Chronic Blockade of NO Synthase Activity Induces a Proinflammatory Phenotype in the Arterial Wall
Prevention by Angiotensin II Antagonism

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Abstract—Chronic blockade of NO production induces hypertension and early occlusive and fibrotic end-stage organ damage owing to vascular lesions in the brain, kidney, and heart. In this study, we evaluated the inflammatory phenotypic changes induced in the arterial wall by chronic N^G-nitro-L-arginine methyl ester (L-NAME) administration and the effect of an angiotensin II receptor (AT_1) antagonist, irbesartan, on these changes. For this purpose, 2 groups of rats received L-NAME in the drinking water (50 mg · kg⁻¹ · d⁻¹) for 2 months. One group received no other treatment and the other was treated with irbesartan (10 mg · kg⁻¹ · d⁻¹). A third group (controls) received neither L-NAME nor irbesartan. After 8 weeks, plasma, aortas, and left ventricles were sampled from all 3 groups. Expression of inducible NO synthase (iNOS) was evaluated at both the mRNA (quantitative reverse transcription–polymerase chain reaction) and the protein (Western blot and immunohistochemistry) level in the aorta. Expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) was evaluated by reverse transcription–polymerase chain reaction, Western immunoblotting, and immunohistochemistry; inflammatory cell infiltration by immunohistochemistry; and fibrosis by Sirius red staining. Chronic L-NAME administration induced the expression of iNOS in the aorta, which was localized in smooth muscle cells as shown by immunohistochemistry and NADPH diaphorase activity. ICAM-1 and VCAM-1 expression was also increased in aortas of L-NAME–treated rats. These phenotypic changes of the vascular wall were associated with inflammatory cell infiltration and fibrosis in the heart. All of these pathological phenomena were prevented by the angiotensin II antagonist irbesartan. The proinflammatory phenotypic changes of the vascular wall induced by blockade of NOS activity could be involved in the interaction between endothelial dysfunction and the development of arteriosclerosis. (Arterioscler Thromb Vasc Biol. 1998;18:1408-1416.)

Key Words: inducible NO synthase ■ cell adhesion molecules ■ macrophages ■ L-NAME hypertension ■ AT_1 receptor

Chronic administration of N^G-nitro-L-arginine methyl ester (L-NAME) into rats induces a dose-dependent increase in blood pressure (BP) associated with a decrease in the cGMP content of the arterial wall.¹,² This model is characterized by evolutive vascular lesions in the kidney,³,⁴ and central nervous system.⁵ The L-NAME model evolves in 2 stages: an early compensated stage characterized by high BP and a later accelerated stage associated with the development of end-organ damage.⁶ Despite the absence of any increase in renin during the early stage and the absence of any influence of blockade of the renin-angiotensin system (RAS) on the vascular wall cGMP content,⁷ L-NAME–induced hypertension is sensitive to blockade of the RAS.⁸⁻¹¹ Probably the main function of NO-induced G-kinase activation is to inhibit the coupling between the heptahelical transmembrane receptors, such as the angiotensin type 1 (AT_1) receptors, and phospholipase activities in smooth muscle cells.¹²,¹³ Conversely, Hou and coworkers¹⁴ have reported an increased sensitivity of heart and coronary artery remodeling to angiotensin II (Ang II) after NO blockade. Beyond this functional regulation, chronic blockade of NO synthase (NOS) can activate the expression of different genes in the arterial wall, such as inducible (i) isoform type II cyclooxygenase,¹⁵ and is associated with the accumulation of endothelial and subendothelial macrophages.¹⁶ Conversely, it has recently been shown that NO regulates vascular cell adhesion molecule (VCAM) expression and modulates redox-sensitive transcriptional events in endothelial cells.¹⁷

In the current study, we evaluated whether chronic L-NAME administration associated with hypertension could modulate the expression of molecules involved in inflammatory processes in the vascular wall and perivascular fibrosis in...
the heart. We also evaluated the effect of an AT receptor antagonist, irbesartan, on L-NAME–induced phenotypic changes. Our results show that chronic L-NAME administration stimulated the expression of inflammatory iNOS in the aortic wall. This iNOS expression was localized in smooth muscle cells as shown by immunohistochemistry and NADPH diaphorase activity. Chronic L-NAME administration also increased endothelial expression of intercellular adhesion molecule (ICAM)-1 and VCAM-1 and the density of intracellular and perivascular inflammatory cells in the myocardium and arterial wall. Ang II antagonism prevented the development of this vascular inflammatory process.

