Renal Damage in Primary Aldosteronism
Results of the PAPY Study

Gian Paolo Rossi, Giampaolo Bernini, Giovambattista Desideri, Bruno Fabris, Claudio Ferri, Gilberta Giacchetti, Claudio Letizia, Mauro Maccario, Massimo Mannelli, Mee-Jung Matterello, Domenico Montemurro, Gaetana Palumbo, Damiano Rizzoni, Ermanno Rossi, Achille Cesare Pessina, Franco Mantero; for the PAPY Study Participants

Abstract—Primary aldosteronism (PA) has been associated with cardiovascular hypertrophy and fibrosis, in part independent of the blood pressure level, but deleterious effects on the kidneys are less clear. Likewise, it remains unknown if the kidney can be diversely involved in PA caused by aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA). Hence, in the Primary Aldosteronism Prevalence in Italy (PAPY) Study, a prospective survey of newly diagnosed consecutive patients referred to hypertension centers nationwide, we sought signs of renal damage in patients with PA and in comparable patients with primary hypertension (PH). Patients (n=1180) underwent a predefined screening protocol followed by tests for confirming PA and identifying the underlying adrenocortical pathology. Renal damage was assessed by 24-hour urine albumin excretion (UAE) rate and glomerular filtration rate (GFR). UAE rate was measured in 490 patients; all had a normal GFR. Of them, 31 (6.4%) had APA, 33 (6.7%) had IHA, and the rest (86.9%) had PH. UAE rate was predicted (P<0.001) by body mass index, age, urinary Na⁺, and mean blood pressure. Covariate-adjusted UAE rate was significantly higher in APA and IHA than in PH patients; there were more patients with microalbuminuria in the APA and IHA than in the PH group (P=0.007). Among the hypertensive patients with a preserved GFR, those with APA or IHA have a higher UAE rate than comparable PH patients. Thus, hypertension because of excess autonomous aldosterone secretion features an early and more prominent renal damage than PH. (Hypertension. 2006;48:232-238.)

Key Words: hypertension, endocrine • aldosterone • mineralocorticoids • kidney • hypertrophy • adrenal gland

The results of large intervention trials and cross-sectional studies (reviewed by Rossi et al) have recently refueled the interest on the deleterious cardiovascular effects of excess aldosterone. Moreover, growing evidence indicates that primary aldosteronism (PA) is a common cause of secondary hypertension: in the Primary Aldosteronism Prevalence in Italy (PAPY) study, a prospective survey of 1180 consecutive newly diagnosed hypertensive patients referred to specialized hypertension centers, aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA) were found in 4.8% and 6.4% of all patients, respectively, thus leading to an overall prevalence of PA of ~11%. It has been contended that this form of secondary hypertension is relatively “benign,” that is, devoid of cardiovascular complications, because of the suppression of the renin–angiotensin system, which plays a substantial role in cardiovascular remodeling and damage.

This view has, however, been challenged by recent data. PA has in fact been associated with widespread tissue fibrosis, vascular remodeling, and excess prevalence of left ventricular hypertrophy and diastolic dysfunction that were corrected by adrenalectomy. A higher incidence of cardiovascular complications, including atrial fibrillation, has also been described. This might be attributed to the aldosterone- and hypertension-driven excess left ventricular hypertrophy, fibrosis, and hypokalemia, which all contribute to prolong the atrioventricular conduction time and thereby facilitate reentry mechanisms. Excess aldosterone has also been causally related to endothelial dysfunction, because the latter was corrected by blockade of the mineralocorticoid receptor.

By contrast with the wealth of data on the adverse cardiovascular consequences of PA, information on renal damage is confined to a small series of APA patients. Hence, it remains unsettled whether the patients with IHA, who usually exhibit less marked aldosterone excess than those with APA, also feature an early renal damage.

A body of evidence indicates that microalbuminuria is a marker of early renal involvement. Moreover, there is general consensus that evaluation of urine albumin excretion (UAE) rate is not only useful for the assessment of overall cardiovascular risk (reviewed by Palatini) but also represents a cost-effective way to identify patients at higher risk of hypertension.
cardiovascular complication and progression to renal fail-
ure. 20, 21 Thus, we aimed at prospectively testing the hypoth-
thesis that PA implies a more prominent renal damage, as
compared with primary (essential) hypertension (PH), by
measuring UAE rate in patients with a normal glomerular
filtration rate (GFR).

