Chapter V

Discussion

Effect of intravenous injection of Russell's viper venom on renal function during intrarenal arterial infusion of thromboxane synthetase inhibitor (TSI) in dogs revealed that the animals recieved the venom alone (group I) had a significant rise in packed cell volume (PCV) within 10 minutes then gradually declined. This evidence is similar to previous studies (Tungthanathanich., 1983; Tongvonchai., 1984). In imidazole treated animals (group II, III and IV) showed persistently significant elevation of packed cell volume which was significantly higher than that of group I. A marked increase in both mean arterial blood pressure and packed cell volume in animals given imidazole were consistent with the previous study in dogs (Harris et al., 1980). The explanation for splenic contraction leading to the expulsionof sequestered red blood cell may be responsible (Harris et al., 1980). It has been reported that an intravenous infusion of epinephrine also caused striking elevation in packed cell volume in intact dogs whereas the rise in splenectomized animals were lower (Mandal et al 1978). Therefore the increase in packed cell volume in present study may be attribute to the contribution of adrenergic stimulation cause the spleen to squeeze red blood cell into circulation. This evidence also observed by the study of Tongvongchai (1984). The present study suggests that imidazole induced an increase in packed cell volume via adrenergic stimulation since an intravenous injection of a number of imidazoline derivative

into rats induced an increase in blood pressure due to peripheral alpha adrenergic receptor stimulation (Boudier et al., 1974).

In previous study in dogs, pretreated with indomethacin prevented profound hypotensive effect of envenomation and the deterioration of renal function was less than control group which recieved the venom alone (Tongvongchai., 1984). This result favored the possibility that TXA_2 might take part in the alteration that produced by Russell's viper venom injection since hypotensive effect of Russell's viper venom was suggested to be due to the release of TXA_2 which might cause pulmonary vasoconstriction leading to restriction of blood return to the heart and decrease in cardiac output (Huang., 1984) and low dose of indomethacin inhibited TXA_2 production (Jeremy, Baradus, Mikhailis, & Dandowa., 1985). Furthermore an intrarenal arterial infusion of Russell's viper venom in dogs increased plasma and urinary TXB_2 which could be reversed by indomethacin (Thamaree, Chaiyabutr, Leepipatpaiboon, Buranasiri, Tosukhowong, Siriwongs, & Sitprija., 1987). But it seems unlikely that indomethacin counter hypotensive effect on Russell's viper venom solely on TXA_2 inhibition because of reduction of cardiac output was not reversed by indomethacin in previous study (Tongvongchai., 1984). Antihypotensive effect of Russell's viper venom by indomethacin may be due to an increase in adrenergic transmitter action of indomethacin (Fredholm, & Hedquist., 1973) which consistent with increase in packed cell volume in indomethacin pretreated envenomated dogs (Tongvongchai., 1984). Therefore improvement of renal hemodynamic and renal function may be secondary to restoration of systemic blood

pressure. In present study, intrarenal arterial infusion of 2 mg/kg/min of imidazole (group III) prior to envenomation also prevents hypotensive effect of the venom but renal hemodynamic and renal function still depressed. This may be the contribution of high dose of imidazole inhibited cyclooxygenase activity (Moncada et al., 1977) leading to over reduction of vasodilatory prostaglandins. In addition, 0.5 mg/kg/min of imidazole (group IV) given in the same manner of group III in this study fails to antagonize hypotensive effect of Russell's viper venom in spite of imidazole alone increases mean arterial pressure. This indicates that cardiac output must be reduced in the greater extent than the increase in vascular resistance. Factors responsible for the decrease in cardiac output may be the reduction of vasodilator prostacyclin (PGI_2) more than the vasoconstrictor TXA_2 in pulmonary vascular bed, combine with an increase in sympathetic activity effect of imidazole potentiated more severe pulmonary vasoconstriction. The more adrenergic activity due to higher dose of imidazole used in group III may account for it's ability to counter hypotension which absent in group IV that imidazole given in a lower dose. Other studies about the role of TXA_2 participated in ARF and imidazole improved renal function, had cited that amelioration by imidazole depended on simultaneous occurance of vasodilator prostaglandin (Yarger et al. 1980). Imidazole not only inhibited TXA_2 but increased PGE_2, PGF_2, and PGI_2 (Partrignani, Filabozzi, Catella, Pugliese. & Patrono. 1984). Therefore the ultimate usefulness of TSI in vivo does not solely depend on the inhibition of TXA_2 synthesis but may be benificial because it diverts endoperoxide toward PGI_2 (Gorman. 1983). The improvement of renal

