Renal Perfusion Pressure Is an Important Determinant of Sodium and Calcium Excretion in DOC-Salt Hypertension

Michael W. Brands and John E. Hall

This study tested the hypothesis that the increased renal perfusion pressure in DOC-salt hypertension is essential for the maintenance of sodium balance and is responsible for the hypercalciuria associated with this model. Twelve chronically instrumented dogs were placed on a high salt intake and mean arterial pressure (MAP) was measured 24 h/day. After a control period, a 17-day DOC infusion period was begun. In six dogs, however, renal perfusion pressure (RPP) to both kidneys was maintained at control levels for the first 12 days of the DOC infusion by the continuous, servo-controlled adjustment of a suprarenal silastic occluder on the abdominal aorta. The servo-controlled dogs had significantly more sodium retention and a greater increase in blood pressure than the six control DOC hypertensive dogs. Urinary calcium excretion in the control dogs began to increase from 24 ± 6 mg/day on day 1 of DOC, and increased progressively to 100 ± 14 and 175 ± 30 mg/day by days 7 and 12, respectively. Plasma ionized calcium decreased, and parathyroid hormone (PTH) (1-84) increased, significantly by day 4. The hypercalciuria was not different in the servo-controlled dogs for the first 7 days of DOC, but was attenuated thereafter. Thus, increased RPP is important in restoring sodium balance and in maintaining the calciuresis in DOC-salt hypertension; however, other mechanisms also are important, particularly during the onset of hypertension. Am J Hypertens 1998;11:1199–1207

KEY WORDS: **DOC-salt hypertension, dog, renal perfusion pressure, sodium, calcium.**

Since McCarron et al[1] first reported an association of hypercalciuria with essential hypertension, there has been considerable interest in the potential role of altered calcium homeostasis in the cause of hypertension. The hypercalciuria has been postulated to be attributable to a primary defect in renal tubular calcium transport, with the cumulative calcium loss leading to other abnormalities in calcium homeostasis including reduced plasma ionized calcium concentration and increased plasma parathyroid hormone (PTH) levels.[2–4] These abnormalities, in turn, have been proposed to induce hypertension through such mechanisms as increased calcium influx into vascular smooth muscle cells[5,6] and activation of the sympathetic nervous system.[7,8] Furthermore, the calcium loss by way of renal calcium leak may be exacerbated by chronically suppressed dietary calcium intake,[9] and dietary calcium supplementation has been reported to correct the derangements in calcium homeostasis and lower blood pressure.[8–11]

Received March 27, 1997. Accepted July 9, 1997.

From the Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi.

This research was supported by HL-11678, HL-51971, and HL-08171 from the National Institutes of Health and by a Grant-in-Aid from the American Heart Association (AHA), with funds contributed in part by the AHA, Mississippi Affiliate.

Address correspondence and reprint requests to Michael W. Brands, PhD, Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216.

0895-7061/98/$19.00
PII S0895-7061(98)00031-4

However, the finding of hypercalciuria in experimental hypertension of known etiology[12–14] suggests that altered calcium homeostasis could be a consequence, rather than an initiator, of the increase in blood pressure. In fact, Barbagallo et al[14] suggested the hypercalciuria in secondary hypertension was due in part to pressure calciuresis, and MacGregor and Cappuccio[15] hypothesized that the hypercalciuria was a consequence of renal and circulatory compensations for an impaired ability of the kidneys to maintain sodium balance; the ensuing derangements in systemic calcium homeostasis were secondary to this calciuresis.

A powerful mechanism for counteracting impaired renal sodium excretory capability and ensuring the maintenance of sodium balance is increased blood pressure.[16] In fact, studies in certain models of secondary hypertension, such as angiotensin II hypertension,[17] have shown that the natriuretic effect of increased blood pressure is required for the establishment of sodium balance while the kidneys are in a sodium-retaining state. Because renal sodium and calcium reabsorption are linked closely, particularly in the proximal tubule,[18,19] it is possible that decreased tubular calcium reabsorption is a consequence of the mechanisms whereby pressure natriuresis restores sodium balance. In support of this potential relationship, Wu and Sonnenberg[20] reported that acute increases in renal perfusion pressure have a direct calciuretic effect, caused by decreased tubular reabsorption. However, it is not known whether this relationship is operative in chronic hypertensive states shown to have attendant derangements in calcium homeostasis.

Massry et al[12] reported that chronic administration of the mineralocorticoid DOCA induced progressive hypercalciuria in dogs, but the role of increased renal perfusion pressure in mediating these changes was not examined. Therefore, the goals of this study were to quantify the role of increased renal perfusion pressure in maintaining sodium balance in the DOC-salt model of mineralocorticoid-induced hypertension, and to test the hypothesis that the increase in renal perfusion pressure also underlies the sustained hypercalciuria in this model.

METHODS

Experiments were conducted in 12 conditioned mongrel dogs weighing between 18.2 and 27.2 kg (average, 21.5 ± 0.8 kg). The experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center, and were carried out according to the "Guide for the Care and Use of Laboratory Animals" from the National Institutes of Health and according to the guidelines of the Animal Welfare Act.

Under sodium pentobarbital anesthesia (30 mg/kg) with aseptic technique, tygon catheters were implanted in the femoral arteries and veins with the tip of one arterial catheter advanced anterior to the renal arteries and the tip of the other arterial catheter placed posteriorly. Through a left flank incision, an externally adjustable Silastic occluder was then placed on the abdominal aorta above both renal arteries. The catheters and occluder tubing were tunneled subcutaneously to the scapular region and exteriorized. The catheters were filled with 1000 U/mL heparin solution and closed.

