Closed Loop Stimulation: A New Philosophy of Pacing

P. ZECCHI, F. BELLOCCI
Università Cattolica, Policlinico Gemelli, Division of Cardiology, Rome, Italy

A.P. RAVAZZI, P. DIOTALLEVI
S. Antonio e Biagio Hospital, Division of Cardiology, Alessandria, Italy

R. AUDOGLIO
S.R.A., Pavia, Italy

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 $INOS^2$ 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/dt_{max} 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 $R^2 = 0.91$). 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.

Key Words

Closed Loop Stimulation (CLS), right ventricular impedance (RVI), contractility rate

Introduction

When chronotropic competence is lost or severely impaired, then dual chamber pacing is the treatment of choice in the consolidated medical practice. It provides rate modulation driven by a sensor that detects signals that are in some way related to the contingent metabolic needs of the patient.

In currently available devices, proper restoration of heart rate depends on two major factors:

- the nature and specificity of the signal detected by the sensor, and
- the complexity of the algorithm regulating the timing of pacing.

Several sensors are of the accelerometric or piezoelectric type, that give signals proportional to body movements or skeletal muscular noise, and, then, are solely specific to detect physical activity. Others detect phenomena related more to metabolic needs (e.g., minute ventilation and evoked QT interval) and, in first approximation, they are more physiologic than the previous ones. The time of response of activity-related sensors is very fast, but limited and sometimes inappropriate to the patient's actual needs; while "physiologic" sensors have a more appropriate response to perfusion demand; their response is nevertheless quite

slow [1]. The combination of the two types of sensors in the same device seems to make rate adaptation more appropriate to physio-metabolic requirements.
Systems that use a single or dual sensor approach continue to have two major limitations. First, rate responsive pacing restores an artificial chronotropy, which only responds to the real metabolic needs in an initial approximation and should be adapted to each patient through careful programming of the algorithm parameters. Second, the lack of control by the autonomous nervous system (ANS) does not allow the device to give a "natural control" of the heart rate in all situations in which modulation is required nor to verify whether the induced rate is appropriate and in accordance with the general status of the patient. In other words, all of these devices are not integrated into the central cardiovascular regulatory system, which operates in closed loop control with the medullary centers. Then, they are unable to verify whether the cardiac output, induced by rate variation, is hemodynamically correct [2].
The INOS² CLS pacemaker (Biotronik, Germany) is the first and only sensor-free device that operates in a closed loop with the cardiovascular system. It detects variations of the myocardial contractility in the right ventricle, measuring the impedance variations generated by changes of myocardium-blood ratio in the volume around the ventricular tip during systole [2-3]. The control signal does not require a specific sensor or a dedicated lead to be detected. Moreover, its rate control algorithm automatically and continually learns a patient's physio-metabolic status, giving rate increments or decrements according to contingency, and requiring programming for lower and upper rate limitation only.
The experience reported in this article relates to an intensive clinical investigation that was conducted in order to evaluate the benefits of CLS using the INOS² CLS system.

The Concept of Closed Loop Stimulation

The concept of CLS represents a completely new philosophy of physiological pacing and improvement of the patients' quality of life. In order to understand CLS fully, a concise review of basic mechanisms of cardiovascular regulation is necessary [4].
The regulation mechanism of the circulatory system is highly complex and provides an appropriate perfusion to all parts of the body in all contingencies. It operates in a closed loop system, which reacts to external influences in a manner that is appropriate to the individual patient. In addition, it maintains an appropriate mean arterial blood pressure (MABP) whenever the organism changes its conditions (e.g., during physical exercise, changes in posture, increases in temperature, mental stress, etc.). When a biologic transducer (e.g., baroreceptor, mechanoceptor, chemoceptor, etc.) detects deviations from the current value in the controlled variable, a message is sent to the central nervous system, that reacts by modulating an countereffect, which, as a result, causes a change in the regulated parameter (e.g., cardiac output).
The primary characteristic of a closed loop control is its negative feedback. This means that whenever a parameter deviation is detected in one direction, the control causes changes in the opposite direction in order to compensate for the deviation.
As the MABP is influenced by both the cardiac output (CO) and the total peripheral resistance (TPR), it is continuously measured by the baroreceptors in the aortic arch and the carotid sinus. The output of the baroreceptors is transmitted and integrated into the medullary circulatory control center with other incoming signals from the cerebral cortex. The sympathetic and parasympathetic branches of the ANS influence both cardiac function and peripheral vasoconstriction, continuously adjusting CO and TPR. Inside the heart, the three parameters that are kept under control are chronotropy, which exerts the largest influence on the CO, inotropy (contractility), and dromotropy (atrioventricular conduction time). Thus, the ability to react to physical and psychological stress greatly depends on the regulation of the cardiac function under normal physiologic conditions.
In patients whose cardiac regulation mechanisms are impaired (e.g., in SSS), the closed loop control of the circulatory system in general is still functional. The circulatory centers attempt to compensate chronotropic and, by consequence, dromotropic incompetence by increasing inotropy, the remaining intact control mechanism. But CO can be regulated by adjusting the contractile force of the myocardium only within certain limits and with increased stress on the myocardial fibers. Thereafter, the patient's maximum exercise and stress capability is severely affected since his the cardiac requirements can no longer be met.
The role of CLS is to maintain natural cardiovascular regulation by integrating the device into the system.

