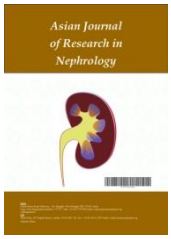

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Sex-related Differences in the Glomerulus and Interstitium in Two-kidney, One-clip Hypertensive Rats

Kabulo Inamfumu Djely [a], Kabulo Katshi Cedric [b,c] and Yves S. Kafuti [b,d*]

[a] Tulane School of Medicine, US.
[b] Dalian University of Technology, China.
[c] University of Lubumbshi, Democratic Republic of the Congo.
[d] University of Kinshasa, Democratic Republic of the Congo.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Arterial hypertension is a common medical condition worldwide and an important predictor of several complicated diseases that can lead to death if not treated. Several factors contribute to the development of arterial hypertension, including physiological, genetic, and lifestyle causes.
Among the constituents that regulate blood pressure, the Renin-Angiotensin-Aldosterone System (RAAS) is one of the most important. This hormonal mechanism controls the hemodynamic stability by adjusting blood pressure, fluid volume, and sodium-potassium balance. As well the RAAS is influenced in a way it functions by many agents such as sex hormones, particularly estrogen. Sex hormones modulate the RAS in various ways and consequently, the RAS displays significant sex-related differences. Estrogen acts on the multiple systems and mechanisms that influence blood pressure (BP) resulting in a decrease or increase of synthesis of different components of the RAAS depending of the sex and the pre or postmenopausal period.
Objective: The aim of this study was to examine if the renal glomerulus and tubulointerstitial injury in 2K1C male rats is greater than the female rats. Additionally, if ovariectomized rats show differences in the degree of renal injury than the 2K1C female rats.
Methods: Thirty-two animal rats were used in the study. The left renal artery of 3 male rats and 4 female rats were clipped in order to develop hypertension and later on develop injury in the renal

**Corresponding author: E-mail: kafutisungu@gmail.com;*

glomerulus and tubulointerstitial so that the tissues could be mounted onto a histological slide and labeled with a CD68 antibody to be later analyzed under the microscope.
Results: The glomeruli and tubulointerstitial inflammation with macrophage infiltration were more severe in the non-clipped kidneys from female 2K1C rats compared to the ones from male and ovariectomized rats. The clipped kidneys from female 2K1C rats in the glomeruli showed an increase in inflammation and macrophage infiltration compared with the clipped kidneys from male and ovariectomized 2K1C rats with not statistical meaning. But non-clipped kidney from female was significantly greater compared with non-clipped kidney from ovariectomized rats ($p < 0.05$). Tubular macrophage infiltration in non-clip female rats was greater compared with male and ovariectomized rats but was not statistical meaningful. Overall, we observed that in the glomerulus as well as in the tubulointertitial, the non-clipped kidneys in both sexes showed a great inflammation with macrophage than in the clipped kidneys.
Conclusion: our experiment did not verify our hypothesis in regard to the expression of hypertension in female rats as opposed to males and ovariectomized rats. Surprisingly, our results showed that glomeruli and tubulointerstitial inflammation with macrophage infiltration were more severe in the non-clipped kidneys from female 2K1C rats showing that renal hypertension was higher in female 2K1C rats than male and ovariectomized rats.

Keywords: Renin-Angiotensin-Aldosterone System (RAAS); angiotensin II; hypertension; sex hormones; two-kidney; one-clip hypertension.