After 1 to 2 weeks of recovery, the dogs were placed in individual metabolic cages in a quiet, air-conditioned room with a 12-h light cycle, and fitted with harnesses containing two pressure transducers (Cobe, Lakewood, CO) mounted at heart level and connected to a polygraph (model 7D, Grass Instruments, Quincy, MA). The harnesses were attached to a flexible vacuum hose that allowed safe routing of electrical lines and tubing to the cage exterior while permitting the dogs to move freely in their cages. Arterial pressure signals from the polygraph were sent to an analog-digital converter and sampled 12 sec each minute, analyzed, and stored by a digital computer, 24 h/day, using customized software. The average blood pressure for each day was calculated from the blood pressures recorded over an 18-h period between 2:00 PM and 8:00 AM daily. Arterial pressure values falling outside preset error limits at any time triggered the activation of a modem, which called a pager carried by the investigator. This allowed any problems to be corrected quickly, even during late-night hours. Before beginning control measurements, the dogs were trained to lie quietly in their cages from 8:00 AM to 12:00 PM for measurements of renal clearances and blood sampling.

Throughout the study, the dogs were fed two cans (477 g/can) of a sodium-deficient diet daily (H/D, Hills Pet Products, Topeka, KS), which provided approximately 7 mmol of sodium, 65 mmol of potassium, and 1720 mg of calcium per day. A high daily sodium intake of 280 mEq/day was maintained by continuous intravenous infusion of approximately 1600 mL/day sterile saline with a roller pump (model 375A, Sage Instruments, Cambridge, MA). In addition, the food was supplemented with potassium chloride to yield a daily potassium intake of approximately 150 mEq. These electrolyte intakes were maintained throughout the experiment. The dogs also were given 5 mL of a vitamin syrup (V.A.L. Syrup, Ft. Dodge Laboratories, Ft. Dodge, IA) each day. All solutions were pumped through disposable filters (0.22 μm, Cathivex, Millipore Corp., Bedford, MA) to prevent contaminants and bacteria from passing into the circulation. Antibiotics were administered daily and

temperatures were monitored regularly for the duration of the study.

Experimental Protocol One to 2 weeks after placement in the cages, a 5-day control period was begun. Subsequently, a continuous intravenous infusion of deoxycorticosterone (DOC, Sigma Chemical Co., St. Louis, MO) at 600 μg/kg/day was initiated in all dogs. In six control dogs, the DOC infusion was maintained for 17 days and renal perfusion pressure was allowed to increase.

In the other six dogs (Servo) renal perfusion pressure was servo-controlled continuously at the same level measured during the control period, before DOC administration. To maintain renal perfusion pressure constant, the aortic occluder was connected to a servo-controlled syringe pump, driven by the output of a proportional servo-control unit that received input from the Grass recorder pressure amplifier.[21] By continuous adjustment of the inflation of the occluder, renal perfusion pressure was maintained within 1 to 2 mm Hg of the set point. It is important to note that renal perfusion pressure was not decreased below control levels; rather, it was maintained at control levels while systemic (anterorenal) pressure increased. After 12 days of DOC infusion/servo-control, the servo controller was stopped and the kidneys were exposed to systemic pressure levels during 5 more days of continued DOC infusion. Importantly, however, the servo-controller was stopped after only 7 days in three Servo dogs due to the severity of the systemic blood pressure increase.

Analytical Procedures Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined from the total plasma clearances of [^{125}I]iothalamate and [^{131}I]iodohippurate, respectively, as previously described.[22] The distribution space of [^{125}I]iothalamate was used as an index of extracellular fluid volume. Plasma and urine sodium and potassium concentrations and plasma-ionized calcium concentration were determined with ion-sensitive electrodes (NOVA Biomedical, Waltham, MA). Urine calcium concentration was determined by atomic absorption spectrophotometry (Instrumentation Laboratory S-12, Andover, MA). Plasma protein concentration was measured by refractometry (American Optical, Buffalo, NY). Plasma renin activity was measured by radioimmunoassay using [^{125}I]angiotensin I (ANGI) from New England Nuclear (Boston, MA) and antibody from Chemicon (El Segundo, CA). Plasma concentration of PTH (1-84) was measured by radioimmunoassay (Nichols). Atrial natriuretic factor (ANF) was extracted from 1 mL of plasma using C_{18} cartridges (Sep-Pak, Waters, Milford, MA), and plasma ANF concentration was determined using [^{125}I]ANF (Amersham Radiochemical, Arlington Heights, IL) and antibody from Research and Diagnostic Antibodies (Berkeley, CA).

Dunnett's test was used for within-group comparisons of experimental days to control values after a repeated measures analysis of variance.[23] Statistical significance was considered to be $P < .05$. All data are expressed as means ± standard error of the mean.

RESULTS

Renal Electrolyte Excretion DOC administration produced a significant decrease in urinary sodium excretion in all dogs on day 1, and the Control dogs escaped from this effect by day 2 (Figure 1). The Servo dogs were divided post hoc into two groups, however, based on different sodium excretory responses to DOC. Three of the Servo dogs transiently escaped (Servo-E) the sodium-retaining action of DOC during the early phase of the infusion, and cumulative sodium balance was 70 ± 25 and 61 ± 16 mmol positive in the Control and Servo-E dogs, respectively, on day 7. The return to a sodium-retaining state in the Servo-E dogs after 7 days of DOC, however, further increased cumulative sodium balance to 171 ± 24 mmol positive by day 12. The other three Servo dogs (Servo-R) retained sodium every day of DOC infusion, and cumulative sodium balance increased progressively during the infusion period to 452 ± 47 mmol positive by day 7.

