Impact of the Ventricular Evoked Response on Heart Transplants

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Summary

Orthotopic heart transplantation is currently a widely performed treatment for end-stage heart disease. Improved immunosuppressive therapy has resulted in prolonged survival of heart transplant recipients, but acute cardiac rejection remains a major cause of death. Endomyocardial biopsy is considered the most reliable method for early identification and monitoring of acute cardiac rejection, but it has some limitations, including risks to the patient, low sensitivity, and relatively high costs. Arbitrary intervals of biopsies may also delay the early detection of acute cardiac rejection. For these reasons, several noninvasive techniques to diagnose acute cardiac rejection have been examined, but none has been proven sufficiently sensitive or specific to replace endomyocardial biopsy. The ventricular evoked response recorded with unipolar endocardial pacing leads represents the summed signal of the action potentials of the surrounding myocardial cells. Therefore, variations in the myocardial action potentials caused by adrenergic stimulation of the myocardium ion current must be reflected in the ventricular evoked response morphology. Fractal coated pacing leads greatly facilitate ventricular evoked response-recordings because of their negligible polarization artifacts and wide-band frequency characteristics. The current results are considered preliminary, since the methodology has not received a final evaluation and the volume of data available up to now is very limited. The primary aim of the present results is to stimulate further acquisition of high-quality intracardiac electrograms and clinical data in order to promote continued investigation of this issue in the future.

Key Words

Heart transplant, acute cardiac rejection, endomyocardial biopsy, ventricular evoked response

Introduction

The current analysis was carried out in order to investigate the hypothesis that low values of the diagnostic computerized heart allograft recipient monitoring (CHARM) parameters, as routinely extracted from the ventricular evoked response (VER), are indicative of a poor prognosis heart transplantation (HTX). The present report provides results for those intramyocardial electrograms (IEGMs) recorded through April 2000 in the course of the CHARM project at the heart transplant center in Curitiba.

Materials and Methods

The IEGMs have been recorded with implanted pacemakers equipped with high-resolution ECG telemetry (Physios CTM01, Biotronik, Berlin) according to the CHARM protocol. The recorded signals have been processed automatically with the established Cortronik IEGM analysis system (Cortronik, Graz, Austria).

The VER parameter under investigation is the corrected T-slew rate of the VER as obtained from the right ventricular endo- or epimyocardial leads (the right ventricular rejection-sensitive parameter as displayed on the Curitiba patient reports). This parameter will be designated as VER_Tslew/c_V in the following, with the "c" indicating correction and the index "c_V" indicating that only signals recorded from the ventricular pacemaker channel (corresponding to a right ventricular lead position in patients with two ventricular leads) have been considered. Figure 1 shows the characteristic points of the VER as well as the definitions of the parameters under investigation. Table 1 shows the definitions of the VER parameters that are involved.

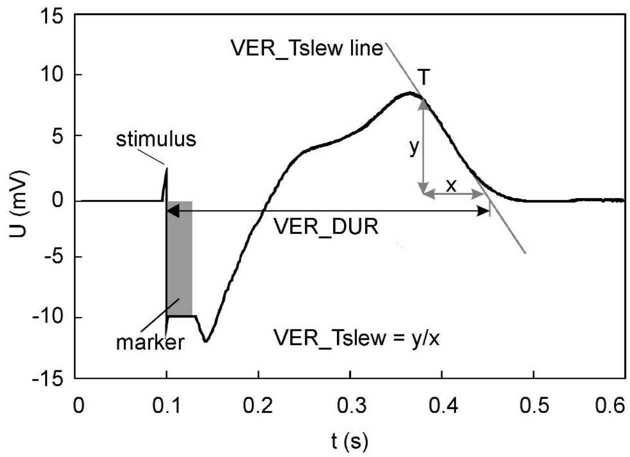

Figure 1. Automatically averaged ventricular evoked response (VER), as obtained from telemetrically recorded intramyocardial electrograms during pacing. The definitions of the relevant characteristic points and parameters are displayed.

