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Sympathetic activity is not increased in L-NAME hypertensive rats

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Santos FM, Dias DPM, Silva CAA, Fazan Jr R, Salgado HC. Sympathetic activity is not increased in L-NAME hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 298: R89–R95, 2010. First published November 4, 2009; doi:10.1152/ajpregu.00449.2009.—The role played by the sympathetic drive in the development of N^G-nitro-L-arginine methyl ester (L-NAME)-induced hypertension is not firmly established. Therefore, the present study was undertaken in conscious rats in which hypertension was induced by treatment with L-NAME over the course of either 2 or 14 days. Mean arterial pressure (MAP) was measured via a catheter placed in the femoral artery, drugs were administered via a cannula placed in the femoral vein, and renal sympathetic nerve activity (RSNA) was monitored using an implanted electrode. Despite the remarkable increase in arterial pressure, heart rate did not change after treatment with L-NAME. RSNA was similar in L-NAME-induced hypertensive rats treated over the course of 2 or 14 days, as well as in normotensive rats. It was also demonstrated that L-NAME-induced hypertensive rats displayed a resetting of the baroreflex control of RSNA to hypertensive levels, with decreased sensitivity over the course of 2 or 14 days. Furthermore, the sympathetic-vagal balance examined in the time and frequency domain and the renal and plasma norepinephrine content did not differ between groups. In conclusion, the evaluation of the sympathetic drive in conscious rats demonstrated that the arterial hypertension induced by L-NAME treatment over the course of 2 and 14 days does not show sympathetic overactivity.

baroreflex; nitric oxide; sympathetic activity.

IN PRIMARY HUMAN hypertension, an overactivation of the sympathetic outflow to the heart, kidneys, and skeletal muscle vasculature has been demonstrated (13, 17). In established hypertension, activity is increased in the sympathetic nerve fibers innervating the blood vessels located in the skeletal muscles (55). The increased cardiac and renal sympathetic nerve firing provides a reasonable mechanism for the development of hypertension (14).

There is evidence to support the hypothesis that nitric oxide (NO) plays an important role in the central nervous system, modulating the cardiocirculatory function by means of a sympathoinibitory effect (19, 43). Thus, NO inhibition may result in the activation of sympathetic activity and an additional increase in arterial pressure (52). Likewise, it is also known that NO levels are diminished in hypertensive humans, providing support for the notion that NO levels play an important role in the pathogenesis of essential hypertension (7, 31, 50).

Experimentally, the chronic blockade of NO synthase (NOS) with a nonspecific inhibitor such as N^G-nitro-L-arginine methyl ester (L-NAME) leads to hypertension that is sustained throughout the period of the blockade (40). Moreover, a number of studies using indirect approaches have suggested an increased sympathetic activity in the experimental model of hypertension achieved via chronic NOS inhibition with L-NAME (5, 29, 46). The decrease in arterial pressure caused by ganglionic blockade has been used to indirectly assess the sympathetic activity in L-NAME-induced hypertension. Using this approach, Sander et al. (45) proposed that sympathetic overactivity may occur only during the onset of L-NAME-induced hypertension, whereas Biancardi et al. (5) suggested that sympathetic overactivity may occur during both the initiation and maintenance of the experimental hypertension. Additional indirect approaches used to assess sympathetic activity include plasma (25, 39, 46) and renal (29, 46) norepinephrine content. Nevertheless, these methods do not yield any differences between the results obtained from normotensive and L-NAME-induced hypertensive rats (25, 29, 39, 46). In the present study, measurements of plasma and renal norepinephrine content were performed to indirectly evaluate sympathetic activity during the initiation (2 days) and maintenance (14 days) of L-NAME-induced hypertension.

It has been suggested that renal sympathetic nerve activity (RSNA) is increased during L-NAME-induced hypertension (29). The only study that directly measured RSNA in L-NAME-induced hypertensive animals was carried out in conscious rabbits treated with L-NAME over the course of 1 wk. The results did not show an increase in RSNA (38). However, since the authors observed an increase in arterial pressure of only 7 mmHg in conscious rabbits, they wondered whether a more significant increase in arterial pressure or the study of another species would reveal increased RSNA (38). Therefore, the major goal of the present study was to investigate the status of RSNA during the initiation (2 days) and maintenance (14 days) of experimental hypertension using conscious L-NAME-induced hypertensive rats displaying significant levels of hypertension.

