REVIEW

The influence of testosterone upon vascular reactivity

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Abstract

Recent clinical studies have reported that testosterone therapy reduces myocardial ischaemia in men with coronary artery disease, and the beneficial modulation of coronary vascular tone by testosterone has been proposed as an effector mechanism. Maintenance of a correct response to vasoconstrictive and vasodilatory agents is essential in the control of vascular tone. Endothelial dysfunction, most commonly manifested through an elevation in vascular tone, is implicated as an initiating factor in conditions such as hypertension and atherosclerosis. Increased sensitivity to vasoconstrictive stimuli is also proposed in the development of heart failure and hypertensive vascular remodelling, while increased coronary vascular reactivity to vasoconstrictive factors is likely further to restrict coronary blood flow through the partially occluded atherosclerotic vessel. Reduced vasodilatation and enhanced vasoconstriction can also lead to vasospasm and exacerbation of anginal symptoms. Testosterone is well known to elicit direct vasodilatation, but its influence upon responses induced by other vasoactive agents is less coherent, and may depend upon the underlying pathogenic process or gender. The aim of this review is to present the data obtained from both the patient and animal studies conducted to date, to ascertain any influence testosterone may have upon the regulation of vascular tone.

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Introduction

The role testosterone plays in the development of cardiovascular disease has increasingly become the subject of current interest (1, 2). Clinical studies consistently report that testosterone therapy, whether administered chronically or acutely, is associated with improvements in myocardial ischaemia in men with coronary artery disease (CAD) (3–6). It has been hypothesised that such improvements in myocardial ischaemia may arise via the beneficial modulation of coronary vascular tone by testosterone (7). Similarly, testosterone replacement therapy in men with chronic heart failure improves exercise duration, heart failure symptoms and quality of life, effects which are independent of an anabolic effect upon the skeletal muscle (8). Since pulmonary and systemic vasodilator drugs are utilised in the treatment of patients with heart failure, these benefits may be due to testosterone exerting a beneficial influence upon systemic and pulmonary vascular tone. Indeed, physiological testosterone therapy has been shown to reduce peripheral vascular resistance in this patient population (9). Epidemiological data support an association between low serum levels of testosterone in elderly men and the presence of aortic and carotid atherosclerosis (10, 11). In addition, an antiatherogenic action of testosterone has been demonstrated in cholesterol-fed animal models (12, 13–15) and in in vitro models of arterial plaque development (16), although aromatisation to 17β-oestradiol is suggested to account for this beneficial action in one (13), but not all (15, 16) studies. While this is a controversial area, such data suggest that testosterone exerts a beneficial influence on the vasculature.

Testosterone induces direct vasodilatation in a variety of vascular beds, an action which is mediated via a non-genomic pathway, independent of the classical nuclear androgen receptor (AR) (reviewed in reference 17). The presence of non-genomic signalling pathways for sex hormones is well recognised (for recent reviews, see references 18 and 19), and testosterone-induced vasodilatation occurs independently of the vascular endothelium and endogenous dilatory mediators, being triggered by modulation of membranous ion channel function (17). However, studies demonstrating an acute vasodilatory action of testosterone upon isolated blood vessels have often been dismissed due to the pharmacological concentration required to induce vasodilatation. There is a clear distinction between the concentration at which testosterone can induce vasodilatation in vivo and in vitro, and also between different in vitro methodologies. Testosterone-mediated
coronary vasodilatation in vivo is reported at concentrations around 100 nM (7, 20), and isolated vessel studies commonly require high (10–100 μM) micromolar concentrations of testosterone to induce vasodilatation (17), while, in isolated cells, vascularly significant alterations in intracellular calcium are observed at low (1 μM) micromolar concentrations (21). Although the first two values are much higher than the normal physiological range (10–30 nM), it is premature simply to discard such observations on this basis. Indeed, the order of potency dependent upon the preparation may be suggestive of the underlying mechanism of action of testosterone, which has a complicated physiology. Unlike most therapeutic agents, endogenous sex hormones such as testosterone are transported in large proportions bound to a designated binding protein, sex hormone-binding globulin (SHBG). The purpose of SHBG is thought to be to maintain the hormone in a biologically inactive state until presentation at the target cell. Upon reaching the target cell, testosterone dissociates from SHBG, and is allowed to enter the target cell, where it is able to bind to the nuclear AR and exert its cellular effects.

