Sex differences in anthracycline-induced cardiotoxicity: the benefits of estrogens

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Sex differences in anthracycline-induced cardiotoxicity: the benefits of estrogens

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Anthracyclines are the cornerstone for many oncologic treatments, but their cardiotoxicity has been recognized for several decades. Female subjects, especially before puberty and adolescence, or after menopause, seem to be more at increased risk, with the prognostic 16 impact of this sex issue being less consistent compared to other cardiovascular risk factors. Several studies imply that sex differences could depend on the lack of the protective effect of sex hormones against the anthracycline-initiated damage in cardiac cells, or on 18 differential mitochondria-related oxidative gene expression. This is also reflected by the results obtained with different diagnostic methods, such as cardiovascular biomarkers and imaging techniques (echocardiography, magnetic resonance, and nuclear medicine) in the diagnosis and monitoring of cardiotoxicity, confirming that sex differences exist. The same is true about protective strategies from anthracycline cardiotoxicity. Indeed, first studied to withstand oxidative damage in response to ischemia/reperfusion (I/R) injury, cardioprotection has different outcomes in men and women. A number of studies assessed the differences in I/R response between male and female hearts, with oxidative stress and apoptosis being shared mechanisms between the I/R and anthracyclines heart damage. Sex hormones can modulate these mechanisms, thus confirming their importance in the pathophysiology in cardioprotection not only from the ischemia/reperfusion damage, but also from anthracyclines, fueling further cardio-oncologic research on the topic.

Keywords Anthracycline cardiotoxicity . Gender differences . Pathophysiology, monitoring, and protection from anthracycline cardiotoxicity

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INTRODUCTION

Anthracyclines are first-line therapies for the treatment of many malignancies; unfortunately, their efficacy is limited by cardiotoxicity (CTX), which is dose-dependent. Recent clinical guidelines on cardiotoxicity from anticancer drugs highlight that identification of subjects at a higher risk is a fundamental step in successful screening and pre-emptive treatment [1-3]. Many factors including cumulative dose, body mass index >30kg/m2 (especially for anti-HER2 compounds) [4], age (elderly and pediatric population treated with anthracyclines) [5-8], concomitant or previous radiation therapy, previous cardiotoxic anticancer therapies, pre-existing cardiovascular disease (CVD) [9], demographic and other CV risk factors, as well as common lifestyle and genetic risk factors may predispose patients to CTX, already at mild to intermediate doses of anthracyclines [1,2,5, 10-12].

In particular, the association between obesity (BMI ≥ 30 kg/m2) and high risk of heart failure has been well established. In addition, previous studies demonstrated that obesity was an important prognostic factor that affected both overall survival and disease-free survival in patients with breast cancer [13]. The mechanisms by which obesity could negatively influence cardiotoxicity are affected by numerous confounding factors. Obesity may increase the expression of pro-inflammatory adipokines and downregulate the anti-inflammatory adipokines, which could result in an adipokine imbalance and maintain a chronic inflammatory state to promote the development of cardiovascular diseases. Second, patients with obesity are more sensitive to the cardiotoxic effects of anthracyclines; an animal model of rats with a high lipid diet showed similar results. Finally, obesity is significantly associated with activation of neurohormones, increased oxidative stress, increased hemodynamic load, and remodeling of the left ventricle[14] .

In addition, ErbB2 (or HER2) seems to be a modulator of oxidative stress, with anti-ErbB2 drugs being able to block protective mechanisms triggered by ErbB2, thus enhancing the oxidative damage induced by anthracyclines. The interactions between anthracyclines and trastuzumab have been extensively studied. Importantly, in breast cancer, coadministration of trastuzumab with ANTs in the first trials increased the latter's toxicity and is now avoided [15–18].

Also, protocols with elevated anthracyclines dosages (cumulative doses higher than 350 mg/m^2) are being seldom used, due to the increased risk of cardiotoxicity.

