CARDIOTHORACIC TRANSPLANTATION

EARLY DETECTION OF ACUTE ALLOGRAFT REJECTION BY LINEAR AND NONLINEAR ANALYSIS OF HEART RATE VARIABILITY

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Objective: The first months after orthotopic heart transplantation are associated with the highest risk of acute allograft rejection. This study explores the utility and reliability of linear and novel nonlinear metrics of heart rate variability as predictors of graft rejection. The underlying hypothesis is that the transplanted heart, in response to inflammatory mediators, alters the dynamic properties of its rhythm-generating system.

Methods: In a cross-sectional study of 45 patients who had undergone heart transplantation, spanning a period of 4 months after the operation, heart rate variability was examined by time- and frequency-domain analysis. The nonlinear features of heart rate variability were studied by computing a pointwise correlation dimension of R-R interval time series. The results of heart rate variability analysis were compared with those of endomyocardial surveillance biopsy studies using the International Society for Heart and Lung Transplantation scoring system.

Results: Duration of heart transplantation itself exhibited a significant ($P < .05$) association with the onset of rejection. Specific predictors of acute rejection based on heart rate variability were identified, including shortening of the R-R interval (from 700 ± 68 to 648 ± 72 ms), an increase in the ratio of low-frequency (0.04-0.15 Hz) to high-frequency (0.15-0.40 Hz) spectral power (from 0.3 ± 0.2 to 0.6 ± 0.4), and a decrease in pointwise correlation dimension values (from 1.7 ± 0.7 to 0.9 ± 0.3 units). Multivariable logistic regression analysis ($R^2 = 0.4$) revealed that the only significant independent risk predictors were pointwise correlation dimension (odds ratio, 2.2 per 0.1 unit) and duration of heart transplantation (odds ratio, 1.7 per week).

Conclusion: Nonlinear measures of heart rate variability provide noninvasive means for identifying patients undergoing cardiac transplantation with acute rejection, thereby enabling the assessment of the time-dependent adaptive response of the donor heart to its host. (J Thorac Cardiovasc Surg 2000;120:737-45)

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Cardiac transplantation is now an accepted form of treatment for end-stage heart disease. In addition to the shortage of donor availability, a remaining persistent problem is the immunologic conflict between the recipient host and the donor heart organ. With the advent of effective immunologic therapy, the ability for early detection of the onset of rejection is expected to directly affect the survival of patients after heart transplantation (HTX). To date, the standard clinical criterion for diagnosing rejection remains endomyocardial surveillance biopsy. The invasive nature of this technique precludes it from being used on a more regular (ie, daily) basis to monitor and detect early changes in allograft immunologic status. A number of noninvasive

alternatives have been pursued to minimize the risk and cost of this demanding diagnostic procedure.^{1,2} The common problem inherent to many of these noninvasive techniques is that, for the purposes of critical decision making, they are lacking in requisite sensitivity and specificity. Nevertheless, there is much to learn from some of the more promising attempts. Importantly, the techniques applied to detect specific changes in the intrinsic properties of the heart, such as indium-labeled antimyosin antibody scanning studies¹ or high-resolution electrocardiographic analysis,² proved to be superior to methods designed to estimate systemic variables, such as cardiac pump function or biochemical-immunologic indices. The primary motivating factor for exploring the dynamic function of cardiac pacemaker activity in the setting of acute rejection was the recognition that intrinsic cardiac mechanisms responsible for generating heart rate variability (HRV) in transplanted, centrally denervated hearts may in fact be disturbed.

