Impaired Renal Adaptation to Stress in the Elderly With Isolated Systolic Hypertension

Sergio Castellani, Andrea Ungar, Claudia Cantini, Giuseppe La Cava, Claudia Di Serio, Barbara Vallotti, Anna Altobelli, Giulio Masotti

Abstract—The aim of this study was to evaluate the renal response in the elderly with isolated systolic hypertension (ISH) when an adrenergic activation, as induced by mental stress, is applied. Renal hemodynamics and kidney neurohumoral response to mental stress were studied in 8 elderly patients with ISH (aged 63 to 82 years) along with 8 elderly normotensive subjects. The study encompassed four 30-minute experimental periods (baseline, mental stress, and recovery I and II). In these patients, the mental stress–induced blood pressure rise was associated with a significant increase in both effective renal plasma flow (I31I-labeled hippurate clearance) and glomerular filtration rate (125I-labeled iothalamate clearance) (+42% and +29%, respectively; P<0.01 for both), without variations in filtration fraction, while elderly normotensives reacted to adrenergic stimulation with renal vasoconstriction but with the glomerular filtration rate constant. Variations in renal vasoactive substances, which paralleled hemodynamics of the kidney, differed in the 2 groups. In normotensives, excretion (radioimmunoassay) of endothelin-1, prostaglandin E2, and cGMP increased during the stimulus (+50%, +54%, and +59%, respectively; P<0.05). In ISH patients the release of these autacoids did not vary in any of the experimental periods. In conclusion, in patients with ISH the renal adaptive capacity to sympathetic activation is impaired, and the data may suggest that the glomerulus passively suffers the blood pressure increase, probably because of the insufficiency of the neurohumoral response, particularly in regard to the increase of endothelin-1. This hemodynamic pattern may predispose ISH patients to a higher risk of renal injury. (Hypertension. 1999;34:1106-1111.)

Key Words: elderly hypertension, isolated systolic renal circulation endothelin prostaglandins

Isolated systolic hypertension (ISH) is the most common form of high blood pressure in the elderly.1,2 Patients with ISH exhibit a higher risk of cardiovascular events than the general population.3–5 Along with these effects, patients affected by ISH more often exhibit abnormal renal function.6 In addition, systolic blood pressure is directly correlated with the incidence of chronic renal failure and end-stage renal disease,7,8 and ISH is present in 12.5% of patients affected by end-stage renal disease.9 It has been hypothesized that hypertensive nephrosclerosis may result from glomerular ischemia as a consequence of small-vessel damage.10 Alternatively, glomerulosclerosis may be the consequence of glomerular hyperfiltration, as in experimental models of hypertension in rats.11 However, no experimental evidence is presently available regarding the mechanisms causing renal damage in humans affected by ISH. It is already known that elderly normotensives react to adrenergic stimulation and to the associated transient blood pressure increase with renal vasoconstriction that is more pronounced and prolonged than in the young. In this condition, glomerular filtration rate (GFR) is maintained but at the expense of glomerular hyperfiltration.12 Therefore, it can be hypothesized that in the elderly patient with ISH, the permanently elevated high blood pressure values may further reduce the renal adaptation capacity already modified by age. To test this hypothesis, in patients with ISH, renal hemodynamic response was studied under a sympathetic stimulation such as that induced by a reproducible mental stress. The renal hemodynamic response to stress was explored together with systemic hormonal activation (catecholamines and plasma renin activity) and renal vasoactive substances such as prostaglandins and endothelin.

Methods

Subjects

Experiments were performed on 8 elderly women affected by ISH aged 63 to 82 years (mean±SD age, 73±6 years), who had given their informed consent to participate in the study. The results were compared with the data observed in 8 healthy elderly female normotensive subjects aged 68 to 82 years (mean±SD age, 75±5 years), contemporaneously studied by the same experimental protocol and described elsewhere.12 We chose only women because
blood pressure was by the method described by Lyem et al. 17 Subjects with cognitive impairment and depressive symptoms, as assessed by the Mini–Mental State Examination18 and the Geriatric Depression Scale, 19 were excluded from the study. If patients were under treatment, treatment was discontinued for 2 weeks before the start of the study.

If patients had been taken for at least 15 days before the beginning of the study. No aspirin or any other cyclooxygenase-inhibiting drug was allowed. The patient was admitted to the study if at both screening and baseline, the difference in the curves between the 2 groups during the experimental period was tested by 2-way MANOVA with multiple comparisons. Significance level was set at 0.05.

### Preliminary Experiments

A preliminary 2-hour experiment in 5 young healthy subjects and 5 elderly subjects was performed to verify the stability and the reproducibility of the measurement of effective renal plasma flow (ERPF), GFR, blood pressure, and heart rate. In this preliminary study, all conditions were the same as in the experimental study except that mental stress was not applied. In this study, blood pressure, heart rate, ERPF, and GFR were all steady.

