Performance of Closed Loop Stimulation in Hypertrophic and Dilated Hearts

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Summary

Previous studies have introduced Closed Loop Stimulation (CLS) as a pacemaker therapy for reestablishing a physiologic heart rate regulation. They were able to prove that right-ventricular intracardiac unipolar impedance measurements are suited to monitor both the right-ventricular and the left-ventricular inotropic cardiac state. Regulating the pacing rate in accordance with myocardial contraction dynamics offers the advantage of including the pacemaker into the natural cardiovascular control loop via negative feedback between the pacing rate and changes in blood pressure. Optimizing the rate regulation in such a manner is especially crucial for patients with congestive heart failure, who have a limited stroke volume, in order to provide a sufficient cardiac output under load. Therefore, this patient population should benefit particularly well from a CLS therapy. Nevertheless, the question arises whether a pathological limitation in contractility could lead to an impairment of the CLS rate regulation. The CLS system comprises automatic initialization and continuous updating of the rate dynamics to compensate for lower or gradually modified contraction dynamics. However, the performance of this function has so far not been explicitly verified in a clinical study. Thus, the primary task of the presented study was to investigate whether and to what degree an effective CLS therapy with adequate pacing rates can be implemented in patients who suffer from a limited contractility. An exercise-tolerant patient population (N = 14; 4 female; ejection fraction at rest for 11 patients: 72 ± 8.6 %) suffering from various degrees of diastolic and systolic insufficiency was selected. During a follow-up examination 3 months after implantation of an Inos^2 CLS pacemaker, various stress tests and echocardiographic examinations were performed, in order to study the cardiac geometry's possible influence on the pacing rate. The study results show that the expected individual heart rate is dependent on the different load steps, and independent from the diastolic state of the left ventricle (diameter, posterior wall thickness). From the study results, it can be concluded that CLS therapy is also suited for patients with limited contractility. Therefore, no restrictions apply to a closer investigation of the benefit of CLS therapy for this particular patient population in further studies.

Key Words

Closed Loop Stimulation, dilated heart, hypertrophic heart, limited contractility

Introduction

Pathological restrictions of the cardiac pumping performance can be divided into two mechanisms, systolic and diastolic insufficiency, as can be seen in Figure 1 [1]. Systolic insufficiency as a result of dilated cardiomyopathy, myocardial ischemia, cardiac infarction, or generally during pressure and volume loads of the heart leads to an extension of the ventricles and a restriction of the heart's ability to contract. While a systolic insufficiency impairs contractility directly, a diastolic function disturbance of hypertrophic ventricles (e.g., hypertrophic cardiomyopathy) also affects the contraction dynamics. In this case, thickening of the

