Chapter V

Discussion

This investigation is studied about the effect of Tetrachlordecaoxide (TCDO) and furosemide (F) on the course of norepinephrine-induced acute renal failure (ARF) in the dog. Animals recieving norepinephrine 0.75 g/min for 40 min consistenly developed a severe but reversible oliguric renal failure. The significant increase in mean arterial blood pressure following NE-infusion with a parallel increase in renal vascular resistance throughout the period of experiments indicate a local vasoconstriction effect of norepinephrine in the kidney (Burke, Duchin, Cronin & Schrier, 1977). Animals recieved norepinephrine infusion had a significant rise in packed cell volume. The explanation for splenic contraction leading to the expulsionof sequestered red blood cell may be responsible. It has been reported that an intravenous infusion of epinephrine also caused stariking elevation in packed cell volume in intact dogs whereas the rise in splencetomized 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.

In the present study, intrarenal infusion of 0.75 ug/kg per min of norepinephrine for 40 min produced a fall in renal blood flow (RBF) after administration in association with the cessation of urine flow on the ipsilateral kidney, while blood flow significantly increased in the contralateral kidney. A reduction in renal blood flow (RBF), glomerular filtration rate (GFR) and rise in renal vascular resistance (RVP) have been uniformly found in the initial phase of several models of ischemic-acute renal failure. Arendshorst (1975) recently studied the effect of 1 hr. of renal artery

occlusion on renal hemodynamics in the rats found that renal blood flow (RBF) was reduced by approximately 40% wheras renal vascular resistance was still increased in thirty to ninety minutes after release of the occlusion. The degree to which the decreased renal blood flow (RBF) can contribute to acute renal failure and also depends on the particular model that is studied. A general consensus exits that RBF the decrement is not related to the decreased glomerular filtration rate in the maintenance phase of ARF, regardless of model of acute renal failure employed. This mechanism may involve an increase in preglomerular resistance, either alone or in association with a decrease in postglomerular resistance (Hsu & Kurtz, 1981). The precise pathophysiologic basis for the increase in renal vascular resistance (RVR) in various forms of acute renal failure (ARF) is still ulclear. Many mechanisms may be involved e.g. endothelial cell swelling (Flores et al, 1972), role of the renin-angiotensin system and role of tubuloglomerular feed back (Thuran, Vogt & Dahlheim, 1976).

In the present results, the contralateral control kidney showed an elevation of the renal blood flow. The mechanism of this change is not clear, whether this change was due to an increase in the renal perfusion by the effect of norepinephrine or this change was similar to the study of unilateral nephrectomy and the reduction of renal mass in the contralateral kidney (Rous & Wakin,1967 ; Hayslett, Kashgarian & Epstein, 1968). However, in the present study four hours after the completion of the norepinephrine infusion,the glomerular filtration rate remained depressed in the left kidney. Several studies using the rat as the experimental model of ischemic nephropathy have suggested that tubular obstruction was the primary event responsible for the decrease in glomerular filtration rate (GFR) (Tanner and Steinhausen, 1976 ; Donohoe, Venkatachalam,

Bernard& Levinsky, 1978). Other studies revealed that the pathophysiologic process related to loss of kidney function such as reduction of glomerular filtration rate (GFR) may be due to diminished cortical blood flow (Hollenbergetal et al.,1970 ; Chedru, Baethke & Oken, 1972). and backflow of filtrate from leaky tubules (Stein et al,1975). In the present study these changes should be occured only on the infused kidney which did not affect to the GFR of the contralateral kidney.

In an attempt to increase renal blood flow to NE-infused kidney, furosemide (F) 10 mg/kg.bw. was administered. Furosemide resulted in a restoration of renal blood flow (RBF) and glomerular filtration rate (GFR) that also was associated with large increase in solute and water excretion. The importance of the rate of solute excretion in the protective effect of furosemide (F) is similar to the previous studies (Teschan and Lawson,1966). The persistance of the apparent diminution in glomerular filtration rate (GFR) may be due to a defect in glomerular permeability (Blantz, 1975; Cox et al.,1974), tubular "leakiness" (Stein, Gottschall, Osygood & Ferris, 1975) in effective net filtration pressure due to persisting tubular obstruction (Tanner and Steinhausen, 1976) or a combination of these. Alteration of glomerular permeability has been suggested by studies of Blantz (1975) in uranyl nitrate-induced ARF and those of Cox et al (1974) in the 2-h NE model. Therefore, a direct effect of furosemide (F) in restoring normal glomerular permeability needs to be considered. Likewise, an increase in solute excretion could reduce transit times through the damaged tubules and allow proportionally less urine to "backleak" into the interstitium. In addition to alteration in glomerular permeability and tubular backleak, a relief of primary or secondary tubular obstruction (Arendshorst, Finn & Gottalk, 1976) during the solute diuresis is a potential mechanism

