Closed Loop Stimulation

Unique physiological rate response for an optimal haemodynamic performance

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Subject Summary

CLS and physiological response

Drug response

Haemodynamic benefits

CLS in pediatric patients

CLS and syncope

CLS for AF reduction

CLS and Heart Failure

45. Brofman P.R.S. et al., PROGRESS IN BIOMEDICAL RESEARCH 2001
"Heart Resynchronization in CHF Patients with Dilated Cardiomyopathy Using a Rate-Responsive Pacemaker Controlled by the Autonomic Nervous System" 93

46. Orlov MV et al., AMERICAN HEART JOURNAL 2010
"Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation" 94

47. Jorde UP et al., EUROPEAN JOURNAL OF HEART FAILURE 2008
"Chronotropic incompetence, beta-blockers, and functional capacity in advanced congestive heart failure: Time to pace?" 96

48. Elhendy A. et al., J. OF AMERICAN COLLEGE OF CARDIOLOGY 2003
"Prognostic significance of impairment of heart rate response to exercise: impact of left ventricular function and myocardial ischemia." 97

49. Tse HF et al., JOURNAL OF AMERICAN COLLEGE OF CARDIOLOGY 2005
"The Incremental Benefit of Rate-Adaptive Pacing on Exercise Performance During Cardiac Resynchronization Therapy" 99

50. Maass A.H., et al., J Cardiovasc Electrophysiol 2009
"Importance of Heart Rate During Exercise for Response to Cardiac Resynchronization Therapy" 101

1 ANS-controlled rate-adaptive pacing a clinical evaluation

Author
J. Witte et al.

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 standardized 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 ischemic changes in the myocardium result in a pacemaker response that is highly dependent on the position of the ischemia. The results of the intracardiac impedance measurements showed that during ischemia 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.

Conclusion 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.

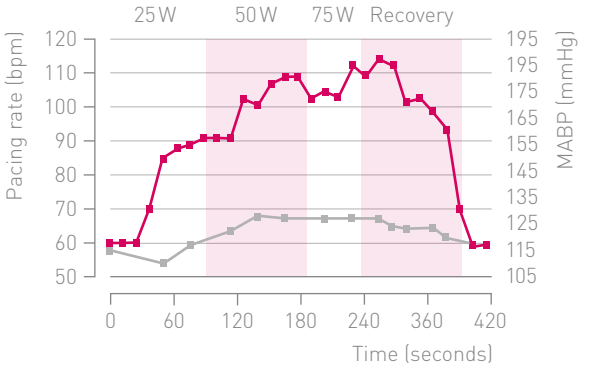


Figure:
Pacing rate and MABP during physical exercise (bicycle ergometry) for a patient with an ANS-pacemaker system.

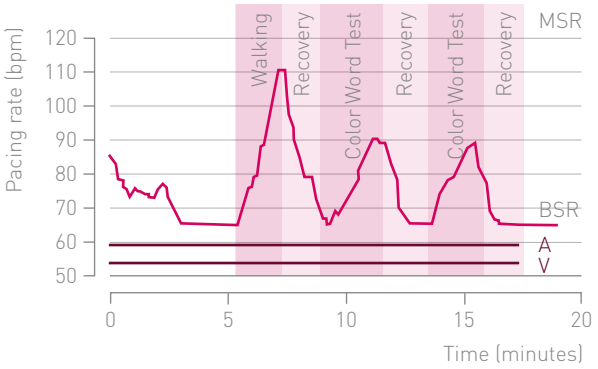


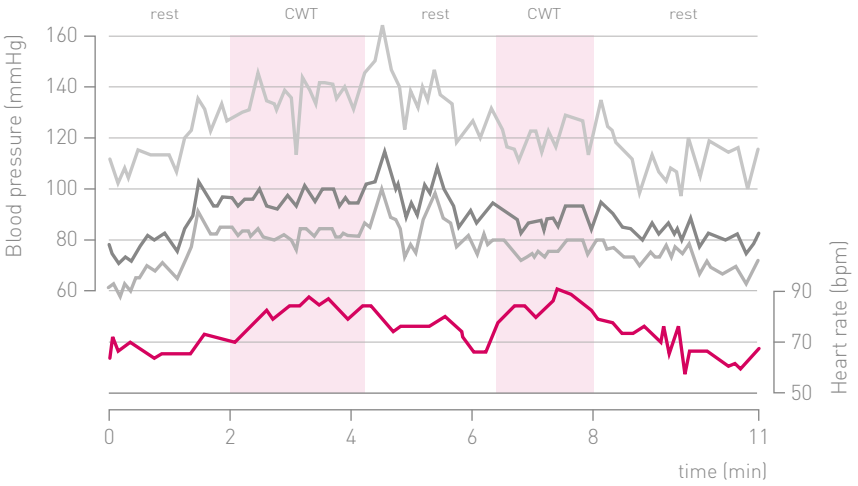
Figure:
Increase in pacing rate with psychological load (colour-word conflict) demonstrates influence of ANS on pacemaker activity

Source: Eur JCPE, 1996

2 Dual Chamber Pacing and Closed-Loop Regulation – Clinical Results

Author
J.C.J. Res et Al.

Summary
Physiological heart rate adaptation is achieved by a new concept monitoring the myocardial contractile state. Since a cardiac parameter is used for evaluating the circulatory demand of the organism, it works independently from the type of load. Furthermore, the rate adaptive principle works with standard pacing leads and does not need any additional sensor. The rate adaptive performance was clinically evaluated for various exercise types. 176 patients (40% female, age 64 ± 14 years) received an Inos DR or InoS2 DR (BIOTRONIK) dual chamber rate adaptive pacemaker. The quality of the rate adaptation in DOOR-mode was validated by applying a set of standardized test protocols. The challenges include physical exercises like bicycle and treadmill ergometry and ambulatory tests. Mental stress was induced by a standardized protocol using mental arithmetic and by color-word-test. During slow walk the rate increased by 9 ± 4 bpm, during brisk walk by 29 ± 10 bpm with respect to the resting value. The observed rate responses are nearly identical to those for healthy subjects. Climbing up stairs caused a maximum pacing rate increase of 28 ± 14 bpm, climbing down stairs resulted in 18 ± 10 bpm in average. During mental stress test a rate increase of 12 ± 3.6 bpm was observed. This value is in good accordance with literature on the same test with healthy subjects (13.6 ± 1.6 bpm). The contractility-controlled rate adaptation is sensitive to different types of exercise. The rate increase observed for the different challenges resembles the values known from literature for chronotropically competent subjects for different physical exercises and for mental stress.



Heart rate (bottom) and blood pressure during two period of mental stress (CWT).

Source: Progress in Biomedical Research, 1997

3 Interindividual Comparison of Different Sensor Principles for Rate Adaptive Pacing

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 analyzed 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 color 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.

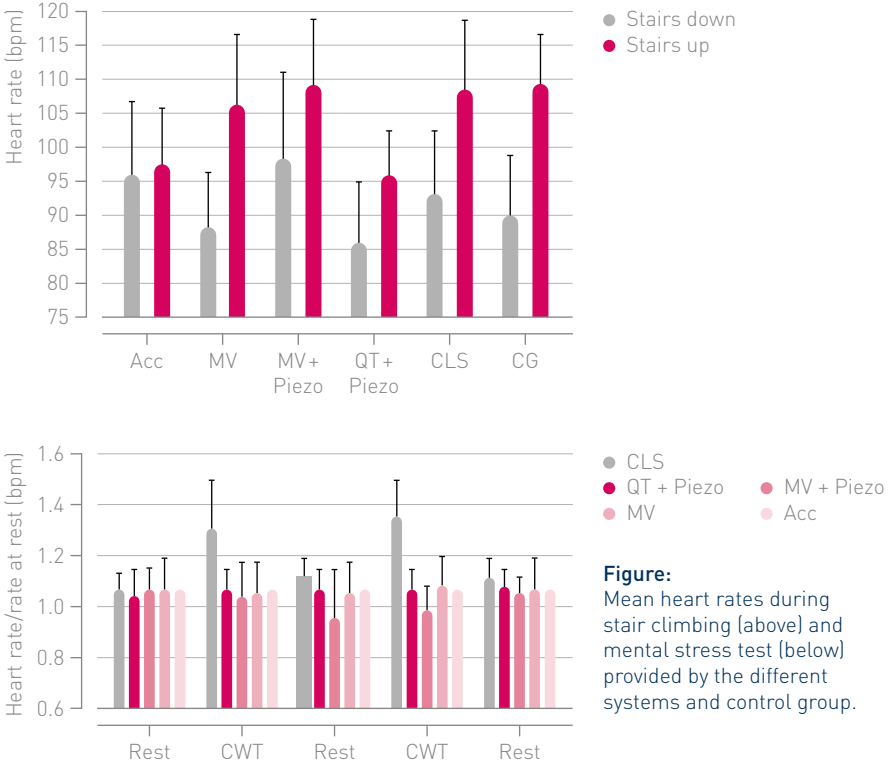


Figure:
Mean heart rates during stair climbing (above) and mental stress test (below) provided by the different systems and control group.

Source: PACE, 1998

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

Author
J. Clementy et al.

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 correlation 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.

Conclusion 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.

Source: American Journal of Cardiology, 1999

5

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

Author
Zecchi et al.

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 (color 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.

Conclusion 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.

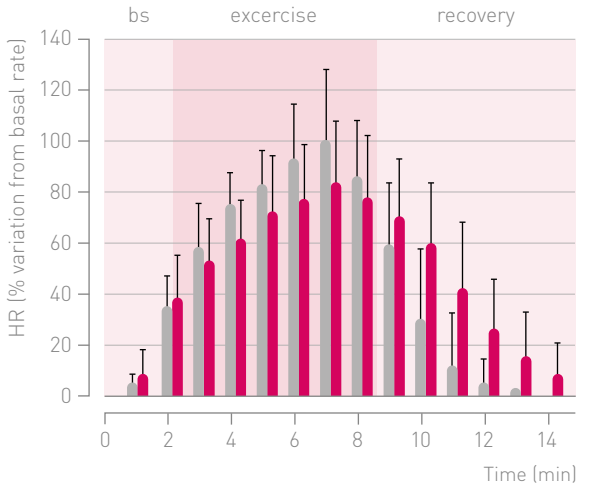


Figure:
Heart rate (HR) adaptation between CLS and accelerometer during treadmill exercise test.

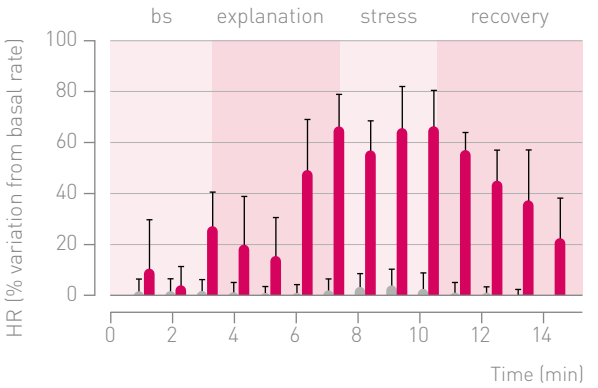


Figure:
Heart rate (HR) trends during acute mental stress. At minute 4, the physician explains the test procedure to the patient; the test starts at minute 7 and ends at minute 11.

Source: Progress in Biomedical Research, 2000

6

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

Author
Zecchi et al.

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.

Conclusion 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.

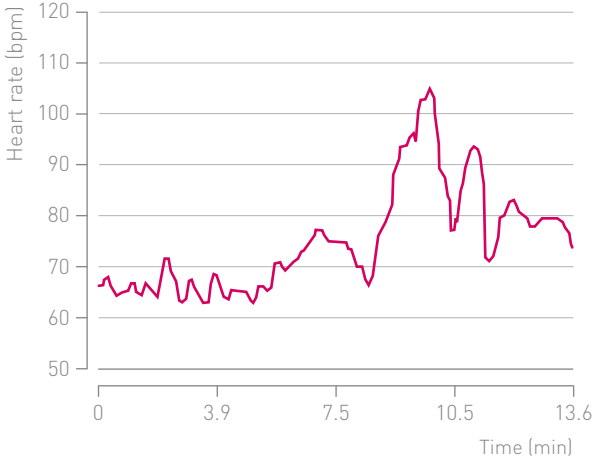


Figure:
Rate trend in a patient programmed to DDD-CLS, during mental stress

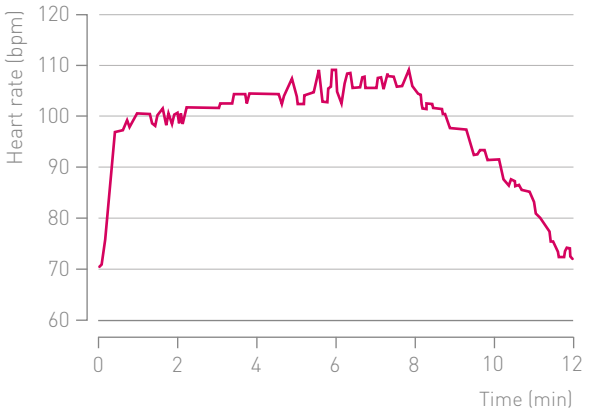


Figure:
Rate trend in a patient programmed to DDD-CLS, during exercise stress test

Source: Progress in Biomedical Research, 2000

7

The Clear Multicenter Study Concept: Comparing Closed Loop Stimulation and Accelerometer Rate-Adaptive Pacing

Author
Osswald et al.

