Small tumor size as favorable prognostic factor after adrenalectomy in Conn’s adenoma

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Abstract

Objective: Primary aldosteronism (PA) due to aldosterone-producing adenoma (APA) is the most common curable form of secondary hypertension.

Design: In order to evaluate blood pressure outcome after adrenalectomy for APA and to identify new favorable prognostic factors, data from 42 consecutive APA patients who underwent adrenalectomy were collected from 2005 to 2007.

Methods: Renin-angiotensin-aldosterone system (upright and postsaline infusion test), serum and urinary electrolytes, office and ambulatory blood pressure monitoring were evaluated at baseline and after a follow-up of 2.7 ± 2.2 years. Drug history and adenoma size at morphological evaluation were also collected.

Results: Multiple regression analysis showed that, before surgery, patients with a small adenoma (diameter < 20 mm) displayed higher postsaline aldosterone values (P = 0.0001), and lower serum potassium levels (P = 0.020), than patients with adenoma > 20 mm. Before surgery, mineralocorticoid receptor (MR) antagonists were used in patients with small APA in greater percentage than patients with bigger adenomas (64 vs 30% respectively, P = 0.037). At follow-up, blood pressure normalized in 63% of the subjects. Recovered patients had a shorter duration of hypertension (P = 0.038), and a smaller adenoma size (P = 0.035). Receiver operating characteristic curves showed that a duration of hypertension ≤ 6 years and an APA size < 20 mm were the best predictors of blood pressure normalization. Patients with APA < 20 mm showed the complete restoration of blood pressure circadian rhythm.

Conclusions: The presence of APA < 20 mm, duration of hypertension equal or less than 6 years, and preoperative MR antagonists use are favorable prognostic factors for hypertension recovery after adrenalectomy.

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Introduction

Conn first described primary aldosteronism (PA), a syndrome characterized by drug-resistant hypertension, suppressed plasma renin activity (PRA), excessive secretion of aldosterone, and hypokalemia (1).

Although previously thought to be a rarity, PA is now considered one of the most common causes of secondary hypertension. Recent evidence shows a PA prevalence of 10% among hypertensives and an aldosterone-producing adenoma (APA) prevalence of 5% (2, 3).

In the last few years, several studies highlighted the negative effects of aldosterone excess on the heart, the blood vessels, the kidney, and the brain (4, 5), as well as on the glucose metabolism and insulin sensitivity (6, 7), indicating the need for a prompt diagnosis of PA and a correct therapeutic approach. While the treatment of choice for APA is unilateral adrenalectomy (8, 9), medical therapy is the best treatment for idiopathic hyperaldosteronism due to adrenal hyperplasia (9–11).

Laparoscopic adrenalectomy has become the treatment of choice and has replaced open surgery for treating benign adrenal tumors, since the first laparoscopic adrenalectomies were performed in 1992 by Gagner (12), Suzuki (13) and Higashihara (14), and co-workers. The transperitoneal laparoscopic approach of an aldosteronoma has many benefits of minimally invasive surgery, including decreased postoperative pain, shortened hospitalization, more rapid convalescence, decrease in overall cost, and decreased morbidity with the smaller incisions and shorter postoperative recovery time (15, 16).

Although it is well demonstrated in the literature that adrenalectomy is beneficial for APA, long-term outcome after surgery has not been extensively studied; in some cases hypertension persists even if adenoma has been
completely removed, and several investigators reported that long-term normalization rate of blood pressure after surgery occurs in no more than 30–70% of the cases (17–19).

Numerous factors have been proposed as predictive factors for hypertension recovering, including age at surgery, response to spironolactone, blood pressure levels on discharge (20), duration of hypertension, family history for hypertension, preoperative ratio of plasma aldosterone to PRA (21), renal damage (22), serum potassium levels, sex (23) and vascular remodeling (24).

The aim of our study is to elucidate long-term blood pressure outcome in patients undergoing laparoscopic adrenalectomy for APA, in an attempt to identify new prognostic factors favorably correlated with blood pressure normalization after successful surgery.

Subjects and methods

Study population

Forty-two consecutive patients with confirmed PA due to an APA have been enrolled in this study, after written informed consent.

