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Analysis of the Ventricular Evoked Response for Use in Cardiac Transplant Monitoring

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Summary

This study presents a new method for non-invasive monitoring of acute rejection after heart transplantation based on the recording of the ventricular evoked response from the stimulated heart using implanted pacemakers and electrodes with fractal surface structure. Parameters derived from the telemetrically obtained epimyocardial electrograms are significantly related to acute rejections of grade 2 and higher as confirmed by endomyocardial biopsy. The results with regard to sensitivity (93%) and specificity (76%) emphasize the potential of this new method and show that many endomyocardial biopsies can be saved without reducing the safe therapy management of the patients.

Introduction

The total number of heart transplantations amounts to about 27,000 with a five-year survival rate of 65 percent.[1] The main post-operative risks are infection and *acute rejection* (AR) which is controlled by immunosuppression. Since only very advanced AR is accompanied by clinical symptoms, AR screening is essential. Despite its severe shortcomings, the gold standard for AR surveillance is repeated *endomyocardial biopsy* (EMB). It is an invasive and expensive procedure, which can be performed only in specialized hospitals and at certain time intervals. Therefore, the relatively normal and healthy life of successfully treated patients can be inconveniently interrupted by EMB. Additionally, EMB offers only limited reliability on the basis of a restricted number of tissue samples that are subjectively evaluated.[2] The aim must be to supplement EMB by complementary methods which render possible a non-invasive, quasi-continuous, objective, and inexpensive surveillance of the patients.

Several investigations have shown the strong influence of AR on the electrical depolarization activity of *epimyocardial electrograms* (EE) from spontaneous heart beats (i.e., QRS or R amplitude), obtained with ventricular electrodes.[3] The development of a new type of electrode with fractal surface structure permits recording of the *ventricular evoked response* (VER) via implanted *pacemakers* (PM), with the same electrode used for stimulating and sensing. A unique feature of this electrode is that only a minor polarization artifact is provoked.[4]

This study assesses the value of parameters derived from telemetrically recorded VERs from paced heart beats as a non-invasive method to detect AR, and provides data on the diagnostic reliability, which can be achieved by comparing VER parameters with histological findings from EMB.

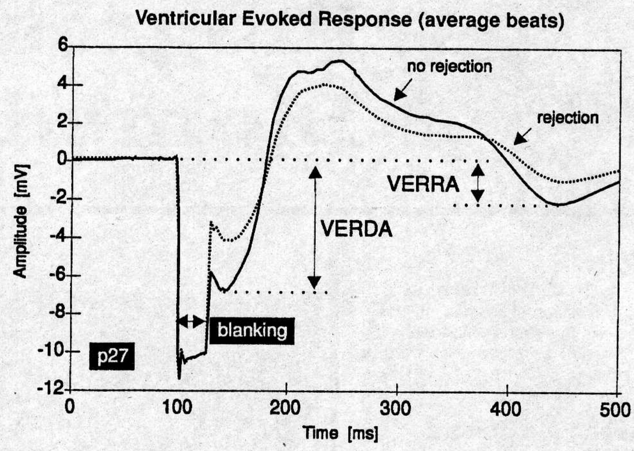

Figure 1. *This figure shows VER averaged signals obtained during an AR rejection episode and with no rejection in the same patient (p27). Two amplitude based parameters are derived from the VER signal as shown. VERDA = VER depolarization amplitude, VERRA = VER repolarization amplitude.*

Materials and Methods

A fractally coated epimyocardial screw-in electrode (ELC 54-UP) was placed at the anterior wall of the right ventricle, and a telemetric PM (Mikros-Biogard or Physios CTM 01) was implanted in the course of each transplant procedure. Immunosuppressive regimen consisted of cyclosporine A, azathioprine and methylprednisolone. EMBs were performed weekly during the first two postoperative months, thereafter with increasing intervals. Histological results were classified according to the grading system of the International Society for Heart and Lung Transplantation.

EEs were obtained using the telemetric PM and a telemetry receiver (Mikros-Biogard or Physios CTM 01, all hardware by Biotronik, Berlin, Germany). Signals were recorded under standardized conditions on the days when routine EMB was scheduled. Additional recordings were taken in the early postoperative period, and in case of acute change of the clinical status such as AR or infection episodes, respectively. Constant pacing parameters (rate, impulse amplitude, impulse duration) were used for all VER recordings in the same patient. In a subset of patients, pacing parameters were changed in order to elucidate the dependency of the VER on the pacing parameters. The EE signals were digitized and stored using a PC-based data acquisition system. Further signal analysis was undertaken on a workstation with specially designed software performing beat detection, beat classification, coherent averaging, and extraction of the parameters from the resulting signal sequence, i.e., the VER depolarization amplitude and the VER repolarization amplitude (Figure 1).

