Growth Hormone as Biomarker in Heart Failure

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KEYWORDS

• Chronic heart failure • Growth hormone • IGF-1 • Anabolic deficiency • Biomarker • Outcomes

KEY POINTS

- The growth hormone (GH) and insulin growth factor 1 axis play a pivotal role in chronic heart failure (CHF).
- Both GH as well as deficiency are associated with impaired functional capacity and poor outcomes.
- GH replacement therapy represents a possible future therapeutic option in CHF.

INTRODUCTION

The neuro-hormonal model has radically changed our understanding of chronic heart failure (CHF) pathophysiology and represented the theoretic background for the implementation of landmark clinical trials, which in turn have dramatically changed the natural history of this disease.[1] This model is rooted in the ubiquitous overactivation of different molecular pathways, such as the sympathetic nervous system, renin-angiotensin-aldosterone, and cytokines' system overexpression, that maintain the heart function within a homeostatic range, after an index event.[2] However, such prolonged overactivity gradually leads to a maladaptive remodeling of the left ventricle architecture and function, with attendant impairment of exercise capacity and occurrence of poor outcomes.[2] The blockade of the sympathetic nervous system (with β-blockers) and the inhibition of the renin-angiotensin-aldosterone pathway (with angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and aldosterone-antagonists) constitutes the bedrock of current pharmacologic therapy for heart failure with reduced ejection fraction (HFrEF),[3,4] taking into account the associated consistent improvements in terms of morbidity and mortality granted by those pharmaceutical classes.[5] However, CHF is still burdened by high mortality (worse than that of many cancers), frequent comorbidities, and, consequently, tremendous associated health care costs.[1] For this reason, in the last decades several other pathophysiologic models were proposed to complement the paradigm of neurohormonal hyperactivity. More specifically, the

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concept is emerging that also downregulation of a portfolio of several biologically active molecules impact on heart failure progression, not the hyperactivation of the systems previously listed. In this regard, multiple anabolic deficiencies have been consistently described in HFrEF[6–8] and, more importantly, are significantly associated with several indexes of physical performance and survival. Chief among these is the reduced activity of growth hormone (GH) and its tissue effector insulinlike growth factor 1 (IGF-1).[9] This review is focused on the involvement of the GH/IGF-1 axis in CHF and its possible use, either as a clinical biomarker or as a potential therapeutic target.

GROWTH HORMONE/INSULINLIKE GROWTH FACTOR 1 AXIS PHYSIOLOGY

Several biological processes require the pituitary secretion of GH. One of the main effects of the interaction between GH and its specific receptors (GHRs) is the activation of a complex signaling cascade that leads to the hepatic production of its major biological mediator IGF-I.

GH and IGF-1 are linked by a long-loop feedback because the IGF-1 produced in the liver in response to GH inhibits GH release through the stimulation of somatostatin release.[9]

The GH/IGF-I axis is regarded as the most powerful anabolic system in nature. Although this pivotal mechanism is still poorly understood, it is well known that the GH/IGF-I axis is responsible for postnatal growth by increasing both bone length and density and muscle mass during childhood and adolescence.[10] Moreover, it has important effects by regulating carbohydrates and lipid metabolism, the latter preferentially on visceral adipose tissue.[11] It has been documented that IGF-I is also released by several other tissues; thus, IGF-1 acts not only as classic endocrine hormone but also in an autocrine and paracrine manner. IGF-1 circulates in blood either free or bound to specific binding proteins that prolong its half-life.[12] To date, 6 IGF-1 binding proteins (IGFBPs) have been identified and represent an elaborate system for regulating IGF-1 activity. In particular, almost 90% of circulating IGF-I is part of a ternary complex, also composed of IGF-specific binding protein 3 (IGFBP-III) and the acid-labile subunit.[13] This complex allows IGF-I to reach several tissues, where it binds to its own receptor (IGF1R), leading to the activation of the PI3K/Akt (phosphatidylinositide 3-kinases (PI3K)/alpha serine/threonine-protein kinase [Akt]) signaling pathway, which in turn promotes cell growth, enhances glucose transport, inhibits apoptosis, and acts along with interleukin 6 to protect cells from tumor necrosis factor (TNF)-α cytotoxicity.[9]

It should be noted that besides the regulation of the somatic growth, this anabolic axis has a significant impact on the cardiovascular system by supporting cardiac growth and performance. The activation of IGF-I receptors expressed in cardiomyocytes determines a direct effect on the reduction of the systemic vascular resistance by inducing the production of nitric oxide, promotes the contractility of cardiomyocytes mainly by increasing intracellular calcium concentration and calcium sensitization of the myofilaments, and preserves capillary density.[14] Of note, both GH and IGF-1 are endowed with growth-promoting properties within the myocardium and increase protein synthesis in the cardiomyocytes.[15]

IGF-1 also induces the reuptake of calcium by the sarcoplasmic reticulum by regulating the sarco/endoplasmic reticulum Ca2+-ATPase (SERCA2), which is involved in diastolic function.

Moreover, several studies performed in experimental models of heart failure demonstrated that GH/IGF-1 activation augments SERCA2 myocardial content, attenuates left ventricular remodeling, and enhances intracellular Akt signaling.[16] In addition, it plays a pivotal role by regulating cardiac growth, cardiomyocyte size, and metabolism by stimulating amino acid uptake for protein synthesis and promoting the transcription of genes specifically expressed in the cardiac muscle.[9] Of note, GH per se increases protein synthesis in the isolated perfused heart by augmenting amino acid trasport.[17]

PATHOPHYSIOLOGY OF GROWTH HORMONE/INSULINLIKE GROWTH FACTOR 1 IMPAIRMENT IN HEART FAILURE

GH deficiency (GHD) is a common finding in CHF with a prevalence ranging from 32% to 53% according to different reports.[14,18,19] IGF-1 has a remarkable positive effect on the cardiovascular system, including antiapoptotic and growth-promoting action, vasodilation and endothelial protection, and increase of cardiac contractility.[9,15] Most of the studies performed in CHF reported reduced IGF-1 serum levels when compared with healthy controls.[18,20–22] IGF-1 levels were remarkably reduced in patients with advanced heart failure[23] or cachexia.[24] Many explanations were provided regarding the underlying mechanism of impaired GH/IGF-1 secretion in CHF. The first hypothesis is rooted in hypoperfusion and reduced oxygen supply, which is the typical hallmark of CHF clinical syndrome. Indeed, 25 children with GHD were evaluated with brain MRI and compared with healthy controls. In these series, pituitary stalk enhancement was