# Effect of Perfusion Pressure on Sodium and Calcium Excretion in the Isolated Dog Kidney[1] (35919)

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(Introduced by G. F. DiBona)

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Numerous experimental observations provide support for the hypothesis that renal tubular transport of sodium and calcium is linked. Increasing sodium excretion by infusing saline, mannitol, glucose, or certain diuretics causes a proportional increase in calcium excretion (1–6). More recently, Gonda *et al.* (7) reported that increasing sodium excretion by infusing vasodilators and raising renal perfusion pressure also augments calcium excretion. However, in their study, it was not possible to separate the contribution of changes in renal perfusion pressure and renal blood flow from possible direct effects of the drugs in mediating the response.

Recent experiments from this laboratory (8) demonstrate that increasing renal perfusion pressure in the isolated kidney causes a natriuresis in the absence of change in glomerular filtration rate and renal blood flow and it was proposed that the natriuresis was secondary to an increase in peritubular capillary pressure, which depressed tubular sodium reabsorption.

In view of the earlier reports describing a relationship between sodium and calcium excretion, it was considered of interest to determine whether a similar pressure stimulus might alter the renal excretion of calcium.

*Methods.* Studies were performed on mongrel dogs, 15 to 25 kg, anesthetized with sodium pentobarbital and ventilated with a Harvard respirator. An isolated perfused kidney was prepared as previously described (8). In brief, a kidney is removed from one dog, placed in a constant temperature-humidity chamber and perfused with blood from the femoral artery of a second dog. Renal venous blood flows into a reservoir and is pumped to the femoral vein of the dog. The dog rests on an adjustable platform; and by raising or lowering the platform, it is possible to alter the perfusion pressure of the isolated kidney without affecting the systemic pressure of the dog.

After the kidney was placed in the chamber, renal arterial pressure was adjusted to about 110 mm Hg. Renal venous pressure was set at 5 mm Hg by adjusting the level of the venous outflow tubing. The dog received priming doses of inulin and *p*-aminohippurate (PAH) followed by a continuous infusion of these substances in 0.9% saline at 1.0 ml/min. Aqueous pitressin was added to the infusion to deliver 0.5 mU/kg/min. In addition, the animal received DOCA, 10 mg, intramuscularly. At least 60 min were allowed for equilibration of solutions and for function of the isolated kidney to stabilize. In 13 experiments, a 30 min control urine was collected from the isolated kidney, while renal arterial pressure was maintained at 110 mm Hg. Then arterial pressure was raised to 160 mm Hg and a second 30 min urine was collected. In 10 experiments, arterial pressure was then restored to control levels and a 30 min recovery urine was obtained.

Urine was collected from a polyethylene catheter secured in the ureter. Midpoint bloods were obtained from the femoral artery of the dog and renal vein of the isolated kidney. Blood and urine specimens were replaced with equal volumes of 0.9% saline to minimize changes in blood volume.

Renal blood flow was measured directly from the renal vein. Renal arterial and venous pressures of the isolated kidney were

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monitored with Statham pressure transducers connected to the arterial and venous catheters by means of T-tubes, and recorded on a Beckman dynograph recorder. Analysis of samples for sodium, potassium, inulin, PAH, protein, and packed cell volume was performed according to methods previously described (8). Total plasma calcium was determined by the method of Hill (9) and urine calcium by the method of Ferro and Ham (10). Ultrafilterable calcium was estimated as 0.65 $\times$ total plasma calcium (11) and was used to calculate the fractional excretion of calcium.

The paired $t$ test was employed in the statistical evaluation of the data.

*Results.* Table I summarizes the results from individual experiments. In the text the data are expressed as the mean $\pm$ 1 SEM.

Sodium excretion: raising renal arterial pressure caused a significant increase in $U_{Na}V$ from 40.8 $\pm$ 7.0 to 113.9 $\pm$ 10.0 $\mu$Eq/min, $p<.001$, and $FE_{Na}$ from 0.8 $\pm$ 0.2 to 2.2 $\pm$ 0.4%, $p<.001$. The increase in sodium excretion was not related to any consistent change in $C_{IN}$ or RBF. Reducing renal arterial pressure was associated with a return of $U_{Na}V$ and $FE_{Na}$ toward control levels.

