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# Doxorubicin induced heart failure: Phenotype and molecular mechanisms

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ABSTRACT

Long term survival of childhood cancers is now more than 70%. Anthracyclines, including doxorubicin, are some of the most efficacious anticancer drugs available. However, its use as a chemotherapeutic agent is severely hindered by its dose-limiting toxicities. Most notably observed is cardiotoxicity, but other organ systems are also degraded by doxorubicin use. Despite the years of its use and the amount of information written about this drug, an understanding of its cellular mechanisms is not fully appreciated. The mechanisms by which doxorubicin induces cytotoxicity in target cancer cells have given insight about how the drug damages cardiomyocytes. The major mechanisms of doxorubicin actions are thought to be as an oxidant generator and as an inhibitor of topoisomerase 2. However, other signaling pathways are also invoked with significant consequences for the cardiomyocyte. Further the interaction between oxidant generation and topoisomerase function has only recently been appreciated and the consequences of this interaction are still not fully understood. The unfortunate consequences of doxorubicin within cardiomyocytes have promoted the search for new drugs and methods that can prevent or reverse the damage caused to the heart after treatment in cancer patients. Alternative protocols have lessened the impact on newly diagnosed cancer patients. However the years of doxorubicin use have generated a need for monitoring the onset of cardiotoxicity as well as understanding its potential long-term consequences. Although a fairly clear understanding of the short-term pathologic mechanisms of doxorubicin actions has been achieved, the long-term mechanisms of doxorubicin induced heart failure remain to be carefully delineated.



## 1. Introduction

Long term survival of childhood cancers is now more than 70% [21]. Unfortunately, adult survivors of childhood cancer are at risk for a variety of treatment-related adverse health outcomes. Using clinical criteria, survivors with a median time from diagnosis of 25 years [range 10–47 years] were assessed for the prevalence of adverse health outcomes. Among them were abnormal pulmonary function (65.2%), auditory (62.1%), endocrine conditions (62.0%), cardiac dysfunction (56.4%), and neurocognitive impairment (48.0%), whereas abnormalities involving hepatic dysfunction (13.0%), osteoporosis (9.6%), kidney dysfunction (5.0%) were less common [37,91]. Anthracyclines, including doxorubicin, are some of the most efficacious anticancer drugs available. Their use has extended over 3 decades despite numerous side effects. The studies of childhood survivors 4 to 20 years after doxorubicin treatment observed significant decreases in fractional shortening and ejection fractions, and that was dependent upon the cumulative dose [2,30,31,33,42,54,55,89,90]. Analysis of heart transplantation patients found doxorubicin as the underlying cause in 2–3% of all cases [7]. Several reviews have been written that focus on the pathophysiology of doxorubicin cardiotoxicity for the patient [15,47,57,80,100]. This review will focus more on the cellular and molecular impacts of doxorubicin on the heart with purpose of more fully delineating the underlying molecular mechanisms that promote cardiotoxicity.

## 2. Chemical structure

Doxorubicin, also known as Adriamycin® or Rubex®, is an anthracycline antibiotic that was discovered from a mutated strain of *Streptomyces peucetius*. Doxorubicin operates on several levels by different molecular mechanisms including an interaction with iron, upsetting calcium homeostasis, altering the activity of intracellular or intramitochondrial oxidant enzymes, and binding to topoisomerases promoting their dysfunction (Fig. 1).

Doxorubicin consists of a naphthacenequinone nucleus and daunosamine, an amino sugar. Doxorubicin has both hydrophilic and hydrophobic regions, allowing it to bind to plasma proteins as well as cell membranes. Doxorubicin is also amphoteric; in having both acidic and basic functions. It is these features that make doxorubicin a versatile compound, allowing it to enter various cellular compartments. Doxorubicin can be reduced intracellularly into doxorubicinol and this metabolite also has biological activity [71]. Doxorubicin can also be reduced to a semiquinone radical by many of the intracellular oxidoreductases. Re-oxidation of this radical resulted in the production of reactive oxygen

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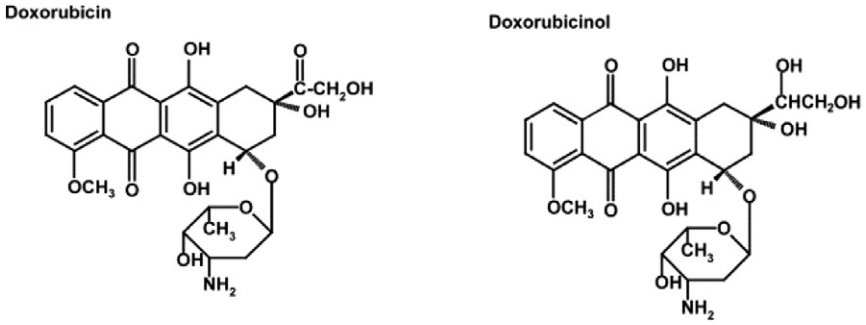


**Fig. 1.** Chemical structure of doxorubicin and its metabolite doxorubicinol. From Wang et.al. [103].

species (ROS). The generation of ROS underlies one mechanism of its antineoplastic and antibiotic capabilities. Excretion is through the liver and kidney with a biphasic half life of 5 min and 30–40 h [43,78]. Alternative forms of doxorubicin including liposomal-encapsulated forms have been developed in an attempt to decreased cardiotoxicity. These forms do not readily exit the vascular system but only in regions where the structures may be disrupted by tumor growth and are likely to have less access to the heart [54]. Various products including Doxil™, Myocet™ and DaunoXome™ are all commercially available. Meta-analysis found that although cardiotoxicity remained a function of cumulative dose, use of liposomal-encapsulated doxothracyclines lowered the incidence of cardiotoxicity [75,94]. More recently, biodegradable microparticles or nanoparticles containing doxorubicin have been explored as a slow release mechanism of doxorubicin therapy [59,63,76].

