Nitric Oxide Attenuates the Renal Hemodynamic Responses to Increased Peripheral and Renal Sympathetic Nerve Activity (44015)

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Abstract. **The role of nitric oxide (NO) in renal function was evaluated under conditions of elevated peripheral and renal sympathetic nerve activity (RSNA), achieved by bilateral carotid occlusion (CO) in anesthetized dogs. Renal function was monitored during CO with the NO system intact and with it blocked by the administration of L-NAME. With NO intact, CO increased arterial pressure and heart rate. With renal perfusion pressure held constant, CO also significantly decreased renal blood flow (RBF) and glomerular filtration rate (GFR) by 46% and 43%, respectively. CO, after L-NAME administration, resulted in a significantly exaggerated renal vasoconstriction. RBF and GFR decreased by 82% and 80%, respectively. Changes in water and sodium excretion were not different between the NO-intact and NO-blocked states during CO. These studies were also performed with the converting enzyme inhibitor, Captopril. The exaggerated renal hemodynamic responses to CO with NO synthesis inhibition were identical with or without Captopril. These findings indicate that under conditions of elevated peripheral and RSNA, NO plays an important role in modulating renal hemodynamics, but not sodium excretion. This effect does not appear to involve angiotensin II.** [P.S.E.B.M. 1996, Vol 212]

Nitric oxide (NO) is an endothelial-derived vasodilator which is known to be produced and act within the kidneys (1–3). NO has the potential to alter renal hemodynamics (3–6), water and electrolyte excretion (2, 3, 7), and possibly renal renin release (8, 9). To assess its physiological capacities, NO synthesis can be competitively inhibited by the administration of L-arginine analogs including N^G-nitro-L-arginine methyl ester (L-NAME) (10).

In studies that have evaluated NO synthesis inhibition in healthy animals, increases in renal vascular resistance (RVR) (4, 6) and decreases in renal blood flow (RBF) (4, 10) have been observed. These studies suggest that in the basal state a fraction of the renal vasculature's vasodilatory component is attributable to endogenous renal NO synthesis. Changes in glomerular filtration rate (GFR) with NO synthesis inhibition are less consistent, with some reports indicating that it is unchanged (3, 6) or decreased (1, 5). The effects of NO blockade on sodium excretion are unclear (2, 3, 5, 7).

There are numerous physiological conditions and pathological states in which peripheral sympathetic nerve activity (SNA) is elevated, including hypertension (11), congestive heart failure (12), cirrhosis (13), and intense exercise (14). During the activation of the sympathetic nervous system, the increase in renal sympathetic nerve activity (RSNA) causes renal vasoconstriction, which leads to changes in kidney function. The role that NO plays in determining renal hemodynamics under these conditions is not well understood. This is an important issue since increased RSNA may increase the production or release of NO

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Received October 16, 1995. [P.S.E.B.M. 1996, Vol 212]
Accepted March 14, 1996.

0037-9727/96/2123-0000$10.50/0

(15). Therefore, NO may serve to modulate, or attenuate, the renal vasoconstrictive effects of elevated RSNA. The present study was designed to address this question by mimicking a condition of elevated SNA in a normal, healthy animal.

To achieve this, bilateral carotid occlusion (CO), inferior to the carotid baroreceptors, was utilized to reflexively increase peripheral and RSNA (16). To determine the role of NO on renal function in animals with elevated SNA, comparisons were made of the renal hemodynamic and excretory response to CO with the NO system intact, versus with NO synthesis inhibited by the administration of L-NAME.

With CO, the baroreceptor-stimulated increase in RSNA may cause renal vasoconstriction directly through the release of norepinephrine, or indirectly, through the stimulation of renin release and the subsequent formation of angiotensin II (Ang II) (17, 18). Studies have shown that NO may influence the vasoconstrictive effects of Ang II (19), and possibly renin release (8, 9, 20). Consequently, experiments were also performed to evaluate the effects of CO and NO inhibition with L-NAME in animals pretreated with the angiotensin-converting enzyme inhibitor, Captopril.