Methods

Experimental Design
Male Wistar rats (IFFA CREDO, Lyon, France) with an initial body weight of 180 g were used for this study. Three groups of rats were subjected to the following experimental regimen for 8 weeks: (1) a control group, with regular tap water to drink (n=10) plus 1 mL water daily by gavage; (2) an L-NAME group (50 mg · kg⁻¹ · d⁻¹ in the drinking water; n=11; Sigma Chemical Co) plus 1 mL water daily by gavage; and (3) an L-NAME group (as above) plus irbesartan (10 mg/kg; n=14) given daily by gavage 1 week after L-NAME administration. The dosage of irbesartan corresponded to a maximal antihypertensive effect in renin-dependent hypertensive rat models. Irbesartan was a gift of Dr Nisato (Sanofi, Montpellier, France).

Systolic BP and heart rate were measured once a week by the tail-cuff method, and body weights were recorded. After 8 weeks of treatment, the rats were euthanized. Blood was sampled into heparinized tubes and plasma was removed by centrifugation. One of the groups was perfused with 10% buffered formalin and embedded in paraffin. Tissue sections were subjected to the following experimental regimen for 8 weeks: (1) a control group, with regular tap water to drink (n=10) plus 1 mL water daily by gavage; and (3) an L-NAME group (as above) plus irbesartan (10 mg/kg; n=14) given daily by gavage 1 week after L-NAME administration. The dosage of irbesartan corresponded to a maximal antihypertensive effect in renin-dependent hypertensive rat models. Irbesartan was a gift of Dr Nisato (Sanofi, Montpellier, France).

Quantitative Analysis of iNOS mRNA
Rat iNOS internal standard was produced by using rat iNOS–specific primers (sense, 5'-CCG TGG TCA GCC CTC AGA GTA CAA-3'; antisense, 5'-TCC GCT TCT TGA GCT GGA AGT-3') as previously described. Rat iNOS cDNA was amplified from rat heart RNA, subcloned, and sequenced. A polylinker fragment (47 bp) was inserted in a unique BsaI site between the same 2 primers used for the comparative analysis. After HindIII linearization, iNOS standard plasmid was purified and precipitated to serve as a template for in vitro transcription. The 2 primers surrounding the 47-bp-insertion site were designed to allow the distinct amplification of iNOS mRNA (227 bp) and of internal standard cRNA (274 bp). Quantification of the PCR products was performed by using radiolabeled primers and by counting the radioactivity of the amplified fragments. The quantitative assay was performed according to Gilliland and coworkers. For each sample, a defined quantity of total RNA was reverse-transcribed with 5 different concentrations of the reverse transcription and PCR amplification reagents for any competitive PCR. The PCR amplification was verified to be exponential. The comparative analysis. After HindIII linearization, iNOS standard plasmid was purified and precipitated to serve as a template for in vitro transcription. The 2 primers surrounding the 47-bp-insertion site were designed to allow the distinct amplification of iNOS mRNA (227 bp) and of internal standard cRNA (274 bp). Quantification of the PCR products was performed by using radiolabeled primers and by counting the radioactivity of the amplified fragments. The quantitative assay was performed according to Gilliland and coworkers. For each sample, a defined quantity of total RNA was reverse-transcribed with 5 different concentrations of the reverse transcription and PCR amplification reagents for any competitive PCR. The PCR amplification was verified to be exponential. The comparative analysis. After HindIII linearization, iNOS standard plasmid was purified and precipitated to serve as a template for in vitro transcription. The 2 primers surrounding the 47-bp-insertion site were designed to allow the distinct amplification of iNOS mRNA (227 bp) and of internal standard cRNA (274 bp). Quantification of the PCR products was performed by using radiolabeled primers and by counting the radioactivity of the amplified fragments. The quantitative assay was performed according to Gilliland and coworkers.