The process whereby the intracellular transfer of testosterone occurs, and that of how the target cell identifies itself to the hormone–globulin complex to initiate dissociation, remain unknown. Identification of membrane receptors for SHBG in a variety of cell types has suggested that the hormone–globulin complex, originally thought to be biologically inert, may in fact be able to elicit cellular responses in designated tissues, or that the SHBG receptor might be responsible for the correct orientation of testosterone within the target cell membrane (reviewed in reference 22). Since the direct vasodilatory activity of testosterone is recognised to be independent of the nuclear AR and proposed to occur via modulation of membrane ion channels (17), this is potentially a very significant hypothesis. Indeed, we have recently demonstrated that physiological concentrations of testosterone can inhibit the main α1C subunit of L-type voltage-gated calcium channels when applied directly to the channel (23). Clearly, the mode of presentation of testosterone to the smooth muscle cell would appear to be critical in determining potency. In order to elicit dilatation in an isolated vessel, testosterone must first diffuse to the vessel surface and then permeate into a large enough number of smooth muscle cells within the vessel to produce a significant response. If SHBG is involved in the presentation of testosterone to the effector proteins within the target cell membrane, the absence of endogenous SHBG in such experiments may explain the marked loss of potency compared with in vivo vascular biology studies.

Another confounding issue between in vivo and in vitro experimentation is the loss of physiological interaction between the endothelial and smooth muscle cell layers (or in the case of denuded vessels the absence of the vascular endothelium per se). In isolated vessel experiments, administration of a precontractile agent is required, often in high concentrations, to induce enough tone from which to measure significant vasodilatation. In contrast, in the in vivo situation, vascular tone is maintained by the balance between endogenous endothelial-derived vasoconstrictive and vasodilatory agents, the release of which is controlled by a plethora of factors such as blood pressure and flow, as well the local tissue oxygen concentration and temperature. The interaction between testosterone and endogenous vasoactive agents is controversial. While endogenous dilatory prostanooids are recognised not to mediate the direct vasodilatory action of testosterone, recent evidence suggests that if the synthesis of prostanooids by cyclooxygenase is blocked, a vasodilatory action is unearthing at physiological concentrations (24). Such observations are consistent with endogenous contractile prostanooids suppressing this direct vasodilatory action of testosterone, and suggest that interaction between testosterone and endogenous vasoactive pathways may play an important role in the regulation of vascular tone.

With these two hypotheses in mind, the role testosterone plays in both the vascular responses induced by other vasoactive agents, and the effect of in vivo administration of testosterone upon vascular reactivity, are likely to be the most relevant to the clinical situation. The aim of the present review is to present and discuss the findings of the studies conducted in these areas, to highlight the role testosterone may play in the regulation of vascular tone.

**Effect of testosterone therapy upon vascular reactivity in man**

While administration of testosterone directly to isolated blood vessels is recognised to elicit vasodilatation (17), the influence of exposure to testosterone upon responses induced by other vasoactive agents has been less closely examined. However, in contrast to investigation into the acute vasodilatory mechanism of action of testosterone, where human studies have yet to be undertaken, a number of patient-based studies have investigated the influence of testosterone therapy upon vascular reactivity in man. Such studies have commonly employed Doppler ultrasound to monitor changes in brachial artery diameter in response to an increase in blood flow following release of a blood-pressure cuff inflated over the forearm, or in response to nitrate administration. Brachial artery reactivity has been established as an accurate and reproducible measurement of endothelial function (25), which correlates closely with endothelial-dependent coronary and peripheral arterial responses (26). The effect of testosterone upon human vascular reactivity is a
complex issue, and may be dependent upon the underlying androgen and/or disease status (Table 1).

