The Ventricular Evoked Response in Pacemaker Therapy

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Summary

This review discusses the use of the intracardiac potential evoked by ventricular stimulation – the ventricular evoked response (VER) – in pacemaker therapy. The theoretical aspects that the evoked response is based on are discussed at the beginning. The paper then examines the preconditions for accurate detection and analysis of the evoked potentials. The most important aspects in this context are the elimination of afterpotentials, which distort the measurement and the signal morphology, as well as optimization of the pacemaker input filters. Various approaches taken in the past to reduce the afterpotential are retraced. The significance of the lower cut-off frequency will also be discussed, as its influence on the signal morphology has not been recognized in the beginning. Already available applications of the VER in monitoring the pacing efficacy in the ventricle, in physiologic rate adaptation, and in monitoring a heart transplant in regard to rejection are addressed in a sufficient detail. A separate section is devoted to research results that have not yet been transferred into pacemaker applications. The emphasis is given on the results from application-oriented studies.

Key Words

Ventricular evoked response (VER), pacemaker therapy

Introduction

This paper intends to give a survey of the use of the evoked ventricular potential in pacemaker technology and therapy. Technical aspects of its use comprise the possibility of an automatic testing or a closed loop regulation, and therapeutical use applies mainly to the monitoring of myocardial cellular activity. The review begins with a brief discussion of the theory behind the ventricular evoked potential. Practical aspects of the measurement procedure are then discussed in greater detail and current applications presented. Possible future applications and expectations for further development are described at the end.

Characterization of the Ventricular Evoked Potential

The excitation resulting from an effective right-ventricular myocardial stimulus can be monitored intracardially and constitutes the ventricular evoked response (VER). Alternative terms include ventricular evoked potential or ventricular endocardial paced evoked response. From an electrical engineering point of view, this signal is a sum signal of all electrical sources in the heart. Its morphology results from the spatial distribution and the temporal development of the electrical multipoles of the excited cardiac cells. Therefore, it is mainly influenced by the electrical parameters of the heart, such as the conduction velocity or the action potential duration. Mechanical-geometrical parameters may also play an important role, since changes in cardiac geometry in the course of a cardiac action result in a rearrangement of the electrical sources. As the contraction velocity determines the rapidity of this rearrangement, it could also influence the evoked potential. However, this assumption has not yet been corroborated by clinical results.

Furthermore, the signal morphology depends on the arrangement of the sensing electrodes, as well as the electrical parameters of the measuring circuit itself. This will be covered in detail in the following section. Apart from these possible influences, i.e., with defined measuring points and minimized technical signal distortions, there is a so-called natural morphology of the evoked potential, reflecting the electrical state of the myocardium. Several examples will later on illustrate that the evoked potentials are directly associated with the patient's myocardial state and cellular electrophysiology. Theoretical studies have confirmed the origin of the VER. They have shown that the VER morphology depends on unipolar recordings of the evoked potential in the amplitude and duration of the underlying action potential and the velocity and anisotropy of the spread of excitation, with mostly the left ventricle contributing to the signal generation [1-2].

Afterpotential and Filter Cut-off Frequency

The morphology of the evoked potentials is decisively influenced by the distance of the electrode poles: The closer the indifferent pole is to the different one, the more localized is the signal. When reducing the distance between the electrode tip and the ring to less than about 5 cm, the local influences become dominant. With a distance of less than 1 cm, the evoked potential even represents a monophasic action potential, if monitored with suitable lead tips [3-5]. The unipolar recording contains information from throughout the heart, i.e., from the immediate vicinity of the electrode tip as well as from more remotely situated parts of the heart. This global character of the unipolar recording has been underestimated for a long time [3,6-7]. In the following, the term VER will be exclusively used for the unipolar recording of the evoked potential, as it has become customary in the newer literature.

Several studies have investigated how the signal morphology is related to the position of the electrode tip, with the emphasis on the positions close to the apex in the right and left ventricle. The results show a high correlation of signals measured at different right-ventricular locations as well as of right- and left-ventricular recordings [8-9]. The evoked potential does not necessarily have to be monitored with the stimulating electrode. However, a number of reasons favor using this electrode as a sensor:

- Fewer electrodes need to be introduced into the heart, which is of particular importance in situations when implantable pacemakers are used for the measurements;
- Convincing correlations of local characteristics of the evoked potentials and myocardial function parameters, such as the refractory period, are attainable only if the stimulation and the monitoring location are very close to each other [10];
- The morphological standardization of the evoked potential and, thus, the interindividual comparability are improved because the excitation always spreads from the monitoring location instead of passing the monitoring electrode in the form of an excitation front similar to the intrinsic signal [11-12].

