Emergence (from chaos?) of Regulatory Order in the Transplanted Heart

J. Yasha Kresh

Depts. of Cardiothoracic Surgery / Medicine, Medical College of Pennsylvania/Hahnemann University, PA, USA

There are many systems in nature in which a large assembly of autonomous parts (agents) interacting locally, in the absence of a high-level global controller, can give rise to highly coordinated and optimized behavior. The complex adaptive behavior of global-level structures that emerges is a consequence of nonlinear spatio-temporal interactions of local-level processes or subsystems. This form of nested co-optation (across levels of organization) constitutes isolated cells, organisms, societies and ecologies. Systems of this type are governed by universal principles of adaptation and self-organization, in which control and order is emergent rather than predetermined, i.e., cannot be derived simply from their concatenated fractions but evolves "relationally", i.e., it emanates from emergent internal requirements of the constitutive “parts within parts”.

Evolution in heart rate variability dynamics was used as measure of the capacity of the transplanted human heart to express newly emergent regulatory order. In a cross-sectional study consisting of 100-patients post (0-10 yrs) heart transplantation (HTX), heart rate dynamics was assessed using pointwise correlation dimension (PD2) analysis. In general, the number of variables required to characterize the time-dependent events of a dynamic system determines its “dimensionality”. PD2 of 4-5 in normal subjects is expected to reflect the minimum number of independent control variables, i.e., degrees of freedom that define the dynamics of the cardiac pacemaker. How precisely the interaction of the components comprising the autonomic nervous system translate into a system dimension that is greater than the mere number of known pacemaker control loops (attributable to the parasympathetic and sympathetic system) remains to be elucidated. Nevertheless, the number of control variables involved in the "regulation" of the HR-dynamics is considerable less than the number of neuromodulators known to alter sinus node automaticity. This is consistent with the view that a dissipative system having a large number of state variables does not traverse the whole of its state-space but operates within a bounded subset, defined by only few variables.

Commencing with the acute event of transplantation, the dynamics of cardiac rhythm formation exhibited a number of phase transitions. Shortly after implantation, the donor heart manifested a metronome-like behavior (PD2~1.0). The dimensional trajectory of HRV reached a peak value of PD2~2.0 at 11 to 100 days post-HTX. The subsequent dimensional collapse to PD2~1.0 at 20-30 month post-HTX was followed by a progressive near linear gain in the functional order of the rhythm generating system, reaching PD2~3.0 at 7-10 years post-HTX (see Figure).

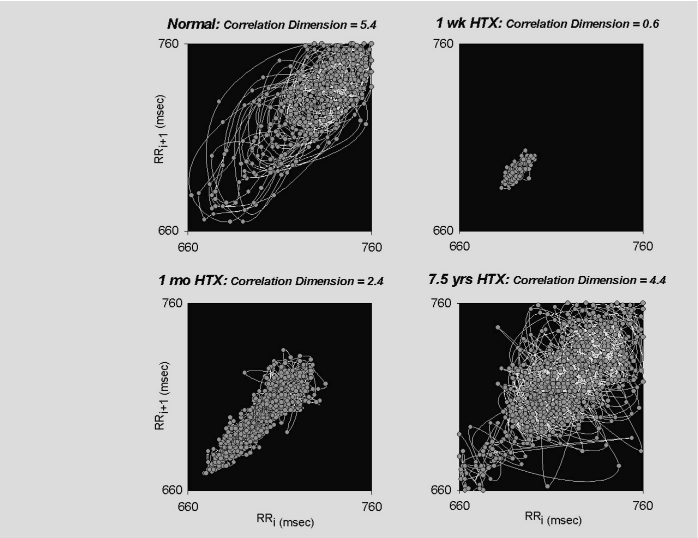

Figure: Phase-plane portraits (Poincare' plots) of cardiac allograft RR-interval time-series, in route to/from complex dynamics with its respective attractor dimension (point correlation dimension-PD2).

The "dynamic reorganization" of the rhythm generating system of the transplanted heart, seen in the first 100 days can be attributed to adaptive capacity of intrinsic control mechanisms carried together with the donor organ. It is important to emphasize that the HRV dynamics in early stage of post-HTX (within first 100 days) are in fact generated by a system devoid of central autonomic control, thus implicating a causative role to the intrinsic cardiac regulation. The fact that a finite

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dimensionality associated with the heart rhythm generator was observed implies that the allograft is not merely a passive participant in the assimilation process within the host "landscape". Importantly, the decentralized heart is capable of expressing new patterns of self-regulation. The fact that the heart can restitute the multi-dimensional dynamics, relatively independent of external command and control, is an impetus for reassessing the prevailing paradigm of cardiac regulation and adaptation.

