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Early Renin Recovery After Adrenalectomy in Aldosterone-Producing Adenomas: A Prospective Study

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ABSTRACT

The aim of the study was to clarify the relationship and the time of aldosterone and renin recoveries at immediate and long-term follow-up in aldosterone-producing adenoma (APA) patients who underwent adrenalectomy. Prospective and longitudinal protocol in a cohort of APA patients was followed in a single center. Among 43 patients with primary aldosteronism (PA), thirteen APA patients were enrolled in this study. Blood was collected for aldosterone, renin, potassium, creatinine, cortisol, and ACTH before and 1, 3, 5, 7, 15, 30, 60, 90, 120, 180, 270, 360 days after adrenalectomy. At diagnosis, most patients (84 %) had hypokalemia and high median aldosterone levels (54.8; 24.0–103 ng/dl) that decreased to undetectable (< 2.2) or very low (< 3.0) levels between fifth to seventh days after surgery; then, between 3–12 months, its levels gradually increased to the lower normal range. The suppressed renin (2.3; 2.3–2.3 mU/l) became detectable between the fifteen and thirty days after surgery, remaining normal throughout the study. The aldosterone took longer than renin to recover (60 vs.15 days; p < 0.002) and patients with higher aldosterone had later recovery (p = 0.03). The cortisol/ACTH levels remained normal despite the presence of a post-operative hypoaldosteronism. Blood pressure and antihypertensive requirement decreased after adrenalectomy. In conclusion, our prospective study shows the borderline persistent post-operative hypoaldosteronism in the presence of early renin recovery indicating incapability of the zona glomerulosa of the remaining adrenal gland to produce aldosterone. These findings contribute to the comprehension of differences in renin and aldosterone regulation in APA patients, although both are part of the same interconnected system.

Introduction

Primary aldosteronism (PA), characterized by high plasma aldosterone and suppressed plasma renin, has been recognized as one of the most common causes of secondary hypertension [1]. However, it is still unrecognized by physicians [2] and has high heterogeneity among centers worldwide [3]. The PA prevalence has been increasing since its first description six decades ago [4, 5] ranging from 5–10 % in the general hypertensive population to 15–26 % in resistant hypertension patients [2, 6].

Unilateral aldosterone-producing adenoma (APA) and idiopathic bilateral adrenal hyperplasia are the most common causes of the autonomous aldosterone hypersecretion. Various genetic abnor-

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malities have been identified in APA and in familial forms of the disease [7]. Clinical practice guidelines have established PA diagnosis recommendations for clinical detection, screening and confirmatory tests, adrenal Computed Tomography (CT) scan, and bilateral adrenal vein sampling (AVS) to differentiate unilateral from bilateral forms of PA [8–10]. APA has been primarily treated by laparoscopic adrenalectomy while the bilateral form of PA mostly treated by mineralocorticoid receptor antagonists [1, 9].

Recently, the Primary Aldosteronism Surgical Outcome (PASO) study established international criteria for clinical and biochemical treatment success in APA patients [11, 12] and a numerical PASO score has been used for the prediction of patient clinical outcome after APA adrenalectomy [13, 14]. The aldosterone excess in patients with unilateral APA chronically suppresses renal renin release and decreases aldosterone secretion from the zona glomerulosa (ZG) of the contralateral adrenal gland [15–17] leading to the ZG insufficiency. Consequently, these patients present low plasma aldosterone after unilateral adrenalectomy and some isolated recent case reports have presented post-operative hyperkalemia as an indicator of post-operative hypoaldosteronism [12, 17–23].

The importance of the post-operative hypoaldosteronism recovery had surfaced since the 1960s [24–27]. However, there has been limited comprehension on renin and aldosterone relationship after APA adrenalectomy since most of the previous studies were retrospective reviews and none evaluated their recoveries using concurrent and consecutive samples at short- and long-term observation periods after adrenalectomy in patients presenting APA. Therefore, we designed the current study to clarify the relationship of serum aldosterone and renin levels at immediate and long-term follow-up, using a prospective and longitudinal protocol, in a cohort of patients with APA who underwent unilateral adrenalectomy in a single tertiary medical center. The second aim was to evaluate the time to reestablish the renin and aldosterone normal secretion after adrenalectomy in APA patients.

