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CHRONIC CHANGES OF HEMATOCRIT VALUE ALTER BLOOD PRESSURE AND GLOMERULAR FILTRATION IN SPONTANEOUSLY HYPERTENSIVE RATS

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Many studies in hypertensive humans and animals have shown that increased blood viscosity is in direct relation with essential hypertension. The aim of our studies was to investigate the effects of chronic hematocrit value changes on arterial blood pressure and kidney function in genetically induced hypertension. To this end, we studied the effects of several interventions, designed to increase/decrease hematocrit, on hemodynamic parameters, vascular reactivity, glomerular filtration and renal function curve in spontaneously hypertensive rats (SHR). Results of our study show that chronic hematocrit value elevation increases blood pressure and peripheral vascular resistance in SHR. On the other hand, chronic hematocrit lowering elucidates blood pressure and peripheral vascular resistance decrease followed by cardiac output rising. Both hematocrit value changes significantly reduce vasodilatory vascular response. Hematocrit lowering induces acute renal failure. Sodium excretion is shifted to higher blood pressure values in high hematocrit value animals and opposite - lower blood pressure values in low hematocrit value animals. Repeated transfusions develop salt sensitive malignant hypertension in SHR. Further studies are necessary to evaluate the degree of kidney damage after chronic hematocrit value changes in SHR.

Key words: experimental hypertension, hematocrit, kidney function curve, vascular reactivity

INTRODUCTION

Hematocrit (Hct) is the proportion of blood volume that is occupied by red blood cells. In humans it is normally within the range from 38% to 48%. The role of hematocrit in the regulation of blood pressure has been seen in the highlight of Whitaker and Winton (1933), the classical concept being that there is a direct relationship between hematocrit value and blood viscosity. Nevertheless, considering Poiseuille's equation (Burton, 1965) blood pressure is directly proportional to viscosity. Numerous studies in normotensive animals have shown

that both acute and chronic wide-range changes in hematocrit value do not influence blood pressure (Hatcher *et al.*, 1954; Richardson *et al.*, 1959; Guyton *et al.*, 1961; Murray *et al.*, 1963; Mc Donald *et al.*, 1974). Experimental induced hematocrit value changes in these studies were found to be associated with similar changes in total peripheral resistance and a reciprocal change in both venous return and cardiac output, so blood pressure remains unchanged. Studies of acute normovolemic anemia also showed an increase in cardiac output as a compensatory response (Champion *et al.*, 2011). In opposite, studies in hypertensive humans and animals (Letcher *et al.*, 1981; Declerk *et al.*, 1980) had shown increased blood viscosity in direct relation with essential hypertension. Przybylski (Przybylski *et al.*, 1997) showed an increased erythrocyte number and concentration of hemoglobin (Hb) in 14 weeks old spontaneously hypertensive rats (SHR). The results of the Strong Heart Study in American Indians showed a clear positive relationship between hypertension and blood viscosity (de Simone *et al.*, 2005). Results of Sušić (Sušić *et al.*, 1982) implicated that heparin induced hematocrit lowering was followed by decreasing arterial blood pressure, without changes in plasma volume in SHR.

Beside the effects on blood viscosity, hematocrit value changes can influence blood pressure via nitric oxide (NO) production. The mechanism of this effect is believed to be due to the essentially irreversible binding of the vasodilator NO by the heme of Hb (Schultz *et al.*, 1993). In physiological conditions, increased blood viscosity induces vasodilatation which neutralizes haemodynamic changes. In the healthy population Hct presents a variability which is not reflected by the variability of blood pressure. This is due to a regulatory process at the level of endothelium, whereby the increase of Hct leads to increased shear stress and the production of the vasodilator nitric oxide (Salazar Vazquez *et al.*, 2010). On the other hand, there is reduced vasodilatation in SHR, due to disturbance of vasoconstriction/vasodilation mechanisms and vascular damages, which taken together lead to increased sensitivity for the change in blood viscosity (Koller *et al.*, 1996). In the kidney, hematocrit value changes elucidate disturbances in renal haemodynamic, glomerular filtration and postglomerular oncotic pressure, shift renal function curve and lead to changes in arterial pressure (Guyton, 1987). Also, many studies have shown nephrotoxicity potential of Hb due to tubular obstruction, free radical production and vasoconstriction (Jaenike, 1967; Shah and Walker, 1988; Thompson *et al.*, 1994).

