Prolonged Zona Glomerulosa Insufficiency Causing Hyperkalemia in Primary Aldosteronism after Adrenalectomy

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Context: Unilateral adrenalectomy is the therapy of choice in aldosterone-producing adenoma (APA). Zona glomerulosa (ZG) insufficiency causing hyperkalemia after adrenalectomy has been described in case reports.

Objective: Our aim was to analyze the clinical relevance of ZG insufficiency causing hyperkalemia after adrenalectomy in a large series of patients with APA.

Design: This was a retrospective chart review.

Setting: The study was conducted at two tertiary university referral centers in Germany.

Patients: Data from 110 patients with confirmed APA adrenalectomized at the centers in Munich and Berlin between 2004 and 2012 were analyzed.

Main Outcome Measures: The primary outcome was the incidence of ZG insufficiency causing hyperkalemia after adrenalectomy; the secondary outcome was the identification of risk factors predisposing for hyperkalemia.

Results: Eighteen of 110 patients (16%) developed postoperative hyperkalemia. The majority of these patients (n = 14) had undetectable plasma aldosterone levels after adrenalectomy; four had low aldosterone levels. In 12 of these patients, hyperkalemia was documented only once and resumed spontaneously. Prolonged hypoaldosteronism accompanied by hyperkalemia was observed in six patients (5% of total cohort). These patients needed continuous mineralocorticoid replacement therapy for 11–46 months. Mineralocorticoid antagonist treatment for 4 wk prior to surgery did not prevent hyperkalemia. In multivariate analysis, preoperatively decreased glomerular filtration rate and increased serum creatinine as well as increased postoperative creatinine and microalbuminuria remained significant predictors of hyperkalemia.

Conclusion: Persistent postoperative hypoaldosteronism with hyperkalemia occurs in 5% of adrenalectomized PA patients through prolonged ZG insufficiency, requiring long-term fludrocortisone treatment. Potassium levels after adrenalectomy must be monitored to avoid life-threatening hyperkalemia. **(*J Clin Endocrinol Metab* 97: 3965–3973, 2012)**

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Abbreviations: AC, Cortisol-corrected aldosterone ratio; ACE, angiotensin-converting enzyme; APA, aldosterone-producing adenoma; ARB, angiotensin-II receptor blocker; AVS, adrenal venous sampling; BP, blood pressure; GFR, glomerular filtration rate; MR, mineralocorticoid receptor; NSAID, nonsteroidal antiinflammatory drug; PA, primary aldosteronism; RAAS, renin-angiotensin-aldosterone system; TTKG, transtubular potassium gradient; ZG, zona glomerulosa.

Primary aldosteronism (PA) is the most common cause of secondary arterial hypertension. Five to 13% of all hypertensive subjects and up to 20% of all patients with refractory hypertension are affected by PA (1, 2). Excessive aldosterone secretion induces increased potassium excretion with hypokalemia, sodium and fluid retention with hypertension, and ultimately increases cardiovascular, renal and metabolic morbidity by blood pressure (BP)-dependent and -independent mechanisms (3–5). Therefore, early diagnosis and specific therapy are of crucial importance (3, 6). The main causes of PA are aldosterone-producing adenomas (APA) and bilateral idiopathic adrenal hyperplasia, accounting for more than 95% of the cases. The therapy of choice is lifetime administration of mineralocorticoid receptor (MR) antagonists in idiopathic adrenal hyperplasia and unilateral adrenalectomy in APA (2).

Adrenalectomy is an effective treatment for APA. Remission of hypertension is seen in 33–72% of patients after adrenalectomy and improvement in the remainder (7–10). Hypokalemia is cured in almost all patients. A pathophysiological consequence of unilateral aldosterone excess is the suppression of contralateral zona glomerulosa (ZG) function via suppressed plasma renin levels. After adrenalectomy this can lead to inadequate ZG function and hypoaldosteronism impairing renal potassium clearance and consequent hyperkalemia. To our knowledge hyperkalemia after adrenalectomy has been described only in case reports (11–13). Yet the severity and incidence of postoperative hyperkalemia has not been investigated. The aim of our study was to analyze the incidence and course of hyperkalemia after adrenalectomy in a large series of APA.

