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Risk Factors Associated with a Low Glomerular Filtration Rate in Primary Aldosteronism

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Context: Primary aldosteronism (PA) is associated with vascular end organ damage.

Objective: We evaluated the newly established German Conn's Registry for evidence of renal impairment and compared the data with those from hypertensive subjects of a population-based survey.

Design: We conducted a case-control study.

Patients and Controls: A total of 408 patients with PA from the Conn's registry treated in five German centers were matched for age, sex, and body mass index in a 1:1 ratio with 408 hypertensive control subjects from the population-based F3 survey of the Kooperative Gesundheitsforschung in the region of Augsburg (KORA).

Main Outcome Measures: We measured serum creatinine and calculated glomerular filtration rate (GFR).

Results: The percentage of patients with a serum creatinine concentration above the normal range of 1.25 mg/dl was higher in patients with PA than in hypertensive controls (29 vs. 10%; $P < 0.001$). Regression analysis showed that age, male sex, low potassium, and high aldosterone concentrations were independent predictors of a lower GFR. Adrenalectomy reduced systolic blood pressure from a mean of 160 to 144 mm Hg. In parallel, we observed an increase in serum creatinine and a decrease of GFR from 71 to 64 ml/min ($P < 0.001$). A similar trend was seen after spironolactone treatment.

Conclusions: In a large cohort of patients with PA, markers of disease activity such as plasma aldosterone and serum potassium are independent predictors of a lower GFR. Specific interventions, such as adrenalectomy or spironolactone treatment, are associated with a further decline in GFR. **(*J Clin Endocrinol Metab* 94: 869–875, 2009)**

Within the last 15 yr, primary aldosteronism (PA) has been reported with increasing frequency (1), and it accounts for more than 10% of the hypertensive population (2). In a retrospective study involving more than 10,000 subjects with hypertension from clinical centers in five continents, application of the aldosterone to renin ratio resulted in a 5- to 15-fold increase in the identification of patients affected by PA (3). In the recent prospective Italian multicenter trial of 1,125 patients with hy-

Abbreviations: BMI, Body mass index; GFR, glomerular filtration rate; PA, primary aldosteronism.

pertension, 4.8% had aldosterone producing adenoma, and 6.4% had an idiopathic bilateral hyperplasia (4).

There is a relative paucity of information about the effects of prolonged aldosterone excess on kidney function. In a small study of 23 patients with PA, left ventricular hypertrophy preceded hypertensive retinopathy and hypertensive renal involvement (5). More recently, in the cross-sectional Primary Aldosteronism Prevalence in Italy (PAPY) Study, renal damage as assessed by 24-h urine albumin excretion rate was significantly more frequent in aldosterone-producing adenoma and idiopathic adrenal hyperplasia than in hypertensive controls (6). A longitudinal study analyzed renal outcome in 50 patients with PA and in 100 subjects with essential hypertension matched for severity and duration of hypertension. The authors showed that restoration of normal albumin excretion from microalbuminuria was significantly more frequent in PA after specific intervention than in essential hypertension (7), despite comparable blood pressure control.

We used the database of the German Conn's Registry to study renal impairment in PA in comparison to subjects with hypertension from a population-based survey. The aim of the study was to identify predictors of impaired renal function in patients with PA.

Patients and Methods

Description of the registry

Founded in 2006, the German Conn's Registry (www.conn-register.de) is a multicenter database analyzing comorbidities and long-term outcome of patients with PA. Participating centers in Berlin, Bochum, Freiburg, Munich, and Wuerzburg included all patients with PA who had been treated between 1990 and 2006 in the registry. Data entry followed a retrospective design. The Ethics Committees of the University of Munich and of the participating centers approved the protocol. Personal data protection laws were strictly observed.

Patients were identified by review of their paper charts (up to 1999), or by review of electronic charts thereafter, using key words associated with PA. The patients were entered into an Access database after pseudonymization. Persons responsible for data entry received intense training in Munich ensuring high quality of data retrieval and homogeneity of the data entry. The quality of entered data was evaluated in 2007. Possible inconsistencies and missing data were validated and corrected if appropriate.

