CHAPTER V

DISCUSSION

The results of the present study show that intravenous injection of crude cobra venom alone caused a marked reduction in systemic arterial blood pressure and narrowing of pulse pressure in the first 15 minutes after envenomation (Group II). These results were similar to the results of Bhanganada and Perry (1963) and Rattanabanangkoon et al. (1978). This hypotension was suggested to be due to vasodilatation in the periphery which resulted from the venom induced release of histamine (Lee, 1979). However, in the present study total peripheral resistance markedly increased indicating a compensatory mechanism for maintenance of blood pressure. A slight increase of heart rate during increment of total peripheral resistance in the present study seemed to be due to sympathetic activity (Prayoonsri Khowean, 1990). A complex pattern of cardiovascular changes results from injection of cobra venom into anaesthetized dogs. An immediate and profound drop in cardiac output and arterial pressure occurred. Many possibilities for maintenance blood pressure may occur during envenomation. One possible mechanism for recovery of blood pressure is a result of sympathetic stimulation (Guyton, 1991). Since, cardiotoxic fraction injection produced an increase in heart rate in the present study. Hemodynamic changes resulting from cobra venom may be attributable to chemical mediators release into circulation. High concentrations of adrenaline and noradrenaline have been demonstrated immediately following injection of endotoxin into the dog (Rosenberg et al., 1961). During 45 minutes after envenomation, packed cell volume markedly decreased from the control value. It might be due to hemolysis of the red cell after envenomation.

The animals pretreated with intravenous infusion of verapamil before injection of crude cobra venom showed a slight reduction of arterial blood pressure (Group III).

Envenomation still produced a marked fall in systemic arterial blood pressure and narrowing of pulse pressure. Progressive reduction in arterial blood pressure was significant longer than that of group II. Cardiac output decreased whereas total peripheral resistance had a tendency to increase. It is possible that there was a synergistic action between verapamil and crude cobra venom was seen. Because verapamil produced a dose-related reduction in cardiac output and stroke volume but the hypotensive effect of the drug could be accounted for almost entirely by peripheral vasodilatation (Ross and Jorgenson, 1967). In the present study, the dose of intravenous infusion of verapamil was 6 μg/kg.bw. that produced no significant reduction in cardiac output (Somchit Eiam-Ong, 1988).

In group IV, cardiotoxic fraction XIII of cobra venom produced a marked reduction in systemic arterial pressure and narrowing of pulse pressure after intravenous injection. Cardiac output initially decreased whereas total peripheral resistance had a tendency to decrease. These results indicate that the compensatory mechanism for maintenance of blood pressure was fail. It possible that the cardiotoxic fraction was more potent than crude venom (Sarkar, 1947).

Animals treated with either crude venom or cardiotoxic fraction XIII slight reduced cardiac output. In contrast, animal pretreated with intravenous infusion of verapamil produced marked a reduction in cardiac output. It is possible that the influence of venom on cardiac output was potentiate by Ca^{2+} channel blocker.

Cardiotoxic fraction showed non significant alteration of all parameters in animal that pretreated with verapamil. These results may be related to the level of intracellular calcium. Since it has been reported that cardiotoxic fraction increase Ca^{2+} influxes (Lin-Shiau et al., 1976, 1986; Harvey et al., 1982), two hypotheses have been proposed for the increased intracellular calcium level. First, cardiotoxin may increase the permeability of calcium into cells (Earl and Excell, 1972). Second, cardiotoxins may form pores in the membrane which favours the influx Na^{+} and Ca^{2+} along the concentration gradients (Louw and Visser, 1977).

