

## Impact of Chaos in the Progression of Heart Failure

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### Abstract

**Purpose of review:** *Cardiologists and researchers are well informed of the advances in chaos theory and nonlinear dynamics and their clinical application in the field of cardiology. Heart failure is a syndrome with a progressive clinical deterioration that involves left ventricular dysfunction and neurohormonal adaptations with a relentless course toward end-stage myocardial failure. In the present paper, a concept of chaotic behavior of cardiac function during heart failure progression is introduced.*

**Recent findings:** *The progressive nature of heart failure discloses a dynamical and non-linear system with properties and characteristics of chaotic behavior related to the initial conditions and the presence of a chaotic attractor. The clinical deterioration of heart failure in a worse clinical state concentrates the characteristics of a complex and unstable system that is stabilized in the form of a strange (chaotic) attractor. The clinical stabilization in the form of a strange attractor is accomplished with help from the self-organized positive feedback stabilization neurohormonal mechanisms. This stabilization period is interrupted by miscellaneous causes with left ventricular remodeling being the most prominent.*

**Summary:** *In human heart failure, there are periods of clinical stabilization in the form of the strange attractor that depends on its initial state, and interruption periods of clinical instability. In the interruption periods small changes of the interrupted causes can produce high clinical instability. Left ventricular remodeling with its functional myocardial deterioration is the most probable cause of the clinical decline and of the progressive nature of heart failure.*

**Keywords:** Heart failure, Chaos in heart failure, Heart failure progression, Strange attractors

### 1. Introduction

The prevalent knowledge of the biological systems is based on the standard scientific perception of natural equilibrium, determination and predictability. Recently, a rethinking of concepts was presented and a new scientific perspective emerged that involves complexity theory with deterministic chaos theory, nonlinear dynamics and theory of fractals. The unpredictability of the chaotic processes probably would change our understanding of diseases and their management.

The mathematical definition of chaos is defined by deterministic behavior with irregular patterns that obey mathematical equations which are critically dependent on initial conditions [1]. The chaos theory is the branch of sciences with an interest in nonlinear dynamics, fractals, bifurcations, periodic oscillations and complexity. Recently, the biomedical interest for this scientific field made these mathematical concepts available to medical researchers and practitioners [2,3]. Any biological network system is considered to have a nominal state, which is recognized as a homeostatic state [4]. In reality, the different physiological systems are not under normal conditions in a stable state of homeostatic balance, but they are in a dynamically stable state with a chaotic behavior and complexity [5]. Biological systems like heart rhythm and brain electrical activity are dynamical systems that can be classified as chaotic systems with sensitive dependence on initial conditions. In biological systems, the state of a disease is characterized by a loss of the complexity and chaotic behavior, and by the presence of pathological periodicity and regulatory behavior. The failure or the collapse of nonlinear dynamics is an indication of disease rather than a characteristic of health.

Heart failure and a variety of other pathologies demonstrate a paradoxical decrease of the nonlinear variability observed in the normal sinus rhythm in healthy people. The chaos theory and the field of nonlinear dynamics are research areas that are related to basic and clinical cardiology. Important classical research fields related to cardiology are the sinus rhythm, ventricular fibrillation and cellular cardiac electrophysiology. Cardiac chaos is related to the purposeful-fluctuations in the instantaneous heart rate or interbeat interval (beat-to-beat variability) in healthy subjects, while in patients with heart failure this phenomenon of heart rate variability (HRV) seems to decrease [6].

There is substantial evidence that the deleterious progression of heart failure and its complicated clinical picture follows the philosophy of chaos theory [7]. Heart failure is a system that displays chaotic behavior and practical unpredictability of future deleterious progression as the small differences in the initial causal conditions can lead to large differences of the subsequent clinical course. The subsequent state of the disease's progression is comprehended as a system that follows a deterministic chaotic attitude in contrast to the concept of rhythm regularity as the classical behavior of a diseased state.

## **2. Chaos theory and nonlinearity**

The chaotic systems are deterministic with no random elements, highly sensitive to initial conditions, and unpredictable. Small differences in the initial conditions have widely varied end-effects, making long-term prediction impossible. There is no standard correlation between cause and effect as small initial perturbations produce big changes and large initial alterations may have little functional consequence.