The aim of our study was to investigate the effects of chronic hematocrit value changes on arterial blood pressure and kidney function. To this end, we studied the effects of several interventions designed to increase and/or decrease hematocrit values on hemodynamic parameters, vascular reactivity, glomerular filtration and renal function curve in SHR.

MATERIALS AND METHODS

Materials

Female adult SHR, weighted about 300 g, were bred at the Institute for Medical Research, Belgrade and fed on a standard chow for laboratory rats

(Veterinarski zavod, Subotica, Serbia). All animal experiments were conducted in accordance with local institutional guidelines for the care and use of laboratory animals. The investigation also conforms to the principles and guidelines of the Canadian Council on Animal Care (CCAC).

Experimental protocol

Three separate experimental studies were performed: haemodynamic measurements, vascular response study and renal function curve - glomerular filtration study. In all mentioned studies the animals were divided in three groups: control non-treated SHR with normal hematocrit (Control); SHR with high hematocrit (HighHct) and SHR with low hematocrit (LowHct). In the HighHct group repeated transfusions of homologous red blood cells (2 mL i.p.) were given three times weekly during the 4 week treatment period. For hematocrit lowering, hemolytic phenyl hydrazine (3 mg/100 g b.m.) was given to the LowHct group three times a week during the 4 week treatment period.

Haemodynamic measurements

Haemodynamic parameters were measured in 24 animals after the 4 week treatment period. All animals were anaesthetised (35 mg/kg sodium pentobarbital; i.p.) and hematocrit samples were collected. Mean arterial pressure (MAP) was determined directly through a femoral artery catheter (PE-50, Clay-Adams, Parsippany, NY, USA), with a low-volume displacement transducer (P23 Db, Statham, Oxnard, CA, USA) and recorded on a direct writing recorder. Cardiac output (CO) was determined by modified Coleman's application of the dye dilution technique as previously described (Coleman, 1974). Total vascular resistance (TVR) was calculated by dividing MAP by CO and expressed as mmHg min 100 g/mL.

Vascular response study

There were 62 animals included in the vascular response study. Each animal was cannulated through the jugular vein and injected with three doses of acetyl-choline (Ach) respectively: 0.25; 0.50; 0.75 μ g/kg b.w. MAP was monitored for each dose. After that, nitric oxide (NO) synthesis inhibitor L-NAME (N^G-L-Arginine Methyl Ester, Sigma; 10 mg/kg b.w. i.v.) was given to randomly selected animals from each group: Low Hct + L-NAME (n=10); Control + L-NAME (n=11); High Hct + L-NAME (n=8). MAP rising was registered 30 minutes after L-NAME injection. Further, three previously mentioned doses of Ach were given to L-NAME pretreated animals and MAP was recorded again.

Renal function curve and glomerular filtration study

The study was performed in 24 animals. Animals were drinking tap water during the first 14 days. Systolic arterial pressure (SAP) and urinary concentrations of sodium (Na⁺) (IL 943-flame photometer, Instrumentation Laboratory, Milan, Italy) were measured at the end of the treatment. In the next two weeks, animals were drinking saline (1% NaCl dissolved in drinking water) and SAP and urinary Na⁺ concentration were measured at the end of the treatment. At

the end of the study, urine and blood samples were collected and urinary and plasma concentrations of creatinine were determined. Glomerular filtration (GFR; endogenous creatinine clearance) was estimated using standard creatinine clearance formula.

Statistical analyses

Results are expressed as mean \pm S.E.M. One-way analysis of variance (ANOVA) was applied. When the ANOVA results were significant, Bonferroni's t-test was used to determine the level of significance and a p value <0.05 was considered to be significant (Primer of Biostatistics, by Stanton A. Glanz).

RESULTS

Hematocrit values and hemodynamic parameters

Hematocrit was significantly lower in LowHct group and higher in HighHct group in comparison to the Control (Figure 1). MAP showed a significant decrease in the LowHct vs. Control group (Figure 2). Opposite, MAP was significantly higher in HighHct group vs. Control. CO was significantly higher in LowHct vs. Control (Figure 2). TVR showed a significant decrease in LowHct vs. Control group (Figure 2). However, TVR was significantly higher in HighHct group vs. Control.

