

Can short-term fasting protect against doxorubicin-induced cardiotoxicity?

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Abstract

Doxorubicin (Dox) is one of the most effective chemotherapeutic agents used in the treatment of several types of cancer. However the use is limited by cardiotoxicity. Despite extensive investigation into the mechanisms of toxicity and preventative strategies, Dox-induced cardiotoxicity still remains a major cause of morbidity and mortality in cancer survivors. Thus, continued research into preventative strategies is vital. Short-term fasting has proven to be cardioprotective against a variety of insults. Despite the potential, only a few studies have been conducted investigating its ability to prevent Dox-induced cardiotoxicity. However, all show proof-of-principle that short-term fasting is cardioprotective against Dox. Fasting affects a plethora of cellular processes making it difficult to discern the mechanism(s) translating fasting to cardioprotection, but may involve suppression of insulin and insulin-like growth factor-1 signaling with stimulated autophagy. It is likely that additional mechanisms also contribute. Importantly, the literature suggests that fasting may enhance the antitumor activity of Dox. Thus, fasting is a regimen that warrants further investigation as

a potential strategy to prevent Dox-induced cardiotoxicity. Future research should aim to determine the optimal regimen of fasting, confirmation that this regimen does not interfere with the antitumor properties of Dox, as well as the underlying mechanisms exerting the cardioprotective effects.

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Key words: Fasting; Doxorubicin; Cardiotoxicity; Cardio-protection

Core tip: Doxorubicin (Dox)-induced cardiotoxicity remains a significant cause of morbidity and mortality in cancer survivors, despite the intensive investigation of potential protective strategies. Studies have shown that short-term fasting induces cardioprotective effects against Dox-induced injury. Importantly, evidence suggests that fasting may enhance the antitumor effects of Dox. Thus, short-term fasting may be a feasible practice that can easily be incorporated into the treatment plans of cancer patients.

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INTRODUCTION

Doxorubicin (Dox) is one of the most effective chemotherapeutic agents currently used in the treatment of hematological malignancies and solid tumors such as breast cancer. It is a quinone-containing anthracycline antibiotic. Its mechanism of antitumor activity has been shown to

involve binding to topoisomerase-II α , thereby resulting in DNA strand breaks and apoptosis^[1]. Despite its effectiveness, its use is limited due to cardiotoxicity. In animal models, Dox has been shown to be hepatotoxic as well, but in humans it is the cardiotoxicity which primarily limits its use^[2,3]. High cumulative doses of Dox are the most powerful predictor of Dox-induced congestive heart failure^[4]. One early study reported that 4% of patients receiving a dose of 500-550 mg/m² and 18% and 36% of patients receiving 551 mg/m² or higher, respectively, experienced heart failure, which is often refractory to conventional therapy^[4,5]. The clinical outcome for these patients is poor^[4]. A variety of approaches to prevent cardiotoxicity have been tested, however, their efficacy has been limited^[4]. Thus, continued investigation of viable strategies to protect the heart from Dox-induced toxicity is of vital importance.

MECHANISMS OF DOX-INDUCED CARDIOTOXICITY

Mechanisms of Dox-induced cardiotoxicity have not been clearly elucidated, but have been shown to involve oxidative stress, mitochondrial dysfunction, and apoptosis. For example, Dox treatment has been shown to increase mitochondrial depolarization, fission, and ROS production while decreasing the rate of ATP synthesis and content^[6-10]. Lipid peroxidation, reduced aconitase activity (a marker of oxidative stress), and alterations in the expression and activity of antioxidant enzymes, such as superoxide dismutase (SOD), are also evident^[11,12]. Oxidative stress and mitochondrial dysfunction can induce apoptosis which leads to loss of post-mitotic myocytes and altered cardiac function^[8,13,14]. It has long been known that Dox can induce oxidative stress *via* semiquinone redox cycling, however it is unclear if this is the specific mechanism of cardiotoxicity since ROS scavengers failed to prevent cardiac toxicity in several studies^[15,16]. Recently, topoisomerase-II β has been shown to be a molecular target of Dox in cardiomyocytes^[17]. Cardiac myocytes do not express topoisomerase-II α , the molecular target in tumor cells^[18]. Zhang *et al.*^[17] demonstrated that cardiomyocyte-specific deletion of topoisomerase-II β prevented Dox-induced cardiotoxicity. Furthermore, the deletion prevented Dox-induced DNA damage and transcriptional changes that are responsible for impaired mitochondrial biogenesis, ROS formation, and apoptosis. Thus, the mechanism of Dox-induced cardiotoxicity may involve molecular targeting of topoisomerase-II β as well as the potential contribution of semiquinone redox cycling.

