Jones TH (ed): Advances in the Management of Testosterone Deficiency.
Front Horm Res. Basel, Karger, 2009, vol 37, pp 183–196

# Testosterone in Chronic Heart Failure

Chris J. Malkin[a] · T. Hugh Jones[b,d] · Kevin S. Channer[a,c]

[a]Department of Cardiology, Royal Hallamshire Hospital, [b]Academic Unit of Diabetes, Endocrinology and Metabolism, Division of Genomic Medicine, University of Sheffield and [c]Faculty of Health and Well-being, Sheffield Hallam University, Sheffield, and [d]Centre for Diabetes and Endocrinology, Barnsley District General Hospital, Barnsley, UK

**Abstract**

Chronic heart failure is common and can be described as a syndrome characterized by impairment of cardiac function associated with a maladaptive metabolic and neurohormonal axis. The thesis that testosterone replacement therapy may be helpful as a treatment for chronic heart failure may seem at first to be unlikely. Testosterone therapy is widely believed to be deleterious to the cardiovascular system and there is a common misconception that the excess of ischaemic heart disease in young and middle-aged males compared to females is a direct effect of endogenous serum testosterone levels. In this chapter we will present the published evidence of the effects of endogenous and therapeutic testosterone on the heart and the human cardiovascular system with an emphasis on the pathologic syndrome of chronic heart failure. There is developing evidence that of all morbid populations, patients with chronic heart failure in particular are likely to benefit from testosterone treatment since the natural history is that of progressive disordered metabolism with catabolic excess and androgen imbalance.


## Introduction

Chronic heart failure (CHF) is a common clinical problem and a major public health issue. The prevalence of CHF in the UK is 1% and in Europe alone it is thought that around 10 million people are affected by CHF [1]. The financial burden required to support this patient group is enormous and in the UK accounts for 4–5% of the NHS budget. Numerous treatment modalities exist – these can be conveniently divided into medical therapies and surgical and device treatments (table 1). Corrective surgery for valvular or congenital disease is rarely curative. Coronary revascularization either by coronary artery bypass surgery or percutaneous angioplasty may also be helpful for a minority. Cardiac transplantation may be offered to selected patients but this modality is limited due to the availability of donor organs. Modern device therapy includes cardiac resynchronization therapy, a technique using multisite pacing to improve cardiac performance and efficiency or implantable cardiac defibrillators designed to prevent sudden

**Table 1.** Medical therapies and surgical and device treatments

| | Treatment modality | Target population | Frequency of use | Effect on symptoms | Effect on mortality |
|---|---|---|---|---|---|
| Surgical | Corrective surgery | Valvular pathology<br>Congenital disease | Infrequent<br>Rare | Improve | Improve |
| | Cardiac transplant | Severe heart failure, unresponsive to other modalities | Rare | Improve | Improve |
| | Revascularization<br>CABG<br>PCI | Proportion of patients with coronary disease | Infrequent | Improve | Improve |
| Device | Cardiac resynchronization | Moderate severity heart failure fulfilling stringent criteria | Rare | Improve | Improve |
| | Cardiac defibrillators | Moderate severity heart failure | Rare | None | Improve |
| Medical therapy | ACE-I<br>ARBs | All | High | Improve | Improve |
| | β-Blockers | All | High | Improve | Improve |
| | Aldosterone antagonists | Moderate severity heart failure | Moderate | Improve | Improve |
| | Diuretics | Heart failure with fluid retention | High | Improve | None |
| | Digoxin | Heart failure with AF | Moderate | Improve | None |

Guide to frequency terms: high: >50% CHF population; moderate: 10–50% CHF population; infrequent: <10% CHF population; rare: <1.5% CHF population. CABG = Coronary artery bypass grafting; PCI = percutaneous coronary intervention; ARB = angiotensin receptor blockers; AF = atrial fibrillation.

death due to malignant ventricular arrhythmias. Most patients however are ineligible for surgical or device therapy and are faced with a clinical condition characterized primarily by breathlessness, poor exercise tolerance and fatigue that is relentlessly progressive. Modern medical therapy for heart failure using combinations of angiotensin-converting enzyme inhibitors (ACE-I), β-adrenergic receptor blockers (β-blockers) and direct aldosterone antagonists improve symptoms and prolong life but do not prevent eventual decompensation to progressive heart failure. Other widely used therapies such as loop diuretics, digoxin and other anti-arrhythmics may improve symptoms and keep patients from unwanted hospital admission but have no demonstrable effect on mortality [1].

