Introduction

To establish an appropriate therapy using rate-adaptive pacemaker systems, the sensor parameters have to be adapted to the individual needs of each patient. Many of these sensor systems require an inappropriately high programming effort to achieve appropriate rate adjustment, prolonging the follow-up procedure in daily clinical routine. An ideal sensor which reacts quickly and adequately to metabolic demands should therefore also be easy to program, and it should not require frequent readjustments [1]. In this context, closed-loop sensors have the advantage of detecting a cardiovascular parameter which is influenced by the heart rate via negative feedback. Consequently, a rise in the sensor signal leads to an increase in the pacing rate, which in turn results in a decrease in the sensor signal. In this manner, the pacing rate can be optimally controlled [2].

The concept of Closed Loop Stimulation (CLS, Biotronik, Germany) is based on an intracardiac imped-

Results of the Protos Survey: Effectiveness of the New Closed-Loop Pacemakers in Clinical Practice

Summary

The new Protos DR/CLS dual-chamber and Protos VR/CLS single-chamber pacemakers have an extended indication and functionality range compared to earlier rate-adaptive pacemaker systems based on monitoring the myocardial contraction dynamics by means of intracardiac impedance measurement. During the Protos survey, 66 patients with DDD(R) or VVI(R) pacemaker indication were followed for 4 weeks after implantation. A total of 60 patients (mean age 72.5 ± 9.9 years, 32 female) with the rate adaptation by means of Closed Loop Stimulation (CLS) activated at hospital discharge were included in the analysis. At the 4-week follow-up, the rate adaptation of 16 out of a total of 43 documented and evaluated exercise tests was classified as adequate. In 26 patients, it was impossible to evaluate the rate adaptation due to a present intrinsic rhythm. In one case, cardiac pacing was observed only at the basic rate despite statistical data of the pacemaker memory that demonstrated a typical histogram with pacing rates higher than the basic rate. Rate adaptation achieved by CLS was comparable to the heart rate variation in chronotropically competent patients with dominating intrinsic rhythm (rest 70.5 ± 10.5 beats/min versus 74.1 ± 13.2 beats/min, 5-min walk test 111.6 ± 22.1 beats/min versus 101.0 ± 19.6 beats/min, stair descending 100.0 ± 7.1 beats/min versus 104.4 ± 20.3 beats/min, stair ascending 106.0 ± 32.1 beats/min versus 109.6 ± 26.0 beats/min). The Protos survey has demonstrated that rate adaptation using the CLS mode in the new Protos DR/CLS dual-chamber and Protos VR/CLS single-chamber pacemakers results in adequate behavior. Additionally, due to a reduction in the effort required to program the device, the follow-up procedure is facilitated.

Key Words

Closed Loop Stimulation (CLS), rate-adaptive pacing, atrioventricular delay
dual-chamber and Protos VR/CLS single-chamber pacemakers (Biotronik), thus making CLS therapy also available to patients with intrinsic activation of the ventricle. The goal of the Protos survey was to evaluate if the Protos DR/CLS dual-chamber and Protos VR/CLS single-chamber pacemakers meet the requirements for rate-adaptive pacemaker systems in clinical practice and if the default setting of the rate-responsive parameters had been optimally chosen. To this end, the routine examinations (pre-operative, implantation, discharge follow-up, 4-week follow-up) and the evaluation of the pacemaker's functionality were documented.

**Materials and Methods**

**Closed Loop Stimulation**

The CLS concept [3-6] offers a therapy for the rate-variable electrostimulation of the heart on the basis of the closed-loop principle. Rate control is based on continuous monitoring of the contraction dynamics of the myocardium by means of intracardiac impedance measurements using a standard ventricular lead. During the different phases of the cardiac cycle (filling phase, isovolumetric contraction, ejection), the blood-to-myocardium ratio and thus the local impedance in the vicinity of the electrode tip varies, making the corresponding impedance changes during metabolic stress characteristic for the rise in ventricular contraction and the cardiac load [7]. By comparing an impedance curve at a given time (impedance values in a range of 50 to 250 ms following ventricular pace or sense) with a reference impedance curve recorded at rest, the pacemaker determines the necessary pacing rate. In this way, the CLS pacemaker is capable of using the intrinsic cardiovascular control for rate adaptation to react adequately to physical [8-13] as well as mental stress [14] and thus to increase the patient's quality of life [15,16]. The new CE-marked (European conformity) Protos DR/CLS dual-chamber and Protos VR/CLS single-chamber pacemakers use an automatic initialization feature that adopts the rate adaptation approximately to the individual patient about 15 min after activating the CLS mode and optimizes it within a few days. A continuous automatic adjustment [17] compensates for changes in the intracardiac impedance due to the growing behavior of the ventricular lead or a change in inotropic drug therapy. To compensate extreme levels of activity, the CLS dynamics can be attenuated or amplified in two steps.
Like the surface ECG, the shape of the intracardiac impedance curve depends strongly on the ventricular event type and can differ considerably between ventricular sensing and pacing. Following successful pre-examinations [18], the impedance curves of all event types can be successfully analyzed in the Protos DR/CLS and Protos VR/CLS. In the Protos DR/CLS dual-chamber pacemaker, intrinsic atrioventricular (A V) conduction with intermittent A V block is supported by an automatic A V hysteresis [19]. The hysteresis also has the purpose of performing a regular update of the various impedance reference curves of ventricular paced and sensed events in order to continuously compensate for changes in myocardial contractility. Since fusion beats [20] cannot be analyzed by the CLS algorithm due to the irregular contraction sequence, the programmed dynamic AV delay that takes into account the sense compensation should be more than 39 ms below the respective intrinsic AV delay. To simplify AV-delay and AV-hysteresis programming, the Protos DR/CLS dual-chamber pacemaker offers new AV-delay statistics that provide information on the delay of the intrinsic AV conduction after atrial paced or sensed events, especially classified in relationship to the underlying heart rate.

