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# Changes of Hemodynamics and Renal Function due to Acute Cadmium Exposure in Rats

**Jae-Joong Kim and Yung Kyu Kim**

*Department of Physiology, College of Medicine, Dongguk University, Gyeongju 780-714, Korea*

**The systolic and diastolic pressures in anesthetized Sprague-Dawley male rats were greatly decreased after single-dose of Cd treatment without significant changes in heart rate. There was a fluid-shift into the third space and/or -loss through the kidney, since plasma $Na^+$ concentration and hematocrit ratio were significantly increased by acute Cd exposure. The present study showed that the sustained hypotensive effect of single-dose Cd on the cardiovascular system might have resulted from the systemic hypovolemia. Furthermore, renal excretion of electrolytes, including $Na^+$ and $K^+$, and urine flow rate were increased by Cd intoxication. Interestingly, the ratio of $Na^+/K^+$ excretion was increased and reached the maximum level 3 hours after Cd injection and returned to the normal level after 7 hours. Nevertheless, there was no difference in the regression analysis of $K^+$ excretion and urine flow rate in both groups. Therefore, the increase in the urine volume seemed to enhance the excretion of $K^+$. This study strongly suggest that the hypotensive effect of Cd is mediated by systemic $Na^+$ loss through the kidney and/or hypovolemia via fluid-shift.**

**Key Words: Acute cadmium intoxication, Hemodynamics, Renal function**

## INTRODUCTION

Cd is one of the most common toxic substances in our environments. The sources of human exposure to Cd include contaminated food and drinks, tobacco, and so on (Goyer & Cherian, 1995). Cd has a very long biological half-life (Friberg et al, 1986; Goyer & Cherian, 1995).

It is known that kidney is a final target organ of Cd intoxication, and chronic exposure to Cd can induce severe nephropathy in humans and animals (Friberg et al, 1986; Goyer & Cherian, 1995). Experimental chronic intoxication with various doses of Cd has been carried out over several weeks and found to cause a Fanconi-like renal failure (Tang et al, 1998; Thevenod, 2003). The nephrotoxicity causes reabsorptive and secretory dysfunction of the renal tubule. In humans and rodents, the main signs of chronic Cd exposures for weeks to years include proteinuria, glucosuria, aminoaciduria, and polyuria (Nordberg & Piscator, 1972; Kim et al, 1988; Liu et al, 1998).

Furthermore, we (Kim, et al, 1988; Kim & Park, 1989 & 1998) and others (Vander, 1962; Doyle et al, 1975; Nishiyama & Nakamura, 1984) previously showed that the renal $Na^+$ reabsorption was increased by Cd exposure in a week. The antinatriuretic effects of subchronic Cd exposure could be mediated by an increase of plasma aldosterone level (Nishiyama & Nakamura, 1984; Kim & Park, 1989). Nishiyama and Nakamura (1984) showed that the aldosterone secretion in adrenal glands is stimulated by Cd exposure in rats. While some investigators observed an increase of plasma renin activity (Perry & Erlanger, 1973) and others did not (Eakin et al, 1980). Therefore, the mechanism of Cd-induced increase of aldosterone secretion remains unclear.

The reduced renal excretion of $Na^+$ in Cd-intoxicated animals can not simply be explained by the increase of plasma aldosterone level, since the renal $K^+$ excretion slightly decreases rather than increases (Doyle et al, 1975; Nishiyama et al, 1986; Kim et al, 1988; Kim & Park, 1998), although aldosterone promotes renal $K^+$ secretion (Young, 1988; Palmer & Frindt, 2000). It has also been known that hypertension is also a symptom of Cd intoxication (Schroeder & Vinton, 1962; Balaraman et al, 1989; Nomiyama et al, 1993; Puri, 1999; Puri & Saha, 2003). The Cd exposure facilitates salt retention, resulting in hypertension. (Perry et al, 1971; Hall & Nasseth, 1979; Ohanian & Iwai, 1980). Satarug et al. (2005) reported that cadmium-induced hypertension is related to the renal tubular damage in human.

Nevertheless, there is a discrepancy for hypertension in Cd-intoxicated animals. Hypertension has never been found among the Japanese itai-itai disease patients. Perry and Yunice (1965) reported that the BP was decreased by a certain dose of Cd, whereas others showed that Cd could induce hypotension in experimental animals (Nomiyama et

Corresponding to: Yung Kyu Kim, Department of Physiology, College of Medicine, Dongguk University, 707 Seokjang-dong, Gyeongju 780-714, Korea. (Tel) 82-54-770-2407, (Fax) 82-54-770-2440, (E-mail) ykim@dongguk.ac.kr

**ABBREVIATIONS:** Cd, cadmium; BP, blood pressure; bpm, beats per min.

al, 1993).