Statistics

Differences between survivors and non-survivors were analyzed as follows. The VER_Tslew/c_V parameter values as obtained during the last follow-ups, either prior to death or prior to the deadline, were grouped with respect to survival according to individual patient status. The two-tailed t-test was used to determine significant differences between the parameter values in the group of survivors and non-survivors. Box plots are provided to help visualize these results. For analysis of the prognostic threshold, a single-threshold discrimination model was used to classify all patients based on the VER_Tslew/c_V values with respect to the survival data. The discrimination outcome was calculated for a number of possible thresholds in terms of the standard diagnostic indices. The threshold that maximized the diagnostic quality index (DQI = the geometric mean of sensitivity and specificity) was finally considered to be the best estimation for the threshold under which parameter values have to be considered indicative of a poor prognosis. For this optimized threshold (26 mV), which is designated as the prognostic threshold in the following study, the fourfold table, diagnostic indices, and the P value for the significance of the discrimination (χ^2-test) are provided.

In order to assess the frequency distribution of follow-ups with VER_Tslew/c_V values below the prognostic threshold, the number of such cases for each patient was calculated for the whole observation period as well as without the first 2 postoperative weeks (> 14th postoperative day). The analyses of deaths within 30 days are performed by repeating the analyses described above after excluding those patients who died but did not undergo a valid follow-up in the 30 days prior to death.

Results

As shown in Table 2, 22 patients are under evaluation. The list on Table 3 explains the meaning of the columns in Table 2. Differences between survivors and non-survivors are shown in Figure 2, and the prognostic threshold is shown in Table 4. Figure 3 and Table 5 show the results after restricting the analysis to only those patients with fatal outcomes who died no later than 30 days after the most recent follow-up.

Discussion

A number of previous studies on HTX patients have already indicated a close correlation between parameters extracted from the VER and clinical findings with

VER Parameter	Definition
VER_Tslew (mV/s)	= x/y, maximum slew rate as obtained from the VER_Tslew line (tangent to the falling part of the repolarization phase at the point of the maximum negative slew rate)
VER_DUR (s)	Duration of the VER as measured from the stimulus to the intersection of the VER_Tslew line with the baseline
VER_Tslew/c (mV)	= VER_Tslew x VER_DUR

Table 1. Definition of the VER parameters extracted from the averaged VERs.

Patient ID	Status	Date of death	Cause of death	Date of last follow-up	VER_Tslew/c_V (mV)	Days before death	Follow-ups ≤ 26 mV
cwb01	***exit***	***20.05.98***	***sepsis***	***03.02.98***	***34.2***	***106***	***5 (4)***
cwb02				13.12.99	50.0		
cwb03	exit	05.12.97	rejection	21.10.97	13.7	45	16 (16)
cwb04				24.02.00	30.7		7 (5)
cwb05				10.04.00	37.3		
cwb06				13.03.00	62.1		
cwb07				05.04.00	50.9		1
cwb08	***exit***	***14.06.99***	***pulm. rejection***	***22.03.99***	***35.6***	***84***	
cwb09	exit	26.07.97	acute rejection	30.06.97	14.8	26	3
cwb10		03.04.00			26.2		19 (17)
cwb11	exit	19.06.98	viral infection	26.05.98	25.3	24	11 (2)
cwb12		13.03.00			28.5		10 (4)
cwb13		05.04.00			36.5		2
cwb14		27.03.00			24.0		24 (16)
cwb15		10.04.00			31.3		
cwb16	exit	15.06.99	acute rejection	05.06.99	17.6	10	3
cwb17		05.04.00			34.2		15 (7)
cwb18	exit	24.04.00	pulm. rejection	05.04.00	24.7	19	2 (1)
cwb19	exit	26.12.99	car accident	29.11.99	23.7	27	5 (2)
cwb20		05.04.00			40.5		2
cwb22	***exit***	***30.04.00***	***acute rejection***	***09.03.00***	***51.2***	***52***	

Table 2. Comprehensive data on all patients who were included for statistical analysis. Patient 21 is not listed here because there were problems with the right ventricular lead; hence, only left ventricular IEGMs could be recorded.

respect to rejection [2,4,6,7]. Specificity, however, was found to be limited, since the method is sensitive not only to rejection but also to other pathological conditions including infection, right heart failure, etc. One theory indicates that low absolute values are generally associated with a bad outcome. This hypothesis could already be supported by initial analyses based on another HTX data pool [5]. The present investigation was performed in order to elucidate further the prognostic impact of the VER after heart transplantation.

