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Mechanisms of Russell's Viper Venom Toxicity on Renal Function; Reversal by Antivenom

Narongsak Chaiyabutr[1,*], Sophon Napathorn[2] and Visith Sitprija[3]

[1]*Department of Physiology, Faculty of Veterinary Science;* [2]*Faculty of Medicine, Chulalongkorn University, Queen Saovabha Memorial Institute,* [3]*Thai Red Cross, Bangkok, Thailand*

ABSTRACT : *Envenoming by Russells viper causes a broad spectrum of renal impairment. Renal failure is an important complication in patients bitten by Russells viper. Experimental work in animals and in vitro has elucidated pathophysiological mechanisms that contribute to life threatening complications and have suggested possibilities for therapeutic intervention. The evidence in experimental animals regarding mechanisms of venom action in relation to changes in either extrarenal or intrarenal factors is presented. The cardiovascular system and renal hemodynamics are affected by venom. Reductions of renal function including renal hemodynamics are associated directly with changes in general circulation during envenomation. Possible endogenous mechanisms for releasing the hormone inducing renal vasoconstriction after envenomation are evident. Hormonal factor such as the catecholamine, prostaglandin and renin angiotensin systems induce these changes. Direct nephrotoxicity of venom action is studied in the isolated perfused kidney. Characteristic polarization of the cell membrane, changes of mitochondrial activity and Na-K ATPase in renal tubular cells are observed. Changes in renal function and the cardiovascular system are observed after envenomation and are reversed by the administration of Russells viper antivenom (purified equine immunoglobulin, Fab_2 fragment). The neutralizing effects are more efficient when the intravenous injection of antivenom is given within 30 min after the envenomation.*

Key Words : *Russell's viper, Renal function, Antivenom*

I. INTRODUCTION

The kidney is the target of the toxic effect of Russells viper venom (RVV) and renal failure is the most important complication in patients bitten by Russells viper (*Daboia russelli*). A broad spectrum of renal involvement following snake envenomation has been reported (Sitprija and Chaiyabutr, 1999; Sitprija and Boonpuckvanich, 1977; Soe-Soe *et al.*, 1990). The mechanism of how RVV toxicity affects renal function remains unclear, although changes of renal function after envenoming have been shown to involve multiple factors relating either to indirect or direct effects of the venom (Sitprija *et al.*, 1987; Chaiyabutr and Sitprija, 1999). The role of venoms has been explained for the cause of impairment of renal hemodynamics during envenomation in the experimental animals. Extrarenal factors, for example, the dysfunction in the cardiovascular system during envenomation, can affect renal hemodynamics (Chaiyabutr and Sitprija, 1999). Other changes of extrarenal factors can affect renal hemodynamics. Hormonal factors such as catecholamine, prostaglandins and the renin-angiotensin system also affect the local renal vasoconstriction.

The clinical features of envenoming from snake bites are explained by the direct action of the venom components on body tissues. The nonspecific effects of the venom, including hypotension, intravascular hemolysis, disseminated intravascular coagulation (DIC), hemoglobinuria and shock, are noted. It is generally accepted that antivenoms are most effective when administered early as quickly as possible after a snake bite. Equine immunoglobulin preparations with antivenom activity have been produced in the Queen Saovabha Memorial Institute (QSMI), and are used throughout the Indochina region for the treatment of Russells viper poisoning. Traditionally, the efficacy of antivenoms has been tested only against the lethal effect of venom; however, a study of the pathophysiological effects of RVV has been reported, particularly on renal function relating to changes in

*To whom correspondence should be addressed

either extrarenal or intrarenal factors (Chaiyabutr and Sitprija, 1999). Thus, an understanding of the mechanisms of actions of venom and antivenom is necessary in order to optimize the parameters of antivenom administration. The effects of antivenom administration have been studied in the experimental model of envenoming dogs in order to assess the appropriate time for neutralizing the RVV effect on the function of the kidneys which are considered to be its sites of action. A review of these studies is presented here.

