Renal Response to Amino Acid Infusion in Essential Hypertension

Luis Juncos, Juan Carlos Cornejo, Encarnacion Pamies-Andreu, Juan Carlos Romero

Abstract In the present study, we evaluated the renal response to a 4-hour infusion of amino acids in essential hypertensive patients, as well as the effects that dietary sodium restriction and enalapril (a converting enzyme inhibitor) had on this renal response. During normal sodium intake, amino acid infusion significantly increased renal plasma flow from 383±58 to 478±51 mL/min and glomerular filtration rate from 82±8 to 100±13 mL/min. All these effects were abolished when the patients received a low sodium diet (40 mmol/d) for 3 days before the amino acid infusion. The administration of enalapril to the patients during sodium restriction restored the amino acid-induced increment in renal plasma flow (from 388±35 to 537±48 mL/min) and glomerular filtration rate (from 88±9 to 103±10 mL/min). Mean arterial pressure remained unaltered under all experimental conditions. The results show that in patients with essential hypertension dietary sodium restriction prevents amino acid-induced increments in glomerular filtration rate and renal plasma flow and that this effect is restored during the simultaneous administration of enalapril. (Hypertension. 1994;23[suppl I]:I-225-I-230.)

Key Words • angiotensin converting enzyme inhibitors • enalapril • diet, sodium-restricted • dietary proteins • aldosterone • renin

It is well known that a high protein intake produces a significant increase in both renal plasma flow (RPF) and glomerular filtration rate (GFR). These effects have been held responsible for accelerating glomerular damage, mainly in patients with preexisting renal insufficiency. However, it is not known if similar deleterious effects are exerted by high-protein diets in patients with essential hypertension. Intravenous administration of an amino acid combination used in parenteral nutrition therapy increases RPF and GFR in normotensive volunteers. In these normotensive individuals, dietary sodium restriction inhibits the renal responses to amino acid infusion; however, administration of a converting enzyme inhibitor during sodium restriction restores the vasodilator renal response.

A similar renal response should not be assumed for patients with essential hypertension. In these patients the kidney endures higher sympathetic tone and higher renal vascular reactivity. Likewise, angiotensin II (Ang II) may contribute to the renal vasoconstriction of hypertension. Hence, renal vasoconstriction is a frequent if not constant finding in essential hypertension. We speculated that these pressor stimuli, seen in hypertensive but not in normotensive individuals, could restrict a protein-induced renal vasodilatation. Furthermore, we felt the basis for such a notion could lie in the activity of the renin-angiotensin system.

This study was designed to answer the following questions: (1) Is the kidney of patients with essential hypertension able to increase RPF and GFR in response to an amino acid infusion? (2) Is the response modified by sodium dietary restriction? and (3) Would the latter be changed by inhibition of the renin-angiotensin system? These observations could have considerable clinical implications concerning the possible effects of a high-protein diet in patients with essential hypertension.

Methods

Nine patients (seven women, two men; age range, 43 to 69 years) with essential hypertension were studied. All patients had diastolic blood pressure measurements in excess of 90 mm Hg on at least three occasions and a history of hypertension for at least 12 months before the study. Secondary hypertension was excluded by a clinical medical examination, urinalysis, serum creatinine, creatinine clearance, serum electrolytes, plasma aldosterone (PA), and 24-hour urinary excretion of vanillylmandelic acid and catecholamines. Renal hypertension was excluded by rapid-sequence intravenous pyelography in all patients. In some patients, radiotopic renogram or renal arteriography was performed to exclude renal arterial disease. All antihypertensive medications were discontinued for at least 3 weeks before the study. Patients then began an isocaloric diet containing 150 mmol sodium, 0.50 g/kg body wt proteins, and free water intake. Urine urea nitrogen was determined as Urinary Urea×0.466. Nonprotein nitrogen excretion was calculated as 29 mg nitrogen/kg per day. Total nitrogen excretion was obtained from the sum of urine urea nitrogen and nonprotein nitrogen. The protein ingestion in grams per day was calculated as the product of total nitrogen excretion and 6.25.

