Ventricular Evoked Responses versus Spontaneous Ventricular Electrograms for Long-term Cardiac Monitoring

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Summary

Serial intramyocardial electrogram recordings have been performed for rejection monitoring in 10 patients after heart transplantation. Signal sequences from the spontaneously beating as well as from the paced heart were obtained non-invasively using implanted telemetric pacemakers. The properties of these intramyocardial electrograms with respect to beat-to-beat variability, long-term reproducibility, and recording site dependency are analyzed. The results show that recordings of the ventricular evoked response during pacing give superior performance for monitoring with respect to all three properties. This allows to conclude, that, compared to spontaneous ventricular electrograms, recordings of the ventricular evoked response are superior for long-term cardiac monitoring.

Key Words

intramyocardial electrogram, telemetric pacemaker, heart transplantation, rejection monitoring

Introduction

Today, heart transplantation is a well accepted therapy for treating end stage heart disease with an annual rate of almost 5000 heart transplants worldwide [11]. The main postoperative risks, i.e. acute rejection and infection, are still serious problems. Hence, early detection of those pathological states is of vital importance for patients after heart transplantation.

Until now, invasive endomyocardial biopsies are used as the standard method for rejection surveillance. The cost of an uncomplicated endomyocardial biopsy has been estimated to be about 1.630 US$ [14]. Considering the invasiveness, the costs, the limited diagnostic accuracy of biopsy [16] as well as the known negative side effects of immunosuppression, the requirement for improved monitoring and adequate therapy management is obvious. An advanced method must enable reliable, non-invasive examinations that can be applied frequently on a low-cost base and during the whole follow-up period [8]. Additionally, the method should support a more adjusted immunosuppressive therapy in order to minimize both risks, i.e. infection and rejection.

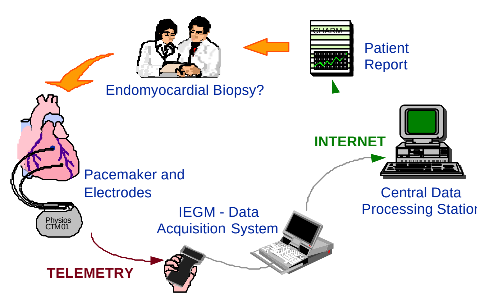

***Figure 1**. CHARM - Computerized Heart Acute Rejection Monitoring*

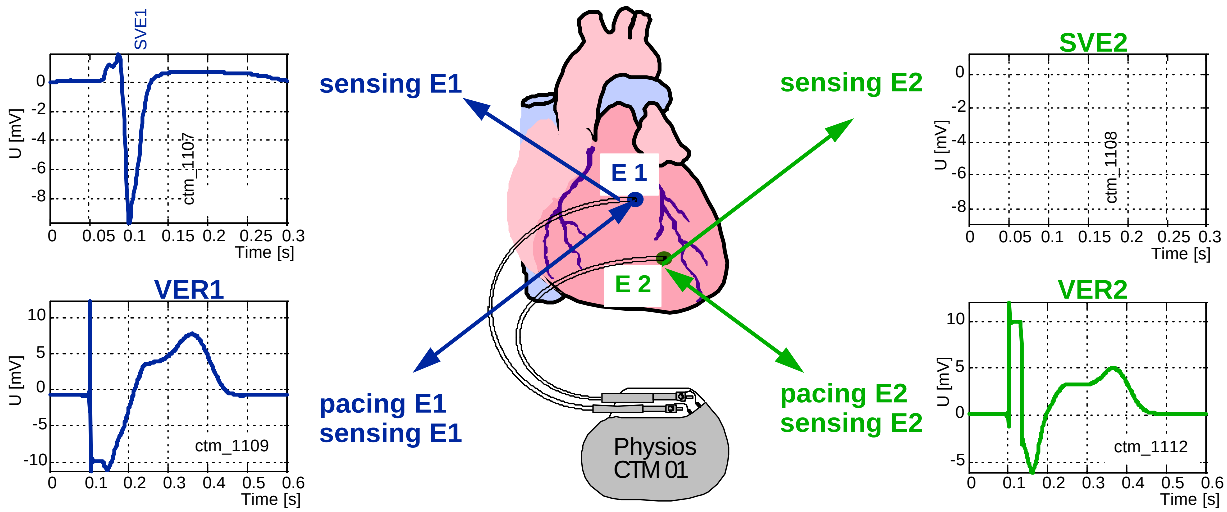

Figure 2. *IEGM recording with a telemetric dual chamber pacemaker and two ventricular, epimyocardial electrodes E1 and E2.*