Summary
The Inos2+CLS cardiac pacemaker is a rate-adaptive, dual-chamber device that incorporates the Closed Loop Stimulation (CLS) principle. It continuously monitors the heart's contraction dynamics through unipolar intracardiac impedance. The CLS system is expected to be superior to the accelerometer sensors that regulate the pacing rate during physical stress based on body movement and acceleration. The planned CLEAR multicenter study plans to compare the rate adaption in Inos2+CLS and Philos DR (accelerometer) pacemakers during a treadmill test, daily activities, and a range of control tests. The objective is to assess the function of the autonomic nervous system and of the cardiovascular control loop. Our study hypothesis is that the CLS system will adequately react during all tests and will not be inferior to the accelerometer sensor. A total of 60 patients will be randomized for Inos2+CLS or Philos DR pacemaker implantation. During the first 6 postoperative weeks, the tests will be carried out in the DDD mode to document the patients' restricted performance capability and chronotropic incompetence. Thereafter, all the tests will be repeated in the respective rate-adaptive mode, and the results of CLS and accelerometer rate adaptive pacing will be compared.

Source: Progress in Biomedical Research, 2002

8

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

Author
M. Martinelli Filho et al.

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 × (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 DDDCLS 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 manoeuvres in the DDD mode, but behaved almost physiologically after sensor activation.

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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.

Conclusion 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.

Source: Progress in Biomedical Research, 2001

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

Author
N. Vijay et al.

Summary
The goal of this prospective, multicenter, clinical study was to validate the safety and effectiveness of Closed Loop Stimulation (CLS). The Inos2+ 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 Inos2+ 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 Inos2+ CLS were fulfilled.

Source: Progress in Biomedical Research, 2001

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Clinical Performances of Automatic Closed Loop Stimulation Systems

Author
Griesbach L. et al.

Introduction
IIn conventional, open-loop rate adaptive pacing systems, the physician tailors pacemaker response by carefully programming several rate responsive parameters for each individual. The Inos pacemaker family (Biotronik, Berlin, Germany) uses contraction dynamics to regulate the pacing rate according to the Closed-Loop Stimulation (CLS) principle. These devices are incorporated into the natural cardiovascular control loop, allowing it to guide the pacing rate, cardiac output, and blood pressure toward optimal values. Internal rate responsive parameters are continually self-adjusted to changing patient conditions and are transparent to the physician, who can program only the basic and maximum closed-loop rate.

This study presents the results from the Rate Behaviour of the Pacing System Inos 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
Seventy-two patients (40.3% women, age 71.6 ± 9.1 years) with sinus node disease were enrolled in the study from January 1998 to December 1999. Fifty patients had sinus node disease in the absence of atrioventricular (AV) block and 22 patients had binodal disease. Inos2 DR, Inos2 CLS, and Inos2+CLS pacemakers were implanted together with conventional tined or screw-in pacemaker leads.

The implanted pulse generators are dual chamber devices using the same algorithm to translate changes of contraction dynamics into pacing rate variation (Fig. 1). 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. This interaction establishes a negative feedback loop that continuously guides the pacing rate towards an optimal value matching current hemodynamic demands. This is equivalent to an artificial sinus node controlled by the baroreceptor reflex in which only the lower and upper rates are programmable.

In their present technical form, CLS systems require ventricular pacing in all heart cycles to ensure stable morphology of the measured intracardiac signal. Dynamic AV delay should be programmed in the way to slightly overdrive spontaneous AV conduction during rest and exercise. Nonpaced ventricular beats are not taken into account for the pacing rate calculation and can cause a gradual decrease of the pacing rate toward the basic rate until ventricular pacing is reestablished. The atrium may be paced, sensed, or both.

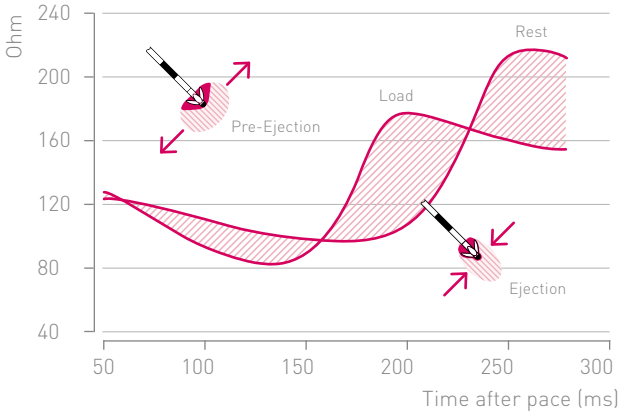

Figure 1. In addition to pacing stimuli, Inos pacemakers deliver short biphasic subthreshold pulses between the tip of a conventional right ventricular lead and the pacemaker housing every 31.25 ms (32 Hz). These pulses allow detection of the intracardiac impedance curve for the period between 50 and 300 ms after ventricular stimulus, which reflects contraction dynamics around the lead tip during the isovolumetric contraction and the beginning of the ejection phase.4 The area below the current curve (load) is compared with the area below the slowly updated reference curve (rest). The "differential area" in between the curves (shaded in gray) is multiplied by a self-adjusting internal rate responsive factor to calculate the CLS pacing rate.

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Results

Pooled 24-hour heart rate trends are shown in Figure 2. The mean incidence of ventricular pacing in the studied population was 99.2%, implying that interruption of the CLS rate adaptation by intrinsic ventricular activity (extrasystoles or intrinsic AV conduction) occurred at a negligible rate. The mean incidence of atrial pacing (CLS-guided rate) during the entire follow-up was 82 ± 18%. The individual 24-hour heart rate trends appeared appropriate in all patients except for two, whose pacing rates were occasionally too fast during the night, causing palpitations. In one of these patients, maximum closed-loop rate was later reprogrammed to 80 beats/min and in the other patient CLS was substituted by the DDD mode. In no other patient was the basic rate or maximum closed-loop rate reprogrammed during the study.

Difference between mean diurnal and mean nocturnal heart rates was highly significant at all three follow-up points ($P < 0.001$), while the variation between follow-ups was insignificant ($P > 0.45$) (Table I). Peak rates during exercise differed significantly for any pair of activities ($P < 0.001$, Table II). Five of 72 patients could not perform the stair climbing/descending test due to insufficient stair facilities at the clinic. Individual heart rates during stair climbing/descending and CWT are illustrated in Figure 3.

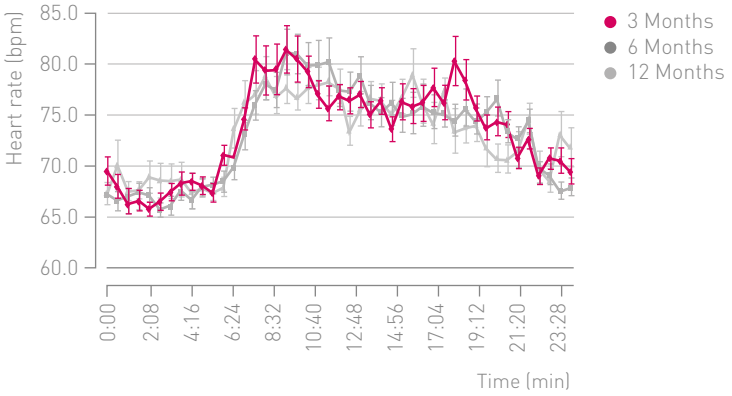

Figure 2. Twenty–four-hour heart rate trends retrieved from the pacemaker memory (mean value ± SE). The trend lines for different follow-up points differed insignificantly at all sample points (unpaired t-test, $P > 0.05$). Mean incidence of atrial pacing during the follow-up was 82 ± 18%.

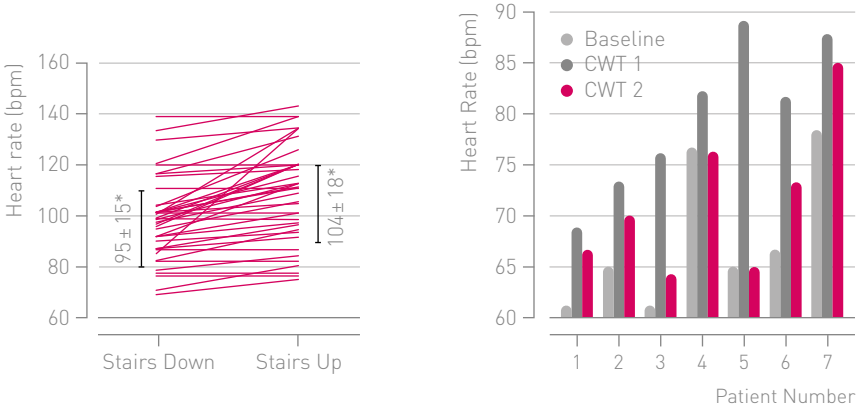

Figure 3. (Panel A) individual peak rates during ascending/descending stairs in 67 patients. Faster rates during climbing were recorded in 82% of the patients and equal rates for climbing and descending in 18% (*$P < 0.001$).). The baseline rate before stair climbing/descending was 70 ± 10 beats/min ($P < 0.001$ compared to either climbing or descending). (Panel B) Individual peak rates during the color-word test (CWT) in seven patients. During the first execution of CWT (CWT 1), the peak rate was 80 ± 8 beats/min. During the repeated execution (CWT 2), the peak rate was 73 ± 8 beats/min. The two values differed significantly from each other and from the baseline rate of 67 ± 7 beats/min ($P < 0.05$). The percent of atrial pacing during CWT was 87 ± 14%, and the peak rates were paced in all seven patients.

Source: PACE, 2003

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Restoration of Circadian Variation and Physiologic Rate Behaviour Through Closed Loop Stimulation: Rapid Study Findings

Author
L. Griesbach et al.

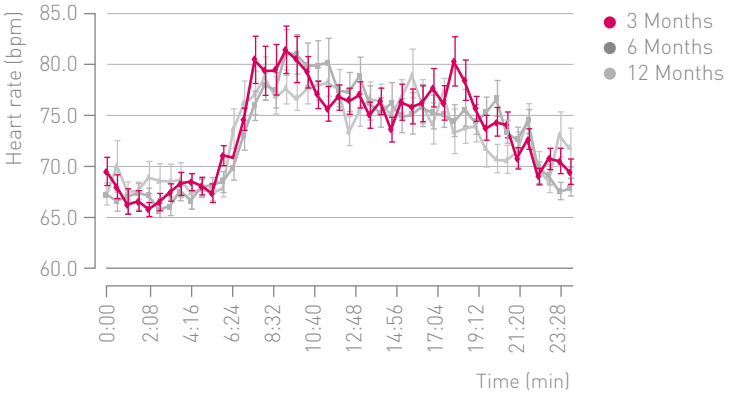
Introduction
This study presents the results from the Rate Behaviour of the Pacing System Inos2 CLS during Daily Life (RAPID) study conducted at 16 European clinics with the aim to evaluate the appropriateness of CLS rate profiles during daily activities and the long-term stability of CLS.

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 of 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. Colour-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 ($p < 0.001$).

Conclusion 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.



Source: PACE, 2003

12

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

Author
B.B. Pavri et al.

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 randomized to either DDDR or DDD-CLS for a period of 4 weeks and completed a range of standardized 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 DDDCLS experienced significant or tremendous improvement compared to only 22% of patients programmed to DDDR.

Conclusion 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 standardized 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

Source: Circulation, 2006

13

Increased Heart Rate During Acute Mental Stress with Closed Loop Stimulation: the Emotional Response 2 Study

Author
S. Neelagaru et al.

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, randomized study and utilized a crossover design with the patients serving as their own control.

Results
A total of 401 patients were enrolled at 36 medical centres. 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 ($p < 0.001$).

Conclusion 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.

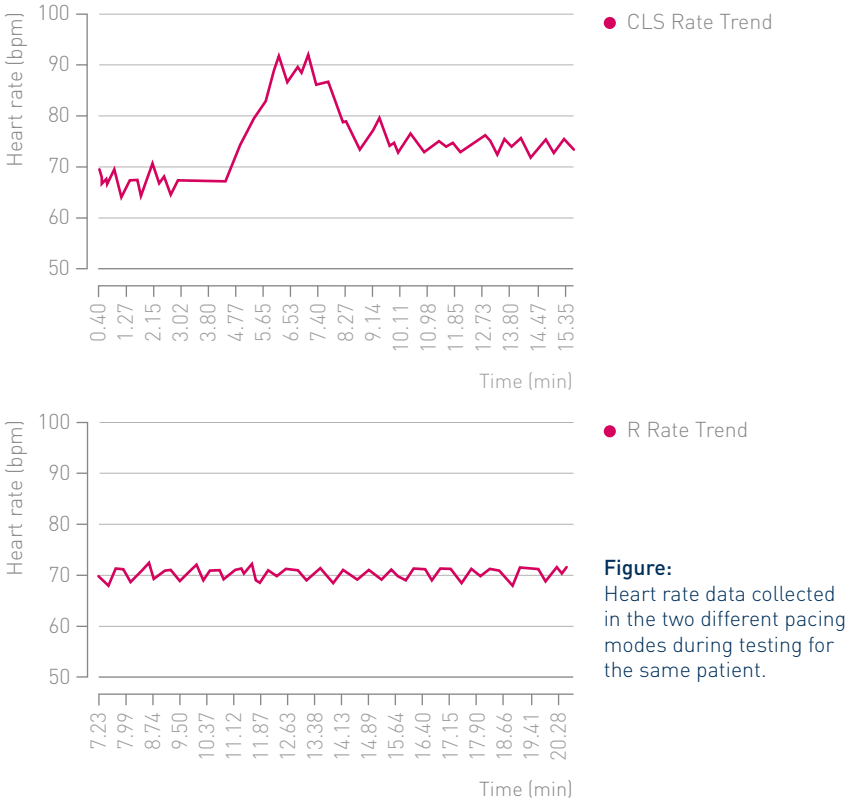


Figure:
Heart rate data collected in the two different pacing modes during testing for the same patient.

Source: Circulation, 2006

14

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

Author
S. Chandiramani et al.

