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Renal Actions of Orthovanadate in the Dog (41452)

JOSE M. LOPEZ-NOVOA, VANESSA MAYOL, AND MANUEL MARTINEZ-MALDONADO[1]

Renal Metabolic Laboratory, Medical and Research Service, San Juan Veterans Administration Hospital, and the Department of Medicine and Physiology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Abstract. The renal effects of orthovanadate (VO_4) were examined in anesthetized mongrel dogs. Orthovanadate was infused into one renal artery in concentrations ranging from 0.075 to 1.5 μmole/min. All major effects were observed only in the infused kidney. Renal vascular resistance (RVR) rose with increasing doses from normal (1.5 mm Hg/ml/min) to as high as 36. In general, the higher the dose the higher the RVR. Identical relationships between dose and response were observed for GFR and RBF which fell dramatically. There was also a fall in the excretion of water, sodium, and potassium. The intense vasoconstriction induced by VO_4 (0.5 μmole/min) was ameliorated by volume expansion (5% body weight with Ringer's saline), papaverine (0.5 mg/min), and acetylcholine (40 μg/min). Despite all these there were only modest increases in fractional sodium and potassium excretion. Systemic hemodynamic changes of VO_4 were a slight increase in mean arterial pressure (99 ± 8 to 107 ± 4 mm Hg), decreased heart rate (100 ± 5 to 82 ± 9 beats/min). It appears that VO_4 has a predominately vascular effect on the dog kidney with no discernible tubular effects under the conditions of these experiments. While the mechanism of the vasoconstriction are not clear they may be related to the effect of VO_4 on the ATPase system of vascular smooth muscle.

The enzymatic complex of Na^+,K^+-ATPase, found on the basolateral surfaces of the renal tubules, is of major importance in the transepithelial transport of sodium (1–4). The recent discovery that vanadate, an oxyanion of vanadium normally present in mammalian tissues (5–7), is a potent inhibitor of Na^+,K^+-ATPase *in vitro* (8) stimulated the study of the effect of this oxyanion in the intact animal. Vanadate has been reported to induce a massive diuresis and natriuresis when administered to rats (9–12). This effect seems to be mainly mediated by a decrease in proximal tubular reabsorption (11). Decreased reabsorption in more distal sites and/or different effects on juxtamedullary nephrons have been suggested (11, 12). In dogs the renal effects of vanadate have been observed only after its systemic administration, but no thorough analysis of its direct effects on the kidney has been attempted. Studies in dogs are of particular interest since this species, in contrast to rats, has a great sensitivity to ouabain, the classical inhibitor of Na^+,K^+-ATPase (13, 14). The present experiments were undertaken to determine by clearance techniques the effect of sodium orthovanadate on renal function in the dog.

Materials and Methods. Mongrel dogs of either sex weighing from 12 to 20 kg were studied. The animals were deprived of food but not of water overnight and all experiments started at 8:00 AM. The dogs were anesthetized with sodium pentobarbital (30 mg/kg iv). Subsequent small doses were administered as needed in order to maintain light anesthesia. Each dog had an endotracheal tube introduced, connected to a Harvard respirator and ventilated with room air. A catheter was placed in the left femoral vein for infusion of inulin (12.5 g/liter) and PAH (5 g/liter) diluted in Ringer's solution at a rate of 0.5 ml/min. Blood pressure was monitored through a femoral artery catheter using a pressure transducer

[1] Reprint requests should be addressed to Dr. M. Martínez-Maldonado, Chief, Medical Service, San Juan, V.A. Hospital, GPO Box 4867, San Juan, P.R. 00936.

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(Statham Instruments, Hato Rey, Puerto Rico) and recorder (Hewlett–Packard, Model 775A, Hewlett–Packard Co., Palo Alto, Calif.). After laparotomy, both ureters were cannulated with polyethylene catheters (PE 100).