Materials and Methods

Animals. Twenty-five adult beagles (12.5 ± 0.9 kg) were used for these studies. In addition to the daily ration of 450 g of Purina Dog Chow, animals were supplemented 1 g/day of NaCl to insure a sodium replete status. Water was provided *ad libitum*. The animals were fasted 20–24 hr prior to surgery.

Surgical Procedures. The dogs were anesthetized with sodium pentobarbital (30 mg/kg iv). The trachea was intubated and the animal was mechanically ventilated with room air. Polyethylene catheters were placed in the jugular vein, the abdominal aorta inferior to the origin of the renal arteries, and the thoracic aorta superior to the kidneys. The jugular catheter was used to administer a priming dose of inulin and para-aminohippuric acid (PAH) in 0.9% NaCl. Inulin and PAH sustain solutions were delivered in saline at an infusion rate of 1.0 ml/min. Both arterial catheters were connected to Statham pressure transducers. To control renal perfusion pressure (RPP), a Blalock clamp was placed around the aorta superior to the renal arteries. The abdominal aortic catheter was used to measure RPP, while the arterial catheter positioned above the clamp monitored mean arterial pressure (MAP). Heart rate (HR) was determined from pulsatile blood pressure. The bladder was approached through a ventral mid-line incision and the left ureter was catheterized. Both carotid arteries were isolated, and the animals were bilaterally vagotomized. After surgery, the animals were allowed an equilibration period of at least 30 min prior to the start of data collection.

Protocols. A total of four experimental protocols were performed. These were designated as Groups 1–4. For three of the groups, the protocol began with a 30-min control period to establish baseline values (CTL I). Following CTL I, the carotid arteries were occluded for a period of 25 min (CO I). Subsequently, CO was released for a 25-min recovery period to reestablish a second control (CTL II). This was followed by a second 25-min period of carotid occlusion (CO II). Thus, this approach with the two periods of CO allowed each animal to serve as its own control. As required, at the beginning of the periods five additional minutes were allowed for equilibration to the changes in MAP, and for adjustment of the Blalock clamp to maintain RPP at CTL I levels, before urine collection was begun. As it has been shown that even a transient increase in RPP may alter renal NO (21), it should be noted that RPP was never allowed to increase with MAP. Blood samples were obtained at 20 min into each period, and urine was collected over the entire period.

Group 1 (CO-NO) intact ($n = 6$) served as a control group and received only saline during CO II. Group 2 (CO + L-NAME) ($n = 5$) received the NO synthesis inhibitor L-NAME (20 mg/kg iv) over 10 min immediately prior CO II. Group 3 (CO + L-NAME + CAPTO) ($n = 9$) received Captopril (3 mg/kg iv) prior to the CTL II period, and L-NAME (20 mg/kg iv) immediately preceding the CO II period. The efficacy of Captopril was confirmed in each animal by the absence of an increase in MAP to exogenous angiotensin I.

Group 4 (L-NAME only) ($n = 5$) was administered L-NAME in the absence of CO. These data were used to determine the effect on renal function achieved by L-NAME administration alone, without the additional changes caused by CO. For this group, after a 30-min equilibration period, a 45-min clearance period was begun (CTL). Following completion of the CTL period, these dogs received L-NAME (20 mg/kg iv) over 10 min. During this infusion and the subsequent 45-min collection period (L-NAME), RPP was maintained at CTL levels. Blood samples were taken 30 min into each period and urine was collected for the duration of the period.

Monitoring and Analytical Procedures. Blood pressures and HR were monitored continuously. They were recorded on a Grass polygraph, as well as digitized and stored on a computer disk. Blood and urine samples were assayed for PAH and inulin concentration. Hematocrit was determined using a microhematocrit centrifuge. Renal plasma flow and GFR were estimated by PAH and inulin clearances, respectively. RBF was calculated from renal plasma flow and the

hematocrit. Serum and urine samples were analyzed for sodium and potassium by flame photometry. All renal data are for the left kidney only.