Patients and Methods

Study population

Data from 110 patients with PA adrenalectomized at the centers in Munich (n = 81) and Berlin (n = 29) between 2004 and March 2012 were analyzed retrospectively. The data were extracted from the Munich and Berlin centers of the German Conn's registry-Else Kröner-Fresenius Hyperaldosteronismus registry. Patients were further analyzed if they had documented follow-up for at least 1 month after adrenalectomy. The diagnosis of PA was made by established criteria (14). In short, the patients had arterial hypertension, an elevated aldosterone to renin ratio and abnormal confirmatory testing by either acute volume loading with 2 liters saline or furosemide stimulation (14–16). The patients were studied without antihypertensive medication during diagnostic procedures whenever possible. If BP required antihypertensive medication, preferably the calcium channel blocker verapamil (maximum dose 240 mg twice daily) and the α-adrenoceptor antagonist doxazosin (maximum dose 16 mg daily), were used. Subtype differentiation was determined using adrenal venous sampling (AVS) as described earlier (17, 18). Ninety-two percent of the patients underwent AVS to differentiate between unilateral and bilateral aldosterone excess. We used a selectivity index of 2 (adrenal vein cortisol to peripheral cortisol) and a lateralization index of 4 or greater for the diagnosis of unilateral aldosterone excess. We assessed the contralateral suppression index in the selective AVS studies, which is defined as the ratio of the cortisol-corrected aldosterone ratio (AC) of the nondominant adrenal gland over the AC of the inferior vena cava ($AC_{NondominantAdrenal}/AC_{inferior\ vena\ cava}$) (19). However, decision for adrenalectomy was not based on suppression of the contralateral adrenal gland. The success rate of AVS was 78% in Munich and 65% in Berlin. Medical records were analyzed to obtain initial demographic data, laboratory values, adrenal imaging, and AVS results. Duration of hypertension and medication was assessed.

Medical treatment before and after surgery

After subtype differentiation, the majority of the patients were treated with MR antagonists to control BP and to correct hypokalemia. The treatment with MR antagonists was based on the individual decision of the responsible physicians. Spironolactone was used primarily, whereas eplerenone was used in patients intolerant to unselective MR antagonists. Eplerenone treatment was continued until the day before surgery. Because of the prolonged half-life, spironolactone was discontinued in most patients 3–7 d before surgery. After surgery, patients continued their usual antihypertensive medication (with the exception of MR antagonists and potassium supplementation) until the first postoperative visit (generally within the first 10 d). Patients were treated with low-molecular-weight heparin for 7 d after adrenalectomy.

Because the procedure of blood sampling has a profound impact on potassium level measurements, blood was drawn by venipuncture without quenching in fasting state by trained staff. The tourniquet was released immediately for several seconds after venipuncture before withdrawing blood. We did not use vacutainers. Blood was brought to the central laboratory and the plasma was separated from the cells as quickly as possible.

Definitions and outcome variables

We determined the incidence of ZG insufficiency [defined as hypoaldosteronism with undetectable plasma aldosterone levels ($<$35 ng/liter) in the presence of a serum potassium $>$5.0 mmol/liter] after adrenalectomy. Patients were classified as having hyporeninemic hypoaldosteronism (suppressed renin levels) or hyperreninemic hypoaldosteronism (stimulated renin levels). Postoperative aldosterone levels were defined as follows: undetectable ($<$35 ng/liter) and low ($<$50 ng/liter). Hyperkalemia was defined as serum potassium greater than 5.0 mmol/liter. Postoperative transient hyperkalemia was defined as hyperkalemia that occurred only once during the first months after adrenalectomy and resumed spontaneously without further intervention. Postoperative persistent hyperkalemia was defined as hyperkalemia that lasted more than 3 months and had to be treated medically.

Outcome variables analyzed included clinical parameters such as systolic and diastolic BP, serum potassium, serum creatinine, glomerular filtration rate (GFR), microalbuminuria, and number of antihypertensive medications at follow-up. The number and dose of antihypertensive medications [β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARB), diuretics, calcium channel blockers, α-blockers, and central-acting sympathomimetics], and non-

steroidal antiinflammatory drugs (NSAID) at diagnosis and follow-up was documented. All variables were assessed prospectively within the registry using standard operational procedures.

We assessed the transtubular potassium gradient [TTKG = (urine [K]/(urine osmoles per plasma osmoles)/serum [K])], which allows the evaluation of mineralocorticoid bioactivity on potassium excretion in the cortical collecting duct in patients with hypo- or hyperkalemia (20, 21). The normal response to hyperkalemia is an increase in aldosterone secretion leading to an increased urinary potassium excretion, with an increase of TTKG to greater than 10 (22). A result of less than 6 in a hyperkalemic patient indicates inadequate aldosterone concentration or effect (20).

Analytical methods

Before 2006, aldosterone was measured using either a commercial RIA (Maia Adaltis Italia S.p.a., Casalecchio di Reno, Italy, and Coat-a-Count, Siemens, Los Angeles, CA) or a chemiluminescence immunoassay (Nichols Advantage, Nichols Institute, San Clemente, CA). Since 2006, all plasma aldosterone measurements were performed with Coat-a-Count-RIA (Biermann DPC, Bad Nauheim, Germany). Since 2007, active renin concentration was measured by the Diasorin assay (Liaison, Saluggia, Italy) in Munich and with the Cisbio assay (Berlin, Germany) in Berlin and before that as renin activity with the Maia Adaltis Italia assay (Casalecchio di Reno, Italy). In our hands, the respective within- and between-assay coefficients of variation were below 9 and 12% for aldosterone and below 5.6 and 12.2% for renin.