It is important to assess the best protocols for early identification of these high-risk patients and for follow-up during cancer therapies, in order to be able to obtain optimal protection from cardiac damage [19]. This paper describes the importance of sex differences in pathophysiology of anthracycline cardiotoxicity, in the assessment and monitoring imaging techniques of this cardiomyopathy, and in the protection from cardiac damage induced by this chemotherapeutic. In terms of protection, here we focus on the role of estrogens, acknowledging that in the CECCY trial, no difference was seen between carvedilol and placebo in both subgroups pre- and post-menopause [20], while in the MANTICORE [21],there is no mention of menopausal status.

SEX DIFFERENCES OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Anthracyclines can lead to cell dysfunction and death by interfering with mitochondrial function, bioenergetics, signaling pathways and redox balance [5,22]. Most of these targets are known to exhibit sexual dimorphism, like "redox features" of cells (i.e., different aspects of redox-associated molecules and enzymes in regard to gender differences in terms of the intracellular production and biochemical activity of reactive species) and expression of mitochondria-related genes at different ages [23,24] In addition to pharmacodynamics, sex-specific differences in pharmacokinetics (absorption, distribution, excretion) may have important clinical consequences, influencing drug side effects. Regarding doxorubicin and its main metabolite doxorubicinol, important intra- and inter-patient variations in pharmacokinetic parameters have been demonstrated [25]. Several authors showed that men have a significantly higher doxorubicin clearance than women [26]. This was supported by the finding of a higher proportion of doxoubicinol detected in the men, which could be related to a greater aldoketoreductase activity. [*27*]. Moreover, doxorubicin and doxorubicinol might accumulate following a reduced expression of p-glycoprotein in females, leading to higher ate of cardiotoxicity [28].

A comparable sex-based difference has been reported for the pharmacokinetics of epirubicin [27]. Therefore, sex-specific characteristics in anthracycline-induced cardiotoxicity can be potentially expected based on both the pharmacodynamic and pharmacokinetic profile.

Experimental data point toward better resistance of females regarding CTX with involvement of mitochondria and less oxidative stress, in fact very few studies have been conducted in humans, with female patients in clinical studies rather appearing to be more susceptible to doxorubicin-induced CTX [1,29,30]. This apparent paradox may be explained because both age and the menopausal state of female patients seem to be the two most important determinants of the sex-specific differences observed in the clinical setting, with higher susceptibility of prepuberal girls and post-menopausal women (Figure 1). Studies in young children receiving anticancer drugs for hematological malignancies [29,31] suggest that prepuberal girls are more susceptible to develop early or late cardiac toxicity than boys of the same age. These data are consistent with absence of female hormones at this age. Unfortunately, no survey has been conducted to specifically assess sex differences in the occurrence of anthracycline cardiotoxicity in adults. Studying the cardiac status of long-term survivors (at least 5 years after therapy) and estimating the features of subclinical cardiotoxicity induced after conventional treatment of lymphoma with doxorubicin, some authors found that male sex was related, together with other factors, to the development of subclinical cardiotoxicity [32]. In cohort studies of cancer survivors, the predicted 10-year cumulative incidence of congestive heart failure for males without or with preexisting cardiac disease is higher than in females [33,34].

In addition, the majority of breast cancer patients are post-menopausal [35], supporting the hypothesis of protection conferred by female sex hormones against doxorubicin cardiotoxicity. Interestingly, doxorubicin itself seems to be likely to cause premature ovarian failure, with a sharp decline in female sex hormones [36].

