The Role of Nitric Oxide in Saline-Induced Natriuresis and Diuresis in Rats (44421)

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Abstract. **This study was designed to determine to what extent nitric oxide (NO) mediates the natriuretic and diuretic responses to acute isotonic saline (0.9 gram % NaCl) volume expansion (SVE, 0.5 ml min^{-1} kg^{-1}). Studies were performed on 49 pentobarbital anesthetized (65 mg/kg) female Sprague-Dawley rats with or without a NO synthase inhibitor, N^{ω}-nitro-L-arginine (LNA). Group 1 received saline at 27 μl/min for 1 hr (baseline) and then SVE for 1 hr; Groups 2–4 received LNA at 10, 150, and 200 μg kg^{-1} min^{-1}, respectively, for 1 hr followed by LNA + SVE. To determine to what extent inhibition of NOS would reverse an ongoing SVE-induced natriuresis and diuresis, Group 5 was saline-volume-expanded for hours 1 and 2 whereas Group 6 was administered SVE during the first hour and then SVE + 150 μg kg^{-1} min^{-1} LNA during the second hour. SVE caused a significant ($P < 0.05$) increase in the glomerular filtration rate (GFR) of Group 1 and the LNA-treated rats (Groups 2–4). This SVE-induced increase in the GFR occurred despite the fact that baseline GFR was significantly lower in the two groups of rats that were infused with the highest doses of LNA (Groups 3–4). SVE was also associated with similar increases in urine flow rate, sodium and potassium excretion, and total osmolar excretion in Groups 1–4. On the other hand, mean arterial pressure (MAP) was significantly higher in Group 2 during SVE + LNA and during the baseline as well as during the SVE periods in Groups 3–4; MAP was also significantly elevated in Group 6 during SVE + LNA. Thus, despite the fact that MAP was higher in LNA-treated rats, sodium and urine flow rates were the same as in Group 1 (i.e., there was no evidence of a pressure natriuresis or diuresis in these animals). Along these lines, there was a small but significant positive linear correlation coefficient ($r = 0.41$, $P = 0.05$) between sodium excretion values and corresponding MAP values in SVE control rats but not in Groups 3–4 during SVE ($r = 0.28$, $P = 0.26$). The current data demonstrate that 1) NO does not mediate SVE-induced hyperfiltration in the rat, 2) NO also does not mediate SVE-induced natriuresis or diuresis, and 3), consistent with other reports, NO appears to mediate pressure natriuresis and diuresis.**

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Nitric oxide (NO) is a vasorelaxant molecule produced by endothelial cells and is released in response to a variety of stimuli (1). In endothelial cells, NO and L-citrulline are formed from the conversion of the terminal guanidino nitrogen atom of L-arginine by a constitutive nitric oxide synthase (NOS) (2). This constantly acting enzyme, as well as neuronal and inducible NOSs can be competitively inhibited by structural analogs of L-arginine such as N^{ω}-nitro-L-arginine (LNA) and N^{ω}-nitro-L-arginine methyl ester (L-NAME). Pharmacologic inhibition of NOSs has helped elucidate the fact that NO is an important regulator of cardiovascular and renal function. Lahera *et al.* (3) have demonstrated in anesthetized rats that L-NAME produced dose-dependent alterations that attenuated sodium excretion and urine flow rate in the absence of significant changes in blood pressure. In the dog, intrarenal NO has been implicated in mediating pressure natriuresis and diuresis as the infusion of LNA (50 μg kg^{-1} min^{-1}) into the renal artery caused a marked reduction of sodium excretion and urine flow rate in response to changes in renal arterial pressure (4). On the other hand, systemic infusion of NO synthesis inhibitors was observed to induce a natriuresis

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and diuresis in the rat (5). This response has been attributed to pressure natriuresis (6), while others have suggested a decrease in proximal tubular reabsorption (7).

