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The impairment of the Growth Hormone/Insulin-like growth factor 1 (IGF-1) axis in heart failure: A possible target for future therapy

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Abstract

Hormonal abnormalities are quite common in chronic heart failure (CHF). The most studied hormonal axis in CHF is the impairment of Growth Hormone (GH)/Insulin Growth Factor-1(IGF-1), which in turn is defined either by a blunted response to GH stimulation test or low serum IGF-1 values. Several independent groups reported that the presence of an abnormal GH/IGF-1 status in CHF is associated with a more severe disease, impaired functional capacity and reduced Survival rates. After the first encouraging results, double -blind controlled trials showed a neutral effect of the GH administration in patients. However, further studies reported positive results, when a GH-therapy is implemented only in those patients presenting a GH deficiency (replacement therapy).

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Introduction

Chronic heart failure (CHF) is a major healthcare issue, being burned by disability, poor outcome and elevated health care costs [1]. Our understanding of CHF has remarkably improved after that the neuro-hormonal model was proposed [1]. This is rooted in ubiquitous over-activation of such patterns (*i.e.*, renin-angiotensin-aldosterone, sympathetic nervous system, inflammatory activation and cytokines), aimed to restoring heart function in a first moment [2,3], but with detrimental effects in the course of the disease [4,5]. The bedrock of current pharmacological therapy of heart failure with reduced ejection fraction (HFrEF) consists of several compounds aimed to blocking the aforementioned molecular pathways, and is associated consistent improvements in terms of morbidity and mortality [6]. Besides the hyperactivation of the aforementioned pathomechanisms, multiple anabolic deficiencies have been consistently described in CHF [7-9]. The impaired activity of Growth Hormone (GH) and its tissue effector Insulin-like Growth Factor 1 (IGF-1) is considered fascinated, given also the possibility of a replacement therapy [10]. This review will be focused on the impairment of GH/IGF-1 axis in CHF, and on the study of GH therapy in CHF.

Effect of GH and IGF-1 on the cardiovascular system

The GH/IGF-I axis is considered the most powerful anabolic system in nature [11]. It drives post-natal growth by increasing both bone length and density, and muscle mass during life [12]. Moreover, it has important effects on metabolism, mainly on visceral adipose tissue [13]. The actions of IGF-1 are mediated by its own receptor (IGF1R), leading to the activation of the PI3K/Akt signaling pathway, promoting cell growth, inhibiting apoptosis and protecting cells from TNF-α cytotoxicity [10].

Furthermore, it owes a significant impact on the cardiovascular system, by sustaining cardiac growth and performance. IGF-1 leads to an increase of the production of nitric oxide (NO), which in turn leads to a reduction of the systemic vascular resistance [14,15]. Moreover, it

increases the contractility of cardiomyocytes mainly by increasing intracellular calcium concentration and calcium sensitization of the myofilaments and preserves capillary density. Last but not least, both GH and IGF-1 are likely to increase protein synthesis in the cardiomyocytes [16]. The reuptake of calcium is also promoted by IGF-1 through the regulation of the sarco-endoplasmic reticulum Ca2+-ATPase (SERCA2), which is involved in diastolic function.

Indeed, animal models of heart failure showed that GH/IGF-1 improves calcium-handling, attenuates left ventricular remodeling and enhances intracellular Akt signaling [17]. In addition, it regulates cardiac growth, cardiomyocyte size and metabolism [10].

Molecular basis of GH/IGF-1 impairment in heart failure

GH deficiency is a quite common feature of CHF with a recorded prevalence from 32% to 53% according to different cohorts [18-20]. The majority of the studies reported also reduced IGF-1 serum values in CHF compared with healthy controls [18,21-23]. Specifically they were remarkably reduced in patients with advanced heart failure [50] or cachexia [24]. GH pulse is down-regulated in CHF and is impaired due to several reasons. A first hypothesis is rooted in hypo-perfusion and reduced oxygen supply, as shown by a proof-of-concept study performed on 25 children with GH deficiency (GHD) undergoing brain MRI. In these report pituitary stalk enhancement were significant impaired in GHD, probably due to a mismatch between arterial perfusion and venous drainage [25]. A primary hypothalamic damage was also theorized by a blunted response to different provocative tests such as Growth Hormone realizing hormone (GHRH), GHRH + Arginine, GH-related peptides 18. Right heart failure and backward liver congestion, which might occur at the end-stages of CHF, may also impair IGF-1 secretion [26,27] Finally, also background therapy of CHF (such as ACE-inhibitors [28] as well as β-blockers [29]) is likely to modify IGF-1 secretion through a direct inhibitions of IGF-1 signaling.

