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BIOTRONIK mbH & o K
Woermannkehre 1
12359 Berl n ermany
Tel +49 (0)30 68905-0
Fax +49 (0)30 6852804
nfo b otron k com
www b otron k com

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Closed Loop Stimulation vs. Conventional DDDR Pacing: Benefits of Hemodynamic Pacing[1]

Authors: P. Zecchi, F. Bellocci, T. Sanna, G. Di Martino, M. Alviti, R. Audoglio

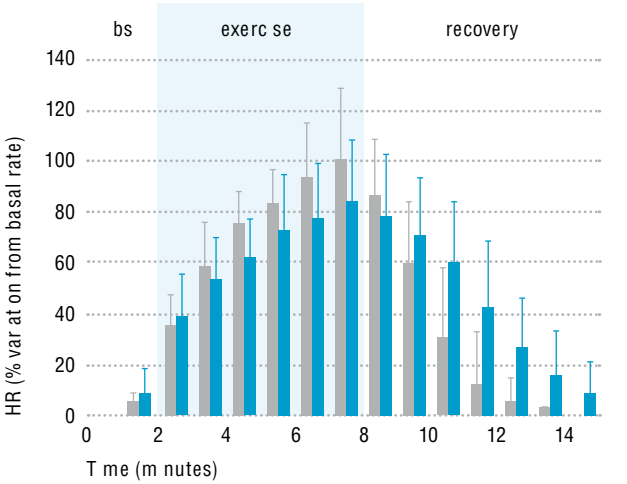
Introduction: The goal of this clinical study is to evaluate the improvements in hemodynamic profile and patients quality of life (QoL), when a previously implanted DDDR pacemaker is selectively replaced with a CLS pacemaker, the rate modulation algorithm based on the principle of Closed Loop Stimulation.

Methods: In seven (7) patients, aged between 56–87 years, all with chronotropic incompetence and advanced AV block, a DDDR pacemaker was replaced with a CLS device. One week before and one month after the pacemaker replacement, patients underwent an ambulatory test sequence, which included exercise stress test (Bruce protocol), mental stress test (colour word test), drug test (isoproterenol) and quality-of-life questionnaire. During the ambulatory tests, both heart rate and arterial blood pressure were monitored.

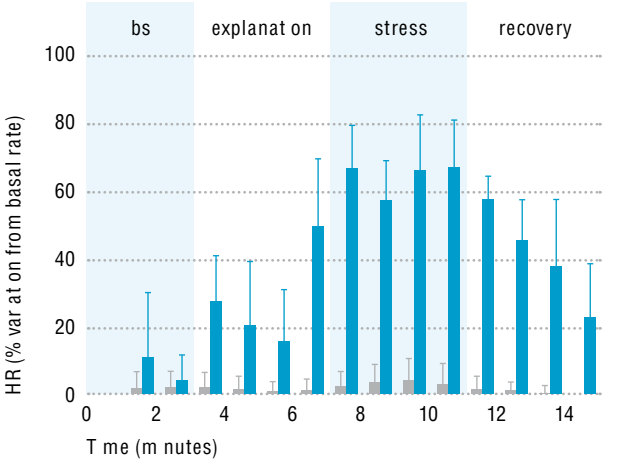
Results: The heart rate modulation was satisfactory in all DDDR pacemakers during exercise testing. Minute ventilation (1) and activity-based pacemakers did not respond to mental stress or to drug infusion. During tests in which rate modulation did not occur, the patients systolic arterial blood pressure reached critical values.

In all patients, the CLS device responded to every test, properly modulating the heart rate and keeping the systolic arterial blood pressure within physiological ranges. All but one patient experienced a substantial improvement in quality of life after replacement.

Conclusions: In conclusion, Closed Loop Stimulation induced a pacing rate modulation, which was always physiological and hemodynamically adequate under all test conditions, and resulted in improved quality of life.



F gure
Heart rate (HR) adaptat on between LS and accelerometer dur ng treadm ll exerc se test



F gure
Heart rate (HR) trends dur ng acute mental stress At m nute 4, the phys - c an expla ns the test procedure to the pat ent the test starts at m nute 7 and ends at m nute 11

Heart Rate Variability Over 24 Hours Closed Loop Stimulation and Motion-Sensor Pacemakers Compared with Healthy Control Group[2]

Authors: O.V. Beliaev, S.V. Berdnikov, S.P. Mikhailov, D.YU. Tobolin

Introduction: The aim of modern pacemaker technology is not only to prolong life but also to provide therapy that is orientated to the patient's individual needs, thus improving their quality of life. With the Closed Loop Stimulation (CLS) pacing concept, the pacemaker becomes part of the natural control loop and, therefore, guarantees adequate pacing rates under all types of mental and physical loads.

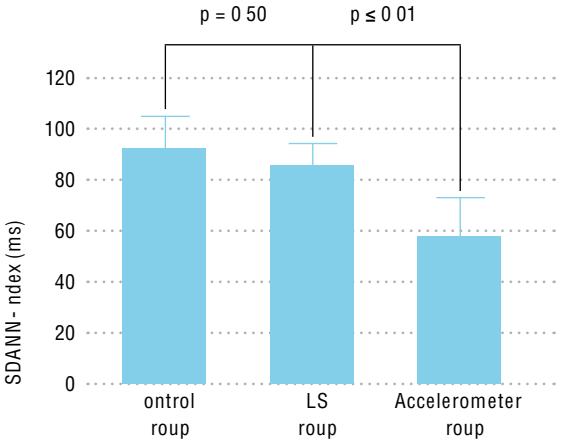
As the pacemaker is part of the natural control loop, the suspicion exists that the pacing rate is mediated by the efferent sympathovagal signals that underlie heart rate variability. Therefore the aim of this investigation is to demonstrate that the CLS pacing delivers a heart rate variability (HRV) similar to those of healthy subjects, and dissimilar to those of patients with systems deriving information for rate adaptation from a motion sensor.

Methods: The investigations to analyse HRV were performed with a total of 71 subjects consisting of two groups of patients, and a control group. The CLS group consisted of 19 patients, the motion sensor rate adaptive group consisted of 32 patients, and a control group of 20 healthy subjects. Both groups of pacemaker patients including the control group underwent 24-hour Holter monitoring for evaluation of heart rate histograms, mean heart rate and for computation of the SDANN index.

Results: The heart rate variability of the CLS group showed a mean SDANN index of 86 ms and no significant difference ($p = 0.5$) to that of the control group (mean SDANN index, 93 ms). The heart rate variability of the motion sensor group, with a mean SDANN index of 59 ms, is significantly different than that of the control group ($p \leq 0.01$).

Conclusions: The results illustrate that CLS provides heart rate variability comparable to that of subjects with healthy sinus nodes due to the integration of the pacemaker into the natural control loop. In contrast, the heart rate variability of the motion sensor group is limited and does not fully correspond to the actual cardiovascular needs of the patients.

It is known from the literature that the SDANN index and the corresponding HRV decreases with increasing age even in healthy persons.



F gure
SDANN ndex of the 3 groups, evaluated from the 24-hour Holter record ngs

Effect of Pacemaker Rate-Adaptation on 24h Beat-to-Beat Heart Rate and Blood Pressure Profiles[3]

Authors: R. Quaglione, G. Calcagnini, F. Censi, M. Malavasi, M. Raveggi, G. Biancalana, P. Bartolini, G. Critelli

Introduction: Dual chamber pacing (DDD) has been shown to provide superior hemodynamic function and work tolerance with respect to single chamber pacing (VVI). This is due to better control of blood pressure with the advantages of AV synchrony and rate responsiveness due to P-wave tracking. A new generation of physiological pacemakers adapt the pacing rate according to an indirect measure of ventricular contractility (closed loop stimulation, DDD-CLS).

