นิพนธ์ต้นฉบับ

Effects of indomethacin on renal hemodynamics, urinary enzymes and thromboxane B_2 following envenomation of Russell's viper in dogs.

Sopit Thamaree*
Narongsak Chaiyabutr** Smai Leepipatpaiboon***
Kanit Buranasiri† Piyaral Tosukowong†
Piroj Sirivongs* Visit Sitprija††

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The effects of indomethacin (5 mg/kg, i.v.) on renal hemodynamics, urinary enzymes, plasma and urinary thromboxane B_2 (TxB_2) following a 40 min intrarenal arterial infusion of Russell's viper venom (RVV, 1.25 ug/kg/min) were studied in anesthetized male mongrel dogs. All parameters were determined before and at every 20 min after envenomation. Urinary enzymes were assayed by colorimetric method. Plasma and urinary thromboxane B_2 (P_{TxB_2}, U_{TxB_2}) were measured by radioimmunoassay after extraction and purification steps. The reduction of mean arterial pressure (MAP) and the increase of urine flow rate (V), P_{TxB_2} and U_{TxB_2} induced by RVV were inhibited by indomethacin pretreatment. Renal blood flow (RBF) and glomerular filtration rate (GFR), relatively unchanged by RVV, were markedly reduced by indomethacin pretreatment. Only urinary N-acetyl-β-D-glucosaminidase (NAG) was increased after envenomation. These results suggest an augmented synthesis of TxB_2 and/or disturbance of active tubular reabsorption of U_{TxB_2}. After the inhibition of prostaglandin synthesis by indomethacin, the reduction of renal function and hypertensive response to RVV may be accounted for by the renin-angiotensin system. The elevation of U_{NAG} indicates a direct nephrotoxicity of RVV.

Reprint requests : Thamaree S. Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok 10500, Thailand.
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* Department of Pharmacology, Faculty of Medicine, Chulalongkorn University.
** Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University.
*** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.
† Department of Biochemistry, Faculty of Medicine, Chulalongkorn University.
†† Department of Medicine. Faculty of Medicine, Chulalongkorn University.

โสภิต ธรรมอารี, ณรงค์ศักดิ์ ชัยบุตร, สมัย ลีพิพัฒน์ไพบูลย์, ชนิษฐ บูรณศิริ, ปิยะรัตน์ โตสุโขวงศ์, ไพโรจน์ ศิริวงษ์, วิศิษฏ์ สิตปรีชา. ฤทธิ์ของอินโดเม็ธธาซินต่อการทำงานของไต, เอ็นซัยม์ในปัสสาวะและธรอมบ๊อกเซน บีทู ภายหลังจากการได้รับพิษงูแมวเซาในสุนัข. จุฬาลงกรณ์เวชสาร 2530 พฤษภาคม; 31(5) : 387–398

คณะผู้วิจัยได้ศึกษาฤทธิ์ของพิษงูแมวเซาที่ฉีดเข้าหลอดเลือดแดงของไตเป็นเวลา 40 นาที ในขนาด 1.25 ไมโครกรัม/กิโลกรัม/นาที ที่มีผลต่อการทำงานของไต, เอ็นซัยม์ในปัสสาวะ และระดับธรอมบ๊อกเซน บีทู ในพลาสม่า และปัสสาวะของสุนัขที่ได้รับการฉีดอินโดเม็ธธาซินเข้าหลอดเลือดดำที่ขาในขนาด 5 มิลลิกรัม/กิโลกรัม (7 ตัว) ก่อนการฉีดพิษงู 40 นาที เปรียบเทียบกับสุนัขที่ไม่ได้รับอินโดเม็ธธาซินมาก่อน (7 ตัว) โดยวัดผลทุก ๆ 20 นาที ภายหลังจากเริ่มให้พิษงูแมวเซา แอ็คติวิตี้ของเอ็นซัยม์ในปัสสาวะวัดโดยวิธีคัลเลอริเมตริก ระดับธรอมบ๊อกเซน บีทู ในพลาสม่า และปัสสาวะวัดโดยวิธีเรดิโออิมมิวโนแอสเซย์ภายหลังขั้นตอนการสะกัดและทำให้บริสุทธิ์แล้ว พิษงูแมวเซาทำให้ความดันเลือดลดลง เพิ่มการขับปัสสาวะและเพิ่มระดับธรอมบ๊อกเซน บีทู ในพลาสม่า และปัสสาวะ ผลเหล่านี้กลับเป็นตรงกันข้ามเมื่อสุนัขได้รับอินโดเม็ธธาซินก่อนได้รับพิษงู เลือดที่ไปเลี้ยงไตและอัตราการกรองที่โกลเมอรูลัสไม่ค่อยเปลี่ยนแปลงเมื่อได้รับพิษงูแต่จะลดลงเมื่อสุนัขได้รับอินโดเม็ธธาซินมาก่อน เอ็นซัยม์ในปัสสาวะที่มีการเพิ่มขึ้นอย่างเด่นชัดภายหลังได้รับพิษงูมีเพียงเอ็น-อะเซทิล-บีดี-ดี-กลูโคสามินิเดส (เอ็นเอจี) ชนิดเดียว ผลเหล่านี้แสดงให้เห็นว่าพิษงูแมวเซาทำให้มีการสังเคราะห์ธรอมบ๊อกเซน บีทู เพิ่มขึ้นและ/หรือมีการรบกวนการดูดซึมกลับของ ธรอมบ๊อกเซน บีทู ที่ท่อไต การที่พิษงูทำให้ความดันเลือดสูงขึ้นภายหลังจากยับยั้งการสังเคราะห์ พรอสต้าแกลนดินส์แล้วน่าจะเป็นผลของระบบเรนิน-แองจิโอเท็นซินที่เด่นชัดขึ้นมา เอ็นซัยม์เอ็นเอจีเพิ่มขึ้น อาจเป็นสิ่งชี้แนะว่าพิษงูแมวเซามีพิษโดยตรงต่อไตก็ได้.

