Noninvasive Patient Monitoring After Heart Transplantation Using the Ventricular Evoked Response - the Hamburg Experience

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Summary

Rejection diagnostics are an important issue in the context of heart transplantation. Endomyocardial biopsy is currently regarded as the "golden standard". However, it is an invasive procedure and reduces the patients' quality of life. Moreover, this procedure cannot be applied on a daily basis. The ventricular evoked response is an intramyocardial signal well suited for standardization, and it can be used for noninvasive long-term monitoring of patients with a heart transplant. In 9 transplant patients, cardiac pacemakers with high-resolution telemetry were implanted to record chronic ventricular intramyocardial signals. The ventricular evoked response was recorded in connection with each endomyocardial biopsy. A special parameter, the rejection sensitive parameter, was defined to evaluate the intramyocardial signals. The biopsy results were compared with the ventricular evoked response results. A rejection degree of ³ 2 determined with the endomyocardial biopsy was judged to be a significant rejection. The average follow-up period was 129 ± 71 days per patient. During this time, 45 endomyocardial biopsies were performed in all 9 patients, and 3 of them showed a rejection degree ³ 2. The rejection sensitive parameter of the ventricular evoked response had a sensitivity of 100 % and a specificity of 75 %. The results of this study indicate the feasibility of safe rejection diagnostics with the aid of intramyocardial signals under the given conditions. The diagnostic rejection sensitive parameter, in connection with a suitable threshold value, could serve as the future basis for a noninvasive procedure to monitor patients after heart transplantation.

Key Words

Heart transplantation, transplant rejection, intramyocardial electrogram, pacemaker monitoring

Introduction

Today, heart transplantation is an established form of treatment for therapy-refractory terminal cardiac insufficiency. Acute rejection of the donor organ remains one of the main problems connected with this procedure. Endomyocardial biopsy (EMB) is still regarded as the "golden standard" in rejection diagnostics [1]. However, this examination method is expensive and invasive, it is burdened with potential risks, and it cannot be repeated with unlimited frequency. For this reason, several procedures for the noninvasive monitoring of heart transplant patients have been developed [2-4]. However, none of these examination methods has been able to gain general acceptance in daily clinical practice.

Earlier studies on this topic have shown that intramyocardial electrograms (IEGM) correlate with rejections determined with the aid of EMB [5]. This study correlates the pacemaker-induced ventricular depolarization (ventricular evoked response, VER) with the EMB.

Materials and Methods

Nine patients were included in the study. Their age at the time of the heart transplantation was 60 ± 4 years

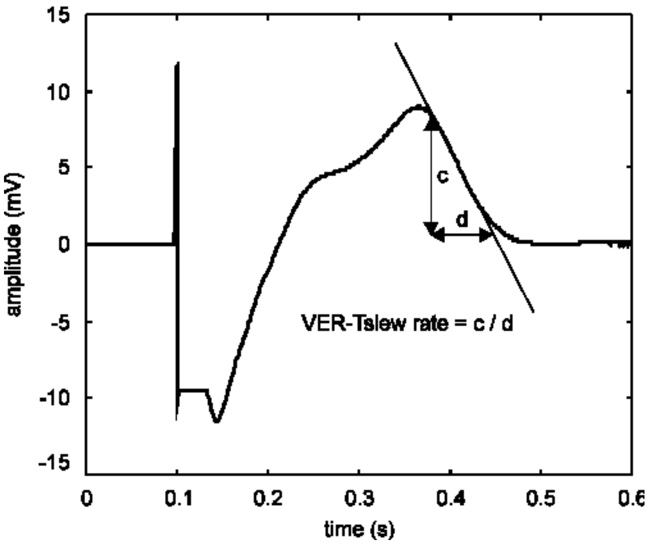

Figure 1. The rejection sensitive parameter is defined as the maximum slope of the descending part of the T wave of the ventricular evoked response (VER T-slew rate).

Pat.-nr.	FUs	EMBs	FU-days
1	18	10	184
2	10	2	44
3	16	8	183
4	12	7	169
5	13	7	177
6	8	1	36
7	9	3	164
8	9	6	180
9	3	1	25
Sum	98	45	1162
Mean	11	5	129
SD	4	3	71
Min.	3	1	25
Max.	18	10	184

Table 1. Statistics on the number of follow-up (FU) examinations, endomyocardial biopsies (EMBs), and the follow-up ranges (FU-days), as obtained for each of the 9 patients individually as well as overall (Pat.-nr. = patient number, SD = standard deviation, min. = minimum, max. = maximum).

(range 54 - 65). During heart transplantation, a dual-chamber pacemaker system (Physios CTM 01, Biotronik, Germany) with a high-resolution telemetry (bandwidth: 0.3 - 200 Hz) was implanted. The signals were measured with two unipolar epicardial screw-in leads with a fractal coating (ELC 54-UP, Biotronik, Germany). One lead was positioned at the right ventricular outflow tract in the vicinity of the septum. The second lead was fixed at the lateral wall of the left ventricle. The pacemaker was implanted subcutaneously in the left abdomen.