There is little information available on the acute effects of Cd on the changes in $Na^+$ excretion related to the BP. The aim of this study was to examine the relationship between functional changes in kidney and cardiovascular system under the condition of acute Cd exposure. Therefore, we examined the acute effects of Cd on the $Na^+$ excretion and BP in anesthetized rats.

## METHODS

### *Animals*

Specific pathogen-free male Sprague-Dawley rats, weighing 250~280 g, were used for all phases of this study. The animals were maintained in the animal care facilities and allowed free access to diet and drinking water *ad libitum* for a week before performing the experiments. The rats were randomly divided into two groups, control (n=4) and Cd (n=4). This study was performed in accordance with the guidelines of the Animal Care Committee of the Medical College of Dongguk University.

### *Anesthesia*

The rats were anesthetized via intraperitoneal administration of thiobutabarbital $Na^+$ (Inactin, 100 mg/kg body weight) purchased from Research Biochemical International (Natick, MA). A tracheotomy was performed, and the trachea was connected to a rodent ventilator (Model 683, Harvard Apparatus; USA).

### *Measurements of BP and heart rate*

To measure BP and heart rate via a pressure transducer (Gould) connected to a polygraph (Model 7E, Grass Instrument Co., USA), the right femoral artery was cannulated with a polyethylene (PE)-50 tubing filled with ammonium heparin (10 IU/ml)-containing saline solution.

### *Urine and blood sampling*

The blood was sampled in the heparinized tube, which contained no $Na^+$, at the end of experiment. Urine was collected by intubation into the urinary bladder and measured urine flow rate with 30-min interval. The concentrations of $Na^+$ and $K^+$ in plasma and urine samples were analyzed with a flame photometer (FLM3, Radiometer, Denmark).

### *Cd administration*

Heart rate and BP were allowed to stabilize and urinary bladder was made empty before Cd was injected into the peritoneum. The dose of Cd was 2 mg/kg body weight and 2 mg of Cd was dissolved in 1 ml of Hartman solution (mM; 130 $Na^+$, 4 $K^+$, 111 $Cl^-$, 27 lactate). Control animals received the same amount of Hartman solution.

### *Statistics*

All values are expressed as mean±standard error. The experimental data were evaluated by the unpaired Student's *t*-test and statistical analysis was determined at $p < 0.05$.

## RESULTS

To examine the acute effects of Cd exposure on the cardiovascular system, systolic and diastolic pressures and heart rate were measured. Peritoneal Cd administration had no effects on BP for the initial 1 to 2 hrs. The systolic pressure of control period was 138±6 mmHg and 127±11 mmHg in control and Cd groups, respectively. As can be seen in Fig. 1, the systolic pressure in control group was not significantly changed during whole experiment period. However, the pressure was significantly lowered 2 hrs after Cd injection and gradually decreased after that. The changes in the diastolic pressure in control and Cd groups were similar to those in the Cd treated systolic pressure (Fig. 2). The values for the control period in control and Cd

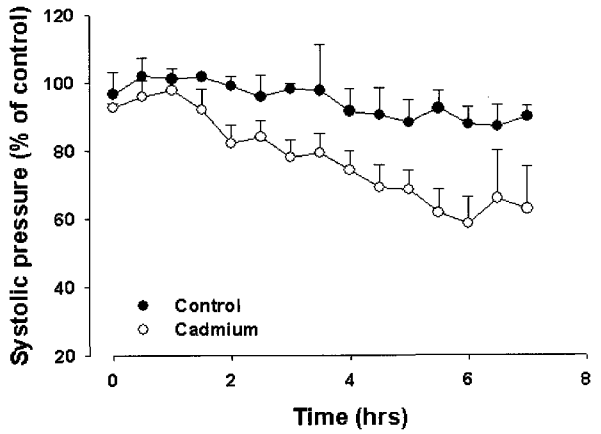


**Fig. 1.** Changes in systolic pressure by Cd treatment. The systolic pressure of the control period in Cd group (138±6 mmHg) was not different from that in control group (127±11 mmHg). The systolic pressure in the Cd group was gradually decreased and significantly different from that in control group 2 hrs after peritoneal injection of Cd.

