Evolution in functional complexity of heart rate dynamics: a measure of cardiac allograft adaptability

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Kresh, J. Yasha, and Igor Izrailtyan. Evolution in functional complexity of heart rate dynamics: a measure of cardiac allograft adaptability. *Am. J. Physiol.* 275 (*Regulatory Integrative Comp. Physiol.* 44): R720–R727, 1998.—The capacity of self-organized systems to adapt is embodied in the functional organization of intrinsic control mechanisms. Evolution in functional complexity of heart rate variability (HRV) was used as measure of the capacity of the transplanted heart to express newly emergent regulatory order. In a cross-sectional study of 100 patients after (0–10 yr) heart transplantation (HTX), heart rate dynamics were assessed using pointwise correlation dimension (PD2) analysis. A new observation is that, commencing with the acute event of allograft transplantation, the dynamics of rhythm formation proceed through complex phase transitions. At implantation, the donor heart manifested metronome-like chronotropic behavior (PD2 $\sim$1.0). At 11–100 days, dimensional complexity of HRV reached a peak (PD2 $\sim$2.0) associated with resurgence in the high-frequency component (0.15–0.5 Hz) of the power spectral density. Subsequent dimensional loss to PD2 $\sim$1.0 at 20–30 mo after HTX was followed by a progressive near-linear gain in system complexity, reaching PD2 $\sim$3.0 7–10 yr after HTX. The "dynamic reorganization" in the allograft rhythm-generating system, seen in the first 100 days, is a manifestation of the adaptive capacity of intrinsic control mechanisms. The loss of HRV 2 yr after HTX implies a withdrawal of intrinsic autonomic control and/or development of an entrained dynamic pattern characteristic of extrinsic sympathetic input. The subsequent long-term progressive rise in dimensional complexity of HRV can be attributed to the restoration of a functional order patterning parasympathetic control. The recognition that the decentralized heart can restitute the multidimensional state space of HR generator dynamics independent of external autonomic signaling may provide a new perspective on principles that constitute homeodynamic regulation.

nonlinear dynamics; heart rate variability; cardiac adaptation; self-organizing systems; homeodynamic regulation

THE HEART IS AN ADAPTIVE ORGAN that responds to changes in its immediate environment by using a number of tissue-specific mechanisms that can be assembled to maintain a homeodynamic (20, 36) balance between its own energetic needs and the constraints of the organism as a whole. Transplanting a heart to a new environment is bound to trigger a number of new interactions between the donor organ and recipient host. Historically, emphasis has been placed on the activation of "body defense" immunologic mechanisms in response to the incorporation of the graft. Within this paradigm, the heart is considered merely a passive participant, amenable to the demands of the host. However, experimental and clinical data indicate that the transplanted heart is endowed with an intrinsic capacity to express newly emergent structural and functional features. This robustness can be illustrated by the plasticity of cardiac allograft, accommodating the requirements of the rapidly developing host. In neonates (8), the oversized donor allografts were shown to abate at 3 mo post heart transplantation (HTX), a phase followed by a process of organ growth, consistent with the normal development of the recipient body size. Another manifestation of this inherent cardiac adaptive potential is made evident by the observation of an ongoing remodeling of allograft vascular luminal geometry (28). These vascular changes may help counteract, to some degree, the deteriorative effects of vasculopathy that are often linked to transplantation and thereby influence the fate of the organ. In general, the dynamics and regulatory principles guiding the adaptive transitions of the donor heart within the habitat of the recipient host remain poorly understood.

Heart rate variability (HRV) analysis has been commonly used to characterize the capacity of neuroendocrine regulatory systems to modify the cardiac chronotropic function on a beat-to-beat basis. Autonomic nervous system metrics of HRV have traditionally used linear estimates of neurohormonal modulators and have been the focus of considerable efforts for the past 15 yr (1, 23, 24). Specifically, spectral decomposition analysis (e.g., parametric and nonparametric estimators) has been used extensively in noninvasive assessment of autonomic nervous system activity in both animal studies and clinical conditions, such as sudden death, coronary artery disease, diabetic neuropathy, and HTX (3, 19, 23, 24, 29). In a normally functioning organ, the sympathetic and parasympathetic nervous systems are the principal mechanisms underlying short-term cardiovascular control, operating on a time scale of seconds to minutes and thus contributing to the complex nature of HRV (1). A prevailing view of the autonomic control is that the centrally denervated transplanted heart is incapable of preserving its short-term regulatory capacity. It is thought that, in humans, a period of many months to years is required to evolve new regulatory patterns of heart rate dynamics (3, 19, 29), attributable to a prolonged course of central reinnervation (18, 35). However, the potential for early post-HTX changes in HRV is plausible, supported by the recognition that the decentralized heart embodies its own means for adaptation and self-regulation (14, 20, 34). This is best exemplified by the regulatory capacity of the intrinsic nervous system to modulate the chronotropic function of an isolated in vitro perfused heart (14). Data obtained in clinical studies confined to the early period after HTX are contradictory, demonstrat-

