Clinical Results of Contractility-Based Closed Loop Stimulation in Patients Treated with Beta-Blockers

D. WOJCIECHOWSKI, C. FAUSER[1], S. BRÜCKNER[2], L. GRIESBACH[3]
Bioengineering Department of the Wolski Hospital and Institute of Biocybernetics and Bioengineering, Polish Academy of Sciences, Warsaw, Poland
[1]Bethesda Hospital, Hoogeveen, The Netherlands
[2]Bernburg Hospital, Bernburg, Germany
[3]Kreiskrankenhaus Kirchberg, Kirchberg, Germany

On Behalf of the RAPID Study Investigators

Summary

Beta-blockers exert negative chronotropic and inotropic influence and can therefore interfere with the rate-adaptive function of pacemakers equipped with a heart contractility sensor. There are concerns that diminished contractile function due to beta-blocker therapy may reduce the magnitude of the signal coming from the contractility sensor and therefore lead to inadequately low pacing rates during daily activities and/or require special sensor calibration in such patients. We retrospectively evaluated data gathered in 102 patients implanted with contractility-driven Closed Loop Stimulation (CLS) Inos² pacemakers within the RAPID study (Rate Behavior of the Pacing System Inos² CLS during Daily Life) to evaluate whether there was a difference in pacing rates during daily activities between patients using beta-blockers and those who did not. Inos² pacemakers perform continuous automatic calibration and adjustment of internal rate-responsive parameters in reaction to changing patient conditions, and allow the physician to influence rate modulation only by programming the basic and maximum closed loop rates. Thirty-four patients used beta-blockers (group A) and 68 did not (group B). The underlying clinical characteristics of the two groups were very similar. A mean incidence of atrial pacing over total follow-up period was 81 ± 15 % (group A) versus 82 ± 17 % (group B, P = ns). Heart rates for group A and group B were compared during physical exercise and over 24 hours. During the day, the mean heart rate was 76 ± 9 versus 76 ± 8 beats/min, respectively, and 69 ± 8 versus 68 ± 6 beats/min during the night (P = ns). There was a highly significant difference between day and night in either group (P < 0.001). At rest, peak rate was 70 ± 7 beats/min (group A) versus 70 ± 10 beats/min (group B, P = ns), for slow walking 85 ± 11 versus 91 ± 12 (P = ns), for stair climbing 101 ± 17 versus 108 ± 18 (P = ns), and for stair descending 92 ± 14 beats/min versus 97 ± 16 beats/min (P = ns). In both groups, the pacemaker clearly differentiated between climbing stairs, descending stairs, and slow walking along a level corridor, with P < 0.05 for any pair of activities. In conclusion, due to a continual self-adjustment of the internal rate-responsive parameters, administration of beta-blockers did not exert a significant influence on, and is compatible with, the CLS therapy.

Key Words

Closed Loop Stimulation, rate-adaptive pacing, contraction dynamics, beta-blockers

Introduction

Beta-blockers are widely used drugs in the treatment of coronary artery disease, cardiac arrhythmia, and heart failure, and are frequently administered to pacemaker patients. Since beta-blockers exert negative chronotropic and inotropic influence, they can interfere with the rate adaptive function of a pacemaker sensing heart contractility. The question arises whether diminished contractile function due to chronic usage of beta-blockers may reduce the magnitude of the signal coming from the contractility sensor and lead to inade-

quately low pacing rates during daily activities and/or require special sensor calibration in such patients.

The RAPID study (Rate Behavior of the Pacing System Inos^2 CLS during Daily Life) was conducted at 16 European clinics to evaluate the appropriateness of the pacing rates provided by the contractility-driven Inos^2 pacemakers (Biotronik, Germany). The study ended in December 2000, and the overall results have been published elsewhere [1]. One third of 102 RAPID study patients used beta-blockers during the study and 2/3 did not. In this work we examined the differences between these two groups of patients in the pacing rates delivered during daily activities.

