The Ventricular Evoked Response and Adrenergic Stimulation: First Results of a Multicenter Clinical Study

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Summary

The ventricular evoked response, i.e., the unsipolarly measured electrical response of the heart to an effective ventricular pacing pulse, is a signal consisting of the sum of myocardial action potentials. Hence, it reflects changes in action potential morphology and the velocity of the spread of myocardial excitation that result from adrenergic stimulation. In the following, we present initial results of a multicenter clinical study investigating the use of the ventricular evoked response as a sensor signal for rate adaptation in pacing. Sixty-seven bicycle ergometry tests were performed with 35 patients. During stepwise load increase, the patients were paced in the DDD mode with low and high basic rates, resulting in triggered ventricular and in dual-chamber pacing, respectively. Patients were also paced in the DDDR mode with rate adaptation according to a load-sensitive parameter derived from the ventricular evoked response. The load-sensitive parameter reacts quickly and with good correlation to load increase and cessation. For 22 patients, a competition of atrial sensed and paced events occurred during DDDR ergometry. For 6 patients, atrial pacing prevailed and yielded heart rate developments comparable to those patients with mainly atrial-sensed events. Therefore, we conclude that the algorithm used for VER analyses is able to correctly extract the information about the adrenergic stimulation from the VER.

Key Words

Ventricular evoked response, adrenergic stimulation, rate-adaptive pacing, physiologic pacing

Introduction

The ventricular evoked response (VER), i.e., the unipolarly measured electric response of the heart to an effective ventricular pacing pulse, is a promising signal for expanding and refining antibradycardia pacemaker therapy. As previous studies have shown, the VER meets important criteria for new diagnostic and therapeutic applications in pacing. It can be measured reproducibly via implantable pacemaker systems, its morphology does not depend on pulse amplitude or width, it shows only small inter-individual changes and it is stable over longer periods [1,2]. Since it is measured in the unipolar mode, the VER incorporates information from a wide area of myocardium, mainly from the left ventricle and septum [3,4]. Theoretical investigations of the VER origin via simulation with finite element methods have additionally revealed that the VER morphology depends on the amplitude and duration of the underlying myocardial action potential and is influenced by the velocity and anisotropy of the spread of excitation [5].

The correctness and reliability of the theoretical considerations and of the clinical studies can be seen by the fact that the VER is already used for first applications in pacemaker therapy such as non-invasive cardiac transplant monitoring and capture control algorithms ensuring effectiveness of ventricular pacing [6,7].

Another consequence that follows from the above-mentioned theoretical considerations is the influence of adrenergic stimulation on the VER morphology. As the underlying myocardial action potential is modified by adrenergic influence, the VER must be modified as well. This has already been corroborated by first clinical investigations that indicate a possible use of the VER for rate adaptation [8,9].
The aim of the present study was to compare the heart rates of patients suffering from different arrhythmias with the VER in order to answer the question whether the VER may be used as a sensor for rate-responsive pacing.

Methods

Patients and Systems
Up to this point, 39 patients (8 f; mean age: 62.5 ± 17.3 years, range: 20 - 84 years) have been included into the investigation. They received the dual-chamber pacemaker Logos and fractal coated ventricular leads TIR 60-BP (56 %), TIR 60-UP (16 %), PX 60-UP (8 %) and PX 53-UP (20 %) (all Biotronik, Germany). The pacemaker Logos is capable of continuously transmitting the intracardiac electrogram from atrium and ventricle and the marker channel to the data recorder and analyzer Unilyzer (Biotronik). The Unilyzer is equipped with a removable flash memory card for storage of several hours of intracardiac signals. Furthermore, the Unilyzer can directly analyze the VER with respect to a predefined parameter and can in response reprogram the signal-transmitting pacemaker. Indications for pacemaker implantations were intermittent or permanent 3rd degree AV block in 63 % of the patients, intermittent or permanent 2nd degree AV block in 18 %, sick sinus syndrome in 16 % with left bundle branch block in 3 %.

