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Computerized heart allograft-recipient monitoring: a multicenter study

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Abstract Computerized heart allograft recipient monitoring (CHARM) is a unique concept of patient surveillance after heart transplantation (HTx), based on the evaluation of intramyocardial electrograms (IEGMs) recorded non-invasively with telemetric pacemakers. Previous open, single-center studies had indicated a high correlation between CHARM results and clinical findings. The present study was initiated to assess the suitability of CHARM for monitoring the absence of rejection in a blind, multicenter context. During the HTx procedure, telemetric pacemakers and two epimyocardial leads were implanted in 44 patients at four European HTx centers. IEGMs during pacing were recorded and transferred via the Internet to the CHARM computer center, for automatic data processing and extraction of diagnostically relevant information, i.e., the maximum slew rate of the descending part of the repolarization phase of the ventricular evoked response (VER T-slew). The study period comprised the first 6 months after HTx, during which the transplant centers were blind to the CHARM results. A single threshold diagnosis model was prospectively defined to assess the ability of the VER T-slew to indicate clinically significant rejection, which was defined as an endomyocardial biopsy (EMB) grade greater than or equal to 2, according to the grading system of the International Society for Heart and Lung Transplantation. All EMB slides from three centers were reviewed blind by the pathologist of the fourth center in order that agreement among the histological diagnoses at the various centers could be assessed. Totals of 839 follow-ups and 366 EMBs were obtained in 44 patients. Thirty-seven patients were alive at the end of the study period. Age at HTx, EMB grade distribution, and rejection prevalence varied significantly between the centers. Review of the EMB results showed considerable differences with respect to classification of significant rejection. Comparison of average VER T-slew values with and without rejection in the 15 patients who exhibited both states revealed significantly lower values under the influence of rejection (97 ± 13% vs 79 ± 15%, $P < 0.0001$). Twenty out of the 25 cases with significant rejection were correctly identified by VER T-slew values below a threshold of 98% (sensitivity = 80%, specificity = 50%, negative predictive value = 97%, positive predictive value = 11%; $P < 0.0005$). Of the EMBs, 48% could have been saved if the diagnosis model had been used to indicate the need for EMB. A high negative predictive value for the detection of cases with significant rejection has been obtained in a prospective, blind, multicenter study. The presented method can, therefore, be used to supplement patient monitoring after HTx non-invasively, in particular to indicate the need for EMBs. In centers with patient management similar to the ones who participated in the study, this may allow a reduction in the number of surveillance EMBs.

Keywords Non-invasive rejection monitoring · Heart transplantation · Rejection · Intramyocardial electrogram

Introduction

After heart transplantation (HTx), rejection surveillance is still achieved by means of invasive and expensive endomyocardial biopsy (EMB). Until now, attempts to develop faster, non-invasive, and frequently applicable methods of transplant monitoring have not resulted in a generally accepted procedure [15]. Computerized heart allograft recipient monitoring (CHARM) is a unique concept for patient surveillance after HTx based on the evaluation of intramyocardial electrograms (IEGMs) that are recorded non-invasively with telemetric pacemakers. Previous open, single-center studies indicated a high correlation between CHARM results and clinical findings [2, 5, 6, 8, 13, 16, 17].

Since 1992 we have developed a pacemaker-based system for the analysis of IEGMs to recognize acute cardiac allograft rejection. The current pacemaker system configuration and the parameters used to detect absence of rejection have been described in detail elsewhere [4, 9, 10, 11, 12, 13, 21, 22]. The present study was initiated to assess the suitability of CHARM for monitoring the absence of rejection in a blind, prospective, multicenter context.

Patients and methods

The clinical study protocol was approved by the ethics committee of all four participating centers, and written informed consent was obtained from each patient.

Clinical patient management

During the HTx procedure, telemetric pacemakers (Physios CTM 01) and two fractally coated epimyocardial leads (ELC 54-UP) were implanted in 44 patients at four European HTx centers. Pacemaker implantation has been described in detail previously [13]. Patient management, immunosuppressive therapy, and the threshold for rejection therapy were subject to individual center preference. The EMB results were graded according to the grading system of the International Society for Heart and Lung Transplantation [3]. All EMB slides from the other three centers were reviewed blind by the pathologist in Graz, in order that the degree of agreement among the histological diagnoses at the various centers could be established.