Because of the retrospective design and the lack of a uniformly accepted diagnostic standard during the study period, the diagnostic criteria for PA varied between the centers. At least three criteria had to be present for inclusion in the registry: 1) elevated aldosterone to renin ratio, or alternatively, suppressed renin and elevated aldosterone concentrations in those patients without aldosterone to renin ratio; 2) serum aldosterone above the middle normal range; 3) abnormal confirmatory testing; 4) adrenal adenoma in histopathology; 5) blood pressure response to adrenalectomy; and 6) blood pressure response to treatment with mineralocorticoid antagonist. Mineralocorticoid antagonists and β-blockers had to be withdrawn for 4 and 1 wk before screening, respectively. The diagnosis of PA was verified centrally by review of all available data.

Extensive clinical data were extracted from patients' charts, including laboratory test results, dynamic testing, medication, adrenal imaging, results of adrenal venous sampling, details of specific medical treatment, surgical treatment, and cardiovascular and cerebrovascular morbidity. Blood pressure was measured with a sphygmomanometer by the physician while the patients were seated.

Study population and control population

Study population

A total of 639 patients with PA were entered into the database. Because of missing data or inconsistencies regarding the diagnosis, 84 patients were centrally excluded from further analysis. The remaining 555 patients with PA were matched with subjects from the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) F3 survey (8) in a 1:1 fashion using age, sex, and body mass index (BMI) as matching variables, leading to a match in 408 patients. Matching tolerance was a maximum deviation of 10 yr for age (mean difference $\pm$ SD, -0.3 ± 2.8 yr) and 2.5 kg/m^2 for BMI (mean difference $\pm$ SD, -0.1 ± 0.6 kg/m^2). In addition, subgroup analysis was performed for duration of hypertensive disease longer than 10 yr and for mean arterial pressure (matching tolerance, 10 mm Hg). Of 408 patients, 359 (88%) had aldosterone to renin ratio screening, 253 patients (62%) underwent confirmatory testing, 139 patients (34%) had adrenal venous sampling, and 97 (24%) of the patients underwent unilateral adrenalectomy, of whom 41 (42%) had prior adrenal vein sampling.

Control population

The KORA F3 survey is a population-based study based on all German residents of the Augsburg region born between 1920 and 1975 and identified through the public record office. For the purpose of this study, all 894 hypertensive subjects were enrolled. Hypertension was defined as blood pressure of at least 140/90 mm Hg and/or current use of antihypertensive drugs. More than 99.5% of the participants were Caucasian. The high standard of the World Health Organization MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project applies to the survey. In 2004, all study participants underwent a standardized interview, physical examination, and blood withdrawal by trained staff. They gave informed written consent on a form from the ethics committee of the Bavarian state board of physicians.

For the patients with PA, creatinine concentrations were measured by automated equipment of the central laboratories of the participating university centers. In the KORA F3 survey, blood parameters were measured by automated equipment in the laboratory of the hospital of Augsburg. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease Study Group (MDRD) equation (9).

Statistics

Results are expressed as mean $\pm$ 1 SD in the case of normally distributed data, and as median plus range in nonnormally distributed data, if not stated otherwise. Significance of differences was determined by Wilcoxon test or Fisher's exact test, as appropriate. A P value <0.05 was considered significant. Multivariate regression analysis was performed using a manual backward elimination to identify potential risk factors for impaired GFR. All the statistical analyses were carried out using R version 2.5.1 software.

Results

Clinical characteristics of the study population

Clinical characteristics of the two study populations are summarized in Table 1. As expected, blood pressure and the number of antihypertensive medications prescribed were significantly higher in subjects with PA compared with control hypertensives. Significant differences were also present with regard to the percentage of patients with diabetes mellitus in the two samples.