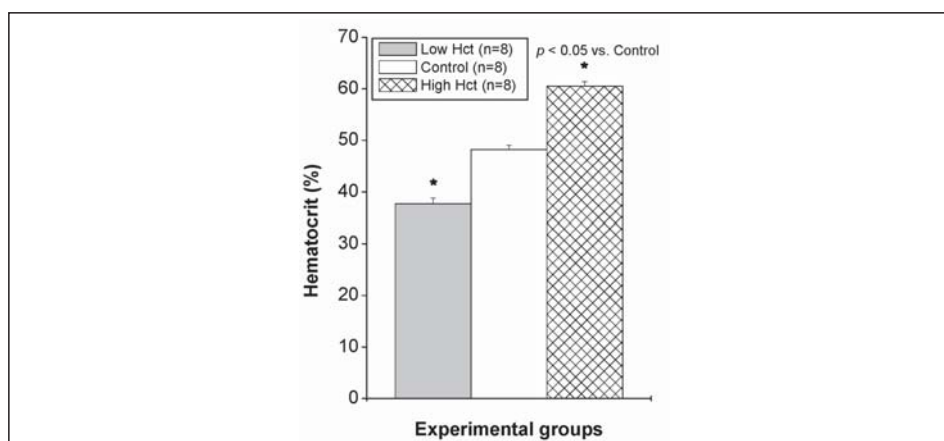


Figure 1. Hematocrit values in experimental groups; n-number of animals

Vascular reactivity

Chronic hematocrit value changes modify acetyl-choline induced vasodilatation in SHR. Both, animals with high, as well as low hematocrit, showed significantly ($p < 0.05$) blunted acetyl-choline induced relaxation in comparison to control animals (Figure 3). MAP was increased in all treated groups after single bolus injection of L-NAME, but only in HighHct group was significantly higher in

comparison to the control. Vasodilatation response to acetyl-choline after L-NAME injection was significantly ($p < 0.05$) blunted in rats with high hematocrit in comparison to control animals (Figure 3).

