

## A Prospective Multicenter Study Demonstrating Safety and Effectiveness of Closed Loop Stimulation

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### Summary

*The goal of this prospective, multicenter, clinical study was to validate the safety and effectiveness of Closed Loop Stimulation (CLS). The Inos<sup>2+</sup> CLS pacemaker monitors and processes the intracardiac impedance signal. Changes in the waveform of this signal are associated with changes in the contraction dynamics of the patient's heart. CLS translates load-dependent variations in cardiac contractility to patient-specific pacing rates. From January 1999 to April 2001, 129 patients (81 male, 48 female; mean age 73 years, range 29 – 92) from 15 centers were implanted with the Inos<sup>2+</sup> CLS pacing system to demonstrate its safety and effectiveness in a prospective clinical study. Data from 52 chronotropic assessment exercise protocol treadmill tests were analyzed to evaluate the appropriateness of the rate-response with various exercise levels. The target slope from the linear regression of the obtained heart rates versus the Wilkoff predicted heart rates was 1.0 (95 % confidence interval 0.65 – 1.35). The overall slope obtained from 52 patients was 0.82 (95 % confidence interval 0.75 – 0.89). The heart rate increases in patients with the CLS algorithm were shown to be of a physiologically appropriate magnitude during standard CAEP treadmill testing. The complication rate was less than the complication rates with other similar rate-responsive devices studied. The observed complication rate of 10.1 % (13 patients) was lower than the criterion used for the primary safety endpoint of 11.5 %. The clinical results gathered during the clinical study demonstrate that the predefined primary study endpoints for efficacy of CLS and safety of the Inos<sup>2+</sup> CLS were fulfilled.*

### Key Words

Rate-responsive pacing, Closed Loop Stimulation, chronotropic assessment exercise protocol, Wilkoff predicted heart rate

### Introduction

The Inos<sup>2+</sup> CLS (Biotronik, Germany) is a multi-programmable, dual-chamber pulse generator with rate-adaptive pacing based on the principle of Closed Loop Stimulation (CLS). This prospective multicenter clinical study was designed to validate the safety and effectiveness of CLS. The basic function of CLS involves the translation of myocardial contractility into patient-specific pacing rates. The result is pacing rate variations that are mediated by the body's own cardiovascular control. Specifically, the pulse generator monitors and processes the intracardiac impedance signal associated

with myocardial contraction dynamics. Changes in the waveform of this impedance signal are associated with changes in the contraction dynamics of the patient's heart due to the heart's inotropic response to exercise and different forms of stress [1-10] which are not properly sensed by other rate adaptive pacemaker systems [11]. By monitoring these changes, the pulse generator can provide a pacing rate that is appropriate and specific to the patient's individual physiologic demands.

This article presents the data collected through April 2001 on 129 patients.

		Atrial pacing threshold	Ventricular pacing threshold	P-wave amplitude	R-wave amplitude	Atrial pacing impedance	Ventricular pacing impedance
<b>Implantation</b>	No. of tests	130	115	133	126	133	133
	Mean $\pm$ SE	0.8 $\pm$ 0.1 V	0.6 $\pm$ 0.1 V	2.8 $\pm$ 0.1 mV	14.3 $\pm$ 0.5 mV	507.8 $\pm$ 10.4 $\Omega$	768.6 $\pm$ 17.6 $\Omega$
<b>Chronic Follow-up (&gt; 60 days)</b>	No. of tests	253	296	262	252	292	301
	Mean $\pm$ SE	1.2 $\pm$ 0.1 V	1.1 $\pm$ 0.1 V	3.0 $\pm$ 0.1 mV	9.9 $\pm$ 0.3 mV	530.3 $\pm$ 8.8 $\Omega$	688.2 $\pm$ 9.3 $\Omega$

Table 1. Summary of the atrial and ventricular lead measurements made at the time of implantation and at subsequent follow-ups. SE = standard error of the mean.

## Materials and Methods

Eighty-one men and 48 women (mean age 73 years, range 29 – 92) from 15 centers were implanted with an Inos CLS pacemaker as well as atrial and ventricular unipolar or bipolar leads with IS-1 compatible connectors. The mean implant duration for all devices was 12.4 months. The data presented in this article is from implant and follow-up visits that took place between January 1999 and April 2001. The average patient in the study was a 73-year-old male with a NYHA class I, as well as indications for a pacemaker to treat sinus bradycardia. Cardiac medications included beta-blockers, ACE-inhibitors, and anti-arrhythmics. Inclusion criteria for the clinical study included meeting the indications for use in accordance with recommendations in the ACC/AHA Task Force Report [12]. The protocol was reviewed and approved by the United States Food and Drug Administration (FDA). Institutional review board approval or ethical committee approval and patient informed consent were obtained prior to enrollment.