Saline volume expansion (SVE) of the extracellular fluid space has been shown to alter a number of renal function variables. Specifically, SVE increases the glomerular filtration rate (GFR, for example, see Ref. 8), renal interstitial hydrostatic pressure and urinary sodium excretion (9). The latter is related to a number of factors including diminished proximal tubular sodium reabsorption (10), increased peritubular capillary hydrostatic pressure and reduced peritubular colloid osmotic pressure (11), decreased renin secretion (12) and plasma renin activity (13), and increased secretion of atrial natriuretic factor (14). It has been demonstrated that in animals with SVE, intrarenal inhibition of nitric oxide synthesis has no effect on the glomerular filtration rate in dogs (15, 16) or rats (17). However, the combined effect of SVE and systemic NO synthesis inhibition on glomerular function and electrolyte excretion has not been studied extensively.

The aim of this study was to determine to what extent nitric oxide contributes to the glomerular hyperfiltration and the increased electrolyte excretion observed in rats acutely volume-expanded with saline. The specific hypothesis to be tested is that the glomerular hyperfiltration and enhanced electrolyte excretion observed with saline volume expansion are the result of increased synthesis of systemic and/or renal nitric oxide. The renal and systemic actions of a nitric oxide synthase inhibitor, N^{ω}-nitro-L-arginine (LNA, 18), were evaluated under steady-state conditions in sodium pentobarbital anesthetized female control and saline volume-expanded rats.

Materials and Methods

Experiments were performed on a total of 49 female Sprague-Dawley rats (187–265 g); all studies were conducted in accordance with institutional guidelines and approved by the Institutional Animal Care and Use Committee. Animals were maintained on standard rat chow and water *ad libitum* until the time of the experiment. On the day of the experiment, rats were anesthetized with sodium pentobarbital (65 mg/kg), and rectal temperatures were maintained at 37 ± 0.5°C with a radiant heat lamp connected to a temperature controller. To facilitate respiration, a tracheotomy was performed using PE-200 tubing. The left femoral artery was cannulated with heat-stretched PE tubing and used for monitoring mean arterial blood pressure (MAP) and for collection of blood samples. The left femoral vein was cannulated with heat-stretched PE tubing and attached to one infusion pump for infusing 3% creatinine in isotonic saline at 27 μl/min ± other agents and to a second pump for infusing an additional 0.5 ml kg^{-1} min^{-1} isotonic saline during the SVE portion of the experiments; the clearance of exogeneously administered creatinine is equivalent to the GFR in female rats (19, 20). The bladder was cannulated with PE-100 tubing for collecting urine. Upon completion of surgery, to facilitate complete collection of urine, animals were placed on their sides above the level of the table. Following a 1-hr stabilization period, two 20-min baseline clearances were collected (since these two clearances were virtually identical, i.e., the animals were in a steady-state, the clearance values were averaged), SVE was then initiated for 1 hr and continued while a second set of 20-min clearances was collected (again, since these two clearances were virtually identical, the values were averaged). A blood sample (approximately 100 μl) was collected after the second baseline clearance and at the conclusion of the study (approximately 500 μl); animals were sacrificed by an injection of a lethal dose of sodium pentobarbital, and the kidneys were removed. Individual protocols are delineated below.

Protocol I: LNA Administered Prior to SVE. To determine to what extent nitric oxide contributes to the glomerular hyperfiltration observed in volume-expanded rats, the potential capacity of the nitric oxide synthase inhibitor, N^{ω}-nitro-L-arginine, to attenuate SVE-induced increases in the GFR was evaluated. Following surgery, rats from Group 1 (n = 7) were infused with 3% creatinine in saline at 27 μl/min for a 1-hr stabilization period; the infusion was continued while two 20-min baseline clearances were collected. SVE (0.5 ml kg^{-1} min^{-1}) was initiated for 1 hr following the baseline clearances, and was continued while two 20-min clearances were collected. By contrast, rats from Groups 2–4 were infused throughout the entire experiment (before and during SVE) with LNA at 10 (Group 2, n = 6), 150 (Group 3, n = 6) and 200 (Group 4, n = 6) μg kg^{-1} min^{-1}. Clearances were collected as described above.