**Observations in men with coronary artery disease (CAD)**

Ong et al. (27) recently employed Doppler ultrasound methodology to study the effects of acute exposure to both high-dose and physiological concentrations of testosterone upon flow-mediated brachial artery vasodilatation, in men with CAD. Compared with placebo, high-dose testosterone significantly increased the circulating plasma testosterone concentration, and was associated with a dramatic increase in brachial artery vasodilatation (27). However, although the acute exposure to physiological levels of testosterone resulted in a small but significant increase in plasma testosterone, no effect was observed upon vascular reactivity (27). Similarly, direct infusion of physiological concentrations of testosterone into the right coronary artery in men with CAD is reported to increase coronary artery diameter and coronary blood flow consistent with a direct vasodilatory activity, but does not modulate acetylcholine-induced increases in these parameters (7). Both acetylcholine and flow-mediated vasodilatation are endothelial dependent, arising as a result of increased nitric oxide (NO) release from the endothelial cells. These data therefore suggest that testosterone is able to upregulate endothelial dependent acetylcholine vasodilatation only at high concentrations. However, the lack of an observed effect at physiological doses may simply be due to the acute nature of these studies.

Indeed, a similar study was subsequently undertaken which produced almost identical findings (28). Kang et al. (28) assessed the effect of a 12-week course of oral testosterone upon brachial artery vasodilatation induced both by increasing forearm blood flow, and by sublingual nitroglycerin, in men with CAD. Compared with placebo, testosterone therapy resulted in a marked increase in both flow- and nitroglycerin-mediated brachial artery vasodilatation, although the plasma levels of free testosterone remained within the physiological range following testosterone therapy. This beneficial effect following longer term exposure to physiological concentrations of testosterone is significant, since it was not observed following acute exposure to similar concentrations in the previous studies (7, 27), and correlates with improvements in myocardial ischaemia following a similar 3-month physiological testosterone replacement regimen, in men with CAD (15). This discrepancy is likely to be a consequence of an insufficient length of exposure to testosterone in the acute studies. Since nitrate-mediated vasodilatation is endothelium-independent, being triggered by NO donation following nitroglycerin degradation, the study of Kang et al. (28) demonstrating a beneficial effect upon both flow- and nitrate-mediated vasodilatation suggests that this modulatory action may actually be intrinsic to the vascular smooth muscle, rather than the upstream signalling pathways of the endothelial cells.

Subcutaneous physiological testosterone therapy has also been shown to increase both flow-mediated and glycerol trinitrate-induced brachial artery vasodilatation levels in women already receiving long-term oestrogen replacement therapy (29). However, the issue of testosterone therapy in women is contentious since it has been demonstrated to increase atherosclerotic burden in female cholesterol-fed animal models (30). Indeed, female to male transsexuals taking high-dose androgens

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**Table 1** Summary of studies investigating the influence of testosterone upon vascular reactivity in man.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Status</th>
<th>Testosterone administration</th>
<th>Vascular assessment</th>
<th>Effect</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>CAD Chronic</td>
<td>i.v. testosterone</td>
<td>High dose physiological</td>
<td>FMD</td>
<td>Ong et al. (27)</td>
</tr>
<tr>
<td>Male</td>
<td>CAD Acute</td>
<td>i.v. testosterone</td>
<td>Physiological</td>
<td>FMD</td>
<td>Kang et al. (28)</td>
</tr>
<tr>
<td>Female</td>
<td>HRT Chronic</td>
<td>s.c. testosterone</td>
<td>Physiological</td>
<td>FMD</td>
<td>Worboys et al. (29)</td>
</tr>
<tr>
<td>Female</td>
<td>TS Chronic</td>
<td>s.c. testosterone or i.m. TE</td>
<td>High Dose</td>
<td>FMD</td>
<td>McCredie et al. (31)</td>
</tr>
<tr>
<td>Male</td>
<td>HG Chronic</td>
<td>Transdermal DHT</td>
<td>Physiological</td>
<td>FMD</td>
<td>Ly et al. (32)</td>
</tr>
<tr>
<td>Male</td>
<td>HG Chronic</td>
<td>Transdermal testosterone</td>
<td>Physiological</td>
<td>FMD</td>
<td>Kenny et al. (33)</td>
</tr>
<tr>
<td>Male</td>
<td>HG Chronic</td>
<td>i.m. TE</td>
<td>Physiological</td>
<td>FMD</td>
<td>Zitzmann et al. (34)</td>
</tr>
<tr>
<td>Male</td>
<td>HG Chronic</td>
<td>s.c. testosterone</td>
<td>Physiological</td>
<td>FMD</td>
<td>Sader et al. (37)</td>
</tr>
</tbody>
</table>

