What is Closed Loop Stimulation ?

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Summary

Improving the patient's quality-of-life has become a focal point in the development of new and optimized techniques for electrostimulation of the heart. In an effort to make such improvements a reality, sensor-controlled rate-adaptive pacemakers try to mimic the heart rate variation in response to the changing exercise state of the patient with artificial external sensors. The Closed Loop Stimulation concept pursues an alternative course: The stimulation device is integrated into the Closed Loop of the circulatory control system. In patients with dysfunctional control mechanisms, the general regulation system is usually still intact. Therefore, it should be possible to preserve natural regulation rather than adding an external control mechanism which is unable to interact with the circulatory system. Analyzing the dynamics of myocardial contraction presents a way to create an interface between the pacemaker and the circulatory control system. A Closed Loop pacemaker based on this concept is already in clinical application. Clinical experience confirms the theoretically expected comparability in heart rate response between healthy people and pacemaker patients with an implanted Closed Loop system. As a consequence of the Closed Loop principle, the regulated heart rate takes into account the individual state and disease of the patient. Heart rates in young, physically fit patients reach much higher levels and dynamic ranges than those in patients with coronary heart disease. Moreover, the Closed Loop concept is not limited to the therapy of chronotropic incompetence. Additional applications, such as the prevention and therapy of arrhythmias, can be developed from these implantable devices that are integrated into the Closed Loop cardiovascular control system.

Key Words

Closed Loop Stimulation, circulatory control system, myocardial contraction

Introduction

New developments in therapeutic and diagnostic devices increasingly highlight the need for not only limiting symptoms but improving the patients' quality-of-life. This important goal is achieved by extending both the functionality and handling properties, thereby making the device safe, effective and easy-to-use. To this end, several innovative tools have been introduced during the last 40 years of implantable cardiac pacemaker development.

In contrast to the currently available sensor-controlled rate-adaptive pacing systems, the concept of Closed Loop Stimulation represents a completely new approach to improving the patients' quality-of-life. The basic simplicity of this concept also minimizes the level of programming required between the physician and the implanted device. The aim of this paper is to illustrate the central concept of this new principle in cardiac pacing and to discuss the resulting consequences of Closed Loop Stimulation in clinical application. The basic mechanisms of cardiovascular regulation are presented as an introduction to the understanding of Closed Loop Stimulation.

Closed Loop Control

Closed Loop Control is a basic principle of regulation in the human body, as well as in various systems in everyday life. In the body, it is used whenever an intrinsic parameter of the organism (e.g., body temperature, blood pressure, blood-glucose level, etc.) needs to be kept within certain limits, in spite of environmental disturbances.

The concept of Closed Loop Control is shown in a simplified form in figure 1. A transducer detects devia-

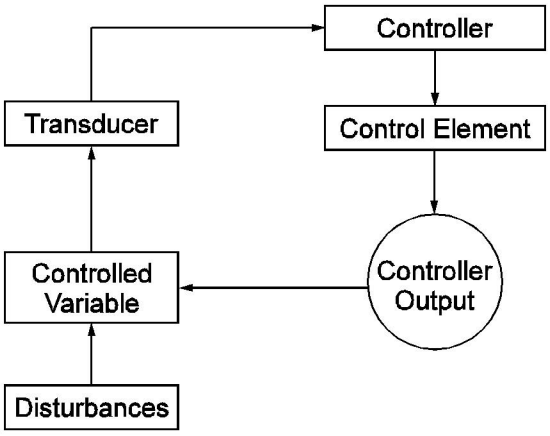

Figure 1. The principle of Closed Loop Control.