The left kidney was exposed, and the left renal vein was catheterized through the ovarian or spermatic vein for venous collections. A hooked 23-gauge needle was placed in the renal artery. The cuff probe of an electromagnetic flowmeter (Gould Statham Sp-2202, Oxnard, Calif.) was placed around the renal artery close to its origin. Renal blood flow in both kidneys was calculated from the PAH clearance and hematocrit. Renal blood flow measurements by flowmeter and clearance methods in the experimental kidney agreed within 5% allowing the use of the PAH method as a reflection of RBF of the right kidney. Arterial blood pressure and renal blood flow were measured continuously throughout the experiment. Also arterial and urine pH, and PCO_2 were frequently monitored using a BMS3MK2 blood microsystem (Radiometer, Copenhagen, Denmark). Heart rate was measured on the pressure graph. An equilibration period of at least 45 min was allowed before any collection was started. All clearance periods were of 20 min duration with arterial and renal vein blood samples collected at midpoint for electrolytes and PAH determinations. Urine and plasma sodium and potassium were measured by flame photometry.

Group I. Vanadate group ($n = 7$). Following three control periods in which Ringer's solution was infused into the left renal artery at a rate of 0.5 ml/min, Na_3VO_4 diluted in Ringer's solution was infused into the renal artery at doses ranging between 0.075 and 1.5 μmole/min. After an equilibration period of 10 min, three periods of 20 min each were obtained. In most of the animals a second dose higher than the first was infused, and the clearance periods repeated.

Group II. Volume expansion, vanadate, and recovery ($n = 4$). Once the surgery was completed, animals were infused with isotonic Ringer's solution at a rate of 1 ml/min/kg of body weight. In addition, mannitol (20 mg/min) was infused throughout the experiment. After three control periods in which Ringer's solution was infused into the renal artery (0.5 ml/min), Na_3VO_4 in Ringer's (1 mmole; 0.5 ml/min) was infused into the renal artery. Three clearance periods were obtained after a 10-min equilibration period, and vanadate infusion was stopped. Then, three further clearance periods were done.

Group III. Volume expansion, vanadate (V), and papaverine (P) group ($n = 5$). Once the surgery was completed, animals were infused with isotonic Ringer's solution at a rate of 1 ml/min/kg of body weight. In addition, mannitol (20 mg/min) was infused throughout the experiment. After three control periods in which Ringer's solution was infused into the renal artery at a rate of 0.5 ml/min, Na_3VO_4 diluted in Ringer's (0.5 ml/min) was infused into the renal artery at a dose of 0.5 μmole/min through the rest of the experiment. After an equilibration period of 10 min, two clearance periods of 20 min each were obtained. Then, papaverine, 0.5 mg/min (diluted in Ringer's; 0.5 ml/min), was also infused into the left renal artery and three further clearance periods obtained. Papaverine infusion was stopped and two more clearance periods were studied.

Group IV. Volume expansion + PAP + V ($n = 6$). A protocol identical to group II was followed, except that papaverine was infused before vanadate.

Group V. Volume expansion + acetylcholine (Ach) + V ($n = 5$). This group was studied in identical fashion as group IV, except that acetylcholine (40 μg/min) was infused instead of papaverine.

Results are expressed as the mean ± SEM of each phase for the experimental (left) and control kidney. The comparisons presented are the differences between experimental phases from the same kidney. The t test for paired and unpaired data was used to analyze the data whenever appropriate.

