



ORIGINAL ARTICLE

# The role of ivabradine in doxorubicin-induced cardiotoxicity: exploring of underlying argument

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## Abstract

This study investigated the potential role of ivabradine (IVN) in the attenuation of doxorubicin (DXR)-induced cardiotoxicity in rats. A total of 28 Swiss-Albino male mice were used, divided into four equal groups: the negative control did not receive any agents ( $n=7$ ), the DXR group received a single dose of DXR 20 mg/kg ( $n=7$ ), the treated group A was pretreated with IVN 5 mg/kg plus DXR ( $n=7$ ), and the treated group B was pretreated with IVN 10 mg/kg plus DXR ( $n=7$ ). The duration of this study was 10 days. Inflammatory biomarkers, including tumor necrosis factor alpha (TNF- $\alpha$ ), lactate dehydrogenase (LDH), malondialdehyde (MDA), and cardiac troponin (cTn-I) serum levels were measured. TNF- $\alpha$ , LDH, MDA, and cTn-I serum levels were higher in the DXR-treated mice compared with the control ( $P<0.01$ ). IVN produced a dose-dependent effect in the reduction of MDA and cTn-I compared to DXR-treated mice ( $P<0.05$ ). Our findings suggest that IVN is an effective agent in mitigating DXR-induced cardiotoxicity due to its anti-inflammatory and antioxidant effects. IVN illustrated a dose-dependent effect in the attenuation of DXR-induced cardiotoxicity through inhibition of lipid peroxidation and cardiomyocyte injury.

**Keywords** Doxorubicin · Cardiotoxicity · Ivabradine · Lipid peroxidation · Cardiomyocyte injury

## Introduction

Doxorubicin (DXR) is a cytotoxic drug belonging to the anthracycline antibiotic class used in the treatment of various malignancies, including leukemia, lymphoma, breast, and ovarian cancers (Jasim et al. 2019). DXR is a hydroxylated form of daunorubicin, which is abundant as a natural

product of many strains of *Streptomyces*. In contrast, only *Streptomyces cesius* can produce DXR, thus other *Streptomyces* strains need to be genetically modified to produce DXR (Al-Kuraishy and Al-Gareeb 2016). In 1996, a gene encoding the conversion of daunorubicin to DXR was discovered (Al-Kuraishy and Al-Gareeb 2016). Acute or prolonged use of DXR is associated with different complications, including

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cardiotoxicity, nephrotoxicity, immunosuppression, bone marrow depression, and gastrointestinal disorders. DXR-induced cardiotoxicity is the most common complication linked with the use of DXR (Al-Kuraishy et al. 2015, 2021a).

DXR-induced cardiotoxicity is thought to be mediated by mechanisms, including reactive oxygen species (ROS) generation, lipid peroxidation, endoplasmic stress, mitochondrial dysfunction, and membrane integrity alteration (Sindhu et al. 2021; Al-Kuraishy et al. 2019, 2022a, b). DXR-induced cardiotoxicity is presented in diverse clinical forms, such as hypotension, arrhythmia, and acute heart failure (Kumari et al. 2020). Chronic use of DXR may lead to the development of congestive heart failure due to the propagation of dilated cardiomyopathy (Xu et al. 2020). Epidemiological and clinical trial studies indicate that DXR causes dose-dependent irreversible cardiotoxicity (Xu et al. 2020). In this state, various therapeutic strategies have been applied to attenuate the development of DXR-induced cardiotoxicity using antioxidants,  $\beta$ -adrenoceptor blockers, and renin–angiotensin system modulators (Lan et al. 2020). However, some of these cardio-protectant agents may interfere with the anticancer effect of DXR. Notably, phosphodiesterase 5 inhibitors, such as tadalafil and sildenafil, can reduce DXR-induced cardiotoxicity without interfering its anticancer effect (Koka et al. 2010; Shah et al. 2021).

