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Pathophysiology and the cardiorenal connection in heart failure. Circulating hormones:biomarkers or mediators

Alessia Buglioni *, John C. Burnett Jr.

Cardiorenal Research Laboratory, Division of Cardiovascular Diseases, Department of Medicine and Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Heart failure (HF) is a syndrome characterized by a complex pathophysiology which involves multiple organ systems, with the kidney playing a major role. HF can present with reduced ejection fraction (EF), HFrEF, or with preserved EF (HFpEF). The interplay between diverse organ systems contributing to HF is mediated by the activation of counteracting neurohormonal pathways focused to re-establishing hemodynamic homeostasis. During early stages of HF, these biochemical signals, consisting mostly of hormones and neurotransmitters secreted by a variety of cell types, are compensatory and the patient is asymptomatic. However, with disease progression, the attempt to reverse or delay cardiac dysfunction is deleterious, leading to multi-organ congestion, fibrosis and decompensation and finally symptomatic HF. In conclusion, these neurohormonal pathways mediate the evolution of HF and have become a way to monitor HF. Specifically, these mediators have become important in the diagnosis and prognosis of this highly fatal cardiovascular disease. Finally, while these multiple neurohumoral factors serve as important HF biomarkers, they can also be targeted for more effective and curative HF treatments.

1. Heart failure

1.1. Definition

Human heart failure (HF) is a condition in which the cardiac pump is not able to provide the appropriate blood supply to diverse organ systems and tissues, and remove deleterious waste products. Thus HF, with its mosaic of signs and symptoms is defined as a syndrome. In this regard, two pathognomonic symptoms are dyspnea and fatigue, with congestion secondary to renal sodium and water retention and elevated venous pressure which favors transudation of intravascular fluid into the interstitium. Most often, it is the elderly who present with HF and have many risk factors which contribute to the development of this syndrome, such as hypertension, diabetes mellitus, renal disease, obesity, sleep apnea and depression [1]. The severity of the clinical manifestations of HF is variable; nevertheless, a progressive condition which may have recurrent exacerbations and requires constant therapeutic interventions is defined as chronic heart failure (CHF), whereas a gradual or sudden onset which requires urgent treatment is acute HF syndrome (AHF) [2].

Relevant to this review is a more contemporary and emerging picture of HF which goes beyond the concept of sodium and water retention and congestion. What is emerging is a concept of a multi-organ syndrome in which multiple deleterious cellular pathways are activated by known and unknown humoral and mechanical mediators. This picture of cascading mechanisms results in tissue remodeling in the heart and kidney and likely in other organ systems, leading to organ fibrosis and end-stage HF. Indeed, it is in such a context that circulating biomarkers may be valuable diagnostic and prognostic entities in addition to serving as protective biochemical factors or deleterious potentiators of HF.

1.2. HFrEF and HFpEF

Although every cell type and chamber of the heart can potentially be involved in the beginning of HF, often there is initially left ventricular (LV) dysfunction linked to an elevation of LV filling pressures. Such a maladaptation secondary to loss of muscle due to myocardial infarction, reduced contractility due to idiopathic cardiomyopathy or increased afterload with hypertension results in a reduced cardiac output and/or increased LV wall tension with a reduced compliance to inflow. When the ejection fraction (EF) of the LV is reduced ($\leq$40%), a condition called "systolic dysfunction", HF is defined as "reduced ejection fraction" (HFrEF). When the EF is $\geq$50%, but there is concomitant impaired relaxation of the left ventricle, a condition called "diastolic dysfunction", along with the presence of pathognomonic signs and symptoms of HF, is classified as "HF with preserved EF" (HFpEF). Subjects with HF and an EF between 40% and 50% are considered as part of an intermediate group [3]. Diastolic dysfunction can also be present in HFrEF [4].

