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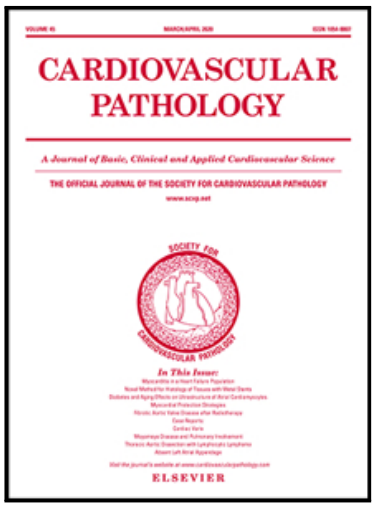

DOXORUBICIN-RELATED CARDIOTOXICITY: REVIEW OF FUNDAMENTAL PATHWAYS OF CARDIOVASCULAR SYSTEM INJURY

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Highlights

- Doxorubicin activates versatile pathways, mainly oxidative and calcium stress, endothelial and metabolic dysfunctions, topoisomerase, and glucose metabolism disturbances with a united endpoint – cardiomyopathy and associated heart failure.

DOXORUBICIN-RELATED CARDIOTOXICITY: REVIEW OF FUNDAMENTAL PATHWAYS OF CARDIOVASCULAR SYSTEM INJURY

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ABSTRACT

Over the years, advancements in the field of oncology have made remarkable strides in enhancing the efficacy of medical care for patients with cancer. These modernizations have resulted in prolonged survival and improved the quality of life for these patients. However, this progress has also been accompanied by escalation in mortality rates associated with anthracycline chemotherapy.

Anthracyclines, which are known for their potent antitumor properties, are notorious for their substantial cardiotoxic potential. Remarkably, even after six decades of research, a conclusive solution to protect the cardiovascular system against doxorubicin-induced damage has not yet been established. A comprehensive understanding of the pathophysiological processes driving cardiotoxicity combined with targeted research is crucial for developing innovative cardioprotective strategies.

This review seeks to explain the mechanisms responsible for structural and functional alterations in doxorubicin-induced cardiomyopathy.

Key words: Cardiotoxicity, Doxorubicin, Chemotherapy, Cardio-oncology.
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Ashot A. Avagimyan is the first and corresponding author of this submission and is part of his Doctor of Medical Sciences (DSc) degree work.

1. Introduction

According to the World Health Organization (WHO), oncological diseases are major contributors to global mortality, ranking second among cardiovascular diseases (CVD) [1]. Advancements in anticancer therapy have significantly improved the survival and quality of life of oncological patients [2].

In today's oncology practice, anthracycline-based chemotherapeutic agents, notably doxorubicin (DOX, also called adriamycin), which has been instituted since 1969, remain a cornerstone for treating malignant neoplasms [3]. DOX is a chemotherapeutic drug that is widely used to treat various types of cancers such as breast cancer, sarcomas, hematologic malignancies, and carcinomas [4]. The tumoricidal properties of DOX are based on its ability to intercalate into DNA, inhibit topoisomerase II, disrupt mitochondrial function, and increase free radical formation, which in turn leads to oxidative damage [5]. However, it is important to note that the precise mechanisms of DOX action are still not fully understood and are currently a topic of debate.

However, the extensive side-effect profile of DOX, including severe cardiotoxic complications, limits its use and often worsens patient prognosis. The incidence of cardiotoxicity has been rapidly growing, extending to younger demographics and those without prior health concerns [6]. Patients attaining stable and prolonged remission from oncological conditions are confronting a wide spectrum of cardiovascular complications, ranging from sinus arrhythmias to decompensated heart failure [7].

While cardiotoxicity is associated with nearly all chemotherapeutic agents, the cardiotoxic effect of anthracyclines is particularly concerning [8]. Historically, cardiotoxicity refers to a subclinical or clinical decline in the left ventricular ejection fraction; however, it now includes the onset of any clinical or subclinical manifestations of cardiovascular metabolism and function [9].

This review describes and evaluates existing data pertaining to the mechanisms governing structural and functional alterations in anthracycline-induced cardiomyopathy.

2. Magnitude of the problem

The magnitude of this concern is confirmed by data from the Pan-European CARDIOTOX-2020 registry, which revealed a 3.6-fold higher incidence of cardiovascular diseases among under-treatment and post-treatment cancer patients than in the general population [10].

The utilization of doxorubicin in clinical settings is restricted by its dose-dependent cardiotoxic nature, which becomes prevalent when the cumulative dose exceeds 400-700 mg/m^2 in adults and 300 mg/m^2 in children [11]. The risk increases exponentially when the cumulative dose exceeds these thresholds. Although a cumulative dose of 400 mg/m^2 poses a 5% risk of cardiotoxicity, it increases to 26% at 550 mg/m^2 [12]. Unfortunately, oncologists are often compelled to prescribe high drug doses. This places clinicians in a quandary, requiring a balance between cardiovascular toxicity and the detrimental impact on oncological prognosis if chemotherapy is withheld.

3. Parallels between oxidative and calcium stress: the final point is mitochondria.

3.1. Oxidative stress

The excessive production of reactive oxygen species (ROS) is a critical factor in the development of anthracycline-induced cardiotoxicity. This overproduction induces oxidative stress, resulting in alterations in cell membranes and intracellular organelles, especially in the mitochondria [13].

ROS formation initiated by DOX is intricate and occurs at several stages. The quinone fragment of anthracyclines is subjected to univalent reduction, forming semiquinone radicals via NADPH cytochrome P-450 reductase activity. Subsequently, the semiquinone form of DOX is oxidized by oxygen molecules, reverting to the initial quinone form and synthesizing superoxide anion radicals [14]. This transformation also causes "leaks" in the electron transport chain, resulting in redox-homeostasis disturbances and activation of multiple proinflammatory cascades [15]. In the presence of Fe^{2+}, H_2O_2 can generate $OH^{\cdot}$, which reacts with DNA, proteins, and lipids, leading to epigenetic damages such as DNA methylation, histone modification, and modification of non-coding RNAs (small interfering RNA molecules, microRNAs, and long non-coding RNAs) [16].

Every subsequent administration of DOX perpetuated this reaction cycle with oxygen molecules, creating more superoxide anion radicals and returning DOX to its original state. This continuous cycle, termed “redox renewal” of DOX, intensifies the cardiovascular damage related to lipid peroxidation (LPO) by generating free radicals [17,18].

Cardiomyocytes have a relatively low level of antioxidant protection, making the myocardium prone to damage by ROS and reactive nitrogen species (RNS). This can result in various morphological patterns such as homogenization, eosinophilic lesions (hypereosinophilia), clumpy decay, myocytolysis, and the development of mixed parenchymal fat-protein dystrophy of the myocardium coupled with replacement and reactive interstitial fibrosis [19]. Notably, the electrophysiological parameters of fat droplets, protein inclusions, and connective tissue differ from those of intact myocardium. These changes can indirectly lead to conduction abnormalities and myocardial fibrosis, contributing to the heart failure development [20].

