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Original Article

Cardiovascular baroreflex sensitivity attenuates by cisplatin-induced toxicity in rats

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Abstract

Introduction: Cisplatin (CP) therapy may disturb cardiovascular system control. The objective of this study was to find baroreflex sensitivity (BRS) in CP-induced nephrotoxicity in rats.

Materials and Methods: Eighteen male and female Wistar rats were randomly assigned to two groups; treated with CP (2.5 mg/kg/day) and the vehicle, for five consecutive days, and then were subjected to surgical procedure to determine BRS using three different doses (0.025, 0.05 and 0.1 mg/kg) of α-adrenergic receptor agonist phenylephrine (PE).

Results: Serum levels of blood urea nitrogen and creatinine, kidney weight, and kidney tissue damage score were increased in CP-treated animals. All doses of PE injection caused MAP increase and HR decrease. However, ΔMAP and ΔHR response to 0.1 mg/kg of PE were significantly lower in the CP-treated group ($P<0.05$). BRS also was increased in a dose-dependent manner by PE in vehicle-treated group, but this was not the case in the CP-treated animals, and significant difference in BRS was detected between the two groups ($P<0.05$) when 0.05 or 0.1 mg/kg of PE were infused.

Conclusion: CP-induced nephrotoxicity attenuates BRS possibly due to peripheral effect on the vascular system.

Keywords:
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Introduction

Cisplatin (CP) is known as a potential drug for chemotherapy, widely used in clinic. However, the drug is accompanied with some major side effects such as nephrotoxicity (Stohr *et al.*, 2007, Nematbakhsh *et al.*, 2012, Nematbakhsh *et al.*, 2012, Okui *et al.*, 2012, Ashrafi *et al.*, 2013, Nematbakhsh *et al.*, 2013, Nematbakhsh *et al.*, 2013, Nematbakhsh and Nasri, 2013) and hepatotoxicity(Cersosimo, 1993, Kohn *et al.*, 1997, Lu and Cederbaum, 2006). This drug also counteract with renin angiotensin system (Cubeddu *et al.*, 1990, Okui *et al.*, 2012); a powerful hemodynamic control system of body fluid and blood pressure in systemic and renal circulation. It is

reported that angiotensin II receptor blockade may prevent CP-induced nephrotoxicity in male (Deegan *et al.*, 1995, Saleh *et al.*, 2009) but not in female (Haghighi *et al.*, 2012) while the sex hormones do not protect the kidney from CP-induced renal toxicity (Nematbakhsh *et al.*, 2012, Pezeshki *et al.*, 2013). Such reports in the literature reveal the important influence of CP on the hemodynamic system in the body and particularly in the kidney. CP reduces renal blood flow (Winston and Safirstein, 1985), glomerular filtration rate (Hansen *et al.*, 1988, Oc *et al.*, 2014), and possibly disturbs blood pressure (Hansen *et al.*, 1988). In addition, according to the literature, CP induces nephrotoxicity in a gender-related manner (Stakisaitis *et al.*, 2010, Eshraghi-Jazi *et al.*, 2011, Haghighi *et al.*, 2012, Pinches *et al.*, 2012, Nematbakhsh *et al.*, 2013, Aydin *et al.*, 2014). Although some data are available in the literature related to kidney and systemic hemodynamic changed by CP (Winston and Safirstein, 1985, Hansen *et al.*, 1988, Oc *et al.*, 2014), the data on the control of systemic blood pressure, which may be disturbed by CP is sparse. It is well known that CP increases the level of oxidative stress, while baroreflex sensitivity (BRS) impairment is associated with oxidative stress (Bertagnolli *et al.*, 2006), and antioxidants may improve BRS (Monteiro *et al.*, 2012). BRS is also reported to be gender- and estrogen-related (Saleh and Connell, 1998, Saleh and Connell, 2000, Goldman *et al.*, 2009, Johnson *et al.*, 2011, Pourshanazari *et al.*, 2013), and it is altered with renal failure (Watson and Di Pette, 1985). CP also disturbs the serum levels of magnesium (Lam and Adelstein, 1986, Bussieres *et al.*, 1990, Goren, 2003, Hodgkinson *et al.*, 2006) and nitric oxide (Wink *et al.*, 1997, Watanabe *et al.*, 2000, Tang and Grimm, 2004, Chanvorachote *et al.*, 2006, Kim *et al.*, 2012), which both influence the BRS(Borgonio *et al.*, 2001, Zhou *et al.*, 2013). Accordingly, we hypothesize that CP therapy may impair BRS directly or indirectly via alteration of CP induced oxidative stress or renal toxicity. To test this hypothesis, the rats were treated with CP and BRS was measured at different doses of α-adrenergic receptor agonist, phenylephrine (PE), infusion.

