

The acute effect of Russell's viper venom on renal functions in rats.

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The renal functions following intraperitoneal injection of 1 mg. per kg. B.W. of Russell's viper venom have been investigated in Wistar rats. Rats were anesthetized with inactin 120 mg. per kg. B.W. intraperitoneally. Arterial blood and urine samples were collected every 30 minutes for three hours following venom injection. After venom injection, the mean arterial pressure (MAP), glomerular filtration rate (GFR) and urine flow rate (UF) declined proportionally, but were followed by a small return. After the second hour, MAP maintained a slight decrease, while GFR and UF gradually decreased until the end of the experiment. The increment of the fractional excretion of sodium (FE.Na) was significant during the second hour, whereas that of potassium (FE.K) rose slightly. These data may indicate that the venom has some important effects in reducing renal functions, both by direct and indirect means, although more detailed mechanisms need to be further investigated.

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ฉีดพิษงูแมวเซาด้วยขนาด 1 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม เข้าทางช่องท้องของหนูขาว 12 ตัว ที่ทำให้สลบด้วยอินแอคตินขนาด 120 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม และศึกษาการทำงานของไตตลอดระยะเวลา 3 ชั่วโมง ภายหลังจากฉีดพิษงู เก็บตัวอย่างเลือดและวัดความดันโลหิตทางหลอดเลือดแดงฟิมอร์ซ้าย เก็บปัสสาวะทางกระเพาะปัสสาวะผ่านหน้าห้อง วัดอัตราการกรองของไตโดยอาศัยอินนูลิน ทันทีทันใดหลังจากฉีดพิษงูพบว่า ความดันโลหิต อัตราการกรองของไต และการขับถ่ายปัสสาวะลดลงเป็นสัดส่วนกัน หลังจากนั้นจะค่อย ๆ เพิ่มขึ้นแต่ไม่ถึงระดับปกติ ภายหลังจาก 2 ชั่วโมงพบว่า ความดันโลหิตลดต่ำลงและค่อนข้างคงที่ในขณะที่อัตราการกรองของไต และการขับถ่ายปัสสาวะลดลงเรื่อย ๆ จนสิ้นสุดการทดลอง ในขณะเดียวกัน อัตราการขับถ่ายต่ออัตราการกรองของไตเพิ่มขึ้นและไปทดสอบสูงขึ้นในชั่วโมงที่สอง หลังจากนั้นจะกลับลดลงอีกเล็กน้อย แต่ยังคงสูงอยู่ จากการทดลองนี้ชี้ให้เห็นได้ว่า พิษงูแมวเซาน่าจะมีผลโดยตรงต่อไต ทำให้การดูดซึมโซเดียมและน้ำกลับได้ลดลงเมื่อเทียบกับอัตราการกรองของไต อย่างไรก็ตามผลทางอ้อมของพิษต่อระบบไหลเวียนเลือดก่อนที่ จะทำให้การทำงานของไตลดลงก็อาจจะมีร่วมไปด้วย เพื่อจะอธิบายให้ชัดเจนจำเป็นต้องทำการศึกษาต่อไปอีก

Acute renal failure is an important complication in patients who survive the early effects of severe viper envenomation.⁽¹⁻⁴⁾ Clinical observations have demonstrated hematuria, oliguria, anuria, hematemesis, decreased platelets and increased fibrinolytic activity.⁽²⁻⁴⁾ No correlation between severity of renal failure and hemostatic abnormality was shown.⁽³⁾ Tubular ischemia or intravascular hemolysis might result in tubular necrosis and subsequent renal failure.⁽⁴⁾

