Progressive nature of heart failure and systems biology

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Abstract

The progressive nature of heart failure (HF) is the predominant cause for the clinical course that the HF syndrome is taking. Systems biology methodology is of the utmost importance to explain and comprehend the built-in mechanisms of adverse clinical progression. Various heart diseases produce myocardial damage with subsequent left ventricular remodeling which is the principal underlying pathophysiological mechanism for the clinical progression of HF. The self-organized positive feedback stabilization mechanisms of left ventricular remodeling, adrenergic stimulation and activation of the renin-angiotensin-aldosterone system and natriuretic peptide systems, are hierarchical adaptive processes. These adaptive processes are responsible for further left ventricular remodeling with subsequent clinical deterioration and for the emergence of clinical phenotypes. These mechanisms are counteracted with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and β-blockers in an attempt to improve the adverse clinical phenomena of HF progression in a new but clinically worse stabilization level. In this review our intention is to underline the progressive nature of the HF syndrome and to demonstrate the significance of ventricular remodeling and the role of self-organized positive feedback adaptive processes.

Key words: heart failure, clinical progress, phenotypes, systems biology, ventricular remodeling

Introduction

Advances in the field of systems biology with progress in our understanding of molecular systems and complex biological networks and constructs, has produced significant applications in the fields of clinical medicine and cardiology. An accepted thesis of current systems biology is that it may be focused on constructing and improving existent but inefficient clinical disease models. It can be expanded from ‘molecular systems’ to ‘cellular’, ‘tissue’, ‘organ’ and ‘disease’ theoretical models. This is a comprehensive and integrating approach that can help us explain complex clinical phenomena.

Heart failure (HF) is a complex entity involving maladaptive biological reactions that produce irregularities and faulty function of multiple organic systems. It is vital to emphasize the progressive clinical nature of HF not only in order to understand the basic pathophysiology but also to change our view for the clinical course of the syndrome. This concept is of immense importance for prognosis and long-term management. The progressive nature of HF reveals a dynamic, self-organized and non-linear biological phenomenon. This concept reveals the chaotic behavior of the syndrome having huge consequences on clinical deterioration and follow-up.

Definition and Terminology of Heart Failure

The HF syndrome has been described as “an abnormality of cardiac structure or function that limits delivery of oxygen to the metabolizing tissues according to their requirements”. It is also a ‘malfunction’ or ‘failure’ of the heart to execute the right or appropriate function that it is supposed to carry out. The terminology or the nomenclature of the various types of HF could be misleading as the ambiguous term ‘heart failure syndrome’ describes only the clinical picture of a symptomatic patient. This terminology follows the patient regardless if he becomes asymptomatic with therapy. Therefore, HF is the clinical syndrome that is characterized by typical symptoms and signs due to underlying cardiac cause which is essential for diagnosis and crucial for therapeutic targeting.
In the International Cardiovascular Forum Journal 2 (2015), different types of HF are described under a variety of terms: according to the left ventricular ejection fraction (EF), time-course or symptomatic severity of HF4. This terminology can describe a number of clinical phenotypes as discussed below in the section of ‘clinical phenotypes’. The HF syndrome is a phenotypically heterogeneous disorder and many different clinical subtypes of HF have been reported. In the medical literature there are many terms used to describe the patients with HF; terms which are associated with the course that the syndrome has taken such as ‘asymptomatic’, ‘chronic’, ‘stable’, ‘decompensated’ (which may happen suddenly or acutely), ‘de novo’ (such as after an acute MI), ‘resolved’ (such as after an acute viral myocarditis), or ‘congestive HF’. According to ESC Guidelines, “many or all of these terms may be accurately applied to the same patient at different times, depending upon their stage of illness”.

