Role of Renal Interstitial Pressure as a Mediator of Sodium Retention During Systemic Blockade of Nitric Oxide

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The role of renal interstitial pressure was examined in mediating the sodium retention induced by blockade of nitric oxide synthesis. The effects of intravenous Nω-nitro-L-arginine-methyl ester (L-NAME), a synthesis inhibitor, on renal hemodynamics, renal interstitial hydrostatic pressure, and sodium and lithium excretion were determined. L-NAME (50 μg/kg per minute) was infused for 75 minutes in Sprague-Dawley rats (n=7) in which renal perfusion pressure was permitted to rise in parallel with systemic arterial pressure and in rats (n=8) in which renal perfusion pressure was servocontrolled constant at basal levels. Infusion of L-NAME raised renal perfusion pressure from 122±6 to 157±4 mm Hg in the nonservocontrolled group but not in the servocontrolled group (118±3 mm Hg). L-NAME decreased renal plasma flow and glomerular filtration rate to the same level in both rat groups. L-NAME significantly decreased sodium excretion (138±0.41 to 0.6±0.14 μEq/min and 1.19±0.46 to 0.30±0.05 μEq/min, respectively), fractional excretion of lithium (25.7±1.7% to 16.7±2.3% and 25.6±4.0% to 18.2±1.7%), and renal interstitial hydrostatic pressure (6.4±1.4 to 3.2±0.9 mm Hg and 6.3±1.8 to 2.7±0.9 mm Hg) in servocontrolled and nonservocontrolled groups. However, there was no significant difference in the renal hemodynamic and excretory responses to L-NAME between the servocontrolled and nonservocontrolled groups. In summary, reductions in sodium excretion during inhibition of nitric oxide synthesis are associated with significant reductions in renal interstitial hydrostatic pressure. Similar responses in sodium excretion and renal interstitial hydrostatic pressure to L-NAME between servocontrolled and nonservocontrolled groups indicate blunted pressure natriuresis and reduced transmission of renal perfusion pressure into renal interstitium during nitric oxide blockade. These data indicate that decreases in renal interstitial hydrostatic pressure may, in part, play a role in mediating the sodium retention of nitric oxide blockade. (Hypertension 1993;21:956–960)

KEY WORDS • hemodynamics • nitric oxide • natriuresis • glomerular filtration rate

Research investigations over the past few years have produced evidence that endothelial cells synthesize several vasoactive substances that modulate vascular smooth muscle function. One of these substances has been identified as nitric oxide. Nitric oxide is a potent activator of soluble guanylate cyclase, which leads to an increase in vascular smooth muscle cyclic GMP and subsequent relaxation.

Recent studies indicate that nitric oxide is produced by the renal vasculature and plays an important role in the regulation of renal hemodynamics and sodium excretion. Systemic administration of nitric oxide synthase inhibitors results in consistent increases in renal vascular resistance. Although some studies have reported inhibition of nitric oxide synthesis to have no effect on or even to increase sodium excretion, most investigations have demonstrated reductions in sodium excretory function when the nitric oxide synthesis inhibitor is given at a constant infusion. The exact mechanisms responsible for the reduction in sodium excretory function have not been fully elucidated. Reductions in sodium excretion may be mediated through reductions in the filtered load of sodium or as a result of an increase in tubular reabsorption of sodium. Enhanced tubular reabsorption of sodium may occur as a result of a direct effect of nitric oxide synthesis inhibition on tubular transport of sodium or via a hemodynamically mediated mechanism by decreasing renal interstitial hydrostatic pressure or medullary blood flow. Although recent preliminary and published reports indicate that nitric oxide may directly influence sodium transport and alter medullary blood flow, the importance of reductions in renal interstitial hydrostatic pressure in mediating sodium retention induced by nitric oxide blockade is not known.

