# Heart Rate Response Using Closed Loop Stimulation in Chagasic Patients

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## Summary

*To treat chronotropic incompetence, rate-responsive pacemakers based upon various sensor signals have been developed. A more attractive form of rate-responsive pacing tries to restore the physiologic control mechanism using information obtained from the autonomic nervous system; it is thus defined as Closed Loop Stimulation. Intracardiac impedance measurements with standard ventricular leads allow monitoring the myocardial contraction status, which depends directly on the sympathetic nervous system tone. Based on this principle, a Closed Loop Stimulation system is realized which will be discussed in the present work, followed by a brief description of its performance in practice. Since 1997, we have implanted cardiac pacemakers controlled by the autonomic nervous system in 160 patients, 87 of them suffering from chronic Chagas' disease. Several examinations were performed, such as clinical exercise protocols, 24h Holter ECG monitoring, evaluation of the physiologic rate response, and monitoring of the arterial blood pressure during the examinations, including emotional and mental stress tests. We have observed that this rate-responsive pacemaker shows long-term stability and has principal advantages over conventional open-loop rate-responsive pacing systems.*

## Key Words

Heart rate response, intracardiac impedance, myocardial contraction, autonomic nervous system, closed loop stimulation

## Introduction

The main task of the cardiovascular system is to supply an adequate and uniform perfusion to all organs of the body. The perfusion level depends on the mean arterial blood pressure (MABP), as well as on the organs' total peripheral resistance (TPR). Therefore, the sustaining of an MABP sufficient to supply enough blood under different conditions, such as physical exercise, different body postures (orthostatic), temperature variation, or mental stress, plays a key role in cardiovascular control. Under normal physiologic conditions, the psychological and physical abilities are highly dependent on the cardiac function regulation by the autonomic nervous system (ANS). Under physio-pathologic conditions (i.e., blood loss, fever), the ANS makes a significant contribution to sustaining the vital functions. In general, the ANS influences the heart not only through the nervous system, but also through the humoral system, which uses hormones, such as adrenaline from the sympathetic nervous system.

If the sinus node function alters, chronotropy as one of the two primary ANS regulation mechanisms will fail. Thus, the ANS cannot regulate the heart rate anymore. Inotropy, the influence on myocardial contractility remains intact. Basically, cardiac output (CO) can be increased, within certain limits, through a sympathetically mediated cardiac contraction increase. However, a maximum increase in the ejection factor by factor of 1.5 usually fails to compensate the blood pressure drop associated with the peripheral arterial vasodilatation in the active muscles. Even with moderate physical exercise, the CO should double to guarantee an adequate perfusion to several muscles in which the demand quadruples.

Without sufficient CO adjustment, the corresponding decrement in the perfusion pressure of the muscle sys-

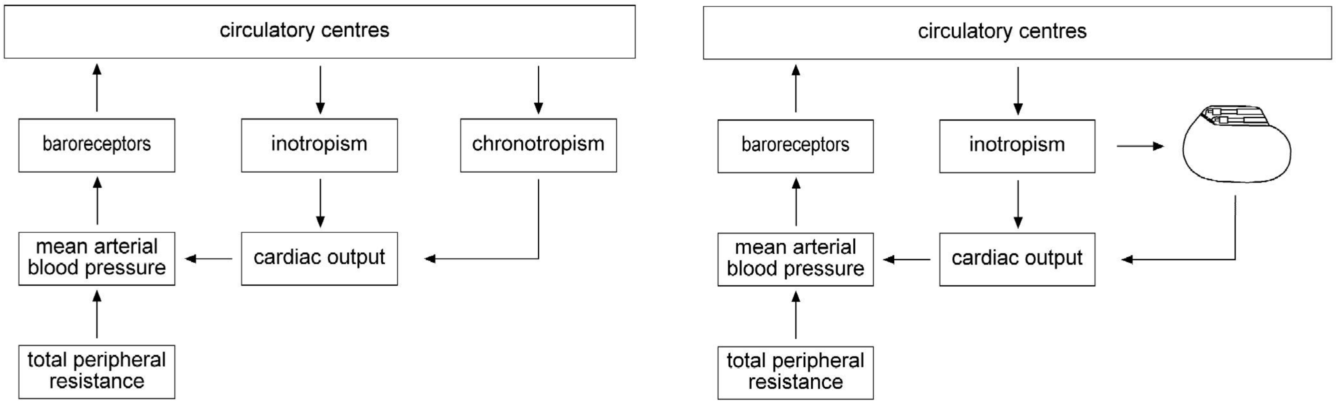


*Figure 1. Natural cardiovascular control loop, whereby heart rate is adjusted according to hemodynamic needs by circulatory centers via the ANS (left); rate regulation by monitoring myocardial contraction dynamics with a CLS pacemaker in case of chronotropic incompetence (right).*