HRV analysis has often been used as a means of risk assessment in patients with acute cardiac events.^{3,4} Studies in patients undergoing transplantation have demonstrated that HRV changes can be sensitive in identifying acute myocardial tissue rejection episodes.⁵⁻⁷ However, the results from these studies are by and large contradictory, reporting an increase⁵ or a decrease^{6,7} in HRV in response to a rejection episode. These inconsistencies are central to the question of whether the HRV-based analysis is discriminatory in detecting the onset of allograft rejection. Most of the HRV studies performed in patients undergoing HTX relied on conventional measures of inherent fluctuations in biologic rhythms, such as time- and frequency-domain methods.^{5,8-10} Recently, a nonlinear system analysis approach gained practical utility in clinical cardiology.^{11-13a} The application of nonlinear analysis is particularly suitable for the study of complex systems, where the magnitude of the response is not proportional or controlled by a given stimulus.¹⁴⁻¹⁶ Specifically, this approach to HRV signal analysis proved to be more discriminating^{4,12} than the conventional techniques used to detect the high-risk, abrupt, autonomic changes preceding acute coronary events (eg, sudden cardiac death). Clearly, because the transplanted heart is devoid of central autonomic regulation, applying nonlinear analysis to assess cardiac allograft function may provide the means to identify changes in its intrinsic regulatory state, reflecting the degree of donor-host functional interactivity that otherwise would not be feasible.

Both linear and nonlinear methods of R-R variability analysis were used in this study. The results demon-

strate that HRV screening is a useful tool for early detection of the onset of acute myocardial rejection.

Methods

Patient population and data acquisition. Forty-five electrocardiograms were recorded in a cross-sectional study of patients who underwent orthotopic cardiac allograft transplantation (by using a biatrial technique). The monitoring time frame was confined to the first 4 months since transplantation. This *observation window* was chosen on the basis of reported peaking risk patterns for myocardial rejection.¹⁷ The study was approved by the institutional review board of the MCP Hahnemann University. Patients were maintained on a standard triple-drug immunosuppression protocol consisting of cyclosporine (INN: ciclosporin), azathioprine, and prednisone. The time series signal epochs were taken in the morning hours before routine serial surveillance of the right ventricular endomyocardial biopsy procedure. Patients were allowed to rest quietly for 5 to 8 minutes before the onset of data acquisition. While the patient remained in a supine position, the electrocardiography signal was recorded for approximately 10 minutes. A total of 800 to 1500 cardiac beats were digitized at a 1-ms sample interval by means of real-time data acquisition software (Windaq/200, Dataq Instruments) and stored for subsequent analysis. Absence of a normal sinus rhythm in the donor heart (atrial fibrillation, pacemaker use, and pharmacologic control) was the sole exclusion criterion. In total, 12 of 57 cases were excluded, thus leaving 45 patient recordings for the analysis.

Cardiac rejection was graded by means of the standard International Society of Heart Lung Transplantation (ISHLT) scale of 0 (no rejection) to 4 (severe rejection). On the basis of the documented severity of rejection, patients were divided into the following two groups: a group of 11 patients showed moderate-to-severe rejection (grade > 1), and the remainder displayed mild or no rejection (grade ≤ 1).

HRV analysis. The R-R interval time series were analyzed offline with R-peak (of the QRS complex) detection software (Windaq, Dataq Instruments) and inspected visually to ascertain proper R-wave identification. The beat-to-beat variations in R-R intervals were used subsequently to ascertain specific quantitative information regarding the dynamic nature of the sinus node pacemaker activity. Linear measures of HRV consisted of computed mean and SDs of R-R intervals for each of the data set points. In addition, power spectral density analysis of the HRV signal was performed by a recursive maximum entropy method (all-poles model).¹⁶ A separate analysis of low-frequency (LF; 0.04-0.15 Hz) and high-frequency (HF; 0.15-0.40 Hz) components of the spectra was carried out.

To extend the ability to analyze complex features of the allograft rhythm dynamics, we subjected the HRV time series to nonlinear signal processing.^{13,18} In general, a system that is characterized by *n*-independent variables can be thought of as residing in an *n*-dimensional space. Depending on the extent of coupling and intensity of internal and external interactions,

Fig 1. Left panels, HRV (R-R interval time series) plots in control and rejecting allografts spanning 800 consecutive beats. Right panels, The associated pointwise correlation dimension (PD2) metric computed for the respective patients. Note the loss in dimension (shift to the left) and the relatively narrowed PD2 histogram for the rejection-afflicted heart.

