

# Cisplatin-induced nephrotoxicity alters blood pressure response to angiotensin II administration in rats

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## Abstract

**Background:** Cisplatin (CP) is an effective chemotherapeutic drug used in the clinic, which is accompanied with nephrotoxicity. CP may also disturb hemodynamics of the circulation system. We have tested the role of CP in mean arterial pressure (MAP) response to graded angiotensin (Ang) II infusion in rats.

**Materials and Methods:** Male and female rats were treated with CP (2.5 mg/kg/day) for a period of 1-week and compared with the vehicle-treated animals. The blood pressure response to Ang II (100–1000 ng/kg/min) was determined under the anesthesia condition. Endothelial permeability of aorta was measured according to the Evans blue uptake. The kidney tissue was also subjected to histological investigation.

**Results:** Significant increase in serum levels of blood urea nitrogen and creatinine and pathological findings in CP-treated rats verified CP-induced nephrotoxicity. Significant difference in percentage of change in MAP response to Ang II between male and female rats was detected in vehicle-treated groups ( $P < 0.05$ ) while in CP-treated animals this response difference was not observed. The groups were not significantly different with regard to the endothelial permeability of aorta while the serum level of nitrite in male rats increased significantly following administration of CP ( $P < 0.05$ ).

**Conclusion:** It seems the different response in percentage of change of MAP to graded Ang II infusion between male and female indicates the effect of CP on renin Ang system parameters.

**Key Words:** Blood pressure, cisplatin, endothelial permeability, renin-angiotensin system

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## INTRODUCTION

Cisplatin (CP) is an effective chemotherapeutic drug used for treatment of various malignant tumors and is accompanied with different side effects including

renal toxicity.<sup>[1]</sup> CP accumulation in kidneys is higher than in any other organ. Thus, kidneys are sensitive to CP-induced tissue damages, which is presented as necrosis of the proximal tubules and apoptosis in the distal part of the nephron.<sup>[2]</sup> The exact mechanism for CP-induced acute renal toxicity is not sufficiently understood, but it seems that the formation of reactive species causing renal damage is involved in the process.<sup>[3]</sup> In the CP-induced nephrotoxicity, some mediators including scavengers of reactive oxygen species, such as superoxide dismutase and edaravone, are in common with those involved in renal failure caused by ischemia/reperfusion.<sup>[3]</sup>

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Angiotensin II (Ang II), the main effector peptide of the renin-angiotensin system (RAS), plays a major role in the maintenance of arterial blood pressure and fluid balance.<sup>[4,5]</sup> Ang II exerts its effects through Ang type I and II receptors (AT1R and AT2R). AT1R activation leads to vasoconstriction, sodium reabsorption, and cell proliferation; while AT2R opposes AT1R-mediated effects, causing vasodilation, sodium excretion, and apoptosis.<sup>[6,7]</sup> The incidence of renal diseases in male is higher than in female.<sup>[8]</sup> The underlying mechanism is unclear, but there is evidence for RAS involvement.<sup>[9,10]</sup> Furthermore, the AT2R: AT1R ratio in females is larger,<sup>[11]</sup> and it is demonstrated that the increase in arterial pressure in response to chronic infusion of Ang II is reduced in females compared with males.<sup>[11-13]</sup>

It has been shown that CP causes hyponatremia,<sup>[14]</sup> which is mediated via impairment of renin-Ang aldosterone system.<sup>[15]</sup> The oxidative stress induced by CP may be attenuated by losartan (AT1R blocker)<sup>[16]</sup> in male rats, while acute blockade of AT1R with losartan does not have a protective role against CP-induced nephrotoxicity.<sup>[15]</sup> In addition, another report has demonstrated that losartan may prevent CP-induced nephrotoxicity in male but not in female rats.<sup>[17]</sup> According to the previous findings,<sup>[15-17]</sup> it seems that CP may affect RAS, which is the major system for systemic hemodynamic controlling.<sup>[4,5]</sup> On the other hand, the different impact of RAS in male and female<sup>[9-13]</sup> and the role of AT1R to protect the kidney against CP provide an idea that systematic circulation may respond differently when CP is present. To test this hypothesis in the current study, we attempted to determine the mean arterial pressure (MAP) response to graded Ang II infusion in male and female rats.