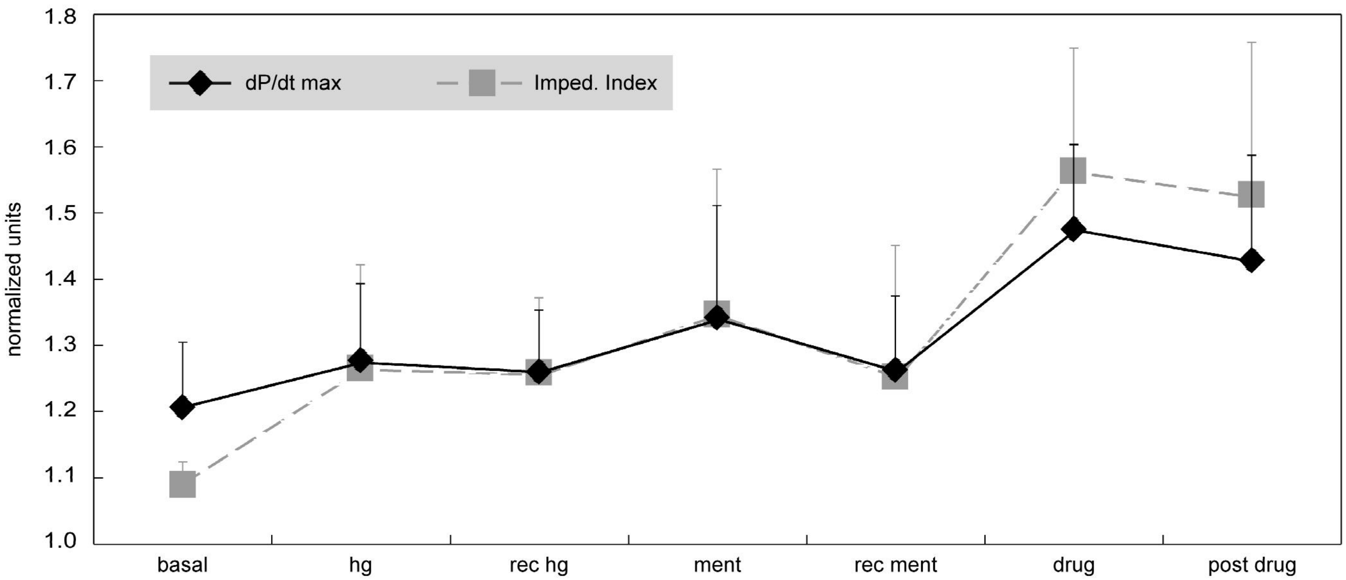

Figure 1. Mean correlation between normalized dP/dt_{max} and impedance index measured by the implanted device and programmed in non-rate responsive DDD mode. The contractility index is expressed in arbitrary units.

In this case, the heart rate will be controlled by the circulatory centers instead of an artificial, and always limited, algorithm. Since the dynamics of the myocardial contractile force still reflect the information from the circulatory center even under patho-physiologic conditions (e.g., sinus node disease, cardiomyopathy, etc.), one possibility of realizing a closed loop pulse generator is to convert the changes in myocardial contractility into individual stimulation rates. With such a device, the pacing rate is linked to the circulatory centers, and an adequate perfusion is enabled under various conditions.

Clinical Experiences

At the present time, more than eighty INOS[2] CLS pacing systems have been implanted in our two Departments of Cardiology. In order to verify the capability of CLS to provide an individual, hemodynamically adequate heart rate control, distinct groups of patients were submitted to different clinical tests. The results and some examples of this experience are reported below.