the measured dimension can range from zero to infinity; the lower the number, the simpler the system dynamics. In the normal range of physiologic response, a dimension of 10 (serving as an upper limit) would resemble white noise. In the intact innervated heart, the HRV dimension was measured to be approximately 4, whereas in the Langendorff-perfused isolated heart, the dimension had a metronome-like (~1) property.¹⁴ A decrease in the computed dimension would imply a loss in the number of active degrees of freedom and a decline in the complexity of the R-R time series.¹³ In this study a loss of complexity in the heart rhythm (HR) dynamics accompanying myocardial rejection served as a marker of the reorganization¹⁸ or/and uncoupling of newly formed graft-host interactions.

Pointwise correlation dimension (PD2) analysis (Enhanced Cardiology Software) was used as the primary tool to extract nonlinear features imbedded in the HRV signal. The main benefit in using the PD2 algorithm is its ability to analyze nonstationary signals,^{11,18} requiring a relatively small data set compared with the classic Grasberger-Procaccia determination of correlation dimension (D2). The most dominant (mode) dimension was extracted from the PD2 histogram (Fig 1) and used in the subsequent statistical analysis.

Statistics. The demographic and HRV data are expressed as means $\pm$ SD. The Student *t* test and χ^2 analysis were used for comparison of continuous and categorical variables, respectively, and tested by the likelihood ratio χ^2 method to determine significant univariate correlates of acute myocardial rejection (ISHLT grade > 1). To select the independent covariates associated with an acute rejection, the significant univariate predictors were reassessed by a forward, stepwise, multivariable, logistic regression. Statistical analysis was performed by use of SigmaStat v2.01 (SPSS Inc, Chicago, Ill) and NCSS 2000 (NCSS Statistical Software, Kaysville, Utah).

Results

Patient population. The HRV analysis using linear and nonlinear time series metrics was carried out in 45 patients up to 120 days after HTX. The mean age of patients was 57.2 ± 9.4 years (range, 26-68 years); 37 were men and 8 were women. These patients were divided into two groups: those with and those without (normal control subjects) documented acute graft rejection (11 and 34 observations, respectively). There were no statistical differences (*P* = not significant) in the demographic variables, including age (58.2 ± 6.4 vs 56.8 ± 10.2 years), sex (11 [100%] vs 26 [76.5%] men), and race (10 [90.9%] vs 30 [88.2%] white subjects, respectively).

Univariate analysis. Fig 1 depicts the characteristic features of HRV signal complexity in two representative patients undergoing HTX, demonstrating distinctly different dimensional attributes of the HR generator. The differences in HR dynamics between the normal (*upper panels*) and rejecting (*lower panels*) allografts are not discernable by merely observing the R-R interval time series (*left panels*) but are made apparent when analyzed by means of PD2 histograms (*right panels*). In general, nonrejecting cardiac allografts manifested a rhythm-generating behavior (average PD2, 1.7 ± 0.7) that was simpler than that seen in normally innervated hearts (PD2, 4.1 ± 0.3).¹⁴ Nevertheless, the allograft HRV dynamics can give rise to complex time series patterns. In fact, the graft rhythm generator exhibited a correlation dimension that was consistently higher than that seen in the isolated centrally denervated heart (PD2, 0.7 ± 0.1 ; Langendorff-perfused rabbit heart

Table I. Linear and nonlinear analysis of HRV in rejecting and nonrejecting (control) patients undergoing cardiac transplantation (univariate statistical analysis)