Figure 2 shows the changes in urinary calcium excretion and cumulative calcium balance in the three groups of dogs. Urinary calcium excretion averaged 24 ± 6, 32 ± 13, and 36 ± 21 mg/day in the Control, Servo-E, and Servo-R dogs, respectively. In the Control dogs, a progressive calciuresis was measured throughout the DOC infusion period, and the increase in calcium excretion in the Servo groups was not different for the first 7 days of DOC. However, in the Servo-E dogs that began to retain sodium again after day 7, a corresponding attenuation in the calciuresis occurred and calcium excretion returned to control levels. This change in calcium excretion also is illustrated by the break that occurred in cumulative calcium balance between the Control and Servo-E dogs beginning on day 8. Also noteworthy is the marked calciuresis that occurred in both Servo groups when servo-control was stopped and renal perfusion pressure was allowed to reach the elevated systemic levels.

Urinary potassium excretion during the control period averaged 117 ± 4, 115 ± 5, and 120 ± 3 mmol/day in the Control, Servo-R, and Servo-E dogs, respectively, and increased to 145 ± 5, 139 ± 4, and 141 ± 6 mmol/day in the respective groups on day 1 of DOC. Potassium excretion remained elevated in the Control dogs, averaging 128 ± 2 mmol/day.

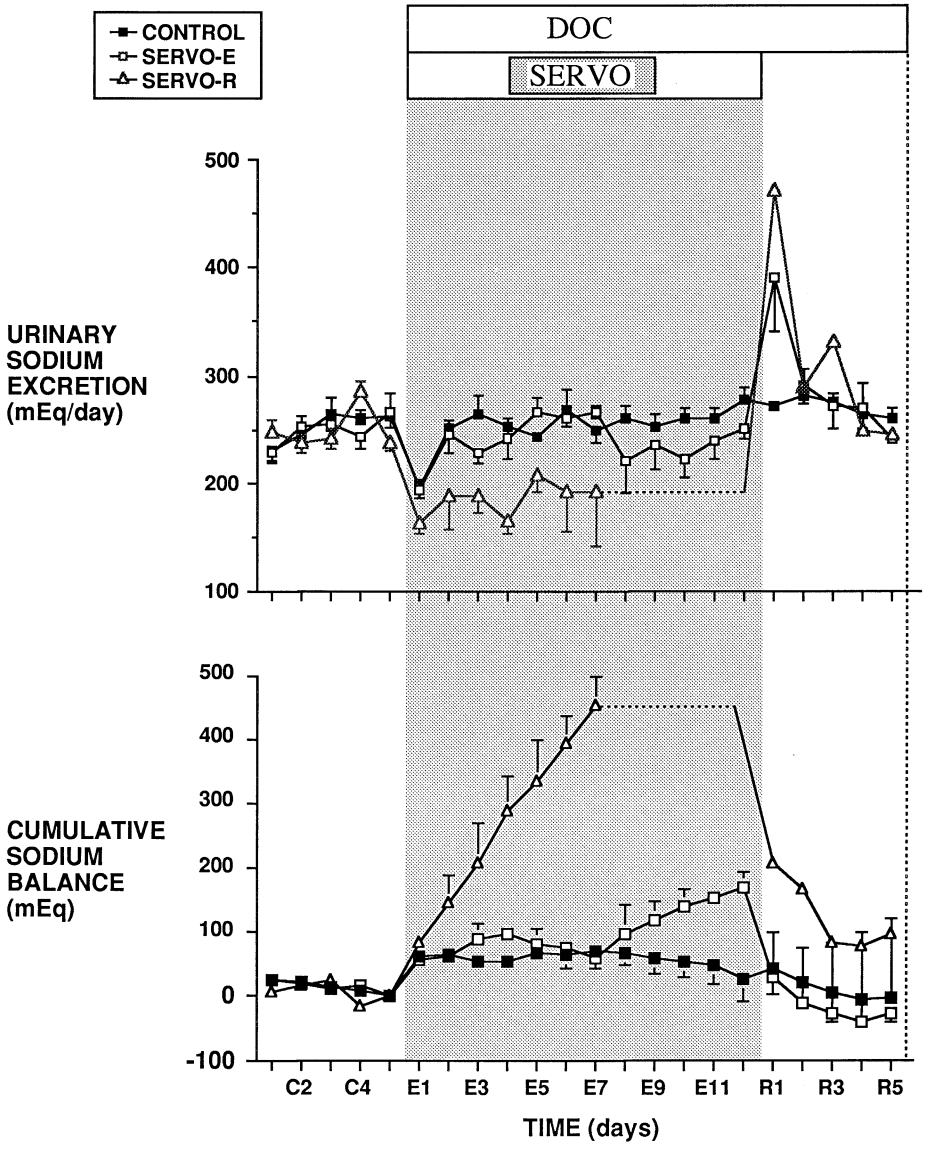

FIGURE 1. *Line graph of urinary sodium excretion* **(top)** *and cumulative sodium balance* **(bottom)** *in the Control, Servo-E, and Servo-R dogs during the control period (C), the period of bilateral servo-control of renal perfusion pressure at control levels during DOC infusion (E), and the post-servo recovery period during continued DOC infusion (R).*

