Closed Loop Stimulation in Patients with Normal and Limited Contractility

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Summary

The integration of the pacemaker into the natural control system is the main idea of Closed Loop Stimulation (CLS). Following publications on the reaction of CLS to various provoked influences, this study collects clinical experiences from patients with different indications and a variation in underlying heart diseases during daily life activities and provoked mental stress. The applicability of CLS therapy in patients with pathologically limited myocardial contractility is the main focus of this article. CLS therapy was applied in 22 arrhythmic patients. Six of them additionally suffered from contractility-limiting diseases such as diabetes mellitus, cor pulmonale, or congestive heart failure. The heart rate behavior over 24 hours and during a mental stress test was analyzed. All patients, regardless of the contractile state, showed distinct circadian variations (day/night difference: 10.8 ± 7.6 bpm) and a rate increase during an arithmetic stress test (increase: 10 ± 9 bpm). The majority of the patients who completed a questionnaire reported an improved quality of life. Thus, the treatment of cardiac arrhythmias with the help of CLS is an adequate method of therapy for pacemaker patients with or without contractility-limiting cardiac diseases.

Key Words

Closed Loop Stimulation, mental stress tests, contractility, pharmacological therapy, RAPID study

Introduction

The theoretical basis and the clinical validation of pacing devices with Closed Loop Stimulation have been discussed in numerous publications in recent years [1-7]. The concept of integrating the stimulator into the natural regulation system, instead of mimicking the behavior of the heart rate with the help of external sensors, is expected to yield various clinical benefits. Advantages include appropriate regulation of blood pressure and heart rate during all situations of daily life as well as compatibility with and possible therapy of secondary diseases. A study by Malinowski that compared the resulting heart rates afforded by CLS therapy with those by different sensor-based pacemakers indicated that Closed Loop Stimulation leads to heart rates comparable to healthy subjects under the investigated forms of load [8].

Encouraged by the promising results of these previous publications, the collection of clinical experiences in patients with different indications and disease states in the Netherlands was initiated in the summer of 1998. CLS systems were implanted at two sites in the Netherlands in the context of the European RAPID study (Rate Behavior of the Pacing System INOS² CLS during Daily Life), which is investigating the long-term stability and adequacy of heart rate behavior in all situations of patient life. This publication presents the preliminary results from the first follow-up of 22 patients receiving CLS therapy.

This special report focuses on the clinical evaluation of the applicability and reliabilty of the system in case of diseases or medications that influence contractility of the ventricular myocardium. As discussed in numerous

articles, CLS systems available to date are continuously monitoring the contraction dynamics of the ventricular myocardium and adjusting the stimulation rate accordingly. Hence, a question of outmost importance is the influence of pathologically or pharmacologically limited contraction dynamics on the resulting cardiovascular regulation in patients with CLS pacemakers, such as diabetes mellitus, congestive heart failure, or the use of beta-blockade. The comparison between patient groups with diseases or medication that do or do not affect the cardiovascular system shall clarify whether CLS therapy still yields appropriate results in patients with limited contractility.

Materials and Methods

Pacemakers with Closed Loop Stimulation (Inos² CLS, BIOTRONIK) were implanted in 22 patients (9 female, 13 male) with a mean age of 72.6 ± 9.8 years. Indications for the pacemaker therapy were AV block and sick sinus syndrome (SSS), as shown in the distribution of indications in Figure 1. Additionally, some patients suffered from secondary diseases such as diabetes mellitus (2 cases), cor pulmonale (2 cases), congestive heart failure (2 cases), and other diseases that do not affect the cardiovascular system, such as Parkinson's disease, polymyalgia rheumatica, and lung cancer.

The patients can be classified according to their secondary diseases, which may blunt cardiovascular responses or directly or indirectly, influence the cardiovascular system. The patients with secondary diseases (SD) (n=6) having cardiovascular effects had a mean age of 73.8 ± 12.7 years, the patient group without secondary diseases having cardiovascular effects (no secondary disease, NSD, n=16) were 72.2 ± 8.8 years of age. The distribution of secondary diseases is illustrated in Figure 2. All patients of the SD group received medication with cardiovascular effects (ß-blockers in 4 cases, hypertonica in 2 cases). Additionally, 4 patients of the NSD group were medicated with ß-blockers. The remaining 12 patients took no medication that had cardiovascular effects.

After implantation of the CLS pacemaker and standard leads (in 3 cases no leads were implanted, just the pacemaker was exchanged), the CLS mode was started using the automatic initialization. The basic rate and the maximum CLS rate were programmed to 60 ppm and 120 ppm, respectively, in all patients. Beside these settings, no other parameter adjustments for rate modulation are necessary with the CLS pacemaker. Three months after implantation, a complete follow-up check was done including threshold and sensing test, and interrogation of the 24-hour trend from the internal pacemaker Holter, and a mental stress test. The mental stress test was designed as an arithmetic exercise (counting backwards from 700 in steps of 7). Furthermore, 15 patients agreed to complete a quality-of-life questionnaire, which intended to compare the present symptomatic level, well-being, and health status to the situation before implantation. Possible answers were "better," "unchanged," or "worse" for each aspect.

