Testosterone, cardiomyopathies, and heart failure: a narrative review

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Testosterone exerts an important regulation of cardiovascular function through genomic and nongenomic pathways. It produces several changes in cardiomyocytes, the main actor of cardiomyopathies, which are characterized by pathological remodeling, eventually leading to heart failure. Testosterone is involved in contractility, in the energy metabolism of myocardial cells, apoptosis, and the remodeling process. In myocarditis, testosterone directly promotes the type of inflammation that leads to fibrosis, and influences viremia with virus localization. At the same time, testosterone exerts cardioprotective effects that have been observed in different studies. There is increasing evidence that low endogenous levels of testosterone have a negative impact in some cardiomyopathies and a protective impact in others. This review focuses on the interrelationships between testosterone and cardiomyopathies and heart failure.

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INTRODUCTION

Testosterone (T) is the principal male sex hormone and is secreted primarily by the testes. Only 1%–2% of testosterone circulates in the blood as free testosterone, and the remaining is bound to proteins including albumin and sex steroid hormone-binding globulin (SHBG). Plasma levels of T vary with circadian rhythm and fluctuate throughout life. Aging is associated with a gradual decline in testosterone levels in men and an increase in circulating SHBG levels. In addition to its anabolic and androgenic effects, testosterone has important effects on the cardiovascular system. The cardiac effects of testosterone are influenced by plasma levels, cellular metabolism, modulation of intracellular pathways, and androgen receptor expression. Androgens exert their physiological effects through a genomic mechanism that is mediated by the androgen receptor, but several possible nongenomic pathways have also been identified (Figure 1). These nongenomic pathways seem to be more rapid than the genomic mechanisms. The nongenomic effects of androgen characteristically involve the rapid induction of conventional second messenger signal transduction cascades, including increases in cytosolic calcium levels and activation of protein kinase A, protein kinase C, and mitogen-activated protein kinase (MAPK).

Several studies have shown that low serum T concentrations are associated with increased cardiovascular risk and mortality. It is not clear whether there is a causative relationship or an indirect association between T concentration and cardiovascular function.

Testosterone replacement therapy (TRT) has been shown to alleviate myocardial ischemia in men with coronary artery disease; increase exercise capacity in men with heart failure; and improve serum glucose levels, hemoglobin A1c (HbA1c) levels, and insulin resistance in men with diabetes and prediabetes. On the other hand, TRT has been linked to prostate cancer, polycythemia, and obstructive sleep apnea, and its long-term effects are unknown.

This review focuses on the interrelationships between testosterone and cardiomyopathies and between testosterone and heart failure.

TESTOSTERONE AND CARDIAC CONTRACTILE FUNCTION

Testosterone influences the cardiovascular system by acting directly on cardiac cells. Cardiomyocytes express receptors for all major sex steroid hormones including testosterone and are thus exposed to their modulatory effects on myocardial cell physiology. Testosterone has an important role in intracellular Ca²⁺ homeostasis. Mediated by the androgen receptor, testosterone activates L-type calcium channels, which increase the intracellular levels of calcium and thus regulate myocardial contractility.

Gonadectomy in adult male rats reduces the contractility of isolated cardiac myocytes, and short-term androgen exposure stimulates the contractility of isolated rat ventricular myocytes. Additionally, in castrated animals, androgen therapy improves coronary blood flow and increases both fractional shortening and peak myocardial oxygen consumption, thereby improving cardiac function.

In an ancillary study of a randomized controlled trial involving men and women with advanced head-and-neck or cervix cancers, the patients were randomly allocated to receive weekly injections of either 100 mg of testosterone enanthate (6 patients, 1 male) or placebo (10 patients) in addition to receiving standard cancer treatment. After 7 weeks of treatment, testosterone improved left ventricular ejection fraction (LVEF: +6.2% ± 4.3%, vs placebo: −1.8% ± 4.3%; P < 0.05) as well as ventricular–vascular coupling.