The study period was limited to the first 6 months after HTx for each patient. During this time the transplant centers were blind to the IEGM results to avoid any treatment bias. Instead of receiving comprehensive patient reports with the trend curves of the derived parameters, the centers received only a list of the recorded IEGMs to confirm successful data acquisition.

IEGM recording and processing

We recorded IEGMs during pacing, i.e., ventricular evoked responses (VERs), frequently during the early postoperative period and always on days on which EMBs were performed, using a notebook-based recording device (SWM/SWD 1000; all pacemaker system components: Biotronik, Berlin, Germany). Recordings were obtained at a pacing rate of at least 100 bpm (in most patients and follow-ups). If required by spontaneous heart rates above 100 bpm, a pacing rate slightly higher than that, but not higher than 130 bpm, was chosen. After the patient had undergone a resting period in the supine position, 1-min IEGM sequences were separately recorded from each electrode and digitized to the portable, laptop-based data acquisition device.

Subsequent to data acquisition, the recorded signals were transferred via the Internet to the CHARM computer center, for data processing and extraction of the diagnostically relevant information. Immediately after new electrogram recordings had been received, signal analysis was performed automatically and without the use of any clinical data. After spontaneous, ectopic or fusion beats had been excluded, all remaining paced heartbeats within each IEGM sequence were averaged so that the representative VER could be computed [20]. Finally, the rejection-sensitive parameter identified in previous studies, i.e., the maximum slew rate of the descending part of the repolarization phase of the VER (VER T-slew), was extracted from the averaged heartbeat according to Fig. 1.

To account for individual absolute values and long-term trends, we normalized the parameter values and expressed them as percentages of the individual adaptive prospective reference values that were calculated as follows, beginning with postoperative day 4 (earlier follow-ups were not considered): from day 4 until day 21 after HTx the maximum value of all previous examinations was used as the reference value. For each follow-up beyond the initial 21 postoperative days the reference value was computed as the mean value of all previous examinations, based on the area under the trend curve up to, but not including, the actual follow-up date (all values from day 4 until day 21 were substituted by the maxi-

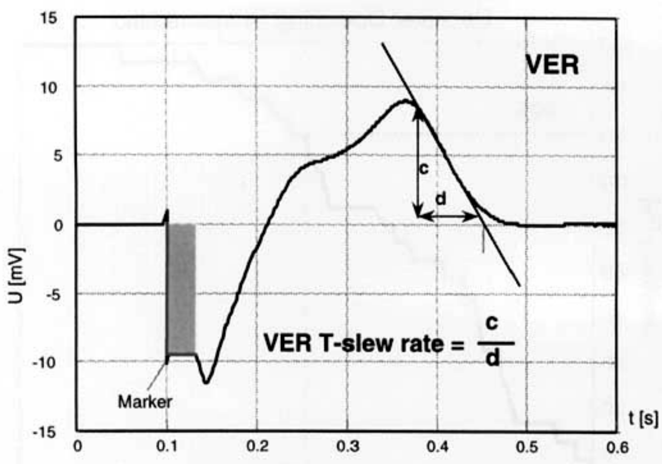

Fig. 1 Averaged VER with the definition of the VER T-slew rate, i.e., the maximum negative slope in the descending part of the repolarization phase of the VER. During the initial 30 ms, pacemaker telemetry transmits a marker instead of the electrogram itself

mum value observed during this period, i.e., by the reference value at the end of the initial 21 postoperative days). Hence, the reference value was always prospectively defined for the following investigation. The final parameter value was computed as the average of the normalized values of both leads.

Statistics

In order to assess the influence of rejection, we grouped the VER T-slew rate values according to whether significant rejection was present (EMB grades ≥2) or not. All observations for each individual patient and state were averaged and merged into a single value. Only patients for whom valid parameter values for both respective states (no rejection/rejection) had been observed were considered for statistical analysis. The two-tailed paired *t*-test was used to test for significant differences between both states.

