Prevalence of primary hyperaldosteronism assessed by aldosterone/renin ratio and spironolactone testing

Sue Hood, John Cannon, Roger Foo and Morris Brown

ABSTRACT – Recent studies have suggested that primary hyperaldosteronism may be present in more than 10% of patients with hypertension. We aimed to estimate the prevalence in unselected patients in primary care, and investigate the influence of current drug treatment upon the aldosterone/renin ratio (ARR) and its prediction of blood pressure response to spironolactone. We measured blood pressure, plasma electrolytes, renin activity and aldosterone in 846 patients with hypertension. Spironolactone 50 mg was prescribed for one month to patients with blood pressure ≥130/85 mmHg and ARR ≥400. The primary outcome measure was to discover the proportion of patients with plasma aldosterone ≥400 pmol/l *and* ARR ≥800 *and* either an adrenal adenoma on computed tomography scan or a systolic blood pressure response to spironolactone ≥20 mmHg. Only one patient had an adenoma, and only 16 (1.8%) had both a plasma aldosterone ≥400 pmol/l and ARR ≥800. By contrast, 119 patients (14.1%) had an elevated ARR but normal plasma aldosterone. In 69 patients out of the 119 who received spironolactone, blood pressure fell by 26/11 mmHg. These patients were normokalaemic but had uncontrolled hypertension despite multiple drugs. The response to spironolactone was best predicted by a low plasma renin, ≤0.5 pmol/ml/h (<10 mU/l), despite treatment with an ACE inhibitor. We concluded that adrenal adenomas are an uncommon cause of hypertension. In the absence of hypokalaemia, a low plasma renin is a sufficient and simple way of detecting spironolactone-responders among patients with resistant hypertension. Only patients with both hypokalaemia and low plasma renin, measured while the patient is off β blockade, require measurement of aldosterone. A plasma aldosterone >400 pmol/l together with renin activity ≤0.5 pmol/ml/h should trigger further investigations for an adrenal adenoma.

KEY WORDS: aldosterone, hypertension, primary hyperaldosteronism, renin, spironolactone

Aldosterone-secreting adenomas were long considered a rare cause of hypertension, with bilateral micronodular hyperplasia accounting for a similarly small proportion – less than 2% – of all hypertension.[1] But recent studies have suggested that primary hyperaldosteronism (PHA) may be present in at least 10% of patients.[2–5] These studies have used biochemical measures of autonomous aldosterone secretion, usually the ratio of plasma aldosterone to renin and the failure of aldosterone to suppress during treatment with salt supplementation. However, as often occurs when the arbiter for diagnosis changes – here, from anatomical to biochemical – the question arises whether the definition of the condition has also changed. There have been concerns, for instance, that a high aldosterone-to-renin ratio (ARR) is driven mainly by its denominator and fails to distinguish PHA from other causes of salt retention and consequent renin suppression.[6,7] And while introduction of ARR as a concept enabled rapid *exclusion* of the diagnosis of PHA in about 90% of hypertensive patients, without the need for hospitalisation or specialist referral, the opposite is true of the fludrocortisone and salt suppression test required in the remaining 10%. This investigation, placing a bias on relatively small studies in specialist centres, may overestimate true prevalence, and is unsuitable to recommend in 10% of all patients with hypertension.

There is arguably little clinical value in recognising an increased prevalence of a condition unless a therapeutic dividend ensues. In our study investigating prevalence of apparent Primary Hyperaldosteronism measured by Aldosterone-to-Renin ratio and spironolactone testing (PHArst), the primary objective was to estimate the proportion of patients in whom measurement of ARR led to either cure (by adrenalectomy) or control (by spironolactone) of the hypertension. We also wished to compare ARR with renin measurement alone in prediction of the spironolactone response. Patients were studied on existing treatment so that we could evaluate the influence of current antihypertensive treatment on plasma aldosterone and renin, and determine which patients in a routine clinic would benefit the most from measurement of these hormones.

