Post-saline infusion test aldosterone levels indicate severity and outcome in primary aldosteronism

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Abstract

Objective: The saline infusion test (SIT) is widely used as a confirmatory test for primary aldosteronism (PA). SIT results are judged as follows: post-test aldosterone levels $< 50$ ng/l exclude PA, whereas levels $> 50$ ng/l confirm PA. We hypothesized that post-SIT aldosterone concentrations indicate the severity of PA and might predict outcome.

Design: The study includes 256 PA patients of the German Conn’s Registry who prospectively underwent SIT. The data of 126 patients with complete follow-up of 1.2 $\pm$ 0.3 years after diagnosis were analyzed. The patients were divided into two groups with post-SIT aldosterone levels of 50–100 ng/l (group 1; $n = 38$) and of $> 100$ ng/l (group 2; $n = 88$).

Results: Patients in group 2 had a significantly shorter duration of hypertension (7.5 vs 11.7 years (median), $P = 0.014$), higher systolic blood pressure (BP; 151 $\pm$ 16 vs 143 $\pm$ 17 mmHg, $P = 0.036$), lower serum potassium (3.3 $\pm$ 0.6 vs 3.5 $\pm$ 0.4 mmol/l, $P = 0.006$), higher 24-h urine protein excretion (7.4 vs 5.4 mg/dl (median), $P = 0.012$), and were more often female ($P = 0.038$). They showed more often unilateral disease ($P < 0.005$) with larger tumors (14 $\pm$ 10 vs 7 $\pm$ 10 mm, $P = 0.021$), underwent more often adrenalectomy (75% vs 37%, $P < 0.005$), required a lower number of antihypertensive drugs after adrenalectomy (1.2 vs 1.2 $\pm$ 2.5 $\pm$ 1.4, $P = 0.001$), had a faster normalization of urinary protein excretion (with medical treatment $P = 0.049$; with Adx $P < 0.005$) at follow-up, and more frequently underlying well-characterized mutation ($P = 0.047$).

Conclusions: PA patients with post-SIT aldosterone levels of $> 100$ ng/l have a more rapid development of PA caused more frequently by unilateral disease with larger aldosterone-producing adenomas. However, this group of patients may have a significantly better outcome following specific treatment.

Introduction

Primary aldosteronism (PA) is the most common form of secondary hypertension and affects up to 10% of all hypertensive patients (1). Patients with PA have an increased risk of developing relevant comorbidities, e.g. vascular, cardiac, or cerebrovascular morbidities and renal insufficiency compared with other hypertensive patients (2, 3, 4, 5, 6, 7). Therefore, it seems mandatory to detect early patients with PA. The aldosterone-to-renin ratio (ARR) is recommended for screening patients with suspected PA (8). The guidelines of the Endocrine Society recommend that patients with a positive ARR measurement should undergo any of four confirmatory tests to
confirm or exclude the diagnosis of PA (8). However, up to
date there is no gold-standard confirmatory test for PA
because all test performances have been evaluated only
retrospectively, in relatively small series of patients and
only in comparison with other tests rather than toward
a conclusive diagnosis of PA (8). In Germany, the most
widely used confirmatory test due to practicability, costs,
and compliance is the saline infusion test (SIT). For the SIT
post-infusion plasma aldosterone levels of <50 ng/l
largely exclude the diagnosis of PA, whereas levels of
>100 ng/l confirm PA. Values between 50 and 100 ng/l
are often described as ‘indeterminate’ in older studies
(9, 10, 11, 12), or interpreted as a mild or early form of PA.

To further investigate clinical, biochemical, and
radiological features in PA with modest (post-SIT aldos-
terone levels of 50–100 ng/l) and with more substantial
elevation of aldosterone levels (post-SIT >100 ng/l), we
analyzed data from the German Conn’s Registry, which
was founded in 2006 to evaluate the diagnosis, treatment,
and outcome of PA in Germany. Owing to the persistent
lack of outcome data in PA patients, we were especially
interested in the clinical outcome of these two groups with
regard to adrenalectomy or medical treatment. We
hypothesized that post-SIT aldosterone concentrations
indicate the severity of PA and might predict outcome.