Russell's viper venom (RVV) is known to cause renal damage including tubular necrosis[1,2], cortical necrosis[3] and glomerulonephritis.[4] Acute renal failure (ARF) which is recognized to be an important cause of death in patients bitten by Russell's viper may partly result from tubulotoxicity of this venom. It has been suggested that a wide variety of enzymes normally excreted into the urine are increased in various disease states including in renal tubular cell injury.[5] The early work of Wellwood et al.[6] had indicated that certain lysosomal enzymes from the proximal tubular cells : N-acetyl-beta-D-glucosaminidase (NAG) and beta-galactosidase (GAL), or from the brush border : gamma-glutamyl-transpeptidase (γGT) and alanine-amino-peptidase (AAP) are early markers of tubular damage induced by aminoglycosides. There was no data on enzymuria despite clinical evidence suggesting a direct tubulotoxicity of RVV.

Furthermore, the reduction in renal hemodynamics clearly observed in experimental dogs envenomated with RVV[7], may also play a role in the initial pathogenesis, in the ischemic model of ARF[8]. It has been proposed that catecholamine release, renin-angiotensin activation[7] and prostaglandin release[9] may be responsible for the impairment of renal function.

In this study the effects of Russell's viper venom on renal hemodynamics, urinary enzymes, plasma thromboxane B_2 (P_{TxB_2}) and urinary thromboxane B_2 (U_{TxB_2}) in dogs pretreated with indomethacin compared to non-pretreated dogs were investigated in an attempt to elucidate the relationship between the nephrotoxicity of RVV and urinary enzymic activities, the role of thromboxane B_2 in renal hemodynamic changes and effects of indomethacin, a cyclooxygenase inhibitor.

Material and Method

Fourteen mongrel dogs weighing 10 to 15 kg were anesthetized by intravenous injection of thiopentone sodium at the dosage of 20-25 mg/kg. Supplementary doses were given as necessary to maintain light anesthesia. A femoral artery was canulated for arterial blood sample collection and for recording of arterial blood pressure and heart rate. The heart rate was recorded on a Grass physiograph. Renal artery was canulated for venom infusion. Femoral vein was canulated for fluid infusion. A polyethylene catheter was introduced into the bladder for urine collection.

Renal plasma flow and glomerular filtration rate were measured by p-aminohippurate and inulin clearances using standard techniques.[10] Renal blood flow was calculated from p-aminohippurate clearance and packed red cell volume. Plasma levels of p-aminohippurate and inulin were maintained approximately at 0.03 mg/ml and 0.20 mg/ml by sustained infusion of isotonic saline solution containing p-aminohippurate (Merck, Sharpe and Dohme) and inulin (Sigma Chemical Co.) following the priming doses. After 40 min of equilibration, urine was collected for 20 min and an arterial blood sample was obtained at the midpoint of urine collection. This served as the control period. Thence, Russell's viper (Vipera russelli siamensis) venom, donated by the Science Division of the Thai Red Cross Society, was given by intrarenal arterial infusion at a dose of 0.05 mg/kg. The lyophilized venom was dissolved in 20 ml of 0.9% sodium chloride solution (NSS). The infusion rate was 0.5 ml/min.

For the indomethacin pretreated group, indomethacin was administered intravenously at a dose of 5 mg/kg, 40 min before envenomation of RVV. Blood sampling and urine collection were made twice over a period of 40 min, after indomethacin pretreatment and at every 20 min after envenomation.

The analysis of urine and blood samples were performed of p-aminohippurate and inulin,[10] sodium and potassium (flame photometric method), chloride (by chloridometer), TxB_2 (as shown in diagram I). Urinary lysosomal enzyme activities were measured by colorimetric method[11-13] as shown stepwise in diagram II.

Diagram I Steps of TxB_2 assay.