All other biochemical variables were assayed in plasma or serum in our central laboratory using standard methods. Serum potassium was measured using flame photometry (ISE Indirect, Cobas Integra, the Roche platform; Roche, Mannheim, Germany). Creatinine-normalized albumin was measured in the morning spot urine (Tinaquant Albumin Gen.2 Cobas Integra, Roche).

Statistics and ethics

If not stated otherwise, results are expressed as mean ± SD or median and the 25th to 75th percentiles for nonnormally distributed variables. Data between groups were compared using an ANOVA test or χ^2 test. For nonparametric testing, a Kruskal-Wallis Test was applied. For multivariate analysis, factors significantly associated with the presence of hyperkalemia in a univariate analysis were inserted into a linear multivariate logistic regression analysis in a backward-stepwise fashion. $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using standard statistical software (SPSS 20, IBM; SPSS Inc., Chicago, IL). The German Conn's registry has been approved by the local ethical committee. Written informed consent was obtained from all subjects.

Results

Patients

A total of 110 patients underwent adrenalectomy because of unilateral aldosterone excess (58 men and 52 women). Mean patient age at diagnosis was 51 ± 12 yr, with all patients being hypertensive (mean BP 151 ± 20/92 ± 12 mm Hg) and being treated with a median of two (two, three) antihypertensive drugs. Ninety-two percent of the patients were hypokalemic at diagnosis. Detailed data are shown in Table 1.

Treatment with MR antagonist before adrenalectomy

We assessed the use of MR antagonists in the preoperative phase. Twenty-four patients (22%) were not treated with MR antagonists before adrenalectomy. Seventy-nine patients were treated with spironolactone at a median daily dose of 50 mg (50; 81 mg) [treatment time 2 months (1; 3 months)] and seven patients with eplerenone at a median dose of 25 mg (25; 50 mg) [treatment time 2 months (1; 7 months)].

Effect of adrenalectomy on blood pressure, renal function, and biochemical remission

The patients visited our clinic after adrenalectomy to assess BP, potassium, and aldosterone to renin ratio to document biochemical and clinical cure of PA. Clinical data are shown in Table 1. The overall decrease of BP was 18 ± 24/9 ± 13 mm Hg with a loss of a median of one (none, two) antihypertensive drug. Thirty-three percent of the patients were treated with ACE inhibitors or ARB, 25% with β-blockers, and 9% with NSAID (see Table 1) postoperatively. In comparison with preoperative renal function, the overall decrease of GFR was 10 ± 17 ml/min. Fifty-two of 110 patients (47%) had plasma aldosterone levels less than 50 ng/liter after adrenalectomy.

Incidence of ZG insufficiency causing hyperkalemia after adrenalectomy

Postoperative hyperkalemia was documented in 18 patients (16%; 14 with undetectable, four with low aldosterone levels). In 12 of these patients, hyperkalemia was transient and occurred only once during the first 3 months after adrenalectomy and abated spontaneously without further intervention (group 1: postoperative transient hyperkalemia). In six patients, the hyperkalemia was prolonged and persisted for 11 months, 11 months, 11 months, 20 months, 24 months, and 46 months after adrenalectomy (group 2: postoperative persistent hyperkalemia). Clinical parameters before and after adrenalectomy are shown in Table 2. The severity of hyperkalemia in group 2 patients varied, ranging from 5.4 to 7.1 mmol/liter. Three patients had potentially life threatening hyperkalemia (maximal serum potassium 6.3, 6.8, and 7.1 mmol/liter) requiring emergency treatment, and the other three patients had clinical relevant potassium levels (maximal serum potassium 5.4, 5.7, and 5.7 mmol/liter), resulting into adjustment of medication. All subjects of group 2 had undetectable aldosterone levels (<35 ng/liter). The patient with the potassium value of 7.1 mmol/liter had a hy-

TABLE 1. Characteristics of the patients before and after adrenalectomy: comparison of the patients affected by postoperative hyperkalemia and without hyperkalemia (values represent mean ± SD unless otherwise specified)