The denervated heart offers a unique experimental model to study the reassembly of the mechanisms responsible for a complex HR dynamics. The transplanted heart cannot benefit from fixed structural arrangement of feedback mechanisms, i.e., homeostatic goal directed behavior. Viewing the heart as an open system may prove to be useful in the understanding of organizational forces involved in restituting a system that exhibits a higher order of behavior. The progressive gain in HRV-dimension indicates some degree of restitution of "functional complexity" to cope with perturbations as they arise. Otherwise, the system would get "stuck in a rut" once it settles in stable environment, where the dynamics of operating point that is restricted in time to a fixed state space attractor.

The observed gain in dimensional complexity may be a product of newly evolved interactions and/or reinforcement of existing local control mechanisms that may facilitate new modes of regulatory function, i.e., emergent order. Specifically, upregulation of existing (dormant, less active) modes of sinus node modulation, such as mechanical stretch or activation of intrinsic neuroendocrine system are possible candidates involved in the emergence of new regulatory patterns.

The biological implications associated with observed HRV-changes post-HTX go beyond the simple characterization of sinus node pacemaker function. In a centrally denervated heart, the modulatory response of cardiac rhythm dynamics is indicative of regulatory function of intrinsic cardiac neuroendocrine mechanisms [1]. The highly distributed nature of the intrinsic cardiac nervous system enables it to integrate changes in the chemical milieu and mechanical state of the myocardium. The organization of complex intrinsic feedback systems constitutes a functional "heart-brain" that may participate actively in the cardiac response to environmental changes. The dynamic interactions among functional components intrinsic to the heart, e.g., neurons and endothelium, give rise to a complex self-regulating organ-system. The transplanted heart, in its encounter with the host, manifests many of the attributes characterizing "complex adaptive systems": network of interacting components, organizational order, multi-functionality, and fluctuation in system parameters. An early surge in dimensional order (PD2) of heart-rate generator proved to be a characteristic feature of donor heart-recipient dynamic interaction. Structural and functional uncoupling resulting from an imposed allostatic load, e.g., organ rejection [2], can trigger a loss/decline in network (hypercycles) of regulatory organization, manifested as a reduction in the dimension of HRV state-space attractor.

The transition in the heart-rate generator "dimension" (gain/loss) may help in quantifying, at least in some reproducible way, the functional reserves and adaptive capacity of the intrinsic control mechanisms. This conceptual framework goes beyond the view that fluctuations in HRV are simply random events. Adaptation of the heart to its host is an impetus for greater level of functional integrity, i.e., higher system dimension, emergence of pattern and order. From a system theory standpoint, a system that is endowed with greater number of degrees of freedom is more robust and has a greater ability to accommodate imposed disturbances. In general, biological systems, independent of hierarchical organization (molecular to multi-cellular), normally operate such that a finite number of regulatory modes can be invoked. It seems that most of physiological time-series data are restricted in dimensional complexity to 3-6 degrees of freedom.

Chaotic systems are very susceptible to changes in initial conditions, i.e., small changes in a parameter of chaotic system can produce very large changes in the output, i.e., poised at the "edge of chaos" [3,4]. This allows the system to switch from one state to another rather quickly. It may be that chaotic regime enables the heart to exert its function such that regulatory changes can be achieved with minimal external input, reminiscent of "self-organized criticality" seen in other physical phenomena. From a standpoint of economy of performance (energy use, responsiveness) there must be some upper limit set on the number of active degrees of freedom (control variables) that can or need be summoned.

The explanatory model of the newly emergent functional order attributable to graft-host interaction may benefit by evoking organizing principles of "co-evolution".

The heart is an organ endowed with an adaptive plasticity (genotypic / phenotypic memory) and capacity to assimilate ("fitness capacity") within the host and in the process modify the environment determining the fate of the body system as whole.

The principles by which "emergent properties" and functional order of self-organizing system, such as the heart, achieve homeodynamic stability provide a non-reductionist framework for understanding how biological system adapt to imposed internal and external stresses, i.e., ischemia, organ/tissue replacement. Thus, the newly emergent dynamics of cardiac rhythm arising after heart transplantation may represent a more stable, versatile and adaptive regulatory order.

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