During the last years our work focused on the evaluation of intramyocardial electrograms (IEGM) for patient monitoring after heart transplantation. The marked influence of cardiac rejection on parameters derived from IEGMs has been shown in a previous study [2]. A recent investigation revealed that IEGM parameters also allow for a close monitoring of the effectiveness of rejection therapies [6]. The system for Computerized Heart Acute Rejection Monitoring (CHARM) is displayed in Figure 1 and has been presented recently [9]. It renders possible further development and evaluation of non-invasive patient monitoring with IEGMs based on a worldwide, multicenter application.

The present paper compares the properties of ventricular evoked response (VER) recordings during pacing with recordings of spontaneous ventricular electrograms (SVE). Beat-to-beat and long-term variability of the signal morphology as well as the relationship of the rejection sensitive parameters, obtained at two different right ventricular positions, are considered.

Methods

Implant:

During the transplant procedure, all patients of the University of Graz heart transplant program receive dual chamber pacemakers (Physios CTM 01, Biotronik, Germany), and two fractally coated epimyocardial screw-in electrodes (ELC 54-UP, Biotronik, Germany) for rejection monitoring. Both leads are placed at the ventricles. Figure 2 shows this implant arrangement. The pacemakers are equipped with IEGM telemetry based on analogue frequency modulation with a bandwidth of 0.33 - 200 Hz. The electrodes feature a fractally coated surface structure that allows to record the VERs a short time after applying a stimulus. The post-stimulus polarization artifact is negligible, although the same electrode is used for stimulating and sensing.

Data acquisition:

In the course of each monitoring session four different

IEGMs are recorded: SVEs and VERs from each of both electrodes. Signal sequences with a duration of one minute are sampled with 666 Hz, using the appropriate telemetry control and data acquisition unit (CTM 1001, Biotronik, Germany).

<u>Signal analysis:</u>

Signal processing takes place at an Internet accessible data processing workstation using a special designed software. Electrograms are transferred from the transplant center to the workstation using the File Transfer Protocol (FTP). Signal evaluation starts automatically after new electrograms have been received and consists of the following major steps:

Heart beat detection

Heart beat detection is based on a comparison of the first derivative of the signal with a threshold. A refractory period of 350 ms around already detected events is used to avoid multiple detection of the same event.

Heart beat classification

Rigorous morphology analysis is completed for each heart beat prior to signal averaging in order to avoid errors in subsequent parameter computing that can be caused by aberrant heart beats (e. g. fusion beats during pacing or ectopic beats during spontaneous beating). This process consists of two steps:

Coarse classification - every single event is checked for a set of specific morphological features (e. g. differentiating between spontaneous and paced heart beats by means of recognizing the calibration impulse preceding paced beats).

Cross correlation classification - to refine the coarse classification by arranging all events identified by the coarse classification (main classes) into homogenous subgroups using a recursively applied correlation technique. The resulting subclasses are characterized by having high correlation coefficients with respect to the normal event averaged from all members of the respective group. The top diagrams of Figure 3 show sections of electrogram sequences and the results of

