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

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Summary

The concept of Closed Loop Stimulation (CLS), recently introduced by Biotronik with the INOS² CLS pacemaker, represents a completely new approach not only to restore proper heart rate, but mostly to improve pacing physiology and patient quality of life. The INOS² CLS detects variations of myocardium contractility by a dynamic measure of right ventricle impedance (RVI) during the systolic phase following a pacing pulse. An INOS² CLS pacemaker was implanted in 40 patients, NYHA Class range I to III, all with chronotropic incompetence and II or III degree AV block. In 8 consecutive patients RVI was recorded during implant and compared with the maximum pressure gradient (dp/dt_{max}) inside the right ventricel (RV) monitored by a multipurpose pressure catheter inserted by femoral vein and positioned in 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. In all patients post-implant follow-up, performed at discharge, 3 and 6 months, included: treadmill exercise test (CAEP), mental stress test (word or color type) and 24 h ECG Holter monitoring. Several typical examples of rate trend during various test conditions are reported to demonstrate the superior hemodynamic performances of CLS pacing. Three patients were selected for a comparative evaluation between INOS² CLS and devices based on single and dual conventional sensor. Even in this case CLS shows 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.

Key Words

Closed Loop Stimulation, physiologic pacing, dp/dt_{max}

Introduction

Sensor driven rate modulated dual chamber pacing is the treatment of choice in the consolidated medical practice for those patients in which the chronotropic reflex is lost or severely impaired. In currently available devices the proper restoration of heart rate depends on two mayor factors: the nature and specificity (i.e. physiology) of the signal detected by the sensor and the complexity of the algorithm regulating the timing of pacing. Several sensors are solely specific to detect physical activity giving signals proportional to body movements or skeletal muscular noise. Other pacemakers detect signals more correlated to metabolic needs (e.g. minute ventilation and evoked QT interval) and, in first approximation, they are more physiologic than the previous ones. Time of response of activity-related sensors is very fast but limited and sometime inappropriate to patient real needs, while "physiologic" sensors have a more appropriate response to real perfusion demand but they response is quite slow [1]. The combination of the two types of sensor in the same device seems to make rate adaptation more proper to physiometabolic requests. Two major limitations remainsin systems using single or dual sensor approach. First, the rate responsive pacing restores an artificial chronotropy, that only in first approximation answers to the real physiometabolic demand, and should be adapted to each patient with a careful programming of the algorithm parameters.

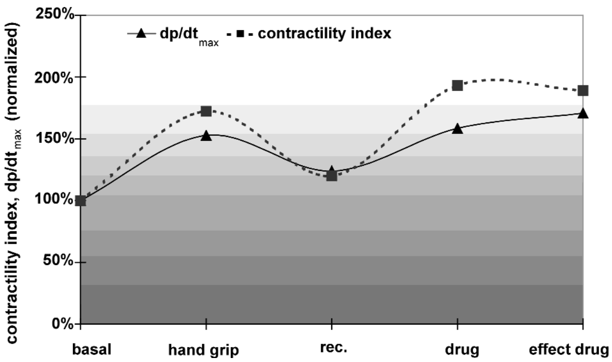

Figure 1. Correlation between mean normalized values of dp/dt_{max} and contractility index averaged ofer 8 patients at different test conditions.

Second, the lack of control by the Autonomous Nervous System does not allow the device to give a "real physiologic control" of the heart rate in all situations in which modulation is required and, moreover, to verify if the induced rate is proper and corresponds to the general status of the patient. In other terms, all these devices are not integrated in the central cardiovascular regulatory system, which operate in closed loop control with medullary centers; then, they are unable to verify, if the cardiac output induced by the rate variation is hemodynamically correct or not [2-4]. Two new pacemakers, using variations of the myocardial contractility in right ventricle (RV) as control parameter, are recently become available: the LIVING BEST (Sorin, Italy) and the INOS² CLS (BIOTRONIK, Germany). The LIVING BEST measures the peak endocardial acceleration (PEA), using a dedicated lead with an accelerometric sensor located inside the ventricular tip electrode. INOS² CLS measures the impedance variations generated by changes of myocardium to blood ratio in the volume around ventricular tip during systole [2, 3]. The control signal detected by the two devices is substantially equivalent, but INOS² CLS does not require a specific sensor or a dedicated lead and, moreover, its control algorithm automatically and constantly learns the patient's physiometabolic status, giving rate increments or decrements according to contingency, and requires to be programmed for lower and upper rate limitation only. Thus, INOS² CLS is a truly closed-loop device fully integrated and managed by the cardiovascular control centers.