Baroreflex function in L-NAME-induced hypertension has been thoroughly examined with regard to the baroreflex control of heart rate (HR) (3, 23, 49, 53). While some authors have described a decreased sensitivity in the baroreflex control of HR (23, 49), others reported either an increase (53) or no change (3) in baroreflex sensitivity. In contrast, few studies were conducted to directly assess the baroreflex control of RSNA in rats (47) or rabbits (38). Ramchandra et al. (38) demonstrated that L-NAME treatment over 1 wk caused a resetting of the baroreflex control of RSNA under hypertensive conditions, combined with decreased sensitivity and no change in the RSNA range. Scrogin et al. (47) showed similar results after 5 wk of L-NAME treatment, but a decreased range of RSNA occurred 1 wk after starting L-NAME treatment. Therefore, in addition to testing the role played by RSNA in the development of L-NAME-induced hypertension, the present study examines the baroreflex control of RSNA.

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Heart rate variability (HRV) and arterial pressure variability in the time and frequency domain (spectral analysis) have been used to evaluate the autonomic modulation of the cardiovascular system (1, 26, 51), particularly under pathophysiological conditions, such as arterial hypertension in humans (18) and experimental models (6, 8, 30, 49, 54). A number of studies have detected increased arterial pressure variability in the time domain, with no change in HRV in the case of L-NAME-induced hypertension (6, 30, 54). However, no previous study has addressed the arterial pressure variability in the frequency domain during L-NAME-induced hypertension. Therefore, another goal of the present study was to investigate, in conscious L-NAME-induced hypertensive rats with significant hypertension, the systolic arterial pressure (SAP) variability and HRV during the initiation (2 days) and maintenance (14 days) of experimental hypertension.

The primary goals of the present study were to investigate the role played by RSNA during the initiation (2 days) and maintenance (14 days) of experimental hypertension, and to evaluate the baroreflex control of RSNA in conscious L-NAME-induced hypertensive rats with remarkable hypertensive levels. In addition, sympathetic function was examined using indirect approaches, such as SAP variability, HRV, and measurements of plasma and renal norepinephrine content.

MATERIALS AND METHODS

All experimental procedures were carried out in accordance with the *Guide for the Care and Use of Laboratory Animals* [Dept. of Health, Education and Welfare, Publication No. (NIH) 85-23, Revised 1985; Office of Science and Health Reports, DRR/NIH, Bethesda, MD]. The experimental protocols used in this research were approved by the Committee of Ethics in Animal Research of the School of Medicine of Ribeirão Preto, University of São Paulo (protocol no. 142/2007).

Animals

Experiments were performed on male Wistar rats (250–300 g) maintained on a 12:12-h light-dark cycle and housed individually with free access to food and water. The L-NAME-induced hypertensive rats were treated with L-NAME (70 mg/kg) by means of gavage during 2 or 14 days, while normotensive rats received tap water. All animals were monitored using the tail-cuff method for indirect arterial pressure measurement on the first day of treatment and on the day before the surgical procedures.

Animal Preparation

Surgical procedures were performed under tribromoethanol (250 mg/kg ip) anesthesia. Each animal underwent surgery to implant polyethylene (PE-50 attached to PE-10) catheters into the left femoral artery for measurement of arterial pressure. In addition to the arterial catheterization, a group of rats was implanted with a catheter (PE-50) in the left femoral vein for drug administration, while the left kidney was exposed through a median laparotomy. A bipolar stainless steel electrode was implanted in a segment of the renal sympathetic nerve. The catheters and the electrode were exteriorized on the nape of the rat.