Despite modern advances in the detection, diagnosis and treatment of CHF the prognosis of this condition is still poor and is no better than the prognosis of most malignancies. Severe heart failure characterized by breathlessness at rest or minimal exertion has an annualized mortality of 50% and even selected heart failure patients managed aggressively within the confines of clinical trials have an annual mortality of around 10% [1].

*Pathophysiology*

CHF is a unique metabolic syndrome characterized by perturbation of numerous endocrine and inflammatory parameters. These changes are important since they relate to the severity of heart failure and directly contribute to deterioration and prognosis. A summary of the heart failure metabolic syndrome is displayed in table 2.

Many of these adaptive parameters are ultimately detrimental and cause worsening of cardiac function and eventually deterioration in severity of heart failure. The natural history of untreated heart failure is very poor with worsening cardiac function, symptoms and death. Strategies to simply increase cardiac muscle contraction with inotropes, for example, merely accelerate the natural history and are associated with a poorer prognosis. In the absence of surgically remedial lesions, modification of these neuro-endocrine responses in heart failure has been explored as potential therapies, with varying efficacy. As discussed above and summarized in table 1, inhibition of the renin-angiotensin-aldosterone axis and blockade of catecholamine receptors are the mainstay of heart failure therapy and will be offered to all patients. Disordered and excess immune activation has been explored with small trials of immunoglobulin and also pentoxyphylline with varying benefit. The possibility of reducing pro-inflammatory cytokines has been intensively investigated and although initial studies of anti-tumour necrosis factor (TNF) 'biological' drugs were promising, definitive benefit has not been borne out in major clinical trials [2].

*Androgen Status in Heart Failure*

It is notable that there is a clear anabolic-catabolic imbalance with an excess of catabolic hormones and a deficiency of many anabolic hormones. This aberration has until relatively recently been ignored, yet there is no doubt that this hormone derangement is a poor prognostic sign and contributes to significant symptoms [3]. Testosterone levels in heart failure in particular are low and this finding alone is a poor prognostic marker [4]. About a quarter of men with moderate severity heart failure have biochemical evidence of testosterone deficiency [5, 6]. One of the most feared clinical signs and a marker of very severe anabolic-catabolic imbalance in heart failure is cachexia [3], defined clinically as the non-intentional loss of 6 kg lean mass over a 6-month period. Cachexia is the most extreme symptom of heart failure and most subjects experience a more gradual catabolic decline. However the fact that severe heart failure can cause muscular wasting and weakness illustrates that the

**Table 2.** The metabolic syndrome of heart failure

| Metabolic axis | Specific compounds | Relationship with CHF | Clinical effect in heart failure | Effect of pharmacologic modification | Available therapies |
|---|---|---|---|---|---|
| Renin-angiotensin | Angiotensin-2 | Relate to severity of CHF and predict deterioration and mortality | Vasoconstriction, fluid retention, myocardial fibrosis | Improve symptoms and mortality | ACE-I ARBs |
| | Aldosterone | | Myocardial fibrosis | Improve symptoms and mortality | Spironolactone, eplenerone |
| Catecholamines | Adrenaline Noradrenaline | Relate to severity of CHF and predict deterioration mortality and sudden death | Risk of sudden death, worsening cardiac function | Improve symptoms and mortality | β-Blockers |
| Glucocorticoid | Cortisol | Elevated | Catabolic | Unknown | None |
| Insulin | | Resistance to insulin action in proportion to severity of CHF | Impaired glucose delivery, catabolic | Unknown | |
| Growth hormone | | Reduced in heart failure, resistance at receptor level | Catabolic | | Recombinant growth hormone |
| Androgens | Testosterone | Reduced in heart failure | Catabolic | Improve endurance | Testosterone |
| | Dehydroepiandrosterone | Reduced in heart failure | Catabolic | Unknown | |
| Immune/ cytokine | TNF | Elevated | Catabolic | None | Monoconal antibodies |
| | IL-1 | Elevated | Catabolic | None | Monoconal antibodies |

ARB = Angiotensin receptor blockers.

condition is not simply a disease of the heart: there are multisystem effects and many of the cardinal symptoms of heart failure such as breathlessness and fatigue are due to abnormal muscle function, impaired mobilization of energy and ultimately loss of lean muscle mass [7]. It is these features of heart failure, intuitively similar to a state of frank androgen deficiency, where the hypothesis of testosterone treatment as an adjunct to heart failure therapy was first described.

