Impairment of Renal Vasodilation With L-Arginine Is Related to More Severe Disease in Untreated Hypertensive Patients

Elena Bello, Carlos Caramelo, Nieves Martell, José María Alcázar, Javier González, María Dolores López, Luis Miguel Ruilope, Francisco Román González, Adela María Rovira, Rosa Gazapo, María José Soldevilla, Santos Casado

Abstract—Data remain insufficient to place the decreased response to L-arginine in hypertensive patients within a consistent pathophysiological sequence. The aim of the present study in patients with essential hypertension was to assess the relationships between the response to L-arginine and a set of relevant clinical and laboratory parameters. In this prospective, interventional study, we administered L-arginine to untreated hypertensive individuals and healthy control subjects and measured the clearance of inulin and of para-aminohippurate and a set of biochemical and clinical variables. L-Arginine infusion revealed major differences between control subjects and 1 subgroup (group B) of hypertensive individuals. Group B hypertensives (n=18) had no increase in inulin clearance and no decrease in renal vascular resistance with L-arginine; however, in another subset of hypertensive patients (group A, n=27), the insulin clearance increased and renal vascular resistance decreased similar to the control group (group C, n=11). The ambulatory blood pressure monitoring in group B showed both an increased mean diastolic pressure and a “nondipper” pattern in the nocturnal regulation of arterial pressure. These findings in group B were accompanied by significant alterations in optic fundus and left ventricle hypertrophy and increased microalbuminuria (all, P<0.05). Furthermore, group B individuals had significantly lower values of HDL cholesterol and a higher baseline atherogenic index, plasma insulin level, and glucose/insulin index. We disclose a previously undescribed relationship between end organ repercussion and decreased renal hemodynamic response to L-arginine. Our results may help to understand the mechanisms that lead to target organ damage in hypertension. (Hypertension. 2001;38:907-912.)

Key Words: L-arginine ▪ hypertension, essential ▪ endothelium ▪ blood pressure monitoring, ambulatory

Despite intense investigative efforts, major basic aspects of the pathophysiology of essential hypertension remain unclear. In recent years, a great deal of attention has been paid to the involvement of endothelium-related mechanisms in the pathogenesis of arterial hypertension.1–8 In particular, the role of the vascular and renal regulatory mediator NO in hypertension has been extensively studied through the administration of the NO precursor amino acid L-arginine.9–12 In these studies, an alteration in the renal vasodilatory response to L-arginine was described, although the findings that have been reported are less than homogeneous.9–12 Therefore, even though the information provided in the aforementioned studies is relevant, the data obtained are incomplete and still must be organized to provide a coherent pathophysiological interpretation. First, to homogenize the information and to eliminate undesired variability, strict criteria are necessary to select patients with essential hypertension. Second, and of extreme importance, no relationships have been sought between the response to L-arginine and markers of severity of hypertension, including 24-hour ambulatory blood pressure measurements (ABPMs) and parameters of target organ damage. Accordingly, the aim of the present study was to assess the putative relationships between the response to L-arginine and a set of meaningful clinical and laboratory variables in restrictively recruited patients with essential hypertension.

Methods
The study was prospective and interventional. The study protocols were approved by the research and ethical boards of the 3 participating institutions, and written informed consent was obtained from all subjects.

Subjects
The participants consisted of 40 whites with untreated essential hypertension (World Health Organization criteria) and 11 healthy...
white control subjects (group C). None of the individuals had evidence of any major disease, and none were taking medications; their plasma cholesterol level was <6.4 mmol/L, and their creatinine clearance (C_{Cr}) was >90 mL/min. Subclinical endothelial damage and putative coadjuvant cardiovascular risk factors were further assessed with measurements of plasma von Willebrand factor, ACE activity, and ferritin. Urine was collected during a 24-hour period on the day before the L-arginine infusion. All of the determinations and procedures, with the exception of the ABPMs, echocardiography, and funduscopy, were also accomplished in a control group of normal individuals who were matched for gender and age with the hypertensive group.

Study Procedure
The L-arginine infusions were performed according to previous studies. No sodium restriction was enforced, but general recommendations for salt control were provided to all subjects. Food intake in the days before the study was unrestricted, but subjects were not allowed to eat during the test.

