Central and peripheral testosterone effects in men with heart failure: An approach for cardiovascular research

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Abstract
Heart failure (HF) is a syndrome recognized as a health problem worldwide. Despite advances in treatment, patients with HF still have increased morbidity and mortality. Testosterone is one of the most researched hormones in the course of HF. Growing interest regarding the effect of testosterone, on a variety of body systems, has increased the knowledge about its mechanisms of action. The terms central and peripheral effects are used to distinguish the effects of testosterone on cardiac and extracardiac structures. Central effects include influences on cardiomyocytes and electrophysiology. Peripheral effects include influences on blood vessels, baroreceptor reactivity, skeletal muscles and erythropoesis. Current knowledge about peripheral effects of testosterone may explain much about beneficiary effects in the pathophysiology of HF syndrome. However, central, i.e., cardiac effects of testosterone are to be further explored.

Key words: Cardiomyocytes; Exercise; Electrophysiology; Heart failure; Vasodilation; Testosterone

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Core tip: Patients with heart failure often have a lower endogenous testosterone level. Testosterone has a number of effects on cardiac and extracardiac structures via genomic and non-genomic mechanisms. We summarize current knowledge about the involvement of testosterone in heart failure syndrome.

INTRODUCTION
Despite many advances in medicine, heart failure (HF) remains one of the leading causes of increased morbidity and mortality among adult population. In recent years, there has been growing interest in...
hormonal disturbances that accompany HF. A body of evidence suggests that several hormones and a variety of metabolic signals may be altered in a way that instigates progression of the disease\cite{11}. Within this framework, testosterone receives vivid research interest.

Many epidemiological studies have found a high incidence of comparably lower testosterone level in men with coronary heart disease, regardless of patient's age\cite{22}. Moreover, population studies have found an association of increased all-cause and cardiovascular mortality with low testosterone levels in general population as well as within a subpopulation of men with coronary heart disease\cite{3-7}.

Testosterone deficiency has been implicated in the pathophysiology of HF, contributing to some characteristics of this syndrome such as reduced skeletal muscle mass, oxygen consumption, reduced exercise capacity and cachexia\cite{8}. The association of serum testosterone levels with clinical severity of HF seems to be present only in non-obese HF patients\cite{9}. In obese patients with HF, lower testosterone levels and a lack of correlation with the disease severity may suggest altered hormonal and hemodynamic mechanisms which could contribute to a better prognosis and the obesity paradox\cite{10}.

To distinguish and classify various cardiovascular, hormonal, muscular and other mechanisms the terms central, i.e., cardiac and peripheral, i.e., extracardiac, effects are used to describe the effects of testosterone on cardiac and extracardiac structures (Figure 1). Those effects are particularly important under the circumstances of nonphysiological testosterone levels (Table 1).

### CENTRAL EFFECTS OF TESTOSTERONE

**Cardiomyocytes**

Testosterone is responsible for protein synthesis and hypertrophy of the cardiac muscle of several investigated species, including humans, through a receptor-specific interaction which results in an increased amino acid incorporation into proteins\cite{13,14}. In a post-infarction model of HF, testosterone supplementation led to a particular type of myocardial hypertrophy with a significant increase in left ventricular mass, but without increase in hypertrophy markers or collagen accumulation\cite{15-19}. It appears that testosterone stimulates the expression of α-myosin heavy chain as opposed to β-myosin heavy chain which is usually seen in pathological cardiac hypertrophy, thus indicating a “physiological” type of cardiac hypertrophy with potentially long term improvement in cardiac function\cite{20}. An animal study of ischemia-reperfusion injury showed that testosterone reduced cardiomyocyte injury by upregulating cardiac α1 adrenoreceptor and possibly by activating cardiac mitochondrial ATP-sensitive potassium (K+) channels\cite{21}.