Statistical Analysis. Repeated measures analysis of variance (ANOVA) was used to determine significant differences between the changes between experimental periods within each group. A paired *t* test was used to determine significant differences between the respective control and CO periods. The percentage changes from CTL I to CO I and CTL II to CO II were also compared by paired *t* test. Control values across groups were also tested by ANOVA. As a *post hoc* test, the Fisher least significant difference was used. A difference was considered to be significant if $P < 0.05$. Throughout the text, tables, and figures, the data are expressed as mean ± SEM.

Results

Group 1. Blood pressures and HR data for Group 1 is shown in Table I. Before, CO, CTL I MAP was 96 ± 7 mm Hg. During CO I, with the reflexive increase in peripheral sympathetic nerve activity, there was a significant increase in both MAP and HR. During the CTL II period, these parameters returned to the baseline values. With CO II, the increments in MAP and HR were identical to those seen during CO I. As intended, adjusting the Blalock clamp was effective in holding RPP constant through the entire protocol (Table I).

In these animals, during CO I RBF and GFR tended to decrease by 15% and 18%, respectively (Fig. 1 and 2). Neither of these changes were significant. During the CTL II period, these parameters increased, with both returning to the CTL I levels. More importantly, in Group 1 animals during CO II, with NO synthesis intact, the decrements in RBF and GFR were identical to those observed during CO I.

The changes in water and electrolyte excretion with the two periods of CO for Group 1 are presented in Table II. During CO I, there was a 45% reduction in urine flow rate ($P < 0.05$). Sodium and potassium excretion tended to decrease, but not significantly. All of these parameters returned to their initial values during CTL II. The decrements in water and electrolyte excretion seen during CO II were essentially identical to those measured during CO I.

Group 2. In this group of animals which received L-NAME during CO II, all of the CTL I parameters were similar to Group 1 except for urinary sodium excretion. During both the CO I and CO II periods, the increases in MAP and HR were also similar to those seen in Group 1 (Table I). However, the increase in MAP during CO II was significantly greater than that seen in Group 1, presumably due to a systemic pressor effect of NO synthesis inhibition (6, 10). There was also a smaller increase in heart rate in CO II in Group 2 than in Group 1, possibly due to the specific bradycardic effect of L-NAME (10). In Group 2, RPP was effectively maintained constant throughout the entire protocol.

As illustrated in Figure 1 and 2, the decrements in RBF ($P < 0.05$) and GFR ($P < 0.05$) during CO I were similar to those seen in Group 1. These values also returned to baseline during CTL II. With subsequent NO synthesis inhibition, during CO II, the decrements in both GFR and RBF were dramatically exaggerated. As shown in Figure 2, for Group 2 animals the percentage decrease in GFR from CTL II to CO II (80%) was significantly greater than the percentage decrease from CTL I to CO I (43%). Similarly, the percentage decrement in RBF during CO II was significantly greater than that seen during CO I (82% vs 46%) ($P < 0.05$). The heightened renal vasoconstriction associated with NO synthesis inhibition, achieved by L-NAME during CO II in Group 2, can not be ascribed to a time-dependent effect, since this response was not observed in Group 1.

In contrast to the changes seen in renal hemody-

Table I. Blood Pressures and Heart Rate

		CTL I	CO I	CTL II	CO II
Group 1	MAP (mm Hg)	96 ± 7	158 ± 15[a]	89 ± 4	158 ± 12[a]
(CO-NO intact)	RPP (mm Hg)	96 ± 7	99 ± 6	90 ± 5	90 ± 4
(*n* = 6)	HR (bpm)	127 ± 6	136 ± 13[a]	118 ± 6	128 ± 7[a]
Group 2	MAP (mm Hg)	108 ± 7	189 ± 8[a]	104 ± 5	214 ± 5[a,b]
(CO + L-NAME	RPP (mm Hg)	106 ± 7	109 ± 7	102 ± 5	103 ± 6
(*n* = 5)	HR (bpm)	109 ± 7	128 ± 8[a]	108 ± 6	115 ± 8
Group 3	MAP (mm Hg)	114 ± 7	173 ± 8[a]	86 ± 4	185 ± 7
(CO + L-NAME + CAPTO)	RPP (mm Hg)	109 ± 7	109 ± 6	81 ± 4	104 ± 6
(*n* = 9)	HR (bpm)	148 ± 7[c]	158 ± 10[a]	141 ± 9	129 ± 8

Note. Mean arterial pressure (MAP), renal perfusion pressure (RPP), and heart rate (HR) during all periods for Group 1, 2, and 3.
[a] $P < 0.05$ versus respective control.
[b] $P < 0.05$ versus Group 1 during the same period.
[c] $P < 0.05$ versus Group 2 during the same period.

