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Exercise Intolerance in Chronic Heart Failure: The Role of Cortisol and the Catabolic State

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Abstract Chronic heart failure (CHF) is a complex clinical syndrome leading to exercise intolerance due to muscular fatigue and dyspnea. Hemodynamics fail to explain the reduced exercise capacity, while a significant skeletal muscular pathology seems to constitute the main underlying mechanism for exercise intolerance in CHF patients. There have been proposed several metabolic, neurohormonal and immune system abnormalities leading to an anabolic/catabolic imbalance that plays a central role in the pathogenesis of the wasting process of skeletal muscle myopathy. The impairment of the anabolic axes is associated with the severity of symptoms and the poor outcome in CHF, whereas increased cortisol levels are predictive of exercise intolerance, ventilatory inefficiency and chronotropic incompetence, suggesting a significant contributing mechanism to the limited functional status. Exercise training and device therapy could have beneficial effects in preventing and treating muscle wasting in CHF. However, specific anabolic treatment needs more investigation to prove possible beneficial effects.

Keywords Chronic heart failure · Exercise intolerance · Skeletal muscle · Myopathy · Catabolism · Cachexia · Cortisol · Hormones

Introduction

Chronic Heart failure (CHF) can be defined as the insufficiency of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues. It is a complex syndrome affecting multifunctionally the systems of the human body. Excessive catabolic state resulting in weight loss and wasting (i.e., cardiac cachexia) is a serious complication of advanced CHF that is associated with reduced survival [1]. First reports of this wasting syndrome "*The flesh is consumed and becomes water*, . . . , *the shoulders*, *clavicles*, *chest and thighs melt away. This illness is fatal*, . . . " [2] come from Hippocratic School of Medicine (Hippocrates c. 460 BC – c. 370 BC).

Nowadays, aging of the population and prolongation of lives by modern therapeutic modalities has led to increased prevalence of heart failure. Approximately 1–2 % of the adult population in developed countries has CHF, with the prevalence rising to ≥10 % among persons 70 years of age or older [3]. In 2010 about 6 million US adults over 18 years of age (2.8 %) had CHF, and it is estimated that by 2030, an additional 3 million people will have CHF, a 25.0 % increase in prevalence from 2010 [4]. In this spectrum, increased advanced CHF incidence is expected in the oncoming decades. A better understanding of the pathophysiological mechanisms involved in excessive catabolism will lead to novel therapeutic strategies in the future.

Exercise Intolerance in CHF

Exercise intolerance is a major clinical manifestation in patients with CHF due to dyspnea and fatigue at low exercise workloads of day life activities. Although central hemodynamic abnormalities are the hallmark of this syndrome, resting hemodynamics failed to explain the reduced exercise capacity [5], and they are unable to estimate the cardiac functional reserve. Studies that investigated the role of the cardiac pump during exercise showed that this impairment was not due simply to an inability of the heart to increase the cardiac output

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during exercise [6], whereas patients had reduced exercise tolerance, and early muscular lactate release despite normal skeletal muscle blood flow [7, 8]. These findings reveal that an intrinsic muscle abnormality, rather than decreased skeletal muscle perfusion, is considered to be responsible for the exercise limitation.

It is widely accepted that significant skeletal muscular pathology [9], including functional, morphologic and metabolic abnormalities of the skeletal muscle, is present in CHF that is now recognized to be the main mechanism for exercise intolerance. Skeletal muscle is structurally and functionally abnormal in CHF [9] and according to the "peripheral muscle hypothesis" [10], impaired skeletal muscle function induces a peripheral ergoreflex hyperactivation, which causes hyperventilation and sympathetic activation, explaining exercise intolerance and, hence, dyspnea and fatigue in CHF patients [10, 11]. This strong relationship of exercise intolerance and skeletal muscle pathology has been demonstrated by significant studies of the last decade, making skeletal muscle myopathy the major debilitating factor of exercise limitation [12•].

The Role of CPET

The need for a global assessment of the CHF patient, including central hemodynamics and the periphery, led to an increasing utilization of the Cardiopulmonary Exercise Test (CPET) in CHF. CPET is a non-invasive, dynamic method, which provides an assessment of the response of the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems to exercise. It has gained widespread application in the assessment of functional status of CHF patients and is a useful test to determine the severity of disease, to provide important prognostic information [13, 14•] and identify candidates for cardiac transplantation [15] or other advanced treatments. It is also the appropriate tool for the exercise prescription of CHF patients and could also assess the efficacy of new drugs and devices. Peak oxygen consumption (Peak VO_2) is the best indicator of exercise capacity and constitutes a significant independent predictor that outperforms clinical variables, right-heart catheterization data and other exercise test variables in predicting outcome in severe CHF [13]. There are also other CPET variables that supply prognostic information: the ventilatory response to exercise (VE/VCO_2 slope) improves the risk stratification of CHF patients [16] and transcends the predictive value of peak VO_2, as it does not require maximal effort [15]; the anaerobic threshold (AT), that does not require maximal effort, and other less well studied parameters like chronotropic response to exercise and parameters of submaximal exercise and of the recovery period. It emerges that the role of CPET becomes of crucial importance in the assessment of exercise intolerance of CHF patients.

Skeletal Myopathy and Cachexia in CHF

CHF is a complex syndrome affecting many body systems. Skeletal muscle myopathy integrates in the vicious cycle of harmful disorders of CHF in body systems resulting in muscle wasting. Muscle wasting is a serious complication of CHF that is characterized by several alterations leading to a catabolic/anabolic imbalance playing a central role in this syndrome. The wasting process affects all body tissues, especially the skeletal muscle (lean tissue) resulting in exercise limitation due to pronounced fatigue and weakness. This process has as an extreme resulting complication the so-called cachexia.