In the elderly with ISH, as well as in the elderly normotensive subjects, mental stress induced an increase of blood pressure and heart rate that was detected only during the administration of the stimulus, without significant difference between the 2 groups (MANOVA). Figure 1 describes the course of the blood pressure. Patients with ISH showed a peak increase of 31 mm Hg in systolic blood pressure, whereas elderly

### Statistical Analysis

All results are presented as mean±SD. Student’s t test for independent samples was used to compare the mean baseline values of the 2 groups. The effects induced by mental stress on each variable were evaluated according to a 2-step statistical analysis: first, an ANOVA for repeated measures was used to evaluate the variations among time periods; second, a post hoc test (least significant difference) was used to detect the differences of values at different times versus baseline. The difference in the curves between the 2 groups during the experimental period was tested by 2-way MANOVA with multiple comparisons. Significance level was set at 0.05.

### Results

#### Baseline Determinations

The hemodynamic and hormonal profiles under baseline conditions are presented in Table 1. In the elderly subjects with ISH, systolic blood pressure was greater than in elderly normotensives (P<0.001), whereas diastolic blood pressure and heart rate were similar. Elderly subjects with ISH did not differ from normotensives in renal hemodynamics and urinary autacoids, except PGE2 excretion, which was significantly less than in elderly normotensives (P<0.01). Baseline values of plasma catecholamines were significantly lower in the elderly affected by ISH than in elderly normotensives (P<0.05 for both).

### Effects of Mental Stress

In the elderly with ISH, as well as in the elderly normotensive subjects, mental stress induced an increase of blood pressure and heart rate that was detected only during the administration of the stimulus, without significant difference between the 2 groups (MANOVA). Figure 1 describes the course of the blood pressure. Patients with ISH showed a peak increase of 31 mm Hg in systolic blood pressure, whereas elderly

### Table 1. Baseline Hemodynamic and Humoral Characteristics of Elderly Patients With ISH and Elderly Normotensives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Elderly With ISH (n=8)</th>
<th>Elderly Normotensives (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>173.6±19.8</td>
<td>134.0±10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.8±4.4</td>
<td>79.5±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>62.5±6.9</td>
<td>63.5±3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>262.6±70.5</td>
<td>377.5±106.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>56.8±25.7</td>
<td>97.0±11.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PRA, ng/mL/hr</td>
<td>0.4±0.3</td>
<td>1.12±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>ERPF, mL/min/1.73 m²</td>
<td>304.3±72.5</td>
<td>367.9±109.4</td>
<td>NS</td>
</tr>
<tr>
<td>GFR, mL/min/1.73 m²</td>
<td>85.6±15.0</td>
<td>94.0±18.8</td>
<td>NS</td>
</tr>
<tr>
<td>FF, %</td>
<td>28.5±3.4</td>
<td>27.0±5.0</td>
<td>NS</td>
</tr>
<tr>
<td>RVR, dyne·s·cm⁻²/1.73 m²</td>
<td>17 000±5000</td>
<td>13 000±7600</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary ET-1, fmol/ERPF</td>
<td>0.20±0.12</td>
<td>0.17±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary cGMP, pmol/ERPF</td>
<td>29.8±17.8</td>
<td>26.4±10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary PGE2, pg/ERPF</td>
<td>19.4±16.3</td>
<td>46.8±15.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urinary 6-keto-PGF1α, pg/ERPF</td>
<td>41.0±30.1</td>
<td>27.3±9.2</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary PGF2α, pg/ERPF</td>
<td>82.4±70.7</td>
<td>31.0±9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary TXB2, pg/ERPF</td>
<td>25.4±19.4</td>
<td>17.3±15.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. DBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PRA, plasma renin activity; FF, filtration fraction; RVR, renal vascular resistance; and ET-1, endothelin-1.
normotensives exhibited a peak increase of 29 mm Hg (+14% and +17%, respectively; \(P<0.0001\) versus baseline for each group). Heart rate rose significantly in both groups during mental stress, with a 15.5% increase at peak in patients with ISH (72.7±9.9 versus 62.5±6.9 bpm versus baseline; \(P<0.0001\)) and a 12.4% increase in elderly normotensives (71.4±6.0 versus 63.5±3.3 bpm versus baseline; \(P<0.05\)).

In patients with ISH, as in elderly normotensives, norepinephrine and epinephrine increased only during mental stress (Table 2). Plasma renin activity remained unchanged during the whole experimental period in the ISH group, whereas plasma renin activity decreased during the recovery periods in elderly normotensives (Table 2).