Variables	Control (n = 34)	Rejection (n = 11)	Regression coefficient	SE	χ^2	P value
Age (y)	56.8 ± 10.2	58.2 ± 6.4	0.02	0.04	0.2	.7
Male sex	26 (76.5%)	11 (100%)	13	429	0.00	1.0
White race	30 (88.2%)	10 (90.9%)	0.3	1.2	0.06	.8
Time after HTX (wk)	5.3 ± 4.0	9.2 ± 4.9	0.2	0.08	5.5	.02
R-R interval (ms)	700 ± 68	648 ± 72	-0.01	0.01	4.0	.05
SD (%)	2.3 ± 1.5	2.0 ± 1.0	-0.2	0.3	0.3	.6
Total power (ms ²)	6.2 ± 7.0	5.0 ± 6.3	-0.03	0.06	0.2	.6
LF power (ms ²)	0.8 ± 0.6	1.8 ± 2.2	0.6	0.3	3.6	.06
HF power (ms ²)	5.3 ± 6.7	3.2 ± 4.6	-0.08	0.08	0.9	.3
LF/HF ratio	0.3 ± 0.2	0.6 ± 0.4	4.7	1.7	7.7	.005
PD2 (units)	1.7 ± 0.7	0.9 ± 0.3	-3.8	1.3	7.9	.005

Continuous variables and ratios are expressed as means ± SD; categoric variables represent the total number of patients (as a percentage of the subgroup). HTX, Heart transplantation; LF, low-frequency component of spectral power; HF, high-frequency component of power; PD2, pointwise correlation dimension.

Table II. Independent predictors of acute myocardial rejection event by multivariable logistic regression analysis

Covariates	Regression coefficient	SE	χ^2	P value	Odds ratio	95% CI	
						Lower	Upper
Intercept	4.0	2.4	—	—	—	—	—
-PD2 (per 0.1 units)	0.8	0.4	4.9	.03	2.2	1.1	4.5
Time after HTX (per 1 wk)	0.5	0.2	4.9	.03	1.7	1.1	2.6

For purposes of presentation, the negative value of PD2 (pointwise correlation dimension) variable is used. SE, Standard error; CI, confidence intervals; HTX, heart transplantation.

model).¹⁹ Moreover, the HRV time series had a positive Lyapunov exponent (0.5-1.2), suggesting the presence of a low-dimensional chaotic process underlying the dynamics of the HR generator. In a rejection-afflicted heart, the measured HRV pointwise correlation dimension histogram peak shifted to an area of significantly lower values (from 2.4 to 0.8; Fig 1). In addition, the observed narrowing of dimensional dispersion in the rejecting heart (as seen in the PD2 histogram) reflects the more constrained dynamics of the HR generator.

The frequency-domain features of the sinus node rhythm were studied by means of power spectral density analysis. As seen in Fig 2, the composite of spectral patterns from the 45 recordings reflects characteristically different features in the rejection-afflicted hearts versus the control hearts. In particular, the ratio of low (0.04-0.15 Hz) to high (0.15-0.40 Hz) frequencies rose significantly ($P < .005$) in the rejecting allografts, signaling a loss in the predominance of HF spectral component seen in the early phase of HTX.

To identify the risk predictors for an acute myocardial rejection, we subjected both linear and nonlinear HRV indices to univariate logistic regression analysis. The summarized results from this analysis are presented in Table I. As seen in this table, the significant uni-

variate predictors of rejection were as follows: an increase in time duration since transplantation, a shortening of the R-R interval, an increase in the LF/HF ratio, and a decrease in the PD2 values. In contrast, the demographic variables, such as age, sex, or race, as well as other linear measures of heart rate dynamics, such as the SD of R-R intervals, total power of the spectrum, or absolute values of LF and HF spectral components, proved to be insensitive to the onset of the rejection event. Importantly, a mild rejection (grade 1a-1b) could not be detected by any of the methods used ($P =$ not significant). In 14 patients undergoing HTX who experienced mild rejection, the LF/HF ratio (0.3 ± 0.2) and PD2 values (1.5 ± 0.7) were similar ($P > .1$) to those seen in the 20 patients in whom the biopsy study did not reveal any degree of rejection (0.3 ± 0.2 and 1.8 ± 0.7 , respectively).