There have been proposed many definitions to explain cardiac cachexia so far. The term cachexia is of Greek origin; it comes from the words "*kakos*" (bad) and "*hexis*" (condition). Anker et al., proposed that weight loss of more than 6 % in a duration above 6 months, in the absence of any other diseases associated with catabolic state (e.g., cancer), should be used to define the presence of cachexia in CHF patients [17]. Incidence of cardiac cachexia is continuously being increased with the aging of the population and prolongation of lives. It is estimated to be about 12–16 % in outpatients [1, 17]. This should be seriously taken into account by the medical community as the cachectic state is a strong independent risk factor for mortality in patients with CHF and combined with a low peak VO_2, it identifies a subset of patients at extremely high risk of death [1]. The need for an effective intervention to reverse the process of muscle wasting should be the next goal of the scientific community.

The pathophysiological mechanisms involved in the wasting process of CHF induce morphologic and functional impairments in different body systems. There have been proposed metabolic, neurohormonal and immune system abnormalities leading to an anabolic/catabolic imbalance, which alongside with deconditioning, malnutrition [18], peripheral hypoperfusion and microcirculatory alterations [19•], oxidative stress [20] and apoptosis [21], play a central role in the pathogenesis of skeletal muscle myopathy.

Skeletal muscle myopathy in CHF is a specific myopathy that is accompanied by functional, metabolic and structural changes. Functional disorders of skeletal muscle are difficult to directly estimate, however, a reduced exercise capacity [14•] is observed due to muscle fatigue and dyspnea at low exercise workloads. Qualitative and quantitative abnormalities of the skeletal muscle induce reduced muscle strength and the generalized weakness [22, 23].

Metabolic abnormalities of the skeletal muscle have been proposed since the 1980's, with studies using magnetic resonance spectroscopy (31P-MRS). The main metabolic disorders include excessive phosphocreatine depletion and acidosis in skeletal muscle during exercise [8, 9, 24–28] and at rest [25], which is correlated with exercise capacity [25]. The levels of oxidative enzymes activity are decreased [27], a

finding combined with the excess acidosis during exercise explains the increase in glycolytic metabolism which is already present at rest.

However, this syndrome includes also significant structural alterations of the skeletal muscle, with the most common and firstly described being the skeletal muscle atrophy [23, 29] resulting from atrophy of the muscle fibers [24, 30]. Another abnormality observed is the shift of fiber type distribution with a significant increase in the proportion of type II (IIb fibers) [9, 24, 26, 27, 30], that are fast twitch and easily fatigued with low aerobic potential fibers, and reduction of type I aerobic fibers [26, 27]. This is another factor explaining the shift to anaerobic metabolism as type IIb fibers are found to be inversely related with exercise capacity in contrast with type I fibers [24]. Similar results come from the alterations in the myosin heavy chain where a shift from the slow oxidative form to the fast is observed [29]. These findings in combination with the metabolic disorders of the skeletal muscle during exercise indicate the dependence on anaerobic metabolism of CHF patients.

Alongside muscle fibers, capillary supply of the skeletal muscle is attenuated, expressed as reduced capillary per muscle area [24] or capillary to fiber ratio [9, 27, 28]. Mitochondrial content of skeletal muscle is reduced in CHF [9, 31] and significantly correlated with the reduced exercise capacity [31].

Each of the above mentioned alterations have been correlated with the exercise intolerance of CHF patients, indicating that skeletal muscle myopathy is the hallmark of exercise limitation in CHF (Fig. 1).

Hormonal Imbalance in CHF

Anabolic Deficiency and the Predominance of Catabolic Factors

In CHF, inflammatory and neurohormonal system activation is a response to the dysfunction of the failing human heart. Activation of the renin-angiotensin system is responsible for the overexpression of the stress hormones; angiotensin-converting enzyme and angiotensin II. Another neurohormonal disorder is the activation of the sympathetic nervous system, which is responsible for peripheral vasoconstriction and increased resting metabolic rate. Inflammatory activation presents with increased levels of cytokines such as tumor necrosis factor a (TNF-a) [32] and interleukins (IL-1, IL-6, IL-8) [33], which are responsible for the direct protein loss of the skeletal muscle [34]. The activation of the neurohormonal and inflammatory systems alongside oxidative stress [20] and apoptosis [21] lead to an anabolic/catabolic imbalance, which is responsible for the wasting process in CHF.

Altered anabolism is the main finding in CHF patients, which present with decrease in dehydroepiandrosterone sulfate (DHEAS) [35], free and total testosterone and circulating and local insulin-like growth factor 1 (IGF-1) concentrations [36, 37, 38••, 39]. More interestingly, the DHEAS level is associated with marked oxidative stress and the disease severity [35]. Moreover, a status of decreased anabolic sex steroids [35, 40, 41], which are associated with patients' survival [37, 40•, 41•], is present in patients with CHF.

In a study by Kontoleon et al. [36], CHF due to idiopathic dilated cardiomyopathy was found to be associated with a significant decrease in growth hormone (GH) levels, in contrast with other studies that found increased GH plasma concentrations in patients with severe CHF [32, 42]. These studies suggest that there is evidence of GH resistance in CHF [43], a pattern of increased GH levels and decreased IGF-1, which is also noticed in patients with cancer. Hambrecht et al., studied the local concentrations of anabolic hormones and the impact of GH/IGF-1 axis on skeletal muscle of CHF patients and demonstrated a reduced expression of the local anabolic IGF that occurs in the presence of normal serum levels of IGF-1 [39]. In the same study, local IGF-1 expression was correlated with skeletal muscle mass, indicating that local IGF-1 deficiency might contribute to a loss of muscle bulk and that altered balance of GH/IGF-1 axis, which is a regulator of muscle hypertrophy/atrophy, plays a central role in the pathophysiology of muscle wasting in CHF. The deficiency of the above-mentioned anabolic hormones is an independent marker of poor prognosis [36, 37].