The experience reported in this article relates to Closed Loop Stimulation (CLS) using the INOS² CLS system.

Materials and Methods

At present time, more than forty INOS² CLS pacing systems were implanted at the Department of Cardiology of the Catholic University of Rome. In order to show the capability of the Closed Loop Stimulation to yield an individual and adequate dynamic heart rate control, integrated into the natural control circuit, some examples and experiences are reported.

Correlation between dp/dt_{max} and contractility index. During implant procedures the correlation between the dp/dt_{max} measured in right ventricle and the contractility index, i.e. the variation of the right ventricular impedance, detected by the implanted device was performed in 8 consecutive patients, 6 males and 2 females, mean age 57.2 years (range 17-76), NYHA Class range I to III, all with chronotropic incompetence and II or III degree AV block. The contractility index was monitored in conventional DDD mode using a special external device (Unilyzer, BIOTRONIK) connected via telemetry to the implanted device; the RV blood pressure was recorded using a temporary multipurpose pressure catheter inserted by femoral vein. During the procedure all patients were submitted to an exercise test (handgrip) and to isoproterenol infusion at standard dosage. The dp/dt_{max} and the contractility index were measured simultaneously. In all test conditions, the resulting correlation between dp/dt_{max} and contractility index was very good (linear regression $R^2 = 0.91$), in according with the experience of other investigators [5].

Results and Discussion

In Figure 1 is shown the correlation between the mean variation (over 8 patients) of the normalized dp/dt_{max} and corresponding variation of the contractility index during sequential phases of the test. Figure 2 shows a typical example of the trend of contractility index, expressed in arbitrary units, and dp/dt_{max} in a male patient, 58 years old, with SSS and intermittent 2nd degree AV block, NYHA Class I.

Response to physical exercise

Figure 3 shows the course of the pacing rate in a male patient, 70 years old, with SSS and 3rd degree AV block, NYHA Class I, during a treadmill exercise test (CAEP protocol) and pacemaker programmed in

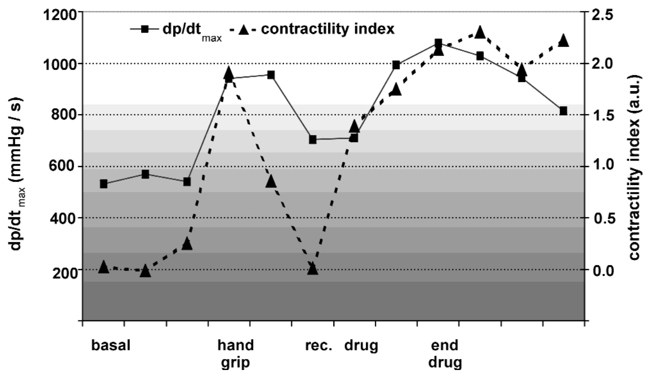

Figure 2. Typical trend of dp/dtmax and contractility index in a patient (male, 58 years) paced in DDD mode.

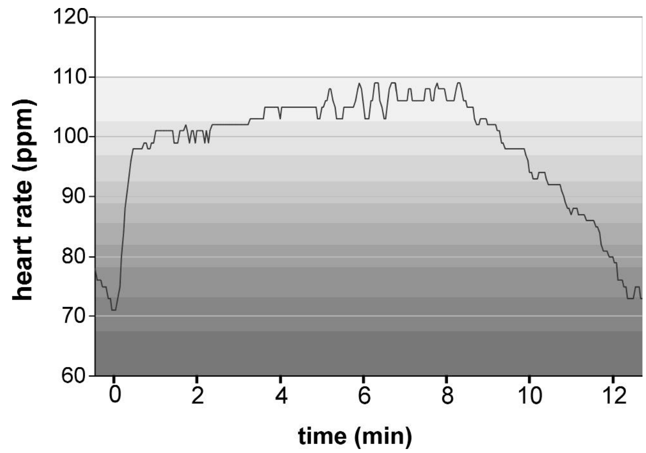

Figure 3. Rate trend in DDD-CLS pacing mode in a patient (male, 70 years) during exercise test.