However, the desire to monitor VER with the stimulation electrode raises the problem of the afterpotential. During the stimulus, the phase boundary between the electrode and the myocardium is charged by polarization. The voltage associated with the polarization artifact is proportional to the charge accumulated at the phase boundary during the stimulus. The charge increases with increasing stimulation current and longer pulse width. In this context, the so-called Helmholtz capacity characterizes the phase boundary's capability to accumulate the charge. With a larger Helmholtz capacity, the given amount of charge will cause a lower afterpotential. As the Helmholtz capacity is directly proportional to the microscopic surface area of the stimulation electrode, electrodes with larger surface areas are more favorable [13].

The polarization artifact is superimposed on the measured VER signal as a temporally varying voltage, thereby distorting the signal [13]. Since the polarization artifact cannot be calculated exactly either in regard to its formation or its decay, but rather depends on the respective stimulation parameters and the properties of the phase boundary that are patient- and situation-individual, it cannot be considered as a fixed offset in the signal interpretation. In order to use the undistorted evoked potential, the polarization artifact must be avoided. To this end, two different approaches have been taken:

- Compensating the stimulation artifact with subthreshold counterpulses;
- Minimizing the polarization voltage by enlarging the electrically active surface of the stimulation electrode (microscopic surface).

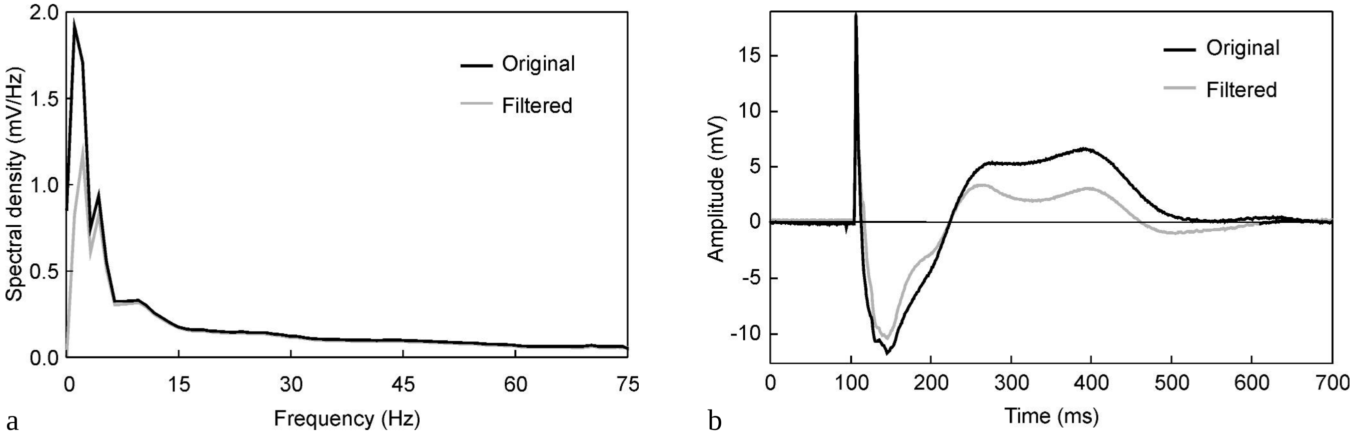

Figure 1. Frequency spectrum of the ventricular evoked response (VER) signal (Panel a). The greatest portion of the signal contents is situated in the frequency range of up to 10 Hz and hardly any components are present at frequencies above 50 Hz. For this reason, a simple high-pass filtering with a cut-off frequency of 2 Hz would lead to a significant modification of the spectrum and thus morphology of the signal (Panel b).

Compensating the phase boundary charge with counterpulses is based on the idea that the charge associated with the stimulation pulse can be neutralized by a pulse equal with respect to the charge accumulated at the phase boundary but with opposite polarity [14]. The neutralization charge can be given either as one event before or after the stimulation pulse proper, or it can be divided to both sides of the stimulation pulse.