II. RUSSELL'S VIPER VENOM COMPONENTS AND COAGULOPATHY

RVV consists of both inorganic component composing of C, H, N, S and O (Ganguly and Malkana, 1935) and organic component of lipid, carbohydrate, amino acid, nucleoside, nucleotide and organic phosphate (Iwanaga and Suzuki, 1979). It also contains many enzymes, including phosphodiesterases, ATPase, hyaluronidase and several isoenzymes of phospholipase A_2 (PLA_2) (Salach *et al.*, 1971). The venom has been separated by means of Sephadex G-75 column chromatography into five fractions (Huang and Lee, 1984). PLA_2 activity has been shown to be concentrated in fractions II and III. Pharmacological effects of PLA_2 in the venom include hypotension (Ho and Lee, 1981), neurotoxicity (Lee and Ho, 1982), local capillary damage and tissue necrosis (Suzuki and Iwanaga, 1970) and anticoagulant action (Boffa *et al.*, 1982). RVV also has hemorrhagin, inducing blood vessel wall damage and bleeding. A persistent incoagulable blood condition occurs about 24 h after RVV administration in experimental animals (Chaiyabutr, unpublished data). The test for coagulopathy has been performed in envenomated animals with intramuscular injection of RVV (1 mg/kg·bw.). The neutralizing ability of antivenom on the action of RVV was also examined. The study was carried out using either extrinsic coagulation pathway by partial thromboplastin time (PTT) or the intrinsic coagulation pathway by prothrombin time (PT). An increase of both PTT and PT was sustained throughout the period of study after giving venom alone (Fig. 1). However, a marked increase in thrombin time (TT) was evident in the first hour after envenomation, suggestive of fibrinolysis and disseminated intravascular coagulation. Markedly prolonged PTT, PT and TT could be reversible in response to antivenom administration when it was given intravenously and immediately.

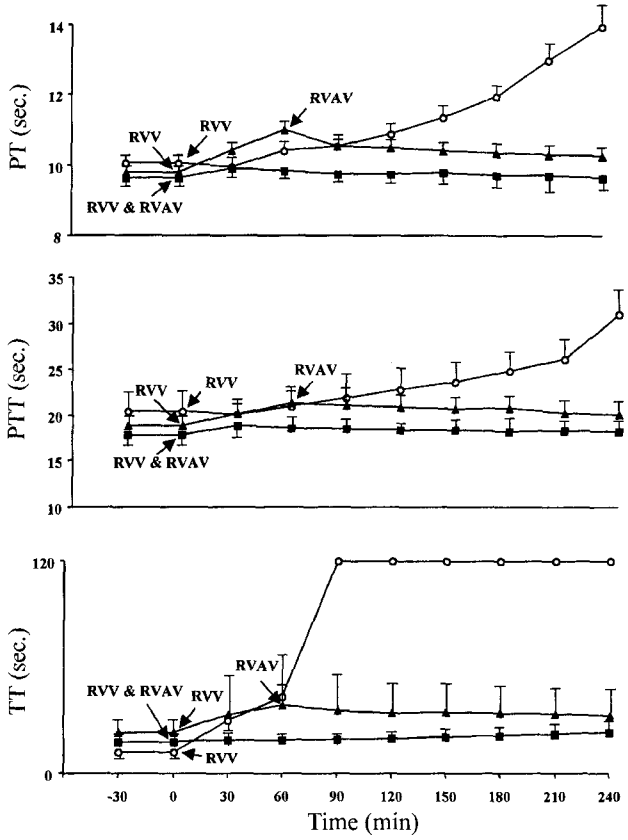

Fig. 1. Effects of antivenom (RVAV) administration on prothrombin time (PT), partial thromboplastin time (PTT) and thrombin time (TT) in experimental animals given Russell's viper venom (RVV). Each curve represents the average (mean±S.E.) obtained from four experimental dogs. Circles, venom alone (1 mg/kg intramuscular injection); squares, venom plus antivenom (20 ml of RVAV intravenous injection which neutralized 10 mg of venom); triangles, venom plus subsequent injection of antivenom.