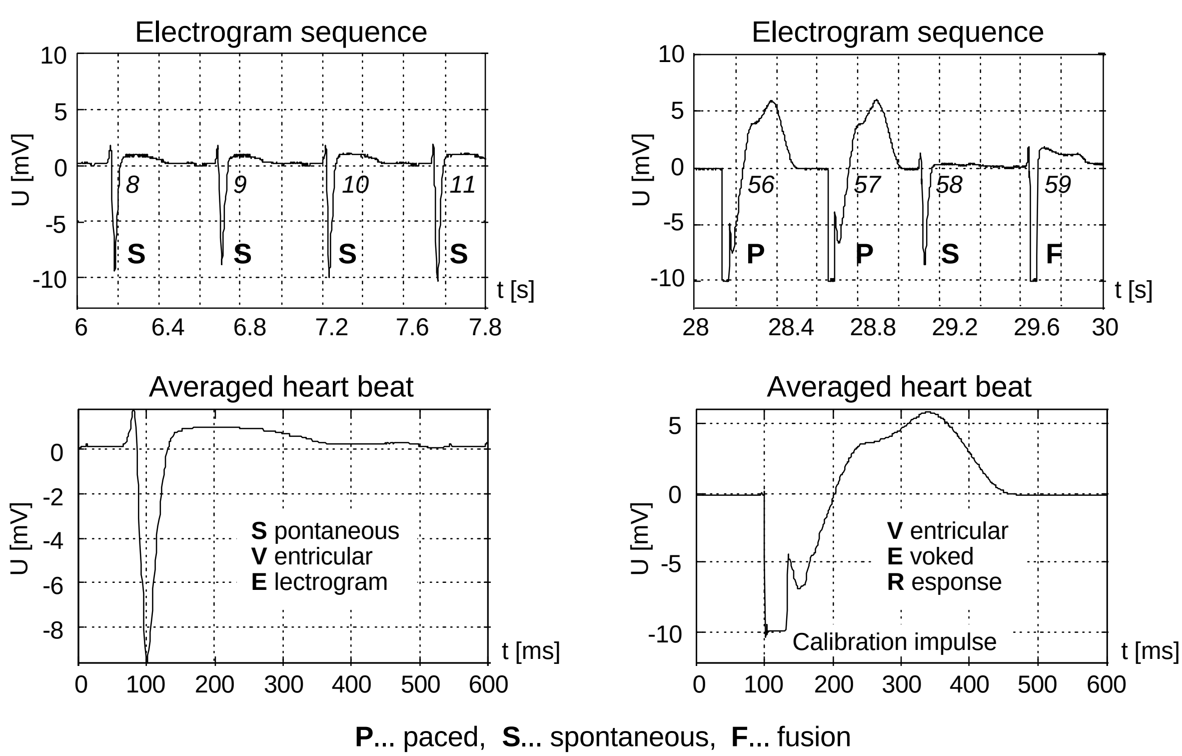

Figure 3*. Signal processing of IEGM sequences; left: SVE, right: VER, top: heart beat detection (italic numbers) and classification (S = spontaneous beat, E = evoked response, F = fusion beat); bottom: averaged heart beats.*

heart beat detection and classification.

Rhythm analysis

Based on coupling intervals and type of the events the rhythm type, the heart rate, and the heart rate variability are computed.

Heart beat averaging

The averaging procedure is carried out to suppress physiological beat-to-beat variations (mainly due to respiration) and to increase the signal-to-noise ratio. The averaging process enhances signal components contained in each heart beat in contrast to asynchronously occurring events like demodulation noise, line interference and physiological beat-to-beat variability. The resulting averaged IEGM consists of all beats of the dominant subclass of the respective main class in the sequence (Figure 3, bottom).

Parameter extraction

A number of voltage and timing values are computed from the resulting averaged heart. The root mean square of the QRS complex of the SVE and the absolute integral over the repolarization phase of VER were found in previous studies [13] to show the highest correlation with respect to histological rejection grading by endomyocardial biopsy. These IEGM parameters are designated the rejection sensitive parameters (RSP).

Statistics:

All transplants with both electrodes placed at the right ventricle and with more than ten follow-ups beyond the 14th postoperative day were considered. Recordings within the first two postoperative weeks were not considered for this analyses to exclude possible early post-ischaemic changes and effects occurring at the electrode-tissue interface in the early time following lead placement. Sequences recorded at spontaneous heart rates or pacing rates above 120 bpm were excluded too.

The differences between SVE and VER were tested using the two-tailed Wilcoxon matched pairs signed rank test, $p < 0.05$ was considered significant.

