A Multicenter Study on Noninvasive Rejection Monitoring of Heart Transplants Using Computerized Processing of Intramyocardial Electrograms

R. BOURGE
University of Alabama at Birmingham, Birmingham, AL, USA

H. EISEN
Temple University, Philadelphia, PA, USA

R. HERSHBERGER
Oregon Health Science University, Portland, OR, USA

A. KELLER
Fairfax Hospital, Falls Church, VA, USA

B. RADOVANCEVIC
St. Luke's Episcopal Hospital/Texas Heart Institute, Houston, TX, USA

G. SCHREIER, P. KASTNER, H. HUTTEN
Institute of Biomedical Engineering, Technical University of Graz, Graz, Austria

Summary

Single-center studies on noninvasive rejection monitoring after heart transplantation (HTX) using intramyocardial electrograms (IEGM) have already been performed and have revealed high correlation with clinical findings. The aim of the present study was to investigate the feasibility of this method on a multicenter basis. During the heart transplant procedure, pacemakers with wide-band telemetry capabilities and two fractal coated, epimyocardial leads were implanted in 30 patients at five transplant centers. Ventricular IEGMs were recorded during both intrinsic and paced activity and digitized to a laptop-based data acquisition device. IEGMs were recorded at frequent intervals-and always on days when endomyocardial biopsies (EMB) were performed-and transferred via the Internet to the central data processing site. Clinical patient management was blinded to the IEGM results and varied considerably between the five centers. Using EMB together with clinical assessment of the transplant revealed 18 cases of clinically significant rejection (SR) beyond postoperative day 27 requiring rejection therapy. The normalized parameter values extracted from the IEGM recordings during pacing associated with SR were significantly lower (86 ± 16% versus 96 ± 22%, $p < 0.005$). The application of a single threshold diagnosis model to the parameter values allowed detecting these cases with a negative predictive value of 98%. Fifty-five percent of the EMBs could have been precluded if the method would have been used to indicate EMB. These results indicate the usefulness of this noninvasive monitoring tool in the transplant population, if confirmed in a prospective study.

Key Words

Noninvasive monitoring, intramyocardial electrogramm, heart transplantation, pacemaker

Introduction

Despite potent immunosuppressive agents, acute cardiac allograft rejection is still a major complication after heart transplantation (HTX). Tight surveillance of the transplant is of crucial importance and predominantly achieved with repeated endomyocardial biopsies (EMB), an invasive and expensive procedure. Though strongly desired, a generally accepted, noninvasive method for rejection monitoring which would reliably allow significant reduction in the number of EMBs does not yet exist [1]. Although high diagnostic reliability has been reported for some noninvasive methods, none of those has found broad clinical acceptance. Most of these proposed methods have not been evaluated in multicenter studies. This may indicate that those methods are not yet standardized enough to be routinely, clinically applicable. Thus clinicians who are not experienced in these methods are not applying them.

Previous single-center studies on cardiac transplant monitoring based on IEGMs and telemetric pacemakers have already shown high correlation with clinical findings [2-6], as well as a high potential of standardization [7]. The aim of the present study was to investigate the feasibility of noninvasive rejection monitoring based on IEGMs in a multicenter context.

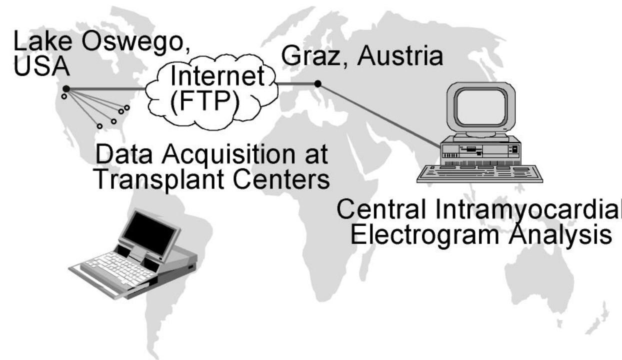

Figure 1. Standardized IEGM processing using the Computerized Heart Acute Rejection Monitoring (CHARM) system.

