Adrenal reserve function after unilateral adrenalectomy in patients with primary aldosteronism

Kyoko Honda

This is a non-final version of an article published in final form in

http://journals.lww.com/jhypertension/Abstract/2013/10000/A_drenal_reserve_function_after_unilateral.15.aspx
Adrenal reserve function after unilateral adrenalectomy in patients with primary aldosteronism

Short title: Adrenal function after uni-adrenalectomy

Conflicts of interest and source of funding: The authors have nothing to declare.

Kyoko HONDA, Masakatsu SONE, Naohisa TAMURA, Takuhiro SONOYAMA, Daisuke TAURA, Katsutoshi KOJIMA, Yorihide FUKUDA, Shiro TANAKA, Shinji YASUNO, Toshihito FUJII, Hideyuki KINOSHITA, Hiroyuki ARIYASU, Naotetsu KANAMOTO, Masako MIURA, Akihiro YASUDA, Hiroshi ARAI, Kenji UESHIMA, Kazuwa NAKAO

aDepartment of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto, Japan

bDepartment of Clinical Trial Design & Management, Translational Research Center, Kyoto University Hospital, Kyoto, Japan

cEBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan
Correspondence

Masakatsu Sone, M.D., Ph.D.

Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine

54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

Tel: +81-75-751-3170; Fax: +81-75-771-9452

E-mail: sonemasa@kuhp.kyoto-u.ac.jp

Word count: 3927 (Introduction through References)

Number of tables: 3

Number of figures: 3

Number of supplementary digital content files: 2
Abstract

Objective: After unilateral adrenalectomy (uADX) in patients with a unilateral aldosterone-producing adenoma (APA), the remaining contralateral adrenal gland is generally considered sufficient to support life. However, few studies have compared adrenal reserve function before and after uADX. Therefore, we closely evaluated adrenal cortisol secretory function before and after uADX in patients with unilateral APA.

Methods: Patients who were diagnosed with APA and underwent uADX for unilateral APA were initially included in this study. Patients with subclinical Cushing's syndrome (SCS) or Cushing's syndrome (CS) were excluded on suspicion of autonomous cortisol secretion. Fourteen patients were finally evaluated. Morning basal serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels were measured, and ACTH stimulation tests under 1-mg dexamethasone suppression (dex-ACTH test) were performed before and after uADX.

Results: No patient developed clinical adrenal insufficiency. Basal cortisol levels were not significantly different before and after uADX. However, basal ACTH levels were significantly elevated after uADX. In addition, peak cortisol levels on the dex-ACTH test decreased in all patients after uADX. The peak cortisol level after uADX was 86.6 (81.4–92.4)% of the level before uADX.
**Conclusions:** The adrenal cortisol secretory response to ACTH stimulation is mildly reduced after uADX in patients with unilateral APA without SCS or CS, although their basal cortisol level is sustained by elevated ACTH. These data will be important as a point of discussion when patients with unilateral APA consider either uADX or specific pharmacotherapy as treatment options.

**Keywords:** primary aldosteronism, unilateral adrenalectomy, adrenal insufficiency, adrenal function, adrenal gland, cortisol
Introduction

Primary aldosteronism (PA) is a group of disorders in which aldosterone production is inappropriately high with suppression of plasma renin. Such inappropriate aldosterone production causes sodium retention and potassium excretion that, if prolonged and severe, may lead to hypertension and hypokalemia. The incidence of PA in patients with hypertension has been considered to be less than 1%, but recent studies have reported a much higher PA prevalence nearing 10% [1–6]. PA is important not only because of its prevalence, but also because patients with PA have higher cardiovascular morbidity and mortality than age- and sex-matched patients with essential hypertension and the same degree of blood pressure elevation [7,8]. PA is caused by unilateral PA, including unilateral aldosterone-producing adenoma (APA), unilateral adrenal hyperplasia (UAH), unilateral multiple micronodules (UMN), and aldosterone-producing carcinoma (APC), or by bilateral PA, including idiopathic hyperaldosteronism (IHA), bilateral APA, and glucocorticoid suppressive hyperaldosteronism (GSH) [1–6]. Among them, APA and IHA account for more than 95% of all PA cases.