The aim of the study was to evaluate the 24-hr beat-to-beat heart rate (R-R) and blood pressure changes during closed loop stimulation (DDD-CLS) pacing and conventional fixed rate DDD pacing with respect to simultaneous activity.

Methods: We continuously and simultaneously measured beat-to-beat heart rate and blood pressure for 24-hr in patients implanted with a closed loop system pacemaker. A randomised crossover comparison of DDD-CLS and DDD pacing was performed using short and long-term analyses.

Results: Seventeen patients (10 males, aged 46 –85 years) were enrolled in the study with 11 completing the protocol. The mean percentage of atrial stimulation was 72.87% during the DDD-CLS and 38.36% in DDD ($p = 0.003$). All patients had 100% stimulation in the ventricle. On average, the percentage increase of paced RR intervals with respect to spontaneous beats was only 7.4% in DDD-CLS, but 20.1% in DDD ($p = 0.0001$).

A significant correlation between spontaneous and paced R-R profiles was obtained only during DDD-CLS ($r_{DDD\text{-}CLS} = 0.77$, $r_{DDD} = 0.23$, $p = 0.01$). Short-term analysis revealed a 3.79% reduction in the escape interval in DDD-CLS and 8.19% in DDD, and the relative fall in diastolic blood pressure was 1.14% in DDD-CLS and 3.18% in DDD.

Conclusions: DDD-CLS provided physiological heart rate fluctuations throughout the duration of the 24-hr test. The blood pressure profiles of paced and spontaneous beats were comparable. The onset of paced rhythm in DDD-CLS resulted in a less pronounced decrease in heart rate and fall in diastolic pressure than in DDD.

Evaluation of the Chronotropic Function of a Closed-Loop Rate-Responsive Dual Chamber Pacemaker Driven by Contractility[4]

Authors: J. Clementy, S. Garrigue, L. Gencel, P. Jais, D.C. Shah, P. Le Metayer, M. Hocini, M. Haissaguerre Chu

Introduction: A promising concept in rate adaptive pacemaker therapy, Closed Loop Stimulation (CLS) aims to adjust the heart rate of chronotropically incompetent patients in accordance with myocardial contractility. CLS monitors the inotropic state of the patient via intracardiac impedance measurement, integrating the system into the baroreceptor reflex.

This study aims to compare the rate modulation of the CLS device to the physiological sinus rate of healthy subjects, focussing on two different aspects: acute responsiveness during daily life exercise and variations due to circadian influences.

Methods: In the Daily Life Exercises sub-study 30 patients implanted with a CLS pacemaker were divided into two groups: Group Manual (19 patients, mean age 69 ± 12 years, manual sensor calibration) and Group Auto (11 patients, mean age 64 ± 9 years, automatic sensor calibration). Patients performed five lifestyle tests in a randomised order including: walking, climbing upstairs, descending stairs, hyperventilation with arm moving and leg flexion with squatting. Additionally the patients performed a symptom limited exercise test and bicycle exercise at 30 and 60 Watts for three mins each. CLS rate modulation was compared with the sinus node obtained from an age matched control group of 18 healthy subjects.

In the Circadian Variation study, 33 patients (mean age 67 ± 9 years) with a CLS pacemaker were divided into three groups. Ten patients were programmed to DDD mode while rate response was activated in the others: 12 with Manual, and 11 with Automatic sensor calibration. Holter trends were obtained in all patients and in the control group in addition to rate histograms and maximal and mean daily hourly rates.

Results: In the Daily Life Exercises study CLS showed an excellent correlation of 92–99 % between sinus rhythm and pacemaker rate modulation during upward and downward stair climbing, walking, hyperventilation and leg flexion. This was independent of the method used for sensor calibration.

In the Circadian Variation study, intermittent rate increases were observed during night-time in six patients due to body rotation. The correlations between mean hourly rate curves during day and night was 84 % in manual calibration and 86 % in automatic mode. These are not statistically different from the control subjects.

Moreover, the 24-hr trends of the pacemaker patients showed circadian variation, which was not statistically significant from that of the healthy control population.

Conclusions: In both the Chronotropic Function and Circadian Rate Modulation studies there was a close correlation between the heart rate trends of the rate adaptive pacemaker patients and those of the healthy control populations. These results demonstrate the effectiveness of the CLS concept in the restoration of natural heart rate variation.

Impact of Closed-Loop Stimulation, Overdrive Pacing, DDDR Pacing Mode on Atrial Tachyarrhythmia Burden in Brady-Tachy Syndrome[5]

Authors: A. Puglisi, G. Altamura, F. Capestro, B. Castaldi, G. Critelli, S. Favale, L. Pavia, G. Pettinati

Introduction: This study was planned to test the hypothesis that in patients with BTS, the restoration of a physiological modulation of heart rate and atrial pacing overdrive, might have a valuable effect on reducing AT burden. Three pacing algorithms were compared in order to verify the hypothesis: Closed Loop Stimulation, DDD+ overdrive pacing and a conventional accelerometer-based DDDR pacing algorithm.

Methods: In this prospective study, with no crossover, 149 (mean age 74±9 years, 48.3% male) patients with BTS were enrolled in 17 Italian centers. Three randomized groups were activated with different pacing algorithms after an observational implant period of one month: the CLS group (74±9 years, 46.1% male) was implanted with Inos^2 pacemakers, the DDD+ (75±8 years, 46.9% male) and DDDR (74±9 years, 52.1% male) groups with Philos DR accordingly.
143 patients reached the 1-month FU, 126 the 4-month and 98 patients the 7-month follow-up. 51 patients dropped, mostly due to occurrence of persistent or chronic AF.

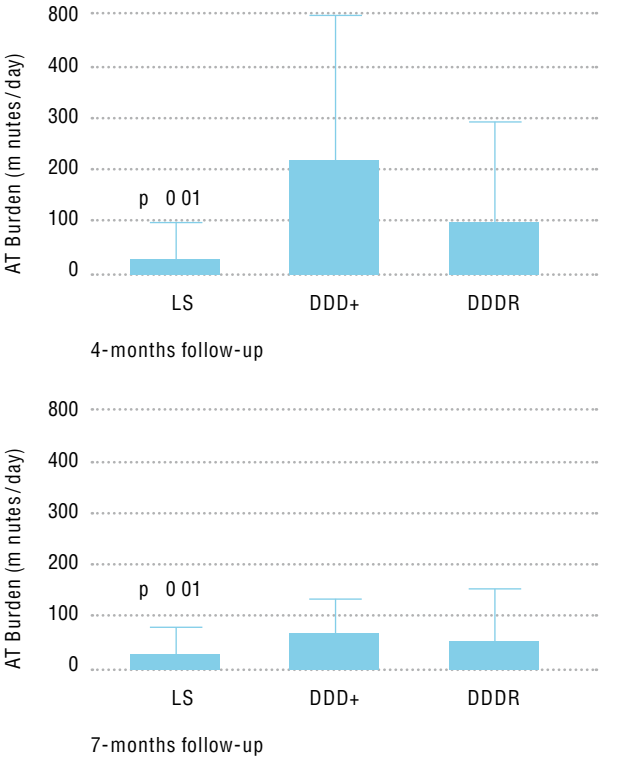
Results: The cumulative duration of AT burden was retrieved from all patients who reached the 4- and 7-month FU.

The lowest AT burden was observed in the CLS group with both, 4- (average 21.1±71.6 min/day) and 7-month (average 20.3±63.1 min/day) FU, while the DDD+ (213.3±535.6 min/day; 63.1±113.8 min/day) and DDDR (94.8±240.5 min/day; 56.0±184.0 min/day) groups showed significantly higher results ($p<0.01$).

Even though the atrial pacing percentage (APP) of CLS and DDD+ was not significantly different, CLS was associated with a lower AT burden.

The APP of DDDR was lower than compared to the other two groups (CLS 89.0±13.2%; DDD+ 97.9±2.7%; DDDR 71.1±26.7% at 7-month FU).

