学位論文

「Novel implantable device to detect cardiac allograft rejection (心臓移植後拒絶反応を早期検知しうる機器の開発)」

指導教授名　宮地 鑑

申請者氏名　宝来 哲也

著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

Novel Implantable Device to Detect Cardiac Allograft Rejection
（心臓移植後拒絶反応を早期検知しうる機器の開発）

論文要旨

背景：
臓器移植後の拒絶反応は、治療成績、予後を左右する重要な因子である。我々の開発した Soul Mate は、移植後心臓に留置された電極線より得られた心筋心電図をワイヤレスで送信のできる埋め込み型の機器である。本実験の目的は、送信された心電図データを解析することにより、移植後の拒絶反応の早期検知を可能とすることである。

方法：
5 頭の犬に、異所心臓移植術を施行し同時に Soul Mate のモニター機器を埋め込んだ。移植後、一定期間後に免疫抑制剤を中止し拒絶反応を誘発した。同時に心筋生検を定期的に行い、拒絶反応の Grade を病理診断した。Soul Mate から得られた心筋心電図波形の 9 個のパラメーター値の変化より、拒絶反応スコアを計算し、病理結果と比較した。

結果：
5 個のパラメーターより得られた拒絶反応スコアは、実際の病理診断と有意な相関があった。さらに有意相関のあった 5 パラメーターの中央値は、病理診断結果と最も強い相関（$r=0.939$, $p<0.001$）が認められ、また、心筋生検病理にて拒絶診断の得られる 1 日前の時点で、感度 85.7%、特異度 100%で拒絶反応を検知しえた。

結論：動物実験モデルにおいて、Soul Mate 拒絶反応モニター機器は、心臓移植後の拒絶反応を非侵襲的に検知することが出来た。Soul Mate は、心臓移植後の拒絶反応を、高頻度にかつ鋭敏に診断しうる機器として使用が可能であることが示唆された。

目次

1. Background

Each year approximately 5,000 patients worldwide undergo heart transplantation (HTx). Despite improved immunosuppressive therapy, acute and chronic allograft rejection remains the most significant factor limiting the success of HTx. Early, precise, and accurate detection of rejection, with subsequent effective management, is important to minimize allograft damage and prolong morbidity-free survival. Currently, the most reliable technique for the diagnosis of acute allograft rejection is endomyocardial biopsy (EMB). However, because of its cost, associated complications, invasiveness, and inability to completely survey the allograft, EMB falls quite short of optimal diagnosis of rejection and, more, does not allow for compulsive daily monitoring. Also, EMB can be performed only in specialized centers, and results are not immediately available. Other simpler, less invasive, more sensitive methods for detecting rejection in real time are critically needed. Electrical activity of the heart is closely related to its functional state, and analysis of intramyocardial electrocardiography (IMEG) has been considered sensitive and specific for allograft rejection [1-4]. The peak-to-peak amplitude (PPA) of the unipolar IMEG has been shown sensitive to a variety of alterations in myocardial physiology [1-6] but has been limited by the inability to easily transmit large quantities of continuous monitoring data. Signal-averaged electrocardiography has helped in the management of HTx rejection in clinical applications [7-9], but it is difficult to perform and not frequently done.

TransWorld Heart™ Corporation (Charlotte, NC, USA) recently developed the Soul Mate® Heart Transplant Monitoring System to monitor electrophysiologic changes with the aim of allowing earlier diagnosis of graft rejection and help with acute and long-term patient management. The Soul Mate uses wireless information

transmission to a centralized data reduction center with Internet accessible daily analysis of nine IMEG parameters recorded from six vectors of the heart. The purpose of this study was to assess the efficacy of this novel device to detect cardiac allograft rejection nonivasively in a canine model.

2. Methods

2-1. Device Description

The Soul Mate Heart Transplant System (Figure 1) records and transfers IMEG data to the TransWorld Central Monitoring Center. The Cardiac Rejection Monitoring Device (CRD™) records IMEG signals through three standard leads, at programmable times of up to 2 min in either bipolar or unipolar configurations. One lead is placed on the epicardial surface of the right ventricle (RV) and two on the left ventricle (LV). The device records information of the following nine IMEG parameters (Figure 2) from QRS complexes for each ventricular configuration at the frequency of 1,000 Hz: Area under dominant peak (AUDP) [mV • ms], area under minor peaks (AUMP) [mV • ms], area under the curve (AUC; sum of AUDP and AUMP) [mV • ms], base to dominant peak amplitude (BDPA) [mV], PPA [mV], nadir electrocardiogram duration (NED) [ms], total electrocardiogram duration (TED) [ms], slew rate of dominant peak upslope (SRDPU) [mV/ms], and slew rate of dominant peak downslope (SRDPD) [mV/ms].

