Spinal Cord Infarcts During Long-term Inhibition of Nitric Oxide Synthase in Rats

S. Blot, DVM; J.-F. Arnal, MD; Y. Xu, MD; F. Gray, MD; J.-B. Michel, MD, PhD

Background and Purpose Chronic hypertension is a major predisposing factor for stroke in humans. It has recently been shown that long-term inhibition of nitric oxide synthase activity causes a gradual time-dependent increase in arterial blood pressure in rats. We used this new animal model of chronic hypertension to study the occurrence and spatial features of infarcts in the central nervous system.

Methods Rats were treated with a nitric oxide synthase inhibitor, N^0^-nitro-L-arginine methyl ester, dissolved in the drinking water at 50 mg/kg per day for 11 weeks. The brains and spinal cords of hypertensive rats with and without motion disturbances were processed for standard microscopic examination.

Results Seventy-nine percent of the hypertensive rats showed motion dysfunctions, especially front leg paralysis, and/or died suddenly when their systolic blood pressure reached approximately 215 mm Hg after approximately 7 weeks of treatment. All of the hypertensive rats with stroke had spinal cord infarcts (90% at the cervical or cervicothoracic level) either alone or combined with brain lesions (30%). These structural alterations ranged from focal areas of pale, spongy tissue to large necrotic sites with vascular alterations, including thickened or fibrinoid degenerated vessel wall, macrophage invasion, and reactive astrocytes.

Conclusions Infarcts occurred in the central nervous system with a high incidence in the spinal cord of hypertensive rats in which nitric oxide synthase was chronically blocked. This location of the hypertensive neuropathologic sequelae contrasts with the model of stroke-prone spontaneously hypertensive rats. The results suggest that nitric oxide is a key factor in spinal cord arteriolar vasomotion and structure in rats.

Key Words • hypertension • nitric oxide • spinal cord • rats

See Editorial Comment, page 1673

recently suggested that neuronal NO takes part in the regulation of vasomotion in the nervous system.12,16-20

The role of hypertension and arterial vasomotion in the pathophysiology of stroke is of considerable importance because hypertension is a frequent disease in humans and a major predisposing factor for cerebrovascular accident. However, until hypertensive strains of rats that frequently suffered cerebrovascular accident became available, studies were limited by the lack of appropriate models. In stroke-prone spontaneously hypertensive rats (SHRSP),21 80% of the male rats more than 100 days old suffer from neurological accidents due to cerebral lesions. Fewer than 10% of these rats have spinal cord lesions.22 In contrast, other experimental models of spontaneous or provoked hypertension do not usually develop stroke.

Moncada et al14,23 used arginine derivatives (N^0^-monomethyl L-arginine [L-NMMA] and N^0^-nitro-L-arginine methyl ester [L-NAME]) to block NO synthase. The endothelial and the neuronal NO synthases appear to be similarly sensitive to these arginine analogues, which are competitive inhibitors of NO synthase.24,25 We have used this sensitivity to develop a new model of hypertension, in which rats are chronically treated with L-NAME. The NO synthase can be dose-dependently blocked, as assessed by the decrease in aortic wall cGMP.26 Acute infusion of L-NAME produces only subtle cerebrovascular pathological changes consistent with focal brain ischemia.8 However, the neurological consequences associated with hypertension due to long-term inhibition of NO synthase activity in rats have not yet
been reported. In the present study male Wistar rats were given L-NAME orally for 11 weeks. This long-term treatment induced a time-dependent increase in blood pressure. Two thirds of the rats showed neurological abnormalities, mainly monoplegia, due to spinal cord infarctions.

Materials and Methods

Experimental Design

Young male Wistar rats (Iffa Credo, Lyon, France) with an initial body weight of 120 to 130 g underwent a control observation period (1 week) before they were divided into two groups and placed on special drinking solutions for 11 weeks. Rats in the control group (n=5) were given regular tap water; rats in the L-NAME group (n=24) were given L-NAME at 50 mg/100 mL of drinking water (50 mg/kg per day). In preliminary experiments we verified that 50 mg/100 mL of drinking water corresponded to a gavage dose of 25 mg twice a day in terms of decrease in vascular wall cGMP and increase in blood pressure. Moreover, the administration of L-NAME in drinking water gave a more stable elevation of blood pressure than gavages.