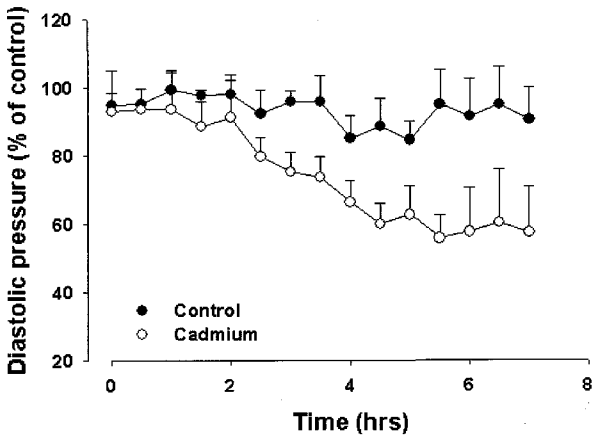


**Fig. 2.** Changes in diastolic pressure by Cd treatment. The diastolic pressure of the control period in Cd group (106±7 mmHg) was not different from that in control group (103±10 mmHg). The diastolic pressure in Cd group was gradually decreased and significantly different from that in the control group 3 hrs after peritoneal injection of Cd.

groups were 106±7 mmHg and 103±10 mmHg, respectively. Compared to control group, the diastolic pressure in Cd group was significantly changed 3 hrs later after peritoneal injection of Cd. Nevertheless, Cd did not alter heart rate throughout whole experimental periods in both groups (Fig. 3). The heart rates in the control period in control and Cd group were 383±7 and 361±10 beats/min (bpm), respectively. These results do not agree with the finding of Cd-induced hypertension.

To further investigate the effects of Cd on the blood compositions, $Na^+$ concentration in the plasma and hematocrit ratio were determined. The hematocrit ratio in Cd group was significantly higher than that in control group (52.3± 3.0% vs. 46.1±0.6%) (Fig. 4, upper panel). Plasma $Na^+$ concentration in Cd group was greater than that in control group (134.5±2.4 mEq/L vs. 130.6±0.4 mEq/L) (Fig. 4, low panel). These data indicate that Cd reduces the plasma volume by extracellular fluid-shift into another space and/or loss through the kidney. We examined the effects of Cd on the renal function including electrolyte excretions and urine flow rate.

The potassium excretion and urine flow rate were increased by 42% and 55% of control levels, respectively (Fig. 5). The urine flow rate and $K^+$ excretion had a linear relationship in both groups, and there was no statistical difference of regression line between two groups (data not shown). These results indicate that the $K^+$ excretion is dependent on the urine flow rate and this relationship is not altered by Cd treatment. The polyuria induced by acute Cd exposure seemed to have resulted from the increase in the excretion of osmotic substances, including electrolytes. Although we did not measure the osmolality, Cd-induced polyuria might have been osmotic diuresis due to increase of $Na^+$ excretion via direct inhibition of $Na^+$ reabsorption by Cd (Fig. 6). Renal $Na^+$ excretion was increased by Cd treatment, however, there was little statistically significant relationship between urine flow rate and $Na^+$ excretion (data not shown). As seen in Fig. 6, Cd had differential effects on the renal excretion of electrolytes: The ratio of $Na^+/K^+$ excretion increased and approached the maximum level 3 hrs after Cd injection and returned to the normal level after 7 hrs (Fig. 6).

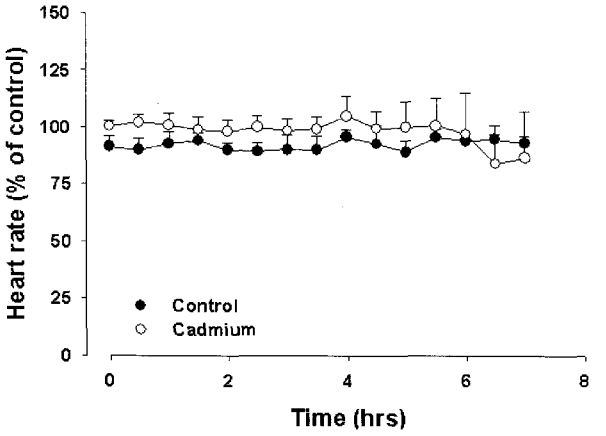


Fig. 3. Effects of Cd on the heart rate. The heart rate of control period in control group was 383±11 bpm and that in Cd group was 361±10 bpm. There were no significant differences between two groups during the period of experiments.