Sensitivity and specificity of the methods. Notably, univariate predictors of myocardial rejection exhibited a disparate discriminatory power in detecting moderate-to-severe myocardial rejection. At a set cutoff value of maximal sensitivity, PD2 analysis showed a specificity of 47.1%, whereas the specificity of the LF/HF ratio, a linear metric of HRV, approached only 20.6%. The corresponding value for the time after HTX was

Fig 2. Loss of spectral reserves in rejecting allografts. Composite graphs of power spectral density were computed by averaging individual patient spectra for rejecting ($n = 11$) and nonrejecting ($n = 34$) HTX groups by the maximum entropy method. The x-axis is scaled by the Nyquist critical frequency (reciprocal of twice the time interval between the average of R-R data points) for each respective group. *LF*, Low frequency; *HF*, high frequency.

even lower (14.7%). This difference is exhibited in Fig 3 by the receiver-operator characteristic curves. The increase in the area under the curve is indicative of a greater predictive value of PD2 compared with the conventional stochastic analysis metric and time variable.

Multivariable analysis. To identify the independent predictors of acute myocardial rejection, we used variables that proved to be significant in a univariate analysis ($P < .05$ in Table I) to build a multivariable logistic regression model. Those covariates, which retained their significance ($P < .05$) in a regression model, are shown in Table II. There were only two predictors of the myocardial rejection event: PD2 (odds ratio, 2.2 per 0.1 unit decrease) and the time after HTX (odds ratio, 1.7 per week). At the maximal sensitivity level (100%), this regression model yielded a specificity of 82.4% ($R^2 = 0.4$, model $\chi^2 = 28.9$), reaching a diagnostic accuracy of 86.7%. The explanatory variables for the model were tested for the presence of association or interaction. This analysis revealed that time after HTX and PD2 were uncorrelated ($R^2 = 0.001$, $P = .80$), which is consistent with the assumptions of multiple logistic regression analysis. When the predictive scores from the model were expressed in a form of the receiver-operator characteristic curve (Fig 3), a significant increase in the discriminatory power of this diagnostic test was demonstrated.

Fig 3. Receiver-operator characteristic (ROC) curves for the pointwise correlation dimension (PD2), low-frequency/high-frequency (LF/HF) ratio, time since transplantation, and scores from multivariable logistic regression model used in detecting myocardial rejection. The larger area under the curve (AUC) is indicative of the greater predictive value of PD2 analysis when compared with other univariate predictors.

Discussion

Limitations of the present study. This study has several limitations. Cross-sectional studies are inherently limiting in accessing individual patient variability, particularly when applied to time-dependent events. Nonetheless, these types of studies are helpful as screening tools for identifying the operating range of HRV metrics under consideration. The relatively small sample size (45 events) may have handicapped the HRV indices to some degree in discriminating between the control and the rejecting state. Because the principal goal of the study was to determine whether HRV-derived indices could be used to detect rejection and not to formulate a comprehensive risk-stratification algorithm, we did not exhaustively examine all the cardiac transplant-related variables, including donor demographics, heart size mismatch, and/or human leukocyte antigen matching. The use of sinus node abnormality as an exclusion criterion should also be considered as a study limitation because it narrowed the subset of patients that were ultimately considered for HRV analysis. It is noteworthy that, to some degree, the high discriminatory ability of HRV analysis compensated for this limitation. In particular, the observed specificity (82%) of the PD2-based model, when

Fig 4. Representative phase-plane portraits (Poincare plots) of cardiac allograft R-R interval time series with and without rejection in route to and from complex (multifractal) dynamics. Compare the *left panel* complex (strange) attractor trajectory pattern to the simpler one (point-cluster in space) shown in the *right panel*. HTX, Heart transplantation; PD2, pointwise correlation dimension; ISHLT, International Society for Heart and Lung Transplantation.

adjusted for the number of the excluded events (12/57), yielded a value of 65%, which is superior when compared with other existing noninvasive tests, such as antimyosin antibody scanning (specificity, ~30%).¹ It implies that the nonlinear HRV analysis, particularly when confined to the early phase of time after HTX, may potentially eliminate the need for routine biopsies in two of three patients undergoing transplantation. Future large-scale prospective longitudinal trials will help validate the general utility of this noninvasive method for detecting myocardial rejection, facilitating a routine monitoring of transplant patients.