**Subjects and methods**

**Design and patients**

The German Conn’s Registry (www.conn-register.de) is a
multi-center database analyzing comorbidities and long-
term outcome of patients with PA (4, 13, 14). Since the
initiation of the prospective phase in October 2008, all
patients actively treated within the centers were entered
in a common database after pseudonymization (15). The
Ethics Committees of the University of Munich and of
the participating centers approved the protocol. Data
protection laws were strictly adhered to.

Clinical data at time of diagnosis were extracted from
patients’ charts including laboratory test results, initiation
of mineralocorticoid antagonist treatment, surgical treat-
ment, cardiovascular comorbidities, and BMI. Blood
was generally drawn in the fasting state. Every 6 and
12 months the patients were seen for follow-up visits
including a clinical examination, laboratory investigation,
and cardiovascular examinations.

The diagnostic criteria for PA in this study were chosen
according to the Endocrine Society practice guidelines (8).
All patients included had an elevated ARR (in sitting
position between 0800 and 1000 h) and an abnormal
confirmatory test (4, 16). Adjustment of medication before
screening and confirmation was performed whenever
possible, using β-blockers, central α-2 agonists, angio-
tensin-converting enzyme inhibitors, angiotensin
receptor blockers, diuretics withdrawn for at least
1 week, and mineralocorticoid antagonists at least for
4 weeks. The diagnosis of PA was centrally verified by
review of all available data.

In the prospective phase of the German Conn’s
Registry, 256 PA patients underwent a recumbent SIT as
confirmatory test. SIT was carried out with a 4-h saline
infusion (2 l i.v.) in supine position between 0800 and
1200 h. Cortisol levels decrease during testing served as
validation to exclude stress-related stimulation of aldos-
terone. A post-SIT aldosterone level >50 ng/l confirmed
the diagnosis of PA.

Only patients with a complete data set at diagnosis
and at follow-up were included. Sufficient data coverage
was available for 126 prospectively recruited patients, who
were included in the final analysis.

Subtype differentiation between aldosterone-
producing adenoma (APA) and bilateral adrenal hyper-
plasia was based on adrenal imaging (computed
tomography or magnetic resonance imaging) and on
adrenal vein sampling (AVS), the latter performed in 94%
of the patients included (n = 118).

AVS was carried out after 2–3 h of resting in supine
position between 0800 and 1200 h as described previously
(17). Selective AVS was assumed for the purpose of this
study, if cortisol of the adrenal vein was 100% higher than
cortisol in the inferior vena cava (cortisol in adrenal
vein/cortisol in inferior vena cava ≥2.0). We used a
lateralization index in AVS of ≥4 to define unilateral
aldosterone secretion.

AVS was successful in 94% of patients (n = 111). For
further analysis, we distinguished between two patient
groups in our prospective cohort: patients who had a post-
SIT aldosterone level between 50 and 100 ng/l (group 1),
and patients with a post-SIT aldosterone level >100 ng/l
(group 2).

Eighty patients in the whole cohort underwent
adrenalectomy: 46 tumor samples from two centers
(Munich and Berlin) were available for DNA isolation
and sequencing. Tumor DNA was extracted and analyzed
as part of recently published studies by Beuschlein et al.
(18) and by Fernandes-Rosa et al. (19).

We defined the outcome as follows:

- Cured (adrenalectomy patients only) = serum
  potassium >3.4 mmol/l and systolic blood pressure (BP)
<140 mmHg and diastolic BP <90 mmHg and no antihypertensives.

Controlled (medically treated patients only)= serum potassium >3.4 mmol/l and systolic BP <140 mmHg and diastolic BP <90 mmHg and on therapy with mineralocorticoid (MR)-antagonists, but no other antihypertensives §.

Significantly improved=normokalemia and systolic BP decrease by ≥10 mmHg and decrease of antihypertensives by ≥1 §.

Slightly improved=normokalemia and (systolic BP decrease by ≥10 mmHg or decrease of antihypertensives by ≥1 §).