On the other hand, the significantly increased levels of cortisol [44], catecholamines [32, 44], angiotensin II and [32, 45] reveal the predominance of catabolic factors. The marked anabolic-catabolic imbalance results in both muscle and fat tissue loss and affects prognosis [32]. This wasting progress resulting in cachexia is more closely associated with hormonal changes than standard indexes of CHF severity [32] suggesting that CHF progresses to cardiac cachexia in the presence of altered anabolic/catabolic balance. Cachectic patients present with a significantly increased cortisol/dehydroepiandrosterone ratio and increased cytokine levels (TNF-alpha, soluble TNF-receptor 1, interleukin-6) [45]. Reduced circulating levels of anabolic hormones and/or increased concentrations of catabolic hormones are correlated to reduced muscle mass, fat tissue and bone mass [45]. Higher levels of serum cortisol have been recently shown to represent an independent predictor of cardiac events [46] and all-cause mortality risk [47] in CHF patients independent of aetiology. A number of studies have investigated the role of cortisol in relation to disease severity such as muscle wasting [45, 48] cachexia [32], increased incidence of cardiac events [46] and mortality [47], whereas an interesting recent study found that cortisol levels in hair correlate with the clinical severity of

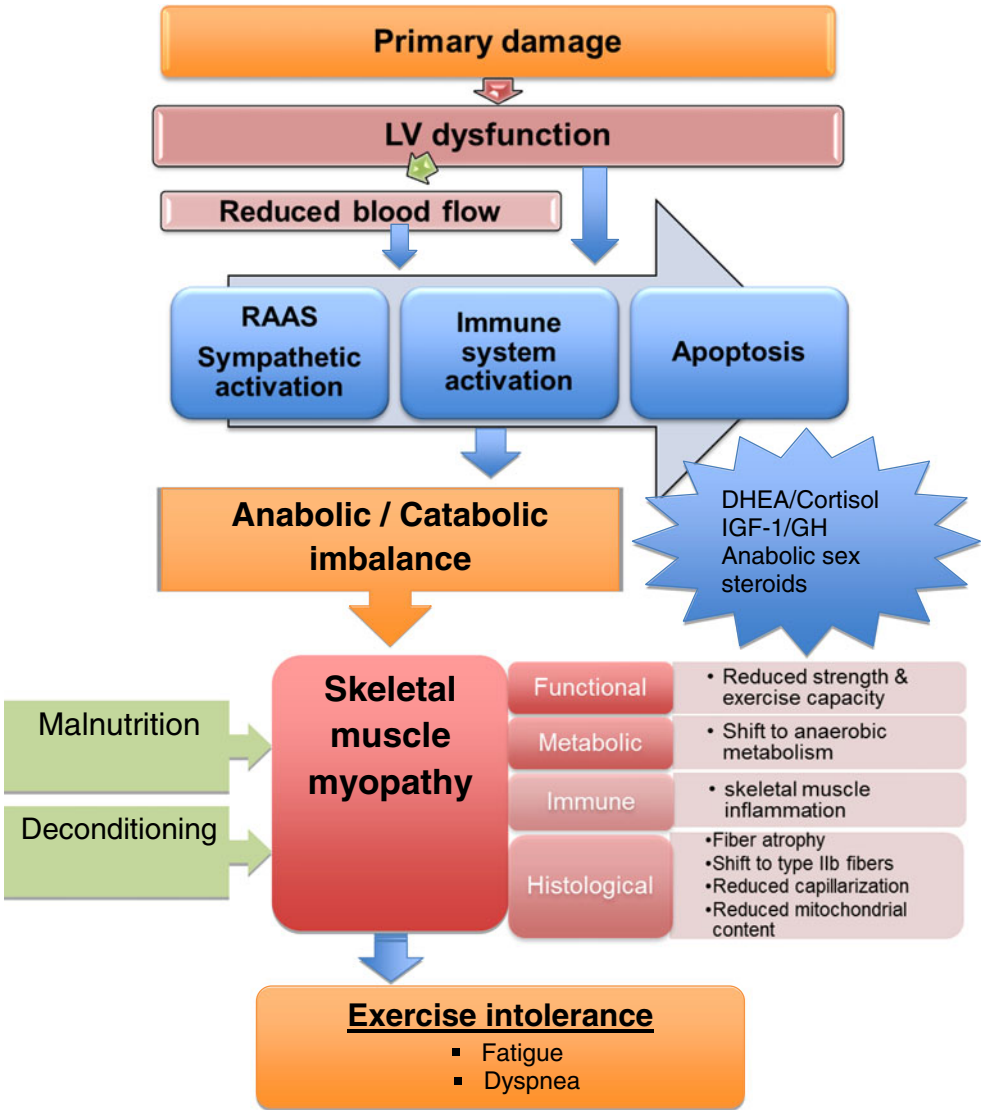

Fig. 1 Mechanisms leading from primary myocardial dysfunction to skeletal muscle myopathy and exercise intolerance in CHF

CHF as assessed by the NYHA score and treadmill exercise capacity [49••].

It has been recently shown that exercise capacity and ventilatory efficiency are related to anabolic impairment of either the adrenal [38••] or the peripheral axis [50] in CHF male patients. However, the relationship of CHF functional impairment with catabolic hormonal status has not been thoroughly investigated yet.

The Role of Cortisol in Exercise Intolerance of CHF Patients

Progression of CHF is associated with activation of neuroendocrine stress response systems including the hypothalamic-pituitary-adrenal axis that modulates the production and secretion of glucocorticoids including cortisol from the adrenal cortex [51]. The prognostic value of serum cortisol levels has been evaluated in a single large study of patients with CHF who were admitted to hospital due to various causes which showed that higher serum levels of both cortisol and aldosterone were independent predictors of increased mortality risk [47]. In this study, serum cortisol levels were within the normal range, meaning that no major activation of the hypothalamus-pituitary-adrenal axis during morning hours was evident in this study, a finding that supports the concept that normal circulating cortisol concentrations are sufficient to activate cardiac mineralocorticoid receptor in heart failure. According to Yamaji et al., high serum cortisol was an independent predictor of cardiac events [46]. However, there was no significant difference in the prediction of cardiac events between patients with high cortisol and low oxidative stress and those in whom both variables were low. Only patients with high levels of both cortisol and oxidative stress showed a significantly higher risk of cardiac events.