tem will result in an inadequate oxygen supply. Therefore, physical capacity will be severely limited, unless the used pacemaker allows an adaptation of the pacing rate related to the exercise level.

Of all strategies used to adapt the heart rate response to cardiac pacing in chronotropically incompetent patients, the most attractive one is restoring the physiologic closed-loop chronotropic control. Conventional pacemakers, which provide rate modulation through sensitivity to physical activity, central venous blood temperature, or respiratory parameters, can only measure specific effects of different activities in an open-loop approximation. Such systems are not capable of reacting adequately to influences where the respective sensor is not being affected; for example, activity sensors are not capable to respond to emotional stress. In general, conventional heart rate adaptation systems are based upon measuring isolated control parameters, which are not part of the cardiovascular control system. Such kinds of system have a reduced specificity for certain types of physiologic and psychological stress in contrast to pacemakers controlled by the ANS. Under physiologic conditions, the ANS adjusts the CO to meet the metabolic and hemodynamic demands. This adjustment is performed by a closed-loop control system, consisting of the baroreceptor reflex controlling the MABP, the afferent passage to the medulla oblongata, the circulation control center in the medulla, the efferent nerves of the sympathetic and parasympathetic nervous systems, the cardiac action as a servo-element for the CO, and the peripheral circulation action as a servo-element for the TPR. In the natural cardiovascular control loop, the ANS transfers relevant hemodynamic information, especially variations of the MABP detected by the baroreceptors, to the circulatory centers, which will adjust inotropic and chronotropic regulation in accordance with the hemodynamic needs. Even in case of chronotropic incompetence, the ANS information remains available in the heart through myocardial contractility (Figure 1). Consequently, a pacemaker monitoring the myocardial contraction status is incorporated in the natural control loop. The corresponding heart rate regulation is called Closed Loop Stimulation (CLS) [1-4]. In principle, closed-loop pacemakers with heart rate adaptation are better than those that function as open-loop systems. Due to the closed-loop heart rate control, they can respond to different physical and psychological circumstances. Our study examined the heart rates resulting after implantation of a CLS pacemaker in a group of 160 patients.

## Materials and Methods

After implantation of an ANS-controlled pacemaker and a manual or automatic (3 - 5 days) calibration procedure, respectively, all patients were subjected to the same examination procedures during each evaluation. Physical exercise was performed according to a standard protocol, using an ergometer and increasing the exercise load gradually, up to 80 % of the maximum level supported by the patient. This process also eval-

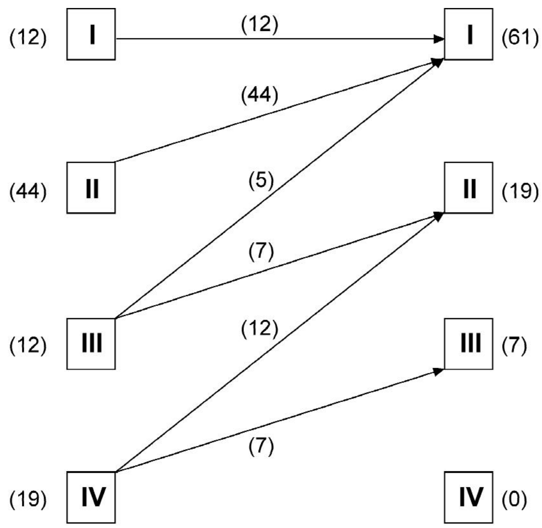


*Figure 2. Pre-implant and post-implant NYHA functional class in 87 patients suffering from the chronic (auto-immune) form of Chagas' disease.*

uated orthostatic effects (to lie, to sit, to stand up), besides walking upstairs and downstairs. The pacing system controlled by the ANS is highly sensitive to changes in the sympathetic tone, and is therefore affected not only by changes caused by physical exercise, but by psychological stress, such as anxiety, excitement, and mental stress, as well.