Many investigators believed that the snake venom might have some direct cytotoxic effect on renal tubular cells,⁽⁵⁻⁷⁾ presumably by the very high concentration in the kidneys.⁽⁸⁾ Recent work was conducted by Huei-chen Huang in 1984,⁽⁹⁾ using phospholipase A₂ isolated from Russell's viper venom.⁽¹⁰⁾ He postulated that the hypotensive effect in rats was probably due to the increase in plasma prostacyclin and thromboxane A₂ levels. He also found the reduction in plasma renin activity.⁽¹¹⁾ The obstruction of glomerular capillaries by coagulated material could also reduce the blood supply to the tubules. Intravascular clotting can enhance intravascular hemolysis and vice versa,⁽¹²⁻¹³⁾ creating a vicious cycle which accentuates the severity of renal failure.⁽⁴⁾ Acute renal failure could be caused by direct effect of venom on vasculature. Arteritis has been observed. The narrowing of vascular lumen could accelerate intravascular coagulation leading to acute renal failure.⁽¹⁴⁾

The effect of Russell's viper venom on renal function has been demonstrated extensively in patients some days following envenomation. Very little has been reported from animal models, especially during the earlier period. This study addressed the role of venom on glomerular filtration rate, urine flow and arterial pressure as well as the fractional excretion of sodium and potassium during the first three hours after venom injection.

Materials and Methods

Experiments were performed on 12 Wistar rats, anesthetized with inactin intraperitoneally, 120 milligram per kilogram body weight. Tracheostomy was performed and the animals were allowed to breathe room air spontaneously. A jugular vein catheter was introduced for administration of 1 percent inulin in Tris-Ringer solution at the rate of approximately 20 milliliters per kilogram per hour. Left femoral artery was isolated and catheterized to record the systemic pressure and collect blood samples. Urine flow rate was measured via bladder catheter.

A period of 45 minutes was allowed to elapse for the stabilization of plasma inulin concentration and general conditions, after which two or three timed collections of urine were taken along with arterial blood samples at the midpoint of each urine collection. The venom was injected at the dosage of 1 milligram per kilogram body weight intraperitoneally. Blood and urine samples were taken every thirty minutes for three hours after venom injection.

At the end of the experiment, both kidneys were excised, stripped of surrounding fat and tissue, blotted dry and weighed. The glomerular filtration rate and urine flow rate were expressed as microliters per minute per gram kidney weight.

Routine measurements of sodium and potassium concentrations in plasma and urine were determined by flame photometry. Plasma and urine inulin concentrations were detected by an anthrone colorimetric technique. The results were shown as the value of mean \pm S.D. The differences were analyzed by the Student's paired t-test.

The Effect of Russell's Viper Venom on Mean Arterial Pressure (MAP), Glomerular Filtration Rate (GFR) and Urine Flow Rate (UF) on Rats (Mean \pm S.D.)

Time (hour)	0	0.5	1.0	1.5	2.0	2.5	3.0
MAP (mm. Hg)	104.50 \pm 6.08	82.00 \pm 7.28 P < .001	88.50 \pm 8.80 P < .001	83.00 \pm 9.98 P < .010	97.50 \pm 9.87 P < .025	87.50 \pm 11.29 P < .005	87.00 \pm 13.21 P < .005
GFR (μ l / min - gm. kidney weight)	104.83 \pm 14.71	76.17 \pm 13.06 P < .001	80.17 \pm 15.21 P < .001	87.92 \pm 19.26 NS	79.92 \pm 13.79 P < .025	72.50 \pm 10.28 P < .001	65.33 \pm 11.53 P < .001
UF (μ l / min - gm. kidney weight)	23.37 \pm 7.84	7.68 \pm 7.43 P < .010	6.82 \pm 6.49 P < .005	8.20 \pm 5.23 P < .010	8.25 \pm 3.83 P < .005	6.81 \pm 3.49 P < .001	5.52 \pm 3.33 P < .001