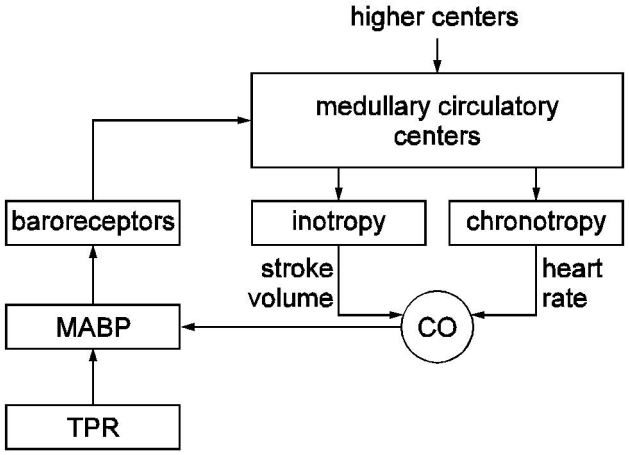

Figure 2. Cardio-circulatory Closed Loop Control.

tions of a controlled variable from its current set point. The controller processes the transducer input and modulates the effector which then causes a change in the regulated parameter. Thus, one of the main characteristics of Closed Loop Control is negative feedback: if the transducer detects parameter deviation in one direction, the control center causes a change in the opposite direction in order to compensate for the deviation.

The circulatory regulation system

The circulatory regulation of the human body is a complex and highly developed system that provides an appropriate perfusion to all parts of the body in all situations of daily life. It is a very specialized Closed Loop system which reacts to external influences in an individual and diverse manner. Maintaining an appropriate MABP under differing conditions (e.g., physical exercise, different postures (orthostasis), temperature changes, or mental stress) is a key part of cardiovascular control.

Figure 2 shows the cardiovascular regulatory system depicted as a Closed Loop. The MABP is affected by both the cardiac output (CO) and the total peripheral resistance (TPR). The MABP, which is the controlled variable, is continuously measured by the baroreceptors in the aortic arch and the carotid sinus. The baroreceptor output is conducted to the medulla oblongata via afferent nerve pathways and are integrated in the medullary circulatory control center with other incoming signals from the cerebral cortex (higher centers). Efferent nerves i.e., the sympathetic and parasympathetic branches of the autonomic nervous system influence cardiac function, as well as peripheral vasoconstriction, resulting in a continuous adjustment of CO and TPR. The most important controlling organ (effector) is the heart and its cardiac output (CO) as determined by the product of stroke volume (SV) and heart rate (HR).

Sinus node depolarization rate is adjusted over a wide range (chronotropic adaptation), thus exerting the largest influence on the CO. Myocardial contractility (inotropic adaptation) and atrioventricular conduction time (dromotropic adaptation) are also affected by the autonomic nervous system. Thus, the ability to react to physical and psychological stress greatly depends on the regulation of the cardiac function under normal physiologic conditions.

To develop a pacemaker capable of interacting with the circulatory system, a detailed understanding of the cellular mechanisms involved in controlling autonomic periodicity and of the influences of neural reflexes on the heart rate is essential. How the nervous system and the heart interact is the subject of study of an interdisciplinary field known as neurocardiology. Neurocardiologic research provides an anatomically precise understanding of the afferent and efferent connections between the brain and the heart via all peripheral neural structures as shown in figure 3.

The ventrolateral nerves in the heart and the neuronal elements around the pulmonary vein complex transmit