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monophosphate (cGMP) pathway.
(ROS) generation, apoptosis, genomic and nongenomic mechanisms, testosterone influences several intracellular mechanisms have been identified. Through CARDIOPROTECTIVE MECHANISMS OF TESTOSTERONE
Longitudinal observational studies of prostate cancer patients have shown that androgen ablation, a treatment option for locally advanced and metastatic prostate cancer, is associated with an increased incidence of cardiovascular diseases (CVD).
In addition to increasing the risk of myocardial infarction (MI) and coronary heart disease (CHD), androgen deprivation therapy is also associated with a decrease in left ventricular longitudinal, circumferential, and radial strain measures, as assessed by speckle-tracking echocardiography.
CARDIOPROTECTIVE MECHANISMS OF TESTOSTERONE
Testosterone has been shown to elicit cardioprotective effects, and several intracellular mechanisms have been identified. Through genomic and nongenomic mechanisms, testosterone influences apoptosis, regulates leukocyte migration and reactive oxygen species (ROS) generation, and the nitric oxide (NO) - guanosine 3’,5’-cyclic monophosphate (cGMP) pathway.
Cardioprotection allows myocardial cells to survive severe stress induced by ischemia–reperfusion or other types of metabolic factors by activating specific intracellular signaling factors, including protein kinases, enzymes, and transcription factors. There is a long list of factors and procedures that promote cardioprotection. The best-known protective mechanism of the heart under conditions of hypoxia is ischemic preconditioning, which was first described by Murry et al. in 1986. In a model of ischemia-reperfusion injury, testosterone was shown to preserve cardiomyocytes by activating ATP-sensitive K channels and upregulating cardiac alpha(1)-adrenoceptors. Ischemic preconditioning is well known to reduce the infarct size in young male rats, but both in the aged heart and the female heart, this protective effect is less evident. Additionally, T reduces the expression of caspase-3, a protein critical for apoptosis.
Testosterone induces ROS generation in vascular smooth muscle cells isolated from normotensive and hypertensive rats, and this effect is followed by an increase in nicotinamide adenine dinucleotide phosphate oxidase. Testosterone protects against angiotensin II-induced vascular remodeling and controls superoxide production through the inhibition of the production of nicotinamide adenine dinucleotide phosphate oxidase.
AMP-activated protein kinase (AMPK) is a serine/threonine kinase that has been implicated in cardiomyocyte metabolism and has cardioprotective properties, such as anti-apoptotic and anti-hypertrophic effects. In vitro studies have shown that short-term stimulation of cardiomyocytes with testosterone increases AMPK phosphorylation through calcium/calmodulin-dependent protein kinase type II (CaMKII).
Altieri et al. compared the effects of pretreatment with sex hormones (testosterone and 17β-estradiol) on doxorubicin-induced toxicity in the rat embryonic cardiac cell line H9c2 and neonatal mouse cardiomyocytes. They showed that testosterone exerted protective effects against senescence caused by doxorubicin by modulating telomere-binding factor 2 via the pathway involving the androgen receptor, phosphatidylinositol 3 kinase, protein kinase B (Akt), and nitric oxide synthase 3. In another study on female embryonic heart H9c2 cells, which express a low number of androgen receptors, testosterone was shown to exert protective effects against 2,4-dinitrophenol, an inhibitor of oxidative phosphorylation. The postulated mechanism is the conversion of 2,4-dinitrophenol to metabolites that activate estrogen receptors and upregulate mitochondrial sulfonyleurea receptor 2B intraexonic splice variant (IES SUR2B) expression.
The heart demands a continuous supply of energy to maintain muscle excitation–contraction coupling, and in heart failure, energy is wasted at the cellular level. In a rat model of doxorubicin-induced cardiomyopathy, decreased effectiveness of all energy-producing systems is observed. Combined administration of testosterone and myocardial extract to rats with doxorubicin-induced cardiomyopathy activates energy supply mechanisms.
Normal cardiomyocytes produce ATP mainly via fatty acid oxidation, but energy substrate utilization may change under pathological conditions. Testosterone improves insulin sensitivity and glucose uptake in the heart, which could lead to an increase in ATP production when cardiac output is increased. Testosterone improves mitochondrial function in cardiac cells by regulating the expression of mitochondrial genes. Androgen levels decrease with age, so cardiac cells exhibit fewer mitochondria, resulting in lower energy production efficiency.
TESTOSTERONE IN HEART FAILURE PATIENTS
Low testosterone levels are frequently seen in men with chronic heart failure (HF), and some studies have associated low testosterone levels with increased mortality; however, the current data are conflicting. The testosterone concentration is lower in men with HF of any etiology than that in healthy men and is correlated with the severity of the disease. There are many possible causes of low T levels in heart failure. Testosterone levels could be low because of chronic inflammation. Pro-inflammatory cytokines (tumor necrosis factor-α...
[TNF-α] and interleukin-1β [IL-1β] and IL-6) are known to regulate the hypothalamic–pituitary axis, resulting in reduced testicular production of testosterone. Another mechanism could be an increase in SHBG levels in the presence of inflammation. This increase in SHBG levels leads to increased estrogen production and decreased T activity. The low level of testosterone in heart failure could also be caused by drugs. Spironolactone, which is both an androgen receptor blocker and an aldosterone receptor blocker, decreases 5α-reductase activity via increased clearance of testosterone secondary to augmented liver hydroxylase activity. Studies suggest that the beneficial effects of spironolactone on cardiomyocytes may be reduced by blocking the anti-apoptotic effect of testosterone and that eplerenone should be used instead. Finally, a hemodynamic factor could be involved in the decrease in testosterone levels, as suggested by the fact that mechanical circulatory support in end-stage cardiac failure has been shown to improve the levels of testosterone in circulation.