DDD-CLS mode. The raising slope of the rate at the beginning of the test and the downing slope during recovery are naturally controlled by contractility variation.

Response to mental and emotional stress

In Figure 4, the course of the pacing rate in DDD-CLS mode in a female patient, 49 years old, with SSS and intermittent 2nd degree AV block, NYHA Class I, is depicted during a mental stress test. The first, small increase in hear rate (peak at 7.5 minutes) matches to the time in which the physician explained the test procedure to the patient. The two peaks that follow relate to the two steps of the test.

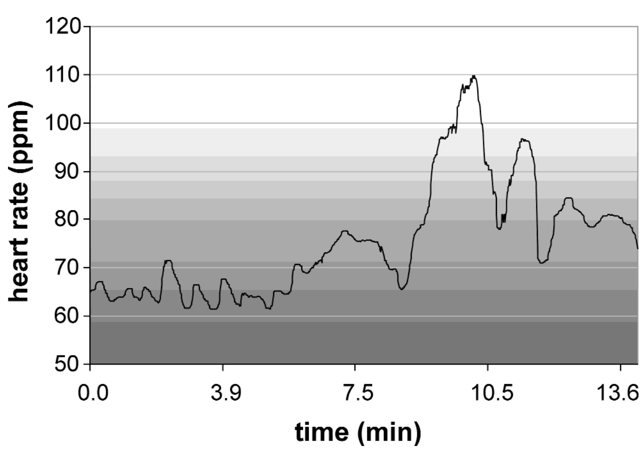

Figure 4. Rate trend in DDD-CLS pacing mode in a patient (female, 49 years) during mental stress.

Rate control during daily life and circadian variations: In all patients a 24 h Holter recording was performed during routine follow-up. All patients reported to have recovered a very good quality of life. Only two patients had seldom sudden wake-up during night with concomitant high pacing rate, probably caused by an hyperactivity of parasympathetic tone during REM sleep, with consequent increase of myocardial contractility. In both patients, the inconvenience disappeared when the sensitivity of the algorithm was reduced by a special re-programming procedure. Figure 5 shows the 24 h trend of heart rate in one of the two previous patients (woman, 49 years old, SSS and intermittent II degree AV block). The hyperactivity of parasympathetic tone is made evident by the large number of high rate peaks that occur even during night. Figure 6 depicts the heart rate during 24 hours in a 67 years old man with SSS, II degree AV block and coronary artery disease. In this patient, the contractility is partially compromised by the coronary disease, but the device properly modulates the rate in an acceptable and safe range of frequency. The evidence that the device operates under the control of the cardiovascular system is represented by the continuous line (6th degree polynomial regression of the rate trend) which corresponds to the natural circadian variations of the heart rate.

Closed Loop Stimulation vs. conventional rate responsive pacing systems

Three patients, all with substantially equivalent characteristics, were selected for a comparative test between closed loop stimulation and conventional

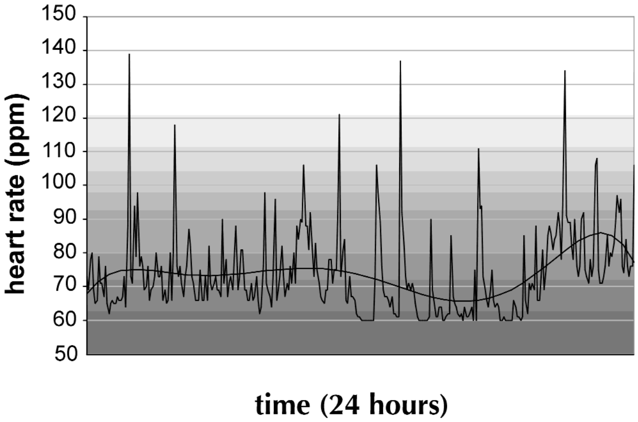

Figure 5. 24 h ECG Holter monitoring in a 49-year-old female patient with hyperactivity of parasympathetic tone during REM sleep.