After giving written informed consent, the patients were admitted to the hospital, weighed, and heart rate and blood pressure measured. All patients fasted from 8 PM the night before the experiment until completion of the study on the following day. During this time water was allowed ad libitum. All the procedures and written consents were approved by the local Institutional Review Committee.

Experimental Protocol

At the beginning of each experiment, a urethral catheter was placed for the collection of urine, and the patients reclined in the supine position and remained in this position for the
duration of the experiment. The clearances of inulin (for determination of GFR) and para-aminhippurate (PAH) for calculation of RPF were measured during diuresis, which was elicited by the oral ingestion of 20 mL water/kg body wt during each clearance period. Priming boluses of inulin (50 mg/kg) and PAH (8 mg/kg) were administered (both diluted in 5% dextrose) over 5 minutes. This was followed by continuous infusions of inulin (0.5 mg/kg per minute) and PAH (0.25 mg/kg per minute) at a total constant rate of 24.66 mL/h by an infusion pump (Harvard Apparatus, South Natick, Mass). After a 45-minute equilibration period, the bladder was emptied, and two consecutive 30-minute control clearances were obtained. Urine volume (UV) and sodium, PAH, and inulin concentrations were measured during each clearance period. Blood samples were obtained at the midpoint of each clearance period from the contralateral arm vein for measurement of plasma inulin, PAH, sodium, potassium, renin activity (PRA), and PA. The values for these two periods were averaged. After the control clearances, a 10% amino acid solution commonly used for parenteral nutrition was infused at a rate of 0.70 mL/kg per hour. The amino acid composition of this solution is shown in Table 1. Because the volume infused each minute varied between 0.72 (patient 4) and 1.07 mL (patient 1), no correction was made in the osmolality of the solution. It was assumed that such small volumes diluted in the much larger extracellular fluid volume did not change plasma osmolality. The amino acid infusion was continued for 4 hours, and urine and plasma variables were measured during the last 30 minutes of each hour.

Baseline Studies

The control studies were conducted after the patients were allowed 3 days of free sodium intake. Twenty-four-hour urinary sodium excretion (UN,V) was measured the day before the amino acid infusion.

Studies During Low Sodium Diet

Negative sodium balance verified by urinary sodium concentration was achieved by an oral dose of furosemide (80 mg) followed by 3 days of a 40-mmol/d sodium and 60-mmol/d potassium diet. Twenty-four-hour UN,V was measured on the third day, and on the fourth day the amino acid infusion was repeated.

Studies During Low Sodium Diet and Treatment With Enalapril

After the completion of the study on the low sodium diet, enalapril (10 mg) was administered orally beginning at 8 PM on that same day and every night for the next 3 days. During this period, the patients were kept on the low sodium diet (40 mmol/d). Another 24-hour UN,V was measured on the third day of enalapril administration, and the infusion study was repeated the following day.

Analysis

Urinary and plasma PAH and inulin were measured by a photocolormetric method. Urinary and plasma sodium and potassium concentrations were determined by flame photometry. PRA was measured by radioimmunoassay using a commercial kit (Gamma Coat Kit, Baxter Corp, Cambridge, Mass). PA was measured by solid-phase radioimmunoassay (Coat-A-Count, Diagnostic Products Corp, Los Angeles, Calif).

Statistical Methods

Data are presented as mean±SEM. The significance of the difference of the recorded values between groups was evaluated with a randomized block analysis of variance and the Newman-Keuls multiple-range test.

| TABLE 1. Composition of the 10% Amino Acid Solution |
|---------------------------------|---------|
| Amino Acid                      | Amount, mg |
| L-Isoleucine                    | 720     |
| L-Leucine                       | 940     |
| L-Lysine L-glutamate            | 720     |
| L-Methionine                    | 400     |
| L-Phenylalanine                 | 440     |
| L-Threonine                     | 520     |
| L-Tryptophen                    | 160     |
| L-Valine                        | 800     |
| L-Arginine                      | 960     |
| L-Histidine                     | 300     |
| L-Alanine                       | 1280    |
| L-Proline                       | 860     |
| Serine                          | 420     |
| Tyrosine                        | 44      |
| Glycine                         | 1280    |
| Osmolality                      | 1000 mOsm/L |
| NaEDTA                          |         |