Protocol
The follow-up period consists of 3 investigations 4 weeks, 3 and 6 months after implantation, respectively. The 4-week examination comprises two bicycle ergometry tests with ergometric load increasing every two minutes by steps of 25 W until the patient is exhausted. The first run is performed with the pacemaker programmed to the DDD mode with a basic rate of 60 bpm. This results in VAT pacing during exercise. In order to reliably avoid fusion beats, the AV delay is shortened (see Table 1). After a sufficient recovery period, the basic rate is reprogrammed to above 100 bpm and the second ergometric run is performed. During both ergometry tests, the ventricular endocardial signal is continuously recorded by the Unilyzer from 2 minutes before start until recovery to the initial rest heart rate.

Follow-up	BR (bpm)	MSR (bpm)	HR at rest (bpm)	AV delay (ms) after AS	after AP
4 weeks					
VAT			80 ± 15	77 ± 7	100 ± 15
DDD	129 ± 10		129 ± 11	77 ± 10	95 ± 4
3 months					
DDDR	67 ± 10	133 ± 10	80 ± 14	73 ± 4	92 ± 7
6 months					
DDDR	65 ± 7	132 ± 9	82 ± 12	73 ± 4	92 ± 6

Table 1. Mean values for programmed basic rate (BR), programmed maximum sensor rate (MSR in DDDR mode), heart rate (HR) at rest and programmed AV delay after an atrial sensed event and after an atrial paced event.

The 3- and the 6-month tests follow the same scheme: The VER is recorded for two minutes in the DDD mode with a basic rate of 60 bpm and short AV delays. The basic rate is then programmed to above 100 bpm and a bicycle ergometry is performed in the same manner as during the 4-week follow-up. Immediately thereafter, the stored VERs are analyzed in a calibration procedure with respect to an optimized load-sensitive parameter δ_{ST} (see next paragraph) and the Unilyzer is prepared for rate-adaptive programming of the Logos according to δ_{ST}. The second exercise test - the so-called "closed loop investigation" - is performed in a simulated DDDR mode, i.e., with instantaneous reprogramming of the pacemaker's DDD base rate by the Unilyzer according to the load-sensitive parameter δ_{ST}.

VER Analyses and Calibration Procedure
The VER is analyzed with respect to the difference in signal amplitude at two points designated the S- and T-point (see Figure 2). These points are determined for each patient individually using a calibration procedure aiming at maximizing the load influence and minimizing rate influence on the amplitude difference. Therefore, the VER was averaged over 5 consecutive beats for 3 different states:

(1) basic rate at rest,
(2) maximum rate at rest, and
(3) maximum rate at maximum load.

Of course, the maximum rate at rest could only be achieved by directly programming the rate as the DDD basic rate. Comparison of (1) and (2) shows the rate effect, whereas the comparison of (2) and (3) yields the pure load effect. The location of S- and T-points are presented as the time after stimulus.

For rate-adaptive pacing, the Unilyzer is prepared with a reference table that is produced during calibration. It contains the appropriate heart rate for any value of δ_{ST} taken during the ergometry at the maximum rate. The supervising physician defines 'appropriate' by determining the minimum and maximum desired heart rate.

Data Analyses and Statistics

The VER data are analyzed with respect to the behavior of the load-sensitive parameter δ_{ST} in response to increasing load during bicycle exercise and subsequent recovery. Close to the end of every load level, mean δ_{ST} and mean heart rate are calculated for 10 consecutive beats and compared to the mean values during rest just before the exercise starts. During recovery, mean δ_{ST} and mean heart rate are calculated at 1, 2 and 5 minutes after exercise termination. For the closed loop investigations at the 3- and 6-month follow-up, the percentage of atrial paced events is taken from the atrial marker channel. Furthermore, the development of the atrial rate during exercise is compared for the following grouping of the patients: less than 35 % of atrial pacing, between 35 and 65 % and more than 65 % of atrial pacing.