Methods
The protocol of the PAPY Study was approved by the Ethical
Committee of the University of Padua and has been described in
details elsewhere; therefore, it will be only briefly recalled. Con-
secutive patients with a new diagnosis of PH, who had been referred
to specialized centers for the diagnosis and treatment of PH nation-
wide in Italy, were enrolled to minimize the chances for any
selection bias. A previous diagnosis of a secondary form of PH, the
patient’s refusal to participate in the study, and associated diseases (eg,
diabetes) and hypertension complicated by congestive heart failure or
renal insufficiency represented the exclusion criteria for this study.
Serum creatinine had to be <115 μmol/L (1.3 mg/dL), and
estimated creatinine clearance (abbreviated Modification of Diet in
Renal Disease Study Group [MDRD] equation) had to be >61
mL/min/1.73 m², which corresponds with the 95th percentile of
the values observed in the entire PAPY Study population. An inform-
ated consent was obtained from each participant.

After the diagnosis of hypertension was confirmed by current
guidelines, 20 mineralocorticoid receptor antagonists (for ≥6 weeks),
diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and
angiotensin II type 1 receptor antagonists (for ≥2 weeks) were
withdrawn. A long-acting calcium entry blocker and/or doxazosin
were allowed if necessary for minimizing the risks of uncontrolled
hypertension. On the day of the screening test, after an overnight
fasting and 1 hour quiet rest in the sitting position, serum and urine
Na⁺ and K⁺ concentration, plasma renin activity (PRA), aldosterone,
and cortisol were measured between 7:00 AM and 9:00 AM, baseline
and again 60 minutes after the oral administration of 50 mg of
captopril. The blood pressure (BP) levels were measured at baseline
and after captopril with a mercury sphygmomanometer using phase V
for diastolic. The aldosterone (in ng/mL/1

1
) PRA (in ng/mL/1

1h
) ratio (ARR), baseline and after captopril, and a score of PA based on
a validated multivariate logistic discriminant function (LDF) score, 22
were then calculated. This score estimates the individual probability
of APA in each patient. Patients with an ARR ≥40 baseline or ≥30
after captopril and/or an LDF score ≥0.50 underwent a saline
infusion test (2 L of 0.9% NaCl solution in 4 hours), and, if
necessary, an imaging test that was composed of a high-resolution
computed tomography with 3-mm slices and/or magnetic resonance
followed by adrenal vein sampling 23 or dexamethasone-suppressed
adrenocortical scintigraphy.

Biochemical Measurements
PRA was measured by radioimmunoassay using commercial kits
(Ren CTK; Sorin Biomedica) in 10 centers or Angiotensina 1 RIA
(Radim) in the rest. Normal range sitting at rest and on a normal Na⁺
diet was 0.2 to 2.8 ng/mL/1

1h
; intra-assay and interassay coefficients of variation (CVs) were within 8% and 10% for both
kits. The assay for aldosterone was performed with the same
diagnostic kit (Aldosterone Mira, Technogenetics) in all 15 centers.
Normal range was 10 to 150 pg/mL ≤1 supine, 30 to 320 pg/mL/1

1h
 upright on a normal Na⁺ diet; intra-assay and interassay CVs assay
were both <5.6%; the cross-reactivity of the antibody for aldoste-
rone for the other adrenal steroids was <0.001%. Cortisol was
measured with a commercial kit (Cortisol bridge, Adaltis); the
intra-assay and interassay CVs of this assay were <6% and 10%,
respectively. The cross-reactivity of the antibody for the other
adrenal steroids was 18% for 11-desoxycortisol, 7.5% for cortico-
sterone, 7.5% for 21-desoxycortic; 7.3% for desoxyxycorticosterone,
6% for 17α-progesterone, and <0.1% for aldosterone and other
known steroids.

