Closed Loop Stimulation and Evaluation of the Effect of the Autonomic Nervous System Using Heart Rate Variability

A.S. MENEZES JR., M.T. DAHER, J.M.R. DE PAIVA, C.M. NASCENTE, H.G. MOREIRA
Universidade Federal de Goiás, Goiânia , Goiás, Brazil

Summary

It is well-known that the sinus node supports an adequate heart rate in response to mental, emotional, and physical stress. A heart rate variability analysis is based on small variations in heart rate caused by sympathetic and parasympathetic activities. A sensor system called Closed Loop Stimulation is believed to be capable of restoring normal sinus node function. This study evaluates the autonomic sensitivity of CLS to a group of pacemaker patients as well as its effect on the autonomic nervous system, according to the heart rate variability, as compared with healthy individuals. A total of 58 patients with an Inos^{2+} CLS pacemaker were included in the study along with 37 individuals without a pacemaker. All patients were connected to a 24-hour Holter, and the heart rate variability time and frequency domain data were collected, indicating a close response between CLS patients and healthy individuals.

KeyWords

Closed Loop Stimulation (CLS), chronotropic incompetence, heart rate variability.

Introduction

Rate-Responsive Pacemakers

Rate-responsive pacemakers are widely used to treat chronotropic incompetence as well as complete atrioventricular (AV) block or sinus node disease. Of the several sensor concepts that have been evaluated since 1980, the activity sensor (accelerometer) and two physiologic models (minute ventilation and QT interval) have been predominantly used in clinical practice. Some devices offer a dual-sensor-based rate adaptation, where a physiologic sensor is combined with an accelerometer to improve the speed of rate response and specificity, sensitivity, and proportionality of the rate response to workload [1].

A major limitation of rate-adaptive pacing is the nonphysiological rate response of the most commonly used activity sensor principles [2,3]. Although this problem has been partly solved with so-called "physiological sensors," rate adaptation in these systems is not always based on hemodynamic parameters which would allow for incorporating the sensor response as a positive and negative feedback, i.e., "closed-loop" system, within the normal circulatory reflex arch. In healthy subjects, cardiac output adaptation during exercise is achieved by modifying both heart rate and ventricular contractility. In subjects with impaired heart rate behavior, the contractility signal can still be used by pacemakers to estimate current hemodynamic demands.

Myocardial contractility can be measured by implantable devices using two different technical approaches. The first solution is based on the recognition of the ventricular endocardial acceleration [4] by a microaccelerometer mounted on the tip of the ventricular unipolar lead. The second technical solution is the measurement of beat-to-beat right ventricular unipolar impedance variations via standard unipolar or bipolar pacing leads [5,6]. The Inos^{2+} CLS pacemaker (Biotronik, Germany) is based on this Closed Loop

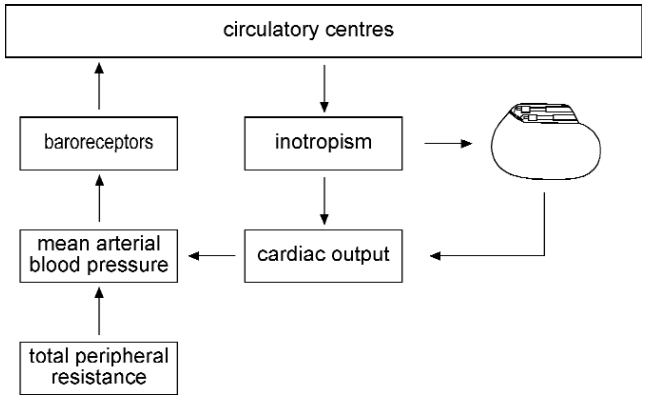

Figure 1. The pacemaker adapts pacing rate according to variations in myocardial contraction dynamics which is called Closed Loop Stimulation (CLS, Biotronik, Germany).

•	SDNN	Standard deviation of all NN intervals
•	SDANN	Standard deviation of the averages of NN intervals in all 5 minute segments of the entire recording
•	rMSSD	Square root of the mean of the sum of the squares of the differences between adjacent NN intervals
•	SDNN index	Mean of the standard deviations of all NN intervals for all 5 minute segments of the entire recording
•	pNN50	NN50 count devided by number of all NN intervals

Table 1. Heart rate variability parameters in time domain (according to [10]).

Stimulation (CLS) principle [7-9]. The pacemaker adapts pacing rate according to variations in myocardial contraction dynamics and is therefore involved in the physiological cardiovascular control mechanism (Figure 1).