Western Blotting
The initial aortic homogenate was treated for protein extraction according to the Trizol reagent protocol (n=5 per group). After complete removal of RNA, proteins present in the phenol–ethanol supernatant were dialyzed against 0.1% SDS at 4°C. After centrifugation, the clear supernatant was used for the determination of protein concentration (Lowry method) and for Western blotting. Two hundred fifty micrograms of total solubilized proteins was electrophoresed on an 8% acrylamide gel and transferred to a nitrocellulose membrane (Hybond ECL, Amersham). The membranes were incubated with the following antibodies, all diluted 1/1000: eNOS (a monoclonal mouse anti-human antibody; Transduction Laboratories); iNOS (a polyclonal rabbit anti-mouse antibody); VCAM-1 (polyclonal goat anti-human antibodies); and ICAM-1 (polyclonal goat anti-mouse; Santa Cruz Biotechnology). Horseradish peroxidase–conjugated immunoglobulin antibodies were used as secondary antibodies at the following dilutions: 1/1000 for eNOS and iNOS and 1/2000 for VCAM-1 and ICAM-1. Detection was performed by using ECL reagents (Amersham). Films were analyzed by densitometry to determine the quantity of protein expressed in each group.

Immunohistochemistry
Transverse cryostat sections (5 μm) of hearts and aortas were cut and immunolabeled with the following antibodies and immunodetection methods. One series of sections was incubated for 30 minutes at room temperature with the following primary monoclonal mouse anti-rat antibodies: ED1 (macrophages diluted 1/1500, Serotec), OX6 (major histocompatibility class II diluted 1/50, Sera Laboratory), OX8 (cytotoxic T lymphocytes diluted 1/50, Sera Laboratory), W3/25 (helper T lymphocytes) (diluted 1/50, Sera Laboratory), and anti-iNOS (diluted 1/50, Transduction Laboratories). Subsequently, sections were incubated with a rabbit anti-mouse immunoglobulin...
antibody for 30 minutes at room temperature, followed by the alkaline phosphatase/anti-alkaline phosphatase enzymatic reaction and fast red staining (Dakopatts). Counterstaining was performed with hematoxylin.

A second series of sections was incubated overnight at 4°C with a polyclonal rabbit anti-iNOS antibody (diluted 1/50 in 50 mmol/L Tris-HCl, pH 7.4), followed by an FITC swine anti-rabbit antibody (diluted 1/20) and examined with an epifluorescence Leitz microscope.

A final series of sections was incubated at room temperature with anti-ICAM-1 and anti–VCAM-1 (diluted 1/50, polyclonal goat anti-mouse antibodies, Santa Cruz Biotechnology), followed by a donkey anti-goat biotinylated antibody (diluted 1/50, Amersham) and detected with the Vectastain ABC-AP kit (Vector Laboratories) and fast red staining. Counterstaining was performed with hematoxylin.

**Histochemical Staining of NADPH Diaphorase**

Transverse cryostat sections (5 μm) of aortas were incubated in 100 mmol/L Tris-HCl, pH 7.6, buffer containing 0.2% nitro blue tetrazolium, 1 mmol/L NADPH-Na₄, and 0.2% Triton X-100 for 2 hours at 37°C. Then the sections were washed with ice-cold 50 mmol/L Tris-HCl, pH 7.4, and mounted with a glycerol-gelatin solution.

**Statistical Analysis**

The results are expressed as mean±SEM. Statistical significance was estimated between groups by 1-way ANOVA followed by Bonferroni analysis. P<0.05 was considered significant.

**Results**

**Body Weight, Heart Weight, Systolic BP, and PRA**

During the 8 weeks, no significant differences in body weights or heart weights were observed between the 3 groups (Table 1). However, the heart weight to body weight ratio was significantly higher in L-NAME rats than in control and in L-NAME+irbesartan groups (Table 1). Long-term blockade of NOS by oral administration of L-NAME resulted in persistent hypertension, reaching a maximum level within 3 weeks (Figure 1). Systolic BP was significantly higher in the L-NAME group versus controls. In the L-NAME+irbesartan group, a significant decrease in BP compared with that in the L-NAME group was observed, but the BP values remained significantly higher than control values. No statistical difference in PRA was observed between the control and the L-NAME groups. PRA significantly increased in the L-NAME+irbesartan group compared with the control and L-NAME groups (Table 1).

