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Review

# Ranolazine in the prevention of anthracycline cardiotoxicity☆

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ABSTRACT

Ranolazine is a selective inhibitor of the cardiomyocyte late inward sodium current, $I_{NaL}$, and features anti-ischemic, antiarrhythmic and ATP-sparing actions. Extensive laboratory data show that anthracyclines can induce the production of reactive oxygen species (ROS). Other laboratory data show that ROS can hyperactivate the cardiac isoform of calmodulin-dependent protein kinase II (CaMKII δ), in turn inducing a hyperactivation of the cardiac late sodium current ($I_{NaL}$) and a resulting cytosolic calcium overload. This, as a consequence of the related sodium overload, can induce a mitochondrial calcium depletion that, in turn, triggers a chronic vicious cycle characterized by mitochondrial $H_2O_2$ production (increased oxidative stress), and NAD(P)H and ATP depletion (energetic stress), both sustaining ROS production. We hypothesize that anthracyclines may induce both $I_{NaL}$ hyperactivation and an oxidative/energetic vicious cycle in cardiomyocytes. These sustained oxidative and energetic stresses may induce low-level cardiomyocyte and cardiac stem cell death by various mechanisms, leading to heart failure in the presence of genetic factors, age, ischemic and arrhythmic events, harmful dietary behaviors, and concomitant diseases. By reducing $I_{NaL}$ in a myocardium particularly vulnerable to apoptotic stress and ischemia ranolazine might thus exert cardioprotection interfering with the vicious cycle of anthracycline cardiotoxicity.


**Contents**



☆ Perspective articles contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

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## 1. Introduction

Anthracyclines are antibiotic drugs with effective anti-tumor cytotoxic activity [1,2]. The most important anthracyclines are doxorubicin (Dox, or adriamycin) and daunorubicin (isolated from *Streptomyces peucetius* var. *Caesius*), epirubicin (a semi-synthetic epimer of doxorubicin), idarubicin (a chemical analog of daunorubicin), aclacinomycin A (or aclarubicin), and amrubicin [1] (Table 1). They are extensively used in the chemotherapy of breast cancer, soft tissue sarcomas, non-Hodgkin's lymphomas, acute lymphoblastic, myeloblastic and myelogenous leukemias [1–5].

The main mechanism of the cytotoxic anti-tumor activity of anthracyclines involves the inhibition of topoisomerase IIα (*TopIIα*), an enzyme that relaxes topological supercoiled DNA thus allowing DNA replication and transcription. Anthracyclines consequently interfere with DNA synthesis and RNA transcription in cancer cells actively engaged in mitosis, inducing cell cycle blocks at the G1 or G2 phases, and favoring the development of cell death [1,6].

The use of anthracyclines as anti-tumor drugs is hampered by their associated cardiotoxicity [2,3,5]. During their post-natal maturation, cardiomyocytes to a large extent withdraw from the cell cycle at the $G_0/G_1$ or $G_2$/M transition phases, blocking DNA synthesis [7]. Anthracycline cardiotoxic and anti-tumor actions are believed to be due to different mechanisms, and there is an active search for developing analogs able to protect the heart without impairing chemotherapeutic efficacy [1,2,5]. Anthracycline cardiotoxicity is due, at least in part, to the generation of reactive oxygen species (ROS) [8–10].

We hypothesize that anthracyclines, through a ROS-dependent mechanism, may cause changes in the sarcolemmal late inward sodium current ($I_{NaL}$) [11], thereby impairing the sodium and calcium intracellular homeostasis, and thus feeding a vicious cycle that maintains oxidative and energetic stresses [12]. We will therefore here discuss the possibility that ranolazine, a selective $I_{NaL}$ inhibitor, by this mechanism attenuates cardiac biochemical and contractile dysfunction induced by anthracyclines.

## 2. Anthracycline cardiotoxicity: clinical characteristics

The clinical expression of anthracycline-induced cardiotoxicity is highly variable, and has been categorized into an acute form, with sudden onset – within 24 h of the rapid anthracycline intravenous infusion – and a late-onset chronic progressive form [4,5,10], characterized by left ventricular systolic dysfunction up to severe heart failure [5,10,13,14] that may not become evident even after 1 year from the first dose of anthracyclines [14], and may be remain subclinical for many years, up to 10–20 years [13]. This latter form preferentially affects the long-term survivors of childhood cancer [13].