Calcium excretion: raising renal arterial pressure also caused an increase in $U_{Ca}V$ from 0.8 $\pm$ 0.2 to 2.3 $\pm$ 0.5 $\mu$Eq/min, $p<.005$. The estimated ultrafilterable calcium remained constant at 3.0 $\pm$ 0.1 mEq/liter for the three periods. Using this estimated value for ultrafilterable calcium, $FE_{Ca}$ measured 1.0 $\pm$ 0.4% during control and increased to 2.6 $\pm$ 0.8% in response to the rise in renal arterial pressure, $p<.025$. When arterial pressure was lowered, calcium excretion returned toward the control level.

In Fig. 1, $FE_{Ca}$ is plotted against $FE_{Na}$ using all the data points from the three periods and demonstrates a significant correlation between the two variables as determined by the method of least squares. A highly significant correlation was also found between $\Delta FE_{Ca}$ and $\Delta FE_{Na}$ with $r = 0.727$ and $p<.01$.

Miscellaneous: PAH extraction, filtration fraction, plasma protein concentration and packed cell volume remained constant during the study. $E_{PAH}$ measured 0.75 $\pm$ 0.02, 0.75 $\pm$ 0.02, and 0.77 $\pm$ 0.02; filtration fraction measured 0.30 $\pm$ 0.03, 0.31 $\pm$ 0.03, and 0.31 $\pm$ 0.03; and plasma protein concentration measured 5.5 $\pm$ 0.1, 5.6 $\pm$ 0.1, and 5.4 $\pm$ 0.1 g/100 ml during the three consecutive periods. Packed cell volume remained constant at 33 $\pm$ 1%.

*Discussion.* These experiments demonstrate that raising renal arterial pressure causes a significant increase in both sodium and calcium excretion and that the magnitude of the change in excretion of one cation is significantly correlated with that of the other. The increase in sodium excretion occurred in the absence of any consistent change in glomerular filtration rate suggesting that the natriuresis was primarily secondary to a decrease in tubule sodium reabsorption. Similarly if it is assumed that raising renal arterial pressure did not alter ultrafilterable calcium, then the constancy of plasma calcium suggests that the increase in calcium excretion also reflected a decrease in tubular calcium reabsorption.

The mechanism whereby an increase in renal arterial pressure augments sodium excretion has intrigued physiologists for many years. The constancy of RBF, $E_{PAH}$, and filtration fraction argues against an alteration in the intrarenal distribution of blood flow as the mechanism mediating the natriuresis and calciuresis. Similarly the constancy of plasma proteins and packed cell volume excludes these variables as factors in the response.

Several groups of investigators have proposed that pressure natriuresis is mediated by an increase in peritubular capillary pressure, which depresses tubular reabsorption of sodium (12–14). In a recent report from this laboratory (8), evidence was presented in support of this hypothesis. It was demonstrated that the natriuresis caused by increasing renal arterial pressure was associated with an increase in proximal tubular pressure but without change in GFR or RBF. Since proximal tubular pressure closely mirrors peritubular capillary pressure (15), it was postulated that the decrease in tubular sodium reabsorption was a function of the increase in peritubular capillary pressure. Although proximal tubular pressure was not measured in the present experiments, the fact that the

