Chronic heart failure is one of the most common heart diseases and is a leading cause of morbidity and mortality. There has been a rapid growth in knowledge and understanding of the pathogenesis of chronic heart failure in recent years. Tumor necrosis factor (TNF-α), a pro-inflammatory cytokine, is found to play an important role on the development and progression of heart failure. Recent evidence suggests that testosterone improves cardiac function and clinical symptoms in patients with chronic heart failure. Recent experimental studies show that testosterone suppresses the biosynthesis of TNF-α while increasing the levels of anti-inflammatory faction, interleukin-10. Therefore, we hypothesize that testosterone may also suppress the biosynthesis of TNF-α and re-balancing the pro- and anti-inflammatory mechanisms in human hearts, leading to significant improvement in cardiac function and symptoms in patients with chronic heart failure.
Testosterone suppresses the biosynthesis of tumor necrosis factor-α and improves cardiac dysfunction during heart failure

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Abstract

Chronic heart failure is one of the most common heart diseases and is a leading cause of morbidity and mortality. There has been a rapid growth in knowledge and understanding of the pathogenesis of chronic heart failure in recent years. Tumor necrosis factor (TNF-α), a pro-inflammatory cytokine, is found to play an important role on the development and progression of heart failure. Recent evidence suggests that testosterone improves cardiac function and clinical symptoms in patients with chronic heart failure. Recent experimental studies show that testosterone suppresses the biosynthesis of TNF-α while increasing the levels of anti-inflammatory faction, interleukin-10. Therefore, we hypothesize that testosterone may also suppress the biosynthesis of TNF-α and re-balancing the pro- and anti-inflammatory mechanisms in human hearts, leading to significant improvement in cardiac function and symptoms in patients with chronic heart failure.

Key words: testosterone, tumor necrosis factor, interleukin, chronic heart failure.
Introduction

Chronic heart failure is a leading cause of morbidity and mortality in all societies. It is a result of a number of cardiovascular disorders, such as myocardial infarction, hypertension, cardiomyopathy or diabetes [1]. The medical treatment of chronic heart failure has undergone a remarkable transition in the past two decades. The approach has changed from a short-term hemodynamic/pharmacological paradigm to a more long-term strategy that aims to favorably alter the biological properties of the failing heart [2, 3]. This strategic transition in therapeutic regimens is evidenced by the introduction of angiotensin-converting-enzyme inhibitors and β-blockers, which have resulted in a significant improvement in the quality of life, survival rate and reduction in hospital re-admissions in patients with chronic heart failure [2, 3].

However, even with the most contemporary evidence-based management, the annual mortality in patients with moderate to severe left ventricular dysfunction still remains more than 20% [1]. Therefore, new therapeutic regimens are being constantly investigated in recent years in the hope to further improve the clinical outcomes of chronic heart failure.

Recent clinical observations have suggested that synthetic testosterone, when administered on a regular basis, relieves clinical symptoms and enhances myocardium and other skeletal muscle capacity in men with moderate to severe heart failure [4, 5]. However, during these relatively small clinical trials, testosterone therapy does not appear to reduce long-term mortality of chronic heart failure despite of the improvement in clinical symptoms and exercise tolerance [4, 5].

It is not entirely clear as to whether testosterone improves the ventricular function and clinical symptoms in men. Recent studies suggest that the cytokine network plays an important role in the pathogenesis and progression of chronic heart failure. Serum tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine, is increased in heart failure
patients, whereas the serum level of interleukin-10, an anti-inflammatory cytokine, is reduced [6]. During heart failure, the imbalance between the inflammatory and anti-inflammatory pathways, or altered TNF-α /interleukin-10 ratio, results in myocardial remodeling, ventricular dilation, myocyte apoptosis and impairment in myocardial contractility [6].

We hypothesize that testosterone, when given as a therapeutic agent, would suppress the biosynthesis of TNF-α and re-address the TNF-α /interleukin-10 ratio. As a result, testosterone prevents ventricular remodeling and improves ventricular function and clinical symptoms in patients with chronic heart failure.

