Noninvasive Patient Monitoring after Heart Transplantation - New Methodological Aspects

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Summary

During the last years, we developed a method for noninvasive cardiac transplant monitoring based on intramyocardial electrograms which are obtained using implanted, telemetric pacemakers and fractally coated electrodes. Besides cardiac rejection, a number of other conditions influence the electrical activity of the transplanted heart. Additionally, the properties of intramyocardial electrograms depend on the position of the myocardial leads, the recording configuration, and whether ventricular evoked responses during pacing, or spontaneous ventricular electrograms are recorded.

This paper presents important aspects of the current methodological concept regarding implantation, data acquisition and processing and concludes that averaged unipolar ventricular evoked responses, obtained from electrogram sequences during pacing with constant pacing frequency, recorded at comparable times of the day, after a resting period of some minutes, together with standardized signal processing yield results with excellent reproducibility and, therefore, are the signals of choice for patient monitoring after heart transplantation.

Key Words

Intramyocardial Electrogram, Ventricular Evoked Response, Telemetric Pacemaker, Heart Transplantation, Noninvasive Patient Monitoring

Introduction

During the last years, we developed a method for noninvasive cardiac transplant monitoring based on intramyocardial electrograms (IEGM). Implanted, telemetric pacemakers and fractally coated electrodes allow daily, noninvasive, electrophysiological examinations of the patients[1,3,4,5,6,9,10]. Up to now, we recorded more than 11.000 IEGMs from 103 patients.

IEGMs can be recorded with various implant configurations and under different conditions, with each methodological approach having its own properties. Based on a number of specific studies on the behavior of these signals under various conditions, we steadily improved the method, ending up with our current implant, recording, and signal

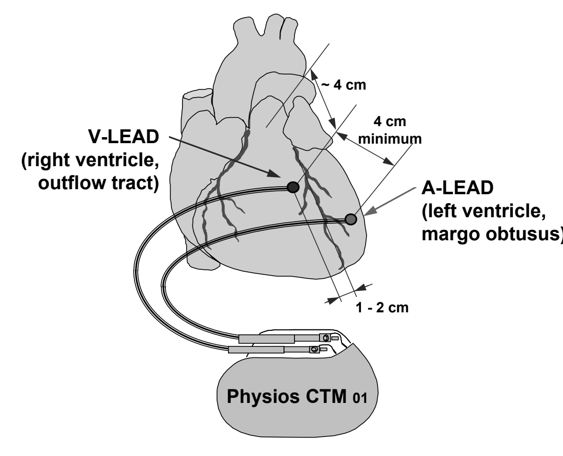

Figure 1. *Preferred implant configuration with the telemetric dual chamber pacemaker and two epimyocardial screw-in electrodes, placed at the right and at the left ventricle, with a distance between both leads of at least 4 cm.*

processing policy. Figure 1 shows the preferred implant configuration.

A number of conditions influence the electrical activity of the transplanted heart. Among them: rejection and infectious disease, immunosuppression, heart or pacing rate, haemodynamics, ventricular dilatation, the time of the day when recordings are performed, and cardioactive drugs. A second group of important factors which significantly determine the electrograms are the kind and position of the myocardial electrodes, the recording configuration, i.e. unipolar or bipolar, and the origin of excitation as well as the depolarization pattern, i.e. recordings during spontaneous beating or during pacing, respectively. Although the presented method basically allows to record and analyze both kinds of electrograms, in patients with the proper implant configuration, we focus on ventricular evoked response (VER) recordings during pacing, which - compared to spontaneous ventricular electrogram (SVE) recordings - have been shown to be superior for long-term cardiac monitoring[14]. After recording, adequate signal processing is necessary not to impair the results.

This paper presents important aspects which have led to the current methodological concept.

Methods

IEGMs are obtained using dual chamber pacemakers equipped with IEGM telemetry (bandwidth: 0,3 - 200 Hz, Physios CTM 01) and various types of fractally coated leads. If the pacemaker system is implanted intraoperatively (during the heart transplant procedure), the leads are implanted epicardially (lead type ELC). If the pacemaker is implanted at a later time, the endocardial approach is used.

IEGM sequences with a duration of one minute are telemetrically received, sampled with 667 Hz and stored using a special pacemaker programming and data acquisition system (SWM/SWD 1000, all appliances so far: BIOTRONIK, Berlin, Germany).

