Use of Closed Loop Stimulation in Reestablishing Full-scale Cardiovascular Regulation

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Summary

Improvements in the therapy of cardiovascular diseases require a detailed understanding of physiologic and pathophysiologic mechanisms of the interaction between heart, vasomotors, and neurohumoral control. Various processes influence the most important parameter for the continuous adequate supply of the organism - the mean arterial blood pressure. Based on this knowledge, a therapeutic concept was developed which supports the cardiovascular system in its main task of stabilizing the adequate perfusion, rather than simply treating particular symptoms. The first successful realization of this therapeutic concept, based on disturbance variable feedforward and a continuous feedback loop, is the Closed Loop Stimulation (CLS). CLS was introduced into clinical practice several years ago. In recent years, the therapeutic application of CLS yielded numerous results reflecting the restored physiologic mechanisms of cardiovascular control. These results demonstrate an effective support of the limited natural regulation system with the help of the CLS pacemaker. As a consequence, CLS is a therapy suitable not only for rhythmologic dysfunctions, but also for a wide range of pathologic structural and cellular changes.

Key Words

Closed Loop Stimulation, cardiovascular control, baroreceptors, pacemaker

Introduction

Since the introduction of Closed Loop Stimulation (CLS) as a therapeutic concept for electrostimulation of the heart, the treatment of pathologic limitations of the cardiovascular system has changed from simply eliminating particular symptoms to a more general support of the cardiac, vascular, and neurohumoral control mechanisms. In the meanwhile, this management method has been established as a standard therapy for the treatment of various diseases of the cardiovascular system, which are not limited to forms of sick sinus syndrome. The basis for the development of this therapeutic strategy and the realization of the clinical applicability was a detailed understanding of the physiology and pathophysiology of the cardiovascular system. This understanding has taken into account the physical, technical, as well as medical aspects, thereby building the prerequisite for an interdisciplinary research and evaluation process.

Physiology of the Cardiovascular System

The starting point for a discussion of the complex structure of the cardiovascular system is the definition of its main task and the corresponding parameters. In order to ensure a continuous supply of all body cells with nutriments, oxygen, other substances, and the disposition of metabolic products, a stable and appropriate perfusion pressure has to be provided by the cardiovascular system [1]. Within that regulation process, mean arterial blood pressure (MABP) and total peripheral resistance (TPR) play a major role, since local metabolic changes directly respond to the vasomotors, while the baroreceptors assess the appropriate perfusion by continuously measuring blood pressure. MABP as a central parameter of cardiovascular regulation, is influenced by numerous factors. These include physiologic variations due to changing organic requirements, as well as the consequences of pathologic structural or cellular changes (Figure 1).

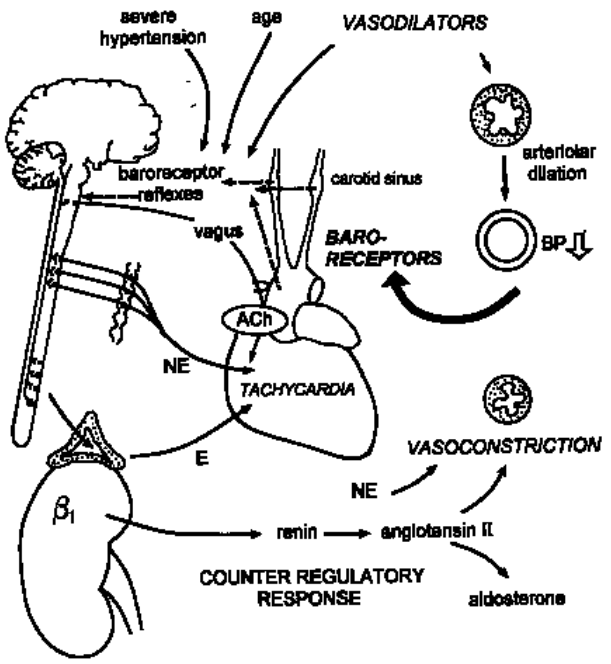

Figure 1. Interaction of mechanisms in cardiovascular control (modified from [2]).