Correlation between dP/dt_{max} and the Contractility Index

During implant procedures, the correlation between the dP/dt_{max}, invasively measured in the right ventricle, and the contractility index, telemetrically detected by the implanted device, was performed in 15 consecutive patients (12 males and 3 females, mean age 64.5, all with chronotropic incompetence and II or III degree AV block, NYHA class range I to III). The impedance index was continuously monitored using a dedicated device (UNILYZER, Biotronik) connected to a lap top PC programmer. During the procedure, all patients were subjected to an exercise test (handgrip according to the patient's limit), a mental stress test, and to isoproterenol infusion (standard dosage). The dP/dt_{max} and the contractility index were measured simultaneously and trends were compared. A good correlation was found between the two parameters (mean R^2 = 0.91) as shown in Figure 1.

Response to Exercise

Sixty-two patients were submitted to a treadmill exercise test (CAEP protocol according to the patient's limit). In all patients, the heart rate (HR) trend was appropriate, with rate acceleration and deceleration in accordance with the individual MABP monitored trend. Figure 2 shows the typical HR course induced by CLS in a 70-year old male patient with SSS, 3rd degree AV block, NYHA class I, during a treadmill exercise test. The rising slope of the rate at the

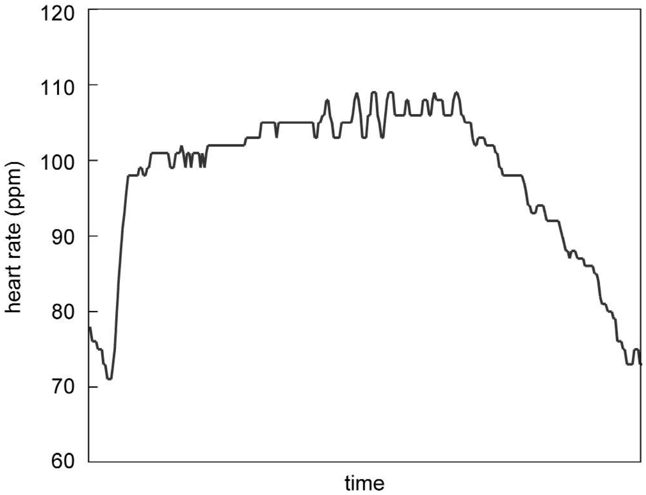

Figure 2. Typical example of induced heart rate trend during treadmill test.

beginning of the test and the downward slope during recovery are naturally controlled by myocardial contractility variations.

Response to mental and emotional stress

Forty-five patients were submitted to a mental stress test (color words - two steps). All patients showed prompt and appropriate HR modulation, not only during the two steps of the test, but even during the test's preliminary phase in which the patient became emotionally involved by the physician's explanation of the test procedures. Figure 3 depicts the course of the paced rate in a 49-year old female patient with SSS and intermittent 2nd degree AV block, NYHA class I, during the mental stress test. The first peak, at min. 7.5, corresponds to the time in which the physician explained the test procedure. The two peaks that follow relate to the two steps of the test.

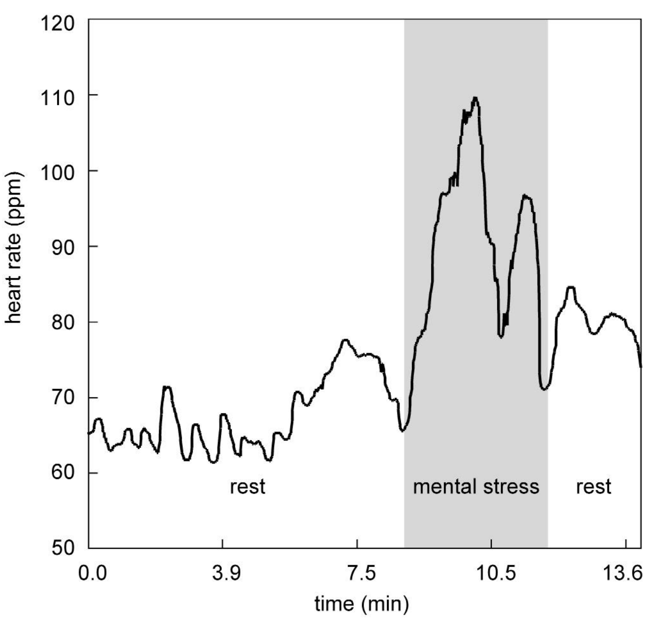

Figure 3. Induced heart rate during mental stress test.