Systemic Effects The progressive increase in cumulative sodium balance in the Servo-R dogs was accompanied by a parallel increase in mean arterial pressure that was 61% ± 8% above the average control pressure of 95 ± 3 mm Hg by day 7 of DOC (Figure 3). After 7 days of DOC infusion, servo-control of renal perfusion pressure was stopped in the Servo-R dogs because of the excessive increase in systemic arterial pressure (systolic blood pressure reaching 250 mm Hg), and subsequent values for this group represent the average of two dogs. In the Control and Servo-E dogs, mean arterial pressure averaged 14% ± 3% and 17% ± 5% above the respective control values of 94 ± 4 and 93 ± 6 mm Hg 7 days after starting DOC. However, the return to a sodium-retaining state in the Servo-E dogs was associated with a progressive increase in mean arterial pressure.

The different responses among the Servo dogs could not be attributed to significant differences in the control of renal perfusion pressure during the DOC infusion, as renal perfusion pressure was within 1% of control in both groups on every day except for a 2% increase on day 7 in the Servo-E dogs, and 2% and 3% increases on days 6 and 7 in the Servo-R dogs that did not escape (Figure 3). Also, the transition of the Servo-E dogs from sodium balance to sodium retention after 7 days of DOC was not linked to a significant decrease in renal perfusion pressure below control levels, as renal pressure averaged 100% to 101% of control from days 8 to 12 in those dogs. When servo-control was stopped in both groups during continued DOC infusion, renal perfusion pressure immediately increased to the level of systemic arterial pressure. This marked increase in renal perfusion pressure induced a pronounced natriuresis (Figure 1), and cumulative sodium balance and mean arterial pressure de-

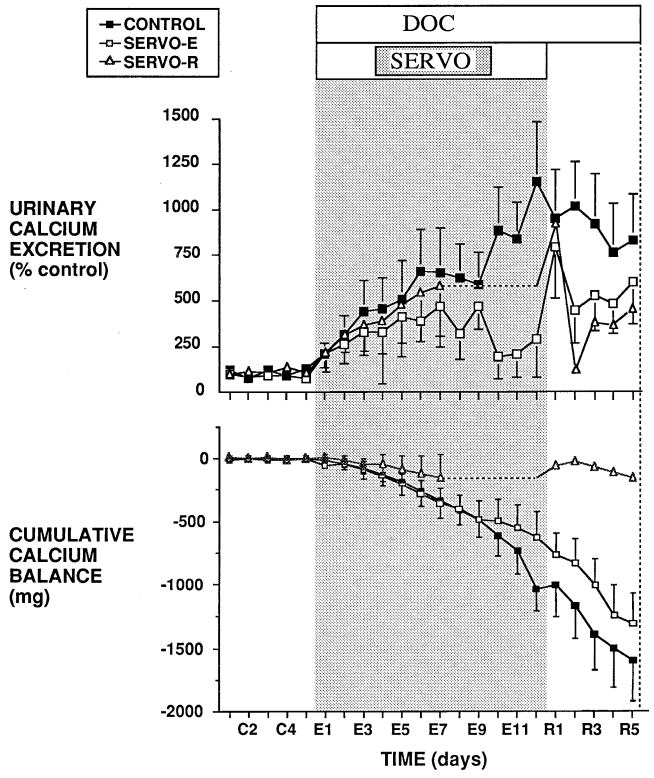

FIGURE 2. *Line graph of urinary calcium excretion* **(top)** *and cumulative calcium balance* **(bottom)** *in the Control, Servo-E, and Servo-R dogs during the control period (C), the period of bilateral servo-control of renal perfusion pressure at control levels during DOC infusion (E), and the post-servo recovery period during continued DOC infusion (R).*

creased to levels not different from those in the Control DOC-salt hypertensive dogs.

The changes in plasma PTH (1-84) (Table 1), although highly variable in the Servo groups due to low subject number, reflect the changes in calcium balance. PTH (1-84) increased commensurate with the negative calcium balance, and the rise in the Control group was statistically significant. In addition, an increase in PTH (1-84) associated with the pronounced calciuresis was measured in the Servo groups on the first day after stopping the servo controller (R1 in the Servo-E dogs and E8 in the Servo-R dogs in Table 1). Statistically significant decreases in plasma-ionized calcium were measured in the Control and Servo-R groups (Table 1; sample loss decreased in from the Control and Servo-E dogs), and the decrease in plasma calcium in the Control and Servo dogs is consistent with the observation that the hypercalciuric responses were not different between groups for the first 7 days of DOC.

Sodium iothalamate space was used as an index of extracellular fluid volume (ECFV), and the changes in that variable closely reflected the changes in sodium excretion and cumulative sodium balance in the three groups of dogs (Figure 4). By day 12, ECFV in the Control dogs had increased by approximately 300 mL, whereas the Servo-E dogs had an increase of >1600 mL. The Servo-R dogs, on the other hand, had retained >1500 mL by day 3 of DOC. The changes in plasma ANF concentration also reflected the changes