Data transfer is achieved by holding the OneLife® Wand over the CRD, and stored data are transferred to the Wand via telemetry. The data are then transferred from the Wand to the Home Call Box through a Bluetooth wireless connection. For data analysis, the Home Call Box automatically sends the data to the Central Monitoring Center.

2-2. Experimental Design

The study protocol was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee. All animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, D.C., 1996).

Five mongrel dogs weighing 26.0 ± 1.6 kg underwent heterotopic cervical HTx [10-12], receiving allografts from five dogs weighing 8.9 ± 0.9 kg. After the HTx and CRD implantation, data were collected and stored automatically by the CRD every 4-6 h and transferred to the TransWorld Central Monitoring Center twice a day.

Biopsy specimens were taken at regular intervals to determine biopsy rejection grade (BG), and the results were compared with analyzed data to evaluate the efficacy of the device.

2-3. Surgical Procedures

Donor dogs were anesthetized with 15 mg/kg of intravenous thiopental, ventilated through an endotracheal tube, and placed in the right lateral position. Through a left thoracotomy, the heart was harvested using potassium crystalloid cardioplegia and placed in cold saline. An atrial septal defect was created by removing the foramen ovale, and the mitral leaflets were removed to create mitral regurgitation. Cardioplegia solution was injected every 20 min.

The recipient dogs were anesthetized with 3 mg/kg of intravenous propofol, intubated and placed on the left side. The right common carotid artery and external

jugular vein were exposed. The brachiocephalic trunk of the donor dog's explanted heart was anastomosed to the recipient's carotid artery in an end-to-side fashion under systemic heparinization (100 U/kg). The donor's main pulmonary artery was anastomosed to the recipient's right jugular vein. After the HTx was completed, screw-in myocardial leads were placed on the lateral wall and posterior wall of the LV and the RV free wall of the donor heart. The leads were tunneled subcutaneously and attached to the CRD, which was placed in the subcutaneous pocket on the back of the animal.

2-4. Immunosuppressive Protocol

The animals were given methylprednisolone (500 mg) during the HTx procedure. On the day of the HTx, oral immunosuppressive therapy was started, consisting of cyclosporine (20 mg/kg/day) and prednisone (0.5 mg/kg/day). The dosage of cyclosporine was adjusted to therapeutic blood levels between 400 and 600 ng/ml. Cyclosporine was discontinued at either 22 or 24 days after the HTx with exception of two animals that were sacrificed during this period of immunosuppressive therapy. Prednisone was continued at the same dose during the entire postoperative course to prevent rebound adrenal insufficiency.

2-5. Surveillance EMB and Pathological Evaluation

Follow-up biopsies were performed through an incision under local and general anesthesia. Three to four full-layer biopsy specimens were taken from the ventricular septum with a biopsy needle (Tru-Cut Biopsy Needle, 18G, Cardinal Health) and fixed in 10% buffered formalin. During the period of cyclosporine administration, a biopsy

study was performed three times per week. After cessation of cyclosporine, daily biopsy studies were performed until the allograft stopped beating.

All biopsy specimens were sectioned at three step levels, stained with hematoxylin and eosin and evaluated for the presence or absence of rejection by a cardiac pathologist, blinded to the status of immunosuppressive therapy, external findings of the allograft, and the data from the device. BG was determined according to the revised classification scheme of the International Society for Heart and Lung Transplantation (ISHLT) [13]. In brief, rejection is classified as Grade 0R (none), 1R (mild), 2R (moderate), and 3R (severe).

2-6. Data Analysis

The median of the noninvasively transmitted IMEG values was obtained during each recording session for 1 day per lead configuration as representative of a single parameter for that day. Two possible input sources were evaluated for each parameter, including the median of the normalized values obtained from six configurations (three ventricular leads in both unipolar and bipolar mode) and from four configurations, excluding the RV lead. In addition, a calculation was performed by taking the parameter "General Median," which was the median of the individual medians of the five parameters (AUC, AUDP, BDPA, PPA, and SRDPU) as input. A sliding baseline consisted of the average values of one parameter over three consecutive days prior to the actual considered date. Calculated rejection grade (CG) 2 was deemed to exist when the value of the parameter was between 50% and 70% of the baseline, and CG 3 when the value was lower than 50%. When the value of a single parameter fell with an

average slope higher than 8% per day or the animal was in CG 2 or 3, the baseline remained frozen.

CGs were obtained each day and compared with BGs taken on the corresponding date. Analysis was also performed between BG and CG just 1 day prior to the acquisition of biopsy data to determine the capability of the Soul Mate as an early rejection detecting device. Correlation coefficients between BG and CG for each parameter were analyzed using SPSS software (version 11.5J, SPSS, Inc., Chicago, IL).

2-7. Statement of Responsibility

I had full access to and take full responsibility for the integrity of the data. All study participants have read and agree to the manuscript as written.