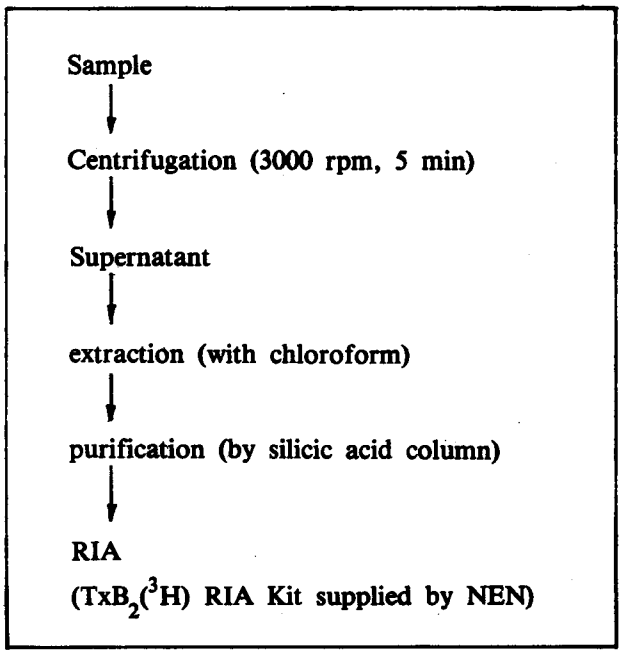
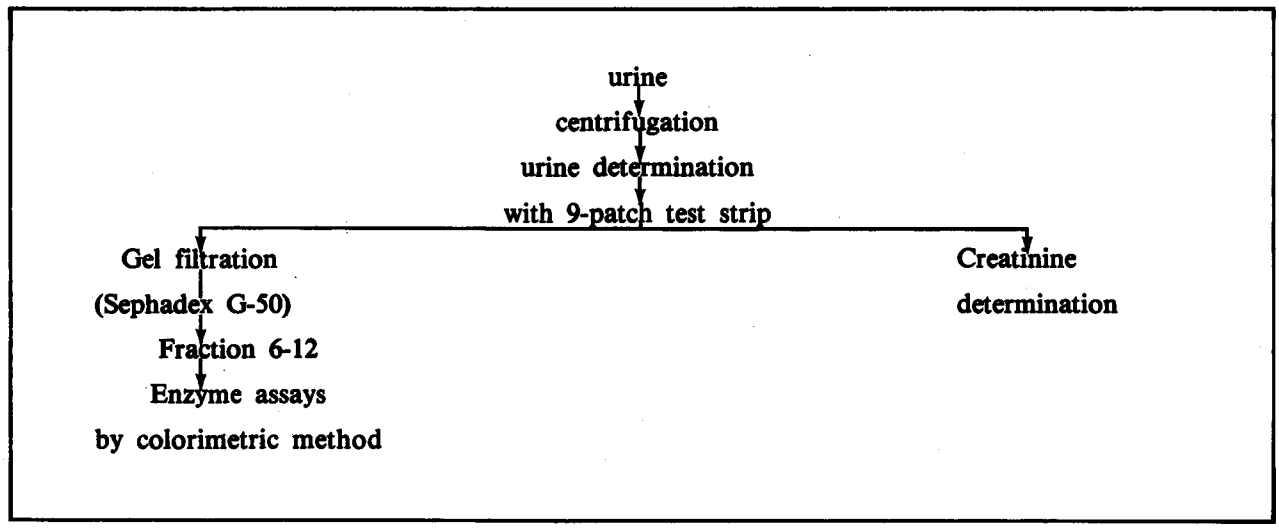


Diagram II Steps of analysis of urinary enzyme activities.



Result

The reduction in arterial blood pressure after envenomation was inhibited by indomethacin pretreatment. Heart rate was slightly decreased in both groups after envenomation (Table 1.) Packed red cell volume was not altered by indomethacin pretreatment but was slightly increased in response to RVV. Renal blood flow (RBF) and renal plasma flow (RPF) were slightly increased during the first 20 min after envenomation but gradually decreased toward the control level, while indomethacin caused a significant decrease in RBF and RPF with further decreases after envenomation. Glomerular filtration rate (GFR), relatively unchanged by RVV alone, was decreased slightly after indomethacin pretreatment and significantly following envenomation. The rising of urine flow rate (V) by 15-65% in response to RVV was inhibited by indomethacin pretreatment (Fig. 1). Urinary excretion of sodium (U_{Na} V), chloride (U_{Cl} V) and potassium (U_K V), and the fractional excretion of sodium (FE_{Na}) and chloride (FE_{Cl}) were increased during the first 20 min of envenomation parallel to the increase in urine flow rate and then declined toward the control level. Indomethacin pretreatment tended to decrease the urinary excretion of sodium, chloride and potassium which gradually increased toward the control level during a 40-min of envenomation. Fractional excretion of sodium, chloride and potassium rose throughout the experimental period but not significantly different from the control (Table 2). The urinary enzyme activity of NAG, significantly increased after the end of a 40-min intrarenal arterial infusion of RVV, was elevated slightly by indomethacin pretreatment and again significantly during envenomation. Other urinary enzyme activities fluctuated but showed a tendency toward an increase after envenomation (Fig. 2). A 7 to 10 fold elevation of urinary TxB_2 was observed during envenomation. Plasma TxB_2 followed a parallel elevation. Indomethacin completely inhibited the rise in P_{TxB_2} and U_{TxB_2}. (Fig. 3, 4)

Table 1 Effect of Russell's viper venom on blood pressure and heart rate.