Analytical Methods
Resting arterial pressure was measured by conventional sphygmomanometry (5 readings within 30 minutes). The study included autoanalyzer determinations; plasma and urinary electrolytes; total, LDL, and HDL cholesterol; and proteinuria by the sulfosalicylic method and inulin (IN) and para-aminohippurate (PAH) concentrations (colorimetric method; Merck). Plasma insulin (RIA; Linco Research Inc), von Willebrand factor (RIA; American Diagnostica), ACE activity (enzymatic analyzer; Sigma Chemical Co); ferritin (nephelometry; Dade-Behring), and microalbuminuria (urinary albumin excretion [UAE], immunoturbidimetry; Boehringer-Mannheim) were also measured. We obtained 24-hour arterial pressure measurements (Spacelabs Medical Inc). Optic fundus was evaluated by staff ophthalmologists and classified according to the Keith-Wagener-Barker classification. ECG and echocardiography results were analyzed by staff cardiologists and classified according to previously reported criteria. In all cases, the physicians were blinded to the clinical data of the patients.

Statistical Analysis
Data are expressed as mean±SEM, and P<0.05 was considered significant. We used Kolmogorov-Smirnov, paired and unpaired Student’s t, and χ² tests and ANOVA followed by Scheffe’s t test and regression analysis; multivariate analysis was performed only on the blood biochemical variables with the multiple linear regression, stepwise method (SigmaStat, Jandel Scientific; and SPSS, SPSS Inc, 1998). The L-arginine effects were calculated by comparing the baseline period with the period of peak effect of the infusion. The rationale for the distribution of the data in groups A, B, and C was based on the experimental results (see Results).

Results
The infusion of L-arginine revealed major differences in the glomerular filtration rate (GFR) and renal plasma flow (RPF) responses between control subjects and 1 subgroup of hypertensive individuals (Figures 1a and 1b). Accordingly, the results are presented with a focus on this difference. Group C denotes the control individuals (n=11), who had increased clearance of IN (C_{IN}) and PAH (C_{PAH}) on L-arginine infusion; group A denotes the hypertensive patients who responded in a similar manner as control subjects, namely, by increasing C_{IN} and C_{PAH}; and group B denotes the hypertensive individuals who had no increase in C_{IN} and a minor increase in C_{PAH} with L-arginine. The absence of response to L-arginine was defined as a <10% increase in C_{IN} with respect to the baseline. To facilitate visualization, the figures show only the baseline and peak values. In group A patients (n=27, 60% of

Figure 1. A, Values of C_{IN} at baseline (left columns) and at the peak effect of L-arginine infusion (right columns). B, Values of C_{PAH} at baseline (left columns) and at the peak effect of L-arginine infusion (right columns). Columns A and B denote the 2 groups of hypertensive patients; column C, the control group. P<0.001 vs group B.

the hypertensive individuals), C_{IN} and C_{PAH} increased with L-arginine in a proportion that did not differ (P=NS) from that observed in the control subjects. In all of the cases, the peak response occurred within 90 to 120 minutes from the beginning of the infusion. However, group B hypertensives (n=18, 40% of the hypertensive individuals) had a markedly diverse response, with no increment in GFR and a minor increase in RPF. As a consequence, the filtration fraction (FF) values for baseline were 0.22±0.1% (group A), 0.19±0.03% (group B), and 0.20±0.05% (group C), and for peak L-arginine effect, the values were 0.21±0.07% (group A), 0.15±0.04% (group B), P<0.05 versus groups A and C and versus baseline), and 0.21±0.05% (group C). In the 3 groups, values of C_{Cr} corresponded to those of C_{IN} (data not shown, P=NS for C_{Cr} versus C_{IN}). Of further interest, no significant changes in mean arterial pressure (MAP) were detected due to the L-arginine infusion (baseline: group A 109±10 mm Hg, group B 115±9 mm Hg, and group C 85±14 mm Hg; peak value of L-arginine effect: group A 106±12 mm Hg, group B 112±10 mm Hg, and group C 80±9 mm Hg; P<0.01 versus group C). Therefore, changes in renal vascular resistance (RVR) in response to L-arginine (Figure 2) were significant.

