Relative Glomerular Hyperfiltration in Primary Aldosteronism

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Experimental and clinical data suggest that primary aldosteronism (PA) may be associated with cardiovascular hypertrophy and fibrosis, in part independent of the BP level. Whether PA may also result in specific deleterious effects on the kidneys was less studied. In 25 patients with tumoral PA, renal studies (urinary excretion of proteins, GFR, and effective renal plasma flow [ERPF], as clearances of technetium-labeled diethylene triaminopentaacetic acid and 131I-ortho iodohippurate, respectively) were performed both before and 6 mo after surgical cure. A control group consisting of patients with essential hypertension (EH) was studied before and after 6 mo of antihypertensive therapy. At baseline, PA and EH patients were similar with respect to demographic data, duration and level of hypertension, and GFR and ERPF. Urinary excretion of albumin and β2 microglobulin were higher in PA than EH (88 ± 26 versus 39 ± 12 and 0.91 ± 0.23 versus 0.26 ± 0.19 mg/24 h, respectively; both P < 0.05). Adrenalectomy was followed by a decrease in arterial BP (by 28 ± 3/13 ± 2 mmHg), urinary excretion of albumin and β2 microglobulin (by 48 ± 19 and 0.53 ± 0.21 mg/24 h, respectively), and GFR and ERPF (by 15 ± 3 and 54 ± 15 ml/min per 1.73 m², respectively). In EH, a similar decrease in pressure was associated with a decrease in albuminuria but no change in GFR or ERPF. In 17 of the 25 PA patients who received a 6-mo treatment of spironolactone, both GFR and ERPF decreased in parallel with BP, similar to what was observed after surgery. These data suggest that PA was associated with relative hyperfiltration, unmasked after suppression of aldosterone excess.


Primary aldosteronism (PA) is a possibly common form of endocrine hypertension in which aldosterone production is inappropriate and at least partially autonomous with regard to physiologic control by angiotensin. In recent years, the widespread use of the plasma aldosterone/renin ratio as a screening test for PA has led to a marked increase in the proportion of hypertensive patients identified as such (1). Whether the diagnostic workup of aldosterone-producing adenomas is cost-effective regarding the potential for curability or effective protection of target organs by specific treatment remains controversial (2). Several experimental and, to a lesser extent, clinical studies suggest that long-term exposure to increased aldosterone levels may result in renal as well as cardiac and vascular toxicity that is in part independent of the BP level (3,4). Target organ damage, as assessed by the measurement of left ventricular mass or urinary excretion of albumin, may be inappropriately high with respect to the BP level in patients with PA (5,6). However, the relationship between albuminuria and renal function parameters is not clear. Specifically, it is not known whether PA-associated albuminuria may relate to a state of hyperfiltration suggested in a study in which GFR was assessed by the measurement of creatinine clearance (7). For investigating the effect of aldosterone excess on renal hemodynamics and function, studies were performed in patients with PA before and after a 6-mo administration of spironolactone as well as before and 6 mo after surgical cure or improvement of hypertension.

Materials and Methods

Patients

Studies were conducted in 25 consecutive patients (eight women and 17 men, aged 33 to 66 yr) who presented with a (subsequently) surgically proven aldosterone-producing adenoma and 25 patients with essential hypertension matched for age, gender, and body mass index as well as the level and apparent duration of hypertension. Primary aldosteronism was suspected on the basis of clinical presentation, i.e., resistant hypertension and/or spontaneous hypokalemia associated with low renin and high plasma aldosterone values, then confirmed by demonstrating lack of aldosterone suppression after saline infusion. Unilateral adrenal adenoma was identified on computed tomography, then adrenal vein sampling or scintigraphy as appropriate. In all patients, adenoma was confirmed by pathology. Ablation of the adenoma by laparoscopic surgery was followed by cure (as defined by a postoperative BP <140/90 mmHg) or improvement (as defined by a decrease in BP by >20% without medication) of hypertension.

Patients with associated diseases (e.g., diabetes) and severe (diastolic BP >120 mmHg) or complicated (by congestive heart failure or renal insufficiency) hypertension were excluded from the study. Serum creatinine had to be <115 μmol/L (1.3 mg/dl), and estimated creatinine clearance (Cockcroft-Gault formula) had to be >90 ml/min.