GFR and UAE Rate
GFR was measured by using the so called “abbreviated equation,”
which takes into consideration serum creatinine, age, gender, and race
(is available at www.kdoqi.org) for easy computation: estimated GFR
(mL/min/1.73 m²) = 186 × (serum creatinine)

1.15×(age)

0.20×(0.742 if female) × (0.742 if female) × (0.742 if female). 24

On the day of the screening test, patients came to the ward with
24-hour urine collections for the determination of creatinine (to
assess the adequateness of urine collection), sodium (to estimate
sodium intake), and potassium. Urinary albumin and creatinine
excretion was measured with commercially available radioimmuno-
assay (H ALB kit-double antibody; Sclavo SpA) or immunoturbi-
dimetry assay kit (Sera-Pak, Bayer). The mean intra-assay and
interassay CVs are within 4.5% and 11.0%, respectively. 26 Urinary
creatinine was measured by Jaffe’s reaction (CV ∼7.2%).

UAE rate was analyzed as milligrams/24 hours ×1 and also after
normalization for milligrams of urinary creatinine. The normal range
of UAE rate was 30 to 300 mg/g ×1 of creatinine (or 30 to 300
mg/24 hours). 24 According to the timed 24-hour UAE rate, samples
were divided into 3 groups: normoalbuminuric (UAE <28.8 mg/24
hours), microalbuminuric (UAE 28.8 to 288 mg/24 hours), and macroalbuminuric (UAE ≥288 mg/24 hours), eg, >200 μg/1). 

Conclusive Diagnosis
On completion of the diagnostic workup, the presence or absence of
PA and its underlying cause were conclusively diagnosed by an
adjudication committee (G.P.R. and F.M.). In patients with an ARR
>40 and/or an LDF score >0.80, APA was initially diagnosed based on
imaging tests, evidence of lateralized aldosterone secretion at
adrenal vein sampling, or adrenocortical dexamethasone-suppressed
scintigraphy. The diagnosis had to be thereafter retrospectively
confirmed at surgery, pathology, and overall by the observation of
cure or improvement of hypertension at follow-up after adrenalect-
omy. To this end, the American Heart Association guidelines 27 were
used: cure was defined as a systolic BP <140 mm Hg and diastolic
BP <90 mm Hg without medications; and improvement was a
systolic and diastolic BP <140/90 mm Hg, respectively, on the same
and/or reduced number of defined daily doses of medications, as
described by the World Health Organization. 28

Statistical Analysis
GFR values were proportioned to 1.73 m² of body surface area.
Quantitative variables were tested beforehand for normal distribution
by graphical plot and Shapiro-Welch test; appropriate transforma-
tions were undertaken for skewed variables until a normal distribu-
tion was attained. PRA, plasma aldosterone, cortisol, and serum
creatinine values required natural logarithm transformation to attain
a gaussian distribution before use for statistical analysis. UAE rate
values required square-root transformation to achieve a normal
distribution. Univariate and multivariate outliers were identified with
the procedure described by Tabachnick 29 and excluded from the
analysis. Univariate outliers were identified as those with z scores
>3.29 that corresponded with P < 0.001. Mahalanobis distances were
assessed by regression analysis to identify multivariate outliers;
cases with χ² > 4.5 (at α = 0.001) were considered outliers. Data are
presented as mean and SEM. One-way ANOVA followed by
Bonferroni’s test was then used to compare normally distributed
quantitative variables between groups. The frequency of categorical
variables was investigated by χ² analysis. Multiple linear regression
analysis (backward, Wald criterion) was used to identify the deter-
novants of GFR and UAE rate with inclusion and exclusion cutoffs
of 0.05 and 0.10, respectively. GFR and UAE rate were then
analyzed after adjustment for the effect of their significant determi-
nants. Significance was set at P < 0.05; SPSS 13.0 for Windows
(SPPS Italy Inc) was used for these analyses.

Results
Anthropometric Characteristics
On locking the database on September 30, 2005, of the 1180
patients that had been enrolled, 490 satisfied the inclusion/
exclusion criteria for this study and had complete UAE rate and GFR data. Their baseline clinical features, shown in Table 1, did not differ from those of the whole PAPY study.