Systolic blood pressure was measured every 2 weeks by the tail-cuff method (W+W electronic recorder model 8005, Aplelab), and body weight was recorded at the same time. The procedure used in the care and euthanasia of the rats was in accordance with the European Community Standards on the care and use of laboratory animals (Ministere de l'Agriculture, France; authorization No. 00577, April 30, 1989).

Morphological Examination

Each rat was evaluated for stroke every week. Rats developing neurological signs were anesthetized with ether 1 to 6 days after the onset of the signs. A thoracotomy was performed, and the left ventricle and aortic trunk were cannulated. The vascular system was flushed with 250 to 300 mL of washout with 0.1 mol/L heparinized phosphate-buffered saline at a pressure of 180 cm H2O via the perfusion cannula. This was immediately followed by perfusion fixation with 250 to 300 mL of 4% formaldehyde in 0.1 mol/L phosphate buffer, pH 7, at a pressure of 180 cm H2O.

The brain was sectioned coronally into three 4-mm-thick slices in the cerebellum, occipital, and frontal areas. The cerebral, thoracic, and lumbar spinal cords were entirely cut into 4-mm-thick slices. Then the slices were dehydrated in graded ethanols and xylene, embedded in paraffin, sectioned at 10 µm, and stained with hematoxylin-eosin or processed for macrophage and smooth muscle cell immunohistochemistry. Macrophages were identified with the ED, monoclonal antibody (a generous gift from Dr Dijkstra, Free University of Amsterdam, the Netherlands);27 smooth muscle cells were stained with a specific anti-α-actin antibody (a generous gift from Dr Gabbiani, Geneva, Switzerland).28 Antibodies were visualized by the phosphatase–alkaline–antiphasphatase alkaline method.29

All rats from the L-NAME group (which had not developed locomotion disturbances or sudden death) that survived to the end of the 11 weeks and those from the control group were examined as described above.

Statistical Analysis

Data are expressed as mean±SEM. Blood pressures and weight were compared by factorial two-way ANOVA for repeated measures. Survival distribution was estimated by the Kaplan-Meier method.30

Results

Clinical Evolution

NO synthase was chronically blocked with oral L-NAME (50 mg/kg per day). This dose was chosen on the basis of previous studies.26 The treatment resulted in a significant, persistent, time-dependent (F=167, P<.0001) increase (F=111, P<.0001) in blood pressure (Fig 1), which reached a maximum at approximately 7 weeks, at which time it was 150% of the pressure in the controls (Table 1).

Between 41 days (when systolic blood pressure of hypertensive rats was maximal) and 76 days of treatment (the end of the study), 15 L-NAME rats showed locomotion disturbances and 5 of them died spontaneously. 4 L-NAME rats died suddenly with no obvious locomotion disturbances (rats with motion disturbances or with sudden death totaled 79%), and 5 L-NAME rats suffered no motion disturbances except weight loss at the end of the 11 weeks. The mean 50% survival rate without clinical neurological signs was 60 days (Fig 2). All the locomotion disturbances were motor abnormalities: tetraparesis or general weakness, monoplegia, and paralysis of either both front legs or both rear legs. Monoplegia occurred mostly in a front leg (Table 2).

![Figure 1](image1.png)

**Figure 1.** Line graph shows systolic blood pressure during treatment with N\(^\text{\textendash}\)nitro-L-arginine methyl ester (L-NAME). The symbol ▲ indicates control normotensive Wistar rats; L-NAME-treated rats. Values are mean±SEM.

