Heart Failure as a Multiple Hormonal Deficiency Syndrome

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The classic neurohormonal model of heart failure (HF) is rooted in the overexpression of neurohormonal molecules. To complement this paradigm, increasing evidence indicates that a variety of hormones and metabolic signals may be downregulated in HF patients. The list of downregulated molecules includes growth hormone (GH), its tissue effector insulin-like growth factor-1 (IGF-1), thyroid hormone, and anabolic steroids.1–4 In addition, HF is complicated by insulin resistance (IR), which ultimately means downregulation of insulin signaling.5,6 This review examines the evidence in support of the concept that HF is a multiple hormonal and metabolic deficiency syndrome (MHD). Particular attention is focused on the relevance of MHD in terms of cardiac performance and physical capacity and its impact on HF progression. Translation of new concepts into potential therapeutic options is also discussed.

IR and HF

A bidirectional link exists between IR and HF. IR predicts HF independently of other risk factors.7 Conversely, patients with HF are predisposed to IR or type 2 diabetes.5,8 In the OPTIMIZE-HF study, 42% of patients hospitalized for HF also had diabetes.9 IR is present in about one third of nondiabetic HF patients and associates with more severe HF symptoms, worse functional capacity, and poor survival.5,6 IR per se, independent of hyperglycemia and hyperinsulinemia, may exert deleterious cardiovascular effects.10

IR specifically involves the myocardial tissue. In a dog model of HF, myocardial glucose uptake was 32% lower (P<0.001) than pre-HF values, and this decrease was associated with reduced translocation of GLUT4 and downregulation of phosphorylated Akt.11 A positron emission tomography study showed impaired myocardial uptake of glucose and increased uptake of free fatty acid (FFA) in HF patients.12

Several mechanisms may explain why HF is complicated by IR. A key factor is adrenergic overactivity. The insulin-antagonistic effect of catecholamines is well established.13,14 Angiotensin II, which is overproduced in HF, may inhibit norepinephrine reuptake in the myocardium. A more recent positron emission tomography study showed that the reduced norepinephrine reuptake occurs with regional IR.15

The failing heart is characterized by a marked fall in phosphocreatine and in the phosphocreatine/ATP ratio.16 In the initial stages of HF, a fetal pattern of metabolic genes re-emerges and causes a major shift in substrate preference, with glucose becoming the primary substrate that is oxidized.17,18 This shift provides 40% to 50% more ATP per oxygen molecule consumed.19 When IR superimposes on HF, the increased FFA flux maximizes myocardial FFA oxidation, whereas glucose uptake is downregulated.20 The consequent reduction in energy production and metabolic flexibility accounts for the so-called “IR cardiomyopathy.”21 The role of impaired glucose uptake is supported by the finding that cardiac-specific overexpression of GLUT1 prevents cardiac dysfunction.22

IR is a new potential target in the treatment of HF.23 However, few measures are able to improve myocardial metabolism. Some of them (diet, physical exercise, and carvedilol among β-blockers) are components of standard HF treatment. Hyperinsulinemia is a powerful tool to overcome IR. However, there are well-grounded reservations regarding insulin use in type 2 diabetics with HF. In a study of 554 patients with advanced HF, insulin-treated diabetes was an independent predictor of mortality (hazard ratio, 4.3).24

Metabolic modulators (trimetazidine, perhexiline, ranolazine) block mitochondrial FFA entry or FFA β-oxidation. However, there are no clinical data about the myocardial and long-term effects of these drugs. Moreover, if myocardial insulin sensitivity is not restored, inhibiting FFA oxidation may further compromise cardiac dysfunction.25

The insulin-sensitizers thiazolidinediones (TZDs) improve myocardial glucose uptake and contractile dysfunction.26–28 Unfortunately, meta-analyses of clinical trials revealed a high incidence of HF symptoms in the TZD arms.29,30 This finding led health authorities (the European Medicines Agency and the Food and Drug Administration) to issue contraindications or warnings against the use of TZDs in HF. However, there are no reports of increased mortality from HF during TZD treatment. Moreover, TZD-related HF does not appear to be due to the worsening of cardiac performance but to peripheral mechanisms (fluid retention and increased vascular permeability).

By activating AMPK, metformin stimulates GLUT4 translocation and glucose uptake in cardiac muscle and in insulin-resistant cardiomyocytes.31,32 Until recently, metformin was contraindicated in diabetics with HF because of the remote
possibility of lactic acidosis. The FDA’s stance has recently changed from contraindication to a black-box warning.