Unilateral adrenalectomy (uADX) is generally recommended for patients with unilateral APA, while pharmacotherapy with mineralocorticoid receptor antagonists is another therapeutic option. uADX in patients with unilateral APA normalizes hypokalemia, improves hypertension
in almost all patients, and fully controls hypertension in approximately 30–72% of patients [2,9].

It is generally considered that even after uADX, the remaining contralateral adrenal gland can sufficiently support life because the adrenal gland is critical for survival and may have a large amount of reserve function for maintenance of homeostasis. A few studies have examined adrenal function or cortisol secretion after uADX [10,11]. For example, Gordon et al. [10] reported reduced plasma levels of cortisol, aldosterone, and catecholamines following uADX for unilateral PA. However, in these earlier reports, only the basal cortisol levels were compared before and after uADX. Meanwhile, some patients can develop relative adrenal insufficiency in extreme illness even if they have two healthy adrenal glands and their baseline cortisol and adrenocorticotropic hormone (ACTH) levels are within the normal range [12,13]. Therefore, patients with one adrenal gland after uADX may be more susceptible to relative adrenal insufficiency compared with patients with two healthy adrenal glands in such a situation, although no clinical studies have proven this. Before irrevocable surgical intervention, it is preferable for both doctors and patients to have precise data about changes in adrenal reserve function by the intervention. Although we cannot predict the risk of relative adrenal insufficiency, evaluation of the basal cortisol level alone is not enough to properly predict the adrenocortical reserve function. The ACTH stimulation test is widely used as a simple method
to identify adrenocortical hyporesponsiveness. The ACTH stimulation test assesses the stress response of the adrenal gland by measuring the adrenal cortisol response to synthetic ACTH.

Thus, in this study, we compared the cortisol response to ACTH by performing an ACTH stimulation test before and after uADX.

In addition, because APA is sometimes accompanied by subclinical Cushing’s syndrome (SCS) or Cushing’s syndrome (CS), their exclusion is important for accurate evaluation.

Therefore, in this study, we investigated adrenocortisol function by comparing basal serum cortisol, plasma ACTH levels, and the cortisol response to ACTH on the ACTH stimulation test under 1-mg dexamethasone suppression (dex-ACTH test) before and after uADX in patients with APA without SCS or CS. The objective of this study was to evaluate residual adrenal cortisol secretory function after uADX in these patients.

**Methods**

We retrospectively analyzed the patients with APA who were admitted to the Department of Endocrinology and Metabolism of Kyoto University Hospital, Kyoto, Japan, and underwent uADX over the past 6 years. The study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki.
Diagnosis of PA

Hypertensive patients who were referred to our hospital were initially screened by determining their aldosterone-to-renin ratio (ARR; the ratio of plasma aldosterone concentration [PAC] to plasma renin activity [PRA]). A positive screening was defined as an ARR over 555 pmol/l per ng/ml/h (>20 ng/dl per ng/ml/h). PRA and PAC were measured in blood samples obtained after 30 min of rest in a supine position in the morning. All antihypertensive drugs with the exception of calcium channel blockers and alpha blockers were stopped at least 4 weeks before the measurement of PRA and PAC [14]. Patients with hypokalemia (i.e., serum potassium level less than 3.5 mmol/l) were allowed to take oral potassium supplementation.