ing both presence (38) and absence (30) of prominent frequency spectral peaks in HRV time series. In part, these discrepancies can be attributed to the dynamic (time dependent) process of allograft assimilation within the host as well as to the methodological limitations in extracting pertinent information from power spectrum analysis (23, 24), particularly when the dominant spectral reserves are grossly attenuated.

The underlying functional order and temporal unfolding of heart rate dynamics have many features attributable to complex nonlinear dynamic systems (6, 9). The capacity of self-organized systems to adapt is embodied in the functional organization of intrinsic control mechanisms. From this vantage point, the heart can be portrayed as if it is an information-generating source in which the regulating inputs are made operational in terms of one of its more conspicuous outputs, i.e., the HRV. Thus the working premise of this study was that regeneration of the complexity in heart rate dynamics can be used to assess the functional capacity of cardiac allograft to express newly emergent regulatory order, stemming from its interactivity with the host environment.

METHODS

Study patients and measurements. One hundred patients at various stages (7 days to 9.7 yr) of postorthotopic cardiac allograft transplantation were recruited for this cross-sectional study. Their mean age was 53.8 ± 1.2 yr (19.5–72.4 yr); 73 men and 27 women were monitored. All patients underwent a standard triple drug immunosuppression protocol consisting of cyclosporine, azathioprine, and prednisone. To obviate the diurnal influences, the time series signal epoch was recorded in the morning hours before the routine serial surveillance right ventricular endomyocardial biopsy study. The patients were allowed to rest quietly for 5–8 min before the data acquisition session. While patients remained in a supine position, 10-min epoch electrocardiographic signals (800–1,500 beats) were recorded and digitized (1-ms resolution) using real time data acquisition software (Windaq/200, Dataq Instruments) and stored for subsequent analysis.

The R-R intervals were analyzed off line using QRS peak detection software (Windaq, Dataq Instruments) and inspected visually to verify proper peak identification. The R-R intervals were then subjected to a nonlinear mathematical analysis using a pointwise correlation dimension (PD2) algorithm (PD2 Software, Enhanced Cardiology). The dominant dimension (mode) was extracted from the PD2 histogram (see Fig. 1) and used in the subsequent comparative analysis. The advantage of the PD2 algorithm is that it requires fewer data points compared with the classic Grassberger-Procaccia (10) determination of a correlation dimension (D2). In addition, it offers an added feature in that it can extract a "dimensional complexity" from a nonstationary signal-generating source (6). Stochastic measures included computed mean and standard deviation of R-R interval for each of the data set points. In addition, power spectral density analysis of the HRV signal was performed using a recursive maximum entropy method (all-poles model) (22). Moderate to severe rejection, documented by biopsy sampling (International Society of Heart and Lung Transplantation grade ≥ 2), and/or absence of normal sinus rhythm (e.g., signal noise, atrial fibrillation, ectopic rhythm, or presence of a pacemaker) were the only exclusion criteria.

Study limitations. In general, cross-sectional studies are inherently limiting when accessing variable responses between individuals, particularly when applied to the analysis of time-dependent events. Nonetheless, when applied to a large sample population, this approach may serve as a screening tool to explore the operating range under consideration. An implied assumption in this study is that the "boundedness" of homeodynamic process is such that the observed regulatory expanse seen in the entire population represents the operating state space of an individual.

Dimensional analysis. The beat-to-beat variations in heart rate are not arbitrary random events but can be used to provide specific quantitative information about the neurohumoral activity modulating the sinus node pacemaker. Spontaneous fluctuations of heart rate reflect the coupling between intrinsic and extrinsic cardiac regulatory mechanisms. These interactions are not simply a linear summation of two autonomic inputs but may be a result of a nonlinear deterministic process (9, 31). To better characterize the regulatory modes of the heart, we made use of dimensional analysis, a technique often used in the study of nonlinear phenomena such as complex (chaotic) dynamics (6, 9, 10).