The effect of Russell's viper antivenom administration on the plasma concentration of RVV in envenomated animals was also examined (Fig. 2). During envenomation, markedly increased levels of circulatory venom were seen in experimental animals. The curve for elimination of RVV from plasma was noted after intravenous injection of antivenom into dogs. The plasma venom concentration, based on ELISA, was apparent at a high level 30 min after intramuscular injection of RVV (1 mg/kg·bw.) but envenomated animals showed a low level of circulatory venom after

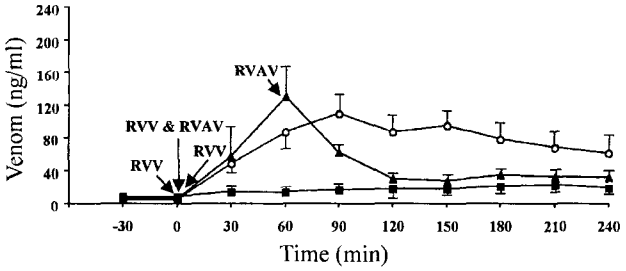

Fig. 2. Effects of antivenom (RVAV) administration on plasma distribution of venom in experimentally envenomated (RVV) dogs. Each curve represents the average (mean±S.E.) obtained from four experimental dogs. Circles, venom alone (1 mg/kg intramuscular injection); squares, venom plus antivenom (20 m*l* of RVAV intravenous injection which neutralized 10 mg of venom); triangles, venom plus subsequent injection of antivenom.

antivenom (purified equine immunoglobulin, Fab_2 fragment 10 mg/dog) was given intravenously and immediately. It can follow from these results that when a neutralizing dose of antivenom is injected intravenously after envenomation, the level of circulating venom is cleared from the circulation after 1 h of administration. In order to speed up neutralization of the venom, the dose of antivenom should be higher than the neutralization dose.

III. CARDIOVASCULAR EFFECTS

It is known that changes in general circulation can affect renal blood flow. A number of studies have been carried out to elucidate the mechanism responsible for impairment of renal function during envenomation. After acute intravenous injection of the minimal lethal dose of 0.1 mg/kg of RVV in anesthetized mongrel dogs, two phases of changes in the cardiovascular system have been observed (Tungthanathanich *et al.*, 1986). During the initial postinjection period, the mean arterial blood pressure and heart rate decreased while total peripheral resistance and renal vascular resistance increased. The decreases in blood pressure and heart rate are sustained for 30 min and return to normal levels within 2 h after venom injection. The pattern of these changes in the first phase is similar to that observed in rats (Chaiyabutr *et al.*, 1985a) and in experimental dogs given either intravenous injection (Chaiyabutr *et al.*, 1996) or intramuscular injection of RVV (Fig. 3). The initial decrease in mean arterial blood pressure during the first phase has

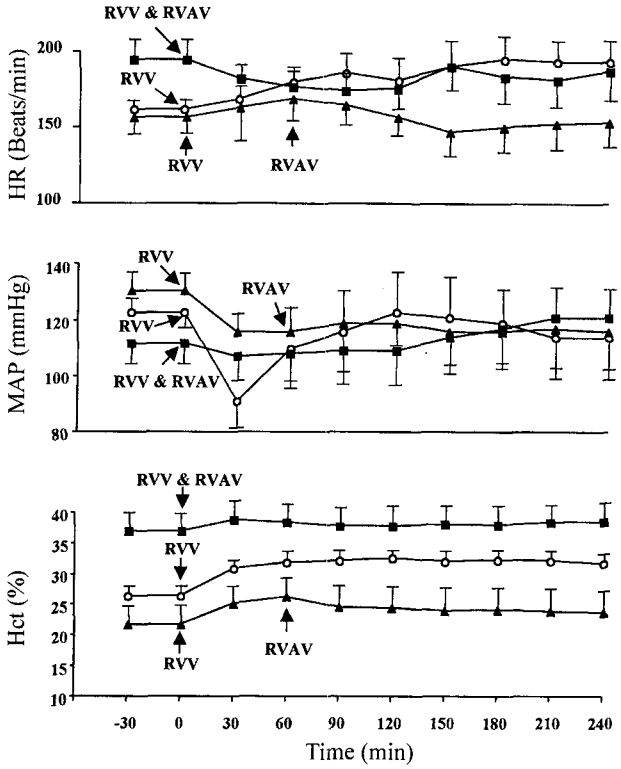

Fig. 3. Effects of antivenom (RVAV) administration on heart rate (HR), mean±S.E.) obtained from four experimental dogs. Circles, venom alone (1 mg/kg intramuscular injection); squares, venom plus antivenom (20 m*l*, of RVAV intravenous injection which neutralized 10 mg of venom); triangles, venom plus subsequent injection of antivenom.

been found not to be due to cholinergic in origin, since atropinization in experimental dogs does not prevent initial hypotension after intravenous injection of venom (Chaiyabutr *et al.*, 1996). The hypotension has been attributed to vasodilatation of capillaries in the hepato-splanchnic area and this was prevented by evisceration (Vick *et al.*, 1967). However, this conclusion may not give a complete explanation, since in dogs either splenectomy (Tongvongchai, 1984) or intravascular volume expansion with dextran solution and a marked decrease in blood pressure and cardiac output are still apparent after envenomation (Chaiyasest *et al.*, unpublished data). This indicates that the spleen is not the major contributor to the total blood volume shifts caused by the effect of the venom. Other organs and/or the venous vascular bed may play an important role (Shoukas *et al.*, 1981).