Materials and methods

Animals

Eighteen male and female Wistar rats (Animal Center, Isfahan University of Medical Sciences, Isfahan, Iran) were used in this research. The rats were housed at the temperature of 23-25 ºC. Rats had free access to water and rat chow. The rats were acclimatized to this diet for at least one week prior to the experiment. The experimental procedures were in advance approved by the Isfahan University of Medical Sciences Ethics Committee. The animals were randomly assigned to two groups and were treated as follows: Group 1 (n=9; four male and five female) received CP (2.5 mg/kg/day) (Nematbakhsh *et al.*, 2013) for five consecutive days, and then they were subjected to surgical procedure to determine the BRS. The animals in group 2 (n=9; four male and five female) were treated similar to group 1 except vehicle (saline) instead of CP.

Drugs

CP, PE, and urethane were purchased from EBEWE Pharma Ges.m.b.H (Utrecht, Austria), Ramopharmin Pharmaceutical Lab (Tehran, Iran), and Merck (Darmstadt, Germany), respectively.

Surgical procedure

The rats were anaesthetized (Urethane, 20 mg/kg i.p.) and the air ventilation tube was inserted into trachea. Catheters were implanted into the femoral vein and artery. The flowmeter probe was placed and fixed around the left common carotid artery, and carotid blood flow (CBF) was monitored by transit-time ultrasound flowmetry (Transonic Systems, Ithaca, NY, USA.). Body temperature was continuously monitored through the experiment. We allowed 30 minutes for the equilibration period.

Experimental protocol

After the equilibration period, male and female rats were subjected to PE injection to determine the BRS. Three bolus doses of α-adrenergic receptor agonist, PE, (0.025, 0.05 and 0.1 mg/kg) were intravenously

Table 1: Baseline measurement for the groups treated with cisplatin (CP) and vehicle. BW: body weight; MAP: mean arterial pressure; SP: systolic pressure; DP: diastolic pressure; CBF: left common carotid blood flow.

Group	*BW (g)*	*MAP (mmHg)*	*SP (mmHg)*	*DP (mmHg)*	*CBF (ml/min)*
1 (CP-treated)	191.0±11.5	84.9±3.5	108.5±5.8	66.6±2.9	2.1±0.3
2 (vehicle-treated)	216.5±17.3	87.8±2.1	106.2±3.4	72.7±1.9	1.7±.2
P value	0.24	0.49	0.74	0.1	0.28

injected. The second and the third doses were injected after recovery from the previous dose. For each dose, the peak amplitude of the resulting pressure and bradycardia responses were considered to determine the changes of mean arterial pressure (MAP) and heart rate (HR). The ratio of HR change (ΔHR) to MAP change (ΔMAP) was calculated and considered as the BRS index. At the end of the experiment, blood samples were obtained via catheter and the animals were sacrificed humanely. To demonstrate the effect of CP and its side effect of nephrotoxicity, kidney function parameter and kidney histological findings are considered as the golden standard.

Measurements

Serum levels of blood urea nitrogen (BUN) and creatinine (Cr) were determined using quantitative diagnostic kits (Pars Azmoon, Iran). Left kidney was fixed in 10% neutral formalin solution and embedded in paraffin. To evaluate the tissue damage, slices were stained with the Hematoxylin and Eosin method. The kidney tissue damage was determined by a pathologist who was blind to the study. Kidney tissue damage score (KTDS) was assigned by the pathologist from 1 to 4, while zero score was considered for normal tissue.