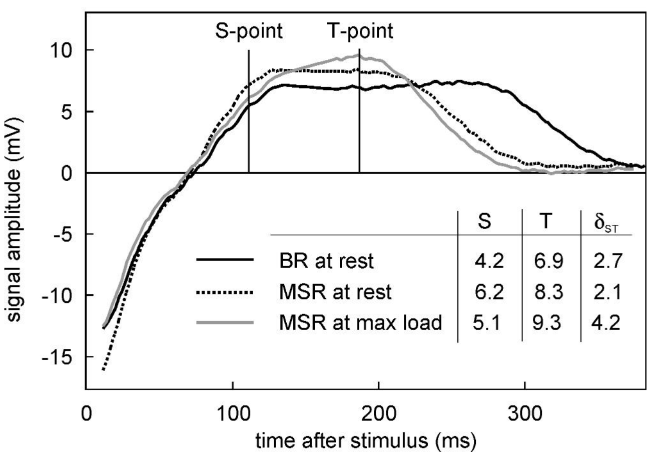

Figure 1. Example for changes in VER morphology and in d_{ST} due to rate increase and bicycle load. A higher rate (BR vs. MSR, at rest) resulted in a shortening of the VER and an amplitude increase at the S- and T-points. The load effect (MSR, at rest vs. at maximal load) is described by an amplitude decrease at S-point and increase at T-point. Hence, rate and load effects could be properly distinguished.

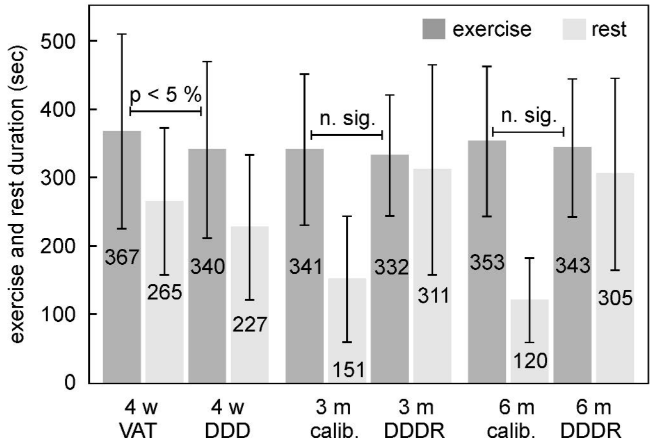

Figure 2. Duration of VER recording during exercise and post-exercise rest for all bicycle ergometry tests.

Where appropriate, data are presented as mean ± standard error of mean (SEM). Statistical significance is tested with the help of the Student-t-test for paired data with a level of significance of < 5 %.

Results

So far, the data of 29 patients have been successfully analyzed for the 4-week tests, the data for 24 patients have been evaluated for the 3-month examination, and the data for 14 have been evaluated for the 6-month examination. At the 4-week follow-up, exercise duration was significantly longer for the first than for the second ergometry run (see Figure 2). For the 3- and the 6-month follow-up, no significant difference between duration of first and second exercise occurred.

4-Week Follow-Up

The load at which patients stopped exercising was 50 W for 25 % of the tests, 75 W for 14 %, 100 W for 32 % and 125 W or more for 29 %.

Table 2 displays the mean locations for S- and T-point and the mean difference, as determined by the calibration procedure. All three values vary over a wide range

