Effect of Reducing Renal Arterial Blood Pressure by Balloon Catheter on Urate Excretion in the Dog.* (28830)

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Previous investigators(1-4) have shown that when renal arterial blood pressure is reduced in the dog, whether by inflation of a balloon-tipped catheter inserted into the aorta above the level of the renal arteries or by direct renal arterial constriction, the excretion of sodium falls at a precipitous rate disproportionate to the reduction in glomerular filtration rate (GFR), under conditions of less than maximal sodium loading of the nephron. In contrast, the excretion of potassium, which unlike sodium involves tubular processes of secretion as well as glomerular filtration and tubular reabsorption, diminishes at a rate less than or proportional to the reduction in GFR(3,4). The present study, using the balloon-tipped catheter technic in the dog(2), shows that renal elimination of uric acid responds like potassium excretion to graded reduction in renal arterial blood pressure. It is further shown that the response to reduction in renal arterial blood pressure in the mongrel dog, under conditions of net tubular reabsorption of urate, is similar to that in the Dalmatian coach hound, under conditions of net tubular secretion of urate.

Methods. The experiments were carried out in 18 mongrel and 4 Dalmatian dogs, 18-22 kg in weight, anesthetized with pentobarbital sodium in a dose of 30 mg per kg. Appropriate priming and sustaining infusions containing creatinine (in some experiments both creatinine and inulin), para-aminohippurate, urate and mannitol were administered. Mannitol was given in amounts of 26 g to prime, and in 5% concentration in the sustaining solution, which was delivered at a constant rate, variously 4 to 8 ml per minute in different experiments. The priming dose of uric acid varied from 0.2 to 1.5 g, the sustaining rate from 2 to 16 mg per minute, to give plasma urate levels over a range of 1.2 mg% to 26.5 mg% in different experiments. Plasma levels of creatinine were maintained at 20-30 mg%, PAH at 2-4 mg%. Through a separate vein, isotonic sodium chloride was given at rates of 3 to 5 ml per minute, to prevent the development of hyponatremia resulting from rapid urine flow rates. Sodium and potassium clearances were measured in 9 experiments, for purposes of comparison with uric acid excretion.

The balloon-tipped catheter was passed *via* a femoral artery to the level of the diaphragm, just above the origin of the renal arteries, as confirmed by fluoroscopy. Mean femoral arterial blood pressure, taken as a measure of the mean renal arterial blood pressure, was monitored by a damped mercury manometer inserted in the contralateral femoral artery. Three or four collection periods were obtained before balloon inflation. By graded degrees of inflation of the balloon, renal arterial blood pressure could be altered, then maintained at the mean pressure desired(2). An equilibration period of 10 to 15 minutes at a particular level of mean pressure was followed by 3 to 6 experimental periods, each lasting 7 to 15 minutes. The level of mean renal arterial pressure was then further altered by varying the degree of balloon inflation, and the process repeated. Finally, the balloon was deflated to permit return of the renal arterial blood pressure to or toward control levels, for appropriate comparison of clearance measurements. Clearance techniques and analytical methods employed were as previously described(7).

Results. Table I depicts a typical experiment in a Dalmatian dog, in which urate was given in a dose of 1.5 g to prime, then at a sustaining rate of 14 mg per minute. The ratio of excreted urate ($U_{urate}V$) to filtered urate (F_{urate}) remained greater than 1.0 throughout this experiment, as in the 3 other

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TABLE I. Effect of Graded Decrements in Mean Renal Arterial Blood Pressure on Renal Hemodynamics and Various Discrete Renal Functions in the Dog.

Mean renal arterial pressure, mm Hg	$C_{creatinine}$ ml/min	$C_{creatinine}$ % control	C_{PAH}, ml/min	C_{cr}/C_{PAH}	P_{ur}, mg %	$U_{ur}V$, mg/min	F_{ur}, mg/min	$U_{ur}V/F_{ur}$	$U_{Na}V/F_{Na}$	U_KV/F_K
D #2534										
150	64	100	213	.30	21.0	14.2	13.5	1.05	.072	.65
95	46	72	169	.27	21.7	11.9	10.0	1.19	.047	.63
75	33	52	126	.26	23.2	10.3	7.7	1.34	.026	.63
60	29	45	116	.25	26.0	8.5	7.5	1.12	.005	.49
155	42	65	138	.30	26.5	11.9	11.0	1.08	.071	.65
M #4134										
140	82	100	210	.39	1.6	.54	1.31	.41	.035	.26
100	69	84	178	.39	1.4	.45	.99	.46	.019	.29
85	60	73	138	.43	1.4	.44	.86	.51	.011	.29
75	55	67	124	.44	1.5	.44	.82	.54	.004	.26
185	62	76	124	.50	1.5	.49	.95	.52	.022	.30
M #4499										
140	85	100	199	.43	4.6	2.02	3.90	.52	.031	.29
90	65	76	175	.37	4.5	1.78	2.92	.61	.035	.35
	67	79	180	.37	4.6	2.15	3.08	.70	.024	.32
70	65	76	165	.39	4.7	2.22	3.04	.73	.020	.32
	61	72	154	.40	4.8	2.18	2.93	.75	.015	.29
160	68	80	167	.41	5.2	2.20	3.52	.63	.043	.43
M #3997										
158	54	100	197	.28	8.1	2.39	4.40	.54		
120	29	53	137	.21	8.1	1.08	2.33	.46		
135	36	66	152	.24	7.9	1.36	2.78	.49		

