Diagnosis of primary aldosteronism: value of different screening parameters and influence of antihypertensive medication

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Abstract

Objective: The aim of this study was to investigate the utility of different screening techniques for primary aldosteronism (PA), including serum aldosterone (SA), plasma renin activity (PRA) and the SA/PRA ratio in hypertensive patients of a tertiary-care centre. Furthermore, the influence of antihypertensive medication on SA and the SA/PRA ratio were studied.

Design: Clinical records of 425 hypertensive patients who had SA and PRA measurements over a 27-month period were analysed retrospectively. Eighty patients were excluded from further analysis because of incomplete data. The remaining 345 patients were classified into the following groups: patients with essential hypertension (EH) (n = 260, 75.4%), patients with primary aldosteronism (PA) (n = 49, 14.2%) and patients with secondary hypertension other than PA (n = 36, 10.4%). Diagnosis of PA was made in accordance with established laboratory criteria (including measurements of SA, PRA, urinary excretion of aldosterone and metabolites, imaging techniques and response to treatment).

Results: Although mean serum potassium values were significantly lower (P < 0.001) in the PA group compared with the EH group, 61% of PA subjects were normokalaemic (3.4–5.2 mmol/l). The SA/PRA ratio alone identified 94% of the patients with PA, but was false positive in 30% of the patients with EH. The SA/PRA ratio together with SA > 150 g/ml increased the diagnostic accuracy, led to the correct identification of 94% of the patients with PA, and decreased the false-positive rate to 3%. A multivariate binary logistic regression analysis based on SA and PRA was performed, which identified PA with 90% sensitivity and 91% accuracy. The SA2/PRA or the SA3/PRA ratio was found useful for simplification of the regression analysis. Antihypertensive medication influenced SA, PRA and the SA/PRA ratio only in EH patients. In EH patients taking β-adrenoceptor antagonists PRA tended to be lower, leading to a significantly higher SA/PRA ratio and therefore increasing the false-negative rate.

Conclusion: To reduce false-positive results in screening for PA, and thereby avoid unnecessary and cost-intensive diagnostic procedures, SA should be taken into account in addition to the SA/PRA ratio as a second screening criterion. Alternatively, the SA2/PRA or the SA3/PRA ratio is more accurate screening tests than the SA/PRA ratio. Beta-blockers should be avoided whilst screening for PA.

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Introduction

Primary aldosteronism (PA) in its classic form (characterized by hypertension, hypokalaemia and metabolic alkalosis) is a rare cause of arterial hypertension, with a prevalence of less than 1% of the hypertensive population (1). However, recent data suggest that the prevalence of PA is considerably higher if appropriate screening techniques are applied. The prevalence of PA using the SA/PRA (serum aldosterone/plasma renin activity) ratio ranged from 2.7% to 32% in selected, normokalaemic patients with arterial hypertension (2–5). Therefore, PA is now considered the most common endocrine cause of curable hypertension. However, which screening test identifies PA unequivocally is still under debate.

Another controversial discussed issue is whether or not antihypertensive medication influences the SA/PRA ratio. As antihypertensive treatment may affect the renin–angiotensin–aldosterone system,
some authors have recommended withdrawal of all antihypertensive drugs for 7–10 days prior to screening with the SA/PRA ratio (6, 7). For example, β-blockers can raise the ratio by suppressing PRA, and angiotensin-converting enzyme (ACE) inhibitors and diuretics may affect the SA/PRA ratio by increasing PRA. Other groups, however, have pointed out that the ratio is a valid screening parameter for PA also under ongoing medication (5, 8).

Identification of PA in hypertensive patients is important as specific therapeutic options are available. Surgery can provide definite cure in the case of an unilateral aldosterone-producing adenoma (APA), thereby obviating a lifetime dependency on costly and potentially harmful antihypertensive medication (9). In patients with idiopathic hyperaldosteronism (IIA), adding spironolactone to the antihypertensive treatment regimen results in better control of hypertension and therefore reduces target organ damage (10, 11).

As discontinuation of antihypertensive treatment for the differential diagnosis of hypertensive patients is often impractical or even dangerous, validation of the impact of antihypertensive therapy on screening parameter is crucial for the clinical practice.