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 utilizes 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 randomized study design, in which pacing mode testing order was randomized.

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 heart rate	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			

Source: PACE, 2007

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

Author
M. Coenen, et al.

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 intra-individually in 131 patients during walking and acute mental stress to assess 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.

Conclusion 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.

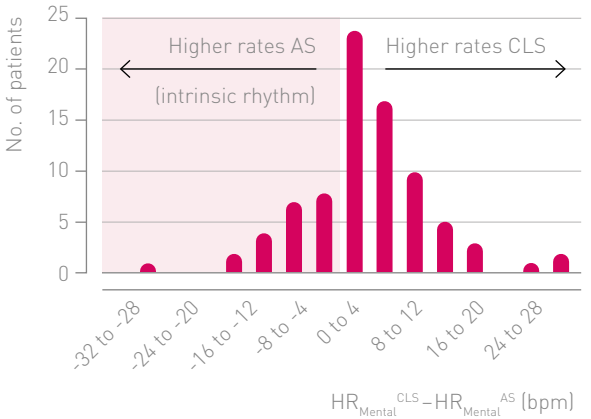

Figure:
Intraindividual difference in HR_{Mental} for CLS versus AS (mean 3.0 ± 9.2 bpm, p = 0.004, N = 84 pairs of data).
HR_{Mental}: mean rate in the period between 60 and 120 sec after starting arithmetic calculations

Source: Europace, 2008

16

Clinical Observations with Closed Loop Stimulation Pacemakers in a Large Patient Cohort: the Cylos Routine Documentation Registry (Record)

Author
M. Lindovskà et al.

Aims
Closed Loop Stimulation (CLS) pacemakers couple pacing rate to myocardial contraction dynamics by monitoring unipolar right ventricular impedance on a beat-to-beat basis. The aim of this large-scale registry was to evaluate the safety and efficacy of the CLS therapy under clinical routine conditions.

Methods and results
A total of 706 patients was enrolled in the clinical investigation 'Registry: CYLOS Routine Documentation' (RECORD) at 57 investigational sites in Europe and Hong Kong. Not to interfere with clinical routine and therapeutic decisions of health care providers, the registry was implemented as a part of the standard follow-up schedule. Two follow-ups were conducted within 12 months of enrolment in order to evaluate typical programming of CLS-related parameters, reasons for their later reprogramming, frequency of patient intolerance to CLS, and physicians' satisfaction with medical benefits and technical performance of CLS in each patient. The investigators' medical and technical notes on CLS rated it excellent in ≈80% of patients, poor in 1.4% (medical benefit) or 0.5% (technical performance), and adequate in rest of the patients. Closed Loop Stimulation functionality was not influenced by pacing site variation within the right ventricle (septal, outflow tract) or by advanced heart failure (New York Heart Association classes II–IV). Permanent or temporary CLS deactivation was undertaken for various reasons in 6.2% of patients. Signs of intolerance to CLS or rate-adaptive pacing were reported by 2.3% of patients. Reprogramming of CLS-related parameters was seldom undertaken, with >90% of pacemakers operating with default settings in the long term.

Conclusion
Clinical performance of CLS was very satisfactory in the large cohort studied.

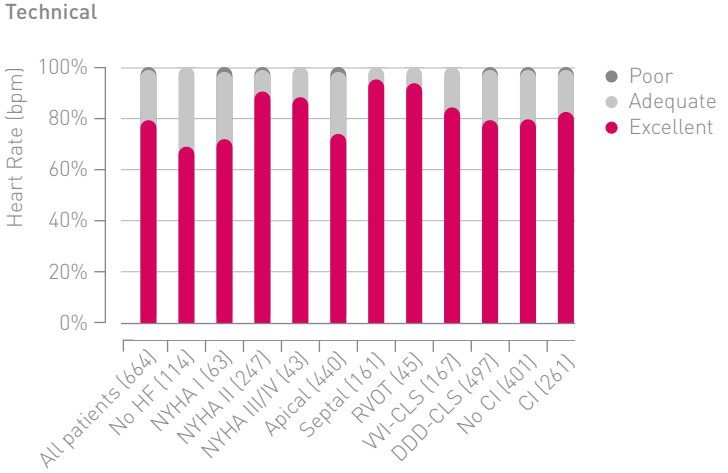

Figure 1. Technical performance of CLS in 664 patients as judged by physicians at last observation carried forward (the second follow-up, n=591; the first follow-up, n=73). The stacked column chart shows, from top to bottom, the percent of patients for whom the score was poor, adequate, or excellent.

Subgroups were formed according to the New York Heart Association functional classification, right ventricular lead position (apical, septal, right ventricular outflow tract), pacing mode, and chronotropic incompetence. The number of patients is indicated in brackets. Note that New York Heart Association functional class and chronotropic incompetence were not known in all patients, whereas in a minority of patients, the ventricular lead position differed from the three major positions included in the chart. The reasons for missing judgement in 42 patients were early study termination (n=36) and Closed Loop Stimulation deactivation unrelated to its performance (n=6). CI, chronotropic incompetence; CLS, Closed Loop Stimulation; DDD, dualchamber pacing; HF, heart failure; NYHA, New York Heart Association functional class; RVOT, right ventricular outflow tract; VVI, single-chamber pacing in the ventricle.

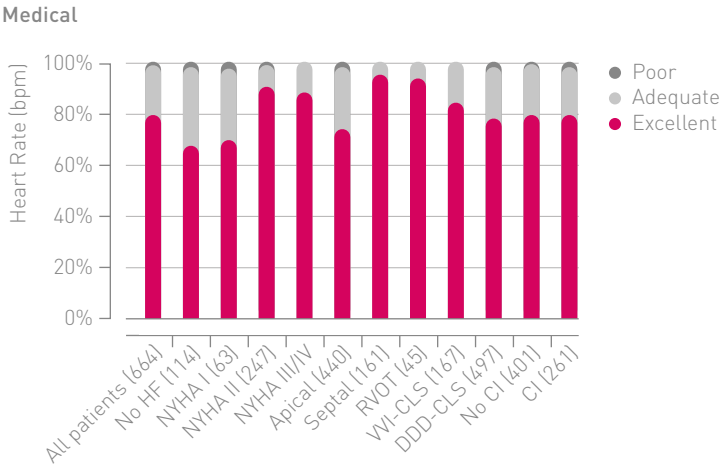

Figure 2. Medical benefit of Closed Loop Stimulation. In 32 (4.8%) of 664 patients, medical benefit and technical performance got different scores, whereof 11 patients had better medical than technical score (e.g. when the patient's well-being and symptoms appeared more favourable than Closed Loop Stimulation performance), and 21 patients had better technical than medical score (e.g. when unfavourable symptomatic or clinical development was observed despite seemingly correct Closed Loop Stimulation performance). CI, chronotropic incompetence; CLS, Closed Loop Stimulation; DDD, dual-chamber pacing; HF, heart failure; NYHA, New York Heart Association functional class; RVOT, right ventricular outflow tract; VVI, single-chamber pacing in the ventricle.

Source: Europace, 2012

Closed Loop Stimulation Is Effective in Improving Heart Rate and Blood Pressure Response to Mental Stress: Report of a Single-Chamber Pacemaker Study in Patients with Chronotropic Incompetent Atrial Fibrillation

Author
R. Proietti et al.

Introduction
Closed-loop stimulation (CLS) is a form of rate-adaptive pacing capable of providing an effective pacing rate profile not only during physical exercise but also during mental stress. To test its effectiveness, CLS and accelerometer sensor (AS) rate response were compared intraindividually during a mental stress test (MST).

Methods
Thirty-six patients (mean age 78.9 ± 6.4 years) implanted with a pacemaker with the CLS algorithm (Cylos, Biotronik, Berlin, Germany) underwent MSTs in different pacing configurations: non rate adaptive mode (VVI), AS mode (VVIR), and CLS mode, respectively. A modified Stroop test was used in order to induce mental stress. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure, and pacing percentage burden were collected for 5 minutes before, during, and 5 minutes after the test.

Results
Mean peak-HR during MST was significantly higher in CLS configuration than in VVIR and VVI modes (92.8 ± 12.6 vs 78.9 ± 6.5 vs 77.8 ± 7.5; P < 0.001). The average HR increase during MST was also higher in CLS configuration than in VVIR and VVI modes (22.7 ± 16.7 vs 8.2 ± 8.6 vs 6.6 } 6.3; P < 0.001). The percentage of pacing beats during MST was higher in CLS configuration than with the other two algorithms (48.4 ± 17.9 vs 27.4 ± 17.5 vs 25.8 ± 17.6; P < 0.001). The average peak-SBP was significantly higher during MST in CLS mode than in VVIR and VVI configurations (172.6 ± 15.5 vs 156.7 ± 12.2 vs 145.5 ± 13.7; P < 0.001). The mean SBP increase showed a similar behaviour (51.8 ± 24.7 vs 18.4 ± 13.7 vs 16.4 ± 10.3; P < 0.001).

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Conclusion CLS algorithm in a single-chamber device is more effective than AS in detecting a hemodynamic demand due to an emotional stress and supplying a proper HR increase. These results are even more surprising compared to previous data in dual-chamber pacemakers, because they imply that CLS algorithm can provide an appropriate rate-modulation in patients with AF and chronotropic incompetence.

Source: Europace, 2012

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Closed Loop Stimulation: A New Philosophy of Pacing

Author
Zecchi et al.

Summary
Rate modulation induced by Closed Loop Stimulation is driven by variations of right ventricular impedance during the systolic phase. The right ventricular impedance appears to be correlated with myocardial contractility, which is modified by the autonomic nervous system in accordance with the real physiologic needs of the patient.

The results of the clinical validation study VICRA (Validation of INOS Contractility Rate Modulation Algorithm) on Closed Loop Stimulation are presented. Eighteen patients, all with chronotropic incompetence and II or III degree AV block, were implanted with an INOS2 CLS pacemaker. In fifteen of these patients, the variations of right ventricular impedance, measured by the implanted pacemaker, were recorded and compared with the dP/dt max invasively monitored in the right ventricle during implantation. Right ventricular impedance and dP/dtmax were measured at rest and during handgrip, mental stress, and drug infusion tests. The correlation between right ventricular impedance and right ventricular dP/dt max was very good (linear regression $R2 = 0.91$). In other groups of patients, Closed Loop Stimulation induced a pacing rate that was always physiologically and hemodynamically adequate in all test conditions, even in patients with coronary artery disease. In conclusion, preliminary results show that Closed Loop Stimulation responds to messages generated by the autonomous nervous system and integrates the pacemaker into the cardiovascular system, thus enabling the heart rate to be managed in accordance with hemodynamics and not by an artificial pacing algorithm.

Source: Progress in Biomedical Research, 2000

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Effect of Autonomic Stressors on Rate Control in Pacemaker Using Ventricular Impedance Signal

Author
M. Santini et al.

Summary
The aim of this study is to evaluate the heart rate adaptation obtained by a pacemaker, based on a measure of ventricular impedance in patients undergoing autonomic challenges. The evaluation procedure was based on the analysis of the mean value (MV) and heart rate variability (HRV) of RR and systolic pressure intervals, according to a set of neurovegetative stressors (controlled respiration in supine position and during active standing; mental stress; handgrip, and noninvasive sinusoidal stimulation of carotid baroreceptors). Each test lasted 5 minutes. Fifteen chronotropic incompetent patients first implanted, were studied three months after implantation. ECG, respiration activity, and noninvasive blood pressure were monitored. HRV was evaluated by spectral analysis. Variability in the low frequency (LF) and high frequency (HF) bands was compared by computing percentage and absolute powers. We found that baseline HR was 72.2±5.5 beats/min, in mental stress was 76.8±7.8 beats/min, in handgrip was 79.2±6.3 beats/min, and in active standing was 80.9±8.6 beats/min ($P < 0.01$, Friedman's test). During active standing, LF component was significantly higher with respect to baseline (25.7% of total power in standing; 9.4% in baseline, $P < 0.01$) and it was synchronous to the LF component of the arterial pressure variability. Carotid activation/deactivation by neck suction induced synchronous changes in the paced rates. In conclusion, closed loop strategy based on ventricular contractility continuously controls heart rate by tracking the sympathetic modulation to the heart.

Source: PACE, 2004

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Rate Response of a Closed-Loop Stimulation Pacing System to Changing Preload and Afterload Conditions

Author
Cron et al.

Introduction
Although various sensor principles have been implemented in rate adaptive pacemakers, the optimal concept providing physiological rate response is still lacking. Most available sensors measure more or less specific effects of physical activity (e.g., body movement, respiratory or metabolic parameters) in a open loop system only (i.e., without a feed back regulation). An optimal sensor concept should provide a heart rate response adjusted to the metabolic demand of different physical or mental stress conditions mimicking the physiological auto-feedback mechanism of heart rate control mediated by the autonomic nervous system. Closed-loop stimulation (CLS), a promising new sensor concept, measures changes in the unipolar right ventricular impedance, which closely correlates to changes of the right ventricular contractility and reflects the autonomic nervous innervation of the heart in a closed-loop approach. This sensor has been validated in several clinical studies under different conditions of physical activity, showing an appropriate and physiological rate response. Nevertheless, in the Author' experience some patients with a CLS pacemaker do not tolerate the rate adaptive mode (DDD-CLS) because of unexplained, inappropriate pacemaker tachycardia, mainly related to postural changes. So far, the close correlation of right ventricular impedance and myocardial contractility has only been validated under experimental steady-state volume conditions. However, it is unknown if changing central volume conditions, affecting the filling of the right ventricle, might influence intracardiac impedance and, thereby, affect the sensor response in a clinically unfavorable way.

The aim of this study was to assess the rate response to rapid changes in pre- and afterload in patients with a dual chamber CLS pacemaker compared to a control group without a pacemaker.

