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Original article

Acute effect of Russell's viper (*Daboia siamensis*) venom on renal tubular handling of sodium in isolated rabbit kidney

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Background: The common complication in cases of poisoning by Russell's viper (*Daboia siamensis*) venom (RVV) is acute renal failure, but the pathogenesis involved in the alteration of kidney function is still not well understood.
Objective: To clarify the role of RVV in the pathogenesis of renal damage, the present study examines the functional short-term alterations acutely induced by RVV in isolated perfused rabbit kidney.
Methods: Effects of RVV on renal tubular handling of sodium including mean perfusion pressure (PP), the renal vascular resistance (RVR), the glomerular filtration rate (GFR), the urinary flow (V) and osmolar clearance (Cosm) were studied in two groups of isolated perfused rabbit kidneys; each group had four isolated rabbit kidneys. RVV was added to the perfusion system to obtain the final concentration of 10 □g/ml.
Results: Immediate decreases in PP and RVR caused by the venom were significantly apparent ($p < 0.05$) in the first 15 min after RVV administration. A gradual rise in both PP and RVR occurred 15 min after the initial reduction of the first phase, but its remained below pretreatment values. The GFR, V, and Cosm decreased significantly throughout experiments after venom perfusion ($p < 0.05$). The total fractional sodium excretion increased significantly after venom perfusion throughout experiments, while significant reductions ($p < 0.05$) of renal tubular handling of sodium were apparent for proximal absolute reabsorption of sodium and proximal fractional reabsorption of sodium including marked reductions of distal absolute reabsorption of sodium and distal fractional reabsorption of sodium of the venom treated kidney. Optical microscopy of treated kidney tissue showed acute tubular necrosis at the end of experiment.
Conclusion: The present study suggests that an administration of RVV in the isolated rabbit kidney causes direct acute nephrotoxicity and acute alterations of main functional parameters that are probably mediated by either the direct action of venom components or an indirect effect from vasoactive mediators released from renal cells of the RVV-treated kidney.

Keywords: *Daboia siamensis,* isolated rabbit kidney, renal tubular handling of sodium, Russell's viper venom

Acute renal failure often occurs in patients envenomated by Russell's viper (*Daboia siamensis*). Hemodynamic alterations, inflammatory reactions because of proinflammatory cytokines and vasoactive mediators, and direct nephrotoxicity are incriminated in the pathogenesis of renal injury [1-4]. Hemodynamic changes because of venom can generate and interact with inflammatory mediators to further enhance renal ischemia. Therefore, renal injury is attributed to a combined effect of the venom and inflammatory reaction from the host. In this respect, isolated renal perfusion by eliminating host factors provides a good methodology by which to study renal hemodynamics of the venom and renal pathological changes. In a study of Russell's viper venom (RVV) in isolated renal perfusion using rat kidney, the glomerular filtration rate was decreased and fractional excretion of sodium was increased in dose dependent fashion [5]. Renal pathology was not studied. Another function study by micropuncture of *Triturus* kidney, RVV caused depolarization of proximal tubular cells [6]. The pathophysiological mechanism for the acute

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effect of RVV on renal function has not been fully elucidated. Supplementary to previous study, the present study on isolated perfusion of rabbit kidney reveals the differential effects of RVV on sodium handling of the proximal tubules and distal nephron and renal pathological changes. The isolated perfused rabbit kidney using in the present study was exploited as an efficient tool for the study of an acute response of renal functions with consecutive sufficient urine sample collections for analysis in every 1 minute interval subsequent to the RVV treatment. The lithium clearance method (C_{Li}) was chosen to estimate the rate of renal proximal and distal tubular reabsorption of sodium in the present study. C_{Li} has been shown to be useful to estimate end-proximal fluid delivery including cortical and juxtamedullary nephrons as a single population [7, 8]. The data obtained may contribute to understanding better the mechanisms involved in alteration of kidney function in the isolated kidney after RVV administration without extrarenal factors.