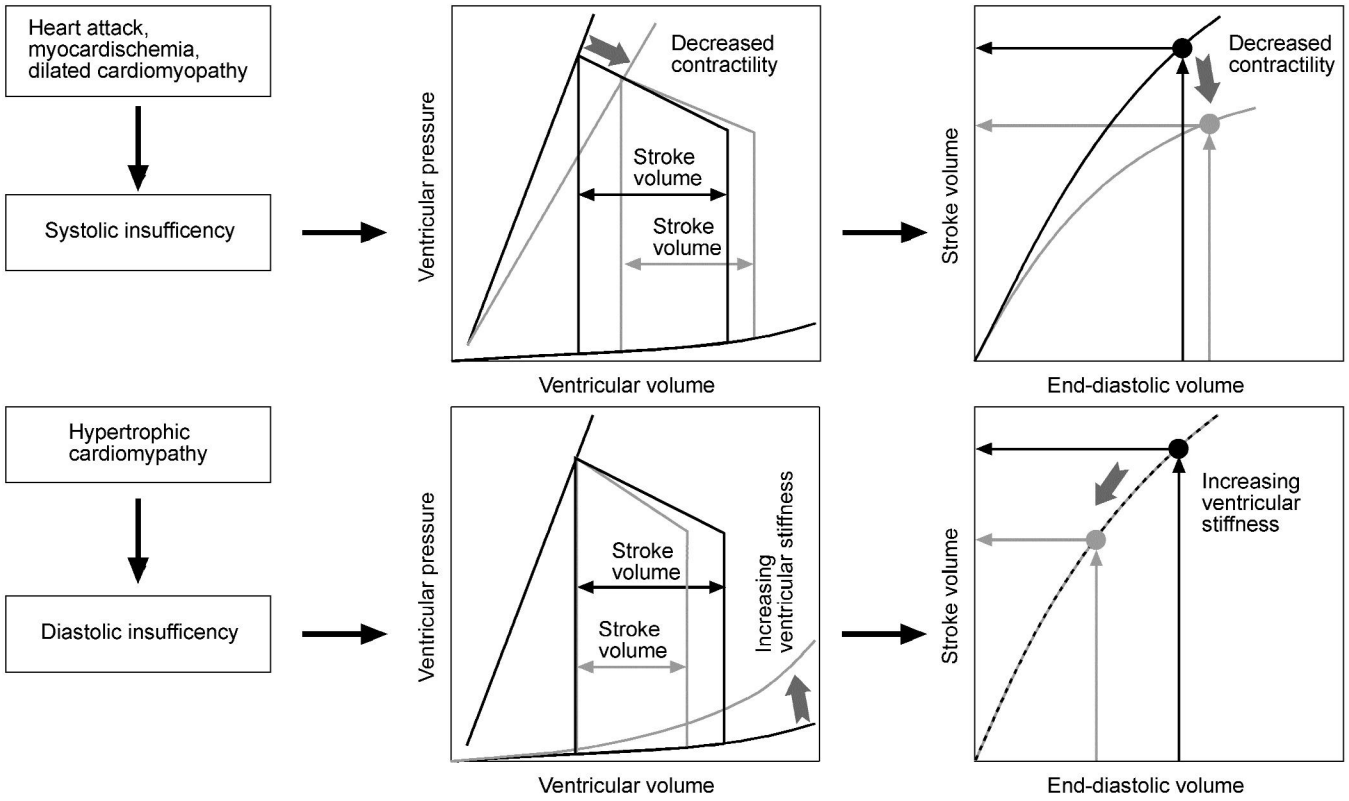


Figure 1. Effects of systolic and diastolic cardiac insufficiency on the contraction dynamics and the stroke volume.

ventricular walls and the septum results in stiffening of the ventricles and a lower end-diastolic volume, thus again decreasing the stroke volume. In the end, physiologic compensation mechanisms can have the result that diastolic and systolic function disturbances merge into each other [2].

A reduced stroke volume can lead to a considerably limited performance, especially in those patients who additionally suffer from permanent or intermittent chronotropic incompetence. In such a case, only the reestablishment of chronotropy with a rate-adaptive pacemaker therapy can achieve an adequate, load-dependent cardiac output [3-4].

Closed Loop Stimulation (CLS) regulates the pacing rate according to the cardiovascular demand by determining and analyzing the myocardial contraction dynamics from right-ventricular intracardiac impedance curves (Figure 2). Osswald et al [5] were able to show a correlation of this measurement signal with the right-ventricular maximum pressure gradient, which is generally accepted as a parameter for the inotropic state of the heart. Moreover, first results with the left-ventricular maximum pressure gradient also show a

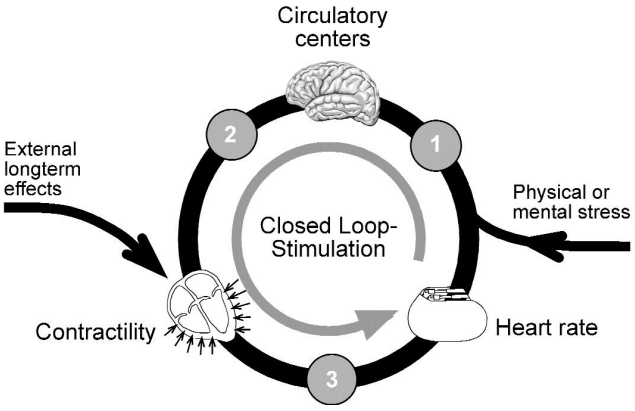


Figure 2. Principle of Closed Loop Stimulation (CLS). Baroreceptors detect a fall in blood pressure during physical or mental load (1), prompting the autonomic nervous system to react with a rise of the contractility (2). The CLS system senses the relative change in the myocardial contraction dynamics through intracardiac impedance measurements (3) and generates a higher pacing rate, thus increasing the cardiac output. Consequently, the blood pressure stabilizes, while contractility and pacing rate are regulated to optimal values. The CLS system's automatic initialization and continuous updating compensate for external long-term influences that affect the inotropic cardiac state.