Tables 1 and 2 show several parameters of the 3 groups at baseline. Both MAP and pulse pressure were significantly higher in the 2 hypertensive groups than in the control subjects. However, at this time, GFR and RPF were similar in all of the groups. The values of putative biochemical markers of endothelial injury were within a normal range in all the subjects, independent of their arterial pressure or type of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{IN}</td>
<td>22±1%</td>
<td>18±0.5%</td>
<td>20±0.3%</td>
</tr>
<tr>
<td>C_{PAH}</td>
<td>21±0.7%</td>
<td>15±0.4%</td>
<td>21±0.5%</td>
</tr>
<tr>
<td>C_{Cr}</td>
<td>0.22±0.1%</td>
<td>0.19±0.03%</td>
<td>0.20±0.05%</td>
</tr>
</tbody>
</table>

Tables 1 and 2 show several parameters of the 3 groups at baseline. Both MAP and pulse pressure were significantly higher in the 2 hypertensive groups than in the control subjects. However, at this time, GFR and RPF were similar in all of the groups. The values of putative biochemical markers of endothelial injury were within a normal range in all the subjects, independent of their arterial pressure or type of
A comparative analysis of several relevant variables allowed further characterization of group B as different from groups A and C. First, the data from ABPM tracings showed both an increased mean diastolic pressure and a clear-cut impairment in the nocturnal downregulation of arterial pressure in the patients from group B (Table 3). However, no differences in mean systolic arterial pressure were evident. The findings from ABPMs were further supported by the significant differences in additional clinical variables, namely, optic fundus and left ventricle overload, as assessed by the ECG (Table 4), and left ventricular hypertrophy, as assessed by the echocardiogram (Table 5). In the latter case, concentric hypertrophy was found in all cases (3 in group A and 7 in group B), except in 1 patient in group B, who had predominant septal hypertrophy. All of the abnormalities in funduscopy were of Keith-Wagener-Barker class I or II.

**Figure 2.** RVR (mm Hg · min⁻¹ · mL⁻¹). Columns A and B denote the 2 groups of hypertensive patients; column C, the control group. *P<0.001 vs groups A and C. **P<0.05 vs baseline group. *P<0.05 vs groups A and B.

The main message of the present study is that the decreased response to L-arginine corresponds to a group of hypertensive patients with more severe organ repercussion, even preceding the appearance of microalbuminuria and before the increase in other markers of vascular damage. As an important part of the same message, the “nondipper” blood pressure pattern, a marker of potential complications, is related herein to the lack of vasodilatation with L-arginine.

The fact that our patients were rigorously selected, recently diagnosed, and previously untreated is crucial for the appraisal of the potential importance of the present findings. Of note, the alterations that we report were detected only on the basis of the response to the L-arginine infusion, and therefore, no previous selection bias occurred. In this setting, the response to L-arginine infusion appears to be sensitive enough to detect endothelium-related hemodynamic disturbances. Actually, other markers may result more from secondary atherosclerotic changes than from hypertension itself. In this regard, in series of diabetic patients, no increase in von Willebrand factor was detected until the appearance of microalbuminuria, thereby supporting its meaning as a marker of advanced vascular injury. Moreover, it should be reemphasized that on the basis of the normality of the baseline plasma creatinine and $C_\text{Cr}$, the alterations in the

Second, even though L-arginine increased UAE in the 3 groups, a higher increment of UAE was evident in group B throughout the study (Figure 3). Third, a moderate but consistent difference was found in plasma HDL cholesterol, which was significantly lower in group B with respect to groups A and C, albeit within values considered normal in the current evaluations of risk factors (Table 2). In the same regard, the atherogenic index was elevated in group B with respect to group A (Table 2). Moreover, on multivariate statistical analysis, a lower HDL cholesterol concentration was the only variable in blood biochemistry that independently predicted the probability of belonging to group B ($P=0.0273$). Additional, meaningful differences of group B with respect to groups A and C included a significantly increased insulinemia at baseline (Table 2). Of further interest, the glucose/insulin index was significantly decreased in group B with respect to groups A and C (Table 2).

**Discussion**

A classic tenet of arterial hypertension was established in the work of Guyton et al., who sustained the primacy of the kidney in the pathogenesis of hypertension. This concept was further supported by studies that showed defects in renal vasodilatation in hypertensive disease. The actual mechanisms involved in this phenomenon are, however, still incompletely understood, and their putative relationships with organ repercussion of hypertension have not been defined.

With the exception of microalbuminuria, no clinical or laboratory variables can be reliably used to distinguish patients with a progressive target organ injury from those who follow a more benign course. Furthermore, the available data do not define the actual importance of the altered renal vasodilatory response to L-arginine in hypertensive patients, a phenomenon that cannot be precisely ascribed to any particular pathophysiological sequence.