In order to evaluate the appropriateness of the rate-response of the Inos<sup>2+</sup> CLS pacing system, the clinical protocol required patients to complete exercise testing according to the chronotropic assessment exercise protocol (CAEP) at one-month post implant. The CAEP is designed specifically for chronotropic assessment and is structured to collect heart rate data at sub-maximal as well as peak exercise intensity [13]. This standardized protocol allows for the verification of the chronotropic response provided by the pacemaker and corresponding to the intensity of the particular activity in patients with typical exercise capacities. Additionally, data was collected during 24-hour Holter recordings in order to evaluate pacing rates during daily activities as well as periods of rest and sleep. Lead measurements, including sensing and pacing

thresholds and impedance, were made at each follow-up interval. Clinical complications during the study were reported and analyzed.

The primary endpoint of the study was to demonstrate that the rate-adaptive CLS algorithm provides rate-response that is proportional to the patient's level of exertion. More specifically, the primary endpoint was an analysis of the sensor-controlled rate as compared to the expected heart rate, which is based on the patient's "Wilkoff" predicted heart rate [13].

## Results

Table 1 provides a summary of the atrial and ventricular lead measurements made at the time of implantation and at subsequent follow-up examinations. All lead measurements were in the range of expected values. A total of 52 patients were included in the CAEP treadmill testing. The primary efficacy endpoint was based on the simple linear regression of the observed rate-adaptive pacing rate with the CLS algorithm versus the expected heart rate during a CAEP treadmill test. According to the relevant FDA guidance document, the target slope from the linear regression of the obtained heart rates versus the predicted heart rates was 1.0. Additionally, the 95 % confidence intervals of the resulting slope should fall within the interval 0.65 – 1.35. The overall slope obtained with all 52 patients was 0.82 with a standard error of the mean of 0.04 (95 % confidence interval 0.75 – 0.89). In 46 patients (88.5 %) a result was demonstrated similar to the Wilkoff predicted heart rates during the treadmill test. The heart rate obtained at the different CAEP stages was nearly equivalent, within 15 % of the predicted heart rate for each of the stages. The average slope for this patient group was 0.83. Figure 1 shows an example of a typical treadmill obtained during CAEP treadmill testing.

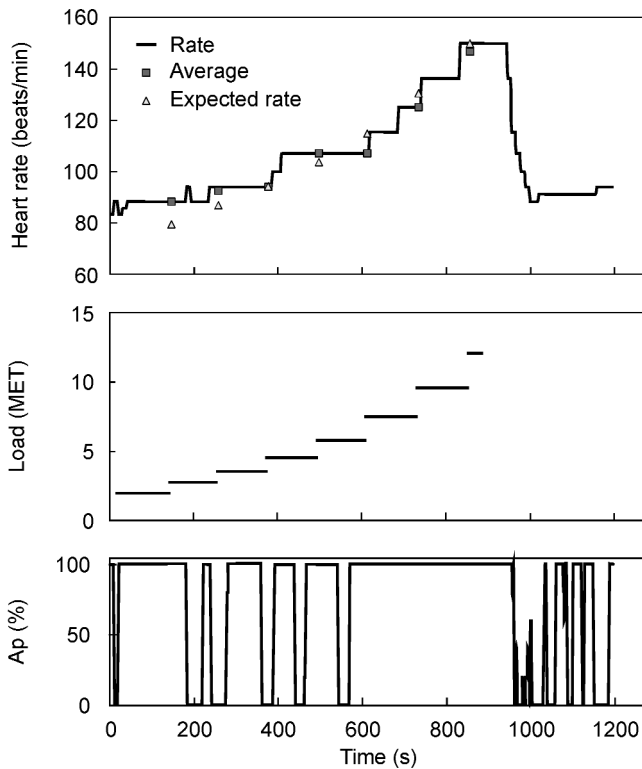


Figure 1. A typical CAEP treadmill result. The average rate of the 30 s end-stage are used for comparison to the expected heart rates. The programmed basic rate was 70 beats/min and the upper sensor rate 150 beats/min. Slope from the linear regression of the obtained heart rates versus the predicted heart rates = 0.87. The CAEP exercise protocol is based on a stepwise increase in workload which is presented here graphically. The percentage of atrial pacing (Ap) is represented to demonstrate that the heart rate was controlled by the device.