**Clinical deterioration**

The clinical picture of a patient with HF is characterized by symptoms (dyspnea, exercise intolerance, fatigue) and signs (edema, rales). These are associated with a lower cardiac output, excessive salt and water retention, reduced functional capacity and decreased quality of life. The clinical picture encompasses a relentless progression to the final end-stage with frequent hospital admissions due to myocardial decompensation, multiple organ dysfunction, neurohormonal activation and renal impairment. Renal dysfunction is secondary to hemodynamic derangements: elevated filling pressure and low cardiac output. The underlying pathophysiological mechanisms and treatment are not the same in all patients with HF despite the similarities in their clinical picture and behavior. Their common progressive clinical instability and deterioration involves left ventricular dysfunction and neurohormonal adaptations. This progressive clinical instability is interrupted by periods of clinical stability which are followed by periods of clinical instability. During the periods of stabilization the clinical state takes the form of a strange (chaotic) attractor with characteristics that depend on the initial clinical conditions and on the self-organized positive feedback stabilization mechanisms of adrenergic stimulation, neurohormonal mechanisms and left ventricular remodeling1-3. Minor clinical changes and further left ventricular remodeling can disturb the stability of the strange attractor and produce clinical instability. Thus, left ventricular remodeling followed by functional myocardial decline is considered as the most potential cause of clinical deterioration and progression of HFS.

The concept of hierarchical organization

At this point it is important to underline both the progressive nature of HF and its hierarchical adaptive multi-level organization. These two mechanisms together produce the appearance of clinical phenotypes. The nature of HF is a non-linear dynamic system that is related to the basic concepts of emergence and self-organization of the biological systems. The systems biology methodology is a promising approach to comprehend the complexity of the HF syndrome and to decode the connections between biological components and networks. In every biological construction of a disease many levels of biologically active networks from genes, proteins, transcripts, metabolites up to the higher hierarchical levels and human phenotypes are included. Each level encapsulates many more fine-grained sublevels that reflect the hierarchical organization of the biological build-up. A disease like HF represents a “disturbed” biological construction that follows the basic hierarchical rules albeit with significant consequences for the human health.

In general, the concept of ‘network’ is correlated with a pattern of interconnections (links) between a set of objects, persons or biological phenomena. In a complex system network there are underlying consequences at the two levels of linkage. At the point of structure it is important to realize what is connected with what and at the point of behavior to appreciate the inter-behavior connections between elements of the same network or between different networks6. The intracellular and extracellular networks from genes, proteins, tissues, organisms and diseases are responsible for supporting normal or abnormal cellular functions. Thus, a disease is represented by biological networks with abnormalities in their construction and/or in their interconnections.

The HF syndrome has the characteristics of a multi-leveled structure with established novel emergent properties in each stage (level of biological network), which together add up to the level of phenotype. The “disturbed” intra- and inter-network connections that affect the emergent properties in each hierarchical level are the responsible factors for the genesis and perpetuation of HF syndrome. It is possible that high-level emergent properties are affected by low-level properties, and in the whole changes in macromolecular function have an impact on the emergent properties of the entire phenotype. Therefore, complex interplay between different levels contributes to the emergent properties that characterize every clinical phenotype. Thus, for the genesis of a clinical phenotype, it is important to assess the corresponding contribution of the intra-protein interactions or of the intra-cellular interactions or of the interactions in higher functional levels. Virtually, “there is a multitude of HF phenotypes and therefore the above mentioned classification of the guidelines is important only as a temporary diagnostic and therapeutic guide”. In the HF syndrome, following the ‘top-down’ direction (functional decomposition) of systems biology, we attempt to elucidate the compensatory regulatory mechanisms (modules) that participate in the genesis, maintenance and progression of clinical HF, as well as the genesis of clinical HF phenotypes (models). In the ‘bottom-up’ direction (functional composition), we analyze the mechanisms of complex biological networks and integrate in the different levels of the malfunctioned system are unraveled.

Adaptive compensatory mechanisms

The progressive model of the HF syndrome is initiated by mechanical myocardial dysfunction and continues with recurrent episodes of clinical deterioration followed by periods of hemodynamic stability and clinical compensation. An early-phase of myocardial stress changes is followed by a later-phase of left ventricular remodeling, which deteriorates after a lengthy period of continuous clinical progression and multi-organ involvement into irreversible myocardial damage. The initiation and the perpetuation of left ventricular remodeling is the outcome of various interacting mechanisms that are following the steps of an adaptive biological system.