PROTECTIVE STRATEGIES AGAINST DOX-INDUCED CARDIOTOXICITY

Currently, available therapies to effectively prevent cardiotoxicity in patients treated with Dox are limited. Thus,

the first line of defense is to limit the cumulative dose of Dox. However, lowering cumulative dose may translate to reduced treatment efficacy^[19]. Another strategy to protect against cardiotoxicity has been to alter the mode of delivery of Dox, such as encapsulation in liposomes, which aims to target the delivery to the tumor, thereby, reducing plasma concentrations of Dox. The United States Food and Drug Administration has approved one liposomal doxorubicin, Doxil^[19]. Shorter-term clinical trials have shown that liposomal doxorubicin can reduce early cardiotoxicity while having the same antineoplastic efficacy as conventional doxorubicin^[19]. Although, liposomal doxorubicin has shown promise in reducing cardiotoxicity, currently, it is still mainstream to use conventional Dox. Utilizing antioxidants or iron chelators to reduce Dox-induced oxidative stress has been another tested strategy, but with limited success^[19]. Dexrazoxane, an iron chelating agent, has shown the most promise in reducing oxidative stress and cardiotoxicity, however, with some limitations. Most studies have shown that Dexrazoxane is safe, however, some have shown that dexrazoxane may cause myelosuppression and also increase the risk of second malignancies^[20,21]. Furthermore, it has been shown that the efficacy of dexrazoxane may vary between sexes, with less benefit in males^[19,22]. Despite extensive investigation and numerous tested strategies to prevent cardiotoxicity, success has been limited. Dox-induced cardiotoxicity still remains a major cause of morbidity and mortality in cancer survivors^[19]. Thus, exploration of additional strategies to prevent Dox-induced cardiotoxicity is paramount.

A cardioprotective strategy that warrants further exploration is fasting. Fasting and/or caloric restriction (CR) has been shown to protect the heart from a variety of conditions and insults. For example, intermittent fasting protects the heart from ischemic damage and attenuates post-MI cardiac remodeling^[23]. Furthermore, calorie restriction has proven protective against coronary artery disease, the process of aging on the cardiovascular system, as well as drug toxicities, including doxorubicin-induced cardiotoxicity^[24-27]. Mitra *et al.*^[26] demonstrated that 40+ days of a 35% calorie restricted diet lead to 100% protection against Dox-induced cardiotoxicity and death while all of the rodents administered with Dox in the *ad libitum* fed group died. However, long term CR regimens, such as this, are not feasible in cancer patients since they typically suffer from malnutrition and other complications. Therefore, short-term fasting may be an alternative approach. Indeed, Raffaghello *et al.*^[28] reported that 48-60 h of complete fasting prevented organ toxicity induced by chemotherapy in various species of female mice, however, etoposide rather than Dox was used in the study. Kawaguchi *et al.*^[29] demonstrated that 48 h of complete fasting prior to Dox administration mitigated the Dox-induced impairment in cardiac function in adult GFP-LC-3 transgenic mice, as determined by left ventricular ejection fraction (LVEF), systolic pressure (LVSP), end diastolic pressure (LVEDP), and +dP/dt. Microscopy revealed attenuation

Table 1 Summary of unpublished data

Dependent variable	Control (mean ± SEM)	Dox (mean ± SEM)	P value
Aconitase activity (nmol/min per milligram protein)	14.46 ± 3.68	23.74 ± 3.25	0.08
SOD activity (units/mg protein)	0.026 ± 0.003	0.026 ± 0.002	0.904
SOD1 content	1025 ± 110.2	949 ± 91.6	0.603
SOD2 content	275.6 ± 23.25	288.1 ± 23.71	0.715
Procaspace-12 content	36.90 ± 6.14	24.28 ± 4.19	0.1
Procaspace-9 content	28.59 ± 1.57	25.33 ± 3.61	0.5
Procaspace-8 content	68.10 ± 11.90	82.90 ± 0.93	0.34
Caspase-3 activity (arbitrary OD/mg protein)	0.951 ± 0.676	0.490 ± 0.295	0.524
Caspase-9 activity (arbitrary OD/mg protein)	1.084 ± 0.809	0.462 ± 0.255	0.451
FIS1 content	563.6 ± 76.6	474.3 ± 68.8	0.4
DRP1 content	1294.9 ± 109.8	1187.5 ± 73.5	0.421
MFN1 content	5443.5 ± 786.8	4607.8 ± 627.0	0.417
MFN2 content	2001.5 ± 456.8	2053.6 ± 330.2	0.926
OPA1 content	6019.5 ± 739.3	6143.6 ± 601.0	0.897
PINK1 content	3343.0 ± 206.9	3422.0 ± 263.4	0.824
Parkin content	4192.0 ± 1009.0	4157.0 ± 1629.0	0.986
p62 content	1895.7 ± 272.7	1896.7 ± 252.2	0.998

Protein content determined by Western blot (units are "normalized OD"). SOD: Superoxide dismutase.

of LV dilatation, myocardial atrophy, and fibrosis^[29]. *In vitro*, a caloric restriction mimetic, 2-deoxyglucose (2-DG), was shown to exhibit cardioprotective properties against Dox using neonatal rat cardiomyocytes isolated from 0-2 d old Harlan Sprague-Dawley rat neonates^[30]. Thus, the literature supports that fasting may be an effective regimen to protect against Dox-induced cardiotoxicity.

