

Doxorubicin-induced Cardiomyopathy: Mechanisms, Diagnosis and Therapeutic Drugs

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Abstract. Doxorubicin (DOX) is an anthracycline drug for cancer treatments, including breast cancer, prostate cancer, and some other types of malignancies. However, doxorubicin is toxic related does, exerting cardiotoxicity most severely on patients. Cardiotoxicity is defined as “toxicity that affects the heart” by the National Cancer Institute. Cardiomyopathy is a major side-effect. There are modern studies which showed there are direct relationship between the severity of DOX-induced cardiomyopathy and the amount of DOX that patients consumed. This review explains the mechanisms of DOX-induced cardiomyopathy, specifically the causes for the oxidative stress, mitochondria’s role in DOX-induced cardiomyopathy, and the relations with NOS ROS, and eNOS that ultimately cause the oxidative stress, which will be a crucial factor for the occurrence of DOX-induced cardiomyopathy. Besides, summarizing the diagnosis imaging modalities including echocardiogram, tissue doppler imaging, cardiac resonance imaging and multigated acquisition, and introduce the drugs that can alleviate cardiomyopathy, which are dexazoxane and liposomal DOX with their mechanisms and experiments results demonstrated.

Keywords: Doxorubicin, cardiomyopathy, oxidative stress, diagnosis, dexazoxane.

1. Introduction

Doxorubicin, also known as DOX (Compound CID: 31703), is a common drug in treatment in breast cancer and tumors. It belongs to the family of Anthracycline which is used for treatment in pediatric cancer in chemotherapy. However, in recent years, it is dented by the modern researchers that there are several side-effects after consumption various doses of the drug, and cardiomyopathy is the most typical one which present in most of patients after chemotherapy with DOX. There are specific calculations which have shown 10% of patients, who used DOX as the major source for treatment in chemotherapy, got DOX-induced cardiomyopathy under ten years [1]. There are also factors like gender and age which will have obviously vary the possibilities of getting this sickness.

Before treating the side effects of DOX chemotherapy or making decision for treating breast cancer patients with DOX continuously, it is essential to diagnose and detect the problem by using sensitive and specific assessment techniques. The current clinical practice commonly used is to take consecutive assessments by imaging [2].

This review summarizes the drug mechanism after consumption of DOX by explaining oxidative stress in distinctive organelles, the diagnosis technique for cardiomyopathy, and therapies for DOX-induced cardiomyopathy.

2. Drug Mechanism inside human body

2.1. Oxidative Stress

Oxidative stress is deemed as one of explanations for the existence of the side-effect after consuming DOX contained drug in chemotherapy. Oxidative stress can be defined as imbalance between free radicals which did not have even electron in any oxygen contained molecules and easily have reaction with other molecules. There are approximately two ways to induce oxidative stress with

DOX, which are mitochondria's dependency ROS and NOS dependency in ROS, and each of them would have unique role in human body [1, 3].

2.2. Mitochondria's Role in DOX-induced Cardiomyopathy

When mitochondria are exposed to DOX medicines, they exert a large amount of effect. Due to the fact that DOX is a cation ion once it enters the human body, it will interact with cardiolipin via electrostatic attraction and bind to the inner mitochondrial layer. It would inhibit protein synthesis due to disruptions in the electron transport chain, because cardiolipin is required for normal protein synthesis. By forming more superoxide ions, the mitochondrial activity is impaired, and ATP is no longer generated, resulting in cardiomyopathy.

However, current study indicates that a small dose of DOX would not produce serious cardiomyopathy, and the effect on mitochondria would likewise be subtle. In the research conducted by Rui A. Carvalho et al., wistar Hans rats (75g-100g) were given DOX at a concentration of 2mg/kg, and the findings were determined using ^{13}C isotopomer analysis [4]. Thus, mitochondria are critical for the pathophysiology of DOX-induced cardiomyopathy, and avoiding mitochondrial dysfunction appears to be a feasible therapy.

2.3. eNOS, iNOS, eNOS relates with DOX-induced Cardiomyopathy

Uncoupling of nitric oxide synthases (eNOS) is a decisive factor in the development of cardiovascular disease, and there is data suggesting eNOS-dependent ROS has a unique effect on DOX-induced cardiomyopathy. Disrupting eNOS transcription through a through a process distinct frothrough a process distinct fromech th thanism distinct from that of cardioprotective genes, mat of cardioprotective genes, mat of cardioprotective genes, may protect against DOX-induced heart dysfunction, damage, and mortality [5]. Additionally, they show that the cardiac pathology caused by DOX is worsened by cardiomyocyte-specific overexpression of eNOS .

