

Animal study of Anthracycline-induced Cardiotoxicity and Nephrotoxicity and Evaluation of Protective Agents

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Abstract

Study background: Anticancer chemotherapy Anthracycline (ANT) antibiotics associated with cardiac and renal toxicity which represents serious complication. In this study, the protective effect of the 2 beta-blockers carvedilol and nebivolol were tested in a rat model of ANT induced cardio and renal-toxicity by repeated intraperitoneal doxorubicin (Dox) administration.

Methods: Six groups of animals were used, each 8 rats divided as control group- received intraperitoneal saline every other day; control carvedilol: rats received carvedilol dose 30mg/kg/day orally; control nebivolol: rats received nebivolol 1mg/kg/day orally; doxorubicin alone: a dose of 3 mg/kg/day was administered intraperitoneal every other day; doxorubicin + carvedilol: carvedilol started at the same day with Dox; doxorubicin + nebivolol: nebivolol started at the same day with Dox. All substances were administered for 12 days. Detection & quantification of doxorubicin-induced heart and renal damage and therapeutic action of beta-blockers was done using Langendorff's technique, echo-cardiographic function examinations, serum creatinine, total proteins and histopathology.

Results: The administration of doxorubicin in the dose of 3 mg/kg/day for 12 days produced pronounced heart impairment, as well as renal nephrotoxic changes. Significant reduction of Doxo-cardiotoxicity and nephrotoxicity in Nebivolol-treated animals more than Carvedilol treated animals.

Conclusions: Coadministration of either carvedilol or nebivolol with doxorubicin was able to ameliorate up to almost contradict doxorubicin-induced myocardial injury, glomerular filtration disturbance and renal tubular damage with upper hand for nebivolol. So, they can be considered a feasible candidate to protect against nephrotoxicity & cardiotoxicity commonly encountered with doxorubicin treatment.

Keywords: Anthracycline; Toxicity; Nebivolol; Carvedilol

Introduction

Doxorubicin (Dox) is one of the most potent broad-spectrum antitumor anthracycline antibiotics, widely used to treat a variety of cancers including breast, ovarian, lung, uterine and cervical cancers, Hodgkin's disease, non-Hodgkin lymphoma, acute leukemia, soft tissue and primary bone sarcomas [1-3]. Because of their great importance in cancer therapy, researchers have expended great efforts trying to prevent or attenuate the side effects of Dox administration. Accordingly, several approaches have been pursued in the 90's, such as dosage optimization, synthesis, and use of analogues or combined therapy. No hopeful results have been found and the application of different Dox-analogues did not show better antineoplastic value or lower toxicity than Dox [4,5].

Many different chemical agents have been examined to prevent ANT-induced cytotoxicity [4,6], and some of them showed promising results. These chemicals includes natural Products e.g. the most commonly used and investigated compounds are vitamins (E, C, A, carotenoids), coenzyme Q, flavonoids, polyphenols, herbal antioxidants, selenium, and virgin olive oil [7].

Some well-known as well as new and potential drugs have been shown to have a significant influence on Dox-induced toxicity throughout different pathways of protection. Stolarska et al. [8] investigated the cytoprotective effect of amifostine against cardiotoxicity due to Dox in the treatment of childhood neoplastic diseases. Doxycycline protection against Dox-induced oxidative stress and apoptosis in mouse testes was observed by Yeh et al. [9]. Liu et al. [10] have compared the roles of dihydropyridine calcium antagonists: nifedipine, nitrendipine, and

amlodipine in Dox-induced nephrotoxicity. Published in vivo studies suggested that clinically available cytokine "erythropoietin" may play a protective role against nonhematopoietic diseases, including cardiotoxicity induced by Dox, infarction and ischemia-reperfusion injury in the heart [11]. Pre-administration of docetaxel protects against Dox-induced cardiotoxicity [12]. Fullerenols act as a free radical scavenger in biological systems has repeatedly demonstrated protective effects against cardio-, hepato- and nephrotoxicity induced by Dox in animal models [13,14].

Despite extensive research, the mechanism of Dox-induced toxicity is still not completely elucidated and neither are the mechanisms of the different chemicals acting as potential protectors. Clinical trials and further studies are warranted to investigate and compare the individual mechanisms of beneficial effects [15].