correlation with the CLS impedance signal [6]. A detailed description of the principle of CLS has already been extensively discussed in earlier publications, using examples from the clinical practice [7-10]. If the intracardiac contraction dynamics are used to control the pacing rate, pathological changes in the inotropic cardiac state can also affect the rate dynamics during physical as well as mental tress. For that reason, CLS pacemakers are equipped with a procedure for automatic initialization and continuous updating. Programming a basic rate (BR) and a maximum closed loop rate (MCLR) has the effect that changes in the contraction dynamics are in the medium-term always reflected in the rate range between BR and MCLR, i.e., the rate range between BR and MCLR is always completely used within a few days. Long-term studies with Inos pacemaker systems did not find any problems concerning the rate stability [11]. On the other hand, there has so far been no special study with the task of determining whether pathological changes of the heart and especially of the contraction dynamics have a negative influence on the rate regulation with CLS. The presented study aims at closing this gap.

Materials and Methods

Fourteen patients (ten male and four female; mean age 71.3 ± 11.8 years) were included in the study. Due to their chronotropic incompetence, all were implanted with an Inos² CLS pacemaker (Biotronik, Germany). To determine the contractile state of each individual patient, an echocardiographic measurement was performed while the patients in supine position, determining the diameter of the left ventricle (diastolic, systolic) as well as the thickness of its posterior wall (diastolic, systolic). In all patients, automatic CLS initialization was activated after the 4-week follow-up with the same programming (BR = 60 beats/min, MCLR = 120 beats/min). During a follow-up after 3 months, the patients underwent a two-step ergometric test in the supine position, according to their exercise tolerance (rest – 25 W – 50 W – recovery, or rest – 50 W – 75 W – recovery). Only 11 patients (eight male, three female) participated in this examination because two patients were not able to participate due to knee problems, and one patient did not show up for the scheduled follow-up. During the ergometric test, each load stage was maintained for 3 min; the recovery phase lasted 5 min. The heart rate was recorded with a pacemaker Holter and, subsequently, read out by a laptop programmer and stored on a disk. Mean values for each load stage are shown here. At the end of each load stage, the blood pressure was measured, and an echocardiographic measurement was carried out. It determined the ejection fraction (EF), the systolic and diastolic thickness of the posterior wall, and the systolic and diastolic ventricular diameters. Normal values from the literature (Table 1) were used for the purpose of comparison [12-18]. The algorithm used in the CLS system to avoid orthostasis-caused rate peaks was deactivated in the study software during this special load test in a supine position. For evaluation, methods of descriptive statistics, the Student t-test ($P < 0.05$ was considered to be statistically significant), and correlation analysis were used.

Results

Performing echocardiographic examinations during exercise poses some difficulties due to the patient's body movements, thus leading to a certain inexactness of the measurement results. To evaluate the individual measurements, the simultaneously determined systolic and diastolic diameters of the left ventricle were used for all examinations. An approximately linear relationship should exist at rest and under submaximum load. The measurement values depicted in Figure 3 resulted

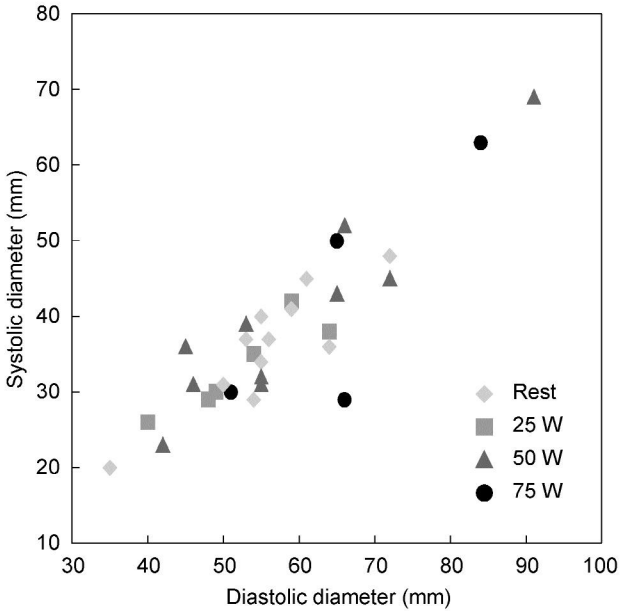
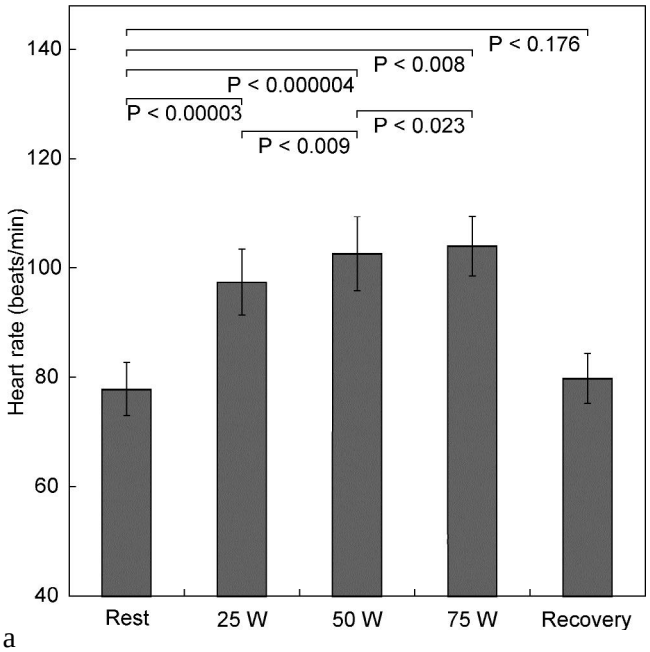