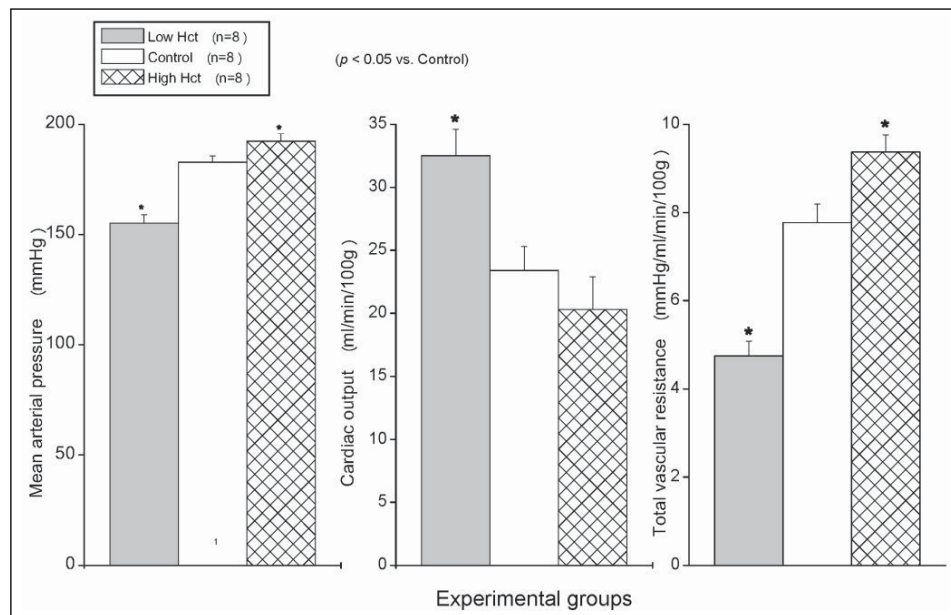


Figure 2. Hemodynamic parameters in experimental groups; n-number of animals

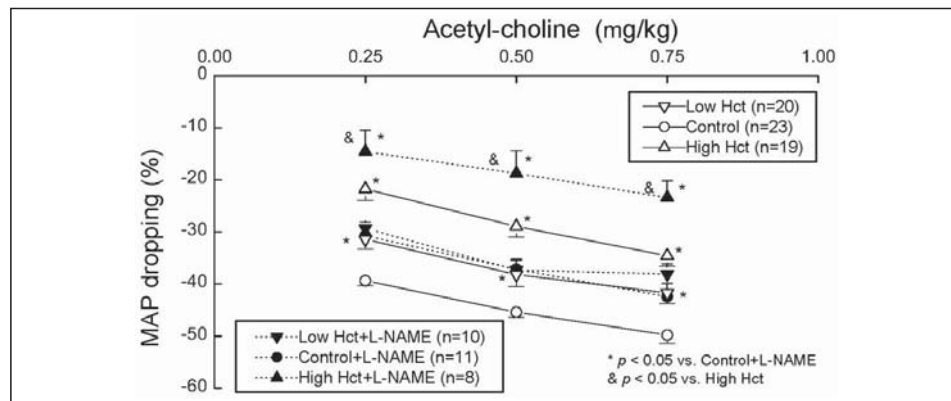


Figure 3. Acetyl-choline induced mean arterial pressure (MAP) dropping in SHR before and after L-NAME treatment; n-number of animals

Glomerular filtration and renal function curve

GFR significantly ($p < 0.05$) dropped in the LowHct group (Figure 4). Renal function curves are shown in Figure 5. Renal function curve of SHR with a normal hematocrit value is almost vertically positioned and right-shifted in comparison to the standard normotensive renal function curve. Renal function curve of the HighHct group is right directed and renal function curve of the animals with low hematocrit value was significantly left-shifted in comparison to control animals.