In the context of discussing the mechanisms underlying the development of doxorubicin-related oxidative stress in the myocardium, the role of Yes-associated protein (YAP) is worth exploring. YAP is a key regulator of the Hippo signaling pathway and plays a crucial role in cell biogenesis. Under physiological conditions, YAP promotes the transcription of antioxidant enzymes such as catalase and superoxide dismutase [21]. However, *in vivo* studies have shown that doxorubicin-based therapy is associated with a significant intramyocardial reduction of YAP1 protein, coinciding with the activation of caspase-3 [22]. Doxorubicin not only inhibits the expression of YAP1 protein and messenger RNA but also leads to increased phosphorylation of YAP1 in the Ser127 domain [23]. Regarding the role of YAP1 in DOX-induced pathways of cellular death, it should be noted that YAP1 overexpression significantly reversed DOX-induced cell death by reducing caspase-3/7 activation [24]. In both H9c2 cells and mouse models, doxorubicin treatment decreased YAP expression and its downstream target genes such as CTGF, Birc5, and Park2 [25]. These findings suggest that doxorubicin affects the expression of YAP and its target genes, ultimately leading to cell death, myocardial fibrosis, and aging.

3.2. Mitochondrial dysfunction

DOX is a cationic molecule with hydrophilic and hydrophobic regions that allow it to penetrate the membranes of cytoplasmic organelles [26]. It predominantly accumulates in the mitochondria, reaching concentrations over 100 times that in the cytoplasm. Because of this accumulation, mitochondria are principally targeted by LPO end-products, specifically 4-hydroxynonenal and 4-hydroxyhexanal [27]. The cationic nature of DOX enables it to penetrate the mitochondrial membrane and irreversibly form a complex with cardiolipin protein, thereby disrupting its function and triggering the production of superoxide radicals [28]. This interaction leads to the uncoupling of oxidative phosphorylation complexes (OXPHOS), diminishing

adenosine triphosphate (ATP) synthesis and elevating the adenosine monophosphate (AMP)/ATP ratio, resulting in cardiomyocyte damage and contractile disturbances mediated by AMP-activated protein kinase (AMPK) [29]. DOX also destabilizes the intracellular energy reserves, affecting the structure and function of mitochondrial creatine kinase, an enzyme critical for converting creatine (Cr) to phosphorylcreatine (PCr), which is essential for replenishing the ATP pool. Furthermore, DOX inhibition of mitochondrial complex I triggers the opening of the mitochondrial permeability transition pore (mPTP), initiating a signaling cascade that results in apoptosis [30].

Cardiolipin is pivotal in maintaining myocardial homeostasis primarily through its involvement in the activation of electron transport chain enzymes. These enzymes include cytochrome C oxidase, NADH cytochrome C oxidoreductase, and cytoplasmic xanthine oxidase [31]. However, this crucial activation is hindered by the binding of DOX to cardiolipin. As these enzymes are integral components of complexes II - IV within the electron transport chain, their impaired activation disrupts oxidative phosphorylation. This leads to an energetic crisis, contractive abnormalities, and worsening cardiotoxicity [15].

Mitochondrial biogenesis occurs through two essential processes: fusion and fission [32]. Fusion is facilitated by outer mitochondrial membrane proteins, namely mitofusin 1/2 (Mfn1/2), and inner mitochondrial membrane proteins such as Optic Atrophy 1 (Opa1). In contrast, fission is regulated by dynamin-related protein 1 (Drp1). Drp1 functions by binding to its outer mitochondrial membrane receptor proteins, including mitochondrial division protein 1 (MTFP1), mitochondrial fission factor (MFF), and mitochondrial fission protein 1 (Fis1) [33].

An in vitro study utilizing the H9c2 cardiomyoblast cell line revealed a significant increase in mitochondrial division due to increased expression of Drp1, p-Drp1ser616, Fis1, and MFF proteins, along with the suppression of p-Drp1ser637. Conversely, a decline in the expression of Mfn1/2 and Opa1 leads to reduced mitochondrial fusion [34]. Further research has shown that DOX administration significantly enhances Drp1-mediated mitochondrial division and fragmentation while suppressing the synthesis of proteins associated with mitochondrial fusion [35]. These findings indicate that DOX disrupts mitochondrial dynamics by inhibiting fusion and stimulating fission, ultimately leading to dystrophic myocardial changes.

3.3. DOX and Nrf2

It is also important to observe alterations in the expression of transcriptional erythroid nuclear respiratory factor-2 (Nrf2). This factor serves as a sensor of oxidative stress. It regulates

the adaptive response to ROS compounds through the production of antioxidants such as glutathione S-transferase (GST), heme oxygenase-1 (HO-1), and NAD(P)H-quinone dehydrogenase 1 (NQO1) [36]. DOX activates the negative regulator of Kelch-like ECH-associated protein 1 (Keap1), which leads to proteasomal degradation of Nrf2 and subsequent suppression of antioxidant enzyme expression [37]. Thus, doxorubicin stimulates ROS production while simultaneously inhibiting the antioxidant defense mechanism in the myocardium [38].

In addition to inducing oxidative stress, DOX stimulates the development of calcium stress in cardiomyocytes through five complementary mechanisms [39]: (1) inhibition of the sodium-calcium exchange channel; (2) dysregulation of ryanodine receptor (RyR), sarcoplasmatic/endoplasmic reticulum calcium ATPase 2 alpha (SERCA2alpha), and phospholamban; (3) activation of calpains, which also induces titin degradation; (4) overexpression of transient receptor potential cation channel subfamily C member (TRPC) 3 and TRPC6 in ventricular cardiomyocytes; and (5) increased phosphorylation of calcium/calmodulin-dependent protein kinase II (CaMKII), promoting CaMKII-dependent sarcoplasmic reticulum calcium leakage. This results in diastolic calcium overload in rat myocytes and a diminished calcium release from the sarcoplasmic reticulum. It is critical to emphasize that excessive calcium accumulation leads to contractile failure and triggers cellular death [40].

The use of doxorubicin results in the breakdown of the interaction between endotheliocytes and cardiomyocytes, which ultimately leads to microcirculatory insufficiency and subsequent disintegration of myocardial function. In mice, doxorubicin treatment leads to a reduction in capillary density within the heart, resulting in an increase in the expression of activin receptor-like kinase (ALK) 4/5 ligands in cardiac cells. The expression of these ligands also decreases EC proliferation in cardiac endothelial cells. Thereby doxorubicin inhibits cardiac endothelial cell proliferation and angiogenesis [41]. This evolves into heart failure, often initially with a preserved ejection fraction, which may then transition to heart failure with a reduced ejection fraction.

A schematic overview of the above-mentioned parallels between DOX, oxidative stress, and mitochondrial dysfunction is shown in Figure 1.