Variable	All patients	Postoperative transient hyperkalemia (n = 12, group 1)	Postoperative persistent hyperkalemia (n = 6, group 2)	Postoperative normokalemia (n = 92, group 3)	*P* value
Age (yr)	51 ± 12 (n = 110)	54 ± 13 (n = 12)	65 ± 9 (n = 6)	50 ± 12 (n = 92)	0.008
Gender (male/female)	58/52 (n = 110)	7/5 (n = 12)	4/2 (n = 6)	47/45 (n = 92)	0.698
Duration of hypertension (yr)[a]	6 (2; 16) (n = 109)	5 (1; 24) (n = 12)	17 (7; 23) (n = 6)	6 (2; 15) (n = 91)	0.177
Follow-up (months)	28 ± 26 (n = 110)	33 ± 30 (n = 12)	21 ± 14 (n = 6)	28 ± 26 (n = 92)	0.562
Minumum potassium (mmol/liter)	2.7 ± 0.5 (n = 100)	2.9 ± 0.6 (n = 12)	2.7 ± 0.5 (n = 6)	2.7 ± 0.4 (n = 82)	0.506
Hypokalemic (%)	92% (n = 100)	83% (n = 12)	100% (n = 6)	93% (n = 82)	0.407
Diabetes mellitus (%)	15% (n = 110)	17% (n = 12)	17% (n = 6)	15% (n = 92)	0.988
Potassium substitution pre-OP (mEq)[a]	40 (3; 120) (n = 90)	40 (0; 100) (n = 11)	70 (30; 130) (n = 6)	40 (12; 120) (n = 73)	0.642
MR ant therapy pre-OP (%)	78% (n = 110)	58% (n = 12)	100% (n = 6)	79% (n = 92)	0.104
Initial systolic BP (mm Hg)	151 ± 20 (n = 104)	168 ± 30 (n = 12)	143 ± 11 (n = 6)	149 ± 18 (n = 86)	0.004
Follow-up systolic BP (mm Hg)	132 ± 15 (n = 106)	135 ± 8 (n = 12)	135 ± 23 (n = 6)	132 ± 15 (n = 88)	0.739
Initial diastolic BP (mm Hg)	92 ± 12 (n = 103)	99 ± 16 (n = 12)	89 ± 7 (n = 6)	91 ± 11 (n = 85)	0.073
Follow-up diastolic BP (mm Hg)	83 ± 10 (n = 106)	86 ± 10 (n = 12)	81 ± 12 (n = 6)	83 ± 10 (n = 88)	0.560
Pre-OP number of antihypertensive drugs[a]	2 (2; 3) (n = 105)	2 (1; 3) (n = 11)	3 (2; 5) (n = 6)	2 (2; 3) (n = 88)	0.424
Post-OP number of antihypertensive drugs[a]	1 (0; 3) (n = 107)	1 (0; 2) (n = 12)	2 (2; 3) (n = 6)	1 (0; 3) (n = 89)	0.340
Treatment with ACE inhibitors/ARB post-OP	33% (n = 99)	25% (n = 12)	33% (n = 6)	35% (n = 81)	0.581
Treatment with β-blockers post-OP	26% (n = 99)	33% (n = 12)	33% (n = 6)	25% (n = 81)	0.556
Treatment with NSAID post-OP	9% (n = 99)	17% (n = 12)	33% (n = 6)	6% (n = 81)	0.064
Aldosterone pre-OP (ng/liter)[a]	282.0 (161.2; 459.0) (n = 107)	287.9 (151.5; 453.1) (n = 12)	480.0 (394.3; 664.8) (n = 6)	275 (160.5; 421.9) (n = 89)	0.096
Aldosterone post-OP (ng/liter)[a]	56.0 (35.0; 87.5) (n = 105)	90.0 (41.5; 148.8) (n = 12)	35.0 (33.0; 35.0) (n = 6)	56.0 (35.0; 85.0) (n = 87)	0.006
Renin pre-OP (mU/liter)[a]	2.8 (1.6; 4.8) (n = 103)	2.7 (1.4; 3.4) (n = 12)	2.9 (1.4; 5.5) (n = 6)	2.8 (1.6; 6.2) (n = 85)	0.729
Renin post-OP (mU/liter)[a]	14.4 (7.9; 31.9) (n = 105)	15.8 (2.8; 35.1) (n = 12)	14.7 (6.1; 108.3) (n = 6)	14.4 (8.1; 30.3) (n = 87)	0.788
Creatinine pre-OP (mg/dl)[a]	0.9 (0.8; 1.0) (n = 107)	0.8 (0.7; 1.2) (n = 12)	1.2 (1.0; 1.5) (n = 6)	0.8 (0.7; 1.0) (n = 89)	0.027
Creatinine post-OP (mg/dl)[a]	1.0 (0.8; 1.2) (n = 109)	1.1 (0.7; 1.4) (n = 12)	1.5 (1.4; 1.9) (n = 6)	1.0 (0.8; 1.1) (n = 91)	0.002
GFR pre-OP (ml/min)	82 ± 22 (n = 107)	79 ± 23 (n = 12)	56 ± 17 (n = 6)	84 ± 21 (n = 89)	0.007
GFR post-OP (ml/min)	72 ± 21 (n = 109)	68 ± 17 (n = 12)	41 ± 8 (n = 6)	74 ± 20 (n = 91)	0.000
BMI pre-OP (kg/m^2)	28.4 ± 5.1 (n = 103)	28.7 ± 5.3 (n = 12)	26.4 ± 2.4 (n = 6)	28.5 ± 5.1 (n = 85)	0.593
BMI post-OP (kg/m^2)	28.7 ± 5.1 (n = 106)	28.9 ± 5.2 (n = 11)	26.9 ± 2.9 (n = 6)	28.7 ± 5.2 (n = 89)	0.690
Microalbuminuria pre-OP (mg/dl) (spot urine)[a]	2.4 (0.9; 7.7) (n = 85)	4.3 (0.8; 13.6) (n = 12)	22.1 (1.9; 47.7) (n = 6)	2.0 (0.8; 5.3) (n = 67)	0.122
Microalbuminuria post-OP (mg/dl)[a] (spot urine)	0.5 (0.5; 1.6) (n = 72)	0.8 (0.5; 2.8) (n = 11)	3.6 (0.8; 17.7) (n = 6)	0.5 (0.5; 0.9) (n = 55)	0.021

