Transpl Int (2000) 13 [Suppl 1]: S225–S227

B. Grasser
F. Iberer
S. Schaffellner
D. Kniepeiss
G. Schreier
P. Kastner
K.-H. Tscheliessnigg

Non-invasive graft monitoring after heart transplantation: rationale to reduce the number of endomyocardial biopsies

B. Grasser · F. Iberer · S. Schaffellner · D. Kniepeiss · K.-H. Tscheliessnigg
Department of Surgery, Division of Transplantation, Karl-Franzens University of Graz, Austria

G. Schreier · P. Kastner
Institute of Biomedical Engineering, Technical University of Graz, Austria

F. Iberer (✉)
Chirurgische Klinik, LKH, Fach 37, A-8036 Graz, Austria
Fax: + 43-316-385-4446

Abstract The endomyocardial biopsy is invasive, reduces quality of life and cannot be repeated daily. Initial studies on noninvasive cardiac graft monitoring have been presented recently. During the heart transplant procedure, we implanted wideband telemetric pacemakers and fractally coated, epimyocardial electrodes. On biopsy days and during each follow-up, intramyocardial electrogram sequences were obtained. The maximum T-slew rate from the ventricular evoked response (VER) was automatically calculated and compared to the biopsy results ($n = 331$, ISHLT grading). The VER T-slew rate was significantly lower during rejection grade 2 or higher. The negative predictive value to exclude rejection was 98%. Using a single threshold diagnosis model, 74% of the biopsies could have been avoided. Noninvasive cardiac graft monitoring can reduce the need for surveillance biopsies and may offer a tool to optimize immunosuppressive therapy after heart transplantation

Key words Graft monitoring after heart transplantation · Intramyocardial electrograms · Rejection after heart transplantation

Introduction

Obligatory graft surveillance in patients after heart transplantation is still achieved with the invasive and expensive endomyocardial biopsy (EMB). Up to now, attempts to develop an alternative, generally accepted procedure have failed.

Since 1992, our group has developed a pacemaker based system for the analysis of intramyocardial electrograms to recognize acute cardiac allograft rejection [4]. We found that the repolarization phase of the paced intramyocardial electrogram contains the most accurate information to indicate absence of rejection [1, 2]. Infection also influences intramyocardial electrograms [3]. The usefulness of this method to avoid EMB without missing relevant rejection after heart transplantation is described in the following study.

Materials and methods

During the transplant procedure, we implanted dual chamber pacemakers (Physios CTM 01, Biotronik, Berlin, Germany) with wideband intramyocardial electrogram telemetry capabilities (0.3–200 Hz) and two unipolar, epicardial screw-in leads with fractal surface structure coating (ELC 54-UP, Biotronik, Berlin, Germany).

All patients received induction therapy with antithymocyt globulin (ATG) and were maintained on triple drug immunosuppressive therapy. Repeated surveillance EMBs guided the indication of rejection therapy with pulsed steroids or polyclonal antibodies, as appropriate. The biopsy results were classified according to the guidelines of the International Society of Heart and Lung Transplantation.

Intramyocardial electrogram recordings were performed at frequent intervals in the early postoperative phase, during each follow-up and on days when EMBs were performed. Recordings were obtained at pacing rates between 100 and 130 bpm, as appropriate. After 5 min rest in the supine position [2], 1 min intramyocardial electrogram sequences of the VER were separately recorded from each electrode and digitized to a laptop-based data acqui-

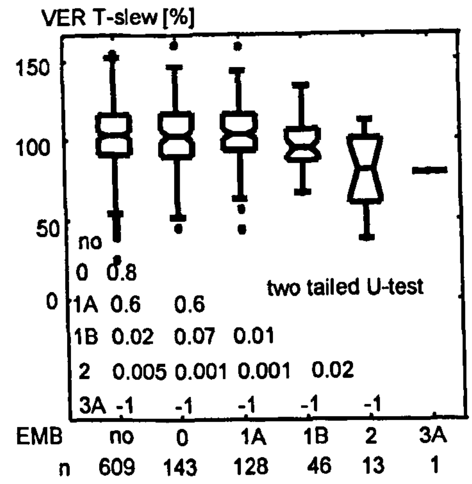

Fig. 1 Differences in the normalized VER T slew rate parameter between different EMB results

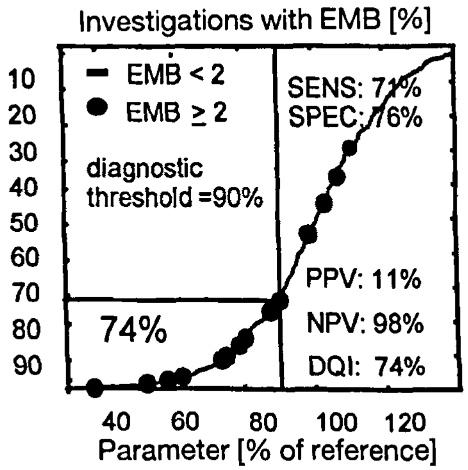

Fig. 2 Application of the single threshold diagnosis model to the normalized VER T-slew rate parameter values and standard diagnostic indices

sition device. Intramyocardial electrograms were transferred via the Internet to the central data processing site in Graz, Austria. After automatic signal morphology checking to exclude spontaneous, ectopic or fusion beats, each intramyocardial electrogram sequence was averaged.