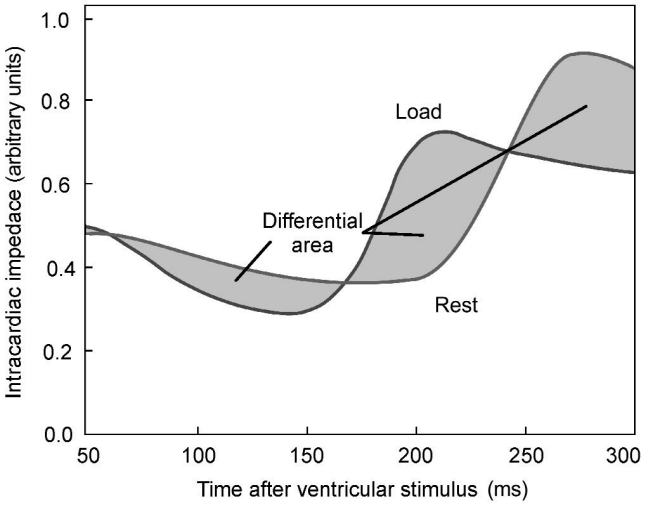

Figure 1. Inos^2 pacemakers inject subthreshold current pulses between the tip of a right ventricular lead and the pacemaker housing, to determine intracardiac impedance curve during the isovolumetric contraction and the beginning of the ejection phase. The impedance increase is thought to correlate with the right ventricular contraction dynamics, and thus, with the inotropic state of the heart. The area below the actual curve (load) is compared with the area below the slowly updated reference curve (rest). The differential area is multiplied by a self-adjusting internal rate-responsive factor to calculate the CLS pacing rate.

Materials and Methods

Pacemaker Description

The RAPID study included patients implanted with dual-chamber Inos^2 DR, Inos^2 CLS, or Inos^{2+} CLS pacemakers, which measure contraction dynamics using impedance cardiography (Figure 1) [1,2]. Since the Inos^2 pacemaker is integrated into the cardiovascular control loop, and uses the control loop to continuously guide the pacing rate, this pacemaker establishes a form of rate-adaptive pacing called Closed Loop Stimulation (CLS) (Figure 2) [1-7].

The device performs continuous automatic calibration and allows the physician to influence rate modulation only by programming the basic and maximum closed loop rates. Conventional programmable rate-adaptive parameters such as rate-responsive factor, rate acceleration/deceleration, sensor sensitivity, sensor blending, etc., are not available. The rate-responsive factor exists only as an internal parameter that the pacemaker continually and automatically adjusts in order to make available the full range of allowed pacing rates – from the basic to the maximum pacing rate. This parameter is determined based on the magnitude of changes in the contraction dynamics observed over a 2 – 3 day period. Even a chronic depression of heart contractility caused by structural heart disease or drug usage should allow the programmed maximum closed loop rate to be reached when needed, since the internal rate-responsive factor is automatically augmented compared with that of normal subjects.

Study Protocol and Data Management

The RAPID study protocol required that pacemakers be programmed to DDD-CLS mode (i.e., CLS) after pacemaker implantation, using parameters selected under physicians' discretion. Follow-up controls took place at 1.5 – 3 months, 6 months, and 12 months after pacemaker implantation. At the beginning of each follow-up control, the rolling 24-hour heart rate trend and counters showing the percentages of paced and sensed events in the atrium and ventricle during the period between the previous and current follow-up examinations were interrogated from the pacemaker memory. Mean daily and nightly rates in each individual were extracted from the 24-hour trends. The "day" was considered to begin with getting up in the morning and to end with going into bed in the evening, according to the patient diary. The in-clinic activity test was performed at the 1.5 – 3 month follow-up. It consisted of 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 slow walking along the flat corridor. A short-term pacemaker rate trend was obtained in conjunction with the in-clinic testing. Heart rates during the initial period of rest, as well as peak rates during stair-climbing, stair-descending, and walking were extracted from the short-term pacemaker trends obtained during in-clinic testing.