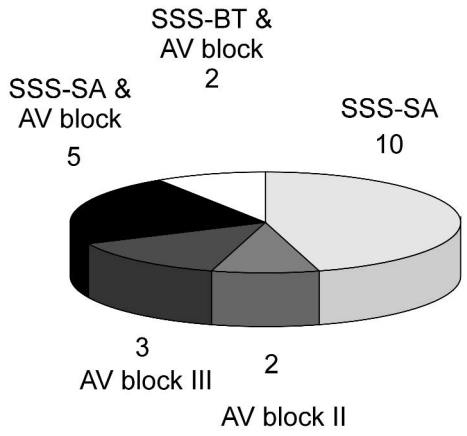

Figure 1. Indications for pacemaker implantation.

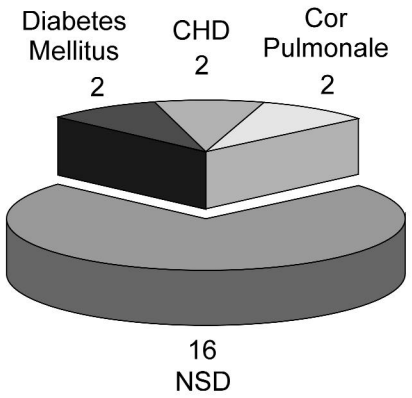

Figure 2. Patient groups with (n=6) and without (n=16) secondary diseases possessing cardiovascular effects.

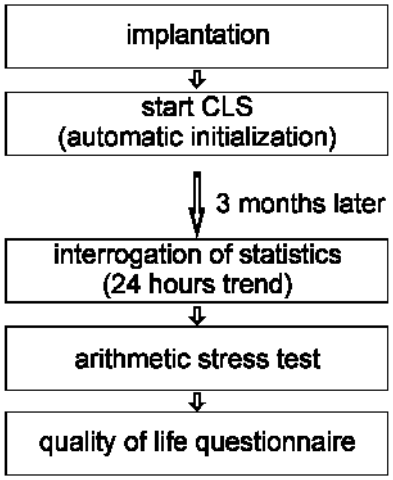

Figure 3. Flow chart of performed investigations.

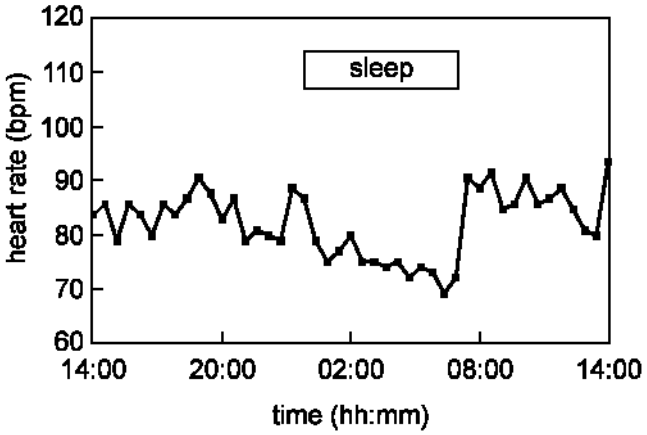

Figure 4. Typical 24-hour trend of a patient from the SD group (diabetes mellitus).

A flow chart of the investigations is depicted in Figure 3. For the analysis of the heart rate results, the mean values for diurnal and nocturnal rates as well as the percentage of intrinsic sinus activity were determined from the interrogated statistical data. The day and night periods were defined according to the patient's diary. Additionally, the mean increases in heart rate during the mental stress test were calculated.

Results

CLS pacemakers were implanted and initiated without complications in all 22 patients. Analyzing the complete patient population, distinct circadian variations were observed. A typical 24-hour trend is shown in Figure 4. The mean difference between day and night rates was 10.8 ± 7.6 bpm. In 77.3% of all patients, the difference between day and night rates was more than 5.0 bpm. Separating the 24-hour trend results from the two patient groups revealed that the disease state does not influence the resulting circadian variation. The day-night difference was 11.3 ± 8.1 bpm for the NSD group, 9.6 ± 7.6 for the SD group (Figure 5). Using the Student's t-test ($p < 0.05$), it was proven that the diurnal rate values were significantly higher than the nocturnal rates for the complete population as well as the two subgroups. The slightly smaller difference between average day and night rates in the SD group was due to a moderately elevated nocturnal rate level, whereas diurnal rates were identical.

The patients were relatively chronotropically incompetent, as the average percentage of intrinsic sinus activity indicates. The fraction of intrinsic atrial activity was 14.3 ± 13.9% for the complete population. With a percentage of 10.0 ± 13.0%, the patients of the SD group were more chronotropically incompetent than the NSD group (18.0 ± 14.4%). In 54.5% of the patients, the fraction of intrinsic sinus activity was below 10%.

