# Multi-Center Investigations with Automatically Initialized Closed Loop Stimulation - Rate Response during Daily Life and Physical Exercise Tests

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## Summary

*The present investigations were performed to test the chronotropic response of a permanent pacemaker system that modulates the pacing rate based on the right ventricular contraction dynamics of the myocardium. With this principle, the pacemaker is integrated into the natural circulatory regulation of the organism and, therefore, provides closed loop regulation for the patient's heart rate. Twenty-six patients (17 male, 9 female; mean age: 69 years; range: 45 to 92 years), mostly suffering from sick sinus node syndrome and AV block, participated in this study. After an automatic initialization time of 3 to 5 days, the pacemaker trend monitor was interrogated. The 24-h pacemaker trends show a very close correlation to the heart rates of healthy elderly subjects, including significant circadian variation. All patients underwent an ambulatory test (sitting, slow and brisk walking, ascending and descending stairs), and 21 patients performed a two-stage ergometry to assess the rate response to physical load. During the ambulatory test, the highest average increase in heart rate was achieved while ascending stairs (41 ppm). In contrast, brisk walking (33 ppm), descending stairs (24 ppm), and slow walking (17 ppm) provoked lower increases - results which are in good accordance with the literature. Ergometry confirmed these results with nearly proportional heart rate increases during the first (28 ppm) and the second (42 ppm) load steps. The heart rate returned to reasonable rest values during recovery within physiologic time periods. The test results of two patients (of differing ages and states of health) emphasized the universality of the closed loop principle for heart rate regulation.*

## Key Words

Cardiovascular regulation, Closed Loop Stimulation, automatic initialization, heart rates, ergometry, ambulatory exercise

## Introduction

Cardiovascular circulatory control of the human body is a complex process to supply the organism with appropriate arterial blood pressure and perfusion and involves various parameters (e.g., heart rate, stroke volume, and total peripheral vascular resistance). Impaired functionality of one of these variables results in a more intense use of the remaining quantities which, therefore, can serve as ideal indicators of the circulatory demand.

The most attractive strategy for reestablishing adequate heart rates is based on the principle of closed loop chronotropic control [1]. Different than conventional rate responsive pacemakers, which measure only specific effects (i.e., body acceleration or respiratory minute volume), a closed loop system derives its information from an internal parameter of the cardiovascular system. Such systems are prepared for demand-oriented heart rates, which are provided upon request from the organism. In principle, the natural atrioventricular conduction is suitable for relaying information about the circulatory demand, but this function may also be impaired or even blockd. The myocardial contraction dynamics, on the other hand, are always affected by the medullary circulatory centers, marking them as an ideal input parameter for rate responsive systems. This concept is principally superior due to the existing heart rate feedback which affords high specificity for physical and mental stress [2]. Named after its primary characteristic, this principle is called Closed Loop Stimulation (CLS). Various studies [2-7] have demonstrated that CLS provides excellent restoration of heart rate, a parameter which will be called "CLS-rate" in the following.

First experience with CLS was gained with a system that required manual, patient-specific initialization. Now, the pacing system has been further developed and is equipped with automatic initialization which provides adequate heart rate response within 3 to 5 days after starting the CLS pacing mode. This pacemaker mode can be activated in all INOS² DR pacemakers (BIOTRONIK), even if the device is already implanted. The performance of the automatic initialization has been validated with ambulatory and ergometry tests, as well as with 24-h heart rate trend recordings. The individual response of the CLS principle is demonstrated by spezimen of two male patients who are both chronotropically incompetent but have a completely different health status. The first patient is athletic and only 45 years of age; he shows no concomitant disease other than sinus node dysfunction and AV block and does not require medication. The Maximum Closed Loop Rate (MCLR), which serves as the upper limit of the regulated pacing rate, was programmed to 140 ppm according to this patient's age. In contrast, the second patient is 78 years of age and suffers from sick sinus node syndrome (SSS), essential hypertension, and coronary heart disease (MCLR: 110 ppm). The second patient receives extensive pharmacological treatment (Digoxin, Isoket, Benazepril, Sotalex, Marcumar).

## Materials and Methods

Twenty-six patients (17 male, 9 female; mean age: 69 years; range: 45 to 92 years) from 14 European clinical centers (see acknowledgments) were investigated. The results are presented with special respect to two subjects (from the centers in Brno, Czech Republic and Landshut, Germany), demonstrating the universal performance of the closed loop principle.

