Preliminary Results of Closed Loop Stimulation (CLS) During Chronotropic Assessment Exercise Protocol

M. HUBMANN, T. RUPPERT, E. LANG
Medizinische Klinik Waldkrankenhaus St. Marien, Erlangen, Germany

R. HARDT
Geriatrische Rehabilitationsklinik Irminen, Trier, Germany

Summary

We evaluated whether the self-initialization and continuous automatic adjustment of Inos² CLS pacemakers (BIOTRONIK, Germany) resulted in optimal pacing rates during a graded treadmill exercise. The study was conducted with eight patients aged 69 ± 7.6 years (range: 56-79 years), at 5 ± 4 months (range: 1-15 months) after pacemaker implantation. The programmed values of basic and maximum pacing rates were 60 beats per min (bpm) and 120-140 bpm, respectively. The slope and the speed of the treadmill were changed incrementally from 2% and 1 mile per hour (stage 1) up to 10% and 4 miles per hour (stage 7), according to a chronotropic assessment exercise protocol (CAEP). Mean arterial blood pressure was monitored during the exercise. Closed Loop Stimulation (CLS) pacing rates in the individual patients were assessed at each stage of the exercise and compared with the expected heart rates calculated according to a formula by Wilkoff et al. Achieved CLS pacing rates and the expected heart rates were then normalized to the 0-1 scale, and linear regression parameters and correlation index were calculated. Good correlation between the expected and CLS heart rates was obtained: $r^2 = 0.98$, $p < 0.05$, $Y = 1.018 X + 0.036$. Pacemaker rate response and mean arterial blood pressure trends during the exercise appeared appropriate in all patients. In the second part of the article, we discuss potential advantages of the CLS over conventional rate-responsive systems in elderly patients (at least 75 years old) and suggest several directions for future prospective clinical trials.

Key Words

Pacing rate, Closed Loop Stimulation, pacing in the elderly, chronotropic incompetence

Introduction

The concept of Closed Loop Stimulation (CLS) via intracardiac impedance (heart contractility) measurements was introduced around 1990 [1,2]. The CLS-based pacing rate adaptation had the potential not only to increase the functional capacity of chronotropically incompetent patients during physical exercise, but also to significantly improve overall quality of life of the patients. The reason for such expectations was a unique CLS feature capable of detecting any change in circulatory demands and, regardless of the origin of the stress (physical, mental, emotional, thermal, etc.), to support it with an adequate cardiac output. Large-scale clinical studies in Europe and Latin America demonstrated appropriate performance of the CLS rate adjustment principle and illustrated potential advantages of the CLS over conventional rate-responsive systems utilizing sensors of acceleration, body vibration, and minute ventilation [3-10].

Pacemaker self-initialization following implantation and continuous automatic adaptation of CLS on a daily basis are new features available in the Inos² CLS dual-chamber pacemakers (BIOTRONIK, Germany). This design was intended to ensure optimal performance of the Inos² CLS pacemaker in each patient and to simplify follow-up procedure by leaving only two rate-responsive parameters to be programmed: a basic pacing rate and a maximum CLS pacing rate.

Study Goals

The aim of the present study was to evaluate whether the automatic initialization and continuous automatic adjustment of the Inos[2] CLS pacemaker would result in appropriate pacing rates during a graded treadmill exercise. Because pacing in the geriatric population is a topic of particular interest for our team [11-13], in the second part of the article we discuss potential advantages of the CLS over conventional rate-responsive systems in elderly patients (at least 75 years of age) and suggest several directions for future prospective clinical trials.

Materials and Methods

Eight patients (2 female, 6 male) who had received an Inos[2] CLS pacemaker in the period from June 1997 to September 1998 were enrolled in the study. The mean age of the patients was 69 ± 7.6 years (range: 56-79). Indications for pacing were symptomatic bradycardia (n=8) secondary to sick sinus syndrome (n=5), carotid sinus syndrome (n=2), or third-degree AV block (n=1). Pacemaker leads implanted with the pacemakers were a fractal coated screw-in bipolar atrial lead (n=8) (Y53-5 BP, BIOTRONIK, Germany) and a fractal coated tined bipolar ventricular lead (n=8) (PX 60 BP, BIOTRONIK, Germany).
A chronotropic assessment exercise protocol (CAEP) was conducted 5 ± 4 months after pacemaker implantation (range: 1-15 months). The programmed values of basic and maximum pacing rates were 60 beats per min (bpm) and 120-140 bpm, respectively. The slope and the speed of the treadmill were changed incrementally from 2% and 1 mile per hour (stage 1) up to 10% and 4 miles per hour (stage 7), with each stage lasting 2 minutes [14]. Mean arterial blood pressure was monitored continuously during the exercise using the method by Riva Rocci.
The CLS pacing rate was assessed at each stage of the exercise and in each individual patient and compared with the corresponding expected heart rates calculated using the following equation, which is explained in Wilkoff et al [14]:

$$HR_{stage} = \frac{[220 - \text{age} - HR_{rest}] \times [MET_{stage} - 1]}{METS_{peak} - 1} + HR_{rest}$$

Thereafter, the achieved CLS pacing rates and expected heart rates were normalized to the 0-1 scale, and linear regression parameters and correlation index were calculated.