Materials and Methods

a) HTX and pacemaker implantation

During the heart transplant procedure, a dual-chamber pacemaker with wide-band IEGM telemetry capabilities (0.3 to 200 Hz) and two fractal coated, epimyocardial leads (Physios CTM 01 & ELC-UP, BIOTRONIK, Germany) were implanted in patients at different transplant centers. Both leads were screwed into the right ventricle; the pacemaker unit was implanted into the left epigastric region.

b) Clinical patient management

Except IEGM recording, the clinical patient management was done according to the center's preference. All EMB results were classified according to the standardized grading system for EMBs of the International Society of Heart and Lung Transplantation [8].

c) IEGM recording and processing

In the course of each follow-up, ventricular IEGMs were recorded during both intrinsic and paced activity and digitized to a laptop-based data acquisition device. IEGMs were recorded at frequent intervals during the early postoperative phase, as well as during special clinical events, and always on days when EMBs were performed. During the data acquisition phase, both the transplant centers and data processing centers were blinded to the IEGM results and clinical data, respectively.

IEGMs were collected at the U.S. relay site and transferred via the Internet to the central data processing site in Graz, Austria, for automatic IEGM analysis using the CHARM system, which has specifically been designed for IEGMs [9] (Figure 1). Signal processing provided an averaged, representative heartbeat electrogram for each sequence. After comprehensive signal quality control, a number of parameter values were extracted from the averaged heartbeat electrograms.

d) Statistics

To account for individual absolute levels and long-term trends, the IEGM parameters of each patient and lead have been normalized and expressed as percentages of individual and adaptive reference values. These reference values have been calculated as the average value observed prior to the actual follow-up with a special initialization procedure during the initial postoperative course, where the maximum parameter value observed previously served as the reference value. After normalization, the final value of the diagnostic parameter has been obtained as the average of the values from both leads.

Beginning with postoperative day 28, all observations have been classified as presenting SR or not, based on whether rejection therapy was initiated. A rejection therapy was defined by administration of an additional immunosuppressant or high steroid dosages.

The differences of the normalized IEGM parameter values of the cases with SR versus without SR have been tested using the two-tailed U-test. A diagnosis model consisting of a single threshold was applied to the normalized IEGM parameter values to test the possibility to detect the cases with SR (χ^2-test) and to calculate the standard diagnostic indices. p values less than 0.05 were considered to be statistically significant.

Center #	Number of patients	EMBs per patient	Rejection therapies per patient	Median of EMB grades
1	8	8	0.9	2*
2	5	7	1.2	2*
3	8	16	1.3	1B
4	6	11	2	1B
5	3	14	2	1A

* p < 0.0001 versus centers # 3, 4, 5 (two tailed U-test), EMB grades 0, 1A, 1B, 2, 3A, 3B, 4 mapped to an ordinal, linear scale from 0 to 6.

Table 1. Statistics on the number of patients, EMBs per patient, rejection therapies per patient, and medians of the EMB results at the five transplant centers during the whole follow-up period.

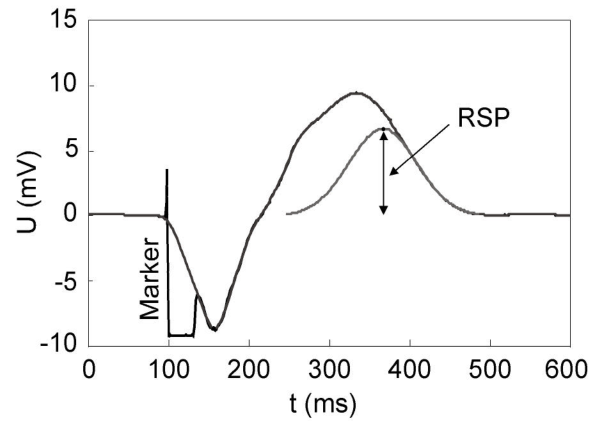

Figure 2. Typical averaged ventricular evoked response as obtained from an IEGM sequence during pacing. The rejection sensitive parameter (RSP) is calculated as the amplitude of a normal distribution, which was fitted to the terminal part of the repolarization phase using least square techniques.

Results

The patient group consisted of 30 patients from five transplant centers. Mean age at HTX was 55 ± 8 years (range: 38 to 67). Through the end of 1997, a total of 923 follow-ups were performed, resulting in 3593 IEGM recordings and 329 EMBs. Follow-up time per patient (time period from the first to the last recording) was 258 ± 113 (19 to 497) days, cumulative follow-up time was 21 patient years. At the end of the observation period, 25 patients were alive. A single pacemaker was explanted from a patient who suffered from severe infection, which also affected the implant. One of the two leads of the patient who received the first implant failed shortly after implantation, monitoring was based on the single remaining lead in this patient. No other complications related to the implanted pacemaker systems have been observed. Patient management in general (immunosuppression, rejection therapy threshold), as well as EMB frequencies and grade distributions, varied considerably between the five centers. The centers can be split into basically two groups characterized by substantial differences in patient management. Centers 1 and 2 show lower numbers of EMBs and rejections per patient but higher average EMB grades as compared to centers 3, 4, and 5 (table 1).