OP, Operative/operatively; ant, antagonist; BMI, body mass index.

[a] Data are median (25th to 75th percentiles).

perkalemia-related hospitalization: he reported dizziness and perioral numbness and needed emergency in-patient treatment, which included increased fluid intake and forced diuresis induced by loop diuretics. Treatment of hyperkalemia included weekly monitoring of serum potassium concentrations, instruction to reduce dietary potassium content, and adjustment of antihypertensive medication (withdrawal of potassium sparing medication like ACE inhibitors or ARB, start of loop diuretics). One patient was treated with oral Na^+HCO^-3 supplementation. Five of six patients needed continuous treatment with fludrocortisone (0.05–0.3 mg/d, n = 5). One patient refused to be treated with fludrocortisone and remained mildly hyperkalemic until the last follow-up. In one patient, fludrocortisone was withdrawn after 14 months, but he had recurrence of hyperkalemia (5.3 mmol/liter). The other patients had ongoing mineralocorticoid replacement therapy at last follow-up (April 2012). Periodic attempts to withdraw fludrocortisone ended so far with recurrence of hyperkalemia.

Analysis of risk factors associated with postoperative hyperkalemia

We performed analysis of risk factors associated with postoperative hyperkalemia and compared the groups of patients with postoperative transient hyperkalemia (group 1;

TABLE 2. Pre- and postoperative characteristics of the patients with prolonged postoperative hyperkalemia

n	Age (yr), sex	Duration BP (yr)	Creatinine pre-OP (mg/dl)	GFR pre-OP (ml/min)	Microalbuminuria pre-OP (mg/dl)	Minimum K (mmol/liter)	Aldo pre-OP (ng/liter)	Renin pre-OP (mU/liter)	Antihypertensive drugs pre-OP	BP systolic pre-OP (mm Hg)
1	70, f	18	0.95	58.2	46.0	2.7	191	2.6	3	160
2	63, f	7	1.2	44.6	7.1	2.4	475	9.0	2	145
3	78, m	30	1.0	72.3	2.3	2.7	793	1.6	2	133
4	54, m	16	1.1	69.8	0.8	3.1	485	3.2	3	139
5	67, m	5	2.4	27.0	52.9	3.4	462	4.3	4	131
6	55, m	21	1.2	62.9	37.0	2.0	622	0.9	7	152

f, Female; m, male; OP, operative; K, potassium.

n = 12), persistent hyperkalemia (group 2; n = 6), and postoperative normokalemia (group 3; n = 92). The patients with persistent hyperkalemia were significantly older at the time of diagnosis than the normokalemic patients (65 ± 9 *vs.* 50 ± 12 yr, $P = 0.026$). They also had significantly worse preoperative renal function (creatinine: 1.2 mg/dl [1.0; 1.5 mg/dl] *vs.* 0.8 mg/dl [0.7; 1.0 mg/dl], $P = 0.001$; GFR: 56 ± 17 *vs.* 84 ± 21 ml/min, $P = 0.024$). Postoperatively, the renal function decreased in all groups but remained the lowest in the group with severe hyperkalemia [creatinine: 1.5 mg/dl (1.4; 1.9 mg/dl) *vs.* 1.0 mg/dl (0.8; 1.1 mg/dl) in group 3, $P = 0.001$, and *vs.* 1.1 mg/dl (0.7; 1.4 mg/dl) in group 1, $P = 0.013$; GFR: 41 ± 8 *vs.* 74 ± 20 ml/min in group 3, $P = 0.000$, and *vs.* 68 ± 17 ml/min in group 1, $P = 0.001$]. In addition, the patients with persistent hyperkalemia had the highest levels of postoperative microalbuminuria [3.6 mg/dl (0.8; 17.7 mg/dl) *vs.* 0.5 mg/dl (0.5; 0.9 mg/dl), $P = 0.013$] (see Table 1). In addition to preoperatively decreased GFR and increased serum creatinine, postoperative creatinine and microalbuminuria also remained significant predictors for postoperative hyperkalemia in multivariate analysis ($P < 0.001$, R = 0.632). Postoperative hyperkalemia was not prevented by prior MR antagonist treatment ($P = 0.104$). Postoperative treatment with ACE inhibitors, ARB, and β-blockers did not differ significantly between the groups (see Table 1). Treatment with NSAID was more frequent in group 2 without reaching statistical significance ($P = 0.064$).

