Hormonal Replacement and Physical Exercise in Heart Failure Treatment: A Systematic Review

EXERCISE AND SPORTS MEDICINE CLINIC

Original Article

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ABSTRACT

Background: Despite the full use of pharmacological and non-pharmacological therapy, morbidity and mortality incidence as a result from heart failure (HF) are still significantly persistent. In the therapeutic context, the inhibition of inadequate neuro-hormonal and metabolic adaptations, as well the information on the anabolic deficiency that develops in HF becomes relevant. However, just recently some studies about the benefits of the testosterone replacement or supplementation therapy (TRT) have emerged. Objective: to review studies that address the TRT in heart failure (HF), particularly those developed in the ideal setting for clinical treatment, including physical exercise program. Methods: the Scielo and Pubmed databases, Cochrane of Systematic Review and Clinical Control Trials from Cochrane Collaboration databases were analyzed. Results: The few studies about TRT in patients with HF showed improvement in hemodynamic function, insulin resistance, functional capacity and neuro-hormonal and neuromuscular responses, highlighted the controversy regarding the influence on the inflammatory profile, and found no changes in function and structure in the central cardiovascular system. However, studies about TRT associated with exercise programs have not been found. Conclusion: the present state of knowledge, although based on a few studies, allows considering TRT in the treatment of patients with HF. The ideal choice of TRT, regarding for example, treatment duration and inclusion and exclusion criteria is not well-defined yet. There is a wide gap in the literature, calling attention to the lack of studies about TRT concomitant with full medical treatment which includes a physical exercise program.

Keywords: stress, high performance, athletes.

INTRODUCTION

Acute heart failure syndrome (AHFS) is the state which derives from the heart being unable to keep blood circulation which meets the needs of the metabolizing tissues or which can only do it under high filling pressure[1]. Heart failure (HF) is usually a chronic condition of progressive evolution and bad prognosis, being its mortality rate around 50% in one year for patients with hospitalization history. Additionally, it causes morbidity and disorders, decreasing quality of life, and being a common condition of great social and economic relevance in our environment. The Brazilian public health system (SUS) spent in the year of 2000 around R$ 4.9 billion in hospital admissions, R$ 5.7 billion in ambulatory care and R$ 2.5 billion in medication, and HF was the most common reason for hospital admission[2]. Initially, compromising of the ventricular function, compensated by the neuro-hormone adaptations and by the activity of inflammatory mediators, occurs. Subsequently, the adaptations worsen the heart and endothelial disorder, causing increasing damage to the peripheral blood flow as well as ventilatory deterioration of the musculoskeletal functions (including sarcopenia), and of the autonomous nervous system, which function with great neuroendocrine alterations[3,4].

There are many studies demonstrating the effectiveness of pharmacological treatments, for example, the spironolactone and angiotensin-converting enzyme, which acts in the renin/angiotensin system axis, and the betablockers, which act in the catecholamine axis[5], besides non-pharmacological therapeutics, with special attention to physical exercise[6,7]. However, the studies on strategies which act in the androgens axis are recent and limited in number, demonstrating that the hormone replacement or supplementation therapy (TRT) has not deserved much attention. This article has the aim to research the literature about the TRT in HF, especially in the ideal scenario, of the complete clinical treatment, which includes a customized program of physical exercises.