The release of substances or hormones, e.g., kinin (Oshima *et al.*, 1969), by the effect of venoms may be responsible. There is also evidence, obtained by

Huang and Lee (1984), that most phosphalipase A_2 (PLA_2) subfractions of the venom had hypotensive actions in rats given 0.1 mg/kg intravenously. Huang (1984a) suggested that PLA_2 fractions in the venom released thromboxane A_2 (TXA_2), prostacycline (PGI_2) and histamine from the perfused guinea-pig lungs, which might cause vasodilation in the periphery, combined with pulmonary vasoconstriction and restriction of blood return to the heart, leading to a decrease in cardiac output and inducing greater hypotensive effects.

In experimental animals, the second phase of bodily response is apparent during 2 h after envenomation. The cardiac output increases, total peripheral resistance decreases and mean arterial blood pressure are restored to normal levels (Tungthanathanich *et al.*, 1986). Restoration of blood pressure following the transient decrease after envenomation has been explained by a release of catecholamine as a compensatory mechanism (Chaiyabutr *et al.*, 1996). Therefore, at the later stage an increase in systemic vascular resistance and packed cell volume are observed. Failure to compensate would lead to death (Chaiyabutr *et al.*, 1984). It would appear that the changes in cardiovascular system in this period are not only induced by catecholamine release but also by other hormones. An increase in the renin-angiotensin activity is believed to be the main mechanism since the study in rats by Chaiyabutr and co-workers (1985a) demonstrated that when the formation of angiotensin II was blocked by a converting enzyme inhibitor (MK-422, enalapril maleate) in either pre- or post-envenomation, the systemic blood pressure decreased without a compensatory mechanism. An elevation of plasma renin activity in victims of Russells viper bite is also noted (Tin-Nu-Swe *et al.*, 1993).

Fig. 3 shows the efficacy of antivenom administration in eliminating signs of circulatory dysfunction in envenoming animals. Antivenom (purified equine immunoglobulin, Fab_2 fragment) was used to neutralize both circulating venom and venom that is being absorbed from the site of injection into the circulation during the period of 4 h after envenomation. The findings of hypotension, changes in heart rate and hematocrit manifestation were not apparent throughout the period of 4 h when antivenom was given intravenously immediately after the envenomation.

IV. RENAL HEMODYNAMIC EFFECTS

A number of studies have proven a relationship between renal hemodynamics and the cardiovascular system after administration of RVV. The effect of RVV on renal hemodynamics has been studied in experimental dogs (Chaiyabutr *et al.*, 1984; Tongvongchai, 1984; Tungthanathanich *et al.*, 1986). RVV causes a marked decrease in general circulation and renal hemodynamics during the initial venom administration. Thereafter the blood pressure and heart rate gradually increase and approach the control level within 2 hours. However, the rate of renal blood flow (RBF), glomerular filtration rate (GFR) and renal fraction (% cardiac output) decrease throughout the period of 2 to 48 hours after application of RVV (Chaiyabutr and Sitprija, 1999). This is due to local vasoconstriction in the kidney which is associated with an increase in renal vascular resistance.