With the aid of pacemaker telemetry, the IEGMs were recorded in a laptop computer during each follow-up and subsequently transmitted via the Internet to the data analysis center in Graz [6]. The pacing rate was programmed to at least 100 ppm (sinus rhythm plus 10 ppm), and the IEGMs were recorded for 60 seconds each. Previous studies have shown that the signal of the paced cardiac actions possesses a better long-term stability than the intrinsic signal [5]. The IEGMs were recorded on days when an EMB was performed; in the early post-operative phase and, in case of clinically conspicuous states, the recordings could take place more often. The responsible pathologist evaluated the EMBs. During the study, the clinic did not receive any information about the evaluation of the IEGMs. In the data analysis center, the quality of the IEGMs was checked after their transmission, and they were evaluated automatically. To detect the presence of rejection reactions, a special parameter was defined and termed the rejection sensitive parameter (RSP) [5]. This parameter is defined as the maximum slope of the descending flank of the T wave in the VER (VER T-slew rate) (Figure 1). Previous studies had shown that this parameter is very well suited for rejection diagnostics.

The data were evaluated in regard to the sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), and negative predictive value (NPV) of the diagnostic model that was used. To determine the optimum threshold value for a diagnosis, maximization of the diagnostic quality index (DQI) was applied. The DQI represents the total performance of the diagnosis and, thus, secures a balanced relationship between sensitivity and specificity. It is equivalent to the geometrical mean value of SENS and SPEC, according to the equation:

$$DQI = \sqrt{SENS \cdot SPEC}$$

Results

Leads and pacemakers were implanted without complications. A total of 98 follow-up examinations were performed, 11 ± 4.5 per patient (range 3 - 18), which can be contrasted with the 45 EMBs carried out. The average follow-up period was 129 ± 71 days per

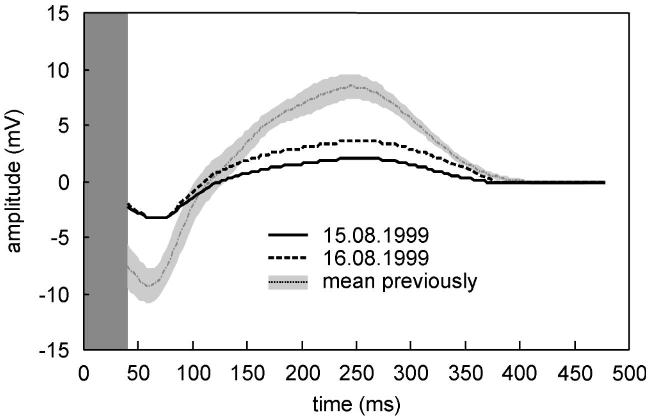

Figure 2. Changes of the VER during a rejection sequence of one patient. The gray-shaded area represents the phase without rejection, the two black lines display the VERs recorded under the influence of hemodynamically significant rejection.

patient (range 25 - 184). Thus, the cumulative observation time added up to 3 patient-years. After an observation period of 190 days, 7 patients were still alive. Table 1 shows the follow-up data. One pacemaker had to be explanted due to an infection of the sternum with mediastinitis. However, this infection was not caused by the pacemaker or the leads. No pacemaker- or lead-caused complications were registered.

The evaluation of the data resulted in a very good correlation between the values of the RSP and the results of the EMBs (Table 2). A threshold value for the VER

$p < 0.01$	EMB < 2	EMB ≥ 2	sum
RSP > 51 mV/s	30	0	30
RSP ≤ 51 mV/s	10	3	13
Sum	40	3	43

SENS = 100 %
SPEC = 75 %
PPV = 23 %
NPV = 100 %
DQI = 87 %

Table 2. Fourfold table for the comparison between the results of endomyocardial biopsies (EMB) and the results of the rejection sensitive parameter (RSP).

T-slew rate of 51 mV/s appeared to be the best for the diagnosis of rejection. Only the absolute values of the VER T-slew rate were analyzed. Furthermore, it was apparent that the VERs of the right ventricle were better suited for diagnosing rejection than the VERs of the left ventricle. For the evaluation, all IEGMs with a VER T-slew rate of < 51 mV/s were classified as rejections. In contrast, all signals with a VER T-slew rate value ≥ 51 mV/s were classified as no rejection. Using this threshold value, all three rejections that had a rejection degree ≥ 2 in the EMB could be correctly diagnosed by means of the VERs in comparison with the EMB. Therefore, the evaluation resulted in a sensitivity of 100 % and a specificity of 75 % for the RSP. The threshold value for the VER T-slew rate was defined in such a way that the DQI reached its maximum value.