Patients and Methods

Patients

We prospectively studied forty-three patients with confirmed PA consecutively referred from September 2016 to February 2020 to the Division of Endocrinology, University Hospital at Ribeirao Preto Medical School, University of Sao Paulo, a Brazilian tertiary center for adrenal diseases. We adopted the protocol for PA clinical diagnosis and etiology differentiation according to The Endocrine Society guideline [9, 10]. The diagnostic differentiation between unilateral and bilateral PA forms was performed using a dedicated adrenal CT scan protocol in all 43 patients. In 26 out of 43 patients, the AVS protocol with continuous cosyntropin infusion was also performed. Cortisol concentrations from the adrenal and peripheral veins were used to confirm successful catheterization, adopting as selectivity index the adrenal:peripheral vein cortisol ratio of 5:1 [9]. To characterize lateralization, we used the cortisol-corrected aldosterone ratio from high-side to low-side of 4:1 [9]. In the setting of failed cannulation of the right adrenal vein, the aldosterone:cortisol ratio of the left adrenal vein compared with the inferior vena cava (LAV/IVC) was used based on Pasternak et al. [28]. We considered as suppression index, the cutoff values ratios of ≥ 5.5 and ≤ 0.5, which predicted left- and right-sided disease, respectively.

Nineteen patients had confirmed APA diagnosis and were enrolled in this study (▶ **Fig. 1**). At the time of the diagnosis, APA patients underwent systematic assessment for aldosterone and cortisol co-secretion [29] by well-established tests for hypercortisolism diagnosis [30]. There were no shift workers among patients. The study was approved by the Ethical Committee of the Ribeirao Preto Medical School, University of Sao Paulo.

Patient blood samples were collected for baseline serum aldosterone and direct renin between 09:00 to 10:00 h, after 2 hours in the upright position followed by 10 minutes seated. Patients had normal sodium intake diet and hypokalemia, if present, was corrected. Drugs affecting aldosterone and DRC were withdrawn for at least 4 weeks. PA detection cut-off levels were serum aldosterone of > 15 ng/dl associated with a suppressed renin concentration of < 5 mIU/l. Diagnosis of PA was confirmed by intravenous saline suppression test using an aldosterone cut-off of > 10 ng/dl. Confirmatory tests were not performed in patients with suppressed direct renin concentration (DRC), plasma aldosterone concentration of > 20 ng/dl, and spontaneous hypokalemia [9].

Study design: post-adrenalectomy prospective longitudinal protocol

Nineteen patients submitted to unilateral adrenalectomy were followed by a prospective longitudinal study protocol. Briefly, serum aldosterone and DRC were measured in the morning before and 1, 3, 5, 7, 15, 30, 60, 90, 120, 180, 270, and 360 days after adrenalectomy. Potassium, creatinine, cortisol, and ACTH levels were also determined. There was a rigorous control of pre-analytical and samples storage phases. Additionally, at the same time points, blood pressure measurement and antihypertensive treatment requirement were obtained. Antihypertensive medications were expressed as defined daily doses (DDD). In addition, prior to the blood collection during the longitudinal protocol, patients were on unrestricted salt intake diet and, when necessary, potassium replacement was prescribed. Subsequently, six patients were excluded due to the following reasons: progressive severity of chronic kidney disease (n = 2), persistent PA (n = 1), loss to follow-up (n = 1), and aldosterone and cortisol co-secretion (n = 2, ▶ **Fig. 1**). The descriptive data of aldosterone and cortisol co-secretion patients were presented separately. Clinical evaluation and the prospective protocol were under supervision of the same endocrinologists (LMM, PCLE, ACM). The same surgeons (CAFM, STJ) performed the unilateral video laparoscopic adrenalectomy.

Assays and laboratory methods

Serum aldosterone and plasma DRC were determined by chemiluminescence immunoassays using DiaSorin kits (Liaison, Stillwater, MN, USA). The limits of detection (LoD) and quantitation (LoQ) at 20 % coefficient of variation (CV) of aldosterone immunoassay were 2.2 and 3.0 ng/dl, respectively [31]. The limit of detection of DRC was 2.3 mIU/l at 11 % CV. The intra- and inter-assay CVs were 4.8 and 6.7 % for aldosterone and 5.8 and 12.8 % for DRC. In our laboratory, the median (5th and 95th percentiles) values for healthy subjects in the upright position are, respectively, 12.5 (4.5 and 30)

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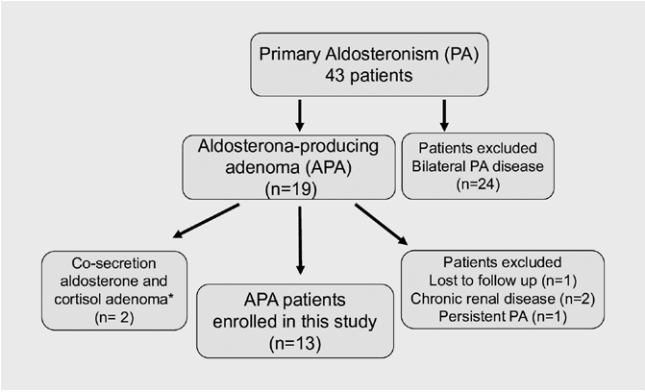