Patients with PA were stratified into those who never had documented hypokalemia below 3.5 mmol/liter (normokalemic PA) and those who had current or past hypokalemia or received potassium supplements (hypokalemic PA). Both groups were

TABLE 1. Clinical and biochemical characteristics of the study population

	Patients with PA				
	Total	Hypokalemic	Normokalemic	Control population	*P*
n	408	262	146	408	
Age (yr)	60 ± 10	60 ± 10	61 ± 10	60 ± 9	Match
Female	155 (38%)	91 (35%)	64 (43%)	155 (38%)	Match
BMI (kg/m^2)	28.7 ± 4.5	28.8 ± 4.6	28.6 ± 4.3	28.8 ± 4.5	Match
Blood pressure (mm Hg)	160 ± 21/94 ± 13	159 ± 22/94 ± 13	160 ± 20/93 ± 12	138 ± 21/85 ± 11	<0.001[a]
Potassium (mmol/liter)	3.6 ± 0.6	3.4 ± 0.5	4.1 ± 0.4	NA	<0.001[c]
No. of patients with diabetes	84 (20%)	54 (21%)	30 (21%)	61 (15%)	<0.05[a]
No. of antihypertensive medications at first visit	2.7 ± 1.8	2.7 ± 1.8	2.6 ± 1.9	1.7 ± 1.0	<0.001[a]
Duration of hypertension (yr)	12 ± 9	13 ± 9	12 ± 9	NA	
No. of patients with duration of hypertension >10 yr	178 (44%)	115 (44%)	63 (43%)	136 (33%)	<0.01[a]
Plasma aldosterone concentration (pg/ml)[b]	247 ± 176	271 ± 196	208 ± 128	NA	<0.01[c]
Mean creatinine concentration (mg/dl)	1.19 ± 0.71	1.20 ± 0.49	1.17 ± 0.98	1.01 ± 0.58	0.01[a]
No. of patients with creatinine concentration >1.25 mg/dl	119 (29%)	84 (32%)	35 (24%)	40 (10%)	<0.001[a] = 0.08[c]

Data are presented as mean ± SD. NA, Not available.

[a] Total number of PA patients *vs.* controls.

[b] Linear rescaled between different methods to a hypothetic normal range of 50–300.

[c] Hypo- *vs.* normokalemic PA.

similar with respect to age, sex, BMI, duration of hypertension history, systolic and diastolic blood pressure values, and number of hypertensive medications per subject, but they differed with respect to prevalence of diabetes and serum aldosterone concentrations (Table 1).

Kidney function of the study populations

The percentage of patients with a serum creatinine concentration above the normal range was significantly higher in patients with PA than in hypertensive controls (29 *vs.* 10%; $P < 0.001$). In addition, patients with PA had higher serum creatinine concentrations (1.19 ± 0.71 *vs.* 1.01 ± 0.58 mg/dl), and a lower mean GFR (65 ± 16 *vs.* 68 ± 15 ml/min; $P < 0.01$; Fig. 1). Subgroup analysis showed that a lower GFR was found in PA of both sexes (data not shown) and in subjects with the hypokalemic and normokalemic variant (Table 1). In addition, a lower GFR was found in all age decades of subjects with PA compared with the KORA population, with the exception of the lowest and highest decade, most likely due to a small sample size (Fig. 2).

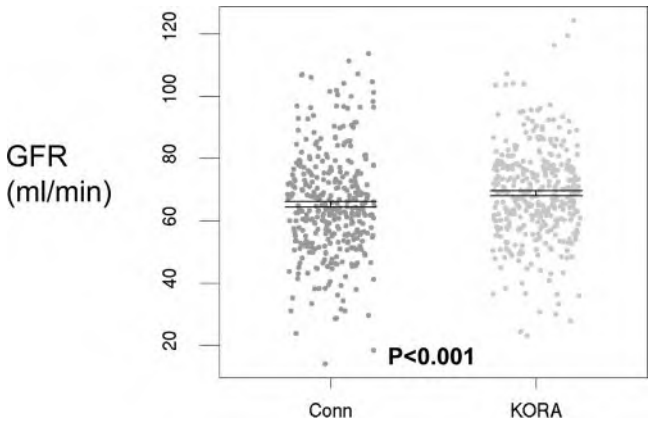

FIG. 1. Individual GFR values and mean GFR + SEM in 408 subjects with PA (*left*) and 408 hypertensive subjects from the KORA F3 survey (*right*).