Human HF, as a self-organized system with positive feedback stabilization mechanisms counteracting the adverse circumstances of heart deterioration. These compensatory mechanisms include the left ventricular remodeling system, the
sympathetic adrenergic stimulation system (SAS), the renin-angiotensin-aldosterone system (RAAS), and the natriuretic peptide systems (NPAs). Other participating compensatory systems are the prostaglandins (PGE2 and PGEI2), nitric oxide systems and cytokine and endothelial activation. The compensatory mechanisms are mobilized in response to mechanical myocardial dysfunction and form critical functional biological complexes selected for adaptation and survival. These compensatory mechanisms that are recruited for clinical stabilization and maintenance of cardiovascular homeostasis generate a new clinical and mechanical reality with progression into a temporary stage of clinical stability. On the other hand, these mechanisms are also responsible for further left ventricular remodeling, HF progression and clinical deterioration. This clinical and hemodynamic stability period is short-lived and soon becomes maladaptive to ventricular remodeling followed by deterioration to a worse clinical and hemodynamic instability period. The continuous neurohormonal stimulation of the myocardium produces geometric changes in the left ventricle having as a result an increase in left ventricular volume and mass, and modification of its form to a more spherical shape (remodeling). This remodeling adaptation is responsible for further deleterious hemodynamic repercussions with contractile dysfunction and significant clinical impact, worsening the clinical picture leading to the congestive phenomena of HF. The repetitive interchange of HF stages, from clinical and hemodynamic stability to a decompensated state with clinical and hemodynamic instability, is detrimental to myocardial function.

The symptomatic human HF syndrome has a significant prevalence, morbidity and mortality, especially for our ageing population with an increased prevalence of important co-morbidities, such as renal failure, diabetes mellitus, hypertension and coronary heart disease. The purpose of HF therapy is to retard remodeling and myocardial damage progression in order to reduce morbidity and mortality, and to relieve the patient from symptoms and clinical signs. The classical clinical picture of a patient with HF is changed with modern therapy. Modern therapy with angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and β-blockers, can retard worsening of myocardial function and clinical deterioration. This notion is based on the assumption that these drugs are blocking the deleterious effects of the compensatory mechanisms. The ACEIs and ARBs drugs are affecting the neurohormonal system and as a consequence cardiac function and LV remodeling. LV deterioration is promoted not only by the activation of the neurohormonal system but also directly from the LV remodeling process itself (ventricular dilatation, impaired contractility, diminished EF) which plays a significant role in HF progression. Thus, the ACEIs and ARBs drugs are regarded as the therapy of choice in order to block LV remodeling and HF progression, and to reduce symptoms and/or mortality.

Besides neurohormonal stimulation and myocardial remodeling, left ventricular decompensation “depends also on atrial contraction, synchronized contraction of the left ventricle and the normal interaction between the right and left ventricles.” In this regard the effect of cardiac resynchronization therapy (CRT) on myocardial function and the long-term clinical repercussions have been demonstrated to be effective in patients with HF.

Models or phenotypes

In general, an observable characteristic or trait is referred to as a phenotype (model), but most often, with the term ‘phenotype’ is described the overall appearance of a biological entity or a disease. The term ‘phenotype’ includes anatomic, physiologic, biochemical, genetic and behavioral traits and their complex relationship with the environment. The stability of a phenotypic trait must be robust which is an indication of a good adaptation to the biological environment. Nevertheless, if the genetic and environmental variations are excessively high, then the phenotype robustness is breaking down, with a change in the equilibrium point and phenotype trait. In evolutionary systems, in order to understand the basic properties of the evolutionary process mathematical approaches were introduced such as the adaptive and phenotype landscapes. These analytical techniques are suitable to study statistical associations between clinical phenotypic traits and allow an improved approach to understanding disease progression. In biology, in the course of constructing a model it is important to start from a simple abstracted picture of biological reality, and gradually to advance to larger complexities. In contrast, in the reality of the clinical domain, the construction of a clinical model is a more difficult task. That is due to the complexities of the participating biological events and particularly from the continuous change of the clinical picture. In HF, the progressive nature of the syndrome gives a more or less approximate and temporary picture of the clinical reality. Therefore, the construction of robust complex clinical phenotypes is difficult in view of the computational complexity incorporated in the model system of continuous progression of HF.