3. Results

The experimental course of each of the five animals, including ISHLT grades of rejection for biopsy specimens, is shown in Figure 3. After the third post HTx day, 44 biopsies were obtained. Figure 4 shows representative histological findings of biopsy specimens taken from experimental animal 2 on day 2, 12, 28, and 31 postoperatively. These findings demonstrate no, mild, moderate, and severe rejection, respectively.

During the experiments, 69,035 individual heartbeats were recorded and analyzed. The six parameters (AUC, AUDP, BDPA, PPA, SRDPU, and General Median) successfully detected rejection in experiments 2 and 3. In experiment 1, the six parameters reported grade 2 rejections not detected by biopsy on the day of the termination, although the allograft had stopped beating, probably because of ischemia caused by a thrombus in its aortic root. In experiment 2, detection was 1 day earlier in

three parameters (AUD, AUDP and General Median) with four configurations, but there was one false-negative episode by the device on day 5. In experiment 3, rapid progression of allograft rejection was observed, leading to complete graft failure and cardiac arrest on day 10. Detection of rejection occurred 2 days earlier than by biopsy in six parameters with four configurations (not considering the RV lead). In experiments 4 and 5, progressive rejection was not observed even after cessation of immunosuppressive therapy. Figure 5 shows examples of the changes in 6 IMEG parameters with time after heart transplantation obtained in experiments 2, 3 and 5 from four configurations.

Table 1 details the comparisons between BG and CG obtained through the General Median parameters from six configurations and four configurations. When rejection grades are classified as negative (grade 0 or 1) or positive (grade 2 or 3), the corresponding diagnostic indices had a sensitivity of 85.7% and a specificity of 97.3% based on data from six configurations, and a sensitivity of 85.7% and a specificity of 91.9% based on data from four configurations. When BG was compared with CG, obtained 1 day prior to biopsy, the indices had a sensitivity of 71.4% and a specificity of 100% based on data from six configurations, and a sensitivity of 85.7% and a specificity of 100% based on data from four configurations. In Table 2, correlation coefficients between CG and BG using each parameter are shown. Significant correlations ($r > 0.75$, $p < 0.001$) were obtained between the biopsy results and the six parameters (AUC, AUDP, BDPA, PPA, SRDPU, and General Median). In the rest of the four parameters, there were no correlations higher than 0.7. The strongest correlation ($r = 0.939$) was obtained using the General Median with four configurations 1 day prior to obtaining the biopsy data.

4. Discussion

A decline in R-wave amplitude from a surface 12-lead electrocardiogram has been considered indicative of organ rejection since the early years of HTx. This decline likely reflects a decrease in functional myocardial cell mass as a result of myocyte injury and necrosis, which occurs with moderate to severe inflammation caused by rejection. Several reports suggest that IMEG recordings are more sensitive and specific for diagnosing graft rejection [1-6, 11]. Recently, IMEG monitoring has been clinically applied for patient management after HTx [14-16]; however, the Soul Mate system has several significant advantages over this method, as it can measure, analyze, and transmit nine IMEG parameters from six vectors. Of nine parameters, five were significantly ($r > 0.75$, $p < 0.001$) correlated to biopsy results and demonstrated the Soul Mate's ability to make an early diagnosis of allograft rejection. By applying the General Median parameter, the strongest correlation coefficient was obtained when BG was compared with CG obtained 1 day prior to biopsy. The sensitivity of 85.7% and specificity of 100% to determine biopsy-proven cardiac allograft rejection demonstrated the capability of this device to more effectively and safely monitor heart transplant patients. Indeed, we believe that the ability of this device to provide more frequent recording of parameters that characterize allograft rejection will allow earlier diagnosis of significant rejection episodes requiring ad hoc immunosuppressive therapies as well as critical fine-tuning of day-to-day maintenance immunosuppressive strategies.

Unfortunately, contemporary management of patients post HTx relies primarily on a "cookbook" approach, with standard multidrug protocols usually prescribed to prevent rejection and maintain graft integrity and optimal function. Immunosuppressive

drugs, however, are toxic and cause renal and hepatic insufficiency as well as the risk of infection and malignancy in these patients that is directly related to the degree of immunosuppression prescribed [17]. Management of immunosuppressive strategies by EMB does not enable daily fine tuning of drug administration and doses that follow a minimalist strategy. The Soul Mate can fulfill this challenge. Indeed, it reported rejection not detected by biopsy on the days of experiment termination. In the absence of significant cellular rejection, allograft failure in this animal could be explained by ischemia from the autopsy findings. However, it may also be explained by the occurrence of antibody-mediated rejection, which, without additional immunohistochemical stains, routine EMB cannot detect. Indeed, in a previous animal study [12], the sensitivity of IMEG was much higher than that of EMB (100% vs. 12.5%) to detect antibody-mediated rejection.