Ivabradine (IVN) is an inhibitor of funny current ( $I_f$ ) channels in the sinoatrial nodal tissue, which decreases heart rate, and it is used mainly in the management of sinus tachycardia. Unlike  $\beta$ -adrenoceptor blockers, IVN does not reduce the force of ventricular contraction, so it is safe to use in heart failure (Su et al. 2020). Of interest, a clinical trial revealed the effectiveness of IVN in decreasing the severity of heart failure and acute coronary syndrome through its anti-inflammatory and antioxidant properties (Su et al. 2020). Thus, the objective of the present study was to investigate the potential role of IVN in the attenuation of DXR-induced cardiotoxicity in rats.

## Materials and methods

This study was performed in the College of Medicine, Department of Clinical Pharmacology and Therapeutic, Al-Mustansiriyah University, Bagdad, Iraq from December 2021 to February 2022. This study was allowed and approved by the Scientific Jury and Editorial Board in the College of Medicine, Al-Mustansiriyah University, according to reference No. 384WTR on 23/4/2021.

### Animals

Twenty-eight Swiss-Albino male mice weighing 200–500 g were obtained from the animal house of the Iraqi Medical

Research Center, Bagdad, Iraq. All experimental mice were kept in sterilized cages (3 per cage) under a 12/12 h light–dark cycle with standard atmospheric conditions. All mice had free access to water and food, and added libitum. To ensure adaptation, all rats were permitted to stay in their cages for 1 week.

### Induction of DXR-induced cardiotoxicity

In this experimental study, each mouse was anesthetized with isoflurane at 2 mg/kg, and then DXR at 20 mg/kg was injected intraperitoneally (IP) using 26G sterile syringes. The mice were observed prudently for any deterioration in their general health. This method was performed according to the Al-Kuraishy and Al-Gareeb (2016).

### Study design

Twenty-eight mice were allocated into four groups: negative control, did not receive any agents ( $n = 7$ ); DXR group, received a single dose of DXR 20 mg/kg ( $n = 7$ ); treated group A, pretreated with IVN 5 mg/kg orally for 10 days plus DXR 20 mg/kg on the 8th day ( $n = 7$ ); treated group B, pretreated with IVN 10 mg/kg orally for 10 days plus DXR 20 mg/kg on the 8th day ( $n = 7$ ). The duration of the study was 10 days. Each experiment was performed according to the Guidelines for Use and Care of Laboratory Animals.

### Biochemical variables

At the end of the study, the mice were sacrificed under general anesthesia, and blood samples were drained from the heart chambers. The blood samples were directly centrifuged at 3000 rpm. The sera were stored at  $-20\text{ }^{\circ}\text{C}$  in a special refrigerator until the time of analysis.

Inflammatory biomarkers, including tumor necrosis factor alpha (TNF- $\alpha$ ), were assessed by ELISA kit methods (MyBioSource, San Diego, USA). In addition, serum lactate dehydrogenase (LDH), malondialdehyde (MDA), and cardiac troponin (cTn-I) levels were measured by the ELISA kit method (MyBioSource, San Diego, USA). Procedures for ELISA kits were performed according to the manufacturer's protocol and instructions. All drugs and reagents were purchased from a private pharmaceutical company.

Data analysis was performed using SPSS (Statistics for Windows version 24.00, 2018, Armonk, NY, IBM Corp, USA). The presented data were expressed as a mean  $\pm$  standard deviation. An unpaired  $t$  test and one-way analysis of variance were applied to detect differences among unrelated groups. The level of significance was applied when  $P < 0.05$ .

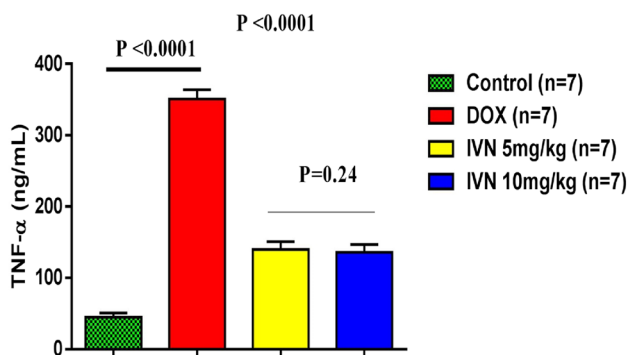
## Results

TNF- $\alpha$  serum level was higher in DXR-treated mice ( $350.85 \pm 12.82$  ng/mL) compared to the control ( $44.91 \pm 6.07$  ng/mL), ( $P < 0.0001$ ). TNF- $\alpha$  serum level was reduced in both doses of IVN 5 mg/kg and 10 mg/kg to  $139.99 \pm 10.93$  ng/mL and  $135.94 \pm 10.79$  ng/mL, respectively, compared to DXR-treated mice ( $P < 0.0001$ ). However, IVN 5 mg/kg had an insignificant effect in reducing TNF- $\alpha$  serum level compared to IVN 10 mg/kg ( $P = 0.24$ ) (Fig. 1).