Water for injection

Results

Effects of Amino Acid Infusion During Normal Sodium Diet

During a normal sodium diet (24-hour UN,V the day before the study averaged 126.3±11.1 mmol), the infusion of amino acids induced a progressive increase in RPF that was significant by the fourth hour (Table 2). These increments in flow from hour 1 to hour 4 averaged approximately 24% above control. Similarly, GFR progressively increased and became significantly elevated above control (22%) by the fourth hour of the amino acid infusion.

Fractional excretion of sodium (FeNa), total UN,V, UV, fractional excretion of potassium (FeK), PRA, and PA remained unchanged (Table 2). During the infusion, neither systolic nor diastolic blood pressure experienced any change of importance. Plasma potassium did not change and averaged from 4.1 to 4.4 mmol/L during the experiment.

Amino Acid Infusion During Low Sodium Diet

The procedures adopted to induce a negative balance of sodium (a single oral dose of 80 mg furosemide followed by 3 days of 40 mmol sodium per day) were effective in reducing the 24-hour UN,V to 27.4±1.8 mmol and the total UN,V to 124±16 µmol/min (Table 3). GFR was significantly decreased by the low sodium diet (from 82±8 to 71±8 mL/min). However, no significant changes were observed in RPF (from 383±58 to 361±45 mL/min). These changes were accompanied by an upward trend in PRA and PA that did not achieve statistical significance. The low sodium diet produced a significant decrease in basal values of diastolic and systolic blood pressures. The remaining parameters were not significantly affected.
During dietary sodium restriction, amino acid infusion failed to alter RPF, GFR, or PRA, which remained fairly stable. In contrast, PA levels decreased to 45% of the control value by the fourth hour of the infusion. Amino acid infusion had no effect on UV, Fe N\textsubscript{a}, or Fe K. Few significant changes were observed in systolic or diastolic blood pressures or in plasma potassium (4.2 to 4.4 mmol/L).

### Changes in Renal Hemodynamics

**Effect of Amino Acid Infusions in Patients on Low Sodium Diet Pretreated With Enalapril**

Patients treated with enalapril for 3 days simultaneously with the low sodium intake exhibited an average 24-hour UN\textsubscript{V} of 34.9±7.6 mmol, which is comparable to that recorded during the low sodium diet without enalapril. However, the administration of enalapril increased control values of GFR (88±9 mL/min, Table 4) 24% above the control value obtained in the same patients during sodium-restricted diets without enalapril (71±8 mL/min, Table 3). However, these values were not significantly higher than those recorded during the control period of a normal sodium intake. Enalapril did not alter basal values of RPF (388±35 versus 361±45 mL/min), UN\textsubscript{V}, UV, Fe N\textsubscript{a}, or Fe K. Similarly, enalapril produced a significant threefold increase in the control values of PRA, whereas control PA was unaltered from 4.4 to 4.1 mmol/L. Enalapril increased control values of systolic blood pressure by 16% (153±4 versus 129±6 mm Hg) without altering the control values of diastolic blood pressure.

During enalapril treatment, the suppressor effects of low sodium diet on amino acid–induced increments in RPF and GFR were reversed. In fact, as shown in Table 4, RPF and GFR were significantly above the control level, reaching values comparable to those seen during amino acid infusion on a normal sodium diet. The mean rise in RPF at 4 hours was 38.4%, well above the 17.0% rise in GFR. This is reflected in a mean 3.5% fall in filtration fraction.