Rate Control in Daily Life

For all 80 patients, during the scheduled 3rd month follow-up a 24-h ECG Holter recording was performed and a simple Quality of Life (QoL) questionnaire was completed. The questionnaire evaluation showed evidence that all patients had recovered a high level of quality in their daily lives.

The analysis of the Holter recordings showed a correct and specific dynamics of HR modulation during the entire monitoring time. A 6th degree polynomial regression of the HR trend was performed for all records. The trend expressed by this mathematical operation matched with the natural circadian variations of the HR, showing evidence that CLS operates under the control of the cardiovascular system.

Only two patients reported a rare, sudden experience of waking-up during the night, with a concomitant high paced rate. The Holter and ambulatory analysis showed that such rate increases were caused by hyperactivity of the parasympathetic tone during REM sleep in one patient and by supine postural conditions in the second, both inducing an increase of myocardial contractility. Two significant examples are reported in the following figures.

Figure 4 shows the 24-hour trend of HR in a 49-year old female patient with SSS and intermittent 2nd degree AV block. The large number of high rate peaks, which occur even during night, makes the hyperactivity of parasympathetic tone evident.

Figure 5 depicts the HR course during a 24-hour period in a 67-year old man with SSS, 2nd 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 frequency range.

In both figures, the continuous line represents the 6th degree polynomial regression of the HR trend, which corresponds to the circadian rate variations.

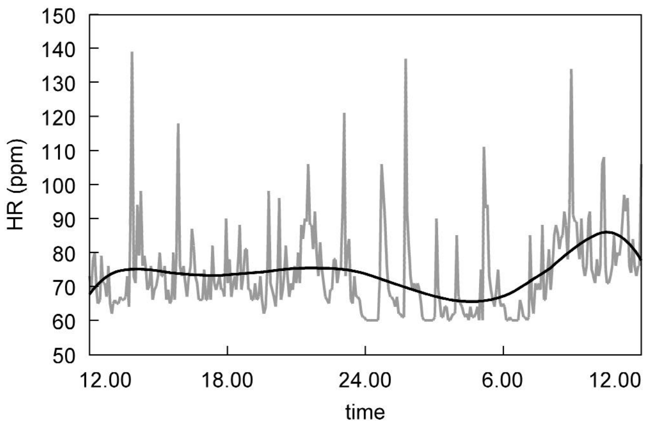

Figure 4. 24-hour rate trend: woman, 49- years old, SSS and intermittent 2nd degree AVB.

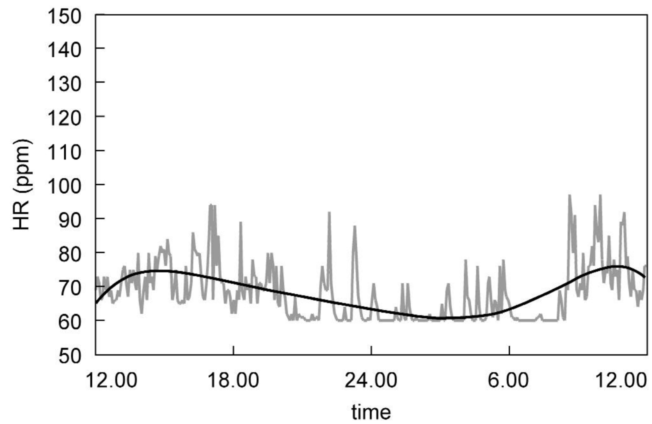

Figure 5. 24-hour rate trend: man, 67- years old, SSS, 2nd degree AVB and coronary artery disease.

Closed Loop Stimulation vs. Conventional Rate Responsive Systems

Three patients, all with substantially equivalent characteristics, were selected for a comparative test between CLS and conventional DDDR pacing. The test was based on a single, consecutive sequence of an exercise test (treadmill, 6 min. walking), a mental stress test (color words - one step), and provocative drug test (infusion of isoproterenol at standard dosage). The HR, the systolic (SABP), and diastolic (DABP) arterial blood pressure were monitored every minute during the test sequence. Common characteristics for all three patients were: male gender, age 70 ± 3, SSS (or sinus node dysfunction) and symptomatic AV block, SABP at rest 130 ± 10 mmHg, DABP at rest 70 ± 10 mmHg, no evidence of coronary artery disease, and the pacemaker implanted at least six months before the test.