Parameter	Control	Indomethacin		Russell's viper venom		NSS
		20 min	40 min	20 min	40 min	20 min
Mean arterial pressure	128 ± 8	not given	not given	118 ± 10**	118 ± 12	117 ± 11
(mm Hg)	122 ± 24	128 ± 22*	130 ± 19*	129 ± 22*	137 ± 17*	140 ± 17†
Heart rate (beats/min)	154 ± 11	not given	not given	147 ± 9	135 ± 10	135 ± 12
	145 ± 21	130 ± 17	128 ± 15	127 ± 21	130 ± 25	134 ± 26

Values are mean ± S.D., n = 7
*P<0.05, **P<0.025, † P<0.01 when compared to the control
NSS = Normal saline solution

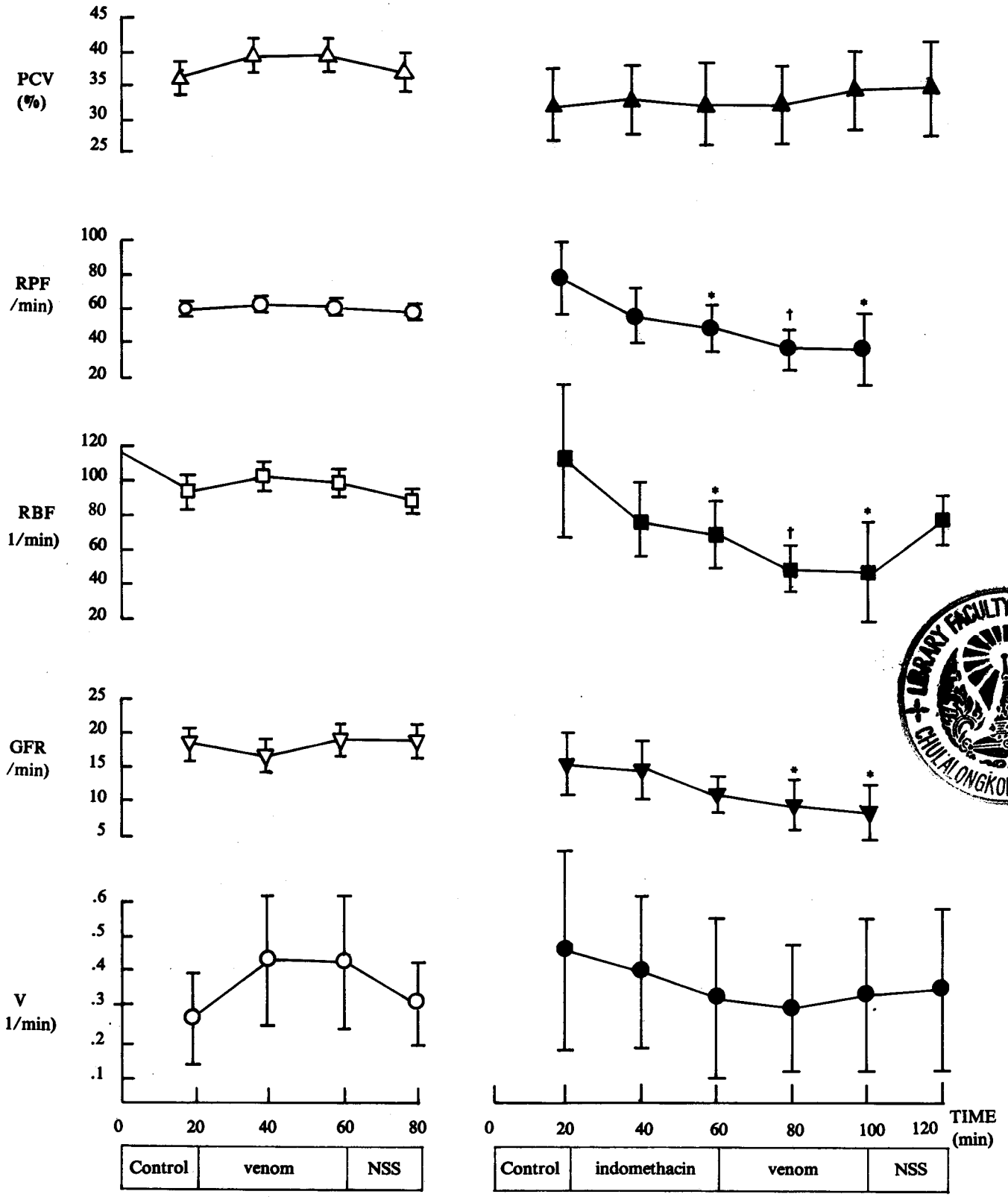


Figure 1 Effects of Russell's viper venom on packed cell volume (PCV), renal plasma flow (RPF), renal blood flow (RBF), glomerular filtration rate (GFR) and urine flow rate (V) in indomethacin non-pretreated (n=7) and pretreated dogs (n=7). Values are mean ± S.D., *P<0.05, † P<0.001 when compared to the control. NSS = normal saline solution.