*Endogenous Testosterone and the Heart*

Male sex is a risk factor for the premature development for coronary disease, with a relative risk ratio of 2.5:1, which is consistent throughout the world despite a widespread variation in the background incidence of coronary disease. This consistent epidemiological ratio infers that for any given genetic profile or exposure to risk factors there is an inherent advantage of being female or a disadvantage of being male [8]. This fact is difficult to explain and currently remains somewhat controversial. There is a widespread belief that higher serum testosterone levels in men compared with women are responsible. The concept stems partly from numerous case reports of adverse cardiovascular events in subjects who abuse high-dose anabolic steroids and partly from the simple association of male status and higher endogenous testosterone levels. Were this to be true then it follows that the higher the testosterone blood level the worse the cardiovascular effect. In fact there is a considerable volume of published data examining this issue, with approximately 40 cross-sectional studies and 8 prospective long-term follow-up studies and there does not appear to be any relationship with the levels of serum testosterone and the risk of atherosclerotic vascular disease. Indeed in many of the cross-sectional studies an inverse relationship is observed, with lower levels of testosterone associated with vascular disease [8]. Similarly in women, endogenous oestrogens appear to be protective and although the recent mega-trials of hormone replacement therapy in postmenopausal women have found hormone replacement therapy to cause an excess of vascular events, most of these effects are driven primarily by prothrombotic mechanisms. In summary, there appear to be sex-specific effects of endogenous sex hormones; in both sexes there is evidence that endogenous sex hormones, testosterone in males and oestrogens in women, are protective against atherosclerotic vascular disease. The clinical challenge is delivering effective therapeutic preparations of hormone replacement. In women for example this has been hampered by prothrombotic and procancerous effects of oestrogen. In men hormone replacement therapy in partial androgen deficiency is a relatively untested field. The prothrombotic effects of oestrogen therapy are not a problem with testosterone treatment since testosterone is a weak activator of fibrinolysis [9]. The risks of malignancy, particularly prostate cancer, are uncertain and require further evaluation.

## Testosterone as a Treatment for Heart Failure

Testosterone is in many ways a logical choice as a treatment for heart failure. Heart failure is a characterized by anabolic deficiency, low-grade inflammation and a loss of muscle mass and strength; these are effects that testosterone treatment even at physiological doses may improve. In addition heart failure is a condition of disordered vascular behaviour specifically peripheral vasoconstriction and increased systemic vascular resistance, testosterone has effects on both the systemic and the coronary vasculature that increase both coronary perfusion and cardiac output.

### Cardiac Effects of Testosterone Treatment

Within the boundaries of the normal physiological range testosterone therapy seems to have relatively little effect on myocardial morphology and function. There is animal data that profound testosterone depletion due to castration in early life regulates the expression of certain calcium ion channels and protein synthesis. In these studies castration was associated with reduced left ventricular (LV) mass, reduced cardiac output and reduced ejection fraction [10]. There is considerably more data on the effects of supraphysiological testosterone treatment on the myocardium. There is general uniformity in cell culture studies, animal treatment studies and observational studies of power athletes known to abuse anabolic androgens that a very high dose is detrimental to the myocardium. The important specific findings from the human observational studies included increased LV mass and hypertrophy, smaller LV cavity dimensions and evidence of early diastolic dysfunction due to stiffening and loss of LV compliance [11].

### Non-Cardiac Effects of Testosterone Treatment

The non-cardiac effects of testosterone therapy are important. Analogous to many of the current pharmacological heart failure treatments, testosterone acts in a positive manner on the maladaptive heart failure metabolic syndrome and the direct effects on the myocardium appear to be less important.

### Body Composition and Physical Strength

Numerous clinical trials of androgen therapy on the effects of body composition and voluntary physical strength exist within the literature. The trials can be broadly divided into those using physiological or non-physiological testosterone therapy and those testing the effects in morbid populations, androgen-deficient males and normal subjects. There is general consistency within the literature, with well-conducted prospective randomized controlled trials finding that testosterone improves anabolic function. This improvement in function is characterized by increased voluntary muscle strength, increased lean (muscle) mass and reduced fat mass [12]. These effects are seen in all patient groups and with testosterone preparations within the physiological replacement range. The morbid populations studied include patients with weight loss and cachexia due to malignancy, HIV infection and inflammatory autoimmune disease.