Follow-up	Location determined by calibration of: S-point mean ± sd (range)	T-point mean ± sd (range)	Difference T-S mean ± sd (range)	Changes compared to last follow up in: S-point mean ± sd (range)	T-point mean ± sd (range)	Difference T-S mean ± sd (range)	Number of patients with changes > 25 ms in S or T
4 weeks	135.9 ± 16.1 (96.8 - 150.5)	215.6 ± 23.9 (193.6 - 317.2)	79.7 ± 28.6 (43.0 - 185.5)				
3 months	134.0 ± 15.0 (99.5 -150.5)	206.5 ± 8.6 (193.5 - 217.7)	72.6 ± 14.4 (59.1 - 110.2)	-3.8 ± 11.8 (-26.9 - 10.8)	-16.1 ± 29.9 (-107.5 - 16.1)	-12.3 ± 31.0 (-104.8 - 24.2)	3
6 months	139.8 ± 19.4 (96.8 - 150.5)	219.1 ± 8.9 (209.7 - 231.2)	79.3 ± 26.3 (59.1 - 134.4)	-1.1 ± 2.7 (-2.7 to 5.4)	19.8 ± 9.2 (0.0 - 21.5)	9.7 ± 9.1 (0.0 - 24.2)	0

Table 2. Location of S- and T-points. Time difference between S- and T-points and changes to previous follow-up. Displayed are mean ± sd and varies with time after stimulus in ms.

of time after stimulus. Nevertheless, the ranges of S- and T-points are clearly separated.

Figure 3 shows the results for the development of the heart rate and the load-sensitive parameter δ_{ST} during the 4-week follow-up. In both runs, δ_{ST} increased continuously with increasing load and decreases during recovery. For the first ergometry test, the mean heart rate rose from 80.0 ± 15.2 bpm (range: 59.9 to 117.2 bpm) at rest to 118.2 ± 16.7 bpm (range: 86 to151 bpm) at the final load level. The associated change in δ_{ST} was 1.7 ± 1.1 mV (range: 0.1 to 4.1 mV). During load increase, δ_{ST} for clearly VER-like signals was always greater than at rest and than at the preceding load level for all patients. However, for two patients, higher load resulted in the onset of intrinsic AV conduction with a conduction time comparable to the programmed AV delay. Hence, the signal morphology changed due to fusion and yielded smaller values for δ_{ST} than in the beginning. During recovery after exercise, δ_{ST} continuously declined for 18 patients immediately after the end of exercise. In 6 patients, the increase of δ_{ST} still continued for part of the first minute of recovery and continuously decreased afterwards. In 3 patients, the post-exercise increase of δ_{ST} lasted until the end of the second minute. In 2 patients, δ_{ST} took on a local minimum in the second minute. The final level of δ_{ST} reached its initial value for 16 patients, was significantly smaller for 3 patients, and was even greater for 10 patients. However, 7 of these 10 patients were monitored for less than 4 minutes and δ_{ST} was still decreasing during the last minute of observation for all 10.

The second ergometry was performed with a mean programmed heart rate of 129 ± 10 bpm (range: 100 bpm to 140 bpm). For 6 patients, the aim of exercising at a constant heart rate was not achieved. Their heart rates increased above the programmed values at maximum load. However, relative changes were about 5 % except for one patient (12 %) and, hence, rate influence on δ_{ST} is minor to load effect. As in the first ergometry test, δ_{ST} was always greater than it was at rest and increased with every load increase for nearly all patients. Only three exceptions occurred. One patient who exercised up to 200 W exhibited no parameter reaction until the beginning of 75 W, and the signal of two patients again consisted of fusion beats at the final load level. Mean increase in δ_{ST} was 2.1 ± 1.2 mV (range: 0.1 mV to 3.8 mV). Recovery was similar to the first ergometry test, i.e., the patients exhibited the same patterns of δ_{ST} decrease and similar time constants.

Three- and 6-Month Follow-Up

As the 3- and 6-month tests followed the same scheme, their results are presented together. The first ergometry tests, in DDD mode with a high basic rate, yielded mean results similar to the corresponding 4-week follow-up tests. Therefore, they are not presented here. However, for some patients significant deviations in rate or δ_{ST} development can be observed between the different follow-up examinations. The detailed analysis of this finding is postponed to the final data analysis after completion of the clinical study. This is expected to occur in Summer 2000.