Protocol II: LNA Administered During SVE. Experiments in Protocol II were designed to determine to what extent inhibition of nitric oxide synthase with LNA reverses the renal and cardiovascular changes associated with SVE. Group 5 (n = 5) was saline volume expanded immediately following surgery. After a 1 hr stabilization period, two 20 min baseline clearances were collected. SVE was continued for a second hour, and then two 20-min clearances were collected. Group 6 (n = 5) also had SVE initiated following surgery and continued throughout the experiment except that following the collection of two 20-min baseline clearances, an infusion of LNA at 150 μg kg^{-1} min^{-1} was added. One hour later, two 20 min clearances were collected.

Analytical and Statistical Procedures. Urine volumes and kidney weights were determined gravimetrically. Creatinine concentrations in blood and urine were measured by the method of Folin and Wu (21). Sodium and potassium concentrations in urine (U_{Na} and U_K, respectively) and in plasma were measured using a flame photometer (Corning 480 Flame Photometer, Medfield, MA). Osmolality of urine and plasma was measured by vapor pressure osmometry (Wescor, UT).

Statistical differences of values between groups were determined using a one-way analysis of variance. Differences within each group were evaluated using Student's t

test for paired data. Linear regression analysis was used to calculate the correlation coefficient, r, between two physiologic variables. Values were accepted as significantly different when the probability (P) of difference was less than 5%. Means ± SEM are reported.

All chemicals and reagents were purchased from Sigma Chemical Company (St. Louis, MO).

Results

Protocol I: LNA Administered Prior to SVE. Glomerular filtration rate (ml min^{-1} g kidney wt^{-1}), mean arterial pressure (mmHg), urine flow rate (V, μl min^{-1} g kidney wt^{-1}), and sodium excretion ($U_{Na}V$, μEq min^{-1} g kidney wt^{-1}) values obtained from rats in Groups 1–4 are summarized in Figure 1. All other renal excretion variables from these four groups are presented in Table I. Compared with Group 1, the baseline GFR (Fig. 1A) was significantly lower in rats treated with 150 and with 200 μg kg^{-1} min^{-1} LNA (Groups 3 and 4, respectively). On the other hand, saline volume expansion produced a significant increase in the GFR in Group 1 rats and in rats that were treated with 10, 150, or 200 μg kg^{-1} min^{-1} LNA (Groups 2–4, respectively). Furthermore, none of the GFR values during SVE was significantly different among the four groups of rats.

Mean arterial blood pressure (illustrated in Fig. 1B) was significantly higher in rats treated with LNA at 150 and 200 μg kg^{-1} (Groups 3 and 4, respectively) compared with Group 1 rats during both the baseline and SVE periods. MAP was also significantly greater in rats that received 10 μg kg^{-1} min^{-1} LNA during the saline expansion period (Group 2).

As noted in Figures 1C and 1D, SVE was associated with significant and similar increases in urine flow rate and sodium excretion rate in Groups 1–4. In addition, none of the values for urine flow rate or sodium excretion rate were different among either baseline or SVE conditions among the four groups of rats.

Table I illustrates that the other excretion variables measured in the current study, potassium excretion (U_KV) and osmolar excretion ($U_{os}V$), again all factored by kidney weight, were not statistically different in corresponding baseline or SVE periods among the four groups. However, each of these variables, increased significantly during SVE.

Protocol II: LNA Administered During SVE. Glomerular filtration rate, mean arterial pressure, urine flow rate and sodium excretion rate data for Groups 5–6 are summarized in Figure 2. As illustrated in Figure 2A, compared with the first hour of SVE, the GFR did not change significantly during the second hour of continued SVE in either Group 5 or in rats treated with 150 μg kg^{-1} min^{-1} LNA during the second hour (Group 6). MAP, illustrated in Figure 2B, did not change significantly in Group 5 during the second hour of saline volume expansion, but did increase significantly with the addition of 150 μg kg^{-1} min^{-1} LNA in Group 6. In addition, MAP in Group 6 during infusion of LNA was significantly greater when compared to the second hour of SVE in Group 5.