Each figure represents the mean of 3 clearance periods. D = Dalmatian coach hound. M = Mongrel dog.

Dalmatians studied, at all levels of mean renal arterial pressure. When the mean renal arterial pressure was lowered from 150 to 75 mm Hg, GFR and F_{urate} concomitantly fell approximately 50% but $U_{urate}V$ declined only moderately, and the ratio of excreted urate to filtered urate rose appreciably. The proportion of excreted sodium ($U_{Na}V$) to filtered sodium (F_{Na}) showed the expected sharp decline, markedly greater in percentage than the fall in GFR; the ratio of excreted potassium (U_KV) to filtered potassium was unaltered. The effective renal plasma flow, as measured by the clearance of para-aminohippurate (C_{PAH}), decreased roughly in proportion to the GFR. On deflation of the balloon, and return of renal arterial pressure to control levels, GFR and C_{PAH} rose, although not to the original levels. Filtered and excreted urate rose too, and the ratio UV/F for urate and Na returned toward control values.

In Table I are also summarized representative experiments in 3 mongrel dogs. In M4134, urate was given in a dose of 0.2 g to prime, then at a sustaining rate of 2.0 mg per minute. In M 4499 and M3977, the priming dose was 1.5 g urate, the sustaining dose was 14 mg/min and 16 mg/min respectively. The ratio of excreted to filtered urate remained below 1.0 in the 3 experiments (as in all others with mongrels), indicating net tubular reabsorption of urate. As mean renal arterial pressure was reduced about 50% in M4134 and M4499, GFR fell to approximately 70% of control, F_{urate} about the same degree. The ratio $U_{urate}V/F_{urate}$ rose somewhat in M4134 and M4499, whereas in M3977 there was a slight decline after smaller reductions in pressure, GFR and F_{urate}. The ratio of excreted to filtered sodium fell markedly, while that for potassium did not. On deflation of the balloon, renal arterial pressure usually rose to a level somewhat above control, due to obscure pressor effects(3). GFR, F_{urate} and $U_{urate}V$ all increased, although not to control levels. UV/F for urate remained elevated above the control, or rose toward control levels. UV/F for sodium returned toward control values, that

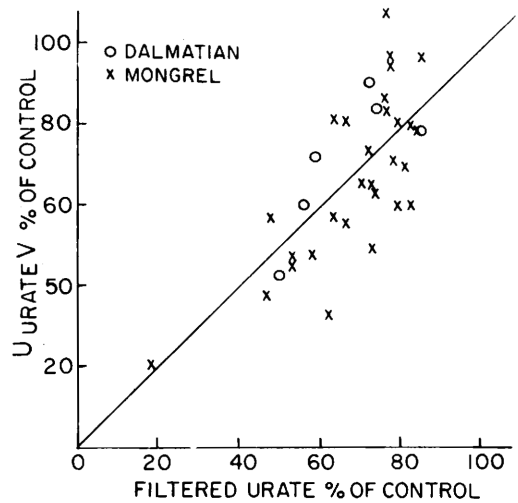

FIG. 1. Effect of reduction in GFR on relationship of $U_{ur}V$, % of control value at initial GFR, to F_{ur}, % of control value at initial GFR. As the GFR is reduced, both parameters decline roughly proportionately in Dalmatian and mongrel dogs. See text.

for potassium exceeded the initial value slightly in some experiments.

Fig. 1 is a résumé of the results in all Dalmatian and mongrel dogs studied. Each point represents the averaged value of 3 or more periods at a particular level of mean renal arterial pressure. The ordinate represents excreted urate, *plotted as % of control value*, and the abscissa filtered urate, *plotted as % of control value*. The diagonal line represents proportionate changes in excreted and filtered urate such that the ratio UV/F would remain unaltered from the control value. On this plot the control points, not shown, would have coordinates at 100% on each axis. In the Dalmatians, at all levels of mean renal arterial blood pressure, net tubular secretion was maintained, UV/F remaining above 1.0. In most cases the decline in excreted urate as GFR was reduced was less than that of filtered urate, so that UV/F rose, and most points fall above the diagonal line. Thus, although both functions declined as mean pressure was reduced, net tubular secretion of urate was maintained in the face of marked reduction in GFR and F_{urate}. A lesser effect of diminution of renal arterial blood flow on the renal tubular secretory mechanism for urate than on GFR is implied.