All patients gave informed consent to the protocol. Renal investigations, as detailed subsequently, were performed both at baseline (after a washout period of 3 wk without antihypertensive therapy) and 6 mo after surgery in the PA group and 6 mo after optimization of antihypertensive therapy in the essential hypertension (EH) group. In addi-
tion, the effect of a 6-mo period of treatment by spironolactone was assessed in 17 of 25 PA patients before surgery.

**Protocol and Analytical Procedures**

Renal function studies were performed during morning hours as described previously (8). After overnight fasting, patients came to the ward with one to two 24-h urine collections for the determination of creatinine (to assess the adequateness of urine collection), sodium and urea (to estimate sodium and protein intake, respectively), albumin (measured by RIA), and β2-microglobulin (by nephelometry). Arterial pressure and heart rate were monitored every 3 min with an automatic device (Dynamap 845 XT; Critikon, France), with reported values being the average of at least 10 measurements obtained in the supine position during renal clearance studies.

GFR and effective renal plasma flow (ERPF) were estimated by urinary clearances of technetium-labeled diethylene triaminopentacetic acid (99mTc-DTPA) and 131I-ortho iodohippurate, respectively, using the constant infusion technique under conditions of water diuresis and timed urine collections. Blood samples were obtained before clearance determination for the measurement of creatinine, electrolytes, plasma aldosterone concentration, and renin activity (RIA using the CEA Sorin kit, Saclay, France).

Filtration fraction was calculated as GFR/ERPF and renal vascular resistance as mean arterial pressure (MAP) × (1 – hematocrit)/ERPF. Intrarenal hemodynamics were assessed through Gomez’s equations (9), using MAP, ERPF, GFR, hematocrit, and total protein values to estimate glomerular hydrostatic pressure (P_G) and arteriolar resistance, either pregglomerular (afferent resistance [R_A]) or postglomerular (effe-

**Statistical Analyses**

Data are presented as mean and SEM. Clearance values were averaged and proportioned to 1.73 m² of body surface area. Variables not normally distributed (e.g., albumin, β2-microglobulin excretion rates) were analyzed after logarithmic transformation. Statistical analysis was carried out using ANOVA followed by Dunnett test and paired t test when appropriate. Linear nonparametric correlation coefficients between the changes in renal function parameters and a number of variables were calculated in univariate regression analysis, then entered in a model of stepwise regression analysis. P = 0.05 was taken as the minimum level of significance.

**Results**

As shown in Table 1, the PA and EH groups did not differ in any of the listed characteristics.

**Basal Renal Function**

As depicted in Table 2, baseline renal function parameters did not differ between PA and EH. Of note, a higher mean value of urinary albumin excretion (whether expressed as mg/24 h or mg/mmol creatinine) was observed in PA patients despite the presence of a similar level of BP. In addition, a marked increase (approximately five-fold) in urinary β2-microglobulin was found in PA patients. As expected, mean supine plasma renin and aldosterone values were markedly lower and higher, respectively, in PA and EH.

**Effect of Treatment on Renal Function**

As shown in Figure 1, surgical ablation of the adenoma was followed by a marked reduction in arterial BP (from 169 ± 4/97 ± 2 to 142 ± 3/84 ± 2 mmHg; P < 0.05), and normal values (<140/90 mmHg) were achieved in 13 of 25 PA patients. GFR and ERPF decreased by 15 ± 3 and 54 ± 15 ml/min per 1.73 m², respectively (both P < 0.05), and filtration fraction was unchanged. Urinary excretion of albumin and β2-microglobulin consistently fell. Body weight, hematocrit, and serum albumin concentration as well as urinary excretion of sodium and urea, both potential determinants of GFR and ERPF, remained unchanged.

In the EH group, treatment that consisted of a combination of thiazide and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in 21 of 25 patients was associated with a fall in BP (–24 ± 4/12 ± 2 mmHg), equivalent to that observed in PA after adrenalectomy. In contrast to the PA group, no significant effect of therapy on GFR, ERPF, and filtration fraction was detected. Urinary excretion of albumin but not β2-microglobulin significantly decreased in parallel with BP. It is interesting that plasma aldosterone concentration also declined in EH, but the final level was higher than the postoperative mean value measured in PA patients.

**Intrarenal Hemodynamics**

When glomerular hemodynamics were estimated by Gomez’s equations, calculated glomerular hydrostatic pressure tended to be higher (63 ± 1 versus 61 ± 1 mmHg) and afferent resistance declined.