The first patient (Figure 6) was implanted with a DDDR pacemaker (Marathon DR, Intermedics, Belgium) that uses an activity sensor. The second patient (Figure 7) received a Talent DR (Ela, France) pacemaker that modulates the pacing rate using two combined sensors: minute ventilation and activity. The third patient (Figure 8) was implanted with an INOS² CLS pacemaker.

Looking at the trends depicted in Figures 6, 7 and 8, three considerations can be advanced:

- All three pacemaker models show a similar, but not equal, response to exercise. The pacemaker operating in closed loop control (INOS² CLS) reacts in a more physiologic manner, during both stress

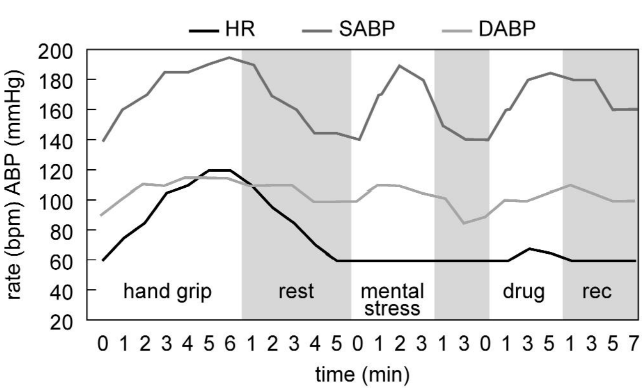

Figure 6. HR, SABP and DABP trends in a patient with a DDDR pacemaker with an activity sensor.

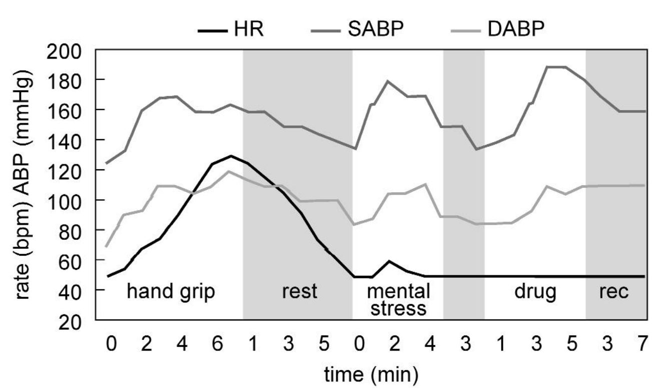

Figure 7. HR, SABP and DABP trends in a patient with a DDDR pacemaker with a dual sensor: minute ventilation and activity.

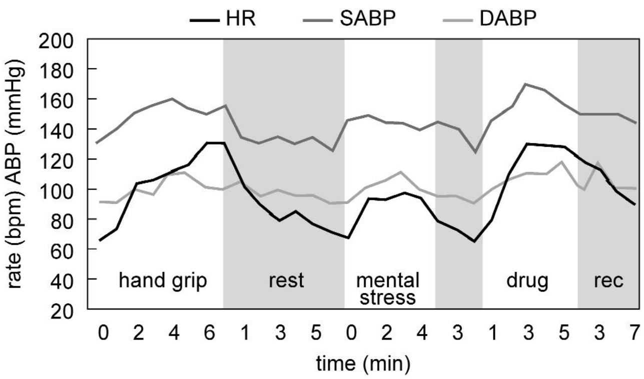

Figure 8. HR, SABP and DABP trends in a patient with an INOS² CLS pacemaker.

increase and recovery, than the other two devices.

- Only the CLS responds to mental stress and drug infusion by properly modulating the HR. The small reactions of Marathon DR that were shown at the end of drug infusion should be attributed to the patient's body movements. During mental stress, Talent DR shows some modulation of HR, which is not sufficient to prevent the excessive increase of SABP.
- In the Marathon DR, SABP rises to high values during each phase of test. With the Talent DR, SABP remains within acceptable values during exercise but increases to high levels during the mental and drug tests. The INOS² CLS follows the trend of the HR, remaining within the physiological range. In all three devices, DABP is less influenced by HR, but in the patient with the INOS² CLS the trend is more linear.

From this comparison, although currently limited in its patient sample size, it seems evident that only the CLS responds to all contingent metabolic needs of the patient and maintains a proper hemodynamic equilibrium [6].

Conclusion

Conventional DDDR pacemakers with simple artificial sensors are unable to re-establish functionality to a complex and dysfunctional cardiovascular system. Closed Loop Stimulation preserves intrinsic circulatory regulation and integrates the pacemaker into the natural control system, enabling the heart rate to be managed by the ANS and not by an artificial pacing algorithm.

Our clinical experience shows that CLS:

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

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

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