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Subjects and methods

The study was undertaken in five general practices, embracing a mixture of urban and rural populations. The diagnosis of hypertension was accepted if patients were receiving treatment, and/or had three blood pressure readings >140/90 mmHg.[8] Patients aged 18–75 were invited to a 30-minute visit at their practice undertaken by a single specialist research nurse. Sitting blood pressure was recorded in triplicate, using the Omron HEM-705-CP, and blood taken after 30 minutes rest for electrolyte, aldosterone and renin activity assay. The hormones were measured by radioimmunoassay at the supraregional reference laboratory, using in-house antisera.[9] In order to expand the lower range of the assay, active renin concentration was also measured in the final 202 samples by the Nichols Advantage assay. Patients in whom ARR was ≥400, or renin ≥0.2 pmol/ml/h, were invited to two further visits, at which blood pressure was measured before and one month after addition of spironolactone 50 mg daily to existing medication; exclusions were patients who had either a blood pressure already below 130/85 mmHg, or a serum creatinine >150 μmol/l, or K^+ >5.5. In three practices, a spiral computed tomography (CT) or magnetic resonance imaging (MRI) scan of the adrenals was performed in all patients with an ARR ≥800, or both an ARR ≥400–799 and fall in systolic blood pressure on spironolactone (ΔSBP_{spiro}) ≥20 mmHg. In the last two practices, scans were performed only in patients meeting the other pre-specified criteria (elevated aldosterone, ARR and (ΔSBP_{spiro}) for diagnosing PHA.

In two practices, we investigated whether Na^+ loading of the distal tubule would unmask hypokalaemia in apparently normokalaemic PHA. All patients in these practices had two visits, two weeks apart, during which they took bendrofluazide 10 mg and slow sodium 150 mmol daily, in addition to existing medication. Blood pressure and blood samples were taken on both visits.

All patients gave written consent and the protocol was approved by the local research ethics committee.

The primary outcome was a composite of elevated plasma aldosterone (≥400 pmol/l) and aldosterone/renin ratio (≥800) together with an adrenal adenoma on CT or MRI scan and/or systolic blood pressure fall on spironolactone of ≥20 mmHg. Secondary outcomes were the proportion of patients receiving each of the main drug classes in whom spironolactone achieved ΔSBP ≥20 mmHg or British Hypertension Society target blood pressure (<140/85 mmHg). We aimed to recruit a sample of 150–200 patients from each practice. If the true prevalence of PHA was between 5 and 10%, the study would have the power to detect such rates with 95% confidence intervals of 2–3%. The characteristics of high and low ARR groups were compared by unpaired t test. Comparison of log-normalised ARR and renin distribution between patients receiving each drug class was performed by Kalmogorov-Smirnov (K-S) and chi-squared test. The influence of ARR and plasma renin activity upon spironolactone response was estimated by multiple regression analysis. Patients who withdrew consent between estimation of ARR and performance of CT scanning or spironolactone testing are included in the analyses of ARR and the intention-to-treat analysis of primary outcome.

Key Points

Primary hyperaldosteronism (Conn's syndrome) is an uncommon cause of hypertension and need not generally be suspected in the absence of typical electrolyte changes (low K^+, high/normal Na^+)

A much commoner syndrome is that of low-renin resistant hypertension, which responds to spironolactone when other drugs (including thiazide diuretics) have apparently been ineffective

A recently introduced immunochemiluminometric assay for plasma renin mass provides a cheap and quick method for detecting both of the above syndromes, whereas the current manual assay for aldosterone can be reserved for patients with low plasma renin and hypokalaemia

Both renin and aldosterone measurements are open to confounding by commonly used antihypertensive drugs. β blockers work by suppressing renin secretion, and cause false-positive elevation of the aldosterone/renin ratio. Calcium blockers can suppress aldosterone secretion, as does hypokalaemia of any cause

Primary hyperaldosteronism is most likely when a high Na^+, low K^+, low renin and high aldosterone are found despite treatment with an ACE inhibitor or angiotensin blocker

Low-dose thiazide-induced hypokalaemia is a reason for considering, not rejecting, the diagnosis of primary hyperaldosteronism

Results

Primary outcomes

In all, 846 patients attended the screens, whose demographic data are shown in Table 1. The renin and aldosterone levels are shown as a scattergram in Fig 1; this illustrates the continuum of the distributions for both hormones and lack of a substantial subgroup of patients with high aldosterone and low renin levels in the top left-hand quadrant. 119 (14.1%) patients had an ARR ≥800, but only 16 (1.8%) patients had both plasma aldosterone ≥400 pmol/l and ARR ≥800. Of these, only three had a plasma aldosterone >500, and one patient >700 pmol/l.