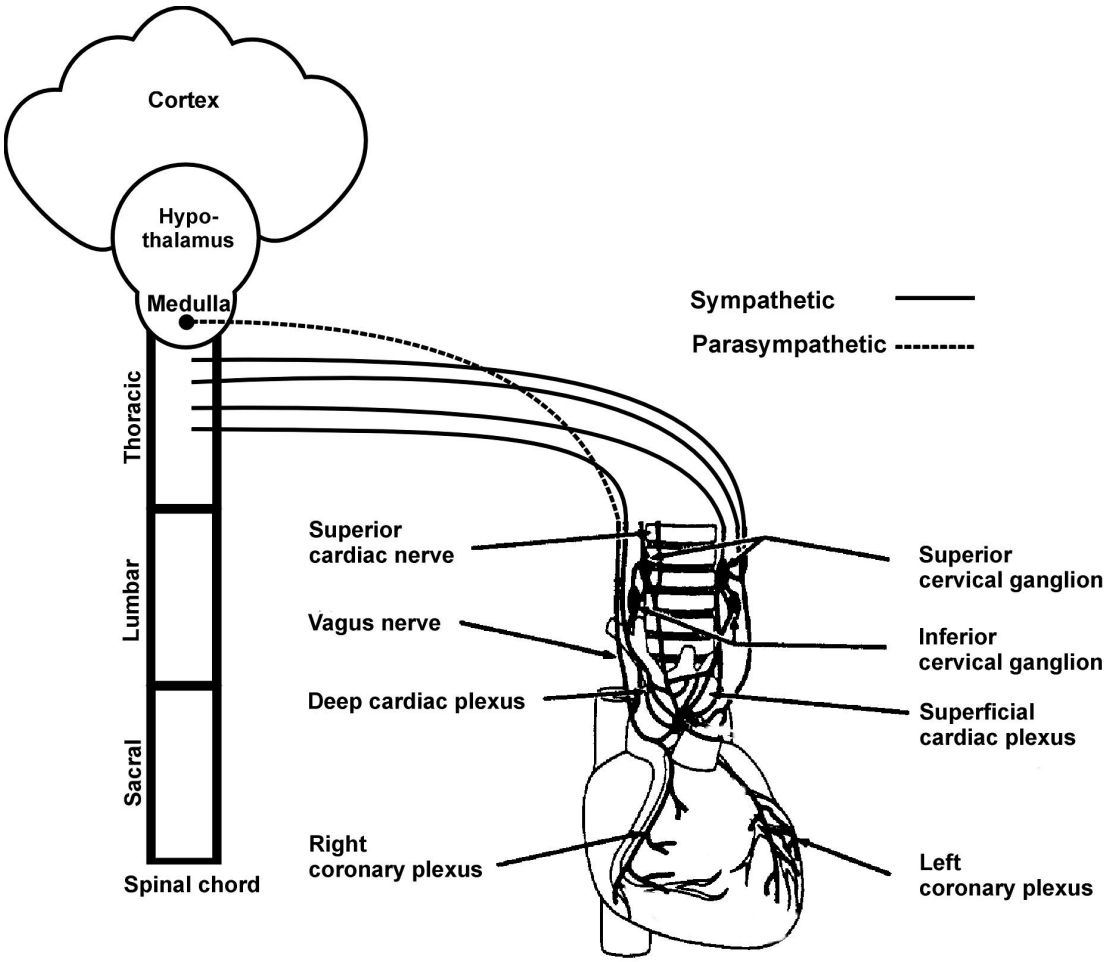

Figure 3. Neurocardiologic innervation.

left sympathetic chronotropic influences, while dissection of the pulmonary artery nerves and tissues between the right pulmonary artery and superior vena cava interrupts right sympathetic control of the heart rate.

The medulla oblongata selectively serves as the central regulatory region, controlling sinoatrial automaticity and atrioventricular conduction. Both ventricles are richly supplied with sympathetic fibers. The predominantly sympathetic control of ventricular inotropy resides within nerves along the dorsal surfaces of the pulmonary artery and along the superior vena cava to its junction with the right atrium.

Separate functions control the heart rate, AV conduction, and myocardial contractile force. They are mediated by the vagus nerve, as well as by selective projections from within the pericardium to the different effector terminals. For many years, it has been assumed that the vagus nerve does not innervate the ventricles. This opinion is still presented in some current textbooks. However, growing evidence indicates a very important role of the parasympathetic nerve in the ventricles, both in healthy and diseased conditions. The presence of acetylcholine and acetylcholinesterase in the ventricular muscle suggests a certain functional role for the vagus nerve, namely reductions in ventricular contractility, ventricular excitability (i.e., increased effective refractory period and ventricular action potential durations), the fibrillation threshold, and the threshold of repetitive extrasystoles.

The facilitating effects of tonic sympathetic activity on the heart are usually strikingly opposed by inhibitory effects of tonic vagal activity. However, the extent of antagonistic influences on the main cardiac functions

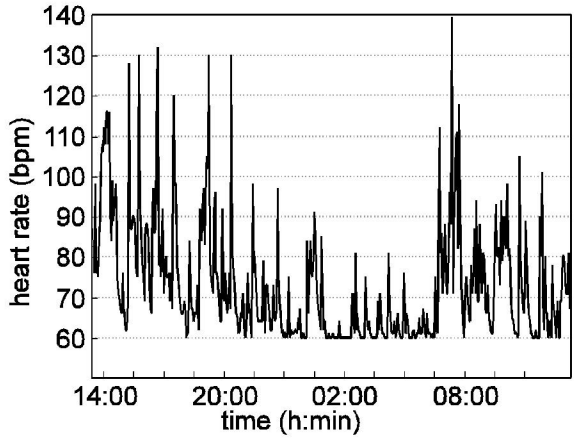

Figure 4. 24-h trend of a young, athletic patient showing circadian variation and high pacing rates during exercise.

