Systems Biology Applied to Heart Failure With Normal Ejection Fraction

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Abstract

Heart failure with normal ejection fraction (HFNEF) is currently the most prevalent clinical phenotype of heart failure. However, the treatments available have shown no reduction in mortality so far. Advances in the *omics* sciences and techniques of high data processing used in molecular biology have enabled the development of an integrating approach to HFNEF based on systems biology.

This study aimed at presenting a systems-biology-based HFNEF model using the bottom-up and top-down approaches.

A literature search was conducted for studies published between 1991 and 2013 regarding HFNEF pathophysiology, its biomarkers and systems biology. A conceptual model was developed using bottom-up and top-down approaches of systems biology.

The use of systems-biology approaches for HFNEF, a complex clinical syndrome, can be useful to better understand its pathophysiology and to discover new therapeutic targets.

Introduction

Heart failure (HF) is a complex clinical syndrome, and the final pathway of different forms of aggression to the cardiac muscle. It manifests as two distinct phenotypes: HF with reduced ejection fraction (HFREF) and HF with normal ejection fraction (HFNEF).

The HFNEF prevalence has increased, so that HFNEF will become the most prevalent phenotype of HF in this decade, affecting mainly elderly individuals of the female sex with multiple co-morbidities[1]. Its pathophysiology has been mainly centered on the presence of left ventricular (LV) structural and diastolic functional changes, which cause an increase in LV filling pressures and intolerance to physical exertion[2-4].

The results of different randomized clinical studies, using drug treatment directed at improving diastolic function, have shown neutral results regarding patients' survival[5-7]. The oslerian approach classically used to describe the mechanisms of disease, as well as the construction of the reasoning that is the basis of treatment for HFNEF might need to be replaced by a new approach that uses systems biology, recently introduced into other areas of internal medicine, such as infectology and oncology. That new approach has led to the development of successful new drugs in those areas, allowing the construction of the so-called personalized medicine, which has propitiated the advance of that concept. That is important mainly because HFNEF is a cardiovascular syndrome with multiple abnormalities of the pathophysiological pathways, which interact through a complex network[8-9].

This review was aimed at presenting recent concepts of systems biology and its potential use in complex cardiovascular diseases, such as HFNEF, a syndrome with multiple pathophysiological abnormalities and still limited therapeutic arsenal in the light of current knowledge.

Keywords

Heart Failure; Stroke Volume; Ventricular Dysfunction, Left; Aged.

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HFNEF and its pathophysiological complexity

From the clinical and epidemiological viewpoints, compared to patients with HFREF, those with the HFNEF phenotype are usually older, more obese, of the female sex and have a history of arterial hypertension and atrial fibrillation [1,10,11].

The diagnosis of HFNEF is currently made from a clinical suspicion (intolerance to exercise) in association with the following Doppler echocardiographic findings, by using tissue Doppler: LV ejection fraction ≥ 50%; final LV indexed diastolic volume < 97 mL/m²; and diastolic functional abnormalities[12,13].

Patients with HFNEF have shown different subcellular abnormalities, such as changes in the extracellular matrix with increased deposits of advanced glycation end-products, collagen profile changes, sarcomeric protein titin isoform switch and hypophosphorilation, increased inflammatory response, and reduced SERCA2 pump activity[14,15]. The changes observed at cellular level were apoptosis, cardiomyocyte stiffness and hypertrophy, which might be responsible for concentric remodeling, even in the absence of LV hypertrophy. Macroscopically, LV hypertrophy and increased left atrial volume are observed, characterizing the major structural changes of patients with HFNEF. Finally, all changes lead to disorder of the cardiovascular system, which, integrated with other systems, will cause or aggravate multisystem abnormalities known as co-morbidities[14] (Figure 1).

Briefly, such structural and functional changes increase the risk of LV diastolic dysfunction. Although patients with HFNEF have LV ejection fraction values considered normal, they have changes in systolic performance, which can be assessed through different systolic function indices, such as

LV contractility, systolic volume, cardiac output and axial systolic shortening velocity (S'). Abnormality of relaxation and increased ventricular stiffness lead to increased LV filling pressures, which are diastolic dysfunction markers[2].

Changes in arterial stiffness and endothelial function are present in different degrees in individuals with HFNEF, contributing to aggravate diastolic dysfunction, increasing afterload and causing or intensifying myocardial ischemia. In addition, abnormalities of the microcirculation can also contribute to intolerance to exercise by hindering the perfusion of skeletal and respiratory muscles, which has been studied in individuals with HFNEF.