Materials and methods

Animal preparation

Adult male white New Zealand rabbits weighing 2 to 3 kg were used in this study. Rabbits were kept in an animal house under controlled temperature (25°C) and light (0600–1800 h) and had unrestricted access to food and water. Animal care and all experimental protocols conformed to the Guide for the Care and Use of Laboratory Animals published by the Ethics Committee of the Queen Saovabha Memorial Institute, Thai Red Cross Society. These recommendations are based on international standards and are in accordance with the principles and guidelines of the National Research Council of Thailand for the Care and Use of Laboratory Animals.

Isolated kidney perfusion and experimental studies

The rabbits were fasted with free access to water 24 h before experiments. The rabbits were anaesthetized with pentobarbital sodium (50 mg/kg body weight). The abdomen was opened by a midline incision, and the left kidney, the renal artery, and the abdominal aorta were exposed. The left kidney was isolated. The animal was given 1000 units heparin intravenously. The left ureter was cannulated with polyvinyl catheter. The left renal artery was prepared for perfusion after careful exposure of the left kidney. The renal artery was separated from its surrounding tissue, and was ligated above the renal artery. A needle cannula (No. 19) was inserted into the renal artery and flushed with heparinized saline (100 units/ml). The kidney was isolated with the renal vein and the ureter intact and immediately transferred to a thermostatically controlled tissue bath organ chamber. The fluid perfusing the kidney flowed from the cut end of the renal vein and the ureter. The isolated kidney was used to employ a recirculating perfusion design by means of a perfusion apparatus ex vivo. The perfusion fluid was maintained at a temperature of 37°C and aerated with a 95% O_2–5% CO_2 mixture. The working perfusate was perfused through the renal artery with an oxygenated modified Krebs–Henseleit solution by means of a recirculating a rotary pump (EYELA, Roller pump, RP-1000). The rabbit kidney was perfused at constant perfusion flow rate (15–20 ml/min) throughout the experiments. The perfusion fluid was a modified Krebs–Henseleit solution as described in a previous report [9] with the following composition: 141 mM Na^+, 5.4 mM K^+, 1.9 mM Ca^{++}, 2.4 mM Mg^{++}, 126 mM Cl^-, 25 mM HCO_3^-, 2.44 mM SO_4^{2-}, 1.5 mM PO_4^{3-}. Bovine serum albumin (BSA fraction V), 6 g/100 ml; 1 mM arginine, 1 mM alanine,1 mM glycine, 100 mg glucose, 50 mg inulin, and 100 mg LiCl were added to the solution resulting in a final perfusate volume of 100 ml. The pH of solution was adjusted to 7.4 and the perfusate in perfusion system was kept at 37°C by a prewarming coil and oxygenation by the addition of a 1.2 μm filter in tissue bath for large organ chamber (Radnoti, chamber for organ isolation procedures, catalog No. 166070, Grass Technologies, Monrovia, CA, USA). Changes of perfusion pressure (PP) in the rabbit kidney were measured using a Statham strain gauge pressure transducer and recorded on the physiograph (Universal Oscillograph, Harvard Apparatus, Edenbridge, Kent, UK).

Twenty to thirty minutes were allowed for the kidney to approach normal or nearly normal function as indicated by a perfusion pressure of 120–140 mmHg and urine flow. After equilibration, the experiments were conducted over 60 min after venom administration. Russell's viper *(Daboia siamensis)* venom was milked and lyophilized at Queen Saovabha Memorial Institute, The Thai Red Cross Society. The lyophilized of RVV in normal saline was added to the perfusion system after the control period of the experiment. The venom was added to the perfusion fluid to obtain the final concentration of 10 μg/ml. This

concentration was adjusted according to our previously described work [10] in experimental animals that the dosage of LD_{50} of RVV by intravenously injection was 0.5 mg/kg body weight. Hemodynamics and renal function were determined at –3, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30 and 60 minutes after addition of RVV to the perfusion fluid.

At each specified time point, perfusion pressure (PP) and the rate of urine flow (V) were recorded. At each specified time point, we determined the sodium and lithium ion concentrations (Flame photometer 410C, Ciba Corning, USA) and osmolality (Osmometer 3D3, Advance Instruments, Norwood, MA, USA) of both perfusate (P) and urine (U) samples. The inulin concentration in both perfusate and urine was determined using the anthrone method [11].