![Figure 1](image) Evolution of systolic BP with time. Evolution of systolic BP measured by tail-cuff method in 3 experimental groups during 8 weeks of the experiment. Data are presented as mean±SEM: —— control group (n=10), —— L-NAME group (n=11), and —— L-NAME+irbesartan group (n=14).

**NO Synthases**

**mRNA Expression**

The results of semiquantitative analysis of RT-PCR are shown in Table 2. No significant difference was found for eNOS mRNA levels between the 3 experimental groups. The amount of iNOS mRNA was significantly increased in L-NAME aortas. Quantitative analysis of iNOS mRNA expression normalized to 100 ng of aortic RNA showed that the amount of iNOS mRNA in the L-NAME group was significantly higher than that in controls or the L-NAME+irbesartan group. No significant difference was observed between controls and the L-NAME+irbesartan group.

**Western Blotting**

Western blots of eNOS and iNOS proteins are illustrated in Figure 2. eNOS protein was expressed in aortas from control, L-NAME-, and L-NAME+irbesartan–treated rats. Densitometric analysis showed no difference among the 3 groups. Expression of iNOS protein was detectable in the L-NAME group and was absent in controls and the irbesartan-treated L-NAME group (Figure 2).

**Histochemistry**

Immunostaining for eNOS showed that the enzyme was present in the endothelium of all arteries, veins, and capillaries.
ies of myocardial tissue (Figure 3). No difference was observed (in the heart and aortic sections) between the 3 experimental groups. Immunofluorescent labeling of iNOS was observed in the arterial wall of the L-NAME group, whereas no immunostaining was detected in either control or the L-NAME+irbesartan group. This immunostaining was strong, and, as shown in Figure 3, the expression of iNOS activity was mainly localized in vascular smooth muscle cells.

The NADPH diaphorase reaction is used as an index of tissue activity for all NOSs (neuronal, endothelial, and inducible). In the 3 experimental groups, endothelial cells were labeled. In the aortas of L-NAME rats, vascular smooth muscle cells were also labeled, confirming the diaphorase activity of the NOS protein found by immunolabeling. Control and L-NAME+irbesartan aortas showed no labeling in the medial layer. Representative photomicrographs are shown in Figure 3.

Adhesion Proteins

mRNA Expression

Results of semiquantitative RT-PCR of the adhesion molecules VCAM and ICAM are shown in Table 2. L-NAME treatment induced a significant increase in aortic VCAM and ICAM mRNA expression compared with controls (F = 6.05, P < 0.01 and F = 4.36, P < 0.05, respectively). Irbesartan treatment normalized VCAM expression and decreased ICAM mRNA expression to an intermediate level not significantly different from that of the L-NAME group.

Western Blotting

Data obtained at the mRNA level were confirmed at the protein level by Western blotting (Figure 4). Expression of VCAM-1 was detected only in L-NAME rats, and no signal was detected in controls or in the irbesartan-treated L-NAME group. Expression of ICAM-1 was observed in all 3 groups, but in the L-NAME group ICAM expression was significantly higher than in controls (F = 5.5, P < 0.05). No difference was found between controls and the L-NAME+irbesartan–treated group or between the L-NAME– and the L-NAME+irbesartan–treated groups.

Immunohistochemistry

Representative photomicrographs are shown in Figure 5. Expression of VCAM-1 was observed in the endothelium and adventitia of pathological arteries in the L-NAME group, whereas in rats treated with L-NAME+irbesartan, as in controls, no VCAM-1 labeling was detected in the endothelium. ICAM-1 labeling was detected in the endothelium of veins of control myocardial tissue, and no changes were observed in the L-NAME or L-NAME+irbesartan groups. No ICAM-1 labeling was observed in the endothelium of conductance arteries. In contrast, arteries of the L-NAME group showed marked labeling in the intimal and adventitial areas, but this labeling was not observed in rats treated with L-NAME+irbesartan.

