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A comprehensive review on the effects of sex hormones on chemotherapy-induced cardiotoxicity: are they lucrative or unprofitable?

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Abstract
Chemotherapy is one of the routine treatment for preventing rapid growth of the tumor cells. However, chemotherapeutic agents, especially doxorubicin cause damages to the normal cells especially cardiomyocytes. Cardiotoxicity induced by chemotherapeutic drugs lead to the myocardial cell injury and finally causes left ventricular dysfunction. It seems that there were some differences in the severity of cardiovascular side effects of drugs used in the treatment of cancers. Sex hormones in male and female play crucial roles in cardiovascular development and physiological function of the heart and blood vessels. Gender differences and sex-specific hormones influence various aspects of cardiovascular health, including ventricular function, mitochondrial autophagy, and the development of abdominal aortic aneurysms. The most important gender related hormones are LH, FSH, testosterone, estrogen, progesterone, prolactin and oxytocin. They exert very important cardiovascular effects via different signaling mechanisms. Sex related hormones are also important in the cardiovascular side effects of chemotherapeutic agents, so that chronic cardiotoxicity induced by anthracyclines is more common in women. During different stages of life (before, during, and after sexual life), the levels of these hormones will be changed. This alterations can affect cardiovascular function during physiological conditions and pathological process. Because of the importance of the sex related hormones in the cardiac function, in this review we tried to comprehensively elucidate the role of these physiological hormones in cardiotoxicity induced by chemotherapeutic agents with emphasizing their signaling mechanisms.

Keywords Sex hormones, Doxorubicin, Cardiovascular system, Cardiotoxicity, Inflammation

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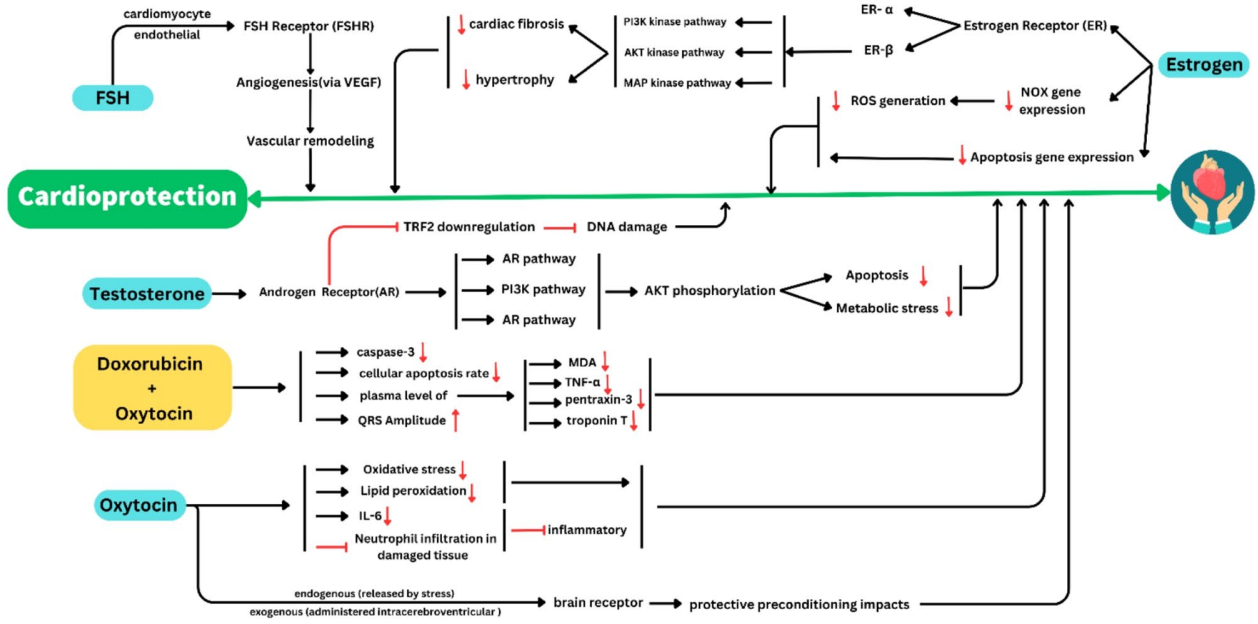
Graphical Abstract



Introduction

National cancer institute defines cardiotoxicity as "the toxicity that affects the heart". This type of damage to the heart could be due to different toxic substances, radiation, viruses, immunotherapy, and chemotherapy drugs. Although still there is much debate about the exact definition of the cardiotoxicity term, there is a consensus that cardiotoxicity affects resting systolic myocardial function, such as left ventricular ejection fraction (LVEF). When environmental stimuli are mild, the heart responds by alteration in calcium homeostasis [1–3]. Changes in calcium concentration disturb cell communication and conduction of electrical impulses, which give rise to reversible arrhythmia [4, 5].

Drug-induced cardiotoxicity is one of the crucial causes of cardiac injury, and anti-cancer drugs are one of the major suspects of this issue. There are two main pathophysiological mechanisms of drug-induced cardiotoxicity [6, 7]. Type 1 cardiotoxicity, induced by drugs like anthracyclines, is caused by the destruction of myocardial cells. It is dose-dependent, permanent, and irreversible. Type 2 cardiotoxicity results from the suppression of myocardial cells' function, and it is reversible. This type of cardiotoxicity is caused by drugs like Trastuzumab, and it is not dose-dependent [8–10]. Apoptosis (programmed cell death) [11, 12], myocardial necrosis [13, 14], myocardial remodeling [15, 16], Ca^{2+} homeostasis disruption [17], formation of reactive oxygen species (ROS) [18], iron complexes [19], mitochondrial dysfunction [20], and inflammation [21] are crucial mechanisms by which cardiotoxicity develops. The utilization of anti-cancer treatments like anthracyclines, Trastuzumab, and Sunitinib is a double-edged sword that can bring cardiotoxicity in conjunction with its benefits [8, 22]. Several studies have focused on drug-induced cardiotoxicity to reduce its impacts on patients' life, and various compounds like Dexrazoxane are used to prevent this issue.

Notably, Interleukin-1 (IL-1) is a pro-inflammatory cytokine integral to immune response, significantly impacting cancer therapy-related cardiac dysfunction (CTRCD) by intensifying inflammation and cardiac injury during and after cancer treatment [23, 24]. Elevated IL-1 levels, often triggered by chemotherapy and radiation, contribute to myocardial inflammation, fibrosis, and apoptosis, leading to severe cardiovascular outcomes, including heart failure [23, 24]. Mechanistically, IL-1 activates pathways like NF-kB and MAPKs, promoting transcription of inflammatory genes that cause endothelial dysfunction, increased vascular permeability, and myocardial remodeling, all key factors in CTRCD [23–25]. Additionally, IL-1 levels are modulated by hormone levels. Stress hormones like cortisol elevate IL-1, while sex hormones such as estrogen and testosterone variably influence inflammation [23, 26, 27]. For postmenopausal women, reduced estrogen can lead to increased IL-1 and higher cardiovascular risk, while hormonal fluctuations during cancer therapy may similarly exacerbate inflammation and susceptibility to cardiovascular events [24, 26]. Understanding the complex interplay between IL-1 and hormonal changes is essential

to developing strategies to reduce cardiovascular complications in cancer patients. A study by Quagliariello et al. highlights IL-1β's role in worsening cardiotoxicity in cancer patients receiving chemotherapy and immune checkpoint inhibitors. It shows that IL-1β not only promotes myocardial damage but also contributes to cancer progression and treatment resistance [28]. The study supports IL-1β inhibition with agents like canakinumab as a strategy to reduce cardiovascular events, aligning with our findings on IL-1's broader inflammatory impact. This focus on IL-1β's specific cardiotoxic effects reinforces its therapeutic potential, especially for high-risk patients in the current SARS-CoV-2 context [28].