No improvement=persistent hypokalemia or no BP improvement according to the above criteria. §, MR antagonist was not counted as an antihypertensive.

**Statistical analyses**

Variables were assessed for normality by Kolmogorov–Smirnov test. Results are expressed as mean±s.d. if not stated otherwise. Differences between the two groups were assessed using Student’s t-test for normally distributed variables and Mann–Whitney U test for non-normally distributed variables. For paired data and for non-normally distributed variables, we used paired Wilcoxon’s test.

For categorial variables and unpaired data we used χ²-test/Fisher’s exact test and for categorial variables and paired data we used McNemar test. A P value <0.05 was considered as significant. Statistical analysis was carried out using IBM SPSS Statistics 20.

**Results**

Of the 126 PA patients included in this analysis, 38 PA patients had a post-SIT aldosterone level between 50 and 100 ng/l (group 1) and 88 PA patients a post-SIT aldosterone >100 ng/l (group 2). Patients of group 2 were significantly more often hypokalemic, had hypertension for a shorter duration, showed higher systolic BP, and a higher proteinuria at time of diagnosis (Table 1). Group 2 contained a higher proportion of female patients than group 1 and showed a significant higher rate of unilateral aldosterone secretion resulting in a higher rate of adrenalectomies (Table 2). In group 1 only 14 patients (37%) had unilateral disease and were adrenalectomized. In comparison with the 66 patients (75%) of group 2 who underwent adrenalectomy, patients of group 1 were significantly older, had lower potassium levels, and more antihypertensive drugs at follow-up (1.2±0.3 years) (Table 3). The tumor size on imaging was significantly larger in group 2 (Table 3).

**Table 1** Clinical and biochemical parameters of 126 prospective PA patients at diagnosis (baseline) depending on post-SIT aldosterone values. Values are means±s.d. (median).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=38)</th>
<th>Group 2 (n=88)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hypertension (years)</td>
<td>16.4±12.5 (11.7)</td>
<td>11.3±11.4 (7.5)</td>
<td>0.014&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at PA diagnosis (years)</td>
<td>53.9±11.3</td>
<td>50.4±12.4</td>
<td>0.142&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male/female</td>
<td>29 (76%)/9 (24%)</td>
<td>50 (57%)/38 (43%)</td>
<td>0.038&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>24-h systolic BP (mmHg)</td>
<td>143±17</td>
<td>151±16</td>
<td>0.036&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>24-h diastolic BP (mmHg)</td>
<td>91.0±11.1</td>
<td>93.7±13.5</td>
<td>0.345&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aldosterone (ng/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-test</td>
<td>183±68.3 (174)</td>
<td>304±189 (247)</td>
<td>&lt;0.005&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post-test</td>
<td>72.5±15.0 (72.3)</td>
<td>220±120 (178)</td>
<td>&lt;0.005&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renin (ng/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-test</td>
<td>4.56±3.62 (3.90)</td>
<td>4.45±5.08 (2.40)</td>
<td>0.405&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post-test</td>
<td>3.07±2.39 (2.76)</td>
<td>3.19±4.07 (1.80)</td>
<td>0.361&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ARR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-test</td>
<td>81.7±73.6 (41.9)</td>
<td>184±312 (87.8)</td>
<td>0.009&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post-test</td>
<td>44.0±40.3 (26.1)</td>
<td>176±251 (117)</td>
<td>&lt;0.005&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GFR (MDRD) (ml/min per 1.73 m²)</td>
<td>91.5±24.4</td>
<td>87.0±23.2</td>
<td>0.335&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.91±0.27 (0.90)</td>
<td>0.91±0.31 (0.80)</td>
<td>0.587&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.5±0.4</td>
<td>3.3±0.6</td>
<td>0.006&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protein in 24-h urine (mg/dl)</td>
<td>19±63 (5.40)</td>
<td>38±91 (7.40)</td>
<td>0.012&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>No. of antihypertensives</td>
<td>1.7±1.2</td>
<td>2.0±1.1</td>
<td>0.299&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29±5</td>
<td>29±5</td>
<td>0.648&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Group 1, post-SIT aldosterone 50–100 ng/l; group 2, post-SIT aldosterone >100 ng/l; BP, blood pressure; ARR, aldosterone-to-renin ratio; GFR, glomerular filtration rate.