One objective of this study was to assess the prevalence of PA in patients of a tertiary-care centre. The subjects were patients who had SA and PRA determinations over a 27-month period. We also investigated the diagnostic accuracy of different screening techniques including the SA/PRA ratio, and the influence of antihypertensive medication on SA, PRA and the SA/PRA ratio.

Subjects and methods

Subjects and diagnosis

Clinical records of 425 patients evaluated for secondary hypertension in our hypertension clinic who had SA and PRA measurements between May 1999 and August 2001 were analysed. Eighty of 425 patients were excluded from further analysis because of incomplete investigation, treatment with spironolactone or loss during follow-up. Subjects treated with antihypertensive drugs other than spironolactone were included in the study.

Of the remaining 345 patients, 36 patients had non-essential hypertension such as renal hypertension (n = 24; 12 patients with renal artery stenosis, eight with chronic glomerulonephritis, two with chronic pyelonephritis, one with nephrosclerosis, one with polycystic kidney disease), or other causes of secondary hypertension (n = 12) including two patients with pheochromocytoma, six with Cushing’s syndrome, one with PICA syndrome (hypertension associated with neurovascular compression at the ventrolateral medulla caused by a looping posterior inferior cerebellar artery), two with medication-induced hypertension, and one with pregnancy-induced hypertension.

Of the remaining 309 patients who were finally enrolled in this study, 49 patients were classified as having PA, resulting in a PA prevalence of 14% (49/345). Two hundred and sixty patients were classified as having essential hypertension (EH). PA was diagnosed based on the following criteria: (1) repeatedly low renin in the presence of high normal or elevated SA resulting in an elevated SA/PRA ratio; (2) at least one positive confirmatory test, e.g. failed suppression of SA after saline infusion, elevated urinary excretion of aldosterone (cut-off 15 μg/24 h), 3α,5β-tetrahydroaldosterone or aldosterone-18-glucuronide (cut-off 70 μg/24 h and 17.5 μg/24 h respectively); and (3) response to treatment, e.g. improvement of blood pressure (BP) and/or normalization of serum potassium after surgery or treatment with spironolactone. Improvement of BP was considered when BP decreased to 140/90 mmHg or less or if antihypertensive medications were not further required or could be reduced in number or dosage following treatment. EH was diagnosed if PA or other causes of arterial hypertension were excluded.

Clinical and laboratory profiles of EH and PA subjects are given in Table 1. Patients with PA had a significantly lower serum potassium than EH subjects (P < 0.001), but 30 (61%) of the PA subjects had a serum potassium level within the normal range (3.4–5.2 mmol/l). In 95% of the PA subjects the serum potassium level was below 4.6 mmol/l. Mean values of SA in hypokalaemic PA subjects were significantly higher than those of normokalaemic patients (470 vs 259 pg/ml respectively, P < 0.05).

In 8.1% of the patients details of the medication were not appropriately documented. These patients were excluded leaving 243 patients with EH and 41 patients with PA for the substudy concerning the influence of antihypertensive medication. These 243 patients were grouped by their antihypertensive treatment. Groups of patients with EH were categorized as those receiving mono-treatment with β-adrenoceptor blockers.

Table 1 Clinical and biochemical parameters of patients with EH and PA, indicated as means±S.D.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>EH</th>
<th>PA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>260</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>128/132</td>
<td>16/33</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.6±16</td>
<td>50.7±11.9</td>
<td>0.96</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8±6.3</td>
<td>27.5±4.3</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>76±107</td>
<td>133±128</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blood pressure, systolic (mmHg)</td>
<td>152±25</td>
<td>164±25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blood pressure, diastolic (mmHg)</td>
<td>91±14</td>
<td>100±13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any medication (no. (%))</td>
<td>184 (77)</td>
<td>35 (85)</td>
<td>0.31</td>
</tr>
<tr>
<td>Antihypertensive drugs (no.)</td>
<td>1.5±1.4</td>
<td>1.9±1.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.37±0.4</td>
<td>3.74±0.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>SA (pg/ml)</td>
<td>123±58</td>
<td>341±319</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PRA (ng/ml per h)</td>
<td>1.1±1.9</td>
<td>0.5±0.8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

To convert values of SA to SI units picomoles per litre (pmol/l), multiply by 319. To convert values of PRA to SI units nanomoles per litre per hour (nmol/l per hour), multiply by 0.75. P values were determined by unpaired t-test.