The various activities of daily life are coupled with numerous individual requirements to the organism, which cause local and global constriction or dilation of the vessels. Increasing workload of certain parts of the organism initially causes vasodilation, in order to ensure an elevated blood flow through the corresponding tissue. With the help of neural and humoral control mechanisms, the heart starts to counteract the decreasing blood pressure by increasing the cardiac output [2]. As these regulation processes act continuously and mostly delay-free, the blood pressure remains stable or shows a slight increase during phases of increased workload despite the significantly decreasing TPR. The baroreceptors, which are continuously monitoring the blood pressure, are the most important natural sensor for providing hemodynamic stability on a beat-to-beat basis [3]. Sudden changes in the TPR are immediately responded by antagonistic variations in the heart rate. This behavior is reflected in the cardiac response to provoked blood pressure changes during Valsalva maneuvers [4-5], as well as in the characteristic heart rate variability [6-7], which indicates continuous pressure stabilizing short-term regulations. A detailed analysis of the neurohumoral mediation of necessary compensatory variations in cardiac output essentially leads to a discussion of the important role of myocardial and circulating catecholamines and their effect on cardiovascular parameters. Changing load stages cause variations in the dynamics of catecholamine release via the medullary circulation center. Hence, a decreased TPR, triggered by higher metabolic needs, initiates a pronounced release of catecholamines and adapts the cardiac output with the help of the known cardiac mechanisms: chronotropy, inotropy, and dromotropy [2].

Pathophysiologic Aspects

Pathologic limitations of the cardiovascular system significantly impact the main parameters, such as blood pressure. The main difference between pathophysiologic and physiologic effects is the lack of balance in pathologic situations and, thus, the inability of the system to appropriately counteract deviations in the perfusion pressure. This limitation can be caused by malfunctions of cardiovascular sensors, neurohumoral balance, or vascular and cardiac mechanisms. In many cases, the initial cellular or structural myocardial changes cause hemodynamic restrictions, which again amplify the progress of the pathologic development. A typical example of this is the congestive heart failure. The diseased myocardial cells lead to morphologic changes of the ventricle, causing congestion. Due to the congestion, the cardiac efficiency is reduced, and increased contraction is necessary to meet the hemodynamic requirements to stabilize the blood pressure. The permanently elevated level of contractility disables recovery phases for the myocardial cells thereby emphasizing the progression of structural changes. A different clinical manifestation of pathologic malfunctions in the cardiovascular control is "neurocardiogenic syncope." An inappropriate slowing in cardiac rate, resulting from sudden augmentation of efferent vagal activity, combined with hypotension generates an abnormal and pathologic reflex effect. The decrease in blood pressure is amplified by the pathologic decrease of cardiac output, instead of by the activation of any compensatory mechanism. The syncopal event is the expression of severe hypotension and bradycardia resulting from this neuro-cardiac reflex [8,9].

Thermodynamic Description

Although the functioning and interaction of the various cardiovascular mechanisms, as well as the wide range

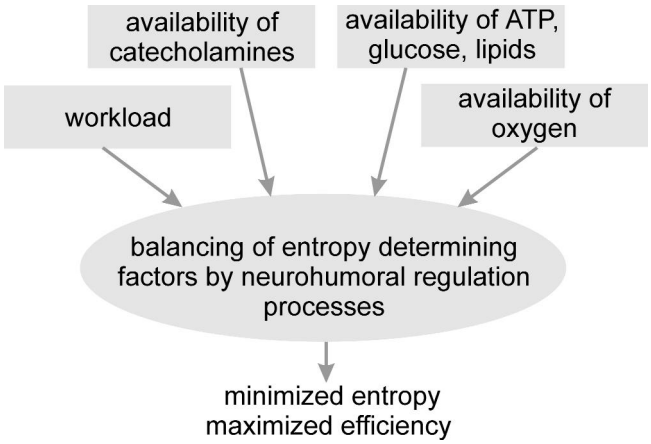

Figure 2. Thermodynamic aspect of cardiovascular regulation.