Calculations for renal function and renal tubular handling of sodium

The flow rate of perfusate to the kidney and perfusion pressure of the system was determined for the renal vascular resistance (RVR) using the standard formula (PP/perfusate flow rate). The clearance (C) of inulin (Cin, GFR), lithium (C_{Li}), and osmolality (Cosm) were measured using standard techniques [12]. Fractional sodium excretion (FE_{Na}) was determined by divided C_{Na} with GFR. The renal tubular handling of sodium was evaluated by determining the proximal absolute reabsorption of sodium (PAR_{Na}), proximal fractional reabsorption of sodium (PFR_{Na}), distal absolute reabsorption of sodium (DAR_{Na}), distal fractional reabsorption of sodium (DFR_{Na}), distal absolute reabsorption of water (DAR_{H2O}) and distal fractional reabsorption of water (DFR_{H2O}).

On the basis of the assumption that lithium is reabsorbed only in the proximal tubules in the same proportion as sodium and water and that lithium is not reabsorbed in the distal tubules, C_{Li} represents the delivery of isotonic fluid at the end of the proximal tubules [8]. The estimation of segmental tubular handling of sodium and water can be calculated using C_{Li} as follows:

Lithium clearance (C_{Li})	$= U_{Li} \times V/P_{Li}$
Proximal absolute reabsorption of sodium (PAR_{Na})	$= (GFR–C_{Li}) \times P_{Na}$
Proximal fractional reabsorption of sodium (PFR_{Na})	$= (1–C_{Li}/GFR) \times 100\%$
Distal absolute reabsorption of sodium (DAR_{Na})	$= (C_{Li}–C_{Na}) \times P_{Na}$
Distal fractional reabsorption of sodium (DFR_{Na})	$= (1–C_{Na}/C_{Li}) \times 100\%$
Distal absolute reabsorption of water (DAR_{H2O})	$= C_{Li}–V$
Distal fractional reabsorption of water (DFR_{H2O})	$= (1–V/C_{Li}) \times 100\%$

Histological examination of the kidney

The kidney tissue was taken after 60 minutes of perfusion in either controlled kidney or treated kidney with RVV. Formalin-fixed and paraffin-embedded kidney tissue was cut into sections and stained with hematoxylin and eosin. Histological examination was performed under a light microscope (Olympus, Tokyo, Japan). The hematoxylin and eosin-stained sections were used to assess changes in glomerulus, proximal and distal convoluted tubules, and collecting ductal epithelia of the isolated kidney after addition of RVV to the perfusate system.

Statistical analysis

The data are presented as mean ± SEM for four different isolated perfused rabbit kidneys in each group. The level of significance for parameters of renal function at $p < 0.05$ using a paired *t* test were evaluated between the pretreated value and value after an addition of RVV to the perfusate system in the same group.

Results

Acute effects of RVV on PP, RVR, GFR, urine flow, Cosm, and FE_{Na} of the isolated kidney (Figure 1)

The present results in Figure 1 show that all renal functional parameters of the controlled isolated kidney were maintained stable throughout 60 min of renal perfusion period. Changes in renal function of the treated isolated kidney showed acute responses after infusion of RVV (10 µg/ml). Immediately after treatment with RVV both PP and RVR of the isolated kidneys significantly decreased with biphasic responses. An initial decrease in PP and RVR was seen, followed by a gradual increase despite continued infusion. A significant reduction ($p < 0.05$) of PP at the first phase was observed 3 to 15 min after venom perfusion in comparison to initial paired control rates in this group (pretreatment = 139 ± 6.3; venom = 119 ± 6.4 mmHg). A significant reduction of

RVR ($p < 0.05$) at the first phase was observed 4–5 min after venom perfusion (pretreatment = 5.3 ± 0.4; venom = 4.4 ± 0.6 mmHg/min/ml). A gradual rise of both PP and RVR occurred 15 min after the reduction of the first phase, but the values remained below initial pretreatment values in all experiments. RVV caused decreases in GFR and urine flow throughout experiments with immediate effect. The maximum reduction of GFR was observed at 10 min after venom perfusion (pretreatment = 1.20 ± 0.19, venom = 0.51± 0.10 ml/min). The maximum reductions of V were observed at 5 min after venom perfusion (pretreatment = 0.79 ± 0.09, venom$_5$ = 0.38 ± 0.20 ml/min). The total fractional sodium excretion showed significant increases ($p < 0.05$) while Cosm decreased after venom perfusion throughout experiments. The maximum reductions of Cosm were observed at 4 min after venom perfusion (pretreatment = 0.82 ± 0.10, venom = 0.37 ± 0.11 ml/min).

