The Ventricular Evoked Response as Monitor for Adrenergic Stimulation

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Summary

We investigated a possible use of the Ventricular Evoked Response (VER) for monitoring of adrenergic stimulation. The dual-chamber pacemaker Logos and fractal leads (BIOTRONIK) were implanted in 8 patients due to sick sinus syndrome and AV block of 2nd and 3rd degree. During three subsequent ergometry runs with increasing load at different pacing rates we telemetrically monitored the VER. As parameter sensitive to adrenergic stimulation the difference in amplitude between two VER points was used. We observed a time delay between load onset and change in difference parameter of less than 10 msec in nearly all patients. Load induced changes in difference-parameter ranged from 0.6 to 6.1 mV (mean: 2.2 ± 1.9 mV). For 6 patients, it was nearly linear in time during load increase. Discrimination of load and rate effects is possible from the sign of change in the difference parameter for all but 1 patient. The latter discrimination is possible by the amount of change associated with load and with rate increase. A possible drawback for a VER based rate control is the observation of fusion beats with a VER-like morphology in two patients. However, the fusion beats always occurred in combination with intrinsic actions. Furthermore, a change from atrial paced to sensed events was associated with an offset in difference parameter for 2 patients. In conclusion, the use of the VER amplitude difference seem a promising concept for automatic monitoring of adrenergic stimulation.

Key words

Ventricular evoked response, adrenergic stimulation, telemetric pacemaker, intracardiac signal recording

Introduction

Technical development in the field of pacemaker therapy is aiming at increasing diagnostic and therapeutic capabilities of the pacemaker. Until recently, pacemakers did not use any information directly from the heart, except timing information. Other parameters influencing the pacemakers performance had to be either programmed by the physician, e. g. pacing amplitudes or sensing thresholds were continuously calculated from external parameters as for example pacing rate in dependence of accelerometer yield. However, within the last 5 to 10 years, the use of new intracardiac signals pushed technology a step further towards the autodiagnostic pacemaker as it was suggested by Auerbach et al. [1]: Capture control ensuring effectiveness of ventricular pacing [2], noninvasive cardiac transplant monitoring [3] - both based on the Ventricular Evoked Response (VER) - or regulation of pacing rate using the concept of Closed Loop Stimulation (CLS) based on measurements of myocardial contractility [4, 5].

Concerning the Ventricular Evoked Response, i. e. the unipolar measured electrical response of the heart to an effective ventricular pacing pulse, former investigations [6] have shown that this signal fulfils the main requirements for diagnostic and therapeutic applications in the electrotherapy of the heart: It can reproducibly be measured via specially designed electrodes and pacemakers and the morphology shows only small interindividual variations and sufficient long-term stability. Furthermore, bicycle ergometry testing revealed that the VER is uniquely related to cardiovascular

demand under physical load [7]. This may offer the possibility to use VER parameters for controlling a pacemakers activity, especially its rate behavior.
Therefore, we investigated a possible use of the VER for automatic monitoring of intrinsic adrenergic stimulation during exercise.

Materials and methods

The dual-chamber pacemaker Logos (BIOTRONIK) is capable of monitoring the VER with sufficient time and amplitude resolution to detect morphological changes in the VER associated with adrenergic stimulation due to physical load. Furthermore, Logos can telemetrically transmit the signals to the recording device UNILYZER 1.4 and 2.2 (BIOTRONIK) thus offering the possibility for continuos storage of VERs on flash memory card for several hours. The recorded data can afterwards be transferred to a PC and automatically be analyzed. We used this feature to monitor the VER during bicycle ergometry testing according to the following scheme: Ergometry load increased in steps of 25 W every 2 minutes up to the patients personal limit or to a maximum load of 125 W. The ergometry had to be repeated three times with different basic rates: 70 ppm, 100 ppm and 131 ppm. Between two ergometries, a recovery period of 20 to 30 minutes was allowed. For each run, VER monitoring comprised the period from 2 minutes before first load increase until 10 minutes after load was stopped. The repetition of the ergometry with different basic rates allows separation of different influences on the VER: The 70 ppm run actually results in VAT mode except for the very beginning, i.e. the pacing rate during load is determined by the patients intrinsic sinus rhythm, which increases during ergometry. This run thus yields the combined changes of the VER due to rate and load increase. During the 131 ppm run pacing rate does not change, hence, VER changes monitor pure load influence. The 100 ppm run is a combination of both with initially overpacing up to a certain load level. Comparative analyses of all three runs should reveal the adequateness of the selected parameter for rate adaptation and especially an unwanted positive feed back effect of rate increase.