of pathologic changes give the impression of incalculable complexity, the system can be described in a very compact way using the terminology of thermodynamics. Based on mechanical explanation of the heart cycle, the efficiency of the heart can be defined as the "relationship between cardiac work output (which mainly depending on stroke volume and mean arterial blood pressure), and myocardial energy consumption, which can be quantified by analyzing the cardiac oxygen uptake." Proceeding to the thermodynamic refinement of the physical description, discussed by Cesarman et al., the entropy of the heart becomes the parameter of global interest, which is indirectly proportional to cardiac efficiency [10-12]. The entropy describes the spontaneous movement of energy towards the random distribution of matter and heat. Hence, the main aim of myocardial as well as all other biological cells is to continuously reduce entropy, thereby maximizing the ability to perform work in a highly effective way. The various mechanisms and subsystems of the cardiovascular system permanently balance all entropy-determining factors, including the availability of glucose, lipides, ATP, oxygen, catecholamines and workload. This occurs in order to counteract the natural tendency of physical systems to approach a random distribution of matter and energy (Figure 2). In this description, the inclusion of periodic cardiac contractions leads to the thermodynamic separation of systole and diastole. The minimization of entropy and, thus, the restoration of excitability and contractility, is subject to mechanical diastole; whereas systole is consuming these energy resources and simultaneously increasing entropy. The knowledge of these thermodynamic aspects enables new possibilities in understanding pathologic limitations within the cardiovascular system. The majority of known pathologic anomalies of the heart, the vascular system and the neurohumoral regulation, can be defined as an inability of the system to appropriately balance the entropy - determining factors, leading to reduced entropy disposition and decreased cardiac efficiency. The resulting pathological biochemical and structural changes draw the system towards a suboptimal working point with the absence of a stable minimum energy production. The analysis of different clinical manifestations emphasizes the applicability of thermodynamic theories for the functionality of the cardiovascular system, as discussed in the two examples above. In patients with congestive heart failure the attenuation of the cellular ability to minimize entropy causes structural changes, which again amplify the initial process of pathologic cellular modifications. In cases of neurocardiogenic syncope, the system's ability to reduce entropy is intact, but the sudden neurohumoral imbalance disables the necessary transfer of minimum entropy into effective cardiac work. With respect to this knowledge, a more global approach for developing and providing therapeutic measures is necessary. Supporting the cardiovascular system is the main task of minimizing entropy production rather than simply treating particular symptoms. This might significantly improve the effectiveness of therapy by initiating remodeling of the structural changes and offering preventative measures.

Concept and Technology of Closed Loop Stimulation

The practical way of supporting the cardiovascular system in this global manner is CLS, which is based on the principle of disturbance variable feedforward. Typical pathologic changes limit the dynamic range of one of several control mechanisms, thereby causing significant delays and deviations in the cardiovascular regulation. The continuous stabilization of an appropriate perfusion is disabled and the metabolic requirements can be fulfilled only within certain limits. As in some physiologic control loops (especially if the control is acting with long reaction times), the disturbance variable feedforward is a method to eliminate these restrictions [1]. The direct transmission of information (about disturbance variables in the control center) significant-

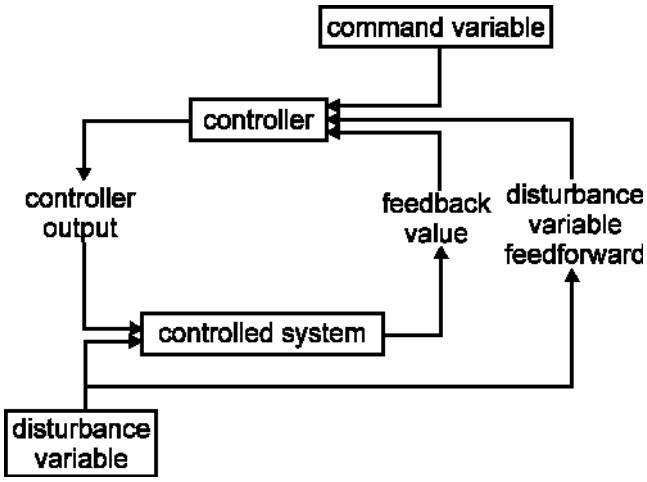

Figure 3. Principle of disturbance variable feedforward for the acceleration of slowly reacting control loops.