Arterial Pressure and RSNA Recordings

Arterial pressure was measured by connecting the arterial catheter to a Statham (model P23XL; Statham, Valley View, OH) pressure transducer, which was attached to a Carrier Amplifier (model 8805B; Hewlett Packard, Palo Alto, CA). Arterial pressure and RSNA were recorded simultaneously. RSNA was amplified and filtered (Cyberamp 320; Axon Instruments) and digitally recorded (10 kHz), using an IBM/PC equipped with an A/D interface (model DI-220; Dataq Instruments, Akron, OH).

Experimental Protocols

All experiments were carried out between 10 AM and 7 PM in conscious, freely moving rats housed in individual plastic cages. Rats were taken to the recording room at least 30 min before the beginning of the experiment, and a quiet environment was maintained to avoid any stress.

Protocol 1 was conducted 24 h after arterial catheterization. Basal pulsatile arterial pressure was recorded for 40 min. After the hemodynamic recordings, the rats were killed by decapitation, the kidneys were rapidly removed and frozen in liquid nitrogen for subsequent analysis of norepinephrine content, blood was withdrawn, and the plasma was immediately extracted by refrigerated centrifugation and filtration and stored at −80°C for posterior analysis.

Protocol 2 was conducted 6 to 8 h after arterial and vein catheterization and electrode implantation, because preliminary experiments had demonstrated no significant difference between MAP and HR measured 24 vs. 6 to 8 h after the surgical procedures. Initially, pulsatile arterial pressure, MAP, and RSNA were recorded simultaneously during a baseline period of 10 min and then continuous measurements were made after the administration of sodium nitroprusside and phenylephrine. Sodium nitroprusside (16 μg/kg) was injected to reduce MAP to ~45 mmHg. All variables were then allowed to return to baseline levels before phenylephrine (8 μg/kg) was injected to raise the MAP to ~160 mmHg when RSNA was absent. These sequences were repeated at least three times. At the end of the experiment, the rats were killed with an intravenous overdose of anesthesia.

Data Analysis

Mean arterial pressure vs. RSNA curve. MAP vs. RSNA curves were constructed after intravenous administration of phenylephrine and sodium nitroprusside. The RSNA signal was rectified, and noise subtracted. RSNA was then integrated using the diastolic arterial pressure as a trigger on a beat-to-beat basis. To compare multifiber RSNA from different rats, the RSNA was normalized as a function of the maximal activity (max = 100%) (42), as determined during the administration of sodium nitroprusside. The MAP vs. RSNA curve, fitted by four-parameter nonlinear sigmoidal regression (27), was plotted. The maximum slope (gain) of the curve was calculated from the first derivative of the sigmoidal fit. The MAP corresponding to the threshold pressure for RSNA activation (MAP_{th}) and the MAP needed to achieve maximum RSNA, i.e., saturation (MAP_{sat}), were calculated from the third derivative of the sigmoidal curve by means of the identification of the first (MAP_{th}) and second (MAP_{sat}) points of maximal inflexion of the sigmoidal curve.

Heart rate and arterial pressure variability analysis. Arterial pressure recordings were processed by computer software that applies an algorithm to detect beat-to-beat inflection points of a periodic waveform, determining beat-by-beat values of systolic and diastolic arterial pressures. Beat-by-beat pulse interval (PI) series were also generated by measuring the length of time between adjacent diastolic pressure readings, and they were used to determine HRV. The overall variability of SAP and PI was assessed by the variance of the time series (51). All time series were obtained from each experimental group, including normotensive rats and L-NAME-induced hypertensive rats treated over the course of 2 and 14 days. The SAP and PI variabilities in the frequency domain were assessed by spectral analysis as follows: the values of SAP and PI were resampled at 10 Hz by cubic spline interpolation to adjust the time interval between beats. The 15-min series, i.e., 9,001 interpolated values of SAP and PI, were divided into 34 segments with 512 values each, overlapping by half. The SAP and PI of each segment were examined visually, and segments with artifacts or large transients were excluded. Each seg-

ment of SAP and PI was submitted to spectral analysis via fast fourier transform after the Hanning window. The spectra of SAP and PI were integrated into bands of low (0.2 to 0.75 Hz) and high frequency (0.75 to 3 Hz).