Results

Figure 1 summarizes the study results. Duration of the walk on the treadmill was 10.0 ± 2.8 minutes (range: 7.0 - 15.0 minutes), depending on the patients' individual capabilities. Rate response appeared to be appropriate in all patients. An individual example of the CLS rate adaptation during the CAEP and the corresponding mean arterial blood pressure trend are illustrated in Figure 2.

The individual patient performance versus patient age was as follows:

Patient Age	Exercise Duration
55 years	13.5 minutes
60 years	15.0 minutes
65 years	11.9 minutes
69 years	9.0 minutes
71 years	8.2 minutes
73 years	7.0 minutes
75 years	7.5 minutes
79 years	8.2 minutes

Discussion

No previous clinical studies have examined the correlation between the expected heart rates calculated according to the Wilkoff model [14] and CLS pacing

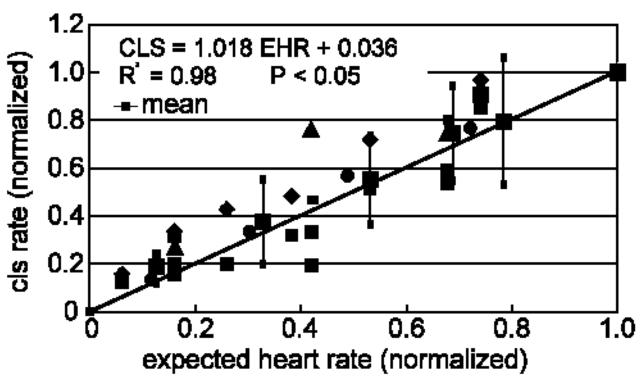

Figure 1. Scatter diagram of normalized CLS pacing rates and expected heart rates (EHR) during the treadmill CAEP. Mean ± standard deviation values are shown for each stage of the exercise. Linear regression equation and correlation index are indicated.

rates. As demonstrated in Figure 1, a very satisfactory correlation between the achieved and desired pacing rates for different workloads during the graded treadmill exercise was obtained in our study (r^2 = 0.98, $P < 0.05$). The used CAEP test is generally regarded as a suitable tool for the evaluation of the subject's exercise capacity, as the physical effort (walking slope and speed) is increased in small steps from minimum to medium and very high intensities, which encourages patients to attempt the next stage. Therefore, the CAEP allows an evaluation of the functional capacity of the subject and his (or her) chronotropic competence for a full range of activities from daily life [14].

Programming the CLS function in the Inos[2] CLS pacemaker is simplified to the degree that no other values than the basic and maximum pacing rates are selected by the physician. This eliminates the possibility of inadequate pacemaker programming and minimizes the risk of suboptimal rate adjustment, which may occur with other rate-adaptive systems [15].

The limitation of the present study is that it was conducted in a relatively small number of patients available for the investigation. The promising findings, however, call for a larger scale study that would verify our observations and demonstrate clinical meanigfullness of the findings. In view of the topic of the next section, the question is whether our study data may serve as an indication of proper CLS performance in elderly patients. According to our criteria for the elderly (patient age of at least 75 years), only two patients in this study belonged to the elderly group. However, a less strict criterion used in the USA (patient age of at least 65 years) was met in six out of eight patients [16]; in all of them the CLS performance was very satisfactory.

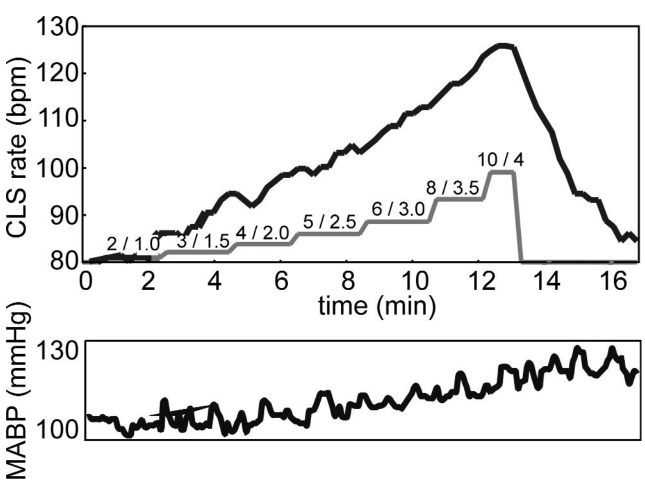

Figure 2. CLS pacing rate profile in beats per min (bpm) and the mean arterial blood pressure (MABP) trend in one patient during the CAEP and in the subsequent rest phase. The numbers in the figure indicate the slope and speed of treadmill, ranging from 2% to 10% (slope) and from 1 to 4 miles per hour (speed).