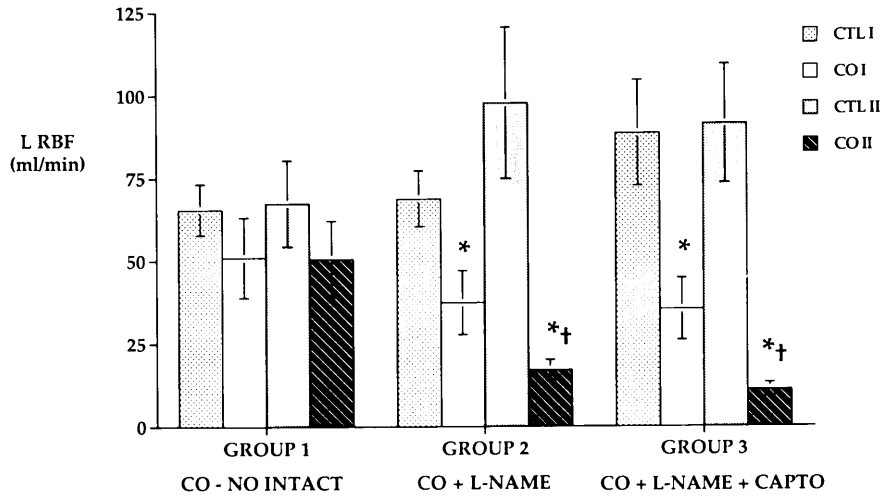

Figure 1. Comparison of changes in left renal blood flow (L RBF) between Group 1 (n = 6) and Group 2 (n = 5) and Group 3 (n = 9). L-NAME was administered immediately preceding CO II in Group 2 and 3, and Captopril was administered to Group 3 only. CTL I and CTL II are the first and second control periods. CO I and CO II are the first and second periods of carotid occlusion. *$P < 0.05$ versus respective control period. †$P < 0.05$ for the percentage change CTL II − CO II versus CTL I − CO I.

namics, in Group 2, NO synthesis inhibition during CO II did not alter the water and electrolyte excretory responses (Table II). The significant decrements in urine volume and sodium and potassium excretion were similar between the CO I and CO II periods. Although the starting values for water and electrolyte excretion were lower in Group 2 than in Group 1, the relative changes seen in these parameters with CO were the same.

These data demonstrate that, during CO and elevated RSNA, the renal vasoconstrictor response was significantly exaggerated by NO synthesis inhibition, whereas the decrements in water and electrolyte excretion were unchanged.

Group 3. In the animals that received Captopril prior to L-NAME during CO II, the MAP and HR values for CTL I and CO I were similar to those of Groups 1 and 2 (Table I). Due to the administration of Captopril, MAP decreased significantly during CTL II. The administration of L-NAME during CO II increased MAP to 185 ± 7 mm Hg, which allowed RPP to be properly maintained at CTL I levels (104 ± 6 mm Hg). With L-NAME, HR did not increase during CO II.

