Effect of testosterone on post-myocardial infarction remodeling and function

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Abstract

Background: Men and women are differently affected by coronary artery disease, suggesting an important role of sex steroids. Moreover, testosterone (T) treatment is increasingly used in elderly males. Therefore, we examined effects of chronic anabolic T administration on left ventricular (LV) remodeling after myocardial infarction (MI).

Methods: Adult male rats were treated with intramuscular placebo, testosterone undecanoate (T), or were orchiectomized. After 2 weeks, animals underwent sham-operation (sham) or left coronary artery ligation. Left ventricular remodeling and function was assessed by serial magnetic resonance imaging (MRI) at weeks 2 and 8 and hemodynamic investigation at week 8.

Results: In sham operated animals T administration increased serum T levels and led to cardiac hypertrophy, but not to an upregulation of ANP mRNA. The \(\alpha/\beta\)-MHC ratio was significantly higher after T treatment due to an increase in \(\alpha\)-MHC. As a potential mechanism for this "physiologic" form of hypertrophy, IGF-1 mRNA expression was significantly increased in T treated animals. After coronary artery ligation, infarct size and mortality were similar among the groups. Left ventricular hypertrophy was enhanced by T treatment. However, in vivo LV end-diastolic pressure and wall stress were decreased by T, whereas other hemodynamic parameters (mean arterial pressure, cardiac output, etc.) remained unchanged. Conclusion: Chronic anabolic T treatment led to a specific "physiologic" pattern of myocardial hypertrophy with a significant increase in LV weight, but without differences in ANP and with an upregulation in \(\alpha/\beta\)-MHC, possibly mediated by IGF-1. Testosterone treatment had no detrimental effects following MI. Reduced wall stress and LVEDP may even improve long-term outcome.

Keywords: Heart failure; Hormones; Hypertrophy; Infarction; Remodeling

1. Introduction

In recent years, several reports have suggested an association of androgenic-anabolic steroid (AAS) use and detrimental cardiovascular effects both in animals and in power athletes (for review, see Ref. [1]). However, studies in humans are mostly case reports or lack adequate control groups [1]. They often do not account for important variables such as age, genetic predisposition, type of exercise, and—most importantly—steroid type and steroid dose (e.g., "stacking"). AASs are a heterogeneous group of substances with a variety of actions depending on their metabolic fate (e.g., aromatization, 5a-reduction) [2] and their interaction with non-androgen receptors and other targets [3]. Due to their clandestine use, their clinical pharmacology is not well understood.

In contrast, male gender appears to be associated with a more favorable outcome following myocardial infarction. Although female gender increases the probability to reach...
the hospital after acute MI, during hospitalization higher rates of death have been found in women younger than 75 years of age compared to men of the same age [4]. Moreover, 2-year mortality after MI was also reported to be higher in women than in men [5]. Gender differences in long-term mortality after MI may be related to gender differences in cardiac remodeling [6] and differences in circulating sex steroids may be of major importance for these findings. Thus one might speculate that higher endogenous androgen levels contribute to a more favorable long-term prognosis after MI in men. Indeed, there is evidence that natural androgens have a neutral or even favorable effect on cardiovascular disease. For example, in the Rancho Bernardo study baseline testosterone (T) was not associated with subsequent cardiovascular mortality in elderly men [7]. Even more, there is some evidence for an association of low T and cardiovascular disease in men [8]. However, the influence of testosterone on progressive ventricular remodeling following myocardial infarction remains to be determined. Therefore, we evaluated the influence of T treatment on left ventricular remodeling following experimental myocardial infarction in male rats, as assessed by magnetic resonance imaging and in vivo hemodynamics.

2. Methods

2.1. Animals, orchiectomy and testosterone administration

All procedures conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. Male Wistar rats weighing 180 to 200 g underwent orchiectomy (ORX) or sham operation. T undecanoate was injected bilaterally deep into the musculi glutaei medii (500 mg/kg body weight every 4 weeks).