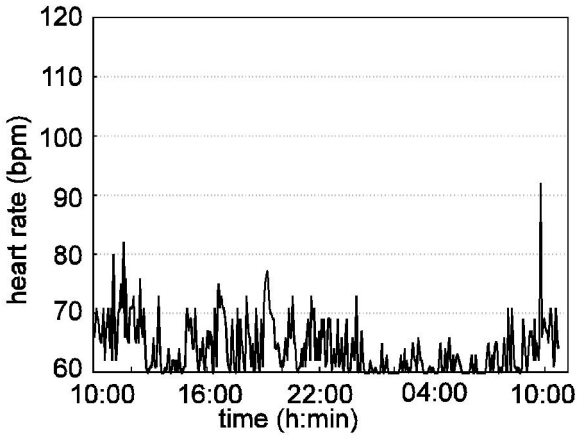

Figure 5. 24-h trend of an elderly patient with coronary heart disease showing circadian variation and only moderate pacing rate increase during exercise.

has a site-specificity ranging from accentuated antagonism, in relation to sinus node automaticity, to a moderate one in controlling AV conduction. Perhaps because the autonomic interactions are rather accentuated in ventricular functions, the vagal influence in the ventricles has been previously overlooked. Indeed, vagal stimulation or intracoronary acetylcholine infusions in animal experiments have only slightly reduced the ventricular contractile force. At the same time, during concurrent sympathetic nerve stimulation or norepinephrine administration, an infusion of acetylcholine or vagus stimulation substantially compensates for the increased contractile force

The concept of Closed Loop Stimulation

Because the cardiovascular system is a complex Closed Loop C ontrol system, it is impossible to reestablish functionality within a dysfunctional circulatory system using simply artificial sensors. Therefore, conventional rate-adaptive pacemakers do not ideally mimic the response of a competent circulatory regulation. Their sensors measure parameters that are only indirectly correlated to the patients' exercise level. Pacing rates based on such information may result in non-physiologic heart rates and inadequate response times to exercise.

In patients with dysfunctional cardiac regulation mechanisms, e.g., in cases of sick sinus disease, rate variation or atrioventricular conduction is limited. Usually, the disease does not affect the Closed Loop Control of the circulatory system in general, as a result the remaining parts of the system, namely: the receptors, the afferent pathways, the central controlling circuits, the efferent vagal and sympathetic neural pathways to the heart with all their interactions and peripherally acting modulators, as well as the myocardium itself, are still functional. The circulatory centers attempt to compensate for the limitations in the control dynamics by forcedly varying the intact control mechanism (e.g., inotropy). But regulating CO by adjusting the contractile force of the myocardium is possible only within certain limits. Moreover, even low levels of exercise or mental stress may lead to increased myocardial wall stress for chronotropically incompetent patients, since the increasing circulatory demand can only be provided by augmenting myocardial contractility. For yet greater stress, the required cardiac demand can no longer be provided, thereby severely restricting the patient’s maximum capacity.

The essence of Closed Loop Stimulation is to preserve the intrinsic circulatory regulation system and to integrate the pacemaker into the regulation system, thus enabling the heart rate to be controlled by the circulatory centers - and not by the pacemaker. In this innovative role, the pacemaker restores the full dynamic range of the heart rate and thus the patient’s maximum load capacity.

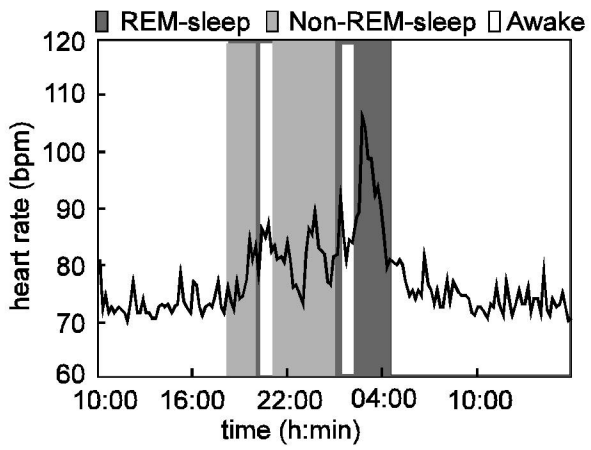

Figure 6. Heart-rate regulation byClosed Loop Stimulation during different sleep phases, recorded in a sleep laboratory.