Glucagon-like peptide-1 is a novel antidiabetic agent that stimulates GLUT1 translocation and myocardial glucose uptake. A 5-week infusion of glucagon-like peptide-1 in HF patients with New York Heart Association class III/IV improved LV ejection fraction (EF) (from 21% to 27% ± 3%; P<0.01) and maximal oxygen consumption. Given its efficacy and good tolerability, glucagon-like peptide-1 and its analogs are promising candidates for the treatment of IR cardiomyopathy.

The Low IGF-1 Syndrome in HF

GH and IGF-1 are essential for preserving both cardiac morphology and performance in adult life. Patients with GH deficiency have impaired cardiac performance, increased peripheral vascular resistance (PVR), and reduced exercise capacity. Table 1 reports the basal, unstimulated serum concentration of IGF-1 in patients with HF. In most studies, IGF-1 was reduced in HF patients and more in patients with either advanced HF or cardiac cachexia. The prevalence of IGF-1 deficiency, defined as an IGF-1 level below the tenth percentile of healthy peers, was as high as 64%.

The finding of low IGF-1 in HF patients is relevant for many reasons. First, individuals with low IGF-1 levels undergo cardiovascular alterations that are reminiscent of those observed in HF patients and are corrected by replacement therapy. These observations demonstrate the continuing ability of IGF-1 to modulate the plasticity of cardiac tissue in adult life. Second, large population-based studies (Framingham, DAN-MONICA, and Rancho Bernardo) show that a low level of IGF-1 is predictive of HF, ischemic heart disease, and cardiovascular mortality. Third, low IGF-1 levels in HF patients are associated with greater cytokine and its severity.

Reduced IGF-1 levels in HF patients may be due to deficient GH secretion or to reduced responsiveness of IGF-1-generating tissues to GH. GH secretion was assessed by the GHRH plus arginine test in 34-well-nourished patients with HF (EF, 23%) and compared with a group of 39 healthy controls. The GH response was markedly impaired in the HF patients (18±3 ng/mL versus 34±5; P<0.01). Also spontaneous GH secretion is defective in HF patients. The mean nocturnal GH and the peak GH were markedly reduced in HF patients with severely compromised LV function (EF, <20%).

With regard to GH resistance, the response of IGF-1 to GH was assessed in 39 patients with HF in good nutritional state and in 42 age-matched controls. After 4 days of 5 or 10 mU/kg per day GH administration, IGF-1 levels in HF patients rose to levels similar to those of the controls, indicating that GH sensitivity was preserved in HF patients. Subsequent studies addressed the issue of GH resistance in HF patients in relation to the presence of cardiac cachexia. The IGF-1/GH ratio was 12-fold higher in noncachectic patients than in cachectic patients with HF. The difference is impressive and, although the IGF-1/GH ratio is a crude index of GH sensitivity, the data strongly suggest that cardiac cachexia causes GH resistance. However, cachexia is not the only cause of GH resistance because the response of IGF-1 to GH administration is extremely variable and may be independent of nutritional problems. This point is well discussed in a recent meta-analysis in which the effects of GH were analyzed in relation to the IGF-1 response.

As yet, no study has evaluated whether administration of customized amounts of GH or IGF-1 will benefit HF patients who have documented GH deficiency and low IGF-1 levels.

The Low-T3 Syndrome in HF

T3 is generated from T4 by the activity of 5’-monodeiodinase. T3 increases cardiac output by affecting all the determinants of cardiac performance (ie, preload, afterload, contractility, and heart rate). An important, non-genomic effect of T3 is exerted in the resistance vessels, where T3 induces relaxation of the vascular smooth muscle cells. This effect of T3 is mediated by the endothelial PI3-K/Akt/endothelial nitric oxide synthase signaling complex. The augmented nitric oxide availability activates guanosine 3’,5’-cyclic monophosphate in the vascular smooth muscle cells with a consequent fall in calcium flux, relaxation, and decrease in PVR.

Patients with HF may have decreased T3 levels, in the presence of normal or near-normal T4 and TSH levels. This hormonal combination defines the low-T3 syndrome, in all likelihood caused by alterations of the conversion mechanisms. In experimental HF, the cardiac activity of type III deiodinase, which converts T4 into rT3 and T3 into T2, was increased 5-fold.