Confirmatory tests for PA

We performed the captopril challenge test and the saline infusion test to confirm the diagnosis of PA in this study. In the captopril challenge test, an ARR of ≥555 pmol/l per ng/ml/h (20 ng/dl per ng/ml/h) 60 min after administration of 50 mg of captopril was considered positive for PA. For the saline infusion test, a PAC of ≥166 pmol/l (6.0 ng/dl) after infusion of 2 L of 0.9% saline was considered positive for PA. Patients who showed positive captopril challenge test results and/or positive saline infusion test results were diagnosed with PA in this study [15].
Diagnosis of APA

Patients with confirmed PA underwent subtype diagnosis prior to surgery. Adrenal CT scanning was performed for initial localization. The definitive test for subtype diagnosis was adrenal venous sampling (AVS) [16]. AVS was performed by expert radiologists with ACTH stimulation as previously described [17]. Adrenal vein cannulation was considered successful if the adrenal vein/inferior vena cava cortisol gradient (selectivity index) was >3.0. We considered lateralization to be present when the aldosterone-to-cortisol ratio (A/C) from one adrenal gland was >3 times the ratio from the other adrenal gland (lateralization ratio) and the A/C in the contralateral adrenal vein was lower than the A/C in the vena cava (contralateral ratio).

Diagnosis of APA required the following: (1) diagnosis of PA by the captopril challenge test and/or saline infusion test, (2) lateralization of aldosterone secretion at AVS, (3) pathological evidence of adrenal adenoma in the adrenal gland with aldosterone hypersecretion, and (4) normalization of PAC after uADX.

Exclusion criteria

The following patients were excluded from this study: patients with autonomous cortisol secretion (i.e., plasma cortisol level of ≥49.7 nmol/l [1.8 μg/dl] after overnight 1-mg dexamethasone suppression) with suspicion of autonomous cortisol secretion, such as that
induced by SCS or CS [18–21] and patients with incomplete data collection (i.e., patients for whom the dex-ACTH test was not performed before or after surgery).

**Blood sampling and dex-ACTH test**

Before and 2 weeks after uADX, blood samples were collected between 0800 and 0900 h after the patients had maintained a supine position for 30 min to measure the basal serum cortisol and plasma ACTH levels. The dex-ACTH test was also performed before and 2 weeks after uADX as follows: 1 mg of dexamethasone was orally administered at 2300 h the night before ACTH injection. At 0900 h the following morning, 250 µg of synthetic ACTH was intravenously injected, and blood samples were collected every 30 min until 120 min after the injection of ACTH. Serum cortisol levels were measured at each time point. The area under the curve (AUC) of the dex-ACTH test was calculated by adding the areas under the cortisol-time curve for the intervals 0–30, 30–60, 60–90, and 90–120 min. This test was repeated 1 year after uADX in six patients who requested reassessment of their adrenocortical reserve function after uADX for a longer duration.

**Blood pressure measurement**

Blood pressures were measured in a quiet, warm room with patients in a seated position with the
arm held at heart level. The blood pressures listed in Table 1 were those obtained the morning after hospitalization.

**Measurements of hormones**

PRA was measured using a commercially available radioimmunoassay (Renin RIA beads; TFB Factories Ltd., Tokyo, Japan). PAC was measured by radioimmunoassay with a commercial kit (Spec-S Aldosterone Kit; TFB Factories Ltd., Tokyo, Japan). Cortisol was measured by an enzyme immunoassay with the E-test TOSOH II (Cortisol) (Tosoh Corporation, Tokyo, Japan) on an automated immunoassay analyzer (AIA-1800; Eiken Chemical Co., Ltd., Tokyo, Japan). ACTH was measured using a commercially available electrochemiluminescence immunoassay (ECL usys A CTH; Roche Diagnostics Corporation, Tokyo, Japan).

**Statistical analysis**

All data were expressed as medians with the interquartile range (IQR). Data obtained before and after uADX were compared using the Wilcoxon signed rank test. A P value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA).
Results

Patients

Twenty-nine consecutive patients underwent operations for unilateral APA from 2006 to 2012 in our hospital. Among them, seven patients with serum cortisol levels of e49.7 nmol/l (e1.8 µg/dl) after overnight 1-mg dexamethasone suppression were excluded from this study because of a suspicion of autonomous cortisol secretion. Another eight patients were excluded because of incomplete data collection. As a result, 14 patients were included in this study. The clinical characteristics of the 14 patients are shown in Table 1. No patients developed clinically apparent adrenal insufficiency. The serum potassium level normalized after uADX in all 14 patients.