## Results

Since 1997, 160 ANS-controlled pacemakers (Inos$^2$ DR, Inos$^2$ CLS, and Inos$^{2+}$ CLS, all from

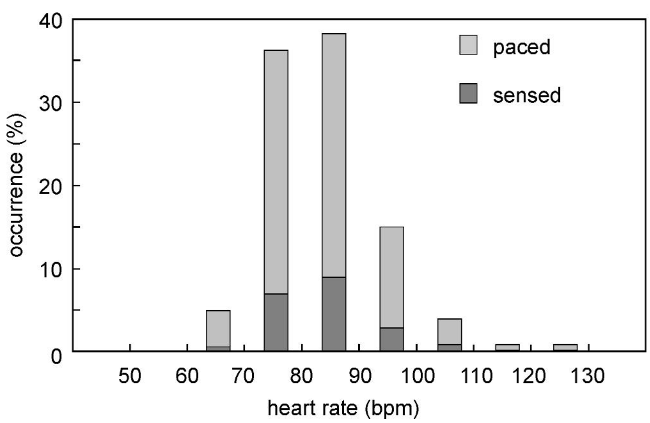


*Figure 3. Frequency histogram of sensed and paced atrial events measured by the pacemaker diagnostic functions during a follow-up period of several months.*

Biotronik, Germany) were implanted in patients (87 male, 73 female) with a mean age of 64 ± 9 years. The mean age is relatively low because 87 patients (54.3 %) suffered from the chronic (auto-immune) form of Chagas' disease. The NYHA functional rating showed an improvement from 2.4 at the pre-implant phase to 1.4 in the post-implant phase (Figure 2). Obviously, adequate heart rate regulation had been restored, which can be seen by, e.g., the appropriate rate distribution that was comparable to that of healthy subjects (Figure 3).
From the mean heart rates of chagasic patients (Figure 4 left), it becomes evident that the response to physical exercise was adequate. Moreover, in contrast to conventional rate-adaptive pacemakers, CLS is able to adjust heart rates according to mental stress, too (Figure 4 right).

## Discussion

It has been reported that artificial cardiac stimulation with rate adaptation improves the symptoms and the patients' quality of life, when compared to fixed-rate stimulation [5-8]. Studied patients whose implanted pacemakers were controlled by the ANS reported a better quality of life and a more active life, and they were more confident about their cardiac condition and their pacemakers. This is not a surprise, since the heart rate adaptation, particularly during exercise, provides them with a protection against myocardial overload. They also noticed a more appropriate heart rate increase with physical activity and psychological stress, associated with routine activities.

### *Comparison to Conventional Rate-responsive Pacemakers*

The presented system monitors the ANS influence on the cardiovascular system by evaluating the myocardial contraction status through measurement of the myocardial impedance. Clinical studies showed a significant advantage of this mechanism for physiologic circulation control of cardiac activity, which maintains the MABP within physiologic limits and offers an improved perfusion of the upper cerebral structures. The pacemakers controlled by the ANS are not encumbered with the disadvantages of rate-adaptive pacing systems that use movement, temperature, and respiratory sensors [9]. Such disadvantages include sensitivity to passive movements (movement sensor), or long response delay, or sensitivity to speech (respiratory sensor); in case of multiple sensors, calibration of the