In a subgroup analysis, further matching for mean arterial pressure between PA and controls resulted in 71 matches (Table 2). PA patients still had a lower GFR (65 ± 17 *vs.* 68 ± 16 ml/min), but this difference was no longer statistically significant. Matching for duration of hypertension of more than 10 yr (n = 51) also resulted in a slightly lower GFR (not significant). Diabetic patients with PA and diabetic controls did not differ significantly with respect to GFR.

Risk factors associated with impaired kidney function in untreated PA

We used a regression analysis with multiple predictors to describe the creatinine concentration in untreated PA. Age, sex, BMI, systolic and diastolic blood pressure at first presentation, length of hypertension history, number of antihypertensive drugs, potassium concentration, and plasma aldosterone and renin concentrations at first diagnosis were used for the initial model. Using a manual backward elimination, age (0.051 mg creatinine per 10 yr; $P = 0.01$) and male sex (odds ratio, 2.9; 95% confidence interval, 1.3–7.3; $P = 0.001$) showed a highly significant effect. In addition, the initial potassium concentration (odds ratio, 1.3; 95% confidence interval, 1.0–5.2; $P < 0.01$), plasma aldosterone concentrations ($P < 0.05$), and presence or absence of the hypokalemic variant of PA ($P < 0.05$) were independent predictors of creatinine concentrations. A weak trend with $P \sim 0.1$ was found for the maximal number of antihypertensive drugs in most models. Albumin excretion in urine was documented in a minority of patients with PA (22%). Therefore, its potential role as a predictive factor of creatinine concentrations was not analyzed in this study.

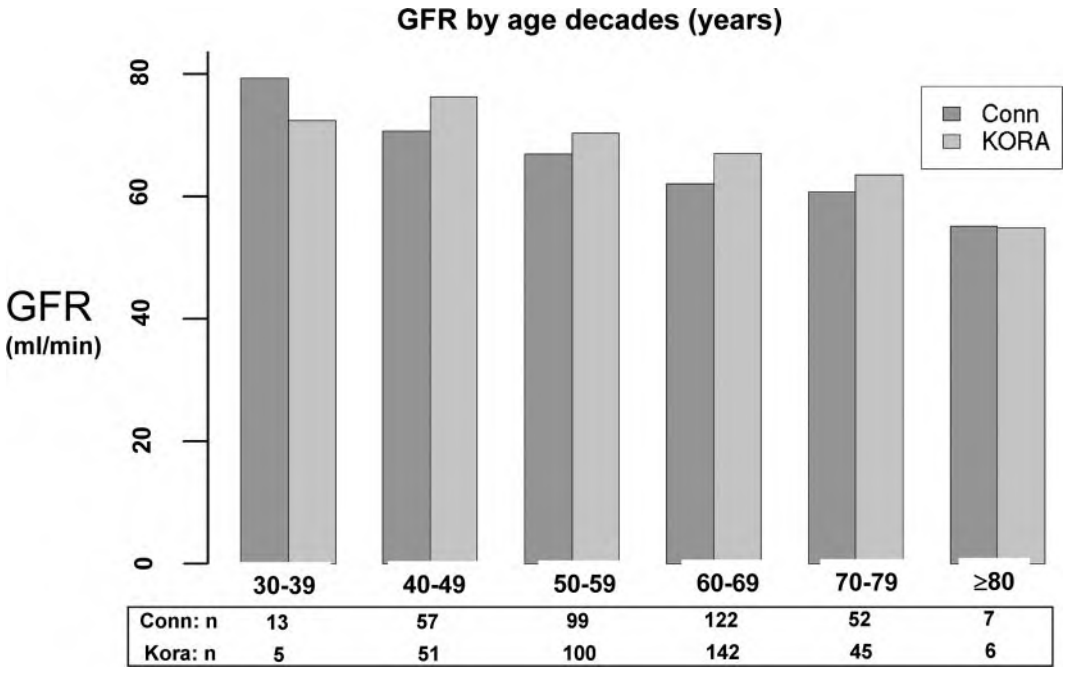

FIG. 2. Mean GFR in relation to age (in decades) in 408 subjects with PA and 408 matched hypertensive subjects from the KORA F3 survey.