Inclusion criteria consisted of cooperative patients implanted with INOS² DR pacemakers and without contraindication to exercise. This study aimed at including chronotropically incompetent patients with maximum spontaneous atrial rates below 100 bpm. In addition to the 8% with normal sinus node function prior to pacemaker implantation, the other patients

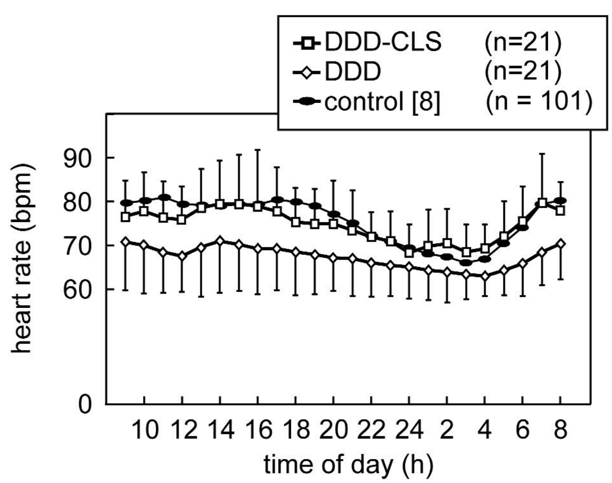


*Figure 1. Hourly averaged heart rates in DDD and DDD-CLS mode of 21 patients during daily life activities. The DDD-CLS trend approaches the 24-h heart rate of healthy subjects [8] very closely.*

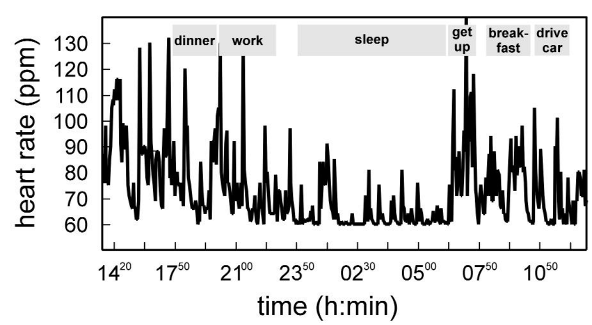


*Figure 2. Closed Loop Stimulation in a young, athletic, but chronotropically incompetent patient is characterized by circadian heart rate variation and increased rates during exercise.*

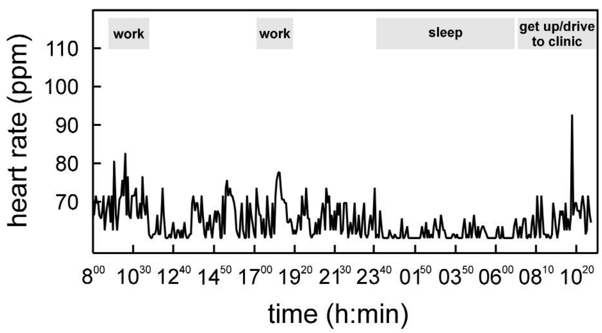


*Figure 3. Closed Loop Stimulation in an elderly, multimorbid, and chronotropically incompetent patient is characterized by circadian heart rate variation but only moderate rates during exercise.*

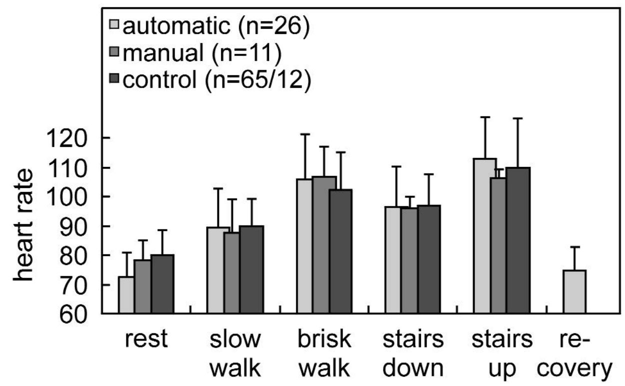


*Figure 4. Averaged heart rates (rest: mean value; walk and stairs: maximum value; recovery: final value) of two CLS patient groups with automatic and manual initialization show close correspondence to a healthy control population (rest, slow walk, brisk walk, n = 65 : [9] / stairs down, stairs up, n = 12 : [10]).*

(92 %) had been diagnosed with SSS. Two-thirds of the SSS patients were classified as bradycardic, while the remaining patients developed sinoatrial arrest. Eighty-one percent of the patients suffered from partial or complete atrioventricular blockade. One patient appeared to be completely chronotropically competent during the exercise tests because the spontaneous atrial rate reached the age-predicted heart rate. The heart rates in the other patients were supported by the CLS-rate, at least partly during higher load.