In studies concerning hematological malignancies, both sexes were treated risk factor for adverse cardiac events and the authors attributed this to a higher baseline cardiac disease in males [33]. In addition, data with hematological malignancies in postmenopausal women suggest that

similar baseline cardiovascular health in elderly men and women leads to similar susceptibility to anthracycline-induced cardiotoxicity [37]. Oxidative stress is well known to play a major role in anthracycline-induced cardiotoxicity. Reactive Oxygen Species (ROS) include several oxygen radicals such as Superoxide ($O^{-2}\bullet$) and hydroxyl radicals ($OH\bullet$), and non-radicals molecules, e.g. hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$). Also the Reactive Nitrogen Species (RNS) comprise radicals such as Nitric Oxide ($NO\bullet$) and Nitric Dioxide ($NO_2\bullet$), and non-radicals, *e.g.* nitrous acid (HNO_2) and dinitrogen tetroxide (N_2O_4)

Overproduction of ROS and RNS induced by anthracyclines determines redox stress, which induces cardiac injury [5], including DNA damage and lipid peroxidation, leading to membrane injury and/or apoptosis and alterations of the enzymatic activity of the mitochondrial redox system. Among altered enzymes are those of the respiratory complexes, the enzymes of Krebs cycle, oxidative phosphorylation, and β-oxidation and nitric oxide synthases (NOSs) [18]. While cross-talk in breast cancer cell lines between estrogen receptors and ROS/Notch/Wnt pathways may play an important role in regulating cell death, differentiation, and angiogenesis [38, 39], a complex inter-relationship between estrogen receptors and enzyme activity involved in redox mechanisms may sustain different oxidative stress that mediates cardiotoxicity in a gender-specific manner. In support of this hypothesis, the work of Gonzalez and colleagues [40] demonstrates that adult tumor-bearing male SH rats are more cardiosensitive to doxorubicin treatment than female or hormone-deficient animals. These results suggest that repro181ductive hormones regulate doxorubicin-induced 182cardiotoxicity and the selective cytotoxic mechanism likely 183functions through the greater activation of oxidative stress 184and apoptosis in male SH rats [40].

SEX DIFFERENCES IN ASSESSMENT AND MONITORING OF ANTHRACYCLINES TOXICITY

Beside the pathophysiology of anthracycline-cardiotoxicity, sex differences may also prompt differential assessment and monitoring of patients who are treated with these drugs.

Transthoracic echocardiography (TTE) is the most useful tool to monitor cardiac function in patients undergoing chemotherapy because of its safety, availability and low cost [41]; nonetheless, there are some sex-related differences that should be considered during a TTE evaluation of patients with suspected cardiotoxicity. Indeed, pathophysiological and epidemiological features, specific of female sex, often imply higher heart rate, smaller ventricles with seemingly higher contractility, supraventricular arrhythmias, and higher prevalence of HFpEF [42,43.]. Although LVEF is a gross and poorly sensitive parameter to evaluate cardiotoxicity, it is still the most used parameter for follow-up of oncologic patients [1,44]. The last TTE recommendations indicate as normal a LVEF (by 2D-modified Simpson's rule) >52% for men and 54% for women [45]. Cardiotoxicity has been defined as a decrease in LVEF of >10% to a value <53% [44] (or <50% independent from sex) [1]. However, LVEF is poorly sensitive for the detection of small changes in LV contractility, particularly if these are limited to few segments and in hypertrophic, small ventricles, as often occurs in women. [46,47].Thus, it should be combined with wall motion score index (WMSI) calculation which enables the identification of early regional damage very common in women treated with trastuzumab [44](Figure 2). A 5-unit fall of contractile reserve at low-dose dobutamine stress echocardiography in women with breast cancer seems to be able to predict subsequent LVEF reduction <50% [48].

