Chapter V

Discussion

The present results show that the effects of Russell's viper venom on cardiovascular and renal functions vary between splenectomized animals and animals pretreated with indomethacin. In the control period, splenectomized dogs had higher heart rate than intact dogs but cardiac output, plasma volume, blood volume and blood pressure were not different. These results are similar to the earlier work on the dog (Ffoulkes - Crabbe et al., 1976). In the present experiment, animal pretreated with indomethacin produced expansion of plasma volume, blood volume, these changes might be attributed to an increase in cardiac output. However, a marked reduction in urine flow rate as well as excretion of sodium in animals pretreated with indomethacin are related to an increase in renal vascular resistance. This evidence clearly indicates vasoconstriction in the kidney. The change in glomerular filtration rate is also determined by an increase in filtration fraction after indomethacin administration (Feigen et al., 1976; Sjodin et al., 1983).

The reduction of cardiac output heart rate, plasma volume and other cardiovascular variables obtained from animals in each group after envenomation are similar to the results of the earlier experiment (see Tungthanathanich, 1983). The Russell's viper venom produced a pooling of blood in the hapato - splanchnic bed of dog (Vick et al., 1967). The initial phase of envenomation probably

caused a decrease venous return and contributed to the low cardiac output concomitantly with decrease in mean arterial blood pressure. It has been shown that if mesenteric arteries are clamped, quite large doses of the venom do not produced any marked effect in the blood pressure. Evisceration prevented the initial hypotension (Vick et al., 1967). The present study indicated the failure of splenectomy to modify the effect of the venom in the initial phase of hypotension. However, it should be emplasized that the spleen is not the major contributor to the total blood volume shifts caused by the effect of the venom. Therefore, other organs and/or venous vascular bed may play an important role. (Shoukas, et al., 1981).

It will be observed that packed cell volume was elevated in intact animal after envenomation. However, splenectomized animals the elevated packed cell volume was not observed. During envenomation period, the hemorrhagic tendency occurred, since the packed cell volume showed tendency to deline at the end of the experiment. These results indicated that bleeding manifestation occur following envenomation (Chugh et al., 1975). Hemorrhage and incoagulable blood were present in both patient victim of snake bite and also in experimental animal after envenomation (Aung - Khin, 1978; Tungthanaich, 1983).

It has been reported that intravenous infusion of epinephrine causes severe renal tubular necrosis in intact animal which elevated in packed cell volume, while renal damage was less severe and absence of elevated paked cell volume in splenectomized animals. Initially, elevated packed cell volume is thought to be an important factor in pathogenesis of acute renal failure (Mandal et al., 1978). The

splenectomy might play an important role to prevent acute renal failure (Bell et al., 1981). Mandal (1982) concluded that splencetomy afford protection against epinephrine induced acute renal failure possible by attenuated the vasoconstriction effects of epinephrine by prostaglandin synthesis and lack of elevated of packed cell volume. Results of the present study are not consistent with data of Bell et al., (1981) and Mandal (1982). Changes in general circulation are similar in either intact or splenectomized animals after envenomation. The elevated packed cell volume seem to less importance in the contribution of decrease renal blood flow. Although an increase in packed cell volume would be expected to increase in blood viscosity which caused a reduction in renal plasma flow and renal blood flow 10 - 20 minutes after that the adjustment was occurred. (Nashat and Portal, 1967). In the intact animal was severely impaired of renal function as compared to the animal in other groups after venom injection. These changes may contribute to the increase of blood viscosity.

The determination of tubular activity indicated that the tubular function decreased significantly after envenomation in the non pretreated animal and remain in the lower level over 3 hour period of the experiment. These results indicate that renin - angiotensin system might be activated after envenomation to be due to an increase in proximal tubular reabsorption of sodium and chloride, thereby decrease distal delivery (Gerber et al., 1981; Henrich, 1981). A decreases in urinary excretion of sodium, potassium and chloride were associated with a decrease in fractional excretion of sodium

and chloride, but fractional excretion of potassium increased. These results might be due to the reduction of systemic blood pressure and renal blood flow which enhance formation of angiotensin. The angiotensin may stimulate aldosterone secretion (Blair-West et al.,(1962) Guyton, 1981). Aldosterone causes excess sodium reabsorption and increase potassium excretion (Knochet et al., 1973; Young et al., 1976). The increase of potassium excretion under the influence of aldosterone might attribute to the decrease in plasma potassium concentration. However, the present results show that the plasma osmolality increase slightly with decrease in urinary excretion of sodium, chloride,osmolar and osmolar clearance, which corresponding to an increase in free water clearance.

