Closed loop stimulation and accelerometer-based rate adaptation: results of the PROVIDE study

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Aims We compared pacing rate adaptation based on closed loop stimulation (CLS) or accelerometer sensor (AS) during acute mental and physical stress in the same patient.

Methods and results One month after Protos (Biotronik, Germany) pacemaker implantation, 131 chronotropically incompetent patients were randomized to AS or CLS for 3 months with crossover. Arithmetic and 6 min walk tests were performed in the non-rate-adaptive mode and AS and CLS rate-adaptive modes, respectively. At the end, patients had to select the individually preferred pacemaker sensor. Heart rate during mental stress was higher (3.0 ± 9.2 bpm) in the CLS than in the AS mode (P = 0.004). Benefit in the walking distance compared with non-rate-adaptive pacing was similar for the two modes: added 27 ± 96 m (AS, P = 0.013) and 30 ± 116 m (CLS, P = 0.025). At the end of the walk, heart rate was higher by 4.8 ± 21.4 bpm in AS than in CLS (P = 0.049). Twice as many patients preferred CLS over AS (P < 0.01).

Conclusion The arithmetic test was associated with a significantly higher heart rate for CLS than for AS, showing a greater sensitivity of CLS-based rate adaptation to mental stress. Performance during physical stress was comparable. Patients preferred CLS.

KEYWORDS Rate-adaptive pacing; Chronotropic incompetence; Closed loop stimulation; Accelerometer sensor; Mental stress; Physical stress

Introduction Rate-adaptive systems are widely used in modern pacemaker therapy.1 They are commonly based on accelerometer sensors which increase pacing rate according to the amount and vigorosity of anterior to posterior thoracic motion.2–5 Accelerometers have proved to deliver an acceptable pacing rate profile in daily life, often needing customized programming by the physician though.5–8 Exercise forms without thoracic movement as well as mental and emotional stress have no impact on the sensor, although they cause a significant increase in heart rate in healthy people.9–11

By measuring an intrinsic parameter that is directly affected by vagal and sympathetic output, the so-called closed loop sensors modify the pacing rate which, in turn, interacts with the autonomic nervous system via the negative feedback.2,5 Should the heart rate be too low or too high, not matching current physiological requirements, a change in detected signal directs the pacemaker towards a more appropriate pacing rate. This principle allows continuous adjustment of the pacing rate to optimal values. In the present study, we use closed loop stimulation (CLS) system that assesses variations in myocardial contractility by beat-to-beat intracardiac impedance measurements.12–17 Pacemakers which incorporate both CLS and an accelerometer sensor (Protos, Biotronik, Berlin, Germany) can be used to compare the two sensors intraindividually.

The objective of the PROVIDE study was to compare CLS and accelerometer during walking and mental stress, and to assess patients’ (subjective) preferences regarding the sensor system.
Methods

Patients

All patients had an accepted indication for the implantation of a single- or dual-chamber pacemaker and chronotropic incompetence based on clinical evidence. Stable prognosis, medication, and geographical location were required for the study duration. Patients gave written informed consent for participation in the study. The research protocol was approved by the local ethics committee and complies with the declaration of Helsinki.

Study design

PROVIDE (PROtos CLS Validation: Improvement in Day-to-day Exercise) was a prospective, randomized, multicenter trial. Patients received a Protos pacemaker and conventional ventricular and atrial (if applicable) pacing leads. Follow-up controls took place at 1, 4, and 7 months after pacemaker implantation. The implanted pacemakers were programmed to a non-rate-adaptive VVI or DDD mode for 1 month after implantation. At the end of the 1-month run-in period, patients were randomized either to the accelerometer-based (DDDR or VVIR) or CLS-based (DDD-CLS or VVI-CLS) rate-adaptive mode. The single- or dual-chamber pacing configuration chosen in the run-in phase had to be maintained after mode randomization. At the 4-month follow-up, the sensors were crossed over. Mental stress test and a 6 min walking test were performed at the 1, 4, and 7 month follow-up in the non-rate-adaptive mode, 'first sensor', and 'second sensor' rate-adaptive modes, respectively. At the end of the 7 month follow-up, patients had to select the individually preferred sensor.