Postoperative hypoaldosteronism in patients with severe hyperkalemia

In all patients with persistent ZG insufficiency (n = 6), hypoaldosteronism was longstanding (11–46 months). In two patients, the hypoaldosteronism was hyporeninemic in nature (secondary hypoaldosteronism; Fig. 1, A–C). The plasma renin and aldosterone values stayed inadequately low over the observation period. In four patients, the hypoaldosteronism was hyperreninemic in nature (primary hypoaldosteronism) (see Fig. 1, A–C). Despite adequate renin secretion, plasma aldosterone levels remained below the limit of detection. The calculation of the TTKG showed decreased values of less than 6 in three of four evaluated hyperkalemic patients, showing inappropriate renal response to hyperkalemia (20).

Contralateral suppression index in AVS

We assessed the contralateral gland suppression index in those patients who had selective AVS prior surgery (n = 77). Five of five investigated patients with persistent hyperkalemia demonstrated a contralateral suppression index of aldosterone in the nondominant gland less than 1, whereas five of seven patients with transient hyperkalemia (71% of investigated patients) and 50 of 67 patients with normokalemia (75% of investigated patients) had a contralateral suppression index less than 1. This difference was not statistically significant ($P = 0.468$).

Discussion

In this study we describe persistent hyperkalemia after adrenalectomy in a subset of patients with APA. All patients had postoperative ZG insufficiency with undetectable plasma aldosterone concentrations despite being hyperkalemic. Risk factors associated with hyperkalemia were higher age and impaired renal function. Hypoaldosteronism persisted for several months and is ongoing at last follow-up in all subjects. Preoperative treatment with MR antagonists did not influence the incidence of hypoaldosteronism and hyperkalemia.

The deleterious and BP-independent consequences of aldosterone hypersecretion on renal function have already been demonstrated (5, 23–25). Discussed mechanisms include direct harmful effects of aldosterone with the up-regulation of MR expression leading to inflammation, fibrosis, and mesangial proliferation (26, 27). On the other side, as a consequence of hyperaldosteronism with vasodilation in afferent and efferent arterioles, glomerular hyperfiltration occurs in the untreated patients. This mechanism might be possibly due to intraglomerular hypertension and elevated sodium reabsorption in the proximal tubule with an increase of glomerular filtration via tubuloglomerular feedback (28, 29). After adrenalectomy, temporary hypoaldosteronism and

TABLE 2. Continued

BP diastolic pre-OP (mm Hg)	Creatinine post-OP (mg/dl)	GFR post-OP (ml/min)	Microalbuminuria post-OP (mg/dl)	K post-OP (mmol/liter)	Aldo post-OP (ng/liter)	Renin post-OP (mU/liter)	Antihypertensive drugs post-OP	BP systolic post-OP (mm Hg)	BP diastolic post-OP (mm Hg)
80	1.1	47.1	6.0	6.4	<27	105.8	1	166	97
84	1.4	36.7	0.9	5.1	<35	35.0	3	146	88
85	1.6	42.0	0.5	5.1	<35	10.4	3	116	67
94	1.3	57.5	1.1	5.1	<35	3.6	2	128	77
92	2.6	24.7	42.4	6.3	<35	367.2	1	105	70
100	2.1	32.7	9.4	7.1	<35	7.6	2	147	88