Patients referred to our clinic for suspicion of PA and adrenal mass were studied on an inpatient basis. All patients consumed a standard hospital diet, with a daily salt intake of 150 mEq/day, and a potassium intake of 50–75 mEq/day. After hospital admission, both at baseline and at follow-up examinations, office blood pressure was measured in seated subjects, who had been quiet for at least 10 min, using a standard mercury sphygmomanometer with the cuff at the level of the heart and with cuff sizes selected on the basis of the measurement of arm circumference. The average of three readings obtained at 1-min intervals was considered for the study.

Basal and dynamic evaluation was performed after discontinuation of any antihypertensive treatment for at least 4 weeks, except for calcium channel and \( \text{\( \beta \)} \)-blockers when required, which were withdrawn at hospital admission. Patients with hypokalemia (plasma potassium < 3.5 mEq/l) had been given adequate oral or i.v. potassium supplements before the hormonal evaluations.

The diagnosis of PA was established as described previously (25). Briefly, PA was suspected for an upright serum aldosterone/uptight PRA ratio (ARR) greater than 40 (ng/dl per ng/ml per h), together with an upright aldosterone value greater than 15 ng/dl, and confirmed with a 4-h i.v. saline infusion (2 l of 0.9% NaCl solution), which was considered positive if the post-test aldosterone value was greater than 7 ng/dl (25). In all patients with confirmed PA, differentiation between an adrenal adenoma and idiopathic aldosteronism was obtained using computerized tomographic (CT) scan of the adrenal glands with 3 mm contiguous slices after administration of a non-ionic iodinated contrast agent (\( n = 37 \)); or magnetic resonance imaging (MRI) in patients with iodine allergy or claustrophobia (\( n = 5 \)), followed by adrenal vein sampling (AVS) for measurement of aldosterone and cortisol (\( n = 26 \)); or dexamethasone-suppressed adrenal scintigraphy with \( ^{131} \text{I} \) cholesterol (\( n = 16 \)). The correct cannulation of adrenal veins and lateralization of aldosterone hypersecretion were defined according to the criteria proposed by Rossi et al. (26). Due to the lack of cannulation of adrenal veins, AVS was successfully repeated in eight patients.

In all our patients with a CT scan or MRI showing a unilateral solitary adrenal nodule and a normal-appearing contralateral adrenal gland we demonstrated a lateralization of aldosterone overproduction through AVS or adrenal dexamethasone-suppressed scintigraphy.

Data about a history of essential hypertension in first-degree relatives and adenoma size at morphological evaluation were also collected.

All patients underwent laparoscopic unilateral adrenalectomy performed by a surgical team with wide experience in abdominal laparoscopy. Patients were operated in the supine positions with no intraoperative complications or mortality; conversion to open surgery was never necessary; postoperative pain was minimal and patients were able to ambulate 12–24 h after surgery and were allowed liquid diet on the first day after surgery. The diagnosis of adenoma was further confirmed at surgery and pathological evaluation in all 42 APA.

From May 2005 to December 2007 a within-subject and longitudinal comparison was carried out after a mean follow-up period of 2.7 ± 2.2 years (range between 9 months and 8 years) from laparoscopic adrenalectomy.

The preoperative diagnosis of APA was confirmed post-surgery by the satisfaction of all the following conditions, in all patients: i) histopathological demonstration of cortical adrenal adenoma; ii) normalization of the renin-angiotensin-aldosterone system and of hypokalemia if present; iii) cure or improvement of hypertension. Hypertension was considered cured for blood pressure levels below 140/90 mmHg without any antihypertensive medications, while considered improved when normal blood pressure was achieved with a reduced number of drugs, compared with the preoperative number.

APA patients who remained hypertensive after surgery were reevaluated at follow-up after discontinuation of antihypertensive treatment for at least 4 weeks (except for calcium channel and \( \text{\( \beta \)} \)-blockers when required).