Conclusions: Patients treated with CLS spent on average a shorter time with atrial tachyarrhythmias as compared to patients treated with DDD+ persistent overdrive algorithm and conventional DDDR pacing mode. Despite the not significant differences in atrial pacing percentage, CLS seems to have a positive effect reducing daily AT burden. Due to the nature of this study further investigation is needed to be conclusive.



F gure
AT burden n each treatment group after 4- and 7-month follow-up

Closed Loop Stimulation in prevention of vasovagal syncope. Inotropy controlled pacing in vasovagal syncope (INVASY): a multicenter randomized, single blind, controlled study[6]

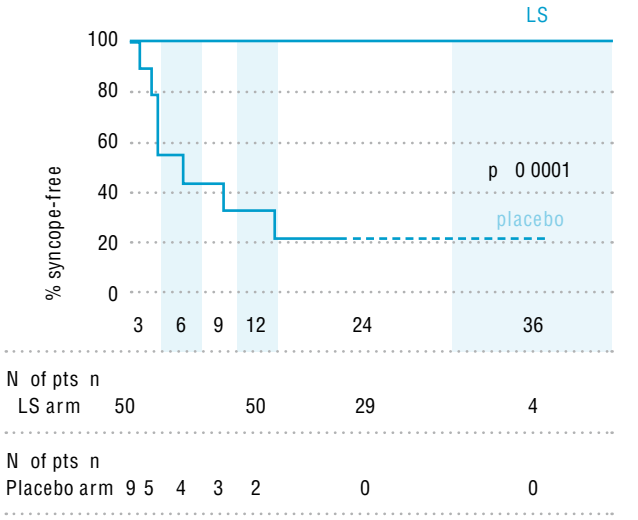
Authors: E. Occhetta, M. Bortnik, R. Audoglio, C. Vassanelli, for the "INVASY" Study Investigators

Introduction: In patients with recurrent, severe, cardioinhibitory vasovagal syncope (VVS), significant bradycardia or prolonged asystole (up to >60 s) and concomitant hypotension, can produce serious physical injuries and psychological impairment, including a substantial limitation of social and working life. During VVS, an increase in myocardial contractility associated with a reduction of ventricular filling produces an increase in baroreceptor afferent flow and a consequent decrease in the heart rate. The CLS algorithm is a form of rate adaptive pacing, which responds to myocardial contraction dynamics. During an incipient VVS it could increase paced heart rate and avoid bradycardia, arterial hypotension and syncope. This study aims to determine, whether CLS is able to prevent recurrence of VVS.

Methods: 50 patients (27 males, mean age 59±18 years) with severe and recurrent VVS and positive Head Up Tilt Test (HUTT) with cardioinhibition received a CLS pacemaker (Inos^2). The primary endpoint was recurrence of two VVS during a minimum of 1 year of follow-up. Randomization between DDD-CLS and DDI mode (40 bpm) pacing was performed only during the first stage of the study (first year): 9/26 randomized to DDI mode (control group) and 17/26 in DDD-CLS mode. All the 24 patients recruited in the second stage of the study (second year) were programmed in DDD-CLS mode. The tested hypothesis was that the implantation of a DDD-CLS pacemaker would reduce the recurrence of VVS by at least 50% compared to the placebo DDI mode pacemaker.

Results: Of the nine patients randomized to the DDI mode, seven had recurrences of syncope during the first year. At the end of the first year the nine patients were reprogrammed to the CLS mode and no syncope occurred after reprogramming. The 41 patients programmed to CLS had a mean follow-up of 19±4 months: none reported VVS, only four (10%) reported occasional presyncope and their quality of life greatly improved. Positive HUTT at the end of the first year failed to predict the clinical response to CLS pacing.

Conclusions: The study demonstrates the effectiveness of CLS pacing in preventing cardioinhibitory VVS. A possible placebo effect of pacemaker implantation occurred in 22% of patients.



F gure
Probab l ty of rema n ng free of syncopal recurrences (Kaplan-Me er est mat on) n 41 pat ents n LS arm and n ne pat ents n the control group (placebo – DDI)

T me s nce random zat on (n month)

Heart Rate Changes during Acute Mental Stress with Closed Loop Stimulation: Report on Two Single-Blinded, Pacemaker Studies[7]

Authors: S. Chandiramani, M.D, L.C. Cohorn, B.S, S. Chandiramani

Introduction: Mental stress affects hemodynamic properties of the heart in patients indicated for a pacemaker, therefore highlighting the need for a rate-adaptive sensor that responds to mental loads. One such sensor utilises Closed Loop Stimulation (CLS), which translates right ventricular contractility into patient specific pacing rates.

Clinical studies utilizing CLS (Emotional Response (ER) and Emotional Response 2 (ER2) studies) have been performed to confirm CLS provides appropriate heart rate response to acute mental stress. The objective of these studies was to compare heart rates during a mental stress test, with the patient's pacemaker programmed to a CLS pacing mode and an accelerometer pacing mode.

Methods: Patients were implanted with a CLS pacemaker and subjected to mental stress testing. The stress test consisted of a relaxation period followed by a colour-word test and an arithmetic challenge test. The ER2 study utilised a randomised study design, in which pacing mode testing order was randomised

Results: Analysis included patients who exhibited at least 80 % sensor-driven heart rates during mental stress testing. Results for both studies demonstrated that CLS provided a statistically higher increase in heart rate during testing compared with an accelerometer pacing mode. The studies also showed that CLS provided a statistically significant higher peak heart rate during testing compared with an accelerometer pacing mode.

Conclusion: The ER and ER2 studies demonstrate that the CLS algorithm responds with an increasing heart rate to acute mental stress in patients exhibiting a high percentage of sensor-driven pacing.

Heart Rate Profile Comparison in ER and ER2 Studies:
CLS Versus Accelerometer

	CLS	Accelerometer	P-Value
ER study (n = 40)			
Peak sensor-driven	83.90 ± 7.5	71.26 ± 5.3	< 0.001
Heart rate increase	18.65 ± 5.77	6.99 ± 3.22	< 0.001
ER2 study (n = 150)			
Peak sensor-driven heart rate	80.47 ± 8.40	70.70 ± 5.99	< 0.001
Heart rate increase	16.16 ± 7.34	6.85 ± 2.56	< 0.001

Data are mean ± SD

Heart Rate Profile Comparison in ER2 Study:
Dual Chamber Versus Single Chamber Pacemakers

	CLS	Accelerometer	P-Value
ER study (n = 91)			
Peak sensor-driven heart rate	79.42 ± 9.03	69.43 ± 5.98	< 0.001
Heart rate increase	16.10 ± 8.27	6.62 ± 2.49	< 0.001
ER2 study (n = 59)			
Peak sensor-driven heart rate	82.09 ± 7.09	72.65 ± 5.51	< 0.001
Heart rate increase	16.25 ± 5.67	7.21 ± 2.65	< 0.001

Data are mean ± SD

ANS-Controlled Rate-Adaptive Pacing
A Clinical Evaluation [8]

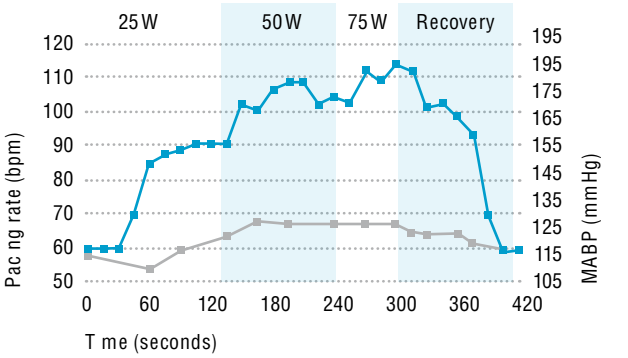
Authors: J. Witte, R. Reibis, A.M. Pichlmaier, E. Enber, K. Malinowski, W. Rodiger, W. Niederlag, E. Wunderlich, R.J. Van Woersem, J.C.J. Res, B. Merkely, F.A. Lucchese, C. Halperin, O.T. Greco, O.V. Beljaev, J. Vaskelyte, M. Schaldach

Introduction: For patients with chronotropic incompetence, the most effective strategy for rate adaptation is the physiologic restoration of closed-loop chronotropic control. Under physiological conditions cardiac output is adjusted by the ANS to meet hemodynamic and metabolic requirements. The adjustment is performed within a closed loop system with mean arterial blood pressure as the controlled quantity. Physical and psychological abilities under normal physiological conditions are greatly dependent on the regulation of cardiac function by the ANS. The aim of this study was to provide an overview of ANS controlled bradycardia therapy. It evaluated the use of CLS in the regulation and restoration of physiological rate response in a range of environments including physical and psychological stress.