Importantly, WMSI has been applied in previous clinical studies. A work from the early son hematological malignancies suggested that the 16-segment evaluationof LV function at rest by WMSI might be superior to global 2D measurement of EF. Moreover, gradual worsening of WMSI during anthracyclines paralleled the decline of radionuclide EF [49]. Also, autopsy studies have shown that the cardiac injury caused by anthracyclines is patchy, and at times is limited to one or more ventricle walls [50]. Therefore, segmental abnormalities can be detected before any global systolic LV dysfunction is apparent. More recently, in childhood cancer survivors (CCS) treated with anthracyclines, platinum, and/or radiotherapy between 1976 and 1999, at 18 years post-treatment, there was an increased prevalence of abnormal WMSI compared to controls, and NT-proBNP was associated to increased WMSI [51]. In addition, CCS with persistent LV regional wall motion

abnormalities (WMA) show reduced LV myocardial performance, evaluated through 3D speckle tracking echocardiography, compared with those without WMA, despite a preserved LVEF. Multiple linear regression analysis identified global radial strain as a significant determinant of the existence of WMA in these patients [52]. 9Indeed, global systolic longitudinal strain (GLS) was recognized to accurately predict a subsequent decrease in LVEF in several studies on women treated with anthracyclines with or without additional agents [53]. A relative percentage reduction of GLS of >15% from baseline is considered abnormal and a marker of early LV subclinical dysfunction in the last position statement [1],based on the results of a study in women with breast cancer treated with trastuzumab, with or without anthracyclines. In this context, it is important to refer to 248meanvaluesforGLSaccordingtosexandage, because values of GLS are slightly higher in women than in men [54]. Kocabay and colleagues reported a mean normal GLS of 20.7±2 for men and 22.1±1.8 for women [55].These values are almost identical to the ones reported by the Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study for the same vendor, showing an effect of gender on GLS values [56]. Interestingly, in early 2019, Barros and colleagues analyzed prospectively the role of LV WMSI among echocardiographic parameters in the prediction of development of cardiotoxicity in breast cancer patients undergoing chemotherapy. In the multivariate analysis using the logistic regression model, LVWMA, LV systolic dimension increase and GLS reduction were strongly associated with cardiotoxicity and could be use full in risk stratification of these patients [57]. In summary, during cardiac toxicity monitoring it is very helpful to refer to current recommendations on the cardiac chamber normal values [45]. It is also strongly recommended not only to use TTE parameters of global function such as EF, volumes, and GLS, but also to refine the analysis through the regional function assessment (WMSI and bull 's eye map of longitudinal strain),in both baseline patient 'sex amination and during follow-up [58]. As for the other cardiac evaluations (valves, atria, right ventricle, pericardium), no particular gender-related difference was found in TTE studies on cardiotoxicity diagnosis and monitoring.

Cardiovascular magnetic Resonance (CMR) is an ionizing radiation-free imaging method accepted as the gold standard for quantifying biventricular parameters. It is well known that biventricular function parameters are strongly correlated to gender and age [59]. Thus, in clinical practice it is strongly recommended to apply cut off values according to gender and normalized to body surface area (BSA) for the volumes and the mass in order to accurately detect cardiotoxicity related to anthracyclines. Many studies showed a significant decrease in LVEF due to chemotherapy treatment. In adult patients LVEF changes seem to be not affected by sex [60]. One study involving 62 long-term survivors of childhood cancer showed a trend toward a male predominance among those with an abnormal LVEF (29% vs 9%; P=0.053) and RVEF (39% vs 18%; P=0.057) [61]. Post-treatment biventricular volumes and LV mass were significantly higher in males, but these parameters were not normalized to BSA [62]. .Moreover, these results can be a consequence of the different morphology of male and female hearts, due to different adrenergic and hormonal states [63], body weight, height, different muscular mass, and body conformation. Importantly, sex differences can be observed in hemodynamics only in patients with normal LV function, but not with HF: Mitoff and colleagues speculated that the intrinsic or extrinsic factors responsible for sex differences in patients with normal cardiac function may be masked by the HF disease state or its treatment [64].

CMR provides an accurate and reliable evaluation of myocardial deformation by tagging techniques and few studies have demonstrated a significant decrease in longitudinal and circumferential deformation in chemotherapy-treated patients compared with controls [65]. In 46 asymptomatic post chemotherapy pediatric patients average circumferential and longitudinal strain magnitude was lower among male subjects, but this finding was due to the fact that gender affects normal values [62] and this issue was not taken in account in the study.