Mesquita et al. and Matsubara have provided a more detailed discussion of the pathophysiology of HFNEF in two recent reviews published in the *Arquivos Brasileiros de Cardiologia*[3,4].

Defining the systems-biology approach

The contemporary translational model of developing scientific knowledge in the medical area has allowed the large-scale use of new effective treatments for diseases. That model, derived from the oslerian system, has established that the presence of a certain disease should be defined as changes in a tissue (anatomico-clinical correlation), from which its pathophysiology can be pursued and a specific therapeutic target developed[16,17]. Based on the advances of molecular biology and using the oslerian view, the identification of individual genes, proteins and cells has been sought, as well as the study of their functions, providing limited information on complex diseases.

Systems biology allows, through the construction of mathematical models, simulations and data processing techniques, the integration of information from the *omics* sciences and clinical-epidemiological data, to provide better understanding of the interactions between the components of live systems and their biological processes[18-20].

Systems biology has its roots in the formulation of the internal environment stability principle by Claude Bernard in 1865, and has gained quantitative formalism with the mathematical description of the potential of action biophysics, first delineated by Hodgkin and Huxley in nervous cells, and soon after extended to the cardiac potential of action by Denis Noble[21]. That approach has been applied in medicine since before the molecular biology revolution. However, in the pregenomic era, systems biology was naturally hindered by the lack of technologies necessary to reach that integration and by the inability to investigate such systems in details[21]. However, in the past decades, scientific advances in the areas of molecular biology, engineering, bioinformatics, and physics, in association with the *omics* sciences (Table 1), enabled the acquisition of more complete information with a greater capacity to define more detailed approaches.

Systems biology, whose major characteristics are shown in Table 2, can be understood as the interaction of different biological systems activated at the molecular, cellular, tissular and organic levels, which can be assessed by use of tools, many of which available in clinical practice[8,22].

Systems biology allows a new understanding of the concept of disease, which can be defined as the lack of cooperation between some of the biological parts in an organic system, resulting in impairment of the entire functioning of the organism[14].