Before uADX, all 14 patients had hypertension and 12 of them were prescribed antihypertensive agents. Two weeks after uADX, the blood pressure normalized without medication in 12 patients and the antihypertensive drugs were reduced in the remaining 2 patients. Six months after uADX, the blood pressure of 10 of the 12 patients remained normal without medication, but the blood pressure in the remaining 2 patients rose again. Medication was restarted in these two patients, although the dose was lower than that administered preoperatively. Therefore, we consider that hypertension was cured in 10 of the 14 patients and improved in the remaining 4 patients, 6 months after uADX.
**Basal ACTH and cortisol levels**

The basal cortisol levels before and after uADX were 303.5 (272.5–364.2) and 296.6 (270.4–357.3) nmol/l, respectively. The basal ACTH levels before and after uADX were 4.4 (2.9–5.8) and 7.0 (4.8–10.5) pmol/l, respectively. The basal cortisol levels were within the normal range in all patients and were not significantly different before and after uADX (P = 0.706) (Fig. 1a). Although the plasma ACTH levels were also within the normal range, they were significantly higher after uADX than before (P < 0.01) (Fig. 1b).

**ACTH stimulation test under 1-mg dexamethasone suppression (dex-ACTH test)**

On the dex-ACTH test, the peak cortisol level in response to 250 µg of ACTH was lower after uADX than before uADX in all patients. The peak cortisol level was mildly but significantly decreased after uADX to 86.6 (81.4–92.4)% of the level before uADX (535.2 [497.3–575.9] vs 649.7 [604.2–700.8] nmol/l; P < 0.01) (Table 2, Fig. 2a). The cortisol AUC was also significantly decreased after uADX to 82.6 (79.0–91.9)% of that before uADX (46703.0 [43888.8–51017.4] vs 58021.8 [55052.4–60867.0] nmol/l/120 min; P < 0.01) (Table 2, Fig. 2b).

**Discussion**

In patients with SCS or CS, autonomous cortisol hypersecretion from the cortisol-producing
adenoma suppresses the hypothalamic-pituitary-adrenal (HPA) axis and cortisol secretion from
the healthy contralateral adrenal cortex. Therefore, adrenal insufficiency often occurs after
uADX. However, in patients with PA without SCS or CS, the HPA axis is not suppressed, and
cortisol secretion from the healthy contralateral normal adrenal cortex is maintained. Therefore,
it is generally considered that adrenal insufficiency does not occur after uADX in patients with
PA without SCS or CS.

Generally, basal cortisol levels are measured to assess adrenal function. However, the basal
cortisol level is markedly variable according to blood sampling conditions, and it is difficult to
evaluate small differences in data obtained with single blood samplings. In addition, evaluation
of the basal cortisol levels alone is not enough to properly predict the adrenocortical reserve
function. To overcome these limitations, we performed the dex-ACTH test to precisely evaluate
adrenal reserve function after uADX. The ACTH stimulation test is generally used to evaluate
adrenal reserve function [22–24], although it is sometimes used to confirm PA by measuring the
plasma aldosterone concentration [25,26]. The ACTH stimulation test following 1-mg
dexamethasone suppression (i.e., dex-ACTH test) is also useful to evaluate adrenal reserve
function [27]. Administration of 1 mg dexamethasone at 2300 h suppresses the HPA axis on the
following morning and can eliminate the effect of endogenous ACTH. Subsequent
administration of a fixed and large amount of ACTH permits evaluation of adrenal responsiveness to the stimulation (i.e., the adrenal reserve function).