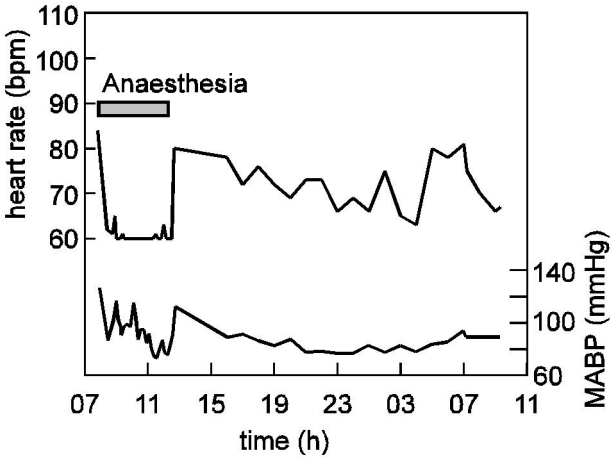

Figure 7. Heart-rate response of Closed Loop Stimulation to general anesthesia.

Even under pathophysiologic conditions (e.g., sinus node disease, cardiomyopathy), the dynamics of the myocardial contractile force still reflect the information from the circulatory center. Thus, one possibility of realizing a Closed Loop pacemaker is to transfer changes in myocardial contractility into individual stimulation rates. With such a device, the stimulation rate is linked to the circulatory center, and adequate perfusion is enabled under various conditions.

Clinical experiences and consequences

The Closed Loop Stimulation concept has been clinically validated in more than 500 patients and has been implemented in a Closed Loop pacemaker system (INOS² CLS, BIOTRONIK). The aim of the validation was to prove the theoretically expected result. Namely, Closed Loop Stimulation yields individual and adequately dynamic heart rates through integration into the natural control circuit. As a consequence of the negative feedback within the Closed Loop Control, the system should not only be able to react proportionally to exercise in every patient, but also to take into account the patient's individual condition and disease state.

The analysis of the stimulation rates in patients with implanted Closed Loop pacemakers shows circadian variation. The individual variations between day and night closely correlate to the rhythm of everyday life. In the case of a young, athletic patient (figure 4) with a high degree of chronotropic incompetence but no other diagnosis, high pacing rates during physical activity are reached. A distinct circadian heart rate variation with elevated diurnal and low nocturnal rates can be observed. The 24-hour trend of an elderly patient with limited physical resilience, a high degree of chronotropic incompetence, and coronary heart disease (figure 5) shows a significant circadian variation as well, but only moderate pacing rates are reached during physical activity.

These two cases demonstrate that circulatory control is still the rate-determining module when using pacemaker with the Closed Loop Stimulation concept. Due to the feedback, the pacemaker does not stimulate with excessively high heart rates which would be harmful to the patient with coronary heart disease. In contrast, the Closed Loop system regulates heart rates appropriately high for the young, athletic patient. The Closed Loop pacemaker has no option of - and no necessity for - manually adjusting additional parameters, such as sensor gain and attack or decay rates. The different levels of heart rate and attack and decay rates are an automatic consequence of maintaining the natural cardiovascular control loop.

In additional investigations of Closed Loop Stimulation, rate response was analyzed during sleep in a chronotropically incompetent patient who had received a Closed Loop pacemaker. Sleep studies have documented that the different stages of sleep correlate to characteristic changes in heart rate dynamics. REM

(rapid eye movement) sleep phases show moderately elevated heart rates; and non-REM phases, the stages of deep sleep, correlate to predominantly low heart rates.