ly accelerates the control and avoids deviations of the controlled variable due to sudden changing requirements (Figure 3). The CLS pacemaker has direct access to the disturbance variable, i.e. the hemodynamic requirement, by monitoring the inotropic mechanism of contraction dynamics. The pacemaker bypasses the diseased sinus node reaction by providing appropriate heart rates. In this way, the continuous and immediate balancing of the different mechanisms is reestablished and the system is able to periodically reduce entropy and perform effective work. This ensures the permanent adequate supply of the organism.
During several years of interaction between technical development and clinical research, a technology for the realization of this principle was designed and validated. Clinical consequences, benefits, and applicability have been analyzed within numerous investigations. Technically, changes in the inotropic state are assessed via unipolar intracardiac impedance measurements. Biphasic subthreshold pulses are injected between the tip of the ventricular lead and the pacemaker housing. The resulting potential difference is measured between the same points. Changes in myocardial contractility result in varying morphology of the measured unipolar intracardiac impedance curve [13-14].

Validation of the System

To examine the correlation between invasively measured inotropy (dP/dt_{max}) and the inotropic values assessed via the impedance signal, the unipolar intracardiac impedance and the right ventricular pressure were recorded intraoperatively for various dosages of dobutamine. The normalized values of the impedance curve changes were compared to the corresponding pressure gradients by linear regression analysis. The calculations resulted in a correlation coefficient of 0.92. The demonstrated high correlation between the impedance and the pressure-based measurements of the cardiac inotropic status indicate that the unipolar impedance signal reliably reflects the inotropic drive, i.e. changes in myocardial contraction dynamics [15].
Based on the proven correlation between unipolar impedance changes and inotropic drive, the realization of a CLS pacemaker based on the monitoring of contraction dynamics is possible. As a consequence of the pacemaker integration into the circulatory regulation system, it is expected that the heart rate for patients with CLS systems is influenced by changes in the level of circulating catecholamines. During a pharmacological stress test using the catecholamine dobutamine, heart rates of patients with CLS pacemakers were examined. The increase in myocardial contractility was measured using an echocardiographic method for dP/dt determination. The patients showed a significantly increaseing stimulation rate during dobutamine infusion. A few minutes after the end of the infusion, all patients reached their original resting heart rate. The inotropic parameter dP/dt_{max} increased in parallel during infusion. These results confirm the hypothesis of a chronotropic reaction to increased catecholamine levels with the CLS pacemaker, by re-synchronizing inotropic and chronotropic control mechanisms [16].

Clinical Implications

A closed loop system, which forwards the disturbance variable input to the cardiac control mechanisms, should continuously provide adequate organic perfusion. As a consequence, it shows the same reactions on external influences and comparable behavior of the cardiovascular parameters as in the healthy organism, as previously discussed. Performing the Valsalva maneuver in patients with the CLS pacemaker yields the characteristic curves of blood pressure and heart rate during the forced expiration, against the pressure of 30 mmHg (Figure 4) [17]. This typical behavior can only be observed, if the pacing rate is controlled by the baroreceptor reflex. Thus, the CLS pacemaker controls

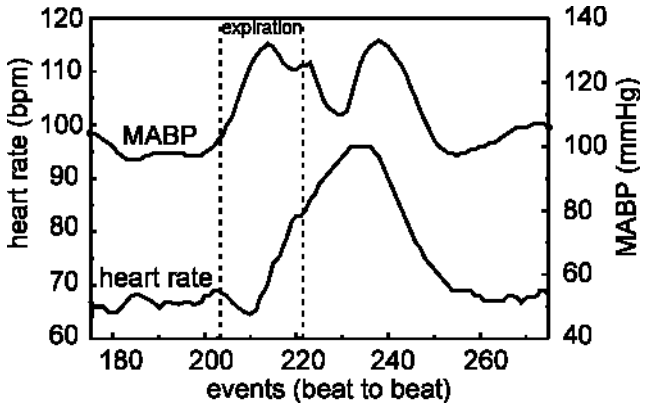

Figure 4. Response of mean arterial blood pressure (MABP) and heart rate of a CLS patient to Valsalva maneuver.