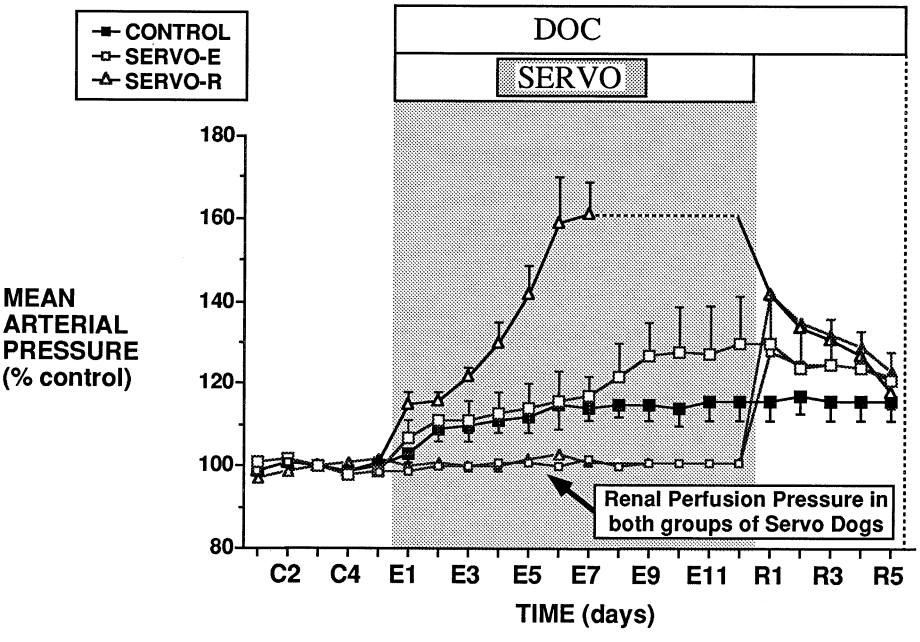

FIGURE 3. *Line graph of mean arterial pressure in the Control, Servo-E, and Servo-R dogs during the control period (C), the period of bilateral servo-control of renal perfusion pressure at control levels during DOC infusion (E), and the post-servo recovery period during continued DOC infusion (R).*

TABLE 1. PLASMA PTH (1-84) AND Ca^{2+} CONCENTRATIONS

Variable	C1	C4	E1	E4	E8	E11	R1	R5
[PTH(1-84)] (pmol/L)								
Control	2.65 ± 0.74	2.65 ± 0.64	3.61 ± 0.53	4.03 ± 0.53*	4.14 ± 0.53*	4.35 ± 0.53*	3.93 ± 0.32*	4.88 ± 0.42*
Servo-E	3.18 ± 1.38	3.50 ± 1.17	3.50 ± 1.59	4.67 ± 0.85	3.93 ± 0.53	4.35 ± 1.06	5.20 ± 0.95	3.93 ± 0.74
Servo-R	3.29 ± 1.27	2.76 ± 1.27	3.08 ± 1.49	3.50 ± 1.27	4.24	—	5.94	4.77
[Ca^{2+}] (mmol/L)								
Control (n = 5)	1.22 ± 0.02	1.21 ± 0.03	1.20 ± 0.01	1.14 ± 0.02*	1.13 ± 0.02	1.14 ± 0.02*	1.16 ± 0.01	1.17 ± 0.02
Servo-E (n = 1)	1.23	1.25	1.21	1.18	1.17	1.16	1.16	1.18
Servo-R	1.25 ± 0.02	1.24 ± 0.01	1.14 ± 0.04*	1.15 ± 0.02*	1.05	—	1.04	1.12

C, control; E, experimental (servo period), R, Recovery. For the Servo-R dogs: E8 = E7 and n = 2 after E4 (see Results). *$P < .05$ *compared to the average of C1 and C2.*

in sodium excretion (Figure 4). Plasma ANF in the Servo dogs increased progressively to levels almost fourfold above control, whereas ANF levels in the Servo-E dogs were not different from the Control dogs until after they began retaining sodium again.

Plasma sodium concentration increased in all groups on day 1 of DOC and tended to remain elevated throughout the experiment, except for transient reductions on day E4 in the Servo-E dogs and DOC day 8 in the Control dogs. Plasma potassium concentration decreased in all groups during DOC infusion. Modest, transient reductions in hematocrit and plasma protein concentration also were measured in each group, with the exception that plasma protein in the Servo-R dogs showed a progressive decrease during DOC infusion, reflective of their more pronounced fluid retention.