(n = 27), ACE inhibitors (n = 12), angiotensin II subtype 1 (AT1) receptor antagonists (n = 9), calcium-channel blockers (n = 13) or those under combined drug treatment. In these groups under combined treatment, the subjects could be assigned to more than one group. Due to the small number of patients with PA, subjects on monotherapy and combined therapy were pooled for sub-group analysis.

**Measurements of SA and PRA**

Tests of basal SA and PRA were performed on an in-patient or out-patient basis. The majority of in-patients had measurements performed in the supine position at 0800 h, while out-patients had measurements taken in the upright and/or supine position. SA and PRA of the first measurement were used for all calculations and figures. If both supine and upright measurements were performed at the first examination, the mean was calculated for further analysis. The aldosterone to renin (SA/PRA) ratio was expressed as the value of SA (pg/ml) divided by PRA (ng/ml per hour). The lower limit of detection for PRA was 0.2 ng/ml per hour and thus was set at 0.2 for the calculation of the ratio. The saline infusion test was performed on an in-patient basis. After resting for 1 h in a lying or sitting position, 21 of 0.9% saline were infused over 4 h. SA was determined before and after infusion. A normal response was defined by a SA level after infusion that was < 85 pg/ml (1).

**Hormone assays**

Aldosterone concentration was measured in serum (SA) and in 24-h urine samples using a commercial RIA kit (BioChem ImmunoSystems, Bologna, Italy) (13), with a normal range for SA of 12–150 pg/ml in the supine position, and 70–350 pg/ml in the upright position. Normal values for urinary aldosterone ranged from 3 to 15 pg/24 h. PRA was measured using a commercial RIA kit (DiaSorin, Saluggia, Italy), with a normal range of PRA of 0.2–2.8 ng/ml per hour in the supine position, and 1.5–6.7 ng/ml per hour in the upright position. The assay for the measurement of PRA involved an initial enzymatic reaction to generate angiotensin I, followed by quantitation by RIA as previously described (14). 3α,5β-tetrahydroaldosterone and aldosterone-18-glucuronide were measured by RIA after extraction and chromatographic purification as described elsewhere (15). The normal ranges for the 24-h urinary excretion of 3α,5β-tetrahydroaldosterone and aldosterone-18-glucuronide are 10–70 μg/24 h and 3.5–17.5 μg/24 h respectively.

**Analysis and statistics**

Sensitivity, specificity, positive and negative predictive values, and accuracy for the different screening tests were calculated in accordance with standard definitions. An unpaired t-test was applied to compare baseline BP and hormonal values between groups and a paired t-test to compare position-related changes of hormonal values. Furthermore, several parameters (SA, PRA, BP, body mass index (BMI), urinary aldosterone, 3α,5β-tetrahydroaldosterone and aldosterone-18-glucuronide) were analysed in a multivariate logistic regression model and by backward elimination concerning their value to distinguish between patients with PA and EH. In addition, the SA/PRA ratio, the function of the logistic regression model (a weighted log SA – log PRA difference), and a simplification of this model (the SA²/PRA ratio) were compared with a receiver-operating characteristics (ROC) curve (16) in terms of slope. An unpaired t-test was applied to compare hormonal values between the different treatment groups. Fisher’s exact test was performed to compare the number of antihypertensive drugs.

**Statistics**

Statistics were analysed using SAS 6.12 software (SAS 6.12, Proc. Logistic, SAS Institute Inc., Cary, NC, USA). P-values of less than 0.05 were considered to indicate statistical significance.