Both the urine flow rate and sodium excretion rate (Figures 2C and 2D) increased significantly during the second hour of SVE compared with the first hour of expansion in both Groups 5 and 6. Neither urine flow rate nor sodium excretion rate was different during the first hour of SVE

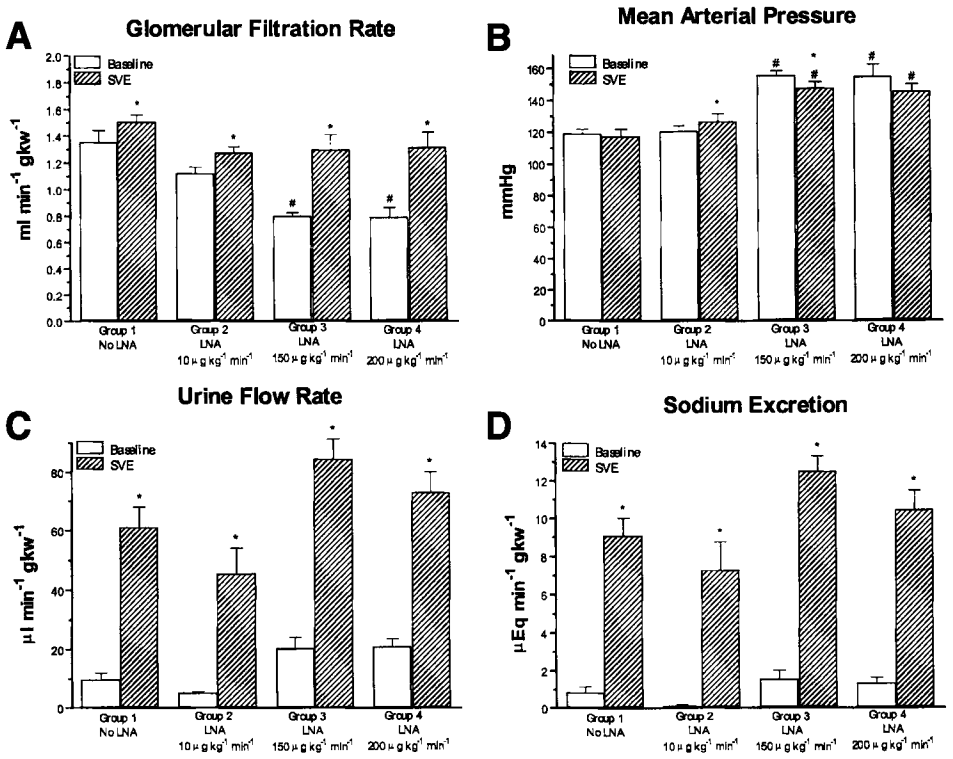

Figure 1. Effects of saline volume expansion (SVE) on (A) glomerular filtration rate (GFR); (B) mean arterial pressure (MAP); (C) urine flow rate (V); and (D) sodium excretion ($U_{Na}V$), normalized per gram kidney weight (kw), in anesthetized rats without LNA (Group 1) or during N^{ω}-nitro-L-arginine (LNA; 10, 150, and 200 μg kg^{-1} min^{-1}; Groups 2–4, respectively) infusion during the second hr of SVE. Data are expressed as mean ± SEM. *Indicates a significant difference ($P < 0.05$) between SVE data and corresponding baseline data, and # indicates a significant difference ($P < 0.05$) between LNA and corresponding control values.

Table I. Effects of SVE on Potassium Excretion (U_KV) and Total Osmolar Excretion ($U_{os}V$), Normalized per Gram Kidney Weight (kw), in Anesthetized Rats Without (Group 1) and With N^{ω}-nitro-L-Arginine Infusion (Group 2 = 10, Group 3 = 150 and Group 4 = 200 μg kg^{-1} min^{-1}, respectively) During the Entire Experiment