The third generation of β -adrenoreceptor antagonists including nebivolol and carvedilol represents a distinct pharmacological entity as compared with other β -adrenoreceptor antagonists [16,17].

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Carvedilol is a cardiovascular drug with a wide therapeutic potential. It is a non selective blocker of α 1 and β -adrenergic receptors, while displaying vasodilating properties has potent antioxidant and antiapoptotic properties [18,19].

In addition to the inhibitory effects on β 1-adrenergic receptors, the novel β -blocker nebivolol has additional hemodynamic properties [20]. In particular, nebivolol is able to stimulate endogenous production of NO by inducing phosphorylation of the endothelial enzyme endothelial NO synthase (NOS; eNOS) [21]. Whereas nebivolol action on NO can result in favorable outcomes at vascular levels, the effects of NO on the heart are not so straightforwardly beneficial.

We designed in this study to establish the effect of Administration of doxorubicin in combination with either carvedilol or nebivolol Beta-blocker agents in order to block its free-radical mediated cardio- and nephro-toxic effect, thus reducing its cardiotoxicity and nephrotoxicity.

Materials and Methods

-Doxorubicin Hydrochloride (DOX): (Pharmacia and Upjohn. Italy).

$C_{27}H_{29}NO_{11}$, HCL. DOX was supplied as a red-orange, hygroscopic, crystalline powder. DOX solution was freshly prepared, protected from light. It was dissolved in saline solution.

-Nebivolol powder (Sigma chemical company). Nebivolol was dissolved in distilled water.

-Carvedilol powder (Sigma chemical company). Carvedilol was dissolved in distilled water.

-Isoprenaline powder (Sigma chemical company). Isoprenaline was dissolved in distilled water.

-Modified Krebs-Henseleit buffer solution of the following composition: NaCl, 118 mmol/L; KCl, 4.7 mmol/L; CaCl, 2.0 mmol/L; MgSO₄ 7H₂O, 1.2 mmol/L; KH₂PO₄, 1.2 mmol/L; glucose, 11.1 mmol/L; and NaHCO₃, 25 mmol/L [22]. All chemicals from Sigma chemical company.

Creatinine kit. DIAMOND

-Total proteins kit. Bio-Analytcs

-PowerLab Data Acquisition and Analysis Systems for Monitoring and recording signals from the isolated rabbit's heart connected to the Langendorff's coronary perfusion set.

-We used 48 male albino rats, of the same age and weight 250-300 g. They were housed under standard laboratory conditions in the animal house of Research Institute of Ophthalmology.

The animals were placed every 2 in a cage, fed a standard rat chow diet and given water ad libitum under a 12 hr light/dark cycle and room temperature. Rats were acclimatized to the environment for one-week prior to experimental use.

This study was approved by our institution's (kasr el eini hospital) Animal Care Committee and the guidelines were strictly adhered to.

-Rats were randomly divided in six experimental groups (8 rats each):

1st group – control saline: treated with 0.5 ml of 0.9 % NaCl /day intraperitoneal every other day.

2nd group – control carvedilol: rats treated with carvedilol dose 30mg/kg/day (in 0.5 ml solution) [23] by oral gavage for 12 days.

3rd group – control nebivolol: rats treated with nebivolol dose 1mg/kg/day [24] by oral gavage for 12 days.

4th group – Dox alone: a dose of 3mg/kg/day (18 mg/kg cumulative total dose) was administered intraperitoneally (in 0.5 ml solution) every other day during 12 days of the experiment [25].

5th group – Dox + carvedilol: rats treated with carvedilol dose 30mg/kg/day by oral gavage for 12 days started at the same day with dox.

6th group – Dox + nebivolol: rats treated with nebivolol dose 1mg/kg/day by oral gavage for 12 days started at the same day with dox.

At the end of the experiment, the animals were subjected to:

1. Blood samples collection after 18 hr fast, from the retro-orbital sinus for determination of: Serum creatinine by the kinetic method according to Menry [26]; while total proteins were measured according to the method of Reinhold [27].
2. Echocardiography was done at the end of the experiment under light ether anesthesia [28].