The investigation of each patient spanned two follow-up with a 3- to 5-day period between the examinations. During the first follow-up, the usual pacemaker interrogation was performed before programming the INOS² DR to DDD-CLS mode with automatic initialization and 24-h trend recording. The patient was given a diary for documenting his or her activities during the 24 hours prior to returning to the clinic for the second follow-up visit. In 4 patients, the automatic initialization procedure was accelerated, so the exercise tests could be performed during the first follow-up. All patients underwent an ambulatory test which included ascending and descending stairs (1 to 2 min each), as well as slow (1 to 2 min) and brisk (3 to 6 min) walking at patient-specific velocities. Each exercise step, except slow walking, was concluded with a recovery period of 3 min. Subsequently, 21 of the 26 patients performed a symptom-limited ergometry with two load steps each lasting 3 min. The second load was set to the predicted patient-specific maximum load, the first step was half that value.

## Results and Discussion

### 24-h trend

Consecutive 24-h trends stored in the pacemaker memory during DDD and DDD-CLS modes are available in 21 patients (see figure 1) allowing an intraindividual comparison of the corresponding average heart rates. The chronotropic incompetence in this patient group is indicated by relative low average rates during DDD mode. The CLS rate exceeds the heart rate during DDD pacing at any time, but the rate elevation during the day is more prominent compared to the nocturnal ones. The very close correlation between the DDD-CLS trend and the averaged 24-h heart rate of a healthy control group [8] serves as an indication for the reestablishment of physiologic heart rates by the CLS principle.

The two patients chosen as examples for the individual response of CLS pacing show circadian variation over 24 h (figures 2 and 3). Apart from this, the younger athletic man reaches high rates close to the individual MCLR during physical activity, but the corresponding heart rates of the older multimorbid man are relatively low due to limited exercise tolerance.

### Ambulatory test

Although it is not possible to measure and normalize the exercise level for ambulatory tests, these examinations have the advantage that they represent a major

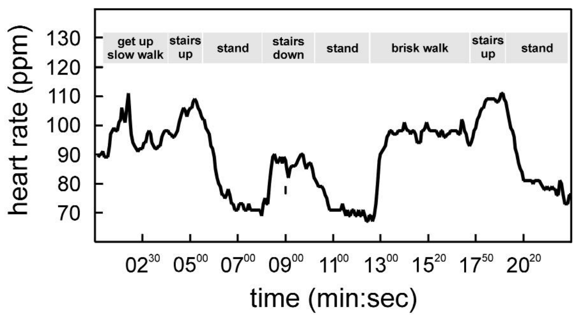


*Figure 5. CLS heart rate of a young, athletic, but chronotropically incompetent patient during an ambulatory test.*

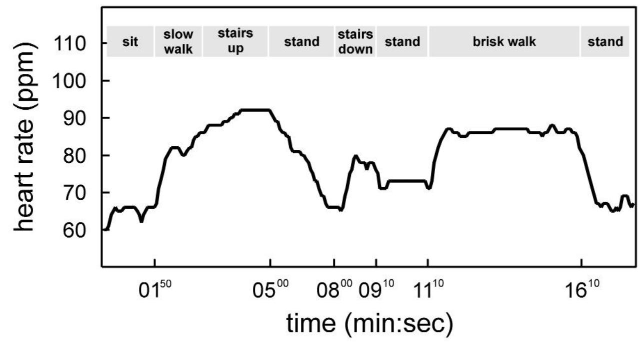


*Figure 6. CLS heart rate of an older, multimorbid, and chronotropically incompetent patient during an ambulatory test.*

aspect of the patient's normal daily life activity. The heart rates in figure 4 represent mean values for rest, maximum values during walking or ascending stairs, and the final rate at the end of recovery. During rest, the averaged heart rate values of CLS with automatic initialization and the control group show the highest difference (72 vs. 80 ppm). This deviation may be caused by the subjects being more or less excited prior to the investigation, since emotional effects affect the sinus rate, as well as the CLS. Compared with rest, the CLS rate (automatic initialization) increased by 17 ppm during slow walking, 33 ppm during brisk walking, 24 ppm during descending stairs, and 41 ppm during ascending stairs. These values correspond to the values of the control group very closely (maximum difference 3 ppm). During recovery, the CLS rate reaches a final value that is only 2 ppm higher than the initial rest rate. The standard deviations of all averaged values are comparable, indicating homogeneous populations. The close correspondence between the averaged heart rates of both the manual [7] and automatic initialization patient group with healthy subjects [9][10] indicates that CLS achieves physiologic heart rates regardless of initialization type.