Table 4 indicates that significantly lower parameter values have been observed during the last follow-up for patients who subsequently passed away. According to Figure 3, if the threshold discrimination model is used, one can establish a prognostic threshold that is able to indicate high-risk cases with high significance and reasonably high diagnostic indices.

A closer look at the three patients who had false negative cases with VER_Tslew/c_V values above the prognostic threshold despite a fatal outcome (rows bold italic in Table 2) reveals that those patients had not undergone a valid follow-up for quite a long period of time, i.e. 52, 84, and 106 days before death. It can be assumed that a correlation between the electrophysiological state - as assessed by a certain IEGM recording - and the clinical state of the transplant will persist only for a limited time. Therefore, a sufficiently high recording frequency is mandatory in order to allow an evaluation of the patient's status. Based on the current data, it seems justified to set the maximum interval between follow-ups in otherwise uneventful patients at about 30 days.

On the other hand, the data in brackets in the right-hand column in Table 2 show that most of the surviving

Column	Meaning	
Patient ID	patient identification	
Status	[empty], alive	patient is still alive at the deadline
	exit	patient passed away
	pm_ex	pacemaker explanted
Date of death	as extracted from the survival data	
Cause of death	as extracted from the survival data	
Date of last follow-up	date of the last follow-up, either before death or before the deadline up to which the data have been included into the statistical analysis	
VER_Tslew/c_V	the value of the duration - corrected VER_Tslew rate parameter as obtained from the right ventricular VER (ventricular pacemaker channel) from the last follow-up	
Days before death	number of days between the last valid follow-up and death	
Follow-ups ≤ 26 mV	number of all follow-ups with parameter values below the prognostic threshold, numbers in brackets indicate how much of these follow-ups occurred after postoperative day 14	

Table 3. Meaning of the columns in Table 2.

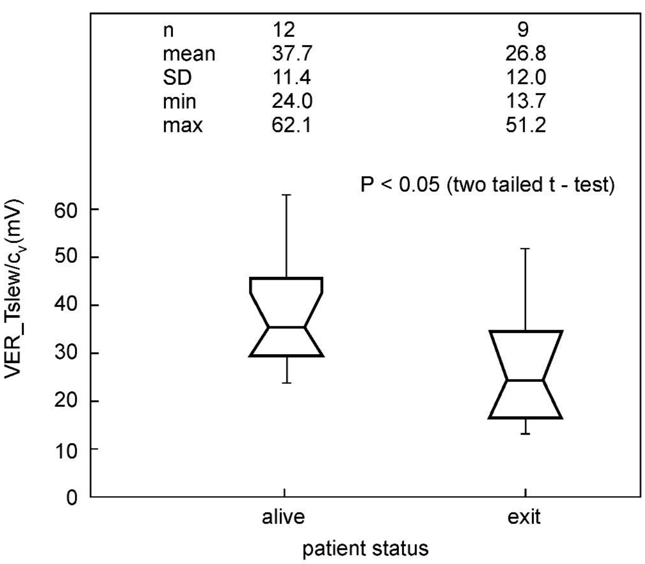

Figure 2. Differences between survivors and non-survivors: Statistics on the VER_Tslew/ c_V values grouped with respect to survival, indicating that those patients who died exhibited significantly lower parameter values during the final follow-up. The horizontal lines from bottom to top mean: the lower limit, the 25th quartile, the median, the 75th quartile, and the upper limit. n = number of patients; SD = standard deviation; min = minimum; max = maximum; and P = significance level.

patients temporarily exhibited parameter values below the prognostic threshold. This occurred particularly, but not exclusively, during the early postoperative period. From this behavior it can be concluded that through appropriate treatment, patients can recover from this risky situation. Hence, physicians are requested to closely examine a patient who exhibits consistently low parameter values and to use the proposed method in order to monitor the success of any associated therapeutic action.