The two-tailed paired *t*-test, ANOVA, and the Kruskal-Wallis test were used to test for significant differences between the various transplant centers regarding age at HTx and EMB scores (ISHLT grades mapped to a linear scale: 0–>2, 1A–>3, 1B–>4, ...). To assess the ability of the VER T-slew rate to discriminate between follow-ups with and without rejection, we applied a diagnosis model consisting of a single threshold to the parameter values. Cases with EMB grades greater than or equal to 2 were considered to represent positive cases in terms of significant rejection. Follow-ups with parameter values below the threshold were considered to represent positive cases in terms of CHARM. Based on a number of possible thresholds, the receiver operating characteristic curve was computed. The standard diagnostic indices sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), and negative predictive value (NPV) were finally presented for the threshold that resulted in the highest value for the geometric mean of SENS and SPEC, i.e., which maximizes the product of SENS and SPEC. The correlation between the classification of follow-ups by EBM result and the diagnostic threshold applied to the VER T-slew rate parameter values was tested with the χ^2 test. *P* values of below 0.05 were considered to indicate significance.

Results

Through December 1999, totals of 839 follow-ups and 366 EMBs were obtained in 44 patients at the four transplant centers. Thirty-seven patients were alive at the end of the 6-month study period. Age at HTx was 54 ± 8 (32–65) years. In two patients, one of the two electrodes failed and IEGM recording was restricted to the remaining electrode in those patients. In one patient, the pacemaker – although not itself the cause – was affected by an infection and was explanted approximately 6 weeks after HTx. No further complications related to the implanted pacemaker system were observed.

Table 1 displays basic properties of the patient subgroups as enrolled at the four investigational sites. Beside considerable differences with respect to the number of follow-ups, EMBs, and rejection prevalence, age at HTx and average EMB grade per patient varied significantly among the four centers.

For 345 of the follow-ups, both a valid EMB diagnosis and a valid VER T-slew rate parameter value were obtained. Twenty-five of these follow-ups were associated with significant rejection in terms of EMB grades greater than or equal to 2. These cases occurred in 17 patients, of whom three experienced two, one patient three, and one patient four follow-ups with significant rejection. One patient died after the initial two EMB procedures had revealed significant rejection and, therefore, without having exhibited a non-rejecting state. Figure 2 displays the comparison of the average VER T-slew values with

Table 1 Basic descriptive statistics (mean ± SD) and frequencies for the patient subgroups at each individual participating center as well as overall. *P* values were obtained by ANOVA for ages, and by the Kruskal-Wallis test for EMB scores

Parameter	Center					*P*
	Graz, Austria	Liège, Belgium	Hamburg, Germany	Vienna, Austria	Overall	
Patients	14	13	9	8	44	
Age at HTx (years)	54.1 ± 8.35	52.3 ± 7.60	60.0 ± 4.15	48.6 ± 9.58	53.8 ± 8.31	<0.05
Follow-ups	353	243	97	118	801	
EMBs	177	88	46	55	366	
Cases ≥ grade 2	6	15	5	1	27	
Rejection prevalence	3%	18%	10%	2%	7%	
EMB score/patient	2.72 ± 0.44	3.30 ± 0.79	2.41 ± 0.65	2.18 ± 0.29	2.73 ± 0.71	<0.001
Review EMB score	[2.72 ± 0.44]	3.16 ± 0.57	2.56 ± 0.68	2.82 ± 0.53	2.84 ± 0.58	NS

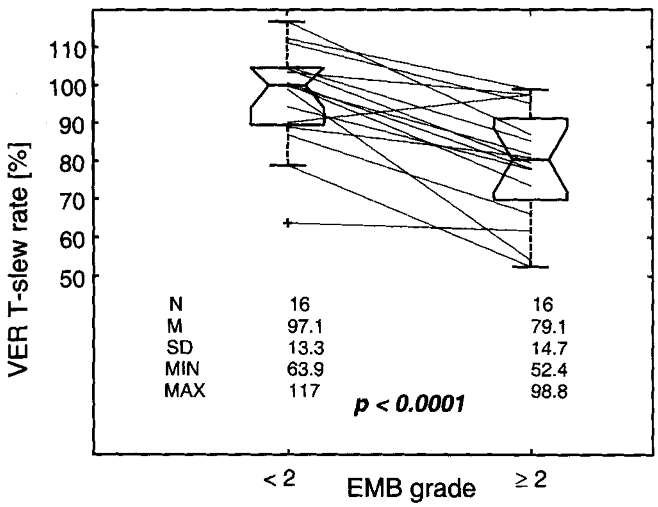

Fig. 2 Box and whisker plots with descriptive statistics regarding the influence of rejection on the normalized values of the VER T-slew rate parameter (*N* number of patients included, *M* mean, *SD* standard deviation, *MIN* minimum, *MAX* maximum). *The horizontal lines from bottom to top* represent the lower limit, the 25th quartile, the median (*MED*), the 75th quartile, and the upper limit. + indicates outliers. The *P* value was obtained with the two-tailed *t*-test for matched pairs and indicates significantly lower values under the influence of rejection, which was also the case individually for all except one patient