<sup>a</sup>Mann–Whitney U test.

<sup>b</sup>Student’s t-test.
Table 2 Baseline features of 126 prospective PA patients depending on post-SIT aldosterone values.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=38)</th>
<th>Group 2 (n=88)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful AVS</td>
<td>35 (92%)</td>
<td>76 (86%)</td>
<td></td>
</tr>
<tr>
<td>Bilateral/unilateral disease</td>
<td>19 (50%)/</td>
<td>18 (21%)/</td>
<td>0.001</td>
</tr>
<tr>
<td>Adrenalectomy, yes/no</td>
<td>14 (37%)/</td>
<td>66 (75%)/</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Group 1, post-SIT aldosterone levels of 50–100 ng/l; group 2, post-SIT aldosterone levels of > 100 ng/l; AVS, adrenal vein sampling.

Twenty-four patients of group 1 and 22 patients of group 2 showed bilateral disease or refused adrenalectomy (n=5) and, therefore, were put on medical therapy. At follow-up, medically treated patients of group 1 showed lower aldosterone levels but a similar ARR as group 2. Protein excretion of group 2 was reduced on medical therapy compared with the time at diagnosis, but was still higher than that of group 1 (Table 4).

BP normalization, normokalemia, and reduction in antihypertensive medication were more often achieved in group 2 than in group 1 (Fig. 1). Patients on medical therapy reached the outcome ‘controlled’ or ‘significantly improved’ only in 25 or 27% (groups 1 and 2 respectively).

Table 3 Clinical and biochemical parameters of 80 prospective PA patients 1.2 ± 0.3 years after adrenalectomy (follow-up) depending on post-SIT aldosterone values at diagnosis. Values are means ± s.d. (median).

<table>
<thead>
<tr>
<th>After ADX</th>
<th>Group 1 (10 m/4 f)</th>
<th>Group 2 (37 m/29 f)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at follow-up visit</td>
<td>58 ± 12</td>
<td>50 ± 12</td>
<td>0.032*</td>
</tr>
<tr>
<td>Aldosterone (ng/l)</td>
<td>90 ± 72 (68)</td>
<td>71 ± 46 (55)</td>
<td>0.536a</td>
</tr>
<tr>
<td>Renin (ng/l)</td>
<td>39 ± 77 (10)</td>
<td>20 ± 24 (10)</td>
<td>0.438a</td>
</tr>
<tr>
<td>ARR</td>
<td>35 ± 75 (12)</td>
<td>10 ± 15 (6)</td>
<td>0.244a</td>
</tr>
<tr>
<td>24-h systolic/diastolic BP (mmHg)</td>
<td>133/84 ± 17/10</td>
<td>134/83 ± 12/9</td>
<td>0.873/0.763a</td>
</tr>
<tr>
<td>GFR (MDRD) (ml/min per 1.73 m²)</td>
<td>77 ± 24</td>
<td>75 ± 23</td>
<td>0.800a</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.3</td>
<td>0.720a</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.0 ± 0.4</td>
<td>4.3 ± 0.5</td>
<td>0.027a</td>
</tr>
<tr>
<td>Protein in 24-h urine (mg/dl)</td>
<td>4.9 ± 2.1 (5.0)</td>
<td>5.6 ± 3.2 (5.0)</td>
<td>0.788a</td>
</tr>
<tr>
<td>No. of antihypertensives</td>
<td>2.5 ± 1.4</td>
<td>1.2 ± 1.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>Tumor size according to pathological</td>
<td>16 ± 11 (n=10); n=1 NH</td>
<td>25 ± 18 (n=49); n=1 NH</td>
<td>0.135a</td>
</tr>
<tr>
<td>report (mm)</td>
<td>n=3 ND</td>
<td>n=16 ND</td>
<td></td>
</tr>
<tr>
<td>Tumor size according imaging (mm)</td>
<td>7 ± 10 (n=12); n=2 ND</td>
<td>14 ± 10 (n=64); n=2 ND</td>
<td>0.021a</td>
</tr>
<tr>
<td>No. of patients with mutation</td>
<td>1 of 8</td>
<td>22 of 38</td>
<td>0.047f</td>
</tr>
<tr>
<td>KCN5</td>
<td>1</td>
<td>16 (8)</td>
<td></td>
</tr>
<tr>
<td>ATP1A1/ATP2B3</td>
<td>0/0</td>
<td>3/1</td>
<td></td>
</tr>
</tbody>
</table>