The counterpulses should not trigger the myocardial excitation, which can be achieved by applying a respectively long pulse duration at a voltage below the rheobase. Stimulation pulse and counterpulses together form a bi- or triphasic pulse configuration. To be able to measure the potential evoked by an effective stimulation, the charge compensation must be completed quickly after the end of the stimulus. This is why the so-called pre-charge part of the stimulus is of major importance for neutralizing the polarization charge. However, this method functions reliably only if the compensation pulse is tuned to the respective conditions by measuring the polarization artifact, in which case an afterpotential reduction of up to 75 % is achieved [15-16]. This method has the drawback that the charge necessary for compensating the stimulation artifact must be taken from the pacemaker battery, shortening its service life. Furthermore, it has been found that the polarization artifact cannot be sufficiently compensated in case of stimulation voltages in the range of 5 V, which may be used with older electrodes [17].

In contrast, the second method maximizes the Helmholtz capacity of the phase boundary, leading to a reduction of the polarization voltage. However, a direct, purely geometrical increase in stimulation area would be associated with a lower stimulation impedance and increased stimulation current, again resulting in an undesired shortening of the pacemaker service life [18-19]. This can be countered by enlarging the electrically active surface at an unchanged geometric surface. Various methods and materials can be used for this purpose. For instance, smooth platinum, iridium, titanium, or carbon electrodes are further processed by sandblasting, laser cutting or mechanical drilling, chemical etching or sintering to enlarge the electrochemically active surface, or they are already deposited as sponge-like, porous, textured, or fractal structures by chemical-physical processes [13,20-25]. The related increase in the electrically active surface (Helmholtz capacity) ranges between 2 for mechanically perforated and 1000 for fractal coated electrodes [13]. The lowest signal distortion can thus be achieved with fractal coating, leading to a reduction of the afterpotential by > 90 % [26].

Aside from the distortion of the evoked potential by the afterpotential, the signal is decisively influenced by the filter properties of the measuring circuit. As the large portion of the power spectrum of the VER is situated in the frequency range from DC to 10 Hz, the lower cutoff frequencies of the electrode and of the measuring circuit should be as low as possible (Figure 1). The

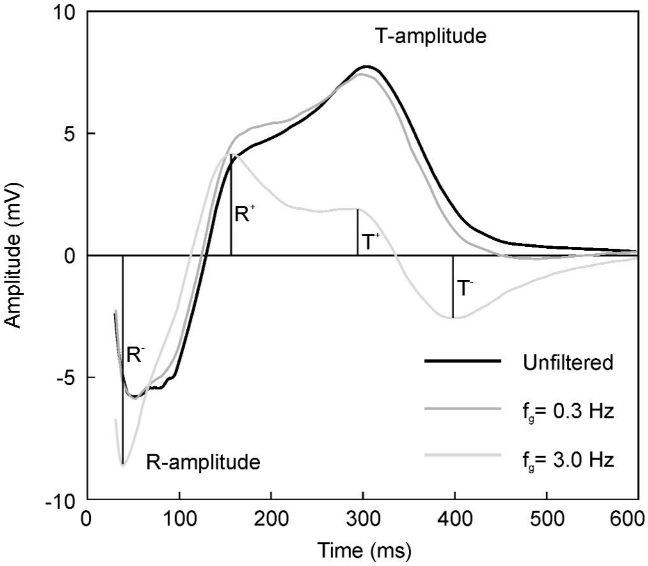

Figure 2. Unfiltered and filtered VER signal using different cut-off frequencies (f_g). Filtering the VER with the cut-off frequencies of 0.5 Hz and 3 Hz results in a slight or a significant modification of the signal morphology, respectively. In particular, the signal parts referred to as R^+, R^-, T^+, and T^- in earlier publications are artifacts of the R- and T-amplitudes and are product of filtering (terminology according to [11]).

desired high-pass properties of the electrode are again decisively influenced by the Helmholtz capacity – the higher the capacity the lower the cut-off frequency. With its high Helmholtz capacity that allows the lower cut-off frequency of about 0.3 Hz, fractal coated electrodes possess ideal properties with respect to signal filtering too [27]. The filter properties of the pacemaker input channel can also lead to changes in the signal. Conventional intracardiac electrogram (IEGM) input filters with the lower cut-off frequencies of 5 Hz, or higher, are not suited for undistorted measurement of evoked potentials. Broadband input filters are more favorable (Figure 2). A number of the applications and pacemaker models discussed in the following exhibit deviations from the prerequisites for ideal signal detection in at least one of the above listed points. In many cases, however, this had no serious impact on their function, although in some cases it had.