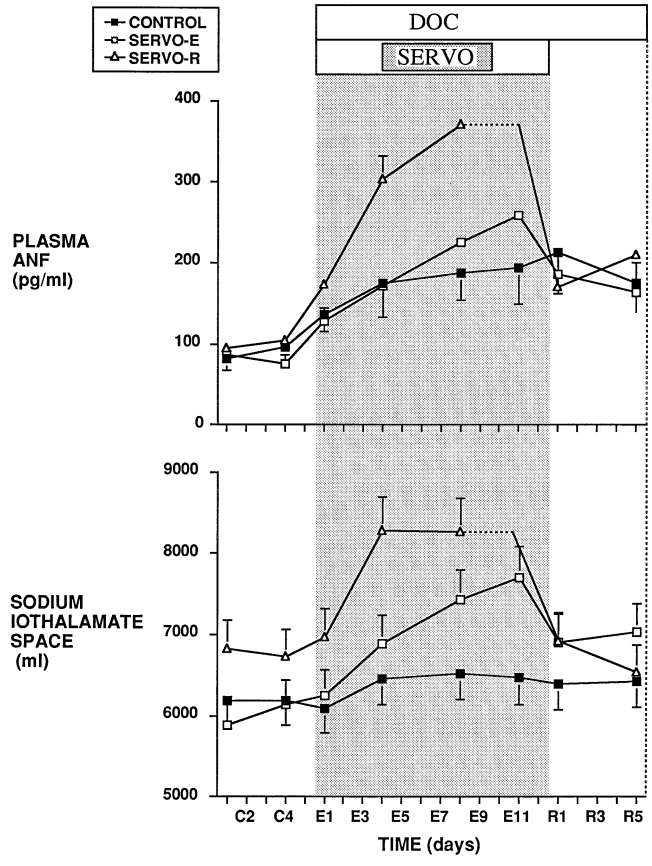

FIGURE 4. *Line graph of plasma atrial natriuretic factor (ANF) concentration* **(top)** *and sodium iothalamate space* **(bottom)** *in the Control, Servo-E, and Servo-R dogs during the control period (C), the period of bilateral servo-control of renal perfusion pressure at control levels during DOC infusion (E), and the post-servo recovery period during continued DOC infusion (R).*

Renal Hemodynamics Glomerular filtration rate increased in all groups on day 1 of DOC infusion (Figure 5). In the Control dogs, GFR continued to increase to 118% ± 4% of control by the fourth day and remained near that level for the remainder of the infusion period. In the Servo-E dogs, GFR also continued to rise on the fourth day of DOC, which was during the period in which this group was in sodium balance similar to the Control dogs. However, by day 8, when those dogs had begun to retain sodium again, GFR had returned to control levels. In the Servo-R dogs, which never regained sodium balance during DOC infusion, GFR was back to control levels by day 4 of the infusion. The between-group differences in renal plasma flow (RPF) showed a pattern similar to those measured for GFR. No change in RPF was found on day 1 of DOC in any group, but an increase to a plateau level approximately 114% above control occurred by day 4 in the Control dogs. In the Servo-E group, no significant change in RPF was measured during DOC, whereas a decrease to 72% of control was measured in the Servo-R dogs.

DISCUSSION

An important finding from this study is that increased renal perfusion pressure is important in maintaining sodium balance in DOC-salt hypertension, although other mechanisms are capable of initiating sodium escape and transiently enabling sodium balance. Like-

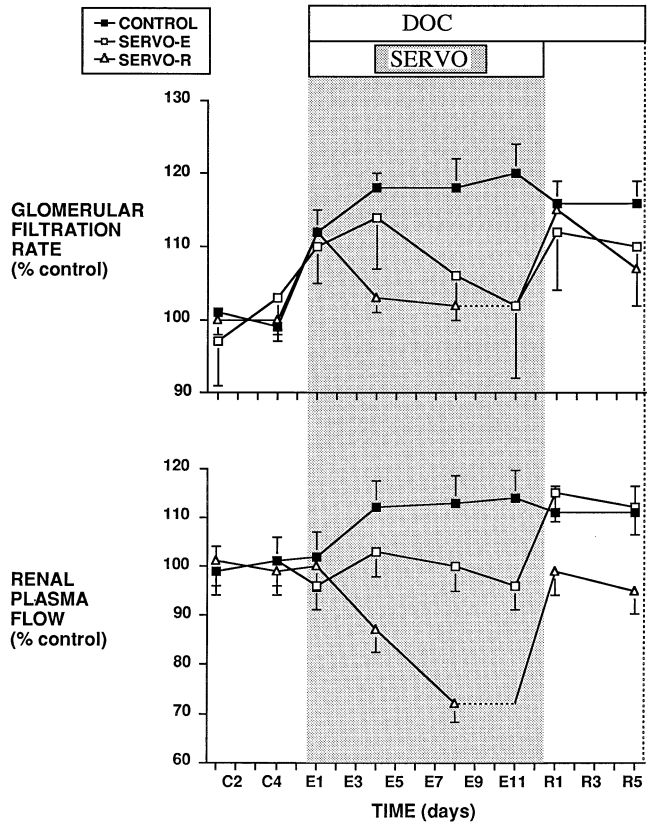

FIGURE 5. *Line graph of glomerular filtration rate* **(top)** *and renal plasma flow* **(bottom)** *in the Control, Servo-E, and Servo-R dogs during the Control period (C), the period of bilateral servo-control of renal perfusion pressure at control levels during DOC infusion (E), and the post-servo recovery period during continued DOC infusion (R).*

wise, the sustained hypercalciuria associated with this hypertensive model is dependent on increased renal perfusion pressure, but increased calcium excretion in the early phases of the hypertension is not dependent on this mechanism. Thus, increased renal perfusion pressure is an important determinant of sodium and calcium excretion in mineralocorticoid hypertension, and the calciuresis may be linked to the mechanisms for maintaining sodium balance.

One explanation that has been proposed for the hypercalciuria in subsets of essential hypertensive patients is that there is a primary defect in cellular calcium transport.[2–4] Moreover, the urinary calcium loss and subsequent systemic changes have been postulated to underlie the hypertension, through effects of hypocalcemia to increase vascular tone either directly or through enhanced sympathetic nervous system activity.[5–8] However, the occurrence of hypercalciuria in experimental models of hypertension, in which the cause of the hypertension is known, suggests that renal calcium loss may be a consequence rather than a cause of the hypertension. In fact, MacGregor and Cappuccio[15] hypothesized that hypercalciuria, as a characteristic of hypertension in general, is secondary to mechanisms acting to maintain sodium balance. Thus, an understanding of the control of sodium balance in the DOC-salt model of hypertension may be an integral component in the evaluation of calcium homeostasis.