function in those dogs treated with imidazole may be due to improvement of renal hemodynamic or a specific action of imidazole (Cadnapaphornchai et al., 1982). In the present study a deterioration of RPF, RBF, and GFR of the treated left kidney were apparent in animals given a higher dose of imidazole (group III). This result may be due to a prolonged infusion of imidazole which induced the accumulation of the drug to the level high enough to exhibit the cyclooxegenase blocking activity (Moncada et al., 1977). The other possibility may be due to sympathomimetic activity of imidazole that aggravates renal hemodynamic in the same manner of epinephrine injection (Mandal et al., 1978) or may be the combination of both. These may be responsible for the locally persistent elevation of RVR in the left kidney of group III & IV which were directly infused with imidazole. However, the depression of renal hemodynamic may be the effect of renin angiotensin system (Navar et al., 1984) especially in case of Russell's viper envenomation (Chaiyabutr et al., 1985). Envenomation induced an increase in FF in the present experiment may be due to renin angiotensin stimulation since an increase in FF accompanied with elevation of packed cell volume have been suggested to be mediated by alteration of efferent arteriolar resistance (Nashat et al., 1967) and the efferent arteriolar resistance should be attributed to the effect of Angiotensin II (Hall et al., 1977; Narvar et al., 1884). Increase in plasma osmolality in imidazole-treated groups may be the result of sympathetic stimulation dues to prolonged infusion of imidazole because it is well known that epinephrine reduced plasma volume by extravasation of fluid which is consistent with elevation of pakced cell volume in these groups. The rise of

plasma osmolality may contribute to urine volume reduction since indomethacin potentiated action of ADH induced an increase in urinary osmolality and decrease in free water clearance (Berl, Raz., Wald. Horowitz, & Crazked., 1977) as well as high dose of imidazole enhanced permeability response to vasopressin in toad urinary bladder (Burch, Knapp, & Haluska., 1979). But these data do not agree with the present study because an alteration of urinary osmolality is variable, urinary osmolality excretion is reduced and free water clearance is increased instead. The possible explanation is that sympathetic over stimulation effect of imidazole is responsible for the reduction of urine formation and the increase in plasma osmolality. Urinary osmolar and electrolytes excretions are all depressed in imidazole-treated groups especially in left kidney. This indicates the impairment of tubular function in these groups.

Fractional excretion of all electrolyte were elevated in the left kidney of group III. This elvation was higher than other groups. The most interesting is FE_{Na}, a minor modification of renalfailure index, an almost perfect diagnostic indicator of acute tubular necrosis (ATN). The classical limit to interprete ATN, FE_{Na} is of 6% and above (Oken., 1981). In this study, the left kidney of group III, FE_{Na} at 50 to 90 minutes after envenomation was higher than that of 6%. In addition to previous study by Mandal (1978) animals with higher hematrocrits also had a more severe acute tubular lesion. High hematocrits in dogs caused a reduction in RPF and GFR (Nashat et al., 1967) which is consistent with the present study. Furthermore ARF with tubular necrosis was described by Sitpreja (1974) in patients

bitten by Russell's vipers. This was later confirmed by Chugh et al (1975). These data may interprete that the treated left kidney of group III falls in the state of ATN. This deterioration may be due to the effect of imidazole which directly infused via the left renal artery. Imidazole may enhance the effect of Russell's viper venom to affect tubular transport activity by unknown mechanism. It is of interest that FE_{Pi} in left kidney of all groups were strikingly transient elevation. This is in agreement with previous study (Tungthanathanich., 1983; Meerut., 1986) Transient increase in FE_{Pi} in the control group and group II at 30 min period prior to imidazole infusion suggests that the effect is primarily due to Russell's viper venom not imidazole. The mechanism of Russell's viper venom affects tubular transport of inorganic phosphorus may be by either cyclic adenosine monophosphate (c- AMP) production or acts as metabolic inhibitor in renal tubular cells (Meerut., 1986). In conclusion, continuous intrarenal arterial infusion of imidazole in envenomated dogs induced an exaggerated deterioration of the infused kidney. Both extrarenal and intrarenal factors are responsible for this alteration. Since prolonged infusion of imidazole did not suppress renal function (Yarger et al., 1980) and an admistration of imidazole for 14 days did not alter renal function in human (Ziper., 1985). The most likely contribution of this renal impairment is that imidazole enhances metabolic toxic effect of Russell's viper venom on tubular cells. Because cyclooxygenase inhibitor, indomethacin, was found to decrease the activity of c-AMP phosphodiesterase in rat kidney (Berl et al., 1977) and imidazole acts as cyclooxygenase inhibitor (Moncada et al., 1977). Recently, it was suggested that Russell's viper venom may

enhance c-AMP production (Meerut., 1986). Many effects of imidazole other than TSI, such as cyclooxygenase inhibitor, sympathomimetic activity suggest that it is unreasonable to exclude TXA_2 from the involvement of Russell's viper venom inducing renal function disturbance.