In general, a system that displays n degrees of freedom or that is characterized by n different (independent) variables can be thought of as residing in an n-dimensional space (36).
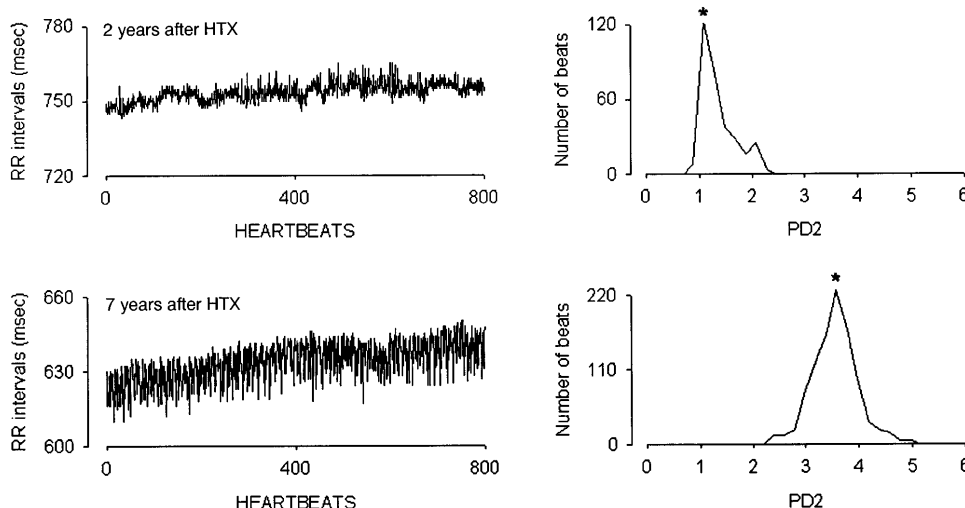

Fig. 1. Dynamic changes of heart rate variability (R-R intervals) in heart transplant patients (HTX). PD2, point correlation dimension. Number of beats in PD2 histogram = n. *Most prevalent dimension used in data analysis.

The term "dimension," as defined in this study, is a measure of the system complexity corresponding to the number of dominant control variables needed to specify the configurational state (behavior) of the system at a given point. Specifically, it is a product of a deterministic formalism by which the evolution of the active modes modulating the cardiac rhythm generator (25) can be quantified. In particular, dimensional analysis is used to document the emergent dynamic changes in HRV response after cardiac transplantation spanning a 10-yr period, acknowledging in advance that the functional order is amenable to change, i.e., evolves over time.

Theoretically, the computed dimension represents a region in phase space (topological attractor) to which all deviating trajectories ultimately settle down; it can be a noninteger, i.e., fractal. In theory, the system dimension can range from zero to infinity; the lower it is, the simpler the dynamics are. In a normal physiological range of activity, a dimension of 10 (serving as upper limit) would resemble white noise (36). In this study, there is no implied precondition that stipulates that the manifested changes in HRV are purely indicative of central reinnervation. Evolution in rhythm complexity is used as a measure of reorganization in cardiac control that may arise over time, de novo and/or by regenerating existing regulatory pathways.

RESULTS

Among the 100 patients studied, only 2 exhibited a PD2 level similar to the normal heart (i.e., 4.1 ± 0.3; see Ref. 21). In general, cardiac allografts manifested a rhythm-generating behavior that was simpler than that seen in normally innervated hearts. Nevertheless, the HRV dynamics of cardiac allografts were not simply periodic but expressed complex time series patterns. In fact, at many post-HTX stages, the cardiac rhythm generator of the allografts exhibited a correlation dimension that was consistently higher than that of the isolated, centrally denervated heart (PD2 0.7 ± 0.1, Langendorff perfused rabbit heart model; see Ref. 16). In addition, the HRV time series had a positive Lyapunov exponent (0.5–1.2), providing additional evidence for a low-dimensional chaotic process underlying the dynamics of the HR generator.

Figure 1 depicts the characteristic features of dimensional complexity in two patients demonstrating distinct dynamic behavior of the HR generator at different post-HTX stages, i.e., 2 yr vs. 7 yr (PD2 values of 1.0 vs. 3.6, respectively). In addition, the observed fluctuation in PD2 (PD2 histogram span; see Fig. 1) provides indirect evidence of the extent of signal nonstationarity present, reflecting the inherent homeodynamic transitions (36) in the state space of the heart rate regulator.