There are significant differences in the clinical profile, etiology, demographics, comorbidities, and management of heart failure depending on left ventricular ejection fraction. Most studies addressing the issue of testosterone in heart failure have examined patients with systolic dysfunction (Table 1).

Jankowska et al. studied the prevalence and prognosis of deficiencies in total and estimated free testosterone, dehydroepiandrosterone sulfate, and insulin-like growth factor-1 levels in 208 men with chronic heart failure (LVEF < 45%) compared to 366 healthy men. In the heart failure group, the median age was 63 years, 81% of the men had ischemic etiology, the median LVEF was 33%, and 28% of the men had diabetes. Deficiency in the circulating testosterone level was most common in patients aged ≤45 years and those aged >66 years when assessed based on both total T (TT) levels (39% and 27%, respectively) and estimated free testosterone (eFT) levels (62% and 36%, respectively). Deficiencies in dehydroepiandrosterone sulfate (DHEAS) and insulin-like growth factor 1 (IGF-1) levels were observed in all age groups among men with chronic heart failure (CHF). There was a statistically significant decrease in TT, eFT, and DHEAS concentrations in subjects with more severe CHF, as assessed by New York Heart Association (NYHA) class, but there was no relationship between decreases in these levels and LVEF or plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Regarding prognosis, deficiencies in the levels of multiple anabolic hormones correlated with increased mortality ($\chi^2 = 26.12, P < 0.0001$). Normal circulating levels of all anabolic hormones were associated with an 83% 3-year survival rate (95% confidence interval [CI]: 67%–98%). In patients with deficiencies in three anabolic axes, survival was 27% (95% CI: 5%–49%).

The prognostic value of androgen hormone levels (total testosterone, sex hormone-binding globulin, and estimated free testosterone) in chronic heart failure with reduced left ventricular ejection fraction (LVEF ≤ 45% measured by echocardiography) was assessed by Wu et al. in 175 men aged ≥60 years. The mean age was 68.5 ± 5 years, 54.9% of the men had ischemic etiology of CHF, and the median follow-up was 3.46 years. The median level of TT was 20.3 nmol l⁻¹ (25th–75th percentile: 17.0–27.2 nmol l⁻¹), and that of eFT was 0.28 nmol l⁻¹ (25th–75th percentile: 0.21–0.35 nmol l⁻¹). The researchers found a relatively high prevalence of reduced serum concentrations of androgens: the prevalence of TT deficiency was 21.7%, and the prevalence of eFT deficiency was 27.4%. Total testosterone and estimated free testosterone levels were inversely associated with left ventricular ejection fraction and NT-proBNP but not with NYHA class; also, they were not significantly associated with survival after adjustment for clinical variables.

Testosterone was associated not only with mortality but also with the length of hospitalization and readmission rate in 110 men with a left ventricular ejection fraction <45% and NYHA class IV heart failure symptomatology.

The prognostic value of testosterone was demonstrated in 167 Chinese men with CHF who were followed up for at least 3 years. Compared with those with normal testosterone levels, patients with low testosterone levels had more severe cardiac dysfunction, a higher prevalence of ischemic etiology, and more comorbidities. Readmission rates were also higher for patients with low testosterone levels than for patients in the normal testosterone group. Predictors of mortality in multivariable models of Cox proportional hazard analyses were LVEF (hazard ratio [HR]: 0.885, 95% CI: 0.829–0.945, P = 0.0003), free testosterone levels (HR: 6.301, 95% CI: 3.187–12.459, P < 0.0001), and glomerular filtration rate (GFR; HR: 0.967, 95% CI: 0.937–0.998, P = 0.0348).