ABBREVIATIONS

2K1C : 2-Kidney-1-Clip;
ACE : Angiotensin-Converting Enzyme;
ADH : Anti-Diuretic Hormone;
ANG (1-7) : Angiotensin (1-7)
ANOVA : Analysis of Variance;
AGT : Angiotensinogen;
AT1R : Angiotensin Type 1 Receptor;
AT2R : Angiotensin on the Expression of the Type 2 Receptor;
ANG II : Angiotensin II;
BP : Blood Pressure;
Ca 2+ : Calcium;
CV : Cardiovascular;
CVD : Cardiovascular Disease;
GFR : Glomerular Filtration Rate;
HBP : High Blood Pressure;
MasR : Mas Receptor;
NO : Nitric Oxide;
PCNA : Proliferating Cell Nuclear Antigen;
RAAS :Renin-Angiotensin-Aldosterone System;
SHRs : Spontaneously Hypertensive rats;
SNS :Sympathetic Nervous System;
Uagt : Urinary AGT;

1. INTRODUCTION

Hypertension is a worldwide epidemic and a multifactorial disease that represents the leading cause of morbidity and mortality. Hypertension significantly impacts the risk of all major cardiovascular events, including stroke, sudden cardiac death, heart failure, peripheral vascular disease, etc.

Estimates suggest that 7.6 million (13.5 %) die from high blood pressure every year globally and 31.1% of the world's population ((1.39 billion people) has hypertension [1], with most (two-thirds) living in low- and middle-income countries. The prevalence is expected to increase to 29% by 2025 [1] which exacts a tremendous economic and public health burden. In the United States, nearly half of the adult population (108 million, or 45%) have hypertension.

The death rate from high blood pressure increased by nearly 11 percent in the United States between 2005 and 2015, and the actual number of deaths rose by almost 38 percent (up to nearly 79,000 by 2015), according to the statistic [2,3]

In general, a higher percentage of men than women of reproductive age have high blood pressure as shown in world health statistics 2012 that estimated the prevalence of hypertension to be 29.2% in males and 24.8% in females [2,3]. Surprisingly, after menopause, more women develop hypertension than men of the same age.

Male-female differences in the development and progression of hypertension and end-organ damage are evident. Studies have suggested that in mostly, hypertension promotes more the progression of renal disease in men than in women. This is attributable to the fact that estrogen is known to have protective effects against the development of hypertension [4].

Estrogen exerts its beneficial influence on vascular endothelium, which is responsible for nitric oxide (NO) production, as well as on various components of the renin-angiotensin-aldosterone system (RAAS) resulting in vasodilation, the opening of Ca2+ activated K+ channels, and reduction of endothelin-1, ANG II, and catecholamine levels [5,6].

As previously reviewed, several studies have shown that in addition to the systemic RAS, intrarenal RAS has been recognized as a major factor in the pathogenesis of hypertension and various renal diseases as well as its independent regulation to the systemic RAS.

In ANG II-dependent hypertension and other renal diseases, Renal angiotensin-converting enzyme (ACE) is maintained or even increased and Angiotensin-converting enzyme 2 (ACE2) counteract the effect of ACE by metabolizing ANG II to generate angiotensin (1-7) [ANG (1–7)] [5]. The classic RAS is the ACE-Ang II-AT1R axis that promotes vasoconstriction to increase Blood Pressure (BP) as well as to increase oxidative stress, fibrosis, cellular growth, and inflammation in pathological conditions. Conversely, the nonclassical RAS is the Ang II/Ang III-AT2R pathway and the ACE2-Ang-(1-7)-AT7R axis. The nonclassical RAS opposes the actions of the Ang II-AT1R axis through vasodilation by increasing in nitric oxide and prostaglandins also reducing oxidative stress [7].

Some studies have shown that the RAS exhibits sex-related differences. This sex difference is explained by sex hormones' effects, particularly estrogen, on the multiple systems and mechanisms that influence blood pressure (BP) [6].

Dr. Shao et al‘s article displayed that the RAAS exhibits sex-related differences linked to gonadal hormones. 2-Kidney-1-Clip (2K1C) male rats exhibit a higher level of angiotensin II in response to activation of the internal renin-angiotensin system (RAS) in both nonclipped kidney and clipped kidneys. Also, some specific differences were seen in clipped kidneys compared to non-clipped kidneys. High level of intrarenal Angiotensinogen (AGT) expression and urinary AGT (uAGT) excretion, as well as important renal damages were observed [8]. However, renal effects in 2K1C female rats are not well established.

