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Intramyocardial electrograms for non-invasive rejection monitoring: initial experience with an infection-specific parameter

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Abstract Non-invasive rejection monitoring based on the analysis of paced intramyocardial electrograms enables repeated or even daily graft surveillance. The rejection-sensitive parameter is calculated from the maximum slope of the descending part of the t wave. Biopsy-proven rejection grade 2 or higher (ISHLT classification) can safely be detected. Nevertheless, infection influences the rejection-sensitive parameter in the same manner as does rejection (99% negative predictive value for rejection grade 2 or higher, 17% positive predictive value). We defined the infection-specific parameter as the time on the O line between the pacemaker stimulus and the crossover with the maximum slope of the descending part of the t wave. Patients were classified prospectively according to infection status: patients without infection and those with clinically apparent infection. Patients with clinically apparent infections had a significantly longer infection-specific parameter. A simultaneous decrease of the rejection-sensitive parameter and an increase in the infection-specific parameter was observed during clinical infection; a decrease in the rejection-sensitive parameter and no changes in the infection-specific parameter were observed during rejection. This preliminary analysis revealed that discrimination of rejection and infection might be possible by the analysis of intramyocardial electrograms.

Key words Heart transplantation · Infection · Non-invasive rejection monitoring · Intramyocardial electrograms · Infection monitoring

Introduction

Survival rates of heart recipients reach 84% at 1 year after heart transplantation. During this time, 60% of the recipients suffer from acute cardiac rejection and 31% from clinically apparent infection [6]. Five years after transplantation, 64% of the transplanted organs have an adequate graft function [7]. Nevertheless, no induction of tolerance to the donor organ is observed and the risk of organ failure due to rejection remains [9].

One of the milestones in cardiac transplantation, the endomyocardial biopsy (EMB), was developed many years ago [2]. To date, the detection of acute and chronic cardiac rejection is based on the EMB, which cannot safely distinguish between rejection and infection. Although it is the current gold standard of acute rejection diagnosis, the disadvantages are that patients are frequently exposed to fluoroscopy and the method is invasive and cannot be repeated daily. Its diagnostic value is hampered by sampling error [10], which is dependent on the pathologist, and there is no clear differentiation between rejection and infection.

Non-invasive rejection monitoring based on the analysis of intramyocardial electrograms enables repeated or even daily graft surveillance. The rejection-sensitive parameter (RSP) enables the detection of biopsy-proven rejection grade 2 or higher (ISHLT classification)

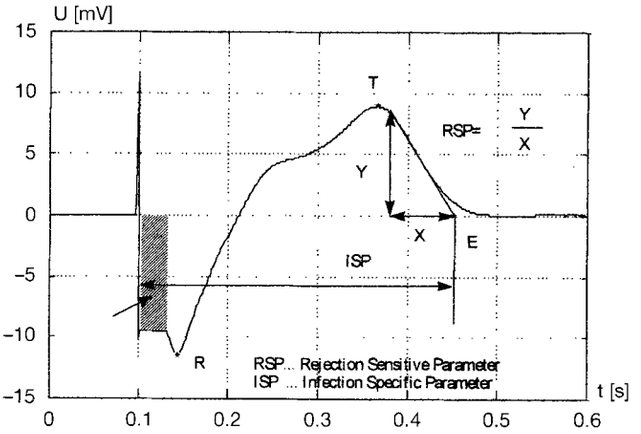

Fig. 1 Definition of the rejection-specific parameter (*RSP*) and the infection-specific parameter (*ISP*)

[1]. Furthermore, the efficiency of rejection therapy can be estimated within 24 h [3].

Nevertheless, infection influences the RSP in the same manner as does rejection (99% negative predictive value for rejection grade 2 or higher, 17% positive predictive value). Differentiation between rejection and infection would substantially increase the value of this method.

Materials and methods

Thirty-three consecutive heart transplant recipients were included in the study. Basic immunosuppressive therapy consisted of cyclosporine A, azathioprine, and methylprednisolone. All patients received induction therapy with antithymocyte globulin. During heart transplantation we implanted the rejection monitoring system, a telemetric pacemaker (Physios CTM; Biotronik, Erlangen, Germany) with unipolar, epimyocardial, fractally coated, screw-in electrodes (ELC 54-UP; Biotronik). The position of the electrodes is over the anterior wall of the right and/or left ventricle, with a distance between electrodes of at least 4 cm. Acute cardiac rejection was monitored by routine EMB and rejection grade 2 or higher (ISHLT classification) was treated with methylprednisolone (1000 mg daily for 3 days). For non-invasive rejection monitoring, recordings of the ventricular-evoked response were performed under standardized conditions, with patients in a supine position without talking or moving, programmed to a pacing rate of 100 beats/min, and at the same time of day [5]. The reproducibility of the ventricular-evoked response is superior to that of spontaneous heart rhythm after heart transplantation [4, 8]. One-minute sequences were recorded with a notebook-based system and sent via the Internet to a Unix workstation. In order to reduce the influence of beat to beat variations and ectopic heart beats, rigorous signal morphology checking and signal averaging was carried out. The RSP and infection-specific parameters (ISP) were calculated from the averaged signal of paced intramyocardial electrocardiograms. The RSP is calculated from the maximum slope of the descending part of the t wave and the ISP as the time on the O line between the pacemaker stimulus and the crossover with the maximum slope of the descending part of the t wave (Fig. 1).

Measurements were taken on biopsy days, twice weekly during hospital stay, during every outpatient clinic, and on days with clinically apparent infection. Patients classified prospectively were into those without and those with clinically apparent infection.

