CHAPTER IV

DISCUSSION

This investigation was designed to determine whether the reversal of ischemic ARF and $HgCl_2$-induced ARF can occur during hypertonic saline infusion. The experimental data showed that during 45 minutes of clamping of the left renal artery or 45 minutes after $HgCl_2$injection, there was a significant reduction of cardiac output and a slightly decrease in both stroke volume and heart rate. However, this systemic response was not related to the changes in body fluid volume, since unalteration in plasma volume and blood volume were observed in both groups of ARF. These results were in agreement with previous reported in rat in $HgCl_2$-induced ARF (Kurtz and Hsu, 1978). A reduction in cardiac output in $HgCl_2$-induced ARF dogs could have been due primarily to a cardiotoxic action of $HgCl_2$ which caused the decrement of myocardial contractility (Kurtz and Hsu, 1978). This effect might not expect in the ischemic ARF dogs. During clamping the left renal artery or $HgCl_2$ injection, the mean blood pressure was apparently increased. Thus the significant decrease in cardiac output of both two models ARF could be not only related to a decrease in heart rate, but also secondary to reflex symphathetic changes particularly during clamping of the left renal artery.(Hsu and Kurtz, 1981)

It was found that after hypertonic saline infusion of both group, the percentage of an elevation of cardiac output in ischemic ARF was more than $HgCl_2$-induced ARF (Fig.2, p.28). The increases in cardiac output in ischemic ARF dogs could be a result of an increase in cardiac

activity (Templeton et al, 1972, Atkin et al, 1973) and increased filling pressure of the heart (Lopes et al, 1981). However, it is not possible to distinguish at present study that the increase in cardiac output in $HgCl_2$ treated dogs during hypertonic saline infusion was due to either increase in myocardial contractility (Koch-Weser, 1963, Wildenthal et al, 1969) or reduction in cardiotoxic effect of $HgCl_2$.

The present study indicates that the decrease in cardiac output related to the decrease in renal perfusion in $HgCl_2$ treated dogs. Similar finding have been reported by Hsu and Kurtz (1981) for both glycerol and $HgCl_2$ models of ARF. Our data show that after hypertonic saline infusion, the increment of cardiac output and renal fraction were disproportionate in both ischemic and $HgCl_2$ models of ARF. Therefore, it clearly indicate that changes in cardiovascular system are not responsible for the decrease in renal fraction in both ischemic and $HgCl_2$ models of ARF (Fig.2, p.28). Since the renal resistance is still in a high level after hypertonic saline infusion.

During thirty minutes after released clamp of the left renal artery, anuria still occured whereas the contralateral control kidney did not show any significant increase in the rate of urine flow. In contrast, an appearance of diuresis or oliguria occured in dogs at 45 minutes after $HgCl_2$ injection. It is therefore indicated that different mechanisms are at play in the generation of ARF. Cell debris and cast caused tubular obstruction have been demonstrated in one hour of renal artery occlusion in rat (Arendshorst et al, 1975). During postocclusion, tubular obstruction was still occured and passive backflow of tubular fluid appeared to be important in the maintenance of the oliguria. However, it is not ascertain from the present study that oliguria in $HgCl_2$-induced ARF was the process of passive backflow. Because continuing renal hypoperfusion still occured after hypertonic saline

infusion. "No reflow" of post-ischemia associated with swelling of renal cells in the kidney has also been reported in rat by Flores et al (1972). That "no reflow" and cell swelling could be reversed by hypertonic mannitol and hypertonic sodium sulfate but isotonic saline and isotonic mannitol were unaffected. The present study indicates that after released clamp "no reflow" can be reversed by acute hypertonic saline infusion. However, the results obtained from the present experiment seem to relate with other extrarenal factors because GFR and RBF were apparently altered in the right control kidney after hypertonic saline infusion.