Funder et al., indicated that if an intracellular redox state changes with tissue damage and generation of reactive oxygen species, cortisol may act as a mineralocorticoid agonist like aldosterone [52], while it has been shown that high circulating levels of aldosterone are clearly capable of damaging all types of striated muscle. This might lend support to the concept that heart failure is a generalized, rather than a cardiac-specific, myopathy [53]. In addition, there is supporting evidence that there is a reciprocal interaction between aldosterone and parathyroid hormone (PTH) levels that may contribute to a higher risk of cardiovascular events [54]. PTH stimulates aldosterone secretion by increasing the calcium concentration in the cells of the adrenal zona glomerulosa as a result of binding to the PTH/PTH-rP receptor and indirectly by potentiating angiotensin 2 induced effects [54]. Recent studies have shown that CHF patients present a secondary hyperparathyroidism that is associated with exercise intolerance [55] and with poor prognosis [56]. The above studies indicate that PTH may also constitute another stimulus that enhances aldosterone detrimental effects in cardiac and skeletal muscles, by a different pathway to that of hypercortisolemia in CHF patients with increased catabolic state (cachexia). Further studies are necessary to clarify better the mechanisms involved.

Previous studies have investigated the role of cortisol in CHF in relation to disease severity such as muscle wasting [45, 48]. A recent study found that cortisol levels in hair correlate with the clinical severity of CHF as assessed by the NYHA score and treadmill exercise [49••]. In another previous study held in our Institute, it was found that cortisol levels were associated with CHF severity after evaluation with a symptom-limited CPET [57••]. Specifically, increased serum cortisol levels were associated with reduced exercise capacity (peak VO_2), inefficient ventilatory response to exercise (VE/VCO_2 slope), chronotropic incompetence and impaired recovery oxygen kinetics, all strong prognostic indices for CHF risk stratification. This study provides evidence of a possible central role of hypercortisolism in the pathophysiological mechanisms of CPET abnormalities in CHF patients.

Many previous studies have described the adverse effects of hypercortisolemia on skeletal muscle structure and metabolism. Cortisol affects skeletal muscles in increasing net protein breakdown and the efflux of amino acids [58, 59]. It has been further shown that the loss of muscle nitrogen is likely due primarily to the effects of cortisol, rather than the also increased circulating concentrations of glucagon and catecholamines, accompanying severe stress [60]. Moreover, cortisol decreases the utilization of glucose by cells, including the skeletal muscles and diminishes the sensitivity to insulin, thus depriving skeletal muscles an energy source and the anabolic action of insulin [61]. Interestingly, these adverse effects of glucocorticoids are present also when the increases in serum cortisol are within the normal range [62, 63].

Therapeutic Interventions for CHF Skeletal Myopathy

Exercise Training

Exercise training induces peripheral muscle adaptations in patients with heart failure and appears to be a suitable intervention to enhance their functional capacity. Exercise training by either a continuous or interval training modality has been shown to have anti-inflammatory effects in the skeletal muscle [64] and to improve the skeletal muscle myopathy [65, 66], the endothelium [67•, 68], the microcirculation [69], the respiratory drive [70], the autonomous nervous system derangement [71], myocardial function [67•, 68] and the aerobic capacity [64–66, 67•, 68–72] of CHF patients. Furthermore, the addition of strength training to aerobic training seems to confer greater beneficial effects in endothelium function and muscle strength than aerobic training alone in CHF patients [73, 74].

Reversal of fiber type distribution to aerobic fibers [65], increased anabolic factors and hormones [72], improvement of aerobic metabolism by increased aerobic enzymes and mitochondria [65, 66, 68] and increased capillarization [67•] of the skeletal muscle imply that skeletal muscle myopathy is partially reversed by exercise training.

It seems that exercise training plays a key role in the vicious cycle of CHF by affecting every parameter of the process from the myocardial dysfunction to the development of skeletal muscle myopathy and exercise intolerance. Therefore, exercise training should be taken seriously into account in the therapeutic regimen of CHF patients and investigation for the suitable form of exercise (continuous-interval, with or without addition of strength training, other forms of exercise) remains a promising field of investigation.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) with a biventricular pacemaker has been also found to improve cardiac function at rest in CHF. However, CRT improves cardiac function and contractility during exercise and VO_2 kinetics [75], thus, this could be a possible mechanism for increased muscle blood flow and the improvement of exercise capacity in CHF patients after CRT [75, 76]. Further studies are needed to demonstrate a possible role of CRT in preventing/reversing cachexia syndrome in patients with advanced CHF.

Left Ventricular Assist Devices

Long term mechanical support with left ventricular assist devices (LVAD) of the advanced failing heart has nowadays become a standard bridge to heart transplantation [77] and a permanent ("destination") therapy for selected end-stage CHF patients [78]. Interestingly, LVAD unloading has been also

shown to potentially "reverse" myocardial remodeling, especially in combination with medical therapy [79]. Recent important data support the use of continuous and non-pulsatile flow LVAD either as a bridge to transplantation [80] or destination therapy with associated substantial left ventricular unloading, haemodynamic improvement and increased survival [81, 82].

However, the impact of LVAD on the human peripheral organs is a controversial issue currently under investigation [82, 83]. George et al. [84], have evaluated the effects of clenbuterol on cardiac and skeletal muscle function during LVAD support showing an increased skeletal muscle mass and strength and prevention of the cardiac function deterioration. In a recent study by Dimopoulos et al. [85•] LVAD induced a progressively significant improvement on exercise capacity with parallel reversal of respiratory skeletal muscle dysfunction indicating that LVAD might also contribute to reversal of skeletal muscle myopathy by increasing peripheral muscles oxidative capacity.