Group 1, post-SIT aldosterone levels of 50–100 ng/l; group 2, post-SIT aldosterone levels of > 100 ng/l; ARR, aldosterone-to-renin ratio; BP, blood pressure; GFR, glomerular filtration rate; NH, nodular hyperplasia; ND, no data available.

*Student’s t-test.

*aMann–Whitney U test.

Aldosterone-to-renin ratio at screening and post-SIT aldosterone showed similar strength as predictors regarding outcome (r=−0.188, P=0.045 and r=−0.182, P=0.041 respectively). Post-SIT aldosterone levels remained significant (P=0.046) after correction for main confounding variables (age, duration of hypertension, and BP).

Forty-six tumor samples from 80 adrenalectomies (58%) were available (eight from group 1 and 38 from group 2). The frequency of well-defined somatic mutations was significantly higher (P=0.047) in group 2 (22 of 38; 58%) than in group 1 (one of eight; 13%). In group 1, only one tumor revealed a mutation in the KCN5 gene, whereas 17 tumors of group 2 showed a mutation in the KCN5 gene (45%), one in the CACNA1D gene (3%), three in the ATP1A1 gene (8%), and one in ATP2B3 gene (3%).

Discussion

Mulatero et al. (20) had demonstrated that the SIT is a reasonably reliable alternative to the more time demanding and expensive fludrocortisone suppression test for the confirmation of PA, showing a specificity of 84% and sensitivity of 88% with a cutoff value of 50 ng/l.
Accordingly, SIT is the most widely used confirmatory test for PA in many countries including Germany. In addition to the SIT, the patients in our prospective cohort underwent AVS to differentiate between uni- and bilateral disease. Thereby, we were able to show that 42% of patients with a post-SIT aldosterone levels between 50 and 100 ng/l had unilateral disease. Furthermore, our analysis indicates that patients with post-SIT aldosterone levels of >100 ng/l had more severe PA with faster development of hypertension, higher systolic BP, lower serum potassium, and higher 24-h urine protein excretion at diagnosis. Importantly, in this group, the percentage of patients with unilateral PA was significantly higher than that in the group with post-SIT aldosterone levels of 50–100 ng/l. This is in accordance to a previous small study showing that patients with APA displayed a smaller reduction in aldosterone levels in SIT compared with patients with bilateral adrenal hyperplasia (20). Another study had shown that patients with higher preoperative BP experienced a greater decrease in BP after adrenalectomy (21).

We found more patients in the group with post-SIT aldosterone level >100 ng/l, who were tested positive for somatic mutations in the removed APA compared with operated patients with a post-SIT aldosterone level of 50–100 ng/l. Previously published data have demonstrated that patients with KCNJ5 mutations are more frequently female and are diagnosed at a younger age (19, 22). This is in accordance with our cohort data, showing a higher percentage of female patients in the group with post-SIT aldosterone level >100 ng/l, and a higher percentage of KCNJ5 mutations.