During CO I, RBF and GFR decreased due to the CO (Fig. 1 and 2). These changes were similar to those seen in Groups 1 and 2. During CTL II, after infusion of Captopril, renal hemodynamics returned to CTL I values, despite the fact that RPP was lower. During CO II, following administration of L-NAME, the de-

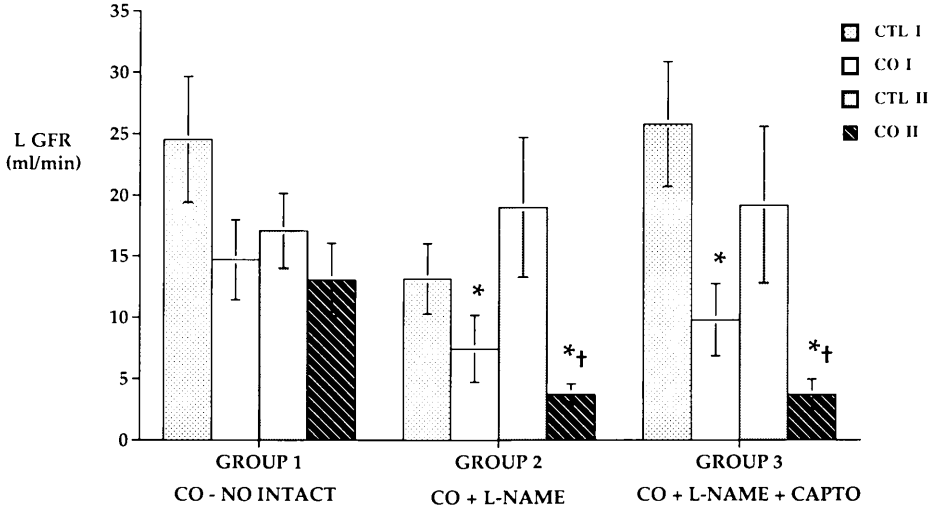

Figure 2. Comparison of changes in left glomerular filtration rate (L GFR) among Group 1 (n = 6), 2 (n = 5), 3 (n = 9). L-NAME was administered immediately preceding CO II in Group 2 and 3, and Captopril was administered to Group 3 only. CTL I and CTL II are the first and second control periods. CO I and CO II are the first and second periods of carotid occlusion. *$P < 0.05$ versus respective control period. †$P < 0.05$ for the percentage change CTL II − CO II versus CTL I − CO I.

Table II. Water and Electrolyte Excretion

		CTL I	CO I	CTL II	CO II
Group 1	UV (ml/min)	0.11 ± 0.02	0.06 ± 0.01[a]	0.13 ± 0.04	0.07 ± 0.03[a]
(CO-NO intact)	$U_{Na}V$ (μEq/min)	23.8 ± 7.0	13.6 ± 2.6	25.1 ± 7.5	15.0 ± 5.6
(n = 6)	U_KV (μEq/min)	9.2 ± 0.8	7.7 ± 1.7	11.6 ± 2.2	6.5 ± 1.8[a]
Group 2	UV (ml/min)	0.04 ± 0.01	0.02 ± 0.01[a]	0.05 ± 0.01	0.03 ± 0.01[a]
(CO + L-NAME	$U_{Na}V$ (μEq/min)	10.0 ± 3.6[b]	4.9 ± 2.2[a]	6.7 ± 1.5	2.6 ± 0.8[a]
(n = 5)	U_KV (μEq/min)	8.1 ± 1.4	4.8 ± 1.6*	12.7 ± 1.5	3.1 ± 1.0*
Group 3	UV (ml/min)	0.12 ± 0.3	0.03 ± 0.01[a]	0.14 ± 0.04	0.04 ± 0.01[a]
(CO + L-NAME + CAPTO)	$U_{Na}V$ (μEq/min)	24.8 ± 7.0	5.1 ± 1.0[a]	27.0 ± 8.1	3.8 ± 1.1[a]
(n = 9)	U_KV (μEq/min)	10.3 ± 1.8	2.5 ± 0.7[a]	12.6 ± 3.1	1.6 ± 0.4[a]

Note. Urine volume (UV), urinary sodium excretion ($U_{Na}V$), and urinary potassium excretion (U_KV) during all periods for Group 1, 2, and 3.
[a] $P < 0.05$ versus respective control.
[b] $P <$ versus group 1 during the same period.

crements in RBF and GFR were significantly greater than that seen during CO I. This response was no different from Group 2, suggesting that Ang II did not play a significant role in the exaggerated vasoconstriction during CO.