### Insulin Resistance

One of the major hormonal derangements in heart failure is resistance to insulin. Insulin resistance is another example of a maladaptive hormone system in the complex syndrome of heart failure. The severity of heart failure is related to the severity of the insulin resistance and impaired insulin-mediated glucose uptake is a powerful independent prognostic marker [3]. The mechanism underlying insulin resistance in

heart failure is obscure, though it appears functionally different than insulin resistance in other morbid populations which in general are characterized by reduced phosphorylation of intracellular postinsulin receptor proteins. It is likely that the cause is multifactorial and involves impaired postreceptor signalling and other neurohormonal and immune alterations present in severe heart failure [13]. It is notable that insulin resistance can be improved; by both conventional heart failure treatments such as ACE-I and β-blockers as well as novel non-pharmacological treatments such as graded exercise. Testosterone treatment has a positive effect on insulin sensitivity both in normal subjects and morbid populations such as obese men and diabetics [14]. A single study has examined the effect of testosterone treatment on insulin sensitivity in CHF. In this small crossover study compared to placebo, testosterone improved fasting glucose and insulin, insulin resistance as measured by HOMA (homeostatic model assessment) index and this was associated with increased lean mass and reduced fat mass [15].

### Inflammation

CHF is a condition of low-grade subclinical inflammation. Inflammatory mediators such as TNF-α and interleukins (IL) such as IL-1 and IL-6 are elevated in heart failure and are mediators of the heart failure syndrome contributing to cachexia and insulin resistance [3]. Testosterone therapy is reported to have positive effects on inflammatory cytokines in hypogonadal men with co-morbid disease such as diabetes and coronary disease [16]. However significant clinical effects in men with heart failure have not been detected in vivo [17], although clinical trials at present are limited and underpowered.

### Endurance and Functional Capacity

The general anabolic actions of androgen therapy are widely accepted. The evidence is less clear regarding the effect of androgens on functional capacity, exercise endurance and effort fatigue. This property is important in patients with chronic catabolic conditions and particularly in patients with congestive heart failure. The cardinal symptoms of CHF are poor exercise tolerance and fatigue. The restriction of exercise varies widely and bears little relation to the level of cardiac dysfunction, abnormal central pressures or haemodynamics. There appears to be a closer relationship with peripheral energy handling and delivery to the skeletal muscles – the so-called 'muscle hypothesis' [7]. These pathophysiological changes include subnormal peripheral blood flow response (impaired vasodilatation), early anaerobic metabolism, early depletion of high energy phosphates, deficient oxidative and lipolytic enzymes and histological changes consistent with muscle fibre loss and de-conditioning. In short many of these 'muscle' changes are consistent with an anabolic deficiency, and studies of exercise treatment in heart failure have found a degree of reversibility and improvement. The hypothesis that testosterone supplementation may augment this is clearly an important issue. There is relatively little published evidence to reliably answer this question. The limited animal data is consistent, with testosterone

therapy, albeit sometimes at supraphysiological doses improving endurance and exercise capacity whereas clinical trials in normal subjects and morbid populations (HIV-infected patients and chronic respiratory failure patients) have yielded inconsistent results. To date two trials have explored the effects of testosterone on endurance capacity in heart failure and both have reported improvements in objective assessments of functional endurance capacity [6, 18]; these trials are explored in more detail in later sections.

*Haemodynamic Effects of Testosterone Therapy*

Testosterone has widespread effects on vascular tone and reactivity. There is substantial evidence within the literature that testosterone is a dilator of the systemic, pulmonary, mesenteric and coronary vascular beds [19]. Although testosterone is a steroid hormone it also has non-steroidal effects and interacts with a cell membrane-bound L-type calcium ion channel, permitting calcium cellular influx and vasodilatation [20, 21]. The vasodilatator properties of testosterone offer therapeutic properties in heart failure and also in related conditions such as angina pectoris caused by coronary heart disease.

## Haemodynamics in Heart Failure

Heart failure is a condition of systemic vasoconstriction, a physiological adaptation to impaired cardiac function and reduced cardiac output. The increase in systemic vascular resistance is maladaptive and contributes to progressive symptoms and deterioration in patients with CHF. Testosterone therapy has beneficial effects on the haemodynamics of heart failure. Experimental data have confirmed that testosterone in vitro is a dilator of preconstricted systemic vessels (isolated from subcutaneous fat) [22]. Furthermore an important in vivo crossover study using invasive haemodynamic monitoring in 12 patients with CHF randomized to 6 h of acute testosterone therapy or placebo in random order has confirmed the thesis that testosterone reduces systemic vascular resistance and consequently increases cardiac output/index (fig. 1) [23]. The levels of testosterone in the treatment phase of this study were in the high physiological range and show that in the short term at least testosterone increases cardiac output as a result of reducing vascular resistance and increasing myocardial stroke volume. Further analysis of these data demonstrates that the patients with the lowest baseline testosterone levels (patients below the median) derived a greater haemodynamic effect. This finding suggests biological plausibility and potentially a dose-response relationship; the observation that patients with a lower baseline serum testosterone derive a greater benefit is a consistent finding and is also found when testosterone is used to treat angina pectoris.