Furthermore, in Okuniewski's experiment in examining the effect of ovariectomy upon the development of hypertension in female rats, it was demonstrated an increase in plasma renin activity in ovariectomized female 2K1C rats which was not observed at the same time in intact female 2K1C rats [9]. Information regarding sex-related differences in the glomerulus and tubulointerstitial is limited. Accordingly, this study is designed to investigate the hypothesis that the renal glomerulus and tubulointerstitial injury in 2K1C male rats is greater than the female rats. Additionally, ovariectomized rats show differences in the degree of renal injury than the 2K1C female rats.

2. MATERIALS AND METHODS

Preparation of 2K1C Goldblatt hypertensive rats. The experimental protocol was approved by the Animal Care and Use Committee at Tulane University**.** The animal was described in our lab group in the previous research [8].

Tissue samples were fixed using 10% formaldehyde. Histologic samples were embedded in paraffin and 4 µm sections were used for immunohistochemical analysis. After the quenching of the endogenous peroxidase activity, sections were incubated with the primary antibody against proliferating cell nuclear antigen (PCNA, Santa Cruz Biotechnology, sc-25280) at 1:1000 dilutions for 1 hour at room temperature. The slides were incubated with appropriate secondary antibodies for 30 minutes. The sections were rinsed in phosphate-buffered saline (PBS), and incubated in 0.02% 3, 3′-diaminobenzidine tetrahydrochloride.

Macrophages were used as experimental cells. The numbers of monocytes/macrophages were examined by immunohistochemistry using a commercially available antibody against CD68 (catalog no. CM033A; Biocare Medical). Immunohistochemistry was performed by a robotic system (Dako autostainer) and counterstained with hematoxylin-eosin. Twenty consecutive microscopic fields were examined for each rat, and CD68-positive cells (brown) were counted in tubulointerstitial and glomeruli in each of the rats using 200 or 400 magnification objectives. The averaged numbers of monocytes/macrophages in tubulointerstitial or glomeruli then were obtained for each rat and a digital camera (DS-U2/L2USB) attached to a Nikon Eclipse 50i microscope. The kidney

sections were arbitrarily selected from each group for analysis.

Thirty-two animal rats were used in the study. Among the thirty-two animals, 3 male rats and 4 female rats were clipped. A 2.5-mm clip was placed on the left renal artery in order to induce high blood pressure. In the male group, 3 kidneys of 3 animal rats (picked randomly) represented the control group, 3 clipped kidneys of 3 animal rats accounted for the left kidney group and 3 non-clipped kidneys of 3 rats constituted the right kidney group. In the female group, 7 kidneys of 7 animal rats represented the control group, 4 clipped kidneys of 4 rats composed the left kidney group and 8 non-clipped kidneys of 8 animals were in the right kidney group. 4 non-clipped kidneys of 4 rats represented the right kidney group of ovariectomized rats.

Table 1. Study protocol

Male			Female			Ovariectomized	
Control	2K1C		Control	2K1C			
	Left	Right		Left	Right	Left	Right
G0M1	G1M1	G1M1	CF1	G1F1	G1F1		OVX-1
G0M2	G1M3	G1M3	CF3	G2F1	G2F1		OVX-2
G0M3	G2M3	G2M3	CF5	G2F3	G2F3		OVX-3
			CF1	G2F4	G2F4		OVX-4
			CF4		2K1C-F1		
			Control2		2K1C-F2		
			Control3		2K1C-F3		
					2K1C-F4		

2.1 Statistical Analysis

Results are expressed as means SE. Data were analyzed by repeated-measures ANOVA with post hoc Newman-Keuls multiple-comparison test within each group and by oneway ANOVA with post hoc Newman-Keuls multiple-comparison test among groups. A value of P 0.05 was considered statistically significant.