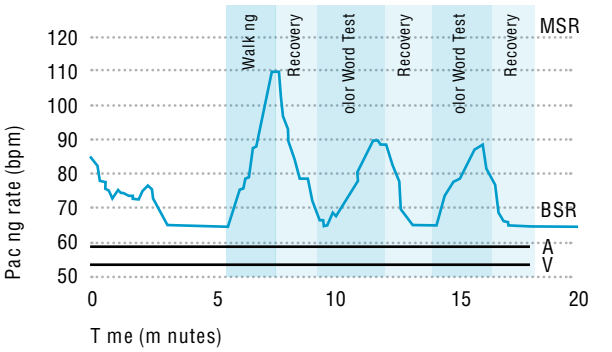
Methods: ANS-controlled pacemakers were implanted in 262 patients (84 dual and 78 single chambered systems) with a mean age of 62 ± 7 years. Successful rate adaptive performance was evaluated following analysis of the 24-hr trend data (stored with the pacemaker memory), and heart rate response to a standardised exercise protocol. Rate adaptive changes under stressful psychological conditions were assessed with the use of colour word conflict tasks. Intracardiac impedance was measured via the tip of the RV stimulation electrode and reflected changes in blood/tissue concentrations around the electrode tip.

Results: Successful rate adaptation was achieved in 93% of single chamber systems, and in 96% of the dual systems both in the 24-hr trending and the exercise protocols. Studies with the ANS-controlled pacemaker have shown that temporary ischaemic changes in the myocardium result in a pacemaker response that is highly dependent on the position of the ischaemia. The results of the intracardiac impedance measurements showed that during ischaemia in the myocardium, the impedance signal changes were similar to that obtained during physical exercise, reflecting enhanced contractility, and similar to expected pathophysiologic response of the circulatory system at such a time.

Conclusions: The results obtained demonstrate the feasibility of the ANS-controlled closed loop pacing system based on the assessment of myocardial contractility. In Sick Sinus patients, changes in heart rate at the beginning of exercise, as well as during recovery correlate with typical physiological responses. There is also clear indication that the ANS-controlled rate adaptation functions effectively during both physical and emotional stress.



F gure
Pac ng rate and MABP dur ng phys cal exerc se (b cycle ergometry) for a pat ent w th an ANS-pacemaker system



F gure
Increase n pac ng rate w th psycholog - cal load (colour-word confl ct) demonstrates nfluence of ANS on pacemaker act v ty

Increased Heart Rate during Acute Mental Stress with Closed Loop Stimulation: The Emotional Response 2 Study[9]

Authors: S. Neelagaru, M.D., S. Ehrlich, M.D., C. Clayhorn, B.S.

Introduction: Closed Loop Stimulation (CLS) is a sensor that translates right ventricular contractility into patient specific pacing rates. The CLS algorithm monitors and processes an intracardiac impedance signal associated with myocardial contractility dynamics on a beat-to-beat basis. Contractility is a cardiac control element integrated into the cardiovascular closed loop system, therefore allowing the CLS algorithm to provide patients with a wider, more physiologic heart rate distribution. The Emotional Response 2 (ER 2) study evaluated the effect of CLS during sensor driven pacing to determine if the sensor provided an appropriate heart rate response to acute mental stress.

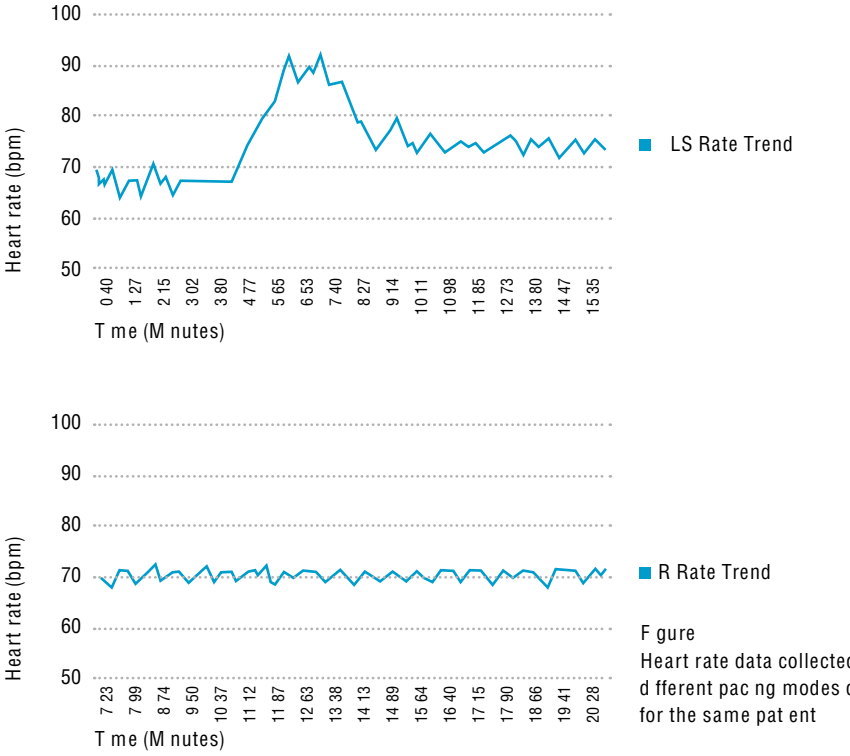
Methods: The ER 2 study compared heart rates during an emotional and mental stress test, whilst the patient's pacemaker was programmed to CLS and compared them with those of the accelerometer or (R) mode. Patients were implanted with a BIOTRONIK CLS pacemaker. The computer directed emotional response test consisted of relaxation slides followed by a colour-word and an arithmetic test. The ER 2 study was a blind, randomised study and utilised a crossover design with the patients serving as their own control.

Results: A total of 401 patients were enrolled at 36 medical centers. Of the total population, 150 patients had at least an 80% sensor-driven heart rate (SDHR) during testing. The average SDHR during testing was 80.47 ± 8.40 bpm compared to 70.70 ± 5.99 bpm while in the R mode ($p < 0.001$).

For patients aged between 40–60 years (n = 11), CLS provided an average heart rate (HR) increase from baseline of 16.05 ± 7.06 bpm during testing versus 5.79 ± 1.67 bpm increase with R mode ($p < 0.001$).

For patients aged >60 years (n = 138), CLS provided an average HR increase from baseline of 16.10 ± 7.36 bpm during testing versus 6.92 ± 2.61 bpm increase with the R mode ($p < 0.001$).

Conclusions: The ER 2 study demonstrated that the CLS algorithm responds with an appropriate heart rate increase to acute mental stress in patients exhibiting a high percentage of sensor driven pacing. The ER 2 study demonstrates that the rate adaptation provided by CLS is consistent with historical controls for age-matched healthy subjects.