Table 2 Effect of Russell's viper venom on sodium, chloride and potassium excretion

	Control	Indomethacin		Russell's viper venom		NSS
		20 min	40 min	20 min	40 min	20 min
$U_{Na}V$ (mEq/min)	40.64 ± 40.52	not given	not given	53.34 ± 36.02	39.36 ± 25.26	29.75 ± 18.04
FE_{Na} (%)	1.81 ± 2.17	not given	not given	3.25 ± 3.19*	1.73 ± 1.28	1.48 ± 1.01
$U_{Na}V$ (mEq/min)	48.4 ± 32.48	38.09 ± 41.14	35.85 ± 38.22	35.75 ± 25.88	41.50 ± 33.44	46.08 ± 37.52
FE_{Na} (%)	2.2 ± 1.1	2.2 ± 1.7	3.3 ± 4.2	14.9 ± 30.1	4.2 ± 2.2	7.3 ± 3.8
$U_{Cl}V$ (mEq/min)	45.85 ± 45.62	not given	not given	59.36 ± 39.13	46.99 ± 30.69	29.84 ± 17.87
$FE_{Cl}V$ (%)	2.32 ± 2.86	not given	not given	4.33 ± 4.76*	2.52 ± 2.05	1.70 ± 1.18
$U_{Cl}V$ (mEq/min)	54.2 ± 50.12	51.19 ± 68.02	43.57 ± 65.71	46.31 ± 43.48	50.91 ± 51.73	54.04 ± 46.62
$FE_{Cl}V$ (%)	2.95 ± 2.25	3.4 ± 2.7	5.1 ± 8.0	5.2 ± 5.5	5.3 ± 3.1	9.2 ± 4.0
U_KV (mEq/min)	11.25 ± 4.85	not given	not given	12.54 ± 4.54	9.78 ± 3.57	9.70 ± 2.09
FE_K (%)	23.53 ± 15.05	not given	not given	32.16 ± 17.03*	20.15 ± 9.92	23.10 ± 8.59
U_KV (mEq/min)	8.74 ± 7.07	6.25 ± 3.65	6.48 ± 4.07	6.65 ± 3.89	8.16 ± 5.21	8.11 ± 4.93
FE_K (%)	18.45 ± 8.1	17.4 ± 9.2	25.3 ± 19.2	27.7 ± 18.0	47.6 ± 50.1	32.9 ± 13.1

Values are mean ± S.D., n = 7
UV = urinary excretion, FE = fractional excretion, Na = sodium, Cl = chloride, K = potassium.
*$P < 0.05$ when compared to the control.