In human physiology and pathophysiology, gender differences and sex hormones are a potential predictor of cardiovascular disease development and outcomes [29]. Sex-specific hormones influence various aspects of cardiovascular health, including right ventricular function, mitochondrial autophagy (mitophagy) in arterial senescence, and the development of abdominal aortic aneurysms [30]. Abnormal levels of sex hormones have been associated with an increased risk of cardiovascular diseases (CVDs) [31]. Estrogen, has been shown to have a protective effect on the cardiovascular system. It stimulates the release of endothelium-derived vasodilator factors and inhibits the renin-angiotensin system, leading to decreased blood pressure, both of which contribute to good heart health [32, 33]. Estrogen deficiency in women and androgen deficiency in men may contribute to cardiovascular disease and high blood pressure [34, 35]. The decline in estrogen with age and menopause is associated with an increased incidence of cardiovascular disease in women [36]. Progesterone reduces blood pressure and inhibits coronary hyperactivity. It has a powerful vasodilator effect which can help improve blood flow [37, 38]. Testosterone and other androgens have cardioprotective effects and may play an important role in the acute regulation of vascular function. In fact, testosterone has beneficial effects on cardiovascular function by inducing rapid relaxing vascular smooth muscle [35, 39]. Estrogen, progesterone, and testosterone receptors are present in blood vessels, which appear to stimulate endothelium-dependent mechanisms of vascular relaxation mechanism and inhibit vascular smooth muscle contraction mechanisms [40].

Gonadotropin hormone-releasing hormone (GnRH) is secreted from hypothalamus in a pulsatile manner and induces the secretion of Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) from anterior pituitary gland. FSH and LH have crucial role in estrogen, testosterone, and other sex steroids secretion [15]. Despite the widespread researches on the pathophysiological functions and effects of sex hormones in cardiovascular system, there is no comprehensive review regarding to the effects of these hormones on the cardiotoxicity. In this paper we tried to elucidate the impacts of sex related hormones including GnRH, FSH, LH, Estrogens, Testosterone, Progesterone, Prolactin, and Oxytocin on drug-induced cardiotoxicity.

GnRH

Gonadotropin-releasing hormone (GnRH) is one of the hypothalamus' releasing hormones. Its pulsatile secretion controls the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) [41]. In the clinical setting androgen deprivation therapy (ADT) is the primary treatment for prostate cancer patients (PCa). The first-line therapeutic agent for ADT is GnRH agonists (Leuprolide, Goserelin, Triptorelin, etc.) which continuously stimulate the anterior pituitary gland to secrete LH and FSH [42]. The alternative treatment for GnRH agonists is GnRH antagonists (Abarelix, Cetrorelix, Degarelix, etc.) which competitively bind to GnRH receptors, and prevent the secretion of gonadotropins, thus preventing testosterone secretion [43]. Despite the positive effects of these drugs on PCa patients, they have several adverse effects, including sexual dysfunction, bone fractures, anemia, loss of libido, vasomotor flushing, osteoporosis, insulin insensitivity, diabetes, and cardiovascular events such as myocardial infarction (MI) and cardiac sudden death (CSD) [44, 45].

Cardiovascular effects of GnRH agonists and antagonists

The association between ADTs and cardiovascular (CV) disorders is still controversial and unclear, but the possibility of CV events induced by GnRH agonists and antagonists are a growing concern due to prevalence of cardiovascular disease (CVD) in cancer patients [43]. Utilization of GnRH agonists is in conjunction with a higher risk for diabetes, MI, and CSD among PCa patients [46]. Another study has shown an increase in CV mortality risk in patients treated with antiandrogens and GnRH agonists [47]. Several subsequent observational studies also have confirmed that the GnRH agonist treatment is correlated with a higher risk of cardiovascular events such as stroke, arrhythmia, and heart failure (HF) [43]. Pooled data from six phase 3 prospective randomized trials recruiting 2328 men (2005–2012) showed that compared with GnRH agonists, GnRH antagonists have higher incidence of CV events among men with preexisting CVD within 1 year of initiating the treatment [48]. Another explanation for CV risks induced by GnRH agonists is the direct effect of these drugs on cardiomyocytes. In addition, QT prolongation was observed in patients who were treated with GnRH agonists for six months due to electrolytes modification [49].

a meta-analysis comparing the risk of cardiovascular events in patients treated with GnRH antagonists

and agonists found that patients treated with GnRH antagonists had a reduced cardiovascular risk compared with those treated with GnRH agonists, particularly in patients with preexisting CV disease [50]. The mechanism by which GnRH antagonists exert their cardioprotective effects is not fully understood. However, it is believed that GnRH antagonists may have a more direct effects on the cardiovascular system than GnRH agonists. GnRH agonists stimulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which can lead to increased testosterone levels. High testosterone levels are associated with an increased risk of cardiovascular events. On the other hand, GnRH antagonists inhibit the release of LH and FSH, leading to reduced testosterone levels. This reduction in testosterone levels may contribute to the cardioprotective effects of GnRH antagonists [51].

LH

Definition and general functions

LH is a gonadotropic hormone secreted by the anterior pituitary gland in response to GnRH secretion from the hypothalamus. Its main function is to induce ovulation and formation of corpus luteum, stimulate ovaries to produce estrogen and progesterone, and stimulate interstitial cells of Leydig in the testis to produce testosterone [52].

Effects of LH on the cardiovascular system

Based on a clinical assessment on 3637 community-dwelling men aged 70–88 years to evaluate the association between testosterone, sex hormone binding globulin (SHBG), and LH levels with ischemic heart diseases (IHD), higher levels of LH were associated with a higher likelihood of IHD events (testosterone levels had a negative relation with IHD risk, and there were no relations between SHBG and IHD risk) [53]. Three hypotheses were proposed to explain the association between LH levels and IHD events: (1)Increased levels of LH are an indicator of low levels of testosterone. Due to the fact that testosterone has a positive impact on the cardiovascular system, this association can be explained. Testosterone inhibits inflammation through reducing pro-inflammatory cytokines [54, 55],(2) higher LH levels have a gonadal-independent harmful effects on the cardiovascular system. LH receptors have been found in extragonadal sites [56] like vascular tissue and smooth muscle [57, 58]. In mouse aorta LH receptor expression was associated with the proliferation of endothelial cells [57]. Rastrelli et al. confirmed that higher serum level of LH was a testis volume-independent predictor of major adverse CV events [59] and (3) Elevated LH levels are an epiphenomenon of other processes which have detrimental effects on the cardiovascular system [53].

Effects of LH on drug induced cardiotoxicity

There is no study assessing the relation between LH and drug-induced cardiotoxicity. More researches and studies on this topic are highly recommended.