Results *A. Renal effects.* The effects of vanadate were observed primarily in the infused kidney, with little if any change in

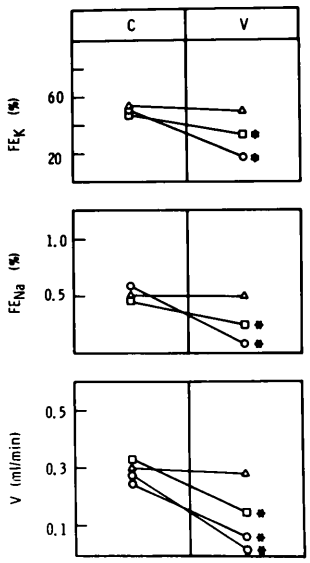

FIG. 1. Changes in urine flow (V), fractional excretion of sodium (FE_{Na}) and potassium in response to intrarenal vanadate (V) infusion at several doses: 0.075 (△), 0.35 (□), 0.5 (○), 1.5 μmole/min (⬭). Asterisks represent significant changes ($P < 0.05$) from previous values.

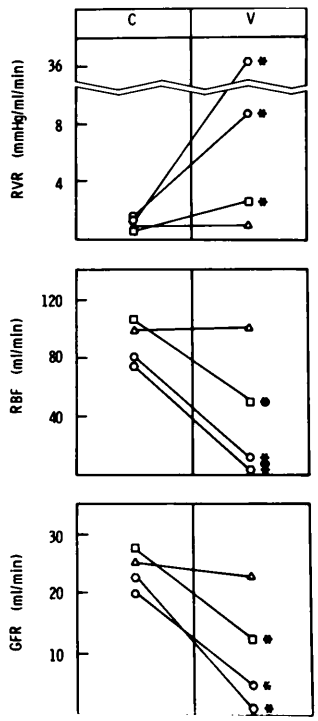

FIG. 2. Changes in glomerular filtration rate (GFR), renal blood flow (RBF), and renal vascular resistance (RVR) in response to intrarenal vanadate infusion at various doses. Symbols as in Fig. 1.

the control kidney. In the tables only values for the experimental kidney are given, whereas in the figures both kidneys are represented. In this particular model the manipulation of the experimental kidney's hilus for insertion of the needle and blood flowmeter and inadvertent stimulation of renal nerves, allows for some of the initial differences in function between the two kidneys. Nevertheless, this model has the advantage that is allows the longitudinal analysis of the changes in the infused kidney, while monitoring the contralateral kidney. In the studies there were only slight changes in the control kidney.

1. Group I. Vanadate. Results from group I are shown in Figs. 1 and 2. Vanadate caused a dose-dependent decrease in GFR, RPF, urinary flow, and sodium and potassium excretion. Doses lower than 0.1 μmole/min did not produce any appreciable effect, whereas a dose higher than 1.5 μmole/min induced a virtual cessation of glomerular filtration and urine production. Glucosuria or proteinuria were not observed.

2. Group II. Volume expansion + vanadate. Results from group II are shown in Figs. 3 and 4. This group received saline and mannitol to determine if volume expansion per se, rather than renal vasodilation, influences the effect of vanadate. Volume expansion prior to vanadate infusion partially prevented the renal hemodynamic effects seen with the compound. Nevertheless, vanadate, infused at a dose of 0.5 μmole/min still caused a marked vasoconstriction, with decrease in GFR, urine flow, and in the absolute and fractional excretion of sodium and potassium. These changes were essentially identical regardless of animal weight. Moreover, although modest, a small but significant reduction in RBF and GFR in the contralateral kidney was observed without changes in water or electrolyte excretion. Filtration fraction increased significantly after vanadate infusion (from 35.8 ± 2.5 to 43.2 ± 2.4%; $P < 0.05$).