Recordings are performed at standardized conditions to avoid as many influences as possible which may be introduced by varying recording conditions (pacing frequency, time of the day, position of the patient, etc.).

After recording, the electrogram sequences together with associated clinical information are transmitted via the Internet to the central data processing station for automated evaluation and report generation[5]. Signal processing comprises of the following major steps[10]:

1. event detection,
2. event classification,
3. averaging of all events assigned to the same class,
4. extraction of the diagnostic parameters from the representative, averaged heart beat electrogram.

Figure 2 shows the definition of the diagnostic parameters extracted from the VER, the rejection sensitive parameter (RSP) and the infection specific parameter (ISP), respectively.

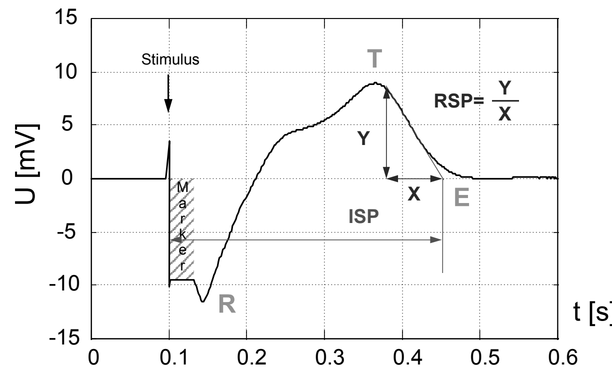

Figure 2. *Definition of the diagnostic VER parameters. RSP (rejection sensitive parameter) = the maximum slew rate in the descending part of the repolarization phase of the VER; ISP (infection specific parameter) = the duration of the VER, measured from the stimulus to the intersection of the slopeline with the baseline.*

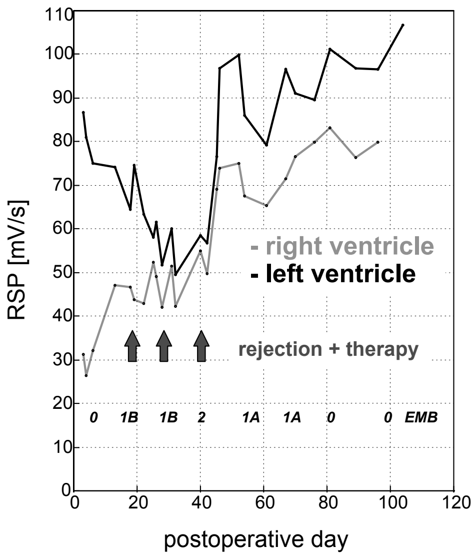

Figure 3. *Trend curves of the RSP values from a patient who exhibited different time courses for the right and the left ventricle during the first postoperative month and suffered from three rejection episodes. Only the third rejection therapy has led to a significant increase of the RSP values as well as an improvement according to endomyocardial biopsy (EMB)*

Results and Discussion

1. Rejection and Infection

The sensitivity of the repolarization phase of the VER to cardiac rejection and rejection therapy in comparison to the results from endomyocardial biopsy have already been shown[1,3,6,10]. The electrical repolarization activity of the transplant, as assessed by the RSP, decreases under the influence of rejection and increases under the influence of successful rejection therapy (Figure 3).

Decreased RSP values, however, may also occur during other pathological conditions like infection or ventricular dilatation. Recently, we observed that the duration of the VER, as reflected by the ISP, is prolonged during severe infection only and presumably can be used to rule out rejection in such cases (Figure 4)[13].

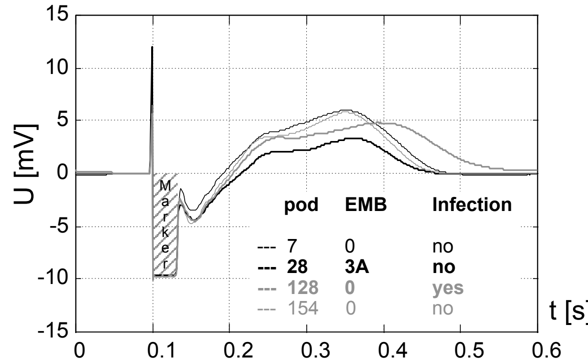

Figure 4. *VERs obtained from a single patient at four different postoperative days (pod). Compared to the recordings on days without rejection or infection (pod 7 and 154), the VER showed decreased repolarization slew rates under the influence of both pathological effects. A markedly increased duration of the VER, however, can be observed under the influence of infection only (EMB - rejection grade according to endomyocardial biopsy).*

2. Telemetric pacemakers

Basically, the IEGM telemetry bandwidth of the Physios CTM 01 covers all relevant signal components of both, SVEs - recorded from the spontaneously beating heart - and VERs - recorded during pacing.