	U_KV (μEq min^{-1} gkw^{-1})		$U_{os}V$ (μosmoles min^{-1} gkw^{-1})	
	Baseline	SVE	Baseline	SVE
Group 1 No LNA (n = 7)	1.26 ± 0.18	1.67 ± 0.10	10.86 ± 1.24	27.56 ± 1.86*
Group 2 LNA 10 μg kg^{-1} min^{-1} (n = 6)	0.72 ± 0.09	1.54 ± 0.02*	7.87 ± 0.50	23.46 ± 2.66*
Group 3 LNA 150 μg kg^{-1} min^{-1} (n = 6)	0.69 ± 0.18	1.63 ± 0.16*	10.58 ± 1.30	39.97 ± 4.62*
Group 4 LNA 200 μg kg^{-1} min^{-1} (n = 6)	0.82 ± 0.17	1.57 ± 0.16*	10.39 ± 1.12	32.81 ± 2.29*

* Indicates a significant difference ($P < 0.05$) between SVE and corresponding baseline data ($P < 0.05$).
Note. Data are expressed as means ± SEM.

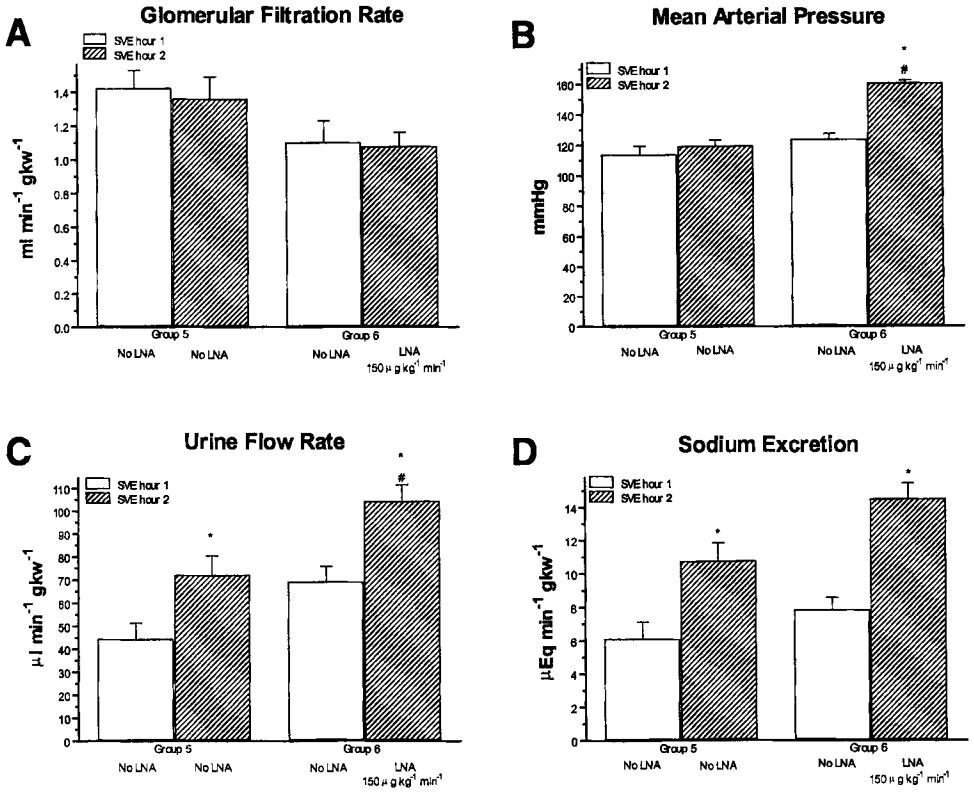

Figure 2. Effects of saline volume expansion (SVE) on (A) glomerular filtration rate (GFR), (B) mean arterial pressure (MAP); (C) urine flow rate (V); and (D) sodium excretion ($U_{Na}V$), normalized per gram kidney weight (kw), in anesthetized rats without LNA (Group 5) or during LNA (150 μg kg^{-1} min^{-1}; Group 6) infusion during the second hr SVE. Data are expressed as mean ± SEM. *Indicates a significant difference ($P < 0.05$) between hour 1 and hour 2, and # indicates a significant difference ($P < 0.05$) between LNA and corresponding control values.

between Groups 5 and 6; however, the urine flow rate was significantly increased in Group 5 in the second hour and with the administration of LNA in Group 6.