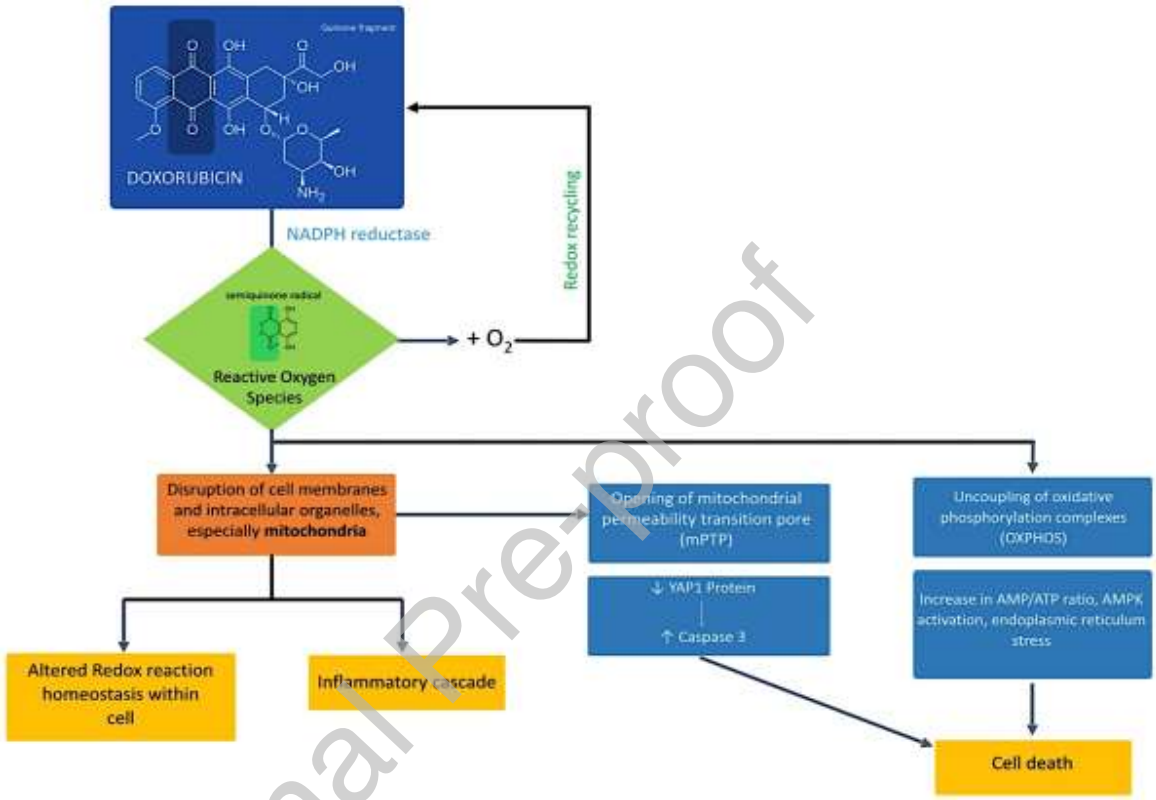

Figure 1. Redox-balance and doxorubicin-induced cardiotoxicity.
YAP1, Yes-associated protein 1

4. Endothelial dysfunction as an "orchestrator" of DOX-induced cardiotoxicity

4.1. DOX and endothelial cells

DOX-related ROS and reactive nitrogen species (RNS) significantly destabilize endothelial activity (dysregulation of endothelin-1, nitric oxide, homocysteine, adrenomedulin, intracellular and vascular cell-adhesion molecules, etc.), inducing a mixed phenotype of endothelial dysfunction (ED) where vasomotor, adhesive, and homeostatic functions are impaired, leading to endothelial-mesenchymal transition and coronary artery injury [42, 43]. This

multifaceted impairment lays the foundation for proatherogenic changes, carries considerable cardiovascular risk, and increases non-high-density lipoprotein (non-HDL) cholesterol in the blood [44].

At the beginning of the continuum of development of doxorubicin cardiomyopathy due to the inflammatory microenvironment, ischemia, and hypoxia of the myocardium, doxorubicin is characterized by an increase in the level of endotlin-1, followed by activation of type A and B receptors, which leads not only to vasoconstriction but also to the release of nitric oxide, adrenomedullin, and prostacyclin [45].

Nitric oxide (NO) is a versatile molecule that is crucial in the pathogenesis of heart failure, ischemia/reperfusion injury, and cardiomyopathy. DOX propagates cardiotoxicity by influencing NO levels in both plasma and myocardial homogenate supernatant [46]. It binds to endothelial nitric oxide synthase (eNOS), prompting the formation of semiquinone radical DOX. This radical reduces free oxygen to superoxide radicals, and in the presence of flavoenzymes, such as NADPH cytochrome P450 reductase and mitochondrial NADH dehydrogenase, DOX completes the one-electron reduction reaction [47]. This interaction with eNOS creates an imbalance between superoxide and NO levels, with a decrease in nitric oxide and an increase in reactive oxygen and nitrogen species formation, contributing to doxorubicin-induced myocardial damage [48].

Humans have three types of NOS: eNOS, iNOS, and nNOS. DOX also amplifies iNOS transcription and protein expression, leading to nitrotyrosine formation and increased mitochondrial superoxide levels in cardiac tissue. This cascade subsequently increases cardiomyocyte apoptosis and myocardial dysfunction [49]. Disruption of NO metabolism leads to excessive formation of RNS, especially nitrosonium cations, peroxynitrite, S-nitrosothiols, nitroxide anions, higher nitrogen oxides, and dinitrosyl iron complexes, which stimulate cell death through the development of nitrosative stress [50].

Xanthine oxidases also play an important role in DOX-mediated oxidative stress by promoting the generation of superoxide anions [51]. The one-electron reduction of DOX, catalyzed by xanthine oxidases, is central to the development of oxidative stress. This significance is evidenced by the cardiovascular damage observed with the application of febuxostat in various experimental models exploring both acute and chronic DOX-induced cardiotoxicity [52].

Thus, the effect of doxorubicin on the endothelium disrupts the interaction between endothelial cells and cardiomyocytes, with the subsequent development of myocardial dysfunction, as shown in Figure 2.