Anthracycline-induced cardiotoxicity is dose-dependent and cumulative [1,2,4,5,10]. The cumulative anthracycline dose is the most important cardiotoxic risk factor [15,16]. Blanco et al. [17] have recently demonstrated increased risk of cardiomyopathy at doses even as low as 101–150 mg/mm$^2$, and that homozygosity for the *carbonyl reductase 3* (*CBR3*) *V244M G* allele contributes to increased risk with low-to-moderate dose regimens. Several recent studies suggest that there is no completely safe anthracycline dose, both in children [18–20] and in adults [4], and that even though "anthracyclines are life-saving", they introduce "a lifetime risk of cardiac events" [4,21].

## 3. Anthracycline cardiotoxicity—mechanisms

### 3.1. Introduction

There is no agreement on the molecular mechanisms through which anthracyclines induce cellular degenerative changes and clinical manifestations of cardiotoxicity. We can distinguish three main hypotheses: (1) the oxidative stress hypothesis; (2) the ternary complex – DNA/Dox/Top-IIβ – formation hypothesis [22]; (3) the alcohol metabolite hypothesis [1,4]. Whichever may be the relative weight of these hypotheses, it is clearer and clearer that the cellular (apoptosis, necrosis, mitochondrial dysfunctions, sarcomere degenerations, DNA-damage) and clinical phenotypic manifestations of anthracycline cardiotoxicity (severe cardiomyopathy with heart failure) are the consequence of the complex interaction of 3 forms of molecular stress: the oxidative stress (ROS production); an energetic/ionic stress (ATP depletion and derangement of calcium homeostasis); and a genotoxic stress (response to DNA-damage).

### 3.2. Molecular pathogenetic hypotheses of anthracycline cardiotoxicity

#### 3.2.1. The oxidative stress hypothesis (Figs. 1 and 2)

*3.2.1.1. Redox-cycling mechanism (Fig. 1).* According to this mechanism, Dox-induced ROS can be produced by the intracellular redox metabolism of the drug through 3 main inter-dependent modalities [1,3,4,8,9,23,24].

*3.2.1.1.1. Enzymatic ROS production (Fig. 1, point 1).* Some enzymes of the NAD(P)H-oxidoreductases family [cytochrome P450, mitochondrial NADH dehydrogenase (complex I of the electron transport chain, ETC), xanthine dehydrogenase, endothelial nitric oxide synthase (reductase domain)] [1] can catalyze the one-electron transfer from NAD(P)H to the quinone moiety in ring C of Dox, resulting in the formation of a semiquinone radical that, in the presence of molecular oxygen ($O_2$), can rapidly regenerate its parental quinone and reduce molecular oxygen to a superoxide radical ($O_2^{\bullet -}$) [1,8,9]. The semiquinone can oxidize and deglycosilate to generate a 7-deoxyaglycone and another $O_2^{\bullet}$ [1,8,9]. The deoxyaglycone is particularly active, being strongly lipophilic, to penetrate and intercalate with lipids, in particular cardiolipin, of mitochondrial membranes. It can generate $O_2^{\bullet}$ and $H_2O_2$ through a futile cycle catalyzed by NADH dehydrogenase of the ETC [1].

*3.2.1.1.2. Formation of ROS by Dox–Fe complexes (Fig. 1, point 2).* Dox binds avidly to iron (Fe) both in the ferric ($Fe^{3+}$) and ferrous ($Fe^{2+}$) forms, generating Dox:Fe complexes (1:1, 2:1, 3:1) [1,8,24,25]. In the presence of enzymes of the NAD(P)H-oxidoreductase family, the Fe of Dox–$Fe^{n+}$ complexes can cycle between the two oxidation states, $Fe^{2+}$ and $Fe^{3+}$ [8,24,25]. The Dox–$Fe^{2+}$ complex, in the presence of molecular oxygen, can generate $O_2^{\bullet}$, but can also reduce $H_2O_2$ (hydrogen peroxide) to $OH^{\bullet -}$ (hydroxyl radical), an extremely harmful radical [8]. The reactions thus far described in the preceding two sections represent the redox-cycling of Dox [1,8,9,24].

The superoxide anion $O_2^{\bullet}$ produced by redox-cycling of Dox can be enzymatically dismutated to $H_2O_2$ and $H_2O$ by superoxide