A spiral CT or MRI scan was performed in 78 patients. Only one definite adenoma was found. This patient, on treatment with a calcium blocker, had a plasma K^+ of 3.2 mmol/l and plasma aldosterone of 428 pmol/l which rose to 758 pmol/l after correction of the hypokalaemia. Possible adenomas, less than 1 cm in size, were seen in two further patients who subsequently underwent adrenal vein sampling. In both cases, elevated aldosterone secretion was found to be bilateral. Six eligible patients (though with plasma aldosterone <300 pmol/l) declined scans.

Secondary outcomes

The measurement of ARR succeeded in identifying patients with a good blood pressure response to spironolactone, which was added to existing treatment in 126 patients with an ARR ≥400. Mean (SD) ΔSBP_{spiro} was 22.7(19.9) mmHg, and 40 patients (37%) achieved the British Hypertension Society target of 140/85 mmHg. Slightly more patients with an ARR ≥800 met the pre-specified outcome for ΔSBP_{spiro} of ≥20 mmHg, than patients with ARR of 400–799 (40 out of 69 (58%), *vs* 23 out of 55, (42%), $p = 0.05$. Of the 16 patients with elevated plasma aldosterone and ARR, only six patients (including the adenoma patient) achieved the 20 mmHg threshold for ΔSBP_{spiro}. The estimated prevalence of PHA by our pre-specified definition was therefore 0.7%.

Factors influencing plasma renin and ARR

The main determinant of ARR was not aldosterone but renin. This was mainly because a linear increase in ARR with aldosterone secretion assumes similar distributions of both hormones – whereas the distributions are usually normal for aldosterone and log-normal for renin. This difference in distribution is apparent from the axes of Fig 1, which additionally shows the contrasting influences of angiotensin-converting enzyme inhibitor (ACEi) (or angiotensin blocker, ARB) and β-blocker therapy on plasma renin. The consequence for the use of ARR is seen in Fig 2, with little overlap between the distribution of ARR for patients on these two types of drugs (K-S Z = 7.12, $p < 0.001$).

Althouth PHArst set out primarily to investigate the diagnostic value of ARR, plasma renin alone was found to be at least as predictive. All patients with an elevated ARR had a plasma renin in the lower half of the distribution, and 57 out of the 64 good responses to spironolactone (ΔSBP_{spiro} ≥20 mmHg) were in patients in the lowest decile for their drug treatment. In a multiple regression analysis of ΔSBP_{spiro} (as dependent variable) upon renin, aldosterone and drug-group (independent variables), there was an inverse correlation between plasma renin and ΔSBP_{spiro} ($\beta = -0.29$, $p = 0.003$); there was, by contrast, no significant correlation between plasma aldosterone and ΔSBP_{spiro}. Because ACEi (or ARB) and β blockade had marked and opposite effects upon renin secretion, a low plasma renin was a better predictor of spironolactone response in patients receiving ACEi than β blockade (Fig 3). Ninety-two of the 126 spironolactone tests were conducted in patients whose β blockade caused a high ARR, and fewer than half these patients had a ΔSBP_{spiro} >20 mmHg. By contrast, only 19 of the ACEi/ARB-treated patients had a high ARR, and ΔSBP_{spiro} exceeded 20 mmHg in 16 of the 19 patients.

Table 1. Patient demographics comparing patients with high and low aldosterone/renin ratio (ARR).