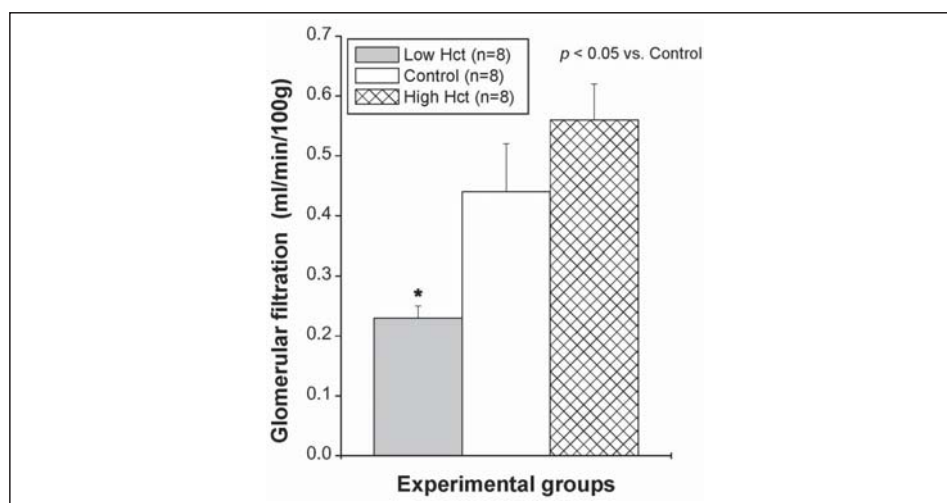


Figure 4. Glomerular filtration in experimental groups; n-number of animals

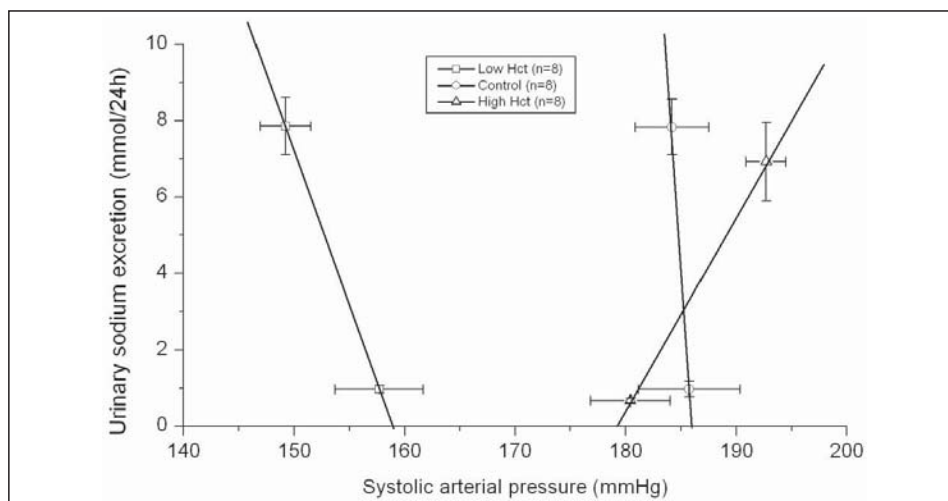


Figure 5. Renal function curves in experimental groups; n-number of animals

DISCUSSION

Results of the present study demonstrate that chronic hematocrit value changes alter blood pressure in SHR. A decreased hematocrit induces CO rise followed by TVR and MAP decrease. On the other hand, increasing hematocrit value induces CO decrease and further TVR and MAP increase. Dintefass and Girolami (1978) have shown a positive correlation among diastolic blood pressure and blood viscosity in patients with a high hematocrit (46%). Isovolemic haemodilution leads to a decrease in hematocrit and plasma fibrinogen, to reduction of blood viscosity and finally to a decrease in arterial blood pressure (Siefge *et al.*, 1981). Also, studies of Sušić (Sušić *et al.*, 1982; 1988; 1992) showed that heparin or phenylhydrazine induced lowering of hematocrit value, followed by arterial blood pressure decrease.

Strazzullo *et al.* (1990) reported increased both hematocrit and hemoglobin values in hypertensive patients. A clear positive relationship between hypertension and blood viscosity was described in the Strong Heart Study in American Indians (de Simone *et al.*, 2005). A four year follow up study of Mandal *et al.* (1993) showed that decreasing of blood viscosity (induced by hematocrit lowering) participates in diastolic blood pressure reduction in hypertensive patients receiving 50 mg of hydrochlorothiazide and there was no change in kidney function. Our results are in accordance to the findings of Mayer *et al.* (1988) that increase in hematocrit values induces high blood viscosity followed by CO lowering, increasing vascular resistance and finally arterial hypertension. Besides, vascular endothelial cells produce the strong endogenous vasodilator molecule NO (Lüscher TF, 1990) which is occupied by an excess of Hb (Schultz *et al.*, 1993) leading to vasoconstriction and blood pressure elevation.

In the present study, chronic hematocrit value elevation significantly blunts Ach induced vasodilatation. Nakai *et al.* (1996) showed that repeated transfusions increase plasma hemoglobin and inhibit circulating NO, opposite to synthetic hemoglobin products which can inhibit both circulating and mio-intimal blood vessel NO. There are two different ways of Hb induced NO inactivation. First, oxyhemoglobin reacts with NO quickly (in 100 ms) producing nitrite ions and methemoglobin ($\text{Hb-O}_2 + \text{NO} \rightarrow \text{NO}_3^-$) and second, deoxyhemoglobin binds NO producing NO-hemoglobin. The net result of both actions is decreased NO bioavailability and vasoconstriction (Schultz *et al.*, 1993). Rioux *et al.* (1994) showed that Hb can neutralize Ach via direct stimulation of cholinesterase activity.

Unexpectedly, hematocrit value lowering significantly blunted Ach induced vasodilatation in our study. It's well known that hypoxia induces elevation in endothelium derived NO production, thus resulting in vasodilatation (Kam and Govender, 1994). Regarding that, it's reasonable to expect a stronger Ach induced vasodilatory response in low hematocrit animals. Our results could be explained by the study of Bassenge *et al.* (1996) that hypoxia due to low hematocrit/hemoglobin concentration stimulates macrophage inducible NO synthase (iNOS) which further inhibits expression of endothelial NO synthase (eNOS) - mediator of Ach induced vasodilatory response. On the other hand, phenylhydrazine as a toxic and hemolytic agent (Williams, 1990) could damage

both endothelial cells and receptors, therefore disturbs vascular response. Both, L-NAME induced MAP elevation and blunted Ach induced vascular response correlate our results with the study of Sharma *et al.* (1995) which implies synergism of hemoglobin induced NO inhibition and L-NAME vascular effects.

Dramatically reduced GRF in LowHct group indicates that these animals have developed acute renal failure (ARF). There are several factors involved in the initiation and maintenance of ARF: decrease of glomerular capillary permeability, back-leak of glomerular filtrate, tubular obstruction and intrarenal vasoconstriction (Nissenson, 1998). Many haemolytic agents, among them phenyl hydrazine and its derivatives can induce ARF (Stefanović, 1989). There are three possible mechanisms of hemoglobin induced kidney injury: tubular obstruction due to macromolecular precipitation of hem protein (Zager and Gamelin, 1989); free radical damages of kidney epithelial cells due to oxidation of iron (Paller, 1988) and ischemic injury due to NO induced hem inactivation (Moncada *et al.*, 1991). However, detailed histopathological analyses is needed to evaluate the degree of renal damage in our study.

