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The pathophysiological role of natriuretic peptide-RAAS cross talk in heart failure

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ABSTRACT

Chronic Heart Failure (HF) is still a disease state characterized by elevated morbidity and mortality and represents an unresolved problem for its socio-economic impact. Besides many of the pathophysiological events leading to advanced HF have been widely disclosed in the past decades, the role of neuro-hormonal dysregulation accompanying HF has to be clearly assessed with the objective of better therapeutic approaches in treating such a disease.

In the present review article, alongside with a brief re-evaluation of general aspects of HF physiopathology, we summarize recent advances in the cross talk between renin-angiotensin-aldosterone system (RAAS) with natriuretic peptides (NPs) which have been shown to play a relevant role in the development of severe HF.

The role of RAAS-NPs interplay has been shown to be crucial in both hemodynamic and tissue remodeling associated to cardiomyocyte dysfunction, leading to advanced impairment of left ventricular performance.

On the basis of these results, the development of drugs resetting both RAAS and NPs system seems to be promising for a successful long term treatment of chronic HF.

1. Introduction

Heart failure (HF) is one of the major problems of public health, associated with a significant rate of mortality, morbidity, hospitalizations and health care expenditure, with the prevalence rising to ≥10% in patients with over 70 years of age [1]. It was estimated that approximately 1–2% of the adult population in developed countries has HF, with more than 5.8 million people in the United States and more than 23 million in the whole world [2].

HF can be defined according to the most recent European Society of Cardiology (ESC) Guidelines (2012) as an "abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)" [1]. In addition, HF is characterized clinically as a "syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function" [1]. Besides, the symptoms and their pharmacological as well as non-pharmacological control of HF are non-discriminating and, therefore, of limited diagnostic value [1–3].

The primary cause of HF is an ischemic cardiopathy, responsible for two-thirds of patients with left ventricular systolic dysfunction. Others main causes of HF are valvular disease, rheumatic disease, myocarditis, alcohol abuse, chemotherapy and hypertension [1]. In other cases, as in the idiopathic dilated cardiomyopathy, it is not possible to establish an exact cause. The predisposing risk factors in the development of HF are the left ventricular hypertrophy, smoking, obesity, hypertension, diabetes and increase in total cholesterol/HDL cholesterol.

Besides effective treatment, over the last two decades, has improved the rate of hospitalization of patients undergoing HF by 30–50% [1], the decrease of mortality is still unsatisfactory and novel pharmacological interventions are required for a better prognosis of patients with severe HF.

The present review will summarize pathophysiological aspects of HF underlying the cross talk occurring between the renin-angiotensin-aldosterone system (RAAS) and the natriuretic peptide (NPs) system alongside with their role for a better pharmacological approach to HF.

2. Pathophysiology of HF

HF is a clinical syndrome in which local and systemic adaptations attempt to maintain and, at the same time, contribute to a dysregulation

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of cardiovascular homeostasis. Although the symptoms and signs of HF are well recognized, the development of the effective therapy for each individual patient is particularly challenging and has to face the complexity of mechanisms involved in the pathogenesis of HF. Different, but not mutually exclusive features, participate to HF pathophysiology (Fig. 1).

Myocardial injury with the decrease in the contractility of the myocardium and the increase in the hemodynamic load drives hemodynamic alterations in HF. These events are often associated with the ventricular remodeling that reflects dynamic changes in the myocyte compartment and extracellular matrix thereby overcomplicating the natural history of the disease.

Cardiomyocyte hypertrophy, abnormalities in intracellular calcium homeostasis and progressive loss of cardiac myocytes together with the increase in myocardial stiffness have a negative impact on ventricular architecture and performance. On the other hand, compensatory mechanisms increase preload involving Frank–Starling mechanism, induce peripheral vasoconstriction, preserving the perfusion of vital organs, and stimulate myocardial hypertrophy that initially maintains wall stress. Renal sodium and water retention, that at first enhance ventricular preload, contribute with time to edema and dyspnea. Moreover, the prolonged activation of several neuro-hormonal vasoconstrictor systems leads to maladaptive remodeling and contributes to the progression of HF with unfavorable prognosis. Additionally, the raise of local and circulating proinflammatory cytokines indicates an inflammatory component present in the pathophysiology of HF. Thus, due to the huge contribution of these pathophysiological processes to activate and maintain HF, any of these steps represents a potential target for therapeutic intervention in the management of chronic HF with the common goal to relieve symptoms and, most important, to improve the quality of life.

2.1. Neuroendocrine players in HF

The primary neuro-hormonal systems involved in the physiopathology of HF are the sympathetic nervous system (SNS), the RAAS and the NPs system. Other vasoactive hormones are arginine vasopressin (AVP), endothelin-1, prostaglandins, kallikrein-kinin and substance P.