According to current concepts, renal circulation is regulated by two hormonal systems: vasoconstriction is mediated by norepinephrine and/or the renin-angiotensin system, while prostaglandin compounds and the kallikrein-kinin system act as vasodilators. The mechanisms of renal hormonal interactions involved in intrarenal vasoconstriction are probably complex. During envenomation, the increase in plasma levels of both the vasodilator and vasoconstrictor have been shown to be critical to systemic and renal hemodynamics (Thamaree *et al.*, 2000). Direct evidence for the involvement of renin-angiotensin activity in response to renal vasoconstriction after envenomation has been obtained both in envenomated animals (Chaiyabutr *et al.*, 1985a) and in victims of Russell's viper bites (Tin-Nu-Swe *et al.*, 1993). The changes of renal hemodynamics in venom pretreated rats are reversible with intrarenal A_{II} blockade [Enalapril maleate (MK-422)]. Of interest is a study by Thamaree *et al.* (1994) which demonstrated renal vasodilatation when the venom was directly injected into the renal artery. Pretreatment of animals with indomethacin, an inhibitor of prostaglandin synthesis, alleviated this hemodynamic effect. This phenomenon may be important in the study of the effect of RVV. A possible endogenous mechanism for releasing the hormone inducing vasoconstriction after envenomation may be the lack of dilatory prostaglandins

(e.g., PGE_2) and/or overproduction of thromboxane A_2 (TXA_2), a powerful renal vasoconstrictor (Gerber *et al.*, 1978). However, according to experimental data by Chaiyabutr *et al.* (1985a), an increase in renal vascular resistance and decrease in renal blood flow in rats given RVV has been also shown to be mediated through renin-angiotensin system activation. Whether an activation of the renin-angiotensin system is mediated indirectly through the action of catecholamine (Vander, 1965) or prostaglandins (Werning *et al.*, 1971) remains to be defined. Furthermore, catecholamine can activate the renin-angiotnsin system as confirmed by the increase in plasma renin activity (Huang 1984b). Recent studies have demonstrated that several hormonal interactions among catecholamines, the prostaglandin system and the renin-angiotensin system are involved in modulating a number of changes in renal function after envenomation. Among these mediators catecholamines appears to be most crucial in compromising renal hemodynamics. Its blockade (prazosin) offers the most protective effects on the renal circulation in snake envenomation (Chaiyabutr *et al.*, 1996).

The effects of the venom on renal hemodynamics are likely to be complex. The mechanism for the release of mediators during envenomation seems to involve inactivation of the calcium ion. The role of calcium on bodily functions, including enhancement of the release of catecholamines from the adrenal medulla and renal nerves, has been extensively reviewed (Rubin, 1970; Kotchen and Roy, 1983). Prolonged calcium depletion prevents stimulation of renin release by catecholamine (Lester and Rubin, 1977). Apart from its stimulation of the hormonal secretion, the rise in intracellular calcium can activate the contractile mechanism of the blood vessel and would lead to an enhanced vasoconstriction. Furthermore, it has been shown that hypocalcemia in parathyroidectomized rats can prevent renal dysfunction from toxic substances (Tomford *et al.*, 1981). The severity of impairment of renal hemodynamics after envenomation seems to be alleviated in hypocalcemic animals due to parathyroidectomy. After RVV administration in parathyroidectomized dogs, patterns of changes in blood pressure and heart rate are similar to those in control animals after administering the venom (Buranakarl and Chaiyabutr, 1990). However, decreases in GFR and RPF with a concomitant increase in renal vascular resistance in parathyroid dogs during initial postinjection of RVV have been shown to be lower than in control animals. This is contrary to the case of animals pretreated with verapamil (voltage dependent calcium channel blocker), which show further aggravation. The GFR and RBF of animals pretreated with verapamil have been shown to decrease to a greater extent in comparison with both parathyroid-intact animals and parathyroidectomized animals after envenomation. Elevation of parathyroid hormone (PTH) of normal animals is expected after envenomation, which coincides with an increase in plasma inorganic phosphorus.

Figs. 4 and 5 show experimental results in dogs for the protective role of Russells viper antivenom (purified immunoglobulin) on renal hemodynamics. Sig-