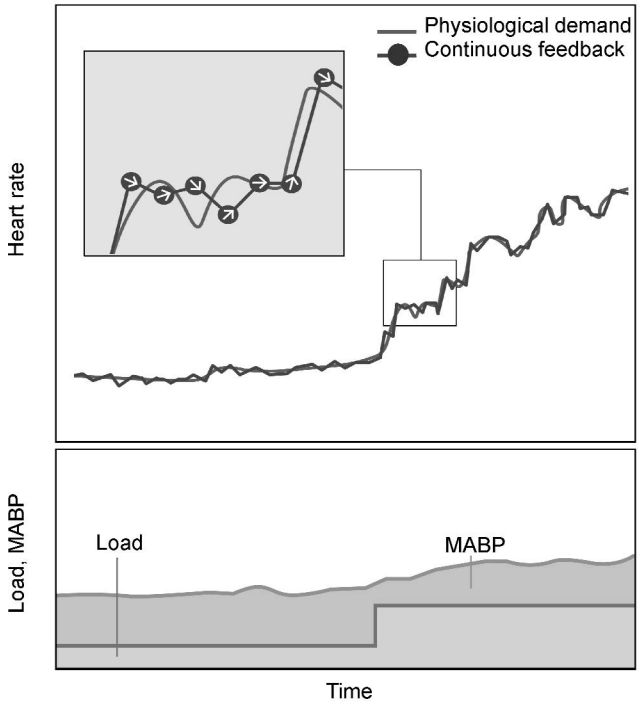

Figure 2. Since contractility and the heart rate interact with each other, a pacing rate that is too slow will cause an increase in contractility due to the baroreceptor reflex (triggered by a suboptimal systemic blood pressure), thereby indicating to the pacemaker that a faster heart rate is necessary. The reverse occurs for a pacing rate that is too fast. In theory, this interaction establishes a negative feedback that continuously guides the pacing rate towards an optimal value matching current hemodynamic demands.
MABP = Mean arterial blood pressure.

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. Results for the two groups of patients were compared using the unpaired two-tailed t-test, except for the gender and pacing indications, which were evaluated using chi-square best-fit analysis. The significance of the intrapatient differences in pacing rates for different activities were assessed with the aid of the paired two-tailed t-test. P values of less than 0.05 were considered significant.

Results

The two patient groups were homogenous with respect to underlying patient characteristics and pacemaker programming (Table 1). Study results are illustrated in Figures 3 and 4, and the statistical significance of the differences between the two groups is evaluated in Table 1. As can be seen, pacing rates during exertion were slightly lower in the beta-blocker group, but the difference was not significant. Both patient groups showed appropriate circadian variation of pacing rates, with adequate pacemaker response to different types of exercise. The differences between mean nocturnal and diurnal rates, as well as among the peak rates during slow walking, stair-climbing, and stair-descending, were statistically significant in both patient groups ($P < 0.05$ for any pair of activities).

Discussion

It has been shown in previous studies [2,8] that the impedance signal measured by an Inos^2 device will be augmented in proportion to the dosage of intravenously administered dobutamine (positive inotropically effective drug), leading to a simultaneous proportional increase in the CLS rate. This finding demonstrated that the measured impedance signal is closely correlated with dP/dt_{max}, and thus comprises a physiological sensor that incorporates the pacemaker into the natural cardiovascular control loop.
Since the measured contractility signal may be affected by various pharmacological agents and the degree of cardiomyopathy, it was important to enable the pacing system to automatically adapt itself to changing patient conditions without the need for manual re-calibration or pacemaker reprogramming. Our study eval-

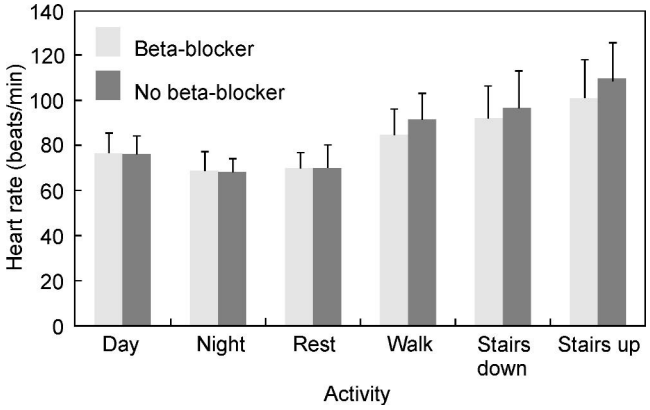

Figure 3. Mean pacing rates during day and night, and peak rates during rest, slow walking, descending and climbing stairs (mean values ± standard deviations).