F gure
Heart rate data collected n the two d fferent pac ng modes dur ng test ng for the same pat ent

Closed Loop Stimulation and Accelerometer-Based Rate Adaptation: Results of the PROVIDE Study[10]

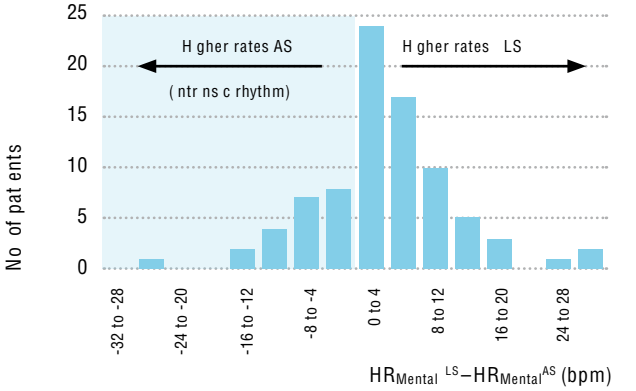
Authors: M. Coenen, K. Malinowski, W. Spitzer, A. Schuchert, D. Schmitz, M. Anelli-Monti, S. K.G. Maier, W. Estlinbaum, A. Bauer, H. Muehling, F. Kalscheur, K. Puerner, J. Boergel, S. Osswald

Introduction: Accelerometers have proven to deliver an acceptable pacing rate profile in daily life, often needing customized programming by the physician though. Exercise forms without thoracic movement as well as mental and emotional stress have no impact on the sensor. Measuring an intrinsic parameter that is directly affected by vagal and sympathetic output, so-called closed loop sensors modify the pacing rate which, in turn, interacts with the autonomic nervous system via negative feedback. Rate adaptive pacing based on Closed Loop Stimulation (CLS) or accelerometer sensor (AS) was compared intraindividually in 131 patients during walking and acute mental stress to asses patients' preferences regarding the sensor system.

Methods: One month after the pacemaker implantation, 131 chronotropically incompetent patients were randomized to either the AS or the CLS group for 3 months with crossover after the 4-months follow-up. Arithmetic and 6-min walk tests were performed in the non-rate adaptive mode (VVI or DDD), AS (VVIR or DDDR) and CLS rate adaptive modes (VVI-CLS or DDD-CLS), respectively. Single- or dual-chamber pacing configuration had to be maintained after mode randomization. After the 7-months follow-up, patients had to select the individually preferred pacemaker sensor.

Results: The mean heart rate during the final minute of mental stress was higher (3.0±9.2 bpm) in the CLS than in AS mode ($p=0.004$). Benefit in the walking distance compared with non-rate adaptive pacing was similar for the two modes: added 27±96 m (AS, $p=0.013$) and 30±116 m (CLS, $p=0.025$). At the end of the walk, heart rate was higher by 4.8±21.4 bpm in AS than CLS ($p=0.049$). Twice as many patients preferred CLS over AS (51%; $p<0.01$). One quarter had no preferred mode.

Conclusions: The arithmetic test was associated with significantly higher heart rates for the CLS than for accelerometer sensor, confirming the expected greater sensitivity of CLS-based rate adaptation to mental stress. There was no difference in the distance covered during 6-min walk between the two sensors. However, patients preferred CLS over accelerometer to a statistically significant degree.



F gure
Intra nd v dual d fference n HR_{Mental} for LS versus AS (mean 3 0±9 2 bpm, p=0 004, N=84 pa rs of data)
HR_{Mental} mean rate n the per od between 60 and 120 sec after start ng ar thmet c calculat ons

An Impedance Sensor (CLS) is Superior to an Accelerometer for Chronotropically Incompetent Patients with Sinus Node Dysfunction: Results of a Pilot Study with a Dual Sensor Pacemaker[11]

Authors: B.B. Pavri, M.D, S. Russell, RN

Introduction: Patients with chronotropic incompetence (CI) depend on pacemakers for rate response. Many sensors, however, do not provide an adequate heart rate (HR) response. Closed Loop Stimulation (CLS) is an impedance sensor, which monitors local right ventricle myocardial-blood pool impedance as a surrogate for cardiac contractility. CLS establishes a resting or baseline impedance curve for each heart beat, and calculates the differential area deviation away from the baseline curve. The purpose of this study was to compare the HR response provided by an accelerometer (DDDR) to that of Closed Loop Stimulation (DDD-CLS) in patients with chronotropic incompetence.

Methods: A total of 18 patients with CI (defined as a mean HR <55 bpm on 24-hr Holter, and AF <20% total time) were enrolled in a single blind crossover trial. Patients were randomised to either DDDR or DDD-CLS for a period of 4 weeks and completed a range of standardised activities including isometric handgrip, deep breathing, Valsalva and postural change. Holter data was assessed after the 4-weeks according to the mean, minimum and maximum HR. The Ansar System was used to provide a snapshot of sympathovagal balance during standard manoeuvres. Patient Quality of Life (QoL) scores were measured and patients classified according to a scale from 0=no improvement to 3=tremendous improvement.

Results: Four of the 18 patients were excluded according to the AF criteria of <20% and one patient failed the criteria for CI. The mean HR increased from 56.3 bpm (baseline) to 71.9 bpm in the CLS patients ($p<0.002$) compared with an increase to 64.7 bpm in the DDDR group ($p<0.046$). Maximum HR increased from 91.6 bpm to 116.3 bpm in the DDD-CLS group ($p<0.001$), compared with 106.7 bpm in the DDDR group ($p=0.058$). Over 75% of patients programmed to DDD-CLS experienced significant or tremendous improvement compared to only 22% of patients programmed to DDDR.

Conclusions: Although Holter-derived minimum and maximum HR were not significantly different between the two sensors, DDD-CLS provided a higher mean HR. It was concluded however that DDD-CLS provided a superior HR response to standardised autonomic manoeuvres as assessed by the Ansar testing. Furthermore DDD-CLS provided better QoL and was selected as the sensor of choice by the majority of blinded patients.

Quality of Life	Baseline	DDD-CLS	DDDR	p value (CLS vs. DDDR)		
Score	0	1.9	0.8	0.006		
Holter Heart Rate (bpm)	Baseline	DDD-CLS	DDDR	p value (BL vs. CLS)	p value (BL vs. DDDR)	p value (CLS vs. DDDR)
Holter Mean HR	56.3	71.9	64.7	0.002	0.004	0.046
Holter Minimum HR	40.3	57.2	57.3	‹0.001	‹0.001	0.681
Holter Maximum HR	91.6	116.3	106.7	0.002	0.058	0.092

F gure
hanges n mean, m n mum and max mum heart rate for LS and accelerometer pacemaker modes

Inter-individual Comparison of Different Sensor Principles for Rate Adaptive Pacing[12]