Current Applications

This section presents three applications of the VER that are already incorporated in several commercially available pacemakers.

Monitoring the Pacing Efficacy

Pacemaker longevity is mainly determined by the capacity of its battery. A considerable part of the electrical energy necessary for operation is used up directly by the pacing current. Therefore, minimizing the pacing current is desirable and can be achieved by taking various measures, for instance by the use of high-impedance leads which exhibit low pacing thresholds and high pacing impedances [28-29] or/and by the application of low energy output [30]. Too low output can lead to ineffective stimulation in case of pacing threshold rise, which constitutes a considerable risk for pacemaker-dependent patients. While such increases in pacing thresholds are mostly observed during the initial postoperative weeks, they can also occur in the electrodes implanted for several months and even years. Additionally, such threshold increases are patient-specific and depend on the lead type and placement [31-32]. Consequently, automatic monitoring of the pacing efficacy is a useful capability for an implantable pacemaker. Presently, several single- and dual-chamber pacemakers from various manufacturers perform automatic capture control. The reliability and usefulness of this pacemaker function have been proven in comprehensive multicenter studies for typical pacemaker population as well as for children and premature infants [33-38]. However, with the use of non-fractal, high-ohmic electrodes, problems with polarization artifacts and insufficient charge compensation occur in up to 10 % of patients [36,39]. For that reason, the use of the sum signal of the electrode tip and ring after bipolar stimulation or an improved compensation of the phase boundary charge are considered as further methods for elimination of the afterpotentials [40-41].

Automatic stimulation effectiveness control is currently used only in implantable pacemakers and during pacemaker follow-up examinations (Figure 3). A demand for the implementation of the similar function in implantable cardioverter-defibrillators (ICDs) can be anticipated, especially with the increasing use of dual-chamber ICDs [43-44].

Rate-adaptive Pacing

Rate-adaptive pacing was among the first applications utilizing evoked potentials. Initial investigations had indicated that the QT interval, i.e., the time between stimulus and evoked T-wave, is a reliable and rate-independent load indicator suitable for a physiologic rate

