CHAPTER I

INTRODUCTION AND AIMS

Acute failure of renal function is one of the most dramatic and important clinical problems in which the physician may be faced. Its importance stem in part from the fact that many patients with acute renal failure (ARF) present the most severe clinical problems from which an individual may completely recover. Thus, both the severity and the reversibility of the situation demand attention.

The most common cause of ARF is renal ischemia, which cause renal function impairment through a combination of renal vasoconstriction, renal tubular obstruction, tubular back leakage of glomerular filtrate, and decreased glomerular permeability (Niranjan and Veith,1979 Steinhausen et al,1978; Eisenhach & Steinhausen, 1973) However, the nature of the cellular insult that produces these changes is unknown. Many factors, for example, a decrease in high energy phosphate supply, increase in free intracellular calcium concentration, loss of cellular synthetic function, activation of membrane degradative processes and generation of endogenous membrane toxins have been postulated to mediate cellular injury during ischemia (Leaf, Cheung, Mills & Bonvnetre, 1983). An understanding on the nature of the cellular insult in ARF would have broad application since ischemia injures all organs. Also, an understanding on the mechanisms of cell injury in ARF.(Mark, Hoidal & Ferris, 1984), renal ischemia causes a rapid decrease in tissue Adenosine triphosphate (ATP) (Hems & Brosnan, 1970) and a rise in the ATP degradation products adenosine, inosine and hypoxanthine (Ossawld, Schmitz & Kemper, 1977). The accumulation of hypoxanthine during renal ischemia might be the generation of highly reactive oxygen free radicals as reactive oxygen species (ROS), since the enzymatic

conversion of hypoxanthine to xanthine by xanthine oxidase generates superoxide radicals ($O_2^{\cdot-}$) as a reduction product of molecular oxygen (Fridovich, 1970). Superoxide radical and its reduction products, hydrogen peroxide (H_2O_2), and hydroxyl radical (OH.) can produce cellular injury through lipid peroxidation of mitochondrial, lysosomal, and plasma membranes, which can alter both membrane structure and function (Fridovich, 1978 Kellogg & Fridovich, 1975).

Increase in ATP degradation resulting in the reduction in ATP levels and, in parallel, enhanced formation of hypoxanthine have been observed in the kidney of rats with ischemic ARF (Mark, Hoidal & Ferris, 1984). It is very likely that ROS generated under these conditions contribute to the cell injury. Oxygen free radicals could theoretically produce damage in renal arteriolar endothelial cells, glomerular mesangial cells and renal tubular epithelial cells.

According to previous experiment (Hansson *et al*, 1983) the decrease in RBF that occurs in ARF was improved by treatment with the oxygen free radical scavengers, Superoxide dismutase (SOD). They concluded that the oxygen free radical scavengers SOD inhibits free radical generation, protected renal function after ischemia. Furosemide and mannitol are two agents that have been frequently employed in experimental and clinical settings to ameliorate or prevent ARF. Mannitol is a known free radical scavenger effective in preventing reoxygenation all injury. It could protect against ischemic imjury by neutralizing toxic free radicals generated. (Hanley & Davidson, 1981). Furosemide, on the other hand, has been shown to affect the concentrations of glycolytic intermediates in the kidney and to inhibit lactate formation (Yoshida & Mitcoff, 1972) So, mannitol and furosemide protect against the development of ARF

by preserving proximal nephron integrity and thereby preventing the debris-producing cellular injury.

In clinical studies, it has been demonstrated that the Tetrachlordecaoxide (TCDO) or Oxoferin, which is an aqueous solution containing a non-metabollic biocatalytically activated oxygen carrier, increased the oxygen supply in hypoxic peripheral tissue and also acted as a bactericide. TCDO (oxoferin) has been shown in invitro studies under the catalysis of certain hemeproteins such as peroxidase (s), myoglobin Fe^{2+} or Fe^{3+} hemoglobin (but not with catalase) to lead to the formation of an active oxygen species. This agent does not posses the same biological and chemical properties as the aggressive free OH^-, the superoxide radical (O_2^-), H_2O_2 and singlet oxygen ($^1O_2$). In addition to the bactericidal properties in inflamed tissue, TCDO also leads to increase blood supply, increase partial oxygen pressure in hypoxic tissue, which likewise appears to occur via the agency of active oxygen species (Youngman, Wagner, Kuhne, & Elstner, 1985).

As of the above mentioned qualification of TCDO. The aim of the present study was to obtain the information about the physiological role of TCDO in dogs induced ARF. Ischemic - ARF model by intrarenal norepinephrine (NE) infusion was carried out in order to determine :

First, whether the reversal of ischemic-ARF occur during TCDO treatment.

Secondly, whether any alterations of renal functions during TCDO infusion.