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Methods

The pacemaker group included 12 patients (10 men, 2 women) with an indication for dual chamber pacing, in whom a INOS2-CLS DDDR pacemaker (Biotronik GmbH & Co., Berlin, Germany) had been implanted for > 3 months. Conventional bipolar passive-fixation leads (Polyrox, Biotronik GmbH & Co.) were implanted in the right ventricular apex and the right atrial appendage. All patients in the pacemaker group were predominantly paced in the right ventricle (i.e., < 20% intrinsic conduction). This was required because the CLS sensor system relies on the measurement of the unipolar ventricular impedance. The control group consisted of 14 patients (13 men, 1 woman) recruited from the cardiology outpatient clinic with stable coronary or valvular heart disease and no history of sinus node dysfunction, chronotropic incompetence, or orthostatic dysregulation.

In the pacemaker group, the rate adaptive mode (CLS, DDD-CLS) was activated at least 2 weeks prior to the study testing. Automatic calibration of the CLS sensor was performed according to the manufacturer's instructions. The lower rate was set to 60 beats/min and the upper sensor rate to 140 beats/min. The technical details of the CLS sensor system have been published elsewhere.6ß-Blocker treatment was discontinued prior to testing. Other cardiovascular drug therapy was continued.

In all patients, a handgrip and a head-up tilt table test were performed to provoke changes in pre- and afterload according to standardized protocols. For handgrip tests the patients were sitting. The handgrip dynamometer was adapted to the size of each subjects hand. The stain gauge was connected to a display placed in front of the subjects to adjust and control the developed force. First, maximal voluntary contraction (MVC) was measured. Then, after 2 minutes of rest the subjects were asked to maintain a submaximal (30% MVC) isometric handgrip contraction for 2 minutes, followed by a 1-minute recovery period. Passive head-up tilt tests were performed with a commercially available tilt table (Huntleigh Akron, Ipswich, Suffolk, England, UK). After 5 minutes of rest in a supine position, patients were rapidly (5 s) tilted to 70 degrees for an additional 5 minutes. Beat-to-beat systolic and diastolic blood pressure and pulse pressure were measured with a continuous noninvasive hemodynamic monitoring system (Finapres 2300, Ohmeda, Engelwood, CO, USA). Intrinsic and paced heart rates were derived from continuous electrocardiographic (ECG) monitoring, using a customized personal computer (PC)-based recording system designed for beat-to-beat analysis of heart rate changes. This system allows determination of heart rates in paced and intrinsic rhythm and as exclusion of premature beats and artifacts. Mean heart rates were calculated in periods of 8 seconds. In the pacemaker group, sensor driven pacing was assumed as long as atrial pacing was detected. Whenever intrinsic heart rate exceeded the sensor indicated rate, sensor activity counts were directly analyzed, using a customized analyzing algorithm (Unilyzer, Biotronik GmbH & Co.) that translated the measured sensor signals into a theoretical sensor rate.

Results

The age of the studied patients ranged from 50 to 87 years. The pacemaker group was significantly older (median age 77 vs 59 years, $P < 0.01$). Male sex was dominant in both groups (83 and 93%, respectively). There are no statistically significant differences in underlying heart disease between the two groups. Hypertensive heart disease tended to be more frequent in the pacemaker population and valvular heart disease more frequent in the control group. Two thirds of the pacemaker patients had high degree conduction disturbances and one third sick sinus syndrome.

Figure 1 depicts heart and sensor rates during head-up tilt testing. The heart rate behavior in the control group during tilting showed a physiological pattern with only a slight increase of the heart rate immediately after tilting and minimal changes during ongoing vertical body position. In contrast to this, tilting the pacemaker patients resulted in a immediate and steep increase of the sensor rate. Peak mean sensor rate was achieved at 72 seconds after start of tilting and was > 20 beats/min faster than baseline. However, within 2–3 minutes the sensor rate decreased slowly towards the baseline level. The differences between the sensor rate in the pacemaker group and the intrinsic heart rate in the control group were statistically significant at all measurements from 24–128 seconds after start of the head-up tilt (ANOVA, $P < 0.01$).

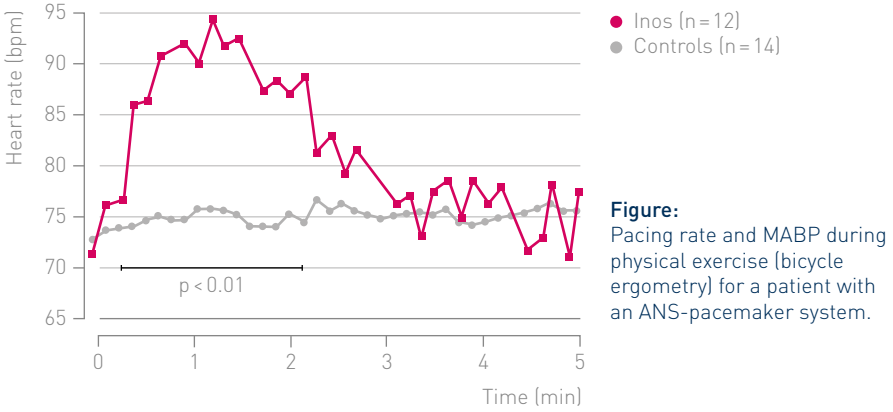

Figure:
Pacing rate and MABP during physical exercise (bicycle ergometry) for a patient with an ANS-pacemaker system.

Figure 1. Mean sensor rates (pacemaker group, Inos) and mean intrinsic heart rates (control group) during tilt table testing (passive head-up tilt starts at 0 minutes). Mean heart rates were calculated in periods of 8 seconds.

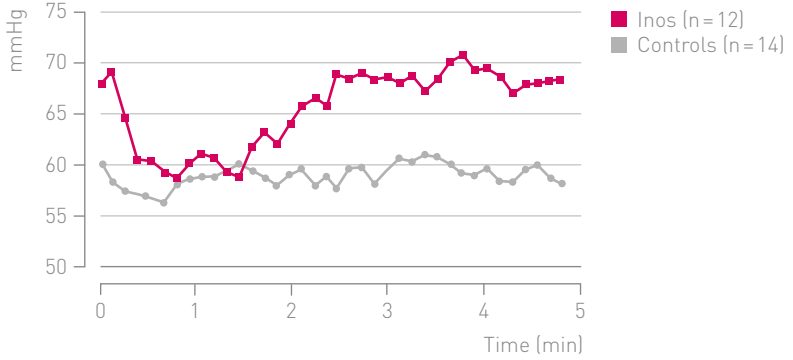

Figure 2. Pulse pressure (i.e., difference of systolic and diastolic blood pressure) throughout tilt table testing in the pacemaker (Inos) and control group (passive head-up tilt starts at 0 minutes).

As shown in figure 2 the blood pressure amplitude (pulse pressure) of the pacemaker population dropped significantly within the first minute after tilting, concomitantly to the excessive increase in the sensor driven pacing rate. This drop in pulse pressure was due to a simultaneous fall of systolic and increase of diastolic blood pressure immediately after tilting. Only a slight decrease of the blood pressure amplitude was noted in the control group.

During handgrip testing, the behavior of the sensor rate in the pacemaker group and the intrinsic heart rate in the control group showed no statistically significant difference. Likewise, systolic and diastolic blood pressure and the blood pressure amplitude did not differ significantly between the two groups. In both groups, heart rate (intrinsic and sensor rate, respectively) and systolic and diastolic blood pressure showed a very moderate, but parallel increase during isovolumetric contraction with a fast return to baseline values after release of the handgrip.

Source: PACE, 2003

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Effect of Rate-Adaptive Pacing on Performance and Physiological Parameters During Activities of Daily Living in the Elderly: Results from the Clear (Cylos Responds with Physiologic Rate Changes During Daily Activities) Study

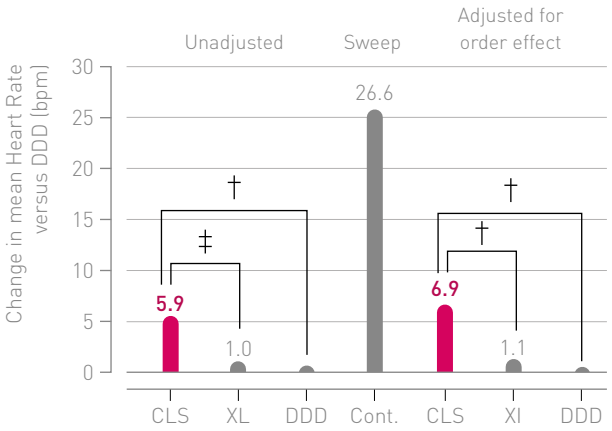
Author
Abi.Samra F.D.

Aims
For most elderly pacemaker patients, evaluation of rate-adaptive pacing using treadmill and bicycle tests is impractical and not representative of typical daily activities. This study was designed to compare the performance and physiological response of the closed-loop stimulation (CLS) rate-adaptive sensor to accelerometer (XL) and no rate sensor (DDD) during typical daily activity testing.

Methods and results
Subjects recently implanted with a Cylos pacemaker completed timed activities of daily life testing, which included walking, sweeping, and standing from a seated position. Activity performance and physiological response from each sensor mode was evaluated for subjects requiring ≥80% pacing. Overall, 74 subjects needed ≥80% pacing during at least one test. An increase in the area swept (CLS vs. XL, 1.67 m2 difference, P=0.009; CLS vs. DDD, 1.59 m2 difference, P=0.025) and a decrease in the prevalence of orthostatic hypotension (OH) after standing 1 min (CLS vs. XL, odds ratio=0.16, P=0.006; CLS vs. DDD, odds ratio=0.18, P=0.012) was observed in the CLS mode as compared with XL and DDD. No statistical difference in walk distance was observed between CLS and XL or CLS and DDD.

Source: PACE, 2004

Conclusion In acute testing, as compared with XL and DDD, CLS provides a more physiological response during the performance of activities of daily living for subjects with ≥80% pacing. This is clinically reflected in better performance during the sweep test as well as a decrease in the prevalence of OH in our elderly population.



Source: EUROPACE, 2013

22

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

Author
S. Osswald et al.

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 analyze 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, normalized 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 (r2 = 0.93) and intrinsic rhythm (r2 = 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 (r2 = 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.

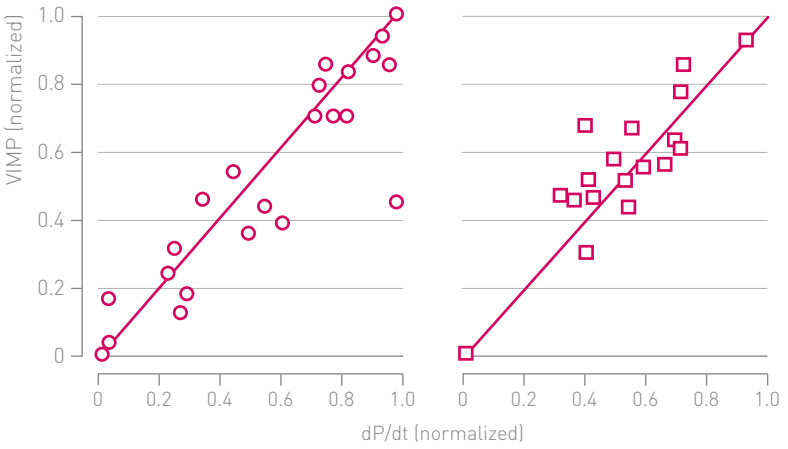


Figure:
Correlation between VIMP and dP/dt $_{max}$ separated for intrinsic and paced rhythm

Source: PACE, 2000

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

Author
D. Wojciechowski et al.

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.

Source: Progress in Biomedical Research, 2001

Clinical Assessment of the Correlation Between Right Ventricular Impedance and Left Ventricular Contractility

Author
A. P. Ravazzi et Al.

Summary
Variation in the right ventricular impedance (RVI) generated by changes in the myocardium-to-blood ratio during systole is the signal used for Closed Loop Stimulation form of rate-responsive pacing, which integrates the pacemaker into the natural cardiovascular control loop. Two previous studies have demonstrated that RVI variations are well correlated ($r > 0.91$) to the variation in right ventricular contractility. The aim of this study was to assess whether a correlation even exists between RVI and left ventricular contractility, which is the main factor in hemodynamic performance. In 15 consecutive patients all of whom showed no evidence of conduction disturbances, RVI and the maximum pressure change (dp/dtmax) in the left ventricle were recorded during diagnostic left heart catheterization. During the procedure, the two parameters were simultaneously measured during an isometric exercise test and left ventriculography, and the variation trends were compared. After the handgrip test, the correlation between variations of RVI and left ventricular dp/dtmax was acceptable ($r > 0.79$). As peripheral vascular resistance and left ventricular afterload increases due to the stress, the sympathetic response influences the contractile status of both ventricles simultaneously; this accounts for the RVI correlation with right ventricular dp/dtmax as previously found by our study group as well as other Author. Left ventriculography affects the preload by increasing the left ventricular diastolic filling during the isovolumetric ventricular contraction. These changes are shared by the right ventricle, accounting for the strong correlation ($r > 0.92$) found between the RVI and left ventricular dp/dtmax during this test. The results of this study demonstrate that the device responds properly to the variation of contractility in the whole heart.

Source: Progress in Biomedical Research, 2000

Autonomic Function During Closed Loop Stimulation and Fixed Rate Pacing: Heart Rate Variability Analysis from 24-Hour Holter Recordings

Author
R. Quaglione et al

Aim
Aim of this retrospective study was to analyze the effect of closed-loop stimulation (CLS) and DDD pacing mode on autonomic balance, and to evaluate heart rate variability (HRV) during CLS stimulation.