In the present study, we found that basal plasma ACTH levels after uADX were significantly higher than those before uADX. The basal serum cortisol levels were within the normal range in all patients and were not significantly different before and after uADX. In addition, on the dex-ACTH test, the peak cortisol level and the cortisol AUC in response to 250 µg of ACTH were mildly but significantly decreased after uADX, which indicates that adrenal responsiveness to ACTH stimulation decreased after uADX. These results suggest that the adrenal reserve function is mildly reduced after uADX but that the basal cortisol secretion is preserved by the increased basal plasma ACTH levels [28].

The peak cortisol level in response to ACTH was significantly lower after uADX than before uADX (P < 0.01) (Table 2). However, the cortisol responsiveness to ACTH stimulation after uADX was maintained at 86.6 (81.4–92.4)% of that before uADX. Among all 14 patients after uADX, 4 had peak cortisol levels of 415–500 nmol/l, 6 had peak cortisol levels of 500–550 nmol/l, and 4 had peak cortisol levels of >550 nmol/l. None of the 14 patients had a peak cortisol level of <415 nmol/l on the dex-ACTH test, and we supposed that no apparent adrenal insufficiency was diagnosed in these patients [22–24]. This may explain why clinically apparent adrenal insufficiency did not occur in our patients after uADX. Our results provide important
evidence that reassures and supports the current clinical opinion of uADX as a safe procedure in PA with minimal risk of significant adrenal insufficiency. On the other hand, our results indicate that adrenal reserve function after uADX is not the same as that before uADX. The change in adrenal reserve function by uADX may result in changes to the patient’s physical potentials that are difficult to be detected during general medical examinations; such changes may include physical stress endurance, or maximum physical ability in sports.

Two weeks after uADX, the blood pressure normalized without medication in 12 of the 14 patients; however, no patients developed hypotension. Furthermore, hyponatremia and hyperkalemia were not observed after uADX. However, the percentage of eosinophils increased significantly after uADX (P < 0.01) (Table 1, Supplementary Table 1, Supplemental Digital Content 1). The amount of circulating eosinophils is often used as a marker for the biological effect of glucocorticoids and adrenocortical function [29,30]. Therefore, the increase in eosinophils might represent a slight reduction in adrenocortical reserve function, although clinically significant adrenal insufficiency did not occur in these patients.

Although the number of cases included in this study was not large, the sample size was sufficient to detect elevated basal ACTH levels, decreased peak cortisol levels, and the cortisol AUC on the dex-ACTH test after uADX with 80% power at the 5% level of significance (Supplementary Table 2, Supplemental Digital Content 2). In addition, the results of the
dex-ACTH tests showed the same tendency in all cases. Therefore, the result that adrenal reserve function mildly decreased after uADX is convincing. Meanwhile, no patients developed clinically apparent adrenal insufficiency, and the basal cortisol levels were within the normal range in all patients and were not significantly different before and after uADX ($P = 0.706$). In fact, if the basal cortisol level decreased to a lower normal range (138.0 nmol/l), we could detect the change with 99% power (Supplementary Table 2, Supplemental Digital Content 2).

We evaluated adrenocortical function 2 weeks after uADX to evaluate the risk for adrenal insufficiency as early as possible once the patient had reached a stable condition after uADX. We can consider that there was little influence of surgical intervention at 2 weeks after laparoscopic adrenalectomy [31,32]. Furthermore, in this study, 6 of 14 patients were observed for a longer duration to verify the long-term outcomes. In the 6 patients, the results 1 year after uADX showed almost the same tendency as those 2 weeks after uADX. Basal plasma ACTH levels after uADX also remained significantly higher than those before uADX. Basal serum cortisol levels remained within the normal range and were not significantly different before and 1 year after uADX (Table 3). Moreover, the cortisol response to ACTH on the dex-ACTH test 1 year after uADX did not return to the preoperative level and remained significantly decreased compared with that before uADX ($P < 0.05$) (Table 3, Fig. 3). Meanwhile, the percentage of eosinophils 1 year after uADX decreased to almost the same level as that before uADX, which
had increased 2 weeks after uADX (Table 3).