### Discussion

**Changes in Renal Hemodynamics**

This study included nine randomly selected patients with essential hypertension who exhibited a wide dispersion in RPF and GFR values that ranged from subnormal to normal levels. This finding most probably reflects the variable renal damage inflicted by variable periods of hypertensive disease. However, the relatively low basal values of hemodynamic parameters also could have been produced by dietary protein restriction imposed 3 days before the study. We performed this maneuver to standardize the renal response to amino acid infusions. Within these experimental conditions, our study demonstrated that amino acid infusions induced increases in RPF and GFR that were inhibited by sodium restriction. The administration of enalapril during the sodium restriction restored the effects of amino acid infusion on RPF and GFR.

These results, although analogous to those reported in healthy individuals, were not expected. Patients with essential hypertension have different basal renal hemodynamics, and they are under the influence of distinct pressor effects. Thus, we expected to see resistance to the vasodilator effects of amino acids. This was not so and shows that patients with essential hypertension are exposed to protein-induced hyperfiltration. The mechanisms responsible for these effects are difficult to identify because the intimate mode of action underlying the vasodilator effects of amino acids are poorly understood. Early hypotheses on the participation of pituitary growth hormone, as well as liver hormones such as glucagon, were ruled out after amino acids were shown to produce significant increases in renal hemodynamics in patients with panhypopituitarism and in animals in whom the liver was functionally excluded from the general circulation. Similarly, the participation of glucagon was eliminated mainly because the infusion of this hormone failed to increase renal hemodynamics.

More recently, the renal response to amino acid infusion has been regarded as a manifestation of endothelial modulatory function. Benigni et al 17 have shown that hyperfiltration induced by a high protein intake in animals with experimental nephrosis was related to a significant increase in 6-ketoprostaglandin F\textsubscript{1a} and suppressed by indomethacin, suggesting that prostacyclin plays a role in the hyperfiltration response to amino acid infusion. Ruizlope et al 4 reported that in normotensive
patients pretreated with indomethacin, the renal response to amino acid infusion was inhibited.

Endothelium-derived relaxing factor, namely, nitric oxide (NO), which is known to be produced from the nitrogen atom contained in the $N$-guanidino group of L-arginine,18 also has been implicated in the amino acid response. In rats, amino acid-induced increments in RPF or GFR are largely prevented by prior administration of an NO inhibitor, $N^\text{O}$-monomethyl L-arginine.19,20 This observation is in agreement with the study of Premen and Dobkins,22 who have shown that amino acid combinations of L- but not D-isomers elevated RPF and GFR, and with Castellino et al,23 who demonstrated that RPF and GFR were increased by a solution of gluconeogenic amino acids containing L-arginine. NO may have taken part in the renal hemodynamic response to amino acids in our patients during a normal salt diet. The suppressed response after sodium restriction could have been caused by depressed NO activity. This notion is supported by the work of Shultz and Tolins 24 showing that NO activity rises during a high salt intake, thus suggesting a role of NO in renal adaptation to variations in sodium intake. An alternative mechanism proposed by Woods et al25 and DeNicola et al21 is that amino acids induce an afferent arteriolar vasodilatation through a tubular glomerular feedback mechanism. However, our results do not allow a distinction among these possibilities.

The involvement of Ang II in the renal response to amino acid infusion is strongly advocated by the suppressive effect of sodium dietary restriction and the restoring action of enalapril. These results are comparable to those reported by Ruilope et al6 in normotensive patients. Moreover, Smolowitz et al26 observed that captopril enhanced the renal response to amino acids in normotensive diabetics. Although these patients were on a normal sodium diet, the results were attributed to the abnormally elevated Ang II levels in this disease.26 The specific mechanism through which changes in the formation of Ang II could influence the responses to amino acid remains unknown. Some investigators have suggested that Ang II could alter the sensitivity of tubular glomerular feedback responses.27 However, others have considered that the intrarenal changes in the