A prospective observational study of 618 men discharged with decompensated HF showed that all-cause mortality was inversely correlated with the quartile of the total testosterone level. On multivariate analysis, TT was independently associated with mortality (HR: 0.929, P = 0.042). Left ventricular ejection fraction and B-type natriuretic peptide levels were not different among quartiles, but the lowest quartile (TT < 300 ng dL⁻¹) had higher levels of troponin, which is a marker of myocardial injury.

Finally, the study by Güder et al. is noteworthy because it also included patients with heart failure and preserved ejection fraction. Free serum testosterone, DHEAS, and SHBG levels were measured in 191 consecutive men with heart failure (mean age: 64 years), 96 of whom had reduced LVEF (< 40%) and 95 of whom had preserved LVEF (>40%). The median observation period was 859 days. Free serum testosterone levels were inversely related to NYHA class, C-reactive protein levels, and NT-proBNP levels. There was no relationship

Table 1: Studies concerning testosterone relation to prognosis in chronic heart failure

| Study            | Patients | Findings                                                                 |
|------------------|----------|--------------------------------------------------------------------------|
| Jankowska et al. | 208 men  | A low T level in all NYHA classes is a marker of poor prognosis          |
| Güder et al.     | 191 men  | FT, but not TT, levels are inversely associated with NYHA class; lower FT and DHEAS levels and higher SHBG levels predict all-cause mortality risk, but this relationship is confounded by indicators of a poor health state |
| Wu et al.        | 175 older men | TT and eFT levels are decreased and related to disease severity but are not independent predictors of mortality |
| Santos et al.    | 110 hospitalized men | A low T level is an independent risk factor for hospital readmission within 90 days and increased mortality |
| Han et al.       | 167 men  | A low T level is associated with increased readmission rate and mortality |
| Yoshihisa et al. | 618 men dis discharged | A low T level is associated with myocardial damage and lower exercise capacity; the TT level is an independent predictor of all-cause mortality |

DHEAS: dehydroepiandrosterone sulfate; eFT: estimated free testosterone; FT: free testosterone; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SHBG: sex hormone-binding globulin; T: testosterone; TT: total testosterone
between free serum testosterone levels and ejection fraction. Lower free testosterone and DHEAS levels and higher SHBG levels predicted all-cause mortality risk (HR: 0.89, 95% CI: 0.82–0.96 per 1 ng dl⁻¹ free testosterone, \(P = 0.004\); adjusted for age and NYHA class), but this was not confirmed after further adjustments. This study suggests that there is no relationship between testosterone levels and the type of heart failure (systolic or nonsystolic).

Data from epidemiologic studies and clinical trials have suggested that testosterone replacement therapy has beneficial systemic effects in testosterone-deficient men with heart failure. Testosterone replacement therapy in patients with heart failure has promising results in improving functional capacity and quality of life. Two meta-analyses, one including four randomized controlled trials (\(n = 198\); 84% men; mean age: 67 years) and the other including eight trials (\(n = 393\); 96% men; mean age: 65 years), showed that TRT could significantly improve exercise capacity, muscle strength, and electrocardiogram indicators without inducing significant changes in ejection fraction, systolic blood pressure, diastolic blood pressure, NT-proBNP levels, TNF-α levels, high-sensitivity C-reactive protein levels, or IL-6 levels. Another meta-analysis of eight randomized controlled trials including 170 patients in the testosterone supplementation group and 162 in the control group showed that testosterone supplementation within a physiological range was not associated with significantly improved exercise capacity, cardiac function, quality of life, or clinical outcome.

**TESTOSTERONE AND MYOCARDITIS**

Sex hormones play opposing roles in the immune system, with estrogen having stimulatory effects and androgens being immunosuppressive. Androgens decrease B-cell maturation, reduce B-cell synthesis of antibodies (Abs), and suppress auto-Ab production in humans. It is known that autoimmune disorders predominantly affect women and that affected men have lower serum concentrations of androgens. Androgens have immunomodulatory properties, suppressing macrophage production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and increasing the production of anti-inflammatory cytokines (IL-10). In male rats with heart failure, testosterone treatment suppresses ventricular remodeling and improves cardiac function by diminishing the imbalance between IL-10 and TNF-α. In contrast, T promotes the pro-inflammatory Th1 and/or Th17-type immune response that is characteristic of acute myocarditis.