Moreover, DOX produced the greatest amount of cardiac ROS in eNOS transgenic animals and the least amount in eNOS knockout mice. Within 30 minutes of DOX therapy, both endothelium-independent and endothelium-dependent vasodilation were remarkably reduced, as was serum nitrate. These observations in humans coincide with the dysregulation of eNOS activity caused by DOX, particularly in the vascular bed [5]. It is controversial whether DOX-induced cardiac dysfunction is caused by inducible nitric oxide synthase (iNOS). Cardiotoxicity caused by DOX has been shown to be increased and shielded by iNOS deficiency [1]. In acute models of DOX cardiotoxicity, no increase in iNOS mRNA levels was observed, although this result appears to be model-dependent, as other research have showed that DOX raises iNOS mRNA levels. The protective effect of iNOS on hearts is caused by the NO production, whereas the cardiotoxic effect is triggered when NO reacts with O_2 , generating absorption of peroxynitrite. Additionally, peroxynitrite is considered to damage DNA, activate poly (ADP-ribose) polymerase, and produce energy imbalances that eventually result in cell death.

In summary, when DOX has been consumed by patients, it will experience the effects which caused by eNOS and released O_2^- , O_2 , NADPH, and NADP^+ . After releasing of these chemicals, it will cause the formation of ROS and ultimately cause oxidative stress (Fig. 1).

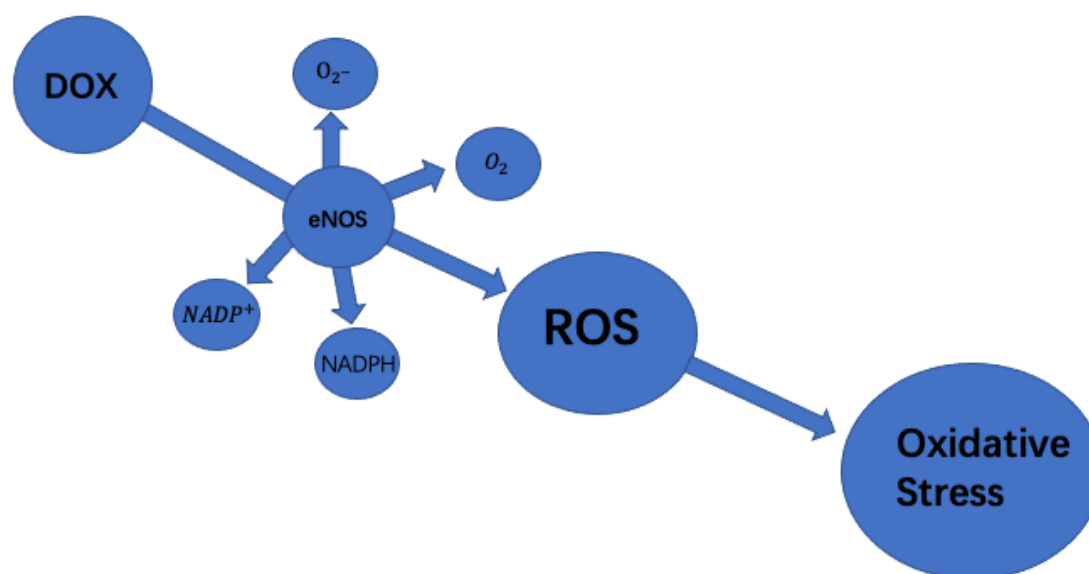


Figure 1. Mechanisms of DOX induced oxidative stress

3. Diagnosis by imaging

3.1. Ecocardiogram

Echocardiogram (echo) is the most frequently used diagnostic modality for DOX-induced cardiomyopathy recently. The left ventricular ejection fraction (LVEF) of patients is usually monitored before, during and after treatment by DOX. However, obtaining and interpreting the images can be variable, which means that patients with cardiac damage induced by chemotherapeutic drugs should not just be measured decreases in their LVEF [6]. It is doubted by some studies that LVEF is not effective as an index of systolic function; instead, diastolic function or combination should be monitored [7, 8, 9]. The most straightforward—2D echo, is not even easy; several ways to measure and calculation of indices of function are required [10]. 3D and 4D can help to get more accurate measurements, but they are not accessible in a wide range [11]. There are multiple advantages of echocardiogram: it is economical compared to other modalities, and patients are not exposed to radioactive materials, for example x-rays [12]; what's more, functional manifestations of other diseases could be visualized to assess the larger vessels or to diagnose regurgitation by combining with Doppler [13, 14]. However, echocardiogram may not be appropriate for high-risks patients due to its lower sufficient predictive power [15].