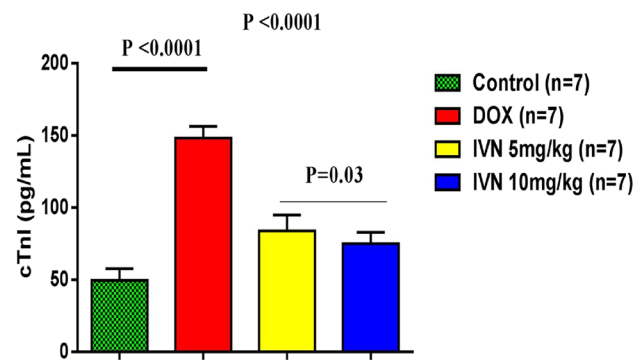
Cardiac troponin (cTn-I) level was higher in DXR-treated mice ( $148.24 \pm 8.82$  pg/mL) compared to the control ( $49.64 \pm 8.08$  ng/mL,  $P < 0.0001$ ). In addition, cTn-I serum level was reduced in both doses of IVN 5 mg/kg and 10 mg/kg to  $83.96 \pm 10.95$  pg/mL and  $75.14 \pm 7.80$  pg/mL, respectively, compared to DXR-treated mice ( $P < 0.0001$ ). However, the effect of reducing cTn-I was significant with IVN 10 mg/kg compared to IVN 5 mg/kg ( $P = 0.03$ ) (Fig. 2).

MDA serum level was higher in DXR-treated mice ( $1.91 \pm 0.12$  ng/mL) compared to the control ( $1.15 \pm 0.20$  ng/mL,  $P = 0.01$ ). MDA serum level was reduced in both doses of IVN 5 mg/kg and 10 mg/kg to  $1.67 \pm 0.10$  ng/mL and  $1.30 \pm 0.11$  ng/mL, respectively, compared to DXR-treated mice ( $P < 0.01$ ). Though, IVN 10 mg/kg had a significant effect in reducing MDA serum level compared to IVN 5 mg/kg ( $P = 0.04$ ) (Fig. 3).

Finally, LDH serum level was higher in DXR-treated mice ( $17.53 \pm 4.05$  IU/L) compared to the control ( $7.95 \pm 2.80$  IU/L,  $P = 0.01$ ). LDH serum level was reduced in both doses of IVN 5 mg/kg and 10 mg/kg to  $14.75 \pm 3.67$  IU/L and  $13.29 \pm 3.33$  IU/L, respectively, compared to DXR-treated mice ( $P < 0.01$ ). Nevertheless, the effect of reducing LDH serum level was insignificant to mice treated with IVN 5 mg/kg compared to mice treated with IVN 10 mg/kg ( $P = 0.09$ ) (Fig. 4).



**Fig. 1** Effects of ivabradine (IVN) on the tumor necrosis factor alpha (TNF- $\alpha$ ) in mice with DXR-induced cardiotoxicity