FSH

Definition and general functions

FSH is the other gonadotropin hormone secreted by gonadotropic cells in the adenohypophysis. FSH triggers the evolution of ovarian follicles, besides it has a prominent role in spermatogenesis by means of sertoli cells [60].

Effects of FSH on the cardiovascular system

FSH affects the cardiovascular system through indirect and direct mechanisms [61]: FSH has a role in angiogenesis, cell division, growth, differentiation, and protein synthesis. FSH receptors are expressed on the endothelial cells and they can promote angiogenesis via a VEGF-dependent mechanism [48, 61, 62]. Furthermore, FSH-FSH receptors (FSHR) signaling could be involved in vascular ring. FSHRs are also expressed on cardiomyocytes [63, 64] which could be the explanation for the alteration in cardiomyocytes' action during ADT therapy. Elevated FSH levels during ADT therapy may cause CV effects due to its role in inflammation, atherosclerosis, insulin resistance, formation of reactive oxygen species, and rearrangement of adipocytes [65]. Studies conducted on mice have shown that volume of dysfunctional fat has an association with FSH receptor concentration [66]. Moreover, dysfunctional fat could lead to metabolic syndrome and CV diseases [67]. FSH levels are also associated with vascular inflammation leading to endothelial dysfunction which is a strong predictor of CV disorders [61, 68]. Besides, FSH increases the reabsorption of calcified regions in the thrombotic plaques leading them to be ruptured and cause CV events [65].

Effects of FSH on drug induced cardiotoxicity

There is not any study evaluating the relation between FSH levels and drug-induced cardiotoxicity. Further studies are recommended to be done on this specific topic.

Testosterone

Definition and general functions

Testosterone is the main male androgen secreted from interstitial Leydig cells in testes in response to LH [69]. Testosterone is the primarily responsible hormone for male sexual development (testicular descent, spermatogenesis, increasing libido, and penis and testes enlargement) and male sexual characteristics (vocal changes, anabolic effects, and male hair pattern) [70]. This hormone is also converted by 5-alpha-reductase in peripheral tissues to its more active form, dihydrotestosterone,

and by aromatase to estradiol [69]. Testosterone is also produced in trivial amounts compared with males by ovaries and adrenal glands in females [71]. It could have a role in female libido and sexual activity due to the fact that in postmenopausal women, decreased testosterone levels are associated with loss of libido and reduced sexual activity [72, 73].

Effects of testosterone on the cardiovascular system

After age 40 the levels of testosterone begin to decrease in men, and this is accompanied by an increase in CV risks [74, 75]. Low physiologic testosterone levels are associated with coronary artery disease (CAD), metabolic syndrome, type 2 diabetes, chronic heart failure (CHF), and altered lipid profiles [43, 76, 77]. Several studies have shown that testosterone replacement therapy (TRT) improves myocardial ischemia in men with CAD [78–80], the capacity of exercise in CHF patients (through proliferation of slow twitch muscle fibers), decrease serum glucose levels, and insulin resistance in diabetic patients [76, 81]. Moreover, testosterone deficiency is also related to metabolic syndrome, diabetes, dyslipidemia, hypertension, and CV adverse effects [76]. Testosterone exerts its impacts through androgen receptor (AR) [43, 82]. Testosterone deficiency can lead to changes in the lipid composition, and decreases triglycerides, total cholesterol, LDL and increases HDL. This increases inflammation, oxidative stress, proliferation and endothelial dysfunction, ultimately causing atherosclerosis and cardiovascular disease [83, 84]. Although few studies state that testosterone supplementation can increase CV risks in hypogonadal men [43, 77], the majority of studies have shown that circulating testosterone has beneficial impacts on the cardiovascular system [43, 76]. Ruige et al. showed that higher testosterone levels decreased CV events in patients>70 years but not in younger patients [85]. Though four other studies also found an inverse association between testosterone levels and CAD severity [81], the mechanism of the relation between testosterone levels and CAD is still undisclosed [76]. An observational study showed that testosterone therapy was associated with MI reduction in high-risk patients [86]. Besides, testosterone has a direct vasodilatory impact on coronary arteries in CAD patients [80]. Antiandrogen monotherapy in prostate cancer patients was associated with a 27% increase in CAD [43, 87].

Effects of testosterone on drug-induced cardiotoxicity

Chronic cardiotoxicity induced by anthracyclines and doxorubicin is more common in women than men. A study on H9C2 cells and neonatal mouse cardiomyocytes was conducted to find whether testosterone or 17β-estradiol pre-exposure has a protective effect against doxorubicin-induced senescence or not. They divided these cells into two groups, the first group was incubated with testosterone or 17β-estradiol 15 min before exposure to 0.1 mol/L doxorubicin for 3 h, and the latter group was exposed to second 3-hour pulse of 0.1 mol/L doxorubicin 14 days after the first directly. They concluded that testosterone counteracts doxorubicin-induced cardiotoxicity; however, 17β-estradiol had partial protecting impacts. Testosterone suppresses doxorubicin-induced cardiotoxicity through AR/PI3K/AKT/TRF2 pathway. AR interaction with PI3K causes an increase in phosphorylation and activity of AKT [88–90]. It also inhibits telomeric repeat binding factor 2 (TRBF2) downregulation, which is a part of the telomere complex and inhibits DNA damage [90]. Inactivating phosphorylation and accumulation of P53 is suppressed by testosterone. Besides, testosterone increases phosphorylation of nitric oxide synthase 3 (NOS 3) in H9C2 cells in a PI3K-dependent manner [91]. Pretreatment with flutamide (a testosterone antagonist), PI3K inhibitor, and nitric-oxide synthesis inhibitor neutralize the testosterone protecting properties [90].

Another study assessed the cardioprotective effects of AR against doxorubicin-induced cardiotoxicity. They used two groups of mice: male AR knockout mice and age-matched male wild-type (WT) mice. These two groups were treated with doxorubicin at a single dose of 20 mg/kg; five day after administration of doxorubicin. The reduction of survival rate, LV function, and oxidative stress caused by doxorubicin administration was more significant in AR knockout mice, besides, they found vacuole formation in myocardial mitochondria, which is an indicating factor of cell damage. Doxorubicin lessens transcription factor A (Tfam), involved in mitochondrial DNA transcription and replication, expression of serine/threonine kinase, involved in intracellular antiapoptotic transduction (AKT) phosphorylation, which is far more prominent in AR knockout mice than WTs. Hence, the androgen-AR system counteracts doxorubicin-induced cardiotoxicity through the AKT pathway and upregulation of Tfam [92].

Estrogens

Definition and general functions

Estrogens (17β-estradiol, estrone, and estriol) are primary female sex hormones secreted by ovaries' developing follicles in a cyclic manner [93]. Estrogens are also produced by the adrenal cortex in both genders and by the placenta in females [94]. In males, small amounts of estrogens are also produced by Leydig cells and germ cells in the testes [95]. Estrogen exerts its effects through nuclear receptors (ERα and ERβ) or membrane receptors (GPR30, ER-X) [94]. Estrogens have a notable role in regulating female reproductive function and secondary sex characteristics [96]. They prepare females' bodies for

mating and maternal care by stimulating breast growth, pelvis bone growth and broadening, vulvar fat deposition, changing vaginal epithelium, long bones' epiphyseal closure, and general growth [94].