Using data gained from EEG, EMG, and EOG (electro oculogram) measurements taken in a sleep laboratory, show that the sleep stages of the patient during Closed Loop Stimulation were ascertained. Additionally, the ECG, respiration frequency, and body position were recorded. Figure 6 shows that Closed Loop Stimulation reestablished the natural dynamics of the heart rate course in this chronotropically incompetent patient.

A final clinical example demonstrates the consequences of integrating the pacing system into the Closed Loop Control of the cardiovascular system. A chronotropically incompetent patient with a Closed Loop pacemaker needing an aortofemoral bypass was monitored peri-operatively under general anesthesia. The surgery lasted 4.25 hours. Before, during, and after anesthesia, heart rate and blood pressure were continuously recorded. Because the Closed Loop pacemaker is an integral part of the circulatory control, the pacing rate should react appropriately to the anesthesia because of the direct influence of narcosis on the neurocardiological control. As shown in figure 7, the stimulated heart rate during anesthesia is significantly affected by Closed Loop Stimulation. In the phases directly before and after the operation, the stimulation rate is at a relatively high level due to the mental stress of the patient who first anticipates the operation and then feels pain. During anesthesia, the heart rate decreases significantly. This rate response, which is comparable to the rate dynamics in healthy people, again shows the consequence of the Closed Loop principle which enables regulation of the heart rate by the natural circulatory control system, rather than mimicking physiologic behavior with artificial external sensors.

Prospects for future applications of Closed Loop Stimulation

The idea of interaction between the pacemaker and the cardiovascular Closed Loop is not limited to therapy for chronotropic incompetence. The importance of the circulatory system in the genesis of cardiac arrhythmias, particularly at the time of acute myocardial ischemia, has become progressively evident from the experimental and clinical observations of many authors [1-5]. It has been shown that within a few seconds of myocardial ischemia, cardio-cardiac sympathetic excitation and vagal depressor reflexes occur. The intensity of increasing sympathetic activity correlates to reduced ventricular fibrillation thresholds and increased coronary vasoconstriction. Myocardial infarction produces areas of mainly sympathetic or vagal denervation. In the case of the latter, it will increase the vulnerability of the heart to arrhythmia and fibrillation during acute, painful, or silent episodes of ischemia.

A number of preventative therapies have been developed and investigated in recent years. Their goal is to prevent malignant arrhythmia in coronary patients by interrupting sympathetic activity or stimulating the vagal influences in the heart with, for example, left stellectomy and efferent electrostimulation of the vagal nerve.

Newer methods for the prevention and therapy of cardiac arrhythmias provide an interesting alternative to pharmacological therapy. The application of Closed Loop systems in arrhythmia therapy offers the opportunity to monitor the cardiovascular system directly and continuously, while receiving spontaneous feedback on therapy efficacy. By monitoring the sympathetic hyperactivity prior to tachyarrhythmia onset, the Closed Loop system can apply, for example, bursts of electrical stimuli to the afferent vagus nerve endings in the right atrial endocardium during the refractory period of the working myocardium.

Deriving from the results of Closed Loop Stimulation for bradyarrhythmia therapy, it can be assumed that a method of antiarrhythmic stimulation with a Closed Loop system is superior to open loop systems. This superiority is due to the continuous feedback gained from being integrated into the circulatory regulation system of the body.

Conclusion

The complexity of the circulatory control system precludes the ability to perfectly reestablish the natural regulation using an ensemble of artificial external sensors. The separate control functions of natural regulation do not collaborate with the artificial sensor-driven heart rate, because the communication interface between the pacemaker and the circulatory system is inherently absent in these open-loop systems.

Integrating the pacemaker into the Closed Loop system of the circulatory regulation can be realized by

connecting the device to the dynamics of myocardial contractility. As the clinical experience shows, Closed Loop Stimulation yields individual, adequate, and patient - specific responses of the regulated heart rates - even in chronotropically incompetent patients. The case reports show how the Closed Loop pacing system automatically accounts patients' condition and disease state without the necessity for manually programming any rate and time factors.

Antibradycardia therapy is only one of many different options for applying the Closed Loop principle in electrostimulation of the heart. In the near future, various strategies for an optimized individual therapy of heart diseases can be developed with this technology. The concept of Closed Loop Stimulation, therefore, opens new avenues of cardiology in which preserving the body's natural functionality is realized to the greatest extent possible.

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