It is not easy to define exactly the reasons for disturbed salt and water excretion in hypertensive humans and animals. Kimura and Brenner (1995) suggested increased preglomerular vascular resistance as a mechanism of not salt-dependent hypertension. In salt-dependent hypertension, these authors proposed lowering of kidney ultrafiltration coefficient and increased tubular sodium reabsorption as mechanisms of developing hypertension. Hu and Manning (1995) showed disturbed sodium excretion, decreased excretion of nitrates and nitrites, right shifted renal function curve and blood pressure elevation in salt sensitive Dahl rats. After NO donor infusion (L-Arginine; 4 mg/kg/min) there was an increased excretion of nitrates and nitrites, left shifting of the renal function curve and returning of blood pressure. This implies that diminished NO production in salt sensitive rats results in right-shifted renal function curve and hypertension developing without changed sodium excretion. Also, results of Boegehold *et al.* (1992) have shown that the non-hypertensive dose of L-NAME (0.1 μ g/kg/min), competitive inhibitor of enzyme NO synthase, induces blood pressure elevation after salt loading (300 meq/day). Taken together, it can be concluded that diminished NO bioavailability in the kidney reduces sodium and water excretion after long-lasting salt loading resulting in salt sensitive hypertension. Also, results of our study lead us to conclude that NO induced hem inactivation could be responsible for blood pressure salt-sensitivity in HighHct group.

In summary, results of our study show that chronic hematocrit value elevation participates in blood pressure and peripheral vascular resistance increasing SHR. On the other hand, chronic hematocrit value lowering elucidates blood pressure and peripheral vascular resistance decrease followed by CO rise. Both hematocrit value changes significantly reduce vasodilatory response, but NO dependent vasodilatory response is significantly blunted only in high hematocrit animals. Hematocrit lowering induces a decline in glomerular filtration and plasma creatinine elevation leading to acute renal failure. Sodium excretion is shifted to higher blood pressure values in high hematocrit animals and opposite -

to lower blood pressure values in low hematocrit animals. Repeated transfusions develop salt sensitive malignant hypertension in SHR. Further study is necessary to evaluate the degree of kidney damages after chronic hematocrit value changes in SHR.

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UTICAJ HRONIČNE PROMENE VREDNOSTI HEMATOKRITA NA KRVNI PRITISAK I GLOMERULSKU FILTRACIJU KOD PACOVA SA UROĐENOM HIPERTENZIJOM

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SADRŽAJ

Brojna ispitivanja izvedena na životinjama i ljudima su ukazala da je povećanje viskoznosti krvi u direktnoj vezi sa hipertenzijom. Cilj naše studije je bio da se istraži uticaj promene vrednosti hematokrita (Hct) na krvni pritisak i funkciju bubrega u urođenoj hipertenziji. U tom cilju, istraživani su uticaj hroničnog povećanja ili smanjenja vrednosti Hct na hemodinamske parametre, vaskularnu reaktivnost, glomerulsku filtraciju i krivu bubrežne funkcije kod pacova sa urođenom hipertenzijom (SHR). Rezultati naše studije su ukazali da hronično povećanje vrednosti Hct dovodi do povećanja arterijskog krvnog pritiska (AKP) i perifernog vaskularnog otpora (PVO) kod SHR. Nasuprot tome, hronično smanjenje vrednosti Hct dovodi do smanjenja AKP i PVO, praćenih povećanjem minutnog volumena srca. Obe promene vrednosti Hct dovode do smanjenja vaskularne reaktivnosti. Hronično smanjenje vrednosti Hct izaziva nastanak akutne bubrežne insuficijencije. Ekskrecija natrijuma je pomešana ka većim vrednostima krvnog pritiska kod pacova sa povećanim vrednostima Hct, a ka nižim kod pacova sa sniženim vrednostima Hct. Hronično povećanje vrednosti Hct dovodi do razvoja maligne hipertenzije kod SHR. Potrebne su dalje studije da bi se utvrdio tačan stepen i priroda oštećenja bubrega nakon hronične promene vrednosti Hct.