![Figure 2](image2.png)

**Figure 2.** Line graph shows survival distribution as a function of time without clinical neurological signs in rats treated with N\(^\text{\textendash}\)nitro-L-arginine methyl ester (Kaplan-Meier method). Control rats suffered no clinical neurological events, and none died (not shown).
Rats with monoparesis or monoplegia could not withdraw the leg when a painful stimulus was applied. Seizure, hemiparesis, or hemiparesis was never noted.

The 9 L-NAME rats that suddenly died, ie, 5 rats a few days after they showed motion disturbances and 4 without any apparent motor disturbances, were not histologically studied. Because the time of death could not be precisely recorded, we thought that spinal cord postmortem alterations would confuse interpretation of histological alterations due to long-term NO synthase blockade. Normotensive rats (n=5) suffered no motion dysfunctions, and none died suddenly throughout the entire study.

**Pathology**

The brains and spinal cords of L-NAME rats and of normotensive controls were examined. The spinal cords of all symptomatic rats (n=10) showed structural alterations of the vascular and/or nerve tissue, most of which were in the cervical area (Table 3).

The pathological foci in the spinal cord were egg-shaped and concentrated in the dorsal or laterodorsal columns (see Fig 4). Morphological changes were never seen in the ventromedial columns. The pathological foci in the gray matter were in the ventral or dorsal horns, either unilaterally or bilaterally. White matter and gray matter were sometimes found together at the same focus but were also involved in multiple separate foci. Spinal alterations occurred equally in the gray and white matter.

Structural alterations ranged from sites of pale, spongy white or gray matter with macrophage invasion and hypertrophied astrocytes to large necroses with vascular alterations and fibrin deposits (Fig 3). Immunohistochemistry showed that the area of infarction was surrounded by a ring of macrophages (ED positive cells; Fig 4c). In some regions the area of sponginess of the neural tissue was even larger, resulting in a more confluent loss of neural tissue and the formation of cystic, sparsely trabeculated cavities (Fig 3b). Most of the neurons in the spongy parenchyma had well-preserved nuclei surrounded by a thin rim of cytoplasm with an ill-defined outline, suggesting lysis or vacuolization of the peripheral cytoplasm (Fig 4a and 4b). The spinal cord contained occasional round neurons in the immediate vicinity of spongy or necrotic regions, with eccentric nuclei and no Nissl bodies in the central part of the cell but persistent Nissl bodies at the periphery (Fig 4a, thin arrow), characteristic of central chromatolysis. The pale, spongy appearance of the nerve tissue indicated edema.

Blood vessels in the vicinity of spongy parenchyma or within regions with severe necrosis had lost smooth muscle cells (Fig 5). The smooth muscle cells in the arterial and arteriolar walls of control normotensive rats were stained with α-actin antibody, whereas there was

**Table 3. Pathological Features of Surviving L-NAME Rats**

<table>
<thead>
<tr>
<th>Rat</th>
<th>Clinical Signs</th>
<th>Time*</th>
<th>Cortex</th>
<th>Basal Nuclei</th>
<th>Cerebellum</th>
<th>Brain Stem</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LFL paralysis</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>FD/AT</td>
<td>0</td>
<td>I/FD/WM/GM</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>2</td>
<td>Weakness</td>
<td>6</td>
<td>0</td>
<td>H/I</td>
<td>0</td>
<td>0</td>
<td>I/FD/WM</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>3</td>
<td>FL paralysis</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/AT</td>
<td>I/FD/AT/WGM</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>4</td>
<td>Tetraparesis</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/FD/WM</td>
<td>0</td>
<td>NE</td>
</tr>
<tr>
<td>5</td>
<td>RL paralysis</td>
<td>1</td>
<td>H</td>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/H/WGM</td>
<td>I/WGM</td>
</tr>
<tr>
<td>6</td>
<td>FL paralysis</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/H/AT/FD/WGM</td>
<td>I/FD/GM</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>FL paralysis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/H/WGM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>RFL paralysis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/WM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>LFL paralysis</td>
<td>4</td>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/H/GM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>LFL paralysis</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/WM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>No sign</td>
<td>...</td>
<td>FD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>I/GM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>No sign</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>H/WM</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>No sign</td>
<td>...</td>
<td>H/I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>No sign</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>No sign</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

L-NAME indicates Nω-nitro-L-arginine methyl ester; LFL, left front leg; FL, front legs; RL, rear legs; RFL, right front leg; H, hemorrhage; I, infarct; FD, fibrinoid degeneration; AT, arterial thrombosis; WM, white matter; GM, gray matter; WGM, white and gray matter; NE, not examined.

