Heart Failure – a review from an evolutionary perspective.

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Abstract

Heart failure continues to be a major health burden. The renewed and rapidly increasing incidence of the syndrome can largely be attributed to heart failure with preserved ejection fraction (HFpEF), which has just recently attracted attention. This cardiac affliction is part of a systemic inflammatory syndrome that is thought to be precipitated by a variety of physiological, particularly metabolic, dysfunctions and maladies. Significant differences in etiology, response to treatment, proteomic profile, pathophysiologic, and histo-morphological aspects distinguish HFpEF from the well-known heart failure with reduced ejection fraction (HFrEF). However, HFrEF and HFpEF both share mechanotransduction, the evolutionarily very ancient, well-shaped response of all living cells and tissues to bio-physical forces. Modified by the individual`s genetic make-up and environmental factors, mechanotransduction takes primacy in the adaptive, principally compensatory response, leading to concentric hypertrophy in HFpEF and eccentric ventricular remodeling in HFrEF. The effects of mechanotransduction are often neglected in our conventional approach to heart failure syndromes. Moreover, as the so-called "relaxed natural selection" may play a significant role in the genesis of diseases, HFpEF may be the result of an adaptive response driven by genetic and environmental factors.

Introduction

Heart failure (HF) may be viewed as the miscarried result (or maladaptation) of intricate morphologic and functional alterations including geometric-structural, cellular and molecular changes arising from the organism`s efforts to compensate for a disturbed cardio-circulatory homeostasis, caused by a threat afflicting the heart and/or the vascular system.

In the process of adaptation, mechanotransduction (MT), a fundamental biological mechanism of living cells and tissues, takes the leading effect. Unfortunately, MT has been neglected in our analysis, explanations and clinical considerations of heart failure pathobiology.

Mechanotransduction

Mechanical forces must be recognized as essential elements in natureand are acknowledged to be "critical regulators in biology" Several vital functions including cell contractility and motility, chromosome movements, cell proliferation and tissue morphogenesis are all regulated through tension forces generated by the cell and united multicellular structures (tissues).

MT designates the basic cellular response to various types of bio-mechanical forces present in physiological and pathophysiological conditions It refers to the conversion of bio-physical forces into biochemical signals and as such describes the cellular response to physical challenges MT is one of the most fundamental biological processes, and is shared by all living cells. MT and its interrelated pathways forming MT have been naturally selected during the very early stages of evolution as the adaptive molecular response to basic environmental forces, which is essential to every living species. Furthermore, concentric hypertrophy is accompanied by increased diffuse interstitial, reactive myocardial fibrosis, a marked inflammatory reaction, and apoptosis. In accordance with the law of Laplace, concentric hypertrophy normalizes the elevated systolic wall stress caused by the imposed pressure load. This condition is hemodynamically characterized by increased and elevated LVEDPs in the presence of a normal or even smaller filling volume with a preserved global LV-EF. Basic facts about MT in HF are depicted in [figure 1].

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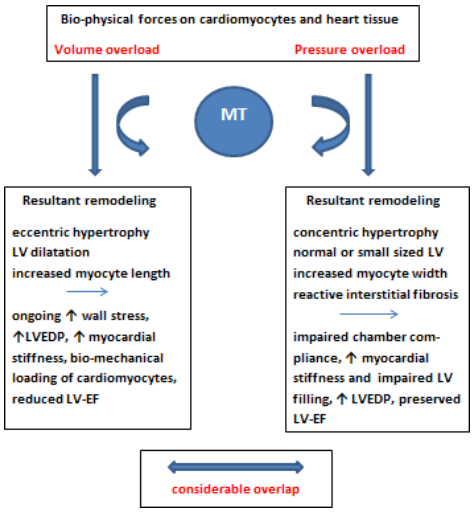

Figure 1: Effects of MT on the heart in case of volume or pressure overload, or both. One effect is leading and predominant, however, note the considerable overlap found in phenotypes!

MT: Mechanotransduction; LV: left ventricle; LVEDP: left ventricular end-diastolic pressure (filling pressure); LV-EF: left ventricular ejection fraction

Heart Failure Phenotypes

Traditional type of HF

The "traditional" type of HF, essentially characterized by impaired systolic properties and performance, and nowadays classified as HFrEF, results in about 60% of the cases from ischemic heart disease. Non-ischemic reasons, mainly dilated cardiomyopathies of various etiologies including genetic, infectious/ inflammatory and toxic genesis, account for up to 40% of all patients suffering from HFrEF.