It has been also suggested that testosterone has an influence on myocardial contractility. Gonadectomy in male rats changed the transcriptional and translational control of genes encoding the L-type calcium (Ca^{2+}) channel, the Na+/Ca^{2+} exchanger, β1 adrenoreceptors, and myosin heavy chain subunits which reduced cardiomyocyte contractile capacity\cite{22,23}.

**Ventricular function**

Among other clinical parameters, several studies have assessed the left ventricular ejection fraction in HF patients who received testosterone supplementation\cite{15-19}. While some animal studies showed that androgens are important for cardiac contractility, such findings were not reported in humans. Despite improvement in exercise capacity and ventilatory efficiency in patients receiving testosterone supplementation, there was no improvement in left ventricular ejection fraction\cite{15-19}.

Higher serum levels of testosterone, most frequently found in athletes using prohibited anabolic androgen steroids, have been shown to cause myocardial hypertrophy\cite{24,25}. However, in a study by Malkin et al\cite{26} patients with HF that received testosterone supplementation had no increase in myocardial mass nor in wall thickness, thus suggesting that testosterone supplementation is safe if kept in physiologic doses.

**Cardiac electrophysiology**

Both endogenous and exogenous sex hormones have been shown to affect cardiac electrophysiology\cite{22,23}. Changes in QT interval are associated with an increased risk of atrial and ventricular tachyarrhythmias, and of sudden cardiac death\cite{24,25}. Several studies have been performed in order to explore the influence of testosterone on QT interval duration. It has been reported that ventricular repolarization was prolonged in castrated men compared with noncastrated men\cite{26}. In addition, women with hyperandrogenism had shorter QT-interval duration than did their respective control\cite{26}. Furthermore a negative linear correlation was found between the duration of QT interval and serum testosterone levels in hypogonadic men after receiving a single intramuscular administration of testosterone\cite{27}.

Low testosterone levels have been also associated with the incidence of atrial fibrillation, particularly in men over 80 years of age\cite{28}. Hence, testosterone supplementation could possibly be beneficial for primary prevention of atrial fibrillation. However, an animal study from 2014, showed that testosterone supplementation in aging rabbits increased arrhythmogenesis by

| Table 1 Effects of nonphysiological testosterone levels |
|--------------------------------------------------------|
| **Supraphysiological** | **Subphysiological** |
| Cardiomyocytes | Hypertrophy | Hypotrophy |
| QT interval | Shortening | Prolongation |
| Vasculature | Vasodilation | Not known |
| Skeletal muscles | Hypertrophy | Hypotrophy |
| Exercise capacity | Increased | Decreased |
| Baroreceptor sensitivity | Increased | Attenuated |

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enlarging adrenergic activity which brought the previous hypothesis in question. Several mechanisms, through which testosterone acts on cardiac electrophysiology, have been proposed. An animal study from 2005 found that testosterone induced a dose dependent shortening of action potential duration through non-genomic enhancement of slowly activating delayed rectifier $K^+$ current and suppressing the L-type $Ca^{2+}$ current. In another animal study, dihydrotestosterone, a metabolite of testosterone, induced QT interval shortening through an increased current density of inward repolarizing rectifier $K^+$ current and by rapidly activating delayed rectifier $K^+$ current. Finally, in another animal study, repolarization of canine ventricular myocardium was significantly modified by testosterone, most likely due to increased expression of ion channel proteins. However, those mechanisms are still being explored and at the moment there is not enough information about the effects of testosterone on cardiac electrophysiology.

**PERIPHERAL EFFECTS OF TESTOSTERONE**

**Vascular effects**

Basic cellular and molecular mechanisms through which testosterone regulates vascular responsiveness are not entirely understood. Animal studies suggest that testosterone affects vascular reactivity by both influencing endothelium-dependent and independent actions in a variety of vascular beds. Vasodilation produces a reduced cardiac afterload and increased cardiac output. Coronary vasodilation improves myocardial oxygenation thereby achieving a beneficiary effect in HF patients.