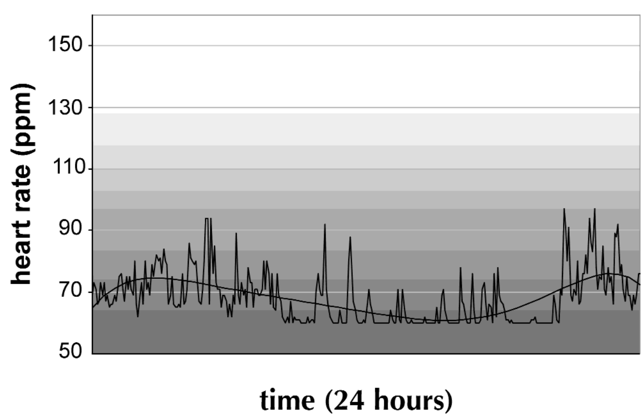

Figure 6. 24 h ECG Holter monitoring in a 67-year-old male patient with coronary artery disease.

DDDR systems. The test was based on a single, consecutive sequence of: an exercise test (handgrip), a mental stress test and an infusion of isoproterenol at standard dosage. The heart rate (HR), the systolic (SABP) and diastolic (DABP) arterial blood pressure were monitored every minute during the test. Common characteristics for all three patients were: male sex, age between 68 and 74 years, SSS (or sinus node dysfunction) and symptomatic AV block, SABP at rest 125-140 mmHg and DABP at rest 75-90 mmHg. Figure 7 shows the trends of a patient an implanted pacemaker model MARATHON DR (Intermedics, Inc., TX), that uses an activity sensor for rate modulation. Figure 8 depicts trends of a patient with a pacemaker model TALENT DR (Ela

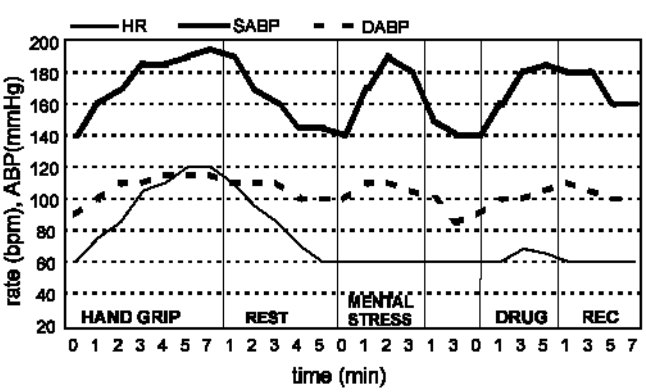

Figure 7. Heart rate (HR), systolic (SABP) and diastolic (DABP) arterial blood pressure in a male patient with single, activity, sensor pacemaker.

Medical, France), that have two combined sensors: minute ventilation and activity. The third patient, which trends are shown in Figure 9, was implanted with an INOS[2] CLS.

Looking at the graphics three considerations can be advanced:

- All three pacemakers show a similar, but not equal, response to physical exercise. The pacemaker operating in closed loop control (INOS[2] CLS) reacts more gradually to exercise and recovers slowly than the other two.
- Only the INOS[2] CLS responds, modulating properly the heart rate, to the mental stress and to drug infusion. The small reactions shoved at the end of the drug infusion and at the beginning of the mental stress by MARATHON DR and TALENT DR respectively should be attributed to body movements of the patient.
- SABP rises to quite high values during each phases of the test in the MARATHON DR, it remains inside acceptable values during exercise in the TALENT DR, but it increases at high levels during mental and drug test. In the INOS[2] CLS, SABP follows the trend of the HR remaining inside the physiological range. DABP is less influenced by HR in all three devices, but, in the patient with the INOS[2] CLS, its trend is more linear.

From this comparison, it becomes evident that only the CLS pacing, integrated in the cardiovascular regulatory system, responds to all contingent metabolic needs of the patient and maintain a proper hemodynamic equilibrium [6].