For early detection of rejection, six parameters with four configurations (not considering the RV lead) appear to have provided the best results. In contrast, Everett and associates [6] concluded that the sensitivity of detecting rejection increased with the increase in the number of leads, using unipolar PPA as a parameter in their animal study. We believe that using the input source without considering the RV lead enables earlier detection of rejection.

One important limitation of this study is that we employed a heterotopic rather than an orthotopic HTx model. The effects of preload and afterload on the course of allograft rejection can be debated. Since the primary purpose of our experiment was to prove the concept that IMEG can detect and quantitate cardiac allograft rejection, we preferred this approach because the graft would not be burdened by the need to maintain an adequate hemodynamic load to sustain animal survival. Another limitation may be

the fact that the immunosuppressive therapy used in this study was not entirely consistent with that employed in humans and that the donor dogs were not crossmatched with recipient dogs. The allograft in experiment 3 suffered from severe rejection and stopped beating on day 10, even though therapeutic cyclosporine blood concentration levels were noted and would have been predicted to have prevented this event (Figure 3). In contrast, the allograft in experiment 4 demonstrated only mild rejection 9 days after the cessation of cyclosporine. Another limitation is that the optimum "cut offs" to determine CG grades (>50 and 70% baseline) and the 5 IMEG parameters used to derive General Median parameter were determined after the study. Also these optimized values are specific to this animal model and may be different for human transplant rejection. Further studies, especially in human, will be necessary to validate the proper cut offs and the IMEG parameters for the General Median calculation.

Finally, the number of animals was small, and the duration of each experiment was short. Further studies are warranted to evaluate the effects of myocardial and electrode fibrosis changes, diastology changes, ischemia (transplant vasculopathy), and/or infection on the sensitivity and accuracy of chronic IMEG parameter measurements to detect rejection. In addition, the effects of therapeutic interventions (such as bolus steroids) on the IMEG parameters have to be evaluated. To further validate results, human clinical trials would be a next step, given the probable safety of the device as extrapolated from experiences with simple pacemakers and defibrillators in HTx patients and demonstration that the unit can detect and monitor acute rejection, as well as transmit data via telemetry.

5. Conclusions

We conclude that the Soul Mate cardiac allograft rejection monitoring system demonstrated the capability, in real time, to accurately and noninvasively detect early acute allograft rejection in a heterotopic canine model. This approach could be used as a noninvasive tool for guiding the frequency and timing of obtaining an EMB. This device would potentially reduce the number of biopsies needed and result in earlier detection and treatment of rejection. Indeed, it is possible that the device could actually replace EMBs and allow vastly more frequent allograft rejection assessment that would assist the clinician with day-to-day, evidence-based adjustments of complicated and toxic immunosuppression cocktails. Further, using the transtelephonic measurements could be beneficial for patients who can be monitored at great distances from the transplant center. There is a potential that the Soul Mate system would offer a method for less invasive and more effective management of HTx patients.

6. Acknowledgments

I am grateful to Dr. Kiyotaka Fukamachi, Lerner Research Institute, Cleveland Clinic, USA, for supervising the present study.