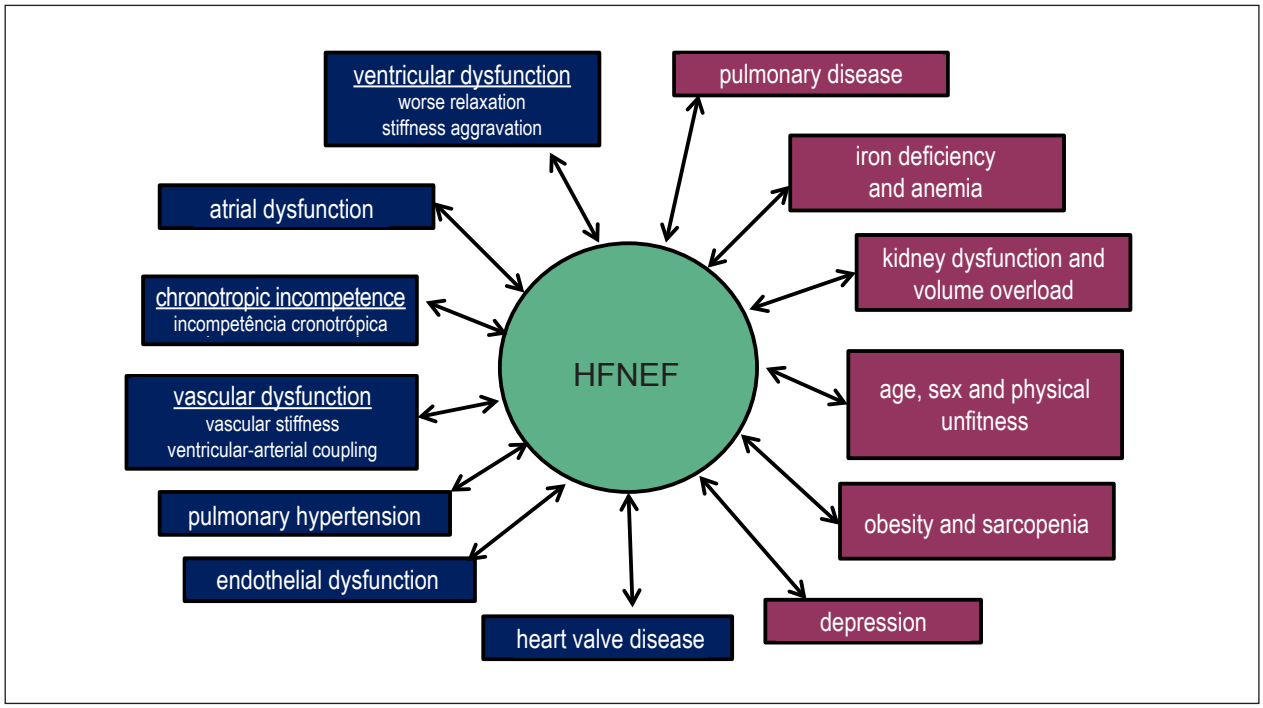

Figure 1 – *HFNEF – pathophysiology and co-morbidities. HFNEF – Heart failure with normal ejection fraction.*

Table 1 - Omics sciences

Genomics	Science that studies all genes, and analyzes their interactions and influences on biological pathways and networks.
Transcriptomics	Science that studies the phenomena involved in mRNA transcription. Through microarray technology, it accesses the expression of thousands of transcribed genes and identifies gene patterns (molecular signature) that can be used as biomarkers for etiology identification, prognostic assessment, and HF treatment.
Proteomics	Science that studies all proteins encoded in the genome; can be used to identify HF prior to the appearance of symptoms, therefore increasing the chances of an earlier and more effective treatment.
Metabolomics	Science that studies the molecular metabolites found in cells, tissues and organs, identifying their regulatory effects on genes and proteins. Used to identify biomarkers in HF.
Epigenomics	Science that studies the mechanisms capable of influencing the reading and interpreting of a chain of genes based on environmental factors on the genome.
Microbiomics	Science that studies the genomes of microbes and their interactions in a certain ecosystem. It is worth noting the study on interactions of intestinal bacteria and trimethylamine-N-oxide production, which propitiate the development of atherosclerosis.

HF: heart failure.

Table 2 - Major characteristics of Systems Biology

• Studies biological systems globally, at molecular level;
• Distinguishes from the classical linear theory: one gene, one protein;
• Integrates knowledge from different disciplines;
• Proposes mathematical models to explain some biological phenomena;
• Manipulates a large amount of data from experimental studies;
• Performs studies that verify the quality of the models described by comparing numerical simulations and experimental data.

According to that concept of disease, two study approaches can be identified: the bottom-up approach, aimed at defining the specificities that compose a structure, enumerating elements and identifying their individual characteristics to obtain an image of the point to be studied; and the top-down approach, which does not need to provide details of the network components, but to understand the general principles of the network to better understand it and to guide the identification of unpredicted elements. Similarly, the bottom-up approach could be compared to a 'link the dots' image, in which the real picture can only be revealed when each dot is duly recognized and linked to the others. The top-down approach can be understood as an impressionist painting, which, when seen from a short distance, does not allow us to identify the whole picture; it has to be seen from a distance, with a more comprehensive view, not requiring excessive details to reveal the image completely. Combining both characteristics, the knowledge on the system analyzed is amplified, allowing the identification of new proposals and pathways[14,19].

The network concept is aimed at providing a structure in which its forming and functional components interact in a self-organized biological network. The networks, rather than the components themselves, create the physiological behavior and disease. Each knot in a network represents a component (a gene, a protein), and the interconnection of the components describes the typical architecture imposed by biological selection and evolution[21] (Figure 2).

Working with networks simplifies complex systems, synthesizing the elements as knots and their interactions as lines between them, and identifies functional groups as module. Many of those biological networks have a topology described as scale-free, in which knots with few connections have priority; when linked to knots that have an elevated number of connections, those are called hubs (Figure 2). That architecture provides a biologically strong evolutionary advantage, considering that there are multiple alternative pathways to go from one knot to the other. In addition, that 'redundancy' enables the networks to more easily adapt to environmental changes. At each level, the network obtains new properties not previewed in the preceding levels, demonstrating the concept of emergent property[8,18]. Failure of the biological networks or incapacity to obtain emergent property at the following level causes disruptions in the physiological mechanisms, generating complex pathological phenotypes.

The network approach might allow a change of paradigm in HF treatment, because, instead of trying to adapt different patients to one single treatment (reductionism), it is aimed at directing the treatment profile at the different patients based on their individual networks (personalized medicine)[23].

The development of that approach is usually centered on a molecular target. However, in complex human diseases, that target is neither easily identified nor directed by one single factor[23].

Recent analyses have shown that a large number of traditional medications do not reach target proteins, but only proteins of the neighboring networks, which can be a reason for the modest effects obtained when some drugs are used for patients with HFNEF[8].