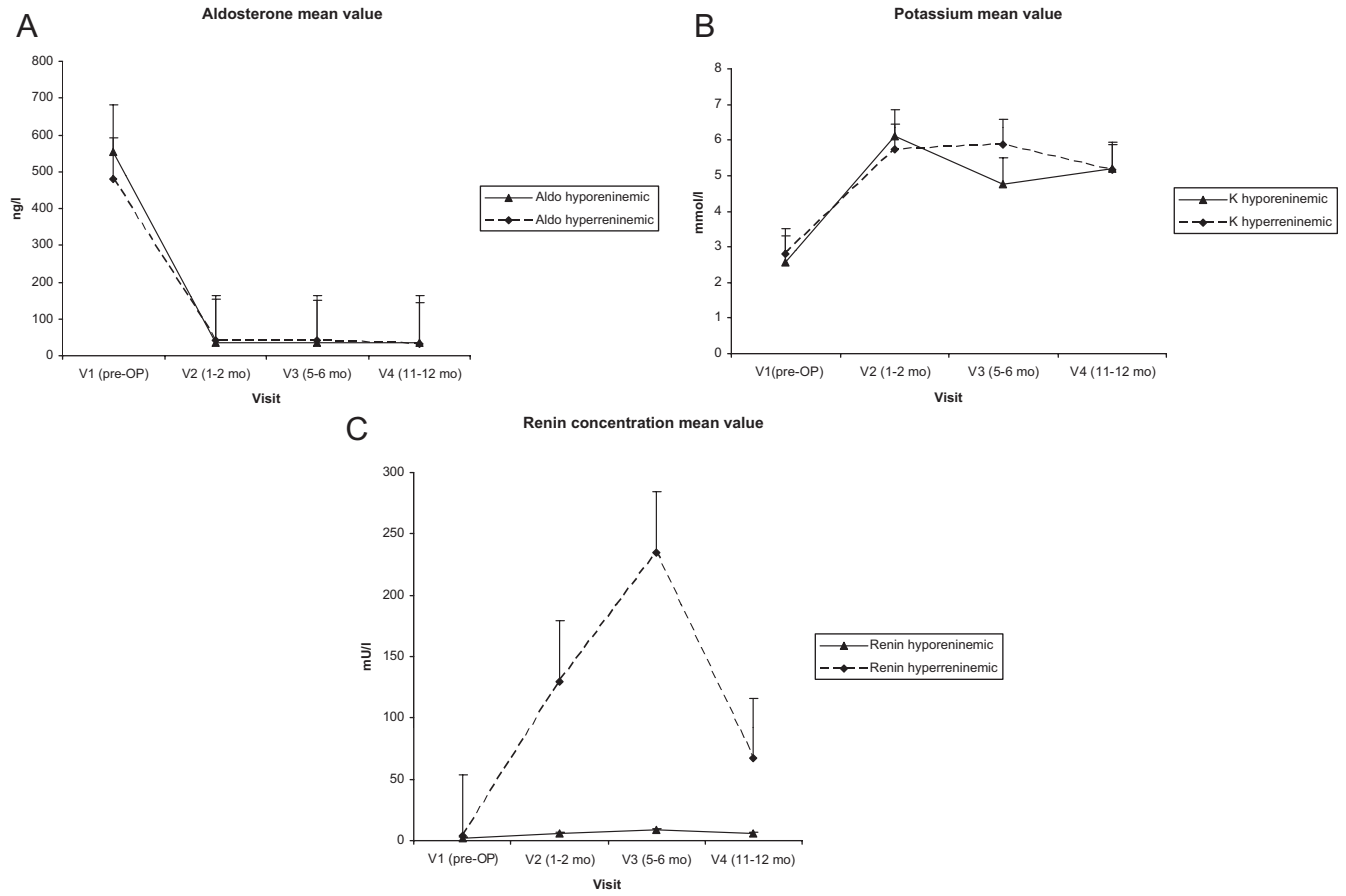

FIG. 1. Mean values of aldosterone (A), serum potassium (B), and renin concentration (C) of the patients with persistent hyperkalemia prior to adrenalectomy [visit (V) 1] and at postoperative visits (V2: 1–2 months; V3: 5–6 months; and V4: 11–12 months): hyporeninemic (n = 2) and hyperreninemic hypoaldosteronism (n = 4). Values are mean ± SEM.

hypotension lead to a decrease of GFR and increase of serum creatinine with the unmasking of the preexisting preoperative renal impairment in some patients (25, 29–31). In our retrospective study of the German Conn's Registry, a significant decline of renal function was demonstrated after adrenalectomy in a large cohort of PA patients (16). In the present study, deterioration of renal function with decreases of GFR and increases of serum creatinine were observed after adrenalectomy in all three groups, but renal function was lowest in patients with postoperative persistent hyperkalemia. Therefore, impaired renal function appears to be a strong predictor of hyperkalemia after adrenalectomy. Also, the use of NSAID was more frequent in patients with persistent postoperative hyperkalemia (33%) and transient hyperkalemia (17%) than in patients with normokalemia (6%) ($P = 0.064$) and might have contributed initially to hyperkalemia. NSAID are known to potentially cause hyperkalemia by reducing prostaglandin synthesis through cyclooxygenase inhibition. Prostaglandins increase potassium excretion by stimulating renin and consecutive aldosterone secretion and maintaining GFR through preglomerular arteriolar vasodilation (32).