Acute effects of RVV on renal tubular handling of sodium (Figure 2)

After the addition of RVV to the perfusate system, PAR_{Na} at the proximal tubule significantly decreased ($p < 0.05$) throughout the experimental period from the initial control rate of 53.7 ± 15.3 µmol/min to 9.5 ± 4.2 µmol/min at 60 minutes after administration of RVV, while the PFR_{Na} decreased from 30.3 ± 6.8% of pretreatment to 13.6 ± 9.3% of the end of experiment. At the distal tubule, there were considerable variations for the calculation in terms of DAR_{Na} and DFR_{Na}, DAR_{H2O} and DFR_{H2O} in the treated kidney, which tended to decrease after venom perfusion.

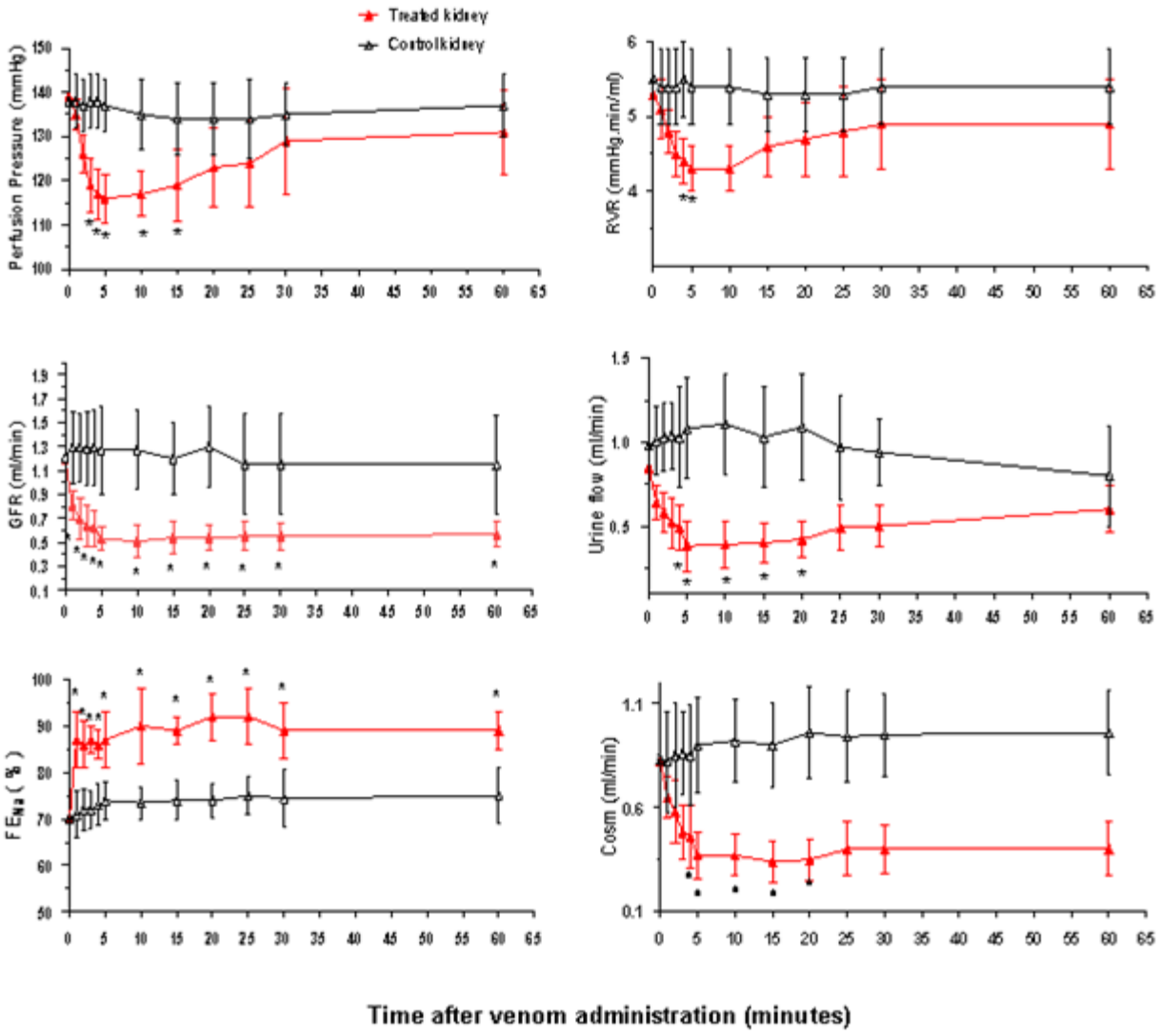

Figure 1. Changes in perfusion pressure, renal vascular resistance (RVR), glomerular filtration rate (GFR), urine flow, osmolar clearance (Cosm), and total fractional sodium excretion (FE_{Na}) of the controlled isolated kidney and the treated kidney after an addition of RVV (Mean ± SEM). Significant differences in changes in comparison with pretreatment were determined using a paired *t* test; *$p < 0.05$