are reported to exhibit impaired nitrate-mediated, but not flow-mediated, brachial arterial vasodilatation (31). However, in males with CAD, testosterone therapy would appear to be associated with potentially beneficial improvements in vasodilatory responses, an observation which is in agreement with the improvements in myocardial ischaemia after testosterone therapy in such individuals.

**Observations in hypogonadal men without vascular disease**

In contrast, clinical studies conducted in hypogonadal men demonstrate a neutral influence of testosterone replacement upon vascular reactivity. Ly et al. (32) initially reported that 3 months of transdermal dihydro-testosterone therapy has no effect upon either flow- or nitrate-mediated brachial artery vasodilatation in hypogonadal men. Similarly, Kenny et al. (33) reported that while 12 months of physiological testosterone replacement had beneficial effects upon the circulating lipid profile in elderly men with low levels of bioavailable testosterone, no change was observed in flow-mediated brachial artery reactivity. However, the low number of patients in the study, and the fact that the number of these patients who actually underwent vascular assessment was significantly lower than those in which lipid levels were measured, may mean that the study was not sufficiently powered to detect any changes in vascular reactivity. In a more thorough study, Zitzmann et al. (34) report that hypogonadal men have increased flow- and nitrate-induced brachial artery vasodilatation compared with a carefully selected control group. While enhanced flow-mediated brachial arterial vasoreactivity in hypogonadal men was not reported in the study of Kenny et al. (33), flow-mediated, but not nitrate-mediated, brachial artery vasodilatation is reported to be increased in men in whom testosterone levels have been therapeutically or surgically lowered, as a treatment for prostate carcinoma (35). Similarly, increased dilatory responses to acetylcholine, but not nitroglycerin, are reported in thoracic aortae from castrated compared with control male rats (36).

Zitzmann et al. (34) report that following 3 months of intramuscular androgen replacement therapy the elevated flow-mediated brachial artery vasodilatation was restored to control levels, although vasodilatation induced by glycerol trinitrate was unaffected. Similarly, Sader et al. (37) reported that flow-mediated brachial artery vasodilatation was lower after receiving a 6-monthly testosterone depot preparation than in the pre-depot (trough) measurement. However, the outcome of this latter study should be interpreted with caution, since the study was not placebo-controlled, it was undertaken in only nine individuals, and there was considerable variation in time following testosterone treatment at which measurements were taken (between 2 and 4 weeks). Furthermore, the observed effect was modest, with no alteration being observed in nitrate-mediated vasodilatation. Taken together, such data suggest that, in hypogonadal men, testosterone deficiency is associated with an upregulation of the endothelial-dependent vasodilatory signalling pathways, which are downregulated once the circulating testosterone profile is restored to within the normal range.

Clearly, it would appear that discrepancies exist between the influence of testosterone in men with cardiovascular disease, where an improvement in vasodilation is observed, and in hypogonadal men, where the influence would appear to be essentially neutral. Although one study reports that testosterone therapy is associated with a clear reduction in vasodilatation in hypogonadal men (34), it must be noted that this merely represents restoration of vascular responsiveness from an elevated state to basal levels, rather than the loss of sensitivity to vasodilatory stimuli. A positive influence upon vascular reactivity may therefore be observed only when vascular reactivity is sufficiently impaired, as is the case in atherosclerotic vessels. Indeed, most of the studies of testosterone therapy in hypogonadal men included only relatively healthy individuals, with the presence of vascular or atherosclerotic disease being an exclusion criterion (32, 34, 35). Consequently, these studies may therefore have unknowingly excluded the patient population in which an effect would be observed. Furthermore, this patient cohort: males with CAD and associated low serum levels of testosterone, is the population in which testosterone replacement therapy may be clinically advantageous, and is the very population in which effects upon vascular reactivity should be investigated.