**Project Design**

The study was performed as a prospective, multicenter survey, without setting any special requirements. The schedule and scope of the follow-up examinations were in accordance with medical standards, and patient guidance was left to the discretion of the attending physician. Data acquisition was performed preoperatively, during implantation, at the hospital discharge follow-up, and at the 4-week follow-up (Figure 1). The required documentation was limited to a standard pacemaker follow-up and an evaluation of pacemaker functionality based on an optional submaximal exercise test [21]. For this purpose, a baseline measurement of the heart rate at the end of a resting phase of at least 2 min and measurements of the maximum heart rate when ascending stairs, descending stairs, or walking for at least 5 min was recommended. The effectiveness of the new automatic CLS initialization had to be evaluated during the discharge follow-up. In case of pacing rates above the basic rate, rate adaptation was classified as detectable. If the intrinsic rate was too low and there were still no pacing rates above the basic rate, the rate adaptation was classified as not detectable for the time shortly after the initialization (due to the fact that an approximate start value was used for determining the pacing rate). The intrinsic rhythm category contains all other cases in which a rise in the pacing rate could not be detected and was also not necessary due to an existing intrinsic rhythm. At the 4-week follow-up, the rate adaptation was evaluated qualitatively. An increasing intrinsic rate during the exercise test was classified as intrinsic rhythm. Cases were judged adequate when a rise in the pacing rate was necessary and also occurred at the necessary magnitude. Accordingly, cases were judged inadequate when a rise in the pacing rate was necessary but did not occur at the necessary magnitude.

**Results**

**Patients**

The survey was performed in the period between the first pre-operative data collection on March 20 and the last 4-week follow-up on May 22, 2003, in eight patients.
Exercise Test at the 4-week Follow-up

At the 4-week follow-up, evaluation of the rate adaptation was not possible due to the presence of an intrinsic rhythm in 26 of 43 cases (60.5%), as demonstrated in Table 4. The rate adaptation of 16 of 43 exercise tests (37.2%) was judged adequate when observing permanent ventricular pacing, permanent intrinsic conduction, as well as intermittent intrinsic conduction or intrinsic ventricular rhythm (Figure 2). In total, 1 of 43 cases (2.3%) was judged inadequate because there was no detectable increase in the pacing rate above the basic rate in the VVI-CLS mode with permanent ventricular pacing. In contrast to the exercise test, the rate trend and the rate histogram obtained between discharge and the 4-week follow-up showed a typical rate adaptation (Figure 3). Additionally, during the surveillance period, the symptoms of the patient, who had been included due to an exchange indication, had improved (Table 5).

There was no significant difference in resting heart rate and the maximum heart rate during submaximal exercise (e.g., 5 min walking, stair descending, stair ascending) comparing the group with intrinsic rhythm and the paced patients with rate adaptation classified as adequate (Figure 4a). The intraindividual differences between the various exercise tests and the basic rate, i.e., the rate increase during exercise, are also in the same range in both groups (Figure 4b).

CLS Parameters at the End of the 4-week Follow-up

At the 4-week follow-up, the final mode setting was as follows:

- DDD/VVI mode in 23 patients, demonstrated as chronotropically incompetent [21,22]
- One patient had a change to the DVI mode
From three patients there is no information on the final mode.

Four patients had a change to the accelerometer-based, rate-responsive mode for investigational purposes due to the discretion of the attending physician.

The remaining 30 patients retained the CLS mode with the following modifications:

- Four cases of reprogramming the maximum closed-loop rate (maximum sensor rate) from 120 ppm to 130 ppm
- Two activations of the parameter Vp required in patients needing permanent ventricular pacing
- One increase of the CLS dynamics (equivalent to a sensor amplification).