Using (My lab 30VET Gold) of Esaote company, the echocardiography was used to evaluate the cardiac functions. Echocardiograms were performed with an echocardiography system equipped with a 4-8 MHz phased-array probe (PA122E) placed over the left parasternal area and rocked through the heart from the apex to the base. Two- dimensional short axis view of the left ventricle and M-mode tracings were recorded through the anterior and posterior left ventricular (LV) walls at the papillary muscle level to measure LV end-diastolic dimension (LVEDD) and LV end-systolic dimension (LVESD); also ejection fraction (EF) and fractional shortening (FS) were recorded. $FS = (End-diastolic\ dimension - End-systolic\ dimension) / End-diastolic\ dimension \times 100\%$.

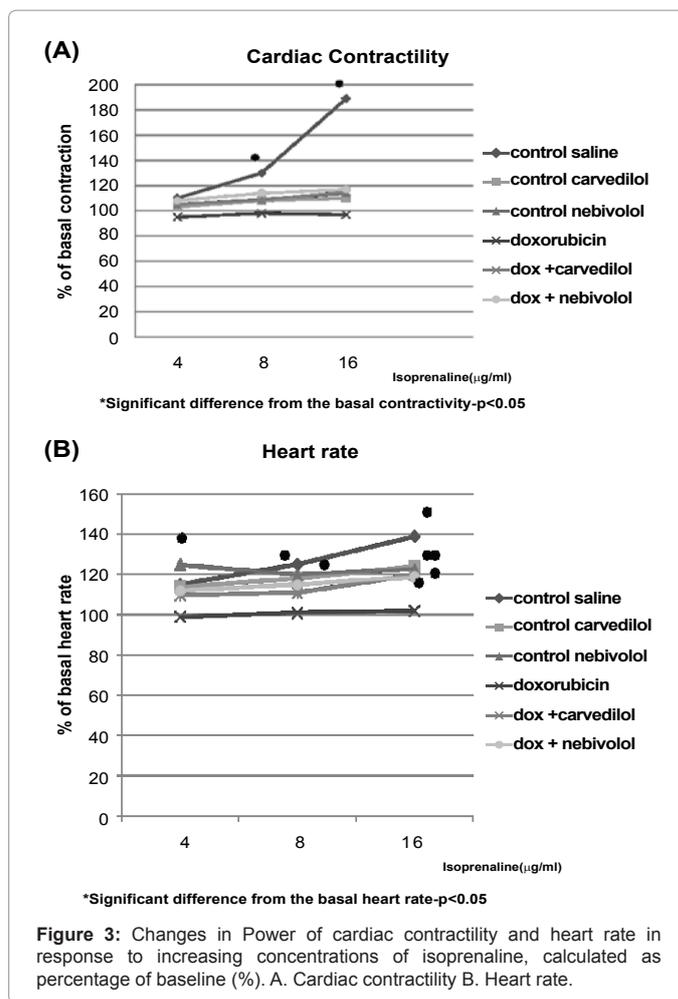
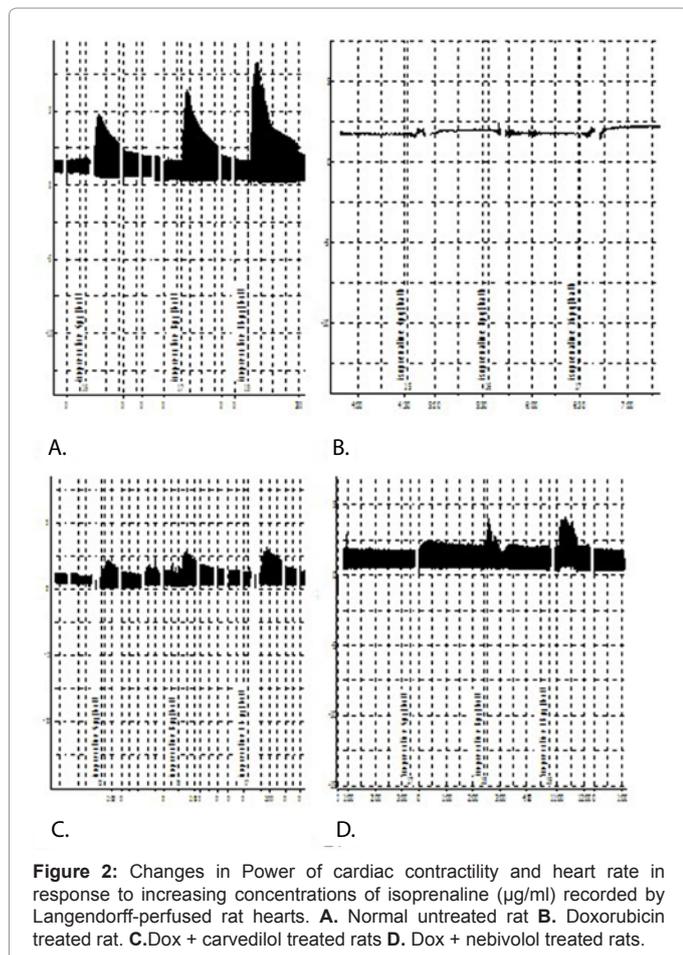
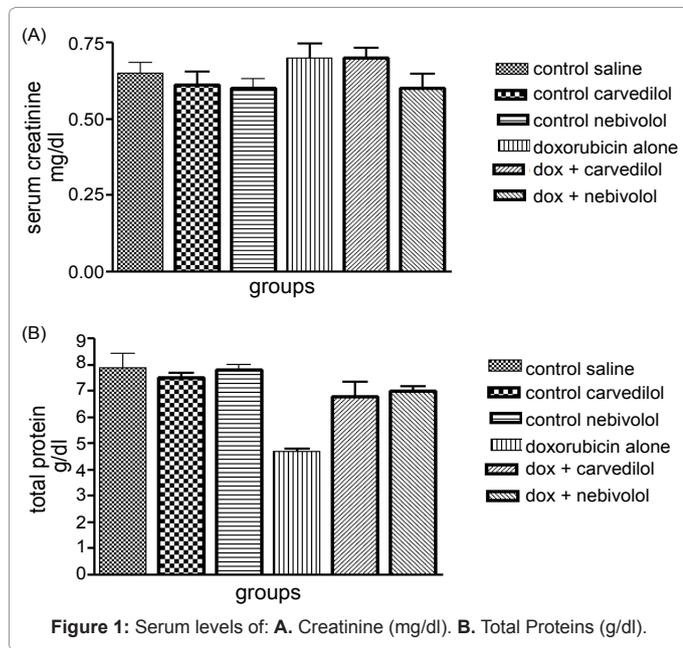
3. Isolated perfused rat heart. Langendorff's technique [29]. The rat hearts were obtained for detection of cardiac contractile strength (inotropic effects) and heart rate (chronotropic effects) using a Power Lab acquisition system.