Potassium excretion decreased significantly during the second hour of SVE in Group 5 (Table II). By contrast, there was no significant difference in potassium excretion following addition of LNA to Group 6. However, potassium excretion during the first hour of SVE in Group 6 was significantly lower compared with the corresponding value in Group 5.

Finally, as also summarized in Table II, the osmolar excretion rate increased significantly from hour 1 to hour 2 in both Groups 5 and 6.

Discussion

Results of the present study illustrate that the nitric oxide synthase inhibitor, LNA, at doses that span more than a 10-fold range, does not attenuate SVE-induced changes in glomerular filtration rate, urine flow rate, or electrolyte excretion when compared with saline volume-expanded rats not treated with the inhibitor. It is also important to note that, the two highest doses of LNA used in the current study appeared to cause maximal increases in arterial blood pressure and maximal decreases in the glomerular filtration rate. In addition, LNA does not reverse or otherwise attenuate ongoing SVE-induced natriuresis and diuresis. Thus, these data strongly suggest that neither systemic nor renal nitric oxide is involved in the natriuresis or diuresis induced by saline volume expansion of the extracellular fluid space.

A number of factors, some of which were summarized previously, are involved in the renal responses associated with saline volume expansion. Of these, a likely candidate for the hyperfiltration associated with SVE is the vasoactive hormone, atrial natriuretic factor (ANF). As demonstrated

Table II. Effects of Saline Volume Expansion (SVE) for 2 hr on Potassium Excretion (U_KV) and Total Osmolar Excretion ($U_{os}V$), Normalized per Gram Kidney Weight (kw), in Anesthetized Rats Without LNA (Group 5) and During Infusion of LNA at 150 μg kg^{-1} min^{-1} During the Second Hour of SVE (Group 6)

	U_KV (μEq min^{-1} gkw^{-1})		$U_{os}V$ (μosmoles min^{-1} gkw^{-1})	
	SVE-hour 1	SVE-hour 2	SVE-hour 1	SVE-hour 2
Group 5 No LNA (n = 5)	2.01 ± 0.16	1.53 ± 0.07*	22.62 ± 1.98	29.27 ± 2.40*
Group 6 LNA Hr 2 150 μg kg^{-1} min^{-1} (n = 6)	1.56 ± 0.06	1.48 ± 0.09	26.15 ± 1.54	39.06 ± 1.83*

* Indicates a significant difference ($P < 0.05$) between Hour 1 and Hour 2 data.
Note. Data are expressed as means ± SEM.

by Khraibi and colleagues (14), infusing a dose of ANF (2 μg kg^{-1} hr^{-1}) that mimics the high plasma concentrations observed during acute volume loading, resulted in a 4-fold increase in the GFR. Furthermore, the vasoactive effects of ANF are not mediated through NO, as the effects of the former are modulated through a particulate guanylate cyclase, whereas the vasoactive effects of NO are mediated through a soluble guanylate cyclase (22). Along these lines, it is of interest to note that two conditions characterized by glomerular hyperfiltration, namely in salt-replete animals with 5/6 nephrectomy and in streptozotocin-induced diabetic rats, the ANF antagonist HS-142-1, reverses the observed hyperfiltration (23, 24).