Increases in renal vascular resistance as a result of nitric oxide synthase inhibition would be expected to decrease renal interstitial hydrostatic pressure. However, increases in renal perfusion pressure during systemic nitric oxide synthesis blockade would increase renal interstitial hydrostatic pressure and tend to offset the effect of renal vascular resistance on renal interstitial hydrostatic pressure. Thus, the role of renal...
interstitial hydrostatic pressure in mediating the sodium retention induced by nitric oxide synthesis blockade remains unclear. Therefore, the objective of this study was to determine the effects of \( \text{N}^\circ \)-nitro-L-arginine-methyl ester (L-NAME), a nitric oxide synthesis blocker, on renal interstitial hydrostatic pressure, renal hemodynamics, and sodium excretion in the presence or absence of increases in renal perfusion pressure.

**Methods**

All experimental procedures involving animals were performed in accordance with institutional guidelines. Experiments were performed on adult male Sprague-Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, Ind.). All rats were fasted overnight before experimentation. For the acute experimental studies, rats were anesthetized intraperitoneally with 100 mg/kg Inactin (Promont GmbH, Hamburg, FRG) and placed on a thermostatically controlled warming table to maintain body temperature at 37°C. A tracheotomy was performed, and a polyethylene 200 tube 3 cm long was inserted into the trachea to maintain an open airway.

Polyethylene catheters (PE-50) were placed in the left jugular vein for maintenance infusion and in the left carotid artery for blood sampling. The right femoral artery was cannulated using PE-10 tubing, and the catheter was advanced into the aorta to the level of the renal artery for continuous measurement of renal perfusion pressure. The carotid and femoral arterial catheters were connected to a model P23DC strain gauge, and arterial pressure was recorded on a polygraph standard expressions. Fractional excretion of lithium was used to estimate proximal tubule handling of sodium.

**Statistical Analysis**

Values are given as mean±SEM. Renal perfusion pressure and renal interstitial hydrostatic pressure recorded at 5-minute intervals were averaged, and one value per period was reported. Multiple data were analyzed by analysis of variance, followed by multiple comparisons made with the Scheffé F test. Statistical significance was considered to be \( p<0.05 \).

**Results**

Figure 1 illustrates changes in renal perfusion pressure, renal plasma flow, and glomerular filtration rate in response to infusion of L-NAME. Infusion of L-NAME raised renal perfusion pressure from 122±6 to 157±4 mm Hg in the nonservocontrolled group but not in the servocontrolled group (118±3 to 118±3 mm Hg). There was no significant change in renal perfusion pressure in the vehicle infusion group (117±4 to 115±5 mm Hg). L-NAME infusion for 75 minutes decreased renal plasma flow significantly from 4.51±0.49 to 1.61±0.41 ml/min in the servocontrolled group and from 4.91±0.36 to 1.80±0.29 ml/min in the nonservocontrolled group. Renal plasma flow in the vehicle-infused rats averaged 4.41±0.48 ml/min and did not change significantly. L-NAME decreased glomerular filtration rate significantly from 7.44±0.19 to 0.81±0.20 ml/min in the servocontrolled group and from 1.96±0.18 to 0.95±0.16 ml/min in the nonservocontrolled group. Glomerular filtration rate in the vehicle-infused rats averaged 1.76±0.18 ml/min and did not change throughout the experiment. There was no significant
difference in renal plasma flow or glomerular filtration rate between the servocontrolled and nonservocontrolled rats under basal conditions and in response to L-NAME.