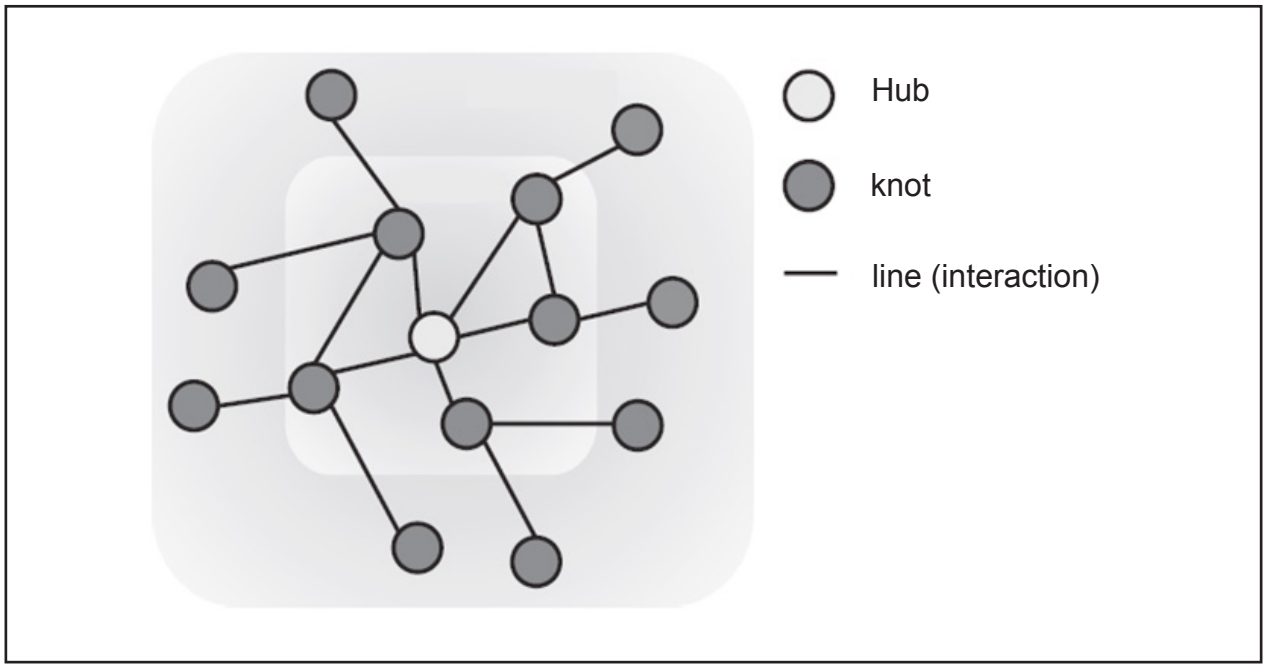

Figure 2 – *Overview of a biological network. Adapted from Chan SY, Loscalzo J. The emerging paradigm of network medicine in the study of human disease. Circulation Res. 2012 Jul 20;111(3):359-74.*

In contrast, a new pharmacology based on biological systems begins to develop aimed at creating new drugs that can be directed at one or more targets involved in the pathophysiological processes of the most relevant networks. That approach begins to be used in cancer and HIV/AIDS, and can become useful for HFNEF, making a new view of HFNEF under the systems biology perspective critical[8].

An HFNEF model using the systems-biology approach

The HFNEF is obviously a complex syndrome, whose pathophysiology and progression remain unclear, which makes the construction of a network model for HFNEF potentially useful and challenging in the current state of knowledge.

The heart involves different structural and functional hierarchic scales, which, through multiple interactions of subsystems, allow normal heart to achieve uniformity despite its structural and functional complexities at different levels[24] (Figure 3). That approach has identified different structural and functional abnormalities of the heart in humans and other animals[7].

From the mechanistic viewpoint, HFNEF can be defined as a complex condition, thus requiring an approach that encompasses the current concepts of systems biology. The analysis of *omic* data is crucial for understanding the factors involved in HFNEF and for identifying biomarkers with diagnostic and prognostic properties for clinical use[5].

By using the systems-biology approach and integrating different abnormalities observed in HFNEF, we propose a model that combines environmental and genetic factors, cardiac and vascular morphofunctional changes, abnormalities in other systems, and interaction with different co-morbidities, developing a holistic view of that syndrome and integrating the bottom-up and top-down methodologies (Figure 4).