The production of aldosterone in the ZG of the adrenal cortex is mainly regulated by renin-dependent production of angiotensin-II, but ACTH and serum potassium also stimulate its secretion (33). Aldosterone leads to urinary potassium excretion through its action on the principal cells of the collecting duct. A pathophysiological consequence of unilateral aldosterone excess is the suppression of contralateral ZG function via suppressed plasma renin levels. In cortisol-producing adrenal tumors (Cushing's syndrome), chronic suppression of CRH and ACTH leads to the atrophy of the contralateral adrenal cortex with the suppression of cortisol production. After adrenalectomy, recovery can be slow with a high risk of life-threatening adrenal crisis. By contrast, recovery of the renin-angiotensin-aldosterone system (RAAS) after unilateral adrenalectomy in APA is usually considered as being relatively rapid and sufficient to avoid the need for mineralocorticoid replacement therapy in the majority of patients. This may be partly due to the fact that in addition to the RAAS, potassium and ACTH also maintain some degree of mineralocorticoid activity in the contralateral adrenal gland (34). Indeed, unlike the markedly atrophic adrenal cortex surrounding a cortisol-producing adenoma, the ZG sur-

rounding an APA is generally not atrophic and can even be paradoxically hyperplastic (35). Yet severe hyperkalemia after adrenalectomy in PA has been defined earlier (11–13). In these patients, inadequate ZG function occurs after adrenalectomy, leading to hypoaldosteronism with impaired renal potassium clearance and consecutive hyperkalemia.

We identified six patients (5%) with severe postoperative hyperkalemia lasting more than 11 months and 12 patients (11%) with transient hyperkalemia in a large series of 110 patients adrenalectomized for APA. The patients with severe hyperkalemia all had prolonged hypoaldosteronism until last follow-up.

Two of the patients had hyporeninemic hypoaldosteronism. Renin levels remained inadequately low throughout the observation period, leading to the diagnosis of secondary hypoaldosteronism. Previous reports of postoperative hyperkalemia also showed undetectable plasma renin activity (11, 13). Through immunohistochemical analyses, Taniguchi *et al.* (11) were able to show that mineralocorticoid production was completely suppressed in the adjacent adrenal tissue of the described patient. On the other side, the zona fasciculata and zona reticularis did not show any atrophy, suggesting a normal hypothalamic-pituary-adrenal axis function. This state might also be present in the contralateral adrenal gland. The reason for the slow recovery of mineralocorticoid synthesis after adrenalectomy is not clear. Possible mechanisms for this hyporeninemic condition may be a delayed recovery of the ZG cell function or permanent irreversible renal target organ damage from hypertension and/or other renal effects of aldosterone excess.

In the other four patients, plasma renin levels increased adequately after surgery but were not followed by a consecutive increase of plasma aldosterone levels. This constellation is typical for primary hypoaldosteronism, similar to a case recently described by Huang *et al.* (12).

Five of our five subjects with selective AVS had low suppression index in the contralateral adrenal gland during AVS prior to surgery. Three of four of our investigated hyperkalemic patients showed TTKG levels less than 6, demonstrating mineralocorticoid deficiency and inappropriate collecting tubule response to hyperkalemia (20).

Preoperative treatment with MR antagonists, which may restore the responsiveness of the chronically suppressed RAAS, did not influence the incidence of hypoaldosteronism and hyperkalemia in our patients. Our data confirm the findings of a historical study that reported hypoaldosteronism despite stimulated renin levels for months to years prior to adrenalectomy (34). Together these data suggest that the degree or the duration of the preoperative treatment might not be sufficient to stimulate aldosterone production in the previously suppressed adrenal gland. On the other hand, discontinuation of spironolactone for 3–7 d as in our study might not be long enough to withdraw effects on the MR, due to the very long half-life of active metabolites. Patients might display effects of spironolactone on RAAS, even after 4–6 wk from interruption. At last, reversal of hyperaldosteronism with a possible normalization of the sensitivity of the ZG to angiotensin-II after long-term MR antagonist treatment has been reported previously by us and others (36–38). A discussed mechanism could be a direct inhibitory effect of spironolactone on adrenal steroidogenesis, possibly explaining the observed hypoaldosteronism (34, 39, 40).

Limitations of our study

The incidence of hyperkalemia might have been overestimated in our study through the following factor: the proportion of patients who were hypokalemic before surgery was very high (92%) compared with other series (*e.g.* 50%) (1, 2). This would imply that our series of APA consisted of particularly severe cases of autonomous aldosterone secretion, resulting in greater suppression of RAAS, and lower potassium, both of which would have led to a greater and more prolonged degree of suppression of aldosterone production by the contralateral adrenal gland.

Therapeutic recommendations

In summary, we describe persistent hyperkalemia after adrenalectomy in patients with APA. Patients with higher age and already impaired renal function prior adrenalectomy appear to be at particular risk of developing potentially life-threatening hyperkalemia. As recommended in The Endocrine Society guidelines, medications impairing potassium clearance and potassium supplementation should be withdrawn on the first postoperative day (2). When hyperkalemia is detected, prolonged monitoring is necessary. When the hyperkalemia does not resolve spontaneously, mineralocorticoid replacement therapy should be initiated. Patients should be instructed to follow a low-potassium and high-sodium diet. Endocrinologists treating patients with PA should be aware of this complication and should monitor potassium levels and renal function in all patients after adrenalectomy.

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