## Haemodynamics in Angina Pectoris

Angina pectoris is a symptom of coronary ischaemia. The most frequent cause of coronary ischaemia is obstructive atheroma in the coronary artery causing blood

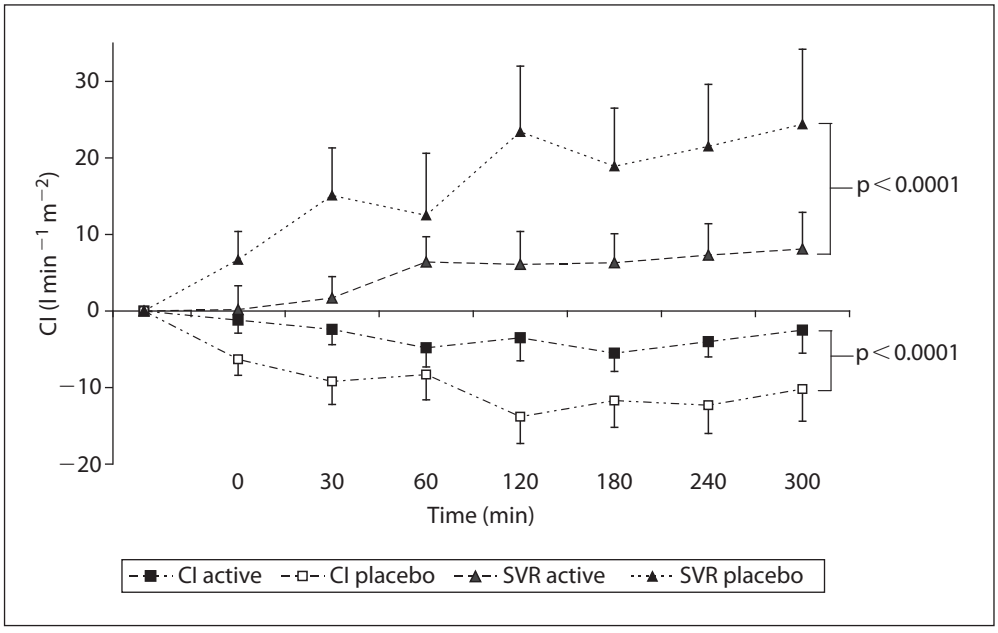


**Fig. 1.** Acute haemodynamic effect of testosterone vs. placebo. Data is change from baseline cardiac index (CI; cardiac output/mass). SVR = Systemic vascular resistance (dyn s $cm^{-5}$). n = 12 patients. Analysis in all cases by ANOVA.

flow limitation. Stable angina is common but unlike CHF has a relatively benign prognosis. Chronic angina can cause restricting symptoms and despite modern therapies including anti-anginal drugs and physical treatments such as coronary artery bypass surgery and coronary angioplasty may severely affect quality of life. Historically testosterone had been used as a therapy for angina and there are several trials from the 1940s attesting to this. Modern trials performed with more scientific methods have found testosterone to be a coronary vasodilator both in vitro and vivo, at physiological doses of therapy [24]. Low-dose testosterone treatment raises the threshold to coronary ischaemia as measured by exercise electrocardiography in an unselected male population with angina. The lower the baseline testosterone level is the greater is the improvement in ischaemic threshold [25]. If a sample of patients with low baseline testosterone levels (androgen deficient) is examined, these subjects derive greater improvement in ischaemic threshold than an unselected sample [26].

*Clinical Trials of Testosterone Therapy in Heart Failure*

There are few trials of androgen treatment in heart failure. A single animal study using a low dose of nandrolone decanoate improved survival in male hamsters with an inherited cardiomyopathy. An unblinded descriptive study of 12 male patients