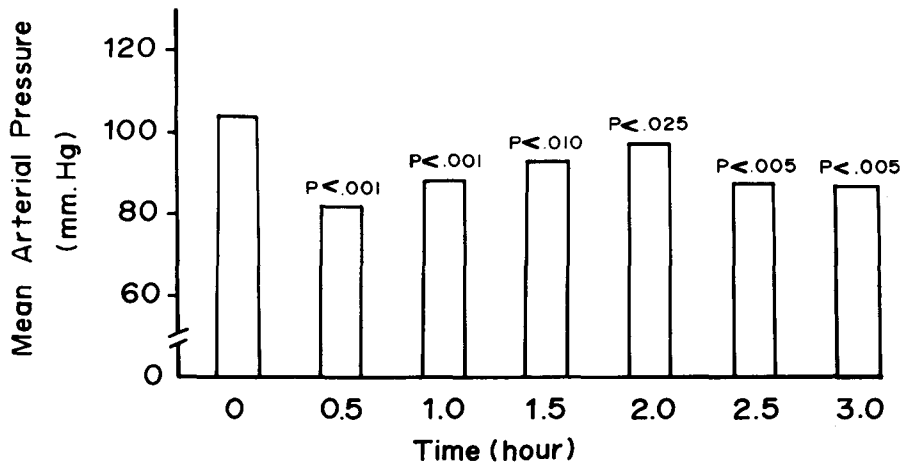


Figure 1 The Effect of Russell's Viper Venom on Mean Arterial Pressure

Results

As illustrated in table and figure 1, following the injection of Russell's viper venom 1 mg per kg body weight intraperitoneally, the mean arterial pressure (MAP) decreased gradually. The MAP decreased from 104.50 ± 6.08 to 82.00 ± 7.28 mm.Hg ($p < .001$) in 30 minutes, and then returned to 97.50 ± 9.87 mm.Hg by the end of the second hour. The decrement in MAP was about 20-30 percent of control value. After 2 hours, it fell again and was maintained at about 87.00 ± 13.21 mm.Hg. The decrement of MAP was statistically significant when compared with that of the control period.

The decrement of glomerular filtration rate (GFR) was seen at 30 minutes following venom injection. GFR dropped from the control value of 104.83 ± 14.71 to 76.17 ± 13.05 microliter per minute per gram kidney weight ($p < .001$). As demonstrated in the table and figure 2, after 30 minutes, GFR increased to 87.92 ± 19.26 microliter per minute per gram kidney weight. The increase was not statistically significant when compared with the control. After one and a half hour, GFR decreased gradually until the end of the experimental period.