The calibration procedure failed in two patients for technical reasons, i.e., signal transmission and recording

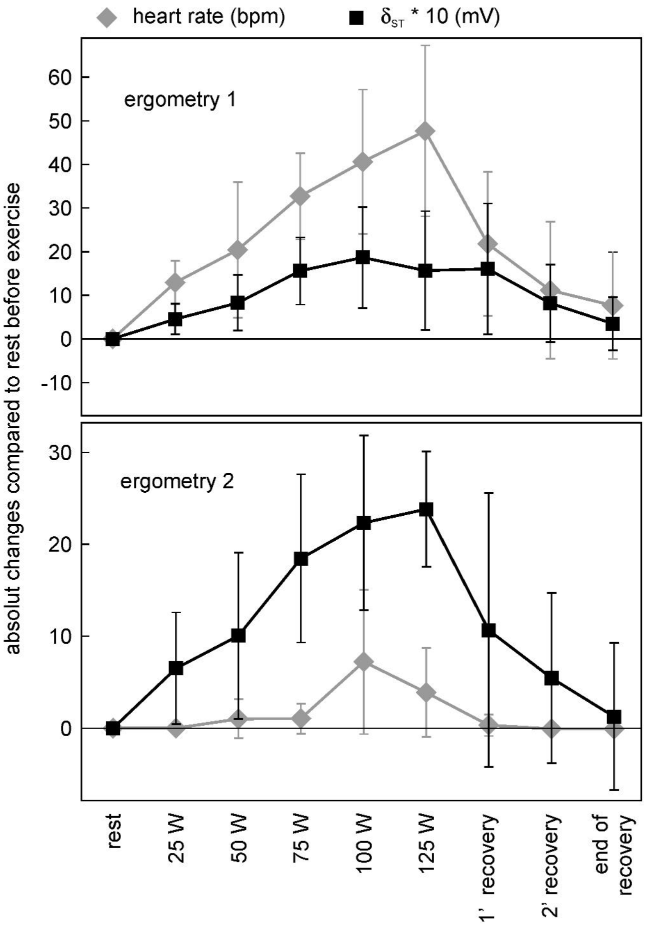

Figure 3. Course of mean heart rate (black) and load-sensitive parameter d_{ST} (grey) during bicycle ergometry with normal basic rate (top) and increased basic rate (bottom) during 4-week follow-up. The decrease in d_{ST} in the 1^{st} ergometry test and in the heart rate in the 2^{nd} ergometry for the transition from 100 W to 125 W is a consequence of the smaller number of patients exercising at 125 W.

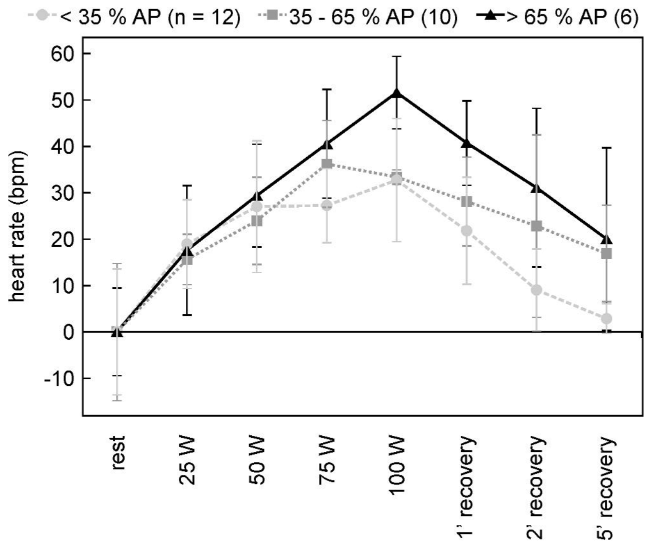

Figure 4. Course of mean heart rate during bicycle exercise in rate adaptive mode during 3- and 6-month follow-up. Results are displayed separately according to the percentage of atrial pacing: less than 35 % (light grey, dashed; mean increase: 20.3 ± 11.1 %), between 35 and 65 % (dark grey, dotted; 49.2 ± 8.4 %) and more than 65 % (black; 90.0 ± 14.1 %) The decrease in heart rate from 75 W to 100 W in the medium group was a consequence of the smaller number of patients exercising at 100 W.