3. RESULTS

Glomeruli and tubulointerstitial inflammation with macrophage infiltration were more severe in the non-clipped kidneys from female 2K1C rats. As to the macrophage infiltration in glomeruli, the clipped kidneys from female 2K1C rats showed a relevant increase in inflammation and macrophage infiltration compared with the clipped kidneys from male and ovariectomized 2K1C rats; however, it was not statistically meaningful. But non-clipped kidney from female was significantly greater compared with non-clipped kidney from ovariectomized rats ($p < 0.05$). Overall, the non-clipped kidneys in both sexes showed a great inflammation with macrophage than in the clipped kidneys.

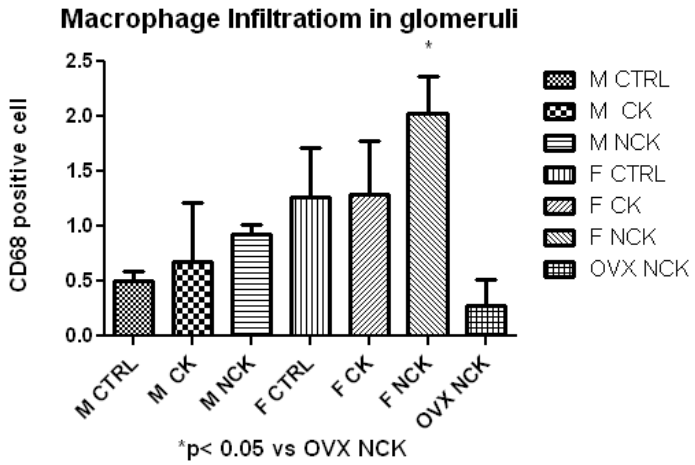

Fig. 1. Macrophage infiltration in glomeruli

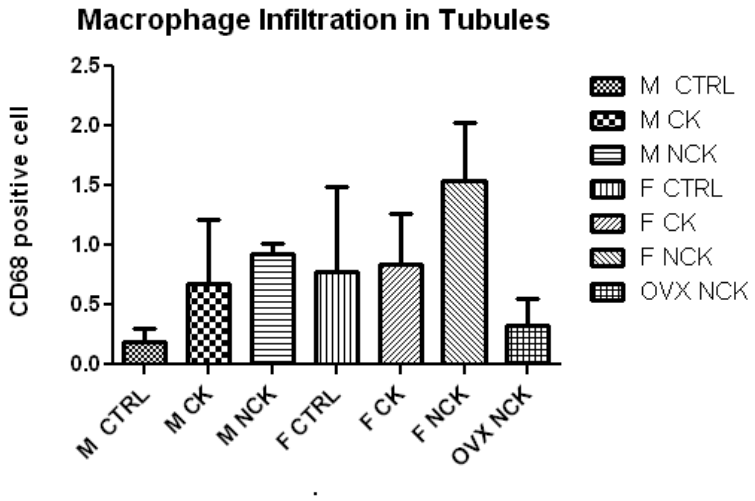

Fig. 2. Macrophage infiltration in tubules

Tubular macrophage infiltration in non-clip female rats was greater compared with male and ovariectomized rats but was not statistical meaningful. The non-clipped kidneys in both male and female rats showed a great inflammation with macrophage than in the clipped kidneys.

CD68, a marker of macrophage infiltration, in glomeruli (A) and tubulointerstitial (B) areas. Averages of 20 fields for each rat were analyzed from paraffin kidney sections (3 μm). The number of CD68-positive cells/mm2 was quantified by an automatic image analysis in glomeruli and tubulointerstitial and expressed as percentage ± SE. *P < 0.05 vs. sham, **P < 0.01 vs. sham, and ##P < 0.01 vs. CK.

4. DISCUSSION

The present study was performed to determine and compare the renal glomerulus and tubulointerstitial injury in both kidneys of male, female and ovariectomized 2K1C hypertensive rats. A key focus was based on results from previous experiments of different researchers.

