events and protection against the evolution of quinine resistance by limiting unsupervised quinine therapy in the community.

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References


Screening for primary aldosteronism — normal ranges for aldosterone and renin in three South African population groups

Brian L Rayner, Jonathan E Myers, Lionel H Opie, Yvonne A Trinder, James S Davidson

Objective. To establish normal ranges for plasma aldosterone, renin and aldosterone/renin (A/R) ratio in South African normotensives under typical outpatient conditions, and to estimate the prevalence of primary aldosteronism (PA) among hypertensives in primary care settings.

Design and methods. One hundred and thirty-six normotensive subjects and 154 sex- and age-matched hypertensives at three primary care clinics had measurements of blood pressure, plasma creatinine, K+, aldosterone, plasma renin activity, and spot urine for urinary Na+/creatinine ratio. Medication was not withdrawn before testing.

Results. Mean plasma renin activity in black normotensive subjects (0.95 ± 1.25 ng/ml/h, mean ± standard deviation (SD)) was significantly lower than in white (2.09 ± 1.12 ng/ml/h; P < 0.0001) and coloured (1.81 ± 1.86 ng/ml/h, P = 0.013) normotensives. Mean plasma aldosterone in black normotensives (306 ± 147 pmol/l) was also significantly lower than in white (506 ± 324 pmol/l, P = 0.0022) and coloured (418 ± 304 pmol/l, P = 0.0148) normotensives. In hypertensives, there were no significant differences in renin or aldosterone levels between the three population groups. Urinary Na+/creatinine ratios, an index of Na+ intake, were not significantly different in the three population groups. None of the normotensives had an A/R ratio > 1 000 plus aldosterone > 750, while 7.1% of hypertensives exceeded these levels, suggesting that they are appropriate criteria for screening for PA.
Although primary aldosteronism (PA) was previously considered to be a rare cause of hypertension, several recent studies, reviewed by Vallotton,1 indicate that the prevalence of PA is actually much higher, ranging from 1.5% to 12% of hypertensives.2 PA is now diagnosed more frequently as a result of several factors, including the recognition that hypokalaemia is not a good screening test,3 the wider availability of aldosterone and renin assays, and the use of the casual aldosterone/renin (A/R) ratio as a screening test.4 This shift in perspective has clinical relevance as PA is potentially curable by unilateral adrenalectomy, is effectively treated with spironolactone, and may not respond well to standard therapy.

The aims of the present study were to establish reference ranges for plasma renin, aldosterone and A/R ratio, and to estimate the prevalence of biochemical PA in hypertensives seen at primary care centres. In view of the fact that ethnic differences in sodium homeostasis and in the renin-aldosterone system have previously been proposed to have importance in the pathogenesis of hypertension,5 a second aim was to clarify whether ethnic differences exist in renin or aldosterone levels, or in the prevalence of PA in South African patients.

Published reference ranges for plasma renin and aldosterone in normotensives have invariably been obtained under controlled conditions of posture (i.e. supine or ambulant) and in many cases under controlled salt intake. These normal ranges are not directly applicable to patients in primary care settings, under variable conditions of posture and salt intake. In addition, mean renin levels have been reported to be lower in black subjects than in whites living in the United Kingdom,6 raising the concern that a high A/R ratio alone may be an inappropriate screen for PA in black population groups. It was therefore necessary to first establish normal ranges for the A/R ratio in normotensives under primary care clinic conditions, in order to estimate the prevalence of PA in hypertensives.

RESULTS

Table I shows the ages and BPs of normotensive and hypertensive subjects in each of the three ethnic groups. Mean plasma aldosterone, renin, A/R ratios and urinary Na+/creatinine ratios are shown in Table II. Plasma aldosterone levels plotted against plasma renin activity for normotensives and hypertensives are shown in Figs 1 and 2 respectively.

There were highly significant ethnic differences in the distribution of plasma renin and aldosterone values among normotensives. Mean plasma renin activity was lower in black normotensives compared with whites and coloureds. The majority of black subjects (70%) had a plasma renin less than 1 ng/ml/h, while this was present in only 16% of whites.

Mean plasma aldosterone was also significantly lower in black normotensives than in whites and coloureds. Only 9% of blacks had a plasma aldosterone greater than 500 pmol/l, while this was present in 34% of whites.