To extract the specific attributes of the time-dependent evolution of the rhythm generator at different post-HTX stages, the 100 patients were divided into 8 groups as summarized in Table 1 and Fig. 2. The time evolution in HR dynamics was made evident by subdividing the first 2 yr into 4 discrete study intervals. The assimilation of the donor heart to the host environment resulted in a distinct trajectory of dimensional changes (ANOVA, $P < 0.001$; power at $\alpha = 0.05$ was 1.00). At the onset of exposure to the recipient (first 10 days; Fig. 2A), the donor heart manifested metronome-like chronotropic behavior (dimension ~1.0). Thereafter, a surge

Table 1. *Heart rate variability as function of posttransplantation time period*

Time After HTX	No. of Patients	Mean R-R Interval, ms	(SD/mean R-R Interval) $\times$ 100, %
0–10 days	6	726.3 ± 15.9	1.7 ± 0.5
11–100 days	27	689.9 ± 13.9	3.4 ± 0.7
101 days–10 mo	15	651.2 ± 23.8	3.8 ± 0.6
10–20 mo	13	657.5 ± 27.0	3.0 ± 0.8
20–30 mo	11	713.5 ± 35.0	2.5 ± 0.9
30 mo–5 yr	9	643.9 ± 26.9	2.8 ± 0.6
5–7 yr	10	646.5 ± 27.8	4.2 ± 0.9
7–10 yr	9	782.4 ± 48.6	3.1 ± 0.7

Values are means $\pm$ SE. R-R interval, heart cycle length; (SD/mean R-R interval) $\times$ 100, coefficient of variation. HTX, heart transplant.

in dimensional complexity reached a peak at 11–100 days (Fig. 2B; gain in ~1 dimension) and was followed by a drop, reaching a minimum at 20–30 mo after HTX (Fig. 2C). A dimensional phase transition occurred at 30 mo after HTX, and it was followed by a progressive near-linear gain ($r = 0.75$, $P < 0.001$) in a system dimension, reaching a maximum (dimension ~3.0) at 7–10 yr after HTX. The post-HTX trajectory depicting the evolutionary trend of HR dynamics did not settle (Fig. 2D) at a fixed plateau, failing to achieve the functional level of the normally innervated heart.

The mean of R-R intervals and standard deviation had poor discriminatory power in delineating the time-dependent evolution of the cardiac allograft (ANOVA for both HR and SD, $P > 0.1$). There was some correlation (see Fig. 3) between the absolute heart cycle length and changes in PD2 (Pearson product moment correlation, $P < 0.05$, $r^2 = 0.06$). In contrast, the standard deviation of R-R interval fluctuations exhibited a weak association with both PD2 and R-R interval.
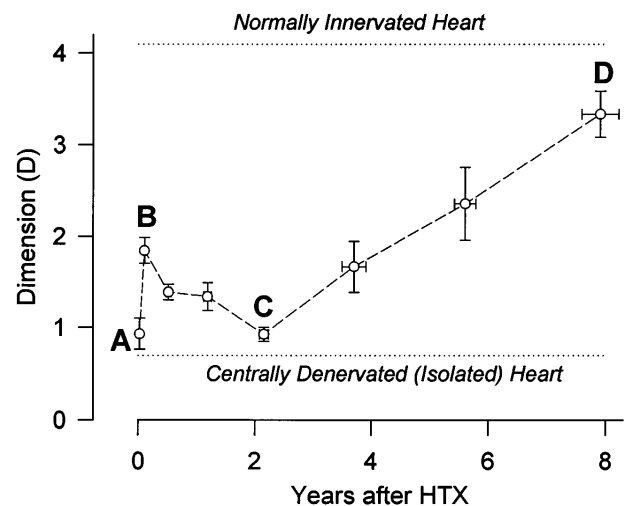