Another aspect of the GFR-related changes in the current study relates to the fact that the baseline GFR values were significantly reduced during infusion of the two higher doses of LNA whereas MAP was significantly elevated, findings that are typically found during inhibition of NOS in the rat (3). As noted above, the effects of LNA on MAP and GFR appeared to be maximal since the changes induced by LNA were similar with the two highest doses (Groups 3 and 4). In the acute setting, the decrease in GFR (25, 26), as well as renal blood flow (27), prompted by NOS inhibition in the rat, has been reported to be mediated by angiotensin II, since angiotensin II receptor antagonists, attenuate these effects. By contrast, inhibiting angiotensin II has no effect on the increase in arterial blood pressure following acute NOS inhibition in the rat (25, 28). During chronic inhibition of NOS, these angiotensin II–mediated events affecting arterial blood pressure are altered. Although not observed in dogs (29), chronic hypertension in the rat induced by long-term NOS inhibition is attenuated by either angiotensin converting enzyme inhibition (30) or by AT_1 receptor blockade (31). Thus, in the current study, the fact that the LNA-induced decrease in the GFR, but not the LNA-induced increase in MAP, was altered by SVE, supports the concept that there are different mechanisms by which these two physiologic variables are regulated by NO in the acute setting. Since it is well established that SVE is associated with a decrease in renin (12), it seems reasonable to speculate that a reduced renin-angiotensin-aldosterone axis during SVE accounts for the reversal in the GFR-related action of LNA, whereas the LNA-related increase in MAP remains unaffected by SVE.

Lahera and co-workers (3) reported that, in nonsaline volume-expanded rats, different doses of L-NAME had differential effects on renal function. At low doses (less than 10 μg kg^{-1} min^{-1}), there was no effect on arterial blood pressure or on renal hemodynamics but a gradual decrease in urine flow rate during the 3-hr duration of the experiment. At higher doses (50 μg kg^{-1} min^{-1}), L-NAME was associated with an increase in urine flow rate and sodium excretion after 3 hr of infusion. In the present study, the lowest dose of LNA (10 μg kg^{-1} min^{-1}) administered for 1 hr prior to SVE did not affect MAP or any of the measured renal variables. On the other hand, despite the fact that none of these values attained statistical significance, there was a trend for urine flow rate, sodium excretion, and other excretion values to be lower in this group of rats. Thus, these results are qualitatively similar to the findings of Lahera *et al.* (3) and Stoos and Garvin (32) suggesting that there are direct tubular actions of NO.

One of the interesting aspects of the results from the current study is that urine flow rate and sodium excretion were similar among Groups 1–4 during saline volume expansion. One would anticipate that, since MAP was significantly higher in Groups 3 and 4, that these variables of renal function would have been significantly greater than corresponding values in Group 1 (i.e., there was no pressure natriuresis or diuresis) Majid *et al.* (4) have reported that administration of an inhibitor of NO synthesis into the renal artery of dogs leads to a marked attenuation in urine flow rate and sodium excretion in response to changes in renal arterial blood pressure. They suggested, therefore, that NO acts as a permissive factor in mediating pressure-induced natriuresis and diuresis, a conclusion that has also been supported by the work of Minami *et al.* in the rat (33). Data from the current study are consistent with these conclusions by Majid *et al.* (4) and Minami *et al.* (33). Specifically, in the present study, there was a small, but nonetheless significant positive correlation ($y = 0.09612x - 2.91422$; $r = 0.41$, $P < 0.05$) between the sodium excretion rate in volume-expanded control rats. By contrast, in saline volume-expanded rats infused with either 150 or 200 μg kg^{-1} min^{-1} LNA (doses that elevated MAP and reduced the GFR during the baseline period), a poor correlation was observed between these two variables ($y = 0.07088x - 1.74831$; $r = 0.28$, $P = 0.26$).

In summary, our results illustrate that several doses of a competitive nitric oxide synthesis inhibitor, N^{ω}-nitro-L-arginine (LNA), spanning more than a 10-fold dosage range, do not attenuate saline volume expansion–induced changes in glomerular filtration rate or electrolyte excretion. In addition, administration of the nitric oxide synthase inhibitor to rats during an ongoing SVE-induced natriuresis and diuresis has no effect on the magnitude of the natriuresis and diuresis. On the other hand, inhibition of NO production is associated with a marked increase in systemic arterial blood pressure, but this is not associated with a larger natriuresis or diuresis. The latter data are consistent with other reports that nitric oxide mediates pressure natriuresis and diuresis.

This study represents a portion of the Ph.D. thesis of W. T. Noonan, M.S., at the University of Cincinnati College of Medicine, Department of Molecular and Cellular Physiology.

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