**Conclusive Diagnosis**

At the end of the thorough diagnostic workup, a conclusive diagnosis was attained in all 490 of the patients. Of them, 64 patients were held to have PA, thus leading to a PA prevalence of 13.1%, with no differences between genders. Of these patients, 33 had IHA, and 31 had APA. On average, the APA patients had lower serum K⁺ than those with IHA, although they did not differ for PRA and plasma aldosterone (Table 1). As anticipated by definition, the APA and IHA patients had lower PRA and serum K⁺ and higher aldosterone than PH patients. They were also older and had higher systolic BP than PH patients, whereas they were similar for the remaining variables, including known duration of hypertension. At the time of the renal function tests, 40% of the patients were untreated, 41% were on a calcium entry blocker or doxazosin, and 19% were on both agents. With the exception of BP values, there were no significant differences of any variables, including UAE rate and hormone values, across treatment groups in either the PA or the PH patients, thus excluding a systematic effect of these treatments on the outcome variables.³⁰,³¹ Likewise, there were no differences in UAE rate, PRA, aldosterone, and cortisol across centers, thus making unlikely a center effect on results of these measurements.

**Predictors of GFR and UAE Rate**

With stepwise regression analyses, we found that plasma aldosterone and body mass index (BMI) significantly predicted GFR, other than age. These 3 variables explained 16% of GFR variance (adjusted $R^2=0.161$; $P<0.001$). Likewise, we could identify that BMI, age, urinary Na⁺ excretion, serum K⁺, and mean BP were significant predictors of UAE rate (Table 2). By contrast, no significant effects of GFR, PRA, aldosterone, and cortisol on UAE rate could be identified. Overall, the 5 variables that remained in the model accounted for only 5.2% of UAE rate (adjusted $R^2=0.052$; $P<0.0001$). Hence, both GFR and UAE rate were adjusted for the effects of its significant predictors for the comparisons between PA and PH patients.

**UAE Rate and Macroalbuminuria and Microalbuminuria by Conclusive Diagnosis**

UAE rate was significantly ($P<0.001$) higher in the patients with PA ($28.1\pm4.3$ μg/mL) than with PH ($18.8\pm1.2$). The results of the comparison of PH patients with PA patients divided into APA and IHA are shown in Figure 1 and Table 3. Although we found no patients with microalbuminuria in this cohort of hypertensive subjects with normal GFR, overall there were more patients with microalbuminuria and less patients with normoalbuminuria in the PA rather than in the PH group ($\chi^2=9.92$; $P=0.002$). The percentage of patients with microalbuminuria by conclusive diagnosis is shown in Figure 2.

**UAE Rate by Serum K⁺**

About half of the patients with APA and 83% of those with IHA had normal serum K⁺ at the time of the screening test. We could, therefore, test the hypothesis that hypokalemia was

**Table 1. Anthropometric and Biochemical Characteristics of the Patients With PH and PA Caused by an APA and IHA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PH (n=426)</th>
<th>APA (n=31)</th>
<th>IHA (n=33)</th>
<th>IHA vs PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45±12</td>
<td>51.5±12</td>
<td>49±12</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg×m⁻²</td>
<td>26.8±4.8</td>
<td>28.3±4.8</td>
<td>27.0±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>147±18</td>
<td>158±19</td>
<td>155±16</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>95±11</td>
<td>96±9.7</td>
<td>100±10</td>
<td>P&lt;0.016</td>
</tr>
<tr>
<td>Serum K⁺, mEq×L⁻¹</td>
<td>4.1±0.4</td>
<td>3.5±0.5</td>
<td>3.8±0.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Na⁺×V, mEq×day⁻¹</td>
<td>154±4.5</td>
<td>132±12</td>
<td>137±8</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine, μmol×L⁻¹</td>
<td>79±18</td>
<td>83±17</td>
<td>83±18</td>
<td>NS</td>
</tr>
<tr>
<td>PRA, ng×mL⁻¹×h⁻¹</td>
<td>1.62±0.13</td>
<td>0.65±0.19</td>
<td>0.5±0.13</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Plasma aldosterone, pmol×L⁻¹</td>
<td>148±5</td>
<td>332±41</td>
<td>303±31</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>ARR, (ng×mL⁻¹)×(mg×mL⁻¹×h⁻¹)⁻¹</td>
<td>24±3</td>
<td>103±25</td>
<td>72±10</td>
<td>P&lt;0.002</td>
</tr>
<tr>
<td>Plasma cortisol, nmol×L⁻¹</td>
<td>140±3</td>
<td>126±6</td>
<td>137±8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Na⁺×V indicates sodium urinary excretion; NS, not significant.