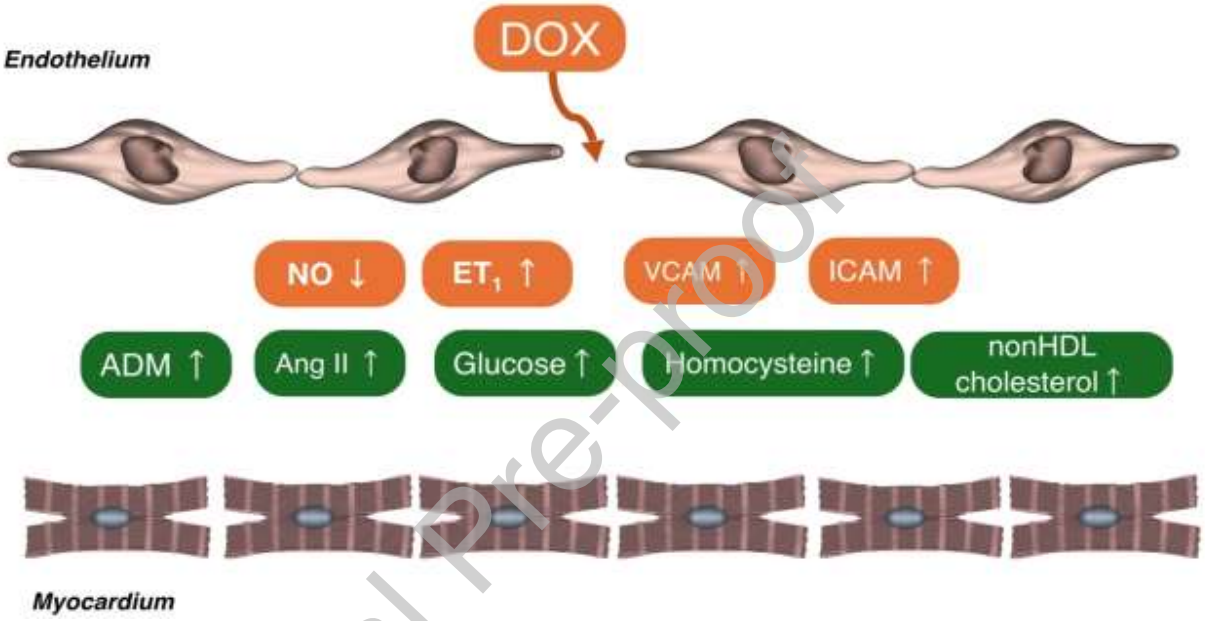

Figure 2. Impaired endotheliocytes-cardiomyocytes cooperation.
DOX, doxorubicin.

4.2. DOX and SMC

It is crucial to consider its impact on smooth muscle cells (SMCs) when discussing its implications in vascular wall remodeling. DOX enhanced SMC tone by disrupting acetylcholine-induced endothelium-dependent relaxation both in vivo and ex vivo. This ultimately leads to a series of cardiovascular changes, namely medial hypertrophy, increased peripheral vascular resistance, added afterload on the heart, and the development of left ventricular myocardial hypertrophy [53]. Endothelial cell apoptosis and a decline in eNOS expression contribute to increased vascular tonus, endothelial mucoid edema, endothelitis, deposition of modified lipoproteins in the intima, and other processes, all contributing to the development of DOX-

induced cardiomyopathy and vasculopathy [54]. Administration of DOX is also associated with a decrease in NO bioavailability, resulting in increased vascular tone, arterial wall stiffness, and formation of inter-endothelial gaps [37].

When we examined the cardiotoxic effects of DOX on SMCs, it is noteworthy that there was a shift in SMC behavior. They switch from a contractile state to a synthetic state, and can even differentiate into macrophage-like cells and migrate to the intima [55]. This phenomenon contributes to low-grade inflammation within the vascular wall, triggering stromal-vascular changes such as mucoid and fibrinoid swelling, necrosis, sclerosis, and hyalinosis, which in turn increases the stiffness of the vascular wall. Another significant concern is the manner in which DOX affects the calcium balance. DOX disturbs calcium homeostasis stress by interfering with Ca^{2+}-ATPase pumps in the sarco/endoplasmic reticulum and cell membranes [56, 57].

Doxorubicin and its metabolite doxorubicinol bind to cardiac ryanodine receptors (RyR2) and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2A) and detrimentally alter their activity, thereby impairing sarcoplasmic reticulum Ca^{2+} uptake [58]. One notable pharmacological action of DOX is its ability to block transient receptor potential vanilloid-2 (TRPV2) channels, which are members of the extensive nonselective cation channel (NSCC) family in cancer cells [59]. However, the role of TRPV channels extends beyond oncogenesis, tumor proliferation, and migration [60]. They also play a role in regulating SMC contraction by controlling calcium influx and maintaining calcium homeostasis [61].

5. Doxorubicin – versatile destabilizer of myocardium metabolism

The myocardium is an energy-dependent and energy-intensive structure. Hence, its metabolism is an adaptive and self-regulating functional biochemical system that switches between metabolic phenotypes to maintain optimal performance under variable conditions [62].

DOX is associated with the disruption of myocardial metabolism. Following the initial doses of DOX, the myocardium activates intrinsic compensatory mechanisms in response to metabolic shifts, aiming to normalize the type of energy substrate. This compensatory response is centered around enhancing the qualitative characteristics of type 1 glucose transporters (GLUT1) [63]. After the first course of DOX therapy, there was an elevation in myocardial GLUT1 recruitment to the cardiomyocyte cell membrane without modifications to the overall level. This increase stimulates the entry into cardiomyocytes [64].

However, it should be noted that the duration and effectiveness of this process depend on various factors, including the dose of the chemotherapy drug, frequency of administration, other components of the chemotherapy regimen (drug-drug synergism), and initial structural and functional state of the heart. DOX also leads to hyperglycemia development via the downregulation of PPARy and AMPk signaling inhibition in skeletal muscles [65, 66]. Thus, the initial elevation in glucose uptake mediated by DOX can be considered as an adaptive response to energy deficiency (an increase in the AMP/ATP ratio).

5.1. DOX and Sirtuins (SIRT) system

Sirtuins (SIRT) are nicotinamide adenine dinucleotide (NAD+)-dependent deacetylating enzymes that play a key role in maintaining normal myocardial function. They participate in many metabolic and homeostatic processes, including gluconeogenesis, fatty acid oxidation, oxidative phosphorylation, and endothelial function [65]. DOX disrupts the functioning of SIRT by inhibiting SIRT3 (a mitochondrial sirtuin) and mitochondrial NAD+-dependent protein deacetylase. Therefore, SIRT3 plays a crucial role in regulating mitochondrial bioenergetics by maintaining optimal redox homeostasis and controlling fatty acid oxidation and pyruvate utilization [67].

Furthermore, anthracyclines inhibit SIRT1 expression, exacerbate DOX-induced cardiotoxicity, and disrupt mitochondrial biogenesis and function. Sirtuin-1 is activated in response to an increase in the AMP/ATP ratio, and is closely related to the influence of AMPK and PCG-1a on energy metabolism. SIRT1 deficiency leads to NF-κB activation. SIRT1 deacetylates peroxisome proliferator-activated receptor-gamma co-activator-1 (PGC-1α), thereby activating a series of genes that contribute to mitochondrial dysfunction. This includes a reduction in the concentration and activity of Nrf1, which intensifies LPO [68].