The HFNEF results from systemic diseases, such as hypertension, diabetes, obesity and coronary artery disease, in association with the female sexual dimorphism. In addition, the aging process influences different cellular and subcellular pathways, promoting functional and structural abnormalities in the heart and great vessels. Recently, abnormalities in the protein folding process have been observed during the abnormal aging of the heart, and can contribute to HFNEF, a phenomenon called "Alzheimer's of the heart".

In addition, experimental evidence has shown that, in the heart of elderly rats, a reduction in the growth differentiation factor 11 (GDF11), which modulates the ligand-receptor activity in cardiomyocytes, contributes to cardiac hypertrophy and to the decreased SERCA2 functional activity, also causing an elevation in B-type natriuretic peptide (BNP) levels. However, when GDF11 levels are restored, a reduction in cardiac hypertrophy and an increase in the SERCA2 pump activity are observed, with consequent restoration of diastolic heart function[25].

Eventually those abnormalities cause intolerance to physical exertion, systemic and/or pulmonary congestion, tissue hypoperfusion and cardiac arrhythmias, such as atrial fibrillation, leading to HF signs and symptoms[26].

Another important concept influenced by the systems biology paradigm is that of the biomarker, considered a clinical status indicator that can be obtained from the integration of multiple biological activity levels in the network. That approach is responsible for guiding the identification of the biomarker based on deep understanding of its biological