Interestingly, patients with post-SIT aldosterone level of >100 ng/l, despite their more severe form of hypertension, responded better to specific therapy than those with a post-SIT aldosterone level of 50–100 ng/l: specifically, 1 year following therapy, they had faster normalization of urinary protein excretion and a better outcome, as defined by serum potassium and BP normalization and no or reduced antihypertensive drugs. For patients with post-SIT aldosterone levels of 50–100 ng/l, at least one of three parameters improved following adrenalectomy in 50% (vs 77%) and after medical therapy in 71% (vs 82%) respectively. Accordingly, the cure rate following adrenalectomy (defined as serum potassium >3.4 mmol/l+BP <140/90 mmHg+no antihypertensive drugs) was only 32% in the high aldosterone group and 7% in the low aldosterone group respectively. Similarly, a controlled status after medical therapy (defined as serum potassium >3.4 mmol/l+BP <140/90 mmHg+on therapy with MR-antagonists, but no other antihypertensive drugs) was achieved in 14% in the high aldosterone group and 4% in the low aldosterone group respectively. The better outcome in the group with post-SIT aldosterone levels of >100 ng/l might be mostly driven by the higher rate of KCNJ5 mutations with higher aldosterone levels, which generally show a better surgical outcome. This might also explain the finding of a recent study describing a better clinical course in patients with the presence of an adenoma rather than hyperplasia (23).

Table 4 Clinical and biochemical parameters of 46 prospective PA patients after 1.2±0.3 years of medical therapy (follow-up) depending on post-SIT aldosterone values at diagnosis. Values are means±s.d. (median).

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Group 1 (19 m/5 f)</th>
<th>Group 2 (13 m/9 f)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at follow-up visit</td>
<td>53±11</td>
<td>56±13</td>
<td>0.490a</td>
</tr>
<tr>
<td>Aldosterone (ng/l)</td>
<td>194±119 (151)</td>
<td>434±348 (354)</td>
<td>0.003b</td>
</tr>
<tr>
<td>Renin (ng/l)</td>
<td>21±27 (10)</td>
<td>41±71 (13)</td>
<td>0.425b</td>
</tr>
<tr>
<td>ARR</td>
<td>34±43 (13)</td>
<td>35±36 (25)</td>
<td>0.620b</td>
</tr>
<tr>
<td>24-h systolic/diastolic BP (mmHg)</td>
<td>138/84±15/6 (136/83)</td>
<td>138/86±26/16</td>
<td>0.562/0.615a</td>
</tr>
<tr>
<td>GFR (MDRD) (ml/min per 1.73 m²)</td>
<td>80±22</td>
<td>73±27</td>
<td>0.277a</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0±0.4 (1.00)</td>
<td>1.1±0.3 (0.9)</td>
<td>0.938b</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.1±0.5</td>
<td>4.1±0.5</td>
<td>0.867b</td>
</tr>
<tr>
<td>Protein in 24-h urine (mg/dl)</td>
<td>5.6±2.7 (5.1)</td>
<td>11.7±12.9 (7.0)</td>
<td>0.032b</td>
</tr>
<tr>
<td>No. of additional antihypertensivesc</td>
<td>1.7±1.0</td>
<td>1.9±1.4</td>
<td>0.653a</td>
</tr>
<tr>
<td>MR antagonist (daily dose in mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>43±19 (n = 18)</td>
<td>49±22 (n = 20)</td>
<td>0.355a</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>80±45 (n = 5)</td>
<td>– (n = 0)</td>
<td>–</td>
</tr>
<tr>
<td>Dose unknown (n)</td>
<td>1</td>
<td>2</td>
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</tr>
</tbody>
</table>