Effects of estrogen on the cardiovascular system

Estrogen receptor (ER) has two main forms: ER-α and ER-β which are respectively encoded by ESR1 and ESR2 [97]. Based on the distribution of these receptors, the tissues' responses will be different [98]. ER-α, localized at or near the plasma membrane, activates endothelial nitric oxide synthase (eNOS) [99], inhibits vascular smooth muscle cell (VSMC) proliferation, and activates PI3K/AKT/MAP kinase pathway [98]. ER-β localized in the nucleus, also activates PI3K/AKT/MAP kinase pathway (Fig. 1), protects against cellular damage, and inhibits cardiac fibrosis and hypertrophy [98].

It is suggested that estrogen deprivation in menopause ages has been related to increased CVD risks [100]. Furthermore, HF-related morbidity and mortality is lower in female patients compared to males, and they respond better to routine treatment compared to male patients [98]. But it is not yet confirmed that these differences are estrogens' effect. Estradiol (E2) induces protecting heat shock protein (hsp) expression leading to enhancing myocyte survival [101]. In rats without estrogen replacement therapy, aged cardiac myocytes showed higher levels of ROS production [98]. Activation of matrix metalloproteinase-2 (MMP-2) and MMP-9 increased during cardiac remodeling with age [102]. In a study conducted on Wistar rats in cardiac fibroblasts, MMP-2 expression was suppressed by E2 administration [108]. Angiotensin II (Ang II) and endothelin-1 activate transforming growth factor beta (TGFβ) and activate fibroblast to myofibroblast transition [103]. Neonatal cardiac fibroblast proliferation induced by Ang II can be inhibited by E2 and this inhibition is blocked by estrogen receptor (ER) antagonist [103, 104]. Interestingly, ERβ, but not ERα, knockout leads to increased cardiac myocyte diameter and; consequently, cardiac hypertrophy in both genders [105].

Effects of estrogen on drug induced cardiotoxicity

Doxorubicin treatment was accompanied by an increase in heart injury serum biomarkers including creatinine kinase and apoptotic genes expression (BAX and caspase 3). The doxorubicin -treated group also showed myofibrillar loss and cytoplasmic vacuolization. Treatment with daily 2 mg/kg subcutaneous E2; not only did estrogen attenuate doxorubicin-induced cardiac damage, but it also had a positive impact on myocardial fibers in rats. Furthermore, E2 inhibited nicotinamide adenine dinucleotide phosphate oxidase (NOX) and apoptotic genes expression (Fig. 1). NOX gene is responsible for ROS generation, which results in cardiomyocyte apoptosis; thus, E2 exerts its beneficial impacts on doxorubicin-induced cardiotoxicity through NOX/ROS/apoptosis pathway (Fig. 1) [106]. Experimental research on male and female Sprague-Dawley rats were conducted to assess the impacts of estrogen, testosterone, and progesterone on doxorubicin-induced cardiotoxicity. Doxorubicin decreased myofilaments maximum active tension (Tmax) which was preserved by estrogen treatment (but not testosterone and progesterone). Besides, doxorubicin

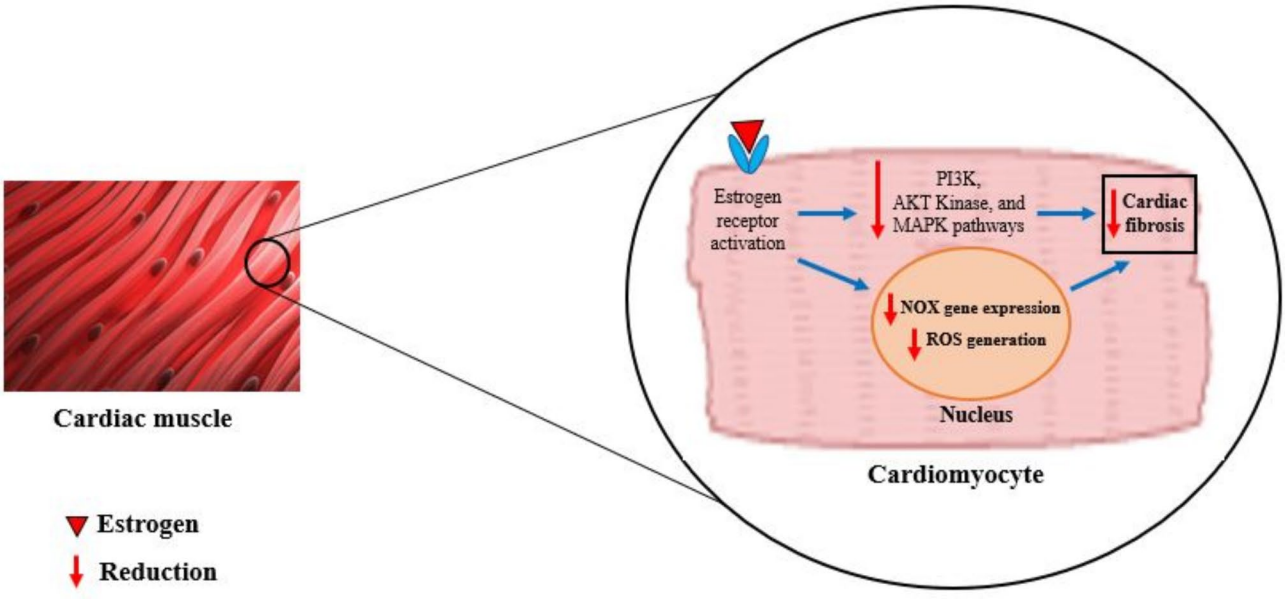


Fig. 1 Mechanisms for decreasing cardiotoxicity by estrogen. NOX; NADPH oxidase, ROS; reactive oxygen species, PI3K; phosphoinositide 3-kinases and MAPK; mitogen-activated protein kinase

increased Ca^{2+} ion sensitivity in the absence of testosterone in male rats but in the presence of estrogen in females and decreased Ca^{2+} ion sensitivity in the absence of estrogen in female rats. Estrogen inhibits the depression of myofilament maximum activate tension through regulating the myosin heavy chain (MHC) isoforms, and inhibiting myofilament proteins oxidative modifications [107]. In ovariectomized rats the effects of endogenous E2, exogenous implanted E2, and progesterone (P4) on doxorubicin-induced cardiotoxicity was evaluated. The results showed that 13 days after doxorubicin injection, doxorubicin-induced cardiotoxicity was suppressed in these animals implanted with E2 pellets. E2 decreased cardiac troponin I (cTnI), oxidative stress pathways, and improved left ventricle reactivity [108]. In rats receiving daily oral gavage of sunitinib (40 mg/kg), neonatal rat ventricular myocytes (NRVMs) and adult rat ventricle myocytes (ARVM) were evaluated to determine sex-differences in sunitinib-induced cardiotoxicity response. Cardiac dysfunction, fetal gene expression (ANF, BNP, and β-MyHC), ventricular dilation (including decreased anterior wall thickness, increased left ventricle systolic volume, and LV mass), decreased fractional shortening (FS), and increased left ventricle fibrosis were prominent in female rats but not in males in response to sunitinib treatment. E2 influences the expression of responsible genes for drug metabolism and efflux including Mdr1 (responsible for sunitinib efflux) and Cyp1A1. Increased expression of Mdr1 and Cyp1A1 induced by sunitinib in female's NRVMs is also blocked by E2. As a result, E2 prohibits the expression of crucial proteins for sunitinib metabolism and efflux, and leads to higher incidence of cardiotoxicity in female rats [109]. In a rat model of hypertrophic cardiomyopathy, a soy-free diet supplemented with phytoestrogens including daidzein and genistein, could protect the female rats against hypertrophic cardiomyopathy sequences, but male with hypertrophic cardiomyopathy were more sensitive and showed impaired cardiac function, decreased fractional shortening, and ventricular dilation. Genistein disturbs several survival pathways by inhibiting RTKs which leads to increased apoptosis by a reduction in anti-apoptotic factor, increasing Bax/Bcl-2 ratio, and raising caspase activity [110].