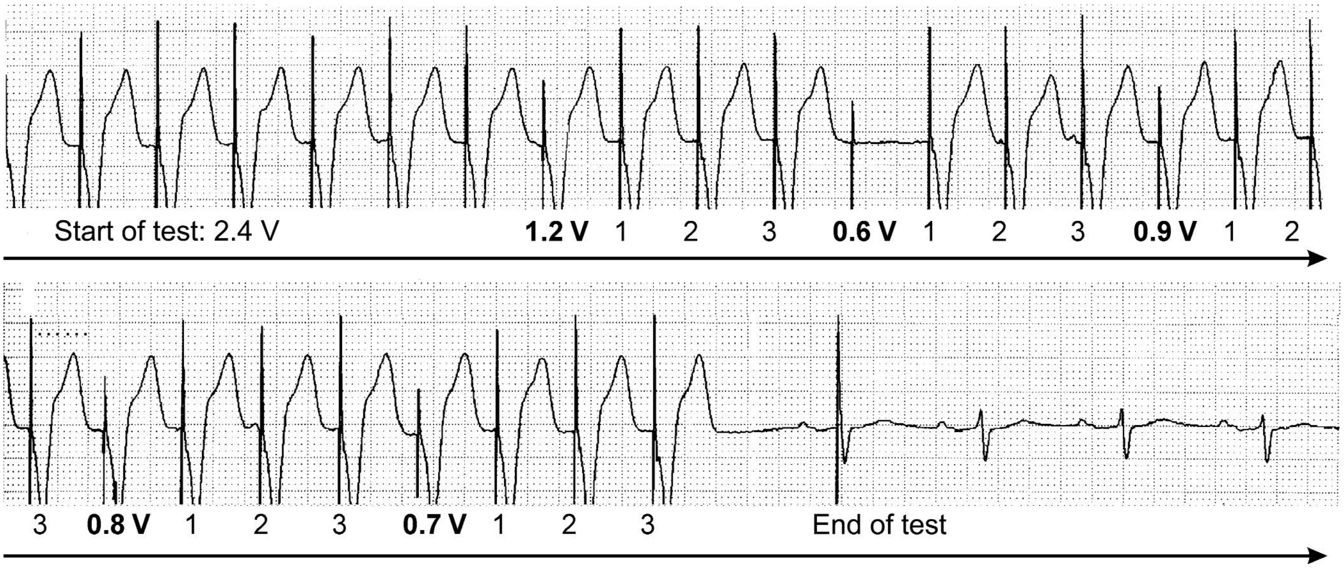

Figure 3. ECG printout of a VER controlled automatic pacing threshold test (pacing threshold = 0.7 V). The test begins with the pacing voltage of the permanent program (2.4 V). Every fourth stimulus, the voltage is reduced to half the value for one stimulus, until the first ineffective stimulus occurs (0.6 V). Each test stimulus is followed by three stimuli with safe output. After ineffective pacing, output is increased by half of the last step and then decreased by steps of 0.1 V. After completing the test, the pacemaker resumes pacing at the permanent program (modified from [42]).

adaptation [45-46]. Later studies showed that the QT interval is not sufficiently rate-independent and that there is a non-linear relationship between the pacing rate and the QT interval, leading to a significant shortening of the QT interval, in particular at higher rates [47]. Additionally, a slow response was apparent in clinical applications and could be improved only by a non-linear assignment of QT intervals and pacing rates [48]. Another problem encountered in the initial phase of a wider clinical application of the QT interval, was difficulty with the reliability and long-term stability of the T-wave sensing, which was partly solved by the use of electrodes with geometrically smaller tips and enlarged electrically active surfaces [49-50]. A combination of QT interval control and piezo sensor has also been realized to improve the correlation between load and pacing rate, but it still exhibits an unsatisfactory response time and a positive rate feedback [51-52].

To improve the load detection and thus the physiologic rate adaptation, the analysis of the evoked potential can be extended from considering exclusively temporal information to morphologic criteria. The first attempt in this context was the evaluation of the ventricular depolarization gradient, defined as the integral over the stimulated R-spike. The depolarization gradient shows a positive load reaction and a negative rate feedback, thus enabling a physiologic rate adaptation without the positive feedback of the QT-interval regulation [52-53]. Rate adaptation by evaluating the depolarization gradient was the first system in which pacing rate could increase during mental stress, and this was due to the direct influence of the sympathetic nervous system on the VER morphology [54-57]. Because it occurred so close to the stimulus, the depolarization gradient is susceptible to signal distortions by an insufficiently neutralized afterpotential.

The T-wave has been studied as another parameter for a physiologic rate adaptation by means of the VER [58-59]. It also shows a clear load effect with a negative rate feedback. The use of this parameter is promising, but so far it has only been realized via an automatic telemetric pacemaker control for study purposes [60-61]. It was found that a high load sensitivity with short reaction times and load proportional pacing rates results from an automatic patient-specific adjustment of the correlation between the T-wave parameter and the rate (Figure 4).

Rejection Diagnostics

A third field that already applies VER analysis with clinical benefits is to monitor patients with a heart trans-

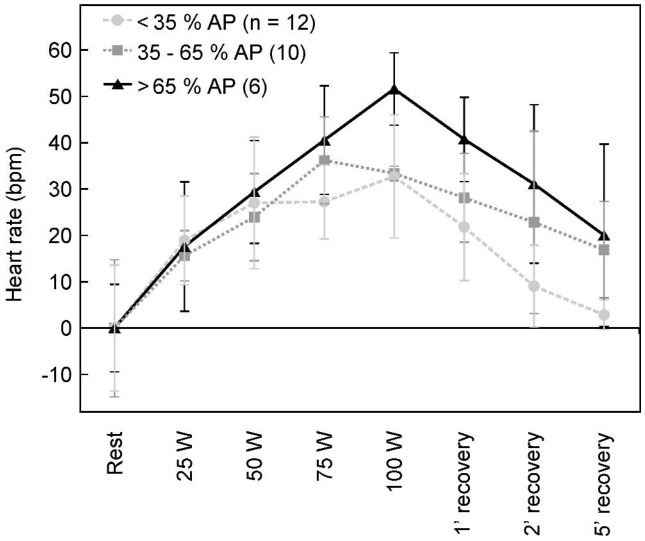

Figure 4. Heart rate development with DDDR pacing based on the T-wave parameter. The patients have been grouped according to the percent of atrial pacing (AP). Significant differences were observed only at the 100 W stage. The decrease in the mean heart rate for the 35 – 65 % AP group when the load was increased from 75 to 100 W was a consequence of the fact that seven patients in this group discontinued the exercise at the 75-W level (according to [61]).