**Role of TNF-α and interleukin-10 in the pathogenesis of heart failure**

In heart failure patients or animal models, not only the serum TNF-α is elevated but also the myocardial synthesis of TNF-α and other inflammatory factors is excessive [6]. The increased biosynthesis and release of TNF-α is largely due to the reduced cardiac output. The biosynthesis of interleukin-10 is also reduced during heart failure [6]. Interleukin-10 is able to down-regulate the production of TNF-α via activation of several transcription factors from the signal transducers [7]. Furthermore, interleukin-10 induces the production of specific cytokine inhibitors, such as interleukin-1 receptor antagonist, and serves as a counter-production mechanism to TNF-α biosynthesis [7]. Therefore the reduced synthesis of interleukin-10 during heart failure also contributes to the over production of TNF-α.

TNF-α is one of the key cytokines important to the development of catabolism during heart failure, causing skeletal muscle wasting and myocardial damages. When over-expressed, TNF-α induces cardiomyopathy, ventricular dysfunction and pulmonary edema [6]. The serum levels of TNF-α is positively correlated with the mortality of chronic heart failure in human subjects [6].

The role of TNF-α and interleukin-10 in the pathogenesis of heart failure is further demonstrated in a recent study in which rat coronary artery was ligated to induce infarct-
related heart failure [7]. Cardiac function, which was assessed by echocardiography, deteriorated progressively after coronary ligation and severe heart failure was seen at 16 weeks after myocardial infarction [7]. Membrane-bound and soluble TNF-α protein fractions were increased 1 and 4 weeks after myocardial infarction, whereas TNF-α mRNA was increased 4 and 8 weeks after [7]. Membrane-bound interleukin-10 protein and mRNA levels were decreased 4, 8, and 16 wk after myocardial infarction. The decrease in the interleukin-10-to-TNF-α protein ratio in all coronary artery-ligated animals correlated with the depressed cardiac function [7]. Furthermore, in animals treated with losartan, an angiotensin II receptor blocker currently used for the treatment of human heart failure, improved cardiac function, membrane-bound and soluble TNF-α and interleukin-10 protein levels, the ratio of interleukin-10 to TNF-α, and interleukin-10 mRNA [7]. These results indicate that a decrease in interleukin-10 and interleukin-10-to-TNF-alpha ratio is associated with the left ventricular dysfunction or heart failure after myocardial infarction.

**Effect of testosterone on ventricular function**

In patients with chronic heart failure, there is an excess of catabolic hormones and a relative deficiency of anabolic hormones [8, 9]. Levels of the weaker adrenal androgen dehydroepiandrosterone and its sulfate are consistently reported to be low in proportion to heart failure severity [8, 9]. This deficiency may be responsible for some of the features of advanced heart failure such as reduced mass of skeletal muscle, abnormal energy handling, cachexia, depression, and fatigue [8, 9]. Testosterone is a hormone that may have therapeutic benefit in chronic heart failure for a number of reasons. It has vasodilatory properties and acute administration of testosterone lowers peripheral vascular resistance, reduces cardiac afterload, and increases cardiac index [4]. These beneficial hemodynamic effects will ultimately improve the cardiac function, clinical symptoms and exercise tolerance of patients.
In a recent randomized, double-blinded and placebo-controlled trial, testosterone at physiological doses was given in 76 men with heart failure over a maximum follow-up period of 12 months [5]. The exercise capacity in the vast majority of the patients was significantly improved with testosterone therapy compared with placebo over the study period. In patients treated with testosterone, symptoms improved by at least one New York Heart Association (NYHA) functional class [5]. However, there were no significant changes in serum tumor necrosis factor levels in this relatively small study, where the anti-inflammatory cytokines such as interleukin-10 were not measured [5].

**The hypotheses**

In human subjects without heart failure, testosterone is known to modulate the immune response, reducing the pro-inflammatory cytokines TNF-α while increasing the anti-inflammatory cytokine, such as interleukin-10 [10]. It has been well documented that pro-inflammatory cytokines TNF-α plays an important role in the pathogenesis and progression of chronic heart failure after myocardial infarction, whereas interleukine-10 counteract the detrimental cardiac effects of TNF-α. Recent studies have demonstrated that testosterone administered at physiological doses improves clinical symptoms and cardiac function in patients with chronic heart failure. Therefore, it is likely that testosterone improves the left ventricular function in heart failure through counteracting the biosynthesis of TNF-α and re-addressing the imbalance between pro- and anti-inflammatory cytokines at the systematic and myocardial levels. This hypothesis can be tested by a large clinical trial in which the levels of TNF-α and interleukin-10 are measured in serum and if possible, in the myocardium before and after testosterone replacement therapy.
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