Except grade 3B (both cases of which were followed by rejection therapy), and given that there were no instances of grade 4, no other EMB grade was consistently regarded to require or not to require rejection therapy. Therefore, a single EMB grade cut-off being relevant to all centers could not be defined. However, using the EMB together with clinical assessment of the transplant led to the initiation of rejection therapy in 15 cases. In 3 cases, rejection therapy was initiated without EMB, based only on strong clinical signs of rejection. All of these 18 cases were classified as SR. In 209 follow-ups with EMBs, no rejection therapy was initiated and these cases were classified not to be associated with SR.

A typical averaged ventricular evoked response, as obtained from an IEGM sequence during pacing, and the definition of the IEGM parameter which was found to give the best diagnostic performance based on the prospective reference value model are displayed in figure 2. This parameter is designated as the rejection sensitive parameter (RSP) in the following.

Figure 3 displays the trend curve of the RSP as obtained in a patient who suffered from two episodes of SR, both being accompanied by markedly decreased RSP values. The first episode of SR started to develop immediately after cessation of induction therapy, a preventive rejection therapy during the very early postoperative period.

The RSP values associated with SR were found to be significantly lower (86 ± 16% versus 96 ± 22%, $p < 0.005$, figure 4).

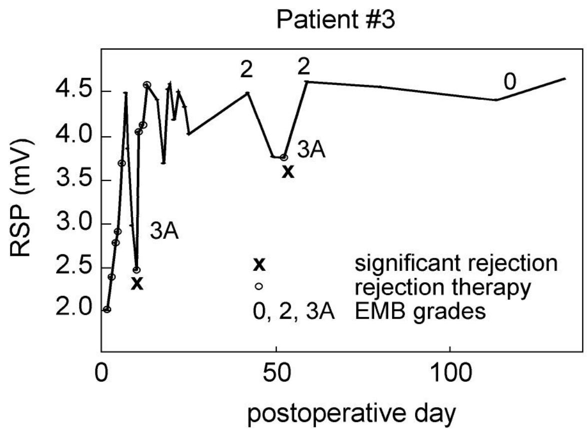

Figure 3. Trend curve of the RSP from a single patient and lead, displaying two episodes of SR (denoted by "X"), and both being accompanied by markedly decreased RSP values. Encircled data points denote initiation or continuation of rejection therapy.

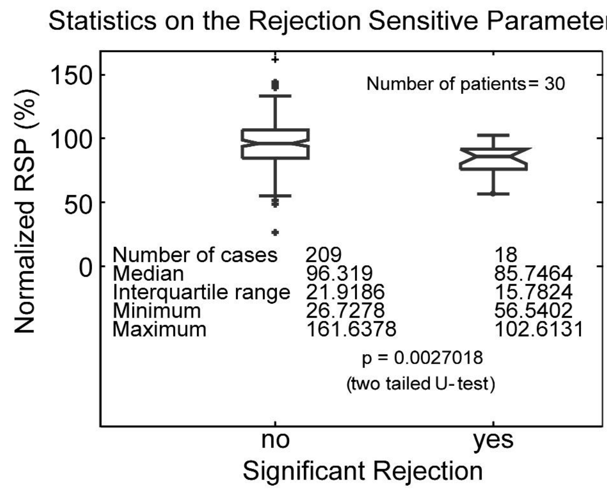

Figure 4. Statistics on the RSP grouped according to whether clinical assessment found SR or not. Application of the U-test indicates that the differences in median are statistically significant.

The application of the single threshold diagnosis model to the RSP is displayed in figure 5.