plant. A rejection of the transplanted heart, which can be detected histologically by myocardial biopsy influences the cellular electrophysiology. This can be detected in the surface ECG or the signal-averaged ECG as well as in the IEGM [62-66]. The sensitivity of ECG-based methods appears insufficient, especially in the early phase after a transplantation and in case of low-degree rejection (degree 1 B) [62, 67]. Moreover, the ECG may also reflect long-term changes that are similar to those during rejection but are consequent to normal integration of the transplanted heart into its new environment and do not require therapy [68].

Therefore, a number of studies have explored whether the use of evoked potentials would lead to an improvement in the detection of transplant rejection [69]. Using the VER, that was evoked and telemetrically measured by implanted single-chamber pacemakers, resulted in a sensitivity of 84 % for rejection of degree 2, or higher, in the initial study with 17 patients [70]. To date more than 100 patients in several multicenter studies have been successfully monitored with implanted pacemakers via VER analysis in the context of CHARM – Computerized Heart Allograft Recipient Monitoring [71-73]. The use of computer and Internet technology makes it possible for the same center to perform the analysis in a highly automated manner, providing a high degree of standardization and reliability [74]. In addition, a large amount of VER data became available through this approach, which could have been used for further development of the detection algorithm. Thus, the transition from one pacemaker generation to the next was completed without difficulties and without temporal gaps in the reliability of the VER analysis results [75,77].

Extending the analysis by using an infection-sensitive parameter led to an improved specificity of transplant monitoring by means of VER analysis. Since an infection influences the rejection-sensitive parameter in the same manner as a rejection, but the infection-sensitive parameter is not influenced by a rejection, a rejection episode can be reliably differentiated from an infection (Figure 5) [76].

The comparability of the conditions under which the IEGM sequences intended for VER analysis have been recorded constitutes another important influence on the sensitivity and specificity of the CHARM measurements. Differences in heart rates, body posture, times of the day, and 5-minute histories for the compared measurements make both rejection-sensitive and the infection-sensitive parameters less conclusive [77-78].

Possibilities for Future Application

Aside from the VER analyses listed in the previous sections, which have already been applied in large patient groups, there are results from individual studies and animal studies that extend the application possibilities for the VER in pacemaker therapy. They will be briefly discussed here.

The desire to gain easy access to medication monitoring by measuring and analyzing the VER already played a role in the first studies about the VER [6]. In particular, it would be advantageous to be able to apply the many influence factors and relationships discovered for the monophasic action potential (MAP) to the VER, which can be measured more easily but is correlated to the MAP [79]. In some cases, studies have indeed already unambiguously shown that the evoked potential can be influenced by drugs, such as amiodarone or bethanidine [80], which prolong phase 2 of the action potential. However, these are individual cases; a comprehensive drug monitoring with the help