Myocardial insults with substantial affliction and/or loss of contractile power lead to marked hemodynamic disorders with altered effective circulating blood volume, basically precipitating HF, and potentially decreased blood pressure due to the critically impaired functional and/or structural systolic properties and capabilities.The loss of myocardial cells (myocardial mass) as in case of myocardial infarctions or dilated cardiomyopathies induces an extra bio-mechanical burden on the remaining viable heart tissue, thereby triggering, via MT,compensatory hypertrophy of the remaining viable cardiomyocytes, which leads to increased muscle mass, in addition to scar formation of the injured region(s) Consequently, the already (through the initial threat) enhanced biomechanical burden on the remaining viable myocardium is further substantially exacerbated by the results of the remodeling effects. Hence, the mechanical burden imposed on the heart muscle and on each cardiomyocyte persists or even aggravates.As bio-mechanical stress on cardiomyocytes precipitates signals for myocardial growth and ventricular hypertrophy, cardiac remodeling continues regardless of the biochemical impact.

As such, the remodeling processes in patients suffering from HFrEF potentially turn maladaptive, if a new steady state cannot be achieved, hence, lead to (worsening) HFand crucially contribute to disease progression.

An overview of the pathobiology of HFrEF is illustrated in [figure 2].

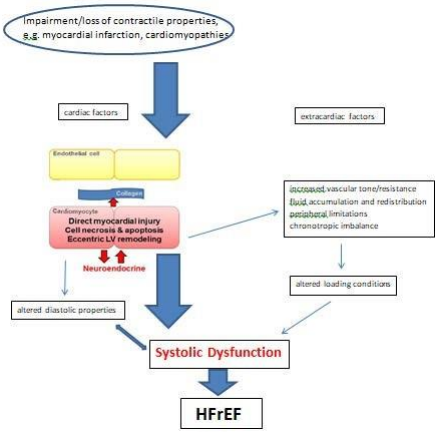

Figure 2: Main pathobiological issues of heart failure with reduced ejection fraction (HFrEF). Modified from Paulus WJ and Tschoepe C, J Am Coll Cardiol 2013; 62: 263 – 271; and Lam, CS and LH Lund, Heart 2016; 102: 257 – 259.

The new type of HF

Since its first description in the literature about 40 years ago, HFpEF has rapidly developed to a serious and epidemic health problem. This newly recognized entity of HF is clearly distinct from HFrEFincluding their main aetiologies and their conflictive response to the same treatment. Moreover, although both conditions display typical findings and symptoms, they differ in their proteomic conditions and profiles (and thus gene expressions), their foremost pathomechanisms and pathophysiologies, their histo-morphological and structural disparities, and even in their remodeling and reverse remodeling processes.

However, HFpEF and HFrEF share many of the common cellular and molecular signaling pathways (e.g. inflammation, neuroendocrine cascades) and thereunder, of course, mechanotransduction.

Since myocardial and cardiomyocyte stiffening means increased myocyte resting tension,these features cause a pressure load and therefore a bio-mechanical burden, hence impose elevated fiber stress on the cardiomyocytes and chamber walls. Subsequently, further signals of myocardial growth and ventricular hypertrophy will inevitably be launched. Consequently, all these alterations result in predominantly impaired cardiac filling mechanicsable to precipitate overt HFpEF. Indeed, all pathophysiological pathways known to be involved in HFpEF will ultimately meaningfully impact diastolic function, thereby causing diastolic dysfunction (DD) (the dominant pathophysiological feature of HFpEF patients), and exerting bio-physical stress on the cardiomyocytes. Moreover, as inflammation and HF

are strongly interconnected and mutually reinforce each other, the underlying inflammatory process, in any way, fuels disease progression.

Consequently, the classic hallmarks of the MT mediated remodeling processes in patients with HFpEFinclude a normal sized or even small LV chamber, an increase in LV wall thickness and LV mass, whereby the LV mass to cavity ratio substantially increases, precipitating concentric hypertrophy. The chamber geometry usually does not relevantly change, and cardiomyocytes may undergo apoptosisand eventually necrosis. The increase in wall thickness allows for compensation of increased systolic wall stress, principally preserving ventricular systolic performance. However, as we know, there are definitely subtle impairments in contractile properties, and concentric hypertrophy generates impaired ventricular compliance and diastolic filling . Moreover, the increase in myocardial cell mass, and the possible significant interstitial fibrosis provokes ongoing and progressive elevated wall stress, often even if the cause of increased load is relieved, and consequently facilitates advanced DD. All these features are suggestive for eccentric remodeling patterns, but may also be due to HFpEF, high output failure, or hypervolemic HF. Moreover, hypertension and hypertensive heart disease may only progress to HFpEF if the patients carry one or two copies of a certain D-allele of the angiotensin-converting enzyme gene. There is an insertion/deletion polymorphism described in hypertensive persons that is found in roughly 50% of them.

For a summary of HFpEF pathobiology, see [figure 3].