Specific Treatment Strategies - Anabolic Treatment

Growth Hormone

Most cachectic and fewer noncachectic CHF patients present with attenuated GH/IGF-1 axis (GH resistance) [43], which is associated with skeletal muscle atrophy and attenuated muscle function and strength. Thus, the potential to increase IGF-1 response to GH treatment, arose early [43, 86–88]. Osterziel et al. [86] found an increase in left-ventricular mass (related to changes of serum IGF-1) in CHF patients treated with GH, but this was not accompanied with any clinical improvement. Acevedo et al. [87] showed that GH administration was associated with an increase in IGF-1, but this was not accompanied to changes in cardiac function and exercise capacity. An interesting study by Cittadine et al. [88] demonstrated that GH therapy in GH deficient patients improved exercise capacity, vascular reactivity, left ventricular function and quality of life, indicating the role of appropriate selection of CHF patients with GH deficiency for replacement therapy. More randomized controlled studies are needed to elucidate its clinical significance in CHF treatment strategy.

Testosterone

Low testosterone levels have been described in CHF patients [36, 37, 38••] and hypotestosteronemia has been found to be associated with poor prognosis [40•, 41•], the skeletal muscle myopathy and exercise intolerance [50] of these patients. Recent studies have tested the hypothesis that testosterone supplementation at replacement doses might constitute a potential therapy to improve reduced exercise capacity. It has been demonstrated that testosterone supplementation improves symptoms of CHF, increases functional capacity, muscle strength and performance in patients with CHF [89–91, 92•]. In addition, [93] have shown that testosterone supplementation during a program of exercise training in CHF patients with hypotestosteronemia was superior to exercise training alone in terms of exercise capacity and muscle strength. These preliminary data indicate that testosterone supplementation, alongside exercise training programs, might play a significant role in the therapeutic regimen of CHF patients, to counteract the exercise intolerance and the skeletal muscle dysfunction.

Conclusions

CHF is a clinical syndrome characterized not only by central haemodynamics but also by peripheral skeletal muscle alterations that lead to early muscular fatigue and dyspnea during exertion. There is nowadays confirming evidence that skeletal muscle presents with several functional, morphologic and metabolic abnormalities that constitute the main underling mechanisms of exercise intolerance in CHF patients. Neurohormonal, immune and metabolic adaptations play an important role in the progression of the syndrome, leading to catabolic/anabolic imbalance that is likely to be responsible for the development of the wasting process. The decreased function of anabolic hormones (GH/IGF-1, Testosterone) and the increased catabolic effects of cortisol are associated with the severity of CHF and it has been shown to be an independent predictor of poor outcome. Specifically, increased cortisol levels predict exercise intolerance, ventilatory inefficiency and chronotropic incompetence in this group of patients, suggesting a significant contributing mechanism to their limited functional status. Exercise training and device therapy (cardiac resychronization therapy / left ventricular assist devices) seem to have a beneficial effect in preventing and treating muscle wasting in CHF and might be useful in a treatment strategy for these patients. More studies are needed to investigate the potential of specific anabolic treatment (GH and/or Testosterone) to prevent and treat cachexia in CHF with an advanced syndrome.

Compliance with Ethics Guidelines

Conflict of Interest Georgios Tzanis, Stavros Dimopoulos, Varvara Agapitou, and Serafim Nanas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet. 1997;349(9058):1050–3. doi:10.1016/S0140-6736(96)07015-8.
2. Katz AM, Katz PB. Diseases of the heart in the works of Hippocrates. Br Heart J. 1962;24:257–64.
3. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137–46. doi:10.1136/hrt.2003.025270.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6–e245. doi:10.1161/CIR.0b013e31828124ad.
5. Franciosa JA, Baker BJ, Seth L. Pulmonary versus systemic hemodynamics in determining exercise capacity of patients with chronic left ventricular failure. Am Heart J. 1985;110(4):807–13.
6. Wilson JR, Martin JL, Ferraro N. Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. Am J Cardiol. 1984;53(9):1308–15.
7. Wilson JR, Mancini DM, Dunkman WB. Exertional fatigue due to skeletal muscle dysfunction in patients with heart failure. Circulation. 1993;87(2):470–5.
8. Massie B, Conway M, Yonge R, Frostick S, Ledingham J, Sleight P, et al. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. Circulation. 1987;76(5):1009–19.
9. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation. 1992;85(5):1751–9.
10. Coats AJ, Clark AL, Piepoli M, Volterrani M, Poole-Wilson PA. Symptoms and quality of life in heart failure: the muscle hypothesis. Br Heart J. 1994;72(2 Suppl):S36–9.
11. Piepoli MF, Kaczmarek A, Francis DP, Davies LC, Rauchhaus M, Jankowska EA, et al. Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. Circulation. 2006;114(2):126–34. doi:10.1161/CIRCULATIONAHA.105.605980.
12. • Middlekauff HR. Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. Circ Heart Fail. 2010;3(4):537–46. doi:10.1161/CIRCHEARTFAILURE.109.903773. *This is a review paper focusing on the role of skeletal muscle myopathy in the exercise limitation of the heart failure patient*.
13. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. Ann Intern Med. 1998;129(4):286–93.
14. • Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Kitzman DW, et al. Cardiopulmonary exercise testing is equally prognostic in young, middle-aged and older individuals diagnosed with heart failure. International journal of cardiology. 2011;151(3):278–83. doi:10.1016/j.ijcard.2010.05.056. *This is a multicenter trial investigating the prognostic role of cardiopulmonary exercise testing in patients with heart failure that focuses not only on elderly (as in other studies) but also on middle-aged and younger patients*.
15. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006. J Heart Lung Transplant. 2006;25(9):1024–42. doi:10.1016/j.healun.2006.06.008.
16. Nanas SN, Nanas JN, Sakellariou D, Dimopoulos SK, Drakos SG, Kapsimalakou SG, et al. VE/VCO2 slope is associated with abnormal resting haemodynamics and is a predictor of long-term survival in chronic heart failure. European journal of heart failure. 2006;8(4):420–7. doi:10.1016/j.ejheart.2005.10.003.
17. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet. 2003;361(9363):1077–83. doi:10.1016/S0140-6736(03)12892-9.
18. Narumi T, Arimoto T, Funayama A, Kadowaki S, Otaki Y, Nishiyama S, et al. The prognostic importance of objective nutritional indexes in patients with chronic heart failure. J Cardiol. 2013. doi:10.1016/j.jjcc.2013.05.007.
19. • Manetos C, Dimopoulos S, Tzanis G, Vakrou S, Tasoulis A, Kapelios C, et al. Skeletal muscle microcirculatory abnormalities are associated with exercise intolerance, ventilatory inefficiency, and impaired autonomic control in heart failure. J Heart Lung Transplant. 2011;30(12):1403–8. doi:10.1016/j.healun.2011.08.020. *This study investigates microcirculatory alterations of heart failure patients by using Near-InfraRed Spectroscopy methodology and its association with the CHF severity as assessed by cardiopulmonary exercise testing parameters*.
20. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol. 2011;301(6):H2181–90. doi:10.1152/ajpheart.00554.2011.
21. Adams V, Jiang H, Yu J, Mobius-Winkler S, Fiehn E, Linke A, et al. Apoptosis in skeletal myocytes of patients with chronic heart failure is associated with exercise intolerance. J Am Coll Cardiol. 1999;33(4):959–65.
22. Harrington D, Anker SD, Chua TP, Webb-Peploe KM, Ponikowski PP, Poole-Wilson PA, et al. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. J Am Coll Cardiol. 1997;30(7):1758–64.
23. Schulze PC, Linke A, Schoene N, Winkler SM, Adams V, Conradi S, et al. Functional and morphological skeletal muscle abnormalities correlate with reduced electromyographic activity in chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2004;11(2):155–61.
24. Mancini DM, Coyle E, Coggan A, Beltz J, Ferraro N, Montain S, et al. Contribution of intrinsic skeletal muscle changes to 31P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. Circulation. 1989;80(5):1338–46.
25. Okita K, Yonezawa K, Nishijima H, Hanada A, Nagai T, Murakami T, et al. Muscle high-energy metabolites and metabolic capacity in patients with heart failure. Med Sci Sports Exerc. 2001;33(3):442–8.
26. Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation. 1990;81(2):518–27.
27. Schaufelberger M, Eriksson BO, Grimby G, Held P, Swedberg K. Skeletal muscle alterations in patients with chronic heart failure. Eur Heart J. 1997;18(6):971–80.
28. Duscha BD, Kraus WE, Keteyian SJ, Sullivan MJ, Green HJ, Schachat FH, et al. Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. J Am Coll Cardiol. 1999;33(7):1956–63.
29. Vescovo G, Serafini F, Facchin L, Tenderini P, Carraro U, Dalla Libera L, et al. Specific changes in skeletal muscle myosin heavy chain composition in cardiac failure: differences compared with