The mean A/R ratio was significantly higher in black normotensives compared with whites. An A/R ratio ≥ 1 000, which has previously been used as a criterion for diagnosis of PA, was present in a large fraction of black (32%) and coloured
Table I. Age and blood pressures in normotensive and hypertensive subjects (mean ± standard deviation)

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>46</td>
<td>55.5 ± 12.7</td>
<td>128 ± 11.2</td>
<td>80 ± 10.4</td>
</tr>
<tr>
<td>Coloured</td>
<td>46</td>
<td>55.0 ± 7.6</td>
<td>130 ± 11.0</td>
<td>82 ± 7.6</td>
</tr>
<tr>
<td>White</td>
<td>44</td>
<td>53.4 ± 12.3</td>
<td>126 ± 11.5</td>
<td>78 ± 5.5</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>56</td>
<td>56 ± 11.0</td>
<td>145 ± 18.2†</td>
<td>93 ± 9.2‡</td>
</tr>
<tr>
<td>Coloured</td>
<td>47</td>
<td>56 ± 7.7</td>
<td>155 ± 17.3§</td>
<td>93 ± 13.1§</td>
</tr>
<tr>
<td>White</td>
<td>51</td>
<td>56 ± 10.4</td>
<td>144 ± 14.9</td>
<td>88 ± 7.7</td>
</tr>
</tbody>
</table>

* Coloured v. white: P = 0.0007.
† Black v. coloured: P = 0.0072.
‡ Black v. white: P = 0.0045.
§ Coloured v. white: P = 0.0012.
¶ Coloured v. white: P = 0.042.

Table II. Mean plasma renin activity, plasma aldosterone, and A/R ratio in normotensive and hypertensive subjects (mean ± standard deviation). Pairwise comparisons of data were performed using two-sample Wilcoxon rank-sum (Mann-Whitney) tests

<table>
<thead>
<tr>
<th>Category</th>
<th>Renin (ng/ml/h)</th>
<th>Aldosterone (pmol/l)</th>
<th>A/R ratio</th>
<th>Urine Na'/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.95 ± 1.26‡</td>
<td>306 ± 147§</td>
<td>1.0504± 1.205</td>
<td>15.5 ± 11.7</td>
</tr>
<tr>
<td>Coloured</td>
<td>1.81 ± 1.86</td>
<td>418 ± 304</td>
<td>1.017± 1.638</td>
<td>12.9 ± 8.4</td>
</tr>
<tr>
<td>White</td>
<td>2.09 ± 1.12</td>
<td>506 ± 324</td>
<td>306 ± 240</td>
<td>11.8 ± 7.8</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2.93 ± 4.40</td>
<td>600 ± 470</td>
<td>609 ± 605</td>
<td>13.2 ± 7.1</td>
</tr>
<tr>
<td>Coloured</td>
<td>1.81 ± 2.07</td>
<td>594 ± 401</td>
<td>1.361 ± 1.938</td>
<td>14.9 ± 11.1</td>
</tr>
<tr>
<td>White</td>
<td>3.69 ± 7.01</td>
<td>577 ± 442</td>
<td>962 ± 1.599</td>
<td>11.7 ± 6.9</td>
</tr>
</tbody>
</table>

* Renin: black v. coloured normotensives: P = 0.0003.
† Renin: black v. white normotensives: P = 0.013.
‡ Aldosterone: black v. white normotensives: P = 0.0002.
§ Aldosterone: black v. coloured normotensives: P = 0.0046.
¶ A/R ratio: black v. white normotensives: P = 0.0003.

Fig. 1. Plasma aldosterone plotted against renin in normotensives. The diagonal line indicates an A/R ratio = 1 000. The shaded area represents a positive screening test for primary aldosteronism.

(19.5%) normotensives, compared with only 4.2% of whites.

Mean sodium intake, estimated by urinary Na'/creatinine ratio, was somewhat higher in blacks than whites (in both normotensives and hypertensives), but these differences were not statistically significant (Table II). While a higher Na' intake is expected to result in a lower renin level, the distribution of renin levels plotted against Na'/creatinine ratio (Fig. 3) suggested that renin levels tended to be lower in black subjects over the entire range of Na' intakes. This was confirmed by stratifying normotensives into three groups defined by tertiles with low, medium or high urinary Na'/creatinine ratios, which showed that renin levels were significantly lower in black subjects than in whites, irrespective of Na' intake (Table III).

In contrast to the normotensives, there were no significant ethnic differences in renin, aldosterone or A/R ratios in the
hypertensives (Fig. 2 and Table II). The profiles of antihypertensive drug usage are shown in Table IV.

**DISCUSSION**

In a recent study we found that 8% of patients at a tertiary hypertension clinic had biochemical results strongly indicative of PA (aldosterone ≥ 1,000 plus A/R ratio ≥ 1,000), and a further 24% had results compatible with PA. Of these patients with biochemical PA, 10% had definite adrenal masses on computed tomography (CT) scan, and a further 6% had probable adrenal masses. Because it was unclear whether this high prevalence of PA was the result of referral bias, the present study was undertaken to investigate the prevalence of biochemical PA among hypertensives in primary care settings. In order to do this, it was first necessary to establish reference ranges for plasma renin and aldosterone in normotensives.

Ethnic differences in sodium homeostasis and in the renin-aldosterone system have previously been reported, and have been proposed to be relevant to the pathogenesis of hypertension. Blacks in the USA have been reported to have a higher incidence of PA and low-renin hypertension. Low-renin hypertension has also been found to be prevalent in Zimbabwean blacks. Recently, variants of the epithelial sodium channel have been found associated with particular ethnic groups. For these reasons, we opted to analyse the renin and aldosterone values according to ethnic group.