Rats were injected intraperitoneally (i.p.) with heparin sodium 5000 IU/kg. They were anesthetized using ether inhalation and then sacrificed. The heart was rapidly excised and placed in ice-cold Krebs-Henseleit buffer bubbled constantly with 95% O₂ and 5% CO₂. Perfusate temperature was maintained at 37°C. The heart was immediately mounted and cannulated in the retrograde mode according to Langendorff method as previously described [29]. The amplitude of ventricular contractions as well as heart rates of different groups was recorded continuously on a Power Lab acquisition system (ADInstruments Pty Ltd, Castle Hill, Australia). Concentration-response curves to isoprenaline (μ g/ml) were constructed to study the inotropic and chronotropic effects.

4. Sections from heart and kidneys were obtained and fixed in 10% neutral phosphate-buffered formalin, dehydrated in ethanol, cleared in xylene and embedded in paraffin. Five-micrometer sections were stained with Hematoxylin and eosin for histopathological examination.

Another set of heart sections were stained by toluidine blue to be

graded for cardiotoxicity. Histopathological changes, including loss of myofibrils and vacuolization of the cytoplasm are used to grade injury on a scale of 1 to 3. Fewer than 5 % of cells show changes of injury are



given a grade 1. Those with changes in 5 to 15 % graded 1.5. While 16 to 25 % were graded 2. 26 to 35 % graded 2.5. Finally, More than 35 % of cells were graded 3 [30].

Statistical analysis

The Stat Plus® program was used for the statistical evaluation; values were compared by an unpaired t- test. Values with $p < 0.05$ were considered significant.