Figure 3. Relationship between the systolic and diastolic diameters of the left ventricle, as measured by echocardiography during various load states.



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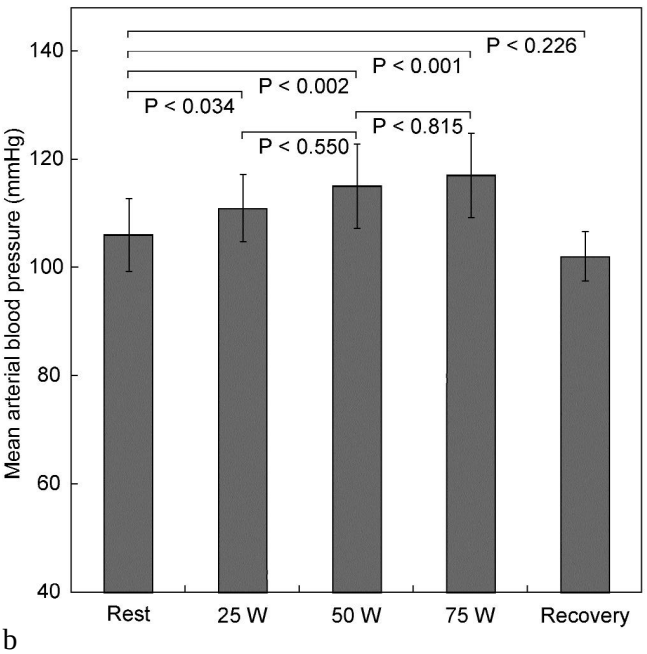

b

Figure 4. Mean values ± standard deviation for heart rate (a) and mean arterial blood pressure (b) in dependence on the load during ergometry. N = 7 patients (rest, 25 W, 50 W, recovery); N = 4 patients (rest, 50 W, 75 W, recovery). The statistical statements are based on a two-tailed paired t-test.

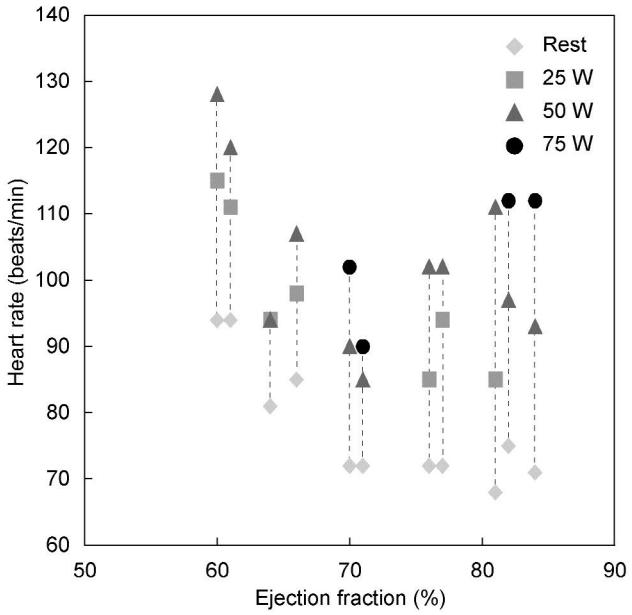

Figure 5. Heart rate in dependence on the ejection fraction measured in the resting position.

