Chapter V

Discussion

The effect of intravenous injection of Russell's viper venom on general circulation in dogs pretreated with MK 422 and imidazole showed a transient fall in mean arterial blood pressure (MAP) while packed cell volume (PCV) significantly rose within 10 minutes (group I). These results are similar to previous studies (Tungthanathanic, 1983; Tongvonchai, 1984). A group of animals pretreated with intrarenal infusion of prazosin after the injection of MK 422 and imidazole showed an immediate fall of arterial blood pressure in 20 minues after envenomation. Progressive reduction in arterial blood pressure was significant longer than that of group I. However, no significant elevation of packed cell volume (PCV) was noted in group II.

The changes in mean arterial blood pressure and heart rate during the first 10 minutes period have been suggested to be due to the vasovagal effect (Chopra and Chowhan, 1934; Lee and Lee, 1979) which could be prevented by vagotomy (Lee and Lee, 1979). Vick and co-worker (1967) proposed that vasodilation and pooling of blood in the hepato-splanchnic area during envenomation and the hypotension were prevented by evisceration. The hypotension action of Russell's viper venom may partly be due to prostacyclin (PGI_2) release, cause vasodilation in the periphery along with the release of leukotriene and histamine from lungs, cause increase lung perfusion pressure, which induce greater hypotension effect (Huang 1984_a, 1984_b). In the present studies, the rise in mean arterial blood pressure following

the transient decrease after envenomation in group I may relate to catecholamines release as a compensatory mechanism. But the elevation in mean arterial blood pressure following transient decrease after envenomation in group II was delayed. These changes may be attributed to the action of prazosin, a selective α_1 -adrenergic receptor antagonist.

A marked increase in packed cell volume (PCV) in animals pretreated with MK 422 and imidazole (group I) were observed. The explanation for splenic contraction leading to the expulsion of sequestered red blood cell (RBC) may be responsible. It has been reported that an intravenous infusion of epinephrine also caused striking elevation in packed cell volume (PCV) in intact dogs whereas the rise in splenectomized animals were lower (Mandal et al., 1978). Therefore, the increase in packed cell volume (PCV) in the present study may be attributed to the contribution of adrenergic stimulation cause the spleen to squeeze red blood cell into circulation. These changes would be reversed by the actions of prazosin.

The effect of Russell's viper venom on renal hemodynamics in the present study (Fig 2-6) demonstrated that the venom produced a marked decrease in renal hemodynamics during the initial venom administration in both kidneys of group I. Although statistical analysis revealed no significant alteration in group I, mean renal vascular resistance showed an increased pattern. An increased renal vascular resistance are believed to contribute to the decrease in glomerular filtration rate and decreased renal plasma flow. A marked increase in renal vascular resistance (RVR) after envenomation in group I seems to be due to the vasoconstriction of the renal

arteriol during hypotension. The previous studies in rats indicated that an increase in renal vascular resistance was probably related to the action of endogenous angiotensin II (Chaiyabutr ed al., 1985). However, in the present study in pretreated dog with the combination of MK 422, imidazole and prazosin (group II) showed significant decrease in mean arterial blood pressure in the initial period while no significant changes in renal vascular resistance of both kidneys were noted. This might be that α_1 -adrenergic receptor was blocked by prazosin.

The previous studies have been shown that there are two discrete noradrenergic binding sites in the renal arteries of dogs which have binding properties expected of alpha 1 and alpha 2 adrenoceptors (Bobik, 1981). Norepinephrine (NE) released from an adrenergic vesicles produces vascular smooth muscle contraction by activation of postsynaptic junctional alpha 1 adrenoceptors. Postsynaptic extrajunctional α_2 -adrenoceptor, when activated by circulating catecholamines, also mediate vasoconstriction (William, 1984). These hypothesis may be applied to explain in the results of renal hemodynamics and renal vascular resistance in envenomated dogs pretreated with prazosin that renal hemodynamics and renal vascular resistance were not altered. However, renal blood flow and renal plasma flow significantly decreased in the first 20 minutes after envenomation of the left kidney which was infused by prazosin throughout the experiment. However, the decrease in glomerular filtration rate and the increase in renal vascular resistance showed no significant difference from the control period in the left kidney. This result may be due to a prolonged infusion of

prazosin which induced the accumulation of the drug to increase α_2 -adrenergic receptor function possibly extrajunctional vascular site (Jeffries et al., 1987). An additional consideration still to be excluded is the possiblity that stimulation of vasoconstrictor α_2 -receptor on the endothelium of renal blood vessels concomitantly released endothelium-derived relaxant factor (EDRF). Thus, it is possible that α_2 -agonists cause less or little vasoconstriction compared with that caused by α_1 -agonists (Strandhoy, 1985).