Figure 2 summarizes changes in sodium excretion and renal interstitial hydrostatic pressure in response to L-NAME. L-NAME infusion decreased sodium excretion significantly from 1.38±0.41 to 0.36±0.14 µEq/min in the servocontrolled group and from 1.19±0.46 to 0.30±0.05 µEq/min in the nonservocontrolled group. Sodium excretion in the vehicle-infused rats averaged 1.23±0.30 µEq/min and did not change significantly. Fractional excretion of sodium also decreased significantly in response to L-NAME in the servocontrolled and nonservocontrolled groups. Fractional excretion of sodium decreased from 0.40±0.15% to 0.23±0.03% in response to L-NAME. Fractional excretion of sodium also decreased to a similar extent in the servocontrolled group (0.53±0.13% to 0.31±0.06%). L-NAME decreased renal interstitial hydrostatic pressure significantly from 6.4±1.4 to 3.2±0.9 mm Hg in the servocontrolled group and from 6.3±1.8 to 2.7±0.9 mm Hg in the nonservocontrolled group. Renal interstitial hydrostatic pressure in the vehicle-infused rats averaged 6.2±0.7 mm Hg and did not change significantly throughout the experiment. There was no significant difference in sodium excretion or renal interstitial hydrostatic pressure between the servocontrolled and nonservocontrolled rats under basal conditions and in response to L-NAME.
VEHICLE (n=7)  
+ NON-SERVOCONT (n=7)  
+ SERVOCONT (n=6)

VEHICLE or L-NAME

TIME (min)

UFR (μL/min)

FELi (%)

Figure 3. Line graphs show effect of N^6-nitro-l-arginine-methyl ester (L-NAME) on urine flow rate (UFR) and fractional excretion of lithium (FELi) in vehicle-infused rats (VEHICLE) and in rats with (SERVOCONT) and without (NON-SERVOCONT) servocontrol of renal perfusion pressure. Values are mean±SEM.

Discussion

Intravenous infusion of an inhibitor of nitric oxide synthesis, L-NAME, resulted in significant increases in arterial pressure and renal vascular resistance and decreases in renal plasma flow, glomerular filtration rate, and sodium excretion. Associated with the reduction in sodium excretory function was a significant decrease in renal interstitial hydrostatic pressure despite marked elevations in renal perfusion pressure.

L-NAME-induced reductions in sodium excretion in our study occurred as a result of a decrease in the filtered load of sodium, an increase in the tubular reabsorption of sodium, or both. Fractional reabsorption of sodium was significantly enhanced by L-NAME. Furthermore, fractional reabsorption of lithium, a marker of proximal tubule sodium reabsorption, was also increased in response to nitric oxide synthesis inhibition.

Inhibition of nitric oxide synthesis could influence tubular reabsorption by a direct effect on tubular sodium transport or by hemodynamically mediated mechanisms via reductions in medullary blood flow or renal interstitial hydrostatic pressure. In support of a direct action of endothelium-derived nitric oxide is the study by Stoos et al indicating that endothelium-derived nitric oxide directly inhibits transport in cultured cortical collecting duct cells. Mattson and colleagues also recently reported that nitric oxide synthesis inhibition decreases papillary plasma flow. In the present study, we report that L-NAME-induced sodium retention is also associated with significant reductions in renal interstitial hydrostatic pressure. Reductions in renal interstitial hydrostatic pressure occurred despite significant elevations in renal perfusion pressure. These changes in intrarenal hemodynamic factors may play an important role in mediating the sodium retention induced by L-NAME.

Results from previous studies examining the effects of systemic endothelium-derived nitric oxide inhibition on sodium excretion have yielded mixed results. Baylis et al reported that bolus intravenous injection of N^6-monomethyl L-arginine (100 mg/kg body wt) increased sodium excretion but bolus injection of L-NAME (10 mg/kg body wt) did not affect sodium excretion. Lahera et al reported that at low doses of L-NAME there were decreases in sodium excretion when there were no increases in blood pressure. However, as the dose was increased and blood pressure increased, there was a natriuretic effect. Recently, Johnson and Freeman reported that the sodium excretion in rats treated with a bolus injection of L-NAME (75 μM/kg body wt) was higher than in vehicle-infused rats, but the natriuresis was prevented when the renal perfusion pressure was maintained at a constant level. They concluded that a rise in renal perfusion pressure induced pressure natriuresis. All these studies suggest that changes in renal perfusion pressure via a pressure natriuresis phenomenon could cause diverse effects on sodium excretion when L-NAME was administered intravenously.