In conclusion, our results suggest that although the basal serum cortisol level is maintained within the normal range, the adrenal reserve cortisol secretory capacity mildly decreases after uADX in patients with APA without SCS or CS. Nevertheless, more than 80% of the reserve capacity was preserved after uADX, which is compatible with the fact that patients generally exhibit no problems in daily life after uADX. Because we compared the adrenal cortisol secretory capacity before and after uADX, our data are important to understand how adrenocortical function changes after removing one adrenal gland. These basic data will be useful as a point of discussion when patients with unilateral PA consider either uADX or specific pharmacotherapy as treatment options based on the possible risks and benefits of both approaches.
Acknowledgements

We gratefully acknowledge the support of the nursing, laboratory, and secretarial staff members in our department and the medical staff members in the departments of urology, radiology, and pathology at Kyoto University Hospital.
References


9 Amar L, Plouin PF, Steichen O. Aldosterone-producing adenoma and other surgically correctable forms of primary aldosteronism. Orphanet J Rare Dis 2010; 5:9.


19 Guignat L, Bertherat J. The diagnosis of Cushing’s syndrome: an Endocrine Society


26 Sonoyama T, Sone M, Miyashita K, Tamura N, Yamahara K, Park K, et al. Significance of adrenocorticotropic stimulation test in the diagnosis of an aldosterone-producing


Figure Legends

**Fig. 1**  Serum cortisol (a) and plasma ACTH (b) levels before and 2 weeks after unilateral adrenalectomy in 14 patients. NS, not significant.

**Fig. 2**  (a) Peak cortisol levels on the ACTH stimulation test under 1-mg dexamethasone suppression performed before and 2 weeks after unilateral adrenalectomy in 14 patients. (b) Cortisol levels at 0, 30, 60, 90, and 120 min after intravenous administration of 250 µg ACTH. Results are expressed as individual values (a) or medians with the interquartile range (IQR) (b).

**Fig. 3**  Peak cortisol levels (a) and cortisol AUC (b) on the ACTH stimulation test under 1-mg dexamethasone suppression performed before, 2 weeks after, and 1 year after unilateral adrenalectomy in six patients.
Fig. 1

(a) Basal cortisol

Before 2 weeks after

0 100 200 300 400 500 600
Cortisol (nmol/l)

NS

(b) Basal ACTH

Before 2 weeks after

0 2 4 6 8 10 12 14 16
ACTH (pmol/l)
P < 0.01
Fig. 2

(a) Peak cortisol

Before 2 weeks after

Cortisol (nmol/l)

(b) ACTH stimulation test under 1-mg dexamethasone suppression

Minutes after intravenous administration of 250 μg ACTH (min)
Fig. 3

(a) Peak cortisol

\[ P < 0.05 \]

(b) AUC

\[ P < 0.05 \]
**Table 1** Clinical characteristics of patients with unilateral aldosterone-producing adenoma before and 2 weeks after unilateral adrenalectomy