Initially, the patients have been supplied with the predecessor of the Physios CTM 01, i.e. the Mikros-Biogard. An important difference between both pacemakers is presented by different lower cut-off frequencies of the IEGM telemetry. This results in different signal morphologies. Figure 5 shows the influence of the IEGM telemetry bandwidth on the VER signal morphology. To account for the changed signal morphology in Physios CTM 01 patients, new parameters have been evaluated as soon as a sufficiently large data pool acquired with the new pacemaker became available. This analysis revealed that the RSP as defined in Figure 2 should be used in Physios CTM 01 patients.

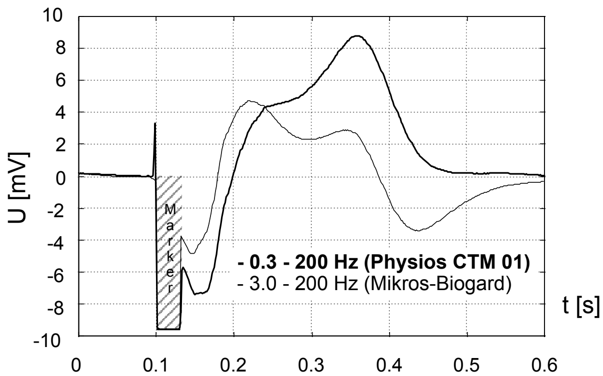

Figure 5. *Influence of the IEGM telemetry bandwidth on the signal morphology of the VER. The bold curve represents a real VER acquired with the Physios CTM 01 pacemaker, the light curve shows what the same VER would look like if recorded with the increased lower cut-off frequency of the Mikros-Biogard of 3 Hz.*

3. Lead type

In order to record IEGMs from electrodes which have previously been used to stimulate the heart, fractally coated leads have to be employed. Non-fractal leads become polarized by the stimulus, resulting in a huge polarization artifact which is superimposed to the intrinsic cardiac signal and impairs meaningful signal processing (Figure 6).

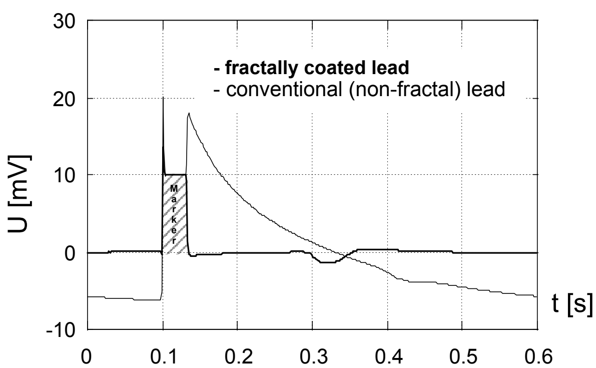

Figure 6. *Comparison of evoked responses obtained in two patients with two different atrial, endocardial leads. Only fractally coated electrodes render possible polarization artifact free recordings of evoked signals a short time after stimulation and with the same electrode being used for stimulation and sensing.*

4. Lead configuration

Basically, each myocyte contributes to the electrocardiogram. This is the case for both, SVEs and VERs. However, the signal which is actually recorded by a certain lead strongly depends on where the depolarization is initiated and how it spreads over the myocardium relative to the position of the recording electrode. It is well known, that unipolar recordings which use the pacemaker case as the indifferent electrode contain much more far field components than bipolar recordings with their relatively small distance between the recording electrodes. Utilizing the special properties of unipolar VERs, it can be achieved to monitor the electrical activity of a large area of the heart (not just the region where the lead contacts the myocardium). This is possible, because the late phase of the VER predominantly contains signal components from a heart region which lies opposite to the recording point, e.g. from the left ventricle in case of a recording lead located at the right ventricle[8]. This behavior of evoked signals can be impressively shown by comparing unipolar and bipolar recordings from one and the same implanted system (Figure 7).