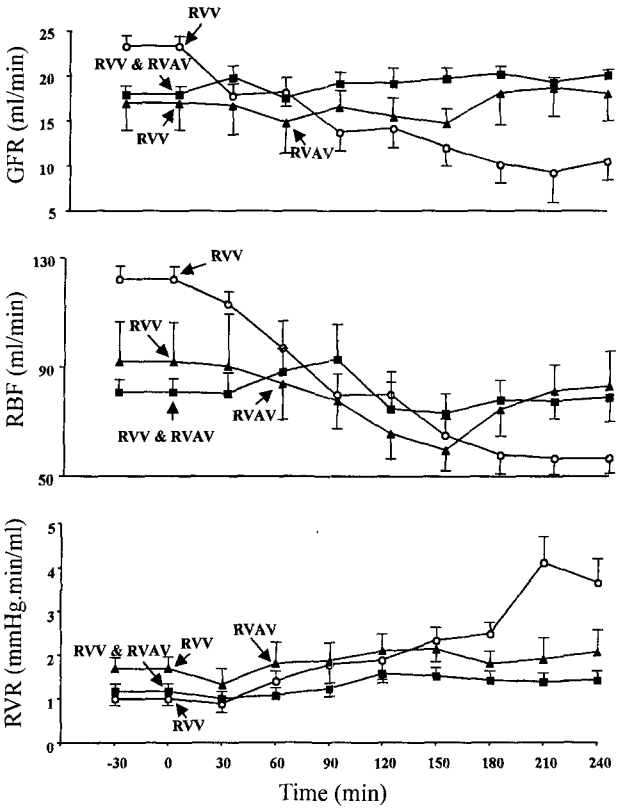

Fig. 4. Effects of antivenom (RVAV) administration of glomerular filtration rate (GFR), renal blood flow (RBF) and renal vascular resistance (RVR) in experimental animals given Russell's viper venom (RVV). Each curve represents the average (mean±S.E.) obtained from four experimental dogs. Circles, venom alone (1 mg/kg intramuscular injection); squares, venom plus antivenom (20 ml of RVAV intravenous injection which neutralized 10 mg of venom); triangles, venom plus subsequent injection of antivenom.

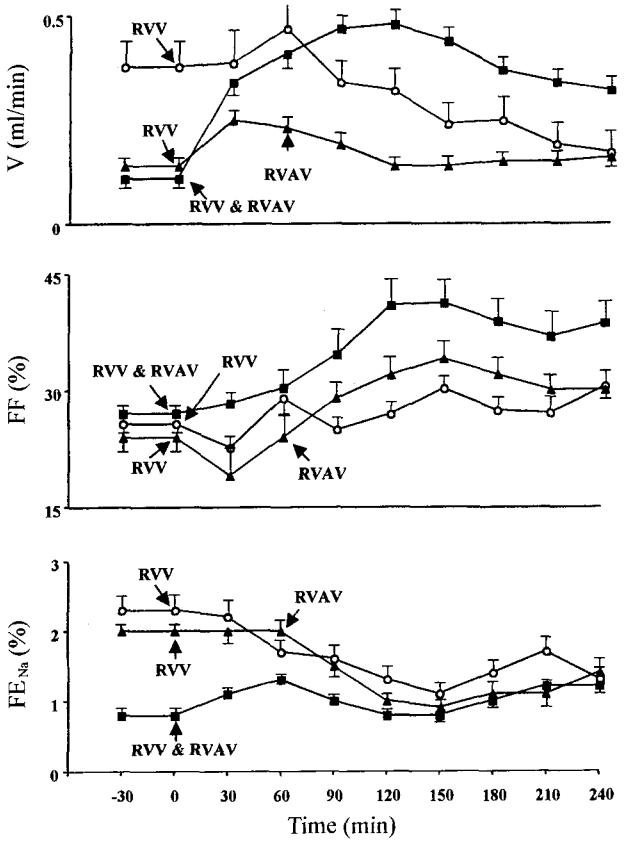

Fig. 5. Effects of antivenom (RVAV) administration on rate of urine flow (V), filtration fraction (FF) and fractional excretion of sodium (FE_{Na}) in experimental animals given Russell's viper venom (RVV). Each curve represents the average (mean±S.E.) obtained from four experimental dogs. Circles, venom alone (1 mg/kg intramuscular injection which neutralized 10 mg of venom); triangles, venom plus subsequent injection of antivenom.

nificant decreases in GFR (using inulin clearance), RBF and RPF (using PAH clearance) and urine flow along with increase in renal vascular resistance were apparent at 30 min after the intramuscular injection of RVV (1 mg/kg·bw.) alone. During envenomation alone, decreases in both GFR and RPF were apparent in proportion. Thus the ratio of the two, the filtration fraction, generally remain unchanged, indicating a predominant increase in afferent vessel resistance during envenomation. In a comparable study with administration of antivenom upon envenoming, no change in renal hemodynamics was noted. There were no significant changes in GFR, RBF and RVR in envenoming animals when antivenom was given immediately. These results indicated that fully reversible venom action could not depend only on the dose of antivenom for optimal efficacy, but rather also upon the appropriate time of administration of antivenom. However, an increase in both urine flow rate and filtration fraction in envenomated animals neutralized with RVAV are attributed to the elimination characteristics of the kidney for low-relative-molecular mass toxin-Fab complexes (Schermann and Pepin, 1996). The renal excretion of venom-Fab complexes also required further investigation for possible tubular reabsorption and re-circulation of free venom toxin molecules.