**Table 2. Results of a Stepwise Regression Analysis (Backward Method) to Identify Predictors of UAE**

<table>
<thead>
<tr>
<th>Variables in the model</th>
<th>β (95% CI)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.115</td>
<td>2.56</td>
<td>0.011</td>
</tr>
<tr>
<td>Age</td>
<td>0.101</td>
<td>2.28</td>
<td>0.023</td>
</tr>
<tr>
<td>Na⁺×V</td>
<td>0.082</td>
<td>1.81</td>
<td>0.071</td>
</tr>
<tr>
<td>Serum K⁺</td>
<td>-0.136</td>
<td>-2.2</td>
<td>0.004</td>
</tr>
<tr>
<td>MBP</td>
<td>0.078</td>
<td>1.71</td>
<td>0.088</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables that did not enter in the model</th>
<th>β</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log (PRA)</td>
<td>0.010</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Log (plasma aldosterone)</td>
<td>-0.090</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>K⁺×V</td>
<td>-0.559</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Log (plasma cortisol)</td>
<td>-0.748</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>-1.479</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted $R^2=0.052$; $F=6.49$; $P<0.0001$; Na⁺×V indicates sodium urinary excretion; NS, not significant.
associated with increased UAE rate. We found an inverse relation between serum $K^+$ and UAE rate ($r = -0.136; P = 0.002$); however, when splitting patients into those with and without hypokalemia, defined with a cutoff of 3.5 mEq/L, no higher UAE rate and no higher rate of microalbuminuria in the hypokalemic than in the normokalemic patients could be found.

**Discussion**

Compelling evidence indicates that hyperaldosteronism implies detrimental consequences on the cardiovascular system (reviewed by Ross et al), but only 2 studies on renal involvement are available. According to their results, UAE rate would be higher in PA than in PH patients, but only patients with APA were studied, and no information on patients with IHA were given. Furthermore, both studies came from the same center, and, thus, the possibility of a selection bias could not be excluded. Based on these data, it was contended that even despite the suppression of the renin–angiotensin system, a renal damage occurs early on in the course of PA. To further investigate this hypothesis, we prospectively measured GFR and UAE rate and urinary creatinine excretion in the PAPY study. At the participating centers, state-of-the-art tests for diagnosing PA were available, thus allowing us to conclusively establish the presence or absence of PA and to accurately identify its underlying cause. Hence, we had a unique opportunity to examine UAE rate in the context of an unequivocal diagnosis of PA subtype and of exhaustive information on hormonal data regarding PRA, aldosterone, and cortisol levels. The impact of these and other variables on UAE rate could, therefore, be examined with unprecedented statistical power.

**Determinants of UAE Rate and Prevalence of Microalbuminuria**

Several factors can affect the UAE rate and thereby the prevalence of microalbuminuria in hypertension. The main

---

**Figure 1.** The bar graph shows the covariates-adjusted UAE rate in the patients with PH and primary aldosteronism because of APA and IHA. (median, interquartile range, and extreme values). In both the APA and the IHA group, the UAE rate was significantly higher than in the PH group.

**Figure 2.** The bar graph shows the prevalence of microalbuminuria in the patients with PH and primary aldosteronism because of APA and IHA.

---

**TABLE 3. GFR, UAE, and Urinary Creatinine Excretion in Patients With PH and Primary Aldosteronism Caused by an APA and IHA**