In the evaluation of anthracycline-induced CTX, CMR has the unique feature of providing information on tissue characterization. In fact, chemotherapeutic agents can cause oedema and hyperaemia, and even cellular necrosis and subsequent fibrosis. No study has evaluated if the prevalence of oedema was different between males and females. Macroscopic fibrosis can be detected

by means of the late gadolinium enhancement (LGE) technique and its presence is a strong prognosticator in all cardiomyopathies [44]. Diffuse myocardial fibrosis can be detected by T1 mapping with the evaluation of the extracellular volume (ECV). Toro-Salazar et al. found that T1 values after contrast administration were significantly lower in 46 long-term survivors in comparison with volunteers, revealing mild diffuse fibrosis [62]. In this study, as well as in a study by Tham et al [66], treated females showed higher mean ECV and lower postcontrast myocardial T1 values compared to males. Similar trends were detected in studies involving healthy subjects, and thus may reflect general sex differences.

In recent years, several *biomarkers* have been tested in the context of anticancer anthracycline-induced cardiotoxicity [67]. However, their use is severely hampered by important sex-specific differences [68]. Specifically, high sensitivity-troponin levels are about 50% lower in women than in men, while NT-proBNP levels are 50% higher [69]. Cardinale et al observed a greater prevalence of women in a group of patients with L-TnI levels > 0.08 ng/mL with a further increase; they also noted that in breast cancer TnI was most commonly positive [70]. However, another study showed that gender had no influence on the occurrence of cTnT positivity [71].

Use of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) to detect subclinical CTX is under investigation and results of published studies are controversial [72-74]. Also, increases of gal3 were found to be not predictive of anthracycline-induced CTX as defined by echo-derived LVEF reduction, and no data are available about differences between the sexes [75].

SEX DIFFERENCES IN CARDIOPROTECTION

Acknowledgment of sex differences in the mechanisms and clinical manifestations of anthracyclines cardiotoxicity may help elucidate cardioprotective approaches and develop therapeutic strategies. The concept of cardioprotection was introduced in the 1960s with pharmacological and reperfusion interventions, following an ischemic damage, and has evolved to include several

strategies that may save the functionality and vitality of cardiac cells jeopardized by ischemia/reperfusion (I/R) or toxic insult [76].

Despite the fact that experimental and pre-clinical studies clearly demonstrate cardioprotective benefits with conditioning strategies, their translation into clinical therapy has been disappointing [77]. This is due to several reasons, including the complexity of the cellular mechanism of cardioprotection. Furthermore, additional confounding factors such as age, comorbidities, comedications and gender may affect the injury, as well as the endogenous cardioprotective aspects triggered by conditioning procedures [78,79]. Cardioprotective strategies that have been first adopted against the oxidative damage that characterizes the ischemia/reperfusion injury, have different outcomes according to the sex analyzed. Estrogens may play a role in modulating protection from anthracyclines cardiotoxicity, too, but their roles in cardioprotection deserve further studies.

A number of studies analyzed the differences in I/R response between male and female hearts, and there are numerous epidemiological data reporting that premenopausal females have a reduced risk for cardiovascular disease [80–86]. In the majority of studies, estrogens are considered 380responsible for the better tolerance to I/R by female hearts [87],as we have already described in a previous section about estrogens protecting from cardiac injury from anthracyclines. Endogenous estrogens may affect with tonic and phasic effects cardiovascular homeostasis in premenopausal females and may interfere with the development of several cardiovascular diseases, including coronary artery disease (Fig. 3). Acting on three receptors (ERs), namely ER α, ER β, and 388GPER, estrogens exert transcriptional regulation. Moreover, GPER is implicated in rapid, phasic signaling via RISK pathway. Indeed, estrogen receptor activation induces the activation of PI3-kinase (PI3K)/Akt signaling converging on nitric oxide (NO) synthases (NOS) [87]. Nitric oxide plays a central role in mechanisms of cardioprotection and may be a key factor in gender differences. Estrogen-induced NO production favors S-nitrosylation (SNO) and closure of L-type Ca2+channels so that cytosolic and mitochondrial calcium overload during ischemia and early reperfusion is reduced [88]. Mechanisms related to the control of Ca2+ homeostasis and mitochondrial function