	Group 1 (ARR <400)	Group 2 (ARR ≥800)	*p* value
Age	59.7 (8.8)	60.0 (8.8)	
Gender (M/F)	300/293	59/57	
SBP (mmHg)	145.6 (19.9)	154.5 (19.5)	0.00001
DBP (mmHg)	88.2 (10.3)	92.2 (10.3)	0.0001
Number of drugs	1.41 (0.80)	1.60 (0.80)	0.02
Na^+ (mmol/l)	140.0 (2.5)	140.3 (2.4)	
K^+ (mmol/l)	4.0 (0.45)	4.1 (0.41)	0.03
Urea (mmol/l)	6.18 (1.82)	5.93 (1.58)	
Creatinine (mmol/l)	97.6 (23.9)	93.1 (14.5)	0.05
Bicarbonate (mmol/l)	28.1 (5.2)	28.2 (2.6)	
Chloride (mmol/l)	103.6 (3.0)	103.8 (3.4)	
Aldosterone (pmol/l)	219 (176)	274 (106)	0.0005
Renin activity (pmol/ml/h)	2.0	0.22	10^{-22}
ARR	93	1122	10^{-22}

DBP = diastolic blood pressure; SBP = systolic blood pressure.
Values are the mean (SD) of each parameter, except for gender, where number of patients is shown.

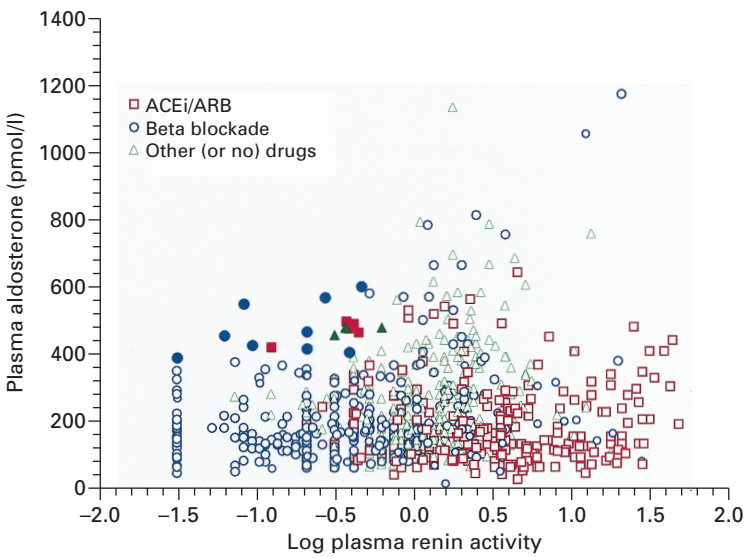

Fig 1. Scattergram of renin and aldosterone values. Renin (activity or mass) and aldosterone were measured in 846 hypertensive patients. Values of renin, but not aldosterone, were higher in patients receiving ACEi or ARB (squares) than in patients on β blockade (circles) or other treatment (triangles). The closed symbols in the upper left quadrant represent the small number of patients whose aldosterone and renin values met the pre-set criteria for diagnosing PHA, namely aldosterone ≥400 pmol/l, and ARR ≥800. Renin mass measurements are shown as renin activity using a conversion factor of 1 pmol/ml/hour = 18 mU/l, estimated in 54 healthy subjects, and confirming a previously published estimate.[33]