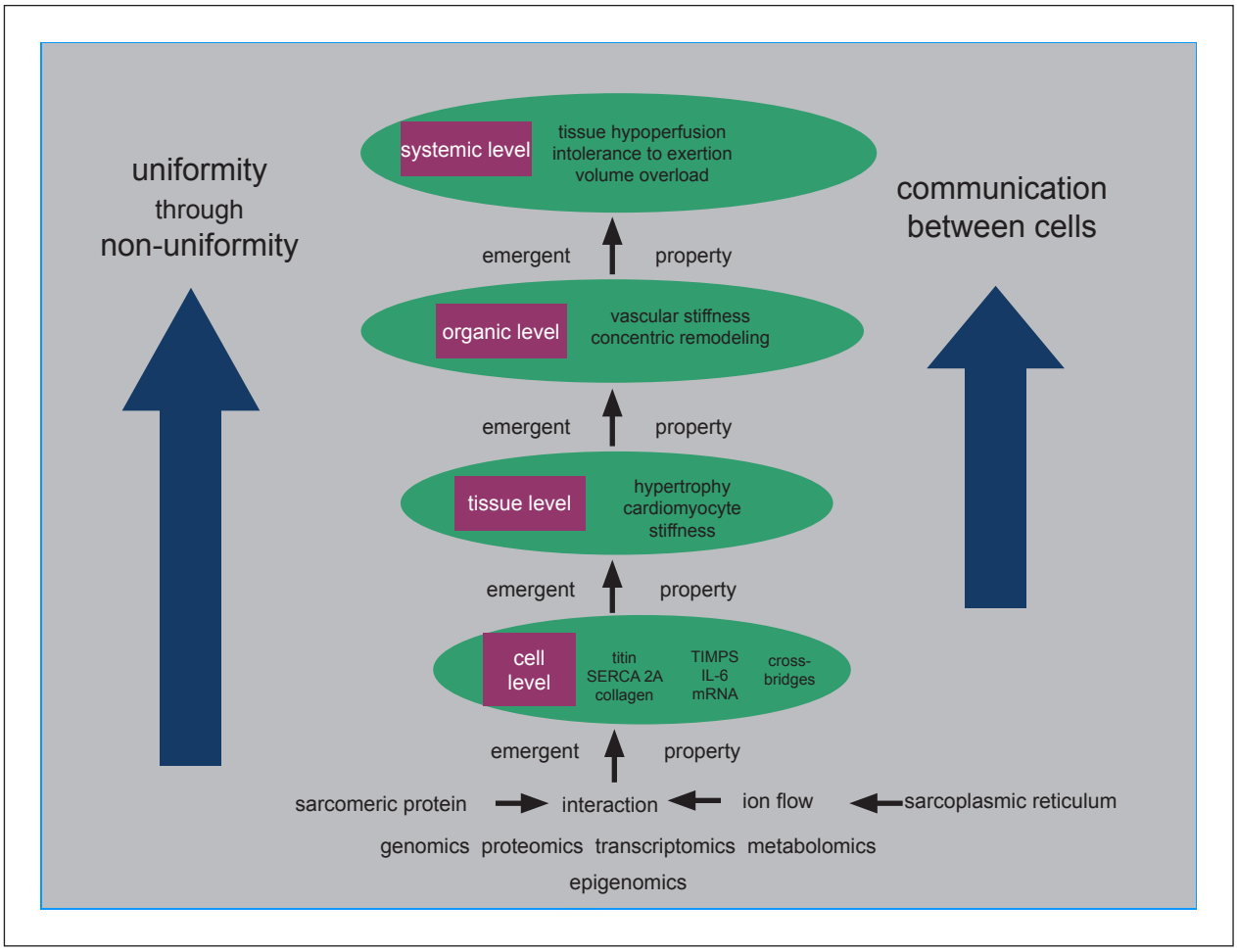

Figure 3 – *Model of the left ventricle as a dissipative structure with emergent properties. Adapted from De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation.2011;123(18):1996-2004.*

mechanism. The BNP, released in the presence of increased intraventricular pressure, is used for diagnostic confirmation and prognosis in HFNEF, and, more recently, has shown therapeutic usefulness in HFREF[18].

Other biomarkers that assess fibrosis, inflammation and necrosis have been studied in HFNEF. Current strategies using micro RNA have shown promise to better characterize patients with HFNEF. In addition, the use of multiple biomarkers in clinical research has introduced an approach similar to that of a system, and can significantly contribute to prognostic assessment and therapeutic response in HFNEF[27].

Understanding the pathophysiological abnormalities in multiple pathways in HFNEF has led to the development of new drugs directed at more than one pathway identified as critical to HFNEF. The LCZ696 is a dual-acting angiotensin receptor-neprilysin inhibitor composed of a neprilysin inhibitor prodrug, AHU 377, and the angiotensin receptor antagonist valsartan. Neprilysin degrades biologically active natriuretic peptides, such as atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide, but not NT-pro-BNP, which is biologically inactive. By increasing active natriuretic peptides, neprilysin inhibitor increases the myocardial generation of cyclic guanosine, which enhances myocardial relaxation and reduces hypertrophy. In addition, natriuretic peptides stimulate natriuresis, diuresis and vasodilation, and can have an additional anti-fibrotic and anti-sympathetic effect. Furthermore, neprilysin contributes to angiotensin collapse, which is the rationale for the dual action of the compound, which inhibits that enzyme and blocks angiotensin action or generation[28] (Figure 5).

The LCZ696 has been tested in patients with HFNEF (PARAMOUNT Study – phase 2) and has shown a more marked reduction in NT-pro-BNP than that caused by the isolated valsartan use. In addition, LCZ696 was better than valsartan to promote left atrial reverse remodeling and to improve those patients' functional class[28].

Briefly, HF understanding from the systems-biology perspective is still limited by the difficulty to integrate data from that complex information system into a biopathological model, mainly because of the several variables that interfere with the existing relationships, such as the genetic variations of each individual and the environmental influence on organisms[8].