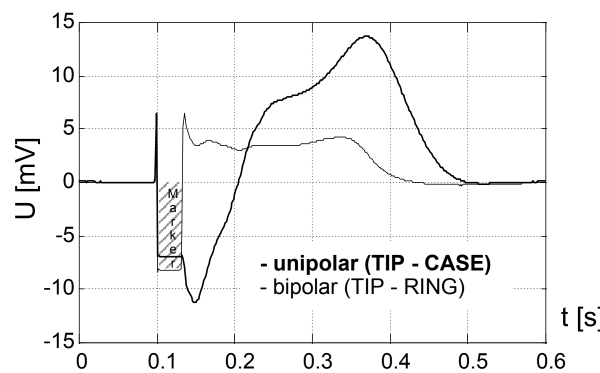

Figure 7. *Comparison of unipolar and bipolar evoked responses - 300 ms after the stimulus, the bipolar signal has already reached the baseline. This indicates that only the unipolar signal contains the electrical activity of heart regions which lie remote from the lead tip.*

Though, up to know, most experience has been obtained with epimyocardial leads, it has already been shown that the same monitoring concept can be applied with comparable results to patients with endocardial implant configuration [2].

5. Recording conditions

Recordings should be performed under as standardized conditions as possible to minimize variations of the diagnostic parameters due to factors like pacing frequency or haemodynamic conditions.

Recordings should be performed at comparable times of the day to minimize the influence of circadian rhythms (Figure 8).

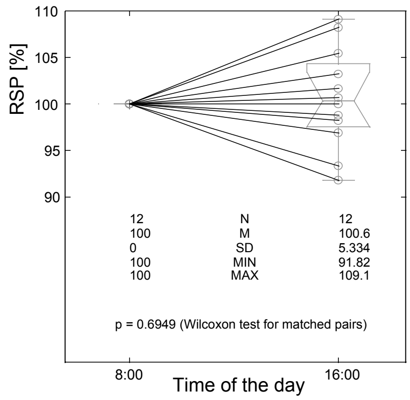

Figure 8. *Changes of RSP of the VER measured at 8:00 (=100%) and 16:00, respectively. Though no general trend has been identified, individual differences of up to ±10% have been observed. Similar results have been reported by other authors for SVE recordings*[7].

Since the repolarization phase of electrocardiograms is strongly influenced by heart rate (Figure 9), one and the same or at least a similar pacing frequency should be used for all recordings of a certain patient. This recording pacing frequency should be well above the patient's spontaneous heart rate to achieve stable paced rhythm and should not exceed physiological values. Pacing frequencies between 100 ppm and 130 ppm present a reasonable range.

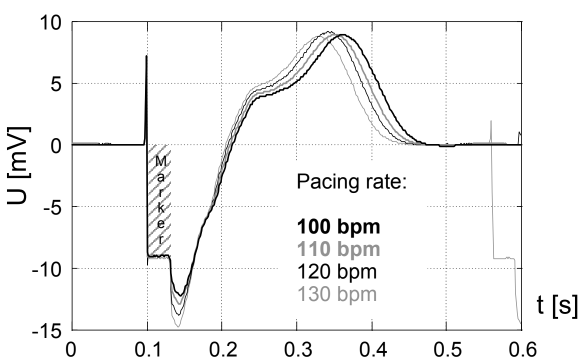

Figure 9. *VERs from a single patient, recorded at different pacing frequencies. The signals show characteristic changes - a shortening of the duration of the signal and increasing amplitudes in the depolarization phase. Recordings during pacing offer the standardization of the heart (pacing) rate.*

A recent investigation has revealed that some minutes are necessary to allow for haemodynamic adjustment after the patients changed their position and/or after the pacemaker has been programmed to the recording pacing frequency (Figure 10).