## MATERIALS AND METHODS

### Animals

A 24 male (weighting 180–220 g) and female (weighting 160–200 g) Wistar rats were housed at the room temperature of 23°C–25°C with a 12-h light/dark cycle and were allowed to acclimatize to the conditions for 1-week. The rats were fed with rat chow and water *ad libitum*. The experiment protocol was in advance approved by the Isfahan University of Medical Sciences Ethics Committee. The animals were divided into four groups ( $n = 6-9$ ) and were treated as follows.

Groups 1 and 2 (male and female, respectively) as control groups received vehicle (saline) for a period of 1-week. Groups 3 and 4 (male and female, respectively) received CP (2.5 mg/kg/day) for a period of 1-week.

### Experimental procedure

At the end of the week, the rats were anesthetized (urethane, 10 mg/kg, i.p.; Sigma, St. Louis, MO, USA) and the trachea was isolated to insert air ventilation tube. Catheters were implanted into the jugular vein and the carotid artery. A catheter was also inserted into the bladder for urine collection. MAP was continuously measured from the carotid artery throughout the experiment and the data were captured as 2 s averages via a data acquisition system. Body temperature was continuously monitored through the experiment. We allowed 30–60 min for equilibration period.

After reaching the equilibrium, a series of intravenous infusions of Ang II (0, 100, 300, and 1000 ng/kg/min) commenced via the jugular vein. Each dose was administered until equilibration for arterial blood pressure was achieved (in about 10 min), and then the measurements were performed for 3–5 min. Following the Ang II infusion, blood samples were obtained, and Evans blue (EB, 10 mg/kg) was infused, and 30 min later, the rats were sacrificed and the kidneys were immediately weighted, and were subjected to pathology staining and investigation.

### Vascular permeability determination

The aorta was removed, opened and washed in saline. Excess water was removed and the aorta wet weight was determined. In order to extract the EB from the tissue, the aorta was kept in 4 ml of formamide at 80°C overnight. The concentration of EB in formamide solution was determined photometrically at a wavelength of 623 nm using standard curves.

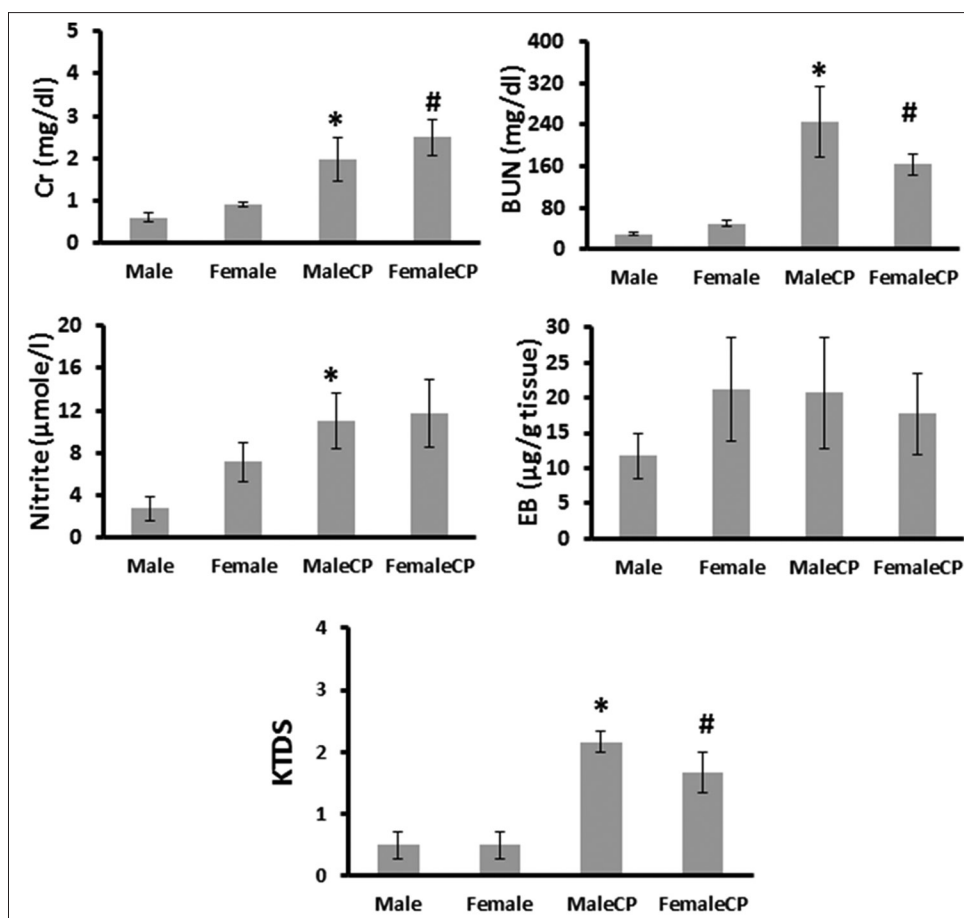
### Statistical analysis

Data are expressed as mean  $\pm$  standard error of the mean. Responses to Ang II infusion were compared via repeated measures anova for the different groups of factors (vehicle, CP) and doses (0, 100, 300, and 1000 ng/kg/min Ang II) and their interactions.  $P \leq 0.05$  was considered statistically significant.