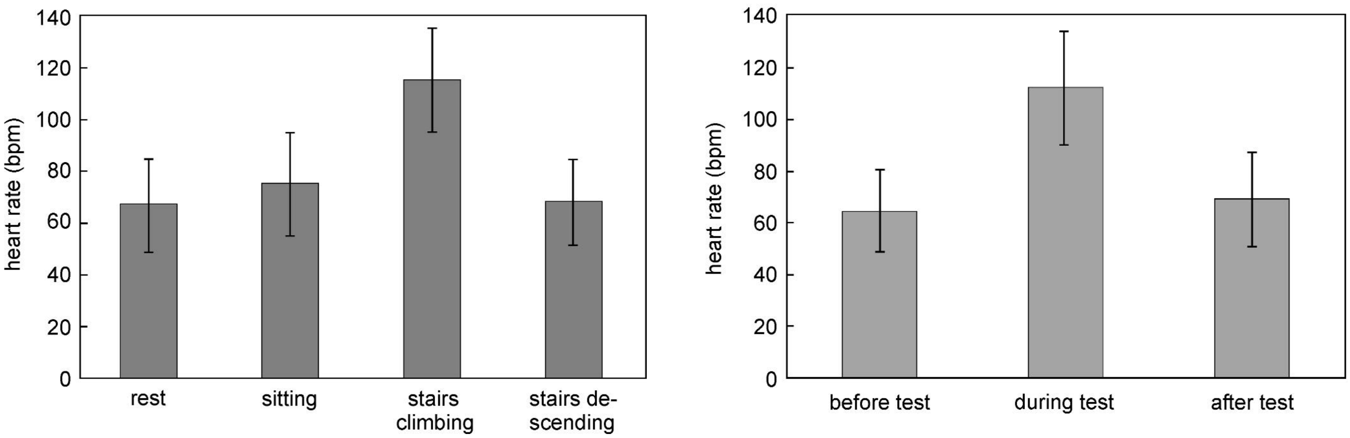


*Figure 4. Variation of mean heart rates in 87 patients suffering from the chronic (auto-immune) form of Chagas' disease during different physical exercise tests (left) and during and immediately after an arrythmetic test (right) .*

different sensor inputs is problematic [10]. The open-loop systems bring an additional external factor to which the systemic circulation must adapt. The ANS-controlled pacemakers do not need adjustments such as gain, sensibility, sensor-response curves increment and decrement, and night program, nor sensor adjustment tests, such as exertion and other exercise.

*Closed Loop Stimulation in Chagas' Disease Patients*

A large group of our patients (87) suffered from the chronic form of Chagas' disease. The clinical symptoms of chronic Chagas' disease include the development of a dilated, diffuse and progressive cardiomyopathy, with alterations in the cardiac dromotropy, chronotropy, and inotropy. The arrhythmogenic form is frequently accompanied by polymorphous ventricular extrasystoles, sustained and non-sustained ventricular tachycardias, AV block, and several hemi-blocks. Sinus node disease usually accompanies Chagas' disease due to its characteristics of autonomic denervation. We usually observe relevant bradycardia and atrial instability with episodes of atrial paroxysmal fibrillation. Fibrillation and atrial flutter are common at late stages. Congestive heart failure is frequently present, which usually evolves slowly, and the signs of right cardiac insufficiency, such as jugular turgescence, painful hepatomegaly, and edema of the lower limbs should be pointed out. Pulmonary and systemic thromboses result from cardiac mural thrombosis [11].

Cardiac pacing plays a fundamental role in the treatment of these patients, who represent today 65 % of our cases. The system chosen consists of the DDD-CLS with short (100 to 150 ms) and dynamic AV interval. Closed-loop cardiac stimulation brings several benefits to Chagas' disease patients, due to its instantaneous auto-regulation. With myocardial contractility as sensor input, rate adaptation is even possible when congestive heart failure is present, so these patients can also benefit from a physiologic adaptation of the heart rate. Right-ventricular bifocal pacing and biventricular pacing have been performed in patients suffering from advanced cardiomyopathy.

## Conclusions

The results obtained during our extensive clinical study demonstrate the applicability of the ANS-controlled closed-loop pacing system, based on monitoring myocardial contractility. The variation of the pacing rate during different types of exercise resulted in a CO sufficient to maintain the MABP within physiologic limits. In sinus node disease patients, the change in the pacing rate at the beginning of the exercise, as well as during recovery, showed a typical physiologic response. There is also a clear indication that the system controlled by the ANS functions during emotional and mental stress. One of the major benefits of closed-loop cardiac stimulation is the correction of the pacing rate during persistent disturbances. Our experience confirmed the excellent stability of the heart rate adaptation performance on a long-term basis for this type of sensor, controlled by the ANS. State-of-the-art devices with Closed Loop Stimulation have optimized diagnosis and statistics features. They are easily programmable and handling of the sensor parameters is easy. Due to their automatic and continuous adjustment of sensor parameters, these systems provide a more physiologic heart rate adaptation.

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