In these Captopril-treated animals, changes in water and electrolyte excretion were also similar to those seen in Groups 1 and 2 (Table II). The decrements in urine volume and sodium and potassium excretion during CO II were also not significantly different from those observed in CO I.

Group 4. The data from Group 2 animals demonstrated an exaggerated renal vasoconstrictor response with CO, as a consequence of L-NAME administration. Since NO, acting as a vasodilator, is one of several determinants of renal vascular tone, this exaggerated response with L-NAME could simply be due to a shift in baseline (i.e., the additive effect of starting at a lower RBF and GFR, plus the vasoconstriction due to CO). In an attempt to quantitate the baseline shift in renal hemodynamics with NO synthesis inhibition, an additional group of animals was studied (Group 4). After a control period, these animals received L-NAME without CO, while RPP was maintained constant.

In this group, baseline values were similar to Groups 1–3 (Table III). With L-NAME administration, MAP rose by 21 ± 3 mm Hg ($P < 0.05$), RPP was maintained constant at 114 ± 6 mm Hg, and HR fell from 117 ± 13 bpm to 68 ± 6 bpm. L-NAME caused RBF to decrease by approximately 35% (Table III) ($P < 0.05$), whereas GFR was unchanged. In these animals with RPP held constant, L-NAME administration did not significantly alter urine flow rate or electrolyte excretion.

Discussion

The purpose of this study was to determine the influence of NO on renal function during elevated SNA. Occlusion of the carotid arteries was utilized because it allowed SNA to be elevated acutely, in a reversible and reproducible manner. Although RSNA was not measured directly, the facts that MAP and HR increased, and that RBF and GFR decreased during CO, provide indirect confirmation that this baroreflex effectively increased peripheral and RSNA. Furthermore, it has been shown by others that CO increases directly measured RSNA by 165 ± 11% (22).

Controlling RPP was an important manipulation in these experiments. Both of the maneuvers applied, occlusion of the carotid arteries and the systemic administration of L-NAME, result in an increase in MAP. This change in RPP, if allowed to occur, would clearly influence renal hemodynamics, as well as sodium excretion. During both CO and the administration of L-NAME, the use of the Blalock clamp was effective in maintaining RPP constant, thus eliminating a potentially confounding variable.

With RPP held constant, CO caused RBF and GFR to decrease by 46% and 43%, respectively. When CO was applied after the administration of the NO synthesis inhibitor L-NAME, RBF and GFR decreased by significantly greater margins, 82% and 80%, respectively. The exaggerated renal vasoconstriction with L-NAME during CO II was clearly not a time-dependent change, since untreated animals had identical responses between the first and second CO. Since RPP was maintained constant, changes in RBF were inversely proportional to changes in renal vascular resistance. These results demonstrate that in normal animals, NO synthesized within the renal vasculature is important in attenuating the renal vasoconstriction in response to increased RSNA; in the absence of NO, the response to increased RSNA is significantly exaggerated. Evidence suggests that activation of the sympathetic nervous system may increase the production of NO (15). The observed changes in RBF and GFR may be due to an elevated production of NO in response to increased RSNA.

In contrast to the hemodynamic results, the water and electrolyte excretory responses did not change af-

Table III. Systemic and Renal Parameters for Group 4 Animals

	Control	L-NAME
MAP (mm Hg)	115 ± 6	132 ± 9[a]
RPP (mm Hg)	113 ± 6	114 ± 6
HR (bpm)	117 ± 13	68 ± 6[a]
L RBF (ml/min)	63 ± 12	41 ± 11[a]
L GFR (ml/min)	14 ± 2	13 ± 3
UV (ml/min)	0.09 ± 0.02	0.09 ± 0.02
$U_{Na}V$ (μEq/min)	31.6 ± 8.0	28.7 ± 7.5
U_KV (μEq/min)	7.9 ± 0.9	7.7 ± 1.2

Note. Mean arterial pressure (MAP), renal perfusion pressure (RPP), heart rate (HR), left renal blood flow (L RBF), left glomerular filtration rate (L GFR), urine volume (UV), urinary sodium excretion ($U_{Na}V$), and urinary potassium excretion (U_KV) for six animals trested with L-NAME in the absence of carotid occlusion.
[a] $P < 0.05$ versus control.

ter L-NAME administration in Group 2 animals. This was surprising considering others have presented evidence indicating that NO has a natriuretic effect (2, 7), and the fact that GFR or the filtered sodium load was less during CO II in L-NAME–treated animals. Filtration fraction, however, between CO I and CO II for Group 2 animals was not significantly different (data not shown).