In the mongrels, there was net urate reabsorption in the control periods, the control ratio of excreted to filtered urate ranging from 0.36 to 0.94, depending upon the rate of urate infusion. As GFR was reduced by balloon inflation, and filtered urate diminished, the decline in excreted urate was close to proportionate in most instances. Except for a greater tendency for the points to fall below the no-change diagonal, *i.e.*, a greater tendency for UV/F to fall off, the distribution of points is similar to that in the Dalmatian.

The declines in excreted urate after balloon inflation correlated as well ($p = 0.05$) with changes in C_{PAH} as with changes in GFR, the ratio GFR/C_{PAH} remaining fairly constant throughout most experimental periods. Lauson and Thompson(3) have shown that for declines in GFR down to 60% of control, tubular transport capacity for PAH is not affected; consequently, within this range, wherein most of the present experimental observations fall, a rough correlation may be drawn between urate excretion and effective renal plasma flow as estimated by C_{PAH}.

Discussion. In the Dalmatian coach hound, in which tubular reabsorption of uric acid is inherently deficient, $U_{urate}V/F_{urate}$ ratios normally approximate 1.0, and values > 1.0, indicative of net tubular secretion of uric acid, are readily achieved by moderate loading with uric acid(5-7). In the mongrel dog, however, $U_{urate}V/F_{urate}$ ratios normally approximate 0.3, and the demonstration of tubular secretion of uric acid is difficult. $U_{urate}V/F_{urate}$ ratios > 1.0 have been achieved in the mongrel dog(6,7), as in the rabbit(8) and in man(9), but only by massive uric acid loading, with vigorous osmotic diuresis and use of drugs that inhibit tubular reabsorption of uric acid. This demonstration that the tubules of the mammalian kidney have not lost the primitive capacity for uric acid secretion implies that under more natural conditions of net tubular reabsorption of uric acid, secretion is occurring but is masked by preponderant reabsorption. The results of the present study are consistent with this interpretation. It is shown that in the Dalmatian, under conditions of net tubular secretion of uric acid, the $U_{urate}V/F_{urate}$ ratios do not decline when the GFR and F_{urate} are reduced up to 50%, and that similarly, in the mongrel dog, under conditions of net tubular reabsorption of uric acid, the $U_{urate}V/F_{urate}$ ratios are but little affected. Moreover, in the mongrel as in the Dalmatian, the relationship of excreted to filtered uric acid over a wide range of filtered uric acid loads more closely resembles the response of potassium, which is subject to tubular secretion, than of sodium.

Summary. Reduction of mean renal arterial blood pressure of Dalmatian and mongrel dogs by inflating a balloon-tipped catheter inserted into the aorta just above the renal arteries resulted in a proportionate decrease in GFR, less decrease in C_{PAH}, a precipitous fall in $U_{Na}V/F_{Na}$, no appreciable change in U_KV/F_K. In the Dalmatian, under conditions of net secretion of urate, $U_{urate}V/F_{urate}$ was unchanged or rose somewhat. A comparable response of $U_{urate}V/F_{urate}$ was obtained in mongrels under conditions of net reabsorption of urate, a result consistent with tubular secretion of urate masked by preponderant tubular reabsorption.

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Immunochemical Studies of Bovine Parathyroid Hormone.* (28831)

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Parathyroid hormone (PTH) is apparently rather weakly antigenic in that the few reported attempts to produce antibodies to it have been only partially successful(1,2,3). However, Tashjian *et al*(3) have recently produced antibodies to bovine PTH, as judged by inhibition of biologic activity and by complement fixation analysis. The present report describes preliminary studies of a) the antigenicity of PTH and b) characterization of the PTH-antiPTH system by several immunochemical methods. Because of the great difficulty in obtaining adequate human parathyroid tissue for hormone extraction, the studies thus far have been carried out with bovine PTH.

Materials and methods. Parathyroid hormone preparation. Starting with fresh frozen bovine parathyroid glands (PTG), 4 different hormonal extracts were prepared: (a) an aqueous extract (A-PTE) prepared by homogenizing fresh frozen PTG in an equal quantity of distilled water, centrifuging, and obtaining the supernatant, (b) an ether precipitate (EP-PTE) (biologic activity 40 U.S.P. units/mg) (4), and (c) a partially purified trichloroacetic acid precipitate (PP-

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