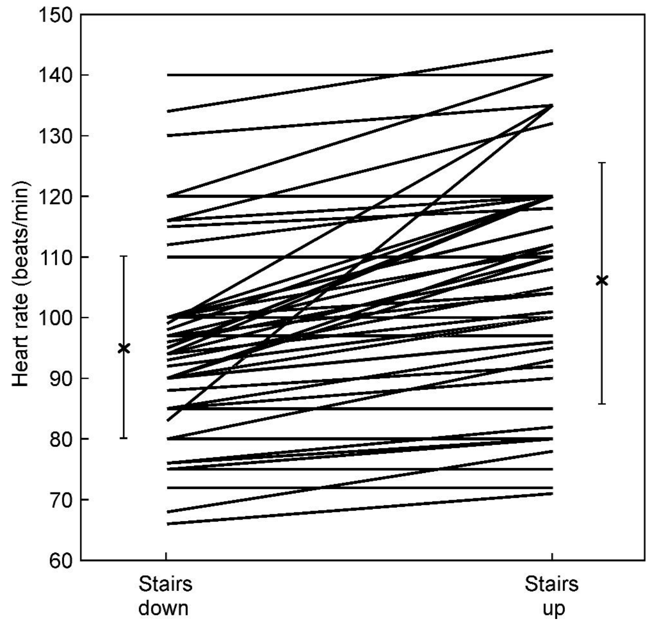

Figure 4. The relationship between maximum heart rates during stair climbing versus stair descending in the individual patients, with mean values ± standard deviations (P < 0.05). Stair climbing was associated with a faster heart rate in 82 % of patients, and in 18 % there was no difference between climbing and descending.

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