We defined the VER T-slew rate parameter as the maximum T-slew rate of the VER. To avoid influences resulting from individual absolute values and the long term trend, the parameter was normalized and expressed as the percentage of the individual adaptive prospective reference value. This value was calculated as the mean area under the curve of all previous examinations and was prospectively defined for the following investigation. The parameter was presented as the average of the value of both leads.

Within a few minutes, comprehensive patient reports are returned via the Internet, which display trend curves and the normalized and absolute values of the derived parameters.

Differences in normalized intramyocardial electrogram parameters between different EMB results were tested with the two-tailed U-test. A single threshold diagnosis model was applied to the normalized VER T-slew rate parameter to test the ability to predict cases with rejection grade 2 or higher and to calculate the standard diagnostic indices using the χ^2-test. Significancy was assumed if $P \leq 0.05$.

Results

The Physios CTM 01 pacemaker was implanted in 37 patients. Mean age at heart transplantation was 57.2 ± 10 (17–71) years. During the observation time, a total of 311 EMBs were performed. The pacing threshold at the time of implantation was 0.63 ± 0.54 V at 0.5 ms pulse and the sensing potential was 11.9 ± 4.3 mV. No adverse events related to the implanted pacemaker system were obtained.

The prevalence of rejection grade 2 or higher in our biopsy results was 4%. The differences in the normalized VER T slew rate parameter between different EMB results are presented in Fig. 1.

The differences in the normalized VER T slew rate parameter between different EMB results values allowed detection of rejection grade 2 or higher with a negative predictive value of 98% ($P < 0.000001$). Results and the standard diagnostic indices are displayed in Fig. 2.

Discussion

This study compares results of the VER T-slew rate parameter and corresponding EMBs. The high negative predictive value of this method suggests its usefulness to exclude rejection after heart transplantation.

The VER, the response of the myocardium to an artificial stimulus, is a well-standardized electrophysiological signal that can be used for non-invasive, long-term monitoring. It enables global heart allograft recipient surveillance for pathologic changes that affect the electrical activity of the heart. Constant intramyocardial electrograms prove the unchanged electrical activity of the myocardium and suggest absence of active rejection, infection or ventricular dilatation. Therefore, inactive or residual cell infiltration of the myocardium might result in false positive biopsy results going with unchanged parameters derived from intramyocardial electrograms (Fig. 2). In contrast, humoral rejection with absence of cell infiltration and negative biopsy results has been detected by a decrease of the VER T-slew rate.

The individual reference value provides center specific definition of the diagnostic threshold and a variable rate of biopsy reduction. Nevertheless, center specific patient management influences the prevalence of rejection in the early postoperative period and the reliability of the individual adaptive reference value. Early rejection results in low reference values and no decrease of the VER T-slew parameter below the reference value is observed. Initially, the confirmation of freedom from rejection is mandatory, to use the reference value for future diagnosis of absence of rejection.

In conclusion, serial intramyocardial electrograms for non-invasive graft monitoring might be useful to reduce the number of biopsies after heart transplantation.

References

1. Grasser B, Iberer F, Schreier G, Schaffellner S, Prenner G, Allmayer T, Wasler A, Petutschnigg B, Müller H, Kastner P, Schaldach M, Hutten H, Tscheliessnigg KH (1998) Influence of circadian rhythm on intramyocardial electrograms for non-invasive rejection monitoring after HTX. In: Bacharova L, Macfarlane PW (eds) Electrocardiology 97. World Scientific Publishing Co. Pte. Ltd, Singapore, New Jersey, London, Hong Kong, pp 347–353
2. Grasser B, Iberer F, Schreier G, Schaffellner S, Kastner P, Prenner G, Hipmair G, Wasler A, Petutschnigg B, Müller H, Hutten H, Schaldach M, Tscheliessnigg KH (1998) Intramyocardial electrogram variability in the monitoring of graft rejection after heart transplantation. PACE 21: 2345–2349
3. Grasser B, Iberer F, Schreier G, Allmayer T, Schaffellner S, Prenner G, Wasler A, Petutschnigg B, Müller H, Tscheliessnigg KH (1998) Intramyocardial electrograms for non-invasive rejection monitoring: initial experience with an infection-specific parameter. Transplant Int 11: 508–511
4. Iberer F, Grasser B, Schreier G, Schaffellner S, Prenner G, Allmayer T, Wasler A, Petutschnigg B, Müller H, Kastner P, Schaldach M, Hutten H, Tscheliessnigg KH (1998) Introducing a new clinical method for noninvasive rejection monitoring after heart transplantation to clinical practice: analysis of paced intramyocardial electrograms. Transplant Proc 30: 895–899