The present study shows that at 30 minutes post-ischemia, the RBF and GFR in the contralateral control kidney decreased 35 % and 21 % respectively. At 10 minutes after hypertonic saline infusion, the reversal of RBF and GFR of the contralateral control kidney in ischemic ARF dogs rose to the control level, while RBF and GFR of the experimental kidney rose to 49 % and 43 % of control values. These results indicate the proportionate increment of both RBF and GFR appearance in ischemic ARF dogs. In comparison with $HgCl_2$ treated dogs, the RBF and GFR fall 57 % and 43 % respectively at 45 minutes after $HgCl_2$ injection. At 10 minutes after hypertonic saline infusion the RBF and GFR rose to 16 % and 2 % of control values(Fig.3, p.29). Although the decreased total RBF may occur during the initial phase of virtually all forms of ARF whereas it may not be related to the early decreases in GFR observed in every instance (Mauk et al, 1977) and this finding might be due to the combination of marked afferent arteriolar vasoconstriction coupled with efferent arteriolar vasodilatation (Reubi et al, 1976). It is not possible from the present study to determine an increase in RBF and GFR disproportionate to be due to the changes of renal arteriole after hypertonic saline infusion of $HgCl_2$ treated dogs.

In both groups, the reduction of RBF was clearly associated with the elevation of renal resistance. However, the precise pathophysiologic basis for the increase in renal resistance in various forms of ARF is still unclear (Stein et al, 1978). Several investigators suggested that renin-angiotensin may be involved. Plasma renin activity has been repeatedly shown to increase in the initial stage of both clinical and experimental forms of ARF (Tu, 1965, Kokot and Kuska, 1969, DiBona and Sawin, 1971). In addition, several groups of patient were observed to have marked elevations of plasma renin activity without the occurrence of ARF (Stein et al, 1978). The present study indicate that 10 minutes after hypertonic saline infusion the magnitude of the decrease in renal resistance of ischemic ARF dogs were more than $HgCl_2$ treated dogs (Fig.4, p.30). The mechanism of these changes are unknown, but it may be due to osmotic change in the water content of the smooth muscle cells or blood vessel during increment of plasma osmolarity and cause to decrease renal resistance (Gazitua et al, 1969, 1971). Hyperosmolar vasodilatation is not caused by the systemic release of histamine or by the effects of prostaglandins have recently been reported by Pinsky et al (1982). The direct local effects of hyperosmolar solution on vascular smooth muscle perhaps mediated by local fluid and electrolyte shifts.

In consideration of U/P osmolarity ratios of 1.1 or less was characteristic of acute tubular necrosis (Eliahou and Beta, 1965, Luke et al, 1970). The present study find that a U/P osmolarity ratios decreased from 1.83 to 0.97 in $HgCl_2$ treated dogs at 10 minutes after hypertonic saline infusion. Thus, it may be interpreted that $HgCl_2$ treated dogs fail to excrete concentrated urine. In contrast, ischemic ARF dogs were not significantly decreased in U/P osmolarity ratios during clamping, after released clamp and hypertonic saline infusion. These finding suggest that renal tubular cell are still responsible

for concentrating urine (Fig.5, p.31).

During post-ischemia for 30 minutes, it was found that low urinary excretion of sodium and fractional excretion of sodium occured in contralateral control kidney, but urinary excretion and fractional excretion of sodium were increased in both kidneys at 10 minutes after hypertonic saline infusion. The fractional potassium excretion was increased in $HgCl_2$ treated dogs whereas there was no changes in fractional potassium excretion of ischemic ARF dogs in either post-ischemia or after hypertonic saline infusion (Fig.6, p.32). These results indicate that the transport mechanism of sodium and potassium in the renal tubule of $HgCl_2$ treated dogs are altered. There are profound and relatively effects of $HgCl_2$ injected to animal. Since it has been noted that mercuric ion bound to plasma proteins is filtered by the glomerulus and interacts with sulhydryl groups in the proximal tubule by inhibition of enzymatic activities along the brush border is observed within 15 minutes. After injection of $HgCl_2$, active transport of Na and K is decreased and an increase in passive backflow occurs (White et al, 1961). This phenomena did not appear in ischemic ARF dogs.

The present study indicates hypertonic saline infusion can improve the renal circulation. The evidence supports the hypothesis that it is the rise in extracellular osmolarity during hypertonic saline infusion by solutes which penetrate cell membranes poorly that shrinks the swollen cell osmotically. The changes in renal functions of ischemic ARF dogs are prerenal failure which the reversal of prerenal failure could be occured rapidly. However, alteration of renal functions during hypertonic saline infusion of both groups of ARF are due to either changes in intrarenal or extrarenal factors.