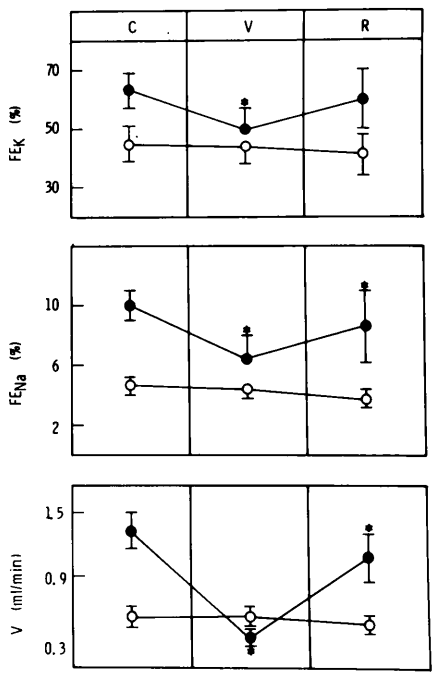

FIG. 3. Changes in urine flow (V). Fractional excretion of sodium (FE_{Na}) and potassium (FE_K) in group II. Left (infused) kidney (●) and right (noninfused) kidney (○) are presented. Asterisks represent significant changes from the previous period ($P < 0.05$).

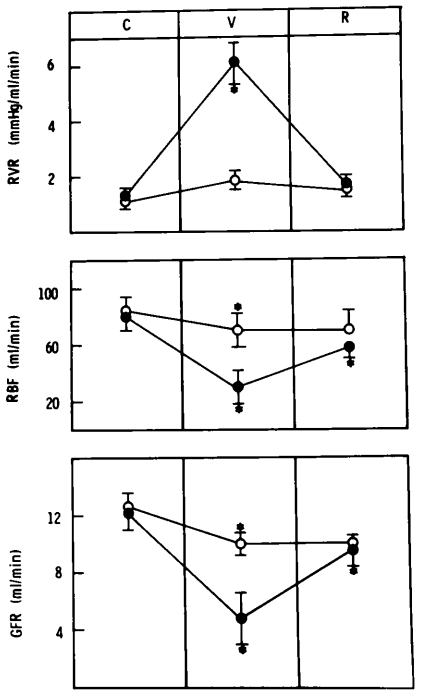

FIG. 4. Changes in glomerular filtration rate (GFR), renal blood flow (RBF), and renal vascular resistance (RVR) in the animals from group II. Symbols as in Fig. 3.

When vanadate infusion was stopped GFR, RBF, FF, and vascular resistance returned toward basal values immediately. From Fig. 5 we can observe that the increase in RBF was prompt and reached its maximal recovery after stopping vanadate within 5 min. GFR and RBF during the recovery period, however, remained lower than control values.

3. Group III. Vanadate + papaverine. Results from group III are shown in Figs. 6 and 7. The effects of vanadate were essentially the same as those seen in group II. Papaverine, however, led to increases in GFR, RBF, and fractional excretion of sodium and potassium. Renal vascular resistance and filtration fraction decreased markedly. When papaverine infusion was stopped, the changes induced by vanadate became manifested: Renal vascular resistance increased abruptly, while there was a sharp fall in RBF, GFR, and V. FE_{Na} and FE_K changed little.

4. Groups IV and V. (Papaverine and vanadate, acetylcholine and vanadate.) Results from groups IV and V are shown in Table I. Only values for the experimental kidney are presented. When papaverine was previously infused, vanadate administration caused hemodynamic changes in the same direction but of lower intensity than when infused alone. In contrast, fractional excretion of sodium and potassium in-

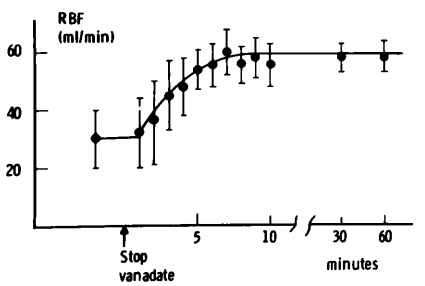

FIG. 5. Changes in renal blood flow (RBF) measured by magnetic flowmeter after stopping vanadate infusion in the left kidney in group II dogs.