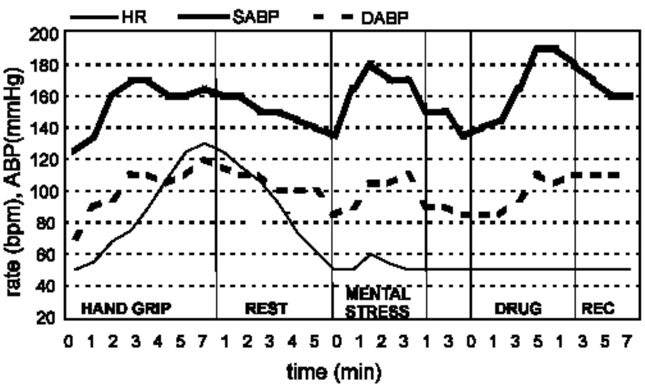

Figure 8. Heart rate (HR), systolic (SABP) and diastolic (DABP) arterial blood pressure in a male patient with dual, minute ventilation and activity, sensor pacemaker.

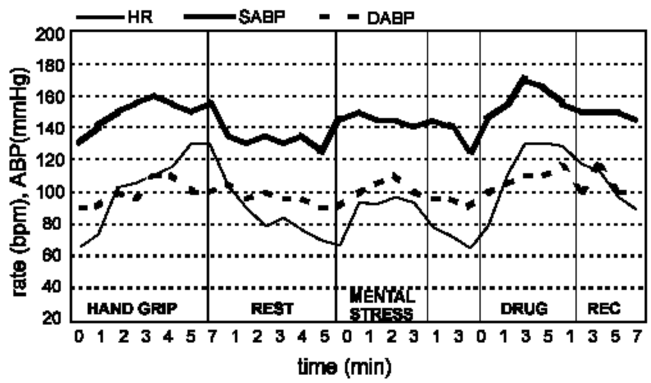

Figure 9. Heart rate (HR), systolic (SABP) and diastolic (DABP) arterial blood pressure in a male patient with Closed Loop Stimulation.

Conclusion

Conventional pacemakers with simple artificial sensors are unable to re-establish functionality to a complex and dysfunctional closed loop cardiovascular system. Closed Loop Stimulation 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.

Our clinical experience shows that Closed Loop Stimulation:

- reacts proportionally to exercise and to unconscious metabolic need in every patient, taking into account individual hemodynamic condition and disease state.
- will not induce excessively high heart rates, which may be harmful to patients with coronary artery disease, and improves their quality-of-life through a proper physiological control.
- can be used in any patient with a previously implanted ventricular lead, since INOS[2] CLS system does not require a specific sensor to detect variations in contractility.

Closed Loop Stimulation is expected not to be limited to therapy of chronotropic incompetence only [7-9]. Neural messages coming from circulatory system play a significant role in the genesis of several cardiac arrhythmias. That way, a closed-loop stimulating device, integrated in the cardiovascular control system, will act as a monitor of the sympathetic activity and may drive preventive therapies in order to avoid or limit effects of the occurring arrhythmic event.

References

[1] Lau CP. Rate Adaptive Cardiac Pacing: Single and Dual Chamber. New York. Futura publishing Co. 1993.

[2] Schaldach M, Hutten H. Intracardiac impedance to determine sympathetic activity in rate responsive pacing. PACE. 1992; 15: 1778-1786.

[3] Pichelmaier AM, Braile D, Ebner E, et al. AND Controlled Closed-Loop Cardiac Pacing. PACE. 1992; 15: 1787-1791.

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

[5] Osswald S, Gradel Ch, Crohn T, et al. Correlation of Intracardiac Impedance and Right Ventricular Contractility During Dobutamin Stress Test. Cardiac Arrhythmias. 1997: 87.

[6] Malinowski K. Interindividual Comparison of Closed Loop Stimulation and Rate-adaptive Sensor Systems. Prog Biomed Res. 1996; 3: 56-60.

[7] Pichelmaier AM, Ebner E, Greco OT, et al. A Multicenter Study of a Closed-Loop ANS-controlled Pacemaker System. PACE. 1993; 16: 1930.

[8] Van Woermsen J, Van Kempen L, Res JCJ, et al. ANS Controlled Closed-Loop Cardiac Pacing - A Multicenter Study. Prog Biomed Res. 1996; 1: 13-16.

[9] Res JCJ, Van Woermsen RJ, Malinowski K, et al. Dual Chamber Pacing and Closed-Loop Regulation - Clinical Results. Prog Biomed Res. 1996; 2: 27-30.