Statistical analysis and diagnostic quality calculations were derived for the whole patient group by normalizing the results of each patient. For this evaluation, all extracted parameters were expressed as percentages of an individual reference value. The reference value was computed as the mean of the parameter values of all recordings for that patient, irrespective of the corresponding EMB result. To use information from the depolarization as well as from the repolarization phase of the cardiac cycle, both respective amplitudes were combined and referred to as the ventricular evoked response amplitude (VERA):

$$\mathrm{VERA} = \sqrt{\mathrm{VER\_dep\_amp}^2 + \mathrm{VER\_rep\_amp}^2}$$

The VERA provides an overall index of the VER's electrical activity. For statistical analysis, the normalized parameter values were grouped according to the associated EMB grades. All cases with EMB grades ≥ 2 were subsumed into one group. For each group, the mean and SD values were computed. P values were calculated with the two-tailed U-Test.

Results

Sixteen consecutive patients (14 males, 2 females) were prospectively included. The mean age of the patients was 49 ± 16 years (mean ± standard deviation), mean follow-up time per patient was 190 ± 128 days. A total of 360 EE recordings with 205 associated EMBs were evaluated. Fifteen ARs with EMB grade ≥ 2 (≥ moderate AR) were observed, 13 of them of grade 2.

EEs changed significantly when AR began to develop. This was found for spontaneous beats (QRSA) as well as during pacing (VERDA and VERRA). The VERRA was the best single parameter and was highly correlated with EMB results. Additional improvement was achieved with the combination of the two VER parameters, *i.e.*, the VERA.

Figure 1 shows signal-averaged VER information from patient (p27), with AR (light line) and no AR following rejection therapy. A significant voltage increase associated with AR therapy was observed. VER recordings were highly reproducible. Figure 2 shows representative results from patient (p29) for the parameters VERDA and VERRA, respectively. VERDA and VERRA values obtained using the standard pacing settings (pulse amplitude = 4.8V, pulse duration = 0.5ms and pacing rate = 100ppm), prior to changing pacing parameters, correspond to the dot at the intersection of the 100% coordinates. The changes to pacing parameters are displayed next to the corresponding data points and describe the influence on the VER parameters with reference to the standard pacing values. It can be seen that most of the values lie within 5% of the standard values, even though pacing parameters were varied by up to 400%. Thus, the influence of major variations in pacing parameters appears to have minimal influence on the VER signal.

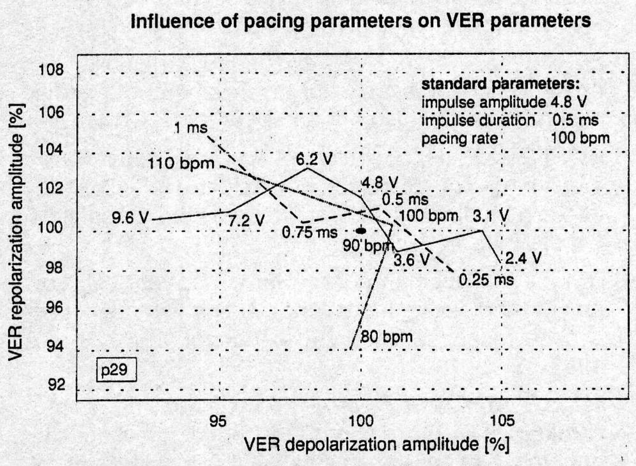

Figure 2. *VER depolarization amplitude and VER repolarization amplitude values of patient (p29) as obtained for a series of recordings with pacing parameter variations (displayed next to the corresponding data points).*

Figure 3 shows the time course for the parameter VERRA in patient (p27). The EMB results are displayed next to the corresponding data points. The AR episode around the 20th postoperative day (EMB grade 3B) was treated with antithymocyte globulin for ten days. This event was preceded by a decreasing VERRA that reached a minimum on the day when AR was diagnosed. Following AR therapy, EMB indicated an improvement of the AR grade to 1A for the third therapy control EMB. The VERRA increase after rejection therapy was closely correlated to the AR improvement. Three clinical infection episodes occurring around the 40th, 80th and 100th postoperative days are also apparent from the time course. The statistical analysis shows that the decrease in VERDA and VERRA with EMB grades >2 were highly statistically significant.

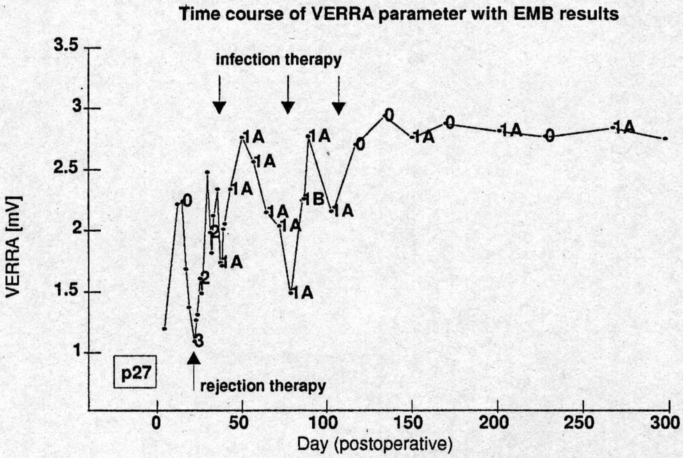

Figure 3. *Time course of VERRA parameter in patient (p27). EMB results are displayed next to their corresponding data points. Institution of rejection and infection therapy are denoted by arrows.*

Figure 4 displays the mean and SD data for the combined parameter VERA and shows that the EMB grade ≥ 2 is associated with a 16% lower amplitude as compared to the overall reference value. This is statistically significantly different when compared to all other EMB grades.