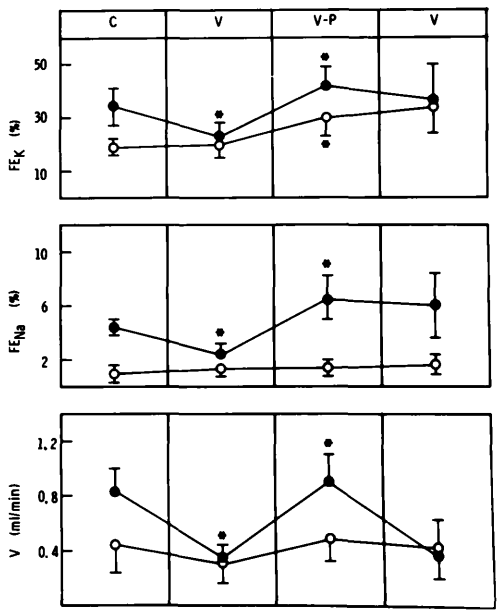

FIG. 6. Changes in urine flow (V), fractional excretion of sodium (FE_{Na}) and potassium (FE_K) in group III. Symbols as in Fig. 3.

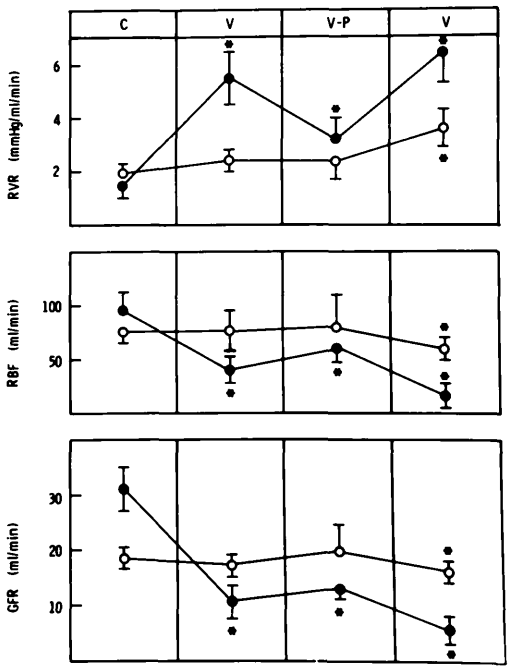

FIG. 7. Changes in glomerular filtration rate (GFR), renal blood flow (RBF), and renal vascular resistance (RVR) in the animals in group III. Symbols as in Fig. 3.

creased, but these increases were not significant. The cessation of papaverine infusion restored the effect of vanadate. Acetylcholine partially prevents the hemodynamic changes induced by vanadate; small but insignificant increments in fractional excretion of sodium and potassium occurred.

There were no changes in the control kidney except in the acetylcholine experiments where there was a fall in RBF and GFR and a rise in renal vascular resistance when the infusion of the vasodilator was discontinued. No doubt this was a result of systemic "spillage" of vanadate.

B. Systemic effects. Table II summarizes the systemic effects of intrarenal infusion of vanadate. There were no changes in blood volume as assessed from the hematocrit. Vanadate reduced heart rate and raised mean arterial pressure, an effect which was totally blocked by papaverine and partially by acetylcholine.

Discussion. Our results demonstrate that infusion of orthovanadate into the renal artery of dogs induces a striking but reversible increase in renal vascular resistance, a fall in renal blood flow and GFR, and sharp declines in urine volume, sodium and potassium excretion. The effects on water and electrolyte excretion seem to be mediated by the changes in renal hemodynamics induced by vanadate. When the fall in renal blood flow returned toward basal levels as a result of acetylcholine or papaverine, urine flow and sodium excretion returned to values near control levels. Fractional excretion of sodium and potassium differed little from basal values, suggesting that direct tubular effects of vanadate to inhibit sodium reabsorption, if any, are modest. The best explanation for the antinatriuresis observed seems to be the changes in renal hemodynamics.