Rats were randomly assigned to one of three subgroups: ORX, non-ORX, and non-ORX and testosterone undecanoate.

2.2. Experimental MI

Two weeks after ORX or non-ORX, MI or sham operations were performed in each group. Thus, together, six experimental groups were studied: (1) non-ORX sham operated (non-ORX+sham, n=8); (2) non-ORX infarcted (non-ORX+MI, n=9); (3) ORX sham operated (ORX+ sham, n=15); (4) ORX infarcted (ORX+MI, n=9); (5) non-ORX, T treated sham operated (non-ORX+T+sham, n=15); and (6) non-ORX, T treated infarcted rats (non-ORX+T+MI, n=9) (Fig. 1). Left coronary artery ligation was induced by a previously described technique [9]. Sham operation was performed using an identical procedure, except that the suture was passed under the coronary artery without ligation. Mortality rate of infarcted rats within first 24 h after the operation was 40 to 50%.

2.3. Magnetic resonance imaging (MRI) measurements and data analysis

MRI experiments were performed on a 7.05 Tesla BIOSPEC 70/21 (Bruker, Germany) under inhalation anesthesia applied by nose cone (isoflurane 1.5%, v/v, supplemented by 0.5 l oxygen per minute). An ECG-triggered fast gradient echo sequence (FLASH) was used with the following parameters: flip angle 30 to 40°, echo time 1.1 ms, repetition time (TR) 3.2 ms, in plane resolution 390 μm and slice thickness 1 mm.

Data analysis was performed as described before [10]. Myocardial infarct size was determined for every slice as the myocardial portion with significant thinning and akinesia or dyskinesia during systole. Diastolic function was assessed by calculation of peak filling rate. In the midventricular slice, all 12 time frames were segmented and the difference between imaging frames calculated. The maximum increase of slice volume during diastolic filling was used for comparison between groups. LV end-diastolic pressure (LVEDP) was used for calculation of global LV wall stress \( WS = 1.33 \times 10^{-3} \times LVEDP \times \frac{216.9+(EDV/MV)}{} \); MV is end-diastolic myocardial volume, 1.33 is a converting factor for mmHg into N/
2.4. In vivo hemodynamics measurements

Eight weeks after left coronary artery ligation or sham operation, hemodynamic measurements were performed as described previously [11]. Left ventricular systolic and end-diastolic pressures (LVSP, LVEDP), mean arterial pressure (MAP) and heart rate (HR) were measured under light ether anesthesia and spontaneous respiration.

2.5. Immunoassays

After 10 weeks, serum T was measured by a commercially available RIA (Diagnostic Products Corporation, USA) with a sensitivity of 0.06 ng/ml. The intra- and inter-assay variabilities ranged between 6–15% and 9–16%, respectively. 17β-estradiol was also measured by a commercially available RIA (Diagnostic Products Corporation) with a lower detection limit of 3.5 pg/ml.

2.6. Northern blot of atrial natriuretic peptide (ANP) and IGF

RNA was isolated and Northern blots were performed as previously described [12]. The ANP probe was a gift of C. Seidman (Boston, MA, USA), the IGF probe was a gift of L. Tsao (Boston, MA, USA).

2.7. Western blot

For Western blots, tissue was lysed in RIPA buffer. Membranes were incubated with a phospho-Akt (Ser473, Cell Signaling, Beverly, MA, USA) antibody overnight, followed by washing and incubation with a matching secondary antibody and autoradiographed. The same membranes were stripped and incubated with an Akt antibody (Cell Signaling) accordingly.

2.8. Quantitative assessment of myocardial collagen

Quantitative myocardial collagen assessment was performed with picrosirius red staining and polarized light as described by Whittaker et al. [13]. Shortly, serial 3 μm sections of the interventricular septum from six rat hearts/group were taken. Sections were examined on a Leitz (Laborlux S) microscope (Leitz, Wetzlar, Germany) using either brightfield or polarized light. Images were analyzed using ScionImage Release 4b (Scion Corporation, USA).