To determine the importance of increases in renal perfusion pressure in influencing the renal interstitial hydrostatic pressure and sodium excretory responses to nitric oxide synthesis inhibition, we examined the renal effects of L-NAME in the presence or absence of...
increases in renal perfusion pressure. In our study, we found no difference in the sodium excretory or renal interstitial hydrostatic pressure response to L-NAME between servocontrolled and nonservocontrolled groups of rats. This finding suggests that pressure natriuresis and the ability for renal perfusion pressure to be transmitted into the renal interstitium can be, under certain conditions, attenuated or abolished by endothelium-derived nitric oxide synthesis inhibition. Several recent studies support these findings. Salom et al.\textsuperscript{17} reported that intravenous infusion of \textsuperscript{N}\textsuperscript{G}-monomethyl L-arginine into rats attenuated the increase in sodium excretion at high renal perfusion pressures. Similarly, Majid and Navar\textsuperscript{18} recently reported that intrarenal infusion of L-NAME markedly reduced pressure natriuresis despite efficient autoregulation of renal blood flow and glomerular filtration rate in anesthetized dogs. Our studies extend these findings by demonstrating that the attenuated pressure natriuresis is associated with reduced transmission of renal perfusion pressure into the renal interstitium. This reduced effect of renal perfusion pressure on renal interstitial hydrostatic pressure may play a role in the attenuated pressure natriuresis response during intravenous administration of L-NAME.

The tendency for renal interstitial hydrostatic pressure to change in response to nitric oxide synthesis inhibition is not only dependent on the degree of change in renal perfusion pressure but also on the level of renal vasoconstriction. If renal perfusion pressure increases much more than renal vascular resistance, one would expect increases in renal interstitial hydrostatic pressure and sodium excretion. However, if renal vascular resistance increases to a greater degree than renal perfusion pressure, no change or even decreases in renal interstitial pressure and sodium excretion could occur. As pointed out in the above discussion, previous studies examining the effects of systemic endothelium-derived nitric oxide synthesis inhibition on sodium excretion have yielded mixed results. The exact reason for these divergent findings is unclear but may be due to many factors, including method and dose of L-NAME administration, anesthesia, and the activity of endogenous vasoconstrictor systems. All of these factors could influence the level at which renal perfusion pressure and renal vasculature resistance changes in response to nitric oxide synthesis inhibition, thus affecting the sodium excretory and renal interstitial responses.

As observed in earlier studies, endothelium-derived nitric oxide synthesis inhibition has significant effects on renal hemodynamics.\textsuperscript{3-6,18} L-NAME (50 \textmu g/kg per minute) used in this study resulted in significant reductions in renal plasma flow and glomerular filtration rate. There was no significant difference in renal plasma flow or glomerular filtration rate between servocontrolled and nonservocontrolled rats despite marked differences in renal perfusion pressure. These results indicate that renal autoregulation was not impaired by L-NAME. This finding is consistent with a number of studies indicating that the autoregulatory capability of the renal vasculature is not affected by endothelium-derived nitric oxide synthesis inhibitors.\textsuperscript{5,18}

In summary, reductions in sodium excretion during endothelium-derived nitric oxide synthesis inhibition are associated with significant reductions in renal interstitial hydrostatic pressure. Similar responses in sodium excretion and renal interstitial hydrostatic pressure to L-NAME between servocontrolled and nonservocontrolled groups indicate blunted pressure natriuresis and reduced transmission of renal perfusion pressure into renal interstitium during endothelium-derived nitric oxide blockade. The association between the renal interstitial hydrostatic pressure data and the sodium excretion data indicates that decreases in renal interstitial hydrostatic pressure may, in part, mediate the sodium retention of endothelium-derived nitric oxide blockade.

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References

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