However, a single pathomechanisms is not able to underline the high reported prevalence of abnormalities of GH/IGF-1 in CHF. Interestingly, these abnormalities are a common finding in several chronic wasting condition characterized by inflammatory activation and cytokine overexpression [11,30-35].

Prevalence and clinical meaning of GH/IGF-1 impairment in CHF

Evidence arising from a wide panel of population studies indicated how Growth Hormone deficiency (GHD) is associated with impaired cardiac performance, increased peripheral vascular resistance and reduced exercise capacity [10] with a positive correlation between GHD severity and cardiac impairment [36]. Indeed, about 30% of CHF patients display a GHD [18,19,37]. Recently, Arcopinto *et al*. demonstrated in 130 CHF undergoing a GHRH+ Arginine provocative test, that the presence of GHD clusters a subgroup of patients with worse clinical status and increased all-cause mortality, higher depression scores, impaired quality of life, presence of left ventricular (LV) remodeling, lower physical performance, and increased NT-proBNP levels38. Interestingly, patients without GHD showed also better right ventricular (RV) function (+18% in RV area change, p=0.03) and lower estimated pulmonary pressures (-11%, p=0.04) [37]. These aforementioned findings might also explain the increased mortality and hospitalization of GHD patients, given the pivotal role of the right heart-pulmonary circulation unit in determining prognosis in CHF [26,38-44]. The assessment of GH status might gather important information also in patients presenting acute heart failure exacerbation. Bhandari *et al*. recently evaluated serum GH concentrations in 537 patients presenting to the Emergency room for acute heart failure (AHF), and found increased GH levels in patients who experienced one of prespecified outcome measures (either death or readmission within 1 year) [45]. A further analysis showed that the addition of GH to ADHERE multivariate logistic model (age, sex, urea, heart rate, and systolic blood pressure), and to ADHERE model + NTproBNP lead to a significant reclassification improvement of both the prognostic scores [45].

With regards to IGF-1 levels, discrepancies were reported among several studies published by independent gorups. Broglio *et al.* [18,46] reported low IGF-1 levels in patients with systolic left ventricle (LV) dysfunction as well as bunted response to GHRH. Anker *et al.* [24] evaluated the GH/IGF-1 axis in cachectic and non-cachectic patients with advanced heart failure, showing that the first group was characterised by a pattern of GH resistance (high GH with low IGF-1). Patients with CHF in NYHA class I and II displayed elevated IGF-1 levels (p=0.005 *vs* control subjects), whereas patients with more severe disease (NYHA classes III and IV) had values comparable to healthy controls as reported by Al-Obaidi [47] supporting the speculation that IGF-1 rises at the initial stages of the disease in order to compensate and restore the heart function at a para-physiological level. On the other hand, as the illness proceeds a condition of impaired IGF-1 secretion up to a frank state of GH resistance may be present [24].

The utmost clinical meaning of low IGF-1 levels in CHF is supported by a consistent body of evidence. Indeed, IGF-I deficiency is associated with inflammatory activation, endothelial dysfunction and a consistent impairment of skeletal muscle performance [22]. Furthermore, a condition of low serum IGF-1 levels is also associated with worse outcomes, as demonstrated by several independent groups [10,23,45,48,49]. Interestingly, a landmark study performed by Jankowska and co-workers showed that the concomitance of more than one hormonal deficiencies (IGF-1, DHEA-S, testosterone) was an independent predictor of mortality in men with HF, shedding lights on the interplay among coexisting anabolic deficiencies [21].

The evaluation of IGF-1 might be helpful not only in the CHF phenotype with reduced ejection fraction (HFrEF) but also in heart failure with preserved ejection fraction (HFpEF). Salzano *et al*. reported lower IGF-1 and higher GHD in HFrEF than HFpEF [50]. Even if lower than in HFrEF, the prevalence of hormone deficiency (HD) in HFpEF was remarkable, considering that more than half of HFpEF had at least 1 hormone deficiency. In this study a major prevalence of atrial fibrillation (AF) in HFpEF was recorded, as expected [51,52]. However, the small sample size did not allow any further investigation regarding the occurrence of AF in patients with hormonal deficiencies and HFpEF. The aforementioned evidences suggest that IGF-1 might be a useful and quick assessable biomarker for the in clinical daily practice, useful for risk stratification and identification a subgroup of patients requiring a more aggressive therapy. Table 1 summarizes the studies evaluating GH/IGF-1 axis in cohorts of patients affected by CHF.

GH therapy in heart failure

Experimental studies reported beneficial effects associated with GH administration on cardiac function, peripheral vascular resistance, and survival [53-55]. In these regards, early treatment of large myocardial infarction with GH reduces pathologic LV remodeling and improves LV function [56]. However, the translation of these results in clinical studies did not lead to unequivocal results. After an initial enthusiasm arising from a wide number of preliminary experiences with open-

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Table 1. Summary of studies on GH/IGF-1 axis as biomarker in heart failure.