METHOD

The search strategy was based on the Cochrane of Systematic Review and Clinical Control Trials from Cochrane Collaboration databases, through the Virtual Health Library (BVS) which enabled evaluation of nine articles related to the topic. In the Medline database the search for original articles was structured in the 'PICO' standard, an acronym for target Patient, Intervention Control, Outcome or Closure which resulted in the following syntax: "(Heart Failure) and (Testosterone or Testosterone 5-alpha-Reductase or Sex Hormone-Binding Globulin or Testosterone Propionate or Testosterone Congeners or 17-Hydroxysteroid Dehydrogenases) and (Asthma, Exercise-Induced or Exercise Therapy or Professional Practice or Professional Review Organizations or Exercise or Exercise Tolerance or Simulation Exercise or Exercise Movement Techniques or Upper Extremity Deep Vein Thrombosis]". Aftwerwards, the "randomized controlled trial (pt) OR controlled clinical trial (pt)OR randomized controlled trials (mh) OR random allocation (mh)OR double-blind method (mh) OR single-blind method (mh) OR clinical trial (pt) OR clinical trials (mh) OR ("clinical trial" (tw]) OR (singl* (tw)OR doubl* (tw)OR trebl* (tw) OR tripl* (tw]) AND (mask* (tw) OR blind* (tw])) OR (placebos (mh) OR placebo* (tw) OR random* (tw)OR research design (mh:noexp) OR comparative study (mh) OR evaluation studies (mh) OR follow-up studies (mh) OR prospective studies (mh) OR control* (tw) OR prospectiv* (tw) OR * (tw]) NOT (animals (mh) NOT humans (mh]) filters were added".

RESULTS

Out of the 44 articles found, six met the selection and relevance requirements according to their scientific evidence power classified according to the Oxford Centre for Evidence Based Medicine guidelines. The references of the selected articles were checked and served as additional information source.

Careful reading of the selected articles led us come to some confirmation, presented as follows in topics.

Testosterone and exercise synergism in heart failure

The anabolic hormones are determinant of the capacity to exercise. Decrease of these hormones is related to age and contributes to gradual worsening of tolerance to exertion in older men[8,9]. Testosterone deficiency and consequent worsening of the anabolism/catabolism ratio is a pathophysiological characteristic of patients, even young ones, with advanced HF[10-14], contributing to the decrease of muscle mass, weakness, fatigue, dyspnea and cachexia. However, the TRT effects in patients with HF, even with severe androgenic deficiency and cachexia clinical episode, have been little investigated until the present moment. A plausible hypothesis is that the synergism between the TRT effects and exercise would provide higher results than isolate effects of the interventions concerning function improvementand muscle mass gain, considering what has been demonstrated in healthy men and in populations with other morbidities[15]. Therefore, the TRT result associated with physical exercise in patients with HF represents a problem to be solved.

Heart failure, catabolism and testosterone

Hypotestosteronemia has been described in patients with HF[10-12]. According to the muscular hypothesis, which is based on the neuro-hormone alteration and altered balance between catabolism/anabolism in favor to catabolism, the disease may progress from a controlled catabolic state to heart cachexia, which is defined as unintentional loss of lean mass above 6kg in six months[16-19]. The deficiency in the testosterone hormone may be a contribution from this process. The low serum testosterone level, frequently found in studies with patients with HF, is considered a marker of worse prognosis, regardless of the predictors of conventional risks and of the cause for the disease[20-22]. The prevalence of hypotestosteronemia (hypogonadism) ranges between 25 and 30%, being the high mortality and morbidity rates associated with the low levels of androgens, even in the absence of cachexia[12,23,24].

Effects of testosterone replacement of supplementation (TRT) in heart failure

1. Central cardiovascular effect: it was verified that the TRT did not promote significant echocardiographic alterations in hypogonadal and eugonadal patients with HF in controlled clinical assays [23-25]. However, this intervention has not been synergically assessed in relation to exercise. On the other hand, abusive anabolic androgens use, common among athletes, causes worsening of heart function, leading to diastolic dysfunction due to increase of left ventricular mass and myocardial hypertrophy[26].

2. Hemodynamic effects: hyper activation of the sympathetic nervous system and depression of the parasympathetic nervous system cause vasoconstriction in the patient with HF. This physiological adaptation in response to the heart failure contributes to physical exertion intolerance. The TRT acts as an acute vasodilator agent and plays a dose-response effect in the vascular bed of the coronary, mesenteric, pulmonary arteries, as well as subcutaneous tissue[27,28], being associated with improvement in endothelial function[29]. The TRT in patients with coronary artery disease (CAD) improved the ischemia limit when promoted increase in coronary blood flow[30], especially among those with lower testosterone levels[31]; this is a relevant fact to be considered, since CAD is a very common etiology for HF. Another study verified that patients submitted to TRT presented decrease of systemic vascular resistance and increase of cardiac debt[32]. In this context, not only the hypogonadal patients, but also the eugonadal patients with lower serum testosterone levels (levels below the mean) were benefited. Additionally, patients submitted to TRT for 12 months improved with maintenance of the blood pressure control and left ventricle function, while these parameters deteriorated in the control group [23]. Adverse effects, such as thromboembolic events have not been described in these studies, perhaps due to the exclusion of patients with high hematocrit levels, or due to their short nature, which did not let adverse effects be evaluated in the long term. Once again, it is worth highlighting that the referred studies have not evaluated the TRT hemodynamic effects associated with physical exercise, denoting the relevance of the need of further studies on this issue.