Predicted heart rate (beats/min)	Estimated rate from regression (beats/min)	Ratio (%)
60	68.1	113.6
80	84.5	105.7
100	100.9	100.9
120	117.3	97.8
140	133.7	95.5
160	150.1	93.8

Table 2. Comparison between the predicted heart rates (HR) and the HR estimated by the resulting formula (Estimated HR = 0.82 x predicted HR + 18.93 beats/min) from the linear regression.

Four patients (7.7 %) demonstrated an over-responsive treadmill performance. The heart rate obtained at the different CAEP stages was significantly higher (15 %) than the predicted heart rate in three or more stages. The average slope for this patient group was 0.96. Two patients (3.8 %) demonstrated an under-responsive treadmill performance. The heart rate obtained at the different CAEP stages was significantly lower (15 %) than the predicted heart rate in three or more stages. The average slope for this patient group was 0.13. Table 2 compares the selected heart rates in the therapeutic range of interest between the predicted heart rates and the heart rates estimated by the resulting formula (estimated HR = 0.82 x HR + 18.93 beats/min) from the linear regression. Overall, the patients reached about 95 % of the programmed upper sensor rate (Maximum Closed Loop Rate = MCLR) in the last stages of exercise. Table 3 shows that 28 patients (53.8 %) obtained a slope greater than 0.825 and 41 patients (78.8 %) obtained a slope greater than the targeted lower confidence limit of 0.625. A group of 42 patients (80.8 %) reached a maximum rate within 20 beats/min of the programmed MCLR and 24 patients (46.2 %) reached the programmed MCLR. Figure 2 shows the normalized obtained heart rate averaged over all analyzed treadmills (n=52) versus the normalized workload, with the 95 % confidence intervals.

There were 86 Holter recordings analyzed. Pacing rates during daily activities and periods of rest and sleep were evaluated. Patients were asked to keep a detailed diary so that changes in their heart rate could be correlated with periods of activity and rest. The secondary purpose of the 24-hour Holter recording was to determine incidence and severity of any pacing or sensing abnormalities. Figure 3 shows an example of a typi-

Criteria	Patients	95 % Confidence interval
Slope > 0.825	28 (53.8 %)	39.5 % - 67.8 %
Slope > 0.650	41 (78.8 %)	65.3 % - 88.9 %
Within 20 beats/min of MCLR	42 (80.8 %)	67.5 % - 90.4 %
Achieved MCLR	24 (46.2 %)	32.2 % - 60.5 %

Table 3. The number and percentages of patients who met certain performance criteria. MCLR = Maximum Closed Loop Rate. Slope from the linear regression of the obtained heart rates versus the predicted heart rates. A total of 52 patients were included.

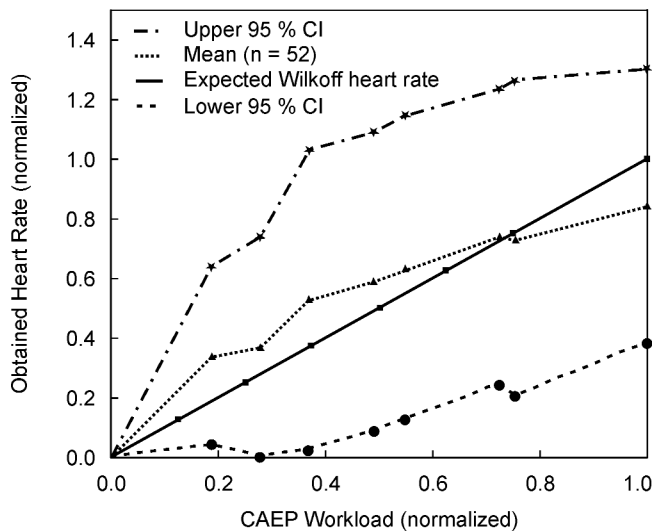


Figure 2. Graphical presentation of the normalized obtained heart rate averaged over all analyzed treadmills ( $n = 52$ ) versus the normalized workload, with the 95 % confidence intervals (CI).

cal Holter result. Thereby, 84 Holter recordings (70 %) demonstrated rate changes correlated to an activity written in the patient diary and appropriate heart rates during periods of rest with a clear circadian variation. Nine Holter recordings (13 %) demonstrated some rate increases that did not exactly correlate with an activity written in the patient diary, possibly because the diary