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>2 weeks after</th>
<th>P-value before vs. 2 weeks after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male : female)</td>
<td>5 : 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>47.5 (40.5–57.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with family history of more than one first-degree relative with hypertension</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with a duration of hypertension of &gt;5 years</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients using antihypertensive drugs</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128.5 (122.8–136.0)</td>
<td>115.5 (105.5–123.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.5 (80.3–94.5)</td>
<td>76.5 (74.0–86.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Estimated GFR (ml/min per 1.73 m²)</td>
<td>73.1 (66.5–82.8)</td>
<td>73.1 (67.0–80.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.3 (3.0–3.6)</td>
<td>4.3 (4.1–4.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oral potassium supplementation (mmol/day)</td>
<td>24 (16–32)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urinary aldosterone (nmol/day)</td>
<td>41.8 (36.7–49.9)</td>
<td>3.9 (2.7–6.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Parameter</td>
<td>Median</td>
<td>Interquartile Range</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
<td>----------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>PAC (pmol/l)</td>
<td>605.2</td>
<td>(486.1–952.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>166.2</td>
<td>(128.8–190.4)</td>
<td></td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>0.1 (0.1–0.4)</td>
<td>0.7 (0.4–1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PAC/PRA (pmol/l per ng/ml/h)</td>
<td>4321.2</td>
<td>(2200.1–8614.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>303.5</td>
<td>(272.5–364.2)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>296.6</td>
<td>(270.4–357.3)</td>
<td></td>
</tr>
<tr>
<td>ACTH (pmol/l)</td>
<td>4.4 (2.9–5.8)</td>
<td>7.0 (4.8–10.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Percentage of eosinophils (%)</td>
<td>2.8 (2.3–4.1)</td>
<td>6.0 (4.9–7.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Laterality of adenoma (left : right)</td>
<td>7 : 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor diameter, mm</td>
<td>14.5 (12.0–19.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PAC, plasma aldosterone concentration; PRA, plasma renin activity; ACTH, adrenocorticotropic hormone; NS, not significant.

Values are medians (interquartile range). Normal values: urinary aldosterone, <27.7 nmol/24 h; PAC, 82.8–439.9 pmol/l; PRA, 0.2–2.7 ng/ml/h; ACTH, 1.5–12.3 pmol/l; cortisol: 138.0–579.4 nmol/l.

For PAC, 1 ng/dl converts to 27.7 pmol/l in the International System of Units (SI units); for urine aldosterone, 1 µg/24 h converts to 2.77 nmol/24 h in SI units; for ACTH, 1 pg/ml converts to 0.22 pmol/l in SI units; and for cortisol, 1 µg/dl converts to 27.59 nmol/l in SI units.
Table 2  Serum cortisol levels (nmol/l) and cortisol area under the curve (AUC) (nmol/l/120 min) during an ACTH stimulation test under 1-mg dexamethasone suppression before and 2 weeks after unilateral adrenalectomy in the 14 patients with unilateral aldosterone-producing adenoma

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>2 weeks after</th>
<th>P-value</th>
<th>Ratio: before vs. 2 weeks after</th>
<th>Decrease in parameters by (2 weeks after / (before)) (%)</th>
<th>uADX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>416.6 (376.6–446.3)</td>
<td>333.8 (310.4–386.3)</td>
<td>&lt;0.01</td>
<td>83.0 (78.1–93.2)</td>
<td>(6.8–21.9)</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>561.5 (528.3–589.0)</td>
<td>430.4 (409.0–483.5)</td>
<td>&lt;0.01</td>
<td>80.3 (77.3–89.9)</td>
<td>(10.1–22.7)</td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>620.8 (577.3–653.2)</td>
<td>507.7 (478.7–537.3)</td>
<td>&lt;0.01</td>
<td>83.7 (80.0–92.1)</td>
<td>(7.9–20.0)</td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>624.9 (595.9–694.6)</td>
<td>532.5 (495.9–575.9)</td>
<td>&lt;0.01</td>
<td>87.5 (78.6–93.4)</td>
<td>(6.6–21.4)</td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>649.7 (604.2–700.8)</td>
<td>535.2 (497.3–575.9)</td>
<td>&lt;0.01</td>
<td>86.6 (81.4–92.4)</td>
<td>(7.6–18.6)</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>58021.8 (55052.4–60867.0)</td>
<td>46703.0 (43888.8–51017.4)</td>
<td>&lt;0.01</td>
<td>82.6 (79.0–91.9)</td>
<td>(8.1–21.0)</td>
<td></td>
</tr>
</tbody>
</table>

uADX, unilateral adrenalectomy; AUC, area under the curve. Values are medians (interquartile range).
Table 3  Adrenal function before, 2 weeks after, and 1 year after unilateral adrenalectomy in six patients with unilateral aldosterone-producing adenoma