2.1.1. The sympathetic nervous system (SNS)

The SNS is activated at the early stages of HF to compensate the reduction of myocardial contractility and to ensure a correct tissue perfusion and tolerance to stressing conditions. The hyperactivity of SNS in the HF is due to a reduction of inhibitory sympathetic reflex and to an increase in the excitatory ones [4]. A prolonged activation of the SNS causes progression of HF, related mainly to induction of excitation-contraction effects and of mechanisms leading to apoptotic cell death of cardiomyocytes [4–6]. The hyperactivation of the SNS that occurs during the HF causes an increase in peripheral vascular resistances, an increased risk of ventricular arrhythmias and the activation of the RAAS [4]. Furthermore, enhanced sympathetic nerve firing is accompanied by additional cardiovascular effects such as increased heart rate, alteration of myocardial contractility, reduction of venous capacitance and, finally, to peripheral vasoconstriction [4] which interact, at the late stages, with cardiac remodeling and dysfunction [7–8]. The molecular mechanisms through which exaggerated adrenergic response

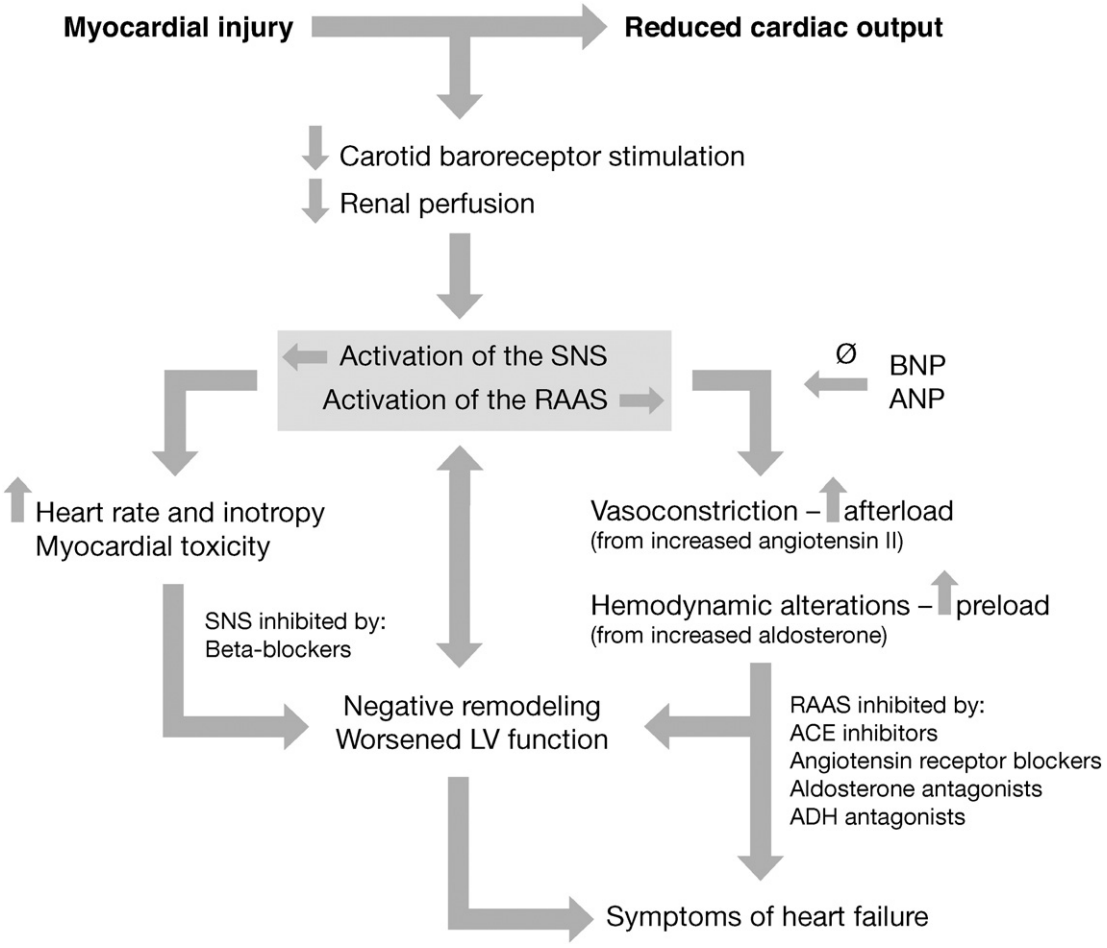

Fig. 1. Heart failure pathophysiology. ACE — angiotensin converting enzyme, ADH — antidiuretic hormone, ANP — A-type natriuretic peptide, BNP — B-type natriuretic peptide, LV — left ventricle, RAAS — renin-angiotensin-aldosterone system, SNS — sympathetic nervous system.

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