* Corresponding author at: Cardiorenal Research Laboratory, Guggenheim 915, Mayo Clinic Foundation, 200 First Street S.W., Rochester, MN 55905, USA. Tel.: +1 507 284 4343; fax: +1 507 266 4710.
E-mail address: buglioni.alessia@mayo.edu (A. Buglioni).

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Interestingly, HFrEF and HFpEF could be additionally distinguished according to a patient's phenotype. Subjects with HFpEF, compared to HFrEF, are more often older women, with a higher body-mass index, greater prevalence of diabetes, atrial fibrillation and a long history of arterial hypertension [5]. The estimated prevalence of HFpEF among subjects with HF is approximately 50% [6,7]. Mortality rate may be higher in patients with HFrEF, however, the high prevalence of HFpEF in the elderly lead to the absolute number of deaths being higher in HFpEF [6]. HFpEF patients principally die from cardiovascular deaths; nevertheless, they also have a higher incidence of non-cardiovascular mortality compared to HFrEF. Subjects with HFrEF are more likely to have cardiovascular related deaths compared to HFpEF patients [5,8].

Structural characteristics of HFrEF and HFpEF are markedly different. In HFrEF the LV is dilated with hypertrophic walls [9]. Histologically, fibrosis is present, cardiac myocytes are elongated and have a smaller diameter than in HFpEF, and their inner myofibrillar density is also reduced. In addition, myocytes are less stiff compared to HFpEF. In HFpEF, the LV cavity has typically a normal volume and the walls are hypertrophic. Histological examination shows collagen deposition and larger, more rigid cardiomyocytes than in HFrEF [4]. Despite diverse cardiac structure and function, the hemodynamic patterns of HFrEF and HFpEF share similarities as well as differences. Clinical symptoms, renal dysfunction, neurohormonal activation, response to exercise, and outcomes may overlap [10]. Nevertheless, increased ventricular and vascular stiffening may play a more important role than an actual volume overload, in acute HFpEF compared to HFrEF. Thus, these two forms of HF are two well distinguished entities, with different pathophysiology and consequently therapeutic approaches. It is possible that HFpEF may evolve into HFrEF and, thus, the two conditions might be considered as “extremes of a single disease” [11].

Treatment and prognosis of cardiovascular disease have dramatically improved over the last decades. Nevertheless, increased mortality and re-hospitalization rates remain high in patients with HF [5]. The American Heart Association Guidelines for the management of HF [3] are clear and straightforward for HFrEF; however, there is lack of consensus in the management of HFpEF [8]. Importantly, therapies such as beta-blockers, angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACE-I), diuretics and mineralocorticoid receptor antagonists (MRAs) which are widely used in HFrEF, do not always have the same beneficial outcome in HFpEF. Most recently, PARAMOUNT [12] was a phase II clinical trial testing the efficacy of a novel compound created by the combination of an ARB, valsartan, with a neprilysin inhibitor (AHU377). Neprilysin is one of the most important enzymes responsible for the degradation of the natriuretic peptides (NPs). The name of this new first-in-class Angiotensin Receptor Neprilysin Inhibitor (ARNI) is LCZ696. The strategy behind this complex molecule is based on the effect targeting two different pathways, both important in the pathogenesis of HFrEF and HFpEF: the renin–angiotensin–aldosterone-system (RAAS) and the NP system [8]. This new drug was added to baseline therapy in n = 301 HFpEF patients and compared to HFpEF subjects with baseline treatment plus valsartan alone. The results of this study showed a greater reduction in NT-proBNP levels in the LCZ696-treated group compared to controls; however, this difference was no longer present after 36 weeks of observation. Further, this reduction in NT-proBNP levels remains to be translated into improved clinical outcomes. LCZ696 has been recently added to standard therapy in chronic symptomatic HFrEF patients: the PARADIGM-HF trial [13,14]. This trial was stopped early (March 2014 instead of October 2014) due to mortality benefit in subjects taking LCZ696 compared to subjects on standard therapy with added ACE-I (enalapril) alone. LCZ696 compared to enalapril also reduced the risk of hospitalization for HF and significantly improved the symptoms of HF. These impressive results have been obtained using a drug that targets at the same time the RAAS and the NP system, and it supports a favorable and enhancing effect of the combination of the two molecules together. LCZ696 may change the therapeutic strategy and the long-term survival of HFrEF patients [15]; however, subjects selected for this landmark trial had a cardiac EF ≤35% and had to tolerate a dose of 10 mg twice a day of enalapril before being considered for taking LCZ696. Translating it into the clinical practice may require careful considerations. Another important trial is TOPCAT that tested the efficacy of spironolactone, an MRA, in HFpEF patients [16]. In this case the investigators selected patients with an EF ≥45%, from the Americas as well as from Russia and Georgia, and it reported that treatment with spironolactone did not reduce the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. However, in a post-hoc analysis spironolactone seemed to benefit patients from the Americas but not those in Russia or Georgia as to reflect a possible diverse approach to the conduct of clinical trials in clinical practice in different countries [17].