2.9. Myosin heavy chain (MHC) protein electrophoresis

Protein for myosin heavy chain electrophoresis was prepared from frozen rat left ventricular tissue. A 40-mg amount of tissue was homogenized in 400 μl of ice-cold sample buffer with protease inhibitors (protease inhibitor cocktail, Roche®). Homogenized tissue was centrifuged for 30 min at 15 000 g, at +4°C. The supernatant was discarded and used for further procedures. A 0.5-μg amount of protein was electrophoretically separated under reducing conditions (Laemmli Sample buffer, Bio-Rad) with 5% β-mercaptoethanol; 6% separation gel with 5% glycerol; 8.7 V/cm for 18 h. The gels were silver stained (Silver Stain Plus kit, Bio-Rad), scanned, and analyzed using ScanPacK 3.0 software.

2.10. Statistical analysis

All data were expressed as mean±standard error of the mean (S.E.M.). Calculations were performed as previously described [14]. For multiple comparisons analysis of variance (ANOVA) was used, followed by Scheffe’s corrections. Statistical significance was achieved if two-tailed P values were less than 0.05. Mortality was calculated by Chi-square statistics.

3. Results

3.1. Baseline characteristics

As intended, T serum levels were supraphysiological after T treatment and below the lower limit of detection after ORX (T vs. placebo, 12.9±1.7 vs. 2.9±0.9 ng/ml, P<0.001). In sham operated and T treated animals no major side effects were observed although T treated animals seemed to be more aggressive. T treatment for 10 weeks significantly reduced body weight, an effect similar to the weight loss seen in estrogen treated female rats. However, skeletal muscle and LV mass increased significantly as measured by MRI (see Figs. 2 and 3 and Table 1). The hormonal status had no influence on LV function and in vivo hemodynamic data (ejection fraction, cardiac output, MAP, LVEDP) (see Table 2).

LV hypertrophy is usually associated with an increase of ANP and a down regulation of the α/β-MHC ratio through an upregulation of β-MHC. However, LV hypertrophy due to T treatment was not accompanied by an increase in ANP mRNA expression and β-MHC, but by an upregulation of the α/β-MHC ratio. This was due to a dose dependent increase in α-MHC by T (Fig. 4). Furthermore, T treatment induced IGF-1 mRNA expression about fivefold in the myocardium when compared to placebo treated animals (see Fig. 5A). Also Akt, a downstream target of IGF, was activated about twofold as demonstrated by its phosphorylation at Ser473 (see Fig. 5B). Collagen
fractional area remained unchanged (non-ORX+sham vs. non-ORX+T+sham vs. ORX+sham, 8.0±4% vs. 7.0±3% vs. 8.9±4%, P=n.s.).

3.2. Characteristics after chronic myocardial infarction

Mean infarct size was 39±2% on average and was not different among groups (see Table 1). Mortality was not significantly different among groups (non-ORX+T+MI vs. non-ORX+MI vs. ORX+MI, 0.53 vs. 0.57 vs. 0.51). As for the sham animals, T treatment significantly decreased the body weight. However, diuretic effects of T treatment could be excluded (sodium, potassium, chloride, and osmolality were not different between the groups). LV
weeks after MI ejection fraction, cardiac output, and mean arterial pressure were reduced in all groups to the same extent when compared to sham operated controls. However, LVEDP was reduced in T treated animals (non-ORX+T+MI vs. non-ORX+MI, 14±3 vs. 26±2 mmHg, P<0.02), but invasive dP/dt max (week 8 post MI, MI+ORX vs. non-ORX+MI vs. non-ORX+T+MI, 7422±643, 6400±529, 7314±812 mmHg/s) was not significantly affected by hormonal status. Furthermore, diastolic wall stress was significantly lower in T treated animals (non-ORX+T+MI vs. non-ORX+MI, 41.4±8.8 vs. 67.1±9.7 N/cm², P<0.05), whereas diastolic peak filling (−dV/dt) as measured by MRI showed no significant difference between treatment groups (ORX+MI 487±69 µl/s, non-ORX+MI 425±94 µl/s, non-ORX+T+MI 562±100 µl/s, P=n.s.).