Plasma and renal norepinephrine determinations. After direct measurement of MAP, the animals were killed, blood was withdrawn after decapitation, and plasma was immediately extracted via refrigerated centrifugation and filtration and stored at −80°C for posterior analysis. The kidneys were immediately removed and frozen in liquid nitrogen for subsequent analysis of norepinephrine content. Plasma and renal norepinephrine content were determined by HPLC as previously described (46).

Statistical Analysis

Data are reported as means ± SE. MAP, HR, plasma and renal norepinephrine, and parameters calculated from the sigmoidal fitting curve (gain, MAP_{th}, MAP_{sat}, and MAP_{50}) were compared among groups via one-way ANOVA, followed by the post hoc Bonferroni test. Differences were considered significant if $P < 0.05$.

RESULTS

Hemodynamic Variables

Table 1 shows the MAP and HR of conscious normotensive and L-NAME-induced hypertensive rats obtained by means of *protocol 1*. NO blockade with L-NAME during 2 or 14 days caused a significant increase in MAP, but did not affect the HR compared with normotensive rats.

RSNA and Baroreflex Control

Figure 1 (*top traces*) illustrates that RSNA was similar in conscious normotensive and L-NAME-induced hypertensive rats treated over the course of 2 and 14 days. The group data of RSNA are shown Fig. 1, *bottom*. The curves displayed in Fig. 2, *top* were constructed from the group data shown (*bottom*). MAP vs. RSNA curves characterized by MAP_{50}, MAP_{th}, and MAP_{sat}, from L-NAME-induced hypertensive rats treated over the course of 2 and 14 days, shifted to the right driven by the increase in MAP. In addition, the curves indicate no change in the range of the reflex during L-NAME treatment, but a significant decrease in baroreflex gain over 2 and 14 days is evident.

SAP and HR Variability

Table 2 shows that NO blockade with L-NAME during either 2 and 14 days did not cause any change in SAP and PI variability, compared with normotensive rats.

Renal and Plasma Norepinephrine Content

Table 3 shows the plasma and renal norepinephrine content of normotensive and L-NAME-induced hypertensive rats treated during 2 and 14 days. These data demonstrate that L-NAME did not increase plasma or renal norepinephrine content in either period of treatment when compared with normotensive rats.

Table 1. *Mean arterial pressure (MAP) and heart rate (HR) of conscious normotensive and L-NAME-induced hypertensive rats treated during 2 and 14 days*

	No. Observations	MAP, mmHg	HR, beats/min
Normotensive	21	111±2	383±7
L-NAME 2 days	14	139±2*	391±13
L-NAME 14 days	9	147±4*	376±14

L-NAME, N^G-nitro-L-arginine methyl ester. *$P < 0,05$ compared with normotensive rats.