Effect of adrenalectomy or mineralocorticoid blockade on GFR in PA

We evaluated the effect of adrenalectomy on renal function in 137 patients. First, we analyzed 51 patients in whom creatinine concentrations were documented immediately before surgery and within 30 d afterward. Whereas systolic blood pressure decreased by 15 ± 27 mm Hg ($P < 0.001$), serum creatinine increased by a mean of 0.11 ± 0.26 mg/dl ($P < 0.001$); GFR decreased by −8 ± 13 ml/min ($P < 0.001$; Fig. 3A). Grouping within an interval of 1000 d before *vs.* 1000 d after surgery over all explorations in all adrenalectomized patients showed the expected drop in blood pressure (mean systolic blood pressure, 161 ± 29 mm Hg before *vs.* 144 ± 20 mm Hg after surgery; $P < 0.001$), paralleled by an increase in serum creatinine concentration and a drop in GFR (from 73 ± 22 to 64 ± 18 ml/min; $P < 0.001$) (Fig. 4). Thus, the decline in GFR appears to develop early within the first month of follow-up without further decline or increase later on.

An analysis of 63 patients with PA undergoing mineralocorticoid blockade with spironolactone showed similar 30-d data: spironolactone in a average dose of 100 mg per day (range, 25 to >150 mg) induced a sharp decrease in systolic blood pressure (−25 ± 31 mm Hg; $P < 0.001$ *vs.* pretreatment blood pressure), an increase in creatinine levels (+0.12 ± 0.30 mg/dl; $P < 0.01$ *vs.* pretreatment values; Fig. 3B), and a drop in GFR (−7 ± 14 ml/min; $P < 0.001$), respectively.

Discussion

The main finding of our study is that markers of disease activity, such as serum potassium and plasma aldosterone, are all inde-

TABLE 2. Subgroup analysis between the study population and hypertensive controls

	n	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	GFR (ml/min)	*P* value (GFR)
Subgroup matching for mean blood pressure					
PA	71	146 ± 16	87 ± 10	65 ± 17	ns
Hypertensive controls from KORA	71	149 ± 16	88 ± 9	68 ± 16	
Subgroup matching for duration of hypertension >10 yr					
PA	51	170 ± 26[a]	99 ± 16[a]	64 ± 15	ns
Hypertensive controls from KORA	51	142 ± 24	86 ± 11	68 ± 16	
Subgroup analysis for presence of diabetes mellitus					
PA	70	165 ± 30[a]	93 ± 18[a]	65 ± 17	ns
Hypertensive controls from KORA	44	139 ± 23	81 ± 12	68 ± 17	

Data are presented as mean ± SD. ns, Not significant.

[a] $P < 0.001$ *vs.* blood pressure of controls.