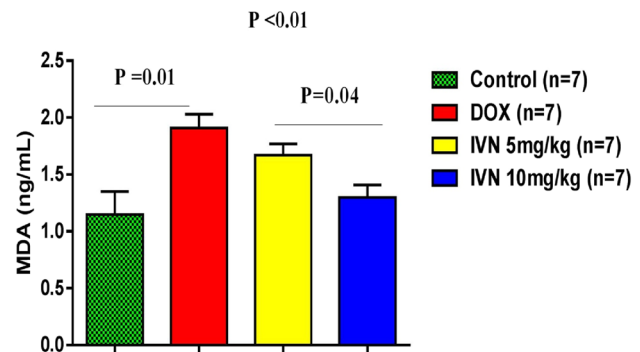


**Fig. 2** Effects of ivabradine (IVN) on the cardiac troponin (cTn-I) levels in mice with DXR-induced cardiotoxicity

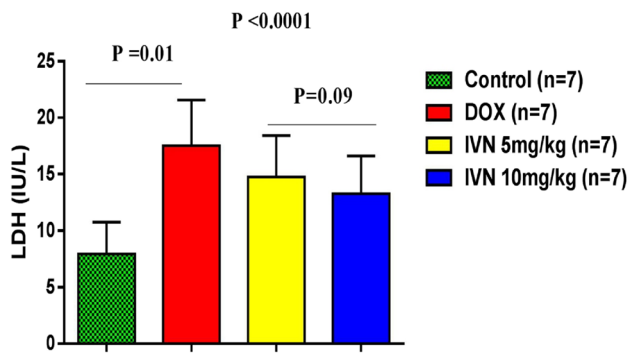
## Discussion

Previous studies have reported that anthracycline-induced cardiotoxicity is approximately 9, and 98% of these cases tend to develop within 1 year. DOX and other anthracycline-induced cardiotoxicities are irreversible in most cases, and 2-year survival has been shown to be 50% when heart failure is caused by anthracycline (Felker et al. 2000). Treatment of DOX-induced cardiotoxicity and associated heart failure is difficult due to the development of resistance to the inotropes (Felker et al. 2000). IVN improves cardiac hemodynamic dysfunction induced by DOX through an increase in stroke volume (Chiu et al. 2019). IVN promotes coronary perfusion and increases left ventricular diastolic filling and cardiac contractility. The positive inotropic effect of IVN is mediated by sarcoplasmic and endoplasmic ATPase activity with a noteworthy reduction of afterload (Yang et al. 2020).

The current study found that IVN had a significant dose-dependent effect in reducing DXR-induced cardiotoxicity. Colak et al. found that IVN had a protective effect against DXR-induced cardiotoxicity in rats (Colak et al. 2012). More specifically, the authors found that IVN-improved



**Fig. 3** Effects of ivabradine (IVN) on the malondialdehyde (MDA) levels in mice with DXR-induced cardiotoxicity



**Fig. 4** Effects of ivabradine (IVN) on the lactate dehydrogenase (LDH) levels in mice with DXR-induced cardiotoxicity

electrocardiographic records and blood pressure alteration in rats with experimental DXR-induced cardiotoxicity (Colak et al. 2012). Besides, it has been suggested that IVN attenuates left ventricular and autonomic dysfunction in DXR-induced cardiotoxicity in rats (El-Naggar et al. 2018). Altogether, these findings underline the protective effect of IVN against DXR-induced cardiotoxicity, which is also confirmed in the present study.

The underlying mechanism of the cardioprotective effect of IVN might be linked to its anti-inflammatory and antioxidant effects (Wang et al. 2022). In the present study, IVN reduced TNF- $\alpha$ , cTn-I, MDA, and LDH serum levels compared to the DXR-induced group. A meta-analysis of randomized trials investigating the effect of IVN on atrial fibrillation illustrated that IVN was effective in the management of atrial fibrillation due to its anti-inflammatory and antioxidant effects (Wang et al. 2022). A previous pilot study by Dominguez-Rodriguez and coworkers demonstrated that IVN had a latent role in decreasing acute coronary syndrome through inhibition of pro-inflammatory cytokines release, including TNF- $\alpha$  (Dominguez-Rodriguez et al. 2012). Likewise, IVN inhibits the expression of inflammatory signaling pathways, such as p38 mitogen activated protein kinase (p39MAPK), in rats with experimental DXR-induced cardiotoxicity (Zuo et al. 2019). Furthermore, a recent study showed that IVN attenuates kindling in rats through its antioxidant effects (Ahmed et al. 2020). Of note, exaggeration of inflammatory reactions and oxidative stress may induce the development of heart failure (Onohuean et al. 2021; Teibo et al. 2021). These findings suggest that the anti-inflammatory and antioxidant properties of IVN could be a potential mechanism in reducing DXR-induced cardiotoxicity.