7. References

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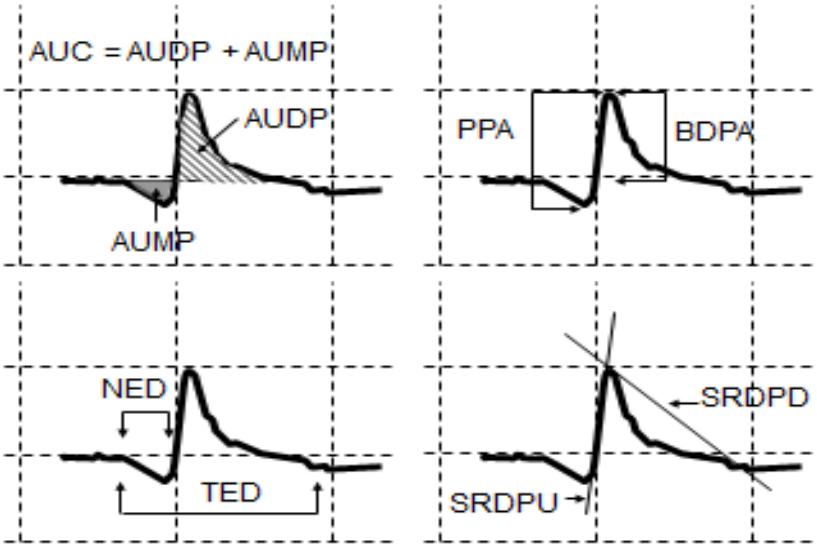
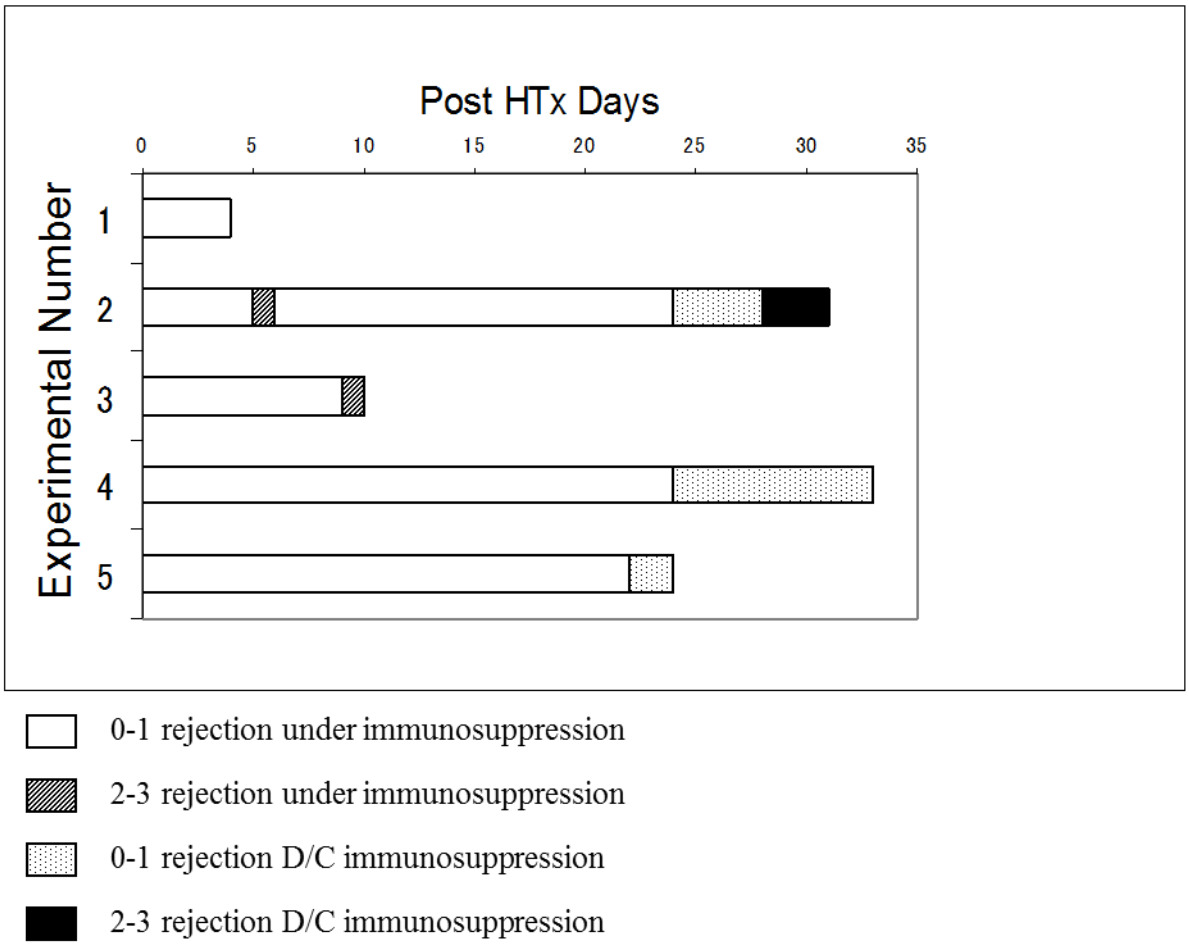
8. Figures

8-1. ***Figure 1.*** The components of the Soul Mate Heart Transplant System.