1st Author	n	Cut-offs	Main findings
		Studies on IGF-1	
Niebauer [22]	52	Lowest level normal subject	Reduced skeletal muscle function, increased TNF-α, CS/ DHEA, NAdr (+49%) and Adr (+136%) in patients with low IGF-1 (<104 ng/ml)
Anker [24]	72	Comparison among groups. No cut-off used	Cachectic patients showed an increase of total serum GH and a decrease of GHBP compared with non-cachectic patients
Al-Obaidi [47]	24	Comparison among groups. No cut-off used	Elevated IGF-1 levels in patients with NYHA class I-II but not in NYHA class III-IV
Jankowska [21]	208	10th percentile of a healthy subjects' population	IGF-1 levels prognostic markers of mortality in multivariable models when adjusted for established prognostic factors
Petretta [49]	82	Log IGF-I/GH <3.45	Low IGF-I/GH ratio independently predicts all-cause mortality
Andreassen [79]	194	Lower quartile of IGF-1	No relevant association between IGF-1 and baseline cardiac status nor prognosis
Watanabe [48]	142	Log IGF1/IGFBP3 less than median value	Low IGF-1/IGFBP3 associated with increased rates of all-cause mortality, cardiac death, and a composite of cardiac death and re-hospitalization
Arcopinto [23]	207	IGF-1 ≤122 ng/ml (derived from a ROC curved analysis)	Low IGF-1 levels independently predict all-cause mortality
Faxen [80]	164	Age- standardized scores of IGF-1	Higher IGF-1 in HFpEF than HFpEF with similar IGF-BP 1 IGF-1 predicts mortality in HFrEF but not in HFpEF
		Studies on GH	
Bhandari [45]	537	GH concentration 0.11 ng/mL and 1.22 ng/mL (based on previous population studies)	GH levels independently predicted 1 year-outcome in HFrEF and increased prognostic information over the ADHERE score and NT-proBNP
Arcopinto [37]	130	Positivity to GHRH + Arginine test and BMI-adjusted cut-offs	GHD patients had impaired functional capacity, LV remodeling, RV performance, elevated NT-proBNP levels and increased all-cause mortality

GH: growth hormone; IGF-1: insulin-like growth factor 1; TNF-α: tumor necrosis factor alpha; CS: cortisol; DHEA: dehydroepiandrosterone; NAdr: noradrenalin; Adr: adrenalin; GHBP: GH binding protein; NYHA: New York Heart Association, IGF-BP: IGF binding protein; ROC: receiver operating characteristic; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ADHERE: acute decompensated heart failure national registry; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; GHRH: growth hormone releasing hormone; LV: left ventricle, RV: right ventricle.

Table 2. Studies on GH administration/replacement in chronic heart failure.

1st Author	Patients (n)	Age (m ± SDS)	Major results	Major side effects
			Studies of GH administration without any GH status assessment	
Fazio [57]	7	46 ± 9	Reduced LV remodeling, improved hemodynamic variable, increase in oxygen consumption, better clinical status	Not recorded
Frustaci [81]	5	28 ± 8.1	Mild reductions in LV end-diastolic diameter and mild improvement in the LV systolic function	Ventricular arrhythmias disappeared after GH withdrawn
Isgaard [64]	22	60± 11	Any significant positive effect recorded on cardiac function, exercise capacity or neuroendocrine activation	Not recorded
Osterziel [82]	50	54 ± 10	GH treatment increased LV mass	Not recorded
Gent-Zotz [58]	7	55 ± 9	Significant reduction in LV volumes; improvement of diastolic function and LV filling pressures. Increased in exercise capacity. Worsening after GH was discontinued	Not recorded
Jose [83]	6	NR	Improvement in functional class	Not recorded
Spallarossa [59]	20	62,1 ± 8	Improved clinical status and duration of the exercise test	Not recorded
Smit [84]	19	65,5 ± 8,5	No beneficial effect on LV function	Not recorded
Napoli [61]	16	54,5 ± 11,3	GH improved endothelial dysfunction and improved non-endothelium-dependent vasodilation. Increased VO_2 max	Not recorded
Acevedo [62]	19	57,7 ± 4,5	Positive correlation between the changes in oxygen consumption and ejection fraction was found in GH treatment group	Not recorded
Adamopoulos [85]	12	50 ± 13,8	Reduction of circulating proinflammatory cytokines and pro-inflammatory molecules, with a final increase in the serum anti-inflammatory/pro-inflammatory balance. Reduction of end-systolic volume and wall stress associated with an increase in contractile reserve	Not recorded
Fazio [63]	22	55± 7	Improved New York Heart Association functional class, cardiopulmonary performance	Not recorded
			Studies of GH replacement implemented after GH status assessment	
Cittadini [19]	56	62 ± 2	Reduction of LV remodeling with significantly improved exercise capacity and cardiopulmonary performance. Improvement of quality of live and reduction of NT-proBNP serum concentration	Not recorded
Cittadini [66]	31	62 ± 2	Reduction in LV volumes and ejection fraction. Marked difference in the aggregate of death and hospitalization for worsening CHF	Not recorded