**Results**

**Comparison between different screening tests**

Three different screening approaches were applied to our patients: (1) the classical screening test: suppressed PRA (e.g. PRA < 0.2 ng/ml per hour in supine and < 1.5 in upright position) and elevated SA (e.g. SA > 150 pg/ml in supine and > 350 in upright position); (2) the SA/PRA ratio (cut-off value 300 pg/ml to ng/ml per hour) (14); and (3) the SA/PRA ratio with SA added as a second criterion. For each approach, sensitivity, specificity as well as positive and negative predictive values were calculated and compared (Table 2). The classical screening criteria were diagnostic in 11 (58%) hypokalaemic and in 15 (50%) normokalaemic patients with PA, and in two (1%) patients with EH, therefore identifying PA with a high specificity but low sensitivity (Table 2). Forty-seven per cent of PA subjects would have been missed in our series if PRA and SA had been used as independent criteria. Using the SA/PRA ratio (cut-off level 300 pg/ml to ng/ml per hour) 18 (95%) and 28 (93%) hypokalaemic and normokalaemic subjects were identified, but in addition 77 (30%) of EH subjects met this criterion (Fig. 1). Increasing the ratio cut-off level to 500 (pg/ml to ng/ml per hour) (3, 9) raised the specificity to 0.85, but dropped sensitivity from 0.94 to 0.78. Applying the SA/PRA ratio (cut-off level 300 pg/ml to ng/ml per hour) plus SA (cut-off level 150 pg/ml) increased the diagnostic accuracy, such as 84% of PA subjects were identified with an overall accuracy of 95% (Fig. 2). Statistical analysis of the accuracy of the SA/PRA ratio was performed using a logistic
regression analysis based on SA and PRA. For the log SA and the log PRA ratio the following regression parameters were calculated: 14.3 and 5.4 (odds ratio 999 and 0.004) respectively. This suggests that, the SA²/PRA ratio or the SA³/PRA ratio, as a simplification of the regression model, performs better in screening for PA than the SA/PRA ratio. Setting the arbitrary cut-off level for the SA²/PRA ratio (regression parameter 6.54; odds ratio 693.062) at 72 000, PA subjects were identified with 92% sensitivity, 89% specificity and 91% accuracy. Setting the arbitrary cut-off level for the SA³/PRA ratio (regression parameter 4.891; odds ratio 120.88) at 8 500 000, PA subjects were identified with 92% sensitivity, 89% specificity and 89% accuracy.

The SA/PRA ratio, the regression model and the SA²/PRA ratio were further compared for the purpose of differentiation of PA from EH using a ROC curve (Fig. 3).

**Influence of antihypertensive drugs on SA and PRA**

When classified for their antihypertensive treatment regimes, no significant differences in the proportion of patients treated with none (28.4% of patients with EH

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**Table 2 Comparison of different screening tests for PA.**

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressed PRA, elevated SA</td>
<td>0.53</td>
<td>0.99</td>
<td>0.93</td>
<td>0.92</td>
</tr>
<tr>
<td>SA/PRA ratio &gt; 300 (pg/ml)/(ng/ml per h)</td>
<td>0.94</td>
<td>0.70</td>
<td>0.37</td>
<td>0.98</td>
</tr>
<tr>
<td>SA/PRA ratio &gt; 300 (pg/ml)/(ng/ml per h), SA &gt; 150 pg/ml</td>
<td>0.84</td>
<td>0.97</td>
<td>0.85</td>
<td>0.97</td>
</tr>
<tr>
<td>SA/PRA ratio &gt; 500 (pg/ml)/(ng/ml per h)</td>
<td>0.78</td>
<td>0.85</td>
<td>0.50</td>
<td>0.95</td>
</tr>
<tr>
<td>SA/PRA ratio &gt; 500 (pg/ml)/(ng/ml per h), SA &gt; 150 pg/ml</td>
<td>0.69</td>
<td>0.98</td>
<td>0.87</td>
<td>0.94</td>
</tr>
<tr>
<td>SA²/PRA &gt; 72 000 (pg/ml)²/(ng/ml per h)</td>
<td>0.90</td>
<td>0.91</td>
<td>0.65</td>
<td>0.98</td>
</tr>
<tr>
<td>SA³/PRA &gt; 8 500 000/(pg/ml)³/(ng/ml per h)</td>
<td>0.92</td>
<td>0.89</td>
<td>0.58</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**Figure 1** Aldosterone to renin (SA/PRA) ratios of patients with EH (n = 260) and normo- (n = 30) and hypokalaemic (n = 19) PA. Values of the SA/PRA ratio obtained at the first measurement are shown. Some patients with an initially low ratio were further studied because of severe, treatment-resistant hypertension and later proved to have PA. To convert values of SA to SI units picomoles per litre (pmol/l), multiply by 2.775. To convert values of PRA to SI units nanomoles per litre per hour (nmol/l per hour), multiply by 0.75.
and 22% of patients with PA; \( P = 0.45 \), one (27.2% and 22%; \( P = 0.57 \)), two (21.8% and 24.4%; \( P = 0.69 \)), three (11.1% and 17.1%; \( P = 0.3 \)) or four and more antihypertensive drugs (11.5% and 14.6%; \( P = 0.61 \)) were evident between EH and PA subjects. Except for \( \alpha \)-adrenoceptor agonists, which were used in a significantly higher proportion of PA patients (\( P < 0.001 \)), no significant difference between EH and PA subjects in the selection of antihypertensive medication was present (data not shown).