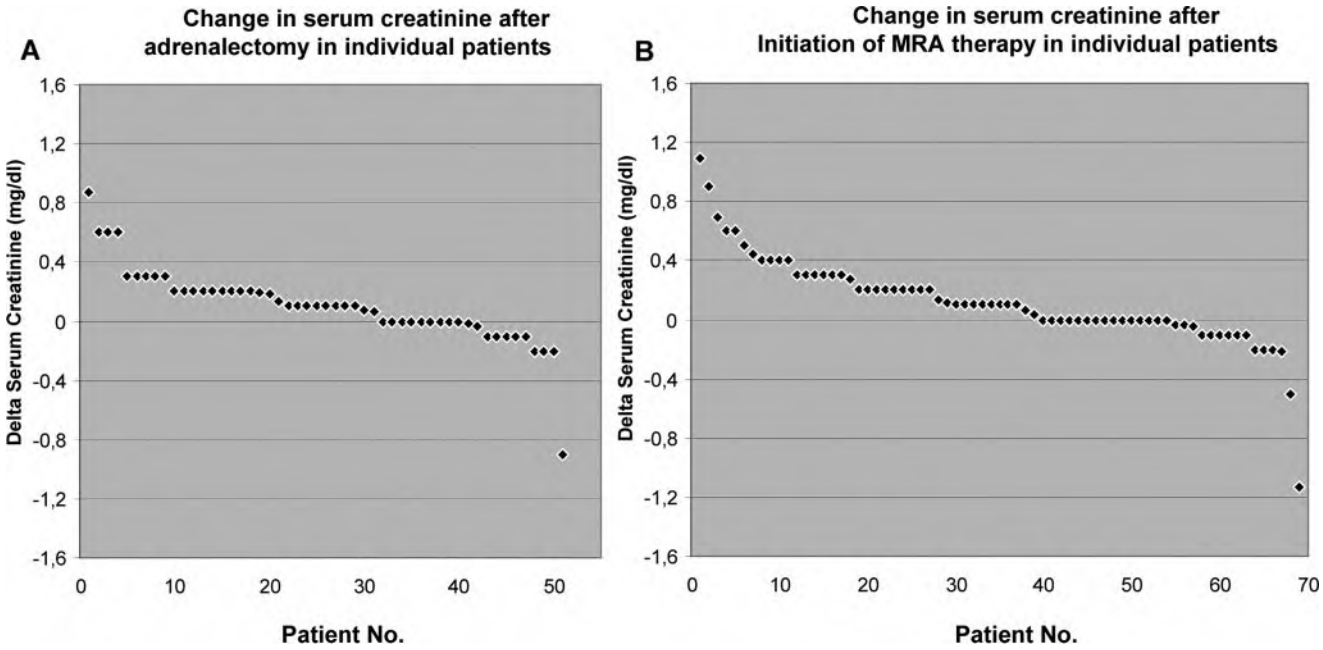

FIG. 3. Individual change in creatinine 30 d after adrenalectomy for aldosterone-producing adenoma (A) or after initiation of mineralocorticoid antagonist (MRA) treatment (B).

pendent predictors of renal impairment in patients with PA. In addition we show that the presence of hypokalemic PA is associated with an adverse renal outcome.

Kidney function in PA

Experimental studies in animal models have demonstrated that inappropriate aldosterone levels for sodium status can produce extensive renal damage (10). Furthermore, there is clinical evidence for elevated aldosterone levels over time contributing to the renal dysfunction seen in PA.

Cross-sectional studies on renal function in PA have shown a high degree of variability in the prevalence of renal damage (6, 11–13). In 1988, Danforth *et al.* (11) were the first to report moderate to severe renal parenchymal damage in renal biopsies of patients with PA.

Halimi and Mimran (12) provided evidence that in comparison to matched patients with essential hypertension, urinary albumin excretion was higher in PA in comparison to essential hypertension. Nishimura *et al.* (13) reported proteinuria and renal insufficiency in 24 and 7%, respectively, of 58 patients with confirmed Conn's adenoma. In the large PAPY trial (6), the adjusted 24-h urine albumin excretion rate was significantly higher in patients with aldosterone-producing adenoma (n = 31) and idiopathic hyperplasia (n = 33) than in 426 essential hypertension patients.

In a recent long-term follow-up study by Sechi *et al.* (7), the authors showed that renal damage in PA is characterized by partially reversible renal dysfunction. Restoration of normal albumin excretion from microalbuminuria after adequate therapy was significantly more frequent in 50 patients with PA than in 100 controls with essential hypertension.