5.2. DOX and Topoisomerase II

The cardiotoxicity of anthracycline drugs is also associated with inhibition of the α and β isoforms of topoisomerase II (Top-2) [69]. Interestingly, the molecular mechanism underlying the anticancer activity of the drug is inactivation of the α-isoform of topoisomerase II (Top II-α) by DOX in tumor cells. By binding to DNA and Top-2, DOX generates a Top2-DOX-DNA triple cleavage complex that triggers cell death [70]. However, similar changes also occur in the myocardium, and the pronounced sensitivity of the myocardium to DOX is attributed to the

relatively high level of top 2-β expression in cardiomyocytes [71]. Experimental studies have shown that species-specific deletion of Top-2β in mouse cardiomyocytes protects against DOX-induced double-stranded DNA breaks, transcriptome changes, and development of progressive heart failure [72].

5.3. DOX and Iron

DOX demonstrates a marked affinity for the plasma membrane owing to the difference in electrophysiological charge (DOX is positively charged, whereas the membrane is neutral). The positive charge of iron further accentuates this affinity, resulting in the formation of a potent and destructive Dox+Fe complex with subsequent ferroptosis development [73]. Doxorubicinol, a DOX metabolite, disrupts iron metabolism by removing iron from the Fe-S catalytic cluster of cytoplasmic aconitase (regulator of iron metabolism). This alteration augments the stability of transferrin mRNA and increases the expression of transferrin receptor (TfR) while concurrently suppressing the translation of iron-sequestering proteins [74]. Moreover, DOX directly inhibits ferritin iron regulatory element (IRE) mRNA in ferritin heavy and light chains, causing ferritin deficiency. This imbalance increases free iron levels and triggers dystrophic changes in cardiomyocytes, particularly coagulation and liquefaction [75].

An increase in the free iron pool results in the formation of ROS. A decreased iron regulatory gene HFE (human homeostatic iron regulator protein) heightens sensitivity to DOX-induced cardiotoxicity, causing increased iron accumulation in the myocardium and severe degenerative changes [76]. It has been confirmed that DOX-related intracellular iron deposits increase oxidative stress, which is a key phase of DOX toxicity. Thus, iron-chelating agents have proven efficacious in decreasing DOX-induced cardiotoxicity [77].

5.4. DOX and renin-angiotensin-aldosterone system (RAAS)

The effect of DOX on the renin-angiotensin-aldosterone system (RAAS) was also notable. DOX is associated with an increase in angiotensin II (AT-II) synthesis and intensified signaling through its receptors [78]. Elevated levels of AT-II are observed in both the myocardium and paraventricular nucleus of the hypothalamus. This suggests that AT-II plays a pivotal role in the pathogenesis of anthracycline cardiomyopathy by influencing remodeling of the myocardium and blood vessels to affect the central mechanisms regulating the cardiovascular system [78]. DOX administration significantly increased the activity of the myocardial isoform of angiotensin-converting enzyme (ACE). This heightened ACE activity stems from integrin activation due to

myocardial hyperfunction [79] and increased infiltration of macrophages in the myocardium, which can express ACE. Notably, myocardial infiltration by these macrophages intensifies with each successive course of DOX-containing chemotherapy [80].

AT-II can initiate apoptosis in ventricular cardiomyocytes via the AT-1R axis of RAAS regulation regardless of the pro-apoptotic potential of anthracyclines. Therefore, the myocardium undergoes extensive damage owing to both the direct toxicity of anthracyclines and apoptosis mediated by AT-II [81]. Moreover, AT-II can cause fibrosis and inflammation in the myocardium via angiotensin receptor-1 (AT-1R). Cardiac fibroblasts, which are responsible for producing matrix proteins, have AT-1R on their surface. When stimulated by AT-II, various signaling pathways are activated, including mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated kinases (ERK1/2). This activation results in the overexpression of collagen type 1 and 3 genes and increases the density and proliferation of fibroblasts. Furthermore, low-grade inflammation associated with angiotensin II acts as a favorable microenvironment to trigger and/or aggravate the mechanisms of myocardial fibrosis. This creates a foundation for various rhythm and conduction disturbances, and the progression of heart failure [82].

5.5. DOX and Cardiac Fibrosis

DOX chemotherapy in cancer patients leads to the blockade of mRNA transfer and impedes the synthesis of matrix metalloproteinase 1 (MMP-1) protein. The subsequent suppression of tumor cell motility activates other MMPs, such as MMP-2 and MMP-9, which in turn promote collagen formation in heart tissues. This triggers the onset of myocardial fibrosis, predominantly by enhancing signals mediated by TGF-β and the phosphorylated form of the transcription factor SMAD3 [83].

Through the aforementioned mechanisms, the pathogenetic continuum of cardiotoxicity results in pronounced morphological changes. These pathomorphological changes in the heart vary from minor microcirculatory disorders to large-focal cardiosclerosis [84], starting in the subendocardial layers of the left ventricle and gradually progressing to involve both ventricles and atria [85, 86].

The induction of myocardial fibrosis can manifest even at doses considered noncardiotoxic. Beyond the previously outlined mechanisms, the stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) signaling pathway is strongly associated with the low-grade inflammatory mechanisms mentioned above [87]. Myocardial fibrosis is accompanied by an elevated expression

of myocardial necrosis, stress, and remodeling markers. These changes can be verified immunohistochemically, by assessing the specific antigen expression of actin, vimentin, desmin, caspase-3, GATA-4, etc. [88], as well as by laboratory markers such as high-sensitivity troponin I (TnI) and N-terminal pro B-type natriuretic peptide (NT-pro-BNP) [89].

It is important to acknowledge that myocardial fibrosis, along with its fatty dystrophy, serves as the morphological foundation for the evolution and progression of multiple rhythm and conduction disturbances, destabilization of a hypertrophied heart, and ultimately, the development of heart failure. These changes occur against the background of ischemia, resulting in acidosis and electrolyte imbalances. The electrophysiological potentials of intact myocardial tissue, zones of lipomatosis, and fibrosis zones differ, leading to blocks of impulse conduction and the generation of ectopic foci of trigger automatism, both in macro- and micro-re-entry types.

A schematic overview of the above-mentioned parallels between DOX, oxidative stress, and mitochondrial dysfunction is shown in Figure 3.