Fig. 2. Time evolution of a pointwise correlation dimension (means $\pm$ SE) in posttransplant patients. At the onset (A, first 10 days), cardiac allograft exhibits a metronome-like chronotropic activity (dimension ~1). A surge in dimension peaked at 100 days (B, gain in ~1 dimension) and was followed by a dimension collapse, reaching a minimum (C, 20–30 mo after HTX). Staring 30 mo after HTX, progressive gain in a system dimension was nearly linear ($y = 0.40x + 0.13$, $r = 0.75$, $P < 0.001$), reaching its maximum value (D) 7–10 yr after HTX. Reference levels for normally innervated and denervated (isolated) heart are included.
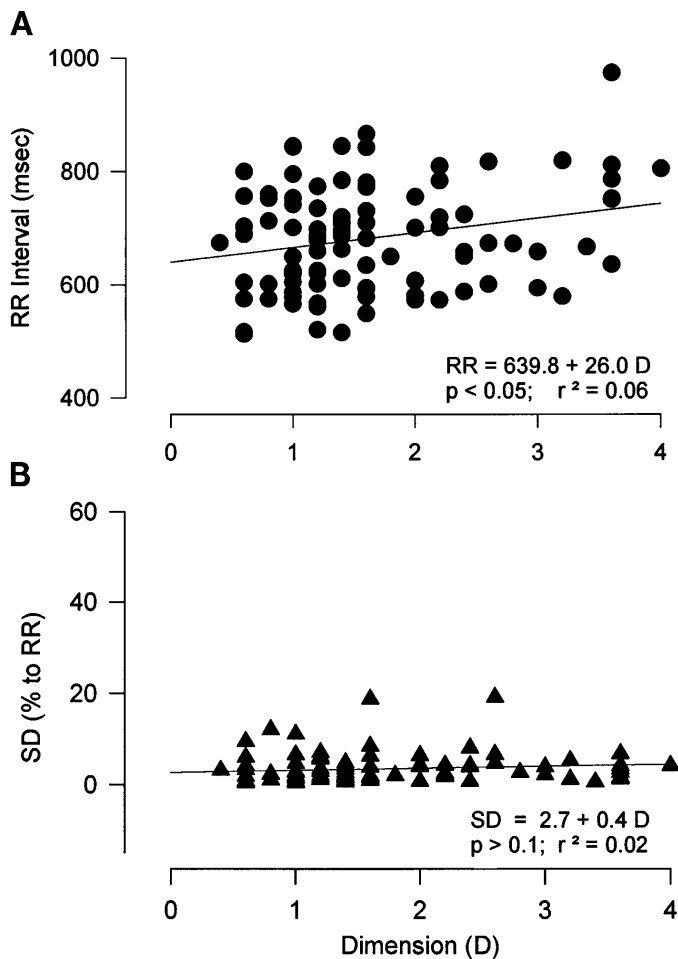
A

RR = 639.8 + 26.0 D
$p < 0.05$; $r^2 = 0.06$

B

SD = 2.7 + 0.4 D
$p > 0.1$; $r^2 = 0.02$

Dimension (D)

Fig. 3. Relationship between point correlation dimension and R-R interval (*A*) and standard deviation (*B*, normalized to R-R interval). Stochastic measures of heart rate and heart rate variability showed low specificity and correlated poorly with PD2 analysis. PD2 vs. mean R-R interval had a correlation of $r = 0.25$ with $P < 0.05$. PD2 vs. standard deviation normalized to R-R interval had a correlation of $r = 0.13$ with $P > 0.1$.

In an attempt to uncover specific oscillatory features that may contribute to the genesis of heart rate dynamics, power spectral analysis was performed. As seen in Fig. 4, the total power of the R-R interval spectra was low in the first 10 days after HTX. At 11–100 days after HTX, it rose appreciably, owing to the resurgence in the high-frequency (HF) component (0.15–0.5 Hz). This response was not sustained; it blunted at 20–30 mo after HTX, resembling the frequency spectra seen at the first 10 days after HTX. The loss of spectral reserve and reduced complexity of the HRV signal was associated with the rise in low frequency (LF) (0.04–0.15 Hz)-to-HF ratio (LF/HF). In late transplants (7–10 yr after HTX), the total power of HRV spectra was greatly accentuated by both LF and HF components.

DISCUSSION

Dimensional analysis of HRV was used to monitor pattern formation in newly evolving determinants of cardiac rhythm dynamics. The new observation of this study is that, commencing with the acute event of

allograft transplantation, the dynamics of cardiac rhythm generation proceed through complex phase transitions. The HRV dimensional changes are characterized by both positive and negative transitional states. The recognition that a gain in a dimensionality of a transplanted, centrally denervated heart can occur at a very early stage after HTX (within first 100 days) points to the role of the primary self-regulating mechanisms that may be recruited as part of the cardioadaptive process. Ultimately, the ability of a donor heart to assimilate and elaborate new functional dynamics is dependent on the graft-host mutual interactivity. It would seem that the cardiac allograft, when transplanted to its new host, is forced to evolve a number of adaptive regimes in response to the acutely imposed changes in its immediate environment, such as immunologic stress and loss of central autonomic control. This is not unlike many other systems in nature where hierarchic organization is the norm, in which the more complex has to evolve from the more simple. The successive evolution of HRV in terms of dimensional hierarchies (see Fig. 2) is consistent with this notion.