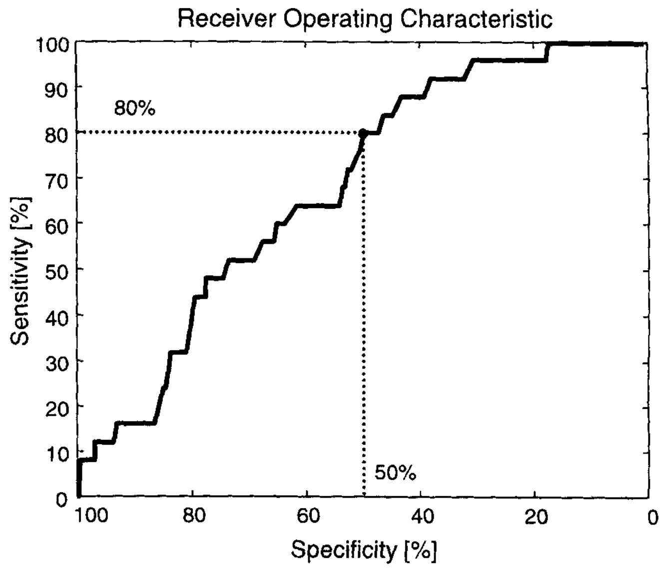

Fig. 3 Receiver operating characteristic of the single threshold diagnosis model used to discriminate follow-ups with versus without significant rejection as defined by EMB grades ≥2. A diagnosis threshold of 98% gives the depicted values of SENS = 80% and SPEC = 50%. Higher thresholds lead to increased SENS but decreased SPEC and vice versa

Table 2 Fourfold table resulting from the application of the single threshold diagnosis model to the normalized VER T-slew rate values indicating the absolute numbers of follow-ups in the four classification categories: true-negative (*TN*), true-positive (*TP*), false-negative (*FN*), and false-positive (*FP*) follow-ups, respectively. The corresponding diagnostic indices were SENS = 80%, SPEC = 50%, PPV = 11%, and NPV = 97%, $P < 0.005$ (X^2-test)

EMBstatus	VER T-slew rate > 98%	VER T-slew rate ≤ 98%
< Grade2	159 (TN)	161 (FP)
≥Grade2	5 (FN)	20 (TP)

Table 3 Comparison of native EMB grades as obtained at three investigational sites and the respective review EMB grades as obtained by blind re-examination of those EMB specimens by the pathologist at the remaining center. *Values in bold italic* indicate cases showing discordant results with respect to significant rejection in terms of grades ≥2

	Grade	Results						
ReviewEMB	3B							1
	3A		***1***			1		
	2		***3***	***2***	2	4		
	1B	7	12	2	***6***	***2***		
	1A	32	16	4	***1***	***2***		
	0	58	8	2		***1***		
Grade Native EMB		0	1A	1B	2	3A	3B	4

and without rejection in the remaining 16 patients who exhibited both states. For each of those patients the values for all available cases with, as well as without, significant rejection, were averaged so that a singe value for each of both states could be obtained. This analysis indicated significantly lower values under the influence of significant rejection (97 ± 13% vs 79 ± 15%; $P < 0.0001$). Additionally, the decrease was present in all but one patient.

Table 2 displays the fourfold table as obtained by application of the diagnosis model to the normalized and combined VER T-slew rate values. Out of the 25 cases with significant rejection as indicated by EMB grades greater than or equal to 2, 20 cases were correctly identified by VER T-slew values below a threshold of 98% (SENS = 80%, SPEC = 50%, NPV = 97%, PPV = 11%; $P < 0.005$). All the five false-negative cases with parameter values above the threshold were associated with EMB grade 2, and none of these cases was considered by the physicians to require rejection therapy. If the diagnosis model had been used to indicate the need for EMB, 48% of the EMBs could have been saved. Figure 3 shows the corresponding receiver operating characteristic.