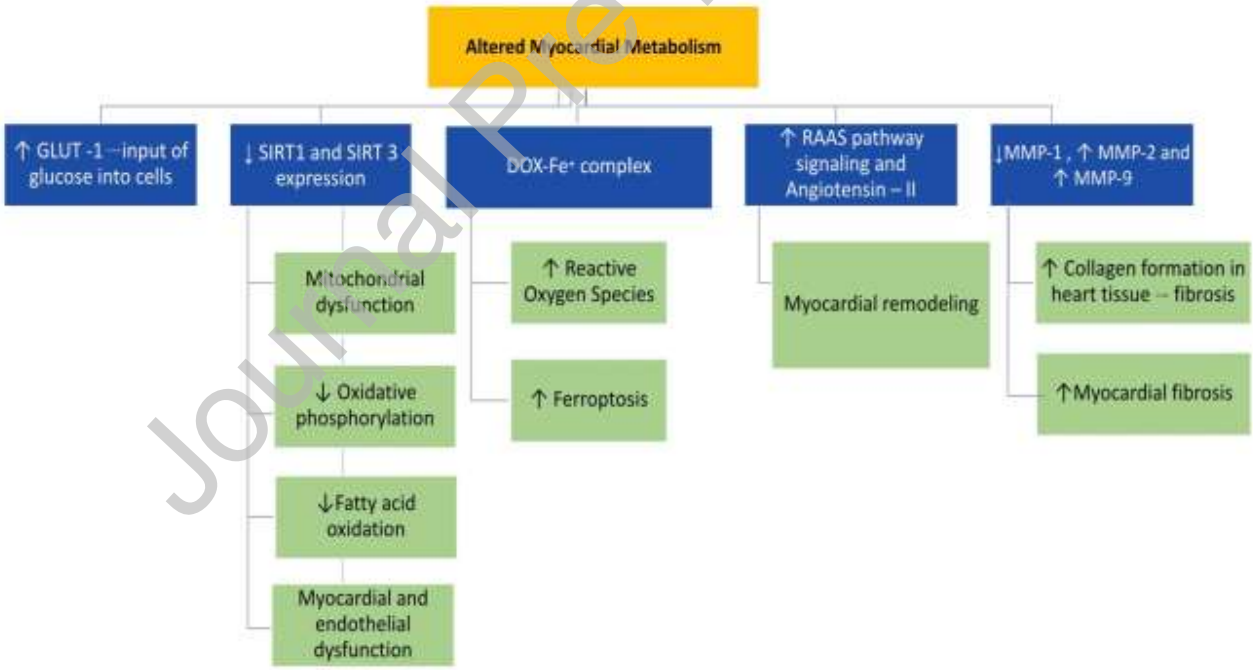

Figure 3. Myocardial metabolism disturbances and doxorubicin-induced cardiotoxicity.
DOX, doxorubicin; GLUT-1, type 1 glucose transporter; Sirt, Sirtuin; RAAS, renin-angiotensin-aldosterone system; MMP, matrix metallopeptidase.

6. Inflammation as an orchestrator in mechanisms of DOX-related cardiomyopathy

When examining the role of the inflammatory cascade in the development of anthracycline cardiomyopathy, inflammasomes have been found to have distinct importance, specifically the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome. It is a multiprotein complex that regulates the production of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-18, and gasdermin D by activating caspase-1 [90]. This inflammasome is triggered by nuclear factor kappa B (NF-κB) signaling, which correlates with DOX-related pathways of myocardial injury. The upregulation of transcription (sometimes referred to as "priming" or "step 1") of various components in this pathway involves NLRP3, inactive proIL-1β and proIL-18 precursor proteins [91]. The pathway begins with an assembled (active) inflammasome complex that realizes its effect through stress signals (e.g., ROS) and leads to the activation of caspase-1.

Caspase-1 catalyzes the cleavage of these cytokines into biologically active forms, resulting in their release from the cells. It has been proven that DOX (a component of anthracycline) is an inflammasome activator, thus through the pathway described, it enhances the production of myocardial cytokines and macrophage infiltration [92]. Upon activation of the inflammasome in cardiomyocytes, there is an increase in the levels of cardiomyocyte 'apoptosis-associated speck-like protein, ' which consists of a caspase recruitment domain (ASC) and cleaved IL-18 [93]. Inflammasome signaling in atrial cardiomyocytes is sufficient to induce arrhythmias, as evidenced by the elevation of inflammasome activation markers in the atria [94].

7. DOX and Myocardial Atrophy

In the context of DOX cardiomyopathy, the mechanisms of myocardial atrophy are worth discussing. The transcription factors that regulate the development of autophagy in the myocardium are forkhead box O (FoxO) factors, namely FoxO1, FoxO3, FoxO4, and FoxO6. Autophagy plays a key role in maintaining homeostasis and the development of myocardial pathology. FoxOs, in this way, are essential regulators of maintaining myocardial muscle mass [95]. FoxO depletion prevents muscle loss and weakness by suppressing the autophagy-lysosome (ALS) and ubiquitin-proteasome (UPS) systems by inhibiting AKT activity [96].

FoxOs regulate the promoters of nearly half of the atrophy genes, such as muscle RING finger 1 (MuRF1), atrogin-1/muscle atrophy gene-1 (MAFbx), and B-cell lymphoma 2 (Bcl-2) 19-kDa interacting protein 3 (Bnip3) [97]. Muscle RING finger 1 (MuRF1) and Muscle Atrophy F-

box (MAFbx)/atrogin-1 were identified over ten years ago as two muscle-specific E3 ubiquitin ligases whose transcription is increased under atrophy-inducing conditions, resulting in their designation as markers of muscle atrophy.

Atrogin-1 and MuRF-1 are two E3 ubiquitin ligases that mediate ubiquitin-mediated protein degradation [98]. DOX activates FoxO1 phosphorylation, thereby increasing the level of FoxO1 in the nucleus, accompanied by an increase in MuRF1 expression. It should be noted that DOX-mediated activation of FOXO1 and its target genes has time- and dose-dependent features. For example, a low dose of DOX (5 mg/kg) does not induce MuRF1 expression. In contrast, a higher dose of 20 mg/kg significantly increased marker levels (mRNA FoxO1 and atrogin-1), which returned to normal seven days after DOX injection [99].

8. Doxorubicin and pathways of cellular deaths

To investigate the endpoint of DOX-induced cardiotoxicity, it is important to recognize the complex nature of the cell death mechanisms involved. Cardiomyocyte death (apoptosis, autophagy, pyroptosis, ferroptosis, and necrosis) plays a pivotal role in the pathogenesis of myocardial fibrosis, diastolic dysfunction, and ultimately heart failure associated with DOX-induced cardiotoxicity [100].

8.1. DOX-related apoptosis

Doxorubicin triggers cardiomyocyte death through various regulated cell death pathways, with apoptosis being the predominant mechanism [101]. By promoting the opening of the mitochondrial permeability transition pore (mPTP), doxorubicin leads to calcium accumulation within the mitochondria, resulting in the disruption of mitochondrial membrane potential (MMP) and the release of cytochrome c, ultimately initiating apoptosis [102]. Oxidative stress resulting from doxorubicin also enhances apoptosis through the peroxidation of cardiolipin, a sensitive marker of oxidative stress, leading to mPTP opening and subsequent cytochrome c release [103].

It is important to note that DOX activates both intrinsic mitochondria-dependent and extrinsic apoptotic pathways. Apoptosis can be divided into three phases: an early stage involving caspase activation and phosphatidylserine expression; an intermediate phase involving DNA fragmentation, chromatin condensation, and membrane phospholipid metabolism; and a late phase characterized by membrane swelling and cell shrinkage [104].