Numerous studies have demonstrated that NO synthesis affects renal hemodynamics (3–6) and tubular electrolyte transport (2, 5, 7) in the basal state. Typical decreases in RBF with NO blockade in normal healthy animals are 15%–40% (3, 10); the decreases in GFR may or may not be significant (1, 3, 5, 6). The exaggerated decrements in RBF and GFR, seen during CO II in Group 2, could have been due to lower starting values in RBF and GFR due to a "baseline shift" in these parameters after NO synthesis inhibition. The experimental protocol for the Group 2 animals did not include a collection period measuring the response to L-NAME alone before the second CO. This extra period was not included because it was determined that the extra time required compromised the reliability seen between the first and second occlusion periods. The possibility of a baseline shift being responsible for the exaggerated renal vasoconstriction was evaluated by studying the Group 4 animals who received L-NAME without CO.

In Group 4, L-NAME caused RBF to decrease by 35% ($P < 0.05$) and GFR by 8% ($P < 0.05$). An important question is whether these declines or baseline shifts were of sufficient magnitude to account for the exaggerated decreases in RBF and GFR observed during CO II in Group 2. Figure 3 shows the value for RBF and GFR for Group 2 during a control period, with CO alone (NO intact), and with CO plus L-NAME. The value for CO-NO INTACT was derived by subtracting the decrement due to CO (Group 2) from the CONTROL values. The last column represents a calculated value to consider the effects of L-NAME alone. This value was derived by subtracting the percentage decrement in RBF and GFR due to L-NAME administration in Group 4 (35% and 8%), from the values for RBF and GFR shown as CO-NO INTACT.

As can be seen in Figure 3, for both RBF and GFR the values calculated were greater, being approximately double the values actually measured during CO plus L-NAME. Statistical analysis of these calculated values was not possible, but these differences indicate that a baseline shift due to L-NAME administration cannot fully account for the exaggerated decreases in RBF and GFR observed with CO while NO synthesis was blocked; these responses are not simply an additive effect of these two conditions. This is most obvi-