Cardiac allograft and HRV. Studies of heart rate fluctuations using conventional time- and frequency-domain analysis of interbeat intervals indicate that, in the human heart, central reinnervation takes many years to develop (3, 5, 19, 29). HRV in cardiac allografts is significantly diminished at 1–2 yr after HTX (30), recovering after 2–3 yr (3, 29) and accentuating further in the fourth through fifth year (19). These HRV changes are consistent with other indicators of improved autonomic function, i.e., norepinephrine spillover (18, 35), central autonomic reflex and exercise responses (5, 18), and "chest pain" syndrome (32). Typically, the early stage of HTX (<2 yr) is characterized by a flat, low-amplitude frequency spectrum. The observed fluctuations in the respiratory HF component
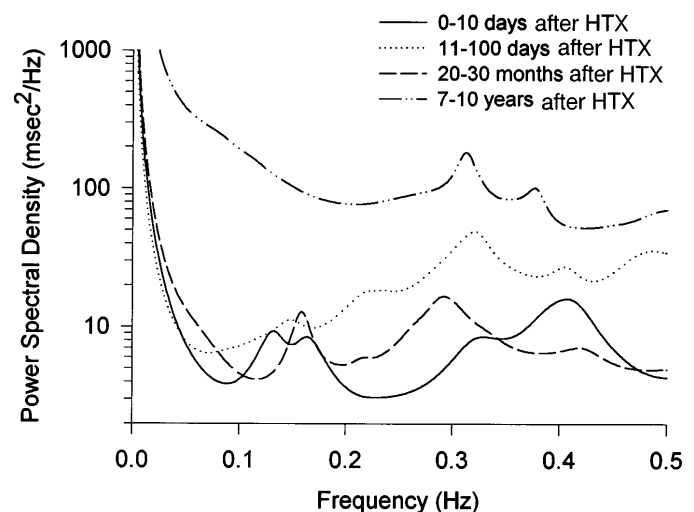

Fig. 4. Emergence of dominant frequencies. Four composite graphs of power spectral density were computed by averaging individual patient spectra for each of the respective HTX groups using maximum entropy method. *X*-axis is scaled using Nyquist critical frequency (reciprocal of 2 times the time interval between average of R-R interval data points) for each respective group.

of the HR spectra (2) are thought to be mediated by mechanical influences of lung inflations and are sustained unaltered during the first 20 mo after HTX (2). When analyzing relatively short time epochs (e.g., 0–10 days or 11–100 days after HTX), we noted a newly evolved HF spectral component (see Fig. 4) implying a presence of an active process by which the regulatory inputs to the HR generator could be altered. Apparently, the control systems associated with the long-term regulatory mechanisms, such as thermoregulation and/or the renin-angiotensin system, had minimal impact on the regeneration of the HRV, because the very-low-frequency (<0.04 Hz) component of the spectra remained relatively invariant during the first 30 mo after HTX (Fig. 4).

Dimensional analysis of heart rate dynamics in HTX. Dimensional analysis of heart rate dynamics in HTX patients (11, 37) is consistent with reported changes in time- and frequency-domain metrics, revealing the delayed onset (~2–3 yr) in establishing HRV signal complexity. Aside from the few isolated observations (37), the available information on characterizing the evolution of HRV during the early phase (<2 yr) after HTX is sparse. Significant changes in the HR dynamics accompanying the early posttransplantation period (Fig. 2) were noted in this study. Importantly, these observations challenge the current assumption of the mechanisms that underlie HRV and the control variables involved in modulating the pacemaker function. In a centrally denervated heart, in the absence of recipient autonomic control, the gain in the correlation dimension is indicative of newly configured cardiac regulatory modes emerging from the encounter of the allograft with the host environment. In contrast, a heart that is acutely isolated from its host (Langendorff preparation) (14, 31) has narrowly restricted dynamic modes and is therefore confined to a metronome-like rhythm (dimension ~1). The recovery and progressive gain in the HRV signal (onset at 30th mo after HTX; Fig. 2, *C* and *D*) is reminiscent of a newly organized pattern described by others (3, 19, 29), implying that the transition is attributable to extracardiac "functional reinnervation". Ultimately, the physiological significance of HRV time evolution has to be reconciled in terms of regulatory attributes that may have been activated and/or recruited in response to the allograft transplantation.