Figure 2 shows an example of a clear rejection reaction in a heart transplant patient. This patient was admitted

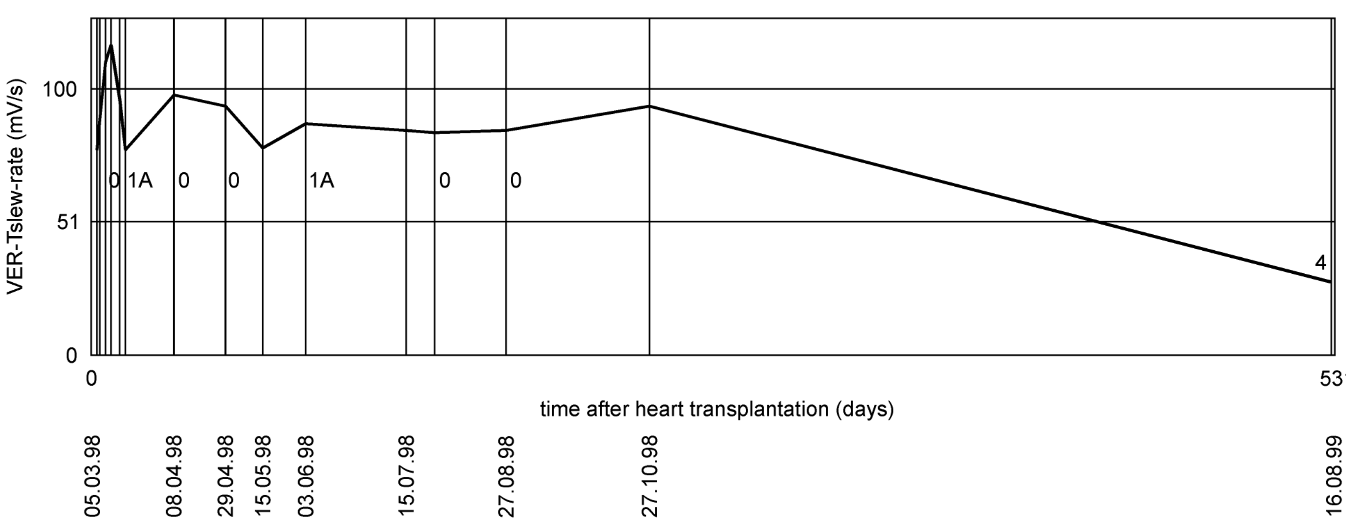

Figure 3. The trend course of the rejection sensitive parameter (VER T-slew rate) as obtained in a single patient who experienced an episode of hemodynamically significant rejection about 530 days after transplant. The numbers within the panel represent the endomyocardial biopsy results.

for emergency care on August 15, 1999, due to bad cardiac function. An immediately performed echocardiogram showed a clearly worsened cardiac function. An acute rejection therapy was started at the same day, and the VER was recorded. This hemodynamically relevant rejection can also be clearly seen in the morphology of the VER. The broad gray line indicates the mean value and standard deviation of the VERs from March 5, 1998, to October 27, 1998. No significant rejection occurred during this period (Figure 3). The signals recorded on August 15 and 16, 1999, show a dramatic change when compared with the previous case history. The VER T-slew rate values decreased from a relatively high value of about 90 mV/s to a value much below the threshold value of 51 mV/s (Figure 3). The entire course of the VER points towards an impaired electrical function of the heart. Under the influence of the initiated rejection therapy, a tendency towards an improvement can be recognized after only one day when looking at the VER (Figure 2) as well as at the trend graph of the VER T-slew rate.

Conclusion

The results of the study show that the presented method enabled safe rejection diagnostics by means of the IEGMs. The diagnostic rejection sensitive parameter, in connection with a suitable threshold value, could serve as the basis for a noninvasive procedure to monitor heart transplant patients. Within the framework of the current study, it was possible to detect all rejections of a degree ≥ 2 reliably. Therefore, the DQI was 87 %. A prospective use of this model would have made it possible to save about 70 % of the endomyocardial biopsies. However, because the number of included patients in this single-center report is relatively small, the results of a multicenter study should be awaited. In regard to the presented data, it should also be considered that all three rejection sequences occurred in one and the same patient.

Rejection diagnostics per home monitoring could be the trend of the future. Heart transplant patients who live very far away from their transplantation centers could transmit the IEGM sequences, which are recorded by a Holter device, to the data analysis center via telecommunication. There, an automatic analysis takes place, and the results are subsequently sent to the clinic. At the clinic, the physician in charge can evaluate the results and begin a suitable therapy. The respective progress of the therapy could be controlled with the same procedure.

Apart from and independent of such long-distance monitoring that might be possible in the near future, a large number of endomyocardial biopsies could soon be avoided with the aid of IEGMs. This would decrease the risk that the invasive intervention poses to the patient and would clearly lower costs per patient.

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