The parameter under investigation, the corrected maximum slope of the repolarization phase of the VER as recorded from the right ventricular lead (VER_Tslew/c_V), is already being used as the primary diagnostic parameter. The most recent parameter value is shown as the last point of the trend curve of the "Rejection Sensitive Parameter /c", as displayed in the lower panel on the right-hand side, as well as in the respective row of the parameter value table on the upper part of the report (see Figure 4). The right ventricular lead has been chosen for the following two reasons:

- Previous investigations based on the data pools of other HTX centers have indicated that these signals

P < 0.01	Alive	Exit	Sum
VER_Tslew/c_V > 26 (mV)	11	3	14
VER_Tslew/c_V ≤ 26 (mV)	1	6	7
Sum	12	9	21

SENS	67 %
SPEC	92 %
NPV	79 %
PPV	86 %
DQI	78 %

Table 4. Prognostic threshold: Fourfold table corresponding to the application of a single threshold in order to discriminate between patients who survived and patients who died. Using an optimized prognostic threshold of 26 mV for the VER_T-slew/cV revealed the displayed diagnostic indices. SENS = sensitivity; SPEC = specificity; NPV = negative predictive value; PPV = positive predictive value; and DQI = diagnostic quality index. The P value obtained with the χ^2-test indicates a significant correlation between the classification by survival and by using the VER_Tslew/c_V values.

P < 0.001	Alive	Exit	Sum
VER_Tslew/c_V > 26 (mV)	11	0	11
VER_Tslew/c_V ≤ 26 (mV)	1	4	5
Sum	12	4	16

SENS	100 %
SPEC	92 %
NPV	100 %
PPV	80 %
DQI	96 %

Table 5. The same analysis as the one shown in Table 4 but excluding patients without a valid follow-up within 30 days prior to death as well as patient cwb19 who died after a car accident

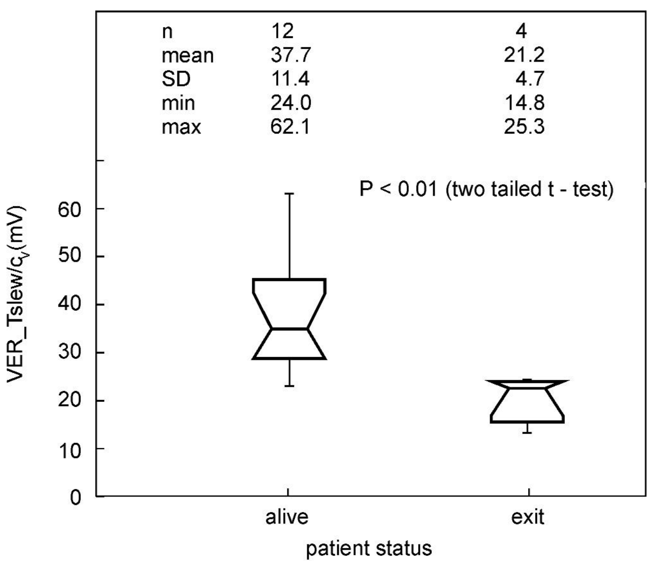

Figure 3. The same analysis as the one shown in Figure 2 but excluding patients who did not undergo a valid follow-up within the 30 days prior to death, and patient cwb19 who died after a car accident.

exhibit a higher prognostic impact than for left ventricular leads, possibly due to better standardization of the right ventricular lead positions.

- In patients with transvenous leads, only right ventricular signals are available.