for the protective effect of furosemide (F). The micropuncture study (Antoine et al, 1978) showed normal rather than low proximal tubular pressure 3 hour after NE in untreated animals with virtually no glomerular filtration rate (GFR) suggesting a component of relative tubular obstruction. Also, with restoration of renal blood flow (RBF) in the NE-treated rats, intratubular pressure were actually increased (Conger & Robinette, 1976). Increase proximal tubular pressure have also been observed in furosemide treated animals (Gottschalk & Mylle,1957). Increased tubular pressure induced by furosemide (F) may lessen the degree of intratubular obstruction and therefore, provide an explanation where by a brisk solute diuresis may contribute to the protection of glomerular filtration rate (GFR) in the ischemic model of acute renal failure (ARF). This hypothesis however, must remain speculative and further studies are necessary to test this possibility. In this regard, however, increasing intratubular pressure through micropipettes inserted in obstruction nephrons has been shown by both Tanner et al (1976) and Flamenbaum et al(1971)to restore function in experimental models of renal failure. Nevertheless, alteration in tubular fluid milicu provoked by a massive solute diuresis, alteration in tubuloglomerular feedback, or increased prostaglandin synthesis by furosemide (F) (Williamson et al, 1975) might have contributed to the protective effect of furosemide (F) in this model of acute renal failure (ARF). Therefore, any potential beneficial effect of furosemide (F) in acute renal failure in man will most likely involve early treatment to induce a high solute excretion rate as urinary losses are replaced. Eventhenthe beneficial effect of furosemide (F) may be primarily to convert oliguric to nonoliguric acute renal failure with its attendant lower mortality and morbidity (Anderson et al.,1977).

In the present study, the Tetrachlordecaoxide (TCDO) .005 mg/kg. bw. were administered in norepinephrine-induced acute renal failure. There were increases in renal blood flow (RBF) glomerular filtration rate (GFR) and urine flow rate (V) of the left kidney of animal treated TCDO after norpinephrine infusion. In the present study, a marked increase in renal vascular resistance in the left kidney after the treatment of these two doses of tetrachlordecaoxide (TCDO) in NE-induced acute renal failure dogs was found. However these increment of all parameters as in above were not significant different from those in the control group (group I). In the right contralateral kidney, there were similar changes in renal vascular resistance (RVR) after norepinephrine infusion of the two TCDO-treated groups as in untreated group (group I). It may propose that tetrachlordecaoxide 0.005 mg/kg.bw. and 0.01 mg/kg.bw. was not affected the renal hemodynamic of norepinephrine-induced acute renal failure animals. In spite of the vasodilatory effect of tetrachlordecaoxide (TCDO) (Youngman et al, 1985), there were no significant different of mean arterial pressure (MAP) in the post norepinephrine infusion period from the untreated group (group I).

The most common cause of acute renal failure is renal ischemia. The nature of the cellular study revealed that renal ischemia results in a rapid decrease in tissue ATP (Hems & Brosnan, 1970) and a rise in the ATP degradation products adenosine inosine and hypoxanthine (Osswald, Schmitz & Kemper, 1977). The loss of adenosine from cells by degradation during ischemia is believed to result in the depletion of adenosine nucleotides, which persists for some time even after reestablishment of blood flow. Another effect of the accumulation of hypoxanthine during renal ischemia might be generation of highly reactive oxygen free radicals since the enzymatic conversion of hypoxanthine to xanthine by xanthine oxidase generates

superoxide radicals ($O_2^{\cdot-}$) as a reduction product of molecular oxygen. Superoxide radical and its reduction products, hydrogen peroxide (H_2O_2) and hydroxyl radical (OH) can produce cellular injury. Tetrachloaradecaoxide is a non-metallic biocatalytically activated oxygen carrier and does not posses the same biological and chemical properties as the superoxide radial($O_2^{\cdot-}$),hydrogen peroxide (H_2O_2) and hydroxyl radical (OH•). As of the above mentioned qualification of tetrachlordecaoxide, it should be modified the magnitude of renal function impairments. In present study it seems likely that tetrachlordecaoxide can affect to the local renal injury tissue which had shown that in the tetrachlordecaoxide treated groups, the values of respiratory quotient(RQ) increased at the fourth hour after norepinephrine infusion when compared with the control (group I) and furosemide treated group (group IV). This result indicates that there is an increase in the renal metabolism. In conclusion, the present study suggests that the therapeutic importance of tetratchlordecaoxide 0.005 mg/kg.bw. and .01 mg/kg.bw.in acute renal failure is not good effective. The other proper doses of this drug should be used in further investaigations.