Methods and Materials
Autonomic balance was estimated by a 24-hour HRV analysis of paced and spontaneous beats in patients implanted with a dual-chamber pacemaker (Inos2+ CLS—Biotronik GmbH, Berlin, Germany) and randomly assigned to CLS or DDD pacing mode. Patients underwent two 24-hour electrocardiogram Holter recordings at the end of each 3-month pacing mode period. Each Holter recording was automatically scanned to extract sequences of consecutive beats of the same type [atrial paced (Ap)- sequence and atrial spontaneous (As)-sequence], lasting at least 130 beats.

Results
Eight hundred and ten sequences were extracted from 15 patients, and the following spectral parameters were evaluated during both CLS and DDD mode: the total power (variance), the absolute and percentage (relative to the total power) powers of the low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) components, as well as the LF/HF power ratio.

Discussion
The two main findings of this study were: in all the patients, CLS seems to mimic short-term physiological HRV, although the variability (total power) was lower than that relative to the spontaneous beats; the HRV of the spontaneous beats had an higher LF/HF when the pacemaker was programmed as DDD respect to CLS, consistent with a shift toward sympathetic predominance.

Source: PACE 2009

26

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

Author
R. Quaglione et al

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 randomized 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-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.

Conclusion 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.

Source: Europace, 2005

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Usefulness of Hemodynamic Sensors for Physiologic Cardiac Pacing in Heart Failure Patients

Author
E. Occhetta et al

Summary
The rate adaptive sensors applied to cardiac pacing should respond as promptly as the normal sinus node with a highly specific and sensitive detection of the need of increasing heart rate. Sensors operating alone may not provide optimal heart responsiveness: central venous pH sensing, variations in the oxygen content of mixed venous blood, QT interval, breathing rate and pulmonary minute ventilation monitored by thoracic impedance variations, activity sensors. Using sensors that have different attributes but that work in a complementary manner offer distinct advantages. However, complicated sensors interactions may occur.
Hemodynamic sensors detect changes in the hemodynamic performances of the heart, which partially depends on the autonomic nervous system-induced inotropic regulation of myocardial fibers. Specific hemodynamic sensors have been designed to measure different expression of the cardiac contraction strength: Peak Endocardial Acceleration (PEA), Closed Loop Stimulation (CLS) and TransValvular Impedance (TVI), guided by intraventricular impedance variations. Rate-responsive pacing is just one of the potential applications of hemodynamic sensors in implantable pacemakers. Other issues discussed in the paper include: hemodynamic monitoring for the optimal programmation and follow up of patients with cardiac resynchronization therapy; hemodynamic deterioration impact of tachyarrhythmias; hemodynamic upper rate limit control; monitoring and prevention of vasovagal malignant syncopes.

Source: Cardiology Research and Practice, 2011

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Closed Loop Stimulation in Patients with Normal and Limited Contractility

Author
G.K.M. Fauser et al.

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 analyzed. 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.

Conclusion 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.

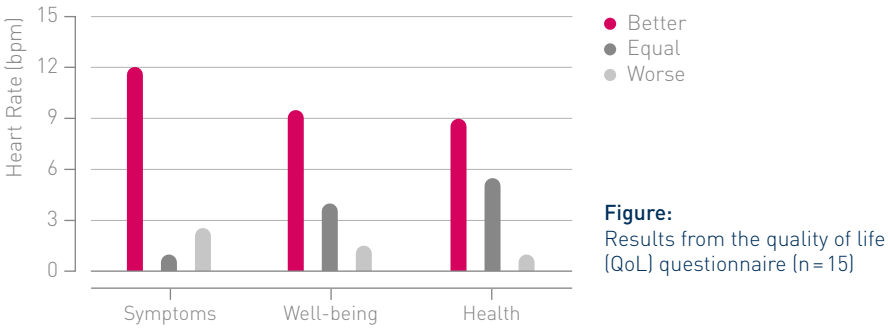

Figure:
Results from the quality of life (QoL) questionnaire (n = 15)

Source: Progress in Biomedical Research, 2009

Rate-Adapting Pacing in a 7-Year-Old Boy Using Ventricular Contractility Information

Author
F. Drago et al.

Background
Pacemaker (PM) therapy seems to be the established choice in pediatric patients with congenital complete atrioventricular block. Recent data have shown how PM therapy reduces mortality and morbidity compared with natural history data previously published, but the appropriate time for the implant is yet to be defined.

1) A relevant problem in pediatric patients regards the choice between single- and dual-chamber PM. In the first decade the use of single-chamber, accelerometric rate-responsive PM (ventricular pacing, ventricular sensing, inhibition response, rate-adaptive; VVIR) is an adequate and cost-effective solution: only a few VVIR patients report PM symptoms within 10 years after implantation.

2) Notwithstanding these interesting results, the benefit of dual-chamber rate-responsive pacing (atrial and ventricular pacing, atrial and ventricular sensing, inhibition and tracking response, rate-adaptive; DDDR), particularly in adolescents and young adults, would suggest the upgrading procedure.

3,4) This procedure involves various complications, mainly related to the choice and positioning of leads.

5,6) New generation rate-responsive PM induce physiologic pacing by adapting the pacing rate upon the indirect measurement of the ventricular contractility (closed loop stimulation, CLS). Contractility is estimated by continuous sampling of the intraventricular electrical impedance obtained by a high-frequency sub-threshold pulse train. The PM records the impedance values under rest conditions (reference curve), then compares the instantaneous impedance values for each ventricular-paced beat with the reference curve: an increase of the impedance curve slope is an indication of increased contractility and this value is used to modulate the pacing rate.

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7) In addition, the system updates the reference curve continuously, to adapt it to the patient's autonomic tone.

8) CLS uses conventional endocardial leads and does not require special settings. It has been shown that, in dual-chamber devices, this mode modulates the heart rate in response to various kinds of autonomic stimuli (either movement or non-movement), 9 – 10) in adult and adolescent populations.

Recently a single-chamber PM featuring the CLS mode has been introduced (ProtosVR-CLS, Biotronik, Berlin, Germany).

A single-chamber physiologic PM, which responds to various stresses (mental or physical), may be an interesting choice for pediatric patients with congenital complete atrioventricular block: it may postpone the upgrade procedure by providing heart rate control according to the maturation of the autonomic tone.

Source: Pediatrics International, 2008

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Beat-To-Beat Heart Rate Adaptation in Pediatric and Late Adolescent Patients with Closed Loop Rate-Responsive Pacemakers

Author

F. Drago et al.

Background

The aim of this study was to evaluate the efficacy of physiological rate-responsive pacemakers (Closed Loop Stimulation-CLS) to pace pediatric and late adolescent patients undergoing rest, mental, standing, and exercise testing. Dual-chamber pacemaker is increasingly indicated for young patients. A new physiological pacing mode based on the indirect measure of ventricular contractility (CLS), has shown interesting results in adults, while no data on pediatric patients are available. RR intervals and beat-to-beat systolic and diastolic pressures were monitored in 12 pediatric patients (6 males, mean age 17 years [12–22 years]) who had a transvenous implant of Inos2+-CLS dual-chamber pacemaker (Biotronik GmbH, Berlin, Germany) and endocardial leads. All the patients showed correct electrical parameters at the implant and during the follow-ups. Paced RR intervals decreased significantly ($F = 7.28$, $P = 0.01$) from 0.85 ± 0.08 seconds (rest) to 0.73 ± 0.10 seconds (mental) and to 0.75 ± 0.010 seconds (standing); systolic/diastolic pressure was significantly higher ($F = 12.2$, $P = 0.002/F = 13.6$, $P = 0.001$) in mental ($134.4 \pm 19.9/74.4 \pm 8.1$ mmHg) with respect to rest ($115.1 \pm 18.3/61.0 \pm 6.1$ mmHg), and standing ($118.7 \pm 23.9/67.3 \pm 0.1$ mmHg). During exercise the paced RR interval showed significant decrease of about 35% from baseline to maximum load ($F = 24.90$, $P = 0.001$) and systolic pressure increased significantly ($F = 4.91$, $P = 0.019$) by about 34% from baseline to maximum load. The comparison between paced and spontaneous rates showed very similar values and trend. In addition, CLS mode does not seem to overrun the spontaneous heart activity, when present. This is a study to evaluate CLS pacing in pediatric and late adolescent patients. The study shows that CLS pacing responds to both physical and non-physical stressors, providing physiological pacing rates, as previously observed in adults.

Source: PACE 2005

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Closed Loop Stimulation Improves Ejection Fraction in Pediatric Patients with Pacemaker and Ventricular Dysfunction

Author:
F. Drago et al.

Background

The aim of this prospective study was to evaluate the effect of the closed loop stimulation (CLS) on the ejection fraction in pediatric patients, affected by complete atrioventricular block (CAVB) or CAVB and sinus node dysfunction (SND), with a previously implanted pacemaker (PM) and ventricular dysfunction. The role of electrical therapy in the treatment of pediatric patients with congenital atrioventricular (AV) blocks has been shown. Conventional right ventricular pacing seems to affect ventricular function. Up to now, the feasibility and the long-term results of biventricular pacing in pediatric patients were not entirely clear.

Methods

In eight pediatric patients with a previously implanted single or dual chamber PM, ventricular dysfunction, and CAVB or SND and CAVB, a dual chamber PM Inos2+-CLS (Biotronik GmbH, Berlin, Germany) was implanted. The effect of the physiological modulation of CLS pacing mode on the ejection fraction was evaluated by Echo-Doppler examination. Measurements were performed before the substitution of the old PM and for up to 2 years of follow-up.

Results

All patients showed correct electrical parameters at implantation and during follow-up. The mean value of the ejection fraction measured before the replacement of the old PM was 36 ± 7%, while after 2 years it was 47 ± 1% (P < 0.003). No patient showed any worsening of the ejection fraction, while only one showed no improvement.

Conclusion DDD-CLS pacing seems to improve ventricular function in pediatric patients with CAVB and/SND in spite of the use of the apical right conventional stimulation.

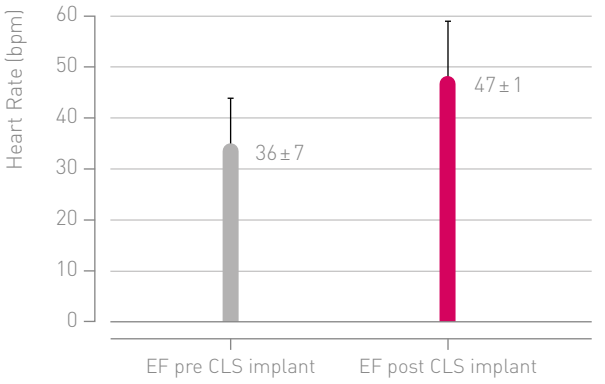

Figure:
Mean Value of ejection fraction before CLS implant and after 2 years

Source: PACE 2007

32

Efficacy of Closed-Loop Stimulation with Epicardial Leads in an Infant with Congenital Atrioventricular Block

Author
A. Di Pino et al.

Background
Pacemaker implantation was performed in a 4-month-old infant for a congenital atrioventricular block (AV) block. The baby presented at birth with a complete AV block and a junctional escape rhythm with a mean heart rate of 50 bpm at the Holter monitoring. Permanent pacing was performed for failure in growth and evidence of progressive dilatation of the left ventricle. We decided to implant a rate responsive pacemaker for the presence of a sinus rate that was not adequate to his metabolic status. A DDD-closed-loop stimulation (CLS) PROTOS pacemaker (Biotronik, Berlin, Germany) was surgically implanted in the abdomen. The pacemaker pocket was tailored between the posterior aspect of the left rectus muscle and the anterior fascia. Inferior sternotomy was adopted for leads positioning. The pacemaker was then programmed in DDDR mode for 30 days and in DDD-CLS mode for the following 30 days. For both stimulation modes, the following parameters were programmed: lower rate at 80 bpm; upper CLS/accelerometer rate at 160 bpm; upper tracking rate at 185 bpm. After these periods, the two pacing modalities were compared on the basis of pacemaker diagnostics.

In DDD-CLS mode, atrial pacing was 48% with respect to 16% of DDDR and keeping higher in all rate ranges.

The 24 h rate trend showed a mean rate during DDD-CLS higher than in DDDR. An echocardiogram performed after 2 months documented a reduction of the left ventricle dilatation, and infant's growing recovered.

Source: EUROPACE, 2008

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The DDDR Closed Loop Stimulation for the Prevention Of Vasovagal Syncope: Results from the Invasy Prospective Feasibility Registry

Author
E. Occhetta et al.

Background
The contraction dynamics of the ventricular myocardium are affected before and during vasovagal fainting suggesting that the Closed Loop Stimulation (CLS) pacemaker could be useful for the treatment of these patients. CLS is
a new concept of heart rate modulation in cardiac pacing. The pacemaker INOS2 CLS (Biotronik, Germany) derives its information for heart rate optimization from myocardial contraction dynamics, by measuring right ventricular intracardiac impedance. The pacemaker becomes an integral part of the circulatory regulation and, therefore, reacts appropriately to different cardiovascular demands.

Methods
In a prospective registry, 34 patients with a history of recurrent vasovagal syncopal events were implanted with INOS2 DDDR CLS pacemakers. The aim of the study was to evaluate both long term clinical outcome, including the first recurrence of syncope, with DDDR-CLS pacing and acute precipitation of vasovagal fainting with DDDR-CLS mode compared with DDD during head up tilt testing.

Results
During a follow up period of 12–50 months, 30 patients experienced no further syncopal events in daily life; 1 patient had no syncope but night palpitations, which were eliminated by pacemaker reprogramming; 2 patients had presyncopal episodes but not syncopes; 3 syncopal recurrences occurred in one patient in chronic atrial fibrillation, possibly not an ideal candidate for implantation.