Results

Serum level of creatinine

Dox-alone group showed statistical significant rise in creatinine levels compared to control groups ($p < 0.05$). Dox-nebivolol treated group showed significant decrease in levels of creatinine compared to dox alone group ($p = 0.0006$), also it showed significant lower creatinine levels compared to dox-carvedilol treated group ($p = 0.0002$) (Figure 1a).

Total proteins

Doxorubicin therapy was shown to decrease total proteins significantly after 12 days as compared to the control values ($p < 0.0001$). Treatment with both carvedilol and nebivolol significantly increased the total proteins concentration compared to dox alone group ($p < 0.0001$), with insignificant difference between the two drugs. However, the concentrations of total proteins are still significantly lower than the control ($p < 0.05$) (Figure 1b).

Echocardiography (Table 1)

LVSD and LVDD were significantly dilated ($p < 0.0001$) in dox-untreated rats, compared to control groups, whereas a significant reduction in both end-diastolic and -systolic volume was observed in both carvedilol and nebivolol treated dox rats compared to dox untreated rats ($p < 0.05$). Also, nebivolol treated dox rats showed significant reduction compared to dox-carvedilol group ($p < 0.0001$).

LV EF values were decreased during the experiment in Dox-receiving animals—from $92 \pm 1.9\%$ in the control to $63 \pm 2.9\%$ at the end of the experiment, the decrease being statistically significant ($p < 0.0001$).

In the carvedilol and nebivolol treated control groups, the LV EF values did not differ significantly from the control group. While in the carvedilol and nebivolol treated dox groups, the LV EF values were not significantly decreased as compared to control groups but significantly higher than dox treated group ($p < 0.0001$).

Percentage fractional shortening (%FS), as derived from the measurements on M-mode echocardiogram, were not significantly different in the three control groups. However, there was a significant reduction at 12 days in dox-untreated rats compared with the other groups ($p < 0.05$).

Isolated perfused rat heart preparation (Langendorff's preparation)

Isoprenaline produced concentration-dependent increase in force and heart rate. The positive inotropic and chronotropic effects of isoprenaline were not significantly different in hearts from the two treated control groups of rats (Figure 2 and 3). However, the positive inotropic and chronotropic effects induced by isoprenaline was significantly reduced ($P < 0.05$) in hearts from the dox group compared to normal untreated and control treated rats ($p < 0.05$) (Figure 2). Both dox treated groups (carvedilol and nebivolol) showed significant improvement in power of cardiac contractility and heart rate (in response to increasing doses of isoprenaline) (Figure 3) compared to dox alone group ($p < 0.05$). There were insignificant change between the Dox + carvedilol and Dox + nebivolol groups ($p > 0.05$) when compared to each other (Table 2).

Histopathological assessments

Heart: There was no abnormal microscopy for the cardiac muscles of all three control groups in the light microscopic examination. Doxorubicin alone group showed 3 as highest recorded grade of cardiac muscle injury (Figure 4A). In dox + carvedilol treated rats group the highest grade recorded was 1.5 which was much lower than those of doxorubicin alone group (Figure 4B). While, dox + nebivolol treated rats groups showed lowest grade of cardiac injury which was 1 (Figure 4C). Both treatment groups showed statistical significant difference compared to the Dox alone group ($p < 0.0001$). Again, dox + nebivolol treated group showed statistical significance difference compared to dox + carvedilol group ($p = 0.03$).

Kidneys: There was no abnormal microscopy for the kidney of all three control groups in the light microscopic examination. On the other hand, light microscopic examination of kidneys' rats of doxorubicin alone group revealed glomerulopathy characterized by mild hyperplasia of mesangium, and moderate tubular atrophy and dilation. Marked albumin (hyaline) casts formation and congestion of interstitial capillaries (Figure 5). In dox + carvedilol treated rats group shows mild increase in mesangium, focal tubular degeneration and dilation. Mild albumin (hyaline) casts formation. In dox + nebivolol treated rats groups revealed only minimal albumin casts formation.

Discussion

The present study shows a prominent cardio and renal-protection elicited by nebivolol, and, to a lesser degree carvedilol in a rat model of doxorubicin-mediated toxicity. Anthracyclines have gained widespread use in the treatment of haematological malignancies and solid tumours, but their cumulative toxicity on the many organs prevents their use at their maximum myelotoxic doses during the optimal number of therapeutic cycles required[31].