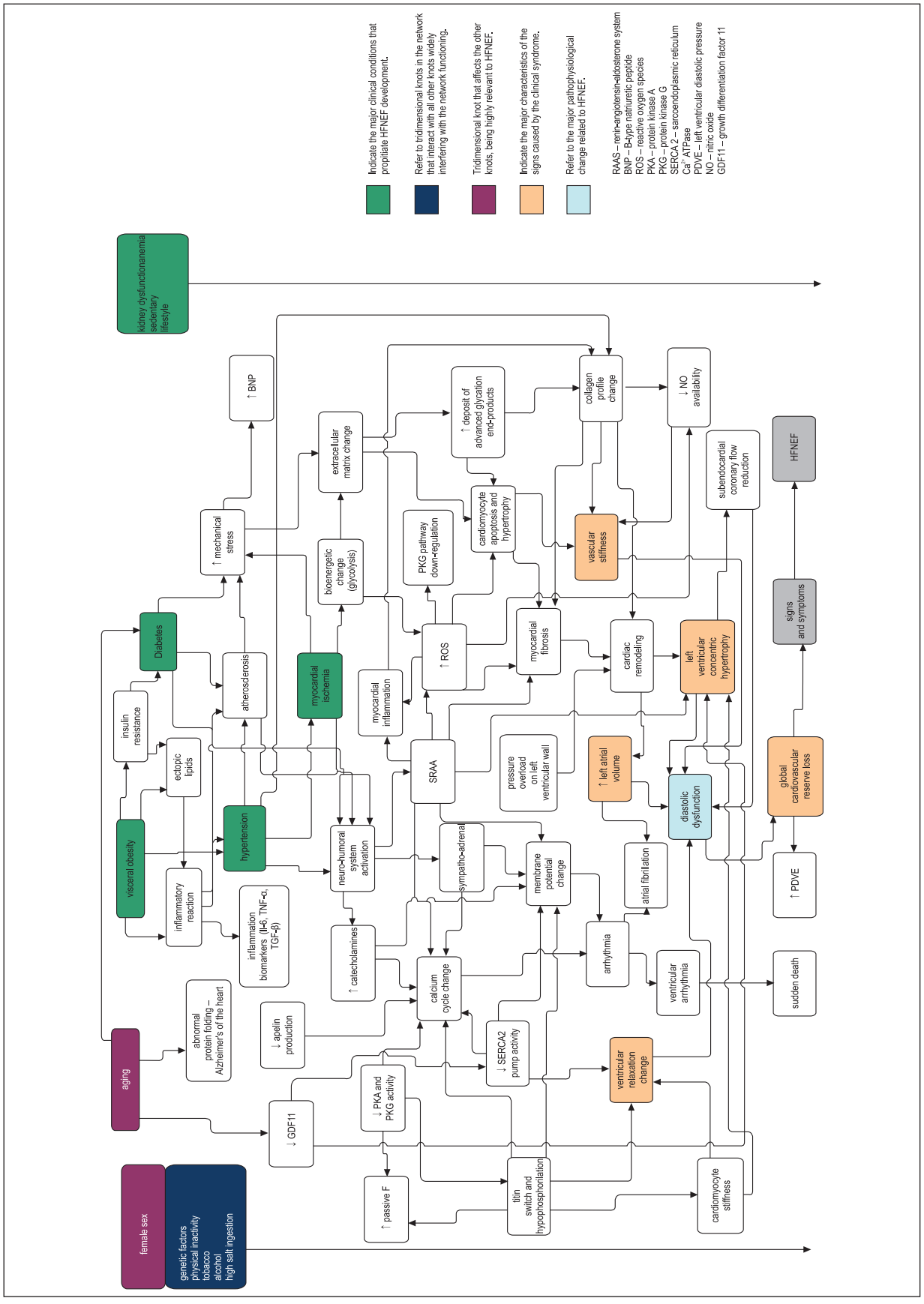

Figure 4 – *Schematic model of a biological network for HFNEF.*

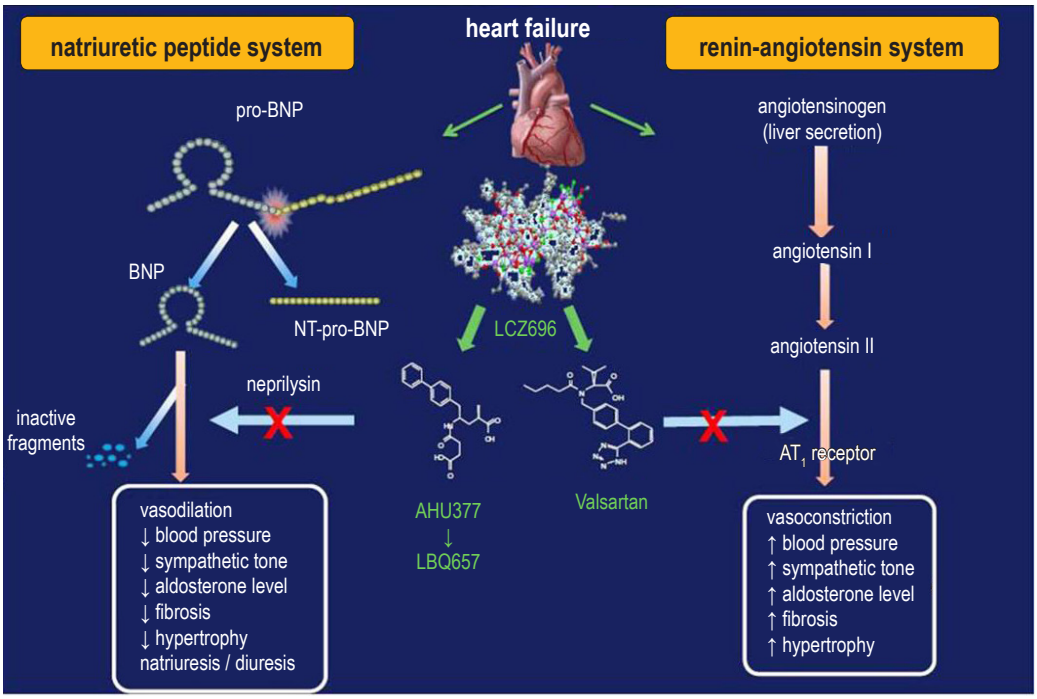

Figure 5 – *Mechanisms of action of the new drug LCZ696 that inhibits neprilysin and blocks the angiotensin receptor. Solomon SD, Zile M, Pieske B, et al; Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) Investigators.Lancet;2012;380:1387-95.*

Conclusion

The systems-biology approach in HFNEF is at an initial stage and can offer the possibility to widen the knowledge on pathophysiology, to refine the diagnosis and to lead to the development of new biomarkers and therapeutic targets.