3.2. Tissue Doppler Imaging (TDI)

Tissue doppler imaging related to echo, is a system that uses ultrasonic signals to reflect frequency changes by moving tissues. TDI is used to evaluate blood flow traditionally, but through measuring high amplitude and low frequency signals, tissue can be assessed instead [16]. Strain and strain rates could also be analyzed by TDI, being able to diagnose subclinical cardiotoxicity [17]. TDI is an effective and non-invasive modality that is ideal for diastolic function, because preload does not affect early diastolic movement, which means it can monitor cardiotoxicity through diastolic changes. However, the drawbacks of TDI include detecting the direction of movement and distinguishing between active and passive motion [18, 19].

3.3. Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance imaging is another modality applied for assessing myocardial function, perfusion evaluation and tissue characterization [20]. There are multiple categories of CMR, including convention CMR, Cine CMR, multi-parametric CMR and contrast-enhanced CMR [15]. Conventional CMR assesses the fundamental cardiac function, but it cannot achieve measurements of 3D intramyocardial deformation compared with Tagging CMR [21].

Table 1. Use and main drawbacks of CMR in the assessment of the myocardium

Type	Use	Drawbacks	References
LGE	Short examination times High contrast-to-noise ratio	Intravenous contrast agent administration needed	[22]
Molecular imaging	Myocyte apoptosis and necrosis	-	[23, 24]
Cine	Ventricular function assessment Measurements of volume, derived mass and deformation	Segmentation required	[21]
Tagging	Ventricular torsion Intramyocardial deformation	Tag time limited in cardiac cycle	[25]

3.4. Multigated acquisition (MUGA)

Multigated acquisition (MUGA), is also called equilibrium radionuclide angiography (ERNA), monitors a radioactive tracer by using a gamma camera. The images taken from the heart are then utilized for creating a movie and calculating the ejection fraction. The extremely reproducible test results make the measurements among observers less mutable [26]. Early research claimed that MUGA is better than traditional echo at measuring the ejection fraction of healthy patients [27]. What's more, MUGA is able to detect patients who should stop continuing treatment before they become symptomatic [28]. MUGA can be performed during break or exercise and as well as assess diastolic dysfunction. Testing under stress performed in each modality detects where the heart does not pump blood as vigorously and consequently receives less oxygen, or the heart muscle has been damaged. The sensitivity of the test can be improved when combining with MUGA, but at the expense of reduced specificity [29]. It has demonstrated by many studies that there are variations in diastolic function via MUGA before LVEF drop being measured [30].

4. Therapies

4.1. Dexazoxane (DXZ)

DXZ is the only drug approved by FDA for DOX-induced cardiomyopathy treatment. A previous study showed that DOX-induced death can be trigger by ferroptosis [31]. Iron is a catalyst for DOX-induced generation of free radicals. Myocardial injury is prevented by dexrazoxane binding to irons that are free or released from intracellular sites following lipid peroxidation [32].

It has been found both in vivo and in vitro that DXZ can be protective for ferroptosis and cardiomyopathy in rats. Male Wistar rats purchased from Vitalriver were divided into DOX group and DOX+DXZ group. Hematoxylin and eosin staining of heart sections and echocardiography were the methods used. Typical images of H & E staining of heart sections of diverse groups of rats suggested that DOX-induced cardiomyopathy was alleviated by treatment of DXZ. According to echocardiographic analysis, the reduction in both left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF) of DOX-treated animals could be reversed by DXZ remedy [33].

4.2. Liposomal DOX

DNA damage and cell death are upregulated by DOX, while downregulated by liposomal DOX in the ventricles.

In previous research, twenty-three domestics pigs were used to determine the effect of liposomal encapsulation of DOX (Myocet/MYO). They were injected intravenously either by DOX dissolved in saline solutions or physiologic saline. The methods consisted of cardiac magnetic resonance (CMR) as well as late enhancement (LE) to evaluate ventricular systolic cardiac function and fibrosis, and transthoracic echocardiography (TTE) to assess the systolic and diastolic functions. The results from CMR+LE indicated that animals treated by liposomal DOX had higher RVEF than those treated by DOX. For pigs received liposomal DOX, higher the LVEF, smaller the left and right ventricular end-diastolic volume index (EDVi) and end-systolic volume index (ESVi). According to the testing of TTE, the left ventricular diastolic function was damaged in DOX-treated animals, while not liposomal DOX pigs or RV systolic dysfunction [34].