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR, mL/min/1.73m²</th>
<th>P</th>
<th>APA (n=31)</th>
<th>P</th>
<th>IHA (n=33)</th>
<th>P</th>
<th>IHA vs PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH (n=426)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted GFR</td>
<td>92±1</td>
<td>P&lt;0.01</td>
<td>85±3</td>
<td>P&lt;0.01</td>
<td>86±3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>UAE, μg/mL</td>
<td>18.30±1.1</td>
<td>NS</td>
<td>25.1±3.8</td>
<td>NS</td>
<td>31.0±7.5</td>
<td>P=0.024</td>
<td></td>
</tr>
<tr>
<td>UCE, g/day</td>
<td>15.1±0.05</td>
<td>NS</td>
<td>1.58±0.2</td>
<td>NS</td>
<td>1.35±0.14</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>UAE/UCE, μg/mL g/day</td>
<td>13.5±0.1</td>
<td>NS</td>
<td>19.5±4.8</td>
<td>NS</td>
<td>311.1±13.4</td>
<td>P&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Adjusted UAE</td>
<td>18.1±0.01</td>
<td>P&lt;0.001</td>
<td>23.0±0.01</td>
<td>P&lt;0.03</td>
<td>20.8±0.02</td>
<td>P&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted GFR indicates GFR adjusted for the BMI, age, and plasma aldosterone; Adjusted UAE, UAE adjusted for the BMI, age, Na⁺, V, serum K⁺, and mean BP; UCE, urinary creatinine excretion.
determinant of UAE rate in subjects with mild hypertension
and no cardiovascular complications seems to be the hemo-
dynamic load, although activation of the renin–angiotensin–
aldosterone system can accelerate the onset of early renal
changes. Moreover, in subjects with more severe hyperten-
sion and associated target organ damage, the augmented
urinary albumin leak is held to be the consequence of
endothelial dysfunction and glomerular damage. Hence, ad-
justment for the effect of significant predictors of UAE rate is
mandatory when undertaking comparisons of groups that may
have an unbalanced distribution of these confounders. By
using regression analysis, we could examine the impact of
renin, aldosterone, and cortisol, both baseline and after
captopril, and several other variables on UAE rate. Although
we could not detect any significant impact of the hormones
and GFR, we found that UAE rate was predicted by BMI, age,
urinary Na⁺ excretion, serum K⁺, and mean BP (Table 2).

UAE Rate in PA and PH Patients
An unbalanced distribution of these covariates across groups
might confound the detection of differences of UAE rate
between PA and PH patients, given the marked differences
observed for some of the variables (Table 1). Hence, to circum-
vent this possibility, we compared the covariates-adjusted UAE
rate across diagnosis groups. This analysis showed that PH
patients had significantly lower UAE rate than patients with PA,
either because of APA or because of IHA, even despite slightly
higher GFR (Table 3 and Figure 1). These differences could not
be accounted for by differences of age, BMI, BP, or serum K⁺,
or urinary Na⁺ excretion between PA and PH patients. Of
interest, there were no significant differences of either raw or
adjusted UAE rates between the PA patients with APA and IHA
(Figure 1). Hence, it would seem that PA, per se, rather than its
underlying cause, implies an early renal involvement. Thus, our
present findings confirm and extend to IHA patients previous
reports in patients with APA. Of note, even despite the
increased UAE rate of PA, we could observe no significant
impact of aldosterone on the UAE rate. Whether this lack of
correlation depends on the intrinsic inaccuracy of plasma aldo-
sterone values, as assessed at a single time point, to reflect the
chronic aldosterone excess and/or on the fact that multiple
factors concur with aldosterone excess to increase the UAE rate.

PA patients were described previously to have relative
hyperfiltration that would be related to the increased UAE
rate and could be unveiled by adrenalectomy. Furthermore,
it was shown that the infusion of aldosterone for 1 week to
normotensive dogs determined a 20% to 24% increase of
GFR, which was associated with an increase of renal perfu-
sion pressure. However, in the present study, GFR was
slightly higher in PH than in PA patients with APA and IHA,
both when raw and when covariate-adjusted GFR values were
compared. Furthermore, we found a weak inverse significant
relation \((r = -0.135; P < 0.001)\) of GFR with UAE rate at
univariate analysis, although this was not significant at
multivariate analysis. Thus, the results of this cross-sectional
study do not seem to support the contention that glomerular
hyperfiltration is a hallmark of chronic PA and accounts for
the observed excess UAE rate. The hyperaldosteronism- and
hypertension-induced nephron loss can be, in our view, a
plausible explanation for the lack of glomerular hyperfiltra-
tion of PA patients in this study. Hence, it would be of interest
to determine whether heterogeneity of GFR across neprons
exists.