Endothelium-dependent effects of testosterone include long term genomic and rapid non-genomic effects. Nitric oxide (NO) is a powerful vasodilator synthesized by the endothelial NO synthase (eNOS) and released, among other tissues, by the vascular endothelium. Testosterone modulates NO release which in addition way is affecting vasoreactivity. It is not fully understood whether this testosterone effect is genomic or non-genomic. There are several proposed mechanisms through which testosterone may act on NO synthesis and release. A study from 2012 showed that testosterone, via non-genomic activation of intracellular signaling pathways and $Ca^{2+}$ influx, increases endothelial NO synthesis and additionally inhibits platelet aggregation. Furthermore, in another study where vascular aging was explored, testosterone increased expression of genes that govern replicative life span which subsequently inhibited endothelial senescence via upregulation of eNOS activity.

In addition to well explored endothelium-dependent mechanisms, several studies investigated endothelium-independent effects of testosterone. The crucial endothelium-independent mechanism, which may underlie the vasodilatory effect of testosterone, involve ion channel function of the smooth muscle cells influencing $K^+$ channel opening and/or $Ca^{2+}$ channel inactivation. In an electrophysiological patch-clamp study, testosterone inactivated L-type voltage-operated
Ca\(^{2+}\) channels and consequently restricted Ca\(^{2+}\) influx and thereby inducing vasodilatation\(^{40}\). Testosterone also shares the same molecular binding site as nifedipine on the subunit of L-type Ca\(^{2+}\) channels which causes channel blockade and may induce vasodilatation\(^{41}\). Moreover testosterone blocks Ca\(^{2+}\) influx via store-operated Ca\(^{2+}\) channels by blocking their response to prostaglandin F\(_2\alpha\)\(^{42}\). As another option, a study from 2008 showed that testosterone activates voltage-operated K\(^+\) channels and/or large-conductance Ca\(^{2+}\)-activated K\(^+\) channels, thereby increasing intracellular K\(^+\) efflux and inducing vasodilatation\(^{43}\).

**Baroreceptor sensitivity**

It has been established that arterial baroreceptor sensitivity is attenuated in HF which is an important adverse prognostic indicator\(^{44}\). In light of this, Caminiti et al\(^{18}\), sought out to investigate the effect of testosterone supplementation on baroreceptor sensitivity in patients with HF. Their results showed an increase in baroreceptor sensitivity in the testosterone treated group. Although they weren’t able to identify the mechanisms through which testosterone enhances baroreceptor sensitivity, several animal studies have shown that testosterone administration improves arterial baroreceptor control of heart rate through an enhancement of cardiac efferent vagal activity\(^{45-47}\). It is possible that this effect takes place at central nervous system sites, because androgen receptors have been identified in brainstem nuclei that are involved in the baroreflex cardiac regulation\(^{48}\).

**Exercise**

Patients with HF have poor exercise capacity test results. This is a consequence of poor left ventricular function, a poor ventilatory efficiency and muscle wasting which is enhanced in HF syndrome leading to early fatigue and limited exercise tolerance. Although peak oxygen consumption (VO\(_2\)) and ventilation to carbon dioxide production ratio (VE/VO\(_2\); slope) express different pathophysiologic segments of the cardiorespiratory response to exercise in HF, they both are facets of that response. Ventilatory efficiency, commonly assessed by the minute VE/VO\(_2\) and VO\(_2\), is a powerful prognostic marker in the HF patients\(^{49}\).

Another important segment in exercise capacity are skeletal muscles. Several morphological and functional irregularities, relatively independent of reduced blood flow, present in the skeletal muscle of HF patients contribute to early lactic acidosis and fatigue during exercise\(^{50}\). These changes are involved in the pathophysiology of HF and have been gathered under the term “the muscle hypothesis”\(^{45}\). According to this hypothesis, exaggerated ergoreflex activation occurs in exercising muscles of HF patient which leads, via activation of sympathetic system, to fatigue and an excessive ventilatory response in a form of dyspnea.