Lee et al. discussed that female rats in the 2K1C model were resistant to hypertension and related organ damage compared with male 2K1C rats. However, this protective effect was eliminated after the ovaries were removed [5].

They implied that the intratubular presence of non-classic RAS [ACE2-ANG (1–7)-MasR] expression could contribute to protecting female rats from hypertension. In male rats, renovascular stenosis promotes an increased expression of intrarenal ACE levels and a decrease in intrarenal ACE2 levels, but the occurrence of these changes in female animals has not been clarified to date according to them [5]. They found that intratubular ACE level was increased in male 2K1C rats but was not augmented in female 2K1C rats 5 wk after the clipping operation. Reciprocally, intratubular ACE2 was increased in female 2K1C rats and decreased in male 2K1C rats 5 wk after the clipping operation. However, these changes were altered in OVX female rats.

Previous studies have reported that medullary ACE and ACE2 activity does not show sex-related differences in hypertensive mRen(2)Lewis rats and that intrarenal ACE mRNA levels are similar between adult male and female spontaneously hypertensive rats (SHRs) [10]. These discrepancies might be due to the use of different measurement methods and different strains of rats. ACE2 is located on the X chromosome; thus, female rats likely present higher ACE2 levels because of the additional gene copy. In contrast, the Sry gene on the Y chromosome is known to augment the promoter of renin, ACE, and angiotensinogen and mitigate the promoter of ACE2 [11]. Female Sprague-Dawley rats demonstrated higher expression levels of AT2R, MasR, and ACE2 in their kidneys than male Sprague-Dawley rats [5].

Thus, the augmentation of ACE2 in female rats could contribute to the protection against

hypertensive organ damage, despite the hypertensive circumstances. However, this is not the case in the kidneys from OVX female rats. Lee et al's experiments showed that OVX increased tubular ACE and AT1R in both kidneys and suppressed the elevation in ACE2 in the clipped kidneys 3 wk after clipping. As a result, the ACE-to-ACE2 ratio was decreased in the clipped kidneys from female 2K1C rats compared with male 2K1C rats and OVX female rats. The increased ACE-to-ACE2 ratio promoted ANG II generation and exacerbated renal damage [12]. The resistance to increased BP and albuminuria was attenuated in OVX female 2K1C rats compared with female 2K1C rats. Estradiol has been reported to attenuate vasoconstriction via estrogen receptor-mediated increases in nitric oxide, and thus OVX could increase BP through vasoconstriction. However, ample evidence suggests that estrogen could be involved in the regulation of RAS components. Renal ACE2 protein expression and activity are decreased in OVX renal-wrap rats compared with female renal-wrap rats, and estrogen replacement recovers ACE2 activity and protein expression [13]. Taken together, these results indicate that intratubular ACE2 might become more abundant in female animals after renovascular hypertension; however, OVX lessened the increase in tubular ACE2 and, conversely, increased tubular ACE. These changes contributed to reducing the protective effect on hypertension in female animals. The shift in the balance between ACE and ACE2 ultimately influenced the expression of intratubular angiotensin peptides in 2K1C rats. Tubular ANG II levels in normotensive male rats are higher than in normotensive female rats, whereas ANG (1–7) levels are similar between the two sexes. After the clipping operation, the clipped kidneys from female 2K1C rats showed higher intratubular ANG (1–7) levels and, reciprocally, lower ANG II levels than those from male rats. Hypertensive male mRen [14]. Lewis's rats exhibit higher levels of medullary ANG II and lower levels of medullary ANG (1–7) than female rats. Moreover, intrarenal ANG (1–7) levels in female SHRs are significantly higher than in male SHRs (40). ANG (1–7), which is an anti-inflammatory and vasodilatory peptide, plays an important role in attenuating the elevation in BP and protecting the kidneys from hypertensive injury [14].