HRV and autonomic control. The major determinants of HRV are autonomic neural inputs that modulate the sinus node activity. Mechanical factors may, to some degree, contribute to the dynamic behavior of a decentralized heart; unlike neural inputs, they remain relatively fixed and thus cannot mediate the long-term evolution of HRV signals in HTX. The observed gain in dimensional complexity (see Fig. 2*B*) associated with a rise in HF of HRV oscillations (see Fig. 4) may be a product of newly evolved interactions and/or reinforcement of existing local control mechanisms. Specifically, upregulation of existing (dormant, less active) modes of sinus node modulation such as mechanical stretch or activation of the intrinsic neuroendocrine system are likely to be involved. A significant number of intrinsic cardiac neurons, having an extensive interconnected network, remain in place and accompany the donor heart (34). The multiple feedback loops making up the intrinsic cardiac nervous system (ICNS) may play a significant mechanistic role in organizing and orchestrating the complex dynamic behavior of a decentralized heart. Recent studies in isolated hearts (14) demonstrated the inherent capacity of this system to regulate sinus node function by engaging an activity of intracardiac reflex-like control mechanisms. Importantly, the chemical activation of ICNS by endogenous peptide (e.g., bradykinin) (16) and ischemic stress (31) was accompanied by a short-lived gain in dimensional complexity of the HR dynamics (rise in PD2 from ~1 to ~2). This response is reminiscent of the early phase after HTX, in which the cardiac allograft is subjected to an altered chemical environment resulting from the immunologic insult. These stressors may initiate a form of allostatic "exploration," promoting new modes of regulatory response.

The next phase of the time advance of organized complexity is associated with a newly established functional order that may arise from reactivating central autonomic neural control mechanisms. An accepted premise based on numerous clinical observations is that in humans the functional reinnervation process begins with activation (~1–2 yr) of sympathetic mechanisms (3, 18, 35) and is followed (>2–3 yr) by partially engaged vagal control (5, 7, 29). The heterogeneous nature of the reinnervation process may lead to an unbalanced sympathetic-parasympathetic interaction. In non-HTX cardiac patients, a predominance of sympathetic tone is accompanied by attenuation of HR generator dimensionality (6). In this study, HRV, characterized by what seems to be simple dynamics (PD2 ~1; Fig. 2*C*), may be a product of dominant sympathetic coherent mode. Associated rise in the LF/HF ratio (comparing periods of 20–30 mo to 11–100 days after HTX; Fig. 4) is suggestive of the relative prominence of sympathetic tone. It is tempting to speculate that at 2 yr after HTX, the dominant mode associated with the intrinsic cardiac homeostats is downregulated as a consequence of resurgence of the central command and control function. This may account for the observed loss in HF power spectra.

Regeneration of the succeeding hierarchic structures, expressed by a progressive evolution of dimensional complexity of HRV (Fig. 2, *C* and *D*), and a rise in the total power of the HRV spectra (Fig. 4) can be attributed to the further reestablishment of central autonomic regulatory modes. In normally innervated human heart, transition to a higher HRV dimension was shown to be associated with parasympathetic accentuation (33). By analogy to this response, the observation in transplant patients can be ascribed to the restoration of functional order patterning parasympathetic control. It is intriguing to consider the posttransplantation modeling pursuit of cardiac control systems as an attempt to emulate the evolutionary

design of "normal" HRV dynamics using its own genotypic and/or phenotypic propensity.

Heart adaptation. A notable observation of this study is that the cardiac rhythm-generating system is not frozen in time but is "engaged" to evolve new patterns of HRV dynamics. The increase in the functional complexity is a reflection of the dynamic interplay of HR generator with the newly constituting constraints of the host habitat. In many biological systems, the increase in system complexity is a natural by-product of a developmental process by which diversity of function and robust evolutionary adaptation are achieved (12). Overall, body systems independent of hierarchical organization (molecular to multicellular) normally operate such that a number of regulatory modes are active. Chaotic systems are very susceptible to changes in initial conditions, i.e., small changes in a given parameter of a chaotic system can produce very large changes in the output (poised at the "edge of chaos") (12, 17). This allows the system to switch rapidly from one state to another. A chaotic regime may enable the heart to operate such that regulatory changes can be achieved with minimal external input, a behavior that is reminiscent of self-organized criticality and often seen in other physical phenomena (17). From a standpoint of economy of performance (energy use), there must also be some upper limit set on the number of active degrees of freedom (control variables) that can or need be summoned. Most of the physiological time series data are restricted in dimensional complexity to 3–8 degrees of freedom (25).