Mental stress test

For mental stress, an arithmetic test was performed, in which the patient had to successively subtract 17 beginning at 1000.9,18,19 Heart rate was documented using a surface ECG strip. Mental stress heart rate (HR_{mental}) was computed as the average rate in the period between 60 and 120 s after starting calculations. The test was preceded by a resting phase of at least 2 min, to diminish potential influence of body movements on heart rate.

Six minute walking test

During the 6 min walk, patients were reminded of the remaining time after 3 and after 5 min. Exercise heart rate (HR_{walk}) was measured immediately after the end of the exercise, and the covered walking distance was documented.

Statistical methods

Statistical calculations were performed with the aid of the SPSS software version 14.0. Continuous data are expressed as mean ± SD. Since the Kolmogorov–Smirnov test showed no significant deviation from normal distribution, the differences were evaluated using the two-sided t-test for paired data. To analyse relative fractions, the Binomial test was applied. A P-value of <0.05 was considered significant.

Results

Patient population

A total of 131 patients (43.5% female) with a mean age of 72.4 ± 10.6 years were enrolled at 17 European clinical centres listed in the appendix. Fifty-one (39%) patients presented with NYHA class I, 45 (34%) with NYHA II, 20 (15%) with NYHA III heart failure symptoms, and for 15 (12%) patients no NYHA class specification was obtained. Sixty-six patients (50%) had a history of atrial flutter or atrial fibrillation. In 100 patients (76%), the pacemaker was implanted for the first time within the PROVIDE study, and 31 patients had pacemaker replacements.

Adverse events

Fifteen serious adverse events were reported: five unrelated to pacing devices (one death, one stroke, one peripheral embolism, one cardiac ischaemia necessitating coronary angiography, one worsening of heart failure), eight related to pacing lead (which was not an issue of this study), one new onset atrial fibrillation (followed by reprogramming from DDD–CLS to VVIR mode), and one patient had palpitations in the DDD–CLS mode. The latter problem was resolved in reprogramming of the optional CLS-dynamics parameter from 'moderate' to 'very low'. In another patient, palpitations in the DDD–CLS mode were classified by the investigator as a non-serious device-related adverse event. The pacemaker was reprogrammed to the DDDR mode. There were no statistically significant differences between the two sensors regarding adverse events.

Premature study termination

In 27 patients, the study terminated prematurely because of adverse events or other reasons. The final sensor selection in this patient group was documented in 18 patients: 4 CLS, 6 accelerometer, and 8 with no rate adaptation. In nine patients, chosen mode was unknown, yet the last mode before lost to follow-up was: eight CLS (including one case of patient refusal to crossover from DDD–CLS to DDDR, one case of withdrawal of patient consent as a result of frequent follow-ups, and one death), and one with no rate adaptation because of the withdrawal of patient consent before randomization.

Data compliance

There are less pairs of data available than patients enrolled because of several kinds of protocol violations, including the use of a rate adaptive instead of a non-rate-adaptive mode at 1-month (baseline) follow-up, change between single- and dual-chamber configurations during the study, use of a non-rate-adaptive mode after randomization, episodes of tachycardia during tests (classified by the investigator), failure to perform mental or walk test according to the protocol, and cases of premature study termination. Changes in medications were not used as a drop-out criterion. Statistical evaluations performed at the end of the study confirmed that, in conditions of crossover study design, there was no statistically significant bias towards any mode caused by medication changes.