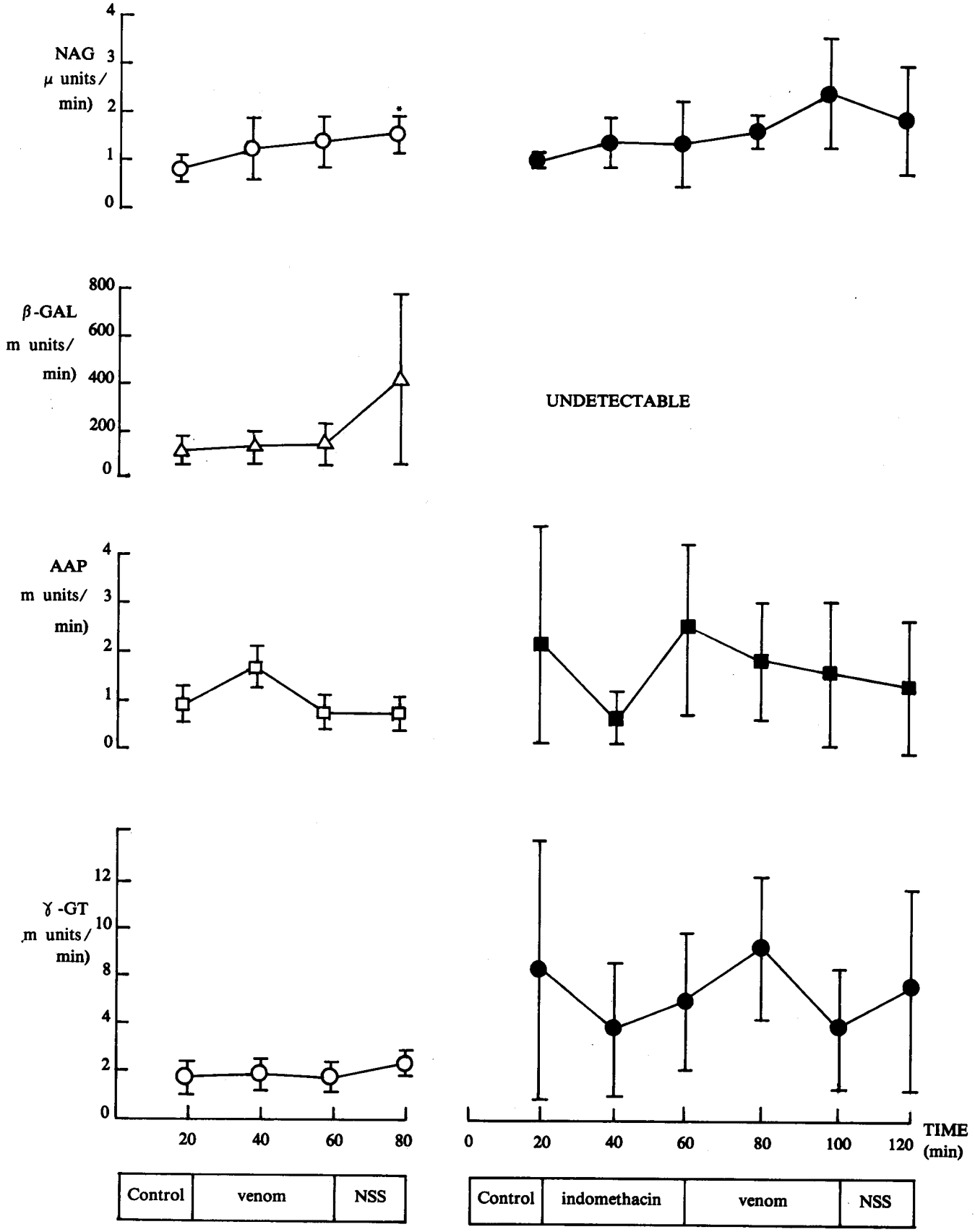


Figure 2 Effects of Russell's viper venom on urinary enzyme activities (n = 7). Values are mean ± S.D., *P < 0.05 when compared to the control. NSS = normal saline solution.