Top2β overexpression induces cardiomyocyte sensitivity to DOX, eventually leading to DNA damage. This is because the formation of DOX-Top2β-DNA complexes induces genotoxic stress, which promotes p53 phosphorylation and initiates DOX-induced apoptosis [105]. An additional pathway of damage to cardiomyocytes involves the peroxisome proliferator-activated receptor (PARP) enzymes formed by DOX oxidative stress, ultimately resulting in apoptotic cell death [106].

8.2. DOX-related autophagy

Autophagy is a cellular process involving degradation and recycling of cellular organelles and structures that can contribute to cell death [107]. Autophagy also plays a crucial role in cellular homeostasis [108].

Doxorubicin has been found to increase the levels of Beclin-1, p62, and microtubule-associated protein 1A/1B-light chain 3 (LC3)-II/LC3-I [109]. Notably, damaged mitochondria can be selectively removed through a process called mitophagy [110]. Upon doxorubicin-driven mitochondrial damage, activation of PTEN-induced kinase 1 (Pink1) and parkin occurs, which serve as markers for damaged mitochondria and initiate mitophagy [111]. Doxorubicin enhances mitophagy, and the use of the mitophagy inhibitor mdivi-1 has shown a protective effect against doxorubicin-induced cardiotoxicity by preserving mitochondrial membrane potential (MMP) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), as well as related signaling pathways [112].

Doxorubicin initially stimulates the formation of autolysosomes, but soon after subsequent injections of doxorubicin, myocardial autophagy is suppressed, with the formation and accumulation of dysfunctional autolysosomes being independent triggers of redox-driven injury [113].

8.3. DOX-related pyroptosis

Pyroptosis is an autonomous, genetically programmed form of cell death that is tightly regulated through inflammasome activation and subsequent induction of proinflammatory caspase-1 (as well as caspases 3, 4, and 11) [114, 115]. This intricate process leads to cell lysis and the release of proinflammatory cytokines, notably IL-1β and IL-18, via inflammasomes [116].

A key trigger of pyroptosis involves activation of caspase-1, which subsequently activates gasdermin D (GSDM-D), a key executioner of pyroptosis. Following cleavage by caspase-1, GSDM-D liberates its N-terminal domain, leading to the formation of pores ranging from 1.1 to

2.4 nm on the plasma membrane [117]. This pore formation facilitates the release of IL-1β and IL-18 [118].

In DOX-induced cardiotoxicity, BNIP3 protein expression is upregulated, thereby stimulating caspase-3 and promoting GSDME-dependent pyroptosis. Perturbations in GSDME function and downregulation of BNIP3 in cardiomyocytes have been implicated in the development of DOX-associated cardiotoxicity in cellular models [119]. Consequently, targeting the interaction between pyroptosis-related molecules such as NLRP3, caspase-1, and BNIP3 represents a promising strategy for mitigating the cardiotoxic effects of doxorubicin.

8.4. DOX-induced ferroptosis

DOX-related elevation in myocardial iron content, discussed in Section 5.3, is a crucial factor in the development of cardiotoxicity due to ferroptosis. Ferroptosis is a form of programmed oxidative necrotic cell death that involves iron-dependent lipid peroxidation [120]. DOX causes ferroptosis, which contributes to cardiotoxicity, and DOX intercalation into mitochondrial DNA decreases heme synthesis, reduces iron utilization, and promotes iron accumulation [121].

DOX causes heme degradation, which releases free iron and impairs heme synthesis necessary for iron use, resulting in iron overload and ferroptosis in the mitochondria. The administration of DOX is also linked to an increase in HO1 levels, which catalyzes heme degradation, leading to the release of Fe^{2+} into the mitochondria [122]. These findings are consistent with increased intracellular iron levels, which are also associated with high mobility group heme 1 (HMGB1) degradation. In DOX rats, *HMGB1* gene knockdown led to a reduction in markers of ferroptosis and myocardial damage [123]. The overexpression of certain enzymes, such as Alas1, or the use of the Alas1 product 5-aminolevulinic acid (5-ALA), has been shown to prevent DOX-driven iron overload in the myocardium [124]. These findings support the crucial role of mitochondrial iron in the induction of ferroptosis and progression of DOX-induced cardiotoxicity.

9. Pathogenic aspects of doxorubicin-induced cardiotoxicity prevention

Despite extensive research, the development of cardiovascular complications in patients with cancer under- and post-treatment remains largely unresolved. In 2022, a collaborative effort between the European Society of Cardiology (ESC), European Hematology Association (EHA), European Society for Therapeutic Radiology (ESTRO), and International Cardio-Oncology

Society (IC-OS) resulted in the publication of the first European guidelines on cardio-oncology [125]. Despite extensive research spanning over seven decades on cardiovascular disease (CVD) related to chemotherapy, the majority of recommendations (guidelines and supporting evidence) are supported by evidence of level B (evidence includes a single randomized, controlled trial or a large, nonrandomized study) and level C (evidence includes expert opinion, small or retrospective studies, or registries) [126].

9.1. Antioxidant approach

Over an extended period, experimental and clinical investigations in the field of cardio-oncology have been based on the principle of restoring normal myocardial redox homeostasis. Various *in vivo* and *in vitro* studies have provided a basis for the potential cardioprotective properties of molecules with antioxidant properties such as curcumin [127], resveratrol [128], ascorbic acid [129], tocopherol [130], melatonin [131], coenzyme Q10 [132] etc. Unfortunately, these substances have not demonstrated significant results in clinical practice. Our research group conducted a preclinical analysis of the cardioprotective properties of trimetazidine, demonstrating significant normalization of the oxidative status, endothelial function, and cholesterol metabolism [133]. These findings provide a potential pathogenic rationale for further clinical studies.

9.2. Iron metabolism based cardioprotection (Iron chelating agents)

In the context of strategies for the prevention of DOX-induced cardiotoxicity, it is noteworthy that one approach focused on normalizing iron metabolism. Dexrazoxane permeates cardiomyocytes and undergoes intracellular biotransformation (hydrolysis) to produce a chelate metabolite with an open-ring structure that binds iron [134]. Consequently, disruption of the anthracycline-iron complex inhibits the formation of iron-induced free radicals that are responsible for ferroptosis. The United States Food and Drug Administration (US FDA) endorses dexrazoxane for cardioprotection during DOX treatment [135]. However, its adoption remains limited, mainly because of concerns raised by the European Medicines Agency (EMA) regarding potential reductions in the efficacy of anti-cancer treatments [136].

9.3. Antidiabetic drugs as a novel instrument in cardio-oncology

It is important to emphasize that the primary criterion for a cardioprotective agent in cardio-oncology is its neutral or “ideal” anti-oncogenic potential [137]. In this context, the impact of sodium-glucose cotransporter type 2 inhibitors is noteworthy, as despite previous oncological

concerns, they are recognized for their diverse mechanisms and, notably, their potential to limit oncogenesis [138, 139, 140], which is particularly crucial within the scope of cardio-oncology.