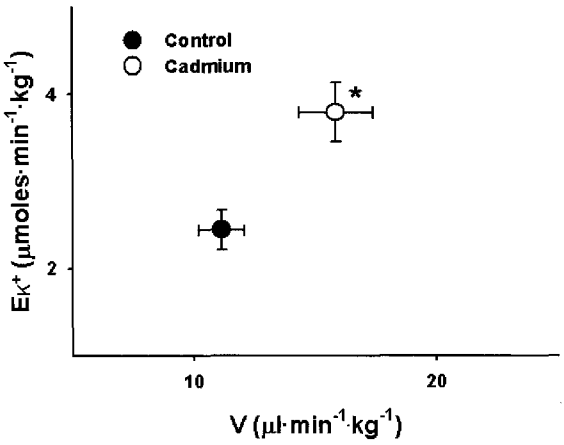


Fig. 5. Increases of renal $K^+$ excretion and urine flow rate in control and Cd groups by acute Cd exposure.

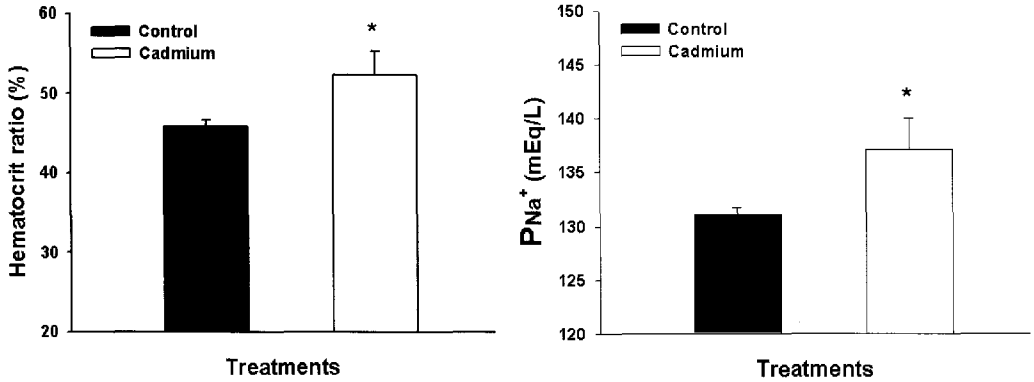


Fig. 4. Effects of Cd on the hematocrit ratio and plasma $Na^+$ concentration. The hematocrit ratio was significantly higher in Cd group (52.3±3.0%) than in control group (46.1±0.6%) (upper panel). The $Na^+$ concentrations of plasma in Cd and control groups were 134.5±2.4 mEq/L and 130.6±0.4 mEq/L, respectively (lower panel). *$p<0.05$, versus control group.

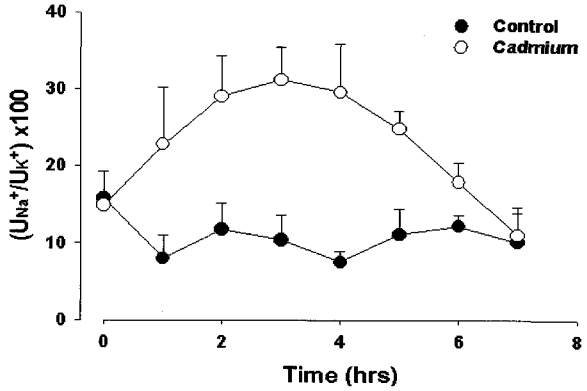


**Fig. 6.** Relative ratio of urinary $Na^+$ excretion to $K^+$ excretion in control and Cd groups.

## DISCUSSION

Cd is a toxic heavy metal and its target organ is the kidney. In recent years, a large number of studies have been carried out to examine the renal effects of Cd intoxication, and clearly demonstrated that Cd toxicity depends upon its dosage, the route of administration, and duration of exposure (Liu et al, 1998). Chronic exposure of Cd induces Fanconi-like syndrome (Kim et al, 1988). However, subchronic exposure of Cd with a dose of 2 mg Cd/kg · day dramatically increases the $Na^+$ reabsorption in the kidney (Kim et al, 1988; Kim & Park, 1998). This antinatriuretic effect of subchronic intoxication of Cd seems to be mediated by increase in aldosterone secretion, since the antinatriuretic mechanisms are well understood (Perry et al, 1971; Nishiyama & Nakamura, 1984; Kim et al, 1998).