Patients with ISH exhibited mental stress–induced changes in renal hemodynamics that were opposite those in elderly normotensives. In the ISH group, mental stress induced an increase in both ERPF and GFR during the administration of the stimulus (+42% and +29%, respectively; \(P<0.01\) for both) and during the first recovery period (+30% and +21%, respectively, versus baseline; \(P<0.05\) for both) (Figure 2).

### TABLE 2. Effects of Mental Stress on Plasma Catecholamines and Plasma Renin Activity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (30 min)</th>
<th>Mental Stress (30 min)</th>
<th>Recovery I (30 min)</th>
<th>Recovery II (30 min)</th>
<th>ANOVA for the Whole Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>(262.6±70.5)</td>
<td>(315.5±121.1)</td>
<td>(260.5±118.0)</td>
<td>(230.5±77.8)</td>
<td>(6.4)</td>
</tr>
<tr>
<td>ISH</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>(377.5±106.0)</td>
<td>(429.6±87.3)</td>
<td>(360.8±88.7)</td>
<td>(328.3±92.9)</td>
<td>(8.4)</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>(56.8±35.7)</td>
<td>(88.6±53.5)</td>
<td>(70.3±57.9)</td>
<td>(46.1±36.5)</td>
<td>(8.3)</td>
</tr>
<tr>
<td>ISH</td>
<td></td>
<td>\†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>(97.0±11.9)</td>
<td>(152.0±37.8)</td>
<td>(102.8±23.6)</td>
<td>(91.8±16.9)</td>
<td>(10.1)</td>
</tr>
<tr>
<td>PRA, ng/mL/hr</td>
<td>(0.4±0.33)</td>
<td>(0.4±0.31)</td>
<td>(0.4±0.19)</td>
<td>(0.2±0.15)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>ISH</td>
<td>(1.2±0.50)</td>
<td>(0.9±0.35)</td>
<td>(0.7±0.29)</td>
<td>(0.8±0.23)</td>
<td>(3.8)</td>
</tr>
<tr>
<td>NT</td>
<td></td>
<td>\†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD; \(n=8\) in both ISH and normotensive (NT) groups. PRA indicates plasma renin activity. 
*\(P<0.05\), †\(P<0.01\), ‡\(P<0.001\) vs baseline.
without any change in filtration fraction. Hence, renal resistance
dropped until the end of the experiment (−24%, P < 0.001
during mental stress; −22%, P < 0.05 during recovery period I;
−16%, P < 0.05 during recovery period II versus baseline).
Conversely, in elderly normotensives, mental stress caused a
prolonged vasoconstriction: ERPF dropped during mental stress
(−20%; P < 0.05) and reached its minimum value during the
second recovery period (−33%; P < 0.01 versus baseline). In
normotensives, GFR remained constant throughout the whole
experiment (Figure 2).

Throughout the whole experiment, in patients with ISH no
significant variations were found in either urinary
endothelin-1 or urinary eicosanoid excretion (Figure 3),
except for TXB2. Urinary TXB2 excretion significantly
dropped in ISH patients (Table 3). This behavior was sharply
different from the variations observed in elderly normotensives,
in whom urinary endothelin-1 increased during mental stress
and recovery period I (+50% and +25%, respectively,
versus baseline; P < 0.05 for both) and urinary PGE2, urinary
6-keto-PGF1α, and PGE2α increased during mental stress
(+54%, +49%, and +53%, respectively; P < 0.05 for each
parameter), while TXB2 remained unchanged (Figure 3 and
Table 3).

In ISH patients, UcGMP did not vary throughout the whole
experiment; on the contrary, in elderly normotensives it rose
significantly during mental stress (41.9 ± 23.4 versus
26.4 ± 10.0 pmol/ERPF during baseline; P < 0.05) and subse-
quently dropped to prestress values by the first recovery
period (Figure 3).

**Discussion**

The present investigation provides experimental evidence
that in patients affected by ISH, the renal adaptation capacity
to adrenergic stimulation is impaired. This hemodynamic
pattern may represent a mechanism of renal injury.

Under baseline conditions, renal hemodynamics of ISH
patients do not differ from those of elderly normotensives. Glomerular
hyperfiltration is present in both groups, as
demonstrated by the high values of filtration fraction com-
pared with values previously reported in young subjects. Most
probably, this hemodynamic and neurohumoral pattern constitutes an
adaptive mechanism to the reduced oxygen supply of those nephrons that undergo...
TABLE 3. Effects of Mental Stress on Urinary Eicosanoids