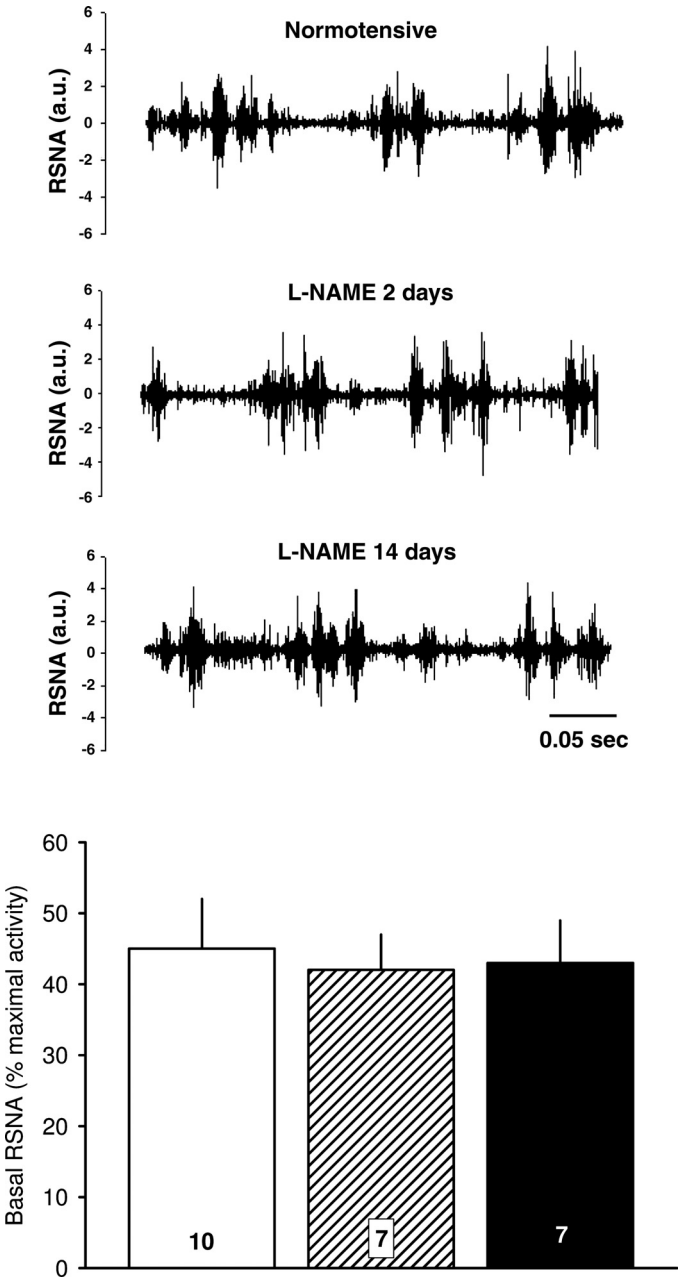

Fig. 1. *Top traces*: raw renal sympathetic nerve activity (RSNA) in arbitrary units (a.u.) from conscious normotensive and N^G-nitro-L-arginine methyl ester (L-NAME) hypertensive rats treated 2 and 14 days. *Bottom*: group data of normalized (%maximum activity) basal RSNA from conscious normotensive and L-NAME hypertensive rats treated during 2 and 14 days. Data are means ± SE of rats from each group. Numbers in bars are number of observations.

DISCUSSION

Examination of RSNA in rats with L-NAME-induced hypertension over the course of 2 and 14 days demonstrated that the sympathetic drive is not augmented in this hypertensive model. This finding was strengthened by the indirect approaches used

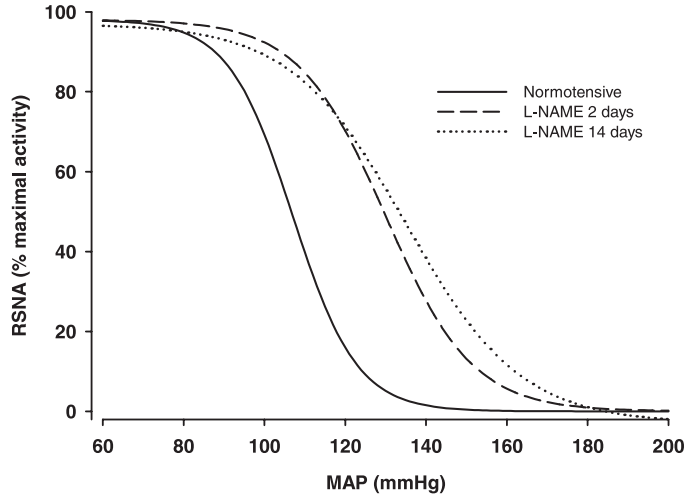

Fig. 2. *Top*: plot shows mean arterial pressure (MAP) vs. RSNA curves, expressed as %maximal activity using 4-parameter logistic sigmoidal regression. *Bottom*: data used to construct the curves. MAP_{50} = MAP corresponding to 50% of RSNA range; MAP_{th} = threshold MAP for RSNA activation; MAP_{sat} = MAP for saturation of discharges. Data are reported as means ± SE of rats from each group.

