INTRODUCTION AND AIMS

It is well known that sodium is the "osmotic skeleton" of the extracellular fluid enabling to maintain its volume against the pull of the intracellular solutes(Michell,1974). An intravenous infusion of sodium salts has been shown to produce beneficial effects in the treatment of patients with hemorrhagic shock, but the mechanism under-lying this response are still poorly understood. Hypertonic sodium chloride infusion has been found to increase the dynamic efficiency of the circulatory system in a period of a critical reduction of blood volume(Velasco et al,1980). There is evidence that an increase in plasma osmolarity induces a wide spread precapillary dilatation(Marshall et al,1959, Gazitúa et al,1969), but the intensity and persistance of this response varies widely as a function of the infuse solutes or the perfused region(Gazitúa et al, 1971).

The acute renal failure(ARF) is often caused related to the prolong blood volume loss(Loew and Meng, 1976, Reubi and Vorburger, 1976). Although the reversal of hemorrhagic shock is able to produce by hypertonic sodium chloride(Velasco et al, 1980, Lopes et al, 1981), but the effects of hypertonic sodium chloride on the reversal of ARF has not determined.

The aim of this study was to obtain more imformation about the physiological role of the hypertonic saline infusion in dogs induced ARF. Ischemic-ARF model by unilateral clamp renal artery and $HgCl_2$-induced ARF have been developed in dogs in order to determine :

First, whether the reversal of ischemic-ARF and $HgCl_2$-induced ARF occur during hypertonic saline infusion.

Secondly, whether any alterations of renal functions during hypertonic saline infusion are due to either changes in intrarenal or extrarenal factors.

BACKGROUND IMFORMATION

RENAL FUNCTIONAL ABNORMALITIES IN CLINICAL ACUTE RENAL FAILURE

Acute renal failure(ARF) is an abrupt deterioration of renal function characterized by retention of nitrogenous compound. The etiology of ARF is varied, but nephrotoxins and renal ischemia are major causes(Chew and DiBartola,1982). This review is largely concerned with the utility of the ischemic and nephrotoxins experimental models. Before discussing the experimental studies of ARF, a brief review of the findings renal functional abnormalities in clinical ARF is warranted. Characteristically, the patients have oliguria, a low urine-to-plasma(U/P) urea and creatinine ratio, a U/P osmolarity of unity, and a high fractional sodium excretion(Levinsky and Alexander, 1976). It has been shown that patients with ARF developed a markedly reduced renal blood flow and a rise in renal vascular resistance(Stein et al, 1978). ARF is not only characterized by oliguria or anuria, but also by isotonicity of urine. This failure to concentrate may continue even when oliguria end off and leads to a polyuric stage. During renal failure and for some time after, the kidney is not able to concentrate urine properly(Bohle et al,1976). However, the phase of recovery deserves emphasis since one of the primary characteristics of ARF is the reversibility of the lesion and the eventual return of all renal functional parameters to essentially normal levels(Stein et al, 1976).

ISCHEMIC ACUTE RENAL FAILURE

Experimental models of ischemic-ARF which have been extensively studied e.g. renal artery clamping, glycerol injection, intra-

renal norepinephrine infusion. A reduction in renal blood flow(RBF),
glomerular filtration rate(GFR) and arise in renal vascular resistance
(RVR) have been uniformaly found in the initial phase of these model.
Arendshorst(1975) recently studied the effect of 1 hr of renal artery
occlusion on renal hemodynamics in the rats. RBF was reduced by approx.
40 % whereas RVR was still increased in thirty to ninety minutes after
release of the occlusion. Daugharty et al (1974) also found a 40 %
decrease in superficial glomerular plasma flow 1 hr after partial renal
artery clamping. Earlier work using the xenon washout method, found
a 19 % decrease in RBF within 10 minutes after intramuscular glycerol
administration, which progressed to a 73 % fall at 24 hr(Ayer et al,
1971). Similar finding have shown in other method such as hydrogen
washout method and radioactive microspheres(Chedru et al, 1972, Hsu
et al, 1976). It has been shown that a dose of 0.25 u/kg per minute
of norepinephrine infused into the renal artery causes a fall in renal
blood flow and urine flow to almost zero and remain at this level for
the length of infusion. After discontinuation of the drug, there is
a slow restoration of blood flow which rarely exceeds 50 % of the
control value at 3 hr (Mauk et al, 1977). If the infusion is given
for 2 hr in the dog, renal function is irreversibly damaged(Cox et al,
1974).

The degree to which the decreased RBF can contribute to ARF
and also depends on the particular model that is studied. A general
consensus exists that RBF the decrement is not related to the decreased
GFR in the maintenance phase of ARF, regardless of model of ARF employed.
This mechanism may involve an increase in preglomerular resistance,
either alone or in association with a decrease in postglomerular re-
sistance (Hsu and Kurtz, 1981). The precise pathophysiologic basis
for the increase in RVR in various forms of ARF is still unclear.