Ambulatory blood pressure measurements

Ambulatory blood pressure monitoring (ABPM) was performed in all subjects before and after surgery with Takeda TM-2430 instrument (A&D, Tokyo, Japan) using oscillometric measurements, at diagnosis and at
follow-up. For the blood pressure analyses, daytime was defined as from 0700 to 2259 h, and nighttime from 2300 to 0659 h. Measurements were taken every 15 min during the daytime and every 30 min at night. Blood pressure thresholds were defined according to the European Society of Hypertension guidelines (27). Individual patient’s blood pressure was classified in normal blood pressure below 140/90 mmHg, and hypertensives higher than 140/90 mmHg or subject to using antihypertensive drugs. The ABPM was considered normal if mean 24 h blood pressure was below 125/80 mmHg, diurnal mean blood pressure below 130/85 mmHg, and nocturnal mean blood pressure below 120/75 mmHg. These parameters are important to avoid the white coat effect, to reveal masked hypertension and to classify subjects as dipper or non-dipper. Dippers were defined as individuals whose nighttime blood pressures dropped by more than 10% compared with their daytime blood pressures.

Biochemical and hormonal assays

All assays were performed in the Central Laboratory. Serum aldosterone (reference range for upright values, 4–31 ng/dl) was measured by a solid-phase RIA kit (Biodata Diagnostics, Rome, Italy). PRA (reference range in the upright position, 1.5–5.7 ng/ml per h) was measured as the generation of angiotensin I in vitro using a commercially available RIA kit (Radim, Rome, Italy). Creatinine (reference range, 0.6–1.4 mg/dl) was determined by standard procedures.

Statistical analysis

Statistical analysis was performed using the StatView version 4.1 software for PC (Abacus Concepts Inc., Berkley, CA, USA), in collaboration with the Department of Statistics of Università Politecnica delle Marche. Data are expressed as mean ± s.e. or median (25th–75th percentile) when appropriate. Statistical significance between groups at baseline was assessed by unpaired t-tests, and a paired t-test was used to compare treatment-related changes within groups. The Mann–Whitney test was used for the data that did not follow a normal distribution. The Pearson χ²-test was used to compare categorical variables. The data were analyzed by ANOVA test for multiple comparisons, as appropriate. The relationship between different variables was examined by linear regression analysis. Multivariate logistic regression analysis was then performed to identify variables independently associated with a resolution of hypertension after adrenalectomy. Collinearity testing was used in order to exclude from the model variables that were interdependent. Observed differences with P<0.05 were considered statistically significant.

Moreover, receiver operating characteristic (ROC) curve analysis was used to choose the best predictor of blood pressure normalization after surgery (i.e. the value with the maximum sensitivity and minimal loss of specificity).

Results

Baseline characteristics

Clinical characteristics of our 42 patients with APA, divided according to gender, are shown in Table 1. The mean age of all patients was 50 ± 11 years; females were significantly younger than males (P=0.040). Males showed a body mass index (BMI) significantly higher than women (P=0.029); no significant

Table 1 Baseline characteristics of studied patients.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>F</th>
<th>M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>42</td>
<td>18</td>
<td>24</td>
<td>0.040</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50±11</td>
<td>46±10</td>
<td>53±11</td>
<td>ns</td>
</tr>
<tr>
<td>Family history for hypertension (n)</td>
<td>28</td>
<td>12</td>
<td>16</td>
<td>ns</td>
</tr>
<tr>
<td>Years since hypertension</td>
<td>8.3±5.6</td>
<td>6.2±4.1</td>
<td>9.8±5.8</td>
<td>0.030</td>
</tr>
<tr>
<td>Drugs used (n)</td>
<td>2.1±0.9</td>
<td>2.0±0.9</td>
<td>2.1±1.0</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/mq)</td>
<td>26.9±3.3</td>
<td>25.6±3.6</td>
<td>27.8±2.7</td>
<td>0.029</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>156±24</td>
<td>152±21</td>
<td>159±25</td>
<td>ns</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>100±15</td>
<td>99±13</td>
<td>101±16</td>
<td>ns</td>
</tr>
<tr>
<td>Na⁺ (mEq/l)</td>
<td>143±2.4</td>
<td>142±2.7</td>
<td>143±2.1</td>
<td>ns</td>
</tr>
<tr>
<td>K⁺ (mEq/l)</td>
<td>3.35±0.44</td>
<td>3.37±0.48</td>
<td>3.37±0.40</td>
<td>ns</td>
</tr>
<tr>
<td>UNa⁺ (mEq/24 h)</td>
<td>152±60.8</td>
<td>152.9±60.8</td>
<td>151.5±66.4</td>
<td>ns</td>
</tr>
<tr>
<td>UK⁺ (mEq/24 h)</td>
<td>54.4±17.3</td>
<td>51.3±16.1</td>
<td>57.4±18.3</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.93±0.25</td>
<td>0.76±0.17</td>
<td>1.1±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>PRA (ng/ml per hour)</td>
<td>0.3 (0.2–0.6)</td>
<td>0.3 (0.2–0.6)</td>
<td>0.3 (0.2–0.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>51.1±32.9</td>
<td>44.7±15.4</td>
<td>56.5±42.3</td>
<td>ns</td>
</tr>
<tr>
<td>ARR</td>
<td>105 (67–186)</td>
<td>103 (73–171)</td>
<td>108 (55–223)</td>
<td>ns</td>
</tr>
<tr>
<td>Postsaline aldosterone (ng/dl)</td>
<td>17.1±11.1</td>
<td>18.8±12.4</td>
<td>15.9±10.2</td>
<td>ns</td>
</tr>
</tbody>
</table>