For each patient and kind of electrogram the following parameters were calculated:

r_E - a measure of the influence of the electrode position on the behavior of the RSPs:

It is defined as the linear correlation coefficient between the trend curves of the RSPs, measured with the two electrodes. High r_E values mean that the trend curves of the RSPs, obtained from both electrodes, run fairly parallel to each other, hence, the electrode position is not critical with respect to rejection monitoring.

r_L - a measure of the long-term reproducibility of the signal morphology:

For each follow-up the linear correlation coefficient of the actual averaged heart beat correlated with the heart beat averaged from all averaged heart beats from previous follow-ups of the same kind is computed. r_L is defined as the median of the correlation coefficients of all follow-ups (mean of both electrodes). High r_L values mean that the signal morphology of the averaged heart beat of a certain patient, electrode, and IEGM type stays the same during the whole follow-up time.

r_B - a measure of the beat-to-beat variability of the signal morphology:

For each follow-up the median of the correlation coefficients of the averaged heart beat correlated with all single heart beats contained in the averaged heart beat is computed. r_B is defined as the median of the medians for all recordings of a certain patient and kind of electrogram (mean of both electrodes). High r_B values mean that the signal morphologies of the single heart beats contained within the averaged heart beats of a certain patient and IEGM type are very similar.

Pat.	**AR$_{MAX}$**	**SVE**			**VER**		
		r_E	**r_L**	**r_B**	**r_E**	**r_L**	**r_B**
1	1B	0.795	0.998	0.986	0.919	0.999	0.999
2	2	0.886	0.996	0.989	0.965	0.997	0.999
3	1B	0.531	0.974	0.978	0.951	0.997	0.999
4	1A	0.696	0.991	0.974	0.990	0.999	0.999
5	1A	0.562	0.983	0.978	0.860	0.995	0.999
6	1B	0.878	0.995	0.983	0.941	0.999	0.999
7	3A	0.954	0.994	0.986	0.985	0.997	0.999
8	1B	0.660	0.997	0.963	0.940	0.997	0.999
9	2	0.758	0.995	0.972	0.963	0.998	0.999
10	2	0.755	0.995	0.991	0.903	0.998	0.999

Table 1. *For all patients: highest observed rejection grade (AR_{MAX}) and the various correlation coefficients (r_E, r_L, r_B) for SVEs and VERs, respectively.*

Results

10 Patients met the inclusion criteria. *Table 1* displays the various correlation coefficients for all patients and both types of electrograms. Additionally, it also shows the highest rejection grade observed in each patient according to the biopsy evaluation scheme of the International Society for Heart and Lung Transplantation [3], denoted AR_{MAX}. Higher rejection grades mean stronger rejection.

The comparison of the various correlation coefficients between the SVE and the VER recordings are displayed in Figure 4, Figure 6, and Figure 7.

For all three measures, the differences of the correlation coefficients between the two electrogram types were found to be statistically significant (r_E, r_L, r_E: $p < 0.01$);

Discussion

Since in the early days of clinical heart transplantation non-invasive rejection screening methods based on electrocardiography were suggested. However, up to now, none has found broad clinical acceptance. Body surface ECGs were found to be no longer reliable after the introduction of Cyclosporine A as a clinical immunosuppressive agent.

Modern pacemakers are equipped with supplementary features that can be utilized for improved cardiac diagnosis and therapy management. Pacemaker telemetry allows to transmit IEGMs to an extracorporeal receiver for further signal processing. These signals have gained much interest as a basis for non-invasive rejection monitoring. IEGMs can be obtained from the spontaneously beating [1, 4, 15] and from the paced heart [5, 2] and give important information on the electrophysiological state of the heart. Fractally coated electrodes feature a negligible polarization artifact after stimulation due to a large capacity of the tissue-lead interface. As a consequence, it is possible to measure IEGMs during pacing with the same electrode to be used for stimulating and sensing.

Because of its intraoperative implantability, the electrode configuration with both electrodes situated at the ventricles (Figure 2) is preferred. Additionally, it offers the possibility to investigate the relationship between signals recorded from two different ventricular sites. The present study shows that correlation of the RSPs from two different right ventricular sites is higher for the VERs compared to the SVEs. Based on experimental results, authors solely using the QRS amplitude from spontaneous heart beats reported that diagnostic accuracy for detecting acute rejection can be improved with a larger number of electrodes [7, 10]. This was thought to be due to focal characteristic of acute rejection as supposed from histological experience, based on endomyocardial biopsy. The model assumes a heterogeneous affection of the electrical activity by acute rejection and predominantly local "views" of the recording electrodes. It was argued that rejection might start far off a lead position and, therefore, might be missed by looking at only the electrophysiological signal recorded with one electrode.