The phenotype incorporates all the elements related to the genotype, including molecules such as RNA, proteins or metabolites. In addition, both the phenotype’s appearance and behavior are modified by environmental constraints. Jameson and Kopp state that in the clinical level, “phenotype is the composite of an organism’s behavior and of observable characteristics or traits, such as its morphology, development, and biochemical or physiological properties.” The same authors comment also that “phenotypic heterogeneity occurs when more than one phenotype is caused by allelic mutations.” Changes in molecules and structures are not visible in the appearance of an organism, but are observable (by Western blotting) and are thus part of the phenotype.

Clinical phenotypes in heart failure

In general, there is the common acceptance of a universal and predictable clinical phenotype, a fact that is based on the larger similar clinical picture and on the assumption that in all patients, despite diverse etiologies, the same regulatory mechanisms are activated. Nevertheless, a cautious clinical approach identifies distinct clinical syndromes (phenotypes) having different clinical characteristics and outcomes. In the concept of ‘clinical phenotype’ different parameters are included: 1) clinical picture, 2) causes and underlying pathophysiology, and 3) satisfactory explanation of the progressive HF worsening. Current systems biology approaches contribute to a successful synthesis and gradual construction of such clinical models.

Mann and Bristow16 proposed a classification with the following phenotypes: a) Cardiorenal, b) Cardiocirculatory or Hemodynamic, c) Neurohormonal, and d) Biomechanical. The cardiorenal phenotype presents with a combined cardiac and renal dysfunction; the cardiocirculatory is associated with a reduced cardiac output; the neurohormonal is based on the assumption that the heart is affected by the neuroendocrine system; and the biomechanical is related to the left ventricular deterioration induced by left ventricular remodeling. These phenotypes are interrelated and in the same patient
two or more of those can coexist during the clinical course of the syndrome17 (Fig 2). The biomechanical phenotype explains better certain emerging therapies, as well as the genesis and progressive clinical deterioration of the syndrome. The construction of a realistic, reliable and robust biomechanical model of HF can be accomplished by integrating knowledge from the molecular and mechanistic data. The construction of a biomechanical phenotype with rigorous determination of each biological step requires meticulous mathematical and statistical structures. This mathematical methodology needed is presently beyond the scope of our current computing capabilities, but these will improve.

The most recent classification of the clinical model system is based on the LV ejection fraction (EF) and includes two clinical phenotypes, the phenotype with a reduced EF (HFrEF) (EF<50%) and the phenotype with preserved EF (HFpEF) (EF>50%)20. A common characteristic in both HFrEF and HFpEF is reduced stroke volume, in the pre-compensatory or un-remodeled state. Remodeling, that is a dominant and adaptive compensatory mechanism, results in a near normalization of stroke volume, increasing the end-diastolic volume (in the absence of hypertrophy) or keeping it at normal levels (in the presence of concentric hypertrophy)20.

In contrast to the above classification, Keulenaer and Brutsaert20, believe that HFrEF and HFpEF are not two distinct clinical phenotypes but represent a continuous disease spectrum of overlapping phenotypes. They presume that this approach is the result of the integrative application of systems biology methodology to the complex nature of HF syndrome. In our opinion, it is more clinically sound to consider the two phenotypes, HFrEF and HFpEF, as two separate clinical entities. This differentiation between the two phenotypes seems to be helpful for clinical, preventive and therapeutic reasons.

In a new proposed concept, the LV remodeling of the HFpEF is attributed to coronary microvascular inflammation in contrast to the remodeling of the HFrEF which is produced by the loss of cardiomyocytes21. Thus, the HFpEF paradigm is associated with a systemic proinflammatory state induced by comorbidities (obesity, diabetes mellitus, chronic obstructive pulmonary disease, and hypertension) and with coronary microvascular endothelial inflammation. Both are considered critical factors for myocardial remodeling in this category of patients.