Progesterone

Definition and general functions

Progesterone is a steroid released from the ovaries and adrenal glands in non-pregnant women and from corpus luteum in the ovaries in response to the anterior pituitary gland hormones during pregnancy. It also is produced by the placenta during pregnancy. This hormone is routinely released in the second half of the ovarian cycle and thickens and prepares the endometrium lining to implant the ovum. In early pregnancy corpus luteum secrets progesterone which inhibits uterus muscle contraction (by inhibiting prostaglandins production) to preserve the pregnancy. Progesterone triggers the secretion of fallopian tubes to nurture the fertilized ovum before implantation; moreover, it has a role in the development of the breasts [52]. Progesterone exerts its effects through a nuclear receptor PR which has two natural isoforms including PRA and PRB [111].

Effects of progesterone on the cardiovascular system

Progesterone receptors (PR) are expressed in the cardiac tissue [108, 112]. This means that the cardiac tissue is responsive to different levels of endogenous and exogenous progesterone concentration [108]. Based on a prospective longitudinal study conducted on Swedish elderly population of opposite-sex twins and 8-year follow-up, increased physiologic concentrations of progesterone were associated with a higher prevalence of CHF, diabetes and mortality independent of renal function biomarkers, inflammatory cytokines, and insulin metabolism [113]. Progesterone has protective effects in the cardiovascular system including lowering blood pressure, inhibiting coronary hyperactivity, and vasodilation [38]. However, medroxyprogesterone acetate has opposing impacts on coronary reactivity, which leads to confusion [114].

Effects of progesterone on drug induced cardiotoxicity

In a rat model of cocaine-induced cardiotoxicity, cardiac muscles of pregnant rats were more sensitive to the cardiotoxic effects of cocaine compared with non-pregnant rats. Based on results, non-pregnant rats showed a biphasic behavior including a positive inotropy, and negative inotropy in response to the higher concentration of cocaine followed by non-functionality of muscles, while pregnant and non-pregnant rats treated with 7 mg/kg progesterone intramuscularly for 3 consecutive days did not show that biphasic response (the positive inotropy was missed) and negative inotropy occurred in response to lower concentrations of cocaine [115]. Based on another study performed on rats, 10 mg/kg oral mifepristone, a progesterone's antagonist, for 3 days has been found to ameliorate cocaine-induced cardiotoxicity [116]. Based on Pokrzywinski et al. study, progesterone suppressed cardioprotective effects of estrogen against doxorubicin-induced cardiotoxicity [108]. This could be explained by progesterone (P4) ability to antagonizing E2 impacts in noradrenaline-treated rats' aorta [117]. Furthermore, exogenous P4 increased tumor growth and did not have any protection against doxorubicin-induced cardiotoxicity [108]. The specific mechanism by which progesterone antagonizes the cardioprotective effects of estrogen in noradrenaline-treated rats' aorta are not

fully understood. However, there are several potential factors and mechanisms may contribute to this phenomenon. Estrogen exerts its cardioprotective effects through estrogen receptors (ERs). There are three types of ERs: ERα, ERβ, and G protein-coupled estrogen receptor (GPER). All three ERs have been identified as functional and present in adult cardiomyocytes [118]. Progesterone can interact with these ERs and interfere with their signaling pathways, thereby antagonizing the cardioprotective effects of estrogen. Estrogen has been shown to have direct effects on the vascular wall, including vasodilation and modulation of vascular response to vasoactive agents. Progesterone may interfere with these vascular responses, leading to a reduction in the cardioprotective effects of estrogen [119].

Prolactin

Definition and general functions

Prolactin (PRL) is a polypeptide hormone which is synthesized and released by anterior pituitary gland. It also could be produced by central nervous system (CNS), immune system, uterus, and mammary gland. Prolactin has a pivotal role in breast development and lactation. Olfaction, light, stress, and nipple stimulation can stimulate prolactin secretion. It also is present in trivial levels in male [120].

Effects of prolactin on the cardiovascular system

Although PRL functions generally is not associated with cardiovascular disease and direct relationship between prolactin and cardiovascular disease is not clear, but it is associated with hypercholesterolemia, hypertriglyceridemia, metabolic syndrome, low HDL levels in women, hypertension, and diabetes in men and thereby increases the risk of cardiovascular diseases. It also has chronotropic and vasoconstrictive effects which disturb endothelial function [121]. Based on a study, high levels of PRL increased carotid intima thickness, blood glucose, insulin resistance, and C-reactive protein which is conducive to atherosclerosis and metabolic abnormalities [122, 123]. Besides, in another animal study, it has been revealed that slight elevation of PRL (0.01 nmol/L) decreases blood pressure (BP) due to increasing nitric oxide (NO), but greater elevation (10 nmol/L) increases BP and HF due to decreasing NO [123–125]. Another cohort study assessing prolactinemia and cardiovascular disorders has found no relation between them. But it revealed that with each 5 mg/dL increase of PRL, the chance of diabetes and hypertension was elevated in men [121, 123]. In an oxidative environment full-length 23-kDa prolactin cleaves into 16-kDa prolactin fragment, which has anti-angiogenic, pro-inflammatory, and pro-apoptotic effects on the cardiovascular system (Fig. 2). This fragment impairs endothelial function, and promotes the release of micro-RNA146 a, which has deleterious impact on cardiomyocytes [126, 127]. Bromocriptine (2.5 mg twice a day for 14 days) associated treatment has found to be effective in improvement of ejection fraction by inhibiting the releasing PRL of the pituitary gland [126, 128, 129]. This study showed that bromocriptine beneficially improved LVEF, while according to the statistics in the text of this article, after taking bromocriptine, LVEF levels decreased from 35% to less than 29%.

Effects of prolactin on anti-cancer drug induced cardiotoxicity

There is no study assessing effects of PRL on drug-induced cardiotoxicity.