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (30 min)</th>
<th>Mental Stress (30 min)</th>
<th>Recovery I (30 min)</th>
<th>Recovery II (30 min)</th>
<th>ANOVA for the Whole Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary 6-Keto-PGF1α, pg/ERPF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>41.1±30.1</td>
<td>39.5±13.7</td>
<td>25.6±14.0</td>
<td>48.5±42.9</td>
<td>0.8 NS</td>
</tr>
<tr>
<td>NT</td>
<td>27.3±9.2</td>
<td>40.7±9.6</td>
<td>30.3±9.5</td>
<td>21.0±9.0</td>
<td>4.0 &lt;0.05</td>
</tr>
<tr>
<td>Urinary PGF2α, pg/ERPF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>82.3±70.7</td>
<td>46.7±27.2</td>
<td>87.8±90.3</td>
<td>62.2±33.5</td>
<td>0.9 NS</td>
</tr>
<tr>
<td>NT</td>
<td>31.0±9.0</td>
<td>47.0±13.1</td>
<td>28.4±11.0</td>
<td>34.5±8.7</td>
<td>1.3 NS</td>
</tr>
<tr>
<td>Urinary TXB2, pg/ERPF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>25.4±19.4</td>
<td>10.6±6.9</td>
<td>13.9±5.2</td>
<td>19.0±8.1</td>
<td>3.9 &lt;0.02</td>
</tr>
<tr>
<td>NT</td>
<td>17.3±15.7</td>
<td>23.5±19.6</td>
<td>16.0±10.2</td>
<td>18.7±10.4</td>
<td>0.8 NS</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=8 for both ISH and normotensive (NT) groups.
*P<0.05, †P<0.01 vs baseline.

In conclusion, this inertia of renal vascular bed probably accounts for the fact that patients with ISH are more prone to develop end-stage renal disease.7–9 The glomerulus, which already exhibits hyperfiltration under basal conditions, is repeatedly exposed to the injury brought about by any further elevations of systemic arterial blood pressure occurring in everyday life, because the pressure increase is not outbalanced by renal adaptation capacity. This is particularly relevant in the elderly, in whom systolic blood pressure variability is greater than in adult patients.31 This hemodynamic pattern may lead to glomerulosclerosis over a period of time.21 The data of our study strongly support the view that

progressive nephrosclerotic changes. This condition stimulates endothelin-1 and PGE2 production,22,23 with resulting overperfusion of the remnant units that exhibit hyperfiltration.

Notwithstanding the similarities in baseline renal hemodynamics, we detected major differences between normotensive and hypertensive subjects in their response to mental stress. In both groups the stimulus caused similar increases in circulating catecholamines, heart rate, and blood pressure, and the mean blood pressure changes were always within the range of renal autoregulation.24 Conversely, with a similar systemic response to stress, renal response in patients with ISH was markedly altered in respect to the response observed in physiological senescence, since the kidney responds to mental stress with vasodilatation, as evidenced by the increase in ERPF. The variations in GFR paralleled the modifications in ERPF, leaving the filtration fraction virtually unchanged. Such response was in sharp contrast to the vasoconstrictive reaction induced by adrenergic stimulation, leaving the filtration fraction virtually unchanged. This reflects the impaired responsiveness of renal vascular endothelium to sympathetic activation. In particular, the association of a defect in endothelin reactivity to sympathetic stimulation with a lack of renal adaptation may support a role of the peptide in the renal vasoconstriction and thus in the mechanisms that protect the kidney against systemic blood pressure increase. The decrease in urinary TXB2 observed in ISH patients could contribute to renal vasodilatation even if its role, according to the literature, is probably not very relevant. In fact, several studies have failed to provide any evidence that renal TXB2 has a role in renal hemodynamic response, and in particular its selective inhibition has not led to an increase in GFR or ERPF in either humans or animals.27,28 The role of renal angiotensin in the impaired renal response to stress cannot be ruled out by our data; nevertheless, Schmieder et al29 found no difference in renal response to mental stress after angiotensin-converting enzyme inhibitor administration. An alternative explanation of renal vasodilatation during stress could be a defect in catecholamine release or a lack in renal response to norepinephrine. In animal experiments, however, it has been recently demonstrated that ganglionic blockade has a very negligible effect on renal hemodynamics under physiological conditions.30

In conclusion, this inertia of renal vascular bed probably accounts for the fact that patients with ISH are more prone to develop end-stage renal disease.7–9 The glomerulus, which already exhibits hyperfiltration under basal conditions, is repeatedly exposed to the injury brought about by any further elevations of systemic arterial blood pressure occurring in everyday life, because the pressure increase is not outbalanced by renal adaptation capacity. This is particularly relevant in the elderly, in whom systolic blood pressure variability is greater than in adult patients.31 This hemodynamic pattern may lead to glomerulosclerosis over a period of time.21 The data of our study strongly support the view that
ISH should be treated like other forms of hypertension not only to prevent cardiovascular mortality but also to prevent renal damage and/or end-organ failure. Further studies will be necessary to identify the antihypertensive drugs with the highest renal protective power.

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References
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