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Conclusion Further studies for detailed understanding of the preventive mechanism of DDDR-CLS pacing in vasovagal syncope are warranted. A randomized multicentre prospective new study (INotropy controlled pacing in VAsovagal SYncope: INVASY) is now in progress to confirm the beneficial effect of DDDR-CLS pacing in a larger group of patients with recurrent vasovagal syncope.

Source: EUROPACE, 2003

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Closed Loop Stimulation in Prevention of Vasovagal Syncope. Inotropy Controlled Pacing in Vasovagal Syncope (Invasy)

Author
E. Occhetta et al.

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 (Inos2). 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.

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

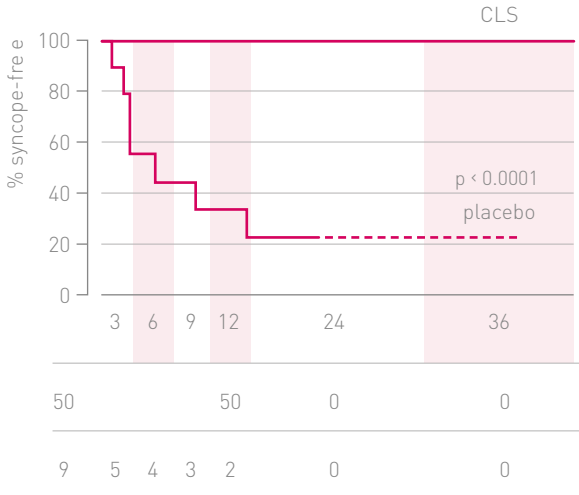


Figure: Probability of remaining free of syncopal recurrences (Kaplan-Meier estimation) in 41 patients in CLS arm and nine patients in the control group (placebo – DDI).

Source: EUROPACE 2004

Preliminary Observations on the Use of Closed-Loop Cardiac Pacing in Patients with Refractory Neurocardiogenic Syncope

Author
K. Kanjwal et al.

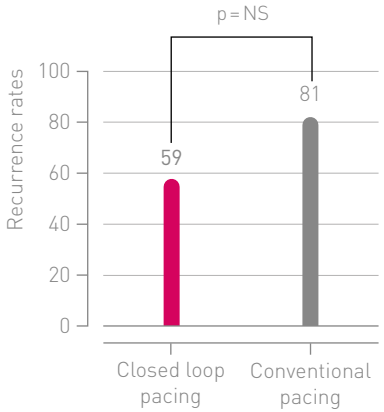
Background
In many patients with recurrent neurocardiogenic syncope (NCS), a significant fall in blood pressure precedes any appreciable decline in heart rate. Closed-loop pacing (CLS) employs a sensing system that measures myocardial contractility, thereby providing a potential way to detect the onset of NCS at a much earlier point in time than that provided by standard pacing systems.

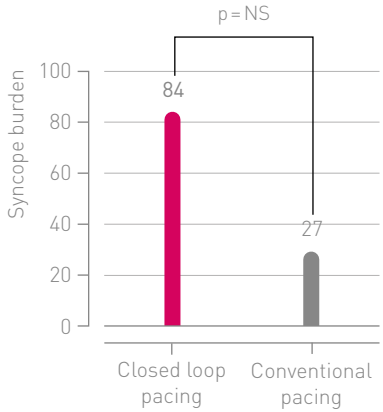
Methods
Patients were included in the study if they suffered from recurrent NCS and met all of the following criteria: (1) They had suffered at least two syncopal episodes in the preceding 6 months. (2) Patients were refractory to (or intolerant of) all conventional, nonpharmacological, or pharmacological treatments. (3) They had evidence of asystole (> 10 s) or severe bradycardia (heart rate < 30 bpm) on implantable loop recorder or during head-up tilt test (HUTT).

Results
Thirty five patients meeting the above criterion received 44 devices. Twelve patients received a standard unit (with rate drop or rate hysterisis response) and 32 patients received a CLS unit (Cylos, Biotronik). The pacemaker implantation was termed successful if there was no recurrence of syncope, if the syncope burden decreased by ≥50%, if only presyncope occurred, or if the syncope occurred but with significant warning symptoms.

Thirty-five patients, 29 females and six males, age 41±11, with refractory NCS underwent pacemaker implantation. Mean follow-up was 9±3 months. Out of 32 patients who received CLS, nine had a conventional pacemaker implanted in the past. Recurrence (59% vs 83%), reduction in syncope burden and pacemaker success (84% vs 25%, P=0.002), and occurrence prodrome/warning signs (40% vs 16%) were much better in the closed-loop group.

Conclusion These preliminary observations suggest that dual-chamber CLS pacing may be promising therapy for refractory NCS. Further randomized trials will be needed to better determine the role of this therapy in refractory NCS.





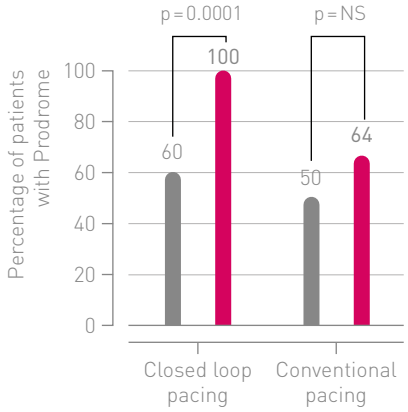


Figure 1:
Recurrence rates in close loop versus conventional pacing

Figure 2:
Pacemaker success and reduction in syncope burden (> 50%) in close loop versus conventional pacing

Source: Journal Interventional Cardiology and Electrophysiology, 2010

Observations on Optimal Programming of Closed Loop Cardiac Pacemakers in Patients with Refractory Neurocardiogenic Syncope

Author
Kanjwal K. et al.,

Summary
There have been few reports on the use of closed loop cardiac pacing in patients suffering from refractory neurocardiogenic syncope. The optimal pacing algorithm using closed loop cardiac pacing has not been well studied. We herein present our single center experience on the specific pacing algorithm, which has been successful in almost 84% of patients.

Introduction
Recurrent refractory neurocardiogenic syncope (NCS) can be a debilitating problem that often proves difficult to manage. Whereas standard cardiac pacing in patients with refractory NCS has yielded mixed results, recent reports have suggested that pacemakers that incorporate closed loop cardiac pacing (CLS) algorithms can be quite effective in decreasing the frequency and severity of syncopal events.1–3 CLS employs a sensing system that measures myocardial contractility, thereby providing a potential way of detecting the onset of NCS at much earlier point in time than that provided by standard pacing systems.1–3 Earlier detection would then allow for pacing to be employed at an earlier point in the syncopal process, potentially enhancing its ability to either prevent (or significantly modify) the syncopal event. The programming algorithm for these patients has not been very well standardized.

In this paper we present a suggested algorithm for programming CLS pacemakers based on our experience in the management of refractory neurocardiogenic syncope over the last 4 years in almost 117 patients: with Evia DR-T 359529 in 30 patients and Cylos DR-T 349799 in 87 patients.

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The CLS system manufactured by Biotronik uses inotropy-based sensors. The earlier model was the Cylos DR-T device and the latest CLS pacer available in the United States market is the Evia DR-T (which employs the same sensor technology). There is no difference in the CLS pacing algorithm between Cylos DR-T and the newer Evia DR-T.

Source: The Journal of Innovations in Cardiac Rhythm Management, 2011

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Closed-Loop Cardiac Pacing vs. Conventional Dual-Chamber Pacing with Specialized Sensing and Pacing Algorithms for Syncope Prevention in Patients with Refractory Vasovagal Syncope: Results of a Long-Term Follow-Up

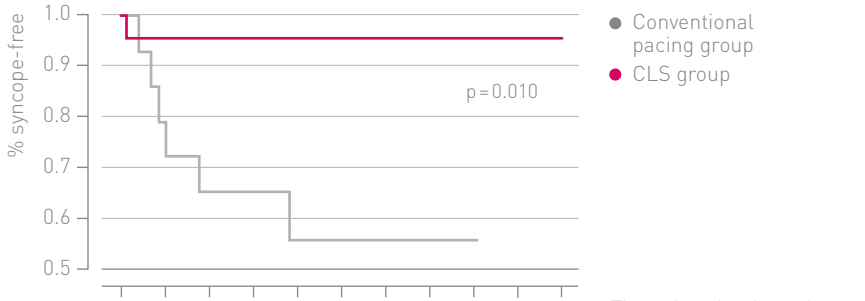
Author
P. Palmisano et al.

Aims
Closed-loop stimulation (CLS) pacing has shown greater efficacy in preventing the recurrence of vasovagal syncope (VVS) in patients with a cardioinhibitory response to head-up tilt test (HUTT) compared with conventional pacing.

Moreover, there is no conclusive evidence to support the superiority of CLS over the conventional algorithms for syncope prevention. This study retrospectively evaluated the effectiveness of CLS pacing compared with dual chamber pacing with conventional specialized sensing and pacing algorithms for syncope prevention in the prevention of syncope recurrence in patients with refractory VVS and a cardioinhibitory response to HUTT during a long-term follow-up.

Methods and results
Forty-one patients (44% male, 53+16 years) with recurrent, refractory VVS (26% with trauma) and a cardioinhibitory response to HUTT who had undergone pacemaker implantation were included in the analysis. Twenty-five patients received a dual-chamber CLS pacemaker (CLS group) and 16 patients received a dual-chamber pacemaker with conventional algorithms for syncope prevention (conventional pacing group): 9 patients with Medtronic rate drop response algorithm and 7 patients with Guidant-Boston Scientific sudden brady response algorithm. During the follow-up (mean 4.4+3.0 years, interquartile range 2.2–7.4 years) one patient (4%) in the CLS group and six (38%) in the conventional pacing group had syncope recurrences ($P < 0.016$). The Kaplan–Meier actuarial estimate of first recurrence of syncope after 8 years was 4% in the CLS group and 40% in the conventional pacing group ($P < 0.010$).

Conclusion The results of this retrospective analysis show that, in order to prevent a recurrence of VVS in patients with a cardioinhibitory response to HUTT, dual-chamber CLS pacing was more effective than dual-chamber pacing with conventional algorithms for syncope prevention in preventing bradycardia-related syncope.



CLS: Closed Loop Simulation;

Source: EUROPACE, 2012

Long-Term Follow-Up of DDDR Closed-Loop Cardiac Pacing for the Prevention of Recurrent Vasovagal Syncope

Author

M. Bortnik et al.

Aims

Vasovagal syncope (VVS) is a common disorder characterized by a drop in blood pressure accompanied with bradycardia; although it is generally considered a benign condition, some patients may be highly symptomatic despite general counselling and/or pharmacological therapy. Closed-loop stimulation (CLS), responding to myocardial contraction dynamics, demonstrated effectiveness in short-term prevention of recurrent VVS. The aim of this study was to evaluate CLS pacing in a long-term follow-up.

Methods

The study involved 35 patients (mean age 59 ± 15 years) with 3 years' follow-up (mean 61 ± 35 months). We compared syncopal events and presyncopes before and after CLS implantation. Mean number of syncopes for patients was six (range 1–24; 212 syncopal spells registered) before pacemaker implantation.

Results

At follow-up, 29 of 35 patients (83%) were asymptomatic; one patient experienced recurrent loss of consciousness but reported an improvement in the quality of life (one syncope or presyncope per month after CLS, vs. one syncope per week and daily presyncopes before CLS). Five patients experienced syncopal recurrences after CLS (range: 1–7, with a total of 15 episodes); in all the cases, the number of post-CLS syncopes was significantly lower.

Source: Journal of Cardiovascular Medicine, 2012

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Dual-Chamber Pacing with Closed Loop Stimulation in Recurrent Reflex Vasovagal Syncope: the Spain Study

Author

G. Baron-Esquivias

Aims

Pacing in vasovagal syncope remains controversial. In this study, the authors evaluated dual-chamber pacing with closed loop stimulation (DDD-CLS) in patients with cardio-inhibitory vasovagal syncope.

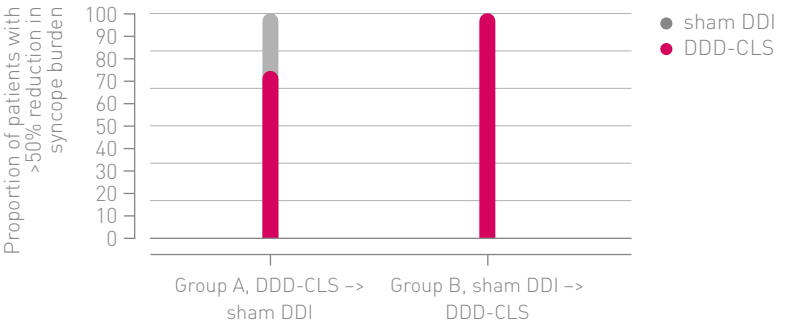
Methods

This randomized, double-blind, controlled study included Canadian and Spanish patients age ≥40 years, with high burden syncope (≥5 episodes, ≥2 episodes in the past year), and a cardioinhibitory head-up tilt test (bradycardia <40 beats/min for 10 s or asystole >3 s). Patients were randomized to either DDD-CLS pacing for 12 months followed by sham DDI mode pacing at 30 pulses/min for 12 months (group A), or sham DDI mode for 12 months followed by DDD-CLS pacing for 12 months (group B). Patients in both arms crossed-over after 12 months of follow-up or when a maximum of 3 syncopal episodes occurred within 1 month.