In a series of 199 patients with HF, 31% of patients with severe HF had low-T3 syndrome, defined as total T3<80 ng/dL. A similar prevalence (34%) was reported in another study of 132 HF patients. In a sample of 573 cardiac patients (mostly affected by ischemic heart disease), a low-T3 syndrome, defined by a free T3 <2 pg/mL, was found in 30% of the patients. After a 12-month follow-up, cardiac and all-cause-mortality was higher in the low-T3 group, and free T3 was the strongest and an independent predictor of death in a multivariate analysis. The value of low T3 as a predictor of poor prognosis was confirmed in a more recent study in 311
patients with HF. The T3 level also correlates with maximal $O_2$ consumption and LVEF. Experimental models of low-T3 syndrome have provided insights into how low T3 affects cardiac biology. After a 4-week caloric restriction, serum T3 decreased remarkably, whereas T4 remained unchanged, as predicted by the low-T3 model. These changes were associated with LV dysfunction, downregulation of SERCA2, and myosin heavy chain shift toward the slower $\beta$ isoform. T3 supplementation normalized cardiac dysfunction. In models of acute myocardial infarction, T3 replacement restored LV function, normalized some of the dysregulated genes (phospholamban, Akt phosphorylation), and inhibited cardiomyocyte apoptosis by inducing Akt phosphorylation.

With regard to clinical studies, 23 patients with advanced HF (EF, 22%) received T3 infusions for 6 to 12 hour. The main finding was the expected decrease in PVR, which was followed by a rise in cardiac output. More recently, a controlled study was performed to assess the effects of a 3-day infusion of T3 in a group of patients with HF and low-T3 syndrome (basal free T3: 1.74 pg/mL). The T3 infusion normalized the low-T3 levels, and resulted in a significant improvement in stroke volume. Interestingly, T3 infusion decreased circulating levels of such key neurohormones and biomarkers, as norepinephrine, aldosterone, and pro-B-type natriuretic peptide.

Although encouraging, the studies of T3 administration to HF patients are very few and short term. The deterrent to robust studies is the concern that T3 may be harmful due to (1) the increased heart rate, (2) the arrhythmogenic effect, and (3) the increased energy demand. These concerns are based on the knowledge that T3 acts on the cardiomyocytes of the sinoatrial node and activates the $\beta_1$-adrenergic receptors. In reality, neither an increase of heart rate nor evidence of ischemia or clinical arrhythmia was observed in any study in which HF patients received T3 or T4, even when serum T3 was raised above the normal range. In contrast, a reduction in heart rate and noradrenergic activity were observed, possibly because of improved hemodynamics.

Acute T3 administration increases stroke volume but not cardiac work, which suggests that T3 acts mainly on PVR and afterload and that T3 does not raise cardiac work or energy demand. Accordingly, PVR and afterload are increased in hypothyroid patients, whereas LV mechanical efficiency, estimated by positron emission tomography methodology, is impaired. In the isolated perfused heart, T3 enhanced cardiac performance without raising oxygen demand. Therefore, the ratio of cardiac work to myocardial oxygen consumption, a reliable measure of myocardial efficiency, was improved. The ability of T3 to reduce the oxygen cost of contractility is a crucial aspect of the T3-HF interaction, given that myocardial energetics play a pivotal role in the progression of HF. This peculiar effect of T3 provides yet another convincing argument in support of T3 as a pharmacological nature of the approach as opposed to the physiological hormonal replacement afforded by T3. This becomes crucial if the goal is to treat selected patients with the low-T3 syndrome.

### Testosterone and HF

In men with HF, serum levels of free testosterone and dehydroepiandrosterone were decreased in proportion to HF severity. The average prevalence of testosterone deficiency, spanning all age classes, was as high as 43%. More importantly, low testosterone and dehydroepiandrosterone are independent predictors of death in men with HF. A reduced testosterone level may be one of the factors that contribute to the anabolic or catabolic imbalance that is characteristically present in many patients with advanced HF. Testosterone receptors are present in endothelial cells, vascular smooth muscle cells, and cardiomyocytes. After binding to its receptors, testosterone may exert both genomic and nongenomic effects.

Testosterone acts on the vascular arterial wall, where it induces vasodilation. This effect is nongenomic because the response is rapid and primarily involves the vascular smooth muscle cells, in which testosterone lowers the intracellular $Ca^{2+}$ flux, secondary to interaction with voltage-operated calcium and potassium channels.

Testosterone induces protein synthesis and hypertrophy in the cardiomyocytes of several species, including humans, through a receptor-specific interaction. In a postmyocardial infarction model of HF, testosterone induced physiological cardiac growth with no increment in hypertrophy markers or collagen accumulation. In a model of ischemia-reperfusion injury, testosterone exerted protective effects on cardiomyocytes by activating ATP-sensitive K channels and upregulating cardiac $\alpha(1)$-adrenoceptor.