*Time between clinical signs and perfusion, in days.
Photomicrographs (low magnification). Hematoxylin-eosin staining of 10-μm paraffin-embedded transverse sections of rat spinal cords showing the range of structural alterations seen after long-term inhibition of nitric oxide synthase: pale vacuolated spongy areas in the white matter (a); cystic, sparsely trabeculated cavity in the gray matter (b); multiple foci of necrotic sites with fibrinoid degeneration of penetrating arterioles and fibrin deposits, with all foci surrounded by reactive cells (macrophages, astrocytes) (c); and control (d) (original magnification ×2.5).

Discussion

Rats given the NO synthase inhibitor L-NAME developed a time-dependent increase in blood pressure. Nineteen of the 24 male rats (79%) developed paresis or paralysis or died suddenly by the end of the 11-week experiment. Light microscopic examination of the central nerve tissue showed that motion dysfunctions were due to spinal cord infarctions. To our knowledge, this is the first report of such neurological events after long-term treatment of rats with L-NAME at 50 mg/kg body.
wt. Previous studies using this model of chronic hypertension (5 mg/kg for 2 months, 60 mg/kg for 6 weeks, and 40 and 70 mg/kg for 7 weeks) did not report these neurological events. The length of time of the treatment appeared to be the critical factor.

The frequency of stroke is close to that reported in SHRSP. However, the clinical presentation and the location of the infarcts were strikingly different. Hemiparalysis never occurred in L-NAME rats, and monoparalysis of a front leg was the main feature. The distribution of the spinal lesions also correlated with the neurological signs, as seen with the high frequency of front leg paralysis and the high frequency of cervical spinal lesions (90%). In contrast, cerebral or medullary stroke has never been reported in non-SHRSP and in other models of secondary hypertension, such as deoxycorticosterone acetate–salt or renovascular hypertensive rats.

The main structural changes encountered were irregular pale staining, sponginess, or edema of the neural parenchyma, which expanded and progressed to cystic cavities, and necrotic foci with invasion by polymorphonuclear cells, macrophages, and reactive astrocytes. These lesions are typical of pale infarcts. Swollen capillaries and petechial diapedetic hemorrhages indicated recent hemorrhagic infarcts. Nonhemorrhagic and hemorrhagic infarcts, together with fibrinoid necrosis of the arteriolar wall, with vessels occluded by fibrin thrombi are neuropathologic sequelae that have been described in both chronic human hypertension and in the genetic
model of SHRSP.23 The fibrinoid degeneration of arterioles, which were sometimes occluded, was frequently observed in the close vicinity of edematous parenchyma or within necrotic sites in the spinal cord or brain tissue of L-NAME rats. This is a morphological hallmark associated with severe chronic hypertension.34–37

The majority of the neurons within the central zone of the lesions were not condensed but were vacuolated or had lysed peripheral cytoplasm (Fig 4). Fairly well-preserved neuronal perikarya were present next to the walls of necrotic cysts, in agreement with the description of Fredriksson et al25 of the gray matter lesions in the SHRSP model. Thus, the pathogenetic processes may be similar, with edema-induced necrosis rather than primary ischemic necrosis.