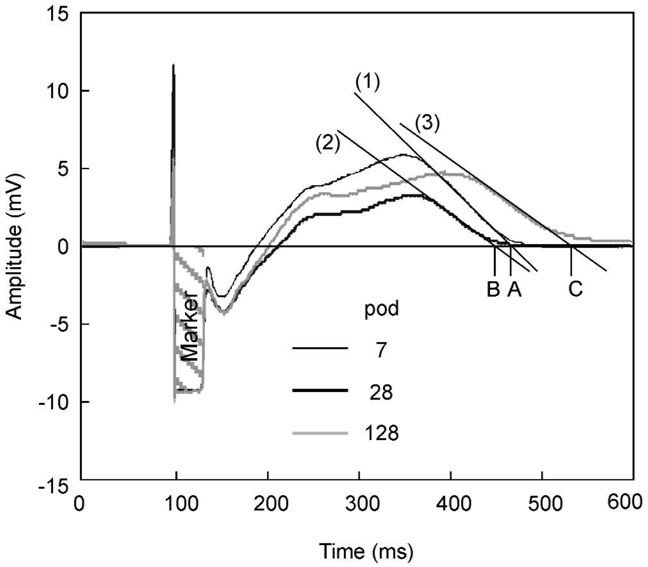

Figure 5. Changes in the VER morphology due to a heart transplant rejection and infection. On the post-operative day (pod) 7, neither rejection nor infection was present. On pod 28, rejection of endomyocardial biopsy (EMB) grade 3A is detected. On pod 128 an infection has developed, but EMB grade was 0, i.e. no rejection. The rejection-sensitive parameter as the tangential on the descending segment of the T-wave decreased both with rejection (1 ® 2) and infection (1 ® 3). In the same time, the infection-sensitive parameter – the time from the stimulus to the zero point of the tangential of the rejection parameter – significantly increased only during infection (A ® C) (according to [77]).

of the VER – e.g., in regard to screening the effect or monitoring the dosage – has not been performed. Possible reason for this is that drug monitoring is neither a task limited to patients with pacemakers, yet concerns a much larger group of people, nor is it a task necessary for the functioning of the pacemaker.

Therefore, a faster realization might rather be expected for tasks that are directly related to the pacemaker function, such as the above mentioned already realized applications of pacing efficacy monitoring and rate adaptation. One of these possible tasks could be an AV-delay programming and optimization. With a morphologic VER analysis, fusion beats can be recognized by a decrease of the T-wave amplitude and the R-spike width [81-82]. Hemodynamic monitoring and optimizing of pacemaker patients is a step in the same direction.

The VER morphology reflects the ventricular geometry, with the amplitude and slope of the R-spike indicating variations of the end-diastolic volume, while the decrease of the T-wave shows changes in the end-systolic volume. These relationships are expected due to the temporal course of the electrical and mechanical activity and have been confirmed for intrinsic as well as paced cardiac actions [83-87]. Again, the correlations are better for paced than for intrinsic actions. Additional correlations have been found for the variations of the QT interval and the T-wave amplitude with the isovolumetric relaxation time and the maximal left-ventricular filling velocity, respectively, after several hours of ventricular pacing [88].

Another field in which it might be worthwhile to apply VER analysis in the future is in the diagnosis and monitoring of certain basic diseases in pacemaker patients. Especially for cardiomyopathies, the VER seems to exhibit a relationship with the kind and degree of the obstruction or dilatation [82,89].

As a last point, the possibility should be mentioned to differentiate between sinus tachycardia and ventricular tachycardia based on VER analysis (integral over the VER) [90].

Conclusions

What can be expected from further development in the use of the VER in pacemaker therapy? So far mainly the initial hopes and ideas have been realized, which were directly connected with the pacemaker function, i.e., increasing safety and improving pacemaker functionality. Rejection diagnostics have been met with interest mainly because it allows complementing and substituting the invasive biopsy with a reliable and easy to handle non-invasive method. However, its implementation requires a close ambulatory control, which is only meaningful for high-risk patients due to financial and time management considerations. Therefore, it seems reasonable to develop in the future only those VER-based optimization methods that are performed only once or a few times during routine follow-up examinations, such as AV-delay optimization.

A possible continuation of the development that began with rejection diagnostics is the possibility of measuring VER parameters during pacemaker follow-up examinations and using them as a progress check or as a therapy indicator for certain basic diseases. To this end, the currently available results should first be extended to larger patient groups and longer observation periods. In the future, it should be feasible to obtain these parameters and their temporal development as continuously stored recordings, which can be presented to the attending physician during a follow-up in the same way as, for example, heart rate trends and histograms are presented today. The next stage of development will be the time- or event-controlled transmission of these parameters per long-distance telemetry to a monitoring station, which will provide the physicians with new options for monitoring and controlling health status and therapy success in their patients.

The mentioned current applications of the VER suggest that monitoring and analysis of this signal is technically feasible and valuable feature in pacemaker technology. The exploitation of the seemingly immense potential of VER for monitoring, analyzing, and controlling the cardiac status has just begun. Very important advantages of the evoked potentials are: stability, reproducibility, and direct access to cardiovascular information. The ongoing development will likely result in increased pacemaker functionality, for instance including automatic optimization of the pacemaker function, the extended therapeutic control, and additional diagnostic capabilities.

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