Our study provides evidence for a lower GFR in untreated patients with PA compared with age-, BMI-, and sex-matched hypertensives from a population-based study in southern Germany. Although the absolute difference (3 ml/min) was small, it proved highly significant because of the large number of subjects studied. This finding is at variance with several studies showing no change in GFR (6, 14) or higher GFR in untreated PA (7). The main reason for this difference is probably linked to differences of the respective control cohorts. At variance to the cited studies, our control cohort was initially not matched for blood pressure and duration of hypertension, two factors associated with an adverse outcome of renal function in hypertension. Long-term effects of high blood pressure might have resulted in a more pronounced renal damage in our PA patients. In line with this explanation is the finding that after matching for blood pressure or duration of hypertension in a subgroup analysis, no significant differences in GFR remained (Table 2).

Risk factors associated with renal damage

Owing to the large number of patients in the German Conn's Registry, multivariate regression analysis could be performed. Our data provide evidence that aside from age and male sex, low serum potassium, high aldosterone concentrations, and the presence of the hypokalemic variant of PA are independent predictors of creatinine concentrations. We compared renal function in patients with PA who never had documented hypokalemia with those subjects who had current or past hypokalemia. This distinction was made to investigate whether the more frequent normokalemic variant of PA is associated with the same degree of end organ damage as the hypokalemic variant. We found a higher prevalence of renal impairment in patients with hypokalemic PA (32 *vs.* 24%; Table 1), exhibiting a borderline significance.

Effect of treatment on GFR

Administration of aldosterone to experimental animals and exogenous mineralocorticoids to humans is associated with a