Myocarditis is a form of inflammatory cardiomyopathy that typically develops secondary to viral infection, often in young, healthy men. It is one of the causes of dilated cardiomyopathy (DCM) and heart failure.

Several experimental studies have suggested that testosterone promotes a type of inflammation that may be involved in fibrosis in the setting of myocarditis.

Human data and clinical studies in this context are lacking. In an in vivo study, male and female BALB/c mice were inoculated with various concentrations of coxsackievirus. Lower viral doses induced severe myocarditis in male mice but caused little injury in females. Sex steroid hormones influence viremia and virus localization; in females given exogenous testosterone and progesterone, the amount of virus in the heart is ten times higher than that in animals given estradiol. The hormones may act by increasing viral receptor expression on endothelial cells and myocytes. Testosterone increases Toll-like receptor (TLR4) and IL-1β expression on CD11b⁺GR1⁺F4/80⁺ macrophages and CD11b⁺CD117⁺ mast cells in male BALB/c mice with myocarditis. Gonadectomy reduces CD11b⁺ inflammation and causes a reversal of the Th1 response in males to a Th2 response. Studies suggest that IL-1β produced by TLR4 is critical for the induction of fibrosis, which leads to DCM.

Serum-soluble interleukin-1 receptor-like 1 (ST2) is a marker of heart failure. Elevated levels predict acute and chronic heart failure mortality regardless of cause. Soluble ST2 (sST2) levels are elevated in young men with myocarditis and correlate with NYHA class III–IV heart failure. Additionally, in several studies, sST2 levels were found to be significantly elevated in healthy men compared with healthy women. In mice with myocarditis, testosterone, but not estradiol, increases sST2 levels. The soluble form of ST2 can promote myocardial damage by binding to IL-33 and blocking the cardioprotective effects generated by the interaction between IL-33 and the transmembrane ST2 ligand.

Testosterone increases the expression of genes associated with cardiac remodeling during acute coxsackievirus B3-induced myocarditis, including tissue inhibitor of metalloproteinases-1 (TIMP-1), serpin A 3n, IL-1β, and neutrophil collagenase (MMP-8). The regulation of IL-1β and serpin A 3n by testosterone in the heart plays a major role in the progression from myocarditis to DCM in males. Serpin A 3n is elevated not only in myocarditis but also in the heart of patients with DCM.

**TESTOSTERONE IN DILATED CARDIOMYOPATHY**

Several studies have shown that the incidence rate of DCM is higher in men than that in women. Women with DCM have better survival than men, which may partly be due to less severe left ventricular dysfunction and a smaller scar burden. The exact reason for this gender-specific discrepancy has yet to be elucidated.

In heart failure studies, female gender has been associated with better cardiac function and survival. In the aging female heart, hypertrophy, apoptosis, and fibrosis are less pronounced than in the aging male heart. Higher testosterone levels in women with polycystic ovary syndrome are associated with cardiovascular and metabolic diseases. Additionally, women with cardiovascular disease have higher levels of free androgen than controls. In postmenopausal women, the ovaries produce significant amounts of androgens, which can increase the incidence of cardiac events in women in the absence of estrogen.

Experimental studies indicate additive cardioprotection when treatment with a combination of estrogen and testosterone treatment is administered. This additive effect could be caused by the synergistic and codependency of these hormones. Additionally, the aromatization of testosterone to estradiol is a critical mechanism involved in the beneficial effect of testosterone on the cardiovascular system. This is supported by the fact that conversion of androgens to estrogens takes place in the heart and by the nongonadal expression of aromatase, which is higher in males than females.

Xiong et al. demonstrated lower T levels (540.8 ± 186.0 pg ml⁻¹ vs 656.3 ± 112.9 pg ml⁻¹, \(P < 0.001\)) but higher SHBG and serum bisphenol-A (BPA) levels in DCM patients than those in controls. Serum BPA levels are statistically significantly associated with increased SHBG levels, but no significant difference in estradiol levels has been noted. Pascual-Figal et al. demonstrated that SHBG levels are associated with the severity of heart failure and a higher risk of cardiac death. Another study that evaluated the association between the BPA concentration and sex hormone levels in 290 men with or without BPA exposure in the workplace showed that exposure to a high amount of BPA impacts the levels of sex hormone levels in men. An increased serum BPA concentration is statistically significantly associated with decreased androstenedione levels, decreased free testosterone levels, decreased free androgen index, and increased SHBG levels.
environmental endocrine-disrupting compound may be associated with the gender disparity in the incidence of DCM.