These results are different from those obtained in rats. In this species vanadate has been found to produce clear-cut increases in urinary volume and sodium excretion when infused as a bolus (10, 11), as continuous infusion (10, 12, 15), or when added to the perfusate of isolated kidneys (16). Micropuncture data suggest that vanadate inhibits sodium and fluid reabsorption

TABLE I. RENAL EFFECTS OF VANADATE DURING RENAL VASODILATION

	V (ml/min)	GFR (ml/min)	RBF (ml/min)	FE_{Na} (%)	FE_K (%)	RVR (mm Hg/ml/min)
			Group IV (n = 6)			
C	1.6 ± 0.5	15.9 ± 2.6	74 ± 9	9 ± 2	40 ± 10	1.6 ± 0.2
P	1.5 ± 0.4	15.2 ± 3.4	77 ± 14	8 ± 2	45 ± 8	1.6 ± 0.2
P + V	1.4 ± 0.4	11.3 ± 2.4*	44 ± 7*	9 ± 2	49 ± 13	2.8 ± 0.7*
V	0.5 ± 0.3*	3.5 ± 2.0*	29 ± 2*	7 ± 2*	53 ± 16	3.9 ± 0.9*
			Group V (n = 5)			
C	1.0 ± 0.1	20.9 ± 3.0	119 ± 21	4 ± 0.5	33 ± 3	1.0 ± 0.2
Ach	2.0 ± 0.8	20.8 ± 3.0	155 ± 21*	6 ± 0.5*	40 ± 5	0.6 ± 0.1*
Ach + V	2.3 ± 0.9	16.8 ± 2.0	120 ± 16*	5 ± 0.5	54 ± 12	1.0 ± 0.1*
V	0.3 ± 0.1*	6.6 ± 1.3*	31 ± 7*	2 ± 0.5*	32 ± 9	5.1 ± 1.1*

Note. All values are means ± SEM. Only the experimental kidney values are presented. C, control; V, vanadate; P, papaverine; Ach, acetylcholine.
* $P < 0.05$ compared to previous value.

in the proximal tubule (11). Furthermore, in rats VO_4 depresses free-water formation at any level of distal sodium delivery, suggesting interference with salt reabsorption in the ascending limb of Henle's loop (12).

In dogs, as well as in the cat, the renal vascular effects of vanadate seem to predominate over the tubular effects (17–19). In these species, vanadate infusion produces vasoconstriction and a decrease in urine flow and sodium excretion. In the rat the hemodynamic alterations in response to vanadate are qualitatively similar, but quantitatively less than in the dog ((10, 15), López-Novoa and Martínez-Maldonado, unpublished observations). In the present experiments, vanadate infused in the renal artery caused a potent renal vasoconstriction, a small increase in MAP, and a decrease in heart rate. Vanadate has been shown to produce vasoconstriction in most mammalian vascular beds and to raise blood pressure (18, 20, 21). It also has a direct action on the contractility of the myocardium (22–24).

Under the present experimental conditions only small alterations in myocardial function and peripheral vascular resistance, as inferred from heart rate and blood pressure changes, took place. The marked preferential renal vasoconstriction in our studies can be explained by the high concentration of the drug in the renal circulation, but a high sensitivity of the renal vasculature to the vanadate cannot be discarded. In this regard, the intravenous administration of vanadate in the cat increases vascular resistance in the areas supplied by the renal artery but not in those supplied by the femoral and carotid arteries (21). Moreover, the kidneys are one of the sites where vanadium reaches highest concentrations in the body (5–7). Vanadium concentration is higher in the cortex, the zone where changes in renal vascular resistance are most likely to occur.