### Table 3. Effects of Amino Acid Infusion in Hypertensive Patients on a Low Sodium Diet

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>1 Hour</th>
<th>2 Hours</th>
<th>3 Hours</th>
<th>4 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPF (mL/min)/1.73 m²</td>
<td>361±45</td>
<td>372±48</td>
<td>388±42</td>
<td>384±54</td>
<td>411±51</td>
</tr>
<tr>
<td>GFR (mL/min)/1.73 m²</td>
<td>71±8</td>
<td>71±9</td>
<td>73±6</td>
<td>72±8</td>
<td>77±7</td>
</tr>
<tr>
<td>UV, mL/min</td>
<td>4±0.8</td>
<td>3.8±0.7</td>
<td>3.9±0.8</td>
<td>3.1±0.7</td>
<td>3.8±0.6</td>
</tr>
<tr>
<td>$U_{\text{NaV}}, \mu$mol/min</td>
<td>124±16</td>
<td>124±16</td>
<td>140±20</td>
<td>136±17</td>
<td>203±53</td>
</tr>
<tr>
<td>$F_{\text{NaV}}, %$</td>
<td>1.5±0.3</td>
<td>1.4±0.3</td>
<td>1.6±0.3</td>
<td>1.5±0.2</td>
<td>2±0.5</td>
</tr>
<tr>
<td>$F_{\text{K}}, %$</td>
<td>23.6±3.5</td>
<td>21.4±3.3</td>
<td>21.4±3.6</td>
<td>19.1±3.3</td>
<td>18.9±2.8</td>
</tr>
<tr>
<td>PRA, ng Ang I/mL/h</td>
<td>3.2±0.5</td>
<td>3.5±0.7</td>
<td>3.7±0.8</td>
<td>2.8±0.7</td>
<td>3.1±0.7</td>
</tr>
<tr>
<td>PA, ng/dL</td>
<td>37.3±8.7</td>
<td>31.5±8.3</td>
<td>25.5±7.6</td>
<td>21.6±3.8</td>
<td>20.2±5*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>153±4</td>
<td>151±5</td>
<td>151±5</td>
<td>151±5</td>
<td>151±5</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84±4</td>
<td>87±4</td>
<td>87±4</td>
<td>85±4</td>
<td>85±4</td>
</tr>
</tbody>
</table>

RPF indicates renal plasma flow; GFR, glomerular filtration rate; UV, urine volume; $U_{\text{NaV}},$ urinary sodium excretion rate; $F_{\text{NaV}},$ fractional excretion of sodium; $F_{\text{K}},$ fractional excretion of potassium; PRA, plasma renin activity; Ang I, angiotensin I; PA, plasma aldosterone; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

*P<.05 vs control period.

### Table 4. Effects of Amino Acid Infusion in Hypertensive Patients on a Low Sodium Diet and During the Inhibition of Converting Enzyme

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>1 Hour</th>
<th>2 Hours</th>
<th>3 Hours</th>
<th>4 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPF (mL/min)/1.73 m²</td>
<td>368±35</td>
<td>450±38</td>
<td>467±44</td>
<td>518±53</td>
<td>537±48*</td>
</tr>
<tr>
<td>GFR (mL/min)/1.73 m²</td>
<td>88±9</td>
<td>100±11</td>
<td>99±9</td>
<td>103±10</td>
<td>103±10*</td>
</tr>
<tr>
<td>UV, mL/min</td>
<td>3.8±0.8</td>
<td>4.1±0.7</td>
<td>3.8±0.7</td>
<td>4±0.7</td>
<td>3.3±0.4</td>
</tr>
<tr>
<td>$U_{\text{NaV}}, \mu$mol/min</td>
<td>144±24</td>
<td>154±20</td>
<td>148±20</td>
<td>157±29</td>
<td>168±25</td>
</tr>
<tr>
<td>$F_{\text{NaV}}, %$</td>
<td>1.3±0.3</td>
<td>1.2±0.2</td>
<td>1.1±0.2</td>
<td>1.2±0.2</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>$F_{\text{K}}, %$</td>
<td>18.3±2.2</td>
<td>16.2±1.8</td>
<td>15.2±2.5</td>
<td>15.2±2.5</td>
<td>12.3±2.1</td>
</tr>
<tr>
<td>PRA, ng Ang I/mL/h</td>
<td>9.9±3.3</td>
<td>8±3.4</td>
<td>7.5±3.4</td>
<td>6.6±2.9</td>
<td>6.2±3.5</td>
</tr>
<tr>
<td>PA, ng/dL</td>
<td>18.6±2.1</td>
<td>16.6±8.3</td>
<td>15.1±3.6</td>
<td>14.4±2.5</td>
<td>13.6±3.7</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>129±6</td>
<td>126±6</td>
<td>126±6</td>
<td>126±6</td>
<td>126±6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79±5</td>
<td>80±5</td>
<td>79±5</td>
<td>77±5</td>
<td>77±5</td>
</tr>
</tbody>
</table>