The results of the arithmetic stress test show the reaction of the CLS system to mental load. From a baseline of 69 ± 3 bpm, the heart rate increased by 10 ± 9 bpm during the mental stress test. The relatively high standard deviation is due to the widely varying mental response of the patients to the mathematical exercises, which ranged from significantly excited to completely unimpressed.

In the quality-of-life questionnaire, three important aspects were addressed: classification of symptoms, general well being and overall perception of health status. A comparison was made in subsequent questionnaires before and after implantation and CLS therapy. In 15 patients two tests were available. The classification was with CLS respectively "better, unchanged or worse" for symptom level 12, 1, 2; for general well being 10, 4, 1 and for overall health perception 9, 5, 1 (see Figure 6). Hence, in the majority of the patient population, CLS therapy improved all aspects of the patient's quality of life. The two patients who reported unfavorable results suffered from progressing diseases — Parkinson's disease in

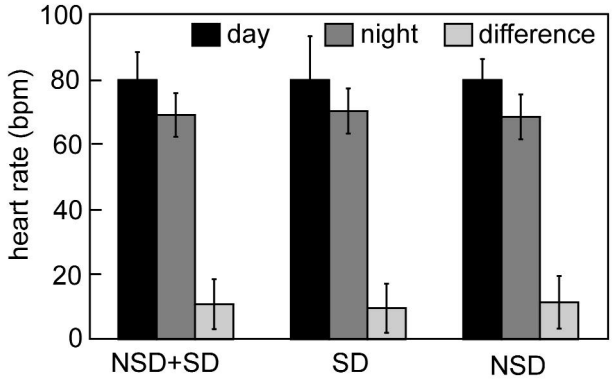

Figure 5. Average diurnal and nocturnal heart rates determined from the 24-hour trends.

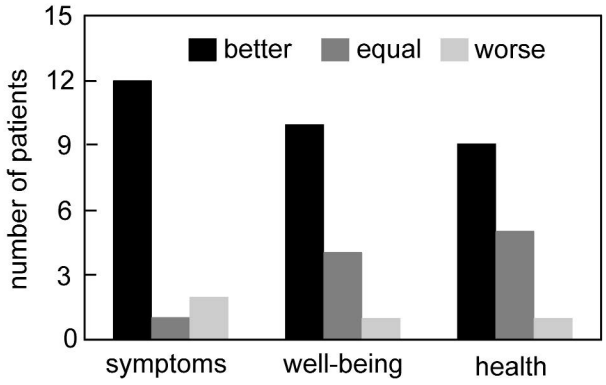

Figure 6. Results from quality-of-life questionnaire (n=15).

one case and progressing cor pulmonale and claudicatio intermittens in the other.

Discussion

The circadian variation in the mostly chronotropically incompetent patients with CLS therapy indicates the reestablishment of intact cardiovascular regulation. More specific proof of the pacemaker's integration in the natural control processes is the resulting increase in heart rate during the mental stress test, a feat that cannot be performed by external sensors [8]. The results confirm the positive clinical experiences of previous investigations, showing heart rate behavior very similar to that of normal individuals.

One of the most important conclusions from the experience collected in the presented investigations is that CLS therapy works even in cases of contractility-limiting diseases and medications. All diseases of the SD group influence the contraction behavior of the ventricular myocardium significantly. The progression of neuropathy caused by diabetes mellitus can be limited with the help of an adequate pharmacological therapy, but decreased inotropic regulation is unavoidable. Hence, the contraction dynamics of the myocardium are restricted [9]. Cor pulmonale leads to a dilation of the right ventricular wall and, thus, progressively decreases the contractility [10]. The limitation of myocardial contractility in patients with congestive heart failure is well known.

With respect to the realization of CLS therapy by monitoring the contraction dynamics of the right ventricular myocardium, the functionality of the system could be reduced in patients with secondary disease, which may blunt cardiovascular responses or directly diminish ventricular contractility. However, the circadian variation of the SD group is similar to that of patients without limited contractility. This result clearly demonstrates that the automatic initialization for the adaptation to patient-specific contraction dynamics and the algorithm for an automatic compensation of long-term changes in the contractility — both features of the investigated CLS device — are working reliably and appropriately. Furthermore, it becomes evident that, even in patients with contractility-limiting diseases, the contraction dynamics still reflect control information from the natural regulation system. With these results and the questionnaire data, the main task of the pacemaker therapy — to improve the patient's quality of life — is fulfilled with CLS therapy, regardless of the individual disease.

Conclusion

The therapy of cardiac arrhythmias with Closed Loop Stimulation reestablishes natural circadian variation. Although the CLS system is realized by monitoring contraction dynamics, CLS therapy can be applied without restrictions in patients with limited contractility, as far as the experience from this investigation indicates. With CLS therapy, a significant improvement in the quality of life resulted for the majority of patients surveyed. The next step of this investigation is to confirm the results with a greater number of patients in each subgroup.

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