It has been proposed that endothelial cell swelling is a self-perpe-
tuating process induce by renal ischemia and maintain by the loss of
the ability to regulate cell volume (Flores et al, 1972). This was
recently rejected by the subsequent experiments of Frega et al (1976)
in the rat. Because there was the rapid return of blood flow in the
particular model of ARF under evaluation. However, utilizing histo-
logic techniques revealed that more than 90 % of straight proximal
tubules were occluded by swollen blebs of desquamated proximal tubular
microvilli (Donohoe et al, 1976). In addition to the obvious mecha-
nical effects of tubular obstruction, several investigator suggested
that tubular obstruction eventually led to afferent arteriole constric-
tion with a consequential fall in intratubular pressure (Arendshorst
et al, 1974, Tanner et al, 1976). This phenomenon would seemingly
explain the eventual reduction in intratubular pressure in the renal
artery clamp model and possibly other experimental form of ARF.

There has been continuing interest in the possible role of the
renin-angiotensin system in the regulation of renal vascular resistance
in ARF. Several investigators have presented the role of tubuloglo-
merular feedback in the pathogenesis of ARF. Specifically, Thurau's
group (1976) has presented several studies which are in line with the
view that tubuloglomerular feedback is operative in several experi-
mental models of ARF and is linked to activation of the renin-angio-
tensin system.

NEPHROTOXIC ACUTE RENAL FAILURE

Uranium administration and mercuric chloride administration
are experimental models which have been extensively studied in the

view of nephrotoxic ARF. Four mechanism have been proposed as being involved in the pathogenesis of ARF : a) renal vasoconstriction, b) tubular obstruction, c) bacleakage of filtrate across damaged tubular epithelium and d) decreased ultrafiltration coefficient. Therefore, the finding in the initial phase of nephrotoxic ARF are less uniform. It has been shown in dog that an initial reduction in RBF of 50-60 % in uranyl nitrate model (Flamembaum et al, 1972, Stein et al, 1975), whereas no change or a modest increase has been found in the rat after treated mercuric chloride (Hsu et al, 1977, Churchill et al, 1977). Several investigators suggested that the renin- angiotensin system may be involved in the pathogenesis of nephrotoxic models of ARF. It found that a high solute excretion per se attenuates the renal function impairment in the mercuric chloride model (Thiel et al, 1976). However, the relation of renin-angiotensin to nephrotoxic ARF is not clear.

According to tubular obstruction in the $HgCl_2$ model in the rat found that a markedly reduced GFR. When the tubule was vented, GFR was restored to normal levels (Flamenbaum et al, 1974). In contrast, no evidence for tubular obstruction has been found in the uranyl nitrate model, but there was increased inulin permeability in both dogs and rats (Blantz et al, 1975, Stein et al, 1975). It has been demonstreated in the $HgCl_2$ treated rat that backleakage of filtrate is operative in this model (Bank et al, 1967). This phenomenon did not occur in normal tubules. These evidences confirm that tubular damage occured in animal treated with $HgCl_2$. A number of recent studies have focused on the change in ultrafiltration coefficient (K_F) which may occur in ARF. In two recent studies, it found that K_F decreased in both mercuric chloride and uranyl nitrate models (Baylis et al, 1977, Blantz et al, 1975).

It has been found that cardiac output (CO) is significanty decreased in $HgCl_2$ model indicates that changes in systemic hemodynamics are involved in the decrease of RBF that occurs during the initial phase of some forms of ARF (Hsu et al, 1977, Kurtz et al, 1978). The decrease in myocardial contractility during a cardiotoxic action of $HgCl_2$ could be a factor in the decreased CO of $HgCl_2$ model (Kurtz et al, 1978).

REVERSIBLE OF ACUTE RENAL FAILURE

Generally, recovery phase of ARF can spontaneously occur, but it spend a long time. Diuresis will cause during recovery phase of ARF. In brief review will consider to experimental of reversible of ARF. Ringer loading can also restore RBF in both the renal artery clamping and norepinephrine models 24-48 hr after the insult without a significant return of GFR (Cox et al, 1974). Similary, there was a marked increase in RBF after Ringer loading in the dog, but oliguria persisted in $HgCl_2$ treated dogs (Baehler et al, 1977). After infusion of acetylcholine into renal artery 1 hr in norepinephrine-induced ARF in the rat caused recovery of RBF, but inulin clearance does not improve because of intra-tubular deposits that cause tubular obstruction (Conger et al, 1981). Propranolol administration is found to result in a decrease in medullary hyaline casts of ischemic model (Solez et al, 1977). Flores et al, (1972) found that renal ischemia, cell swelling, "no reflow" and subsequent renal dysfunction occurring after obstruction to the renal arteries were corrected by the administration of hypertonic mannitol, hypertonic sodium sulfate. Renal dysfunctions, however, are unaffected by an equivalent expansion of the extra cellular fluid volume in either

loaded with isotonic saline or isotonic mannitol (Flores et al, 1972).
Bailey et al (1973) showed that pretreatment of rats with varying doses
of frusemide protected against both the acute tubular necrosis (ATN)
and ARF of all the models except for glycerol where the ATN and ARF
was aggravated.