may be important in determining gender differences not only in response to I/R, but also to anthracycline challenge. The importance and gender differences of NO pathway in regulating the expression of genes relateddirectlyandindirectlytocardiomyocyteCa2+ handling have been recently confirmed by Bienvenu and coworkers [89].

Recently, Murphy and colleagues have demonstrated a characterization of the sex-dependent cardiac SNO proteome [90]. Interestingly, higher level of SNO in membrane fractions derived from female hearts with respect the level found in male hearts have been described, [91]. The same group also showed that female hearts display higher cardiac eNOS expression and that the estrogen-dependent NOS activation/phosphorylation induces NO production, which in turn enhances SNO protein levels and consequently a cardioprotective phenotype occurs. Conversely, in male hearts, the expression of eNOS is reduced, with minor production of nitric oxide derivative and SNO protein levels [90]. The cardioprotective effects of SNO proteins are demonstrated in several reports [92]. In female hearts, it has been also demonstrated that enhanced S-nitrosoglutathione reductase (GSNOR) activity may play a role in the cardioprotective pathway by limiting protein SNO from accumulating to levels that are at risk to trigger deleterious nitrosative stress [90].

As we have already described in a previous section, estrogens are very important not only in modulating the ischemia/reperfusion damage, but also in protecting from cardiac injury from anthracyclines. Indeed, oxidative stress and apoptosis are shared mechanisms between the I/R and anthracyclines heart damage. Hence, anthracyclines are better tolerated in female adult cardiomyocytes [93] in experimental models [40]. Intriguingly, regardless of any therapy, cancer itself can induce cardiac atrophy and autophagy in a sexually dimorphic way, with estrogens conferring protection against cancer-induced cardiac atrophy and body weight loss by signaling through its receptor [94].

Other mechanisms of doxorubicin cardiotoxicity are related to mitochondrial dysfunction and down-regulation of energy metabolism signaling pathways [5,22]. In male rats, doxorubicin treatment resulted in important alterations in mitochondrial function, which appeared unaffected or remarkably

preserved in treated females [95]. Moreover, mitochondrial dysfunction and energy metabolism signaling pathways seem associated with early cardiotoxicity in males but not in females [95], with doxorubicin altering mitochondria more severely in males, as evidenced by a downregulation of gene expression of mitochondrial biogenesis, mitochondrial function and mitochondrial dynamic, decreased mitochondrial respiration, and mitochondrial DNA content. Also, a sex-specific impact of doxorubicin on the heart phospholipidome, especially on cardiolipin, an essential mitochondrial lipid, has also been shown [96].

We have shown recently that estrogens may influence the cardiotoxicity of antineoplastic drugs, with the activation of GPER mitigating the cardiotoxic effects of Doxorubicin (Dox), thus suggesting GPER as an interesting pharmacological target to limit the detrimental myocardial effects of Dox treatment [97]. Some animal studies show that females develop less cardiomyopathy and nephropathy than males after chronic administration of anthracyclines [98,99], but such protection is abrogated after ovariectomy [99]. On the other hand, 17-β-estradiol confers protection against cardiac injury in ovariectomized rats treated with Dox [100]. These observations seem to indicate a protective role of female hormones. Intriguingly, it has been also observed that testosterone is able to protect from ANT-induced damage in cardiac myocytes in vitro [101].