The values of SA, PRA and the SA/PRA ratio were compared in PA and EH subjects for each antihypertensive treatment group (Figs 4–6). Significant influences on SA and PRA by antihypertensive medication were shown only for patients with EH but not for PA subjects. In the group of EH subjects treated with calcium-channel blockers, SA and PRA were higher compared with SA and PRA in EH subjects without antihypertensive treatment (calcium-channel blocker monotherapy: SA 156±60 vs 126±46 pg/ml, \( P = 0.0451 \); PRA 2±1.4 vs 0.8±0.6 ng/ml per hour, \( P = 0.0494 \); calcium-channel blocker plus other antihypertensive drugs: SA 127±79 vs 126±46 pg/ml, \( P = 1 \); PRA 1.5±1.9 vs 0.8±0.6 ng/ml per hour, \( P = 0.0027 \)). As both parameters, SA and PRA, were altered in the same direction, there was no influence on the SA/PRA ratio (calcium-channel blocker monotherapy: SA/PRA ratio 283±221 pg/ml to ng/ml per hour; calcium-channel blocker plus other antihypertensive drugs: SA/PRA ratio 227±210 vs 238±152 pg/ml to ng/ml per hour in patients without antihypertensive medication. \( P = 0.36 \) and 0.72 respectively). In EH subjects treated with ACE inhibitors (mainly in combination with diuretics) (ACE inhibitor monotherapy: PRA 1.4±1.3 vs 0.8±0.6 ng/ml per hour, \( P = 0.0039 \); ACE inhibitors plus other antihypertensive drugs: PRA 1.8±2.2 vs 0.8±0.6 ng/ml per hour, \( P = 0.0008 \); AT \(_1\) receptor antagonists (AT \(_1\) receptor antagonists monotherapy: PRA 1.5±2.1 vs 0.8±0.6 ng/ml per hour, \( P = 0.0205 \); AT \(_1\) receptor antagonists in combination with other antihypertensive drugs: PRA 1.6±4 vs 0.8±0.6 ng/ml per hour, \( P = 0.08 \) and \( \alpha \)-adrenoceptor agonists (PRA 1.5±1.4

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**Figure 2** The aldosterone to renin (SA/PRA) ratio plotted against SA for patients with EH (n = 260) and PA (n = 49). PRA values lower than 0.2 ng/ml per hour were set at 0.2. Dotted lines show the cut-off values for the ratio (300 pg/ml to ng/ml per hour) and for SA concentration (150 pg/ml). To convert values of SA to SI units picomoles per litre (pmol/l), multiply by 2.775. To convert values of PRA to SI units nanomoles per litre per hour (nmol/l per hour), multiply by 0.75.

**Figure 3** Comparison of ROC curves for the model of the logistic regression analysis (black line), for the SA/PRA ratio (blue line) and for SA\(^2\)/PRA ratio (red line). The logistic regression model resulted in a remarkable incremental value, shown by the shift to the left of the ROC curve, as compared with the SA/PRA ratio. The approximation SA\(^2\)/PRA ratio has a slope very close to that of the logistic regression function.
vs 0.8±0.6 ng/ml per hour, \( P = 0.0015 \)) PRA was elevated compared with the control group. However, the SA/PRA ratio was not affected significantly. In EH subjects taking only \( \beta \)-blockers, PRA was slightly lower (PRA 0.6±0.4 vs 0.8±0.6 ng/ml per hour, \( P = 0.1037 \)) and SA/PRA ratio was significantly higher (SA/PRA ratio 321±230 vs 238±152, \( P = 0.0406 \)) compared with those without treatment.