HRV analysis of acute rejection. Early detection of acute myocardial rejection is critically important for instituting an optimal management of the patient undergoing HTX. In this study nonlinear measures of HRV provided a noninvasive metric for identifying patients undergoing HTX with acute rejection. In contrast, conventional stochastic measures of HRV, such as time- and frequency-domain methods, had a lesser discriminatory power. Previous attempts to discern the onset of myocardial rejection by means of HRV analysis relied primarily on traditional stochastic measures. Sands and colleagues,⁵ using frequency spectral analysis of HRV,

observed an association between the onset of myocardial rejection and gain in power spectral density. In contrast, Zbilut and colleagues^{6,7} observed that the cardiac rhythm fluctuations were attenuated in rejection-afflicted hearts. Others⁸⁻¹⁰ did not discern specific changes in HRV spectra accompanying rejection.

These apparent contradictions are in part related to methodologic limitations of power spectrum analysis,^{3,20} principally because the spectral energy in HTX is grossly attenuated. In addition, time- and frequency-domain analysis of R-R intervals provides a restricted view of the information embedded in the HR dynamics. In contrast, dimensional analysis, when applied to the HRV time series, can account for nonlinear interactions between the multiple variables modulating the rhythm-generating system of the heart. It is important to appreciate that different metrics of HRV characterize specific features of the short-term regulatory mechanisms responsible for beat-to-beat cardiac rhythm fluctuations. Although PD2 was more discriminatory in detecting the rejection state of the patients in this study, the specific attributes of power spectral analysis (ie, LF/HF ratio) had nonetheless significant univariate predictive power (Table I).

An important consideration when implementing a new methodology designed to characterize the functional state of the graft is the recognition that the emerging HR dynamics is a product of a time-dependent assimilation process of the donor organ within the environments of the recipient and host. In particular, the rejection incidence displays a specific pattern¹⁷: an early high risk (first 1-4 months) followed by a low persistent risk, spanning over a period of many years. Neglecting to appreciate this temporal pattern may have contributed to the disparity of the reported studies.^{5,10} The data from both univariate and multiple-regression analysis (Tables I and II) highlight the importance of time after HTX as an independent risk factor in predicting acute rejection in early stages after transplantation.

Importantly, as demonstrated by this study and by others,⁷ a mild degree of myocardial rejection (grades 1a-1b) was not amenable to detection by HRV analysis. This may additionally help explain the inherent limitations of previous studies.^{5,9} In clinical practice, episodes of mild rejections are not routinely treated.

Time evolution of cardiac rhythm dynamics after HTX. The cardiac allograft is not merely a passive muscular pump responsive to the demands of a host but in fact is a functional neuroendocrine organ system^{14,18,21,22} actively participating in the assimilation process that is able to adaptively elaborate new struc-

tural and functional features (ie, remodeling).^{23,24} We have recently demonstrated^{14,19} that the rhythm dynamics of a newly transplanted heart are not held constant but proceed through a set of phase transitions. At implantation, the donor heart manifested metronome-like chronotropic behavior (PD2, ~1.0). At 11 to 100 days, the dimensional complexity of HRV reached a peak (PD2, ~2.0), followed by a loss in dimensional complexity at 20 to 30 months after HTX. Thus, in analyzing HRV it is important to define the time frame after HTX within which the regulatory properties are to be assessed. For example, limiting the observation time frame to the very early (<10 days) or late (>20-30 months) stages of HTX, where HRV level is attenuated, can potentially diminish the discriminatory power of any detection scheme on the basis of HRV analysis alone. This point is best illustrated in Fig 4, where HRV dynamics are confined within a 2-dimensional phase-portrait. The observed return maps can be interpreted as the projections of a multidimensional phase-space trajectory of an attractor underlying the HR generator. Fig 4 depicts the typical dynamic patterns of HRV for a normal volunteer compared with three patients undergoing HTX. Two patients at 1 and 4 weeks after HTX were free of rejection, and one patient (at 8 weeks after HTX) had a documented episode of severe rejection. Clearly, the shape and the phase-plane excursions are distinctly different. The attractor in the normally innervated heart displays a wandering pattern. Within 1 week after HTX, the trajectory of the attractor is grossly simplified, converging to a point in space. The dynamics pattern of HRV at 4 weeks after HTX attains a geometrically ordered temporal cone-like structure, pointing to an emergence of a new dynamic state of the HR generator. This characteristic response is lost in its entirety in the rejection-afflicted hearts.