Inflammatory Cells

A dramatic increase in macrophage density (ED, immunolabeling) was observed in the fibrotic interstitial areas in hearts of the L-NAME group (Figure 6). Macrophages were also present in the perivascular areas. In some arteries, the intimal area was also labeled. Macrophages were absent in the arterial wall of the L-NAME+irbesartan group. A regular network of a few helper T cells was present in control myocardial tissue (W3/25 immunolabeling). Alteration of this regular network was evident in fibrotic regions of the L-NAME–treated group (Figure 6). Co-administration with
irbesartan prevented this alteration of helper T cells, and this group showed the same regular network as controls.

The increased density of macrophages and helper T cells in the interstitial and perivascular spaces observed in L-NAME arteries was confirmed by the detection of an increase in major histocompatibility class II molecule expression (OX6) in the same areas. Only in the interstitial pathological areas of the L-NAME myocardium were some cytotoxic T cells (OX8) observed.

Myocardial Fibrosis

Representative photomicrographs of Sirius red–stained myocardium are shown in Figure 6. Fibrosis was localized in perivascular and interstitial areas of myocardial tissue of L-NAME–treated rats. Irbesartan prevented the development of fibrosis induced by L-NAME administration.

Discussion

The current study shows that beyond the functional regulation of BP, chronic blockade of NOS by L-NAME was associated with phenotypic modulations within the arterial wall involving proinflammatory protein expression and infiltration of inflammatory cells. Furthermore, the Ang II antagonist irbesartan, which prevented the BP rise in this model, was also able to prevent these proinflammatory modulations.

We observed that chronic L-NAME administration was associated with the induction of iNOS expression within the arterial wall, whereas expression of the constitutive eNOS isoform did not change. The overexpression of iNOS in the vascular wall was detected at both the mRNA and protein level, and its localization in smooth muscle cells was demonstrated by both immunostaining and staining for NADPH diaphorase activity. Usually, expression of the inducible isoform of NOS is considered to be controlled by cytokines and endotoxins but may also be affected by other factors stimulating protein kinase C and redox signaling pathways, which are able to activate c-Jun, c-Fos, and nuclear factor-κB. In the current study, we observed infiltration of inflammatory cells capable of releasing such cytokines, which could mediate the increase of iNOS expression. However, expres-

![Figure 3. Photomicrographs of eNOS and iNOS in arterial wall. eNOS was detected similarly in the 3 groups of rats. In contrast, iNOS was just detectable in aortic medial areas of controls and in irbesartan-treated L-NAME rats but was greatly increased in medias of rats administered L-NAME. These data were confirmed by NADPH diaphorase reaction, which stained endothelium of the 3 groups of rats (control endothelium only shown) and medial layer only of the L-NAME–administered rats. Original magnification, eNOS ×20; iNOS ×25; and NADPH diaphorase staining ×100.](http://atvb.ahajournals.org/DownloadedFrom)
sion of iNOS could also be induced by the protein kinase C pathway in smooth muscle cells, and hypertension per se could induce such signaling in these cells.33 It has recently been shown that iNOS expression is higher in cultured smooth muscle cells from spontaneously hypertensive rats than in cells from normotensive controls.34 Chronic blockade of NO production by L-NAME is characterized by chronic reinforcement of phospholipase and protein kinase pathways in these cells.11 We have previously shown that chronic L-NAME administration increased expression of the inducible type II isoform of cyclooxygenase,15 which is sensitive, as is iNOS, to interleukins and to the activation of the protein kinase C pathway.35–37

Another important point is that the expression of proinflammatory proteins such as iNOS could participate in the prooxidant stage of the model. Indeed, in the presence of the arginine antagonist L-NAME, the NADPH reductase and the nitric oxidase activities of NOSs could be decoupled. Detection of NADPH diaphorase activity in the L-NAME group provides evidence of this decoupling. Therefore, in the presence of L-NAME, NOSs could probably catalyze an NADPH-dependent formation of activated oxygen intermediates (see Reference 38 for a review).

VCAM-1, which is considered to be an inducible form of adhesion molecule compared with the more constitutive ICAM-1, was also increased in endothelial cells of L-NAME–administered rats. Recruitment of arterial endothelial cells for ICAM-1 expression was also observed. In the presence of L-NAME,诺Ss could probably catalyze an NADPH-dependent formation of activated oxygen intermediates (see Reference 38 for a review).