disuse atrophy as assessed on microbiopsies by high resolution electrophoresis. Heart. 1996;76(4):337–43.
30. Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. International journal of cardiology. 1988;18(2):187–95.
31. Massie BM, Simonini A, Sahgal P, Wells L, Dudley GA. Relation of systemic and local muscle exercise capacity to skeletal muscle characteristics in men with congestive heart failure. J Am Coll Cardiol. 1996;27(1):140–5. doi:10.1016/0735-1097(95)00416-5.
32. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation. 1997;96(2):526–34.
33. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. Heart. 2004;90(4):464–70.
34. Li YP, Schwartz RJ, Waddell ID, Holloway BR, Reid MB. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. FASEB J. 1998;12(10):871–80.
35. Moriyama Y, Yasue H, Yoshimura M, Mizuno Y, Nishiyama K, Tsunoda R, et al. The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. J Clin Endocrinol Metab. 2000;85(5):1834–40.
36. Kontoleon PE, Anastasiou-Nana MI, Papapetrou PD, Alexopoulos G, Ktenas V, Rapti AC, et al. Hormonal profile in patients with congestive heart failure. International journal of cardiology. 2003;87(2–3):179–83.
37. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006;114(17):1829–37. doi:10.1161/CIRCULATIONAHA.106.649426.
38. •• Pastor-Perez FJ, Manzano-Fernandez S, Garrido Bravo IP, Nicolas F, Tornel PL, Lax A, et al. Anabolic status and functional impairment in men with mild chronic heart failure. Am J Cardiol. 2011;108(6):862–6. doi:10.1016/j.amjcard.2011.05.016. *This study investigates the role of hormonal anabolic impairment showing its association with exercise intolerance in heart failure*.
39. Hambrecht R, Schulze PC, Gielen S, Linke A, Mobius-Winkler S, Yu J, et al. Reduction of insulin-like growth factor-I expression in the skeletal muscle of noncachectic patients with chronic heart failure. J Am Coll Cardiol. 2002;39(7):1175–81.
40. • Guder G, Frantz S, Bauersachs J, Allolio B, Ertl G, Angermann CE, et al. Low circulating androgens and mortality risk in heart failure. Heart. 2010;96(7):504–9. doi:10.1136/hrt.2009.181065. *This is a prospective cohort study about anabolic sex steroid deficiency in heart failure and its association with poor prognosis*.
41. • Wehr E, Pilz S, Boehm BO, Marz W, Grammer T, Obermayer-Pietsch B. Low free testosterone is associated with heart failure mortality in older men referred for coronary angiography. European journal of heart failure. 2011;13(5):482–8. doi:10.1093/eurjhf/hfr007. *This is a prospective study that included 2078 patients referred for coronary angiography showing that low free testosterone levels are associated with heart failure mortality*.
42. Mangieri E, Croce CT, Tanzilli G, Lomurno A, Mangiaracina F, Bonifacio V, et al. Blood levels of somatotropic hormone in patients with various degrees of heart failure. G Ital Cardiol. 1994;24(7):845–52.
43. Anker SD, Volterrani M, Pflaum CD, Strasburger CJ, Osterziel KJ, Doehner W, et al. Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. J Am Coll Cardiol. 2001;38(2):443–52.
44. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation. 1989;80(2):299–305.
45. Anker SD, Ponikowski PP, Clark AL, Leyva F, Rauchhaus M, Kemp M, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. Eur Heart J. 1999;20(9):683–93. doi:10.1053/euhj.1998.1446.
46. Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, et al. Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure: the impact of oxidative stress. Circ Heart Fail. 2009;2(6):608–15. doi:10.1161/CIRCHEARTFAILURE.109.868513.
47. Guder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation. 2007;115(13):1754–61. doi:10.1161/CIRCULATIONAHA.106.653964.
48. Anker SD, Clark AL, Kemp M, Salsbury C, Teixeira MM, Hellewell PG, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. J Am Coll Cardiol. 1997;30(4):997–1001.
49. •• Pereg D, Chan J, Russell E, Berlin T, Mosseri M, Seabrook JA et al. Cortisol and testosterone in hair as biological markers of systolic heart failure. Psychoneuroendocrinology. 2013. doi:10.1016/j.psyneuen.2013.07.015. *This is a prospective study that evaluated hair cortisol levels in patients with heart failure. The results of this study showed that hair cortisol levels correlate with heart failure severity as assessed by exercise capacity (metabolic equivalents) and NYHA classes.*
50. Jankowska EA, Filippatos G, Ponikowska B, Borodulin-Nadzieja L, Anker SD, Banasiak W, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. Journal of cardiac failure. 2009;15(5):442–50. doi:10.1016/j.cardfail.2008.12.011.
51. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. Lancet. 2007;370(9592):1089–100. doi:10.1016/S0140-6736(07)61305-1.
52. Funder JW. Mineralocorticoid receptors: distribution and activation. Heart Fail Rev. 2005;10(1):15–22. doi:10.1007/s10741-005-2344-2.
53. Burniston JG, Saini A, Tan LB, Goldspink DF. Aldosterone induces myocyte apoptosis in the heart and skeletal muscles of rats in vivo. J Mol Cell Cardiol. 2005;39(2):395–9. doi:10.1016/j.yjmcc.2005.04.001.
54. Tomaschitz A, Ritz E, Pieske B, Fahrleitner-Pammer A, Kienreich K, Horina JH, et al. Aldosterone and parathyroid hormone: a precarious couple for cardiovascular disease. Cardiovascular research. 2012;94(1):10–9. doi:10.1093/cvr/cvs092.
55. Agapitou V, Dimopoulos S, Mpouchla A, Samartzis L, Tseliou E, Kaldara E, et al. Serum intact parathyroid hormone levels independently predict exercise capacity in stable heart failure patients. International journal of cardiology. 2011;146(3):462–4. doi:10.1016/j.ijcard.2010.10.123.
56. Schierbeck LL, Jensen TS, Bang U, Jensen G, Kober L, Jensen JE. Parathyroid hormone and vitamin D–markers for cardiovascular and all cause mortality in heart failure. European journal of heart failure. 2011;13(6):626–32. doi:10.1093/eurjhf/hfr016.
57. •• Agapitou V, Dimopoulos S, Kapelios C, Karatzanos E, Manetos C, Georgantas A, et al. Hormonal imbalance in relation to exercise intolerance and ventilatory inefficiency in chronic heart failure. J Heart Lung Transplant. 2013;32(4):431–6. doi:10.1016/j.healun.2012.12.011. *This is a prospective study that demonstrates the anabolic deficiency and the enhanced catabolic status in heart failure and the association with exercise intolerance. The results of this study have shown that cortisol and dehydroepiandrosterone levels were both independent predictors of VO_2peak, while cortisol*