Most of the structural alterations were old neuropathologic sites, as revealed by the presence of macrophages. Because the rats were killed at least 1 day after symptoms had occurred, these lesions could explain the motion disturbances. The L-NAME rats that died spontaneously were not autopsied, and therefore the cause of death cannot be clearly identified. Most SHRS8 die of cerebral stroke, with cerebellar herniation interfering with central autonomic regulation.22

Despite the histological similarities of the lesions, most of the infarcts were in the spinal cord in L-NAME rats, in contrast to the cerebral location of the lesions in the genetic model of SHRSP and in human hypertension. Indeed, the incidence of spinal lesions is less than 10% in human hypertension34 and in the genetic model of SHRSP,22 whereas that of cerebral lesions is 100%. Moreover, spinal cord infarcts are always combined with cerebral lesions. The incidence of spinal cord infarcts in L-NAME rats was 100% (with 90% of them in the cervical area), whereas brain lesions only occurred in 30% of cases. In addition, cerebral lesions were always combined with spinal lesions in L-NAME rats.

More than 20 years ago, Steiner et al38 found that the ratio of cGMP to cyclic AMP (a more uniformly distributed intracellular messenger) was higher in the spinal cord and in the cerebellum than in other parts of the mouse nervous system. More recently, neuronal NO synthase has been shown to be constitutively present in the central nervous system, with high levels in the cerebellum, the olfactory bulb, and the spinal cord in rats.9,12,13 Although NO mediates the effects of glutamate in elevating cGMP in the cerebellum,39 the distribution of NO synthase in brain does not resemble that of guanylate cyclase,14,15 suggesting that NO has multiple functions in the brain. In particular, several authors have recently suggested that NO might participate in the regulation of cerebral blood flow6,9,12,17,20 directly or indirectly by the release of calcitonin gene-related peptide.40

In the spinal cord of rats, Wu and Li41 recently indicated that long-term inhibition of NO synthase can be protective of spinal root avulsion. In their study nitroarginine was injected daily at a dose of 50 mg/kg per day IP in adult Sprague-Dawley rats that underwent cervical ventral spinal root avulsion. At the end of the study (3 or 6 weeks), the authors showed that nitroarginine significantly reduced the death of motoneurons due to spinal root avulsion, and therefore long-term inhibition of NO synthase might have potential therapeutic action in this neuronal injury. This differs from our results. However, this striking difference may be due to the different targets involved in the two studies. In the study of Wu and Li, nitroarginine was chronically used to block NO synthase induction (inducible NO synthase) in response to mechanical injury of the spinal root. In our present study the arteriolar wall was the spontaneous target of long-term NO synthase blockade during an experimental design of longer duration. Nevertheless, Wu and Li did not report vascular lesions in the spinal cord in their model of long-term nitroarginine administration (3 to 6 weeks).

In addition to being the NO synthase substrate, it should be remembered that arginine participates in other metabolic functions, including α-ketoglutarate metabolism and polyamine synthesis. Inhibition of NO synthase from arginine may therefore have unsuspected effects through these other mechanisms.40 Also, in relation to possible non–NO-related nitroarginine effects, L-NAME has been demonstrated to act in vitro as a muscarinic antagonist.42 However, deesterification of L-NAME to nitroarginine occurs very rapidly in vivo, at the first liver passage, and nitroarginine did not display this muscarinic antagonist effect. Moreover, in our experiment with chronic oral L-NAME intoxication, acute hemodynamic responses (cardiac frequency and blood pressure) to intravenous injection of acetylcholine were not blocked (data not shown).

Both the endothelium and neurons in the central nervous system can generate NO from L-arginine. NO can act as a paracrine agent and can diffuse up to 100 μm from its site of release.43,44 It can stimulate the soluble guanylate cyclase of the vascular smooth muscle cell and lead to cGMP generation and subsequent relaxation. Several anatomic and physiological observations indicate that neuron-derived NO helps to regulate vasomotion. First, neuronal NO synthase is present in the perifascicular thalamic nucleus, a region of the brain that increases cerebral blood flow when activated by microstimulation.14 NO synthase immunoreactivity also occurs in nerve fibers in the outer, adventitial layers of cerebral blood vessels, being concentrated in large cerebral arteries9,45 and in the distal branch.45–46 The source of these NO synthase-containing fibers appears to be the sphenopalatine ganglion.45 In the spinal cord, the fibers of the intermediolateral system have a special relation with the vasculature, suggesting that NO may help to couple neural activity with regional blood flow in the spinal cord.12 Second, functional studies showing that NO synthase inhibitors produce cerebroarterial vasoconstriction in vitro15 and decrease cerebral blood flow in vivo47–49 provide evidence that the nitroergic vasodilator nerve is involved in the control of cerebrovascular tone in vivo.10 NO generated in response to the activation of receptors for the excitatory amino acid N-methyl-D-aspartate in vivo is neurally derived and not due to a direct vascular effect. NO might mediate increases in local blood flow during increases in neuronal activity, in response to excitatory amino acids.17