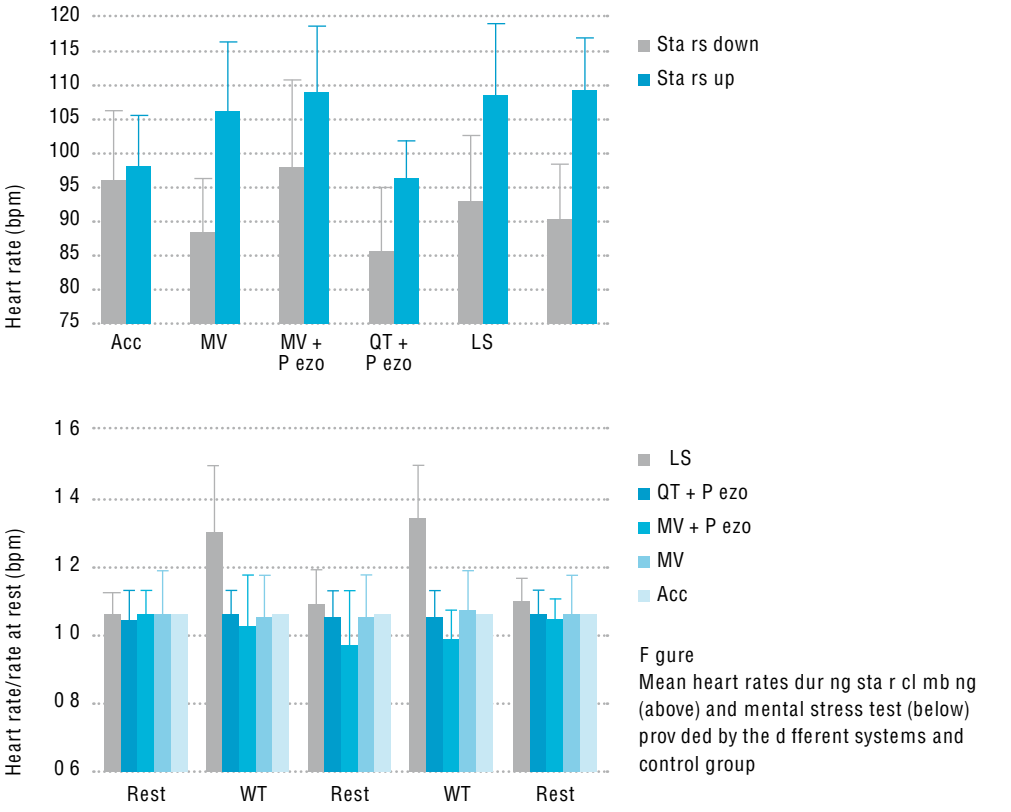
Author: K. Malinowski

Introduction: In recent years a multitude of rate adaptive sensor signals have been developed to adapt the pacing rate to the physical load of the patient. In contrast to those systems the closed loop stimulation (CLS) represents a new concept, which regards the pacemaker as part of the cardio-circulatory system. The pacemaker converts the body's sympathetic activity into a more appropriate heart rate.

Methods: The study compared closed loop stimulation and the different sensor systems that evaluate external parameters for rate adaptive pacing, with a control group. To this end, 27 patients and 15 patients with a healthy sinus node (control group) were subjected to physical and mental stress tests. The recorded results were analysed with regard to the maximum rates reached during the stress.

Results: The analysis of the recorded rate trends showed a higher heart rate when going up stairs, with the exception of the accelerometer (up 97.8±7.7 beats/min; down 95.5±10.4 beats/min). The CLS generated heart rates during stair climbing were almost identical to those of the control group (climbing: CLS 108.3±10.5 beats/min; control: 109.3±7.4 beats/min). The dual sensor systems, QT + piezo and MV+ piezo differed mainly in their absolute pacing rates. Compared to the control group, MV + piezo calculated a rate that was excessive during stair descending due to piezo overvaluation (descending: MV + piezo 98.6±6 beats/min; control 89.6±8.5 beats/min). The accelerometer sensed no significant difference between climbing and descending, setting pacing rates between 95 and 100 beats/min. During the colour word test (CWT) only the CLS showed the expected rate increase (rest: CLS 65.3±4.5 beats/min; CWT 83±14.1 beats/min) followed by the appropriate fall during the relaxation phase.

The results showed that none of the studied sensor-controlled systems was able to determine an adequate pacing rate under all of the various load states. The dual sensor or blended systems experience problems in balancing the input of the two sensor signals when calculating the pacing rate. The evaluation of a single external parameter, such as the acceleration of the upper body with the accelerometer also failed to provide an adequate pacing rate in many stress situations. In contrast to all sensor systems, CLS achieved a heart rate in agreement with those of the reference group in all physical and mental stress situations.



F gure
Mean heart rates dur ng sta r cl mb ng (above) and mental stress test (below) prov ded by the d fferent systems and control group

Closed-Loop Stimulation Using Intracardiac Impedance as a Sensor Principle: Correlation of Right Ventricular dP/dt $_{max}$ and Intracardiac Impedance during a Dobutamine Stress Test [13]

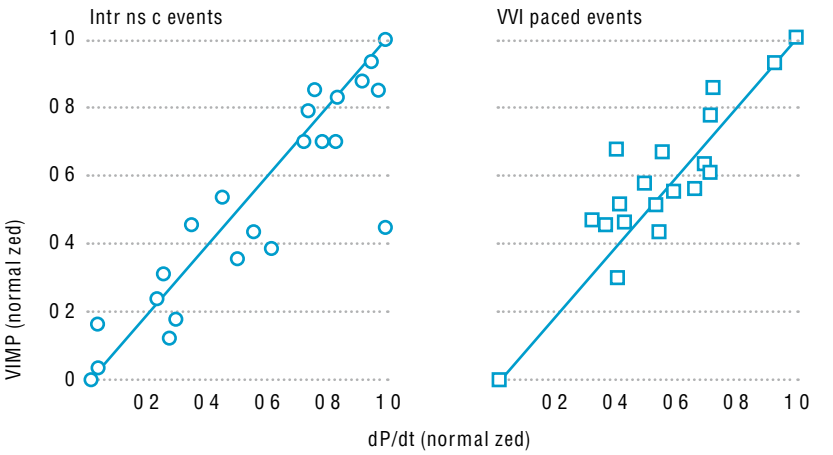
Authors: S. Osswald, T. Cron, C. Graedel, P. Hilti, M. Lippert, J. Stroebel, M. Schaldach, P. Buser, M. Pfisterer

Introduction: Changes in the unipolar right ventricular impedance during the cardiac cycle are related to the changing blood volume (low impedance) and tissue (high impedance) around the tip of the pacing electrode. During myocardial contraction impedance continuously rises reaching its maximum in late systole. This impedance increase is thought to correlate with right ventricular contractility, and thus with the inotropic state of the heart. In CLS pacemakers, information from the changing ventricular impedance (VIMP) is integrated into the closed loop regulation of the rate response. The aim of this study was to analyse the effects of increasing Dobutamine challenge on RV contractility and the measured impedance signals.

Methods: In 12 patients (68 ± 12 years) undergoing a CLS pacemaker implantation (BIOTRONIK), a right ventricular pigtail catheter was inserted for continuous measurements of RV-dP/dt $_{max}$ and simultaneous VIMP signals during intrinsic and ventricular paced rhythm. A stress test with a stepwise increase in intravenous Dobutamine (5–20 g/kg per min) was then performed. To assess the relationship between RV contractility and measured sensor signals, normalised values of dP/dt $_{max}$ and VIMP were compared by linear regression.

Results: There was a strong and highly significant correlation between dP/dt $_{max}$ and VIMP for ventricular paced ($r^2 = 0.93$) and intrinsic rhythm ($r^2 = 0.92$), although the morphologies of the original impedance curves differed substantially between paced and intrinsic rhythm in the same patient. Furthermore, VIMP correlated well with sinus rate ($r^2 = 0.82$), although there were at least four patients with documented chronotropic incompetence.

Conclusion: We conclude that, for intrinsic and ventricular paced rhythms, sensor signals derived from right ventricular unipolar impedance curves, correlate closely with dP/dt $_{max}$, and thus, with a surrogate of right ventricular contractility during a Dobutamine stress testing. Our results suggest that inotropy-sensing via measurement of intracardiac impedance is highly accurate and seems to be a promising sensor principle for physiologic rate adaptation in a closed-loop pacing system.



F gure
orrelat on between VIMP and dP/dt $_{max}$ separated for ntr ns c and paced rhythm

Cardiac Pacemakers Controlled by Autonomic Nervous System-Driven Sensor and Related Neurohumoral Aspects[14]

Authors: M. Martinelli Filho, S.A.D. Nishioka, H. Lopes, J.C. Oliveira, A.A. Pedrosa, S.F. Siqueira, and R. Costa

Introduction: A sympathetic sensor-driven pacing system is an important means of physiologic correction of chronotropic incompetence. The aim of this study was to evaluate changes in heart rate mediated by a sympathetically driven pacemaker compared with normal sinus function.