Nonetheless, one of the most intriguing findings of the current study was the dose-dependent effect of IVN in reducing cTn-I and MDA serum levels in rats with DXR-induced cardiotoxicity. Our results highlight the effectiveness of IVN in decreasing DXR-induced cardiotoxicity

through inhibition of lipid peroxidation and cardiomyocyte injury. Boshra et al. illustrated that IVN could mitigate cardiomyocyte injury by inhibiting the apoptosis and generation of ROS, which has been known to trigger the development of lipid peroxidation in mice with DXR-induced cardiotoxicity (Boshra and Shalaby 2015). In virtue of its anti-inflammatory and antioxidant properties, IVN could be a potential candidate in the mitigation of DXR-induced cardiotoxicity.

In its clinical perspective, IVN might be a pioneer drug in attenuating cardiotoxicity, mainly in patients with heart failure, arrhythmias, and malignancies treated by DXR. It has been shown that unlike  $\beta$ -blockers, IVN does not decrease ventricular force (Su et al. 2020; Al-Kuraishy et al. 2021b, 2022c, d; Lawal et al. 2021) and can also reduce COVID-19-induced cardiovascular complications due to its anti-inflammatory and antioxidant properties (Al-Kuraishy et al. 2021c, 2022e; Batiha et al. 2021, 2022). In addition, IVN facilitates a pleiotropic cardioprotective effect against isoproterenol-induced acute cardiac injury by increasing the ventricular fibrillation threshold (Simko et al. 2021). A clinical trial conducted by Izco et al. showed that acute heart failure patients could benefit from heart rate reduction, as myocardial consumption and oxidative stress are related to tachycardia. IVN could have a clinical role in attenuating catecholamine-induced tachycardia (Izco et al. 2020). Combined with trimetazidine, IVN reduces the risk of acute cardiac injury in patients undergoing percutaneous coronary intervention as a result of an anti-ischemic effect mediated by a decrease in myocardial oxygen consumption (Chen 2021). It has been shown that IVN induces the release of protective microvesicles from endothelial cells, which promote cell proliferation and reduce cardiac necrosis following ischemic reperfusion injury (Ramirez-Carracedo et al. 2020). IVN promotes expression of extracellular matrix metalloproteinase is induced, which prevents the development of myocardial necrosis (Ramirez-Carracedo et al. 2020). Thus, IVN can be used as a prophylactic agent to prevent the development of acute cardiac injury as shown in DXR-induced cardiotoxicity.

Consequently, IVN could be effective in treating patients with heart failure and arrhythmias during DXR chemotherapy.

## Conclusion

The anti-inflammatory and antioxidant effects of IVN render this drug an effective agent in mitigating and preventing DXR-induced cardiotoxicity. Remarkably, this study revealed the dose-dependent effect of IVN on the attenuation of DXR-induced cardiotoxicity due to the inhibition of lipid peroxidation and cardiomyocyte injury. In this state, large-scale experimental, preclinical, and clinical studies are warranted to validate our experimental findings.

**Author contributions** Conceptualization: HMA, HKI, and AIA-G. Data curation: HMA, HKI, and AIA-G. Formal analysis: HMA, AIA, HKI, MME, and GEB. Methodology: HMA, HKI, and AIA. Investigation: MME, GEB, and AY. Visualization: HMA, AIA, HKI, MME, ASA, HAK, and GEB. Writing—original draft: HMA, HKI, MME, GEB, and AIA. Writing—review & editing: HMA, HKI, AIA, MME, AY, ASA, HAK, and GEB. All authors have read and agreed to the published version of the manuscript.

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**Availability of data and materials** All data generated or analyzed during this study are included in this published article.

## Declarations

**Conflict of interests** The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval** This study was performed in the College of Medicine, Department of Clinical Pharmacology and Therapeutic, Al-Mustansiriyah University, Baghdad, Iraq from December 2021 to February 2022. This study was allowed and approved by the Scientific Jury and Editorial Board in the College of Medicine, Al-Mustansiriyah University according to the reference No. 384WTR in 23/4/2021.

**Consent to participate** Not applicable.

**Consent to publish** Not applicable.

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