Kontoleon et al. compared 23 men with NYHA class II–IV heart failure due to idiopathic dilated cardiomyopathy and LVEF ≤35% to 20 healthy men and found significantly lower FL levels in men with heart failure (48.6 ± 23.8 pmol l⁻¹ vs 105.0 ± 17 pmol l⁻¹, P < 0.001). Naderi et al. assessed the levels of several hormones and markers in 33 men with idiopathic dilated cardiomyopathy and NYHA class II–III heart failure. The free testosterone level was within the normal range, and there was no association between free testosterone levels and LVEF, NT-proBNP levels, or high-sensitivity C-reactive protein (hsCRP) levels. There was a weak correlation between free testosterone levels and 6-min walking test (6MWT) distance.

In a study reported only in abstract form, which included men with dilated cardiomyopathy and heart failure, a combination of intramuscular testosterone injections and standard HF therapy significantly improved patients’ clinical status.100

**HYPERTROPHIC CARDIOMYOPATHY**

Hypertrophic cardiomyopathy (HCM) is a genetic disorder inherited as a Mendelian autosomal dominant trait. Although the prevalence of HCM in the general population should be equal between the two genders, studies have shown a higher predominance in male patients than in female patients. Differences in phenotypic expression could be caused by social and endocrine factors. Some familial hypertrophic cardiomyopathies, such as Danon disease, are more severe in males than in females,101 but in other forms, women are more symptomatic than men, often due to outflow tract obstruction, and show a higher risk of progression to advanced heart failure or death.102 In patients without obstruction, on magnetic resonance imaging, females have a lower left ventricle (LV) remodeling index (LV mass/LV end-diastolic volume) than males, suggesting a difference in LV remodeling in HCM.103 There are differences in remodeling between males and females.104

In animal models, testosterone has been found to enhance cardiac remodeling, whereas estrogen is protective.105 In a mouse model of myocardial infarction, there is an obvious gender difference in cardiac remodeling and function. Male mice have a higher incidence of cardiac rupture and a lower LVEF than females. Additionally, in males, castration significantly reduces both mortality and rupture. Testosterone replacement adversely affects myocardial healing and cardiac remodeling during the acute phase of myocardial infarction (MI) in both male and female mice. Moreover, this effect is more pronounced in castrated females.106

In another study, testosterone deficiency induced by orchidectomy in rats was shown to alter the pattern of late remodeling postinfarction, with a lower degree of pathological cardiac hypertrophy and an improvement in contractile parameters.107

The main effect of testosterone on post-MI remodeling may occur in myocytes, mainly through the induction of hypertrophy via androgen receptors108 and increased apoptosis.109 In humans with heart failure post-MI, the rates of myocyte necrosis and apoptosis are higher in men than in women, and these differences are associated with the earlier onset of the disease in males than in females.109

The effects of gender and reproductive hormones on cardiac mass have led to the hypothesis that testosterone influences human left ventricular hypertrophy. Androgen activity is regulated through both AR-dependent and AR-independent mechanisms. Testosterone induces hypertrophy via a direct AR-mediated pathway110 and through cytosolic and nuclear signaling pathways. Testosterone activates the nuclear factor of activated T cells (NFAT) in cardiac myocytes through calcineurin activation and glycogen synthase kinase3 (GSK-3β) inhibition.111 The transcriptional activity of NFAT is regulated tightly by intracellular Ca²⁺ through calcineurin.

*In vitro* treatment with testosterone leads to GSK-3β inhibition and increases in intracellular levels of calcium and activation of calcineurin and NFAT, resulting in cardiomyocyte hypertrophy.112

Deletion of GSK-3β in mice leads to hypertrophic cardiomyopathy secondary to cardiomyoblast hyperproliferation.113 Therefore, GSK-3β has antihypertrophic and antiapoptotic roles114 and could be a viable drug target.