GH: growth hormone; m: mean; SDS: standard deviation; LV: left ventricle; VO_2 max: peak oxygen consumption; NR: not reported; NT-proBNP: n-terminal fragment of the brain natriuretic peptide; CHF: chronic heart failure.

labeled pilot studies [57-63], two larger randomized controlled clinical trials [60,64] ended with neutral results. These inconsistent results might be explicated by several reasons: a different study duration, the insufficient target dose, the use of inadequate end-points and the lack of GH status-assessment [65]. Interestingly, a post-hoc analysis of a double-blind placebo-controlled study of GH-administration, those patients who significantly increased IGF-1 due to GH administration displayed a significant improvement of left ventricle systolic function, whereas those without IGF-1 increase did not experienced any improvement [60]. This led to the speculation that GH should be probably administered only in those patients with an impairment of GH/IGF-1 status. Furthermore, GH therapy should not be administered in end-stage CHF patients, which are probably already in a GH resistance state [24]. Given this magnitude, our group implemented a randomized, single-blind controlled trial, aimed in comparing the effect of GH replacement therapy in CHF with concomitant GH deficiency [19]. In this study only patients with CHF and a positive GHRH + arginine provocative test were enrolled [19]. We recorded in the group treated with GH a net improvement of quality of life score (Minnesota living with heart failure questionnaire decreased from 46 ± 5 to 38 ± 4; p<0.01), LV systolic function (LV ejection fraction improved from 34 ± 2 to 36 ± 2%; p<0.01), peak oxygen uptake (from 12.9 ± 0.9 to 14.5 ± 1 ml/kg· min, p<0.01) a decrease of circulating N-terminal pro-brain natriuretic peptide levels (from 3201 ± 900 to 2177 ± 720 pg/ml; p<0.006), while no relevant changes were observed in the control group19. After these encouraging results, we decided to prolong this study to a 4-year follow up [66]. After a 4-years follow-up, GH replacement therapy was still associated with LV reverse remodeling (increase of LV ejection fraction from 10 ± 3 in the treated group *vs* -2 ± 5% in the control group, p:0.001), end a dramatic increase in peak VO2 (treatment effect of 7.1 ± 0.7 in the treated group *vs* -1.8 ± 0.5 ml/kg· min in control group, p<0.01). A marked difference in the aggregate of death and hospitalization for worsening CHF in replacement therapy arm was also recorded (31 events in the control group *vs* 17 in the GH treated patients) [66]. Of note a significant correlation between IGF-1 serum levels and peak VO2 was found (r: 0.59; p<0.05). Notwithstanding the well-described negative effects of GH administration on glycemic control, no worsening in glycosylated hemoglobin were reported in this study [66]. in However, the usefulness of GH replacement therapy must be still proved in robust double-blind placebo-controlled trial. Table 2 summarizes the studies evaluating GH administration/replacement in CHF.

Future prospective and conclusions

The interplay between hormones and the cardiovascular system is complex [11,66,67-76]. The importance of the somatotropic axis in cardiovascular homeostasis were extensively described in the last 3 decades. Chronic Heart Failure represents a prototype of the interaction between GH/IGF-1 pathway in a chronic cardiovascular impairment status [77]. Indeed, according with most of studies, patients with an impaired GH/IGF-1 status are affected by a more aggressive disease, limited functional and exercise capacity, overexpression of neurohormonal peptides, a more severe left ventricle remodeling and poorer outcomes (mortality and hospitalization). For this reason, a prospective multicenter clinical registry aimed in investigate the impact of multiple and concomitant Anabolic Deficiencies (including therefore also GH and IGF-1 assessment, testosterone, insulin resistance, thyroid, *etc*.) on clinical status, exercise capacity, neurohormonal activation, left ventricle architecture and function, quality of life, hospitalization and mortality rate in patients affected by CHF was implemented recently and was named T.O.S.C.A (Trattamento Ormonale nello Scompenso CArdiaco), whose preliminary results will be available within few months [8,78].

Furthermore, several open-label studies reported the potential beneficial effects of GH replacement therapy as a possible future therapeutic strategy in CHF in a double-blind randomized controlled trial.

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