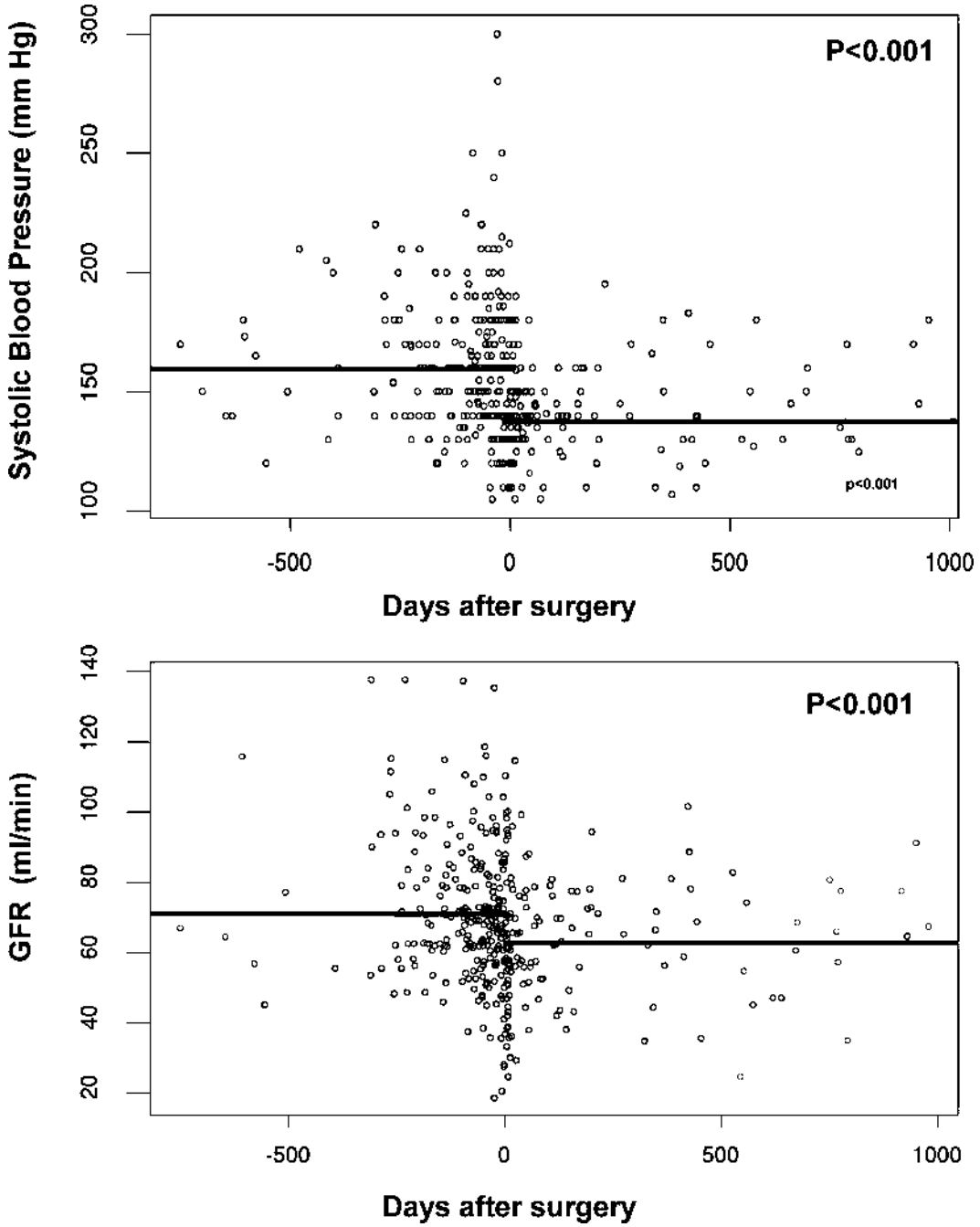

FIG. 4. *Top*, Individual systolic blood pressure values up to 1000 d before and 1000 d after adrenalectomy for aldosterone-producing adenoma. *Bottom*, Mean GFR up to 1000 d before and 1000 d after adrenalectomy for aldosterone-producing adenoma. A single patient may be plotted several times.

transient increase in extracellular fluid volume followed by a return to sodium balance (15). The mechanism of the escape from the sodium-retaining effect of aldosterone involves the pressure natriuresis phenomenon (16), mediated by natriuretic peptides (17) and nitric oxide (18). The occurrence of escape is associated with a proportional increase in GFR and renal plasma flow by approximately 20% (16). Accordingly, Ribstein *et al.* (14) showed in 25 patients with PA that adrenalectomy was followed by a decrease in arterial blood pressure, urinary excretion of albumin, GFR, and effective renal plasma flow, whereas in patients with essential hypertension, a similar decrease in pressure was associated with a decrease in albuminuria but no change in GFR or effective renal plasma flow.

Similar data were reported from the prospective, monocentric longitudinal study by Sechi *et al.* (7) involving 50 patients with PA and 100 patients with essential hypertension. During the initial 6-month period after intervention, the mean GFR decreased by −13.6 ml/min in patients with PA, but only by −2.1 ml/min in patients with essential hypertension despite similar blood pressure values. The decline in PA occurred early (first 30–90 d). Subsequent declines in GFR were similar in this study in patients with PA and those with essential hypertension for the

next 9 yr of follow-up. These data suggest that aldosterone excess is associated with glomerular hyperfiltration and that the decline in GFR has to be considered a specific functional response to treatment in PA. In a more extensive analysis from the same center (19), it was shown that the decrease in GFR after intervention was significantly greater in patients with higher pretreatment plasma renin and aldosterone levels.

Our data confirm this observation. Adrenalectomy or mineralocorticoid treatment induced the expected drop in blood pressure within 30 d. In parallel, there was an increase in serum creatinine and a drop in GFR, respectively. These data are in line with those of Ribstein *et al.* (14) and Sechi *et al.* (7), suggesting that effective treatment of mineralocorticoid excess removes renal hyperfiltration and may uncover the real extent of renal damage associated with PA.

Limitations of our study

The present study has several limitations that may have introduced a bias. First, the design of the patients' registry was retrospective, which may have affected data quality. Second, patients with PA were treated over a long period of time (1990 to 2006). Third, initial diagnostic criteria for PA varied between centers because of a lack of generally accepted diagnostic algorithm for PA at that time. Every case was, however, uniformly reviewed before listing in the registry. Nevertheless, this may have affected the homogeneity of the patients' cohort. A case control study between a patients' cohort (PA) and a control cohort from a population-based study can affect data quality because clinical evaluation may differ between clinical practice in university hospitals and an epidemiological cohort studied in a clinical center following good clinical practice criteria.

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