Programmed pacemaker parameters

Single-chamber pacing configuration was used in 55 patients (42%) and dual-chamber in 76 patients (58%). The programmed lower pacing rates (in bpm) were: 60.0 ± 4.7 (non-rate-adaptive mode), 60.6 ± 4.4 (accelerometer), and 60.6 ± 4.4 (CLS), without significant intraindividual differences. The programmed maximum sensor rates (in bpm) were: 121.7 ± 7.7 (accelerometer) and 119.9 ± 4.8 (CLS). The rate responsive parameters were programmed at the physician’s discretion. The investigators selected 'moderate CLS Dynamics' (factory setting) in all but four...
patients, who had ‘high’, high’, ‘low’, and ‘very low’ CLS
dynamics. The latter was reprogrammed from ‘moderate’
between 1 and 4 month follow-up, see Adverse events
section. The mean sensor gain of the accelerometer was
7.3 along the 1–40 scale (factory setting 4).

Mental stress test

Figure 1A illustrates the sensitivity of the CLS sensor to
mental stress in a patient without intrinsic rhythm. The latter was reprogrammed from ‘moderate’
between 1 and 4 month follow-up, see Adverse events
section. The mean sensor gain of the accelerometer was
7 ± 3 along the 1–40 scale (factory setting 4).

Figure 1A Heart rate trends during mental stress test in DDD mode (left), DDD–CLS mode (middle), and AS-based DDDR mode (right) in a
patient without intrinsic rhythm. The lower parts of (A) show percentage of pacing of nearly 100% in all three modes. Only DDD–CLS mode
resulted in an increase in heart rate from 60 bpm to an average value of 65 bpm. (B) Intraindividual difference in HRMental for CLS vs. AS (mean
3.0 ± 9.2 bpm, P = 0.004, n = 84 pairs of data). HRMental, mean rate in the period between 60 and 120 s after starting arithmetic calculations;
AS, accelerometer sensor; CLS, closed loop stimulation.

Figure 1B Intraindividual difference in HRMental for CLS vs. AS (mean
3.0 ± 9.2 bpm, P = 0.004, n = 84 pairs of data). HRMental, mean rate in the period between 60 and 120 s after starting arithmetic calculations;
AS, accelerometer sensor; CLS, closed loop stimulation.

Mental stress test

Figure 1A illustrates the sensitivity of the CLS sensor to
mental stress in a patient without intrinsic rhythm. However, in many patients, sinus rate interfered with the
sensor signal (normal clinical situation), leading to marked
variations in the intraindividual differences in HRMental for CLS vs. accelerometer (Figure 1B; Table 1). With the ran-
domized crossover study design, the impact of the intrinsic
rhythm could be filtered out substantially, yielding a mean
difference in HRMental for CLS vs. accelerometer of 3.0 ±
9.2 bpm (P = 0.004, 84 data pairs, Figure 1B). In addition,
the randomized crossover design eliminated the potential
influence of a period effect because of familiarization to
the mental stress test in conditions of its repetitions.

Six minute walking test

The gain in distance covered during 6 min walk compared
with non-rate-adaptive pacing was similar for the two
modes: added 27 ± 96 m with the accelerometer (P =
0.013, 81 pairs of data) and added 30 ± 116 m with CLS
(P = 0.025, 79 pairs of data, Figure 2). Thereby, the accele-
rometer sensor produced higher HRWalk values than CLS by
4.8 ± 21.4 bpm (P = 0.049, 81 pairs of data, Figure 3).
Either sensor, however, significantly increased heart rate
compared with the non-rate-adaptive pacing, the accele-
rometer by 14.1 ± 18.1 bpm (P < 0.001, 81 pairs of data)
and CLS by 10.0 ± 18.4 bpm (P < 0.001, 79 pairs of data,
Figure 3).

Preference of pacemaker mode

At the end of the study, twice as many patients preferred
CLS over the accelerometer sensor, which reached statistical
significance (Table 2). One quarter of the patients had no
preferred mode.

Subgroup analyses

Any subgroup analysis was not pre-defined by the study pro-
tocol. It was conducted with the aim to examine possible
meaningful directions for future research, rather than to
produce additional significant evidence within the present
study. Pairs of complementary patient groups compared
with each other were: male vs. female, patients who were
younger vs. older than the median patient age of 75 years,
patients with atrioventricular block at enrolment vs. other
patients, NYHA class II or higher vs. other patients, patients with single- vs. dual-chamber pacing configuration, distance covered during 6 min walking test at 1 month follow-up below median vs. other patients.