The mechanisms by which Cd affects cardiovascular regulation remain controversal. The Cd exposure facilitates salt retention, resulting in hypertension (Hall & Nasseth, 1979; Ohanian & Iwai, 1980). Nevertheless, there is a discrepancy for hypertension in Cd-intoxicated animals. Hypertension has never been found among the Japanese itai-itai disease patients. Perry and Yunice (1965) reported that the BP was decreased by Cd, whereas Cd has also been reported to induce hypotension in experimental animals (Nomiyama et al, 1993).

Moreover, there is little information available on the acute effects of Cd on $Na^+$ excretion related to the BP. For the reasons outlined above, therefore, we understood studying the relationship between cardiovascular and renal effects of Cd during acute exposure to Cd. In this study, we employed the same dose of Cd as used, in order to compare with our previous studies (Kim et al, 1988; Kim & Park, 1989 & 1998) and also to simultaneously examine the effects of single-Cd treatment on both cardiovascular system and renal functions.

Both systolic and diastolic pressures were decreased by single-dose Cd treatment without significant changes in heart rate (Figs. 1~3), however, these results are different from others: Balaraman et al, (1989) and Hall and Hungerford (1982) showed that acute intraperitoneal administration of 1mg of Cd had a pressor effect. Probably, one of the reasons for the difference might be the use of different anesthetics or dosages of Cd.

A large number of studies on the neural control of the circulation have been performed under general anesthesia. Therefore, to understand the effects of anesthesia on neural control mechanisms, responses should be obtained before and after anesthesia under a situation where each animal is used as its own control. When 1mg of Cd (intraperitoneal injection), arterial pressure did not rise in conscious rats, but there was a pressor effect of Cd (~0.25 mg/kg, i.p. inj.) in pentobarbital-anesthetized rats (Hall & Hungerford, 1982). We could not obtain any information on the action of thiobutabarbital on cardiovascular system in this study, whereas Zatzman and Thornhill (1988) reported that thiobutabarbital slightly reduced BP and baroreflex response in marmot. We could not exclude the possibility of interaction of Cd with anesthetics in *in vivo* studies, and also we are not certain whether there is a species-dependent response.

The systolic and diastolic pressures were significantly decreased 2 and 3 hrs after single-dose of Cd treatment, respectively. The delay time could implicate that it takes a certain time to absorb Cd administrated into the peritoneum and affect cardiovascular system. Nevertheless, the reason of the time gap between changes in systolic and diastolic pressure is not clearly known. This hypotensive effect of single-dose of Cd treatment might be mediated by fluid-shift or -loss through the kidney, since $Na^+$ concentration of plasma and hematocrit ratio were increased by Cd treatment. Therefore, the sustained effect of Cd on the cardiovascular system might have resulted from systemic hypovolemia. It is unlikely to alter the autonomic nervous system by a single-dose of Cd treatment since there was no observable change in heart rate. Nevertheless, the possibility that the cardiovascular reflex mechanism might be blocked by Cd could not be eliminated.

$K^+$ excretion and urine flow rate were increased by acute Cd exposure and $K^+$ excretion was dependent on the urine flow rate, similar to control group. The polyuria induced by Cd intoxication seemed to be caused by osmotic diruesis, including increase of $Na^+$ excretion (Fig. 6). It is likely that absorbed Cd directly inhibited $Na^+$ reabsorption and exhibited natriuresis. These effects of single Cd exposure on the renal excretion of electrolytes were reversible. However, hypotensive effect of Cd might result from fluid-loss through the kidney, probably osmotic diuresis. This possibility is strongly supported by the last that significant change of blood pressure by Cd administration was delayed by 2~3 hrs, which corresponds almost with maximum inhibition of $Na^+$ reabsorption.

In conclusion, the results in this study suggests that the hypotensive effect of acute Cd exposure was mediated by systemic $Na^+$ loss through the kidney and/or hypovolemia via fluid-shift in the body. Since the results in this study are greatly different from our earlier studies on the effects of subchronic exposures with the same dose of cadmium (Kim et al, 1989; Kim & Park, 1989 & 1998), we postulate that the antinatriuresis induced by subchronic Cd exposure in our previous studies seems to be mediated by completely different process, such as stimulation of aldosterone secretion. Further studies are needed to clarify how repetitive Cd exposures induces antinatriuresis (Vander, 1962; Kim & Park, 1998) from natriuresis which is induced by single treatment of Cd in this study.

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