▶ **Fig. 1** Flow chart of the prospective and longitudinal study in patients with primary aldosteronism. *These patients were analyzed separately.

ng/dl for serum aldosterone and 16.9 (4.2 and 40) mIU/l for DRC. To convert aldosterone from ng/dl to nmol/l multiply by 0.027.

Serum cortisol and plasma ACTH levels were determined using standard immunoassays [30]. To convert cortisol from µg/dL to nmol/l multiply by 27.59 and ACTH from pg/ml to pmol/l multiply by 0.2202. The cut of ≤ 2 µg/dl of serum cortisol levels after the overnight 1 mg dexamethasone test excluded endogenous hypercortisolism. Serum potassium and creatinine were measured using Atellica CH Analyzer (Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA). All assays were determined at the Endocrinology and Clinical Chemistry Laboratories at the University Hospital.

Definitions of criteria for postoperative outcomes

Complete biochemical surgical success was defined when plasma aldosterone levels were < 5 ng/dl, according to PASO study consensus [11]. The PASO criteria for clinical and biochemical surgical success can be classified as complete, partial, or absent. We evaluated these criteria at 1, 3, 6, and 12 months after surgery [11–13].

For biochemical criteria, we defined serum aldosterone levels (ng/dl) lower than 2.2 as undetectable, between 2.2 and 3 as very low, and between 3 and 4.9 as low, based on our laboratory reference values. We arbitrarily considered post-operative aldosterone and renin recoveries when serum aldosterone level and DRC were > 3 ng/dl and ≥ 5 mU/l, respectively. These values should be observed on two subsequent blood collections and remained throughout the study. Hypokalemia and hyperkalemia were defined as serum potassium of ≤ 3.5 and ≥ 5.5 mmol/l, respectively [11, 17].

Statistical analysis

Data were analyzed for descriptive statistics and expressed as the mean ± SEM or median and the 25th to 75th percentiles (interquartile range) when appropriated. Results below the LoD of the assay were considered as the value of the limit of detection.

Two independent investigators (LMM and ACM) reviewed the data looking at post-operative recovery days of serum aldosterone and renin for each patient, with concordant observations. The difference (days) between the recoveries of DRC and serum aldosterone for each patient was also calculated.

The paired samples for each patient were analyzed by non-parametric paired Wilcoxon signed-rank test. Categorical variables were compared using Fisher's exact test. Data analyses were carried out with the statistical package GraphPad PRISM 8 (GraphPad Software, 2020, La Jolla, CA, USA). Significance was assumed when $p < 0.05$.

Results

Nineteen patients diagnosed with APA (11 M/8 F, age 48 ± 14 years) underwent unilateral adrenalectomy were initially included in the prospective protocol. Among them, nine patients were young (median age 26 years – range: 17 to 37 years) with spontaneous hypokalemia, marked aldosterone excess (median 68 ng/dl), and unequivocal radiological features of unilateral cortical adenoma on adrenal CT scan. Therefore, according to the current guidelines, they did not require AVS before proceeding to unilateral adrenalectomy [9]. APA patients who underwent AVS had a median lateralization index of 44 (range: 8.3–119) while in the bilateral PA group, the median lateralization index was 1.7 (range: 1–2.6). APA patients presented the aldosterone:cortisol ratio of the left adrenal vein compared with the inferior vena cava of 9.1 (range: 6–34) and 0.4 (range: 0.7–0.4) for left and right lateralization, respectively. Among the PA bilateral group, the median suppression index was 1.6 (range: 1–4.7).