The chaotic behavior is a characteristic of complex and nonlinear systems. Therefore, from a mathematical or biological perspective the nonlinear systems demonstrate a chaotic behavior and in each level of complexity are emerging new properties not predicted from the interaction of component elements. Also, the chaotic systems manifest similar characteristics at different levels of scale (fractal scaling), and in an imaginable 'phase space' they are forming areas of chaotic attraction with great detail and complexity called 'strange attractors' which have a fractional dimension. A strange attractor is an attractor with non-integer dimension with a local topological structure. Thus, a large set of initial conditions leads to orbits that converge to a region in n-dimensional phase space occupied by the strange attractor which is a complicated set with a fractal structure and high sensitivity to initial conditions. The area of the imagined phase space under the dominance of the attractor is called the 'basin' of the attractor.

The method to display a chaotic system is the plotting of its trajectory with time. A complex and dynamic system is described as having 'n' variants, with each one to occupy one dimension, and the trajectory of each variable is plotted with time in an 'n' dimensional graph or phase space [8]. In a particular area of the phase space a variable's trajectory forms a pattern called strange attractor having an optimum size and behaving as a constraint (limitation) to further increase. Thus, chaotic systems are not random and when their behavior over time is appropriately displayed in phase space, constraints are evident which are described by 'strange attractors' [9]. Therefore, any biological disturbance can reach a size optimum which behaves as a constraint of further increase and acts as a kind of strange attractor in the phase space. The term 'constraint' refers to a boundary or limitation on what is biologically possible. Fractal (strange) attractor, has a fractional dimension and is underlying chaotic systems [10]. Thus, the measurement of strange attractor's dimension determines how chaotic is the system and reveals that chaos possesses a dimension. Also, there is a relationship between the properties and behavior of a dynamical system and the topology of the attractor.

Fractals are the modes generated by mathematic equations resulting in chaotic systems. The fractal geometry concept is expanded to the biological sciences and led to significant progress in understanding complex functional properties and structural features in normal and diseased states [11]. Chaotic systems display statistical self-similarity or recurring patterns at every scale in biological or non-biological systems. Biological systems such as the branching of the circulatory and bronchial systems are following a fractal model. Circulatory structures have a fractal pattern for rapid and efficient transport as they are providing extended surface area, more than other spatial organization [8]. A biological system with an irregularity constant over different scales is a fractal. Fractals are important for the description of the natural irregularity of physiological systems. Their irregularity is not random and is demonstrated to have spatial or temporal correlation [12].

### 3. *Chaos in cardiology*

At the present time, clinical evaluation is based on various parameters rested on clinical experience and epidemiological studies. The same clinical parameters assess progression of a disease and evaluate the underlying risk of sudden cardiac death. It is significant in clinical practice the development of sophisticated methods from nonlinear dynamics in order to advance medical diagnostics. In an early date, Mackey and Glass [13,14], suggested that irregular physiological rhythms might be associated with deterministic chaos. In the philosophy of medicine, chaos theory has limited implications for the analysis of the concept of disease and the concept of causation, because chaotic processes are fully deterministic and unpredictable due to extreme sensitivity to initial conditions [15]. In contrast, the complexity theory has substantial implications for our knowledge and practice in medicine. Thus, the unpredictability of chaotic processes produces practical problems in diagnosis, prognosis, and treatment, but may be very important in understanding the physiological processes and disease entities [15].

Preliminary studies supported the hypothesis that methods from nonlinear dynamics are able to evaluate heart rate fluctuation and identify patients at high risk for sudden cardiac death. In an early publication, it was suggested that the reduction of the HRV in a subgroup of patients with increased cardiac mortality after myocardial infarction, was due to an autonomic imbalance marked by increased sympathetic and decreased vagal nervous activity [16]. Significant physiological information about the heart is the time between two consecutive beats, known as the interbeat interval which varies constantly.

The fluctuation of the normal heartbeat period (irregular periodicity) is not explained completely by a linear approach and it was proposed that it is a nonlinear deterministic procedure [17]. Also, Goldberger [17] discovered that heart rates show fractal patterns but it is still inconclusive why the fractal patterns break down in diseased hearts. The human heart exhibits deterministic chaotic behavior under normal circumstances, while the unhealthy heart is presented by immutability and predictability. Hence, in cardiac rhythm, the normality is represented by a chaotic interbeat interval (beat-to-beat variability) while a regular heart beat is a sign of disease and predictor of imminent cardiac arrest [18]. It appears that a regular beat follows pathological conditions like end-stage heart failure, while normal irregularities are signs of normal heart function (Figure 1). The electrocardiograms of healthy individuals demonstrate complex nonlinear dynamics and deterministic chaotic behavior, but not stochastic (non-deterministic). In healthy people, the chaotic behavior is displayed by short-term variations of beat-to-beat interval, but in patients with heart failure there are periods with non-chaotic fluctuations [19]. A decrease of the normal nonlinear variability is observed in different cardiovascular diseases and before ventricular fibrillation [20]. Stochastic analyses like standard deviation or power spectrum, display reduced sensitivity and specificity compared to the dimensional measures (attractors) [21]. Thus, a reduced standard deviation of interbeat interval may predict an increased mortality of the group, but cannot identify the individuals who will develop fatal arrhythmogenesis. In contrast, the attractor dimension of the same data can specify which patients will have sudden death. The explanation for the increased sensitivity and specificity of the dimensional measures or attractors is the fact that they are deterministic and therefore more accurate in biological systems and medicine to detect disorders [22].