ACE2 is the main enzyme that catalyzes the conversion of ANG II to ANG (1–7). The predominant activation of ACE2 and ANG (1–7) could help mitigate the increases in BP and albuminuria in female 2K1C rats. Intratubular ANG II was slightly decreased in the nonclipped kidneys from male 2K1C rats. Previous studies have demonstrated an elevation in intrarenal ANG II in both kidneys from 2K1C rats during the initial hypertensive period (2– 4 wk after the clipping operation). In contrast to these studies, the angiotensin peptides were measured during the maintenance phase of hypertension (5– 8 wk after the clipping operation). Their results suggested that the elevated intrarenal RAS might start to decrease during the transition period to chronic hypertension. Additionally, the peptides were measured from frozen samples and likely degraded by the enzyme activity contained within the tissue. Their study revealed that the transcript of medullary AT1R was elevated in OVX female rats compared with malerats, not only in normotensive status but also in renovascular hypertensive status. In addition, intratubular AT1R showed a significant increase in both kidneys from the OVX female 2K1C rats compared with female 2K1C rats. In contrast, mRNA levels of AT2R were increased in female kidneys, regardless of OVX or renal arterial clipping. ANG II has been demonstrated to stimulate vasoconstriction, Na reabsorption, and tissue damage via AT1R but plays a role in vasodilation and antiproliferation via AT2R [15].

AT1 binding and AT1R mRNA were higher in male animals than in female been thought to interfere with the action of ANG II by upregulating renal AT2R and downregulating AT1R; thus, the lower AT1-to-AT2 receptor ratio might be connected to the decrease in BP in female animals [15]. Similar to ACE2, the AT2R gene is located on the X chromosome, and thus sex differences in AT2R could be reasonable. Intratubular MasR was increased in female 2K1C rats compared with male 2K1C rats 5 wk after the clipping operation but did not show sex differences 3 wk postoperation. ANG II infusion induces significant increases in MasR expression only in female SHRs, and sex-related differences in BP are abolished by a MasR antagonist during the response to ANG II infusion [16]. Renal blood flow has been shown to be decreased in female Wistar rats but not male rats after MasR blockade [17]. These data implicate MasR as a sex-specific receptor, and the sex-related differences in renal MasR levels could contribute to the BP responses to ANG II. The data demonstrate that the shift in the balance of angiotensin peptide receptors toward those with vasodilatory effects could contribute to lower BP,

reduce albuminuria, and prevent cardiac hypertrophy in female 2K1C rats [18-37].

However, our experiment did not support our hypothesis. We did not expect to see the opposite of previous findings. Yet, we were surprised to see that glomeruli and tubulointerstitial inflammation with macrophage infiltration were more severe in the non-clipped kidneys from female 2K1C rats showing that renal hypertension was higher in female 2K1C rats than male and ovariectomized rats. Many reasons may explain these findings. First, the choice of animals was done based on two different providers. This constituted an issue as it was difficult to assess the environmental differences between the animal groups which could influence their development. Second, the number of animals were not sufficient for conclusive results in this experiment. Some groups, such as the control male and the clipped kidneys from 2K1C male rats only included 3 animals. In addition, we were unable to obtain species for ovariectomized clipped kidneys. This obstacle was a major issue in order for us to obtain objective results.

5. CONCLUSION

Our experiment did not meet our expectations in regard to the expression of hypertension in female rats as opposed to males and ovariectomized rats. Lee et al posited that estrogen could have a protective effect on female rats and lead to a lesser rate of hypertension in them. Nevertheless, our experiment revealed opposite results. Given the multiple obstacles encountered during the research, namely the insufficient number of ovariectomized rats and the dual origin of rats that could influence their responsiveness to the experiment, a more refined protocol is needed taking in account all the limitations mentioned above. Moreover, the study could be redirected toward researching other factors that favor the expression of hypertension beyond the absence or the presence of estrogen.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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