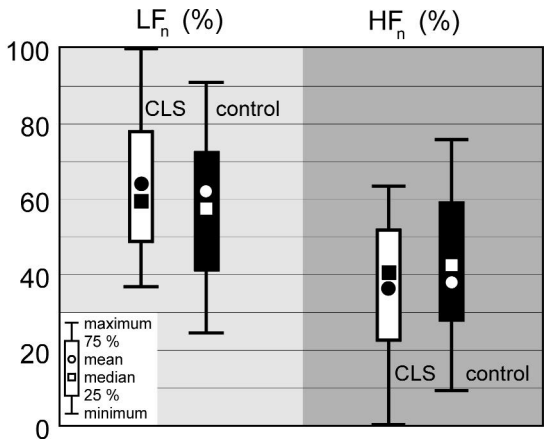

Figure 5. Statistics of normalized power spectral density HF_n-part and LF_n-part of heart rate variability at rest for CLS patients and control group.

the heart rate based on neurohumoral regulation, and establishes a continuous feedback loop between pacemaker and cardiovascular system.

The analysis of heart rate variability confirms the active rate-controlling role of the baroreceptors for patients with CLS pacemaker therapy. Parasympathetic and sympathetic activities cause characteristic fluctuations in heart rate that are related to special frequency ranges. In 16 patients with CLS pacemakers and in a control group of 16 chronotropically competent subjects, a high quality ECG was performed at rest and during exercise. The data regarding heart rate variability was automatically deducted from ECG recordings by using special software for analysis. Power spectral density 1 week after CLS initialization consisted of a well-pronounced LF- and HF-part indicating parasympathetic and sympathetic influence. No difference in the normalized power values was found in the comparison between CLS and control group, indicating a strong correlation of heart rate variability between CLS and sinus node (Figure 5) [18].

While the control mechanisms maintain an appropriate level of blood pressure during load, heart rate and oxygen consumption increase in parallel. A well-proven method for monitoring hemodynamic parameters, the cardio-pulmonary exercise test, affords the opportunity to investigate the ability of CLS therapy to adequately meet metabolic requirements. Patients with CLS pacemakers performed an exercise test, which was monitored with an ergospirometric device. During the test, oxygen consumption measurements were obtained with continuous breath-by-breath sampling and the heart rate was recorded using the internal pacemaker's Holter. The resulting heart rates showed a course identical to that of the oxygen consumption, demonstrating the adequacy of the heart rates mediated by the CLS device [19].

The most important factor for investigating the clinical relevance and possible benefits of a therapy is a detailed analysis of the behavior during daily activities, in order to assess the recovery of an optimal quality of life for the treated patients. The behavior rate of 30 patients with CLS devices was compared with sinus rates of healthy subjects during daily activities, including walking, squatting, climbing stairs, hyperventilation and ergometry. The correlation between sinus rhythm and stimulated rate in CLS patients showed values between 95% and 99% for the different forms of physical activity (Figure 6). In addition, circadian variation during 24 h was analyzed yielding a correlation coefficient of 87% in a comparison of CLS rates and natural sinus node behavior [20].

Similar results have been found during a study comparing the behavior rate of CLS therapy with the rate adaptation of conventional sensor systems during daily activities. Patients with implanted CLS devices responded to every kind of exercise in a way comparable to the control group [21].

Experiences with the Therapy of Various Cardiovascular Diseases

The results demonstrate that the CLS system supports the cardiovascular regulation in a physiologic way.

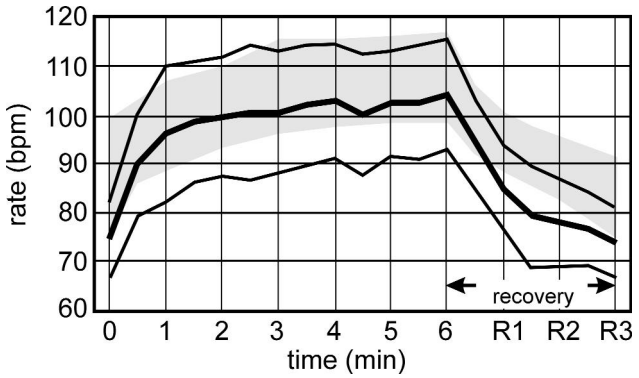

Figure 6. Heart rate of CLS patients during daily activities test. Example of walking test.