**Table 1.** Values of Several Clinically Relevant Variables at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=27)</th>
<th>Group B (n=18)</th>
<th>Group C (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±12.3</td>
<td>40±12.2</td>
<td>36±12.2</td>
</tr>
<tr>
<td>M/F, n</td>
<td>16/11</td>
<td>12/6</td>
<td>7/4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75±16</td>
<td>73±7</td>
<td>69±6.6</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.69±0.1</td>
<td>1.70±0.06</td>
<td>1.68±0.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5±2.2</td>
<td>24.5±1.8</td>
<td>23.5±0.5</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>109±10*</td>
<td>115±9*</td>
<td>85±14</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>58.1±12*</td>
<td>59.9±16*</td>
<td>42.7±18</td>
</tr>
<tr>
<td>CO/m³, mL · min⁻¹ · m⁻²</td>
<td>67±15</td>
<td>67±20</td>
<td>65±15</td>
</tr>
<tr>
<td>von Willebrand factor, U/mL</td>
<td>0.8±0.2</td>
<td>0.7±0.1</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>ACE activity, U/L</td>
<td>36.2±13.4</td>
<td>27.1±12.4</td>
<td>39.7±13.9</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>94±73.7</td>
<td>93±64.1</td>
<td>74±27.5</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; PP, pulse pressure. *P<0.05 for groups A and B vs group C.
TABLE 3. ABPM Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=27)</th>
<th>Group B (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg 24 h</td>
<td>146±14</td>
<td>148±13</td>
</tr>
<tr>
<td>DBP, mm Hg 24 h</td>
<td>93±6</td>
<td>99±9*</td>
</tr>
<tr>
<td>Nocturnal SBP decrease (&gt;10%), % (n)</td>
<td>92 (25)</td>
<td>72* (13)</td>
</tr>
<tr>
<td>Nocturnal SBP decrease (&lt;10%), % (n)</td>
<td>4 (1)</td>
<td>22* (4)</td>
</tr>
<tr>
<td>Paradoxical nocturnal SBP increase, % (n)</td>
<td>4 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Nocturnal DBP decrease (&gt;10%), n (%)</td>
<td>85 (23)</td>
<td>67* (12)</td>
</tr>
<tr>
<td>Nocturnal DBP decrease (&lt;10%), n (%)</td>
<td>11 (3)</td>
<td>22* (4)</td>
</tr>
<tr>
<td>Paradoxical nocturnal DBP increase, n (%)</td>
<td>4 (1)</td>
<td>11* (2)</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

*P<0.05 group A vs group B.
†Expressed as percent of patients with an SBP decrease of >10%.
‡Expressed as percent of patients with an SBP decrease of <10%.
§Expressed as percent of patients with a DBP decrease of >10%.
¶Expressed as percent of patients with a DBP decrease of <10%.

patients of group B would have remained unnoticed. In the same regard, the alterations found in the present study were mild enough to be overlooked.

To understand the renal abnormalities in essential hypertension, the differences between group A and B form the keystone of our findings. At first glance, group B can considered within the framework of impaired functional reserve described in hypertensive patients.25,26 The absence of a decrease in RVR with L-arginine is illustrative of the inadequate response in group B; of additional interest, the decrease in FF found with L-arginine in group B suggests the existence of particularly altered glomerular dynamics in a subset of hypertensive patients.

Of crucial importance, group B patients have several parameters of a more severe degree of hypertension. In this setting, the absence of renal vasodilatation with L-arginine has been relevant for defining a subset of patients with increased organ damage due to hypertension. This picture includes the data of ABPM, UAE, ECG, echocardiographic and optic fundus alterations. On this basis, it is tempting to speculate that the absence of renal vasodilatation with L-arginine discloses a major regulatory failure. This failure, by blunting the daily adaptive changes in RVR, creates a rather more fixed resistance in the renal vascular territory that may lead to a sustained cardiovascular overload.

Of further interest, even though others have related an increased UAE to a more severe organ repercussion of arterial hypertension, UAE has not been specifically related to alterations in renal functional responses, as we report in the present study.

Differences between the results of different investigations concerning the magnitude of the effects of L-arginine on GFR, RPF, and MAP can usually be traced to diversity among the experimental conditions. The existence of a subset of hypertensive patients who do not respond to amino acid infusions by increasing GFR was suggested in previous investigations. In 1 study, 11 of 34 hypertensive individuals were nonresponders; in 8 of the 11, the UAE was above the normal range. Other studies did not found alterations in the increase of GFR induced by an oral protein load in
hypertensive individuals; however, if the results of these studies are reanalyzed individually, a subset of individuals with a blunted increase in GFR and RPF can be detected (eg, 2 of 15 in the study by Valvo et al,30 3 of 16 in the study by Cottone et al31).