V. RENAL TUBULAR EFFECTS

It is known that the first place to search for direct nephrotoxic effects of the venom is in the renal tubules. Nephrotoxicity expresses itself as tubular cell damage, which leads to a reduction in electrolyte and water reabsorption, a loss of urinary concentrating power and polyuria. A number of reports of both *in vivo* and *in vitro* studies indicate the direct effect of RVV on renal function. The direct effects of venom in the isolated perfused rat kidney (IPRK) include a reduction of the glomerular filtration rate and a rise in fractional excretion of sodium, changes which depend on the dosage of venom (Ratcliffe *et al.*, 1989). A more detailed study of the toxic effect of venom on the IPRK by Willinger *et al.* (1995) showed reductions of renal perfusate flow and the glomerular filtration rate. The reduction of tubular reabsorption of sodium ions was apparent with an increase in fractional excretion of sodium (FE_{Na}) and water. The initial decrease in FE_{Na} in envenomated animals given RVV alone (Fig. 5) can probably be attributed to increased aldosterone and angiotensin activity secondary to hypotension. The urine flow rate showed both oliguric and polyuric phases during envenomation. A more detailed study by electron microscopy of perfusion IPRK revealed extensive glomerular destruction and lysis of vascular walls, and various degrees of epithelial injury occurred in all tubular segments. The direct effect of venom on renal tubules is also confirmed using micropuncture studies by measurement of the transmembrane potential in the proximal tubule of a Triturus kidney. The RVV causes depolarization in a dose-dependent manner, similar to the effect of 2-4 dinitrophenol, an inhibitor of Na-active transport (Chaiyabutr *et al.*, 1985b). This result indi-

cates that a direct physical interaction probably takes place between the venom and the composition in the cell membrane, which leads to a change in the characteristic polarization of the cell membrane or venom interacting directly with the specific site that controls the transport of ions across the cell membrane. It appears that RVV could affect the mitochondrial activity, the major part of cellular energy generations. Renal cortical mitochondrial oxygen consumption decreased while the P/O ratio increased when using succinate as a substrate after 40 h of envenomation (Julsukon *et al.*, 1995). Another study clearly supports this tubulotoxicity of RVV resulting from the inhibition of Na-K ATPase activity of renal tubular cells in both the renal cortex and medulla (Buranakarl *et al.*, 1997). Other evidence of renal damage by RVV is the rise in urinary N-acetyl-β-D-glucosaminidase (NAG), which is an index of renal tubular injury (Thamaree *et al.*, 1994).

RVV would directly affect most animal tissue including erythrocytes. The venom causes a marked increase in red blood cell volume *in vitro* (Chaiyabutr *et al.*, 1987). Changes in cell volume would be attributed to the action of venom phospholipase activity on the cell membrane. An *in vitro* study indicates that alteration of red cell volume is affected by venom in heparinized blood, but it does not appear in blood using a calcium chelating agent (e.g., K-EDTA) as an anticoagulant (Chaiyabutr, unpublished observations). This result suggests that the action of venom components, especially phospholipase A_2, on cell membrane would depend on the majority of the free calcium ions in the blood. The increase in red cell volume could increase blood viscosity leading to further decrease in renal blood flow. However, red cell volume is not affected by venom when a neutralizing dose of antivenom is injected intravenously and immediately (Fig. 3).

In conclusion, RVV clearly has both direct and indirect effects on the renal function. Experiments performed on the action of antivenom *in vivo* demonstrate that it has the optimal characteristics for efficacy. The impairment of renal functions has been shown to appear in coincidence with a high level of the plasma venom concentration at 30 min. after intramuscular injection of the venom in experimental animals. The severity of impairment of renal functions after envenomation could be alleviated by administration of the specific antivenom. The Russells viper antivenom (purified equine immunoglobulin, Fab_2 fragment) has a protective role against acute renal failure following Russells viper envenomation, when it is given immediately after the envenomation.

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