The parameter selected for monitoring the adrenergic stimulation is the difference in amplitude between two VER points at fixed time after stimulus (Figure 1): The first one - the so-called S-point - is at the beginning of the nearly horizontal plateau phase about 100 to 150 ms after stimulus. The second one - the T-point - is just before the signal's maximum amplitude at the highest programmed rate. The exact location is determined in a calibration procedure ensuring maximum load effect and minimum rate effect in the parameter's changes. The calibration procedure is performed after termination of the three ergometry runs using VERs recorded during rest at minimum programmed rate and at maximum programmed rate and during maximum load at maximum rate.

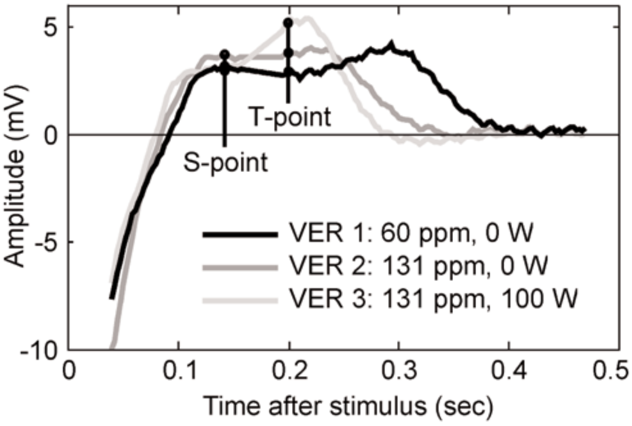

Figure 1. The difference-parameter: It is calculated as signal amplitude at T-point minus signal amplitude at S-point. Hence, it is independent of rate effects (VER 1 vs. VER 2), but strongly rises with load increase (VER 2 vs. VER 3).

Data analyses focuses on four points of interest:
1) Time delay between load increase and parameter reaction,
2) correlation between parameter and load,
3) rate influence and, finally,
4) event type influence.

Results

Eight patients (pts) - 5 males, 3 females - with a mean age of 71 ± 10 years (mean ± standard deviation) have been included into the study. They all received the DDD pacemaker Logos (BIOTRONIK) and fractal coated atrial (YP 60 BP) and ventricular leads (TIR 60-UP (1 x); PX 60-UP; all: BIOTRONIK). Indications for implantation were AV block of 2nd degree type Mobitz in 1 pt, AV block of 3rd degree in 3 pts, trifascicular block in 1 pt and sick sinus syndrome in 3 pts.

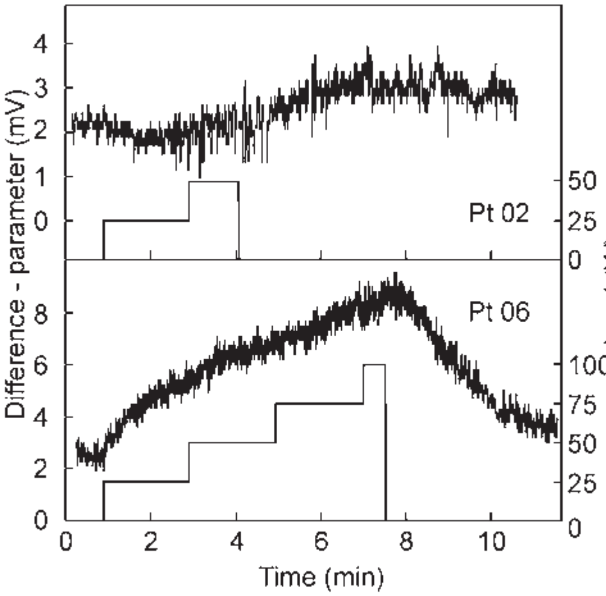

Figure 2. Time delay between load onset and parameter change: Patient 2 (top; pacing rate 100 ppm) shows a time delay of several minutes from load onset to parameter increase and even more pronounced from load cessation and parameter decrease (The initial parameter decrease is still a result of the preceding 70 ppm-run!). For the other patients (e. g. pt 09, bottom, 140 ppm) reaction times of the difference parameters are much shorter.