**Table 1. General clinical parameters in patients with PA and EH**

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>EH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>8/17</td>
<td>8/17</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49 ± 2</td>
<td>50 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.8 ± 0.6</td>
<td>26.9 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>92.0 ± 2.2</td>
<td>91.1 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>169 ± 4</td>
<td>170 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>97 ± 2</td>
<td>99 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 1</td>
<td>63 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. PA, primary aldosteronism; EH, essential hypertension.*
lower (9900 ± 900 vs. 10600 ± 700 dyn/s per cm\(^{-2}\)) in PA than EH groups. Adrenalectomy resulted in a significant decline in glomerular hydrostatic pressure (by 3.8 ± 0.9 mmHg; \(P < 0.05\)) and afferent resistance (by 1600 ± 600 dyn/s per cm\(^{-2}\); \(P < 0.05\)). No significant change in efferent resistance was detected. In EH, antihypertensive treatment was associated with a significant decrease in afferent but not efferent resistance and no change in glomerular hydrostatic pressure.

**Correlation Studies**

The decline in GFR observed after surgical cure of PA was inversely correlated with baseline GFR \((r = -0.50, P = 0.01)\) and baseline glomerular hydrostatic pressure \((r = -0.42, P = 0.04)\). It was directly correlated with the decline in ERPF \((r = 0.67, P < 0.001)\) but not the decrease in BP. In the PA group, a positive correlation between the change in GFR and baseline plasma potassium (Figure 2) but not basal or postoperative aldosterone or renin was obtained. In multivariate analysis, baseline GFR, the decline in ERPF, and preoperative plasma potassium remained significant determinants of the change in GFR.

**Reactivity of the Renin-Angiotensin System**

In 15 of 25 PA patients, the effect of captopril administration was assessed before and after surgery. Adrenalectomy was associated with restoration of a detectable response to acute blockade of the renin-angiotensin system with respect to BP (MAP, \(-1.1 \pm 0.8\) before versus \(-3.9 \pm 0.8\) mmHg after surgery; \(P < 0.05\)) and plasma renin activity (0.05 \pm 0.04 versus 0.83 \pm 0.30 ng/ml per h; \(P < 0.05\)). No significant effect of captopril on GFR or ERPF was observed before or after removal of the adenoma.

**Effect of Spironolactone Treatment**

Spironolactone treatment (75 to 225 mg given for 6 ± 1 mo in 17 of 25 PA patients) was associated with an effect similar to
that of removal of adenoma, i.e., a marked decline in BP (by 31 ± 4/16 ± 2 mmHg) as well as GFR and ERPF (by 17 ± 4 and 58 ± 19 ml/min per 1.73 m², respectively). Urinary excretion of proteins also decreased, from 135 ± 27 to 25 ± 8 mg/24 h for albumin and from 735 ± 183 to 178 ± 19 μg/24 h for β2-microglobulin (both P < 0.05).

Discussion

In these studies conducted in patients with PA, a decline in GFR was observed after consistent improvement of arterial pressure associated with suppression of the effect of aldosterone excess by spironolactone or adrenalectomy. In contrast, reduction in BP of a similar magnitude by antihypertensive therapy had no effect on renal function in patients with EH of similar duration and severity. The study population consisted of patients with normal renal function, and the observed decrease in BP remained well within the expected range of renal autoregulatory capacity, thus ruling out its failure as a likely cause of the postoperative decline in GFR (10).

Suppression of aldosterone excess was probably associated with a decrease in extracellular and intravascular fluid volumes, as suggested by an increase in circulating renin levels at baseline and after acute administration of captopril. It is doubtful that such a moderate decrease in intravascular volume (body weight, hematocrit, or serum albumin did not change) or recovery of reactivity of the renin system would result in a decrease in renal hemodynamics and function. In fact, no response of ERPF or GFR to captopril administration was observed after surgery. Of note, it was previously reported that PA patients who were treated by adrenalectomy recovered normal levels of plasma renin activity and aldosterone within 1 mo after surgery (11). Some authors observed a prolonged postoperative aldosterone suppression attributed either to renin suppression resulting from prolonged inhibition of the juxtaglomerular apparatus (12) or to a decreased adrenal mass (13).