Another hypertrophic mechanism regulated by androgens involves activation of the mTORC1/S6K1 axis through IP₃/Ca²⁺ and MAPK kinase (MEK)/extracellular-regulated kinase (ERK) 1/2.115 Hypertrophied cardiomyocytes increase glycolysis-dependent ATP production, and glucose uptake is stimulated by testosterone, which involves the participation of the CaMKII and AMPK signaling pathways.116

Poorer survival in males than in females has been reported in a variety of rat models of cardiac hypertrophy and heart failure involving pressure (aortic banding) or volume (fistula) overload, with androgens being the important drivers of pathological cardiac hypertrophy.116 Compared to normal testosterone levels, testosterone deficiency in rats with severe left ventricle volume overload results in less cardiac hypertrophy, less LV dilation, better function, and a strong tendency for better survival of the animals.117 Castration in male guanylyl cyclase-A-deficient mice alleviates not only cardiac hypertrophy but also cardiac fibrosis.118

Testosterone can be transformed by the enzyme 5α reductase to 5α-dihydrotestosterone (DHT), a more potent androgen with five times more affinity for the androgen receptor and a ten-fold more potent effect on signaling.1 It has been speculated that the conversion of testosterone to DHT is required for regulation of some of the effects of androgen on the cardiovascular system. DHT induces cardiac hypertrophy *in vitro* and in rats.119 Antiandrogenic therapy with finasteride, which inhibits the transformation of testosterone to DHT, attenuates cardiac hypertrophy and left ventricular dysfunction in mice of both sexes.120

Androgen receptor (AR) plays an important role in cardiac development and function. This is highlighted by the phenotype of AR knockout animals. Compared with wild-type animals, AR knockout mice exhibit a significant reduction in cardiac hypertrophy and cardiac fibrosis induced by angiotensin (Ang) II.121 Flutamide, an AR antagonist, remarkably alleviates cardiac hypertrophy.122

The effects of physiological androgen levels on cardiac remodeling and hypertrophy remain controversial, and further research is necessary to understand their roles.

**RESTRICTIVE CARDIOMYOPATHY**

Restrictive cardiomyopathy (RCM), the least common cardiomyopathy, is characterized by the presence of restrictive ventricular physiology with a normal or reduced ventricular volume and normal wall thickness.123

There have been few studies on sex differences in RCM, but these studies have shown a higher occurrence but better survival in females than in males.103 However, RCM represents a heterogeneous group of cardiac diseases with different pathophysiological processes, clinical presentations, treatments, and prognoses.124 Endomyocardial fibrosis is a form of endemic restrictive cardiomyopathy primarily observed in Africa, Latin America, and Asia. The exact epidemiology, etiology, and pathogenesis of endomyocardial fibrosis remain unknown, and it is characterized by endocardial fibrosis of the apex and inflow tracts...
of the right ventricle, left ventricle, or both. It is more common in children and young females, and affected males have clinical feminization. In a study of 19 male patients with endomyocardial fibrosis, testosterone serum levels were significantly lower in patients than those in controls. Fibrosis also occurs in skeletal muscle, and patients exhibit skeletal muscle atrophy. Transforming growth factor (TGF)-β and Ang II are pivotal in the progression of cardiac fibrosis. Androgens can regulate the effects of TGF-β and Ang II.

Cardiac amyloidosis is the most common form of restrictive cardiomyopathy in high-income countries. It is characterized by deposition of amyloid protein in the cardiac muscle and surrounding tissues. Hereditary transthyretin-related amyloidosis ATTR-CM is a condition more commonly reported in men than in women. Some biological characteristics associated with female gender protect against myocardial involvement in familial ATTR. Females have a less aggressive disease phenotype than males at the time of diagnosis, and have a higher left ventricle ejection fraction. Wild-type transthyretin cardiac amyloidosis is a common aging phenomenon in the elderly population. It predominantly affects elderly men, and affected men have a greater increase in LV thickness than affected women.

Fabry disease, a form of restrictive cardiomyopathy, is an X-linked lysosomal storage disease most often associated with renal dysfunction and death due to renal failure. The disease affects both men and women of all ethnic groups, but men are usually more severely affected. In α-galactosidase A knockout mice, a model of Fabry disease, AR activity is increased in the heart and kidneys. Castration and consequent hypogonadism or AR antagonism therapy alleviates heart and kidney phenotypes in Fabry disease model mice.