3. Insulin resistance: it is a condition commonly found in patients with HF. Its mechanism is not totally clear; however, it is believed that it is related to deficiency in the number of GLUT 4 receptors in the skeletal musculature cells and to the post-receptors signaling[33], being considered a marker of worse prognosis. Conventional pharmacological therapy and exercise practice decrease glucose intolerance. Two studies[24,34] reported improvement in insulin resistance in patients with HF submitted to testosterone replacement. However, these studies did not evaluate the association between TRT and rehabilitation program with exercise, which could offer a better result.

4. Functional capacity: exertion and fatigue intolerance is the-main clinical manifestation in HF, but this magnitude not always-reflects the level of ventricular dysfunction. Vasodilation worsening to exercise, predominance of the anaerobic metabolism and high-energy phosphates depletion are some alterations found in the skeletal musculature which collaborate to the fatigue and exertion intolerance onset. Imbalance between ventilation and oxygen consumption associated with the muscular alterations, stimulated by the bad adaptation of the neuromuscular perception (ergoreflex), which results in hyperventilation and dyspnea is observed[17]. In HF, the treatment through exercise promotes improvement in the musculoskeletal structure and function as well as of hyperventilation induced by exertion (higher ventilatory efficiency), which results in increase of exercise tolerance[18]. In the few investigations carried out, muscle strength and physical performance improvement derived from the TRT were demonstrated[13,23,24]. In one of the studies IM testosterone was applied for three months[13]. In another study[23], the patients were submitted to transdermal testosterone application and were followed for one year. The studies, controlled clinical assays, corroborated the results of muscle strength improvement and physical performance. In the study with the longest duration, improvement in the functional class in 35% of the patients treated and in only 8% of the untreated with testosterone was observed. In agreement with the refereed studies, Caminit*et al.*[24] evaluated

the testosterone buildup effects (testosterone undecanoate) in 70 patients for three months and found strength and muscle power improvement, fatigue index decrease, as well as improvement in performance measured by the VO_2 peak and distance reached in the six-minute walk test.In these clinical assays, with concordance in their outcome, hypogonadal and eugonadal men were evaluated, but the exercise concomitant influence has not been studied.

5. Neuro-hormonal and neuromuscular effect: the ergoreflex activation is caused by accumulation of metabolites in the skeletal muscles during physical activity, with pulmonary ventilation, hemodynamic parameters and nervous system exacerbation[35], with the presence of correlation between the ergoreflex activation and dyspnea and exertion intolerance[7,19]. The study by Caminiti*et al.*[24] examined the correlation between oxygen consumption and ventilation (VE), and it was confirmed that the patients who received testosterone presented significant reduction of the VE/VCO_2 curve, which implies in higher ventilator efficiency as well as improvement in exertion tolerance, suggesting that testosterone attenuates the ergoreflex activation in patients with HF. Additionally, Caminiti *et al.*[24] explored the effects of the testosterone replacement in the arterial baroreceptor sensitivity mediated by the vagus nerve, where the HF is characterized by the sympathetic activation and depression of the baroreceptors response, which implies in worse prognosis[36]. The study presented improvement in the baroreflex sensitivity in patients treated with testosterone; however, the activity mechanism involved in this effect was not clear. Once again, the study did not evaluate the exercise effect in the TRT context.