Heart Rate Variability

In clinical practice, normal-to-normal (NN) intervals are measured using ECG curves. Thereby, NN intervals are distinguished from common RR intervals (time distance between two R points in ECG) by excluding ventricular extrasystoles, which are caused by different processes. Further study of heart rate variability is performed statistically [10], e.g., by calculating standard deviation (SDNN) and other defined parameters (Table 1) in the time domain. The frequency domain analysis is performed using a fast Fourier transform of the NN intervals as a function of time. This leads to power spectral density (PSD), which represents a distribution of variance ($SDNN^2$) on variability frequencies, i.e., integrating PSD over the complete frequency range of outcomes ($SDNN^2$).

Because variability frequencies are defined as small-scale fluctuations in heart rate, the frequency range that is less than 0.5 Hz is of interest. At least there are specific frequency domains, which are affected differently by parasympathetic and sympathetic activities of the autonomic nervous system. Oscillations inside the vasomotor system, including the baroreceptor reflex, are in the order of 0.1 Hz. At higher frequencies, respiratory sinus arrhythmia is present, which is caused by interaction of the respiratory and the cardiovascular systems. Regulatory systems acting on low time scales, e.g., thermoregulation, cause fluctuations in the very low frequency range (0.003 – 0.04 Hz), but these systems are not of interest in this study

Naturally, it is not useful to analyze single frequencies due to insufficient resolution and overlapping of the different mechanisms but, nevertheless, two frequency intervals are found to be suitable as indicators of sympathetic and parasympathetic activities. The integral of the PSD carried out over the low frequency interval from 0.04 Hz to 0.15 Hz is defined as LF power, and the integral carried out over the high frequency interval from 0.15 Hz to 0.4 Hz as HF power, respectively. While the LF power is mostly but not exclusively affected by sympathetic activity, the HF power is predominantly parasympathetically influenced [10]. Thus, relative values $LF_n = LF/(LF + HF)$ and $HF_n = HF/(LF + HF)$ are useful.

Objectives

It has been shown that heart rate variability is a risk factor for sudden cardiac death [11] or a marker for further applications [12,13] because it is a marker of sympathetic or parasympathetic activities of the autonomic nervous system. By measuring the heart rate variability in CLS patients and healthy subjects, it can be clarified whether the autonomic nervous system has an impact on Closed Loop Stimulation.

Materials and Methods

This study protocol was approved by the human ethics committee, and a written, informed consent was obtained from all 58 pacemaker patients and 37 control

	Pacemaker group	Control group
No. of patients	58	37
Age (years)	57 ± 9	52 ± 8
Based cardiomyopathy	Chagas disease	None
NYHA class	I	I
Medication	None	None
Diabetes	None	None
CAD	None	None
Implant indication	DNS symptomatic	Without pacemaker
EF (%)	62 ± 3	65 ± 10
Implantation time (months)	8 ± 3	–

Table 2. Characteristics of the pacemaker patients and the healthy control individuals. DNS = delayed neurological sequelae; EF = ejection fraction; CAD = coronary artery disease.

individuals (Table 2). Patients suffering from sick sinus syndrome (chronotropic incompetence) and indication for implantation of a DDDR pacemaker received an Inos^{2+}CLS pacemaker in combination with active fixation leads (Y60BP, Biotronik) in the right ventricle and right atrial appendage. Thereby, patients with unstable coronary disease, uncontrolled hypertension, or who were on beta-blocking agents that could not be discontinued were not enrolled in the study. The patient group was characterized by Chagas' disease, NYHA class I, and all presented with the symptoms of delayed neurological sequelae (dizziness, syncope, dyspnea). In contrast, the healthy individuals were enrolled after exclusion of any specific or significant disease. All patients and healthy subjects underwent the 24-hour ECG Holter to collect heart rate variability data in the time and frequency domains. Student's t-test was used to evaluate the results, whereby a p-value < 0.05 was considered significant.

Results

The circadian variation of heart rate variability in a pacemaker patient is shown in Figure 1. Lower values of the SDNN, rMSSD, and pNN50 parameters during nighttime indicate a reduced activity of the autonomic nervous system. An example of the frequency analysis of a 24-hour ECG in a pacemaker patient is presented in Figure 2, showing a predominant LF part in comparison with the HF part. The statistical analysis of all patients and healthy individuals is presented in Table 3.