Myocardial infarction increased ANP and β-MHC, as expected. However, as for the sham animals the characteristic molecular changes of hypertrophy (MHC ratio or ANP; see Fig. 4) were not different between the groups despite clear hypertrophy in the T group. Again, T treatment led to a non-significant dose dependent increase in α-MHC. No differences in the collagen content of the remodeling myocardium were detected (non-ORX vs. non-ORX+T vs. ORX, 16.8±8% vs. 16.6±5% vs. 19.0±11%, P=n.s.).

4. Discussion

Not only is there an increase in the therapy with AASs in younger men with chronic disease over the last years [15], but also in the use of testosterone T in elderly males with an age-related decline in endogenous T secretion ("male menopause") [16]. However, it is still an unsettled matter, whether this decline represents a true hormonal deficiency or a physiological adaptation. T supplementation is, therefore, rather a pharmacological interven-

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**Table 1**

Animal characteristics and hormone determination

<table>
<thead>
<tr>
<th></th>
<th>ORX+ MI</th>
<th>ORX+ T+ MI</th>
<th>Non-ORX+ T+ MI</th>
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<th>Non-ORX+ MI</th>
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<td>15</td>
<td>8</td>
<td>15</td>
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<td>MI size (%)</td>
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<td>BW (g)</td>
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<td>402±11¹</td>
<td>438±23</td>
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<td>EF (%)</td>
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<td>CO (ml/min)</td>
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<td>139.6±5</td>
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<td>HW/BW</td>
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<td>3.38</td>
<td>4.34¹</td>
<td>4.78¹‡</td>
<td>4.74¹‡</td>
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<td>∆LV mass (mg)</td>
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<td>+132±21</td>
<td>+164±24¹</td>
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<td>+171±44</td>
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<td>17β-E2 (pg/ml)</td>
<td>&lt;3.5⁵</td>
<td>&lt;3.5</td>
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<tr>
<td>T (ng/ml)</td>
<td>&lt;0.01¹</td>
<td>3.2±0.8</td>
<td>23.7±3.7⁷</td>
<td>&lt;0.01¹</td>
<td>1.8±0.1</td>
<td>21.6±3.1*</td>
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*P<0.02 MI/Plac vs. MI/Test; †P<0.04 S/Plac vs. S/Test; †P<0.0001 S/ORX vs. S/Test; †P<0.0001 MI/ORX vs. MI/Test; †P<0.05 MI/Plac vs. MI/Orx; †P<0.05 sham vs. MI.

MI size=Assessed by MRI; HW=heart weight (measured by scale); BW=body weight 10 weeks after treatment randomization; ∆LV mass=assessed by MRI (difference week 10 and 2); ∆EDV=increase in end-diastolic volume assessed by MRI (difference week 10 and 2); T=testosterone serum levels, 17β-E2=17b-estradiol.
Table 2

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<th>In vivo hemodynamics</th>
<th>ORX+ sham</th>
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<th>Non-ORX+T+ sham</th>
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<td>312±14</td>
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<td>LVSP (mmHg)</td>
<td>147±5</td>
<td>142±6</td>
<td>136±2</td>
<td>126±4</td>
<td>121±3</td>
<td>132±9</td>
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<tr>
<td>LVEDP (mmHg)</td>
<td>9±1</td>
<td>8±2</td>
<td>8±1</td>
<td>21±3</td>
<td>26±2*</td>
<td>14±3*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>131±4</td>
<td>127±5</td>
<td>119±3</td>
<td>102±6</td>
<td>104±5</td>
<td>119±5</td>
</tr>
</tbody>
</table>

*P<0.02 MI/Plac vs. MI/Test; †P<0.0001 S/Plac vs. MI/Plac; ‡P<0.01 S/ORX vs.MI/ORX.