In conclusion, the treatment for HF and, particularly, HFpEF remains a challenge that certainly warrants new alternative and novel therapeutic approaches, in the acute setting as well as in CHF.

2. Neurohormonal activation in HF

2.1. From asymptomatic to symptomatic HF

Despite different pathophysiologies, HFrEF and HFpEF share the activation of three major neurohormonal systems: the NP system, sympathetic nervous system (SNS) and the RAAS. The neurohormonal activation has laid the foundation of the field of HF biomarkers. The initial phase of HF syndrome is usually asymptomatic. The stretched cardiomyocytes of the failing heart secrete NPs primarily from the atria [18] to reduce the hemodynamic impairment secondary to vasoconstriction and sodium retention due to the SNS and RAAS [1]. More specifically, the SNS augments inotropic function and peripheral vasoconstriction [19], whereas the RAAS maintains and expands intravascular volume and renal perfusion through vasoconstriction in the kidney and active tubular sodium reabsorption.

The human NPs system consists of three structurally similar but genetically distinct hormones: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP and BNP are primarily synthetized in the heart whereas CNP is produced mainly by the endothelium and kidney. ANP and BNP act through the membrane-associated particulate guanylate cyclase A (GC-A) receptor. CNP preferentially binds to the particulate guanylate cyclase B receptor (GC-B). There is a third receptor for the clearance of NPs, NP receptor type C (NPR-C), which may also have proliferative actions in cardiomyocytes and anti-fibrotic actions in cardiac fibroblasts [20,21]. Only GC-A and GC-B, after binding their specific peptides, produce the second messenger cyclic guanosine 3′,5′-monophosphate (cGMP). Importantly, cGMP mediates diverse cardiovascular actions which involve suppression of cellular proliferation, inhibition of inflammation [8], reduced platelet activation [22] and preservation of myocardial function and structure [23]. The elevation of plasma NPs and, subsequently, cGMP levels may be viewed as a compensatory response to reduce the initial cardiovascular maladaptation present in HF. NPs have numerous and remarkable actions including natriuresis [24], inhibition of aldosterone synthesis [25] and enhancement of vasodilation [26]. NPs are not the only contributors to the increase of cGMP levels. Nitric oxide (NO) acting through soluble guanylate cyclase, the other guanylate cyclase receptor, through cGMP production may modulate inflammation [27], myocardial contractility [28] and endothelial dysfunction [29]. However, NO bioavailability may be reduced in HF [30], contributing to a state of relative cGMP deficiency. NPs, together with NO, attempt to compensate for hemodynamic dysfunction characterizing the initial stage of HF, through cGMP activation. However, the SNS, which releases catecholamines, induces opposing effects and, additionally, can directly activate the RAAS [31]. The peripheral vasoconstriction, including vasoconstriction of the renal arteries, induced by SNS can also lead to glomerular hypoperfusion followed by renin release from the kidney, and