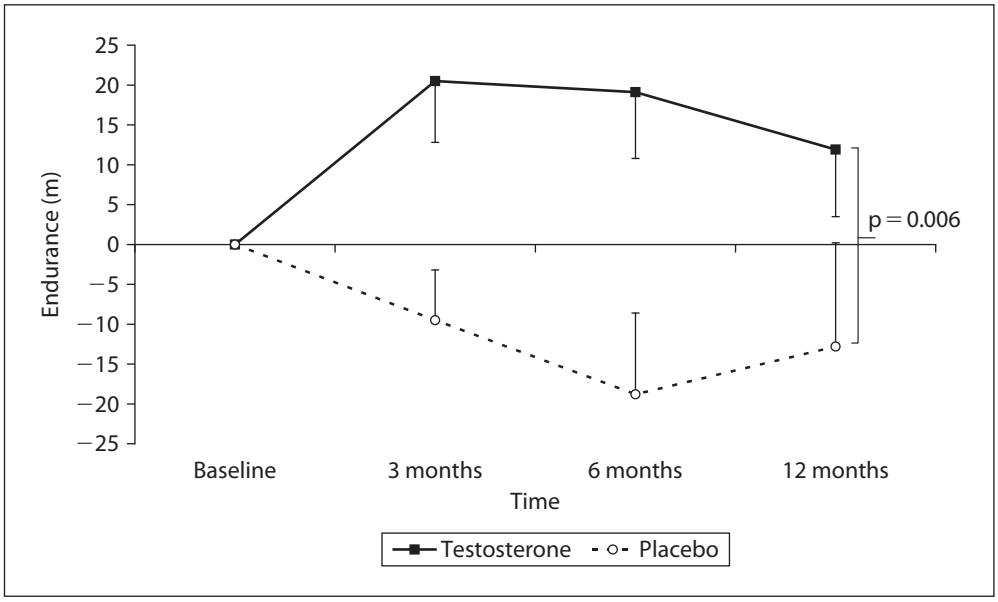


**Fig. 2.** Effect of testosterone on endurance in patients with CHF. Change of endurance from baseline as measured by the incremental shuttle walk test.

found improvements in echocardiographic parameters (reduced LV diameter, reduced LV mass) and reductions in brain natriuretic peptide (a serum marker of heart failure severity) [27]. The only prospective double-blind studies of testosterone treatment in heart failure are from the same scientific research group. Initially designed as a pilot study Pugh et al. [18] using fortnightly intramuscular testosterone (Sustanon 100®) found testosterone to improve mood, symptom scores and endurance (using an incremental shuttle walk test). In the larger follow-up study to this pilot [6], this time using daily testosterone patches (Androderm 5 mg vs. placebo) the effect on endurance was confirmed. Testosterone was found to increase exercise capacity as measured with an incremental shuttle walk test (fig. 2) and improve symptoms as determined by NYHA class. The improvement in exercise capacity in this study was less than observed in the pilot, in which larger doses of testosterone were administered; this suggests that there may be a dose-response relationship. Examination of the pooled data (fig. 3) confirms that the patients treated with intramuscular testosterone in the pilot study achieved higher serum levels of testosterone and greater increases in functional capacity than patients in the patch-treated study. These data suggest that the biological effects of testosterone on functional exercise capacity are related to the serum levels reached in vivo. Furthermore consistent with this notion was that there was a positive correlation with the increase in exercise capacity and serum bio-available testosterone at 3 and 6 months [6].

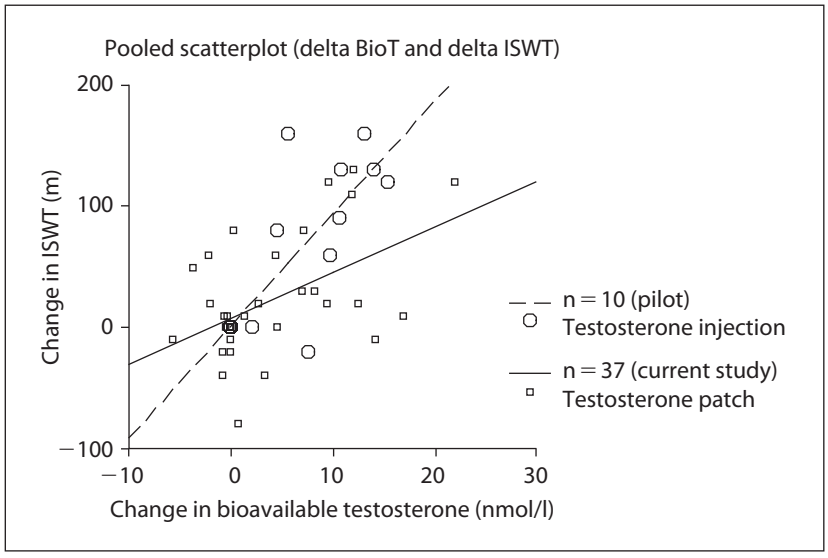


**Fig. 3.** Posttreatment testosterone level and shuttle walk distance. Increase in serum bioavailable testosterone after 3 months' treatment and change in endurance. Studies: pilot (n = 10) Pugh et al. [18]; current (n = 37) Malkin et al. [6] (adapted with permission from the *European Heart Journal*). ISWT = Incremental shuttle walking test.