during the first exercise was erroneous. With correctly stored signals, calibration is, however, always possible. The mean locations for S- and T-points and the mean differences (see Table 2) were close to the values at the 4-weeks follow-up for most of the patients. However, one patient showed a change in the T-point of more than 100 ms, two others showed a change of between 25 and 30 ms from the 4-week to the 3-month follow-up. Changes between the 3- and 6-month investigations were minor. As in the 4-week follow-up, all three values still varied over a wide range of time after stimulus and the ranges of S- and T-point were still clearly separated. In the DDDR mode pacing, the load at which patients stopped exercising was 50 W for 29 % of the tests, 75 W for 24 %, 100 W for 24 % and 125 W or more for 23 %.

For 6 patients, the percentage of atrial pacing during DDDR ergometry was greater than 65 % in at least one test; 4 of them are even paced continuously in the auricle. Twelve patients exhibited less than 35 % of atrial pacing in both rate adaptive tests. The medium range, i.e., 35 to 65 % of atrial pacing, was observed for 12 patients in one or even both follow-up examinations. Figure 4 shows the development of the mean heart rate for the closed-loop investigations. Rate increase was not significantly different for the three groups except at 100 W, where heart rate was greater for the 'more than 65 % APace' group. Irrespective of pacing type, rate always increased with higher load in all patients. During load increase, intermittent changes in atrial event type can be observed in all three groups: for 2 patients with less than 35 % APace, for 5 patients in the medium range group and for the 2 in the third group patients with less than 100 % APace.

During recovery, the heart rate continuously decayed for nearly all patients. In the group with mainly ASense, the - intrinsic - heart rate for 1 patient

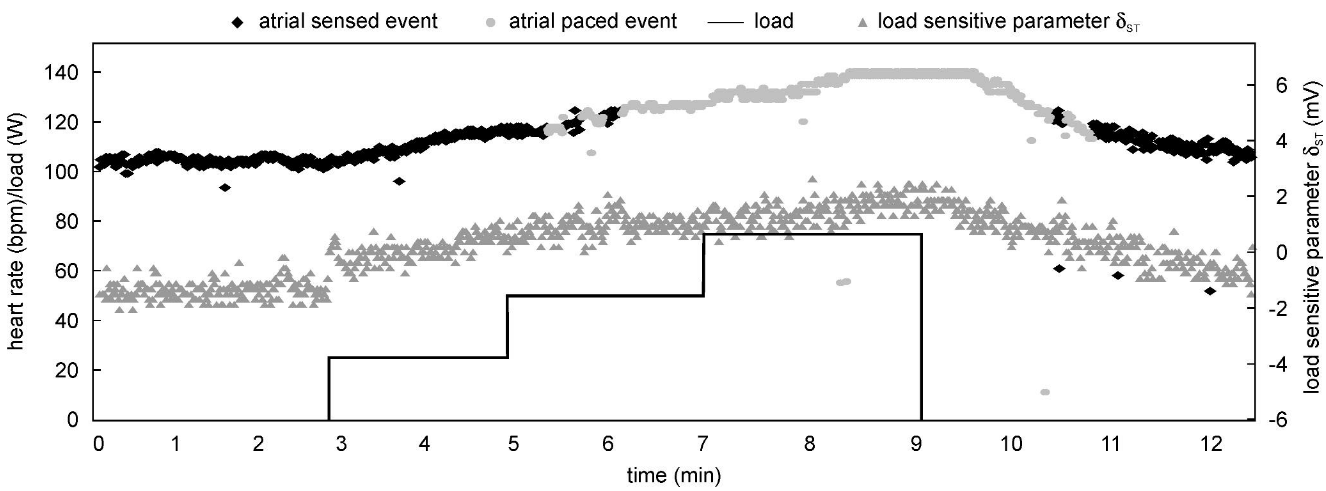

Figure 5. Course of heart rate and load-sensitive parameter d_{ST} for patient S.R. at 3-month follow-up (see 'Results' for detailed discussion).