One must keep in mind that a lead's position strongly influences the absolute values of the parameter. However, due to a limited number of patients available for the present analysis, a separate analysis of patients with transvenous leads (nine patients) and epimyocardial leads (12 patients) has not been performed; all patients were pooled into a single group. For the same reason, the present analysis did not consider different causes of death. However, looking at the very low parameter values of the two patients who died of acute cardiac rejection within 30 days after the most recent follow-up, i.e. patients cwb09 (14.8 mV), and cwb16 (17.6 mV), indicates that acute rejection is, of course, a pathological effect covered by the prognostic concept. Moreover, acute rejection, due to its direct effect on the transplant, seems to be one of the strongest influencing factors on the VER. Patient cwb22, who also died of acute rejection 66 days after HTX, does not pose a problem for this theory (in spite of having a value of 51.2 mV) since the most recent follow-up in this patient was conducted more than 50 days prior to death, which is obviously much too long to monitor an

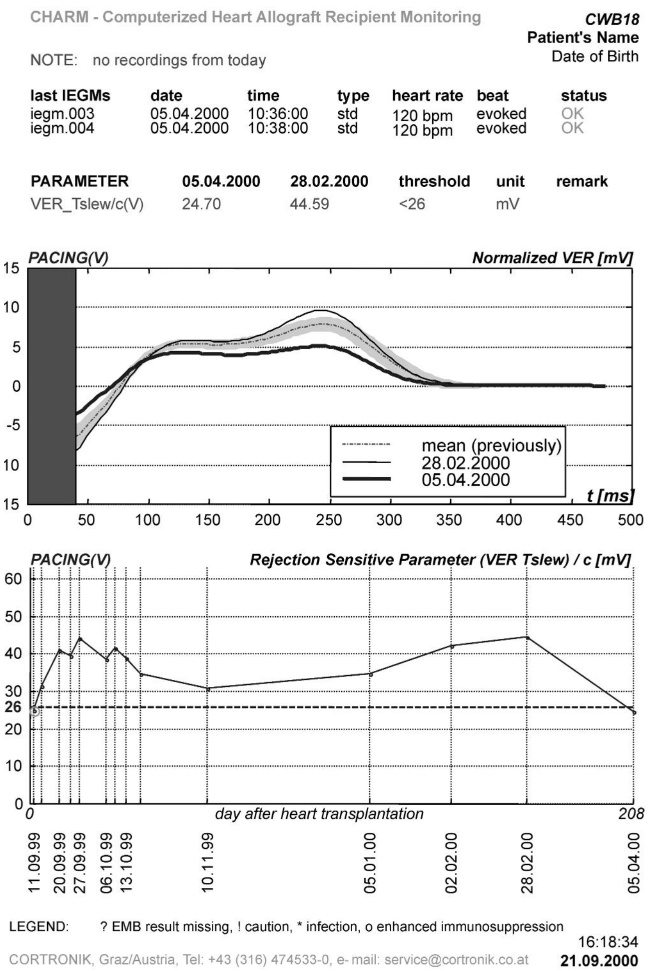

Figure 4. CHARM report of patient CWB18 who died 19 days after the last recording when the VER_T-slew/c fell below the threshold of 26 mV. The upper panel shows the signal morphology of the most recent recording compared to those of previous recordings.

acute effect like rejection or other potential cardiac risk factors, particularly during the early postoperative period.

The current prognostic threshold of 26 mV is a first estimation of the optimal threshold based on the data that are currently available, and will be confirmed or modified when new data become available.

Conclusion

Correlating the VER_Tslew/c_V values that were obtained during the most recent follow-up with the outcome in patients after HTX indicates the strong prognostic impact of this parameter. A prognostic threshold can be established with lower parameter values that are strongly indicative of impending complications or a bad outcome. In such case, patients should be carefully examined and closely monitored. In order to exploit the monitoring capabilities fully, CHARM follow-ups must be performed at regular and sufficiently short intervals. As a general and important recommendation that is in accordance with our present knowledge, the interval between follow-ups should not exceed 30 days.

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