Previous studies from this laboratory have demonstrated that the reestablishment of sodium balance when the kidneys are in a sodium-retaining state, such as during chronic administration of angiotensin II, is dependent on the natriuretic effect of increased renal perfusion pressure, termed pressure natriuresis.[16,17] During chronic administration of the antinatriuretic agent DOC, sodium balance is maintained by an increase in distal tubular sodium chloride delivery to compensate for the mineralocorticoid-mediated increase in distal tubular sodium reabsorption. Because sodium and calcium reabsorption are linked closely in the proximal tubule,[18,19] we speculated that distal calcium delivery also would increase, possibly overwhelming distal tubular calcium reabsorptive capacity, thus resulting in calciuresis. Furthermore, because of the importance of increased renal perfusion pressure in facilitating the return to sodium balance in other models,[16,17] we hypothesized that blocking pressure natriuresis would prevent both the sodium escape and the hypercalciuric responses.

The report by Wu and Sonnenberg[20] supported the hypercalciuric component of this hypothesis by indicating that increased renal perfusion pressure can increase calcium excretion directly, and the two- to threefold increase in 24-h calcium excretion we measured when normal pressure kidneys were exposed to the elevated systemic pressure (ie, when the renal occluder was released) was consistent with that finding. However, the observation that increased renal perfusion pressure can increase calcium excretion does not address whether the increased renal perfusion pressure in hypertension is responsible for the associated, sustained hypercalciuria.

This was tested in the present study by protecting the kidneys from the increased perfusion pressure in DOC-salt hypertension, a form of secondary hypertension associated with hypercalciuria and derangements in systemic calcium homeostasis.[12–14] Overall, the results confirmed that increased renal perfusion pressure contributes significantly to the hypercalciuria, particularly in the sustained phase of the hypertension. However, it also is clear that the initial increase in urinary calcium excretion was not dependent on elevated renal arterial pressure, but the mechanism is not known. Consistent, however, with the hypothesis of MacGregor and Cappuccio,[15] the changes in cal-

cium excretion in this study were linked closely with the changes in sodium balance.

The results from this study demonstrated that pressure natriuresis was an important mechanism in allowing sodium balance to be achieved during chronic DOC administration. When renal perfusion pressure was prevented from increasing during DOC infusion, significantly more sodium and water were retained and a greater increase in systemic arterial pressure occurred. However, these results also revealed that other mechanisms besides pressure natriuresis were capable of transiently increasing sodium excretion (Servo-E dogs), and therefore maintaining sodium balances during DOC infusion.

This does not indicate that pressure natriuresis was unimportant, however, because the ability to maintain sodium balance independent of pressure natriuresis was transient. After 7 days, sodium balance and arterial pressure began to increase significantly in the Servo-E dogs. Furthermore, in the Servo-R dogs, a return to sodium balance was completely prevented by blockade of pressure natriuresis, and precipitous increases in sodium balance and systemic blood pressure ensued. Similarly, we recently reported that dogs with reduced kidney mass and blockade of pressure natriuresis were able to increase sodium excretion when given a high sodium intake, but they retained much more sodium and had a greater increase in systemic arterial pressure than did dogs with pressure natriuresis intact.[24]

The mechanisms that enabled some dogs with pressure natriuresis blocked to increase sodium excretion in this study are not clear. Differential suppression of the renin-angiotensin system during DOC infusion cannot explain these results because plasma renin activity was below the lower limit of detection in all groups throughout the study due to chronic high salt intake. Many natriuretic factors have been proposed to mediate, or contribute to, the sodium escape phenomenon,[25–27] and in this study we measured the ANF response to DOC infusion. ANF increased in proportion to the increase in cumulative sodium balance in each group. This suggests that the failure to achieve sodium balance was not due to an inability to increase ANF levels. In fact, in the Servo-E dogs plasma ANF levels were not different than levels in control dogs during that period in which they were in sodium balance, thus suggesting that ANF was not responsible for their transient ability to escape the antinatriuretic actions of DOC. However, other factors, such as nitric oxide, oubain-like factor, renal prostaglandins, and the renal kallikrein-kinin system, also could have played a role.

A factor that was associated with sodium escape during DOC infusion was increased GFR, as sodium balance was maintained only when GFR was significantly elevated above control. On the first day of DOC infusion, GFR increased in all dogs coincident with a significant decrease in urinary sodium excretion. Because the antinatriuretic effect of DOC involves a mineralocorticoid action to increase sodium reabsorption in the distal nephron, the increase in GFR could serve as a mechanism to increase sodium delivery. By the second day of DOC infusion, urinary sodium excretion had risen back to control in the Control group and in the Servo-E dogs, and the measurement of renal function on day 4 suggested that GFR had continued to increase in those two groups throughout that period. However, in the other Servo dogs, GFR was back to control levels by day 4 and they never returned to sodium balance during DOC. Furthermore, the transition of the Servo-E dogs back to a state of chronic sodium retention also was associated with a decrease of GFR back to normal levels. These associations, therefore, suggest that the ability to maintain sodium balance during DOC-salt hypertension may be dependent on an elevated GFR.

The calcium excretory responses also were related closely to the changes in GFR. In each group, elevated GFR was associated with hypercalciuria. The only exception was the continued elevation in calcium excretion in the Servo dogs on days 4 to 7 when GFR had returned to control levels. However, in the other Servo-E dogs, the decrease in calcium excretion coincided with the decrease in GFR. Moreover, in all the servo-controlled dogs, a pronounced increase in GFR accompanied the hypercalciuria when renal perfusion pressure suddenly was allowed to increase during recovery.