Unpublished data from our laboratory (Table 1) may also suggest that short-term fasting may provide cardioprotection against Dox. Six-week old male F344 rats were treated with a single injection of Dox (20 mg/kg) or saline. Tissues were harvested for analysis 24-h post injection with the aim of determining the effects of Dox on the mitochondrial dynamics and mitophagy machinery. In order to remove the external variable of Dox-induced anorexia, we fasted both groups of animals upon treatment. Studies have shown that animals treated with Dox reduce their food and water intake by up to 70% for several days^[31]. Using this experimental design, the results were unexpected. Dox did not affect any markers of oxidative stress or apoptosis that were assessed in the heart. Dox did not affect aconitase activity, superoxide dismutase (SOD) activity, nor the protein content of cytosolic SOD1 and mitochondrial SOD2. Expression and activation of caspase-12, caspase-9, and caspase-8 were assessed *via* Western analysis, as well as caspase-3 and -9 enzyme activities, and were not affected by Dox. As previously mentioned, the original aim of the study was to investigate the effects of Dox on the mitochondrial dynamics and mitophagy machinery with the hypothesis that Dox treatment would increase the protein content of FIS1 and DRP1 (fission regulators) and decrease the content of MFN1, MFN2 and OPA1 (fusion regulators) thus favoring mitochondrial fission, which is most often associated with oxidative stress, mitochondrial dysfunction and apoptosis^[32-34]. Under the current fasting conditions, Dox did not affect the content of any of these primary regulators. Regulators of mitophagy were also

assessed. Dox did not affect the content of PINK1, Parkin, or p62 (a marker of mitophagy) under these fasting conditions. We do know that Dox exerted a biological effect in these animals since many of these variables were altered in the liver. Furthermore, the treatment significantly affected the proteome lysine acetylation status in the heart, inducing deacetylation (Figure 1), although the significance of this observation is currently unknown. Because previously published studies have reported that acute Dox treatment does affect many of these variables and processes^[8-11,35-37], we believe that complete fasting of the animals in our study may have exerted an unintended cardioprotective effect against the Dox-induced insult. However, further investigation is required to confirm our interpretation of the data. Although this work was done using an acute model of Dox cardiotoxicity, since short-term fasting may be able to protect against the high dose used in the acute model, it is likely that it may also be protective against lower doses used in chronic models of Dox cardiotoxicity which mimics more closely the clinical use of Dox in patients. In summary, short-term fasting may extend similar benefits as longer term CR in regards to cardioprotection against Dox-induced injury.

MECHANISM OF FASTING-INDUCED CARDIOPROTECTION AGAINST DOX TOXICITY

Fasting and caloric deprivation affect a plethora of cellular processes such as mitochondrial dynamics and biogenesis, energy metabolism, oxidative stress, autophagy, and survival signaling pathways, thus making it difficult to discern the mechanism(s) responsible for the cardioprotection^[38-42]. Kawaguchi *et al.*^[29] concluded that the protection against Dox-induced injury extended by 48-h of fasting prior to treatment was due to restoration of autophagy. Autophagy is a conserved process among eukaryotic cells