Given the obesity epidemic and metabolic complications associated with chemotherapy, there has been a shift from an antioxidant-focused to a metabolism-stabilizing approach. Fundamental translational studies have shown the effectiveness of newer antidiabetic drugs, including metformin [141], dapagliflozin [142], semaglutide [143], and tirzepatide [144], in preventing cardiometabolic complications of chemotherapy. Our research group evaluated the cardioprotective reserve of dapagliflozin in a toxic-ischemic cardiomyopathy model [145] and conducted a meta-analysis of the effectiveness of dapagliflozin administration for preservation of the left ventricular ejection fraction, which yielded promising results [146]. Based on our own data, the administration of dapagliflozin resulted in the normalization of myocardial oxidative status, endothelial function, lipid metabolism, and C-reactive protein levels, with subsequent normalization of TnI and Nt-Pro-BNP levels.

9.4. RAAS inhibitors (ACE blockades), β-blockers and statins in the scenario of real clinical practice

Analyzing the above-mentioned first European recommendations at the time of their publication (2022), the preferred strategy in cardio-oncology is non-specific for DOX-related cardiotoxicity and is based on RAAS inhibitors (Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEi), β-blockers (BBs), and statins. It is important to acknowledge that a considerable number of patients do not respond favorably to this strategy [147]. Additionally, the strategy of combining RAAS inhibitors with beta-blockers lacks data regarding the incidence of HF [148].

DOX administration has been found to increase the activity of cardiac angiotensin-converting enzyme and angiotensin II, leading to overexpression of angiotensin II type 1 receptor (AT1R) [149]. This process results in oxidative stress, inflammation, fibrosis, and apoptosis of cardiomyocytes, ultimately leading to cardiotoxicity. Although RAAS inhibitors have been suggested as potential protective agents against DOX-induced cardiotoxicity, recent meta-analyses have indicated that their use may not significantly reduce the risk of overt heart failure and CV mortality [150].

Studies have shown that BBs and ACEI/ARBs can mitigate the decline in LVEF during trastuzumab and anthracycline treatments. Compared with placebo, patients receiving BB or

ACEI/ARB treatment exhibited significantly higher LVEF levels during trastuzumab treatment, but not during anthracycline treatment [151]. These findings suggest that both treatments can protect breast cancer patients from cardiotoxicity.

The PRADA study (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) [152] involved 120 patients undergoing AC therapy with or without trastuzumab, who were randomized to receive therapy with ARB (candesartan), BB (metoprolol), or placebo. The candesartan group exhibited a modest decline in LVEF compared with the placebo group, whereas no significant change in LVEF decline was observed in the metoprolol group. The PRADA EXTENDED trial [153], with a 2-year follow-up, showed no significant difference in LVEF reduction between groups.

Preliminary results from the SAFE (Cardiotoxicity Prevention in Breast Cancer Patients Treated with Anthracyclines and/or Trastuzumab) study evaluated the effect of bisoprolol, ramipril, or their combination in reducing subclinical cardiac damage associated with DOX [154].

Studies on the use of preemptive statins to prevent DOX-induced cardiotoxicity have reported mixed results. Although multiple studies have suggested promising outcomes, data obtained from different related clinical trials, such as PREVENT [155], STOP CA [156], and SPARE-HF [157], are discutable and sometimes difficult to compare. A meta-analysis of nine studies involving 5532 patients, revealed that patients who did not receive statins had a greater decline in LVEF after chemotherapy than those who did. Moreover, chemotherapy patients who received statins had a significantly higher final mean left ventricular ejection fraction and lower risk of incident heart failure than those who did not. However, the change in the mean difference for left ventricular end-diastolic volume (LVEDV) between the statin and non-statin groups was not statistically significant [158].

10. Conclusion

In this review article, our research group explored the fundamental aspects of DOX-induced cardiotoxicity, encompassing several aspects, especially oxidative stress, mitochondrial dysfunction, topoisomerase blockage, myocardium metabolic disturbances, inflammation-related pathways, and subsequent analysis of diverse pathways of cardiac myocyte death. The primary objective of developing new treatment modalities should focus on inhibiting DOX's multicellular action of DOX, which affects various cell types in the heart and vessels, and underscore the need

for additional research to understand DOX-related cardiovascular complications. Unfortunately, there are currently no specific guideline-based approaches for preventing DOX-induced cardiotoxicity. The recommended approach has a low level of evidence and corresponds to a significant number of nonresponders. A more detailed understanding of the pathogenetic mechanisms is the basis for developing a multi-omics fingerprint for preventive protocols to reduce the incidence of cardiovascular complications in doxorubicin-treated patients. Moreover, heart failure can manifest clinically in different phenotypes and endotypes, which is why a more targeted evaluation of DOX-driven cardiotoxicity should be employed in a real clinical setting in the era of personalized medicine.

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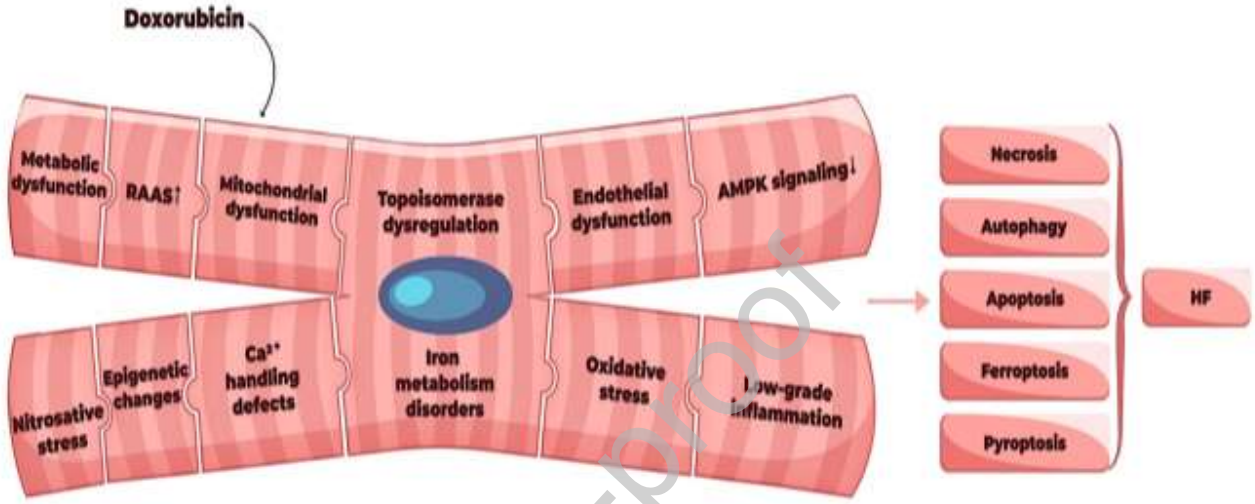
GRAPHICAL ABSTRACT



RAAS, renin-angiotensin-aldosterone system; HF, heart failure

Conflict of Interests:
N/A