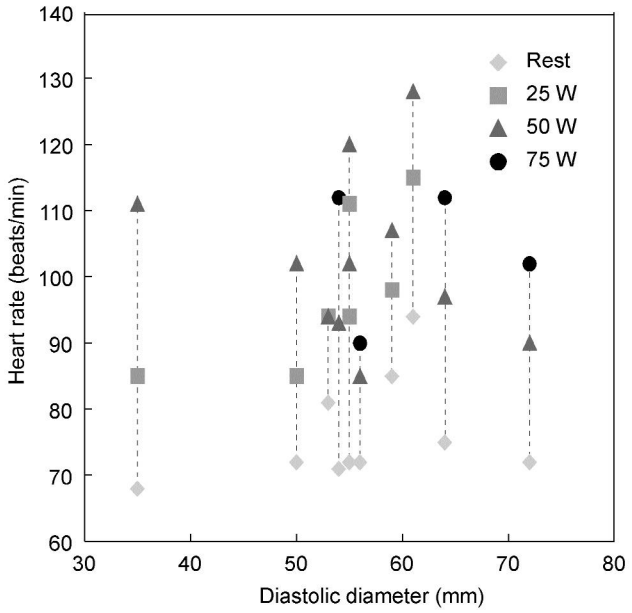

Figure 6. Heart rate during various load states in dependence on the diastolic diameter of the left ventricle (measured in the resting position).

in such a relationship if a realistic measurement error of a magnitude of < 10 % is assumed. Thus, the measurement values listed in Table 1 reflect the pathological state of the left ventricle of the individual patients with great accuracy. The values clearly show that both patients with hypertrophic and with dilated ventricles were included in the patient population. The mean pacing rates and blood pressure values of all patients for

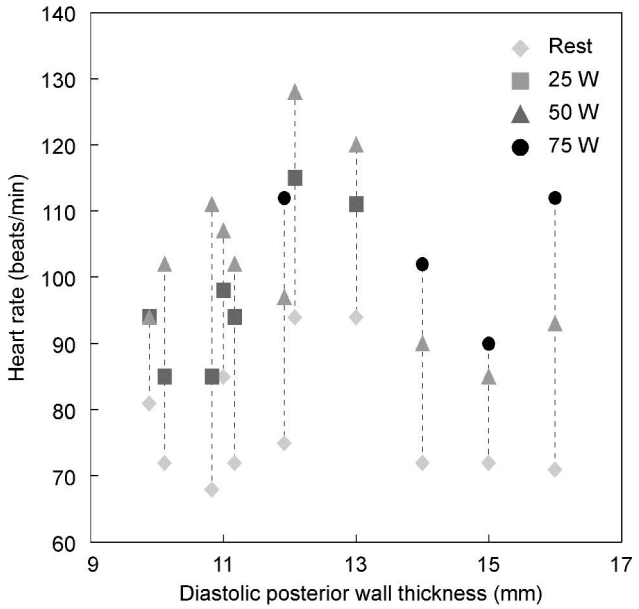

Figure 7. Heart rate during various load states in dependence on the diastolic posterior wall thickness of the left ventricle (measured in the resting position).

	Mean (mm)	SD (mm)	95 % Confidence interval (mm)	References
Diastolic diameter				
Adults	4.7	0.56	3.7 – 5.6	[12]
82 adults	4.7	-	3.7 – 5.6	[13]
40 adults (19 – 68 years)	5.0	0.4	-	[14]
Men	4.9	0.5	≤ 5.8	[15]
Women	4.4	0.5	≤ 5.3	[15]
Systolic diameter				
Adults	3.5	0.6	2.7 – 3.7	[12]
40 adults (19 – 68 years)	3.0	0.3	-	[14]
Men	3.1	0.5	≤ 4.1	[15]
Women	2.7	0.5	≤ 3.7	[15]
Diastolic posterior wall thickness				
137 adults	0.9	-	0.6 – 1.1	[13]
22 adults (22 – 61 years)	0.83	0.18	-	[16]
20 adults (19 – 63 years)	0.9	0.2	-	[17]
78 men	0.89	0.14	≤ 1.17	[18]
55 women	0.80	0.15	≤ 1.09	[18]
Systolic posterior wall thickness				
20 adults (19 – 63 years)	1.5	0.3	-	[17]

Table 1. Normal values for the left-ventricular diameter and posterior wall thickness taken from the literature.

the different load stages are graphically depicted in Figure 4. The results show an adequate rise in pacing rate for each load step. After the recovery phase, the values returned to the initial value.