was the only independent predictor of ventilatory inefficiency (*Ve/Vco₂ slope*).
58. Brillon DJ, Zheng B, Campbell RG, Matthews DE. Effect of cortisol on energy expenditure and amino acid metabolism in humans. Am J Physiol. 1995;268(3 Pt 1):E501–13.
59. Gore DC, Jahoor F, Wolfe RR, Herndon DN. Acute response of human muscle protein to catabolic hormones. Ann Surg. 1993;218(5):679–84.
60. Gelfand RA, Matthews DE, Bier DM, Sherwin RS. Role of counterregulatory hormones in the catabolic response to stress. J Clin Invest. 1984;74(6):2238–48. doi:10.1172/JCI111650.
61. Qi D, Rodrigues B. Glucocorticoids produce whole body insulin resistance with changes in cardiac metabolism. Am J Physiol Endocrinol Metab. 2007;292(3):E654–67. doi:10.1152/ajpendo.00453.2006.
62. Simmons PS, Miles JM, Gerich JE, Haymond MW. Increased proteolysis. An effect of increases in plasma cortisol within the physiologic range. J Clin Invest. 1984;73(2):412–20. doi:10.1172/JCI111227.
63. Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Viscovo L, et al. Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab. 2000;85(4):1440–8.
64. Gielen S, Adams V, Mobius-Winkler S, Linke A, Erbs S, Yu J, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J Am Coll Cardiol. 2003;42(5):861–8.
65. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. J Am Coll Cardiol. 1997;29(5):1067–73.
66. Hambrecht R, Niebauer J, Fiehn E, Kalberer B, Offner B, Hauer K, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol. 1995;25(6):1239–49. doi:10.1016/0735-1097(94)00568-B.
67. • Erbs S, Hollriegel R, Linke A, Beck EB, Adams V, Gielen S, et al. Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. Circ Heart Fail. 2010;3(4):486–94. doi:10.1161/CIRCHEARTFAILURE.109.868992. *This is a randomized trial providing evidence of the beneficial effects of exercise training in patients with advanced heart failure. Exercise training improved LV function, exercise capacity, and peripheral circulation (endothelial function, and skeletal muscle neovascularization*).
68. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115(24):3086–94. doi:10.1161/CIRCULATIONAHA.106.675041.
69. Gerovasili V, Drakos S, Kravari M, Malliaras K, Karatzanos E, Dimopoulos S, et al. Physical exercise improves the peripheral microcirculation of patients with chronic heart failure. Journal of cardiopulmonary rehabilitation and prevention. 2009;29(6):385–91. doi:10.1097/HCR.0b013e3181b4ca4e.
70. Tasoulis A, Papazachou O, Dimopoulos S, Gerovasili V, Karatzanos E, Kyprianou T, et al. Effects of interval exercise training on respiratory drive in patients with chronic heart failure. Respir Med. 2010;104(10):1557–65. doi:10.1016/j.rmed.2010.03.009.
71. Dimopoulos S, Anastasiou-Nana M, Sakellariou D, Drakos S, Kapsimalakou S, Maroulidis G, et al. Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2006;13(1):67–73.
72. Hambrecht R, Schulze PC, Gielen S, Linke A, Mobius-Winkler S, Erbs S, et al. Effects of exercise training on insulin-like growth factor-I expression in the skeletal muscle of non-cachectic patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2005;12(4):401–6.
73. Anagnostakou V, Chatzimichail K, Dimopoulos S, Karatzanos E, Papazachou O, Tasoulis A, et al. Effects of interval cycle training with or without strength training on vascular reactivity in heart failure patients. Journal of cardiac failure. 2011;17(7):585–91. doi:10.1016/j.cardfail.2011.02.009.
74. Bouchla A, Karatzanos E, Dimopoulos S, Tasoulis A, Agapitou V, Diakos N, et al. The addition of strength training to aerobic interval training: effects on muscle strength and body composition in CHF patients. Journal of cardiopulmonary rehabilitation and prevention. 2011;31(1):47–51. doi:10.1097/HCR.0b013e3181e174d7.
75. Tomczak CR, Paterson I, Haykowsky MJ, Lawrance R, Martellotto A, Pantano A, et al. Cardiac resynchronization therapy modulation of exercise left ventricular function and pulmonary O(2) uptake in heart failure. Am J Physiol Heart Circ Physiol. 2012;302(12):H2635–45. doi:10.1152/ajpheart.01119.2011.
76. De Marco T, Wolfel E, Feldman AM, Lowes B, Higginbotham MB, Ghali JK, et al. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. Journal of cardiac failure. 2008;14(1):9–18. doi:10.1016/j.cardfail.2007.08.003.
77. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N Engl J Med. 1998;339(21):1522–33. doi:10.1056/NEJM199811193392107.
78. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43. doi:10.1056/NEJMoa012175.
79. Birks EJ, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med. 2006;355(18):1873–84. doi:10.1056/NEJMoa053063.
80. Lahpor J, Khaghani A, Hetzer R, Pavie A, Friedrich I, Sander K, et al. European results with a continuous-flow ventricular assist device for advanced heart-failure patients. Eur J Cardiothorac Surg. 2010;37(2):357–61. doi:10.1016/j.ejcts.2009.05.043.
81. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241–51. doi:10.1056/NEJMoa0909938.
82. Drakos SG, Terrovitis JV, Anastasiou-Nana MI, Nanas JN. Reverse remodeling during long-term mechanical unloading of the left ventricle. J Mol Cell Cardiol. 2007;43(3):231–42. doi:10.1016/j.yjmcc.2007.05.020.
83. Russell SD, Rogers JG, Milano CA, Dyke DB, Pagani FD, Aranda JM, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation. 2009;120(23):2352–7. doi:10.1161/CIRCULATIONAHA.108.814863.
84. George I, Xydas S, Mancini DM, Lamanca J, DiTullio M, Marboe CC, et al. Effect of clenbuterol on cardiac and skeletal muscle function during left ventricular assist device support. J Heart Lung Transplant. 2006;25(9):1084–90. doi:10.1016/j.healun.2006.06.017.
85. • Dimopoulos SK, Drakos SG, Terrovitis JV, Tzanis GS, Nanas SN. Improvement in respiratory muscle dysfunction with continuous-flow left ventricular assist devices. J Heart Lung Transplant. 2010;29(8):906–8. doi:10.1016/j.healun.2010.03.013. *This prospective study has demonstrated for the first time that left ventricular assist device implantation induces a significant improvement in respiratory muscle function of heart failure*