Another mechanism that could provide an explanation for the postoperative fall in GFR is the removal of the state of escape from the renal effects of aldosterone excess. Administration of aldosterone to experimental animals and exogenous mineralocorticoids to humans is associated with a transient increase in extracellular fluid volume followed by a return to sodium balance (14). The mechanism of the escape from the sodium-retaining effect of aldosterone involves the pressure-natriuresis phenomenon (15), mediated by natriuretic peptides (16) and nitric oxide (17). The occurrence of escape is associated with a proportional increase in GFR and renal plasma flow by approximately 20% (15). It is interesting that a role for aldosterone as a mediator of relative or absolute hyperfiltration has been suggested in other experimental settings, including diet-induced obesity, where administration of the aldosterone antagonist eplerenone markedly attenuated glomerular hyperfiltration (18).

Kimura et al. (7,19) demonstrated that dietary sodium restriction reduced MAP of PA patients. After removal of adenoma, the slope of the renal function curve (i.e., the linear regression of urinary sodium excretion on MAP) was enhanced, and its extrapolated x-intercept was shifted leftward. This approach allowed the authors to estimate whole kidney ultrafiltration coefficient by dividing GFR by effective filtration pressure (assumed to be the difference between MAP on normal sodium diet and the x-intercept). Such calculations and Gomez’s formulas gave similarly elevated values for glomerular capillary pressure. In these studies, adrenalectomy was associated with a consistent fall in calculated glomerular capillary pressure and a selective fall in the preglomerular resistance. In addition, the decline in GFR was correlated with baseline glomerular hydrostatic pressure (the higher the glomerular pressure, the more marked the fall in GFR), thus suggesting that intraglomerular pressure may be a determinant of the relative hyperfiltration found in hyperaldosteronism.

Experimental models allowed a more direct assessment of the effects of mineralocorticoid excess on intraglomerular hemodynamics. It was reported that in vitro addition of aldosterone may exert a direct and rapid vasoconstrictive effect on the efferent renal arteriole (20) or that aldosterone abolished the vasoconstriction induced by potassium chloride at the afferent (preglomerular) level (21). In uninephrectomized rats with desoxycorticosterone-salt hypertension, glomerular injury resulted from elevation in glomerular capillary flow and pressure, and discontinuation of desoxycorticosterone administration was associated with a partial recovery of glomerular injury and a consistent decrease in albuminuria (22). Whether the fall in GFR observed after adrenalectomy may result from the removal of the renal escape to aldosterone through a reduction in nitric oxide (17,23) or, on the contrary, less aldosterone suppression of nitric oxide bioavailability (24) needs further studies with direct assessment of the potential intermediate mechanisms.

As already reported (5,6), albuminuria was higher in patients with PA than in patients with EH matched for the level of BP, thus suggesting that the relation between albuminuria and BP may be enhanced by aldosterone. Alternatively, the “excessive” urinary excretion of albumin found in PA may be a consequence of a defect in tubular reabsorption, also reflected by an increased urinary excretion of β2-microglobulin. β2-Micro-
globulin is a low molecular weight protein that is freely filtered and almost completely reabsorbed by proximal tubular cells. In these studies, the increased level of urinary β2-microglobulin was entirely reversed after surgery or after chronic mineralocorticoid receptor blockade by spironolactone, which in addition normalized the serum potassium level, thus suggesting that observed renal abnormalities may result from hypokalemic nephropathy. Potassium depletion has long been known as a cause of tubular dysfunction. Whether prolonged potassium depletion leads to permanent renal damage in humans has remained controversial. Interstitial fibrosis was found mainly in biopsies from patients with chronic laxative or diuretic abuse. It is interesting that in these studies, the magnitude of the postoperative decline in GFR was correlated with the degree of hypokalemia.

Finally, removal of aldosterone excess—and its hyperfiltering influence—by surgery or spironolactone may have unmasked a state of reduced GFR secondary to renal damage. This is at variance with the long-held tenet that hypertension in patients with PA is relatively benign and that hypertensive patients with low renin are protected against vascular complications. In fact, later studies demonstrated that PA may result in significant target organ damage, including proteinuria, which appeared as a marker for an increased risk for complications. A group of 136 PA patients, Beevers et al. (32) reported on a 15.5% prevalence of renal vascular and parenchymatous abnormalities. Oelkers et al. (33) observed an alteration in renal function after spironolactone administration in PA patients with biopsy-proven marked nephrosclerosis. A study of long-term outcome of renal function after adrenalectomy would be of interest.

References
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