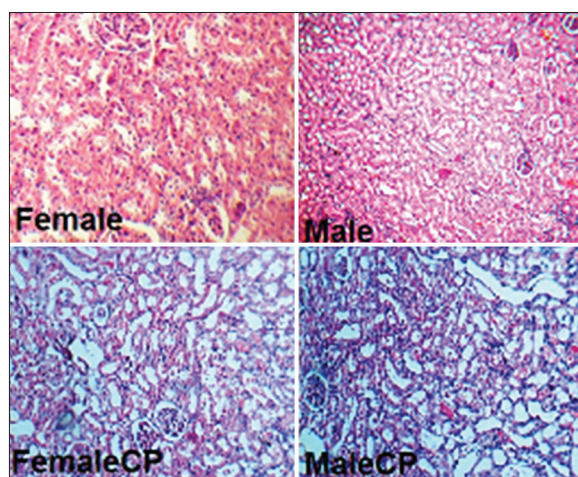
## RESULTS

### Effect of cisplatin

Cisplatin increased serum levels of blood urea nitrogen (BUN) and creatinine (Cr) in both genders significantly ( $P < 0.05$ ,) [Figure 1]. The pathological findings also confirmed nephrotoxicity induced in the CP-treated animals. The images of kidney tissue samples are demonstrated in Figure 2. Kidney tissue damage score in the CP-treated animals was significantly different from the vehicle-treated groups [Figure 1]. The groups were not significantly different



**Figure 1:** The serum levels of blood urea nitrogen, creatinine, and nitrite; aorta endothelial permeability (Evans blue uptake), and kidney tissue damage score in four experimental groups. \*and # indicate significant difference from the control group of the same gender. Male, female, male cisplatin (CP), and female CP represent the male and female treated with vehicle and CP, respectively



**Figure 2:** Image (×100) of kidney tissue samples. More tissue damages were seen in cisplatin-treated groups. Arrows indicates the tubular damages. No damages were seen in normal male and female tissue

with the regard to the endothelial permeability of aorta. In addition, the serum level of nitrite was increased by CP in both sexes, and the increase was statistically significant in male rats ( $P < 0.05$ ).

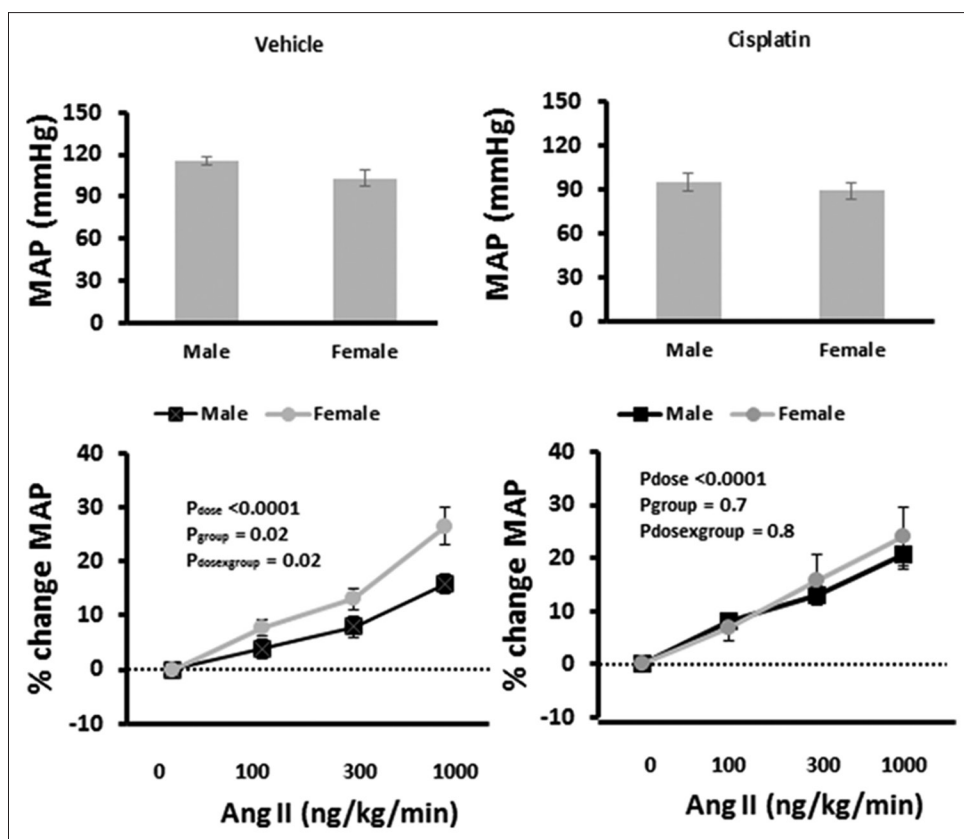
### Mean arterial pressure response to angiotensin II infusion