Other secondary outcomes from this study included improved physician-assigned symptom scores, increased voluntary muscle strength, maintenance of systolic blood pressure, increased LV cavity length by echocardiography and a trend to a reduction in LV mass. There were no significant changes in 'hard' clinical outcomes such as unplanned hospitalizations or mortality. The secondary outcomes were interesting; the echo data suggest LV remodelling – a potential benefit in CHF. Systolic blood pressure decreased in the placebo group over the 12 months' follow-up. This is a part of the natural history of heart failure and is an adverse prognostic sign; however, the systolic blood pressure in the testosterone group was maintained (fig. 4).

*Safety Issues*

Testosterone replacement therapy appears to be safe. Long-term concerns that testosterone treatment may promote coronary disease of impaired cardiac function are not apparent within the boundaries of physiological replacement and in fact there is substantial evidence that this may be beneficial. Fluid retention, listed as an acknowledged side effect of testosterone treatment, is very rarely seen. There are realistic concerns over the risk of prostate malignancy. Prostatic malignancy should be excluded prior to commencing testosterone therapy by measurement of prostate-specific antigen and digital examination [see chapter by Morgentaler and Schulman, pp. 197–203].

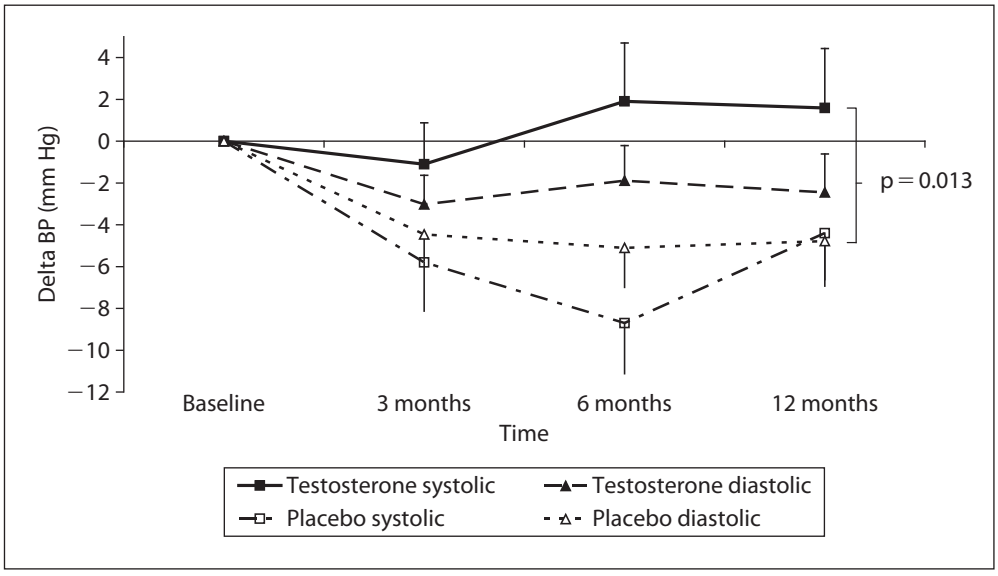


**Fig. 4.** Change in blood pressure from baseline (delta BP). Analysis by ANOVA in each case: change in systolic BP ($p = 0.013$), change in diastolic BP ($p = 0.1$).

## Conclusions

Heart failure is a condition of high mortality, chronic debilitating symptoms and recurrent hospitalization. Novel therapies should either improve morbidity or survival or both; ideally therapy should be widely applicable, inexpensive and show benefit in the presence of co-existing heart failure therapies. Although testosterone replacement therapy cannot be advocated for women, testosterone treatment could be used cheaply in a high proportion of men in whom prostate malignancy had been excluded. It is estimated that the prevalence of biochemical androgen deficiency in males with heart failure is 25%; even in those men with testosterone levels within the normal range it can be argued that within the context of the hormonal imbalance of heart failure this represents a relative androgen deficiency. The effect on survival in heart failure is unknown; clinical trials have not yet been powered to detect any difference. The current evidence base of testosterone treatment in heart failure is small but consistent in reporting positive outcomes. At present, the use of testosterone for heart failure has not filtered into widespread clinical practice. This reflects the limited evidence base but there is also considerable anxiety and suspicion from cardiac specialists in particular to prescribe a male sex hormone to treat a cardiac condition. In this area endocrinologists may need to take a lead. Initially CHF patients with biochemical testosterone deficiency should be treated and followed up to provide registry data. However, larger clinical trials are urgently needed to reduce perceived

anxieties about testosterone treatment within the cardiology community who advise and write guidelines on the management of CHF.