Methods: Nine men and six women (aged 37–80 years) with atrioventricular block and a pacemaker controlled by a closed-loop system were studied. Group I patients included eight patients with chronotropic incompetence, and Group II included seven patients with normal sinus function. All patients underwent the Valsalva manoeuvre and head-up tilt table testing with measurements of plasma catecholamines and renin activity.

Pacing was initially programmed in the DDD mode at a lower rate of 60 beats/min, with an upper rate limit of 0.85 x (220-age/years) beats/min; the pacemakers were then programmed to DDD-CLS (DDDR) in Group I and VVI-CLS (VVIR) in Group 2.

The second phase of the study consisted of nitro-glycerine and phenylephrine infusions, and the third phase involved physiologically provocative manoeuvres. The second and third phases were performed in three patients from each group with sensor activity On and Off.

Results: In Group I, heart rate changed only during tilt in the DDD-CLS mode. In Group II, heart rate changes were comparable in both groups. Catecholamine levels in Group I were higher during DDD than during DDD-CLS pacing ($p<0.05$). In Group I, heart rate did not change during phases II and IV of the Valsalva manoeuvre in the DDD mode, but behaved almost physiologically after sensor activation.

A late and paradoxical response to nitro-glycerine was observed in groups I and II, and a similar response to phenylephrine was observed in group I. During physiologic manoeuvres, significantly greater variations in heart rate were observed during DDD-CLS than during DDD pacing.

Conclusions: Sympathetic sensor-driven pacing provides physiological modulations of the heart rate in patients with atrioventricular block and chronotropic incompetence, comparable to that of patients with healthy sinus nodes.

Restoration of Circadian Variation and Physiologic Rate Behaviour through Closed Loop Stimulation: RAPID Study Findings[15]

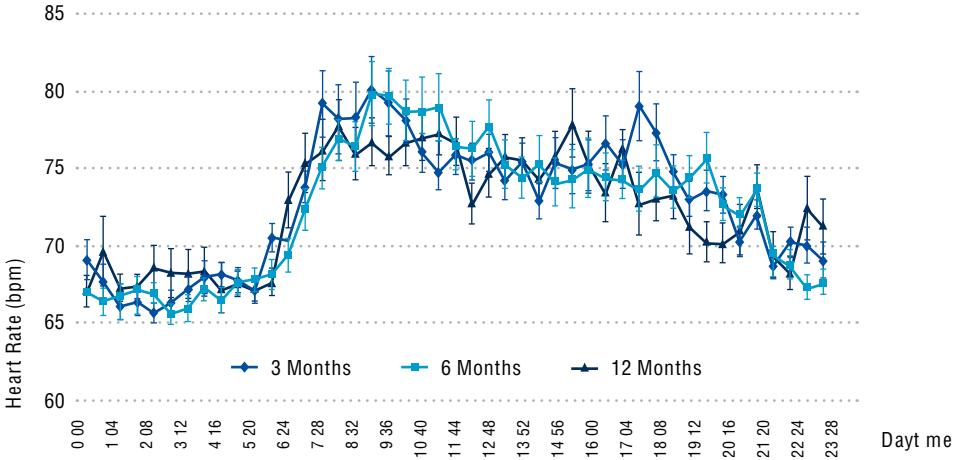
Authors: L. Griesbach, B. Gestrich, D. Wojciechowski, G. Weyers, J. Toenges, M. Schier, D. Danilovic, on behalf of the RAPID Study Investigators

Introduction: This study presents the results from the Rate Behavior of the Pacing System Inos² CLS during Daily Life (RAPID) study conducted at 16 European clinics with the aim to evaluate the appropriateness of CLS rate profiles during daily activities and the long-term stability of CLS.

Methods: 72 patients (40.3 % female, age 71.6 ± 9.1 years) with sinus node disease were enrolled in the study. 50 patients had sinus node disease in the absence of AV block and 22 patients had binodal disease. Inos² DR, Inos² CLS and Inos²⁺ CLS pacemakers were implanted together with conventional active pacemaker leads. The CLS function was enabled after implantation, with a basic rate 0f 60 ± 3 bpm, max. Closed Loop Rate 123 ± 10 bpm, paced AV delay 162 ± 12 ms at the basic rate and 106 ± 15 ms at 130 bpm. Patients returned for 3 follow-up examinations at 1.5–3 months, 60 months, and 12 months after implantation. At the beginning of every follow-up, the rolling 24-hour heart rate trend and counters showing percent of paced and sensed events in the atrium and ventricle were interrogated from the device. The patients were provided with a diary so that corresponding activities could be retrieved. An exercise test was performed during the first FU, comprising stair climbing and descending and walking along a level corridor under daily life circumstances. Color-Word-Tests were performed in order to evaluate the influence of mental stress.

Results: The mean incidence of ventricular pacing was 99.2 %, implying that interruption of the CLS rate adaptation by intrinsic ventricular activity occurred at a negligible rate. The mean incidence of atrial pacing was 82 ± 18 %. The individual 24-hour heart rate trends appeared appropriate in all patients, except for 2, whose pacing rates were occasionally too fast. Reprogramming the max CLS rate or switching to DDD mode resolved the issue. Diurnal and nocturnal heart rates were highly significant at all three follow-up points ($p = 0.001$). Peak rates during exercise differed significantly for any pair of activity ($p < 0.001$).

Conclusions: The 24-hour heart rate trends collected in 72 patients over the 1-year observational period indicated stable CLS performance and appropriate circadian variations in all patients except for two, requiring reprogramming. The study indicated the potential of CLS to distinguish between different physical and mental loads and to provide appropriate pacing rates.



F gure
Twenty–four-hour heart rate trends retr eved from the pacemaker memory (mean value ± SE)
The trend l nes for d fferent follow-up po nts d ffered ns gn cantly at all sample po nts (unpa red t-test, p > 0 05) Mean nc dence of atr al pac ng dur ng the follow-up was 82 ± 18 %

Clinical Benefits of Closed Loop Stimulation Preliminary Results of an Intensive Validation Study[16]

Author: P. Zecchi, F. Bellocci, L. Zanchetta, R. Audoglio

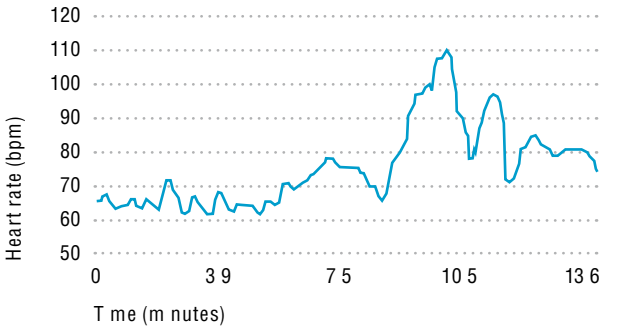
Introduction: The recently introduced concept of Closed Loop Stimulation (CLS) represents a completely new approach, not only in the restoration of appropriate heart rates, but also in terms of improving pacing physiology and quality of life. CLS detects variations in myocardial contractility via a dynamic measurement of right ventricular impedance (RVI) during the systolic phase following a paced pulse.

Methods: A CLS pacemaker was implanted in 40 patients with NYHA Classifications ranging from I to III, all with chronotropic incompetence and Type II or III degree AV block. In eight consecutive patients RVI was recorded during implant and compared with the maximum pressure gradient (dP/dt_{max}) inside the right ventricle (RV), as monitored by a multipurpose pressure catheter, inserted via the femoral vein and positioned in the RV apex.