CONCLUSIONS

The studies we reviewed suggest there are sex differences in the triggering of specific cardioprotective signaling pathways in response to cardiac injury. Tonic and phasic estrogen actions on specific receptors may explain many of gender differences in I/R injury, in cardiotoxicity from anthracyclines, in post-ischemic systolic recovery and in conditioning protection. The intricate inter-relationship between estrogen receptors, NOS activity, and other related or not related mechanisms, acute and chronic conditions, and their roles in cardioprotection deserve further studies, with large clinical studies and more complex preclinical models that take into account sex differences, in order to get more insight into clinical applicability of novel approaches for diagnosis and protection from

anthracycline cardiotoxicity. Considering the impact that confounding factors including gender differences have on the triggering cardiac injury as well as on the effects of cardioprotective therapies, extrapolation from animal findings to clinical relevance in humans should be made cautiously [102],since estrogens may play a role of in increased risk of malignancy, with the majority of post-menopausal women having ER + breast cancer.

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FIGURE LEGENDS

Figure 1

Sexual dimorphism of anthracycline cardiotoxicity

Figure 2:

Bull's eye map of LV longitudinal strain showing early reduction of myocardial deformation at the basal LV segments (especially of the septum and anterior wall) in a woman treated with anticancer therapies.

Figure 3:

Estrogens and cardioprotection

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Figure 1

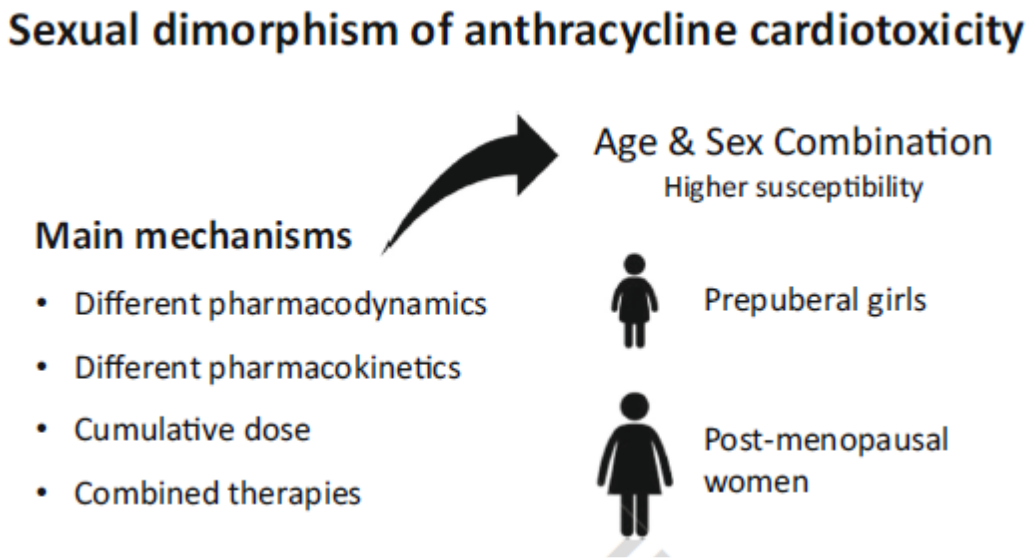


Figure 2.