EDP=End-diastolic pressure; LV=left ventricular; MAP=mean aortic pressure; SP=systolic pressure.

4.1. Testosterone-induced ventricular hypertrophy

In both sham animals and infarcted animals T induced cardiac hypertrophy without changes in ANP mRNA. However, T treatment favored the expression of α-MHC and not of β-MHC as usually expected under conditions of pathological cardiac hypertrophy. Thus T-induced hypertrophy is associated with a more “physiologic” phenotype than the substitution of a true deficit. Safety issues of androgen administration are thus of growing importance. This concerns in particular cardiovascular effects of T, as coronary heart disease is highly prevalent in elderly males. Therefore, we have analyzed the effects of T under baseline conditions and in the clinically most relevant experimental heart failure model, the rat coronary artery ligation model.

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Although not tested in our study, these effects are most likely the result of direct steroid hormone action on cardiac myocytes. Androgen receptors in the heart have been described for several species including rats and humans [17] and are known to mediate hypertrophy in cardiac myocytes [18]. However, despite a clear hypertrophic response, as assessed by [3H]phenylalanin incorporation, T did not increase ANP secretion in neonatal rat ventricular myocytes in vitro in accordance with our results. Furthermore, previous studies have also demonstrated that castration favors the expression of the β-MHC form, whereas T enhances the expression of α-MHC mRNA [19]. This regulation was independent of hemodynamic load or cardiac hypertrophy in stroke-prone spontaneous hypertensive rats [20]. Thus, the observed changes in myosin heavy chain expression (MHC) are most likely the consequence of direct androgen effects on cardiac myocytes. Moreover, as in our study, androgen-induced cardiac hypertrophy using nandrolone decanoate did not change cardiac collagen content [21]. Administration of this androgenic steroid in high doses—alone or in combination with exercise—was not associated with alterations in either the quantity or the quality of left ventricular collagen. However, it was associated with an increase of end diastolic stiffness, an effect that we did not observe. As discussed below, these differences might be due to the dose regimens used or due to the different metabolism of testosterone, e.g., estradiol generation due to aromatase activity.

What could the mechanism for this kind of hypertrophy without pathological hypertrophy markers or collagen accumulation be? Although not formally tested, the explanation may be related to the dose-dependent T-induced increase in IGF-1 mRNA expression and the activation of its downstream targets like Akt. IGF-1 but not growth hormone is known to activate a hypertrophic response in neonatal myocardial cells [22]. Moreover, IGF-1 mRNA levels and protein content are increased after induction of hypertension in the rat suggesting that IGF-1 may be involved in mediating left ventricular hypertrophy. Further, it has been demonstrated that IGF-1 administration enhances ventricular hypertrophy and function during the onset of experimental cardiac failure in rats [23]. More-
Fig. 5. Expression of IGF-1 and Akt following treatment with testosterone. Male rats were treated for 10 weeks with either placebo (PLAC) or testosterone (TUD) or underwent orchiectomy (ORX). Cumulative data from independent experiments are shown (* $P \leq 0.05$, ** $P \leq 0.001$, vs. TUD). (A) TUD treatment increased myocardial IGF expression about fivefold ($n=10$). Data have been normalized to GAPDH mRNA content (arbitrary units). (B) Also, there is an about twofold activation of Akt visualized by phosphorylation of Akt at Ser473. Data have been normalized to total Akt. Akt is an important downstream target of IGF.