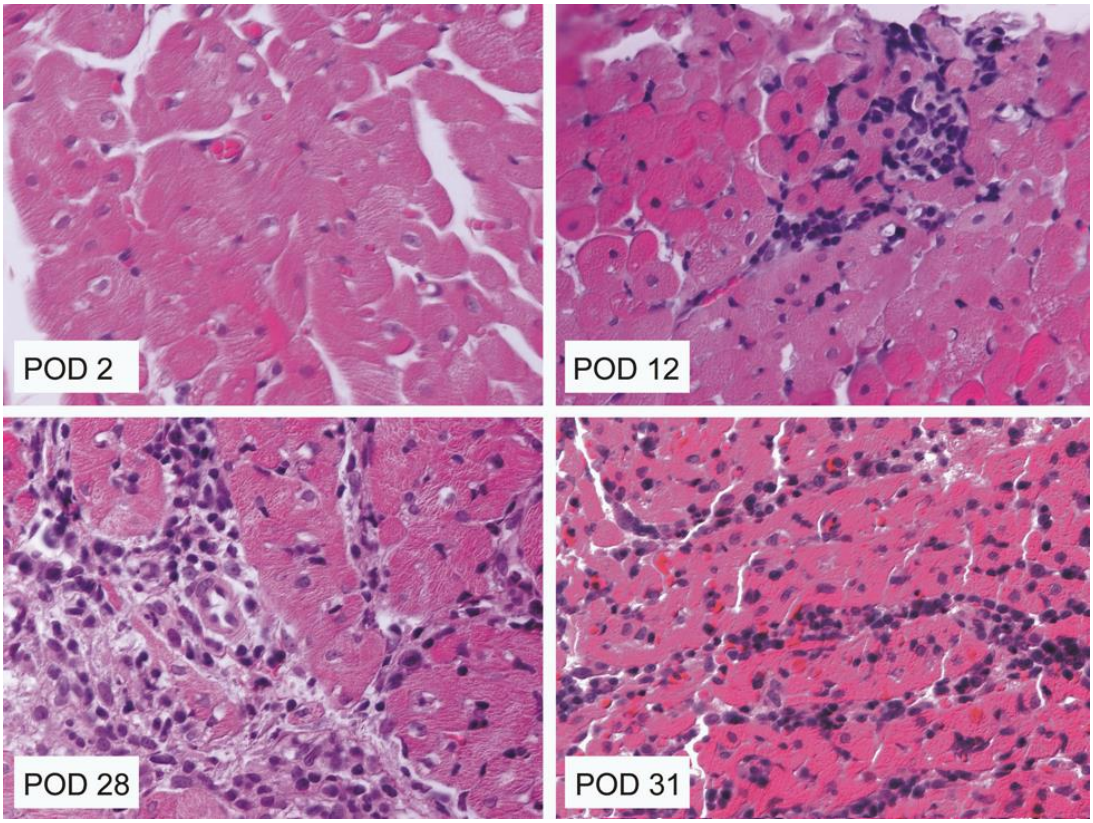
8-2. ***Figure 2***. Nine IMEG parameters, recorded and analyzed.



8-3. *Figure 3.* Summary of the experimental time course of the five dogs. In experiments 1 and 3, the animal was sacrificed before the cessation of the cyclosporine regimen. In experiments 2, 4, and 5, cyclosporine administration was stopped on POD 24, 24, and 22, respectively. D/C, discontinuance; POD, postoperative day**.**



8-4. ***Figure 4***. Histological findings from biopsy specimens (experiment 2). These slides from postoperative days (POD) 2, 12, 28, and 31 after HTx are representative of no rejection, mild rejection, moderate rejection, and severe rejection, respectively (hematoxylin and eosin × 400).



8-5. *Figure 5*. The daily changes in the ratio of the 6 individual IMEG parameters over their sliding baseline in the cases where rejection occurred (Figure 5a: Experiment 2 and Figure 5b: Experiment 3) and in the case where rejection did not occur (Figure 5c: Experiment 5). The y axis value is a measure of the degree of increase or decrease in the recorded IMEG parameter from its sliding baseline (average value recorded over the previous 3 days). The black vertical line indicates the day when immunosuppression was ceased. CG in the x-axis is from General Median data.