**Involvement of endogenous hormone receptors**

A number of observations from these studies may be suggestive of the involvement of endogenous (o)estrogen receptors (ERs) or the AR in the action of testosterone. Testosterone is readily converted into 17β-oestradiol by aromatase, which is expressed in vascular tissue (38, 39), and 17β-oestradiol is known to improve vascular reactivity in women and men (40, 41). In addition, the observation that physiological testosterone therapy also increases both flow-mediated and glycerol trinitrate-induced brachial artery vasodilatation in women (29) makes such an action a possibility. However, in contrast, the rapidity of the improvement in flow-mediated brachial artery vasodilatation in men following testosterone treatment (27) suggests that this arises as a direct action, rather than following enzymatic conversion to an alternative agent. Similarly, considerable evidence precludes the involvement of 17β-oestradiol in testosterone-induced vasodilatation,
since aromatase inhibition and ER antagonism do not attenuate this response (reviewed in reference 17).

In contrast, the observation that flow-mediated brachial artery vasodilatation is enhanced in hypogonadal men (34), and in men in whom testosterone levels have been therapeutically or surgically lowered (35), may be a consequence of the involvement of the AR in the response. The lower level of endogenous testosterone in these two patient groups may result in upregulation of the AR, through which a beneficial action upon the vascular endothelium may be exerted. In agreement with this hypothesis, castrated male rats exhibit increased endothelial-dependent dilatory responses to acetylcholine (as in castrated/ hypogonadal men) (36), while testosterone deficiency combined with a mutated, non-functional AR in the testicular feminised mouse is associated with reduced endothelial-dependent vasodilatation (42).

However, since no studies have directly investigated these hypotheses, such actions involving the ER or AR remain purely speculative. Clearly, further work is required to determine the influence of these genomic pathways in the mechanism of action of testosterone.

Effect of testosterone therapy upon vascular reactivity in animals

Animal experiments have the advantage over patient studies in that the duration of dosing with testosterone can be more tightly controlled, without the confounding influence of varied concurrent medications or disease states. Furthermore, once the period of exposure to testosterone is completed, vascular reactivity to a variety of vasodilatory and vasoconstrictive agents can be assessed in isolated vessels from a variety of vascular beds. Similarly, the simple addition of testosterone to the organ bath in isolated vessel experiments can be employed to study the effects of acute exposure to testosterone upon vasodilator and vasoconstrictive stimuli. A number of animal studies have employed such methodology to determine the effect of chronic and acute exposure to testosterone upon vascular reactivity (Table 2).

Vasodilator responses

To date, only two studies have investigated the effect of chronic testosterone therapy upon reactivity to vasodilatory agents. Adams et al. (30) demonstrated that 8 months of testosterone therapy increased coronary vasodilatation to acetylcholine, but not nitroglycerin, in vivo, in atherosclerotic female cynomolgus monkeys. Similarly, testosterone therapy is reported by Tatchum-Talom et al. (43) to increase acetylcholine (but not sodium nitroprusside)-mediated femoral arterial vasodilatation in vivo, in female spontaneously hypertensive rats. Both these studies mirror the previous female human studies (29), and are in agreement with the hypothesis that testosterone replacement has a beneficial effect upon the dilatory capability of vessels in cardiovascular disease, although at the level of the vascular endothelium rather than the smooth muscle. However, as discussed previously, these observations should be interpreted with caution since they were restricted to female animals. The lack of experimental data on the effect of chronic testosterone exposure upon vasodilatory responses in male animal models is clearly a significant omission from the current literature.