patients in parallel with exercise capacity as assessed with a VO_2 peak.

86. Osterziel KJ, Strohm O, Schuler J, Friedrich M, Hanlein D, Willenbrock R, et al. Randomised, double-blind, placebo-controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy. Lancet. 1998;351(9111): 1233–7. doi:10.1016/S0140-6736(97)11329-0.
87. Acevedo M, Corbalan R, Chamorro G, Jalil J, Nazzal C, Campusano C, et al. Administration of growth hormone to patients with advanced cardiac heart failure: effects upon left ventricular function, exercise capacity, and neurohormonal status. International journal of cardiology. 2003;87(2–3):185–91.
88. Cittadini A, Saldamarco L, Marra AM, Arcopinto M, Carlomagno G, Imbriaco M, et al. Growth hormone deficiency in patients with chronic heart failure and beneficial effects of its correction. J Clin Endocrinol Metab. 2009;94(9):3329–36. doi:10.1210/jc.2009-0533.
89. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. Heart. 2004;90(4): 446–7.
90. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. Eur Heart J. 2006;27(1):57–64. doi:10.1093/eurheartj/ehi443.
91. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol. 2009;54(10):919–27. doi:10.1016/j.jacc.2009.04.078.
92. • Iellamo F, Volterrani M, Caminiti G, Karam R, Massaro R, Fini M, et al. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. J Am Coll Cardiol. 2010;56(16):1310–6. doi:10.1016/j.jacc.2010.03.090. *This is a double blind randomized control trial that investigated the role of testosterone supplementation in females with heart failure and showed an improvement in exercise capacity*, *insulin resistance and muscle strength*.
93. • Stout M, Tew GA, Doll H, Zwierska I, Woodroofe N, Channer KS, et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. Am Heart J. 2012;164(6):893–901. doi:10.1016/j.ahj.2012.09.016. *This novel double blind randomized control trial investigated the role of testosterone supplementation and exercise training in male patients with hearing and testosterone deficiency. The study showed that testosterone supplementation alongside exercise training improved exercise capacity*, *muscle strength and quality of life*.