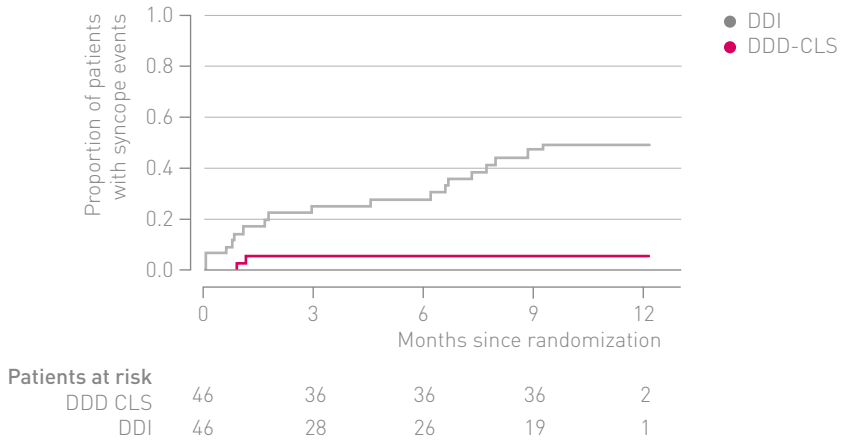
Results

A total of 46 patients completed the protocol; 22 were men (47.8%), and mean age was 56.30 ± 10.63 years. The mean number of previous syncopal episodes was 12 (range 9 to 20). The proportion of patients with ≥50% reduction in the number of syncopal episodes was 72% (95% confidence interval [CI]: 47% to 90%) with DDD-CLS compared with 28% (95% CI: 9.7% to 53.5%) with sham DDI mode (p = 0.017). A total of 4 patients (8.7%) had events during DDD-CLS and 21 (45.7%) during sham DDI (hazard ratio: 6.7; 95% CI: 2.3 to 19.8). Kaplan-Meier curve was significantly different between groups in time to first syncope: 29.2 months (95% CI: 15.3 to 29.2 months) versus 9.3 months (95% CI: 6.21 months, NA; p<0.016); odds ratio: 0.11 (95% CI: 0.03 to 0.37; p < 0.0001).

Conclusion DDD-CLS pacing significantly reduced syncope burden and time to first recurrence by 7-fold, prolonging time to first syncope recurrence in patients age ≥40 years with head-up tilt test–induced vasovagal syncope compared with sham pacing.



Proportion of patients with ≥50% reduction in syncope burden according to allocated pacing mode. Group A (DDD-CLS x 12 months crossed to sham DDI x 12 months): 72% (95% confidence interval [CI]: 47 to 90) with the DDD-CLS mode (blue) compared to 28% (95% CI: 10 to 53) paced in the sham DDI mode (orange) reached the primary efficacy outcome (p = 0.0172, Mainland-Gart). Group B: (Sham DDI x 12 months crossed to DDD-CLS x 12 months) 0% sham DDI versus 100% (95% CI: 40 to 100) DDD-CLS (p = 0.003, Mainland-Gart). DDD-CLS = dual-chamber pacemaker with closed loop stimulation; sham DDI = dual-chamber pacemaker implantation but without pacing activity.



Time to first recurrence of syncope in both pacing mode sequences. Group A (DDD-CLS first/sham DDI) versus group B (sham DDI/DDD-CLS). During a mean of 22.2 ± 5.1 months of follow-up, in an intent-to-treat analysis, the Kaplan-Meier model by treatment sequence estimated a longer median onset to first syncope in group A compared with group B (29.15 months vs. 9.30 months; p = 0.0158).

Source: Journal of American College of Cardiology, 2017

Cardiac Pacing in Severe Recurrent Reflex Syncope and Tilt-Induced Asystole (BIOSync CLS)

Author
M. Brignole et al.

Background
The benefit of cardiac pacing in patients with severe recurrent reflex syncope and asystole induced by tilt testing has not been established. The usefulness of tilt-table test to select candidates for cardiac pacing is controversial.

Methods
We randomly assigned patients 40 years or older who had at least two episodes of unpredictable severe reflex syncope during the last year and a tilt-induced syncope with an asystolic pause longer than 3 seconds, to receive either an active (pacing ON; 63 patients) or an inactive (pacing OFF; 64 patients) dual-chamber pacemaker with closed loop stimulation (CLS). The primary endpoint was the time to first recurrence of syncope. Patients and independent outcome assessors were blinded to the assigned treatment.

Results
After a median follow-up of 11.2 months, syncope occurred in significantly fewer patients in the pacing group than in the control group (10 [16%] vs. 34 [53%]; hazard ratio, 0.23; P<0.001). The estimated syncope recurrence rate at 1 year was 19% (pacing) and 53% (control); at 2 years, 22% (pacing) and 68% (control). A combined endpoint of syncope or presyncope occurred in significantly fewer patients in the pacing group (23 [37%] vs. 40 [63%]; hazard ratio, 0.44; P=0.002). Minor device-related adverse events were reported in 5 patients (4%).

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Conclusion In patients aged 40 years or older, affected by severe recurrent reflex syncope and tilt-induced asystole, dualchamber pacemaker with CLS is highly effective in reducing the recurrences of syncope. Our findings support the inclusion of tilt testing as a useful method to select candidates for cardiac pacing. (ClinicalTrials.gov identifier NCT02324920, Eudamed number CIV-05-013546)

Kaplan–Meier Curves Comparing Survival Free of Symptoms.

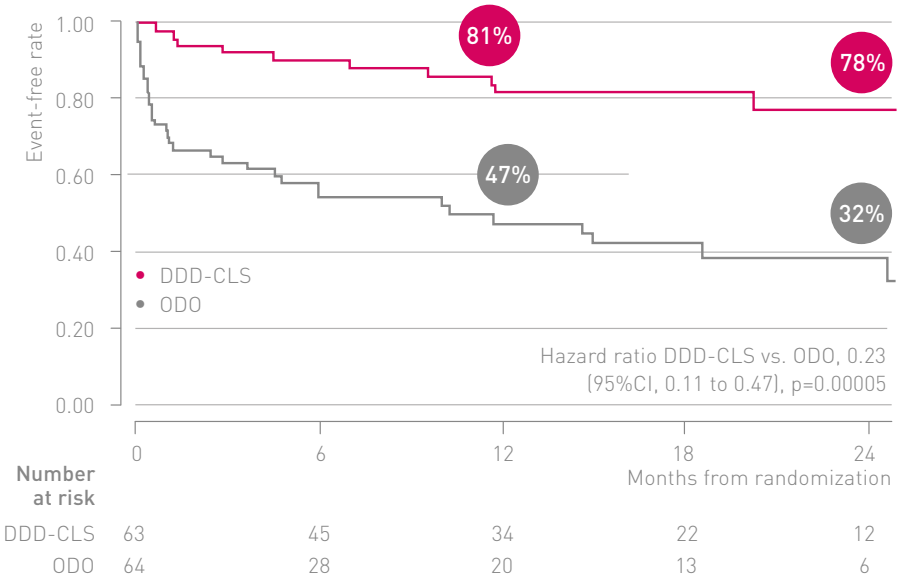

Figure 1:
Survival free of syncope recurrence for CLS-paced patients versus placebo (primary endpoint)

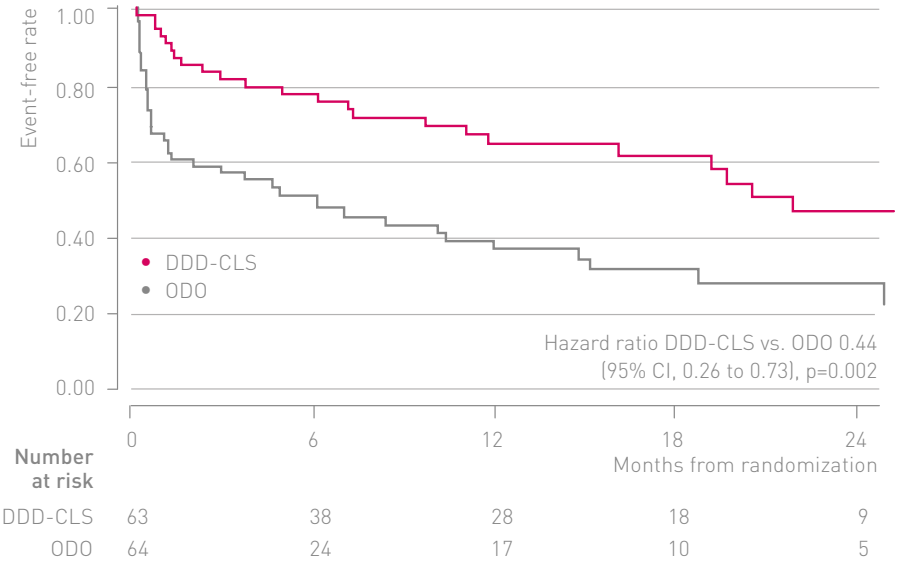

Figure 2:
Survival free of recurrence of syncope/pre-syncope for CLS-paced patients versus placebo (secondary endpoint)

Source: European Heart Journal, 2020

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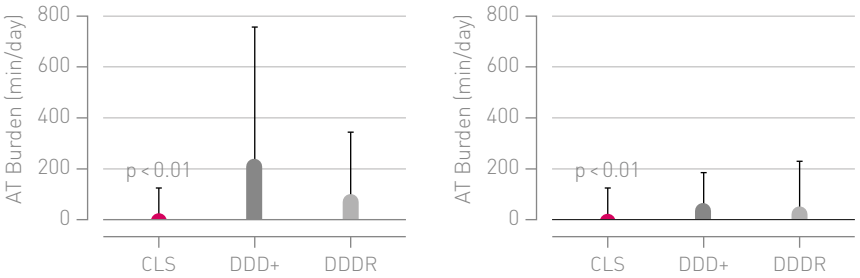
Impact of Closed-Loop Stimulation, Overdrive Pacing, DDDR Pacing Mode on Atrial Tachyarrhythmia Burden in Brady-Tachy Syndrom

Author
A. Puglisi et al.

Aims
Atrial overdrive pacing algorithms increase Atrial Pacing Percentage (APP) to reduce Atrial Tachyarrhythmia (AT) recurrences in patients with Brady-Tachy Syndrome (BTS). This study aimed to compare AT burden and APP in BTS patients treated with conventional DDDR pacing, DDD+ overdrive or Closed-Loop Stimulation (CLS).

Methods and results
One hundred and forty-nine BTS patients were included (72 male, mean age 74 ± 9), who received a dual chamber pacemaker (Philos DR or Inos 2+CLS, Biotronik GmbH, Berlin, Germany) programmed in DDD at 70 min–1. At 1-month follow-up, DDDR, DDD+ or CLS algorithms were activated according to randomization. Follow-up visits for data collection were performed at 4 and 7 months. Non parametric statistical tests (Kruskal–Wallis H-test, Dunn test, Spearman coefficient) were used to analyse not-normally-distributed samples. At 7 months, AT burden was significantly lower in CLS group (20.3 ± 63.1 min/day, $P < 0.01$) compared to DDDR (56.0 ± 184.0 min/day) and DDD+ group (63.1 ± 113.8 min/day). APP was higher in CLS (89.0 ± 13.2%) and in DDD+ group (97.9 ± 2.7%) than in DDDR group (71.1 ± 26.7%, $P < 0.001$). The correlation found between AT burden and APP was very weak: at 7-month follow-up the Spearman coefficient was –0.29 (P = NS) in CLS, –0.52 ($P < 0.01$) in DDD+, –0.22 (P = NS) in DDDR.

Conclusion Atrial overdrive showed the worst performance in terms of AT burden reduction and should not be preferred to heart rate modulation approaches that still have to be considered as a first choice pacing mode in BTS.



Source: European Heart Journal, 2003

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Overdrive Versus Conventional or Closed-Loop Rate Modulation Pacing in the Prevention of Atrial Tachyarrhythmias in Brady-Tachy Syndrome: on Behalf of the Burden II Study Group

Author
A. Puglisi et al.

Background
Optimizing dual-chamber pacing to prevent recurrences of atrial tachyarrhythmias (AT) in sinus node dysfunction is still debated. Despite the large number of studies, efficacy of sophisticated preventive algorithms has never been proven. It is not clear whether this is due to imperfect study designs or to a substantial inefficacy of pacing therapies.

Aim
To intraindividually compare AT burden between an atrial overdrive and two heart rate modulation approaches: a conventional accelerometric-sensor-based DDDR mode and a contractility-driven rate responsive closed loop (CLS) algorithm.

Methods and Results
Four hundred fifty-one patients with Brady-Tachy syndrome (BTS), severe bradycardia, and a documented episode of atrial fibrillation were enrolled. One month after implant, each pacing therapy was activated for 3 months in random order. A simple log transformation was used to handle large and skew AT burden distributions. Estimates were adjusted for false-positive AT episodes and reported as geometric means (95% confidence interval). A significantly higher AT burden was observed during overdrive, 0.14% (0.09%, 0.23%) (adjusted, 0.12% [0.07%, 0.20%]). Both DDDR and CLS performed better: respectively, 0.11% (0.07%, 0.17%) (adjusted, 0.08% [0.05%, 0.14%]), 0.06% (0.03%, 0.09%) (adjusted, 0.04% [0.03%, 0.07%]). All the comparisons were statistically significant. During overdrive significantly more patients had AT episodes of duration between 1 minute and 1 hour. No significant differences were observed for longer episodes.

Conclusion Atrial overdrive showed the worst performance in terms of AT burden reduction and should not be preferred to heart rate modulation approaches that still have to be considered as a first choice pacing mode in BTS.

Source: PACE, 2008

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

Author
O.V. Beliaev et al.

Summary
The aim of modern pacemaker technology is not only to prolong life but 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 method, the pacemaker becomes part of the natural control loop and, therefore, guarantees adequate pacing rates under all kinds of mental and physical loads. To prove this integration of the pacemaker into the cardiovascular system, the heart rate variability of 19 patients who received CLS pacemakers was determined and compared with a control group consisting of 20 healthy patients and with a group of 32 patients who received rate-adaptive pacemakers with a motion sensor. Both groups of pacemaker patients and the control group underwent 24-hour Holter monitoring. The heart rate variability of the CLS group shows 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 the control group ($p < 0.01$). The results illustrate that CLS provides heart rate variability comparable to that of healthy people 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 correspond to the actual needs of the patients.