After exclusion of the six patients, 13 APA patients (9 M/4 F) were fully analyzed. They had mean body mass index of 31 ± 9.8 kg/m^2. Hypertension had been diagnosed at the median age of 31 years (interquartile range 17–37 years) in these patients. However, PA diagnosis were performed later at the median age of 47 years (interquartile range 34–63 years). PA diagnosis occurred with a mean delay of 15.2 years (7.5–24.5). The huge variation in the time of PA diagnosis reflects the delay in the diagnosis of PA. Indeed, at diagnosis, ten patients had been previously treated with various antihypertensive drugs, including spironolactone, by nonspecialized medical services, which delayed the PA screening and diagnosis. Only years later, patients were admitted to the university hospital to properly proceed to PA investigation after withdrawal of interfering medications, such as diuretics and spironolactone for at least four weeks. At diagnosis, the median aldosterone levels were 54.8 (24.0–103) ng/dl while DRC were 2.3 (2.3–2.3) mU/l. The mean adrenal nodule size at pathology evaluation was 1.5 ± 0.8 cm. One-year post-adrenalectomy, mean systolic and diastolic blood pressure decreased from 146 ± 31 to 131 ± 11 mmHg ($p = 0.09$) and from 91 ± 17 to 81 ± 13 mmHg ($p = 0.1$), respectively. The antihypertensive daily requirement was also reduced from DDD 6.1 ± 2.5 to 1.7 ± 1.4 ($p = 0.001$) being 30.7 % normotensive with no medications.

In pre-operatory period, 7 out of 13 patients have not been treated with spironolactone. In one patient spironolactone withdrawal occurred four weeks before surgery while in five patients, the drug withdrawal occurred 2 days before surgery. The majority of patients (84 %) had hypokalemia at diagnosis, with potassium levels of 2.5 ± 0.5 that increased progressively, achieving levels of 4.8 ± 0.6 mmol/l ($p = 0.0002$) one year after adrenalectomy. Hyperkalemia was observed post-operatively in 38 % of patients fifteen days after surgery and decreased progressively to normal values. Two patients received fludrocortisone post-operatively (patients 7 and 8). All patients were followed for at least 12 months. In patients

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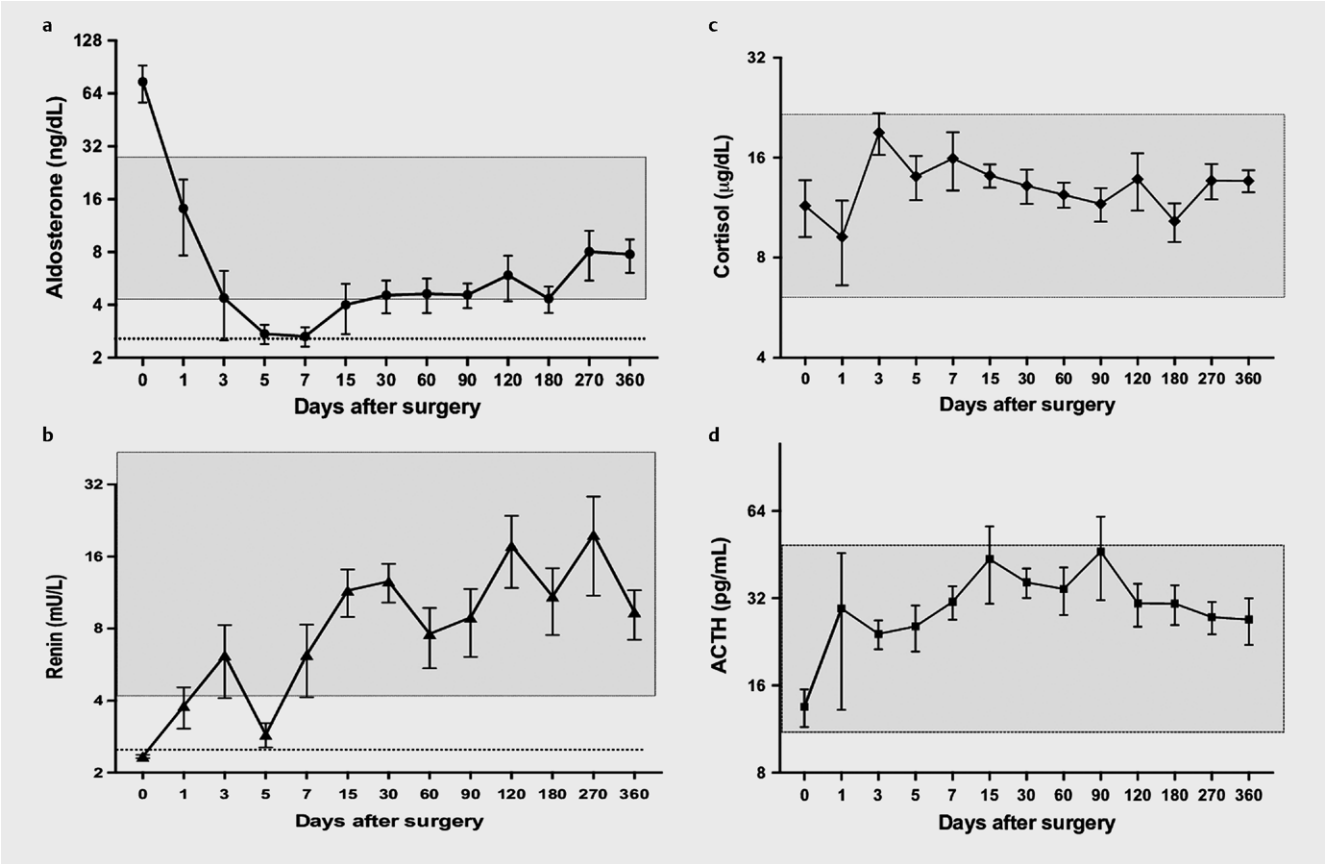
who were still hypertensives after the surgery, antihypertensives that did not interfere with the assessment of renin and aldosterone were prescribed, such as amlodipine, hydralazine, clonidine, or diltiazem. Thus, post-operatively no patients were on spironolactone and diuretics on post-operative period.