Testosterone is important to myocardial contractility. Gnadenectomy in male rats reduced the expression of genes encoding the $L$-type $Ca^{2+}$ channel, the Na+/Ca$^{2+}$ exchanger, $\beta(1)$-adrenoceptors, and myosin heavy chain subunits. In parallel, cardiomyocyte contractile capacity deteriorated. The role of testosterone was explored in a recent clinical study in 25 patients with Klinefelter syndrome and 25 matched controls. There was evidence of systolic dysfunction in the patients, as documented by reduced peak systolic velocities ($4.4 \pm 1.3$ versus $5.3 \pm 1.0$ cm/s, $P<0.01$) and strain rate ($-1.3 \pm -0.3$ versus $-1.6 \pm 0.3$ s$^{-1}$, $P<0.01$).

The notion that testosterone deficiency affects cardiac function encouraged studies of testosterone replacement in patients with HF. In a controlled study, a single dose of testosterone (60 mg orally) was given to 12 patients with New York Heart Association class II–III HF. Testosterone decreased PVR and afterload, and cardiac output was conse-
quently higher than in the placebo study. These results prompted a more robust clinical study in which 76 men with moderately severe HF were randomized to receive testosterone or placebo for 12 months. Testosterone, administered by means of an adhesive skin patch (5 mg/day), raised the serum testosterone level by 40%. Testosterone did not affect LV morphology or function but improved exercise capacity, as shown by the significant increase in shuttle walk distance ($P=0.006$). The clinical severity of HF improved by at least 1 New York Heart Association class in 35% of patients treated with testosterone and in 8% of patients given placebo ($P=0.01$). Testosterone also enhanced dominant handgrip strength ($P=0.04$). The data suggest that the functional improvement was due to an effect of testosterone on skeletal muscle. Even so, the data are of interest given the relevant role that peripheral abnormalities play in HF progression.

A collateral observation, pertinent to HF, is that testosterone replacement therapy may exert beneficial metabolic effects. Thirteen patients with moderate to severe HF received either replacement testosterone treatment or placebo for 4 weeks. IR was estimated by the homeostatic model index (HOMA-IR). Testosterone treatment improved IR ($-1.9\pm0.8$ HOMA units; $P=0.03$), and the response was inversely correlated with the increase in bioavailable testosterone. The improvement in IR was associated with an increase in total body mass ($+1.5$ kg; $P=0.008$) and a decrease in body fat mass ($-0.8\%$; $P=0.02$).

### Summary

The MHD model extends the classic neurohormonal theory and its application by focusing on restoring HF-related metabolic or hormonal deficiencies. Each component of MHD is associated with impaired functional capacity and poor clinical outcome. However, the replacement approaches so far attempted have provided additional benefits on top of standard therapy (Table 2). There are no data regarding the crucial question of whether life expectancy is also improved.

Because the number of deficiencies has a profound impact on the progression of HF and outcome. In HF patients with concurrent deficiency of testosterone, dehydroepiandrosterone, and IGF-1, the 3-year survival rate was as low as 27% versus 75% when only 1 anabolic hormone was defective.

Another important issue is the definition of hormonal or metabolic deficiency. Whereas IR is diagnosed by the HOMA-IR and the insulin clamp tests, and GH deficiency is easily identified by the GHRH plus arginine test, a standardized procedure for GH resistance has not yet been officially recommended. The low-T3 syndrome is currently diagnosed by an arbitrarily low-T3 value in the presence of near-normal T4 and TSH. With regard to testosterone and dehydroepiandrosterone, the Endocrine Society has recently issued guidelines for the diagnosis of androgen deficiency in adult men.

A final, but fundamental, question relates to the meaning of the MHD syndrome. MHD may be one outcome of HF as a complex multiorgan disease. In this scenario, the pituitary gland might be a particular target of HF, with consequent dysfunction of cell lines that control the production of some of the hormones involved in the MHD syndrome. In this case, MHD must be searched for and rectified by adequate hormonal supplementation. If MHD is an ensemble of biomarkers that are not mechanistically linked to HF, MHD may be useful only for staging and monitoring purposes. Finally, if MHD represents the body’s attempt to limit energy dissipation, we must acknowledge such an adaptive response and leave the status quo.

The evidence presented in this review strongly suggests that MHD is not a simple disease marker or a compensatory response. Even assuming that it originates as an adaptive reaction, ultimately, each hormonal deficiency is associated with reduced functional capacity and, more importantly, is a powerful and independent predictor of poor clinical outcome. This finding in itself justifies the implementation of robust clinical trials to determine whether either single or multiple hormone replacement is a workable strategy to adopt in HF patients in addition to current pharmacotherapy.

### Disclosures

None.
References


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