HRV in the transplanted heart. In an intact and normally innervated heart, the variability of the heart rate is thought to reflect a dynamic coupling between the sympathetic and parasympathetic neural control mechanisms and the sinus node pacemaker activity. In a centrally denervated heart, the modulatory response of cardiac rhythm dynamics is indicative of the presence of intrinsic cardiac regulatory mechanisms.^{14,19,21,22} The exact nature of these mechanisms is not clear. Several homeostatic factors have been implicated. Respiratory mechanical factors may contribute to the dynamic behavior of a graft²⁵; unlike neural inputs, they remain relatively fixed and thus are unlikely to mediate both the evolution of HRV signals after HTX and loss of signal complexity after acute rejection. Another plausible hypothesis is that HRV in

the patients undergoing HTX is mediated by irregular firing of the sinus node, in which the L-type calcium channels are altered by rejection.²⁶ Unfortunately, this thesis remains without experimental evidence. Our data in rejecting grafts do not support the likely increase in HRV nor the expected decrease in HR (because of proposed block of cardiac calcium channels) implied by this mechanism.

The postulate of this study is that cardiac allograft has a built-in capacity for neuroendocrine-mediated self-regulation,^{14,19,21,22} which is reflected in the complexity of the generated HR variability. The rejection-induced changes in the graft-host functional and structural integrity of intrinsic cardiac regulators would lead to a loss of cardiac rhythm complexity. There is supporting evidence for this proposition. Immunohistochemical and functional studies of human²⁷ and canine²⁸ cardiac allografts revealed that the decentralized heart is endowed with intrinsic neural elements; a significant number of intracardiac neurons having an extensive interconnected network remain in place and accompany the donor organ within its host. In the intact canine model, controlled stimulation of efferent cardiac parasympathetic nerves resulted in an increase in time- and frequency-domain indices of HRV,²⁹ implying that neurons that reside within the organ are responsible for generating the beat-to-beat fluctuations in the cardiac rhythm. Using the isolated Langendorff-perfused rabbit heart, we have recently demonstrated that direct chemical activation of the cardiac neuroendocrine system by endogenous kinins^{19,21,22} or ischemic stress^{18,22} elicited notable changes in the dynamics of cardiac rhythm (ie, a rise in HF component of the spectra and an increase in PD2 value). With this in mind, a relative loss of HF components, seen in rejecting hearts (Fig 2 and Table I), may represent a decreased firing from intrinsic cholinergic neurons, mediating the HRV in the immunologically stressed graft. Interestingly, the variability of the native normally innervated sinus node pacemaker in patients undergoing HTX was shown to be inversely related to severity of rejection.⁸ This fact supports the notion that acute rejection can manifest itself in the form of functional uncoupling of regulatory systems, modulating cardiac pacemaker activity.

Summary

The transplanted heart, in its encounter with the host, manifests many of the attributes embodied in complex adaptive systems: network of interacting components, organizational order, multifunctionality, and fluctuation in system variables. The early surge in the dimensional complexity (PD2) of the HR gen-

erator proved to be a characteristic feature of dynamic interaction between the donor heart and the recipient host. An acute rejection episode upsets the re-established homeodynamics that are responsible for cardiac self-regulation. Rejection stress may lead to structural and functional uncoupling of regulatory mechanisms controlling the sinus node function, thus giving rise to a loss in dimensional complexity of HRV. This observed dynamic reorganization of the HR-generating system may represent an expression of the adaptive robustness that is attributable to the intrinsic control mechanisms.

In conclusion, multidimensional phase-space analysis may prove to have clinical utility in evaluating the autoregulatory reserves of the heart, thus providing noninvasive metrics for assessing functional viability and serving as an early marker of cardiac allograft rejection (maladaptation) in early stages after transplantation.

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