After envenomation in group I, tubular functions decreased significantly over 60 minutes period of the experiment. The significant decreases in $U_{Na}V$, FE_{Na}, $U_{Cl}V$ and FE_{Cl} were closely related to the decrease in filtered load (filtered load = GFRxP) following envenomation. It was confirmed by the finding that prazosin abolished this effect in group II. The fall in arterial pressure has been known to activate two major systems, the sympathetic nervous system and the juxtaglomerular apparatus (Sullivan, 1982). Alterations in adrenergic neural tone may influence sodium reabsorption and excretion by several pathways. Renal adrenergic nerves have been known to contact with the basement membranes of tubule cells. $Alpha_1$ adrenoceptor activation are probably responsible for the increased Na^+ reabsorption from the proximal tubule (Strandhoy, 1985). In contrast, an α_2 - adrenoceptor activation results in either net sodium and water retention or excretion, depending on the agent mediating the adrenylate cyclase activation. The distal tubular cAMP has been known to increase by vasopressin in the isolated perfused kidney, sodium and water retention. Concomitant α_2 -adrenoceptor activation with epinephrine reverses this effect (Pettinger, et al., 1987). In addition, the effect of Russell's viper venom on $U_{Na}V$, FE_{Na}, $U_{Cl}V$ and FE_{Cl} has been shown to decrease at

2 hours after envenomation (Tungthanathanich, 1983). Recently, it was suggested that Russell's viper venom may enhance cAMP production (Meerut, 1986). Therefore, if cAMP is increased by Russell's viper venom, concomitant α_2 -adrenoceptor activation with norepinephrin, it will reverse the effect of Russell's viper venom. Accordingly, both kidneys in group II which treated prazosin were not different.

Unlikely, urinary sodium excretion in both groups, urinary potassium excretion slightly increased throughout the experiment as compared with the control period in group I, whereas, significant increase was observed in group II after envenomation. This may be due to potassium secretion of distal tubule and collecting duct (Pitts, 1968). However, the decrease of glomerular filtration rate was not significant in group II.

The rate of urine flow was not different between group I and group II after envenomation and the rate of urine flow of both groups did not significant decrease from the control period of each group. However, anuria in the initial period of envenomation in group I was present. It be due to the hypotension and decrease in filtered load.

The present experiments show that changes in urine osmolality excretion associated with changes urine electrolyte excretion which is probably due to the decrease in filtered load in both groups. Free water tubular reabsorption significantly increased in group I but it was not apparent in group II after immediate envenomation. However, free water tubular reabsorption slightly decreased in the initial period following increase after envenomation which corresponding to the increase in osmolar clearance of both groups. These results suggest that the action of ADH is probably present in the last period of enveno-

mation. Changes in the urine to plasma concentration ratio (U_{osm}/P_{osm}) of osmolality in control period and envenomation period are not different of both groups (data is not shown). These results indicate that renal tubular activity of both groups of animals still have a normal functions of concentrating ability of the urine. Although renal failure could be due to hypovolemia, hypotension and disseminated intravascular coagulation leading to renal ischemia (Sitprija and Boonpucknavig, 1977), some clinical evidence suggests a direct tubulotoxicity of the venom (Chaiyabutr, ed al., 1985). In the present study, no direct effect of the venom on the tubular cell was observed. No evidence of acute renal failure was observed which may be due to an inadequate dose of venom administration and also too short observing period of the experiment.

In conclusion, the effects of Russell's viper venom which caused hypotension might stimulate sympathetic activity. The elevation in mean arterial blood pressure following transient decrease after envenomation in animals pretreated with MK 422 and imidazole (group I) was suspected to be due to the effect of catecholamine . The elevation in mean arterial blood pressure after envenomation was abolished by prazosin, α_1 -adrenergic receptor (group II). A marked increase in packed cell volume (PCV) after envenomation in group I without prazosin probably related to the splenic contraction during the elevation of catecholamine. This change was not apparent in group II.

The effects of Russell's viper venom produced a marked decrease in renal hemodynamics in both kidneys of group I which was related to a marked increase in renal vascular resistance. The

changes in renal tubular functions were closely related to the decrease in filtered load and hypotension following envenomation in group I. The action of prazosin can abolished these effects in group II.