Potential Benefits of CLS in the Elderly

We have previously demonstrated that elderly patients (≥ 75 years old) had similar indications for pacing as the younger population, and we corroborated findings of other clinical groups that the need for implantation of sophisticated, physiological pacing devices did not decrease with patient age [11-13,16-20]. The most obvious contraindication for implanting the simplest, single-chamber ventricular (VVI) devices in the elderly is a greater likelihood of later patient symptoms and morbidity (and higher medical costs in the long term) due to the development of atrial fibrillation and/or pacemaker syndrome, which could be significantly reduced by using dual-chamber (DDD) pacemakers [11-13,16-21]. Conventional pacemaker sensors (activity and minute ventilation) were most suitable for detecting vigorous physical activity. The value of rate-responsive pacing in the elderly was doubtful, because these patients were unlikely to undertake strenuous or fast-moving physical exercise. The sensitivity and specificity of the conventional pacemaker sensors to lower levels of exercise and other forms of physiological stress were not sufficient to ensure reliable detection of more discrete variation of metabolic demands and support it with an adequate cardiac output. After the inception of the CLS concept, which is highly sensitive and accurate in rate adjustment because it is always guided by the feedback from the cardiovascular system [1-10], the potential value of rate-responsive pacing in the elderly needs to be reconsidered.

First of all, when the current pacemaker rate is lower than necessary for the ongoing stress condition, cardiac output in chronotropically incompetent patients will increase through increased heart contractility and/or through a redistribution of the available cardiac output via changes in the local vascular tone within the body. Increased blood perfusion of the critical parts of the body that are presently under the greatest stress may be achieved via local vasodilatation concomitant with vasoconstriction in other (non-focused) body organs and tissues, resulting in their hypoperfusion. There are at least four potential negative consequences of this suboptimal circulation regulation when compared with the situation of necessary cardiac output always being obtainable via accurate heart rates provided by the CLS rate-responsive pacemaker.

First, the compensatory circulatory mechanisms-changes in contractility and vascular tone may not be sufficient to ensure adequate cardiac output and perfusion of body organs under the peak stress (e.g., muscles during exercise, the brain during mental activity, etc.), thereby decreasing the patients' functional capability, the repertoire of daily activities, and the patients' quality of life. Second, by overstressing the myocardium with frequent increases of heart contractility without sufficiently long resting periods, the functional status of the myocardium could be impaired in the long term, and the NYHA classification index deteriorates. Third, it is well known that the flexibility and regeneration capability of older organisms are reduced, while the fragility of the structures are increased. Therefore, the consequences of the overstress imposed on the regulatory circulatory mechanisms and on other organs due to hypoperfusion (suboptimal metabolic processes) may result in accumulated fatigue and accelerated degeneration and aging of the involved organs and tissues.

Apart from the previous considerations that were at the organic level, psychological factors should not be overlooked. Thus, the fourth negative consequence of inadequate circulatory regulation may arise from the patient's frustration and/or depression caused by the limitations in his or her physical, mental, or emotional functional capability. Unfavorable psychological conditions could weaken someone's immune system and general health condition independently from the organic disorders.

Although it will be difficult to find objective criteria to set up clinical studies evaluating the potential subtle and long-term advantages of the CLS rate-responsive principle, some clinical trials assuming the following directions may be attempted. First, improved functional capacity for all types of daily life activities and better quality of life and psychological condition in elderly patients may be demonstrated for the CLS versus conventional DDD or rate-adaptive pacing systems in a larger patient population with a multicentric study organization. Improved patient survival might also be demonstrable in conjunction with the CLS, but this will require a longer follow-up period and precisely determined patient inclusion and exclusion criteria to limit potential influence of confounding variables.

In view of the demonstrated capability of CLS to improve the NYHA classification index through preservation of the cardiac contractile reserves [4,10], prospective clinical trials should be conducted in patients with a dilated cardiomyopathy. Furthermore, atherosclerosis is generally more advanced in the elderly and associated with a greater incidence of angina pectoris than in the younger pacemaker patient population. The observed interactions between the CLS and cardiac ischemia during the routine percutaneous transluminal coronary angioplasty (PTCA) procedures indicated that symptoms associated with angina pectoris might be alleviated for the ischemia occurring at the right side of the heart. Namely, episodes of cardiac ischemia will influence local myocardial contractility and, therefore, the CLS pacing rate [4,22]. Ischemia at the right side of the heart will thus result in a lower CLS rate, and the lower pacemaker rate will reduce cardiac workload and metabolic demands, potentially alleviating symptoms and negative effects of the ischemia. Prospective clinical trials in pacemaker patients with angina pectoris originating from ischemia at the right side of the heart might demonstrate symptomatic benefits in patients paced according to the CLS versus patients implanted with conventional pacing systems.