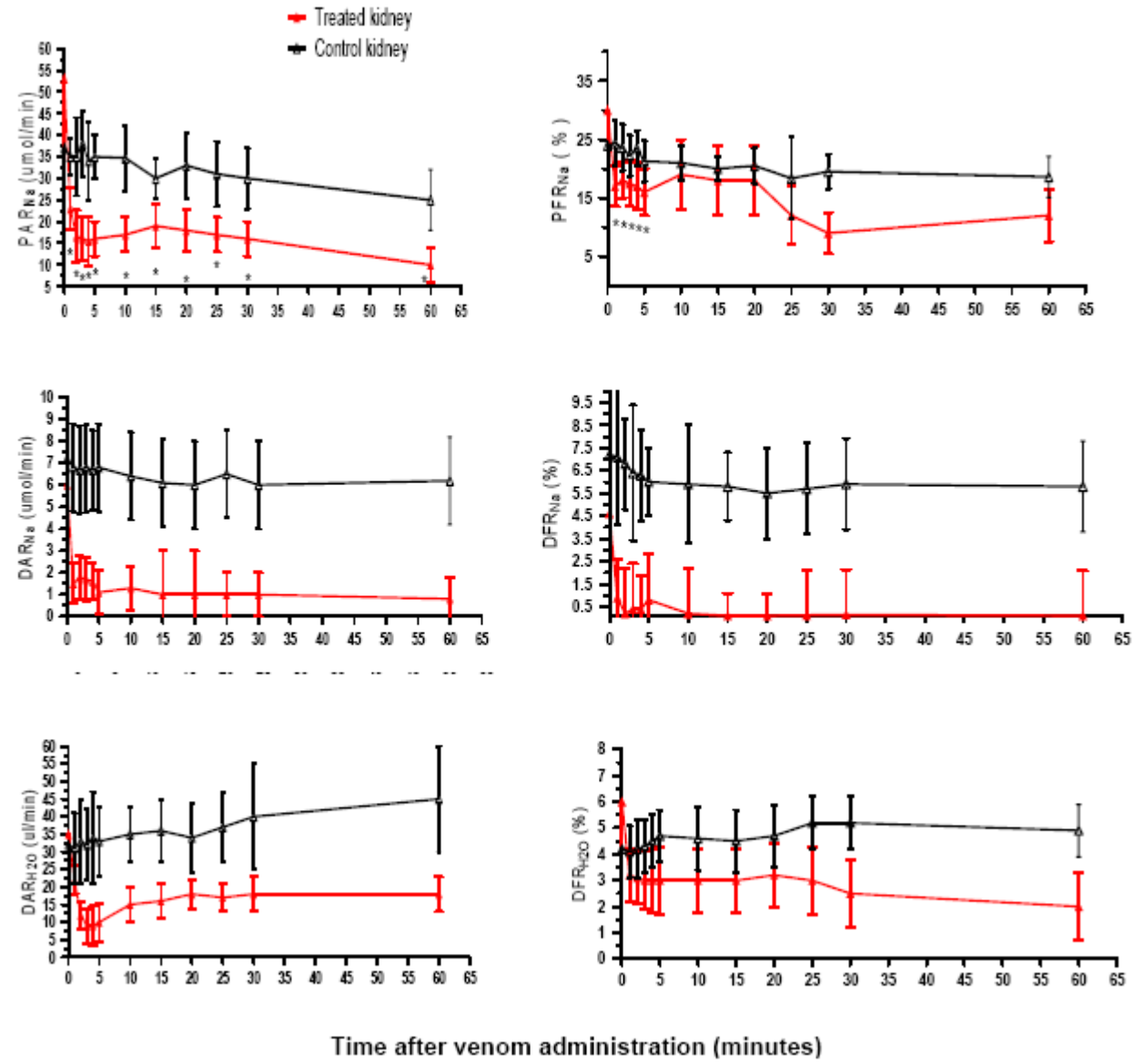

Figure 2. Changes in proximal absolute reabsorption of sodium (PAR_{Na}), proximal fractional reabsorption of sodium (PFR_{Na}), distal absolute reabsorption of sodium (DAR_{Na}), distal fractional reabsorption of sodium (DFR_{Na}), distal absolute reabsorption of water (DAR_{H2O}), and distal fractional reabsorption of water (DFR_{H2O}) of the controlled isolated kidney and the treated kidney after the addition of RVV (Mean ± SEM). Significant differences in changes compared with pretreatment were determined using a paired *t* test; $*p < 0.05$.

Comparison of representative histological images of the isolated perfused rabbit kidneys between control kidney and venom treated kidney

Figure 3 shows representative histological images of the isolated perfused rabbit kidney treated with RVV and the normal controlled isolated perfused rabbit kidney. After exposure to venom for 60 min, optical microscopy showed changes in both glomerular and tubular parts stained with hematoxylin and eosin. The dilatation of the kidney tubules with a moderate congestion and the presence of kidney tubular necrosis were apparent in some samples. The glomerulus revealed dilated capillary slits and accumulation in homogeneous pale-pink proteinaceous substance in capillary. Proximal convoluted tubular epithelium revealed severe hydropic degeneration; enlarged, cloudy swelling in the cytoplasm, accumulation of eosinophilic homogeneous intracytoplasmic and intraluminal substance; compatible with a hyaline cast. Some tubules showed a moderate degree of acute tubular necrosis, tubulorrhexis, and disruption of the tubular basement membrane. The distal convoluted tubular epithelium showed a moderate degree of hydropic degeneration, and disruption from the tubular basement membrane. Collecting ductal epithelium revealed hydropic degeneration, marked cytoplasmic swelling, and accumulation of proteinaceous debris in their lumina.