Doxorubicin 18 mg/kg cumulative total dose - induced cardiomyopathy in the form of impaired LV EF, fractional shortening, LVDD and LVSD dilatation; marked impaired contractility with decrease in heart rate, with failure of β -adrenergic response to isoprenaline together with cardiac muscle injury.

Calcium homeostasis disturbances related to the appearance of oxidative stress could explain why the response to isoprenaline was attenuated in the dox-treated group. The dysfunction of sarcoplasmic reticulum could induce changes in intracellular calcium concentrations [32], leading to impairment of cardiac contractility and/or relaxation. Moreover, it has been reported that anthracycline treatment could induce the reduction of β -adrenergic receptor density on myocardial membrane [33].

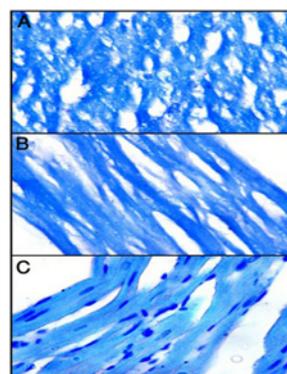


Figure 4: Different sections of rat's hearts with Toluidine blue stain (x1000): **A:** Doxorubicin untreated group showed marked loss of myofibrils and vacuolization of cytoplasm. **B:** Doxorubicin-Carvedilol treated group showed partial preservation of myofibrils and moderate cytoplasmic vacuolization. **C:** Doxorubicin- Nebivolol treated group showed best preservation of myofibrils and minimal vacuolization of cytoplasm.

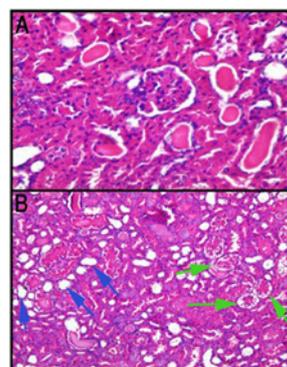


Figure 5: Sections in rat kidneys of Doxorubicin untreated group showing. **A:** Mild increase of mesangium and marked hyaline casts formation (Hematoxylin & eosin x400). **B:** Areas of tubular hydropic degeneration (Green arrows) & tubular atrophy (Blue arrows) (Hematoxylin & eosin x100).

Groups	Echocardiographic Cardiac Functions			
	LV end-systolic dimension (LVSD) (mm)	LV end-diastolic dimension (LVDD) (mm)	Ejection fraction (EF) (%)	Fractional shortening (FS) (%)
control saline	2.8±0.015	8.9±0.01	92±1.9	59±1.3
control carvedilol	3±0.03	7±0.015	90±2	56±1.4
control nebivolol	3.2±0.012	6.8±0.02	89±1.6	55±1.1
doxorubicin alone*	9±0.05	12±0.15	63±2.9	30±1.5
dox + carvedilol†	4±0.02	8.8±0.025	80±1.7	51±1.3
dox + nebivolol‡§	4.7±0.014	8.6±0.016	88±2	45±1.6

*All measures of Dox alone group significantly different from control groups $p < 0.0001$
 † All measures of Dox-Carvedilol group was significantly different from Dox alone group $p < 0.05$
 ‡ All measures of Dox-Nebivolol group was significantly different from Dox alone group $p < 0.0001$
 § All measures of Dox-Nebivolol group was significantly different from Dox-Carvedilol group $p < 0.05$

Table 1: Effect of carvedilol and nebivolol on Doxorubicin induced Cardiac Echocardiographic changes. Values are expressed as mean±S.D. (n=8)

Groups	Power of cardiac contractility (gm)	Heart rate (bpm)
control saline	3.778±0.7104	326.2±18.59
control carvedilol	2.579±0.4133	231.3±19.04
control nebivolol	2.658±0.3995	235.7±14.94
doxorubicin alone*	1.433±0.2861	75.33±12.09
dox + carvedilol†	2.170±0.2445	258.5±28.06
dox + nebivolol‡§	2.071±0.2263	250.3±29.93

*All measures of dox alone group was significantly different compared to control groups $p < 0.0001$
 † Cardiac contractility and heart rate were significantly different in dox-carvedilol treated group compared dox alone group $p = 0.0001$ & < 0.0001 respectively
 ‡ dox-nebivolol treated group showed significant difference in cardiac contractility and heart rate compared to dox alone group $p = 0.0002$ & < 0.0001 respectively
 § No significant difference between measures of dox-nebivolol and dox-carvedilol treated groups $p > 0.05$

Table 2: Cardio dynamic Measurements in Langendorff-perfused rat hearts. Data are presented as mean ± S.D. (n=8).