▶ **Figure 2** and ▶ **Table 1** show the longitudinal mean (± SEM) values of serum aldosterone (▶ **Fig. 2A**) and DRC (▶ **Fig. 2B**) of the 13 APA patients obtained before (day 0) and 1, 3, 5, 7, 15, 30, 60, 90, 120, 180, 270, and 360 days post-adrenalectomy. High preoperative serum aldosterone levels rapidly decreased to undetectable levels between the first and seventh postoperative days. All patients attained aldosterone levels < 5 ng/dl at the immediate post-operative period, characterizing the complete biochemical surgical success. The lowest mean aldosterone levels were observed between the fifth to seventh days, when 85 % of patients presented undetectable (< 2.2 ng/dl) or very low (< 3.0 ng/dl) levels. From 15th to 90th postoperative days aldosterone levels were between 4 and 5 ng/dl (low normal range). Three months from on, serum aldosterone levels gradually increased to the normal range. The median postoperative recovery time was 60 days (interquartile range 15–225).

The suppressed preoperative DRC became rapidly detectable between the 15th and 30th days after surgery, attaining plasma values ≥ 5 mU/l in 92 % of patients (12/13). DRC remained in the normal range for all subsequent days throughout the study (▶ **Fig. 2B**, ▶ **Table 1**). The median DRC postoperative recovery time was 15 days (interquartile range, 5–30) after surgery. In 77 % of the patients, the DRC recovered earlier than aldosterone levels while both hormones recovered simultaneously in 23 %. Thus, the recovery of aldosterone took longer than renin recovery (60 vs. 15 days; p < 0.002).

There was no association between the recovery of aldosterone and DRC with age at diagnosis, duration of hypertension, potassium levels, spironolactone or fludrocortisone treatments. However, patients with aldosterone levels ≥ 52 ng/dl at diagnosis presented later renin (> 15 days; p = 0.02) and aldosterone (> 60 days; p = 0.03) recoveries. There was no relationship between the age at PA diagnosis and the day in which the lowest post-operative serum aldosterone levels were attained (r = 0.2, p = 0.5). Moreover, there was no relationship between the preoperative treatment with spironolactone and the aldosterone (p = 0.16) and DRC (p = 0.19) recoveries.

All thirteen APA patients presented complete biochemical success at 1, 3, 6, and 12 months post-adrenalectomy, according to the PASO criteria (▶ **Table 2**). However, complete clinical success was observed only in 30 % of the patients, while 70 % presented par-



▶ **Fig. 2** Prospective and longitudinal levels of serum aldosterone (**a**) plasma renin (**b**), serum cortisol (**c**), and plasma ACTH (**d**) obtained in the morning before (day 0) and 1, 3, 5, 7, 15, 30, 60, 90, 120, 180, 270, and 360 days after adrenalectomy in thirteen APA patients. Data are presented as mean (± SEM). The horizontal dotted lines represent the limits of detection for serum aldosterone (2.2 ng/dl) and plasma renin (2.3 m IU/l) levels. The grey area represents the laboratory normal morning levels (5th–95th percentiles) for each hormone.

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▶ **Table 1** Prospective and longitudinal follow up of aldosterone, renin, cortisol, ACTH, potassium, and creatinine levels in thirteen patients with aldosterone-producing adenomas before (pre-op) and 1, 3, 5, 7, 15, 30, 60, 90, 120, 180, and 360 days after unilateral adrenalectomy.