Discussion

The present study documents the first multicenter study on telemetrically recorded IEGMs for noninvasive patient monitoring after heart transplantation. The initial aim was to compare the IEGM results directly with the EMB results. Despite the limited diagnostic accuracy of EMBs, as shown in a number of studies [10-12], EMB is still considered to be the gold standard for diagnosis of cardiac rejection. The present multicenter data, however, do not reveal a close correlation between certain EMB grades and the initiation of rejection therapy. Thus, clinical patient management was only in part based on EMB and, to a large extent, considered further rejection indicators and clinical signs of rejection as well. The definition of SR for cases where rejection therapy was initiated provides a measure independent of the strategy how this decision is made at a certain transplant center. Moreover, the introduction of SR allows focusing on the main question: whether it is necessary to further evaluate the transplant in order to decide on rejection therapy. If indicated by noninvasive monitoring, an EMB may than be performed as part of this assessment. Though the diagnostic performance has been evaluated retrospectively, the presented IEGM processing model to assess the electrophysiologic status of the transplant at a certain follow-up uses only information from previous follow-ups; it can thus be applied in a fully prospective way.

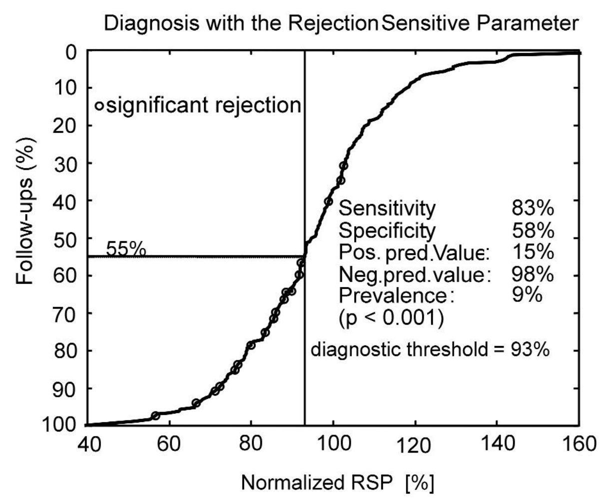

Figure 5. Application of a single diagnostic threshold to detect the cases with SR (encircled data points) indicates significant correlation between the clinical and the IEGM parameter classification ($p < 0.001$). Using a threshold of 93% revealed the diagnostic indices as displayed within the figure. 55% of the EMBs could have been precluded if the RSP values would have been used to indicate EMB. The three cases of SR above the threshold (false negative cases) occurred in 2 patients with multiple episodes of SR (three in each patient) interlaced with infection episodes.

Some initial IEGM follow-ups are necessary to establish the reference values. The exact period of time required to get a reliable estimation for the reference value, however, depends on the kind of patient management, with induction therapy being of particular importance. It may take significantly longer to establish the reference value if induction therapy is not administered, due to the lack of an observation period without rejection. The results indicate, however, that after three to four postoperative weeks a reliable reference value can be obtained in all patients. Thereafter, the method can be used to reliably exclude rejection for patients who show RSP values above the threshold and to substantially reduce the number of EMBs. The three false negative cases according to figure 5 (SR present and RSP values above the threshold) occurred in two patients with multiple rejection episodes (three in both patients) that were interlaced with infection episodes. Re-examination of these complex clinical courses revealed that the decision to initiate rejection therapy in those cases were borderline.

The optimal threshold and, therefore, the highest EMB reduction possible, will vary for different centers due to discrepancies in patient management. The present data obtained at five transplant centers with substantially different patient management, however, give reason to assume that a considerable percentage of EMBs can be saved at most centers.

Efficient and uniform information management is mandatory for extended clinical studies, particularly on a multicenter scale. Specifically designed for this purpose, the Computerized Heart Acute Rejection Monitoring (CHARM) system for standardized processing of IEGMs and clinical data has again proven its usefulness. Although quasi on-line evaluation was not utilized in the course of the present study, CHARM is already capable of providing results in such a fashion. This allows consideration of IEGM results for clinical patient management during a fully prospective clinical study. The next step will be to extend the concept to a home monitoring system-not only for sparing patients EMBs but also routine examinations in the hospital.

Conclusion

Noninvasive cardiac transplant monitoring using telemetric pacemakers is a well standardized method which can by applied on a multicenter basis. The very high negative predictive value of the rejection sensitive parameter for detection of episodes, for which rejection therapy was initiated, highlights the usefulness of this noninvasive monitoring tool in the transplant population. If these results can be confirmed in a prospective study, biopsies can be reduced by a considerable percentage. This would offer a method for less invasive and more efficient patient management after heart transplantation.

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