F, females; M, males; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Na⁺, plasma sodium; K⁺, plasma potassium; UK⁺, urinary potassium; UNa⁺, urinary sodium; PRA, plasma renin activity and ARR, upright serum aldosterone to plasma renin activity ratio. Data are reported as mean ± s.e. or as median (25th–75th percentile).
differences for systolic and diastolic blood pressure levels were observed. The duration of known hypertension showed a significant difference between males and females ($P=0.030$), being longer in males. In 14 patients (33%), no family history for hypertension was reported.

High plasma aldosterone levels and low or undetectable PRA were reported in all patients; ARR was greater than 40 without any difference between males and females. Hypokalemia was present in 19 out of 42 patients (45%), with an average value of 3.35 mEq/l. Creatinine serum levels were higher in males than females ($P=0.001$). The mean number of drugs used before hospital admission was 2.1 ± 0.9 and 50% of patients received a mineralocorticoid receptor antagonist (MR blocker).

The 24 h blood pressure registration showed the loss of physiological circadian rhythm (systolic diurnal mean: 144 ± 17 mmHg, diastolic diurnal mean: 86 ± 12 mmHg; systolic nocturnal mean: 139 ± 21, diastolic nocturnal mean: 81 ± 11 mmHg).

Twenty patients presented with an adenoma of the right adrenal gland (48%), while 22 patients had an adenoma in the left adrenal gland (52%); mean adenoma size determined through imaging techniques was 21 ± 9 mm (range between 8 and 48 mm). No significant differences were observed between males/females as for dimension (21 ± 11 mm for males and 22 ± 8 mm for females) and localization (males: 38% right adrenal and 62% left adrenal; females: 59% right adrenal and 41% left adrenal).

Compared with patients whose adenoma was > 20 mm diameter, patients presenting with an adenoma less than 20 mm size showed higher upright serum aldosterone levels ($63 ± 20$ vs $38 ± 17$ ng/dl, $P=0.009$), higher aldosterone postsaline infusion values ($23 ± 12$ vs $12 ± 3$ ng/dl, $P=0.0001$), and lower plasma potassium levels ($3.22 ± 0.13$ vs $3.48 ± 0.25$ mEq/l, $P=0.020$; Fig. 1). According to adenoma size, there were no significant differences regarding systolic blood pressure ($157 ± 25$ vs $154 ± 23$ mmHg), diastolic blood pressure ($102 ± 16$ vs $98 ± 13$ mmHg), and duration of hypertension ($8.4 ± 6.4$ vs $8.3 ± 4.7$ years). Patients with a smaller adenoma used MR blockers before surgery in greater percentage than patients with adenoma ≥ 20 mm diameter: 14 subjects with adenoma less than 20 mm used MR antagonists (64%) and only 6 with adenoma ≥ 20 mm (30%) ($P=0.037$).

Linear regression analysis showed that adenoma size was inversely correlated with upright aldosterone levels ($r^2: 0.119$ $P=0.003$) and postsaline aldosterone ($r^2: 0.145$ $P=0.01$), and directly correlated with plasma potassium levels ($r^2: 0.173$, $P=0.01$). No correlation was observed between tumor size and duration of hypertension. Multiple regression analysis showed that the correlation remained significant for both postsaline aldosterone ($P=0.03$) and plasma potassium levels ($P=0.01$).