Over, cardiac specific overexpression of IGF can rescue tropomodulin overexpressing transgenic mice from the development of a dilated myopathy and premature death [24]. Of note, IGF-1 treatment caused no induction of cardiac collagen synthesis in rats further supporting the concept of a role of local IGF-1 in androgen-induced hypertrophy. To our knowledge induction of cardiac IGF-1 expression and of its downstream targets by T has not been described before. However, it has been shown that androgens are necessary for the local production of IGF-1 within skeletal muscle, as induction of hypogonadism in normal young men results in a reduction in IGF-1 mRNA levels in skeletal muscle [25]. In addition, treatment of hypogonadal elderly men led to an increase in IGF-1 mRNA levels in muscle biopsy specimens [26]. Thus, skeletal muscle and cardiac muscle may respond in a similar fashion to T by increasing local IGF-1 production.

4.2. Testosterone and myocardial infarction

We found no evidence for cardiac toxicity of T administration despite a 10-fold increase in T levels after testosterone undecanoate administration compared to placebo administration. Neither infarct size nor procedure-related mortality was influenced by T status. In contrast, there was a tendency to an improved hemodynamic outcome: LVEDP was significantly reduced in T treated animals together with wall stress without differences in diastolic filling rates following MI.

These findings may seem to be somehow contradictory to the notion that the use of AASs is associated with significant cardiac toxicity in athletes and in experimental animals. In vitro direct cardiac toxicity has been described for a variety of AAS using ventricular myocytes [27]. Toxicity varied widely between different agents. T esters were especially more toxic than T itself (e.g., T enanthate and T cypionate) [28]. However, since, in practice, T esters act as depot preparations from which T is gradually released, these findings have little bearing on the clinical pharmacology of androgens. Moreover, toxic effects observed in vitro required steroid concentrations several orders of magnitude above those used in our study or for treatment of chronic disease in humans.

The cardiovascular risk of AAS in humans is difficult to assess due to their clandestine use. It is largely based on case reports [1]. High doses of a variety of substances are often used as part of “stacking” protocols with unpredictable toxicity. In contrast, no adverse cardiovascular effects were observed in randomized trials using supraphysiological T doses [29]. Furthermore, in support of our findings, van Kesteren et al. [30] investigated mortality and morbidity in transsexual subjects treated with cross-sex hor-
mones. No serious morbidity was observed which could be related to androgen treatment in female-to-male transsexuals. However, it has to be kept in mind that cardiovascular effects were not analyzed in detail in these studies.

4.3. Study limitations

This study has several limitations. First, we did not assess other possible aspects of T side effects such as changes in thrombogenic activity or lipid changes that may negatively affect long-term survival after MI. Secondly, although the evidence of an IGF-1 mediated hypertrophy by androgen treatment is intriguing, this was not formally proven. Other, so far undiscovered relevant pathways related to testosterone might exist. For example, T is known to reduce the release of TNF (tumor necrosis factor) [31], a factor that seems to be related to disease progression in heart failure [32]. Furthermore, T is necessary for the expression of the angiotensin receptor [33], again a protein that is related to the development of heart failure. Other potential mediators regulated by T and of importance in the pathophysiology of heart failure include TGF-β (transforming growth factor) [34] and VEGF (vascular endothelial growth factor) [35]. Thirdly, T can be aromatized to estrogens. In our study, anabolic T administration led to a concomitant increase in estradiol generation due to aromatase activity in peripheral tissues including the heart itself. Thus, the effect of T administration on the heart may be a consequence of combined estrogen and androgenic activity.

In summary, chronic anabolic T treatment had no detrimental effects following MI. This treatment led to specific pattern of myocardial hypertrophy with a significant increase in LV weight, but without an increase in ANP mRNA and without decreasing α/β-MHC, possibly mediated by local IGF-1. This may indicate a physiological form of hypertrophy, with potential long-term improvement in cardiac function, in contrast to hypertrophy as an unfavorable component of pathological remodeling.

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References