Figure 4 shows that the correlation of the RSPs of the SVE is in fact significantly lower than the correlation of the RSPs of the VER. The influence of rejection can not be the cause of poorer correlation, because the correlation for both signal types tends to be higher for

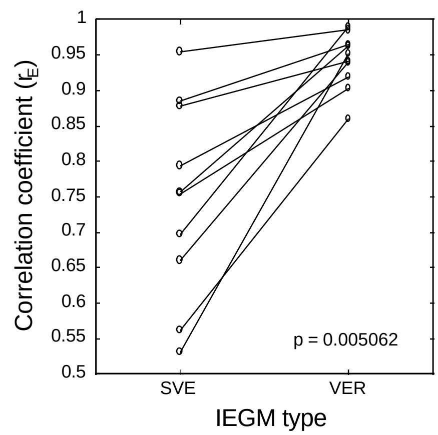

***Figure 4**. Comparison of the correlation coefficients r_E between SVE and VER recordings as a measure of the influence of the electrode position.*

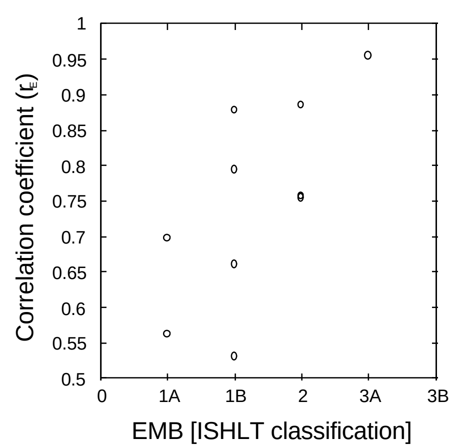

***Figure 5.** Correlation coefficients r_E for SVE recordings and the strongest rejection for each patient referring to the International Society of Heart and Lung Transplantation (ISHLT).*

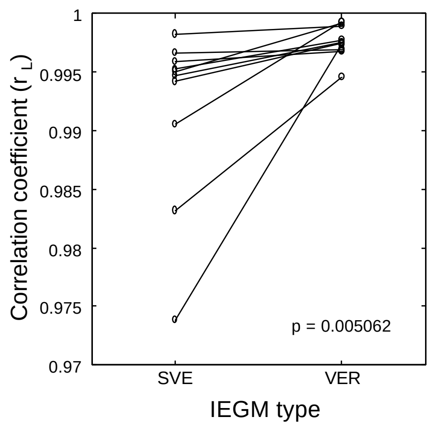

Figure 6. *Comparison of the correlation coefficients r_L between SVE and VER recordings as a measure of long-term reproducibility of the signal morphology.*

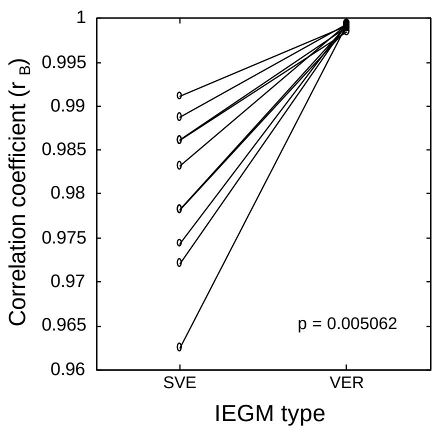

Figure 7. Comparison of the correlation coefficients r_B between SVE and VER recordings as a measure of beat-to-beat variability of the signal morphology.

patients who experienced stronger rejection (Figure 5).

The second parameter, r_L, revealed that the long-term reproducibility of the signal morphology was higher for VERs compared to that of SVEs, although, the amplitudes of the signals may change, e.g. under the influence of rejection. Similar results have been obtained in a previous study on patients with single chamber pacemakers [12].

The third parameter, r_B, indicates that VER recordings contain significantly less beat-to-beat variability of the signal morphology, compared to SVE recordings, although, the amplitudes of the single heart beats may change, e.g. under the influence of respiration.

These results indicate that recordings of VERs during pacing offer better standardization with respect to heart rate (can be kept constant in a patient's recording series), and excitation formation (constant origin at the electrode). Additionally, pacing provides superior conditions for signal processing, e.g. a distinct fiducial point for averaging.

Conclusion

Recordings of IEGMs offer new non-invasive diagnostic opportunities. This is the case particularly for VER recordings during pacing. The VER is a well standardized electrophysiological signal, which, compared to SVEs, shows superior properties for long-term cardiac monitoring.

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