**Outcome of adrenalectomy and favorable prognostic factors**

All patients underwent unilateral laparoscopic adrenalectomy. At follow-up evaluation, (mean follow-up 2.7 ± 2.2 years, range between 6 months and 8 years) all patients showed a normalization of aldosterone (51.1 ± 33 vs 18.4 ± 15.6 ng/dl, $P=0.0001$) and PRA levels (0.43 ± 0.29 vs 2.5 ± 2.9 ng/ml per h, $P=0.004$) as well as of serum potassium levels (3.35 ± 0.44 vs 4.3 ± 0.68 mEq/l, $P<0.0001$). Twenty-six patients out of 42 (63%) recovered from hypertension. Forty-six percent of patients were females and 54% were males. Blood pressure levels improved in all remaining patients (Table 2). Nearly 70% (n = 11) of our patients who remained hypertensive after surgery had a family history positive for hypertension. Table 3 shows the patients’ pre-adrenalectomy data stratified by blood pressure outcome post-surgery: patients who remained hypertensive used a mean of two drugs (2.2 ± 0.7).

**Table 2** Postadrenalectomy anthropometric and clinical features of studied patients according to blood pressure outcome.

<table>
<thead>
<tr>
<th></th>
<th>Cured (n = 26) (63%)</th>
<th>Improved (n = 16) (37%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M (n)</td>
<td>12/14</td>
<td>6/10</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>28 ± 5</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129 ± 16</td>
<td>149 ± 8</td>
<td>0.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77 ± 10</td>
<td>88 ± 11</td>
<td>ns</td>
</tr>
<tr>
<td>Na⁺ (mEq/l)</td>
<td>143 ± 3</td>
<td>141 ± 21</td>
<td>ns</td>
</tr>
<tr>
<td>K⁺ (mEq/l)</td>
<td>4.25 ± 0.64</td>
<td>4.10 ± 0.50</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1 ± 0.40</td>
<td>1.02 ± 0.22</td>
<td>ns</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>2.9 (1.0–2.4)</td>
<td>1.7 (1.3–4.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>18.5 ± 19.2</td>
<td>20.2 ± 6.4</td>
<td>ns</td>
</tr>
</tbody>
</table>

F, females; M, males; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Na⁺, plasma sodium; K⁺, plasma potassium and PRA, plasma renin activity. Data are reported as mean±s.e. or as median (25th–75th percentile).
similar to recovered patients (2 ± 1.1). Fifty percent of the patients used MR blockers: 61% of them recovered and 25% remained hypertensive after surgery (P = 0.029).

Moreover, a significant difference for the duration of hypertension was observed: recovered patients had a shorter duration of hypertension than patients who remained hypertensive (10.3 ± 5.1 vs 6.9 ± 4.9 years, P = 0.038). Adenoma size was smaller in recovering patients (18 ± 9 vs 24 ± 8 mm, P = 0.035; Table 3).

Considering the gender differences, as previously stated, females had significantly shorter duration of hypertension and, although the difference was not significant, recovered more often than males (67 vs 58%, P = ns). Recovered females (n = 18) used less drugs (1.8 ± 1.0 vs 2.6 ± 0.5, P = ns), and had a smaller adenoma (18 ± 6 vs 28 ± 9 mm, P = 0.012). Recovered males (n = 24) had slightly smaller adenoma size compared with patients who remained hypertensive (18 ± 11 vs 21 ± 8 mm, P = ns). No differences were observed for the number of drugs used before surgery in recovered/not recovered males (2.3 ± 1.2 vs 2 ± 0.8 respectively). Without reaching statistical significance, both recovered males and females had shorter duration of hypertension compared with hypertensives: in females 5.8 ± 4.3 vs 8.4 ± 4.2 years and in males 8.2 ± 5.7 vs 11.3 ± 6.4 years.

Considering tumor size, patients with adenoma smaller than 20 mm diameter showed, after surgery, a significant reduction of both diurnal and nocturnal, systolic, and diastolic blood pressure values, and the complete restoration of blood pressure circadian rhythm. Although an improvement of blood pressure levels was observed, no significant differences were found in patients carrying an adenoma bigger than 20 mm (Table 4).