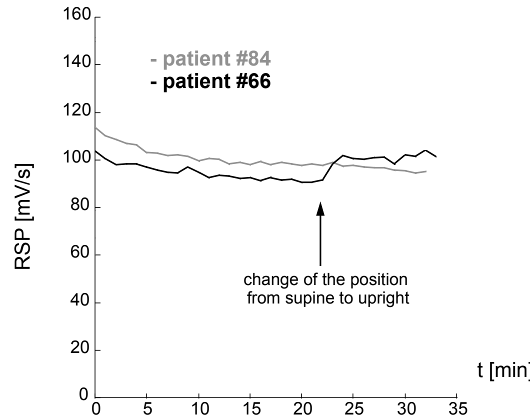

Figure 10. *Trends of the RSP values as obtained in two patients from a number of subsequent one minute recordings. The recordings have intentionally been started immediately after the patients had laid down and after programming the pacemakers to the recording pacing frequency. Additionally, patient #66 was requested to stand up, about 22 minutes after the start of the recording sequence (indicated by the arrow).*

Hence, to avoid different haemodynamic states of the patients at different follow-ups, patients should rest and lie in supine position for at least five minutes prior to the actual start of the recordings with the pacemaker already being programmed to the pacing frequency used for recording.

6. Epimyocardial lead position

A previous study focusing on the dependency of IEGM properties from the lead position revealed high correlation between the time course of parameters extracted from VERs which have been recorded from two different right ventricular leads[11]. From the increasing number of patients with the second lead located at the left ventricle becomes evident that - after the initial postoperative month - the same holds true in those patients. However, different trend courses have been observed in a number of patients during the initial postoperative course (Figure 3). The time courses of the parameter values during the early period after transplantation seem to be significantly influenced by adaptation processes of the ventricles to the new haemodynamic environment. It is hypothesized that low and subsequently increasing parameter values at the right ventricle reflect the initially larger and subsequently decreasing dilatation of the right ventricle compared to the left ventricle. Hence, implanting the leads at different ventricles may supply valuable information regarding the haemodynamic performance of the transplant in the early postoperative phase.

These results indicate that the exact position of the leads is not crucial, since - except in cases of inhomogeneous dilatation - both trend curves are well correlated. However, the absolute values of the parameters do depend on the actual lead position. Hence, each patient has to be used as his own reference by referring the current values to the ones observed previously. This means that the current state of a patient can be assessed only if previous follow-ups under well known clinical conditions are available. This would not be necessary if the interindividual differences of the RSP absolute values could be reduced to an extent where a certain value could unambiguously be assigned to "normal" or "pathological". A necessary step towards this aim is to standardize the lead positions as far as possible.

A recent investigation has shown that the standard implant configuration with two ventricular leads can additionally be used to noninvasively assess the ventricular propagation time[12]. Since the relative error of such measurements decreases with increasing distance between both leads, the interelectrode distance - as measured on the surface of the heart - should not be less than 4 cm.

7. Recording duration

The recording duration of one minute has been chosen to provide the classification and averaging algorithms with a sufficient number of heart beats to compute the averaged, representative heart beat electrogram from each IEGM sequence. Averaging is mandatory to increase the signal-to-noise ratio and to decrease the influence of beat-to-beat variabilities. Those effects introduce beat-to-beat changes of about 10% of the diagnostic parameters if calculated from single heart beats.

Rigorous beat classification and morphology checking are necessary for each heart beat prior to averaging to exclude aberrant beats like spontaneous or fusion beats which can be found in a considerable percentage of recordings (Figure 11).

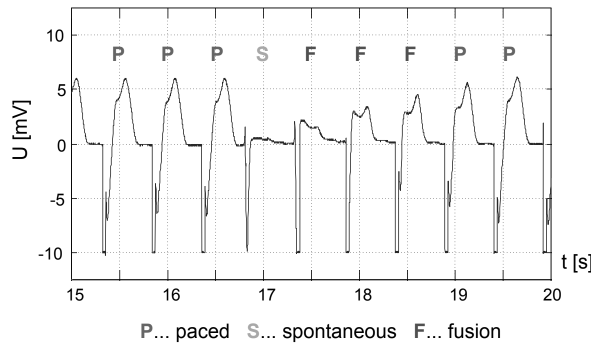

Figure 11. *IEGM section, containing not only VERs but also a spontaneous beat and some fusion beats. Comprehensive signal processing has to be carried out to receive the representative, averaged heart beat electrogram.*

Conclusion

Ventricular evoked responses from unipolar electrogram sequences during pacing with constant pacing frequency, recorded at comparable times of the day and after a resting period of some minutes, together with standardized signal processing utilizing rigorous heart beat classification and averaging yield results with excellent reproducibility and, therefore, are the signals of choice for noninvasive patient monitoring after heart transplantation.

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