This is in agree with Filomena de Nigrisa et al. [34] who evaluated the cardiac toxicity of ANTs by the left ventricular pressure developed under a constant perfusion pressure (LVDP), the rate of variation of this parameter during systole (contractility) (LV/dt)max and during diastole (relaxation) (LV(dP/dt)min. Also Paulo et al. [35] confirmed that DOX induces oxidative stress, mitochondrial dysfunction, and histopathological lesions in the cardiac tissue in DOX-induced mitochondrial-mediated cardiomyopathy.

Also, Doxorubicin-induced glomerulopathy is evident by decrease in both serum creatinine and total proteins, associated with swelling and vacuolation of epithelial cells, moderate tubular atrophy and dilation; marked albumin (hyaline) casts formation and congestion of interstitial capillaries. These results are consistent with previous studies reported by other investigators [36,37] that doxorubicin induced nephrotoxicity in normal rats.

According to the reported results for Dox-induced toxicity, almost all organs can be attacked and damaged via the formation of free oxygen radicals and some of the organo-specific pathways. Several mechanisms have been proposed to account for Dox cardiotoxicity, e.g., free radical stress, calcium overloading, and mitochondrial dysfunction [38,39].

The exact mechanism of doxorubicin-induced nephrotoxicity is not yet known. However, it has been suggested by many investigators that cellular damage induced by doxorubicin is mediated by the formation of an iron anthracycline free radical, which in turn causes severe damage to the plasma membrane [40].

Administration of either carvedilol or nebivolol alone in normal rats did not result in significant reduction of normal heart rate in isolated perfused langendorff heart.

Chronic administration of beta-blockers without additional effects produces reactive up-regulation of beta-receptor density [41]. In addition, beta-blockers reduce nocturnal melatonin production [42]. Indeed, under conditions with a physiologically low sympathetic tone,

i.e. at rest and during recovery, carvedilol failed to significantly decrease heart rate.

The beneficial effect of beta blockers (BBs) on anthracycline induced toxicity, they exert a significant protective effect on the cardiac and renal toxicity induced by doxorubicin in this rat model. Coadministration of either carvedilol or nebivolol with doxorubicin was able to ameliorate up to almost contradict doxorubicin-induced myocardial injury, glomerular filtration disturbance and renal tubular damage with upper hand for nebivolol.

Recent developments in cell biology allow us to understand that not all BBs are equal, as their intracellular mechanisms of action can be very different [43].

A study by Filomena de Nigrisa et al. [34] show a beneficial effect of BBs on anthracycline treated hearts. In particular, the use of nebivolol or carvedilol with anthracyclines have reduced the release of glutathione (GSSG) and reduced glutathione (GSH). Since the most important property of carvedilol is antioxidative profile and nebivolol predominantly effects nitric oxide (NO) pathway, the common protective pathway of nebivolol and carvedilol could be the intrinsic beta blocker properties coupled to antioxidant and NO release. Previous studies showed that patients treated with β_1 -selective antagonists without intrinsic sympathomimetic activity (ISA) had more adrenoceptors than control subjects [44] and that the adenylate cyclase activation by the β -adrenoceptor agonist isoprenaline is also enhanced in this situation [45]. The ISA is therefore an important criterion for the therapeutic usefulness of BBs in heart failure patients.

The cardiac effects of BBs are varying in human cardiac tissue. The cardiodepressant effects of beta-blocker may not correlate with its β_1 -selectivity but result from the combined effects of β_1 -selectivity, intrinsic sympathomimetic properties and inverse agonism [46].