	Beta-blocker group	No beta-blocker group	P-value
Number of patients	34	68	-
Age	70 ± 8	72 ± 8	0.74
Men	19	44	0.59
Women	15	24	0.50
Atrioventricular block	8	17	0.89
Sinus node dysfunction	16	34	0.84
Binodal disease	8	14	0.76
Other pacing indication	2	3	0.75
Programmed basic rate	60 ± 2	60 ± 4	0.91
Programmed maximum closed loop rate	120 ± 5	122 ± 10	0.83
Percent of atrial pacing (total follow-up)	81 ± 15	82 ± 17	0.82
Mean daily rate (total follow-up)	76 ± 9	76 ± 8	0.97
Mean nightly rate (total follow-up)	69 ± 8	68 ± 6	0.89
Resting rate	70 ± 7	70 ± 10	0.99
Peak rate for slow walking	85 ± 11	91 ± 12	0.10
Peak rate for climbing stairs	101 ± 17	108 ± 18	0.20
Peak rate for descending stairs	92 ± 14	97 ± 16	0.30

Table 1. Comparison of patient characteristics and study results for the beta-blocker versus no beta-blocker group (mean values ± standard deviations). Statistical significance of the observed differences is indicated.

uated the newest generation of CLS devices (Inos^2) that perform a continuous slow update of the reference impedance curve and adapt the internal rate-responsive factors in order to associate the patient condition at rest with a pacing rate close to the programmed basic rate and to associate maximum exertion with the programmed maximum closed loop rate. A pacing rate that is too fast can occur only within several minutes of the administration of a new medication – until differential area is diminished by reference curve updating. In the long-term, no abnormalities in pacing rate are expected thanks to the automatic adjustment of the internal rate-responsive factor in reaction to the altered contractile function [9].

Conclusion

Our study indicated that pacing rates during daily activities in Inos^2 pacemakers did not differ between patients using beta-blockers and those without beta-blockers, despite the minimal need for pacemaker programming. In both groups, the physicians freely selected basic and maximum closed loop rates in the individual patients, disregarding the ongoing pharmacological treatment. As no additional CLS programming was necessary, pacemaker handling was easy, and adequate pacing support during daily activities was obtained regardless of the contractile status of the heart.

Clinical Investigators

B. Gestrich (Trier, Germany); L. Griesbach (Kirchberg, Germany); D. Wojciechowski (Warsaw, Poland); C. Fauser (Hoogeveen, The Netherlands); W. Dänschel (Chemnitz, Germany); G. Weyers, (Bergisch Gladbach, Germany); P. Meyer and A. Schleich (Mindelheim, Germany); T. Unger (Halberstadt, Germany); S. Brückner (Bernburg, Germany); J. Tönges (Bernkastel-Kues, Germany); H. Bechtold (Crailsheim, Germany); B. Unger (Neuruppin, Germany); W. Fischer (Peißenberg, Germany); J. Isbary (Bieberach, Germany); M. Fleischer (Marktredwitz, Germany).