6. Inflammation and testosterone use: HF occurs with the subclinical inflammation state, with citokines increase as tumor necrosis α (FNTα) factor, interleukin-6 (IL-6) and interleukin-1 (IL-1). The activity of the inflammatory interleukins causes depression in the hypothalamus-hypophysis-gonadal axis, where the consequent hypotestosteronemia state contributes to worse prognosis. In studies with humans, there has been disagreement concerning the positive effect of the testosterone replacement in the improvement of the circulating profile of inflammatory citokines. The study performed by Pugh *et al.*[37] reported that the TRT has no effect on the improvement of the FNTα levels in patients with HF. On the other hand, Malkin*et al.*[31] reported that in hypogonadal men who received TRT no reduction of the post-inflammatory citokines levels (FNTα and IL-1) and increase of anti-inflammatory citokines (IL-10) activity occurred. No studies on the ultrasensitive C-reactive protein levels in patients with HF submitted to TRT and exercise have been found.

Table 1. Clinical essays: testosterone replacement and heart failure.

Author	N	Duration/ weeks	Intervention	Exercise program	Effects	Adverse effect
(Caminiti, Volterrniet al. 2009) Italy	70	12	IM Testosterone unde canoate every six weeks	Not available	↑ testosterone levels; ↑insulin sensitivity; ↑ peak VO_2; ↑muscle strength ↔Heart function and structure (echocardio) ↓ fatigue index	Not available
(Malkin, Jones et al. 2007) UK	13	12	IM testosterone (sustanon 250) every two hours	Not available	↑ insulin sensitivity ↑ total body mass ↓ fat mass	Not available
(Malkin, Pugh et al. 2006) UK	76	54	Androderm (adhesive) 5mg / day	Not available	↑muscle strength ↑exercise tolerance ↑functional class ↔heart function a and structure	cutaneous allergic reaction.
(Pugh, Jones et al. 2005) UK	94	12	IM and transdermal testosterone 5mg/day	Not available	↔ FNTα	Not available
(Pugh, Jones et al. 2004) UK	20	12	Sustanon 100 every two weeks	Not available	↑muscle strength ↑exercise tolerance ↑functional class	Not available
(Malkinet al. 2004) UK	27	12	IM testosterone enanthate	Not available	↑ IL-10 ↓ IL-1 ↓ FNTα	Not available

↑: improvement or increase; ↓: worsening or decrease; ↔: without alteration or maintenance.
T; Mara LS; Ulbrich A. Rev Bras Mes Esporte- Vol.17,Nº6-Nov/Dec,2011.

Testosterone replacement therapy, undesirable effects

There is evidence that the TRT can be beneficial for a large number of patients, including those with coronary disease, and the endogenous testosterone is not related to the increase of mortality or vascular disease[38-40]. However, considering the risk of prostate cancer, the long-term TRT is an issue which demands prospective studies of long duration. Conversely, there is indication that low levels of endogenous testosterone are associated with more aggressive prostate cancer. Interestingly, meta-analysis data and other careful studies report that high levels of endogenous testosterone and hormone replacement therapy are not associated with the increase of prostate carcinoma[41-43]. Despite the findings of these studies, previous investigation on prostate cancer and subsequent follow-up of all patients who will be submitted to the TRT is recommended[44,45].

After careful review on testosterone and HF,Malkin*et al.*[5] concluded that the current knowledge status enables us to recommend to the internal medicine specialists to consider the TRT to male patients with moderate and severe HF and hypotestosteronemia, since in these patients the hormone therapy would represent a hope for quality of life improvement as well as reduction in the high death risk. In this context, further investigation with the purpose to establish the TRT safety connected to correct conventional treatment, which includes an exercise program, is suggested.

CONCLUSIONS

The current knowledge, despite being based on few investigations, lets us consider the TRT for the treatment of patients with HF with the aim to improve their function and quality of life. The ideal TRT way concerning for example, treatment duration and inclusion and exclusion criteria, has not been well-defined yet.There is a wide gap in the literature which calls attention to the absence of studies on the TRT concomitant with the complete clinical treatment including a physical exercise program.

All authors have declared there is not any potential conflict of interests concerning this article.

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