Group 1, post-SIT aldosterone levels of 50–100 ng/l; group 2, post-SIT aldosterone levels of >100 ng/l; ARR, aldosterone-to-renin ratio; BP, blood pressure; GFR, glomerular filtration rate.
*aStudent’s t-test.
*bMann–Whitney U test.
*cMR antagonist was not counted as an antihypertensive.
A recent paper by Steichen et al. (28) has summarized the studies on outcome of adrenalectomy in PA patients and calculated a pooled cure rate of 42% regarding BP as the only outcome parameter, and with significant heterogeneity across the series. In fact, hardly any study has provided a combined outcome analysis of BP and antihypertensive medication. However, the authors pointed out that adrenalectomy usually results in a significant decrease in systolic BP and in the number of antihypertensive medications prescribed (29). Steichen et al. (28) analyzed adrenalectomy series in PA patients also regarding factors influencing the outcome, which were also highly variable among the studies. However, factors which seem to have a significant negative effect on the outcome were male sex, older age, family history of hypertension, longer duration of hypertension, higher preoperative BP, more drug classes, higher BMI, higher serum potassium concentrations, lower estimated glomerular filtration rate, or higher 24-h urinary aldosterone-to-/ active renin ratio (21, 28). In our study, we could confirm that sex, age, and duration of hypertension influence outcome; however, a higher preoperative BP was not relevant in our cohort. Our data suggest that low post-SIT aldosterone levels (50–100 ng/l) may be an additional indicator of less successful outcome. However, this needs to be validated in other cohorts. Sawka et al. (30) suggested that a higher pre-operative ARR might result in a better outcome after adrenalectomy. This is in accordance with our finding showing higher ARR in the group with post-SIT aldosterone levels of >100 ng/l.

The only prediction model validated to date is a study with 100 patients who underwent adrenalectomy for PA with validation in an independent series of 67 patients.

Our cure/controlled rate is similar to that of a small study with 24 PA patients who showed a cure rate of 33% after adrenalectomy (25). Possible reasons for the overall rather low cure rate in our study may be the long-lasting insufficiently treated hypertension due to delayed diagnosis in patients with PA. Other studies, which reported a better outcome (23), usually used only one outcome parameter, e.g. BP, and used often less strict definitions for ‘cure’ such as a BP <160/95 mmHg (26). In an Italian study with 50 patients who underwent adrenalectomy, the BP outcome was 30% in remission, 53% markedly improved, and 18% showing mild improvement (27). These outcome rates might again be better than in our series due to the shorter duration of hypertension and due to the less stringent definition of outcome.

Figure 1
Outcome data in 126 PA patients with adrenalectomy (A) or medical therapy (B) depending on post-SIT aldosterone values at diagnosis. Group 1 (black bars), post-SIT aldosterone levels of 50–100 ng/l and group 2 (white bars), post-SIT aldosterone levels of >100 ng/l. Cured (adrenalectomy patients only) = serum potassium >3.4 mmol/l and systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg and no antihypertensives. Controlled (medically treated patients only) = serum potassium >3.4 mmol/l and systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg and on therapy with MR-antagonists, but no other antihypertensives §. Significantly improved = normokalemia and systolic blood pressure decrease by ≥10 mmHg and decrease of antihypertensives by ≥1 §. Slightly improved = normokalemia and systolic blood pressure decrease by ≥10 mmHg or decrease of antihypertensives by ≥1 §. No improvement = persistent hypokalemia or no blood pressure improvement. §, MR antagonist was not counted as an antihypertensive.

A recent study (24) investigating unilateral adrenalectomy in bilateral primary hyperaldosteronism has shown that hypertension was cured in 15% of patients and improved in 20%. Also the proportion with controlled hypertension was significantly higher after adrenalectomy (65%) than before (25%). This suggests that unilateral adrenalectomy might be beneficial in some patients with bilateral disease (24), which should not be ruled out per se regarding the rather disappointing outcome data in our cohort.
from another center (31). In this study, a high percentage of patients continued to require antihypertensive medications to control their BP. The best predictors for cure of hypertension following adrenalectomy were a number of antihypertensive medications of ≤2, a BMI ≤25 kg/m², duration of hypertension ≤6 years, female sex (31), and age (2, 30). We confirm in our study that male patients had a poorer outcome than female patients. Nevertheless, the underlying causes of persistent hypertension after PA therapy remain controversial (28). One additional aspect might be that a patient with treated PA is not immune to essential hypertension.

In conclusion, PA patients with post-SIT aldosterone levels of >100 ng/l have a more rapid development of PA caused more frequently by unilateral disease with larger APAs. They showed a better outcome regarding BP, potassium normalization, and reduction in the number of antihypertensive drugs. We suggest that the post-SIT aldosterone level is a predictor for the remission probability of PA post adrenalectomy.

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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