ROC curve analysis showed that among the continuous variables correlated with the resolution of hypertension after adrenalectomy, the best predictors of blood pressure normalization were the duration of hypertension ≤ 6 years (sensitivity 67%, specificity 71%) and adenoma size < 20 mm (sensitivity 81%, specificity 52%; Fig. 2).

### Discussion

This study evaluated the cure rate of PA due to APA and identified prognostic factors of recovering after unilateral laparoscopic adrenalectomy.

The primary goals of APA treatment are correction of the biochemical features of PA and improvement, if not complete resolution, of hypertension. In the present study, surgical management of APA led to the normalization of serum potassium levels and set the aldosterone and PRA levels within the normal range, in all patients. Moreover, 63% of our APA patients were cured of hypertension (blood pressure below 140/90 mmHg, without the aid of antihypertensive medications), while blood pressure levels improved in the remaining patients. Such results are in line with the literature data reporting a rate of blood pressure normalization ranging between 30 and 70% (19, 24). This broad range comes from studies performed with different data collection methods and with different definition of cure/improvement of hypertension (18, 19, 21, 28).

### Table 4 Effects of adrenalectomy on ambulatory blood pressure monitoring results according to adenoma size.

<table>
<thead>
<tr>
<th>Adrenal adenoma</th>
<th>Before surgery</th>
<th>Post-surgery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 mm (n = 22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diurnal SBP (mmHg)</td>
<td>146 ± 12</td>
<td>135 ± 11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diurnal DBP (mmHg)</td>
<td>88 ± 11</td>
<td>77 ± 7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nocturnal SBP (mmHg)</td>
<td>140 ± 18</td>
<td>123 ± 14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nocturnal DBP (mmHg)</td>
<td>81 ± 10</td>
<td>72 ± 7</td>
<td>0.0020</td>
</tr>
<tr>
<td>&gt; 20 mm (n = 20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diurnal SBP (mmHg)</td>
<td>146 ± 18</td>
<td>142 ± 13</td>
<td>ns</td>
</tr>
<tr>
<td>Diurnal DBP (mmHg)</td>
<td>88 ± 13</td>
<td>85 ± 12</td>
<td>ns</td>
</tr>
<tr>
<td>Nocturnal SBP (mmHg)</td>
<td>136 ± 16</td>
<td>130 ± 26</td>
<td>ns</td>
</tr>
<tr>
<td>Nocturnal DBP (mmHg)</td>
<td>79 ± 11</td>
<td>77 ± 16</td>
<td>ns</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are reported as mean ± s.d.
Considering the predictors of outcome of adrenalectomy, we observed that in our patients the cure of hypertension after surgery was associated with a shorter duration of hypertension, pre-surgery treatment with MR antagonists, and adenoma size smaller than 20 mm, but not with other factors previously reported to be associated with a favorable blood pressure outcome such as age, sex, BMI, aldosterone levels, number of antihypertensive agents, and a family history of hypertension (18–20, 28).

In agreement with the previous studies (18, 19, 24), in our group of patients, duration of hypertension can be considered as a prognostic factor; shorter hypertension duration gives a higher recovery percentage. In particular, the ROC curve analysis showed that the best predictor of hypertension recovery after surgery is the duration of hypertension equal to or shorter than 6 years, in accordance with a recent study by Zarnegar et al. (18). In this regard, we can hypothesize that aldosterone excess for long time could induce detrimental and irreversible effects on the cardiovascular system, such as cardiac fibrosis, left ventricular hypertrophy (29–31) or vascular remodeling with increased intima-media thickness (24), responsible for hypertension persistence in spite of aldosterone normalization after surgery.

On the other hand, longer hypertension history is often present in older patients, so maintenance of hypertension could also depend on the onset of essential hypertension that cannot be cured by adrenal surgery.

Although females recovered slightly more often than males in our population, the first were younger than males, their BMI was lower and, more importantly, their hypertension was lasting less. Before surgery, there were no differences as for the number of medications used by men and women. However, recovered women used fewer drugs than those who remained hypertensive and noteworthy MR antagonists were used in a larger percentage in these women. This is a possible demonstration that the targeted action of this drug can counteract aldosterone excess.