## 3. Detection and cardiotoxicity

The increased risk of cardiac dysfunction from doxorubicin can manifest acutely during treatment or chronically weeks to years after treatment has ceased. Cardiac dysfunction may present across a board spectrum of symptoms that may range from arrhythmias to overt heart failure. Several standard approaches of cardiology have been applied towards the detection of cardiotoxicity, including electrocardiography, echocardiography, biopsy, scintigraphy, serum analysis, and genomic markers. However, not all protocols have proven to be helpful.

Standard echocardiography provides visualization of heart structure and can detect cardiac dysfunction via measures. Radionuclide based tests, such as radionuclide angiocardiography and ventriculography, when performed serially before, during, and after treatment are more sensitive to changes in cardiac function [32]. More recently, the use of radial strain has been studied. Strain is a measure of the deformation of the myocardium that occurs during the cardiac cycle and is determined by the change in length of the tissue relative to its original length [28,51]. Doxorubicin induced damage causes myocyte death and the injured regions do not function as well as normal tissue resulting in dyssynchrony and deformation. In both human and animal studies two-dimensional strain echocardiography appeared more sensitive than standard echocardiography protocols providing additional insight into doxorubicin induced cardiac injury [36,65].

Serum biomarkers for cardiac injury more commonly used to detect ischemia may also reflect acute doxorubicin-induced cardiomyopathy. Although elevated circulating levels of cardiac troponin T have been reported, the increases are not quantitatively consistent with the degree of doxorubicin-induced cardiac injury [72,85]. Stronger correlations of circulating brain-type natriuretic peptide to doxorubicin-induced cardiac dysfunction have been demonstrated than with the atrial natriuretic peptide [85]. Distinct from cardiac troponin T that indicate cardiomyocyte damage, the natriuretic peptides reflect an early response to cardiac insufficiency. More recently, the use of circulating genomic biomarkers in monitoring and predicting doxorubicin-induced heart failure is also currently being investigated. These animal studies have examined changes in expression of microRNAs. Of the potential markers, both miR-208 and miR-216B were responsive to doxorubicin treatment and that miR-216B did appear dose-dependent responsive to doxorubicin [70,98]. However, similar to radiolabeled antibodies elevated circulating levels are only detectable as a following indicator to myocyte damage.

Although used but not clinically practical, histopathological results from endomyocardial biopsies are very sensitive in detection of late-onset cardiotoxicity [72]. Alternatively, combination radiolabeled antibodies with scintigraphy is also useful. Antimyosin antibodies bind intracellularly to the heavy chain of myosin but can only do so when cell membrane integrity is compromised, allowing for localization exclusively to damaged cardiomyocytes. Carrió et al. demonstrated that increased uptake of $^{111}$In labeled antimyosin in patients with sarcomas being treated with doxorubicin was predictive of future progression of cardiotoxicity [17]. Patients with higher uptake levels of the antibody at intermediate cumulative doses of doxorubicin initially showed no simultaneous decline in left ventricular ejection fraction. However, as treatment continued, these patients with previous high uptake levels were more likely to develop cardiac dysfunction or mild congestive heart failure as a result of increased cumulative exposure than those patients with lower uptake levels at the intermediate cumulative dose. Valdés Olmos et al. investigated the sensitivity of $^{111}$In-antimyosin and scintigraphy in detecting early cardiac injury in breast cancer patients receiving low doses of doxorubicin [99]. After comparing measurements of myocardial uptake of the antibody to other assessments of cardiac dysfunction, such as left ventricular ejection fraction, it was concluded that localization of $^{111}$In-antimyosin was representative of myocyte injury, even at low cumulative doses of doxorubicin (120–150 mg/m$^2$). These findings suggest that progressive myocyte injury precedes clinically significant cardiac dysfunction, and use of this technique may help determine and individual patient's risk of developing heart failure in response to increasing doses of doxorubicin. However, there is little information about the usefulness of this marker in predicting late-onset cardiotoxicity, which if accurate, could have a major impact on the prevention of doxorubicin-induced congestive heart failure, especially in survivors of childhood cancer.

Acute cardiotoxicity that may appear during treatment or shortly thereafter presents with abnormal changes in heartbeat, which may or may not be seen with non-specific ST-T wave changes in electrocardiograms [82,88,101]. Acute episodes have been reported to occur in up to 40% of patients given doxorubicin [50]. The occurrence of an acute episode has not been predictive of late onset cardiac dysfunction [74].

Beyond the early effects, sub-acute cardiotoxicity may present within a few weeks to a few months. These effects may be attributed to altered $Ca^{+2}$ dynamics, increased oxidative stress, or altered myocardial energetics [23,26,68,71]. Delayed effects have been reported in studies of childhood survivors 4 to 20 years after doxorubicin treatment where significant decreases in fractional shortening and ejection fractions were observed [2,30,31,33,42,54,55,89,90]. There appears to be a relationship between delayed development of congestive heart failure