	NR (10)	L-NAME 2d (7)	L-NAME 14d (7)
Gain (%max/mmHg)	-3.48 ± 0.4	-2.48 ± 0.4*	-2.00 ± 0.3*
Range (% max)	98 ± 2	98 ± 2	100 ± 1
MAP_{50} (mmHg)	107 ± 3	130 ± 4*	135 ± 4*
MAP_{th} (mmHg)	124 ± 2	154 ± 5*	167 ± 5*
MAP_{sat} (mmHg)	88 ± 5	104 ± 6*	102 ± 6*

*P<0.05 compared with normotensive rats (NR).

to examine sympathetic function, including SAP variability, HRV, and renal and plasma norepinephrine content. In addition, it was also observed that the baroreflex control of RSNA was already reset to hypertensive levels 2 days after the initiation of hypertension, while a decreased sensitivity of the baroreflex control of RSNA was detected 2 and 14 days after the onset of hypertension.

Table 2. *Mean values of pulse interval and systolic arterial pressure variances*

	Normotensive	L-NAME, 2 days	L-NAME, 14 days
No. observations	17	12	12
	Pulse Interval		
Variance	21±2	23±2	27±6
LF, ms^2	0.98±0.13	1.27±0.33	1.19±0.39
HF, ms^2	5.79±0.47	5.66±0.92	8.42±2.22
LF, nu	14±1	12±2	17±2
HF, nu	86±1	83±2	88±2
LF/HF, nu	0.17±0.02	0.22±0.03	0.14±0.02
	Systolic Arterial Pressure		
Variance, $mmHg^2$	16±2	21±2	23±2
LF, $mmHg^2$	4.96±0.8	5.64±0.96	6.76±0.94

Values are means ± SE of low frequency (LF), high frequency (HF), and LF/HF powers of pulse interval, and LF powers of systolic arterial pressure of conscious normotensive and L-NAME-induced hypertensive rats treated during 2 and 14 days; nu, normalized units. *$P < 0,05$ compared with normotensive rats.

Hemodynamic Variables

The hypertensive levels obtained in L-NAME-induced hypertensive rats in the present study were similar to those previously observed after 4 wk of treatment with L-NAME (40). Despite the increase in MAP, HR did not change after L-NAME treatment, and this observation is consistent with most reports in the literature (3, 5, 6, 11, 30, 46, 54). Nevertheless, studies have also shown an increase (10, 49) or decrease (25, 29, 39, 46) of HR in this hypertensive model. These discrepancies could be attributed to different methodological approaches, such as the route (per os vs. intravenous) of L-NAME administration, the dose of the NOS inhibitor, the HR acquisition (conscious vs. anesthetized), and the species studied (rats, dogs, and rabbits).

RSNA

There is considerable controversy concerning the role played by RSNA in mediating the elevation of arterial pressure in

Table 3. *Mean values of plasma and renal norepinephrine content of normotensive and L-NAME –induced hypertensive rats treated during two and fourteen days.*

Norepinephrine	Normotensive	L-NAME 2 days	L-NAME 14 days
Plasma (ng/ml)	5,5±0,77 (5)	5,7±1,14 (5)	6,8±1,33 (7)
Renal (ng/g)	125±9 (14)	106±12 (5)	110±10 (9)

Parentheses display the number of observations.