Figure 4. Densitometric analysis of Western blots of VCAM-1 (left) and ICAM-1 (right) in aortas from the 3 groups of rats. Proteins were electrophoresed on an 8% acrylamide gel and transferred to nitrocellulose membranes. Membranes were then probed with antibodies to VCAM-1 or ICAM-1. Blots were analyzed by densitometry, n=4 per group. *P<0.05, **P<0.001 versus controls; †P<0.05, †††P<0.001 versus L-NAME–treated rats.

This study has demonstrated that the Ang II receptor (AT1) antagonist irbesartan can prevent most of the effects induced by L-NAME treatment. The beneficial effect of irbesartan cannot be explained by the reversal of NO blockade, because Ang II antagonists or angiotensin-converting enzyme (ACE) inhibitors have no such properties, as demonstrated by the persistent low levels of cGMP within the arterial walls of rats treated with L-NAME and ACE inhibitors.7 Therefore, the efficiency of the blockade of the RAS in hypertension, as well as in the prevention of phenotypic changes induced by chronic L-NAME administration, could be tentatively explained by extracellular communication or intracellular signaling. In terms of communication, L-NAME administration was not associated with detectable activation of renin endocrine secretion in the early stage of L-NAME–induced hypertension.8 ACE expression is increased at the tissue level by L-NAME administration,7 suggesting a paracrine rather than endocrine activation of the RAS.

In addition to extracellular communication, chronic blockade of NO production could potentiate the signaling pathways induced by Ang II–AT1 receptor interactions in target cells11.
It has recently been proposed that the main effect of NO in smooth muscle cells is to inhibit the coupling between heptahelicoidal transmembrane receptors and phospholipase activities by a G kinase–dependent mechanism. Conversely, we have recently proposed that NO blockade amplifies the coupling between the Ang II receptor and the downstream signaling pathways. Therefore, blockade of the Ang II–AT<sub>1</sub> receptor interaction is a means of downregulating the phospholipase and redox signaling pathways at another step than NO. As we observed for the regulation of vasomotor tone, such a mechanism could also partly explain the efficiency of Ang II antagonism in preventing smooth muscle cell phenotypic modulation induced by chronic L-NAME administration.

Moreover, Ang II antagonism prevents not only smooth muscle phenotypic changes but also overexpression of adhesion molecules on the endothelium. It has recently been demonstrated that endothelial cells also possess Ang II receptors. The effect of Ang II on endothelial cells has not been completely elucidated because Ang II could stimulate not only NO production but also the generation of reactive oxygen intermediates in these cells. Furthermore, NO down-regulates and N<sup>G</sup>-methyl-L-arginine upregulates the tumor necrosis factor–induced VCAM expression in endothelial cells in vitro. Therefore, chronic L-NAME administration could increase expression of adhesion molecules in the endothelium. This effect could be reversed by blocking AT<sub>1</sub> receptors on endothelial cells in vivo. Clozel and coworkers have demonstrated that ACE inhibition was able to prevent the margination of monocytes/macrophages in the model of spontaneously hypertensive rats. However, our data differ from those of Kato et al., as in their work losartan did not prevent the accumulation of ED<sub>1</sub>-positive monocytic cells in the intima. This could be explained by the different experimental designs of these studies, because losartan was administered together with Ang II at a lower dose and during a shorter period than in our study. Nevertheless, the long-term consequences of Ang II–endothelial cell interactions in the presence and absence of NO remain to be explored.

In conclusion, the current study has shown that beyond the effect on vasomotor tone, chronic blockade of NO production induces the expression of proteins sharing prooxidative and

Figure 5. Photomicrographs of immunostaining for VCAM-1 and ICAM-1 in coronary arterial wall. VCAM-1 was present only in arterial endothelium of L-NAME–treated rats. ICAM-1 was detectable in venous endothelium in all 3 groups of rats but in arterial endothelium only of L-NAME–treated rats. Original magnification ×20.
proinflammatory properties in both smooth muscle and endothelial cells of the vascular wall in rats. This study also demonstrated that irbesartan, an AT1 receptor antagonist, was able to prevent the development of such phenotypic changes in the arterial wall and therefore to inhibit inflammatory cell infiltration and fibrosis development in this model.

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