The close association between GFR and urinary sodium excretion suggests that the ability to chronically escape the antinatriuretic action of DOC is dependent on the ability to increase GFR. Furthermore, because this ability was impaired by servo-controlling renal perfusion pressure, these results indicate the importance of increased renal perfusion pressure in GFR control and in the maintenance of sodium balance in DOC-salt hypertension. Moreover, these results provide the first experimental evidence that hypercalciuria in this form of hypertension also is dependent on increased renal perfusion pressure and may be linked to the mechanisms for maintaining sodium balance. However, the hypercalciuria that occurred when renal perfusion pressure was prevented from increasing early in DOC-salt hypertension indicates that mechanisms in addition to pressure calciuresis also are important.

REFERENCES

1. McCarron DA, Pingree PA, Rubin RJ, et al: Enhanced parathyroid function in essential hypertension: a ho-

meostatic response to a urinary calcium leak. Hypertension 1980;2:162–168.

2. Cirillo M, Galletti F, Strazzullo P, et al: On the pathogenetic mechanism of hypercalciuria in genetically hypertensive rats of the Milan strain. Am J Hypertens 1989;2:741–746.
3. McCarron DA: Calcium metabolism and hypertension. Kidney Int 1989;35:717–736.
4. Robinson BF: Altered calcium handling as a cause of primary hypertension. J Hypertens 1984;2:453–460.
5. Bohr DF: Vascular smooth muscle: dual effect of calcium. Science 1963;139:597–599.
6. Dominiczak AF, Bohr DF: Cell membrane abnormalities and the regulation of intracellular calcium concentration in hypertension. Clin Sci 1990;79:415–423.
7. Hatton DC, Scrogin KE, Levine D, et al: Dietary calcium modulates blood pressure through α_1-adrenergic receptors. Am J Physiol 1993;264:F234–F238.
8. Kim S, Ouchi Y, Iijima S, et al: Central neural mechanism contributing to attenuation of angiotensin II-induced hypertension in rats on dietary calcium supplementation. Clin Exp Hypertens 1993;15:307–323.
9. Sowers JR, Zemel MB, Zemel PC, Standley PR: Calcium metabolism and dietary calcium in salt-sensitive hypertension. Am J Hypertens 1991;4:557–563.
10. Resnick LM: Uniformity and diversity of calcium metabolism in hypertension. Am J Med 1987;82(suppl 1B): 16–26.
11. Hatton DC, McCarron DA: Dietary calcium and blood pressure in experimental models of hypertension. Hypertension 1994;23:513–530.
12. Massry SG, Coburn JW, Chapman LW, Kleeman CR: The effect of long-term desoxycorticosterone acetate administration on the renal excretion of calcium and magnesium. J Lab Clin Med 1978;71:212–219.
13. DiPette DJ, Greilich PE, Kerr NE, et al: Systemic and regional hemodynamic effects of dietary calcium supplementation in mineralocorticoid hypertension. Hypertension 1989;13:77–82.
14. Barbagallo M, Resnick LM, Sosa RE, et al: Renal divalent cation excretion in secondary hypertension. Clin Sci 1992;83:561–565.
15. MacGregor GA, Cappuccio FP: The kidney and essential hypertension: a link to osteoporosis? J Hypertens 1993;11:781–785.
16. Hall JE, Mizelle HL, Hildebrandt DA, Brands MW: Abnormal pressure natriuresis: a cause or a consequence of hypertension? Hypertension 1990;15:547–559.
17. Hall JE, Granger JP, Hester RL, et al: Mechanisms of escape from sodium retention during angiotensin II hypertension. Am J Physiol 1984;246:F627–F634.
18. Duarte CG, Watson JF: Calcium reabsorption in proximal tubule of the dog nephron. Am J Physiol 1967;212: 1143–1147.
19. Suki WN, Rouse D: Renal transport of calcium, magnesium, and phosphorus, *in* Brenner BM, Rector FC Jr (eds): The Kidney. WB Saunders, Philadelphia, 1991, pp 320–423.
20. Wu X, Sonnenberg H: Effect of renal perfusion pressure on excretion of calcium, magnesium, and phosphate in the rat. Clin Exp Hypertens 1995;17:1269–1285.
21. Hester RL, Granger JP, Williams J, Hall JE: Acute and chronic servo-control of renal perfusion pressure. Am J Physiol 1983;244:F455–F460.
22. Hall JE, Guyton AC, Farr BM: A single-injection technique for measuring glomerular filtration rate. Am J Physiol 1977;232:F72–F76.
23. Bruning JL, Kintz BL: Computational Handbook of Statistics. Scott, Foresman and Co, Glenview, Illinois, 1987.
24. Hall JE, Mizelle HL, Brands MW, Hildebrandt DA: Pressure natriuresis and angiotensin II in reduced kidney mass, salt-induced hypertension. Am J Physiol 1992;262:R61–R71.
25. Gonzalez-Compoy JM, Romero JC, Knox FG: Escape from the sodium retaining effects of mineralocorticoids: role of ANF and intrarenal hormone systems. Kidney Int 1989;35:767–777.
26. DeWardener HE, Clarkson EM: Concept of natriuretic hormone. Physiol Rev 1985;65:658–659.
27. Marin-Grez M, Oza NB, Carretero OA: The involvement of urinary kallidrein in the renal escape from the sodium retaining effect of mineralocorticoids. Henry Ford Hosp Med J 1973;21:85–90.