Recent studies have shown that testosterone supplementation improves exercise capacity, peak VO\(_2\) and VE/VO\(_2\); slope\(^{46-48}\). The mechanism through which testosterone affects cardiorespiratory parameters in HF patients can be in part explained by the association of muscle ergoreflex overactivity with VE/VO\(_2\); slope\(^{52}\). Animal studies have indicated that anabolic androgens attenuate muscle fatigue in response to exercise, though the precise mechanism of this effect has not been identified\(^{53,54}\). Combination of exercise training and testosterone supplementation may beneficiary change muscle structure and function\(^{50,55}\). This may attenuate muscle ergoreflex activity and ventilatory response to exercise in HF patients and consequently improve exercise test results\(^{50,55}\).

**Erythropoiesis**

Further mechanism of testosterone that could explain improvement in exercise capacity and ventilatory response is the increase in hemoglobin level and oxygen delivery. A body of evidence suggests an association of lower hemoglobin levels with increased risk of hospitalization, poorer clinical status and death due to HF\(^{56,57}\).

Testosterone has a strong stimulatory effect on erythropoiesis\(^{58-60}\). Suggested mechanisms of this effect are stimulation of intestinal iron absorption, erythrocyte iron incorporation and hemoglobin synthesis\(^{60}\). Although testosterone was found not to affect erythropoietin or soluble transferrin receptor levels, it is possible that testosterone has a direct effect on the bone marrow hematopoietic stem cells through the induction of insulin growth factor-I via androgen receptor-mediated mechanisms\(^{61-63}\).

**CLINICAL IMPLICATIONS**

Testosterone deficiency is an independent risk factor of worse outcome in patients with HF of both sexes\(^{64}\). Testosterone supplementation results in positive physiological and biochemical changes in patients with HF and testosterone administration acutely increases cardiac output and reduces peripheral vascular resistance\(^{15,65}\). In addition, transdermal testosterone administration induces coronary vasodilation and increases coronary blood flow and improves angina threshold in patients with coronary artery disease\(^{66,67}\).

An interesting question is whether testosterone may be helpful in women as it prove useful in men? As opposed to men, it seems that testosterone is not a significant factor of sudden cardiac arrest in women\(^{68}\). The only testosterone supplementation study that included female patients with HF showed no difference in effect on functional capacity and muscle strength therefore indicating no differences in possible mechanisms of action between male and female HF patients\(^{69}\).

Another interesting issue is a possibility of the interplay among testosterone therapy and other endogenous anabolic hormones. Growth hormone and insulin growth factor-I levels are important for
preserving both cardiac morphology and performance in adult life[11]. Individuals with low insulin growth factor-I levels undergo cardiovascular alterations that are reminiscent of those observed in HF patients and are corrected by replacement therapy[70,71]. An interaction also exists between testosterone and insulin growth factor-I through androgen receptor-mediated mechanisms[61-63]. Whether testosterone acts directly on insulin growth factor-I or indirectly by influencing the growth hormone is to be investigated.

FUTURE RESEARCH

Testosterone is currently one of the most investigated hormones in the course and prognosis of HF syndrome. Over the past decade, growing interest has widened research targets that could contribute to symptoms and pathophysiology of HF on all body systems. Studies have been performed in order to establish whether testosterone can be included in the standard therapy for HF patients with a low testosterone level. Several unanswered questions should be addressed in future studies: (1) are the effects of exogenous testosterone on tissues, organs and body systems the same as the effects of endogenous testosterone? (2) is there a difference between the routes of testosterone administration which could be important for testosterone supplementation? (3) what is the role of testosterone on cardiac fibrosis and remodeling[34,71]? and (4) has testosterone adverse effects in the elderly, particularly in those with an advanced ischemic or other heart disease[62]?

In conclusion, current knowledge about peripheral effects of testosterone may explain much about beneficiary effects in the pathophysiology of HF syndrome. However, many fields of testosterone’s central, i.e., cardiac effects are to be further explored.

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