The most interesting finding was that, for CLS mode, patients with NYHA class I tended to have lower HR Walk and HR Mental than patients in worse physical condition (NYHA II/III). The mean HRWalk was 84.8 ± 16.4 (NYHA I) vs. 97.1 ± 17.9 bpm (NYHA II/III, P = 0.0012, t-test for independent samples not adjusted for multiple analyses). The mean HRMental was 67.5 ± 9.2 (NYHA I) vs. 74.4 ± 11.4 bpm (NYHA II/III, P = 0.002). No corresponding trend was found for accelerometer-based pacing.

Discussion

CLS vs. accelerometer

Performance of CLS has been evaluated over the years, with favourable clinical results.\textsuperscript{12,15,20–32} Intraindividual comparisons of CLS with the accelerometer sensor were not available until recently, since no pacing device integrated both sensors. Thus far, three other study groups presented preliminary comparative data, suggesting that CLS is superior to accelerometer-based rate-adaptive pacing regarding acute mental stress, isometric handgrip, deep breathing, Valsalva maneuver, postural change, and quality of life.\textsuperscript{33–35} No study compared the two sensors during physical exercise.

In the present study, we evaluated the difference in heart rates between CLS and accelerometer sensor during arithmetic test and at the end of a 6 min walk test, and we also compared the distances covered during the 6 min walk; AS; accelerometer sensor; CLS, closed loop stimulation.

The most interesting finding was that, for CLS mode, patients with NYHA class I tended to have lower HRWalk and HRMental than patients in worse physical condition (NYHA II/III). The mean HRWalk was 84.8 ± 16.4 (NYHA I) vs. 97.1 ± 17.9 bpm (NYHA II/III, P = 0.0012, t-test for independent samples not adjusted for multiple analyses). The mean HRMental was 67.5 ± 9.2 (NYHA I) vs. 74.4 ± 11.4 bpm (NYHA II/III, P = 0.002). No corresponding trend was found for accelerometer-based pacing.

Table 1 Interindividual descriptive analysis

|                        | DDD/VVI               | Accelerometer sensor | Closed loop stimulation |
|------------------------|-----------------------|----------------------|-------------------------|
| **HR-mental**\textsuperscript{a} |                       |                      |                         |
| Number of tests        | 106                   | 99                   | 99                      |
| Mean ± SD (bpm)        | 69.7 ± 12.4           | 67.2 ± 8.9           | 71.1 ± 10.9             |
| Median (bpm)           | 65                    | 64                   | 70                      |
| Range (bpm)            | 54–128                | 50–96                | 50–109                  |
| **Distance of 6 min walk** |                       |                      |                         |
| Number of tests        | 103                   | 101                  | 94                      |
| Mean ± SD (m)          | 394 ± 200             | 426 ± 200            | 430 ± 219               |
| (m)                    | 360                   | 400                  | 382                     |
| Range (m)              | 434–1370              | 78–1560              | 123–1600                |
| **HR-walk**\textsuperscript{b} |                       |                      |                         |
| Number of tests        | 103                   | 98                   | 92                      |
| Mean ± SD (bpm)        | 80.6 ± 16.8           | 94.1 ± 18.6          | 90.7 ± 18.0             |
| Median (bpm)           | 78                    | 92                   | 92                      |
| Range (bpm)            | 56–128                | 64–140               | 52–146                  |

\textsuperscript{a}Heart rate measured in the period between 60 and 120 s after starting arithmetic calculations.

\textsuperscript{b}Heart rate measured immediately after 6 min walk termination.