Source: Progress in Biomedical Research, 1999

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Performance of Closed Loop Stimulation in Hypertrophic and Dilated Hearts

Author
E. Ebner et al.

Summary
Previous studies have introduced Closed Loop Stimulation (CLS) as a pacemaker therapy for reestablishing a physiologic heart rate regulation. They were able to prove that right-ventricular intracardiac unipolar impedance measurements are suited to monitor both the right-ventricular and the left-ventricular inotropic cardiac state. Regulating the pacing rate in accordance with myocardial contraction dynamics offers the advantage of including the pacemaker into the natural cardiovascular control loop via negative feedback between the pacing rate and changes in blood pressure. Optimizing the rate regulation in such a manner is especially crucial for patients with congestive heart failure, who have a limited stroke volume, in order to provide a sufficient cardiac output under load. Therefore, this patient population should benefit particularly well from a CLS therapy. Nevertheless, the question arises whether a pathological limitation in contractility could lead to an impairment of the CLS rate regulation.

The CLS system comprises automatic initialization and continuous updating of the rate dynamics to compensate for lower or gradually modified contraction dynamics. However, the performance of this function has so far not been explicitly verified in a clinical study. Thus, the primary task of the presented study was to investigate whether and to what degree an effective CLS therapy with adequate pacing rates can be implemented in patients who suffer from a limited contractility. An exercise-tolerant patient population ($N = 14$; 4 female; ejection fraction at rest for 11 patients: $72 \pm 8.6\%$) suffering from various degrees of diastolic and systolic insufficiency was selected. During a follow-up examination 3 months after implantation of an Inos2 CLS pacemaker, various stress tests and echocardiographic examinations were performed, in order to study the cardiac geometry's possible influence on the pacing rate. The study results show that the expected individual

heart rate is dependent on the different load steps, and independent from the diastolic state of the left ventricle (diameter, posterior wall thickness). From the study results, it can be concluded that CLS therapy is also suited for patients with limited contractility. Therefore, no restrictions apply to a closer investigation of the benefit of CLS therapy for this particular patient population in further studies.

Source: Progress in Biomedical Research, 2001

Heart Resynchronization in CHF Patients with Dilated Cardiomyopathy Using a Rate-Responsive Pacemaker Controlled by the Autonomic Nervous System

Author
P.R.S. Brofman et al.

Summary
In this study, four patients with congestive heart failure (CHF) due to dilated cardiomyopathy were treated with a heart resynchronization therapy in combination with the Closed Loop Stimulation (CLS) rate-adaptive pacing. Before the implantation, the patients had a prolonged PR-interval and the left bundle branch block. The heart resynchronization has been achieved by a dual-chamber CLS pacemaker. A unipolar Y-adapter was plugged in the ventricular port of the pacemaker. The right ventricular lead was connected to the negative pole (cathode) and the left ventricular lead to the positive pole (anode) of the Y-adapter, while the atrial lead was connected to the atrial port. The patients were evaluated before pacemaker implantation, after the first 15 days and 30 days after pacemaker implantation, and every 3 months thereafter. All patients exhibited a clear improvement in the ejection fraction and cardiac output, a greater exercise capacity, and a decrease in the diastolic diameter of the left ventricle after pacemaker implantation. In all but one patient, the duration of the QRS-complex was reduced.

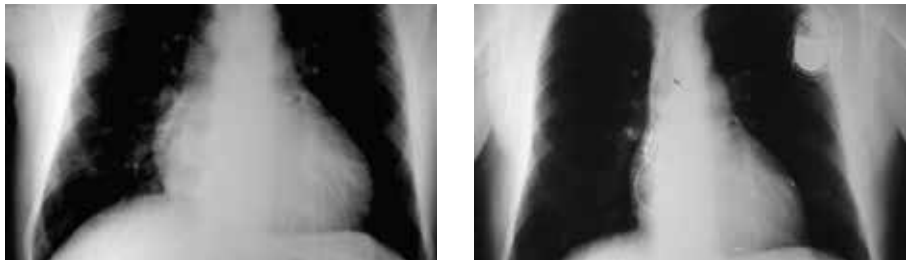

Figure 1. X-ray pre- (panel a) and post-implantation (panel b) of a biventricular pacemaker system (male patient, aged 48).

Source: Progress in Biomedical Research, 2001

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Biventricular Pacing Improves Cardiac Function and Prevents Further Left Atrial Remodeling in Patients with Symptomatic Atrial Fibrillation after Atrioventricular Node Ablation

Author
M.V. Orlov et al

Background
Randomized trials have demonstrated benefits of biventricular (BiV) pacing in patients with advanced heart failure, intraventricular conduction delay, and atrial fibrillation (AF) postatrioventricular (AV) node ablation. The AV Node Ablation with CLS and CRT Pacing Therapies for Treatment of AF trial (AVAIL CLS/CRT) was designed to demonstrate superiority of BiV pacing in patients with AF after AV node ablation, to evaluate its effects on cardiac structure and function, and to investigate additional benefits of Closed Loop Stimulation® (CLS) (BIOTRONIK, Berlin, Germany).

Methods
Patients with refractory AF underwent AV node ablation and were randomized (2:2:1) to BiV pacing with CLS, BiV pacing with accelerometer, or right ventricular (RV) pacing. Echocardiography was performed at baseline and 6 months, with paired data available for 108 patients.

Results
The RV pacing contributed to significant increase in left atrial volume, left ventricular (LV) end-systolic volume, and LV mass compared to BiV pacing. Ejection fraction decreased insignificantly with RV pacing compared to significant increase with BiV pacing. Interventricular dyssynchrony significantly decreased with BiV compared with RV pacing. Closed Loop Stimulation® did not result in additional echocardiographic changes; heart rate distribution was significantly wider with CLS. All groups showed significant improvement in 6-minute walk distance, quality-of-life score, and New York Heart Association class.

Conclusion In conclusion, RV pacing results in significant increase in left atrial volume, LV mass, and worsening of LV contractility compared to patients receiving BiV pacing post-AV node ablation for refractory AF. Closed Loop Stimulation® was not associated with additional structural changes but resulted in significantly wider heart rate distribution.

Source: American Heart Journal, 2010

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Chronotropic Incompetence, Beta-Blockers, and Functional Capacity in Advanced Congestive Heart Failure: Time to Pace?

Author
UP Jorde et al.

Background
Chronotropic incompetence (CI) is often seen in subjects with chronic congestive heart failure (CHF). The prevalence of CI, its mechanisms and association with beta-blocker use as well as exercise capacity have not been clearly defined.

Methods and results
Cardiopulmonary exercise tolerance testing data for 278 consecutive patients with systolic CHF was analyzed. CI, defined as the inability to reach 80% of maximally predicted heart rate was present in 128 of 278 subjects (46%). The prevalence of CI was highest in those with most impaired exercise capacity (72, 48, and 24% for subjects with a VO2 of b14.0, 14.0–20.0, and N20.0 ml/kg/min respectively; p = 0.001). While subjects with CI had lower peak exercise heart rate (114 vs. 152 bpm), and lower peak VO2 (15.4 vs. 19.9 ml/kg/min), they were equally likely to be on chronic beta-blocker therapy (74% vs. 71%; p = 0.51).

Heart rate and norepinephrine (NE) levels were measured during exercise in a separate cohort of 24 subjects with CHF. There was no difference in beta-blocker dose between subjects with and without CI, however, exercise induced NE release and Chronotropic Responsiveness Index, a measure of post-synaptic beta-receptor sensitivity to NE, were lower in subjects with CI (1687 ± 911 vs. 2593 ± 1451 pg/ml p = 0.08; CRI 12.7 ± 5.7 vs. 22.1 ± 4.7, p = 0.002).

Conclusion CI occurs in N70% of subjects with advanced systolic CHF irrespective of beta-blocker use and is associated with a trend toward impaired NE release, post-synaptic beta-receptor desensitization and reduced exercise capacity.

Source: European Journal of Heart Failure, 2008

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Prognostic Significance of Impairment of Heart Rate Response to Exercise: Impact of Left Ventricular Function and Myocardial Ischemia

Author
A. Elhendy et al.

Objectives
The goal of this research was to study the association between heart rate (HR) response to exercise and the risk of death and myocardial infarction (MI) after adjustment for left ventricular (LV) function and myocardial ischemia.

Background
Chronotropic incompetence during exercise testing is associated with increased mortality. It is unknown whether LV dysfunction or ischemia accounts for this.

Methods
We studied 3,221 patients (age 59 ± 12 years; 1,701 men) who underwent treadmill exercise echocardiography. We considered two markers of chronotropic incompetence: 1) failure to achieve 85% of the maximal predicted HR, and 2) low (< 0.8) chronotropic index. The independent association between HR response and end points was evaluated by an adjusted risk (AR) model, which included clinical parameters, ejection fraction, and the severity of ischemic wall motion abnormalities.

Results
Target HR was not achieved in 495 (15%) patients. Low chronotropic index was observed in 793 (25%) patients. There were 129 deaths (41 cardiac) during a median follow-up of 3.2 years. Myocardial infarction occurred in 65 patients. Low chronotropic index was associated with cardiac death (AR, 1.54; 95% confidence interval [CI], 1.18 to 2.04; p = 0.002) and MI (AR, 1.37; 95% CI, 1.09 to 1.69; p = 0.007). Failure to achieve 85% of maximal predicted HR was associated with increased mortality (AR, 1.49; 95% CI, 1.02 to 2.22; p = 0.04) and cardiac death (AR, 2.13; 95% CI, 1.10 to 4.17; p = 0.03).

Conclusion Impaired chronotropic response to exercise is associated with increased mortality and cardiac events even after adjusting for LV function and the severity of exercise-induced myocardial ischemia.

Source: Journal of American College of Cardiology, 2003

The Incremental Benefit of Rate-Adaptive Pacing on Exercise Performance During Cardiac Resynchronization Therapy

Author
HF Tse et al.

Objectives
The purpose of this research was to investigate the effect of using rate-adaptive pacing and atrioventricular interval (AVI) adaptation on exercise performance during cardiac resynchronization therapy (CRT).

Background
The potential incremental benefits of using rate-adaptive pacing and AVI adaptation with CRT during exercise have not been studied.

Methods
We studied 20 patients with heart failure, chronotropic incompetence (< 85% age-predicted heart rate [AP-HR] and < 80% HR reserve), and implanted with CRT. All patients underwent a cardiopulmonary exercise treadmill test using DDD mode with fixed AVI (DDD-OFF), DDD mode with adaptive AVI on (DDD-ON), and DDDR mode with adaptive AVI on (DDDR-ON) to measure metabolic equivalents (METs) and peak oxygen consumption (VO2max).

Results
During DDD-OFF mode, not all patients reached 85% AP-HR during exercise, and 55% of patients had < 70% AP-HR. Compared to patients with > 70% AP-HR, patients with < 70% AP-HR had significantly lower baseline HR (66 ± 3 beats/min vs. 80 ± 5 beats/min, $p = 0.015$) and percentage HR reserve (27 ± 5% vs. 48 ± 6%, $p = 0.006$). In patients with < 70% AP-HR, DDDR-ON mode increased peak exercise HR, exercise time, METs, and VO2max compared with DDD-OFF and DDD-ON modes ($p < 0.05$), without a significant difference between DDD-OFF and DDD-ON modes. In contrast, there were no significant differences in peak exercise HR, exercise time, METs, and VO2max among the three pacing modes in patients with > 70% AP-HR. The percentage HR changes during exercise positively correlated with exercise time ($r = 0.67$, $p < 0.001$), METs ($r = 0.56$, $p < 0.001$), and VO2max ($r = 0.55$, $p < 0.001$).

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Conclusion In heart failure patients with severe chronotropic incompetence as defined by failure to achieve > 70% AP-HR, appropriate use of rate-adaptive pacing with CRT provides incremental benefit on exercise capacity during exercise.

Source: Journal of American College of Cardiology, 2005

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Importance of Heart Rate During Exercise for Response to Cardiac Resynchronization Therapy

Author
A. H. Maass

Summary
Cardiac resynchronization therapy (CRT) is an established therapy for patients with severe heart failure and mechanical dyssynchrony. Response is only achieved in 60–70% of patients.

Methods
We retrospectively examined consecutive patients in whom a CRT device was implanted. All underwent cardiopulmonary exercise testing prior to implantation and after 6 months. The occurrence of chronotropic incompetence and heart rates exceeding the upper rate of the device, thereby compromising biventricular stimulation, was studied. Response was defined as a decrease in LVESV of 10% or more after 6 months.

Results
We included 144 patients. After 6 months 86 (60%) patients were responders. Peak VO2 significantly increased in responders. Chronotropic incompetence wasmore frequently seen in nonresponders (21 [36%] vs 9 [10%], P=0.03), mostly in patients in SR. At moderate exercise, defined as 25% of the maximal exercise tolerance, that is, comparable to daily life exercise, nonresponders more frequently went above the upper rate of the device (13 [22%] vs 2 [3%], P<0.0001), most of whom were patients in permanent AF. Multivariate analysis revealed heart rates not exceeding the upper rate of the device during moderate exercise (OR 15.8 [3.3–76.5], P=0.001) and nonischemic cardiomyopathy (OR 2.4 [1.0–5.7], P=0.04) as predictive for response.

Conclusion Heart rate exceeding the upper rate during moderate exercise is an independent predictor for nonresponse to CRT in patients with AF, whereas chronotropic incompetence is a predictor for patients in SR.

Source: Journal of Cardiovascular Electrophysiology, 2009