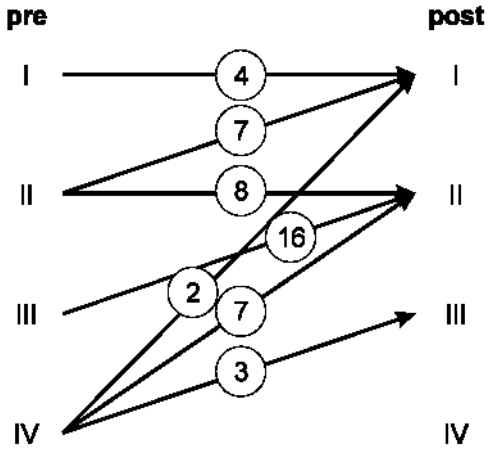

Figure 7. Evolution of NYHA functional class in chagasic patients during 12 months follow-up of pacemaker.

Thus, the re-established balance of the different cardiovascular and neurohumoral mechanisms should not only provide load specific modulation of the heart rate, but also improve the situation of patients with diseased myocardium. This is achieved by interrupting the progression of structural changes and initiating remodeling processes. The consequences of treating congestive heart failure with the help of feedback-controlled electrostimulation have been investigated in a clinical study. In 16 pacemaker patients with congestive heart failure (with a mean LV ejection fraction of 50.1%) a pacemaker exchange was performed with an upgrade from a non-rate modulation to a CLS system. In these patients the maximum work capacity increased from 38.2 W to 94.5 W, and NYHA classifications of I and II increased from 33% to 83%. The results indicate that cardiovascular regulation supported by CLS, respond physiologically to physical load in patients with congestive heart failure. Moreover, diminishing signs of heart failure and a general positive shift in NYHA classification results from this therapy method [22].

Similar results were observed in a study investigating CLS therapy in patients with Chagas disease. In 47 chagasic patients with the CLS device, the behavior of blood pressure and heart rate during changing workloads from 25 to 100 W and the NYHA class were assessed before and after implantation. The patients reached heart rates of 120 bpm during exercise and thereby showed a restoration of the originally limited physiological mechanisms. In 74% of the investigated patients the NYHA class improved by 1 or 2 steps following the pacemaker implantation (Figure 7) [23].

The treatment of vasovagal syndrome with the application of CLS was subjected to several clinical investigations as well. Since the pacing rate in CLS increases according to contractility rise during the presyncopal increase of vagal tone, it is expected to prevent the failure of sympathetic tone and counterbalance the increase of vagal tone. Hence, the system should limit atrial hypotension, bradycardia, and avoid the occurrence of syncope. All investigated patients with CLS therapy had no syncopal events during tilt testing (Figure 8) and were free of syncope following start of CLS therapy [24-26].

Conclusion

This summary of selected investigations of CLS therapy demonstrates the successful integration of the pace-

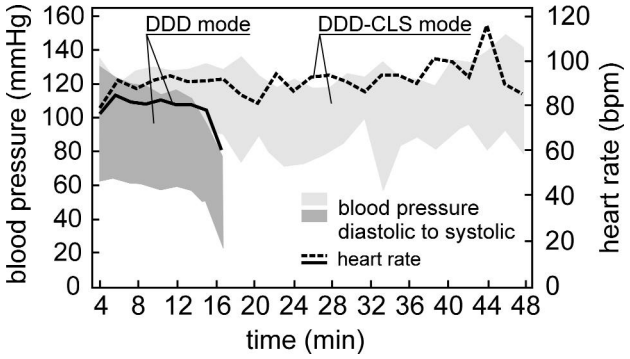

Figure 8. Trend of arterial blood pressures and heart rate during head-up tilt test in DDD and in DDD-CLS mode.

maker into the natural cardiovascular control loop. The above described effects of different physiologic processes on cardiovascular mechanisms, and the resulting behavior of the mean arterial blood pressure are similarly observed in patients with CLS therapy. This indicates the optimal support of the system in maintaining efficient supply to the organism. Moreover, the ability of the CLS system to counteract progressive structural changes, thereby offering improvements to the patient's prognosis, indicates the importance of this physiology-oriented approach for a successful therapy. Returning to the thermodynamic description of the cardiovascular system, CLS can be characterized as an auxiliary mechanism for balancing entropy-determining factors in cases of pathologic limitations of one or more natural regulation modules.

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