According to Table 3, review of the EMB results reveals considerable differences, with respect to the classification of significant rejection in terms of results with grades greater than or equal to 2, between the native pathologists and the Graz pathologist. For example, cases which the Graz pathologist considered to be of grade 1A were found to be of grades 0–3A by the pathologists from the other centers and vice versa. From a total of 26 cases in which at least one side found significant rejection, only eight were unambiguously classified as such by both sides, giving sensitivities of 57% or 40%, depending on which side one assumes to be correct. The corresponding SPEC values of 92% or 96%, on the other hand, were high, i.e., there was a much higher agreement with respect to negative diagnoses.

Discussion and conclusions

The high SENS and NPV, as obtained in this prospective, blind, multicenter study, suggest the use of the method as a non-invasive tool to screen the patient and indicate the need for EMB only in cases of VER T-slew rate values below the threshold. In the present study population, this would have saved approximately half of the EMBs without missing a single case of the EMB results that finally led to the initiation of rejection therapy. The method is easy to use, and the new VER T-slew value together with the reference value are available within minutes after the IEGM recording procedure, which itself takes approximately 5 min for a single patient.

In 1992 we started to develop a pacemaker-based method for the analysis of IEGMs in order to detect acute cardiac allograft rejection non-invasively. Initial investigations were encouraging [1, 21]. After fractally coated leads became available, we started to record IEGMs during pacing, i.e., VERs in addition to the ones recorded from the spontaneously beating heart [4]. Subsequent studies revealed that VERs show superior properties for long-term cardiac monitoring in terms of a higher signal reproducibility and long-term stability [11, 22]. This led us to focus more and more on the VER [2, 14]. Eventually, other investigators obtained comparable results in similar studies [5, 6, 8, 17]. Recently, comprehensive results from our single-center experience have been reported [13]. In order that the possibility of a prospective and multicenter application of the proposed method could be assessed, a multicenter study was initiated, which was based on the very same methodological approach.

The basic idea behind the present study design was to interfere only minimally with routine clinical patient management as performed at most centers. It can, therefore, be expected that the results are not dependent on a very special kind of basic immunosuppression or rejection therapy regimen. The overall correlation between EMB results and IEGM results, however, was slightly lower than that in the previous single-center study [13], but this had to be expected because of (a) the prospective study design and (b) much more variability due to differences in patient management (EMB evaluation, therapy cut-off, immunosuppression, etc.). This notion is supported by additional analyses based on reference EMB grades, individual center diagnostic thresholds, and additional VER parameters, which were able to demonstrate somewhat higher diagnostic indices. Surprisingly, the use of only the signals from the right ventricular electrodes also resulted in a higher correlation between EMB grades and VER T-slew rate values, mostly in terms of higher specificity. Further studies are necessary in order for possible differences in the behavior of right and left ventricular VER signals to be investigated.

A number of cases that showed decreases in VER T-slew rate values without being associated with significant rejection, i.e., false-positive cases, were associated with clinical observations of infection or cardiac dysfunction (e.g., right ventricular dilatation), preceded episodes of significant rejection, and occurred within the first two postoperative months or in the course of the last follow-ups in patients who finally died. This suggests that many of these cases may have been associated with possibly undetected rejection or other cardiac diseases. On the one hand, this limits the specificity of the method. On the other hand, such episodes may also be worth being detected in terms of a generalized heart monitoring concept.

In contrast to the presented method, which is based on a well-defined data-acquisition procedure and an objective data-analysis method, the results of the comparison of native and review EMB results make it evident that considerable uncertainties exist in the histological diagnosis of rejection. This limited interobserver reproducibility and other shortcomings of EMB diagnosis have already been shown by a number of authors [7, 18, 19, 23, 24]. These are significant factors that generally limit the correlation between histological and electrophysiological methods for assessing rejection in heart transplants, in particular in a multicenter setup.

In conclusion, high sensitivity and a negative predictive value for the detection of cases with significant rejection were obtained in a prospective, blind, multicenter study. The presented method can, therefore, be used to supplement patient monitoring after HTx non-invasively, in particular to indicate the need for EMBs. In centers with patient management similar to the ones who participated in the study, this may allow a reduction in the number of surveillance EMBs. Uncertainty in the histological diagnosis of rejection is a significant factor that generally limits the correlation between histological and electrophysiological methods for assessment of rejection in heart transplants.

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