5. Conclusion

This review discussed the basic information of DOX and the cardiomyopathy induced by DOX. The most proposed mechanism is that DOX induced oxidative stress is related to oxidative stress. With four types of imaging modalities explained in the article, cardiomyopathy can be monitored and assessed, which is beneficial to for medicating the negative effects of DOX treatment. DXZ and liposomal DOX can alleviate cardiomyopathy triggered by DOX, with their mechanisms and experiments demonstrated. Further studies are required to explore better ways of preventing or treating DOX-induced cardiomyopathy.

References

- [1] Y. Octavia, C.G. Tocchetti, K.L. Gabrielson, S. Janssens, et al., Doxorubicin-induced cardiomyopathy: From molecular mechanisms to therapeutic strategies, *J. Mol. Cell. Cardiol.* 52 (2012) 1213–1225.
- [2] T.R. Mancilla, B. Iskra and G.J. Aune, Doxorubicin - Induced Cardiomyopathy in Children, *Compr. Physiol.* (2019) 905–931.
- [3] K. Renu, A. V.g., T.P. P.b. and S. Arunachalam, Molecular mechanism of doxorubicin-induced cardiomyopathy - An update, *Eur. J. Pharmacol.* 818 (2018) 241–253
- [4] R.A. Carvalho, R.P.B. Sousa, V.J.J. Cadete, G.D. Lopaschuk, et al., Metabolic remodeling associated with subchronic doxorubicin cardiomyopathy, *Toxicology.* 818 (2010) 92–98.
- [5] T.G. Neilan, S.L. Blake, F. Ichinose, M.J. Raher, et al., Disruption of nitric oxide synthase 3 protects against the cardiac injury, dysfunction, and mortality induced by doxorubicin, *Circulation.* 116 (2007) 506–514.
- [6] S. C. Bull, M. L. Main, G. R. Stevens, J. H. Goldman, et al., Cardiac toxicity screening by echocardiography in healthy volunteers: A study of the effects of diurnal variation and use of a core laboratory on the reproducibility of left ventricular function measurement, *Echocardiography.* 28 (2011) 502–507.
- [7] F. Dodos, T. Halbsguth, E. Erdmann & U. C. Hoppe, Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults, *Clin. Res. Cardiol.* 97 (2008) 318–326.
- [8] H Sawaya, I. A. Sebag, J. C. Plana, J. L. Januzzi, et al., Early detection and prediction of cardiotoxicity in chemotherapy-treated patients, *Am. J. Cardiol.* 107 (2011) 1375–1380.