Days	Aldosterone ng/dl	Renin mIU/l	Cortisol µg/dl	ACTH pg/ml	Potassium mmol/l	Creatinine mg/dl
Pre-op	74.5 ± 17.7	2.3 ± 0.1	11.5 ± 2.2	13.5 ± 2	3.7 ± 0.2	1.1 ± 0.1
1	14.1 ± 6.5	3.6 ± 0.8	9.2 ± 2.6	29.5 ± 16.3	3.8 ± 0.1	1.4 ± 0.2
3	4.4 ± 1.9	6 ± 2.1	19.0 ± 2.7	24.1 ± 2.7	3.8 ± 0.2	1.2 ± 0.2
5	2.7 ± 0.3	2.7 ± 0.4	14 ± 2.1	25.6 ± 4.6	4.0 ± 0.2	1.1 ± 0.1
7	2.6 ± 0.3	6 ± 2.1	15.9 ± 3.2	31.1 ± 4.1	4.5 ± 0.1	1.3 ± 0.1
15	4 ± 1.3	11.5 ± 2.6	14.1 ± 1.1	43.6 ± 13	5.2 ± 0.2	1.5 ± 0.2
30	4.5 ± 0.9	12.6 ± 2.3	13.2 ± 1.6	36.3 ± 4.2	5.1 ± 0.2	1.4 ± 0.1
60	4.6 ± 1	7.5 ± 2.2	12.4 ± 1.1	34.4 ± 6.4	5.2 ± 0.1	1.3 ± 0.2
90	4.6 ± 0.7	8.8 ± 2.8	11.6 ± 1.4	46.4 ± 14.9	4.9 ± 0.2	1.3 ± 0.1
120	6 ± 1.7	17.6 ± 5.9	13.8 ± 2.7	30.7 ± 5.2	5.0 ± 0.2	1.4 ± 0.2
180	4.3 ± 0.7	11 ± 3.4	10.3 ± 1.4	30.7 ± 4.8	4.9 ± 0.1	1.5 ± 0.2
270	8 ± 2.5	19.7 ± 8.7	13.6 ± 1.7	27.5 ± 3.5	4.8 ± 0.1	1.4 ± 0.1
360	7.8 ± 1.7	9.3 ± 2.1	13.6 ± 1	27.0 ± 4.9	4.8 ± 0.2	1.4 ± 0.1

Values represent the mean ± SEM.

▶ **Table 2** Categorization of degrees of biochemical and clinical success according to International Consensus Definitions for Cure of Primary Aldosteronism (PASO) system applied at 1-, 3-, 6- and 12- months after adrenalectomy.

Patients	PASO		PASO		PASO		PASO	
	1 month		3 months		6 months		12 months	
	Clinical	Biochemical	Clinical	Biochemical	Clinical	Biochemical	Clinical	Biochemical
1	C	C	C	C	C	C	C	C
2	A*	C	P	C	P	C	P	C
3	P	C	P	C	P	C	P	C
4	P	C	P	C	P	C	P	C
5	P	C	P	C	P	C	P	C
6	P	C	P	C	P	C	P	C
7	P*	C	C	C	C	C	C	C
8	P	C	P	C	P	C	P	C
9	P	C	P	C	P	C	P	C
10	P	C	P	C	P	C	P	C
11	P	C	P	C	P	C	P	C
12	P*	C	C	C	C	C	C	C
13	C	C	P*	C	C	C	C	nr

C: Complete clinical or biochemical responses; P: Partial clinical or biochemical responses; A: Absent clinical or biochemical responses; NR: Not reported; * Represents discordant PASO criteria at 1 or 3 months versus 6 and 12 months.

tial clinical success at 6 and 12 months after surgery. Complete biochemical and clinical success at 12 months was observed in 23 % (3/13) of the patients. The PASO performance at 3 months was concordant with 6- and 12-months evaluation in 92 % (12/13) of the patients. However, at one month, the PASO clinical score present-

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ed lower concordance with 3-, 6- and 12-month evaluation (69, 77, and 77 %, respectively).

The morning serum cortisol and plasma ACTH levels remained in their normal range during the whole longitudinal protocol as shown in ▶ **Fig. 2C, D** and in ▶ **Table 1**. Of note, two female patients, aging 60 and 61 years-old, presented aldosterone and cortisol co-secretion but no Cushingoid features. They had preoperative morning suppressed ACTH levels (< 10 pg/ml) and cortisol of 14 and 16 µg/dl, with no suppression after overnight 1 mg dexamethasone (13 and 3.5 µg/dl, respectively). Serum cortisol dropped to undetectable levels (< 2 µg/dl) after surgery and recovered (> 5 µg/dl) after 60th and 15th post-operative days. These two patients required hydrocortisone postoperatively and subsequently prednisone and fludrocortisone replacement. The pre-operative DRC were 2.9 and 2.3 mIU/l and serum aldosterone levels were 12 and 38 ng/dl. Serum aldosterone decreased to undetectable levels from 1st to 5th postoperative day and remained undetectable or very low even after 360 days. After two years of follow-up, aldosterone and DRC returned to normal levels. Both patients presented hyperkalemia after adrenalectomy.