increased from minutes 2 to 5. In this group, 6 patients were intermittently paced in the atrium. In the medium-range APace group, 2 patients exhibited an intermediate increase in the second minute of recovery, one of them with atrial paced events, the other with sensed events. In this group, competitive changes between APace and ASense occurred for 7 patients, whereas 3 were continuously paced during recovery. In the third group, no exceptions from continuous rate decay occurred, but for one patient the decay was very slowly. He would have needed an extrapolated time of 30 minutes to recover to the initial heart rate.

Figure 5 shows an example of an ergometry test with event-type changes for higher load and during recovery. As this patient had a relatively high intrinsic rate of 102.6 ± 1.0 bpm at rest, the heart rate calculated from δ_{ST} did not affect pacemaker timing in the beginning. Nevertheless, δ_{ST} reacted quickly and significant to load onset. Until reaching the middle of the 50 W level, the rate resulting from δ_{ST} had sped up to the intrinsic rate. Hence, several event-type changes occurred. Finally, δ_{ST} took over and the patient was continuously paced in the atrium until 1.5 minutes of recovery. As the maximum sensor rate was reached in the middle of the final load level, the further increase in δ_{ST} with ongoing load did not affect the pacing rate. The decreasing δ_{ST} did not immediately result in a decreasing heart rate, but only after the rate was lower than MSR after about half a minute of recovery.

Discussion

The results of our multicenter investigation corroborate previous single-center findings: Measurement and analysis of the ventricular evoked response with an implantable pacemaker is possible in an easy and reliable manner [9]. The monitoring of the adrenergic stimulation of the heart by bicycle ergometry using a selected VER parameter yielded closely correlated courses of load and VER parameter.

However, for optimized recognition of the load influence without disturbing rate effect, the load sensitive parameter δ_{ST} has to be individually adapted to each patient. This is clearly indicated by the wide ranges of values for the S- and T-points. The reproducibility of the S- and T-point determination is unclear. Changes occur for a minor number of patients between the 4-week and the 3-month follow-up, but not from 3 to 6 months after implantation. However, this might also be a consequence of the different calibration procedures: For the 4-week examination, the ergometry with maximum sensor rate is the second ergometry test, whereas during 3- and 6-month follow-up it is the first. Hence, stability of S- and T-point location has to be further investigated.

Another problem is that of fusion beats. Although the AV delay after atrial sensed events was programmed to 80 ms, fusion beats occur for 2 patients due to the onset of fast intrinsic AV conduction with higher load and resulted in abrupt changes in δ_{ST}. As the pacemaker recognizes only paced or sensed events, it falsely interprets such parameter changes as changes in the adrenergic stimulation. This problem can only be solved by using additional criteria to identify fusion.

Irrespective of these problems, on-line rate adaptation using the load-sensitive parameter δ_{ST} yields satisfying results. During load increase and subsequent recovery, the course of heart rate for mostly atrial paced patients is very similar to the patients whose heart rate was mainly determined by sinus nodal activity. The competition of intrinsic and pacemaker atrial activity in most of the patients for at least part of the follow-up examinations shows the correctness of the pacing rate determined from δ_{ST}. Unexpected findings like intermittent increase in paced heart rate at the beginning or in the middle of the recovery period cannot be interpreted as draw-backs, as these observations are found with atrial intrinsic activity as well.

In conclusion, the first results of our multicenter investigation clearly indicate that monitoring the adrenergic stimulation is possible using the selected VER parameter δ_{ST}, and allows direct rate adaptation with acceptable performance, i.e., comparable to healthy sinus node rhythm.

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