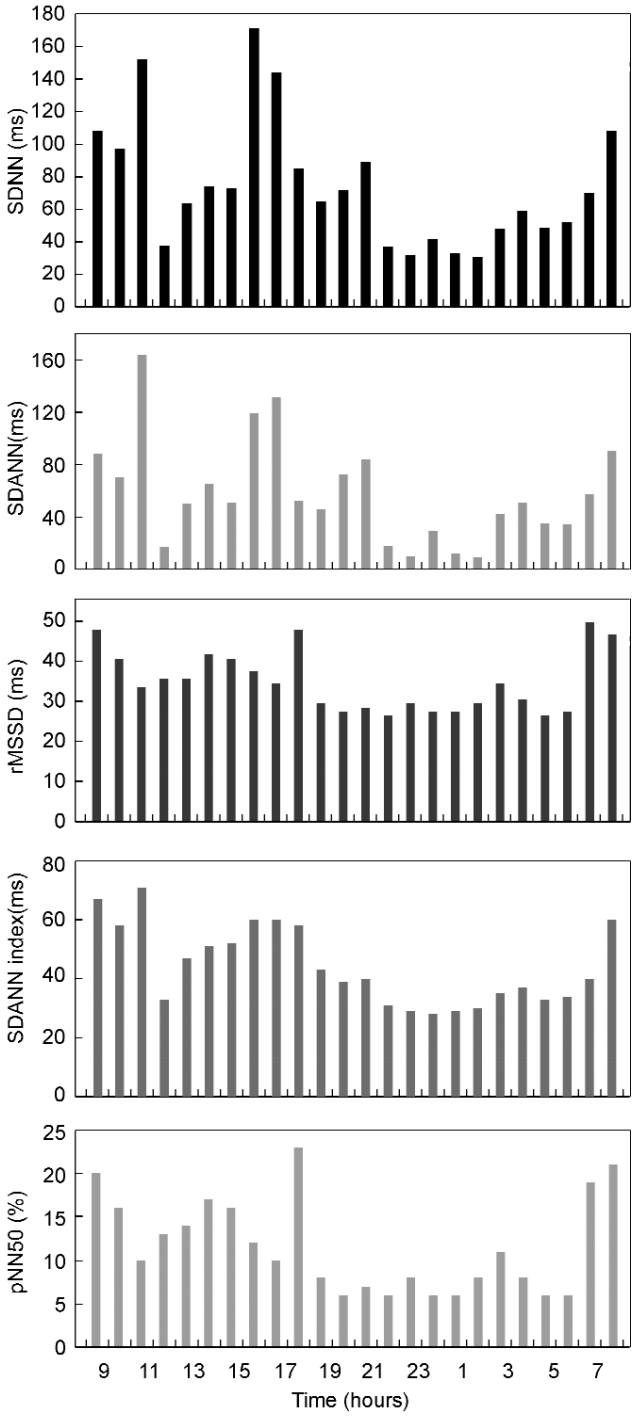

Figure 2. Typical 24-hour trend of heart rate variability parameters in time domain (defined in Table 1) in a pacemaker patient showing increased activity during the daytime.

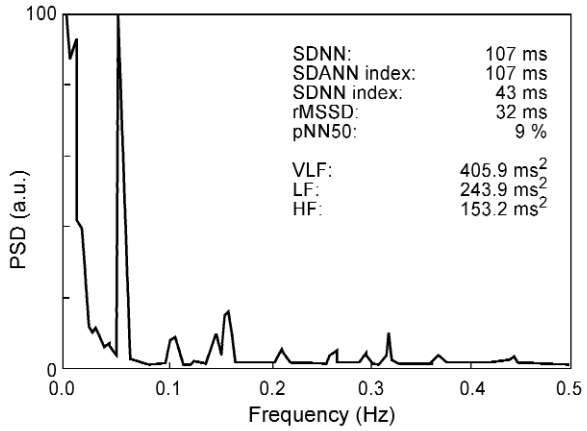

Figure 3. Frequency domain analysis of heart rate variability in a pacemaker patient. Power spectral density is given in arbitrary units (a.u.). Very low frequency part (integration the range 0.003 – 0.04 Hz), low frequency part (integration in the range 0.04 – 0.15 Hz), and high frequency part (integration the range 0.14 – 0.4 Hz), as well as the time domain parameters (defined in Table 1) are shown.

	Pacemaker group	Control group	p-value
HR (bpm)	76 ± 4	77 ± 6	n.s.
SDNN (ms)	118 ± 10	128 ± 12	n.s.
SDANN (ms)	97 ⊥ 5	116 ⊥ 7	n.s.
SDNN index (ms)	55 ± 3	53 ± 4	n.s.
rMSSD (ms)	35 ± 6	36 ± 5	n.s.
pNN50 (%)	9 ± 2	11 ± 2	n.s.
VLF-24h (ms^2)	1913 ± 27	1765 ± 35	n.s.
LF-24h (ms^2)	295 ± 51	718 ± 60	< 0.01
HF-24h (ms^2)	171 ± 69	148 ± 70	n.s.
LF_{max} (ms^2)	3436 ± 110	996 ± 56	< 0.001
HF_{max} (ms^2)	290 ± 85	759 ± 61	n.s.

Table 3. Heart rate variability analysis of a 24-hour ECG (mean value ± standard deviation) of the corresponding time and frequency domain parameters in both the pacemaker group and healthy control group (n.s. = not significant). See text for detailed information.