In the DIAMOND study, Huikuri et al [23], reported the application of nonlinear dynamics to the study of HRV signal in patients after a myocardial infarction. They suggested that the loss of short-term correlation properties of the interbeat intervals predict arrhythmic and total mortality. Probably, a continuous sympathetic activation and a decreased vagal tone reduce the complexity of HRV and induce the interbeat interval to be less adaptable and capable to cope with a continuously changing body and cardiac environment [24,25].

The reduction of variance and the low-frequency spectral component of HRV are related to an increased mortality in heart failure [26]. Also, the chaos analyses on the HRV of fifty patients with heart failure and survival analysis showed that the chaos level is the best predictor of mortality [27]. Methods based on chaos analysis and nonlinear indices provide valuable clinical information and predict fatal cardiovascular events in post-infarction patients and in patients with heart failure. Although the concepts of chaos theory and nonlinear dynamics remain still at a distance from the current practices of clinical medicine, they cover an important scientific field that needs further interdisciplinary research [28]. In an attempt to elucidate the underlying mechanisms of cardiovascular dynamics, Wessel et al [29], stressed the importance of the dominant influence of respiration on heart beat dynamics. They supported the hypothesis that the observed fluctuations are explained by respiratory modulations of heart rate and blood pressure.

Molon et al [30], in sixty heart failure patients implanted with cardiac resynchronization therapy (CRT) assessed if a HR-related complexity predicts adverse clinical and cardiovascular events in one year. They used a set of linear indices of HRV and demonstrated that heart failure patients with lower baseline complexity-related indices, present worse clinical outcome.

#### **4. *The physiology of heart failure progression***

The syndrome of heart failure has a progressive pattern that starts with a myocardial mechanical insufficiency. The sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and the natriuretic peptide systems are stimulated in response to the mechanical insufficiency [31]. These compensatory mechanisms increase myocardial contractility, peripheral vasoconstriction, fluid and sodium retention and left ventricular remodeling. The compensatory mechanisms produce an ephemeral hemodynamic stability, but subsequently become maladaptive with a myocardial deterioration and hemodynamic instability. The persistent neurohormonal stimulation of the myocardium increases left ventricular volume and mass, and changes the configuration of the left ventricle to a more spherical shape. This geometric change of the left ventricle is called cardiac remodeling and has deleterious hemodynamic effects with further deterioration of heart failure syndrome. The recurrent interchange of heart failure phases, from clinical compensation with hemodynamic stability to a decompensated state with clinical and hemodynamic instability, is detrimental to myocardium. Every episode of decompensation can induce irreversible myocardial damage, and increases inflammatory cytokines that may motivate myocardial cells apoptosis [32]. Thus the decompensated periods followed by irreversible myocardial damage may contribute to the progression of heart failure. After an episode of decompensation and a short-lived clinical improvement the patient returns to another period of stabilization with an additional burden in myocardial function.

Objectives of heart failure treatment are to reduce mortality, to relieve symptoms and signs, and to prevent progression of myocardial damage and remodeling of the myocardium. It appears that the angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers delay heart failure progression and the deterioration of myocardial function. This improvement in myocardial function is based on the assumption that the compensatory mechanisms of SNS and RAAS are responsible for the activation of cardiac remodeling and heart failure progression. A substudy of the Studies of Left Ventricular Dysfunction Treatment Trial (SOLVD) demonstrated that enalapril prevented progression of left ventricular dilation and systolic dysfunction in patients with mild or moderate heart failure [31,33]. Other studies showed that carvedilol decreased the left ventricular end-diastolic and end-systolic volume index, and increased left ventricular ejection fraction in patients with mild heart failure [34]. Also, the impact of cardiac resynchronization therapy (CRT) on myocardial function has been investigated in patients with heart failure. In the randomized studies scheduled for six months of follow-up was found an up to 15% reduction in left ventricular end-diastolic diameter and an up to 6% increase in the ejection fraction [35,36]. Despite the above encouraging results definite therapeutic answer to the relentless progression of heart failure needs prospective studies with a long-term follow-up.