In contrast, an apparent inhibitory influence upon vasodilatory stimuli is observed in isolated vessels following acute testosterone incubation. Hutchison et al. (44) studied the effect of acute exposure to testosterone upon vasoreactivity to acetylcholine and nitroglycerin in isolated rabbit aortae harvested from three experimental groups: i) animals fed solely on a high-cholesterol (HC) diet, ii) animals fed on a HC diet and exposed to environmental tobacco smoke (HC + ETS), or iii) controls. The vasodilatory response to acetylcholine was reduced by a similar extent in vessels harvested from the two experimental animal groups, indicative of pathological endothelial dysfunction. In conflict with the above hypothesis, Hutchison et al. (44) demonstrated that incubation with physiological concentrations of testosterone further reduced the dilatory efficacy of acetylcholine in the vessels obtained from the HC + ETS group, suggesting a detrimental action of testosterone in atherosclerotic vessels (44). However, testosterone had no inhibitory action in vessels harvested from the HC rabbits, despite these vessels also exhibiting a much higher level of aortic atherosclerosis compared with controls (44). Such intrastudy discrepancies are hard to explain and may be a consequence of the study being conducted in a small number of animals. Furthermore, the inhibitory action of testosterone upon acetylcholine-mediated vasodilatation in the HC + ETS vessels only just reached statistical significance. A larger study therefore may have better addressed these issues. However, acute incubation with physiological concentrations of testosterone is also reported to attenuate endothelial-dependent vasodilatation induced by bradykinin in isolated porcine coronary arteries (45) and by adenosine in rat coronary arteries in vivo (46).

Vasoconstrictor responses

Animal studies conducted in the late 1960s and early 1970s reported alterations in pressor responses to vasoconstrictive stimuli in vivo following androgen treatment (47, 48). More recently, Schror et al. (49) demonstrated that intramuscular testosterone treatment was associated with subsequent increased coronary arterial constriction to the prostaglandin F2α (PGF2α) analogue U46619, in isolated perfused
**Table 2** Summary of studies investigating the influence of testosterone upon vascular reactivity conducted in animal models.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Sex</th>
<th>Testosterone administration</th>
<th>Vascular assessment</th>
<th>Effect</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Modulation of dilatatory stimuli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic cynomolgus monkey</td>
<td>Female</td>
<td>Chronic s.c. injection</td>
<td>Coronary arterial dilatation to ACh nitroglycerin</td>
<td>↑</td>
<td>Adams et al. (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>supraphysiological levels</td>
<td>Femoral arterial dilatation to ACh SNP</td>
<td>↑</td>
<td>Tatchum-Talom et al. (43)</td>
</tr>
<tr>
<td>Spontaneously hypertensive rat</td>
<td>Female</td>
<td>Chronic s.c. injection</td>
<td>Femoral arterial dilatation to ACh SNP</td>
<td>↑</td>
<td>Tatchum-Talom et al. (43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>supraphysiological levels</td>
<td>Dilatation to ACh–control</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td>Isolated rabbit aortae</td>
<td>Male</td>
<td>Acute organ bath incubation</td>
<td>Dilatation to ACh–control</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>physiological levels</td>
<td>Dilatation to SNP–control</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to SNP–HC</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dilatation to NA–control</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to NA–HC</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to NA–HC and ETS</td>
<td>↓</td>
<td>Hutchison et al. (44)</td>
</tr>
<tr>
<td>Isolated porcine coronary artery</td>
<td>?</td>
<td>Acute organ bath incubation</td>
<td>Dilatation to BK</td>
<td>↓</td>
<td>Teoh et al. (45)</td>
</tr>
<tr>
<td>Rat</td>
<td>Male</td>
<td>physiological levels</td>
<td>Coronary arterial dilatation to adenosine</td>
<td>↓</td>
<td>Ceballos et al. (46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Modulation of contractile stimuli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated guinea pig heart</td>
<td>Male</td>
<td>Chronic i.m. injection</td>
<td>Coronary arterial constriction to U46619</td>
<td>↑</td>
<td>Schror et al. (49)</td>
</tr>
<tr>
<td></td>
<td>Male and female</td>
<td>supraphysiological levels</td>
<td>Contraction to PGF(_2)(_a)-female</td>
<td>↑</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to KCl-Female</td>
<td>↑</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to PGF(_2)(_a)-male</td>
<td>↑</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to KCl-male</td>
<td>↓</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to ET-1</td>
<td>↓</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to 5-HT</td>
<td>↓</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to U46619</td>
<td>↓</td>
<td>Farhat et al. (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction to KCl</td>
<td>↓</td>
<td>Perusquia &amp; Villalon (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calcium-dependent contraction</td>
<td>↓</td>
<td>Perusquia &amp; Villalon (52)</td>
</tr>
</tbody>
</table>