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>2 weeks after</th>
<th>P-value</th>
<th>1 year after</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>before vs.</td>
<td></td>
<td>before vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 weeks after</td>
<td></td>
<td>1 year after</td>
</tr>
<tr>
<td>Number of patients</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male : female)</td>
<td>3 : 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.0 (47.3–57.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Cortisol (nmol/l)</td>
<td>291.1 (229.0–371.8)</td>
<td>280.0 (247.6–320.7)</td>
<td>NS</td>
<td>230.4 (218.7–320.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Basal ACTH (pmol/l)</td>
<td>3.4 (2.7–5.1)</td>
<td>5.8 (4.4–7.3)</td>
<td>&lt;0.05</td>
<td>5.9 (3.8–7.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak cortisol (nmol/l)</td>
<td>663.5 (622.2–752.5)</td>
<td>555.9 (522.8–615.9)</td>
<td>&lt;0.05</td>
<td>573.9 (547.0–658.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cortisol AUC (10⁶ nmol/l/120 min)</td>
<td>5.920 (5.580–6.888)</td>
<td>4.933 (4.466–5.785)</td>
<td>&lt;0.05</td>
<td>5.078 (4.693–5.925)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Percentage of eosinophils (%)</td>
<td>2.8 (2.6–3.0)</td>
<td>7.0 (5.3–7.9)</td>
<td>&lt;0.05</td>
<td>3.2 (2.3–3.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropin hormone; AUC, area under the curve; NS, not significant. Values are medians (interquartile range). Peak cortisol and cortisol AUC are the results on an ACTH stimulation test under 1-mg dexamethasone suppression.
**Supplemental Digital Content 1**

**Supplementary Table 1** Details of differential white blood cell count

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>2 weeks after</th>
<th>P-value before vs. 2 weeks after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white blood cell count (/µl)</td>
<td>4650 (4400–5900)</td>
<td>5450 (4600–6425)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>62.7 (57.2–65.4)</td>
<td>59.1 (57.3–67.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>29.4 (24.2–33.9)</td>
<td>27.7 (22.4–29.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>5.4 (4.4–5.9)</td>
<td>5.8 (4.9–6.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2.8 (2.3–4.1)</td>
<td>6.0 (4.9–7.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.5 (0.3–0.7)</td>
<td>0.7 (0.4–0.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Supplemental Digital Content 2**

**Supplementary Table 2**  Calculation of power to detect a change 2 weeks after unilateral adrenalectomy for a before-2 weeks after data of 14 patients

<table>
<thead>
<tr>
<th></th>
<th>Alternative hypothesis (change 2 weeks after)</th>
<th>SD</th>
<th>Correlation between before and 2 weeks after</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cortisol (nmol/l)</td>
<td>±165.5*</td>
<td>92.5†</td>
<td>0.71†</td>
<td>0.99</td>
</tr>
<tr>
<td>Basal ACTH (pmol/l)</td>
<td>±2.56†</td>
<td>3.09†</td>
<td>0.65†</td>
<td>0.93</td>
</tr>
<tr>
<td>Peak cortisol on dex-ACTH test (nmol/l)</td>
<td>±114.5†</td>
<td>95.0†</td>
<td>0.77†</td>
<td>0.99</td>
</tr>
<tr>
<td>Cortisol AUC on dex-ACTH test (nmol/l/120 min)</td>
<td>±11318.8†</td>
<td>9582.8†</td>
<td>0.78†</td>
<td>0.99</td>
</tr>
<tr>
<td>Percentage of eosinophils (%)</td>
<td>±3.25†</td>
<td>1.89†</td>
<td>0.55†</td>
<td>0.99</td>
</tr>
</tbody>
</table>

SD, standard deviation; dex-ACTH test, ACTH stimulation test under 1-mg dexamethasone suppression.

* Based on difference between a lower normal range (138.0 nmol/l) and the observed baseline median before unilateral adrenalectomy.

† Based on the observed change, SD, or correlation.