Statistical analysis

Data was expressed as mean ± standard error of the mean. Student's t-test was applied to compare the quantitative parameters measured between the two groups. In addition, the Mann-Whitney test was used to compare KTDS between the groups. The p-value less than 0.05 was considered statistically significant.

Results

Effect of CP

The serum levels of BUN and Cr increased in CP-treated animals, and they were significantly different from the values obtained for the vehicle-treated group ($P<0.05$) (Fig. 1). The tissue histology findings confirmed that kidney tissue damage score (KTDS) in the CP-treated group was significantly higher than that in the other group (Fig. 1). The CP-induced kidney tissue damage is also characterized by increase in kidney weight/100g of bodyweight (10, 17, 18), and this ratio in group 1 was significantly greater than that in group 2 (group 1: 0.775±0.023 g; group 2: 0.677±0.025 g, $P<0.05$). All these findings confirmed the effect of CP on the kidney.

Baseline data

At the day of surgery, no significant differences were detected in animal weight between the groups. Before starting the bolus injection of PE, no statistically significant differences were seen in MAP, systolic and diastolic pressures, and CBF between the groups (Table 1).

BRS index, ΔHR, ΔMAP, and ΔCBF

All doses of PE injection caused MAP increase and HR decrease in the two groups. However, ΔMAP and ΔHR were lower in the CP-treated group. By injection of 0.1 mg/kg of PE, the ΔMAP in CP- and vehicle-treated groups were 49.01±5.98 and 65.90±5.79 mmHg, respectively ($P<0.05$). However, ΔHR in CP- and vehicle-treated groups were decreased as -34.90 ±13.10 and -90.44±14.73 beats/min, respectively