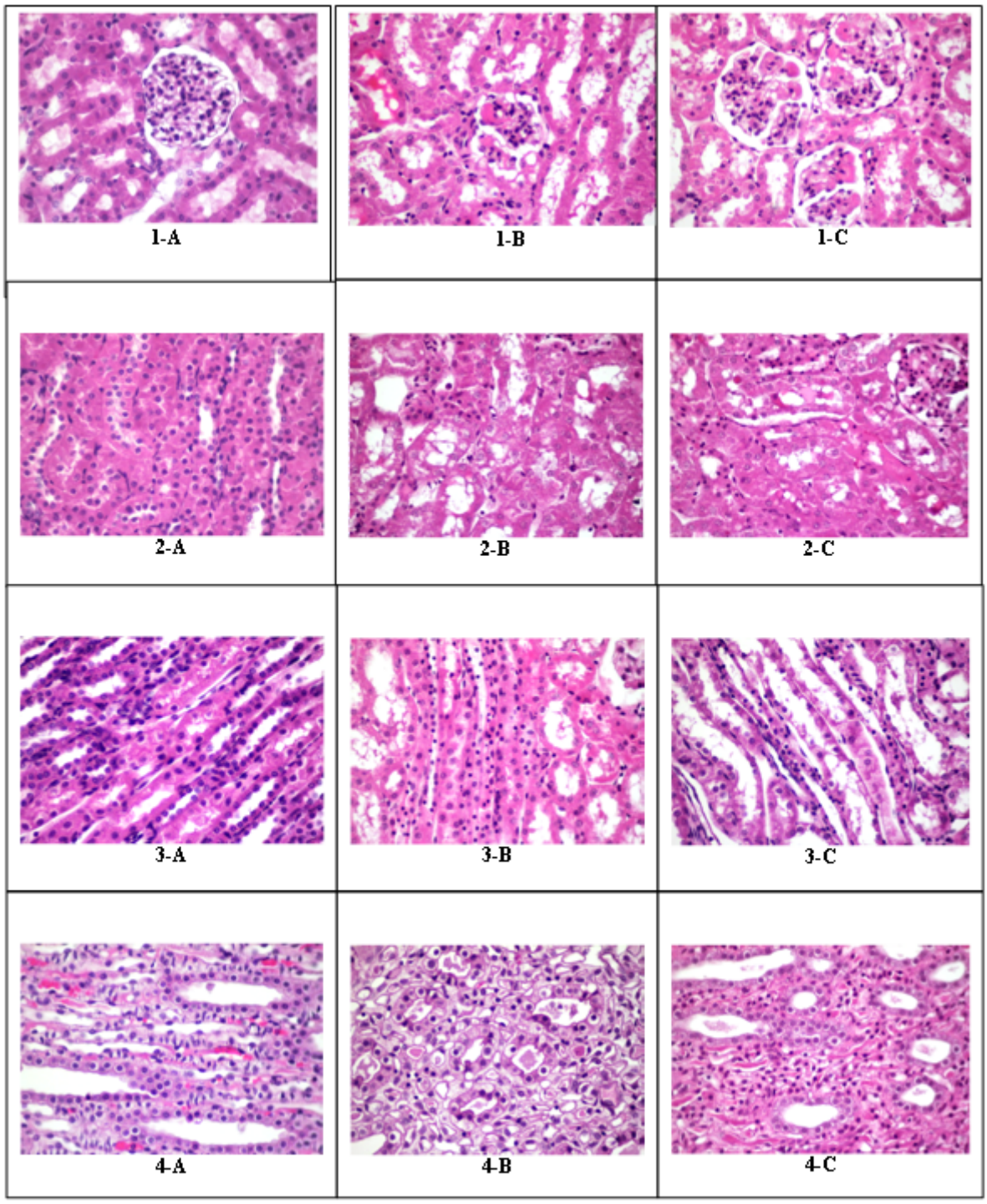

Figure 3. Representative histological images of an isolated rabbit kidney that was taken after 60 minutes of perfusion in either controlled kidney or treated kidney with RVV. The kidney was stained with hematoxylin and eosin (magnification ×400). **1-A:** No abnormal findings of glomerulus in controlled isolated kidney. **1-B, 1-C:** Glomerulus of treated kidney show dilated capillary slits, accumulation of homogeneous pale-pink proteinaceous substance in the capillary. **2-A:** Normal proximal convoluted tubules of controlled kidney. **2-B, 2-C:** Proximal convoluted tubules of treated kidney show severe hydropic degeneration; enlarged, cloudy swelling in cytoplasm, accumulation of eosinophilic homogeneous intracytoplasmic and intraluminal substance; compatible with a hyaline cast. Some tubules show moderate degree of acute tubular necrosis, tubulorrhexis, and disruption of the tubular basement membrane. **3-A:** Normal finding of controlled distal convoluted tubules. **3-B, 3-C:** Distal convoluted tubules of treated kidney show moderate degrees of hydropic degeneration, disruption from the tubular basement membrane. **4-A:** Normal finding of controlled collecting ducts. **4-B, 4-C:** Collecting ductal epithelia of treated kidneys showing severe hydropic degeneration, marked cytoplasmic swelling, and accumulation of proteinaceous debris in their lumina.