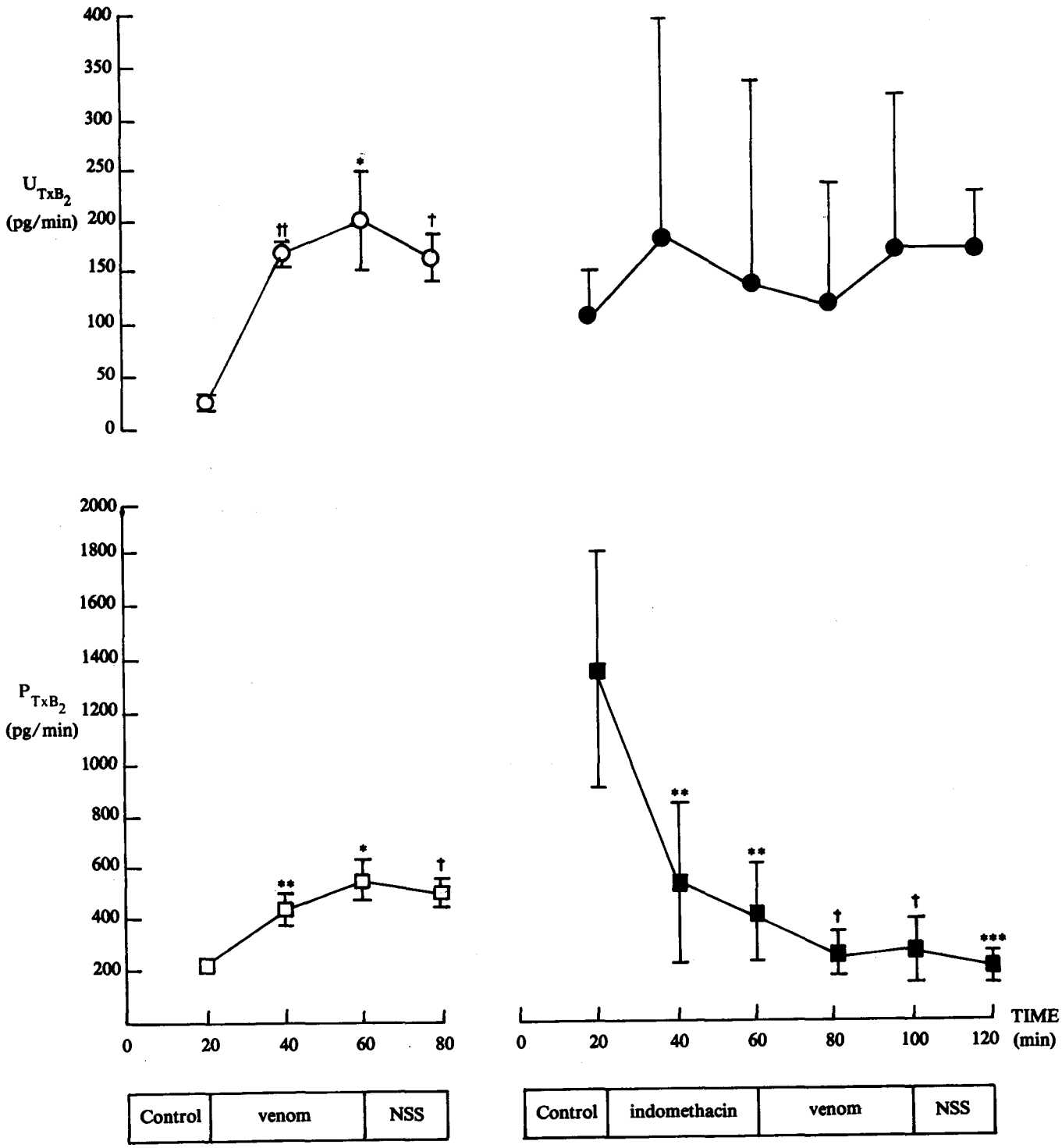


Figure 3 Effects of Russell's viper venom on the urinary and plasma levels of thromboxane B_2 in the indomethacin non-pretreated (n = 7) and pretreated dogs (n = 7). Values are mean ± S.D., *P < 0.05, **P < 0.025, † P < 0.01, ***P < 0.005, †† P < 0.001 When compared to the control. NSS = normal saline solution.

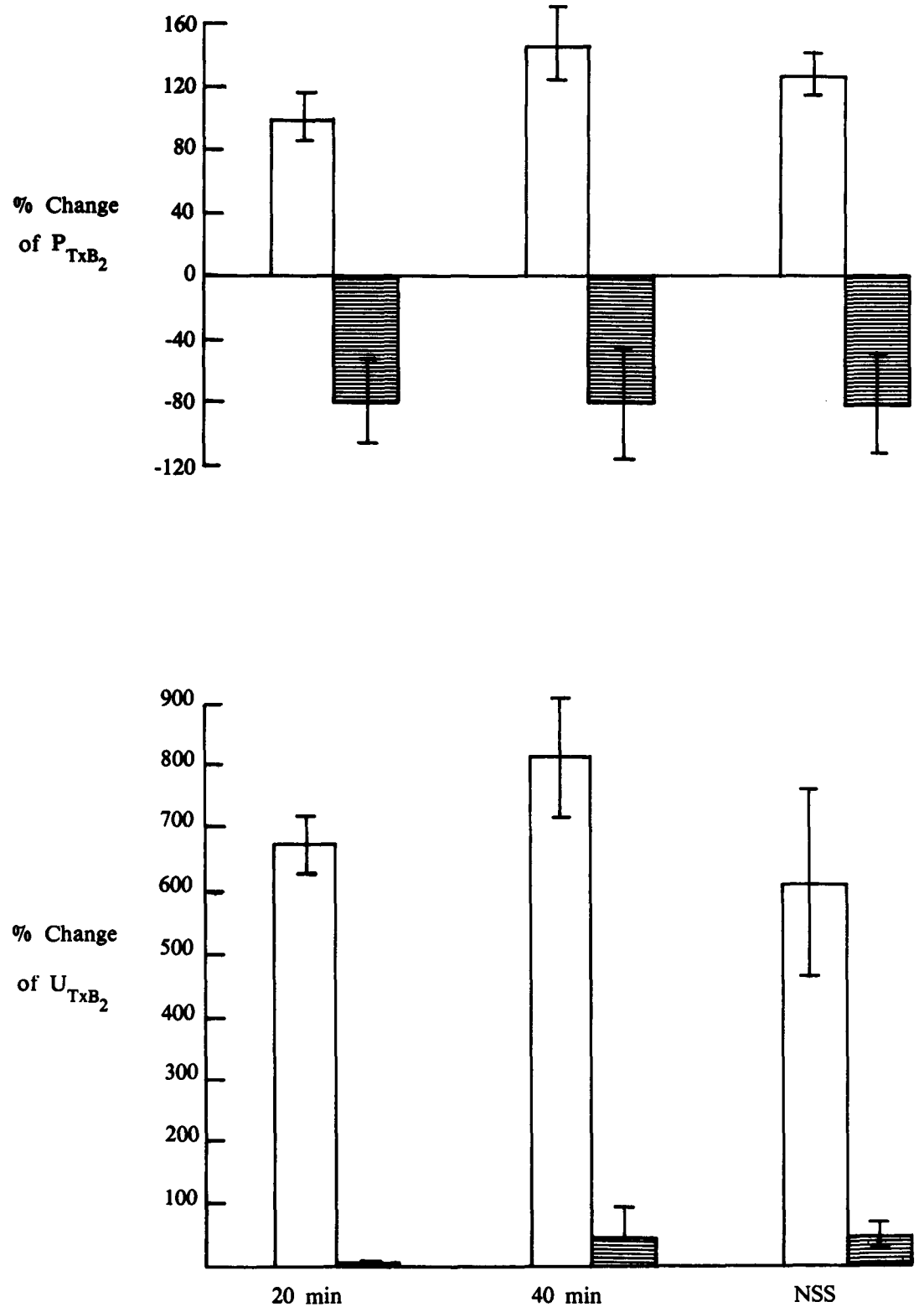


Figure 4 Comparing of the percentage changes from the control level of the plasma and urinary thromboxane B_2 (P_{TxB_2} and U_{TxB_2}) between the indomethacin non-pretreated □ and indomethacin pretreated ■ dogs after 20 min and 40 min of envenomation and a 20-min infusion of normal saline solution (NSS). Each bar is mean ± S.D. of 7 dogs.