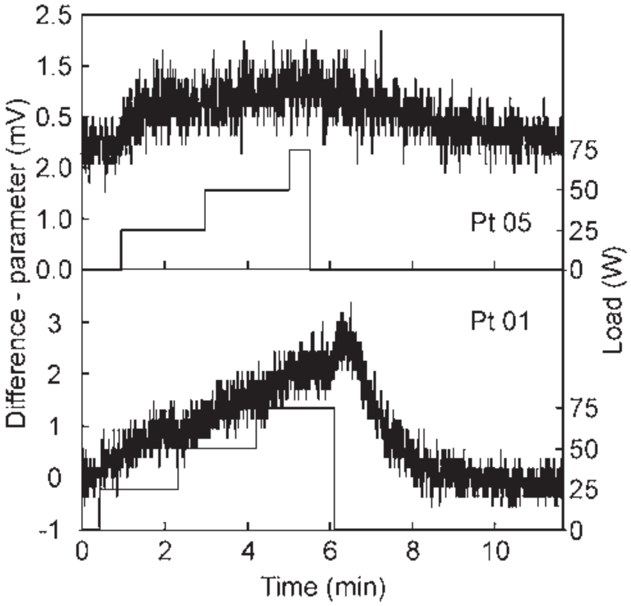

Figure 3. Linearity of difference parameter: Reaction to continuous load increase differs between patients. Whereas the majority shows a nearly linear increase with ergometry time (bottom), patient 05 strongly reacts in the first load step but shows no or only small changes in step 2 and 3.

Five patients had experienced scopes prior to implantation. The patients medications comprised antiarrhythmics class 1 C (2 pts), beta-blockers (2 pts), ACE inhibitors (4 pts), calcium antagonists (1 pt), digitalis (1 pt) and antihypertensives (2 pts).

Fifteen follow up investigations were successfully completed. However, due to different reasons, e. g. technical limitations or orthopaedic or pulmonary problems, only 27 runs yield satisfying results: 10 with a base rate of 70 ppm, 11 with 100 ppm and 6 with 131 ppm. Mean maximum heart rate achieved during the 70 ppm run was 106 ± 19 ppm. For the 100 ppm runs in 4 investigations the final heart at was greater than 100 ppm: 121 ± 9 ppm. Mean load duration was 5:36 ± 1:30 minutes with no significant differences between the different pacing rates (70 ppm: 5:43 ± 1:36 min; 100 ppm: 5:27 ± 1:42 min; 131 ppm: 5:39 ± 1:05 min). Recovery between subsequent runs lasted 9:52 ± 2:56 min or 2.0 ± 0.6 times the preceding load phase.

Time delay between onset of load and change in difference parameter is less than 10 msec in all but 1 patient (Figure 2). For this patient, significant reaction of the parameter to load increase and, even more pronounced, to load decrease is delayed for several minutes. This reaction is reproducible with this patient in all three follow up investigations. For all other patients, an immediate reaction to load onset and a reaction to load cessation within 5 to 40 seconds can be observed irrespective of pacing rate and mode, respectively.

The changes in the difference-parameter between rest and load range from 0.6 to 6.1 mV with a mean of 2.2 ± 1.9 mV. They slightly differ with rate and mode, respectively: 70 ppm / VAT: 1.9 ± 1.7 mV, 100 ppm: 1.7 ± 1.2 mV and 131 ppm: 3.3 ± 3.0 (Mean and sd are calculated using the worst case for all patients, i. e. the smallest change in the up to three corresponding investigations). The greater value for 131 ppm is a consequence of the fact that 131 ppm at rest means overpacing, i. e. actual rate is too high for actual load level.

As important as the absolute amount of change in amplitude is the way it changes. For 6 patients, the change is nearly linear in time during load increase, whereas for 1 patient, the initial change is more pro-

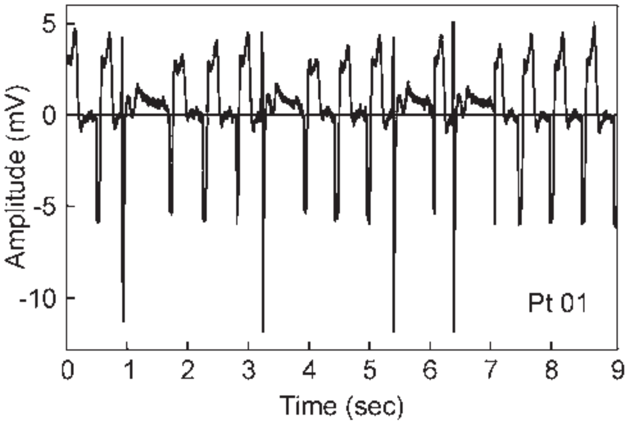

Figure 4. VER, fusion beat and intrinsic action: A sequence recorded in VAT-mode during first ergometry in patient 01 with several changes between VERs, fusion beats and intrinsic actions. Intrinsic actions clearly differ from VERs. However, there is a continuous transition phase between VER and fusion beat, especially affecting the part of the signal containing the T-point.

nounced than the change associated with later load increase (Figure 3).