Thereby, we calculated the heart rate variability parameters in each subject for the complete 24-hour ECG and took the mean value ± the standard deviation in both groups. In addition, LF and HF were calculated for consecutive 5-minute periods. From the maximum value during 24 hours HF_{max} and LF_{max} in each subject, the mean value ± the standard deviation was found in both groups

Mean heart rate as well as the most important heart rate variability parameters in time domain, e.g., SDNN index, SDNN index, rMSSD, pNN50, and frequency domain parameters, e.g., VLF, HF, HF_{max} are similar in both groups. In contrast, a large, significant difference in the LF_{max} and LF frequency domain parameter of the pacemaker group was found compared with the control group, which demonstrates a possible extensive sympathetic activity for 24 hours in the pacemaker patients.

Discussion

According to Malinowski [14], the advantages of CLS over other types of pacemakers are demonstrated on the basis of measurements of heart rate variability. Only CLS pacing provides well-pronounced variations of the heart rate due to interaction with the autonomic nervous system, which could be an indicator of a better prognosis for CLS patients. It was also shown that these variations are similar to those of the control group without pacemakers. In both cases, increasing LF_n power and decreasing HF_n power, respectively, is observed in cases involving physical strain due to more pronounced sympathetic activity versus parasympathetic activity, which demonstrates the strong consistency of CLS pacing with intrinsic heart rate stimulation by the sinus node. From these results, it is natural to assume that CLS pacemakers perform in a way that is comparable to the physiological sinus node, which is the basic approach to increasing a patient's quality of life. Nevertheless, due to the small number of patients, a study with sufficient sample size for statistical data analysis was still lacking. To close this gap, we analyzed heart rate variability in a large number of patients and healthy individuals.

In our study we have observed almost the same results, although the rate of sympathetic tone in CLS is enhanced compared with the control group in light of the 24-hour ECG Holter. Such behavior is similar to pathophysiological mechanisms in patients with any degree of heart failure when the level of epinephrine tends to enhance the sympathetic tone. Thus, our results might be explained by the different state of health

in the two groups. Nevertheless, further analysis is needed to explain this specific behavior in detail, e.g., by direct measurement of epinephrine concentration.

References

[1] Clémenty J, Barold SS, Garrigue S, et al. Clinical significance of multiple sensor options: Rate response optimization, sensor blending, and trending. Am J Cardiol. 1999; 83: 166D-171D.

[2] Clémenty J, et al. Dual chamber rate responsive pacing system driven by contractility: Final assessment after 1 year follow-up. PACE. 1998; 21(Part II): 2192-2197.

[3] Lau CP, Butrous GS, Ward DE, et al. Comparison of exercise performance of a rate adaptive right ventricular cardiac pacemaker. Am J Cardiol. 1989; 63: 833-838.

[4] Clementy J, Kobeissi A, Garrigue S, et al. Validation by serial standardized testing of a new rate-responsive pacemaker sensor based on variations in myocardial contractility. Europace. 2001; 3: 124-131.

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

[6] Bernhard J, Lippert M, Ströbel JP, et al. Physiological rate-adaptive pacing using closed-loop contractility control. Biomed Tech (Berl). 41 (Ergänzungsband 2); 1996: 13-17.

[7] Christ T, Brattström A, Kühn H, et al. Effect of circulation catecholamines on the pacing rate of the Closed Loop Stimulation pacemaker. Prog Biomed Res. 1998; 3: 143-146.

[8] Osswald S, Cron T, Gradel C, et al. Closed-loop stimulation using intracardiac impedance as a sensor principle: Correlation of right ventricular dP/dt_{max} and intracardiac impedance during dobutamine stress test. PACE. 2000; 23: 1502-1508

[9] Novak M, Hoffmann G, Schaldach M. Multi-center investigations with automatically initialized closed loop stimulation-rate response during daily life and physical exercise test. Prog Biomed Res. 1998; 3: 147-151.

[10] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation. 1996; 93: 1043-1065.

[11] Algra A, Tijssen JG, Roelandt J, et al. Heart rate variability from 24-hour eletrocardiography and the 2 year risk for sudden death. Circulation. 1993; 88: 180-185.

[12] Malpas SC, Mailing T.J. Heart-rate variability and cardiac autonomic functions in diabetes. Diabetes. 1990; 39: 1177-1181.

[13] Baumer J, Frey AW, Adt M. Analysis of heart rate variability: Background, method, and possible use in anesthesia. Anästhesist. 1995; 44: 677-687.

[14] Malinowski K. Interindividual comparison of different sensor principles for rate adaptive pacing. PACE. 1998; 21(Part II): 2209-2213.

Contact
Dr. Antônio da Silva Menezes Jr.
Rua T-38, No. 738, Apto 204
Edfício Halley, Setor Bueno
74223-040 Goiânia, Goiás
Brazil
E-mail: hertz@terra.com.br