i.m.: intramuscular, s.c.: subcutaneous, 5-HT: 5-hydroxytryptamine, ACh: acetylcholine, BK: bradykinin, ET-1: endothelin-1, KCl: potassium chloride, NA: noradrenaline, PGF\(_2\)\(_a\): prostaglandin F\(_2\)\(_a\), SNP: sodium nitroprusside, HC: animals fed a high-cholesterol diet, ETS: animals exposed to environmental tobacco smoke, ↑: improvement, ↓: deterioration, ↔: neutral effect.
guinea pig hearts. Similarly, Farhat et al. (50) reported that 2 weeks of subcutaneous testosterone treatment was associated with an elevation in the vasoconstrictor response to both PGF2α and KCl in isolated porcine coronary arteries obtained from female animals, but only to KCl in vessels from males. Such findings suggest that testosterone therapy is associated with an elevation in vasoconstrictor activity. However, these data were complicated further by the observation that while subcutaneous testosterone therapy was associated with a significant increase in the circulating testosterone level in females, in males serum testosterone fell by 90% after therapy. Consequently, these potentially deleterious changes in vascular reactivity in the male animals in this study (50) actually resulted from a reduced circulating testosterone profile.

An equally confusing picture is observed following acute exposure of isolated vessels to testosterone. Teoh et al. (51) report that acute incubation with physiological concentrations of testosterone is associated with enhanced vasoconstrictor responses to ET-1, 5-HT and U46619, in isolated porcine coronary arteries. Unfortunately, the sex of the animals utilised in this study is unknown, as the tissue was obtained directly from an abattoir. Consequently, it is unknown whether the apparent sex-dependent alteration of contractile vasoreactivity reported by Farhat et al. (50) following chronic modulation of testosterone levels is maintained or reversed following acute exposure. In contrast, a potentially beneficial inhibition of contractile vasoreactivity following exposure to testosterone is reported by other investigators. Perusquia and Villalon (52) report that incubation with testosterone significantly attenuates the contraction of isolated rat thoracic aortae induced by KCl and noradrenaline. Similarly, acute exposure to testosterone is reported to inhibit the increase in intracellular calcium elicited by KCl and PGF2α in isolated smooth muscle cells (21, 53), an action which ultimately triggers contraction.

Summary

Human studies suggest that testosterone replacement is associated with an improvement in vascular reactivity in men with CAD. Both long-term physiological testosterone replacement and acute exposure to higher doses of testosterone are reported to improve endothelial-dependent flow-mediated vasodilatation and endothelial-independent nitrate-mediated vasodilatation in men with CAD (27, 28). This improvement of vasodilatory reactivity in men would appear to be restricted to diseased vessels. A different profile of vasoactivity is observed in hypogonadal men, where enhanced endothelial-dependent vasodilatation is observed (34), which may arise from AR upregulation. This is corrected following testosterone restoration (34). However, animal studies are inconclusive. Chronic exposure to testosterone via supplemental therapy and acute exposure of isolated vessel preparations to testosterone are reported to exert a positive (21, 30, 43, 52, 53) neutral (44) or negative (45) effect (46), which is likely to be a consequence of the diverse models utilised. To date, animal studies have employed varied species (monkey, pig, rabbit, rat and guinea pig), vascular beds (coronary, femoral and aortal), disease states (normal, experimental atherosclerosis and experimental hypertension) and androgen exposures (chronic, acute, physiological and supraphysiological). Importantly, to date, no studies have investigated the influence of long-term physiological testosterone therapy upon vascular reactivity in male (or female) animals. Consequently, further study is warranted into the effects of chronic and acute testosterone exposure upon selected vasoconstrictor and vasodilatory responses in both diseased and non-diseased vessels. Only then will a clearer indication of the true influence of testosterone upon vascular reactivity, and the underlying mechanisms, be obtained.

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References

Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in men with coronary artery disease. 

Testosterone enhances flow-mediated brachial artery reactivity in atherosclerosis in rabbits.

Gender-specific differences of testosterone on atherogenesis in cholesterol-fed rabbits.

Vascular reactivity is impaired in genetic androgen deficiency. 


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