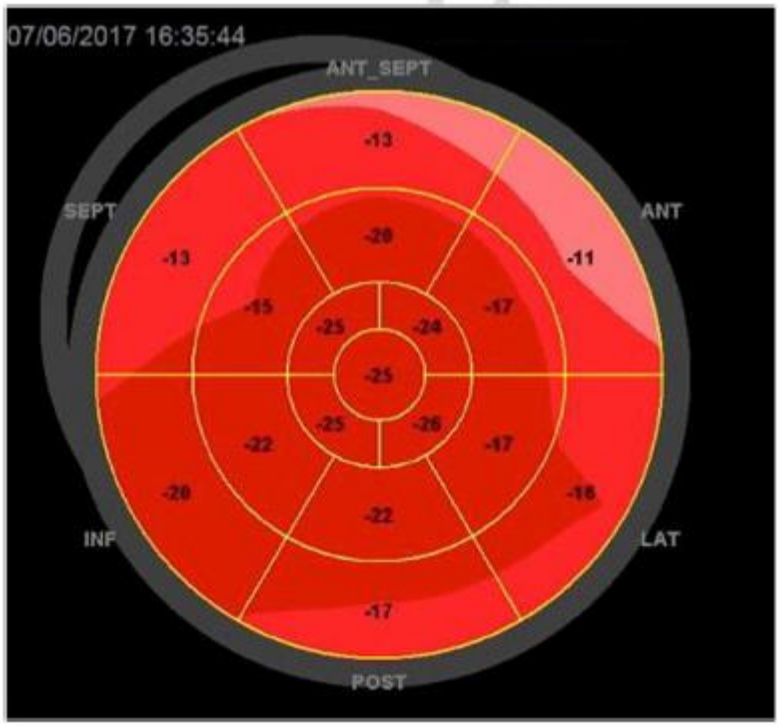
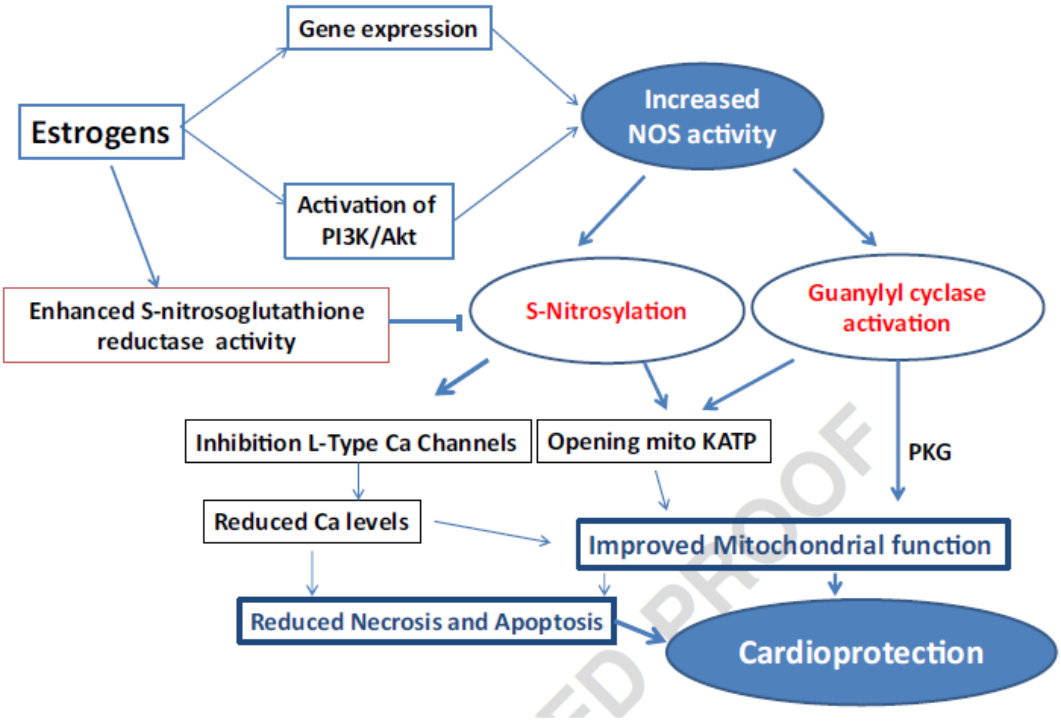


Figure 3


Gene expression
Estrogens
Increased NOS activity
Activation of PI3K/Akt
Enhanced S-nitrosoglutathione reductase activity
S-Nitrosylation
Guanylyl cyclase activation
Inhibition L-Type Ca Channels
Opening mito KATP
PKG
Reduced Ca levels
Improved Mitochondrial function
Reduced Necrosis and Apoptosis
Cardioprotection