No significant influence of medication on mean SA and mean PRA values was seen in patients with PA. However, SA and consequently the SA/PRA ratio was higher (albeit not significantly) in patients treated with \( \alpha \)-adrenoceptor blockers and \( \alpha \)-adrenoceptor antagonists, probably reflecting more pronounced PA causing severe hypertension which required administration of second-line medications.

**Discussion**

**PA screening with SA and PRA**

The data presented herein support previous findings (2, 4) demonstrating a high prevalence of PA (12%) in hypertensive patients referred to a tertiary-care centre.

Screening for PA in specialized hypertension clinics solely on the basis of the SA/PRA ratio using a cut-off value of 250, 300, 750, 1000 (expressed in pg/ml to ng/ml per hour) has revealed a prevalence of 9.5%, 12%, 16.6% and 17% of PA respectively (3, 17, 4, 5). However, prevalence rates reported in these studies are likely to be biased because hypertensive patients were recruited from specialist referral centres. Lim and co-workers, who recruited patients from a single family physician practice, found a raised SA/PRA ratio (>750) in 14.4% of the study population (18). The authors estimated a sensitivity of their cut-off ratio of 93% and concluded that one in ten hypertensive patients in this primary care population had PA, a proportion very similar to that found in specialized referral clinics. Obviously, the definition of a positive SA/PRA ratio varies considerably between investigators. In our study, although the calculation of SA/PRA ratio was useful in identifying patients with PA, the predictive value was low. This limitation is due to the fact that normal or low-normal SA levels were highly amplified by very low PRA levels, leading to a high SA/PRA ratio and consequently to a false-positive result if only the ratio is applied as the screening test.

However, better diagnostic accuracy was obtained if the SA concentration was included as a second criterion. A similar screening approach in other studies showed prevalences of PA of 32% and 18% respectively (10, 19). Cut-off values of SA/PRA ratio and of SA
concentration were set at 1000 pmol/l to ng/ml per hour (equivalent to 360 pg/ml to ng/ml per hour) and 500 pmol/l (equivalent to 180 pg/ml), and 200 (pg/ml to ng/ml per hour) and 150 (pg/ml) respectively. However, it has to be pointed out that not all subjects who screened positive underwent confirmatory studies. The minimum incidence based on biochemically confirmed cases from an unselected Chinese hypertensive population examined by Loh et al. was 5% (19). Rossi et al. investigated 206 selected hypertensive subjects, 32 (13%) of whom had a confirmed APA (20). Based on a retrospective analysis of biochemical tests the authors developed two three-variable models for a logistic multivariate discriminant analysis (MDA) for the screening of PA using PRA, serum potassium and either baseline SA or captopril-suppressed SA. Applying captopril-suppressed SA, patients with Conn’s adenoma were identified with 100% sensitivity and 81% accuracy. When this model was prospectively applied at two institutions a 100% sensitivity and 90% accuracy for the detection of Conn’s adenoma was achieved. In our study the logistic regression model, based on SA and PRA, provided good sensitivity and specificity in the screening for PA. To simplify this model, we calculated the accuracy of the SA^2/PRA and SA^3/PRA ratios, which are close to the optimized model, but may be easier to calculate in clinical practice. Both functions performed better than the conventional SA/PRA ratio (Table 2), suggesting that the SA^2/PRA ratio might be a better screening test than the SA/PRA ratio. It has to be pointed out, however, that the value of the SA^2/PRA ratio must be tested prospectively before its use can be recommended.