Discussion

This report is the first to perform a prospective and longitudinal protocol with simultaneous measurement of serum aldosterone and renin levels in patients with APA at immediate and long-term time course after adrenalectomy. Our original data reveals that the preoperative suppressed renin levels became rapidly detectable after surgery and attained normal values from the 15th post-operative days in the great majority of patients. The current study also demonstrates that DRC recovery occurs much earlier than aldosterone (median 15 vs. 60 days) after adrenalectomy. Thus, the borderline persistent hypoaldosteronism remains, even in the presence of detectable DRC. This finding indicates that renin deficiency does not seem to be the main cause of sustained post-operative hypoaldosteronism in patients with APA who underwent surgery.

In the present study, we observed a long delay between the beginning of hypertension and the PA diagnosis as well as a higher incidence of hypokalemia (84 %) at the diagnosis, suggesting patients with severe hyperaldosteronism. Indeed, the median aldosterone levels before surgery in our study were higher (54.8; 24–103 ng/dl) than those described in two multicenter (28.2 and 34.9 ng/dl) studies [17, 23] and in another referral center (34.8 ng/dl) in Brazil [32]. However, in all these studies, the frequencies of hypokalemia (92, 91.9, and 80 %) were similar to ours (84 %) and much higher than those accepted in the last guideline [9], in which hypokalemia has been described in only one-third of the APA patients. The different rates of hypokalemia can be due to where the patients are seen, whether a primary care setting or referral centers [3].

Post-operative studies evaluating the adrenal function in APA have been described for almost six decades [12, 17, 23–27] shown the persistency of low urinary or plasma aldosterone after unilateral adrenalectomy. However, most of these studies are retrospective [12, 17, 23]. Also, in the previous large series, the post-operative renin and aldosterone levels were assessed from one [17] to three months following surgery [26]. More comprehensively, the present study focuses on evaluating these hormones from the immediate first post-operative days.

Our data on the DRC in APA patients reveal that preoperative suppressed renin concentrations became rapidly detectable and achieved normal values around the second postoperative week in the majority of patients. This very early DRC recovery after removal of APA had not been previously described. In previous reports, the renin recovery occurred either between one or three months after surgery [17] or persisted high until 24 months post-operative [26]. These differences may be ascribed to different methods to measure renin, such as DRC in present study or other commercial renin assays [17] or plasma renin activity [26]. However, these differences may also be attributed to clinical diversity or the severity of the disease among these studies. We could ask if the spironolactone treatment in the immediate pre-operatory period in some patients would interfere with the assessment and the recovery of DRC and aldosterone in post-operative period. Our data on suppressed renin until 5 days post operatively in all patients, including those who had been treated with spironolactone before the surgery, clearly demonstrate that this drug did not interfere either with the assessment of DRC and aldosterone nor with the time of recovery of these hormones post-operatively.

We also demonstrated that in all APA patients, high preoperative serum aldosterone levels rapidly decreased to undetectable levels during the first week after adrenalectomy. Then, aldosterone levels gradually increase but yet at the lower normal range. This finding agrees with previous long-term studies that showed a persistent postoperative hypoaldosteronism after surgery [17, 26].

Our results also show that in three-quarters of the APA patients, aldosterone recovered later than renin whereas in one-quarter they recovered simultaneously. One possibility to explain the different aldosterone and DRC recovery times is that chronic suppression of JGA in the kidney rapidly gains function, allowing the renin secretion to return to normal, in contrast to the gradual recovery of the adrenal ZG. This phenomenon can be due to the differences between renin and aldosterone regulation, although both hormones, besides angiotensin II, are part of the same endocrine interconnected system [33]. Indeed, the JGA, the primary source of renin circulation, acts as a sensing device regulated by multiple factors, such as the blood pressure, the sodium chloride delivery to the macula, and by the β-adrenergic activation. Also, angiotensin II may exert a renin inhibition by a short-loop feedback mechanism and by the action of atrial natriuretic peptide (ANP). Of note, elevated preoperative ANP levels in APA patients dropped after surgery [26]. Therefore, we hypothesized that as soon as hypervolemia and blood pressure reduction occur at the immediate period of adrenalectomy, these multiple factors contribute to the early recovery of the renin secretion. In contrast, the biosynthesis and secretion of aldosterone from ZG cells is a tightly-regulated process under the primary control of Angiotensin II and plasma potassium levels, and partially influenced by other factors such as ACTH concentrations, which usually acts a potent but transient aldosterone secretagogue. Biglieri et al. [24] and Bravo et al. [25] in their seminal studies demonstrated that, after APA adrenalectomy, urinary aldosterone excretion is reduced with no increase neither by direct stimulation with angiotensin II or corticotrophin administration nor by indirect stimulus through sodium intake restriction.