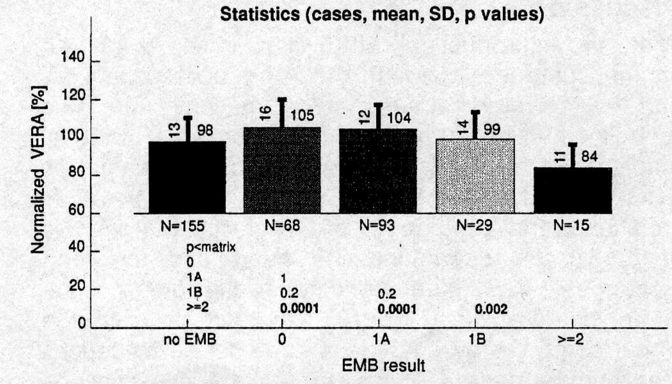

Figure 4. *Results of the statistical analysis. Normalized parameter values were grouped according to the associated EMB grades. The number of cases (N), mean values and SD (top of the bars) are displayed. P values for all combinations of groups 0, 1A, 1B and ≥ 2 are displayed as a 'p< matrix'.*

A single threshold was used as a retrospective diagnostic model. Sensitivity (SENS) and specificity (SPEC) were computed for that threshold which maximized the terms SENS x SPEC, this was termed the diagnostic threshold.

Figure 5 shows that using this threshold yielded a SENS of 93%, a SPEC of 76% and a diagnostic threshold of 95%. By using the diagnostic threshold as shown, 14 of 15 cases of moderate AR were correctly detected. The intersection of the diagnostic threshold line with the cumulative frequency curve gives a value of 71%, which is an estimation of the percentage of EMBs, which could have been avoided if the diagnostic model were applied as an indication to perform EMB.

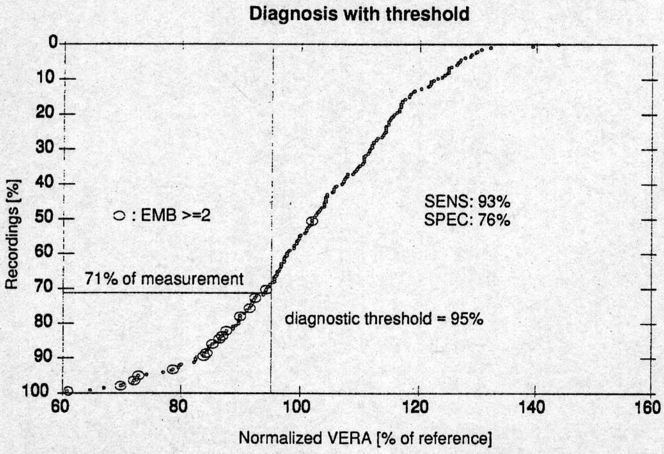

Figure 5. *Application of the diagnosis model. Beginning in the lower left corner, the normalized values of all recordings for all patients were plotted in ascending order. The encircled ones were associated with an EMB grade ≥ 2.*

Throughout the follow-up period no infections or technical failures of the PM systems were observed.

Discussion

With the introduction of cyclosporine A as an immunosuppressive agent, the AR process changed, and the conventional surface ECG became unreliable for AR detection, because small decreases in signal amplitude due to AR can be masked by non-specific ECG fluctuations, such as diurnal and day-to-day variations, and any change of the electrical properties of the tissue separating the heart and the lead electrodes, e.g., pleuropericardial effusion.[5] Since intramyocardial electrograms are very close to the signal source, they show less non-specific influences than body surface ECGs. Our previous investigations have already shown the influence of AR on EEs from spontaneous heart beats.[6] To use information from the repolarization phase, our measurements were extended to recordings of the VER. The use of the VER offers a better standardization for the measurements of electrophysiological signals, because the heart rate can be kept constant in a patient's recording series. To our knowledge, only one other study has employed paced EEs to detect AR, which described a decline of the evoked T-wave amplitude due to AR. Daily recordings via externalized epimyocardial ventricular electrodes, provided for perioperative pacing, were performed during the first three postoperative weeks. Thereafter, the temporary electrodes had to be removed.[7] The high correlation between VER parameters and EMB results shows that histologically proven moderate AR is associated with change in the electrical activity of the transplanted heart. Since fractally coated pacing leads enable reliable telemetric measurements of the VER, this influence can be monitored via telemetrically obtained EEs.

Conclusions

An improved diagnosis of AR detection by means of recording and analysis of VERs was achieved in a real clinical application. Serial recordings of VERs offer the chance to meet the requirements for a non-invasive monitoring of AR with a substantial reduction of EMB frequency. To confirm these results, a multicenter study is currently underway both in Europe and the United States.

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