Currently, the combination of a reductionist view with a holistic view is still necessary to better understand HFNEF, which involves a network of complex interactions between biological entities in different scales.

Thus, the complex pathophysiology of HFNEF and the lack of a treatment capable of reducing its impact on mortality make it the ideal cardiovascular condition for a new approach using systems biology, allowing the development of future therapeutic targets.

Author contributions

Conception and design of the research: Mesquita ET; Writing of the manuscript: Mesquita ET, Jorge AJL, Souza Junior CV, Cassino JPP; Critical revision of the manuscript for intellectual content: Mesquita ET, Jorge AJL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251-9.
2. Mesquita ET, Jorge AJ. Insuficiência cardíaca com fração de ejeção normal – novos critérios diagnósticos e avanços fisiopatológicos. Arq Bras Cardiol. 2009;93(2):180-7.
3. Roscani MG, Matsubara LS, Matsubara BB. Heart failure with normal ejection fraction. Arq Bras Cardiol. 2010;94(5):652-60.
4. Mesquita ET, Socrates J, Rassi S, Villacorta H, Mady C. Heart failure with preserved systolic function. Arq Bras Cardiol. 2004;82(5):494-500.
5. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362(9386):777-81.
6. Cleland JG, Tendera M, Adamus J, Freemantle N, Pçonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27(19):2338-45.

7. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456-67.

8. Chan SY, White K, Loscalzo J. Deciphering the molecular basis or human cardiovascular disease through network biology. Curr Opin Cardiol. 2012;27(3):202-9.

9. Chan SY, Loscalzo J. The emerging paradigm of network medicine in the study of human disease. Circ Res. 2012;111(3):359-74.

10. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006;355(3):260-9.

11. Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. J Am Med Assoc. 2003;289(2):194-202.

12. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007;28(20):2539-50.

13. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J. 2005;26(21):2277-84.

14. Louridas GE, Lourida KG. A conceptual paradigm of heart failure and systems biology approach. Int J Cardiol. 2012;159(1):5-13.

15. Borbély A, Papp Z, Edes I, Paulus WJ. Molecular determinants of heart failure with normal left ventricular ejection fraction. Pharmacol Rep. 2009;61(1):139-45.

16. Norman G. Medical education: past, present and future. Perspect Med Educ. 2012;1(1):6-14.

17. Chen R, Snyder M. Systems biology: per**sona**lized medicine for the future? Curr Opin Pharmacol. 2012;12(5):623-8.

18. Lusis AJ, Weiss JN. Cardiovascular networks: systems-based approaches to cardiovascular disease. Circulation. 2010;121(1):157-70.

19. Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56-68.

20. Maclellan WR, Wang Y, Lusis, AJ.Systems-based approaches to cardiovascular disease. Nat Rev Cardiol. 2012;9(3):172-84.

21. Dewey FE, Wheeler MT, Ashley EA. Systems biology of heart failure, challenges and hopes. Curr Opin Cardiol. 2011;26(4):314-21.

22. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation. 2011;123(18):1996-2004.

23. Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. J Am Coll Cardiol. 2012;60(1):9-20

24. Brutsaert DL. Cardiac dysfunction in heart failure: the cardiologist's love affair with time. Prog Cardiovasc Dis. 2006;49(3):157-81.

25. Lee RT, Loffredo FS, Steinhauser ML, Jay SM, Gannon IJ, Paancoast JR, Yalamanchi P, et al. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell. 2013;153(4):828-39.

26. Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction--Alzheimer's disease of the heart? N Engl J Med. 2013;368(5):455-64.

27. Azuaje FJ, Dewey FE, Brutsaert DL, Devaux Y, Ashley EA, Wagner DR. Systems-based approaches to cardiovascular biomarker discovery. Circ Cardiovasc Genet. 2012;5(3):360-7.

28. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380(98):1387-95.