Discussion

Important findings in this study include decreased PP because of decreased RVR, decreased GFR, decreased urine flow, and decreased tubular Na^+ reabsorption. Eliminating proinflammatory cytokines and vasoactive mediators from the host decreased RVR secondary to vasodilatation should indicate the direct action of venom on the renal vasculature. The role of RVV on hemodynamic alterations via the modulation of ion channels activities represents a promising interpretative key [13]. Closing of vascular Ca^{++} (L-type) and Na^+ channels (ENa) opening of vascular K^+ channels (K_{Ca} and K ATP) are among the possibilities. Alternatively, vasodilatation could result from the effect of PLA_2, a major fraction in RVV, on the cell membrane in generating PGE_2 that causes vasodilatation through the diminution of myosin light chain kinase. Decreased PP and RVR have been observed in a number of venoms from *Bothrops* species [14-16] and *Crotalus durissus terrificus* (tropical rattlesnake) [17]. Decreased GFR was attributed to decreased glomerular filtration pressure, which was in turn attributed to decreased pressure in the glomerular afferent and efferent arterioles. The second phase showing increased perfusion pressure, which indicates vasoconstriction is of physiological interest and suggests autoregulation of the renal blood flow [18]. Decreased perfusion pressure because of vasodilatation, would possibly inactivate vascular calcium activating K^+ channels (K_{Ca}) causing depolarization and opening of Ca^{++} channels. Increased cytosolic Ca^{++} would cause vasoconstriction and increased perfusion pressure. At this stage GFR remained low because of the low intraglomerular pressure resulting from constriction of glomerular afferent arterioles. The urine flow remained low throughout the experimental period as a result of the low GFR.

Decreased tubular Na^+ reabsorption is consistent with a previous study [5] using RVV in isolated perfused rat kidney. In our study using lithium as a marker for the evaluation of the Na^+ profile delivery in the renal tubule, decreased absolute tubular Na^+ reabsorption was observed in both proximal tubule and distal nephron indicating inactivation of Na^+-H^+ exchange (NHE_3) in proximal tubules and Na^+ channels (ENaC) in the distal nephron. It has been shown that RVV inhibits Na^+-K^+-ATPase activity of renal tubules in both the renal cortex and medulla [19]. Increased cytosolic Na^+ would decrease Na^+ reabsorption through downregulation of NHE_3 and ENaC at the apical border of renal tubules. Alternatively, RVV may directly inhibit NHE_3 and ENaC activities. The urinary excretion of sodium seemed to decrease relatively less than GFR and thus the total fractional sodium excretion was increased. A net decrease in total tubular transport of sodium after addition of RVV would create a low osmotic diuretic effect resulting in a decrease in osmolar clearance (Cosm) and led to a decrease in the rate of urine flow. Therefore, pathologically, tubular necrosis was demonstrated at the end of experiment. This is not surprising. Although it is possible that tubular injury was the direct effect of RVV, through venom enzymes such as PLA2 and metalloproteinase [20], ischemic injury because of renal vasoconstriction cannot be excluded. Study using renal cell culture is required to clarify this.

RVV altered the structural integrity of both glomerulus and renal tubules with severe hydropic degeneration and disruption of the tubular basement membrane including moderate degree of tubular degeneration (**Figure 3**), resulting in dilatation of the renal tubule and subsequent slowing of the passage time of tubular fluid in distal sites.

Conclusion

The present results provide information for an increased understanding of the mechanism of action of RVV, which either directly or indirectly affected the structure and function of renal cells. The study was extended to demonstrate that the acute effect of RVV significantly decreased PP and RVR in the isolated kidney with biphasic responses to treatment. An initial decrease in PP and RVR was seen, followed by a gradual increase despite continued infusion, but PP and RVR remained below pretreatment values. The presence of renal vasodilatation by RVV can probably be attributed to the marked decrease in renal sodium tubular reabsorption leading to vasodilatation with ionic exchange occurring in the renal vascular membrane. The study of the effect of RVV on segmental renal tubular handling of sodium in the isolated rabbit kidney revealed acute inhibition of both proximal and distal absolute reabsorption of sodium. Changes in GFR and renal tubular handling of sodium after the RVV perfusion may be of pathophysiological significance of RVV in the kidney.

The authors have no conflicts of interest to declare.

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