TABLE I. Summary of Data from Individual Experiments.[a]

| | $U_{Na}V$ (μEq/min) | | | $FE_{Na}$ (%) | | | $U_{Ca}V$ (μEq/min) | | | $FE_{Ca}$ (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | E | R | C | E | R | C | E | R | C | E | R |
| 1 | 22.4 | 43.5 | 26.7 | 0.3 | 0.6 | 0.4 | 0.5 | 0.9 | 0.4 | 0.4 | 0.6 | 0.3 |
| 2 | 102.8 | 160.4 | 111.0 | 3.1 | 5.1 | 3.3 | 3.2 | 3.3 | 3.1 | 4.9 | 5.8 | 5.4 |
| 3 | 28.5 | 81.9 | 23.5 | 0.6 | 1.9 | 0.8 | 1.2 | 2.8 | 1.1 | 1.2 | 3.1 | 1.9 |
| 4 | 43.1 | 148.5 | 61.0 | 1.3 | 4.6 | 2.5 | 2.0 | 6.5 | 2.2 | 2.9 | 9.7 | 4.1 |
| 5 | 8.4 | 137.5 | — | 0.2 | 2.5 | — | 0.6 | 3.7 | — | 0.8 | 4.2 | — |
| 6 | 26.6 | 92.8 | 29.3 | 0.5 | 1.9 | 0.7 | 1.0 | 4.1 | 1.4 | 1.3 | 4.7 | 1.9 |
| 7 | 60.5 | 143.4 | — | 1.4 | 2.8 | — | 0.3 | 0.9 | — | 0.3 | 0.8 | — |
| 8 | 16.0 | 133.4 | 45.9 | 0.3 | 2.2 | 0.7 | 0.1 | 1.2 | 0.2 | 0.1 | 0.9 | 0.4 |
| 9 | 44.2 | 116.1 | — | 0.7 | 1.8 | — | 0.4 | 0.7 | — | 0.3 | 0.5 | — |
| 10 | 18.6 | 70.7 | 36.3 | 0.3 | 1.0 | 0.5 | 0.3 | 2.8 | 0.1 | 0.2 | 1.8 | 0.1 |
| 11 | 44.3 | 80.6 | 42.5 | 0.5 | 0.9 | 0.6 | 0.6 | 1.3 | 0.9 | 0.3 | 0.7 | 0.1 |
| 12 | 51.6 | 137.6 | 74.7 | 0.7 | 2.0 | 1.0 | 0.2 | 1.2 | 1.2 | 0.1 | 0.8 | 0.8 |
| 13 | 63.2 | 133.6 | 70.2 | 0.9 | 1.7 | 1.0 | 0.2 | 0.5 | 0.4 | 0.1 | 0.3 | 0.3 |
| Mean | 40.8 | 113.9 | 52.1 | 0.8 | 2.2 | 1.2 | 0.8 | 2.3 | 1.1 | 1.0 | 2.6 | 1.5 |
| ±SEM | 7.0 | 10.0 | 8.7 | 0.2 | 0.4 | 0.3 | 0.2 | 0.5 | 0.3 | 0.4 | 0.8 | 0.6 |
| $p$ | <.001 | <.001 | | <.001 | <.001 | | <.005 | <.025 | | <.025 | <.05 | |

renal response to the pressure stimulus was practically identical to that seen in the earlier study suggests that a similar change in proximal tubular pressure occurred.

The significant correlation between fractional sodium and calcium observed in these experiments is in general agreement with the observations of other investigators (1–7). However, in those studies in which sodium excretion was augmented by extracellular volume expansion (1–6), the regression line of fractional calcium excretion on fractional so-

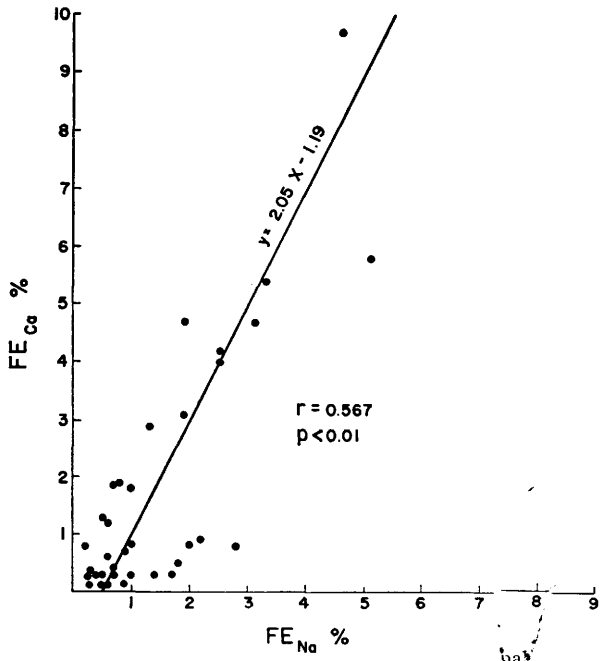


FIG. 1. Fractional calcium excretion ($FE_{Ca}$) plotted against fractional sodium excretion ($FE_{Na}$) for all periods. The regression line is determined by the method of least squares.