#### **5. *HF progression is a chaotic or a stochastic process?***

In heart failure, the concepts of chaos theory and nonlinear dynamics are focused mainly in the HRV analysis for its prognostic capacity. Moreover, chaos theory and systems biology methodology are important tools to understand the clinical progression of heart failure syndrome. In the present paper, a concept of chaotic behavior of cardiac function during progression of heart failure is introduced. This concept differs from the classical knowledge of chaotic behavior of the heart rhythm under normal circumstances and the appearance of rhythm regularity during heart failure.

In the concept of the chaotic behavior of cardiac function deterioration, the heart failure progression in a worse clinical state has the characteristics of a complex and unstable system which in an imaginable 'phase space' is stabilized in the form of a strange attractor of optimum size. The optimum size of the strange attractor is behaving as a kind of constraint to further increase. The progression of heart failure and the related underlying mechanisms can be linked to a chaotic behavior and explained with systems biology methodology and molecular, network and phenotype data integration [7]. The human heart failure is interpreted as a complex and unstable system with periods of molecular and clinical stabilization in the form of a strange attractor, and self-organized positive feedback stabilization mechanisms of adrenergic stimulation, left ventricular remodeling, and activation of the RAAS and natriuretic peptide systems.

Thus, the stabilization mechanisms are considered compensatory processes produced by activation of various neurohormonal pathways in an endeavor to maintain cardiac function and end-organ perfusion [37]. The stabilization period in the basins of attractors can be interrupted by a variety of minor or major deleterious causes, and then the molecular and clinical instability returns with the heart deteriorating into a decompensated situation. The above compensatory processes become maladaptive and partly are responsible for the return of the clinical instability. Natural history studies implicate the progressive left ventricular remodeling as the most probable cause of the clinical deterioration [38]. The left ventricular remodeling involves alterations in myocardial cells' biology and myocardial loss, changes in extracellular myocardial matrix, and alterations in left ventricular chamber geometry. Heart failure progression is an open biological system and the stabilization state (attractor) is attained from different clinical and biological initial conditions (biological convergence).

It is also possible, the unsteady and fluctuating initial conditions and the deteriorating clinical situation to stabilize in the basins of different attractors (biological divergence). The previously described stabilization mechanisms are recalled for a new stable clinical equilibrium state in the basins of a new strange attractor, but this is accompanied with a further progression of heart failure and a worse clinical picture (Figure 2). The clinical stability during the period of the strange attractor should not be confused with a rigid and stereotyped behavioral homeostasis but should be considered as part of the chaotic behavior of the whole system of heart failure progression. Thus, both clinical stabilization and formation of a strange attractor indicate that the chaotic process is rather an adaptive biological mechanism that follows the downward spiral of heart failure progression. Both constitute a temporary physiological adaptive mechanism that is activated in response to the inevitable progression of heart failure. The chaotic strange attractor maintains a maximum flexibility and stability that increases the prospects of survival. A rigid clinical situation is not adaptive and not able to react to the mechanical myocardial changes or to the deterioration of the surrounding environment. The path of the downward spiral of heart failure progression differs from patient to patient, and is determined by the initial deteriorating conditions in the beginning of each decompensated period.

A stochastic or random process is the counterpart to a chaotic or deterministic process. In a stochastic process even if the initial conditions are known, the process can follow many possibilities. Evaluating a heart failure scenario, myocardial cells often measure their local environment through the interaction of diffusible chemical signals with membrane receptors [39]. This process is stochastic for a single receptor, but the cell has many receptors which are reducing the variability by averaging. This explanation doesn't exclude the possibility of stochastic effects taking place in many biological signaling pathways with important implications for heart failure progression.