The mechanism of the renal vasoconstriction is not clear. Renal vasoconstriction disappears promptly after vanadate infusion is stopped and can be relieved by papaverine or acetylcholine infusion. Inhibition of Na^+,K^+-ATPase would result in a reduced transmembrane gradient of Na^+ concentration, which would slow the Ca^{2+} efflux through the Na^+-Ca^{2+} exchange mechanism in the membrane. The increase in the intracellular concentration of calcium would lead to contraction (23). Vanadate also inhibits the sarcoplasmic Ca^{2+}-ATPase which is considered to be responsible for active Ca^{2+} uptake leading to reduced cytoplasmic Ca^{2+} concentration (26–28). Since vanadate inhibits ATPase from inside cells, prompt reversal of vasoconstriction upon stopping its infusion suggests either rapid metabolic clearance or easy dissociation from the enzyme. Papaverine reduces Ca^{2+} influx into cells (29) while acetylcholine, by increasing Na^+ influx most likely enhances Ca^{2+} efflux through a Ca^{2+}-Na^+ exchange

TABLE II. CHANGES IN HEMATOCRIT, HEART RATE, AND MEAN ARTERIAL PRESSURE

	Hematocrit (%)	Heart rate (beats/min)	MAP (mm Hg)
	Group II (n = 4)		
C	33 ± 5	110 ± 5	99 ± 8
V	34 ± 5	97 ± 5*	107 ± 4*
R	34 ± 6	85 ± 10	95 ± 6*
	Group III (n = 5)		
C	34 ± 2	130 ± 9	147 ± 3
V	36 ± 2	120 ± 10*	155 ± 3*
V + P	37 ± 2	125 ± 8	155 ± 5
V	39 ± 2	117 ± 9*	166 ± 7*
	Group IV (n = 6)		
C	39 ± 2	132 ± 9	113 ± 9
P	38 ± 2	136 ± 8	103 ± 12*
P + V	38 ± 2	129 ± 8	107 ± 13
V	38 ± 3	110 ± 9*	108 ± 20
	Group V (n = 5)		
C	38 ± 1	140 ± 9	99 ± 8
Ach	37 ± 1	133 ± 11	95 ± 11
Ach + V	39 ± 2	126 ± 9	108 ± 10*
V	39 ± 2	108 ± 6*	124 ± 7*

Note. All values are means ± SEM. C, control; V, vanadate; P, papaverine; Ach, acetylcholine.
* $P < 0.05$ compared to previous value.

mechanism (25). These effects suggest that vanadium induces marked renal vasoconstriction by increasing Ca^{2+} concentration in the cytosol. While the mechanism for the partially protective effects of volume expansion is not clear it might also involve change in cytosolic calcium concentration. Since this proposal is at present speculative further experiments are required to corroborate it.

The mechanism for the lack of consistent effect of vanadate on renal sodium and water reabsorption cannot be adequately explained by these experiments. Nevertheless some major possibilities can be considered. First, the dose of vanadate used could have the ability to act in the vascular bed but not reach the Na^+,K^+-ATPase of the tubular cells. In support of the possibility, Steffen *et al.* (30) have reported that rats fed chronically with vanadate present marked increases in blood pressure but do not demonstrate increases in sodium excretion. This indicates a dissociation between vascular and tubular actions of vanadate. A second possibility is that while vanadate inhibits tubular ATPase, the natriuresis is not manifested. This could be the result of an increase in peritubular oncotic pressure with a fall in hydrostatic pressure due to the increased filtration fraction.

Finally fractional reabsorption could be decreased in the proximal tubule, but the excess sodium and water reabsorbed in more distal sites of the nephron. A similar hypothesis has been advanced by Higashi and Bello-Reuss to explain the lack of diuretic and natriuretic response to the infusion of a bolus of 0.5 μmole of vanadate at a time when proximal tubular reabsorption was clearly reduced.

In summary, vanadate has profound but reversible renal hemodynamic effects in the dog in which it does not exhibit clear tubular effects. The vasoconstriction may be partially reversed by volume expansion, papaverine, or acetylcholine. The precise mechanisms of the vascular effects of vanadate are not known, but may be related to inhibition of vascular smooth muscle ATPases and changes in cytosolic calcium

content. The mechanism for the difference between rats and dogs in response to vanadate is not clear at present.

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