Figures 5 and 6 present the ambulatory trends of the above-mentioned younger athletic patient and the older multimorbid patient. Both patients show pacing rates proportional to load, particularly when comparing stairs ascent with stairs descent. Additionally, a pacing rate plateau is reached during prolonged submaximal exercise (i.e., brisk walking for 6 min). During each recovery period, the CLS-rate starts to decrease immediately. In contrast, the rate amplitude, as well as the attack and decay rate of the pacing rate, is patient-specific, depending on the patient's condition and health status.

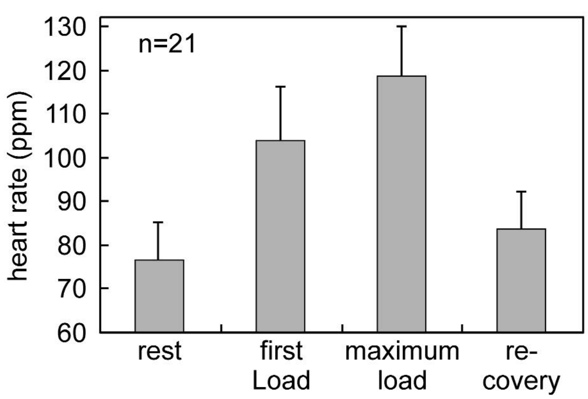


*Figure 7. Averaged heart rates with CLS (automatic initialization) during ergometry (rest: mean value; first and maximum loads: maximum value; recovery: final value).*

**Ergometry**

Standardized conditions exist during ergometry testing. The CLS-rate (automatic initialization) increased by 28 ppm during the first and 42 ppm during the second load step (figure 7). With two patients, ergometry was stopped prematurely because their maximum exercise capacity had been reached. The recovery period of 3 min seems to be too short since the final rate is 7 ppm higher than the initial rest rate (76 ppm). The sample ergometry trends of the younger athletic patient and the older multimorbid patient (figures 8 and 9) show immediate and quick rate increases to load onset and further rate increases during the second load step. The young and athletic patient tolerates high exertion levels with proportional maximum CLS-rates. The blood pressure increases with exercise but stays

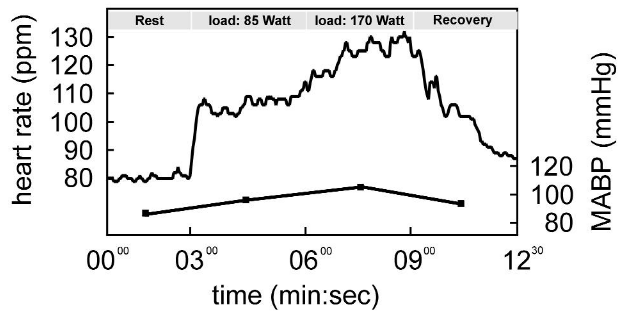


*Figure 8. CLS heart rate of a young, athletic, but chronotropically incompetent patient during ergometry.*

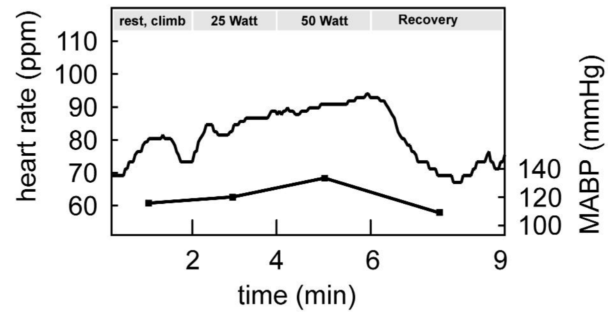


*Figure 9. CLS heart rate of an older, multimorbid, and chronotropically incompetent patient during ergometry.*

within physiologic limits during the entire test. The older patient could perform only at low levels of exercise due to his constitution. During rest, as well as during exercise, the blood pressure was elevated, which may be partially due to the emotional stress of the clinical investigation. Obviously, the response time of the system remains unaffected by the patient's specific disease, but the attack and decay rates are reduced.

## Conclusion

The results obtained during the clinical study demonstrate adequate responses of the regulated heart rate - even in chronotropically incompetent patients. The pacemaker adapts to the individual patient automatically without any need for programming special parameters. The achieved heart rates over 24 h during daily life, as well as those during short exercise tests, show close correspondence with values from healthy control groups. Nevertheless, the CLS-rate shows patient-specific profiles because of the patients' specific conditions and states of health. The new concept of automatic initialization renders the previous manual procedure superfluous, thus, the time needed for follow-up visits is shortened. In addition, the automatic initialization is permanently running when the CLS mode is active, ensuring long-term system stability.

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