L-NAME-induced hypertension. The renal nerves have been extensively studied in several experimental models, especially L-NAME-induced hypertension. It has been demonstrated that bilateral renal denervation in rats delayed the onset and attenuated the maintenance of L-NAME-induced hypertension (29). Consequently, the authors suggested that the renal nerves play a pivotal role in the development of arterial hypertension induced by chronic NOS inhibition (29). In contrast, Granger et al. (16) and Reinhart et al. (39) did not confirm that the renal nerves play a role in the onset of L-NAME-induced hypertension in dogs. A number of studies have used several indirect approaches, such as the examination of the magnitude of the fall in arterial pressure caused by ganglionic blockade, to examine the role of sympathetic nerve activity in the development of arterial hypertension. The decrease in arterial pressure induced by ganglionic blockade was greater in rats with L-NAME-induced hypertension compared with normotensive rats (5, 45). This suggests that the increase in sympathetic activity was responsible for the development of arterial hypertension caused by chronic NOS inhibition. However, ganglionic blockade does not differentiate the role played by the increase in nerve activity from the role played by the increased responsiveness of the vasculature to normal sympathetic discharges (4, 32). A number of studies that attempted to directly characterize the role of sympathetic activity in several experimental models have used RSNA recordings (12, 56). This approach has already been applied in heart failure (35), acute NO blockade (37), stress (22), and L-NAME-induced hypertension (38) when RSNA recordings failed to demonstrate sympathetic overactivity. In the present study, RSNA did not change 2 and 14 days after initiating L-NAME administration. This finding is consistent with the data obtained by Ramchandra et al. (38) in rabbits, even though the hypertensive levels obtained in the published study were slightly above the normotensive levels. Therefore, the normal sympathetic activity observed in conscious rats exhibiting remarkable hypertensive levels in the present study is in line with the only previous report that directly assessed RSNA in conscious rabbits (38). Nevertheless, this finding does not rule out the possibility that L-NAME-induced hypertensive animals display an increased vascular reactivity to normal sympathetic activity (4, 32).

Baroreflex Control of RSNA

To date, few studies have used RSNA recordings to characterize the baroreflex control of sympathetic activity in conscious L-NAME-induced hypertensive animals. To our knowledge, this type of study has been performed only once in rabbits (38) and rats (47). The results of the present study indicate that L-NAME-induced hypertensive rats exhibited a resetting of the baroreflex control of RSNA to hypertensive levels, combined with a decreased sensitivity of the baroreflex over 2 and 14 days after the onset of hypertension. Thus, it seems that NO inhibition has the ability to change baroreflex function during the development of hypertension, as suggested by Wang et al. (54) who found that rats with L-NAME-induced hypertension displayed lower baroreflex gain than two-kidney, one-clip and DOCA salt hypertensive rats. Because NO inhibits mitogenesis and proliferation of smooth muscle cells in culture (15), chronic as opposed to acute inhibition of this mechanism may affect vascular distensibility, which would ultimately affect the interaction between the vessels' smooth muscle and baroreceptor endings (2, 33). Moreover, it is well known that prolonged hypertension affects vascular compliance, influencing the mechanoelectrical transduction of the baroreceptors (2), which is certainly involved in the resetting mechanism and decreased baroreflex sensitivity (9). NO may modulate baroreceptor function by decreasing the tension imposed on baroreceptor nerve endings by means of vasodilatation and also by exerting a direct effect on baroreceptor nerve terminals. Indeed, endothelial and neuronal NOS-derived NO could be involved in the modulation of baroreceptor resetting and sensitivity (20, 24, 11, 15). In isolated rabbit carotid sinus preparations, NO or NO donors elicited inhibition of baroreceptor activity that was not related to NO-induced vasodilatation (28). In our laboratory, an in vivo rat study indicated that NO may contribute to rapid baroreceptor resetting during acute hypertension and affected baroreceptor sensitivity through a COX-dependent mechanism (44). However, it is not clear whether changes in baroreflex function under conditions of L-NAME-induced hypertension are due to adjustments in the afferents, central integration, or efferents of the reflex arc.

SAP and HR Variability

The analysis of HR and SAP variability in the time and frequency domain is a tool widely used to assess cardiovascular autonomic modulation (1, 26, 51), particularly under pathophysiological conditions, such as arterial hypertension in both human (18) and experimental models (6, 8, 30, 49, 54). The present study showed that the variance of PI did not differ between groups of normotensive and L-NAME-induced hypertensive rats. There are few reports in the literature addressing HRV under conditions of L-NAME-induced hypertension. Nevertheless, the results from the present study are consistent with those obtained by Wang et al. (54) and Persson et al. (36), who showed that acute and chronic treatment of NOS with inhibitors did not affect HR variability. Similarly, it was observed in the present study that the power of LF and HF PIs did not differ between normotensive and L-NAME-induced hypertensive rats. Accordingly, there was no difference in the sympathetic-vagal balance of the heart between the two groups. Therefore, it can be concluded that L-NAME-induced hypertensive rats do not show increased cardiac sympathetic modulation. The results of the present study contrast remarkably with those obtained in pathophysiological situations involving sympathetic overactivity in humans (18, 34) and in experimental conditions (41). Moreover, the lack of baseline tachycardia observed in L-NAME-induced hypertensive rats is consistent with the normal sympathetic activity in this hypertensive model.