Results of non-invasive rejection monitoring were compared to the results of the EMB according to the classification of the ISHLT [2] and to the infection status, as prospectively classified.

Statistical analysis was performed using the unpaired, two-tailed U-test; significance was assumed if $P < 0.05$.

Results

The RSP significantly was lower in patients with rejection grade 2 or higher (Fig. 2, left). Nevertheless, the RSP was also significantly influenced by clinically apparent infection (Fig. 2, right), which resulted in a negative predictive value for rejection grade 2 or higher of 99%, and a positive predictive value of 17%.

The ISP remained unchanged in patients with rejection grade 2 or higher (Fig. 3, left) whereas clinically apparent infections significantly influenced the RSP (Fig. 2, right) and the ISP (Fig. 3, right). An example of the behavior of the intramyocardial electrograms during infection and rejection is presented in Fig. 4.

Patients with clinically apparent infections had a significantly higher ISP. A simultaneous decrease of the

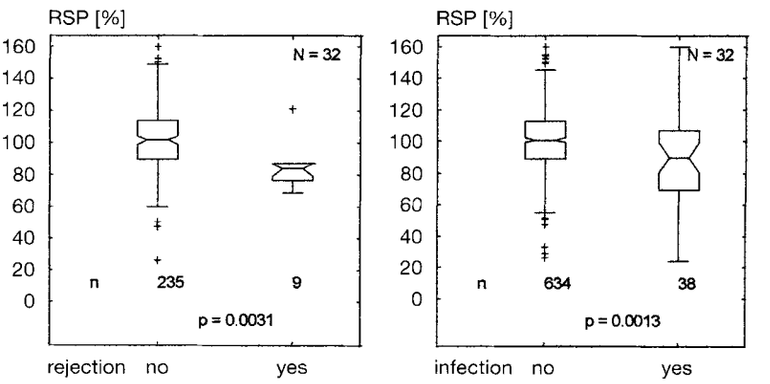

Fig. 2 Influence of rejection (*left*) and infection (*right*) on the RSP

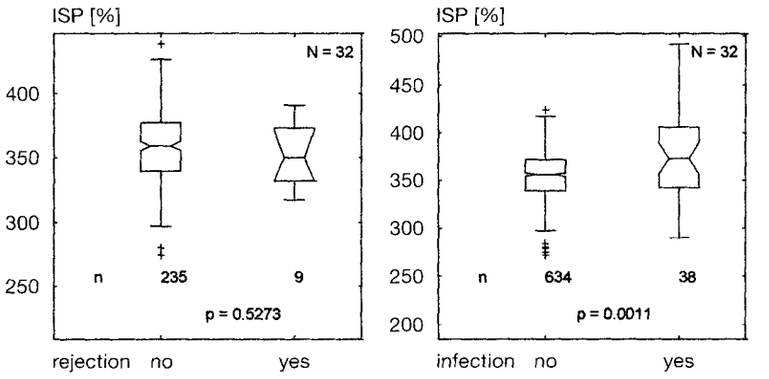

Fig. 3 Influence of rejection (*left*) and infection (*right*) on the ISP

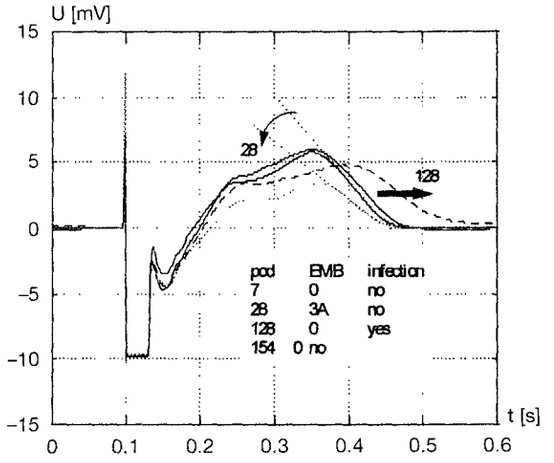

Fig. 4 Influence of rejection on day 28 and infection on day 128 on the same patient. Figures on days 7 and 154 compare favorably as an example of the high reproducibility of intramyocardial electrograms (*pod* postoperative day, *EMB* endomyocardial biopsy)

RSP and an increase of the ISP was observed during clinical infection, a decrease of the RSP and no changes in the ISP were observed during rejection (Figs. 2–4).

Discussion

Differentiation between rejection and infection may be difficult after heart transplantation. Local and general infection presents with various symptoms and at different locations. Moreover, appropriate and reproducible definitions of infection are lacking. Our prospective classification of patients into two groups (clinically apparent infection and no infection) was a rough differentiation to enable the comparison of the actual infection status to that predicted from the results of our method.

The RSP enables the reduction of EMBs without missing a biopsy result grade 2 or higher. Moreover, frequent monitoring might detect more rejection episodes at an earlier stage. On the basis of the RSP alone, however, no differentiation between rejection- and infection-induced decrease of the RSP can be made.

The results of this study might contribute to the discrimination between cellular rejection and infection-related leukocyte infiltration by non-invasive graft monitoring after heart transplantation. The value of the method (tailored immunosuppressive therapy, repetitive non-invasive diagnosis of the immunological status of the graft, monitoring of rejection therapy) could be further improved.

The reason for the different behavior of intramyocardial electrograms during rejection and infection remains unclear; an explanation of how infection causes the prolongation of the signal is not available. To evaluate which kind of infection prolongs intramyocardial electrograms, further studies and the appropriate classification of infection are mandatory.

In conclusion, analysis of the ventricular-evoked response for RSP and ISP revealed that discrimination between rejection and infection might be possible.

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