TABLE I. (Continued).

| | $C_{IN}$ (ml/min) | | | RBF (ml/min) | | | $P_{RA}$ (mm Hg) | | |
|---|---|---|---|---|---|---|---|---|---|
| | C | E | R | C | E | R | C | E | R |
| 1 | 48.0 | 50.4 | 45.3 | 145 | 143 | 146 | 89 | 143 | 95 |
| 2 | 23.5 | 22.8 | 24.1 | 131 | 128 | 116 | 108 | 149 | 102 |
| 3 | 34.8 | 29.2 | 19.7 | 217 | 206 | 187 | 99 | 153 | 101 |
| 4 | 26.3 | 25.8 | 19.1 | 154 | 145 | 106 | 101 | 148 | 103 |
| 5 | 31.6 | 36.3 | — | 189 | 216 | — | 102 | 152 | — |
| 6 | 30.1 | 32.6 | 27.0 | 173 | 150 | 128 | 100 | 153 | 103 |
| 7 | 31.7 | 33.9 | — | 243 | 225 | — | 108 | 162 | — |
| 8 | 43.5 | 42.4 | 43.0 | 257 | 243 | 240 | 120 | 173 | 121 |
| 9 | 45.1 | 44.7 | — | 253 | 259 | — | 116 | 173 | — |
| 10 | 45.7 | 45.7 | 46.7 | 180 | 179 | 164 | 122 | 180 | 124 |
| 11 | 56.0 | 58.7 | 48.8 | 164 | 159 | 155 | 125 | 177 | 123 |
| 12 | 49.7 | 46.9 | 50.0 | 275 | 277 | 298 | 115 | 169 | 113 |
| 13 | 51.0 | 54.0 | 49.4 | 279 | 274 | 271 | 117 | 173 | 112 |
| Mean | 39.8 | 40.3 | 37.3 | 205 | 200 | 181 | 109 | 162 | 110 |
| ±SEM | 2.9 | 3.1 | 4.1 | 14 | 15 | 21 | 3 | 4 | 3 |
| $p$ | NS | <0.05 | | NS | NS | | <.001 | <.001 | |

[a] $U_{Na}V$ = absolute sodium excretion; $FE_{Na}$ = fractional sodium excretion; $U_{Ca}V$ = absolute calcium excretion; $FE_{Ca}$ = fractional excretion of calcium; $C_{IN}$ = inulin clearance; RBF = renal blood flow; $P_{RA}$ = renal arterial pressure; C = control period; E = experimental period; R = recovery period.

dium excretion had a slope of about 1. In several studies the slope was increased above 1 using furosemide (6) or mercurial diuretic (2) suggesting that these drugs may have altered calcium transport by some additional mechanism unrelated to sodium transport. In the present experiments, the regression line describing the relation between fractional calcium and sodium excretion has a slope of 2. Although this steeper slope may reflect a response peculiar to the isolated kidney, the possibility exists that raising renal arterial pressure may alter tubular calcium transport to some extent independent of changes in sodium excretion.

*Summary.* 1. The effect of increasing renal arterial pressure on sodium and calcium excretion in an isolated kidney was studied. 2. Increasing renal arterial pressure by about 50 mm Hg caused a significant increase in both the absolute and fractional excretion of sodium and calcium in the absence of consistent changes in GFR or RBF. 3. A significant correlation was found between calcium and sodium excretion and provides additional evidence that the transport of these two cations is linked.

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