Conclusion

Our study confirmed findings of other investigators that the CLS-based pacing rate adaptation via intracardiac impedance measurement provides a very satisfactory clinical performance. Our article however, contributed to the existing literature by demonstrating a high correlation between the achieved CLS pacing rate and the expected pacing rate (calculated according to the formula available in literature [14]), for different workloads during the graded treadmill exercise ($r^2 = 0.98$, $P < 0.05$). Due to its sensitivity to all circulatory demands, CLS-based pacing rate adaptation incorporated in the Inos² CLS pacemaker may be particularly advantageous in chronotropically incompetent elderly patients.

References

[1] Schaldach M. Automatic adjustment of pacing parameters based on intracardiac impedance measurements. PACE. 1990; 13: 1702-1710.

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

[3] Pichlmaier AM, Braile D, Ebner E, et al. Autonomic nervous system controlled closed loop cardiac pacing. PACE. 1992; 15:1787-1791.

[4] Schaldach M, Urbaszek A, Ströbel JP, et al. Rate-adaptive pacing using a closed-loop, autonomic nervous system controlled pacemaker. J HK Coll Cardiol. 1995; 3:22-32.

[5] Witte J, Reibis R, Pichlmaier AM, et al. ANS-controlled rate-adaptive pacing - A clinical evaluation. EUR JCPE. 1996; 6:53-59.

[6] Res JCJ, van Woersem RJ, Malinowski K, et al. Dual-chamber pacing and closed-loop regulation-Clinical results. Prog Biomed Res. 1997; 2(1): 27-30.

[7] Schaldach M. What is Closed Loop Stimulation? Prog Biomed Res. 1998; 3(2): 49-55.

[8] Malinowski K. Interindividual comparison of different sensor principles for rate adaptive pacing. PACE. 1998; 21:2209-2213.

[9] Andrade JCS. Cardiac contractility sensor evaluation in a DDDR system - A multicenter study. Prog Biomed Res. 1998; 3(3): 137-142.

[10] Vaskelyte J, Medzevicius A, Kazakevicius T, et al. Clinical experience with closed loop pacing systems in patients with congestive heart failure. Prog Biomed Res. 1998; 3(4): 210-213.

[11] Hardt R, Hubmann M, Lang E. Indikation zur Herzschrittmachertherapie und Aggregatwahl im höheren Lebensalter. Geriat Forsch. 1998; 8: 23-32.

[12] Hardt R, Hubmann M, Lang E. Herzschrittmachertherapie in der Geriatrie. Teil II: Psyschophysische Leistungsfähigkeit nach Schrittmacherimplantation - eine vergleichende Studie. Geriat Forsch. 1998; 8: 69-85.

[13] Hardt R. Herzschrittmachertherapie: Hightech-Medizin für die Geriatrie. Geriat Forsch. 1998; 8: 59-61.

[14] Wilkoff BL, Corey J, Blackburn G. A mathematical model of the cardiac chronotropic response to exercise. J Electrophysiol. 1989; 3:176-180.

[15] Sulke N, Dritsas S, Chambers J, et al. Is accurate rate response programming necessary? PACE. 1990; 13: 1031-1044.

[16] Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). J Am Coll Cardiol. 1996; 31: 1175-1209.

[17] Gammage M, Schofield S, Rankin I, et al. Benefit of single setting rate responsive ventricular pacing compared with fixed rate demand pacing in elderly patients. PACE. 1991; 14: 174-180.

[18] Channon KM, Hargreaves MR, Cripps TR, et al. DDD vs. VVI pacing in patients aged over 75 years with complete heart block: A double-blind crossover comparison. QJM. 1994; 87: 245-251.

[19] Lamas GA, Pashos CL, Normand SL, et al. Permanent pacemaker selection and subsequent survival in elderly Medicare pacemaker recipients. Circulation. 1995; 91: 1063-1069.

[20] Lamas GA, Orav EJ, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual chamber pacing. N Eng J Med. 1998; 1097-1104.

[21] Linde C. How to evaluate quality-of-life in pacemaker patients: Problems and pitfalls. PACE. 1996; 391-397.

[22] Witte J, Reibis R, Ströbel J, et al. The response of the intracardiac impedance signal to provoked regional ischemia during PTCA. Prog Biomed Res. 1996; 1(1): 5-8.