The reason for the cardioprotective effects of carvedilol in ANT-induced cardiomyopathy (CMP) may occur through the potent

antioxidant activity of carvedilol. Both carvedilol and its metabolites were shown to have antioxidant effects [47]. It was reported that free oxygen radicals in failing heart were reduced by administration of carvedilol [48]. This antioxidant activity of carvedilol is attributed to its ability to chelate free iron [49], which is widely implicated in enhancing the free radical-mediated toxicity caused by doxorubicin.

However, other possible mechanisms may involve the protection of carvedilol. Sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2) may be another key factor in ANT-induced cardiotoxicity. Doxorubicin causes down-regulation of SERCA2 messenger RNA in animals with cardiac dysfunction [50]. In addition, ANT has been noted to stimulate the release of Ca^{2+} in cardiomyocytes [51]. Treatment of carvedilol is also associated with inhibition of apoptotic signaling pathways [52]. Because apoptosis plays a highly significant role in ANT-induced CMP [53], the antiapoptotic properties of carvedilol could be another important factor in protection from ANT-induced CMP.

A study by Wawaimuli et al. [28] was designed to test the effectiveness of carvedilol, against Dox-induced cardiotoxicity and nephrotoxicity in rats. Carvedilol down-regulated matrix metalloproteinase-2 expression in the heart, increased nephrin expression in the kidney, and attenuated the increased protein expression of NADPH oxidase subunits in heart and kidney. Moreover, carvedilol reduced myocardial and renal apoptosis and improved the histopathological changes in heart and kidney induced by Dox.

The prominent cardioprotective effects of the third-generation beta-blocker nebivolol against anthracycline-induced cardiotoxicity, using the model of an isolated perfused rat heart, were examined by de Nigris et al. [25] Sprague-Dawley rats were treated with Dox and daunorubicin in combination with nebivolol or carvedilol. The co-treatment of beta-blockers and anthracyclines had reduced the release of GSSG and GSH. A more significant reduction was shown with nebivolol than with carvedilol. Also, significant reductions of CK and troponin T activities were observed when the hearts were treated with nebivolol. At the same time, GSHPx, MnSOD, and nitrite/nitrate release were increased after the co-treatment. Three cardiac parameters have been used to evaluate the cardiac toxicity of both anthracyclines and beta-blocker-anthracycline combinations. The left ventricular pressure developed under a constant perfusion pressure (LVDP), then the variation rates of this parameter were observed during contractility (LV/dt)_{max} and relaxation (LV(dp/ dt)_{min}. Nebivolol in combination with anthracyclines had exerted the most significant protection of heart tissue.

It has been demonstrated that nebivolol affected vasodilatation through NO production, stimulated NO release, enhanced NO bioavailability and prevented NO deactivation [54]. A study by Angelo et al. [54] demonstrated that nebivolol stimulates NO production in the heart. This action of nebivolol is exerted via a signaling pathway starting from the activation of β_3 -adrenergic receptors and leading to overexpression of inducible NO synthase.

Nebivolol, a last-generation beta blocker, which is a selective β_1 -adrenergic receptor antagonist, it leads to (i) an increase in the renal NO excretion (ii) a significant increase in the renal plasma flow and glomerular filtration rate (GFR)[56], (iii) suppression of the renin-angiotensin aldosterone system and inhibition angiotensin II[56,57], and reduces endothelin-1[58], and (iv) has an antioxidant effect [59].

Alexandros et al. [60] compared the efficacy of nebivolol versus carvedilol on left ventricular (LV) function and exercise capacity in patients with nonischemic dilated cardiomyopathy (NIDC). Both

nebivolol and carvedilol appear relatively safe, with beneficial effects on LV systolic and diastolic function as well as exercise capacity in patients with NIDC after 12 months' treatment. However, carvedilol exhibits more favorable effects on LV function than does nebivolol.

Conclusions

A coadministration of either carvedilol or nebivolol with doxorubicin was able to ameliorate up to almost contradict doxorubicin-induced myocardial injury, by a mechanism not related to their β -adrenergic receptor antagonism. Also, they improved glomerular filtration disturbance and renal tubular damage with upper hand for nebivolol. So, either drug, especially nebivolol, must merit serious consideration as an adjunctive therapy to protect against cardiotoxicity and nephrotoxicity commonly encountered with doxorubicin treatment.

Further investigations are needed to explore the possible mechanisms of the protective actions of carvedilol and nebivolol.

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