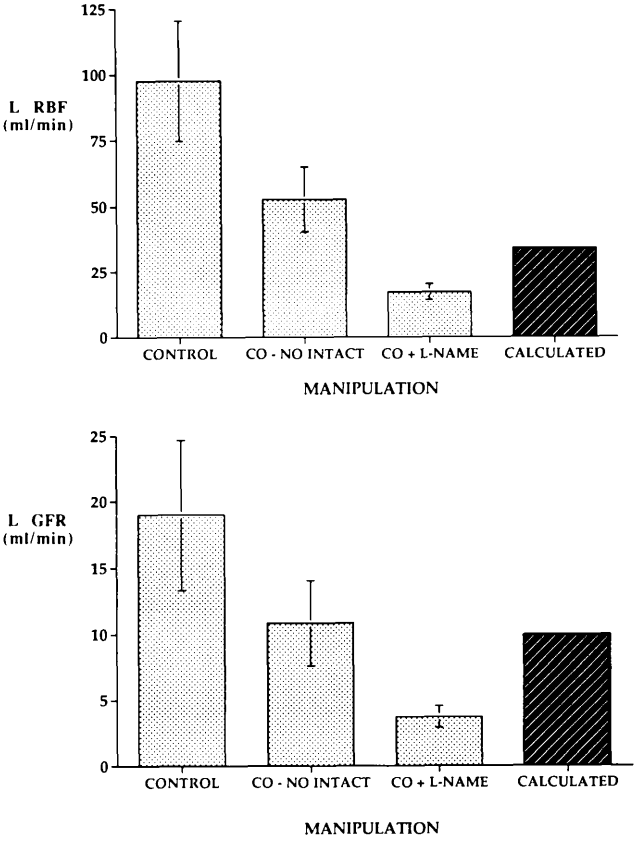

Figure 3. Comparison of L RBF and L GFR values for control, CO alone, CO in combination with L-NAME, and a calculated value representing the change due to CO plus a baseline shift induced by L-NAME. All values from Group 2. CONTROL, data from CTL II, representing no intervention; CO-NO INTACT, values due to CO with the NO system intact (this was derived by subtracting the decrement due to CO from the control values); CO + L-NAME, data from the CO II period, representing animals during CO after NO synthesis blockade; CALCULATED, values representing the additive effect of L-NAME administration and CO, derived by subtracting the percentage decrements due to L-NAME administration in Group 4 from the CO-NO intact values.

ous for GFR since, as we observed and what has been reported by others (1, 3, 6), L-NAME alone did not significantly lower GFR.

Therefore, we conclude that under conditions of elevated peripheral and RSNA, NO plays a significantly greater role in controlling renal hemodynamics than under basal conditions. This is supported by studies by Granger, who found that NO modulated the renal vasoconstrictor effects of norepinephrine (23).

There are at least two mechanisms that could explain why or how L-NAME exaggerated the renal vasoconstrictor response to CO. First, there are reports that increased RSNA may increase renal NO synthesis or release (15). Since NO is a vasodilator, augmented NO synthesis along with increased RSNA would serve to limit the adrenergic vasoconstriction. When NO synthesis was inhibited by L-NAME, the constriction was much greater because the dilator responsible for counterbalancing it was no longer present. An alternate explanation is that the increase in RSNA with CO may have been augmented by L-NAME, since there are data suggesting that systemic administration of L-NAME may increase sympathetic outflow (24, 25). The circulating L-NAME may cross the blood-brain barrier and directly stimulate the central nervous system to increase sympathetic nerve activity (24). This possibility should be evaluated by directly measuring renal nerve activity during CO with and without L-NAME.

Occlusion of the carotid arteries is known to increase the release of renin (17, 18), which subsequently elevates levels of Ang II. Increased Ang II could contribute to the decreases in RBF and GFR seen during CO. There are also studies which show that NO attenuates the constrictive responses of Ang II *in vitro* (19). Thus, the exaggerated vasoconstriction obtained in Group 2 during CO II could involve an interaction of NO with Ang II. We tested this possibility by administering Captopril to Group 3 animals. The data clearly show that the renal hemodynamic and excretory responses to CO with L-NAME were totally unaltered by the administration of Captopril, suggesting that the response observed does not appear to involve Ang II. These data are consistent with the results obtained by Baylis *et al.* (26) who found that the renal constrictor effects of NO synthesis inhibition in conscious rats did not involve Ang II.

There are numerous physiological and pathophysiological states which are associated with increased peripheral and RSNA. These include hypertension (11), congestive heart failure (12), cirrhosis (13), and intense exercise (14). The difficulty in extrapolating these results to define the role of NO as a determinant of renal function in some of these states is that many other complexities and confounding variables may be present. For example, it has been suggested that hypertensive subjects may be deficient in terms of NO synthesis (27, 28). In studies conducted with chronically hypertensive animals, there was an attenuation in the endothelial dependent dilation response to acetylcholine (which induces NO production in endothelial cells) (29). In the condition of heart failure and cirrhosis, there are other chronic endocrine changes, such as markedly elevated renin-angiotensin II or circulating catecholamines: compounds which may influence the response to NO synthesis inhibition. Also, in the disease states very little is known about NO production or release, or the vascular responsiveness to NO. The results from this study may be more applicable to conditions in normal healthy subjects where there are acute changes in SNA that alter renal function. Examples would include postural reflexes and acute exercise.

In summary, the results from this investigation indicate that NO synthesized within the renal vasculature is important in attenuating the renal vasoconstriction in response to increased RSNA. This response does not appear to involve Ang II.

Supported by funds from the New Jersey State Agricultural Experiment Station.

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