Chapter V

Discussion

The results of the present study show that intravenous injection of Russell's viper venom caused a marked reduction of systemic and renal hemodynamics rapidly in the first five minutes of envenomation (Group I) The pattern of these changes are similar to the earlier experiments (Tungthanathanich , 1983 ; Chaiyabutr et al., 1984 Tongvongchai , 1984). The transient hypotensive action may be due to the release of prostacyclin (PGI_2) , cause peripheral vasodilation along with the release of leukotriene and histamines from lung, cause increase pulmonary perfusion pressure which restricts blood return to the heart leading to a decrease in cardiac output (Huang 1984_a , 1984_b) and these changes would be antagonized by indomethacin. In the present study , pretreatment of indomethacin in group IV demonstrates an alleviation of hypotensive effect as the earlier study which suggests that indomethacin may prevent hypotension by interfering of histamine release or inhibition of prostaglandin release (Tongvongchai , 1984).

A marked sustain rise of plasma norepinephrine level in the first 10 minutes after envenomation has been shown to dominate in control dogs (group I). This might be due to transient hypotension induced by Russell's viper venom activates sympathetic activity to release of norepinephrine as a compensatory mechanism (Hall and Hodge, 1971). causing increase in systemic vascular resistance and raise of blood pressure (Tungthanathanich et al ., 1984). Pretreated with prazosin (an α_1-adrenergic receptor antagonist) in animals of group II

revealed to completely inhibit norepinephrine level during envenomation throughout the experiment and caused a delay recovery in mean arterial pressure following transient hypotension. These changes might be attributed to the effects of Vipera russelli venom on the release of norepinephrine mediated by α_1-adrenergic receptor which reversed by prazosin without compensatory mechanism as the envenomated animals in group I. The delay of blood pressure recovery in this study was agree with previous experiment by intrarenal arterial infusion of prazosin before envenomation (Kidmungtangdee , 1989).

However , the release of circulating norepinephrine has been affected in animals either pretreatment of enalapril maleate (an angiotensin II blocker) or indomethacin (a prostaglandins inhibitor) respectively. The present experiment demonstrates that in the first 10 minutes , enalapril maleate showed a greater extent to lower plasma norepinephrine than prazosin while indomethacin showed to be a weaker blocker. The results suggested that enalapril maleate may inhibit A II formation which usually act on sympathetic nerve terminals to enhance neurotransmitter release (Duling , 1988) and the release of renin mediated by prostaglandins (Gerber et al ., 1981). It has been also reported in endotoxemic dogs that an immediate rise in angiotensin level and a latter variable rise in catecholamine level were noted. The early rise in circulating level of angiotensin in dogs suggested that the renin - angiotensin system may be more active in stress situations in dogs given endotoxin (Hall & Hodge , 1971) and these mechanism probably occur in dogs given Russell's viper venom in the present study.

A marked increase in packed cell volume associated with an

elevation of norepinephrine level relating to renal disturbance are demonstrated in envenomated animals (group I). It has been reported that intravenous infusion of epinephrine cause severe renal tubular necrosis in intact animal which elevates in packed cell volume and could be diminished by splenectomy (Mandal et al., 1978). The increase in packed cell volume would expect to increase in bloood viscosity by vasoconstriction which cause a reduction in renal plasma flow and renal blood flow (Nashat and Portal , 1967). However , the changes in norepinephrine level , packed cell volume and severity of changes in renal functions could not be determined in envenomated animals pretreated with prazosin , enalapril maleate or indomethacin (group II , III and IV). This might be other factors partly to involve in modulating of this phenomenon.

The changes of renal hemodynamics and blood pressure in the early phase of venom injection could be ascribed to increase level of angiotensin (Chaiyabutr et al., 1985). During hypotension , an activation of sympathetic nervous system via intrarenal baroreceptor to release renin might expect to occur and/or the sympathetic activation direct to stimulate juxtaglomerular cell to secrete renin which mediated by prostaglandins (Gerber et al ., 1981 ; Henrich , 1981). Therefore , an increase in renal vascular resistance in group I would be account for an increase in angiotensin II causing renal arterial vasoconstriction (Tungthanathanich et al ., 1984). the present study shows that angiotensin II blockage seemed to rapidly decline in renal vascular resistance and increase renal plasma flow , renal blood flow and glomerular filtration rate (group III) within 30 minutes following envenomation while α_1-adrenergic blocker (group II) has a beneficial effect to recover renal hemodynamics in the latter. Another possible explanation for renin

release in these findings is a direct nephrotoxic effect of Russell's viper venom on the renal vasculature , causing the generation of renin and leading to increase systemic angiotensin II level with a progressive decline in systemic blood pressure which may be the stimulus for the delayed release of catecholamines (Hall & Hodge , 1971). However , both enalapril and prazosin in this experiment are effective to improve renal function in envenomated animals which agree to those reports using MK-422 (enalapril maleate) intravenously in envenomated rats (Chaiyabutr et al., 1985) and intrarenal infusion of prazosin in envenomated dogs (Kidmungtandee, 1989), In addition , the reduction of norepinephrine level by prazosin and enalapril maleate (group II and III) seemes to relate with the improvement of renal circulation in the present study.

A marked increase in renal vascular resistance while the reduction of renal functions has been demonstrated in envenomated animals pretreated with indomethacin (group IV). The effect of indomethacin enhanced the action of Russell's viper venom on kidney functions might be due to an inhibition of prostaglandin synthesis , causing lack of vasodilatory prostaglandin to regulate renal functions. These changes are similar to the results of previous study (Thamaree et al ., 1987).

The present study shows that during envenomation , a disturbance of renal tubular functions were observed (group I) . The decrease in urine flow rate coincided with a decline in urinary excretion and fraction excretion of sodium and patassium were seen. One possibility can be explained that the stimulation of Alpha-adrenergic receptor might lead to increase proximal tubular sodium reabsorption via intracellular

cyclic-AMP (Schrier, 1974). Another possibility can be suggested that a decrease in filtered load of Na^+ and K^+ during envenomation can contribute to a reduction of Na^+ concentration in distal tubule and might induce an increase renin-angiotensin activity (Thurau and Boylan, 1976; Chaiyabutr et al., 1984). These changes of tubular function have been attenuated by action of prazosin and enalapril (group II and III) while indomethacin (group IV) has shown to enhance the severity of tubular disturbance.

In conclusion , an elevation of plasma norepinephrine level induce by Russell's viper venom is correlate to changes in renal functions (group I). Inhibition by prazosin , enalapril and indomethacin are lower circulating norepinephrine level (group II , III and IV) which could suggest that the release of norepinephrine after envenomation may be mediated by renin - angiotensin system and/or prostaglandins. Enalapril is the strongest blocker in the early phase of envenomation and prazosin is stronger inhibitor in the latter , causing improvement of renal functions. Indomethacin is a weaker inhibitor of norepinephrine level and enhances the viperine effect to impair renal functions. However , the relationship between norepinephrine level and renal functions remains unclear in this experiment , this might be another factor partly to involve in regulating of this phenomenon.