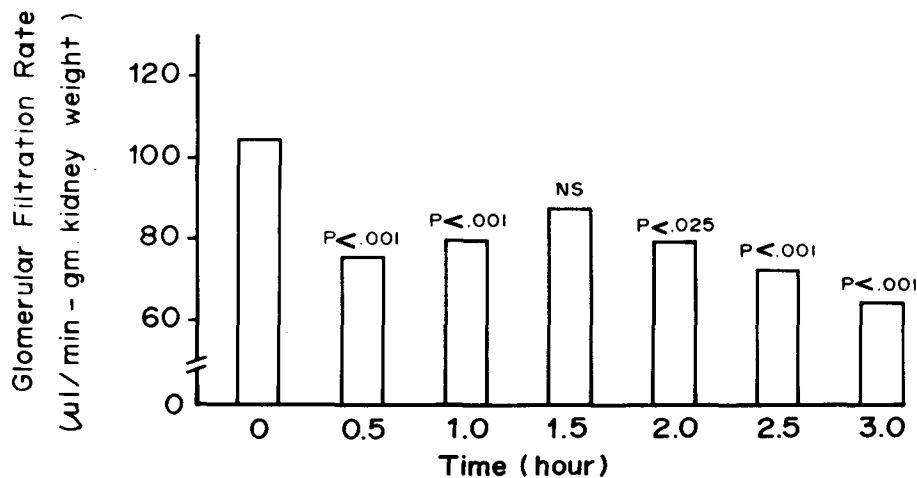


Figure 2 The Effect of Russell's Viper Venom on Glomerular Filtration Rate

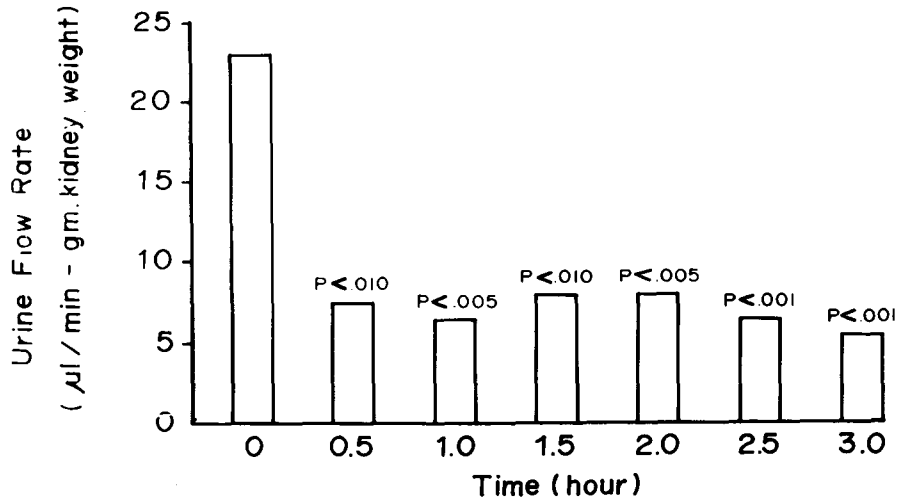


Figure 3 The Effect of Russell's Viper Venom on Urine Flow Rate

The urine flow rate (UF) decreased immediately after venom injection from 23.37 ± 7.84 to 7.68 ± 7.43 and lasted until the end of the first hour (figure 3). During the second hour, UF increased from 6.82 ± 6.49 to 8.25 ± 3.83 microliter per minute per gram kidney weight. However, after 2 hours, UF fell continuously throughout the experimental period as shown in table and figure 3.

Figure 4 and 5 demonstrate the changes of fractional excretion of sodium (FE.Na) and potassium (FE.K) following venom injection. The FE. Na rose significantly during the second hour ($p < .025$), whereas the FE.K increased slightly. After 2 hours, the fractional excretion of both electrolytes showed a small decline.

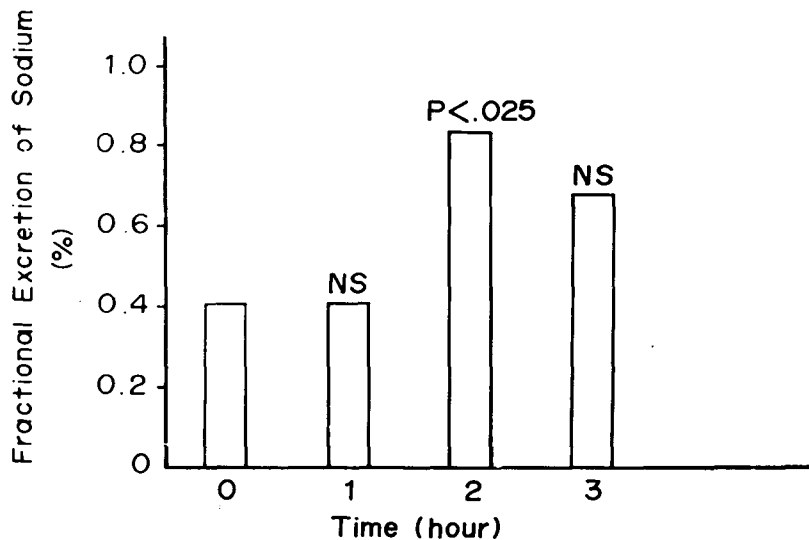


Figure 4 The Effect of Russell's Viper Venom on Fractional Excretion of Sodium

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