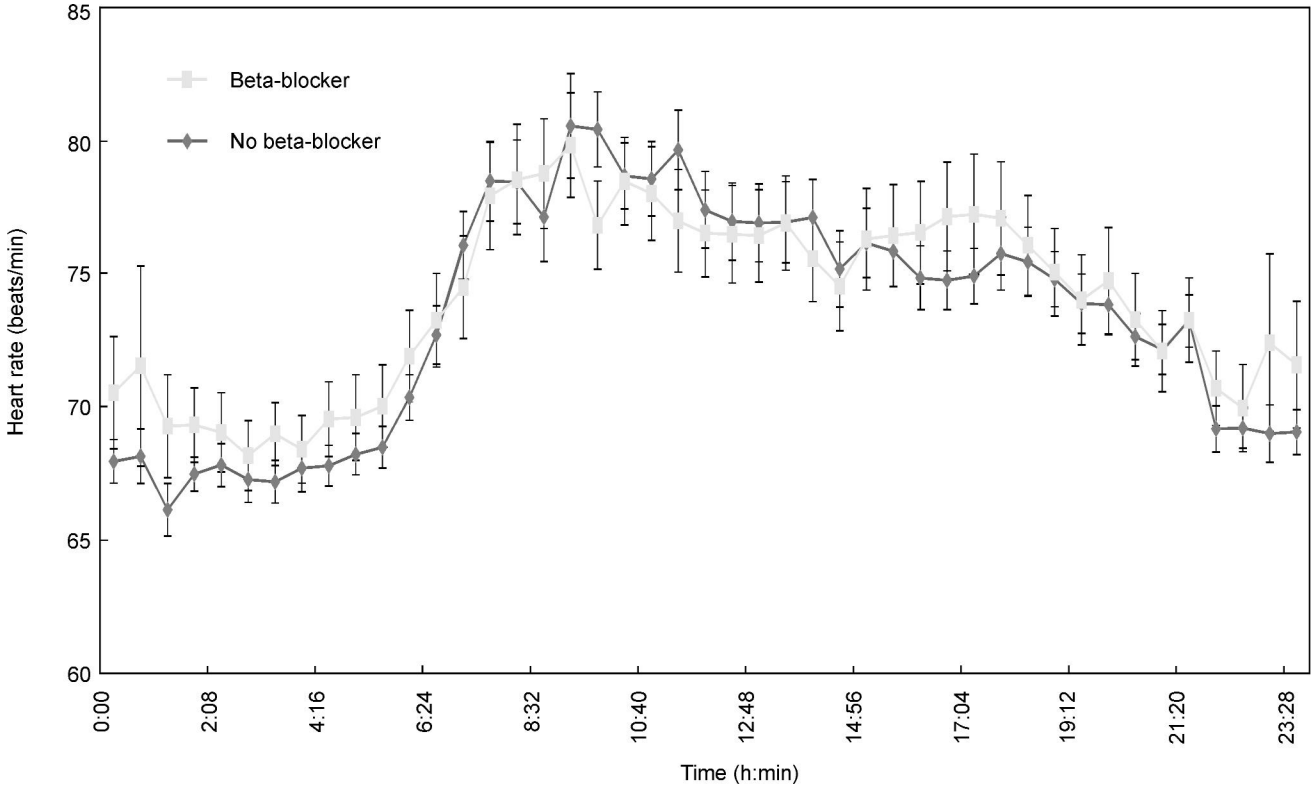

Figure 4. 24-hour heart rate trends retrieved from the pacemaker memory (mean value ± standard error).

References

[1] Griesbach L, Gestrich B. Restoration of circadian variation and physiologic rate behaviour through Closed Loop Stimulation: RAPID study findings. Prog Biomed Res. 2001; 6: 81-86.

[2] Osswald S, Cron T, Grädel C, et al. Closed Loop Stimulation using intracardiac impedance as a sensor principle: Correlation of right ventricular dP/dt max and intracardiac impedance during dobutamine stress test. PACE. 2000; 23: 1502-1508.

[3] Schaldach M. What is Closed Loop Stimulation? Prog Biomed Res. 1998; 3: 49-55.

[4] Schaldach M. Cardiac output optimization by hemodynamic pacing rate control. In: Santini M (editor). Progress in Clinical Pacing 2000. Rome: Centro Editoriale Pubblicitario Italiano (CEPI). 2000: 552-561.

[5] Lau CP. The range of sensors and algorithms used in rate adaptive cardiac pacing. PACE. 1992; 15: 1177-1211.

[6] Malinowski K. Interindividual comparison of different sensor principles for rate adaptive pacing. PACE. 1998; 21: 2209-2213.

[7] Zecchi P, Bellocci F, Ravazzi AP, et al. Closed Loop Stimulation: A new philosophy of pacing. Prog Biomed Res. 2000; 5: 126-131.

[8] Christ T, Brattström A, Kühn H, et al. Effect of circulating catecholamines on the pacing rate of the Closed Loop Stimulation pacemaker. Prog Biomed Res. 1998; 3: 143-146.

[9] Ebner E, Krätschmer H, Schaldach M. Performance of Closed Loop Stimulation in hypertrophic and dilated hearts. Prog Biomed Res. 2001; 6: 87-93.

Contact
Dr. Dariusz Wojciechowski
Bioengineering Department
Wolski Hospital and
Institute of Biocybernetics and Bioengineering
Polish Academy of Sciences
Kasprzaka 17
01-211 Warsaw
Poland
Telephone: +48 22 632 1443
Fax: +48 22 632 6944