Figure 2 (A) Intraindividual difference in DistWalk for AS vs. no rate adaptive DDD or VVI pacing: added 27 ± 96 m (P = 0.013, 81 pairs of data). (B) Intraindividual difference in DistWalk for CLS vs. no rate adaptive DDD or VVI pacing: added 30 ± 116 m (P = 0.025, 79 pairs of data). (C) Intraindividual difference in DistWalk for CLS vs. AS: −8 ± 102 m (P = ns, 84 pairs of data). DistWalk, distance covered during 6 min walk; AS, accelerometer sensor; CLS, closed loop stimulation.

**Mental stress test**

Closed loop stimulation increased heart rates significantly compared with the accelerometer by a mean of 3.0 bpm. When comparing our data with the literature, one should bear in mind that we calculated the mean heart rate during the final (second) minute of the arithmetic test, whereas others may have focused on the peak rate.\textsuperscript{34,35}
This difference as well as their exclusion of those patients who were not paced at least 80% during the test is a plausible reason why Neelagaru et al. 34 and Charindamani et al. 35 obtained a greater difference between heart rates in CLS vs. the accelerometer (mean, 9.3 bpm) than that seen in our study. Although no study evaluated whether CLS-based rate adaptation during mental stress translates into a better achievement (score) of the test, preliminary data show higher quality of life of patients during CLS phase compared with the accelerometer phase.33

### Six minute walking test

Distance covered during the walk was similar for the two sensors, although CLS exerted slightly lower heart rates than the accelerometer sensor. This was due to lower CLS rates in patients in better physical condition (NYHA class I), in whom the 6 min walk represents a submaximal exercise, whereas in patients with NYHA II/III this effort approaches a maximal exercise.36 The CLS seems to be able to identify patients who depend less on higher heart rates for adequate cardiac output. In contrast, the accelerometer increases the rate similarly in all patients, or even more in stronger patients who walk more vigorously, although they actually need less chronotropic support than weaker patients. This hypothesis represents a study rationale for the multicenter CONFIRM trial (Closed Loop Stimulation: Heart Failure Indexing and Rate Modulation), which started recently.

### Preferred mode

Although twice as many patients preferred CLS over accelerometer (Table 2), CLS was not the final choice in at least 24% of patients who preferred accelerometer and in 25% of patients who did not perceive a relevant difference between sensors. These findings suggest that there might be an optimal sensor system for each patient, which underscores the need of individual programming possibilities in dual sensor systems.

### Chronotropic incompetence

Our study protocol did not impose any specific criteria for the evaluation of chronotropic incompetence for patient inclusion in the study, allowing physicians from 17 clinical centres in Germany, Switzerland, and Austria to apply their standard rules from clinical practice. Doing so, we hoped to obtain the results applicable to daily practice, rather than to a specific subset of patients extracted from a broader population. Our data are comparable with the results of a prospective study of Chandiramani et al., 35 although they retrospectively excluded patients with chronotropic competence from the analysis. In the present study, the attending physicians decided to leave the pacemakers in a rate responsive mode in 111 (89%) of 122 patients in whom the final physicians’ decision on pacing mode was known (Table 2). This decision was made based on study results and patients’ preferences. It confirms initial judgment on chronotropic incompetence in the vast majority of cases. Besides, distance covered during the 6 min walk was significantly longer in any rate responsive mode than for non-rate-adaptive pacing.

### Study limitations

The study was not blinded, which might have resulted in a certain bias of patients towards any of the pacing modes used. Considering the fact that CLS was not generally broadly spread or favoured over the accelerometer at the participating centres before and during study execution, the authors do not have the impression that bias played a major role in subjective decisions.
Our study was one of the first to intrindividually compare accelerometer as the state-of-the-art sensor in rate-adaptive pacing and CLS regarding several clinical parameters of interest. The number of patients is too small to evaluate mortality, morbidity and quality of life.

Conclusion

The arithmetic test was associated with a significantly higher heart rate for the CLS than for the accelerometer sensor, confirming the expected greater sensitivity of CLS-based rate adaptation to mental stress. There was no difference in the distance covered during the 6-min walking test between the two sensors. Patients preferred CLS over accelerometer to a statistically significant degree.

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