The present studies also indicated that animals pretreated with indomethacin alleviates the hemodynamic effect of Russell's viper venom in both intact and splenectomized dogs. In the pretreated animal the initial fall in mean arterial blood pressure was less than that of non-pretreated animal after envenomation and recovered to control level in a short time as compared to non pretreated aniamls. One explanation for this might be that indomethacin inhibited prostaglandin synthesis, which expected to be released into plasma after Russell's viper envenomation. Indomethacin may modify some, but not all of protection, The most pronounced modification was the prevention by delayed reduction in systemic arterial blood pressure. The other characteristic of the delayed shock phase were still apparent. Cardiac output was still reduced.

The present study has shown that there were closed relationship to decrease in mean arterial blood pressure, renal plasma flow, renal blood flow, glomerular filtration rate and increase in renal vascular resistance followed by envenomation. It was confirmed by the finding that indomethacin abolished this effect. In both intact and splenectomized dogs without pretreated with indomethacin, these were marked decrease in renal plasma flow, renal blood flow and glomerular filtration rate after venom injection. During hypotension renal blood flow decrease in direct proportion to the fall of systemic blood pressure. The mechanism of action of indomethacin on renal functions after envenomation is not clear. It seems reasonable to postulate that systemic hypotenion after Russell's viper venom injection might activate the nervous system via the intrarenal baroreceptor to release renin. Because of the juxtaglomerular apparatus is innervated by sympathetic nerve. The suggestion would be that sympathetic activation direct stimulates the juxtaglomerular cell to secrete renin (Gerber et al., 1981; Henrich, 1981). Prostaglandin appear clearly to be an intermediary step in the function of the baroreceptor for renin releases (Henrich et al., 1979; Seymour and ZeHr 1979). Increased activity of renin-angiotensin system has been implicated as a cause of elevated renal vascular resistance associated with a reduced in renal blood flow and glomerular filtration rate (Hall et al., 1977; Ploth and Navar 1979). Thus indomethacin administration does not only inhibit prostaglandin but also inhibit the release of plasma renin activity (Rumpt et al., 1975; Frolich et al., 1976). The decrease of renin - angiotensin system has effect on renal function. Certainly, it has been clearly shown in the present study

that the animals pretreated with indomethacin shows improve renal function as compared to non-pretreated animals. However, it is difficult to draw any valid conclusion from the present experiment regarding the ultimate effect of indomethacin on renal function after Russell's viper venom injection. The question as to whether indomethacin is affording protection against by inhibiting prostaglandin synthesis or whether it has a separate and more fundamental action such as alter in general circulation. It should be noted that increase in blood volume and cardiac output were observed in pretreated animals on per-envenomation period.

The immediate fall in systemic arterial blood pressure after venom injection is comparable to that obtained in endotoxin shock (Erdos et al., 1967; Parratt and Sturgess, 1974). The rise in portal pressure and the initial sudden hypotension in endotoxin shock is usually attributed to pooling of blood in the liver. Early fall in systemic blood pressure could be prevented by evisceration (Hinshaw et al., 1958). These finding are in agreement with the effects of Russell's viper venom induced hypotension in dog (Lee et al., 1948; Vick et al., 1967). Many reports have been supported that indomethacin abolished the effect of endotoxin induced hypotension (Erdos et al., 1967; Culp, 1971; Parratt and Sturgess, 1974). It was suggested that indomethacin prevent hypotension might either interfere the release of histamine or inhibit the release of prostaglandin.

In conclusion, the present studies demonstrate that the Russell's viper venom affected cardiovascular and renal functions. The changes of renal function probably are due to change in systemic

circulation contributed to sudden fall in arterial blood pressure followed by decrease in blood flow through the kidney. The mechanism of the action seems to be mediated by activation of prostaglandin synthesis. However, indomethacin pretreated abolishs these effects. On the other hand Russell's viper venom may have direct toxic effect on the kidney, eventhough renal failure has been noted in some cases of Russell's viper bite without hypotension (Sitprija and Boonpucknavig, 1979). The pathogenesis mechanisms which take part in the development of acute renal failure following Russell's viper envenomation are not clear (Varaguman and Panabokke, 1970; Aung-Khin, 1978). The present studies also indicate that the effect of Russell's viper venom on pathophysiology of kidney in intact or splenectomized animals are not different.