Computerized Heart Rejection Monitoring Using High Resolution Pacemaker Telemetry

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Summary

The noninvasive monitoring of the ventricular evoked response through high resolution pacemaker telemetry is compared to the endomyocardial biopsy in the diagnosis of acute heart transplant rejection. Paced unipolar ventricular electrograms were recorded in 13 heart transplant recipients after each biopsy. The signals were digitized on a laptop-based computer and transferred via Internet to the central processing site where the Rejection Sensitive Parameter (RSP) was extracted. Clinical patient management was not compared to the electrogram results during the first six months post implantation. The application of a single-threshold diagnosis model to the RSP value allowed the detection of grade 3 rejection episodes with 100% sensitivity, 76% specificity, 100% negative predictive value and 35% positive predictive value. Using RSP as an easily repeated, non-invasive follow up tool of heart transplant recipients, the number of endomyocardial biopsy (EMB) might be markedly reduced (67%), leading to a potential positive cost/effective analysis.

Key words

Heart transplantation, rejection monitoring, ventricular evoked response, diagnostic functions

Introduction

Although the survival of heart transplant recipients markedly improved since the introduction of cyclosporin, early detection of rejection episodes remains a major challenge. Allograft rejection is not a steady phenomenon but occurs in sporadic waves, extending over a few days or weeks. The patient usually remains asymptomatic until a significant myocardial damage results in heart failure. To initiate a successful therapy at early stage, the diagnosis must be made before clinical features of cardiac failure occur.

Endomyocardial biopsy is the gold standard of rejection monitoring. Nevertheless, this procedure is invasive, expensive and cannot be repeated too frequently to optimally control immunosuppression. Those limitations have spurred the search for reliable, non-invasive and easily repeated monitoring rejection tools.

Acute rejection results in cellular infiltrates, edema and eventually myocardial necrosis. Those factors are considered to alter the electrophysiological properties of the myocardium. Before the introduction of cyclosporine A, those diffuse and massive lesions allowed the detection of rejection by monitoring the amplitude of the surface ECG. Immunosuppression with cyclosporine A resulted in more focal lesions with minimal edema making standard ECG inaccurate for the detection of rejection. Epicardial ECG monitoring, already suggested by Sewell et al. [1] in 1968, regained interest. Preliminary studies showed a significant relation between intramyocardial electrogram amplitudes and endomyocardial biopsy results [2-5].

Nevertheless, attention progressively focused of the repolarization phase of the paced QRS. Indeed, ionic abnormalities due to cell necrosis, and alterations of transmembranic ionic transportation could alter repolarization. The monitoring of the evoked T-wave amplitude using an externalized QT-driven pacemaker exhibited a significant fall of this parameter preceding by an average of 2 days the diagnosis of rejection by endomyocardial biopsy [6]. Long-term monitoring of ventricular evoked response and evoked T-wave amplitude by means of an implanted pacemaker implemented with high resolution telemetry capabilities con-

firmed these initial observations [7, 8]. In-depth analysis of the evoked T-wave signal disclosed the potential interest of monitoring the maximum slew rate of the T-wave repolarisation phase [9]. The purpose of our study was to evaluate the clinical usefulness of extracting this parameter from telemetrically recorded paced ventricular electrograms in the detection of grade 3 or higher acute cardiac allograft rejection.

Methods

Since August 1997, after informed consent, 13 patients (11 men, 2 women, age: 51 ± 8 years) undergoing heart transplantation received a dual chamber pacemaker, the Physios CTM 01 (Biotronik, Germany), connected to two ventricular unipolar epimyocardial screw-in leads with fractal coating (ELC 54-UP, Biotronik, Germany). The electrodes were respectively placed on the right ventricular outflow tract and the left ventricle (margo obtusus) during the transplant procedure.

The Physios CTM is implemented with high speed telemetry (bandwidth: 0.3 to 200 Hz) and allows a high sampling frequency of intracardiac signals, up to 667 Hz. During the follow up examinations, the electrograms were transmitted through high resolution telemetry on a laptop computer, digitized and transferred to the central processing site (Cortronik, Graz, Austria). One minute paced electrograms sequences were recorded on each ventricular lead every alternate day after heart transplantation and after each biopsy. The measurements were performed after a 10 minute resting period, at a constant pacing rate and energy and at the same time of the day in order to minimize the effect of diurnal variations of the signal [9].

The signal processing includes a beat classification: only paced ventricular evoked response are averaged. The Rejection Specific Parameter (RSP) corresponds to the maximum negative slew rate of the descending slope of the repolarization phase of the averaged signal. The RSP values are normalized for each patient and new results are compared with the average of all previous results. A 20% downward shift of RSP from patient specific reference value is considered as abnormal. During the first six months post transplantation, the results of the signal processing were not passed to the investigators. As reference monitoring tool, biopsies were performed at days 10, 20, 30, 45, 60, 80, 110, 140 and 180.