To evaluate the rate response at a variety of pathological states, the heart rates of each individual patient were studied in more detail in the following. Figures 5 to 7 show the heart rates of each patient for each load against the EF (range 60 % – 84 %, 72 ± 8.6 %), the diastolic ventricular diameter (35 – 64 mm, 55.7 ± 9.3 mm), and the diastolic posterior wall thickness (10 – 16 mm, 12 ± 2 mm). All ventricular parameters were determined at rest and reflect the patients' state of health. According to the chosen representation, three vertically superimposed points equal the data from one patient. Heart rate dependence on both the diastolic diameter and the posterior wall thickness of the left ventricle at rest were shown despite a wide scattering of the inter-individual patient data (Figures 6 and 7). Accord-ing to Tables 1 and 2, about half of the patients had di-lated or/and hypertrophic ventricles; thus, any possible limitation of the CLS rate regulation should be reflected in the data. However, obviously no clear correlation can be observed between the load-dependent rate and the left-ventricular diastolic diameter (correlation coefficients: $R^2 = 0.1$; $R^2 = 0.5$; $R^2 = 0.04$, $R^2 = 0.004$) or the left-ventricular diastolic posterior wall thickness (correlation coefficients $R^2 = 0.04$; $R^2 = 0.6$; $R^2 = 0.1$; $R^2 = 0.1$), both determined at rest and thus comparable with the values from literature in Table 1.

Discussion

Mainly patients with pathological changes of the left ventricle were included in the presented study. The entire patient group showed a statistically significant increase in heart rate and blood pressure from rest to the two different load stages. In contrast, the difference between the initial rest situation and the recovery phase at the conclusion of the ergometric test, as well as between the two load stages was statistically not significant. While the first result is to be expected from a physiologic rate regulation, the second result can be

	Patient number 1	2	3	4	5	6	7	8	9	10	11	Mean	SD
Diastolic diameter (mm)	53	50	55	59	55	61	35	64	56	54	72	54.1	8.0
Systolic diameter (mm)	37	31	34	41	40	45	20	36	37	29	48	35.1	7.1
Diastolic posterior wall thickness (mm)	10	10	11	11	13	12	11	12	15	16	14	12.1	2.0
Systolic posterior wall thickness (mm)	16	19	18	16	17	19	17	23	24	24	19	19.3	3.2

Table 2. Measured values of the study group for left-ventricular diameter and posterior wall thickness. Abnormal parameters according to Table 1 are indicated.

explained by the fact that the ergometric load does not linearly depend on the actual load under the unusual load conditions during ergometric testing in a supine position. Therefore, the difference between the first and the second load stage might not be large enough for the patient, so that no statistically significant rise in heart rate could be observed due to the small number of patients.

The analysis of the echocardiographic measurements shows a moderate EF variation. These values are still within the normal range (66 ± 6 %) [19] , thus it can be assumed that the exercise tolerance of the patients was not significantly limited. The individual patient data show a wide variation of the individual measurement data due to the adjustment of the CLS system to the individual state of each respective patient. Despite this scattering, an increase in heart rate with decreasing EF is obvious. This observation is in agreement with the need to generate a sufficient cardiac output. Obviously, the pacemaker compensates for a lower ejection performance with a higher pacing rate. CLS systems support the patient's intrinsic rhythm if it is adequate. In some patients, the sinus rhythm became dominant during high loads, resulting in rates higher than the MCLR of 120 beats/min.

The most important study results were gained from analyzing the left-ventricular diastolic diameter and the left-ventricular diastolic posterior wall thickness. The diastolic diameter determined at rest exceeds the physiologic limit of 55 mm in half of the patients. Nevertheless, no heart rate dependence on this cardiac parameter can be observed. The same results for the diastolic posterior wall thickness determined at rest, where values below 12 mm are within the normal range. Even the three patients with more hypertrophic ventricles between 14 and 16 mm show about the same rate dynamics as the rest of the study group.