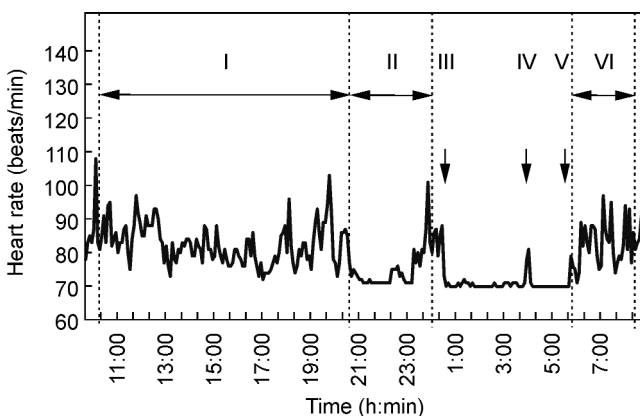


Figure 3. A typical example of a 24-hour Holter recording. The heart rates are presented in 5-min averages. I = getting home, walking, shopping, yard work, dinner, wash dishes; II = TV; III = to bed; IV = bathroom; V = got up; VI = eating breakfast, dressing. The overall mean rate was 78.8 beats/min, the programmed basic rate was 70 beats/min, and the upper sensor rate 139 beats/min.

was incomplete or the patient did not include all activities, which can be expected. No sensing or pacing abnormalities were observed.

There were 15 complications reported over the cumulative implant duration of 1600.7 months (133.4 years). The complications included lead revisions ( $n = 11$ ), pneumothorax ( $n = 3$ ), and explant due to pocket infection ( $n = 1$ ). The clinical investigators did not classify any of these complications as being related to the investigational pulse generator. The calculated rate for complications was 0.12 per patient. The rate of complications per year was 0.112. Overall, this complication rate is within the expected rate and within the pre-defined 95 % confidence intervals.

### Discussion and Conclusion

In conclusion, the heart rate increases in patients with the CLS algorithm were shown to be of physiologically appropriate magnitude during standard CAEP treadmill testing. Additionally, the slope of regression plots of observed heart rates on Wilkoff-based predicted rates were at or near the expected value. For comparison, the clinical studies of other rate-adaptive devices have demonstrated the following mean slopes, resulting from the simple linear regression of the obtained rate-adaptive pacing rate versus the expected heart rate during a symptom limited exercise test:

- The dual sensor, accelerometer and minute-ventilation, system Kappa 700 (Medtronic, USA) demonstrated a mean slope of 0.81 (95 % confidence interval 0.76 – 0.86) [14].
- The dual sensor, QT-interval and minute-ventilation, system Diva (Vitatron, The Netherlands) demonstrated a slope of 0.82 (95 % confidence interval 0.77 – 0.87), for the blended sensor QT = activity [15].
- The dual sensor, accelerometer and minute-ventilation, system Pulsar Max (Guidant, USA) demonstrated a mean slope of 0.81 (95 % confidence interval 0.73 – 0.89) for the blended sensor and a mean slope of 0.83 (95 % confidence interval 0.74 – 0.92) for the minute ventilation sensor [16].

The observed complication rate of 10.1 % (occurring in 13 of 129 patients) was lower than the criterion determined for the Primary Safety Endpoint. Therefore, the study showed that the complication rate is comparable to the complication rate of other similar

studies [14-16]. The observed complication rate in the clinical study was also well below rates demonstrated in the clinical studies of other rate-adaptive devices. For comparison,

- the Kappa system demonstrated 17 % of patients with complications and a complication rate per device year of 0.45 [14];
- the Diva system demonstrated 22.1 % of patients with complications and a complication rate per device year of 0.21 [15]; and
- the Pulsar Max system demonstrated an acceptance criterion of a 3-month complication rate less than or equal to 14.6 % [16].

In conclusion, the Inos<sup>2+</sup> CLS system has fulfilled the predefined endpoints of the study, which supports the safety and efficacy of Closed Loop Stimulation.

### Clinical Investigators

The Inos<sup>2+</sup> CLS Investigator Group included the following investigators who are listed in alphabetical order: F. Abi-Samra (Ochsner Medical Center, New Orleans, LA); W. Bailey (Lake Charles Memorial Hospital, Lake Charles, LA); G.C. Bauknight (Providence Hospital, Columbia, SC); L. Constantin (Lehigh Valley Hospital, Allentown, PA); J. Daubert (University of Rochester Medical Center, Rochester, NY); J. Espinosa (Instituto Mexicano Del Seguro Social, Guadalajara, Mexico); R. Florek (Legacy Health System, Portland, OR); D. Guy (Nebraska Health System, Omaha, NE); M. Holland (Boulder Community Hospital, Boulder, CO); M.J. McGreevy (Sharp Grossmont Medical Center, LaMesa, CA); J. Olson (Swedish Medical Center, Seattle, WA); R. Reeves (Baptist Montclair Medical Center, Birmingham, AL); J. Roth (Medical College of Wisconsin, Milwaukee, WI); N. Vijay (HealthOne Hospital System, Denver, CO); B. Weinstock (Northside Hospital & Heart Institute, St. Petersburg, FL).

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