Thus, endothelial and neuronal NO synthases may act in concert to influence vascular smooth muscle in the nervous system.6,20,50,51

Rats treated chronically with L-NAME provide a novel model of hypertension in which endothelial NO synthase can be dramatically blocked, as assessed by the 10-fold decrease in aortic cGMP.26 As the endothelial
and the neuronal NO synthases appear to be similarly sensitive to this arginine antagonist, they are probably both inhibited in the model.25 The arterial lesions predominating in the spinal cord strongly suggest that NO is important in the vasomotion, structure, and permeability of these arteries. NO is a potent vasodilator of arterial rings and of arteries in vivo.2,22 The chronic increase in blood pressure, and consequently in wall tension, is well known to determine medial smooth muscle hypertrophy. NO can also directly influence the arterial structure because it inhibits the proliferation of vascular smooth muscle cells in tissue culture.53 In L-NAME rats, both direct and pressure-dependent mechanisms probably contribute to the arteriolar thickening and fibrinoid necrosis leading to infarction. This event might also be favored by the removal of the anti-platelet-aggregation effect of NO.3,4,5,24

Finally, hypertension and NO synthase blockade could be dissociated during chronic intoxication with L-NAME. L-NAME rats develop cerebrovascular lesions that are histologically similar but located differently than those seen in other models of hypertension, such as SHRSP. Therefore, both hypertension and NO synthase blockade are probably associated in the production of neurological lesions in the spinal cord of L-NAME rats.

Acknowledgments

We thank Liliane Louedec and Georges Salmon for animal care, Philippe Bozin for the photomicrographs, Annie Depar-"ude, Dr Patrick Dreyfus for constant encouragement, and Dr Elaine Parrish for help with English.

References


---

**Editorial Comment**

Nitric oxide (NO), the gaseous free radical biological messenger molecule, is an important regulator of vascular smooth muscle responsiveness. Long-term inhibition of NO synthase activity causes a gradual time-dependent increase in arterial blood pressure in rats. In the accompanying article, Blot and colleagues use this as an animal model of chronic hypertension. They show that when treated with the NO synthase inhibitor N°-nitro-l-arginine methyl ester for 11 weeks, rats develop profound hypertension and neurological sequelae. After 7 weeks of treatment, 79% of the rats showed neurological abnormalities and/or died suddenly. All the hypertensive rats with neurological abnormalities had spinal cord infarcts either alone or in combination with brain lesions. This markedly contrasts with the model of stroke-prone spontaneously hypertensive rats, and these data suggest that NO is a key factor in spinal cord hemodynamics.

In view of the postulated role of NO in a variety of pathological states, this is a potentially important study that should prompt investigators to proceed with caution in designing or implementing therapeutic trials with NO synthase inhibitors. Inhibition of the endothelial enzyme is probably the main culprit in the neurological sequelae observed in the accompanying study. This further illustrates the need for selective inhibitors of the various isoforms of NO synthase. The development of selective NO synthase inhibitors will hopefully allow the treatment of disorders due to derangement in the formation of NO without the accompanying sequelae.

Ted M. Dawson, MD, PhD, Guest Editor
Department of Neurology and Neuroscience
The Johns Hopkins University School of Medicine
Baltimore, Md

---

**Reference**

S Blot, J F Arnal, Y Xu, F Gray and J B Michel

Stroke. 1994;25:1666-1673
doi: 10.1161/01.STR.25.8.1666
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/8/1666

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/