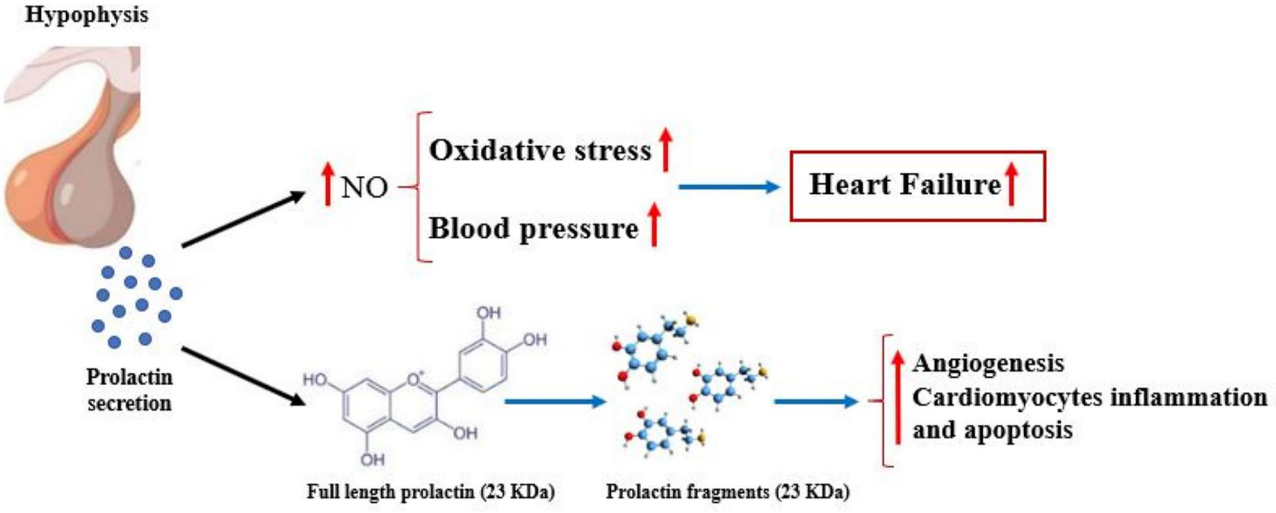


Fig. 2 Effects of prolactin on cardiovascular system. NO; Nitric Oxide

Oxytocin

Definition and general functions

Oxytocin is a peptide hormone made by the paraventricular nucleus in the hypothalamus and released by neurohypophysis (posterior pituitary gland). This hormone's primary functions are increasing contractility of the uterus, especially during labor to help delivering baby, contraction of myoepithelial cells surrounding alveoli of the breasts to evacuation their milk to the nipple, and contraction of fallopian tubes to help the sperm reach the ovum [52]. It is also involved in female sexual arousal [130]. Oxytocin is also produced in same amounts in male mammals but its functions in male gender are ambiguous; it could have a role in ejaculation and sexual behaviors [131].

Effects of oxytocin on the cardiovascular system

Oxytocin receptors (OTRs) and Vasopressin receptor 1a (V1aR) [132, 133] have been found in the heart and vascular beds of humans and rats [134–139]. Synthesized oxytocin (Syntocinon) in the heart supports cardiac function and development; besides it decreases cardiovascular reactivity to stress [140]. OT also exerts a slight vasoconstriction in peripheral arteries through binding to V1a receptor [141, 142]. In hypovolemic condition, cardiac OTRs increase atrial natriuretic peptide (ANP) release [134, 135, 143]; however, it is not confirmed in human [144, 145]. Oxytocin exerts a cardioprotective role in pathophysiological conditions [140]. Mesenchymal cells transfected with oxytocin are immune to apoptosis; besides, when MI is experimentally induced in rats, continuous delivery of 10^{-6} m oxytocin during perfusion gives rise to cardiac healing, reduction of inflammation, and angiogenesis [146]. Oxytocin has vagomimetic and NO generating action which leads to decreased heart rate by increasing diastole duration; thus it increases heart muscle oxygenation [147]. Işeri SO et al. showed that by opening mitochondrial K^+ATP channels, oxytocin inhibits the synthesis of reactive oxygen species; consequently, it has antioxidant impacts [148]. Antioxidants and coenzyme Q10 (CoQ10) may play important roles in addressing hormone-related cardiovascular diseases and managing the cardiovascular impacts of anticancer therapies [149]. Oxidative stress, heightened by hormonal changes such as menopause or hormonal therapies, can lead to endothelial damage, contributing to conditions like hypertension and atherosclerosis [150, 151]. Antioxidants, including vitamins C and E, selenium, and flavonoids, help mitigate this damage by neutralizing free radicals, enhancing nitric oxide bioavailability for better vasodilation, and reducing inflammation [152]. Furthermore, antioxidants with hormonal modulation properties, such as phytoestrogens, can balance estrogen's beneficial vascular effects. CoQ10, a vital mitochondrial antioxidant, supports cardiac health in patients undergoing anticancer therapies like chemotherapy by counteracting treatment-induced oxidative stress and potentially improving cardiac function and fatigue symptoms [153]. While some clinical evidence supports these roles, further studies are essential to establish guidelines for their preventive use in cardiovascular health, especially within oncology and hormone-related contexts [154]. A study by Quagliariello et al. presents a nano-encapsulation method to enhance CoQ10's bioavailability, addressing the limitations of its traditional oral use [155]. By loading CoQ10 in nano-emulsions (NEs) coated with chitosan and hyaluronic acid, the researchers achieved high stability and improved protective effects against doxorubicin and trastuzumab toxicities in cardiomyocytes and hepatocytes. Key findings showed that CoQ10-loaded NEs enhanced cell viability and reduced lipid peroxidation and inflammatory markers (e.g., leukotriene B4, p65/NF-κB, IL-1β, and IL-6), highlighting significant cardioprotective and hepatoprotective effects [155]. This aligns with our study's aim to explore effective strategies for reducing oxidative and inflammatory damage during cancer therapies, supporting further preclinical evaluation of nano-encapsulated CoQ10 in cardio-oncology contexts.

Furthermore, stress-released endogenous oxytocin and intracerebroventricular (ICV) exogenous oxytocin have protective preconditioning impacts on ischemic-reperfused rat hearts through brain receptors [156].

Effects of oxytocin on doxorubicin-induced cardiotoxicity

In a study conducted on 40 male Sprague-Dawley rats, 32 rats were given doxorubicin (2.5 mg/kg/day) intraperitoneally (i.p) in six days, and eight rats were considered as a normal group. This study demonstrated that the best therapeutic result has been seen in doxorubicin + oxytocin group including the least expression of caspase-3, better tissue integrity, lower cellular apoptosis rate, the highest QRS amplitude, and the least plasma malondialdehyde (MDA), tumor necrosis factor alpha (TNF-α), pentraxin-3, and Troponin T levels. Oxytocin hinders oxidative, apoptotic, and inflammatory reactions in the cardiac tissue. It exerts its beneficial impacts via preventing neutrophil infiltration in damaged tissue, decreasing TNF-α and Interleukin 6 (IL-6) levels, and reducing ROS and lipid peroxidation (Fig. 3; Table 1) [157].