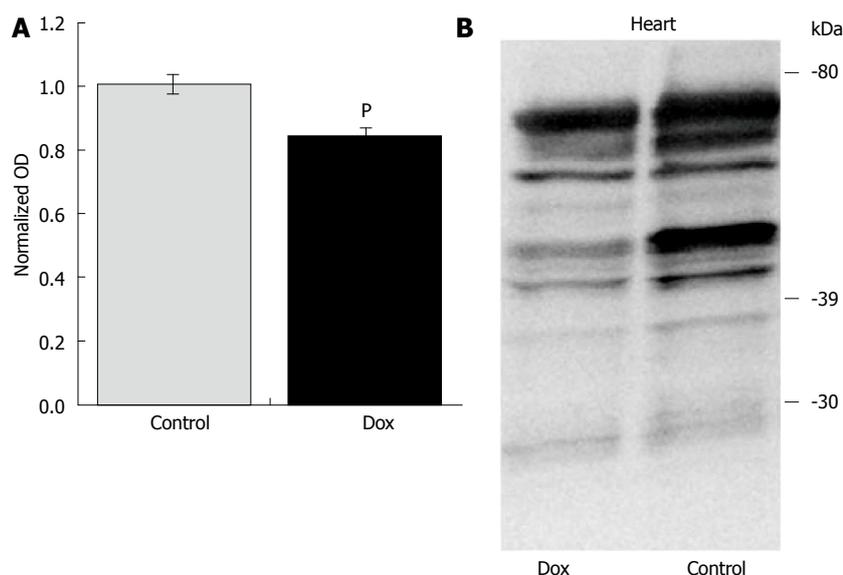


Figure 1 Acute doxorubicin treatment induces proteome lysine deacetylation in the hearts of fasted animals. A: Graphical representation of results; B: Representative Western blot. $P = 0.0016$.

that sequesters cellular material *via* formation of a multi-membrane-bound vacuole, an autophagosome, followed by degradation of the material *via* fusion of the autophagosome with a lysosome^[43]. Autophagy can enhance cellular function and survival by degrading damaged or unwanted proteins and organelles such as mitochondria, as well as by modulating apoptosis^[44]. Indeed, stimulation of autophagy has been shown to be cardioprotective from a variety of damaging stimuli^[44]. Kawaguchi *et al.*^[29] reported that the inhibition of autophagy by Dox was due to inhibition of AMP-activated protein kinase (AMPK). Prior fasting prevented the Dox-induced inhibition of AMPK. Although fasting was able to reverse the effects of Dox on autophagy, no experimental methods were employed to identify restoration of autophagy as the underlying factor for cardioprotection. Furthermore, no other processes known to be affected by fasting were assessed in the study. Moreover, several studies have shown that stimulation of autophagy contributes to Dox-induced cardiotoxicity and protection is provided *via* inhibition of autophagy^[43]. Thus the role of autophagy in Dox-induced cardiotoxicity, whether protective or pathological, is still under question. Therefore, the underlying mechanism(s) of fasting-induced cardioprotection against Dox remains to be determined and is likely due to a combination of mechanisms^[30].

EFFECTS OF FASTING ON TUMOR CELL KILLING

It is critical that a potential cardioprotective agent or regimen does not interfere with the goal of cancer treatment. CR has long been shown to have antineoplastic effects. CR can slow the intrinsic rate of aging and prevent the onset of age-related pathologies, including cancer^[45,46]. Furthermore, CR mimetics, such as 2-DG, have been shown to inhibit tumor growth^[47]. Moreover, 2-DG has been shown to enhance the antitumor efficacy of Dox both *in vitro* and *in vivo*^[48,49]. Short-term (48-60 h) fast-

ing was shown to enhance death of cancer cells, prevent organ toxicity, and increase survival in chemotherapy treated mice, however the chemotherapy tested was etoposide, not Dox^[28]. Interestingly, Raffaghello *et al.*^[28] noted that fasting longer than 60 h worsened outcomes. Thus, there may be a window of optimal duration of fasting to maximize beneficial effects. Many of the benefits of fasting and caloric restriction have been shown to be, at least in part, due to decreased circulating levels of insulin and reduced insulin-like growth factor-1 receptor (IGF-1R) signaling^[50,51]. Seventy-two hours of fasting reduced circulating IGF-1 by 70% and increased the level of the IGF-1 binding protein (IGFBP) by 11x^[52]. Survival time, after Dox treatment, was extended by delaying metastasis of highly aggressive melanoma and prevented Dox-induced toxicity in liver-specific IGF-1-deficient (LID) mice compared to non-LID mice^[52]. Ninety days after inoculation with the melanoma cancer cells, all non-LID mice that were treated with Dox had died from either cancer metastases or Dox toxicity. 60% of LID mice treated with Dox were cancer-free with no signs of toxicity^[52]. Thus, the evidence supports that fasting may be a safe regimen to use in conjunction with Dox in order to prevent cardiotoxicity.

CONCLUSION

In conclusion, Dox-induced cardiotoxicity remains a significant cause of morbidity and mortality in cancer survivors despite the intensive investigation of potential protective strategies. Studies have shown that short-term fasting induces cardioprotective effects against Dox-induced injury. Importantly, evidence suggests that fasting may enhance the antitumor effects of Dox. It seems that short-term fasting would be a feasible practice that can easily be incorporated into the treatment plans of cancer patients. Thus, short-term fasting is a strategy warranting further exploration. Further studies, both preclinical and clinical, should reveal the optimal regimen of fasting,

confirmation that this regimen does not interfere with the antitumor properties of Dox, as well as the underlying mechanisms exerting the cardioprotective effects.

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