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The observed post-operative hypoaldosteronism in the presence of normal renin might occur due to the ZG incapability of the remaining adrenal gland to produce aldosterone. Indeed, the enzymes involved in aldosterone synthesis, such as cholesterol side chain cleavage, 3beta-hydroxysteroid dehydrogenase, and 21-hydroxylase were expressed in the adenoma but were completely absent in the ZG of the adjacent normal adrenal tissue [15]. The mechanism involved in aldosterone synthesis suppression seems similar to the observed after removing of a cortisol secreting adenoma, when insufficient cortisol production by the contralateral adrenal occurs despite normal ACTH secretion [34]. Moreover, in patients with adrenal Cushing's syndrome, the adrenal recovery time was tightly related to the degree of previous hypercortisolism [35]. Similarly, here, we demonstrate that APA patients with aldosterone levels higher than 52 ng/dl at the diagnosis needed longer time to achieve renin and aldosterone recoveries with no association with age at diagnosis and duration of hypertension.

Our data on normal serum cortisol in APA patients after unilateral adrenalectomy confirm previous studies using urinary 17-OHCS levels or plasma cortisol measured by fluorometric assay [24, 25]. The present study also shows, for the first time, that plasma ACTH levels remained in the normal range during all the post-operative periods in APA patients, despite the presence of hypoaldosteronism. These results are in accordance with the role of ACTH as a mild regulator of aldosterone secretion when compared with angiotensin II and potassium stimuli.

We also found aldosterone and cortisol co-secreting adenoma in 2 out of 18 patients (11 %), similar to other small series (4 to 16 %) [36]. However, the co-secretion seems to be more frequent by a steroid metabolome analysis [29]. Both patients presented a transitory postoperative hypocortisolism, with recovery at 15 and 60 days after unilateral adrenalectomy, but aldosterone and renin levels recovery times were longer than two years.

Regarding the clinical applications of the results, we suggest that to assess complete biochemical surgical success, plasma aldosterone should be obtained between the 3rd and 7th days after surgery, whereas serum potassium and creatinine weekly until one month after surgery. We also suggest repeating renin and aldosterone measurement at 30th and 60th postoperative days to detect their recoveries. Finally, our data also indicates that PASO criteria at three months, in opposition to PASO at one-month, maybe an early indicator of clinical and biochemical success, reflecting the well-established PASO at 6- and 12-month evaluation after APA adrenalectomy.

The limitations of our study are, at first, the small sample size compared with retrospective multicenter studies [13, 17]. Another limitation might be the long delay between the beginning of hypertension and the PA diagnosis as well as the higher incidence of hypokalemia at the diagnosis, suggesting patients with severe hyperaldosteronism. Therefore, the conclusions of the present study should be restricted to PA patients with severe clinical and biochemical features, which are not the majority PA patients diagnosed in several specialized centers. Finally, the arbitrary criterion that we assumed to characterize the postoperative aldosterone levels recovery has never been described and it might be questioned. One of the most important strengths of our study is the prospective and longitudinal nature of its protocol in a single tertiary medical center. Thus, our study originally contributes to clarify the outcome of APA patients, mainly at the immediate postoperative period.

In conclusion, our prospective and longitudinal study shows immediate recovery of plasma renin at median of 15 days while serum aldosterone recovery occurs later at 60 days. The borderline persistent hypoaldosteronism, even in the presence of normal DRC, indicates that more than renin deficiency, the ZG incapability of the remaining adrenal gland to produce aldosterone justifies the prolonged post-operative hypoaldosteronism in APA patients who underwent surgery. This study also shows the adequate cortisol-ACTH relationship despite the presence of a post-operative hypoaldosteronism. Taken together, these findings contribute to the comprehension of conceptual aspects of the aldosterone-renin relationship following complete removal of aldosterone-producing adenoma.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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