Based on available information and on the present results,
we would like to propose another mechanism. UAE rate is
held to reflect endothelial damage or dysfunction; moreover,
excess aldosterone has also been causally related to
endothelial dysfunction in experimental and clinical stud-
ies. Thus, the more marked early renal damage found in
PA patients, as compared with PH without hyperaldosteron-
ism, might reflect endothelial dysfunction. Of note, with
excess aldosterone this may occur even despite the suppres-
sion of the renin–angiotensin system, which was held to
minimize the detrimental effects of high BP on the cardio-
vascular system. Because we could obtain no information on
oxidant stress and endothelial function in this study, this
hypothosis remains contentious. However, it is consistent with
the fact that removal of APA, with ensuing correction of
hyperaldosteronism, was followed by a decrease in the UAE
rate.16

UAE Rate by Serum K⁺
K⁺ supplementation has been shown to protect against
stroke and endothelial dysfunction in hypertensive rats. Moreover, K⁺ prevents nephron loss by exerting a protective
action on renal tubules, arteries, and glomeruli. Hence, hy-
pokalemic nephropathy has been contended to be responsible for
the increased UAE rate in PA patients, but this hypothesis has
never been formally tested. Hypokalemia is held to be a
hallmark of PA, although normokalemia is currently detected
more often than hypokalemia in PA cases. In accord with
this view, the majority of the patients not only with PH, but
also with PA, had normal serum K⁺ in the PAPY at the time of
the screening test. We could, therefore, test the hypothesis
that hypokalemia was associated with the UAE rate. Interest-
ingly, we found an inverse relation (Figure 3) between UAE
rate and serum K⁺. The latter remained among predictors of
UAE rate in the regression model (Table 2), thus suggesting
a role for hypokalemia in raising the UAE rate. However, the

![Graph](image-url)
correlation was a weak one \((r = -0.136).\) Moreover, when splitting groups into those with and without hypokalemia, UAE rate and the rate of microalbuminuria were no higher in the patients with than in those without hypokalemia. Thus, it would seem that a diagnosis of PA, rather than the presence of hypokalemia, per se, implies an increased risk of microalbuminuria. Nonetheless, our present results do support the hypothesis that hypokalemia is a determinant of early renal damage, as revealed by microalbuminuria, in hypertensive patients with PA, albeit not a major one. Whether correction of hypokalemia with \(K^+\) supplementation can correct microalbuminuria even despite leaving BP unaffected in PA patients remains to be investigated.

In summary, we showed that in newly diagnosed hypertensive patients referred to specialized centers for arterial hypertension, PA implies an early and more prominent renal involvement, as compared with PH. This renal damage precedes the overt decrease of GFR and is unrelated to the suppression of the renin-angiotensin system, as revealed by microalbuminuria, in hypertensive patients with PA, albeit not a major one. Whether correction of hypokalemia with \(K^+\) supplementation can correct microalbuminuria even despite leaving BP unaffected in PA patients remains to be investigated.

**Perspectives**

Considering the very high prevalence of arterial hypertension in the general population and the high proportion of cases because of excess aldosterone and given the reported association of plasma aldosterone with the risk of developing high BP, research should be aimed at further identifying the mechanisms by which hyperaldosteronism exerts its deleterious effects on the kidney. Follow-up studies with assessment of markers of oxidant stress and endothelial dysfunction and with direct measurement of renal blood flow and GFR would be important in PA patients treated by adrenalectomy or mineralocorticoid receptor antagonists to clarify these mechanisms.

**Appendix**

A list of all PAPY study participants is provided in Table 4.

**Sources of Funding**

This study was carried out under the auspices of the Società Italiana dell’Ipertensione Arteriosa.

**Disclosures**

None.

**References**


Renal Damage in Primary Aldosteronism: Results of the PAPY Study
Gian Paolo Rossi, Giampaolo Bernini, Giovambattista Desideri, Bruno Fabris, Claudio Ferri, Gilberta Giacchetti, Claudio Letizia, Mauro Maccario, Massimo Mannelli, Mee-Jung Matterello, Domenico Montemurro, Gaetana Palumbo, Damiano Rizzoni, Ermanno Rossi, Achille Cesare Pessina and Franco Mantero
for the PAPY Study Participants

Hypertension. 2006;48:232-238; originally published online June 26, 2006;
doi: 10.1161/01.HYP.0000230444.01215.6a
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/48/2/232