The association found in our study between the nondipper pattern of arterial pressure and the lack of renal vasodilatation with L-arginine has not been previously described and can be of importance for understanding the pathogenesis of the nondipper phenomenon, which has been considered a marker of impaired prognosis for progressive renal insufficiency in hypertensive individuals.32 Our data suggest that the nondipper pattern is associated with a profound disturbance in renal vasodilatation to physiological stimuli, such as amino acids.

The finding of a significant correlation between HDL cholesterol levels and the pertinence to group B highlights the importance of the putative pathological value of a small decrease in HDL cholesterol, even at levels considered of little cardiovascular risk. This finding deserves to be further studied in more extensive series of individuals, because it suggests that the normal range of HDL cholesterol may have to be reappraised in the setting of arterial hypertension. Even though we cannot support a direct mechanistic hypothesis for the relationship of HDL cholesterol and the lack of a renal response to L-arginine, 33 and insulin resistance could in part account for our results.

Our results suggest that the absence of a renal response to L-arginine may be pathophysiologically related to a more marked target organ damage and to the nondipper pattern in ABPMs. However, it cannot be established from the present study whether the changes observed were permanent or reversible. In this regard, recent studies have demonstrated that a relatively prolonged administration of L-arginine to spontaneously hypertensive, old rats may have a beneficial influence on several hemodynamic parameters.34 Of additional interest, an association between decreased arm blood flow response to acetylcholine and left ventricular hypertrophy was recently reported,35 which may be related to the present findings; unfortunately, the data in the aforementioned study did not provide information on changes in RBF similar to those measured by strain-gauge plethysmography in the arm.35 From a mechanistic point of view, our present findings with L-arginine, as well as those of the studies that used acetylcholine,3–7,35 probably are related to a deranged response of NO/cGMP-dependent pathways; however, an analysis of the precise cellular mechanisms involved is beyond the scope of the present study.

Our findings provide experimental evidence to support the view that the kidney has a central role in the pathogenesis of arterial hypertension and in the end-organ repercussion and offers a new mechanistic framework in which to interpret previous knowledge.

**TABLE 4. End Organ Repercussion of Arterial Hypertension**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A, % (n)</th>
<th>Group B, % (n)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>Normal</td>
<td>Abnormal†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78 (21)</td>
<td>22 (6)</td>
<td>44 (8)</td>
</tr>
<tr>
<td>Funduscopoy</td>
<td>74 (20 classification 0)</td>
<td>26 (6 classification I, 1 classification II)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44 (8)</td>
<td>56 (10)*</td>
<td></td>
</tr>
<tr>
<td>UAE &gt; 20 µg/min</td>
<td>Normal</td>
<td>Abnormal†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86 (23)</td>
<td>14 (4)</td>
<td>78 (14)</td>
</tr>
</tbody>
</table>

Classifications 0, I, and II indicate degree of the Keith-Wagener-Barker classification. *P<0.05 between groups A and B. †See text for criteria of abnormality.

**TABLE 5. Echocardiographic Measurements**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior wall thickness, mm</td>
<td>10±1.3</td>
<td>12.5±2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal wall thickness, mm</td>
<td>10.1±1.4</td>
<td>11.8±1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>RWT*</td>
<td>0.4±0.05</td>
<td>0.52±0.09</td>
<td>0.002</td>
</tr>
<tr>
<td>LV diameter, systole, mm</td>
<td>32.3±2.8</td>
<td>30.4±5.1</td>
<td>0.02</td>
</tr>
<tr>
<td>LV diameter, diastole, mm</td>
<td>45.5±4.8</td>
<td>49.8±5.6</td>
<td>0.03</td>
</tr>
<tr>
<td>LV mass index, g</td>
<td>150±30</td>
<td>182±50</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>64.5±3.6</td>
<td>71±4.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; EF, ejection fraction; RWT, end-diastolic relative wall thickness.

Values are mean±SD.

**Figure 3. UAE (µg/min).** Columns A and B denote the 2 groups of hypertensive patients; column C, the control group. *P<0.002 vs groups A and C. †P<0.001 vs groups A and C.
Acknowledgments

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References

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