Pure rate effect can be calculated from comparison of the difference parameters at rest at 70 ppm and at 131 ppm. The difference between the two ranges from -1.2 mV to 0.9 mV, only one patient shows a positive difference. Mean difference of the negative values is only -0.4 ± 0.5 mV. Hence, for all but 1 patient, the discrimination of load and rate effect is directly visible from the sign of the change in the difference parameter. For the one patient with positive difference due to rate increase, a comparison to the amount of change associated with load increase is helpful: Increase from 0 to 100 W results in a change in difference parameter of 4.3 mV (70 ppm), 3.3 mV (100 ppm) and 5.7 mV (131 ppm). Thus, it is at least 3.6 times greater than the change induced by rate increase.

The final aspect to deal with is a possible influence of event type on the difference parameter. This comprises atrial and ventricular event. Of course, ventricular sensed events do not have to be considered, as the VER can only be measured after a ventricular pace per definition. However, the possibility of fusion beats with a morphology reminding that of a VER must be taken into account. Such fusion beats were observed for two patients (cf. fig. 4), though never as fusion beats and VERs alone, but always in close vicinity to intrinsic actions.

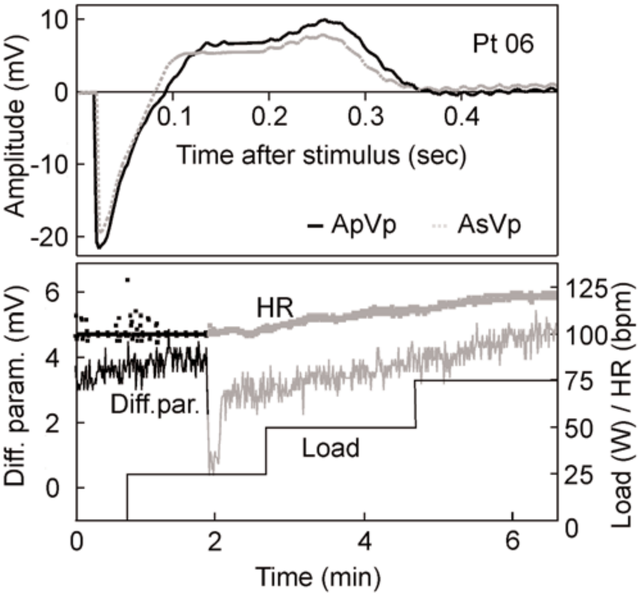

Figure 5. Influence of atrial paced and sensed events: For two patients the change from Ap to As during the 100 ppm run is associated with a small change in VER morphology resulting in an abrupt change in difference-parameter.

The change from atrial paced to atrial sensed events is associated with a remarkable offset in 2 of the 4 pts whose rates go beyond 100 ppm in the 100 ppm run: a reduction of 28% and 57%, respectively, of the total change during load increase (Figure 5).

Discussion

The concept tested in this investigation for monitoring of adrenergic stimulation aiming at physiologic rate adaptation in cardiac pacing seems promising. The difference-parameter extracted from the VER shows sufficient load dependence. For the majority of patients, the answer to changing cardiovascular demand occurs fast and unequivocal. However, influence of medication should still be investigated in more detail.

A positive feed-back of rate increase can reliably be avoided. Discrimination of rate and load effect can directly be made from the sign of change in difference parameter for most of the patients. For the others, the amount of change associated with variations of rate and load, respectively, differs to a sufficient extent.

A linear interpretation of parameter change in terms of pacing rate is appropriate for most patients. However, for some patients with a very pronounced change in parameter to load onset, this may result in temporary high rates in response to even small loads. This question cannot be answered but by Closed Loop investigations, i. e. in the case that rate adaptation is really performed according to the difference parameter.

Our investigations have further shown the necessity to avoid fusion beats by programming short AV delays both after atrial pacing and sensing. Therefore, rate adaptation based on the VER should be realized together with automatic AV-scan and -search. The influence of the atrial event type is of course no problem as the event type is always known to the pacemaker. It can therefore easily be handled with an automatic offset correction.

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