**NONCOMPACTION CARDIOMYOPATHY**

Noncompaction cardiomyopathy is a rare structural myocardial disorder of acquired or congenital origin characterized by prominent trabeculations and recesses in the LV walls. Stöllberger et al. reported that the prevalence of noncompaction cardiomyopathy is higher in males than in females, females exhibit more extensive disease, and that mortality is the same between males and females. There are no data regarding the possible involvement of testosterone in this disease.

**ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)**

ARVC is a genetic form of primary cardiomyopathy in which the right ventricle myocardium is typically replaced by fibrous tissue and fat, with scattered residual myocardial cells, resulting in structural changes such as myocardial thinning, localized or generalized dilatation of the right ventricle, and an increased risk of ventricular arrhythmias and sudden death. Because ARVC is an autosomal-dominant disease, an equal number of men and women are genetically affected. However, recent large studies have revealed a male predominance, with 75% of the patients being male and 25% of the patients being female, and have shown that men have a higher all-life risk of ventricular arrhythmias. Although total cardiac mortality is similar between sexes, women with ARVC have a significant risk for HF. Differences in ARVC phenotypic expression may be affected by sex hormones. A gender difference in the ventricular repolarization rate due to a potassium channel (Kv1.5) was reported to be androgen dependent in mice.

Akdis et al. measured the levels of testosterone and other hormones and biomarkers in 54 ARVC patients (72% male) who were followed up for a median of 1.1 years. The researchers found that total and free testosterone levels are significantly increased in males with major arrhythmic events (defined as sudden cardiac death, survival after sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia, or arrhythmic syncope). Total testosterone levels >13.5 nmol l\(^{-1}\) predicted unfavorable outcomes with a sensitivity of 84% and a specificity of 75%. For free testosterone levels, a cutoff of >264 pmol l\(^{-1}\) had a sensitivity of 74% and a specificity of 75%, and for bioavailable testosterone, a cutoff level of >6.2 nmol l\(^{-1}\) had 79% sensitivity and 75% specificity. Moreover, testosterone plasma levels in male ARVC patients are higher than those in healthy males. In an induced pluripotent stem cell-derived ARVC cardiomyocyte model, testosterone worsens and estradiol alleviates cardiomyocyte apoptosis and lipogenesis, which are hallmarks of ARVC.

**TAKOTSUBO CARDIOMYOPATHY**

The mechanism of Takotsubo cardiomyopathy (TTS) is still elusive, but there are several etiological theories, such as catecholamine-induced acute myocardial injury, vasospasm (epicardial coronary and/or microvascular), impairment of the coronary microcirculation, and myocardial stunning. Due to its predominance in postmenopausal females, it has been suggested that sex hormones may play a role in the disease, but the limited available data are contradictory.

Cardiomyocyte contractility studies have demonstrated that estrogen and testosterone exert contrasting inotropic actions and modulate Ca\(^{2+}\) handling differently. Myocytes from female patients with elevated Ang II levels appear to be more susceptible to contractility deficits, which may explain the female predominance among TTS patients. Brenner et al. analyzed the levels of sex hormones in postmenopausal women with TTS and age-matched females with and without myocardial infarction and found significantly higher estrogen levels at hospital admission in TTS patients than in age-matched females. Male sex is considered a mortality predictor in TTS. Male patients have a higher frequency of both chronic comorbidities and acute illnesses associated with low serum testosterone levels, and this could be an interesting topic for future study.

**CONCLUSIONS**

Cardiovascular disease remains a major cause of death, particularly in men and postmenopausal women. The cardiovascular protection observed in females has been attributed to the beneficial effects of estrogen, but little is known about the effects of testosterone. Evidence from basic science and clinical studies has shown that testosterone influences the cardiovascular system, but these effects are still poorly understood and contradictory. Additionally, the effects of testosterone may be different under normal physiological conditions and in pathological states. Testosterone could simultaneously benefit and harm the cardiovascular system through different pathways. Testosterone deficiency is common in men with dilated cardiomyopathy and heart failure, and studies have shown an association between low testosterone levels and poor cardiovascular outcomes.

**AUTHOR CONTRIBUTIONS**

RD, ID, and OM contributed to the conception of the work, conducted the study, revised the draft, and agreed with all aspects of the work. TAB contributed to the conception of the work, revised it critically for important intellectual content, and agreed with all aspects of the work. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

**COMPETING INTERESTS**

All authors declare no competing interests.
Testosterone and cardiomyopathies

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