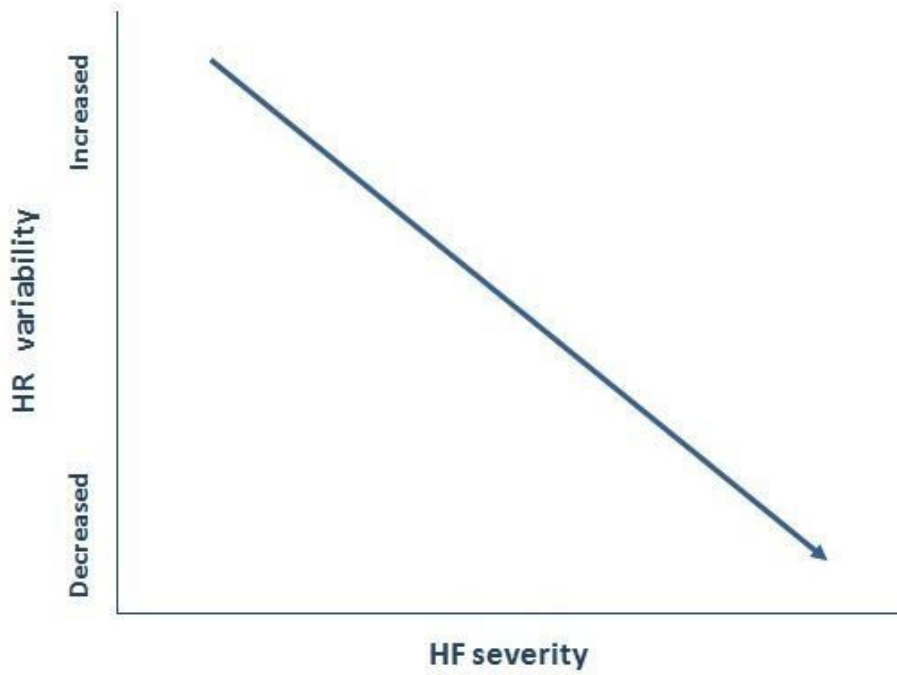
## 6. Conclusion

In human heart failure, the clinical stabilization in the form of the strange attractor, depends on its initial state and can be interrupted by dynamic minor or major causes. During the interruption period small changes of the interrupted causes can produce high clinical instability. The heart failure progression scenario gives the impression of a system that is more accurately explained by chaos theory than by a stochastic process. Probably, the stochastic effects are taking place only in the biological signaling pathways and don't explain the clinical behavior of heart failure progression that is entirely a chaotic phenomenon.

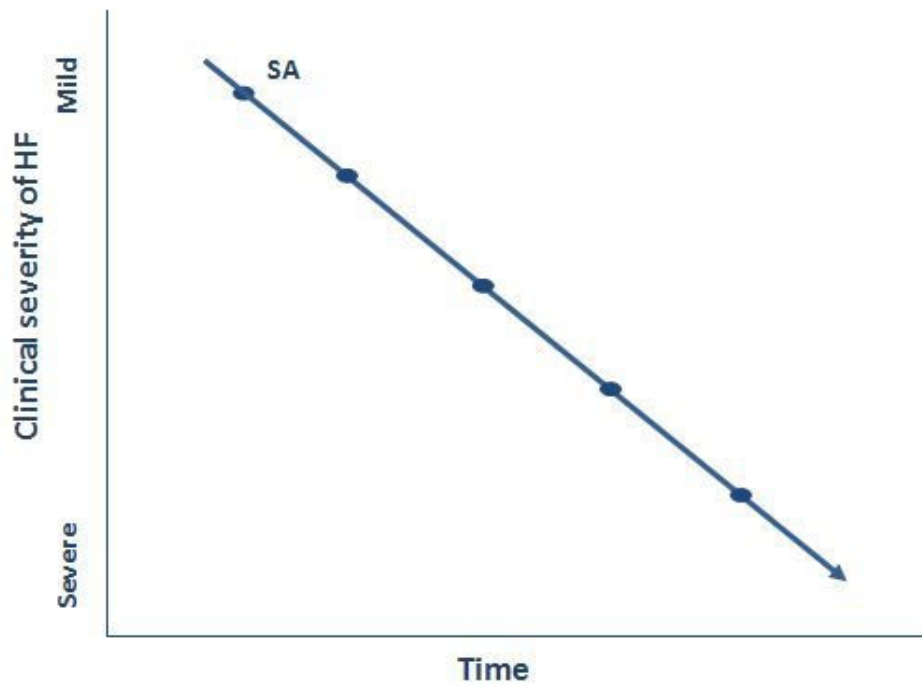
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**Figure 1.**The normality is characterized by a chaotic beat-to-beat variability while a regular heart beat is a sign of heart failure, HF (Heart Failure), HR (Heart Rate).



**Figure 2.**The recurrent periods of clinical stability and the formation of strange attractors indicate an adaptive biological mechanism that follows the path of the downward spiral of heart failure progression, HF (Heart Failure), SA (Strange Attractor).