Considering the MAP response to graded Ang II infusion in the vehicle-treated rats, a significant difference was observed between the genders ( $P < 0.05$ ); a greater response was detected in female rats. However, the difference between sexes was not observed in the CP-treated groups [Figure 3].

### DISCUSSION

Our findings demonstrated that CP abolishes the gender difference in MAP response to Ang II administration. The major side-effect of CP therapy is nephrotoxicity,<sup>[2,18]</sup> and the kidney tissue damage (toxicity) is verified by increase in BUN and Cr levels. Such observations were reported by others in different studies.<sup>[19-21]</sup>

The role of RAS have been evaluated in different studies related to CP-induced nephrotoxicity.<sup>[15,16]</sup> Although the data reported were different, losartan as AT1R blocker was found to be a nephroprotectant agent in male rats but not in female animals.<sup>[17]</sup>



**Figure 3:** Mean arterial pressure (MAP) in male and female rats treated with vehicle (control) and cisplatin before angiotensin II (Ang II) infusion as baseline data (top). The percentage change of MAP in response to Ang II infusion (below) indicate a significant difference between male and female rats in vehicle-treated groups ( $P < 0.05$ )

Losartan also has antioxidant effects,<sup>[22]</sup> but it seems the nephroprotective role of losartan is related to RAS activity. In the current study, the response to Ang II infusion was found to be different in male and female rats while this difference was vanished by CP. The gender difference response to Ang II administration was reported by others.<sup>[11,23]</sup> In our study, MAP response to Ang II in female was higher than that in male. Gandhi *et al.* found the same pattern of response to Ang II infusion while they reported that the difference was not statistically significant. However, the dose of Ang II used in their study<sup>[23]</sup> was lower than that administered in the current study. The gender difference may be attributed to different expression levels of AT1R and AT2R in males and females.<sup>[11]</sup> CP promotes the vasoconstriction effect of Ang II in male more than that in female. Possibly, CP affects sensitivity of the receptor to Ang II. Therefore, it seem that CP-induced nephrotoxicity is gender related as shown previously,<sup>[17]</sup> and this difference may be depends on RAS receptors. It is known that AT2R: AT1R ratio also is greater in female,<sup>[11]</sup> and possibly AT1R blockade potentiated the role of AT2R, so kidneys of female receive a grater blood flow that transport more CP and leads to more tissue damage.<sup>[17]</sup>

Cisplatin disturbs endothelial cells by activating the cell death signaling pathway sand reactive oxygen species generation. This leads to endothelial cell apoptosis and necrosis.<sup>[21,22]</sup> Study of a cell line of dermal microvessels showed that CP alters endothelial function and causes the proliferation, inflammation, and fibrinolysis; and decreases endothelial cell survival by induction of apoptosis.<sup>[24]</sup> It has been also suggested that platinum-based drugs directly induce vascular endothelial dysfunction and may be a risk factor for atherosclerosis.<sup>[25]</sup> CP-induced nephrotoxicity disturbs glomerular capillaries, including endothelial cells, in rats,<sup>[18]</sup> and may damage vascular system.<sup>[23]</sup> Accordingly and based on this background, it is anticipated that CP may alter vascular permeability. However, in our study no significant change was observed in aorta permeability determined by EB. Duration of CP therapy may be the main reason for such finding. Finally, we found that CP increased the serum level of nitric oxide metabolite, and such finding is consistence with other reports.<sup>[26]</sup> The mechanism is not exactly clear, but early vascular response to CP may involve.



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