## References


1 Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al: Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–1140.

2 Anker SD, Coats AJ: How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002;86:123–130.

3 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;96:526–534.

4 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;114:1829–1837.

5 Kontoleon PE, Anastasiou-Nana MI, Papapetrou PD, Alexopoulos G, Ktenas V, Rapti AC, et al: Hormonal profile in patients with congestive heart failure. Int J Cardiol 2003;87:179–183.

6 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;27:57–64.

7 Coats AJ: Heart failure: what causes the symptoms of heart failure? Heart 2001;86:574–578.

8 Wu FC, von Eckardstein A: Androgens and coronary artery disease. Endocr Rev 2003;24:183–217.

9 Malkin CJ, Pugh PJ, Jones TH, Channer KS: Testosterone for secondary prevention in men with ischaemic heart disease? QJM 2003;96:521–529.

10 Scheuer J, Malhotra A, Schaible TF, Capasso J: Effects of gonadectomy and hormonal replacement on rat hearts. Circ Res 1987;61:12–19.

11 Urhausen A, Albers T, Kindermann W: Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? Heart 2004;90:496–501.

12 Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, et al: Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005;63:280–293.

13 Kemppainen J, Tsuchida H, Stolen K, Karlsson H, Bjornholm M, Heinonen OJ, et al: Insulin signalling and resistance in patients with chronic heart failure. J Physiol 2003;550:305–315.

14 Kapoor D, Goodwin E, Channer KS, Jones TH: Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006;154:899–906.

15 Malkin CJ, Jones TH, Channer KS: The effect of testosterone on insulin sensitivity in men with heart failure. Eur J Heart Fail 2007;9:44–50.

16 Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH: The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004;89:3313–3318.

17 Pugh PJ, Jones RD, Malkin CJ, Hall J, Nettleship JE, Kerry KE, et al: Physiologic testosterone therapy has no effect on serum levels of tumour necrosis factor-alpha in men with chronic heart failure. Endocr Res 2005;31:271–283.

18 Pugh PJ, Jones RD, West JN, Jones TH, Channer KS: Testosterone treatment for men with chronic heart failure. Heart 2004;90:446–447.

19 Jones RD, Pugh PJ, Jones TH, Channer KS: The vasodilatory action of testosterone: a potassium-channel opening or a calcium antagonistic action? Br J Pharmacol 2003;138:733–744.

20 Scragg JL, Jones RD, Channer KS, Jones TH, Peers C: Testosterone is a potent inhibitor of L-type Ca(2+) channels. Biochem Biophys Res Commun 2004;318:503–506.

21 Hall J, Jones RD, Jones TH, Channer KS, Peers C: Selective inhibition of L-type $Ca^{2+}$ channels in A7r5 cells by physiological levels of testosterone. Endocrinology 2006;147:2675–2680.

22 Malkin CJ, Jones RD, Jones TH, Channer KS: Effect of testosterone on ex vivo vascular reactivity in man. Clin Sci (Lond) 2006;111:265–274.

23 Pugh PJ, Jones TH, Channer KS: Acute haemodynamic effects of testosterone in men with chronic heart failure. Eur Heart J 2003;24:909–915.

24 Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P: Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100:1690–1696.
25 English KM, Steeds RP, Jones TH, Diver MJ, Channer KS: Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. Circulation 2000;102: 1906–1911.
26 Malkin CJ, Pugh PJ, Morris PD, Kerry KE, Jones RD, Jones TH, et al: Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. Heart 2004;90: 871–876.
27 Tomoda H: Effect of oxymetholone on left ventricular dimensions in heart failure secondary to idiopathic dilated cardiomyopathy or to mitral or aortic regurgitation. Am J Cardiol 1999;83:123–125, A9.

Dr. Chris J. Malkin
Department of Cardiology
Royal Hallamshire Hospital, M Floor, Room M131
Glossop Road, Sheffield S10 2JF (UK)
Tel. +44 114 2713445, Fax +44 114 2712042, E-Mail Chris.malkin@sth.nhs.uk