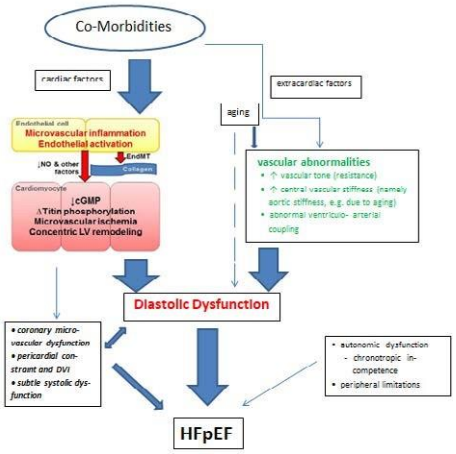

Figure 3: Main pathobiological issues of heart failure with preserved ejection fraction (HFpEF). Modified from Paulus WJ and Tschoepe C, J Am Coll Cardiol 2013; 62: 263 – 271; Lam, CS and LH Lund, Heart 2016; 102: 257 – 259; Juillere, Y et al., Arch Cardiovasc Dis 2018; 111: 766 – 781.

cGMP: cyclic Guanosinmonophosphat; Δ Titin: stiffer isoform of titin; NO: nitric oxide; EndMT: endothelial-mesenchymal transition; DVI: diastolic ventricular interaction.

Discussion

Cardiac remodeling is intended to achieve a new mechanical and biological steady state, allowing the heart to adapt to altered physiological and pathological conditions which affect hemodynamic homeostasis. In case of HFpEF, it is the increase in cardiomyocyte resting tensionthat exerts bio-physical forces (pressure load) and thereby launches MT mediated pathways. Moreover, the elevated resting tension is primarily the result of the enhanced cardiomyocyte, and extra-cellular myocardial tissue, stiffness that is attributed to the prevailing inflammatory condition. The latter is predominantly caused by comorbidities as described in the new paradigm of HFpEF pathobiology.

Bio-mechanical forces, directly propagated via the cytoskeleton and/or indirectly through several signaling pathways, lead to the activation of the nucleus. This results in altered gene expression and maladaptation promotes a reprogramming of foetal genes enabling principally adaptive processes to unfold. Consequently, gene expression is demonstrably different in volume and pressure overload. Moreover, it is predominantly the foetal reprogramming which allows for the phenotypic variability, the so-called phenotypic plasticity, the heart is equipped with. Foetal reprogramming may have been the only way during evolution to address substantial alterations in hemodynamic homeostasis, as it principally makes it possible to re-develop and re-construct the heart. It is thus a result of genetic material chosen by natural selection. To this adds the unpredictable interplay between the genetic and hemodynamic preconditions and the various co-morbidities and thereby diverse conditions: HF patients show overlapping phenotypic characteristics, indicating that “biological traits and co-morbidities intersect in varied combinations” with no single trait shaping the phenotypic appearance.

However, if the hemodynamic disruption and the cardiac dysfunction persist, exceeding the adaptive potential and capacity, and exert ongoing physical stress on cardiomyocytes, overt HF will occur and the ongoing remodeling effects become maladaptive. Moreover, the bio-mechanical stress imposed on the cardiomyocytes through the remodeled heart tissue unfortunately engenders a further bio-mechanical burden which critically contributes to disease progression. Indeed, it has been proposed that the re-activation of the foetal gene program may play a crucial role in the pathogenesis of chronic HF leading to adverse cardiac remodeling.

Conclusion

MT is an ancient and evolutionarily well-shaped cellular response pathway to bio-physical forces that is shared by all living cells and tissues. In the heart, indeed a paradigmatic organ whose cells and tissues are continuously subjected

to several bio-mechanical forces, MT takes primacy in the attempt of cardiac cells and tissue to adapt to altered physiological and pathological conditions. Unfortunately, MT has been largely neglected in our approach and considerations of HF pathobiology. Moreover, the results of MT mediated remodeling may be substantially modified by genetic and environmental factors.Thus, relaxed natural selection, in addition to environmental influences, is suggested to markedly impact the genesis and course of HFpEF, a distinct entity within the heart failure cluster, only recognized in recent studies, but already of endemic dimensions.

References

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007; 93:1137-46.
2. Tanai E, Frantz S. Pathophysiology of Heart Failure. Compr Physiol. 2015; 6:187-214.
3. Bozkurt B, Khalaf S. Heart Failure in Women. Methodist Debakey Cardiovasc J. 2017; 13:216-223.
4. Kurmani S, Squire I. Acute Heart Failure: Definition, Classification and Epidemiology. Curr Heart Fail Rep. 2017; 14:385-392.
5. Price JF. Congestive Heart Failure in Children. Pediatr Rev. 2019; 40:60-70.
6. Dharmarajan K, Rich MW. Epidemiology, Pathophysiology, and Prognosis of Heart Failure in Older Adults. Heart Fail Clin. 2017; 13:417-426.
7. Snipelisky D, Chaudhry SP, Stewart GC. The Many Faces of Heart Failure. Card Electrophysiol Clin. 2019; 11:11-20.
8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/ AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62:e147-239.
9. Figueroa MS, Peters JI. Congestive heart failure: Diagnosis, pathophysiology, therapy, and implications for respiratory care. Respir Care. 2006; 51:403-12.
10. González A, Schelbert EB, Díez J, et al. Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives. J Am Coll Cardiol. 2018; 71:1696-1706.