The present study is the first to examine the effect of L-NAME on SAP variability in the frequency domain. It has been frequently observed that LF oscillations of the SAP are strongly associated with the sympathetic modulation of vascular tone (34, 21). Thus, in the present study, spectral analysis was used to assess the sympathetic modulation in L-NAME-induced hypertension. The LF band of SAP was comparable between normotensive and L-NAME-induced hypertensive rats. This finding led to the conclusion that sympathetic modulation is not augmented in this hypertensive model. Previous experiments have shown that rat models displaying remarkable

sympathetic overactivity, including SHR (48) and congestive heart failure (42), exhibited an increased LF band of SAP. Therefore, the results of the present study associated with SAP variability in the frequency domain are consistent with the notion that the vascular sympathetic modulation is not increased in L-NAME-induced hypertension. The present study also demonstrated that the SAP variance of L-NAME-induced hypertensive rats was not different from that of normotensive rats. This finding is in contrast with previous observations (6, 30, 54) of L-NAME-induced hypertensive rats treated over longer periods, i.e., 4 and 6 wk. However, the development of hypertension over longer time periods may explain the discrepancy in the present study.

Plasma and Renal Norepinephrine Content

The present study showed that treatment with L-NAME over the course of 2 or 14 days did not change the plasma norepinephrine content. This finding supports the notion that L-NAME-induced hypertension does not involve sympathetic overactivity. These data are in agreement with previous observations of normal plasma norepinephrine content in L-NAME-induced hypertensive dogs (39) and rats (25, 46) treated with L-NAME for 1, 2, or 4 wk. In addition, the present study also showed that the renal norepinephrine content was comparable for normotensive and L-NAME-induced hypertensive rats. These findings are consistent with those of Scrogin et al. (46) and Matsuoka et al. (29), who showed normal renal norepinephrine content in L-NAME-induced hypertensive rats.

In conclusion, the evaluation of sympathetic activity in rats with L-NAME-induced hypertension over the course of 2 and 14 days by means of RSNA recordings demonstrated that the sympathetic drive is not augmented in this hypertensive model. This finding was strengthened by means of the indirect examination of sympathetic function through the measurement of SAP variability, HRV, and renal and plasma norepinephrine content. In addition, it was also observed that the baroreflex control of RSNA was already reset to hypertensive levels 2 days after the initiation of hypertension, whereas a decreased sensitivity of the baroreflex control of RSNA was detected over 2 and 14 days after the onset of hypertension.

Perspectives and Significance

There is evidence to support the hypothesis that NO plays an important role in the central nervous system, modulating the cardiocirculatory function by means of a sympathoinibitory effect (19, 40). Thus, NO inhibition may result in the activation of sympathetic activity and an additional increase in arterial pressure (48). Likewise, it is also known that NO levels are diminished in hypertensive humans, providing support for the notion that NO levels play an important role in the pathogenesis of essential hypertension (7, 28, 46). From the experimental point of view, chronic blockade of NOS with a nonspecific inhibitor such as L-NAME leads to hypertension that is sustained throughout the period of the blockade (37). Moreover, a number of studies that used indirect approaches have suggested increased sympathetic activity in the experimental model of hypertension achieved via chronic NOS inhibition with L-NAME (5, 26, 42). Although it is difficult to precisely translate findings obtained from experimental models to clinical conditions, the lack of a sympathetic overactivity observed in the present study in a hypertensive model characterized by reduced NO levels indicates that the association between sympathetic overactivity (13, 17) and deficiency of NO generation (7, 28, 46) is not unquestionable in essential hypertension.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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