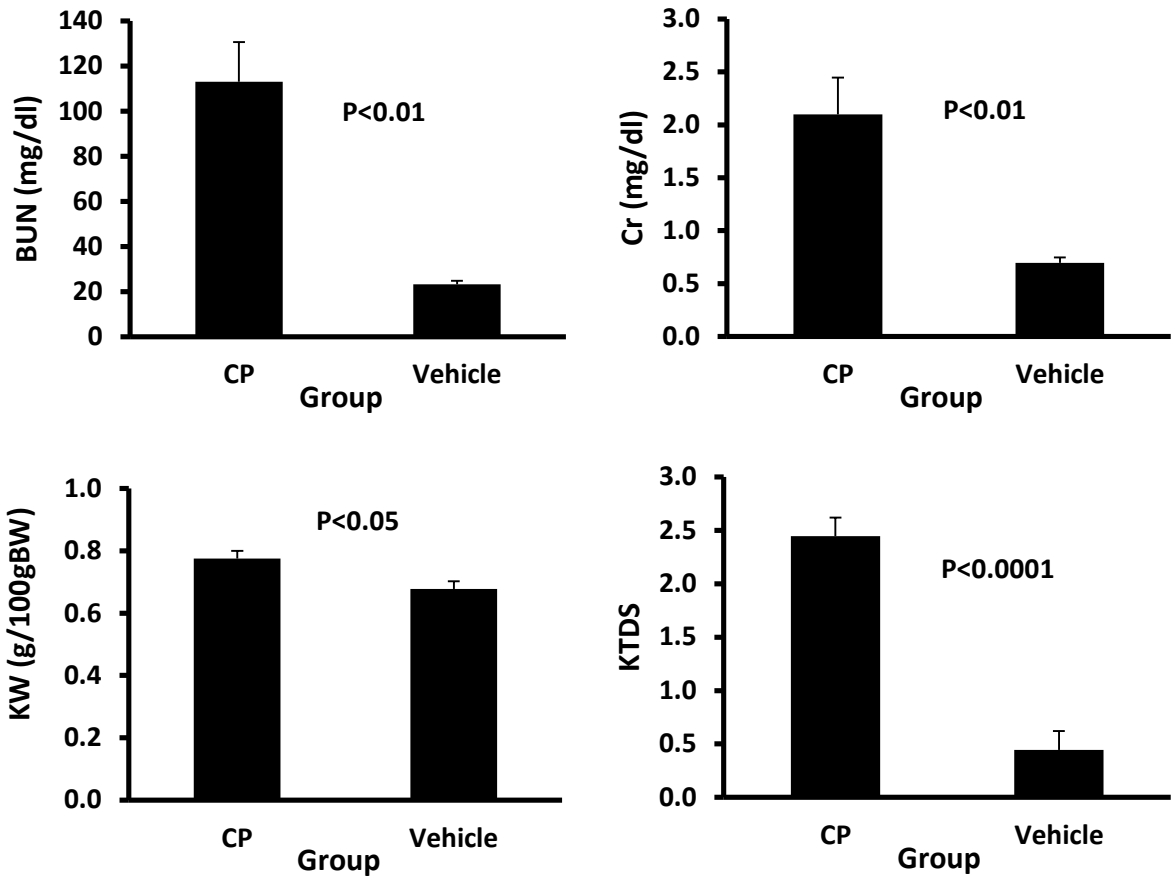

Fig 1: Effect of CP on serum levels of blood urea nitrogen (BUN) and creatinine (Cr), kidney weigh g per 100 g of bodyweight (KW/100 g BW) and kidney tissue damage score (KTDS). CP and vehicle stand for groups 1 and 2 treated with CP and vehicle, respectively.

(P<0.05). BRS increased in a dose-dependent manner by PE in the vehicle-treated group, but such finding was not obtained in the CP-treated animals. Significant difference in BRS was detected between the two groups (P<0.05) when 0.05 or 0.1 mg/kg of PE were infused. Approximately, the mean value of BRS by infusion of 0.05 or 0.1 mg/kg of PE was three times larger in the vehicle-treated than that in the CP-treated group. The change in CBF response to PE infusion in the CP-treated group was larger than that in the other group. However, this response was statistically significant at the dose of 0.01 and 0.05 mg/kg of PE infusion (P<0.1) (Fig. 2).

Discussion

CP is used in clinic for chemotherapy, and nephrotoxicity and hepatotoxicity are its most common side effects. In addition, CP disturbs the hemodynamic function of kidney. BRS is an index for blood pressure control system. This system automatically works to prevent blood pressure alteration via cardiovascular system. In this study, we had one major finding. CP-induced nephrotoxicity attenuated BRS using PE. To the best of our knowledge, the present study is the first to investigate the BRS in a CP-treated model. The effect of CP on hemodynamics system was considered before. It is reported that hypertension may develop in CP-treated patients years after treatment (Hansen *et al.*, 1988). Renal blood flow and renal vascular resistance also may be disturbed by CP as a result of reduction in glomerular filtration rate and blood flow (Winston and Safirstein, 1985). CP does not readily cross the blood-brain barrier, but it may involve in endothelial injury (Ito *et al.*, 1995, Kohn *et al.*, 1997, Yu *et al.*, 2008, Eguchi *et al.*, 2010). However, in animals treated with CP, heart rate as well as BRS for renal sympathetic nerve activity reduced (Khan *et al.*, 2014), and bilateral renal