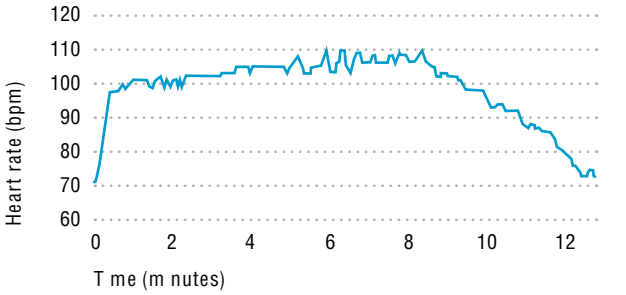
RVI and RV dP/dt_{max} were assessed at rest and during handgrip, rest after handgrip, drug infusion (isoproterenol) and recovery after drug admission. In all patients a post-implant follow-up was performed at discharge, 3 and 6 months, and included the following: treadmill exercise test (CAEP), mental stress test (word or colour type) and 24-hr ECG Holter monitoring.

Results: Several examples of rate trends during various test conditions demonstrated the superior hemodynamic performance of CLS pacing. Three patients were selected for comparative evaluation between CLS devices and devices based on single and dual conventional sensors.

Conclusions: In all cases CLS showed better rate control and hemodynamic response than conventional rate responsive pacing. Preliminary results show that CLS pacing preserves intrinsic circulatory regulation and integrates the pacemaker in the natural control system, enabling the heart rate to be managed by the Autonomous Nervous System and not by an artificial pacing algorithm.



F gure
Rate trend n a pat ent programmed to DDD- LS, dur ng mental stress



F gure
Rate trend n a pat ent programmed to DDD- LS, dur ng exerc se stress test

Closed Loop Stimulation in Patients with Normal and Limited Contractility[17]

Authors: G.K.M. Fauser, P.J.P. Kuijer

Introduction: The integration of the pacemaker into the natural control system is the main concept of Closed Loop Stimulation (CLS). Following publications on the reaction of CLS to various provoked influences, this study collects clinical experiences from patients with different indications and a variation in underlying heart disease during daily life activities and provoked mental stress.

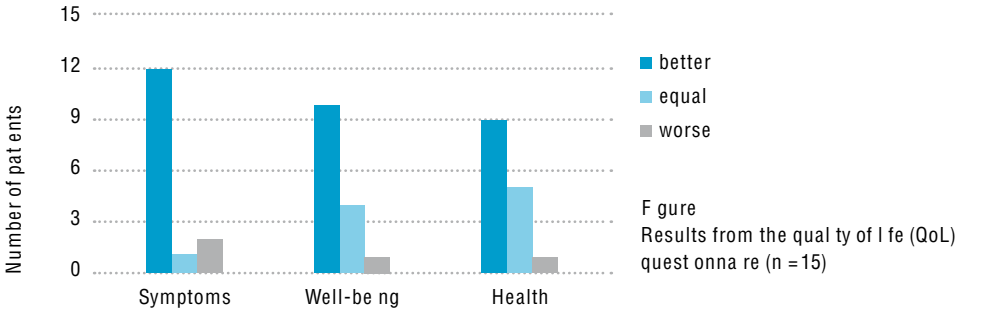
The main focus of this article is the applicability of CLS therapy in patients with pathologically limited myocardial contractility.

Methods: CLS therapy was applied in 22 arrhythmic patients with a mean age of 72.6±9.8 years. Indications for therapy were AV block and Sick Sinus (SSS), and additionally six of them suffered from contractility limiting diseases such as diabetes mellitus, cor pulmonale, or congestive heart failure. The heart rate behaviour over 24 hours and during a mental stress test was analysed. Furthermore 15 patients completed a quality of life (QoL) questionnaire, which intended to compare the present symptomatic level, well-being and health status to the situation before implantation.

Results: All patients, regardless of their contractile state, showed distinct circadian variations with mean differences between day and night rate of 10.8±7.6 bpm). Detailed analysis of the 24-hour trend results of the different patient groups revealed that disease status did not influence the resulting circadian variation.

The results achieved during the arithmetic stress test showed the reaction of the CLS system to various mental activities, which increased the heart rates by a mean of 10.0±9.0 bpm (from a baseline of 69±3 bpm). The majority of the patients who completed the QoL questionnaire reported an improved quality of life, although the low number of respondents meant that the result did not achieve significance.

Conclusions: The treatment of cardiac arrhythmias with the help of CLS is an adequate method of therapy for pacemaker patients with or without contractility-limiting cardiac diseases.



F gure
Results from the qual ty of l fe (QoL) quest onna re (n =15)

Clinical Results of Contractility-Based Closed Loop Stimulation in Patients Treated with Beta-Blockers[18]

Authors: D. Wojciechowski, C. Fauser, S. Brueckner, L. Griesbach

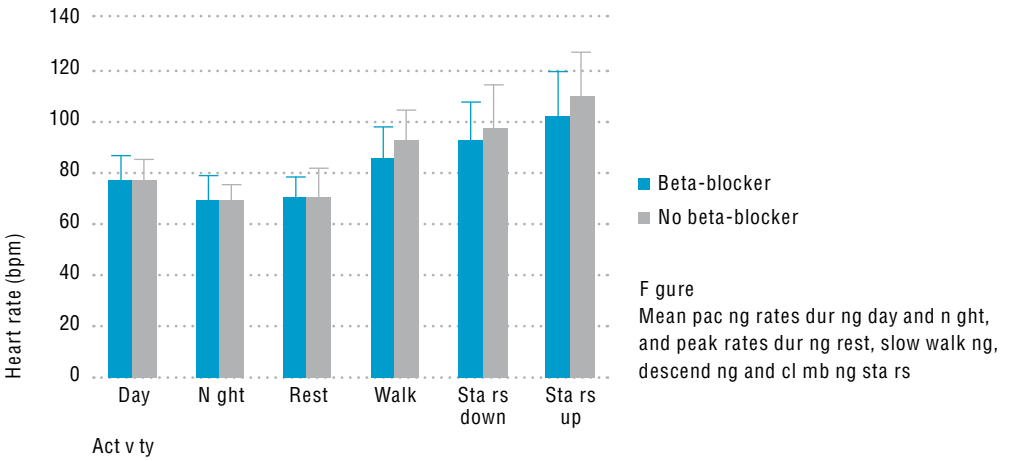
Introduction: Beta-Blockers exert negative chronotropic and inotropic influence and can interfere with the rate adaptive function of pacemakers equipped with a heart contractility sensor. There are concerns that diminished contractile function due to beta-Blocker therapy might reduce the magnitude of the signal coming from the contractility sensor and therefore lead to inadequately low pacing rates during daily activities and/or require special calibration in such patients.

The investigators retrospectively evaluated data gathered in 102 patients implanted with contractility driven Closed Loop Stimulation (CLS) pacemakers within the RAPID study (Rate Behaviour of the Pacing System, CLS during Daily Life). The study evaluated whether there was a difference in pacing rates during daily activities between patients using beta-blockers and those who did not. CLS 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 simply by programming the basic and maximum closed loop rates.

Methods: Patients enrolled in the RAPID study were programmed to DDD-CLS mode after implantation, with follow-ups taking place at 1.5 – 3 months, 6 months and 12 months post-implant. Mean daily and nightly rates in each individual were extracted from the 24-hour trends. Activity tests performed at follow-up consisted of stair climbing, a rest period, descending stairs and slow walking along a flat corridor.

Results: Thirty-four patients used Beta-Blockers (Group A) and 68 patients who did not (Group B) were analysed. The underlying clinical characteristics of the two groups were very similar. A mean incidence of atrial pacing over the total follow-up period 81 ± 15 % (Group A) versus 82 ± 17 % (Group B, p = NS). Heart rates for Group A and B were compared during physical exercise and over a 24-hour period. 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, the peak heart 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 (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.

Conclusions: Due to the continual self-adjustment of the internal rate-responsive parameters, administration of beta-blockers did not exert a significant influence on, and are compatible for use with CLS therapy.



F gure
Mean pac ng rates dur ng day and n ght, and peak rates dur ng rest, slow walk ng, descend ng and cl mb ng sta rs

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