Discussion

The results from our studies show that Russell's viper venom directly infused via renal artery at the dose of 1.25 μg/kg/min can slightly affect the systemic circulation and renal hemodynamics. The reduction of mean arterial blood pressure may be attributable to splanchnic vasodilatation.[14,15] It is believed that Russell's viper venom causes vasodilatation through its effect on prostaglandins and kinin release as well as other slow reacting substances.[9,16] Our results showed a parallel increase of P_{TxB_2} and U_{TxB_2} due to Russell's viper venom despite no marked change in hemodynamics. The increased P_{TxB_2} and U_{TxB_2} may have partly been the result of augmented synthesis of TxB_2 in the renal vasculature. The vasoconstrictor action of TxB_2 may be counteracted by other renal hormones including vasodilatory prostaglandins. Indomethacin, a cyclooxygenase inhibitor, given prior to envenomation can completely inhibit the rise in P_{TxB_2} which accompanied the marked increase in blood pressure in response to the venom. Activation of renin-angiotensin system may be responsible for the hypertensive effect of the venom since, in other study, angiotensin converting enzyme inhibitor has been shown to attenuate this effect[17]. The slight elevation of packed cell volume in both groups was presumably due to splenic contraction.[7] Although the renal blood flow and glomerular filtration rate were relatively unchanged after envenomation, it should be noted that urine flow rate was increased by approximately 15-65%, accompanied by an increase in urinary excretion of sodium, chloride, potassium and thromboxane B_2 as well. They could be accounted for by a direct tubular dysfunction since thromboxane B_2, like uric acid, is actively reabsorbed from the proximal tubule.[8]

Recently it has been reported that Russell's viper venom induced depolarization of the proximal tubular cell possibly by 3 mechanisms. [19] It has been proposed that the failure of the proximal tubular reabsorption of sodium giving rise to a sodium overload in the distal tubular urine can induce the secretion of renin by the macula densa.[20] The activation of angiotensin could induce a decrease in the renal blood flow and cortical ischemia followed by a decrease in glomerular filtration rate. The reduction in renal blood flow may be modulated by the production of vasodilatory prostaglandins, PGI_2 and PGE_2, in the kidney.[21] We did not detect any production of PGI_2 and PGE_2 but clearly observed a decreased renal blood flow and glomerular filtration rate in response to Russell's viper venom after inhibition of prostaglandin synthesis by indomethacin. The activation of renin-angiotensin system could likely account for this. Our result may have reflected the role of angiotensin II on prostaglandin production which McGiff et al[22] were the first to demonstrate and was subsequently confirmed by many investigators.[21,23,24] Urine flow rate changes similar to renal blood flow and glomerular filtration rate during the first 20 min of envenomation then rose despite the decrease in renal blood flow and glomerular filtration rate. Urinary excretion of sodium, chloride and potassium seemed to have decreased relatively less than the decrease in glomerular filtration rate and therefore the fractional excretion of sodium, chloride and potassium were increased. This result suggested that the inhibition of tubular reabsorption of sodium presumably occurred at sites proximal to the distal nephron thus a definite amount of sodium reached this part of the nephron and a small amount under reabsorption in exchange to potassium. Aldosterone, responsible for sodium reabsorption in the distal nephron, may be increased primarily due to the increase in angiotensin II. The correlation between plasma aldosterone concentration and plasma renin activity has been described by Zadik and Kowarski,[25] that the decrease in plasma renin activity is most likely the primary cause of the lower plasma aldosterone concentration; possibly, the opposite may be true. Elevated level of NAG probably indicated the evidence of renal injury corresponding to other types of renal disease or injury previously reported.[26,27] The measurement of AAP, γ-GT or β-GAL appeared on the contrary, to have had little significance. In summary, Russell's viper venom at this dose may directly alter the active reabsorption in the tubular cells. Elevation of P_{TxB_2} and U_{TxB_2} indicated the augmentation of synthesis and/or alteration of tubular reabsorption. Activation of the renin-angiotensin system seemed to have been responsible for the decrease in the renal blood flow and glomerular filtration rate. Experimental data on plasma renin activity changes should be worked out. It remains to be determined whether the levels of prostacycline (PGI_2), PGE_2 and aldosterone are changed and if so, what role they may eventually play in renal hemodynamic changes. Renal histological changes should be performed in accompaniment with a study on urinary enzymes.

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