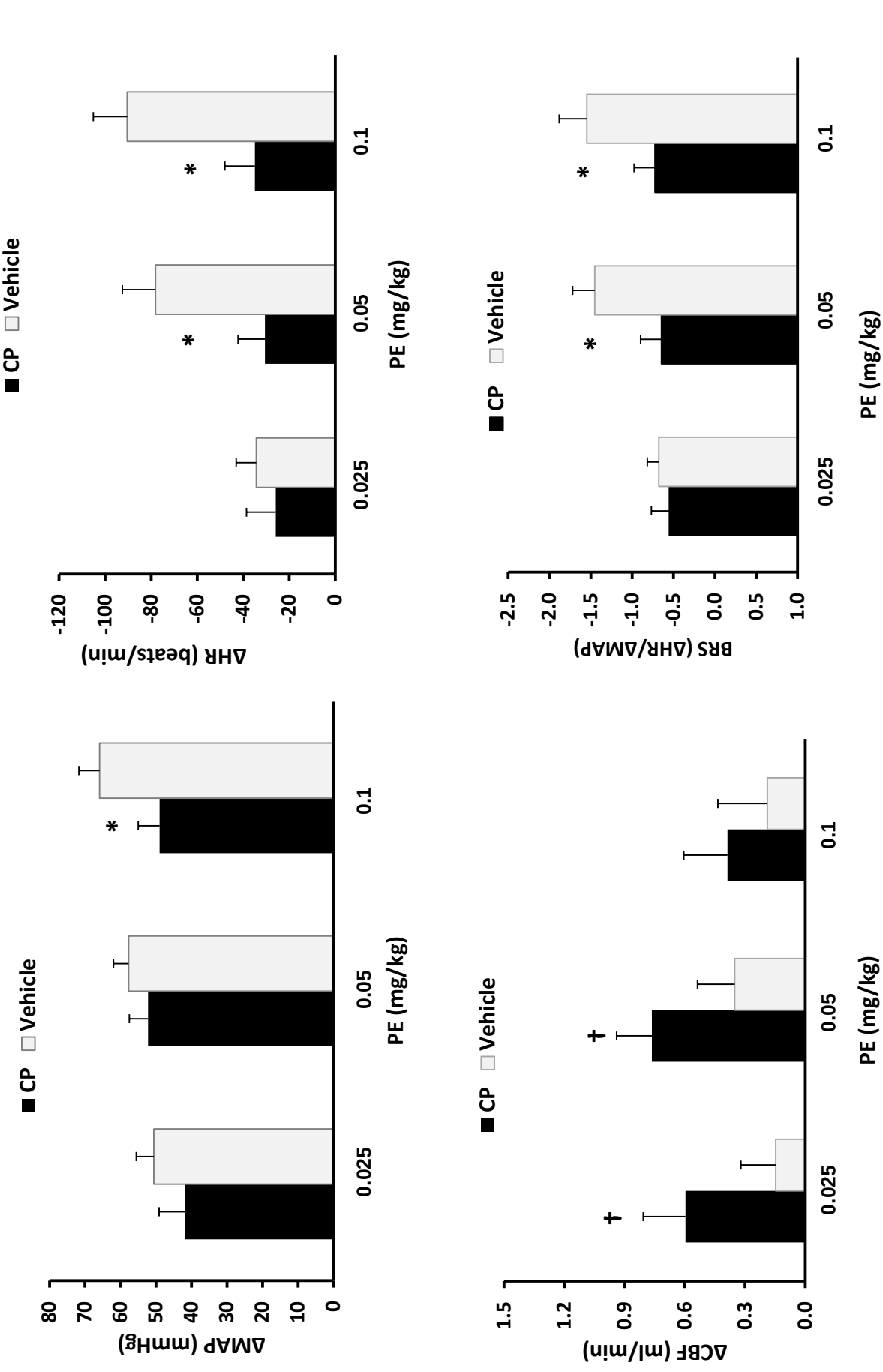

Fig 2: Mean arterial pressure (MAP), heart rate (HR), baroreflex sensitivity (BRS), and left common carotid blood flow (CBF); groups 1 and 2 treated with CP and vehicle, respectively.

denervation restored BRS (Khan *et al.*, 2014).Therefore, it seems that reduced BRS by CP may be related to CP-induced kidney dysfunction or due to kidney sympathetic nerve disturbance.

The different doses of PE did not alter CBF while both MAP and HR were changed by PE in non-CP treated rats. This finding reveals the important role of vascular resistance. As MAP increased by PE, the vascular resistance also increased to maintain blood flow. Such observation was not detected in CP-treated animals; and instead of change in HR, CBF altered. It is reported that CP may disturb vascular function and vascular resistance (Daugaard *et al.*, 1987). Accordingly, it seems that the effect of CP may be peripheral instead central.

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Conflict of interest

The authors have no conflict of interests to declare.

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