The present study reveals highly significant differences in plasma renin activity, aldosterone and A/R ratio between the three ethnic groups among normotensives. Both plasma renin and aldosterone levels were significantly lower in the black group than in whites and coloureds. Because of their low renin values, a high proportion of normotensive black subjects (32%)}
and to a lesser extent normotensive coloured subjects (19.1%) had an A/R ratio ≥ 1.000, compared with only 4.2% of whites. 

In previous studies of predominantly white population groups, a high A/R ratio has often been used as a sole criterion for diagnosing PA, with varying cut-off points for diagnosis of PA. A/R ratios greater than 1.385, 1.390, 1.950, 1.831, 1.100 and 1.500 have been used as cut-off points (expressed in the same units as the present study). In addition to the A/R ratio, Young required an absolute aldosterone level greater than 416 pmol/l for diagnosis of PA.

The present data show that a high A/R ratio cannot be used as the sole criterion for screening for PA in black and coloured patients, as the high prevalence of low renin levels in normotensives would lead to an unacceptably high false-positive rate. It is necessary to include an additional criterion in order to exclude the large number of low-renin patients who do not have PA. An elevated plasma aldosterone level would serve this purpose, but our previous results, as well as other data, have shown that many proven cases of PA do not have an unequivocally elevated aldosterone level. As there is an overlap in aldosterone levels between PA and low-renin essential hypertension, any aldosterone level chosen as a cut-off point will inevitably be a compromise between sensitivity (pick-up of cases of PA) and specificity (false-positives due to low-renin hypertension). No normotensives in our series had A/R ratios > 1.000 plus aldosterone > 750, suggesting these criteria as reasonable cut-off points for screening for PA.

To determine whether the lower renin and aldosterone levels in black normotensives were the result of higher Na⁺ intakes, we estimated sodium intake by the Na⁺/creatinine ratio in a spot urine sample, which has previously been shown to correlate well with 24-hour sodium excretion. Mean Na⁺/creatinine ratios were higher (though not statistically significantly) in black subjects, but this was not a major factor contributing to their lower renin levels, as stratifying the subjects into groups with low, medium or high salt intake showed that black subjects had lower renin levels across the full range of salt intakes.

In considering possible reasons for the lower renin and aldosterone levels in black normotensives, the most direct hypothesis is that the low-renin state is secondary to, and compensates for, a relative tendency to retain sodium. A sodium-retaining tendency could be mediated by differences at many points in the complex control loops governing sodium homeostasis.

Mutations in the β- or α-subunits of the epithelial sodium channel (ENaC) have been identified as the cause of Liddle’s syndrome, a rare cause of hypertension with low renin and aldosterone levels. While the Liddle’s mutations are rare, a polymorphic variant of the βENaC, which has altered function in vitro, is present in 6% of African Americans and is reported to be associated with hypertension in blacks in London. The prevalence of epithelial sodium channel mutations in South African populations is unknown. Differences in the secretion or action of dopamine, atrial natriuretic peptide and renal prostaglandins have all been proposed as possible mechanisms for salt retention in low-renin hypertension.

If the sodium-retention hypothesis is correct, it follows that the black normotensive subjects may have normal BP because they have successfully decreased their renin secretion in response to a salt-retaining tendency. Conversely, the higher renin and aldosterone levels observed in black hypertensives (compared with normotensives) may reflect an inappropriate level of renin and aldosterone secretion in the face of the putative sodium-retaining tendency, and may therefore be a causative factor in these patients’ hypertension. However, it is very likely that the renin and aldosterone levels in the hypertensives in the present study have been markedly altered by the use of antihypertensive drugs (Table IV). Diuretics, used by 90% of black hypertensives, are known to increase renin and aldosterone, and are therefore likely to be a significant factor contributing to the higher levels of renin and aldosterone seen in black hypertensives compared with normotensives. Beta-blockers suppress renin secretion, while angiotensin-converting enzyme (ACE) inhibitors increase it, and it is therefore not possible to speculate on the overall effect of combinations of these drugs in the white hypertensives.

Of the 154 hypertensives, 7.1% (11 patients: 3 black, 3 coloured, 5 white) fulfilled the criteria for PA derived from normotensive data as described above (A/R ≥ 1.000 plus aldosterone ≥ 750). This is clearly a first approximation, and the true prevalence of PA in the primary care setting will require further testing after withdrawal of hypertensive drugs, as we have proposed.

In summary, we have established normal ranges for plasma aldosterone, renin and A/R ratio in South African normotensives under outpatient conditions. Screening of hypertensives in primary care settings indicated that 7.1% require definitive investigation for PA.

Sources of support for this study were the National Kidney Foundation of South Africa, the Southern African Hypertension Society, and Searle (South Africa).

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