Figure 5a

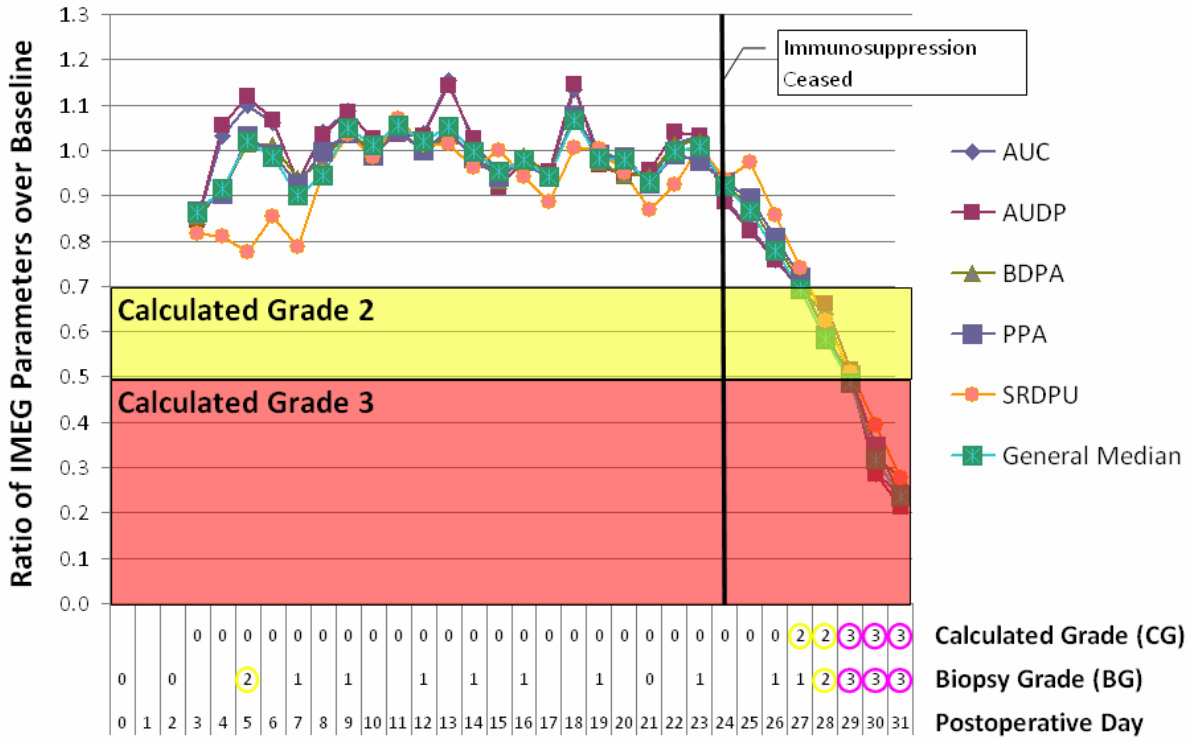


Figure 5b

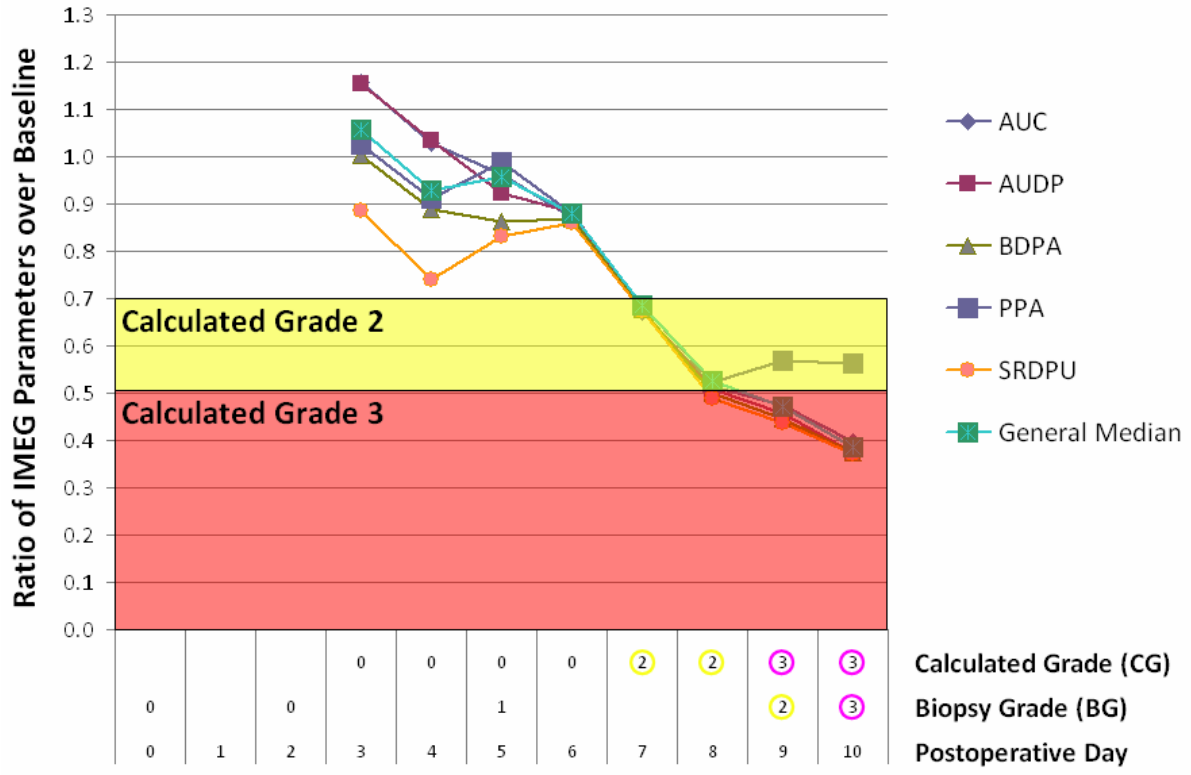
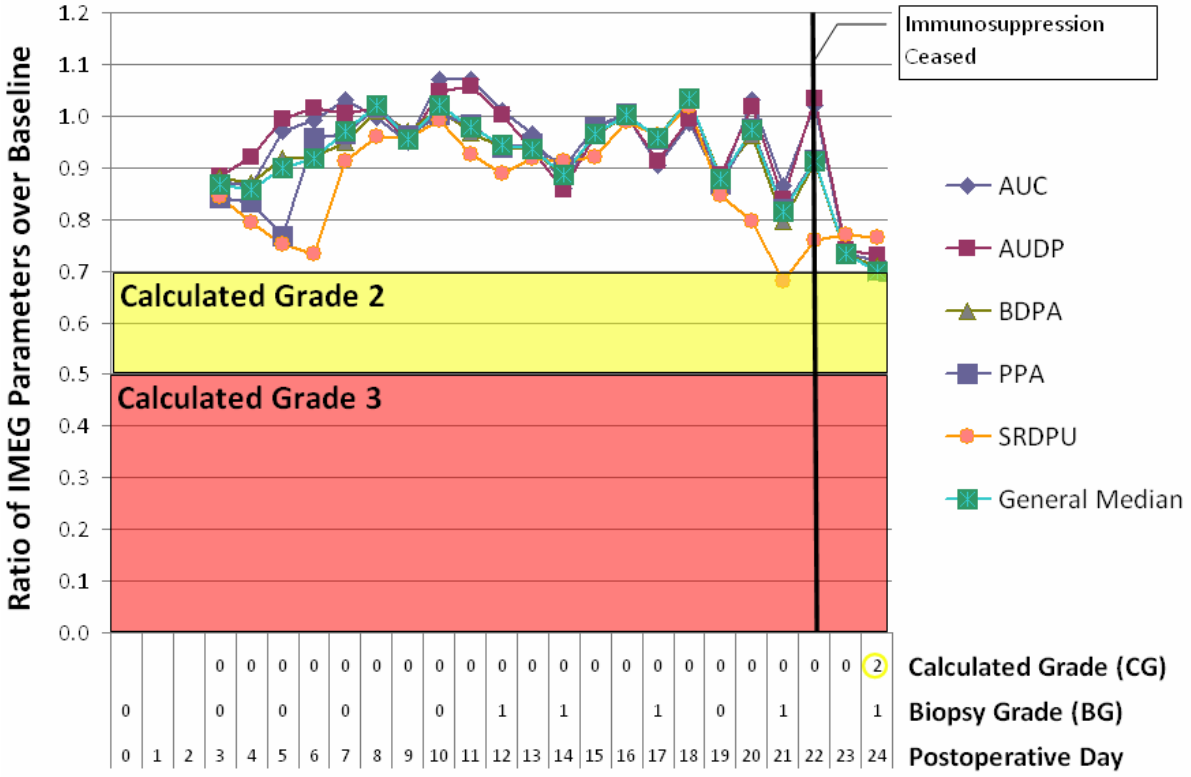


