CHAPTER I

INTRODUCTION AND AIMS

Vanadate is an oxyanion derivation of the ubiquitous trace metal, vanadium, which occurs in various concentrations in air, water, soil, microorganism, plants, animals and human. This agent is normally ingested in foods. Northeastern Thailand has been known to be the vanadium-rich environmental area. Vanadium has been shown to occur in the urine of 30 % of the people in this region studied (Visith Sitprija et al., 1990). Vanadium is both a physiologically and pharmacologically active substance by a low concentration. A functional role, however, has not been identified. It has been suggested that vanadate may serve as a regulator or modifier of many enzymes and play a vital role in intermediary metabolism (Nechay et al., 1986). Trace amounts of vanadium can be detected in most mammalian tissue; the highest concentrations are often found in the kidney especially in the renal cortex. It is excreted in the urine and is accumulated by renal cells in the course of its elimination (Bogden et al., 1982).

An intravenous or intrarenal-arterial administration of vanadate produces potent vasoconstrictor effects, increased the arterial blood pressure, fell cardiac output (Inciarte et al., 1980; López-Nova and Garrido, 1986; Sánchez-Ferrer et al., 1988) and decreased renal blood flow and glomerular filtration rate (Higashi and Bello-Reuss, 1980; Hatfield and Churchill, 1981; López-Novoa, Mayol, and Martínez-Maldonado, 1982; Benabe, Cruz-Soto, and Martínez-Maldonado, 1984; Kannika Chankasem, 1991). Cardiovascular effects of this agent have also been indicated to relate the sodium pump inhibition which play a role in the etiology of

volume expanded, low-renin type of hypertension (López-Novoa et al., 1982; Sundet et al., 1984). The hemodynamic changes have been shown to accompany by a decrease in renin secretion and vascular ATPases system (López-Novoa et al., 1982; Jadhav and Jandhyalo, 1983). Inhibition of Na^+-K^+ATPase by vanadate would lead to cell depolarization in smooth muscle by increasing the influx of calcium or decreasing the efflux of calcium from the cell. Inhibition of calcium pumps could also reduce calcium efflux from the cytoplasm of muscle cell. The increase in cytoplasmic calcium from any of these mechanisms may serve as a stimulus for vasoconstriction. Vanadium-induced alterations in sodium pump activity also occur in the neuronal tissues and affect to increasing the release of noradrenaline from adrenergic sympathetic nerve ending (Inciarte et al., 1980; Sánchez-Ferrer et al., 1988). It has been suggested that vanadate can produce cardiovascular alterations by a mechanism mediated via the autonamic central nervous system (Hom, Chelly, and Jandhyalo, 1982). The mechanism of the hemodynamic actions of vanadate is still not clear.

There are, however, marked differences of renal function in the response to vanadium among different species. Vanadate is a potent diuresis and natriuresis in rat (Day et al., 1980; Higashi and Bello-Reuss, 1980; Hatfield and Churchill, 1981; Westenfelder, Hamburger, and Garcia, 1981). Earlier studies by clearance technique, isolated renal tubular cell and micropuncture experiments demonstrated that vanadate inhibited proximal sodium, chloride, water, bicarbonate and glucose reabsorption and p-aminohippurate (PAH) secretion. Vanadate decreased potassium secretion and also depressed both free water formation and salt reabsorption along the assending limb of Henle's loop (Higashi and Bello-Reuss, 1980; Westenfelder, Hamburger, and Garcia, 1981; Edwards and Granthm,1983a). Vanadate inhibited the initiation of the vassopressin which induced increase in hydroosmotic permeability at a site distal tubule. The effect of vanadate on cyclic-AMP formation and rapid decrease in the

lumen-negative transepithelial voltage decreased free water and sodium reabsorption in the cortical collecting tubule (Edwards and Grantham, 1983b) and in toad bladder (Arruda and Westenfelder, 1983). In vivo studies in dogs indicated that vanadium caused a pronounced reduction of the urine flow and sodium excretion, which was probably mediated by marked renal vasoconstriction. Fractional reabsorption of sodium and water could be decreased in proximal tubule, but the excess sodium and water reabsorption occurred in distal sites of the nephron (Higashi, and Bello-Reuss, 1980; López-Novoa, Mayol, and Martínez-Maldonado, 1982).

It has been known that proximal and distal renal tubular acidosis are assumed to be a generalized defect in HCO_3^- and H^+ transport in renal tubular cells. The defect may relate to the activity of Na^+-K^+ATPase, HCO_3^-ATPase, H^+ATPase, H^+-K^+ATPase and Na^+-H^+ exchange which is either directly or indirectly interfered by vanadium (Arruda, Sabatini, and Westenfelder, 1981; Westenfelder, Hanburger, and Garcia, 1981; Visith Sitprija et al., 1990; Kannika Chankasem, 1991; Dafnis et al., 1992). However, there have been no detailed studies in either mediators or enzymes are responsible for renal function during acute intravenous sodium metavanadate administration in the dogs.

Thus, the purpose of the present study was to investigate the ***in vivo*** effects of intravenous sodium metavanadate infusion on cardiovascular, renal hemodynamics, and renal tubular function espectially proximal and distal tubular functions. Further examinations were performed to elucidate the mechanisms responsible for the alterations whether were mediated by interfering adrenergic sympathetic nervous system via the alpha-1 adrenergic receptors (using prazosin, selective alpha-1 adrenoceptor blocker) or beta-1 adrenergic receptors (using atenolol, selective beta-1 adrenoceptor blocker) or changes in renin-angiotensin system (using enalapril maleate,

converting enzyme inhibitor) and/or a direct result of the actions of vascular or renal tubular cell ATPase system (using acetylcholine, increasing sodium influx likely enhances calcium efflux through a sodium-calcium exchange, and verapamil, decreasing calcium influx through a voltaged-dependent calcium channel) in anesthetized dogs using conventional clearance techniques.