Electrocardiographic studies from the effect of cobra venom showed that the change of T-wave was noted within a few minutes after envenomation. The P-R interval became progressively longer and the ventricular complexes were wider. These results indicate an impairment of conduction system in the heart. Myocardial damage has been observed as the dominant features of the action of the venom. The development of aberrant ventricular complexes may follow. Similar electrocardiographic changes was also observed in cats, isolated heart of rabbit and dogs (Gautrelet et al., 1934; Feldberg and Kellaway, 1937b; Kellaway and Trethewie, 1940; Lee et al., 1971). Conversely, cobra venom produced no markedly changes in cardiac output and stroke volume. It might be due to action of other component in crude cobra venom. In group IV, cardiac output and stroke volume had a tendency to decrease after cardiotoxic fraction injection and markedly decrease in animal pretreated with verapamil before envenomation. It is possible that synergistic effect between verapamil and cobra venom affected on the heart.

Changes in renal hemodynamic were related to changes of general circulation. Diminution of effective renal blood flow, effective renal plasma flow and glomerular filtration rate as well as the increase of renal vascular resistance after envenomation in the present study might be due to sympathetic response to hypotension, thereby resulted in renal vasoconstriction (Guyton, 1991). In group II, cobra venom produced markedly alteration in renal hemodynamic at 15 minutes after venom injection. As same as group III that pretreated animal with verapamil, cardiotoxic fraction induced decrease in effective renal plasma flow, effective renal blood flow and glomerular filtration rate that was more prolonged than other groups. It may be postulated that cardiotoxic fraction exert more vasoconstriction than crude cobra venom. It indicates that verapamil had no effect on renal hemodynamic and this was probably due to the low concentration of verapamil.

Intravenous injection with cardiotoxic fraction caused a marked increase in fractional excretion of sodium during 15 minutes after venom injection, after that there was no difference from the control in the present study. It should be noted that reduction in Na^+-K^+ ATPase activity was apparent after envenomation. Similar results

have been reported in various cell, e.g. Yoshida sarcoma cells, human and dog blood erythrocytes, ox brain and rat brain (Lankisch et al., 1972; Zaheer et al., 1975; Khelif et al., 1985; Bougis et al., 1989). In the previous study, the cytotoxic fraction from Indian cobra venom was found to inhibit Na^+-K^+ ATPase activity of membrane fragments of various cells. It was suggested that cardiotoxin bound to membrane lipids that were associated with the ATPase enzyme and, thereby, blocked the sodium pump. The consequent intracellular accumulation of ions would lead to osmotic lysis (Zaheer et al., 1975).

The present data showed an increment in fractional excretion of sodium, potassium and chloride at 15 minutes after cardiotoxic fraction injection. Cardiotoxic fraction also produced an increase in fractional water excretion. It is possible that water was excreted with electrolyte along the tubules. It may speculate that cardiotoxic fraction affected the function of renal tubule, that would be further clarify.

In group IV, cardiotoxic fraction induced a marked increase in plasma potassium concentration at 15, 30 and 45 minutes of the experimental period. It is possible that increment of plasma potassium concentration in the present study was a consequence of hemolysis after envenomation. At 45 and 60 minutes after cardiotoxic fraction injection, there was an increase in fractional excretion of potassium in consequent of increase in plasma potassium concentration. The present experiments demonstrated that an intravenous injection of cardiotoxic fraction caused reduction of blood bicarbonate concentration, blood pH and urinary acid excretion. All experiment results above indicated that acidosis may be induced after envenomation. This can be supported by an increase in respiratory rate after envenomation. Some mechanism was proposed : potassium ion competed with proton secretion because of the elevation of plasma potassium concentration. Thus, hydrogen ion secretion decreased while potassium excretion increased.

In conclusion, the present study demonstrated that the cobra venom affected both cardiovascular system and renal functions. The changes of renal function may be due to changes in systemic circulation contributed to fall in arterial blood pressure

followed by a decrease in blood perfusion to the kidneys. The mechanism of the action is likely to be due to the stimulation of sympathetic activity. Cardiotoxic fraction produced increase in fractional excretion of sodium, potassium and chloride. It is indicated that the function of renal tubule was affected. Acidosis may be induced by cardiotoxic fraction. Potassium ion may compete with proton secretion resulting on increase in plasma potassium concentration during acidosis.