In our patients, the use of MR antagonists per se appears to be significantly predictive of hypertension recovering. At variance with other studies reporting the preoperative use of spironolactone as MR antagonist (32, 33) this compound was not used in any of our patients because of its known anti-androgenic side effects. Therefore, canrenone or potassium canrenoate was preferred. In our cohort, this treatment appears to be of prognostic value for blood pressure normalization after surgery. In fact, in more than two-thirds of the patients taking MR antagonists, normalization of blood pressure levels after adrenalectomy was observed. However, it is equally plausible that the association between MR antagonists use and postoperative cure of hypertension is indeed due to the fact that small APA, being more active, have been treated more frequently with MR antagonists.

Pre-surgery levels of aldosterone have been proposed as an unfavorable prognostic factor for hypertension recovery (34); the highest levels correlated with hypertension persistence. However, in the present study, as well as in Fukudome’s (22), there was no correlation between aldosterone levels before surgery and persistence of hypertension.

Interestingly, in our patients, a significant inverse correlation between the size of the adenoma and aldosterone levels was observed, both for upright and postsaline infusion aldosterone, while adenoma dimensions directly correlated with serum potassium levels. These observations highlight that small adenomas (i.e. adenomas with diameter less than 20 mm) seem to be characterized by a more pronounced aldosterone secretion, compared with bigger ones. Interestingly, the presence of an APA smaller than 20 mm was also a predictor of hypertension recovery after surgery, as shown also by the ROC analysis. Recently, similar results have been found by Omura et al. (35) who reported that hypertension cure rate was higher in patients with microadenoma. However, at variance with Omura and colleagues, who found that...
microadenomas were less active (lower aldosterone levels, lower ARR, and higher potassium levels), in our study small APA are characterized by a more pronounced aldosterone secretion. In this regard, it is important to underline that in Omura’s paper the presence of a microadenoma was defined at pathology for adenomas with a diameter of less than 7 mm; however, considering our cutoff (i.e. diameter of 20 mm), 86% of their patients had an adenoma smaller than 20 mm so it is clear that it is quite difficult to compare the results of these two papers.

It is possible to speculate that smaller adenomas are characterized by a more marked aldosterone secretion, the removal of which, in the presence of an early diagnosis, is more likely related to PA cure. In this view, the histopathological examination of removed APA would be extremely helpful in order to look for specific characteristics of the adrenal gland in relation to the adenoma dimensions, to see if adenomas bigger than 20 mm present themselves with aspects of hyperplasia or if adjacent areas appear to be hyperplastic. It could be hypothesized, indeed, that bigger adenomas present hyperplastic aspects that from a clinical point of view correspond to a less marked aldosterone hypersecretion, with a less evident picture of PA, and therefore are not diagnosed for a long period with subsequent organ damages responsible, in the end, for the persistence of hypertension after adrenalectomy. It is noteworthy that in the present study we found that small adenomas were responsible for higher aldosterone levels (both in the upright position and postsaline) and for lower serum potassium levels compared with adenoma bigger or equal to 20 mm diameter.

In addition, our results showed that the presence of a small adenoma defines patients with a better response of blood pressure levels also in terms of recovery of the circadian rhythm, evaluated with the ambulatory blood pressure measurements. It is well known, indeed, that patients with PA loose blood pressure circadian rhythm and become non-dipper, a condition associated with an increased risk for cardiovascular events (36, 37). In our patients, 24 h blood pressure monitoring showed that after surgery patients with small adenoma restored blood pressure circadian rhythm at variance with patients with a bigger adenoma.

In conclusion, in order to avoid inappropriate and prolonged therapy and to prevent irreversible organ damage, an early and correct diagnosis of APA is mandatory, as in a high percentage of cases diagnosis means recovery. Our results confirm that adrenalectomy can be performed safely and, in the majority of patients with APA, with good outcomes leading to hypertension resolution in nearly two-thirds of the cases, especially when hypertension is treated with specific drugs such as MR antagonists, concomitant essential hypertension is absent, patients have a short history of hypertension and, as observed in the present study for the first time, the adenoma is of small size.

Therefore, duration of hypertension of 6 years or less, preoperative MR antagonists use, and the presence of an adrenal adenoma smaller than 20 mm, represent favorable prognostic factors for hypertension recovering after surgical removal of APA.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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