Conclusion

Chemotherapeutic agents-induced cardiotoxicity is one of the crucial causes of cardiac injury. Gender differences and sex hormones are potential markers affecting incidence of cardiovascular diseases by influencing various aspects of cardiovascular health. Estrogen and androgen deficiency may contribute to cardiovascular diseases. Conversely, reduction of estrogen is associated

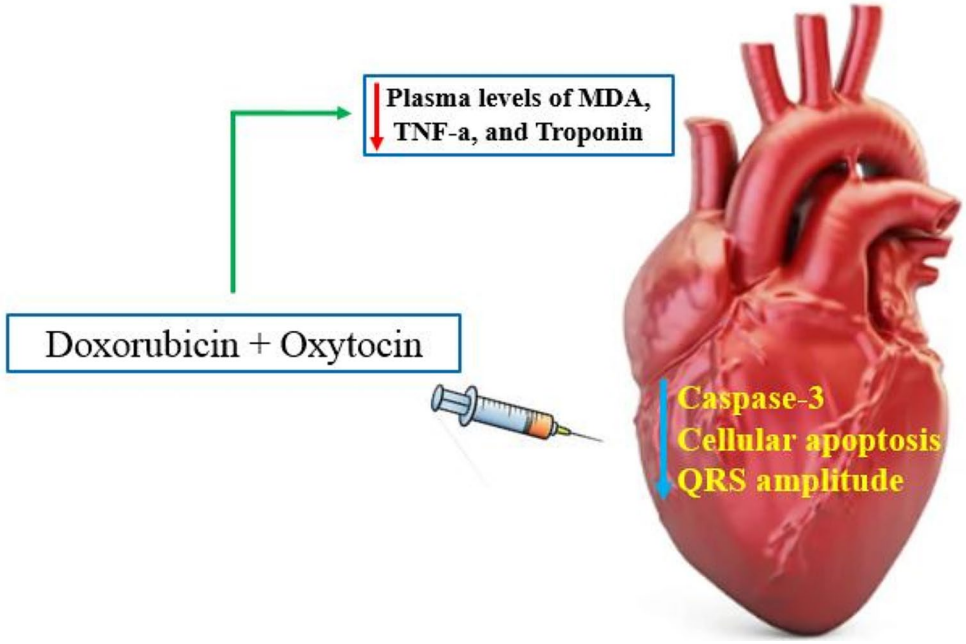


Fig. 3 Effects of oxytocin in doxorubicin induced cardiotoxicity. MDA; malondialdehyde and TNF-α; tumor necrosis factor-α

with an increase in incidence of cardiovascular diseases. For this reason, cardiotoxicity induced by anthracyclines and doxorubicin is more common in women. Regarding to the cardiovascular effects of sex specific hormones in the cardiotoxicity, this review suggests that testosterone decreases doxorubicin-induced cardiotoxicity through AR/PI3K/AKT/TRF2 pathway and preventing DNA damages, estrogen exerts its beneficial impacts on cardiotoxicity through NOX/ROS/apoptosis pathway, progesterone suppresses cardioprotective effects of estrogen against doxorubicin-induced cardiotoxicity and oxytocin decreases cardiotoxicity via anti apoptotic, anti-inflammatory, and anti-oxidant effects.

Table 1 Summarizing the effects of sex related hormones and the analogues of them in the cardiotoxicity induced by chemotherapeutic agents

Ref.	Study model	Drug	Dosage / administration route	Outcome of therapy
[48]	Pooled data analysis from six phase 3 prospective RCT. 2,328 men with pathologically confirmed prostate cancer and naïve to androgen deprivation therapy (ADT). **Randomization**: Men were randomized to receive either a GnRH agonist or a GnRH antagonist for 3–7 months	**GnRH Antagonist**: Degarelix ($n=1491$). **GnRH Agonists**: Leuprolide ($n=379$). Goserelin ($n=458$). **Antiandrogen (Bicalutamide)**: Given to some patients for 1 month as flare protection.	**GnRH Antagonist (Degarelix)**: Administered as per study protocol, details on specific dosage were not provided. **GnRH Agonists (Leuprolide, Goserelin)**: Administered as per study protocol, with some patients also receiving bicalutamide for 1 month. **Administration Route**: Not explicitly mentioned, but typically these are administered via injection.	Men with preexisting cardiovascular disease treated with a GnRH antagonist had a significantly lower risk of cardiac events within 1 year compared to those treated with GnRH agonists (Hazard Ratio: 0.44; 95% CI, 0.26–0.74; $p=0.002$). The absolute risk reduction was 8.2%, with a number needed to treat of 12. Cardiac events occurred only in the longer trials; none occurred in the shorter trials. **Conclusion**: GnRH antagonists may reduce the number of cardiac events in men with preexisting cardiovascular disease compared to GnRH agonists.
[53]	Prospective cohort study 3,637 community-dwelling men aged 70–88 years. **Duration**: Mean follow-up was 5.1 years (range 0.1–7.2 years).	**Primary Focus**: Testosterone and its associated hormones (SHBG and LH)	**Testosterone**, **SHBG**, **and LH levels** were assessed in participants.	**IHD Events**: 17% of men experienced an ischemic heart disease (IHD) event, with 160 of these being fatal. **Testosterone**: Higher levels of total and free testosterone were associated with fewer IHD events, but these associations disappeared after adjusting for prevalent IHD and other cardiovascular risk factors. **SHBG**: No link was found between SHBG levels and IHD events. **LH**: Higher LH levels were associated with increased risk of IHD events, both before and after adjusting for other factors.
[82]	Observational study of 37,443 men with local or regional prostate cancer.	Androgen deprivation therapy (ADT) with: **1.Gonadotropin-releasing hormone (GnRH) agonists** **2.Oral antiandrogens** **Combined androgen blockade (GnRH agonists + oral antiandrogens)** **3.Orchiectomy**	GnRH Agonists: Administered as injections with dosage intervals accounted for by estimating treatment duration. Oral Antiandrogens: Administered orally, with treatment duration accounting for persistent effects up to 8 weeks after the last dose. Orchiectomy: Surgical removal, with patients remaining in this treatment category permanently.	**GnRH Agonists**: Associated with increased risks of diabetes (adjusted hazard ratio [aHR] = 1.28), coronary heart disease (aHR = 1.19), myocardial infarction (aHR = 1.28), sudden cardiac death (aHR = 1.35), and stroke (aHR = 1.22). **Combined Androgen Blockade**: Increased risk of coronary heart disease (aHR = 1.27). **Orchiectomy**: Increased risks of coronary heart disease (aHR = 1.40) and myocardial infarction (aHR = 2.11). **Oral Antiandrogen Monotherapy**: Not associated with significant increases in any outcomes studied.

Table 1 (continued)