**AV-delay Measurement at the 4-week Follow-up**

Figure 5 shows the default settings for the dynamic AV delay and the AV hysteresis. The area shaded in light grey shows the permitted range for intrinsic conduction. The dark grey area is considered a risk range for potential fusion beats that can occur in the case of an intermittent AV block. As part of the survey, the intrinsic AV delay was measured after atrial intrinsic events (66 ± 14 beats/min), during slight overdrive pacing (81 ± 11 beats/min), and during higher overdrive pacing (102 ± 10 beats/min). Taking into account the programmed sense compensation (default value −45 ms, mean value 41 ± 14 ms) for comparison of the intrinsic AV delay after atrial sensing and atrial pacing, a longer AV delay results with increasing overdrive pacing at rest compared to the physiologic shortening at
stress [23]. Therefore, the dynamic AV delay for higher heart rates can only be optimally programmed with simultaneous or previous stress. As an alternative, the AV-delay statistical data of the Protos DR/CLS pacemaker can be used to program sense compensation, dynamic AV delay, and AV hysteresis. This statistical information on the intrinsic AV delays after atrial paced and sensed events is in accordance with the previously described measurements (Figure 6).

**Discussion**

The new automatic initialization for CLS provides an approximate start value for determining the pacing rate from the intracardiac impedance values, which may not be too high for safety reasons. Therefore, the few cases of undetectable rate adaptation directly after activating the CLS mode are within expectations.

At the 4-week follow-up, the DDD-CLS and VVI-CLS modes were adequate in 16 of 43 patients (37.2%). Only one of 43 (2.3%) exercise tests was inadequate because no increase in the pacing rate above the basic rate could be observed. All existing data indicate that this patient was still adequately supplied over a longer period because the patient history showed an improvement compared to the preoperative diagnostics, and the rate adaptation was comparable to that of other chronotropically incompetent patients according to the statistical data in the period between the discharge and 4-week follow-ups. Because the patient had a change to the accelerometer-based, rate-responsive mode for investigational purposes due to the discretion of the attending physician, further analysis of the CLS mode can be performed earliest at the next regular follow-up. The additional follow-ups, adverse effects, or the only death within the surveillance period were not related to the specific pacemaker properties. There were no sensor-specific events causing a reprogramming of the mode setting.

At the end of the 4-week follow-up, the CLS mode was the final mode setting in 50% of the patients which reflects the wide use of pacemaker systems with incorporated sensor for rate-responsive pacing [24]. These results indicate that preoperative diagnosis of chronotropic incompetence is limited, e.g., due to changes in

**Table 5. History of the patient without rate adaptation during an exercise test at the 4-week follow-up.**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Preoperative diagnosis</th>
<th>4-week follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>General condition</td>
<td>low</td>
<td>good</td>
</tr>
<tr>
<td>Exertion tolerance</td>
<td>low</td>
<td>adequate</td>
</tr>
<tr>
<td>Heart rate</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Palpitation of the heart</td>
<td>at no time</td>
<td>at no time</td>
</tr>
<tr>
<td>Difficult breathing/dyspnea</td>
<td>frequent</td>
<td>at no time</td>
</tr>
<tr>
<td>Syncopes</td>
<td>at no time</td>
<td>at no time</td>
</tr>
<tr>
<td>Dizziness</td>
<td>infrequent</td>
<td>infrequent</td>
</tr>
<tr>
<td>Chest pain/angina pectoris</td>
<td>at no time</td>
<td>at no time</td>
</tr>
<tr>
<td>Cerebral symptoms</td>
<td>infrequent</td>
<td>at no time</td>
</tr>
</tbody>
</table>

**Figure 4. Panel a) Mean heart rate at rest and maximum heart rate during various exercise test for two subgroups with intrinsic rhythm and with adequate pacing as classified by the investigators. Panel b) Mean intraindividual difference values between the various exercise tests and the basic rate and corresponding standard deviations. For each value, standard deviations and number of cases are presented.**
antiarrhythmic medication. On the other hand, postoperative diagnosis including pacemaker statistics will improve sensitivity and specificity. Thus, rate-adaptive pacemakers are the method of choice, whereby activating or deactivating the rate-adaptive mode should be decided individually on the base of all information available.

**Conclusion**

The Protos survey has demonstrated that the CLS mode in the new Protos DR/CLS dual-chamber and Protos VR/CLS single-chamber pacemakers allow appropriate rate-responsive pacing with minimal programming effort. Due to the extended functionality and indication of the new pacemaker family, studies with a large sample size can be performed.

**Limitations**

To complete this project within a short time, the indication for DDD(R) or VVI(R) pacemaker therapy was selected as the enrollment criterion, allowing for the inclusion of chronotropically competent patients, as long as activating the rate-adaptive mode over 4 weeks was not contraindicated. A survey does not allow for a protocol with fixed parameter settings and also no interventions into the therapy decisions of the study physicians. Thus, only optional, non-standardized tests were used, not allowing a specific statistical analysis of the data. This approach was justified by the intention to test the CLS properties of the new Protos DR/CLS and Protos VR/CLS in everyday clinical practice.

**References**