The heart contains multiple nested loops of nonlinear interacting regulators (homeostats), making it amenable to chaotic behavior and therefore to a finer and/or rapid adaptation. The postulate of this study was that effective adaption serves as an impetus for building greater complexity. Indeed, sustained periodicities (predictability) of cardiac rhythm are often associated with "unhealthy" events (tachycardia and bradyarrhythmia). A healthy young person shows a greater complexity in HRV than an older person (9). The cardiac allograft is devoid of many extrinsic regulatory regimes and consequently is entirely dependent on its own built-in regulatory schema for seeking out an optimal course of action. It seems that the intrinsic capacity for evolving complexity in HRV dynamics confers a certain degree of cardiac protection. In patients exhibiting acute rejection, the early surge in dimensional complexity of the HRV signal was notably suppressed (15). Moreover, it has been documented that as much as 80% of sudden cardiac death and the increase in an arrhythmia incidence were confined to a period starting at the second year after HTX (26). These events are coincident with the loss of "intrinsically mediated" dimensional HRV complexity (see Fig. 2*C*) and reappearance of a dominant "sympathetic" mode (attractor). Importantly, in nontransplant cardiac patients, the loss in the dimensionality of the HR signal was shown to be a sensitive precursor of sudden death (6).

The cardiac rhythm-generating system, accommodating a set of local constraints, is forced to elaborate new functional order in response to the ongoing donor-host assimilation process (resurfacing extracardiac functional neural connections). These events are reminiscent of "coevolution"-mediated adaptive processes, by which the cardiac allograft and its new host reestablish dynamics closely resembling the normal heart. Interestingly, while evolving from a simple regulatory mode (dimension ~1) to a much greater dynamic capacity (dimension ~3), the evolutionary trend of the HR-generating system is such that it never reaches a plateau, an observation that highlights the fact that in the time frame limited to 10 yr the system continues its "assembly," modifying the underlying dynamics but never being truly adapted. Consistent with general studies of autonomic neural control of the cardiac pacemaker, observations confined to the late post-HTX stage demonstrate only partial reinnervation (7, 18, 35), implying that a deficiency in function of extrinsic reflex loops persists.

HTX provides a unique opportunity to study the reassembly of mechanisms responsible for complex HR dynamics. The denervated heart cannot benefit from fixed functional and structural arrangement of feedback mechanisms, i.e., homeostatic goal-directed behavior. The paradigm of the heart as a complex open system may prove to be useful in the understanding of organizational principles involved in regenerating the dynamics of a system and the means by which a new functional order can emerge. The recognition that the decentralized heart restitutes the multidimensional state space of HR generator dynamics somewhat independently of external autonomic signaling may provide a new perspective on the important attributes that constitute homeodynamic regulation.

Perspectives

Ultimately, the challenge to graft-host adaptation lies beyond merely conquering the immunologic conflict; it may require newly organized modes of self-regulation of the allograft within its assimilating environment. The implication and understanding of the newly emergent functional order attributable to the graft-host interaction may be better served by considering organizing principles of coevolution that are resurfacing in studies of complex adaptive biologic systems (17). Coevolutionary adaptation dictates that each participant in this assimilation process, while satisfying its "selfish" predisposition, deforms the environment ("fitness landscape") and constraints of its neighbor(s), giving rise to an emergent joint effect that will be favorable to both. The heart is not made independently and then assembled; it arises from interactions within the developing organism. The "self-serving" behavior of the cardiac allograft, when transplanted, may in a significant way dictate the course of reestablishing a functional autonomic control within the recipient body. An active role of a target tissue (organ) during the reinnervation has been demonstrated in a number of biological models (4, 13, 27). It is now recognized that the "target" tissue not only releases factors activating neurite growth (27) but also determines the anatomic

direction of the process (13) and the functional expression of the reconstructed neural connections (4). Indeed, a natural by-product of allograft that survives over time is an observed gain in degree of functional complexity of heart rhythm. The newly attained order represents a form of "self-organization," a response to "natural selection" of the donor heart in its attempt to assimilate within the "new landscape" of the recipient.

The heart is an organ endowed with adaptive plasticity (genotypic and/or phenotypic memory) and the capacity to assimilate ("fitness capacity") within the host and, in the process, modify the environment determining the fate of the body system as a whole. The expectation is that the paradigm of complexity will provide a nonreductionist framework for understanding the principles by which "emergent properties" and functional order of self-organizing systems ultimately achieve (homeo)dynamic stability. In such a construct, the integrative action of the living organism cannot be gotten from its concatenated fractions but is evolved "relationally," i.e., it emanates from emergent internal requirements of the parts.

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