**Personalized management**

The present article is focused on clinical HF phenotypes in order to have a comprehensible picture of the nature of HF clinical progression. Furthermore, emphasis is addressed to a more personalized therapeutic approach. Novel strategies are needed to intervene promptly in the initial stage of disease progression in order to implement individualized therapies. The diversity of HF clinical subgroups (different phenotypes) needs an individualized therapy with the help of an integrated approach. A more sophisticated methodology is required in clinical screening and novel technologies are necessary to devise tailored therapeutic approaches.

The personalized genomic effect in cardiology and in clinical practice remains questionable for many heart diseases. The availability of various microarray data and the identification and comparison of single nucleotide polymorphisms (SNPs) between patients with HF and healthy individuals, so far, have not demonstrated any significant relation to the clinical phenotypes. Therefore, today, the translational genomic research for HF patients has limited applications, but its future clinical value seems unquestionable and the integration of genomics into clinical cardiology practice will be increasingly productive and rewarding. A rigorous monitoring system, data comparisons and interdisciplinary communication between clinicians and researchers can in future resolve the challenges of clinical translation of genomic research22. Scientists and researchers from different scientific areas should cooperate with cardiologists and other medical practitioners to translate knowledge from molecular biology and apply it to the clinical practice.

In general, our knowledge of the biological facts that are implicated in the genesis and progression of the HF syndrome is incomplete. The present limited knowledge doesn’t extend to every cellular biological effect. It doesn’t extend to the entire complex biochemistry of the DNA ladder, transcriptional messages, and enzyme or protein assemblage. Hundreds of malfunctioning biochemical factors that interact and integrate in different levels of the hierarchy from the cell to phenotype are implicated. We are in need of an overall structure to integrate all the faulty functions that are taking place. In the future a rational and comprehensible whole is required to integrate modules to a comprehensible clinical model.

Advances in pharmacogenomics and pharmacoproteomics proved to have significant implications for the diagnosis and therapy in specific groups of patients with HF. Novel promising personalized therapies could be addressed to three mitochondrial areas responsible for the development of the clinical HF syndrome; mitochondrial biogenesis, mitochondrial...
oxidative stress and mitochondrial iron handling. Targeting these underlying mitochondrial mechanisms the focus of research is turning to the mitochondrial dysfunction of the failing heart, a crucial factor for the demise of efficient contractile myocardial function.

In dilated cardiomyopathy, the role of circulating autoantibodies against cardiac proteins is important. Immunoadsorption (IA), by removing the circulating autoantibodies and the subsequent use of immunoglobulin G (IgG) is a novel therapeutic approach with significant improvement of symptoms and EF24. In IA/IgG responders and non-responders the myocardial gene expression patterns were different for genes of oxidative phosphorylation and mitochondrial dysfunction. This therapeutic approach and other subsequent strategies of genomic analyses may be important for more personalized therapy in the future with an appropriate selection of patients who will be responders.

In current clinical cardiovascular practice, the progress made in the field of –omics, has allowed the advance of a more individualized approach to disease management with the use of emerging cardiac biomarkers. The cardiac endocrine role is important for cardiovascular and renal system regulation, integration and homeostasis. The NPs are cardiac natureative hormones produced and secreted by atrial and ventricular cardiomyocytes. They are increased in HF patients due to myocardial cellular stretch or wall stress. The levels of NPs are increased in HF patients because of their biological role to maintain renal sodium excretion and balance, as well as to preserve volume and pressure homeostasis. The atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP) and the inactive NT-proBNP cleaved from the pre-prohormone BNP, have wide clinical applications as cardiac biomarkers. Cardiac biomarkers are useful clinical tools to yield information for diagnosis, prognosis and response to therapy for all phenotypes of HF, HfPEF or HFpEF, and chronic or acute HF. Nevertheless, the present available therapy overlooks the structural and functional changes underlying the myocardial mechanisms of HF and, instead, treats only the neuroendocrine and vascular patterns were different for genes of oxidative stress and mitochondrial dysfunction

Conclusion
Human HF is a complex and self-organized biological entity that is progressive with clinical and myocardial deterioration. A more sophisticated methodology and knowledge are required in clinical screening while new technologies are necessary to predict a tailored therapeutic approach.

Conflict of interest
None declared

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