Figure 5c



9. Tables

9-1. ***Table 1.*** *Comparison between biopsy grade and calculated grade*

Configuration/Parameter	CG 0 or 1	CG 2	CG 3
Six configurations			
BG 0	7	1	0
BG 1	19	0	0
BG 2	1	2	0
BG 3	0	1	3
Four configurations			
BG 0	7	1	0
BG 1	27	2	0
BG 2	1	1	1
BG 3	0	0	4
Six configurations			
(1 day prior to biopsy)			
BG 0	8	0	0
BG 1	29	0	0
BG 2	2	1	0
BG 3	0	3	1
Four configurations			
(1 day prior to biopsy)			
BG 0	8	0	0
BG 1	29	0	0
BG 2	1	2	0
BG 3	0	1	3

CG, calculated rejection grade; BG, biopsy rejection grade

9-2. *Table 2.* *Correlation coefficient results*

Config-urations	AUC	AUDP	BDPA	PPA	SRDPU	General median	AUMP	NED	TED	SRDPD
6 Conf.[a]	**0.834****	**0.833****	**0.885****	**0.870****	**0.832****	**0.885****	0.122	0.354*	0.550**	0.551**
4 Conf.[b]	**0.787****	**0.834****	**0.896****	**0.817****	**0.837****	**0.820****	-0.228	-0.009	0.550**	0.571**
6 Conf. day-1[c]	**0.869****	**0.931****	**0.881****	**0.881****	**0.763****	**0.881****	0.175	0.387*	0.397*	0.628**
4 Conf. day-1[d]	**0.884****	**0.931****	**0.890****	**0.881****	**0.852****	**0.939****	-0.17	0.084	0.397*	0.628**

Correlation coefficient using the data obtained from [a]all six configurations, [b]four configurations excluding the RV lead, [c]all six configurations 1 day prior to the biopsy data, and [d]four configurations, excluding the RV lead, 1 day prior to the biopsy data.

AUC, area under the curve; AUDP, area under dominant peak; BDPA, base to dominant peak amplitude; PPA. peak to peak amplitude; SRDPU, slew rate of dominant peak upslope; AUMP, area under minor peaks; NED, nadir electrocardiogram duration; TED. total electrocardiogram duration; SRDPD, slew rate of dominant peak downslope.

The data in bold indicate $r > 0.75$

$*p < 0.05$, $**p < 0.001$