**PA screening with serum potassium**

Screening of hypertensive patients for PA has usually been restricted to those who presented with unprovoked or readily induced hypokalaemia (1, 21). Our study, in which 61% of the patients with PA were normokalaemic and would have been missed if screening was based solely on electrolyte disturbances, confirms the poor predictive value of hypokalaemia in the diagnosis of PA. In accordance with this notion, a recent study reported all of the PA patients being normokalaemic with a mean serum potassium level of 3.9 mmol/l (3), whereas other series showed a percentage of normokalaemic patients with any form of PA of 71% and 33% (10, 5). Apparently, the pre-test probability of hypokalaemia varies between the different forms of PA where hypokalaemia is more often found in patients with APA with a reported incidence of 70–80% (9, 22). In our series, 95% of the PA subjects had a serum potassium level below 4.6 mmol/l. In the present study, significantly higher SA values were found in hypokalaemic patients compared with normokalaemic PA subjects. Similar results have been reported by others and it was therefore assumed that normokalaemic PA represents the common, but milder, presentation of the disease, whereas the hypokalaemic variant represents only severe cases (23).

**Influence of medication on screening for PA**

In this study we retrospectively analysed in a cross-sectional design the influence of antihypertensive medication on the aldosterone to renin ratio in a large cohort of patients with EH and PA. While the design of this study is not ideal, it nevertheless allows some conclusions concerning the screening for PA with the SA/PRA ratio. Clearly, a longitudinal study of patients with determination of the SA/PRA ratio without medication and after administration of a defined antihypertensive regimen would have been more appropriate. However, it is difficult to discontinue medication in severely hypertensive patients for at least 7 days, the period required for appropriate wash-out in such a study. The lack of a longitudinal and prospective study design is, at least in part, compensated by the large number of EH and PA subjects in our study. Apart from α-adrenoceptor agonists, which were significantly more frequently prescribed to PA subjects, there was no significant difference in the antihypertensive medication between EH and PA subjects. The
frequent use of α-adrenoceptor agonists in patients with PA might have two reasons: first, hypertension in PA was more severe and therefore second-line anti-hypertensive drugs had to be added for treatment; second, prior to testing SA and PRA, antihypertensive medication had been switched to drugs that are believed to have little effect on SA and PRA. There is no general agreement on whether it is necessary to discontinue antihypertensive therapy before screening for PA using the SA/PRA ratio. 5, 22–28. In the present study, patients were examined whilst continuing antihypertensive therapy other than spironolactone.

Based on the results presented herein, screening for PA with SA and PRA is influenced by antihypertensive medication in patients with EH. In particular, ACE inhibitors, AT1 receptor blockers, α-adrenoceptor agonists and calcium-channel blockers seem to increase, whereas β-adrenoceptor blockers seem to reduce PRA. This effect is important for EH subjects taking β-adrenoceptor blockers as the SA/PRA ratio is increased due to a beta-blocker therapy and thus an increase in the aldosterone to renin ratio (27). However, as SA was not influenced by antihypertensive medication except calcium-channel blockers in our study population, diagnostic accuracy would remain high if screening with the SA/PRA ratio plus SA had been applied to diagnostic accuracy would remain high if screening calcium-channel blockers in our study population, influenced by antihypertensive medication except one to renin ratio (27). However, as SA was not without alteration of SA in patients with EH under significant suppression of the plasma renin concentration and therefore implies no diagnostic pitfall. Similar increased PRA tends to result in a lower SA/PRA ratio and therefore implies no diagnostic pitfall. Similar results were reported by Seifarth et al., who found a significant suppression of the plasma renin concentration without alteration of SA in patients with EH under β-blocker therapy and thus an increase in the aldosterone to renin ratio (27). However, as SA was not influenced by antihypertensive medication except calcium-channel blockers in our study population, diagnostic accuracy would remain high if screening with the SA/PRA ratio plus SA had been applied to our cohort of EH and PA patients, even if established antihypertensive therapies are not withdrawn.

Summary

In conclusion, screening with the SA/PRA ratio in combination with SA concentration > 150 pg/ml performed better than the ratio alone. However, this retrospective study must be followed by prospective validation of this screening technique in our population. Alternatively, more accurate screening than with the SA/PRA ratio is possible with the SA2/PRA and the SA3/PRA ratios as suggested by the regression model presented. Using the SA/PR ratio plus SA screening of PA is not influenced by antihypertensive medication. If using the SA/PRA ratio alone, one must be aware that β-blockers might increase the false-negative rate.

References

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