- [9] S. Tassan-Mangina, D. Codorean, M. Metivier, B. Costa, et al., Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: Early and late alterations of left ventricular function during a prospective study, *Eur. j. echocardiogr.* 7 (2006) 141–146.
- [10] N. G. Bellenger, M. I. Burgess, S. G. Ray, A. Lahiri, et al., Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance. Are they interchangeable? *Eur. Heart J.* 21 (2000) 1387–1396.
- [11] C. Jenkins, K. Bricknell, L. Hanekom, & T. H. Marwick, Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography, *J. Am. Coll. Cardiol.*, 44 (2004) 878–886.
- [12] R. S. Jiji, C. M. Kramer, & M. Salerno, Non-invasive imaging and monitoring cardiotoxicity of cancer therapeutic drugs, *J. Nucl. Cardiol.* 19 (2012) 377–388.
- [13] S. Guendouz, O. Buicuic, M. Kirsch, N. Benaïem, et al., Restrictive cardiomyopathy associated with left ventricle and left atria endocardial calcifications following chemotherapy, *J. Am. Coll. Cardiol.* 57 (2011) 1633.
- [14] C. Y. Karabay, G. Kocabay, A. Kalayci, R. Zehir, et al., Mitral regurgitation due to papillary muscle dyssynchrony during trastuzumab treatment, *Cardi.* 117(2011) 296–300.
- [15] M. Aissioui, D. Périé, F. Cheriet, N. S. Dahdah, et al., Imaging of early modification in cardiomyopathy: The doxorubicin-induced model, *Int. J. Card. Imaging.* 29 (2013) 1459–1476.
- [16] C. Y. Ho, & S. D. Solomon, A clinician's guide to tissue Doppler imaging, *Circulation.* 113 (2006) 396–398.
- [17] C. A. Geisberg, & D. B. Sawyer, Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage, *Curr. Hypertens. Rep.*, 12 (2010) 404–410.
- [18] L. Kapusta, J. M. Thijssen, J. Groot-Loonen, T. Antonius, et al., Tissue Doppler imaging in detection of myocardial dysfunction in survivors of childhood cancer treated with anthracyclines, *Ultrasound. Med. Bio.* 26 (2000) 1099–1108.
- [19] L. Kapusta, J. Groot-Loonen, J. M. Thijssen, R. DeGraaf, et al., Regional cardiac wall motion abnormalities during and shortly after anthracyclines therapy, *Med. Pediatr. Oncol.* 41 (2003) 426–435.
- [20] I. Eitel, F. von Knobelsdorff-Brenkenhoff, P. Bernhardt, I. Carbone, et al., Clinical Characteristics and Cardiovascular Magnetic Resonance Findings in Stress (Takotsubo) Cardiomyopathy, *JAMA.* 306 (2011) 277–286.
- [21] H. Childs, L. Ma, M. Ma, J. Clarke, et al., Comparison of long and short axis quantification of left ventricular volume parameters by cardiovascular magnetic resonance, with ex-vivo validation, *J. Cardiovasc. Magn. Reson.* 13 (2011) 40.
- [22] W.G. Hundley, D.A. Bluemke, J.P. Finn, S.D. Flamm, et al., ACCF/ACR/AHA/NASCI/SCMR 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance, *Circ.* 121 (2010) 2462–2508.
- [23] V. Positano, A. Pingitore, A. Giorgetti, B. Favilli, et al., A Fast and Effective Method to Assess Myocardial Necrosis by Means of Contrast Magnetic Resonance Imaging, *J. Cardiovasc. Magn. Reson.* 7 (2005) 487–494.
- [24] D.E. Sosnovik, E. Garanger, E. Aikawa, M. Nahrendorf, et al., Molecular MRI of Cardiomyocyte Apoptosis with Simultaneous Delayed-Enhancement MRI Distinguishes Apoptotic and Necrotic Myocytes In Vivo, *Circulation.* 2 (2009) 460–467.
- [25] V.Y. Wang, H.I. Lam, D.B. Ennis, B.R. Cowan, et al., Modelling passive diastolic mechanics with quantitative MRI of cardiac structure and function, *Med. Image Anal.* 13 (2009) 773–784.

- [26] L.-F. de Geus-Oei, A. M. C. Mavinkurve-Groothuis, L. Bellersen, M. Gotthardt, et al., Scintigraphic Techniques for Early Detection of Cancer Treatment-Induced Cardiotoxicity, *J. Nucl. Med.* 52 (2011) 560–571.
- [27] J. Walker, N. Bhullar, N. Fallah-Rad, M. Lytwyn, et al., Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging, *J. Clin. Oncol.* 28 (2010) 3429–3436.
- [28] I. Mitani, Doxorubicin cardiotoxicity: Prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiology in the current era, *J. Nucl. Cardiol.* 10 (2003), 132–139.
- [29] J. H. McKillop, M. R. Bristow, M. L. Goris, M. E. Billingham, et al., Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity, *Am. Heart J.* 106 (1983) 1048–1056.
- [30] M. Salerno, Multi-modality imaging of diastolic function, *J. Nucl. Cardiol.* 17 (2010) 316–327.
- [31] X. Fang, H. Wang, D. Han, E. Xie, et al., Ferroptosis as a target for protection against cardiomyopathy, *PNAS.* 116 (2019) 2672–2680.
- [32] E. Tahover, A. Segal, R. Isacson, O. Rosengarten, et al., Dexrazoxane added to doxorubicin-based adjuvant chemotherapy of breast cancer, *Anticancer Drugs.* 28 (2017) 787–794.
- [33] H. Zhang, Z. Wang, Z. Liu, K. Du, et al., Protective Effects of Dexazoxane on Rat Ferroptosis in Doxorubicin-Induced Cardiomyopathy Through Regulating HMGB1, *Front. Cardiovasc. Med.* 8 (2021).
- [34] M. Gyöngyösi, D. Lukovic, K. Zlabinger, A. Spannbauer, et al., Liposomal doxorubicin attenuates cardiotoxicity via induction of interferon-related DNA damage resistance, *Cardiovasc. Res.* 116 (2020) 970–982.