The automatic initialization and continuous updating of the CLS system required only the programming of a basic rate and a maximum closed loop rate (study parameters: BR = 60 beats/min, MCLR = 120 beats/min), i.e., no patient-specific parameters were programmed. Nevertheless, an adequate, individual rate regulation resulted, independent of the hypertrophic or/and dilated state of the left ventricle. Thus, the study confirms the reliability of Inos CLS pacemakers also for patients with systolic or diastolic function disturbances due to limited or changed contraction dynamics.

Conclusion

Patients suffering from congestive heart failure and chronotropic incompetence can benefit from reestablishing the rate regulation with a suitable pacemaker system. In this context, CLS should be particularly well suited because its rate regulation is based on negative feedback about the inotropic state of the heart. This study aimed at testing the influence of dilated or hypertrophic hearts on the rate regulation of CLS systems. Although, the small patient number did not allow performing an interindividual statistical comparison between different groups (normal group, group with hypertrophic ventricles, group with dilated ventricles), by using descriptive statistics and correlation analysis it was possible to show that the heart rates of patients with Inos^2 CLS pacemakers are independent of the size and thickness of the left ventricle. Thus it can be concluded that limited or modified contraction dynamics of the myocardium are compensated by the CLS system.

References

[1] Silbernagel S, Lang F. Taschenatlas der Pathophysiologie. Stuttgart, New York: Thieme Verlag. 1998: 224-227.

[2] Opie L. The Heart. Physiology from Cell to Circulation. Third Edition. Philadelphia, New York: Lippincott-Raven Publishers. 1998: 475-511.

[3] Salo RW, Auricchio A. Mechanisms of benefit in pacing of patients in heart failure. Herzschr Elektrophys. 1999; 10: 16-22.

[4] Auricchio A, Salo RW. Acute hemodynamic improvement by pacing in patients with severe congestive heart failure. PACE. 1997; 20: 313-324.

[5] Osswald S, Cron T, Grädel, 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.

[6] Ravazzi AP, Carosio G, Diorallevi P, et al. Clinical assessment of the correlation between right ventricular impedance and left ventricular contractility. Prog Biomed Res. 2000; 5: 478-481.

[7] Schaldach M. What is Closed Loop Stimulation? Prog Biomed Res. 1998; 3: 49-55.

[8] Schier M, Müssig D. Use of Closed Loop Stimulation in reestablishing full-scale cardiovascular regulation. Prog Biomed Res. 1999; 4: 489-495.

[9] Anelli-Monti M, Anelli-Monti B, Mächler H, et al. Closed Loop Stimulation – Ein neues Herzschrittmacher-Konzept zur Frequenzadaptation mittels eines Kontraktilitätsensors. J Kardiol. 1999; 6: 21-25.

[10] Clementy J, Garrigue S, Gencel L, et al. Evaluation of the chronotropic function of a closed-loop rate-responsive dual chamber pacemaker driven by contractility. Prog Biomed Res. 1999; 4: 171-175.

[11] Greco GT, Ardito RV, Souza DRS, et al. Long term experience with a contractility (ANS) driven pacemaker sensor in patients with chronic chagasic myopathy. Prog Biomed Res. 1999; 4: 181-184.

[12] Biamino G, Lange L (editors). Echokardiographie. Frankfurt: Hoechst Aktiengesellschaft. 1983: 44.

[13] Feigenbaum H. Echocardiography. 4th edition. Philadelphia: Lea & Febiger. 1986: 622.

[14] Manyari DE, Duff HJ, Kostuk WJ, et al. Usefulness of noninvasive studies for diagnosis of right ventricular dysplasia. Am J Cardiol. 1986; 57: 1147-1153.

[15] Devereux RB. Echocardiography: state of the art-1984. Cardiology. 1984; 71: 118-35.

[16] Hahn B, Bohn I, Strauer BE. Functional evaluation of left ventricular dynamics by use of 2-dimensional echocardiography: comparison with left ventriculography and assessment of normal 2-dimensional echocardiographical values. Z Kardiol. 1982; 71: 445-451.

[17] St. John Sutton MG, Reichek N, Kastor JA, et al. Computerized M-mode echocardiographic analysis of left ventricular dysfunction in cardiac amyloid. Circulation. 1982; 66: 790-799.

[18] Devereux RB, Lutas EM, Casale PN. Standardization of M-mode echocardiographic left ventricular anatomic measurements. J Am Coll Cardiol. 1984; 4: 1222-1230.

[19] Herold G. Innere Medizin. Köln. 1995: 149-165.

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