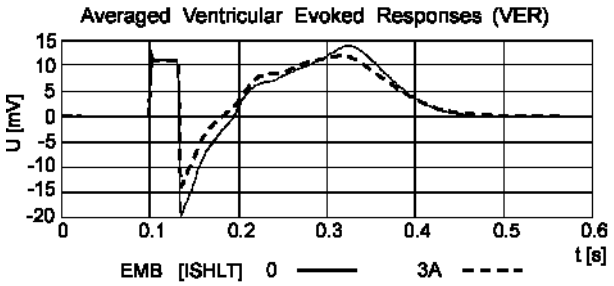

Figure 1. Example of Ventricular Evoked Response with/ without rejection. Signals of patient 3 recorded during a grade 3A rejection episode (dotted line). Please note the downward shift of the repolarization phase compared to the signal recorded outside rejection.

Results

On May 1st, 1999, 9 pts achieved the 6 months follow-up (FU range: 11.9 ± 7.2 months). 2 pts died (one from systemic Aspergillus infection 2 months post transplantation (PT), one from a cerebral hemorrhage 2 months PT). They underwent a total of 219 follow-up examinations and 73 endomyocardial biopsies which were graded according to the classification of the International Society for Heart and Lung Transplantation. Histological analysis classified 8 biopsies as corresponding to a rejection grade 3A (prevalence 11%), 5 as grade 2, 7 as grade 1B, 25 as grade 1A, and 28 as normal.

Using a two tailed U-test, a significant difference was found between the RSP signals acquired during grade 3 rejection episodes and RSP signals acquired during other follow ups (95.2% ± 18.1% vs. 74.2% ± 5.5%, $p < 0.01$). Each RSP signals corresponding to grade 3 rejection episodes were inferior to 80% of patient specific normalized reference value. An example of the intramyocardial electrogram alterations recording during a rejection episode is displayed in Figure 1.

A diagnosis model consisting of a single threshold testing showed the ability RSP to predict the cases with significant rejection on EMB (χ^2-test, $p < 0.0001$). When a downward shift of 20% of patient specific normalized RSP is considered as abnormal, grade 3 rejection episode would be detected with a 100% sensitivity, a 76% specificity, a 100% negative predictive value, and a 35% positive predictive value. Using RSP monitoring as a non invasive monitoring tool of heart transplant recipients to determine biopsy indications, 67% of biopsies would have been avoided (Figure 2).

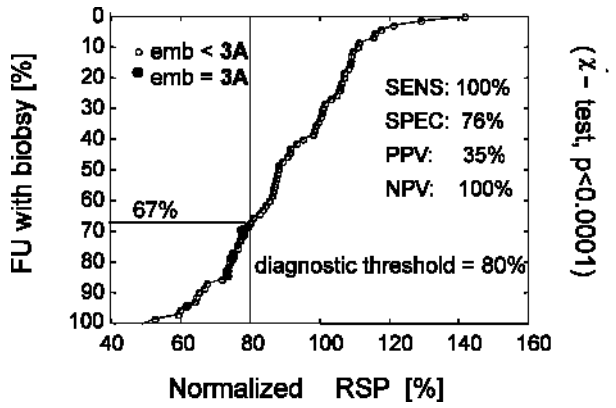

Figure 2. RSP recorded outside grade 3 rejection (O) and RSP recorded during grade 3 rejection episodes are displayed. All RSP values corresponding to grade 3 rejection episodes are below the 80% threshold. The intersection of the diagnostic threshold line with the cumulative frequency curve gives a value (67%) which corresponds to the percentage of biopsies which could have been avoided if RSP monitoring was applied as a screening tool to perform a biopsy.

Discussion

Endomyocardial biospsy is an invasive procedure which is associated with a complication rate ranging between 0.3% and 1.3%. Its processing and interpretation may delay diagnosis of rejection for several days. Furthermore, the detection of rejection is dependent upon the frequency of biopsy, providing snapshots, while the immune response of the recipients against the allograft and the resulting effects on allograft function are continuously on-going.

The purpose of our study was to assess the usefulness of the monitoring of the patient specific negative slew rate of the repolarization phase in the detection of rejection graded 3 of ISLHT classification. Indeed, there is a progressive consensus in regarding grade 3 as the clinically relevant histological grade triggering medical treatment [10, 11]. Although the diagnostic performance presented in that study was evaluated retrospectively, this method might be applied in a fully prospective way. Indeed, investigators were blinded to RSP results during the first six months post transplantation. The 100% sensitivity associated with a 100% negative predictive value of the RSP parameter makes the monitoring of epimyocardial electrogram a potential useful noninvasive screening tool in the detection of significant rejection episodes. However, as RSP reference values are patient specific and derived from the average of previous results, some initial follow ups are necessary either during induction therapy or during an observation period without rejection.

Conclusion

In conclusion, Computerized Heart Acute Recipient Monitoring based on remote analysis of the ventricular evoked response is promising. Using this diagnostic parameter, the number of endomyocardial biopsy might be markedly reduced, leading to a potential beneficial cost/effectiveness analysis. Future perspectives include individual tailoring of immunosuppressive drug treatment in order to minimize secondary effects due to steroid treatment.

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