RPF indicates renal plasma flow; GFR, glomerular filtration rate; UV, urine volume; $U_{\text{NaV}},$ urinary sodium excretion rate; $F_{\text{NaV}},$ fractional excretion of sodium; $F_{\text{K}},$ fractional excretion of potassium; PRA, plasma renin activity; Ang I, angiotensin I; PA, plasma aldosterone; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

*P<.05 vs control period.
formation of Ang II involve reciprocal alterations in the synthesis of NO in a manner such that the inhibition of Ang II formation or blockade of Ang II receptors favors the expression of the effects of NO stimulation. Recently, DeNicola et al.1 showed that pretreatment with the Ang II receptor antagonist DuP 753 restores the glomerular and tubular response to glycerine during NO inhibition, suggesting that NO is a physiological antagonist of Ang II. These findings support our results after angiotensin converting enzyme inhibition. It could therefore be assumed that much of the renal effect produced by the amino acid–mediated stimulation of NO was curtailed by the presence of Ang II.

The amino acid infusion during angiotensin converting enzyme inhibition caused a percent rise in RPF twice as large as that of GFR. Thus, filtration fraction decreased substantially (3.5%). This predominant effect on RPF could only indicate a significant reduction in efferent arteriolar resistance. In other words, blood flow through an amino acid–dilated afferent arteriole encounters little resistance through the also dilated efferent arteriole. Other reported effects of angiotensin converting enzyme inhibition on renal hemodynamics, such as increased RPF or afferent vasodilation, could not explain the drop in filtration fraction during amino acid infusion.

It should be mentioned that the average increments in GFR and RPF during amino acid infusion with a normal sodium diet are within the range reported by other investigators in a normotensive population.2,5,8,10

Changes in Excretory Function, Plasma Renin Activity, and Plasma Aldosterone

As reported by others,32 the amino acid infusions induced a downward trend in PRA during a normal sodium diet as well as during dietary sodium restriction with the concomitant administration of a converting enzyme inhibitor that could be attributed to a stimulation of endothelium-derived relaxing factor.33,35 However, this issue deserves further investigation.

Similarly, the administration of amino acids produces a consistent fall in PA values during a low sodium diet that appears to be independent of fluctuations in PRA. These decrements in PA also occurred in the absence of any significant changes in plasma potassium concentration. The mechanism by which amino acids influence aldosterone secretion is uncertain.

The observations of this study have important clinical implications because they indicate that (1) in untreated essential hypertensive patients, an increase in circulating amino acids is capable of exposing the glomeruli to the same degree of hyperfiltration as that shown by other investigators to accelerate glomerular damage; (2) such a deleterious effect of amino acids on glomerular function is likely to be ameliorated by negative sodium balance, a condition routinely obtained by sodium dietary restriction and/or the administration of diuretics in patients with essential hypertension; and (3) the protective effects of sodium restriction on glomerular hyperfiltration rate appear to be reversed by the administration of enalapril. However, because of the observed fall in filtration fraction, the clinical significance of these acute effects of amino acids should be carefully evaluated to understand the more prolonged beneficial effects that have been reported during long-term treatment with converting enzyme inhibitor.31

Acknowledgments

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