Ref.	Study model	Drug	Dosage / administration route	Outcome of therapy
[87]	The study involved male ARKO mice (androgen receptor knockout mice) and their wild-type (WT) littermates. Additionally, Rat H9c2 cardiac myoblast cells were used in cell culture experiments.	**Doxorubicin (DOX)**	**Mice**: 20 mg/kg DOX administered via intraperitoneal (i.p) injection. **Cell Culture**: H9c2 cells were treated with DOX at a concentration of 1 µM.	**Mice**: DOX treatment reduced the survival rate of both male WT and male ARKO mice, with a significantly lower survival rate in ARKO mice (28% vs. 68% in WT). DOX treatment caused early-phase left ventricular dysfunction, more severe in ARKO mice. ARKO mice exhibited more pronounced mitochondrial damage, increased cardiac superoxide production, and higher levels of lipid peroxidation in response to DOX. DOX treatment led to increased apoptosis of cardiac cells in both WT and ARKO mice, but ARKO mice showed a significantly higher number of apoptotic cells and a lower Bcl-2-to-Bax ratio. DOX treatment resulted in suppressed Akt phosphorylation and reduced Tfam expression in the myocardium of ARKO mice, indicating greater susceptibility to DOX -induced cardiotoxicity. **Cell Culture**: Testosterone, when used as an AR agonist in H9c2 cells, enhanced Akt phosphorylation and Tfam expression via an AR- and PI3K-dependent pathway, indicating a protective mechanism against DOX -induced cardiotoxicity.
[108]	Prospective, longitudinal study **Population**: Elderly Swedish men and women (opposite-sex twins) **Age**: 71 to 80 years at baseline; 82.4 years at follow-up **Sample Size**: 425 subjects (230 men, 195 women) at baseline; 277 subjects (132 men, 145 women) at follow-up	**Hormone Studied**: Progesterone (physiologic concentrations)	**Administration Route**: Natural physiologic serum concentrations measured; no external administration **Time Points**: Baseline (1996) and 8-year follow-up (2004)	Higher serum progesterone levels were significantly associated with increased mortality ($P < 0.001$) and congestive heart failure (CHF) ($P < 0.01$) at follow-up. The association with CHF remained significant even after adjusting for inflammatory markers (CRP), cystatin, and insulin levels. **Conclusion**: Elevated physiologic concentrations of progesterone in elderly individuals were associated with an increased prevalence of CHF and higher mortality rates, independent of other risk factors.
[110]	**Experimental Design**: The study included: Principal study with 8 nonpregnant, 10 pregnant, and 6 nonpregnant progesterone-treated rats. Preliminary study with 6 additional nonpregnant rats. Control studies with 1 nonpregnant, 1 pregnant, and 1 progesterone-treated nonpregnant	**Cocaine HCl**	**Cocaine Concentrations**: Ranging from 10^-16 M to 10^-4 M, added to the muscle bath at 30-minute intervals. **Progesterone Dosage (for pretreatment)**: 7 mg/kg, administered intramuscularly for 3 consecutive days.	**Nonpregnant Rats**: Muscles remained functional up to 10^-4 M cocaine. Positive inotropy (increased dT/dt) was observed up to 10^-7 M, with negative inotropy at higher concentrations. **Pregnant and Progesterone-Treated Nonpregnant Rats**: All muscles became nonfunctional at 10^-5 M cocaine. These groups exhibited only negative inotropy with increasing cocaine concentrations. **Proportion of Nonfunctional Muscles**: Significant differences were observed among the groups at certain cocaine concentrations. **Parameter Measurements**: Peak tension (PT), time to peak tension (TPT), and rate of tension formation (dT/dt) were used to assess muscle response. The negative inotropy in pregnant and progesterone-treated groups was due to decreased PT and TPT.

Table 1 (continued)

Ref.	Study model	Drug	Dosage / administration route	Outcome of therapy
[111]	Rat Papillary Muscles • **Groups**: Untreated (Control) ($n=12$) Progesterone (7 mg/kg) for 3 days ($n=12$) Progesterone (7 mg/kg) for 3 days + RU 486 (10 mg/kg) for 3 days ($n=12$) Progesterone (7 mg/kg) for 3 days + single low dose RU 486 (10 mg/kg) ($n=6$) Progesterone (7 mg/kg) for 3 days + single high dose RU 486 (50 mg/kg) ($n=6$) RU 486 (10 mg/kg) for 3 days ($n=6$) RU 486 (10 mg/kg) for 3 days without exposure to cocaine ($n=6$)	**Progesterone**: 7 mg/kg **RU 486 (Mifepristone)**: Low dose: 10 mg/kg High dose: 50 mg/kg	**Progesterone**: Administered daily for 3 days **RU 486**: Administered daily for 3 days or as a single dose 1 h before decapitation.	**RU 486 Reversal of Progesterone-Enhanced Cardiotoxicity**: RU 486 treatment effectively reversed the increased sensitivity to cocaine-induced cardiotoxicity that was observed in rats pretreated with progesterone. **Functionality at Higher Cocaine Concentrations**: Papillary muscles from rats treated with RU 486 (either for 3 days or as a single high dose) remained functional at significantly higher cocaine concentrations (up to 10^-3 M) compared to those treated with progesterone alone, which became nonfunctional at much lower concentrations (around 10^-7 M). **Positive Inotropy with High-Dose RU 486**: The group treated with a single high dose of RU 486 exhibited a biphasic response, showing positive inotropy at lower cocaine concentrations, followed by negative inotropy at higher concentrations. This pattern was absent in the group treated with a single low dose of RU 486, which only displayed negative inotropy. **RU 486 Alone**: In the absence of cocaine, RU 486 alone did not significantly affect papillary muscle contractility, indicating that its protective effects are specific to the context of cocaine exposure.
[130]	Female Sprague-Dawley rats were used, weighing between 225–250 g. The rats were utilized to study the synthesis, release, and effects of oxytocin (OT) in the heart.	**Oxytocin (OT)**.	Peripheral injection of oxytocin was administered intravenously (i.v.) in previous studies referenced. During the experiment, OT was also analyzed through heart homogenates, perfusion of isolated hearts, and RT-PCR of cardiac tissues.	OT was synthesized and released by the rat heart, particularly in the atria. OT presence in the heart influenced the release of atrial natriuretic peptide (ANP). Peripheral injection of OT in rats decreased mean arterial pressure in a biphasic manner: an initial pressor effect followed by a prolonged decrease in arterial pressure. OT's natriuretic properties may contribute to blood volume regulation. OT was shown to reduce heart rate and force of atrial contractions, suggesting a role in cardiac output and blood volume reduction
[131]	the study involved adult female and immature female Sprague Dawley rats. The immature female rats were specifically implanted with a silastic tube containing diethylstilbestrol (DES), an estrogen analogue, for 48 h.	**Diethylstilbestrol (DES)**, an estrogen analogue	The DES was administered via implantation in a silastic tube for 48 h.	DES also increased oxytocin (OT) levels in the vena cava from 3497 ± 350 to 7756 ± 445 pg/mg protein but did not affect OT concentration in the aorta.

Table 1 (continued)

Ref.	Study model	Drug	Dosage / administration route	Outcome of therapy
[145]	To investigate the therapeutic effects of liraglutide, oxytocin, and granulocyte colony-stimulating factor (G-CSF) in a doxorubicin (DXR)-induced cardiomyopathy rat model. 40 male Sprague–Dawley rats.	40 male Sprague–Dawley rats. **Groups**: **Normal Group**: 8 rats with no treatment. **DXR Group**: 32 rats administered with doxorubicin to induce cardiomyopathy, divided into 4 subgroups: **Placebo (DXR + Saline)**: 8 rats treated with 0.9% NaCl saline solution. **DXR + LIR**: 8 rats treated with liraglutide. **DXR + OX**: 8 rats treated with oxytocin. **DXR + G-CSF**: 8 rats treated with filgrastim (G-CSF).	**Doxorubicin (DXR)** **Liraglutide (LIR)** **Oxytocin (OX)** **Filgrastim (G-CSF)** **Placebo**	**Doxorubicin (DXR)**: **Dosage**: 2.5 mg/kg/day intraperitoneally (i.p.), administered every other day for 6 doses (total dose 15 mg/kg). **Liraglutide (LIR)**: **Dosage**: 1.8 mg/kg/day i.p. for 15 days. **Oxytocin (OX)**: **Dosage**: 160 µg/kg/day i.p. for 15 days. **Filgrastim (G-CSF)**: **Dosage**: 100 µg/kg/day i.p. for 15 days. **Placebo**: **Dosage**: 0.9% NaCl saline solution, 1 ml/kg/day i.p. for 15 days.

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Competing interests
The authors declare no competing interests.

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