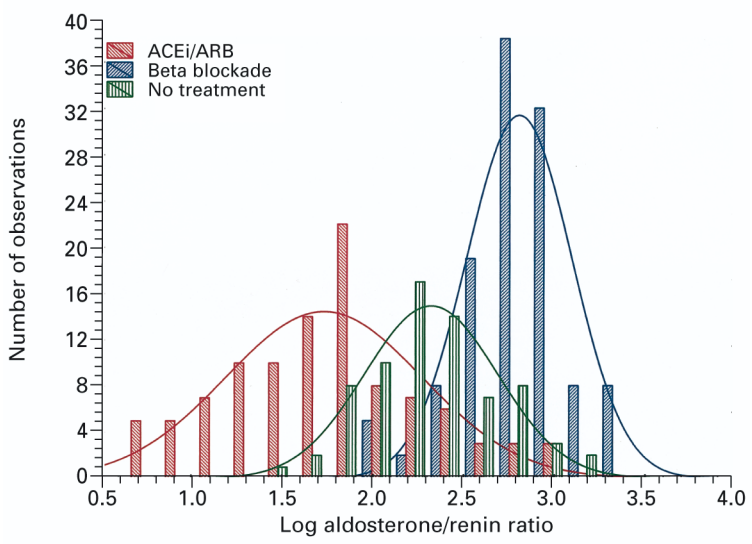

Fig 2. Influence of current drug treatment on the aldosterone/renin ratio. The aldosterone/renin ratio is plotted as a frequency distribution for patients receiving ACEi/ARB, β blockade, or no treatment. Omitted for clarity are the results for patients on calcium blockade, diuretics, or combinations of ACEi/ARB and β blockade; these distributions did not differ significantly from that for untreated patients.

Their mean (SD) response to spironolactone (29±20 mmHg) exceeded that in β-blocked patients (17±18 mmHg) (t = 2.37, $p = 0.019$).

Comparison of high- and low-ARR patients

Unlike the picture expected in patients with classical Conn's syndrome, our patients with an elevated ARR (but, in most cases, normal plasma aldosterone) had normal plasma electrolytes. As shown in Table 1, which compares patients at the top and bottom of the ARR distribution, the distinguishing feature of the former was not a low K^+ or high bicarbonate, but the presence of apparently resistant hypertension. Patients with an elevated ARR had a blood pressure that was on average 9/4 mmHg higher than the lower ARR patients – despite receiving significantly more therapy for their hypertension.

Sub-study of distal tubular Na^+ loading

In 289 patients studied before and after two weeks treatment with 10 mg bendrofluazide and 150 mmol slow sodium daily, there was no significant change in plasma Na^+ but plasma K^+ fell by 0.30 (0.36) mmol/l ($p = 0.0009$). However, the fall in plasma K^+ did not correlate with ARR or plasma renin activity, or predict the ΔSBP_{spiro}. In the single adenoma patient, the K^+ fell from 3.7 to 3.2 mmol/l.

Discussion

For more than 30 years, after dampening of initial enthusiasm for the diagnosis, PHA was considered a rare cause of hypertension.[10,11] The proposal to use ARR for diagnosis[12] led to many studies in which the prevalence of PHA was estimated at more than 10% of patients with hypertension.[4,7,13–21] Some authors have required elevation of plasma aldosterone concentration, as well as the ratio, which is driven mainly by a low plasma renin.[6] Others, however, have described patients with apparent adenomas in the absence of elevated plasma aldosterone levels.[22–24]

Our findings support the need for elevated plasma aldosterone as well as ARR when looking for an anatomically curable cause of PHA. Our estimate of 0.7% prevalence of patients with PHA supports both clinical impression and classical accounts of PHA in which positive scans are uncommon in the absence of hypokalaemia and a plasma aldosterone at least two-fold above normal.[25] False-negative aldosterone values can be caused by hypokalaemia, by calcium blockers, or by diurnal variation.[26] Hypokalaemia itself can be masked by calcium blockade or salt depletion.[26] By performing adrenal imaging in most patients with elevated ARR, regardless of the K^+ or aldosterone value, we aimed to minimise the chance of false negatives. Some have argued that scans are less sensitive than adrenal vein sampling; but state-of-the-art spiral CT or MRI (as used in this study) routinely detects nodules of ≥1–2 mm diameter, whereas only a handful of radiologists in the UK can claim >75% success rates for sampling both adrenal veins. Moreover, the larger adrenal adenomas can be easier to locate laparoscopically, and their removal is more likely to cure hypertension than removal of radiologically normal glands. Published reports cite only 50% cure of hypertension in series that include adrenalectomies performed without a positive scan.[22,24,27] In conclusion, we would not advocate further investigation of patients lacking hypokalaemia, elevated aldosterone excess or anatomical abnormalities on a scan.

On the other hand, we found a high prevalence of patients in whom measurement of the aldosterone/renin ratio correctly predicted that target blood pressure would be achieved by addition of spironolactone. We set 20 mmHg as the pre-specified threshold, being substantially (three-fold) greater than the mean response to open-label addition of second- or third-line treatment in the INSIGHT trial.[28] It seems likely that low-renin patients with resistant hypertension are those most likely to benefit from the recent British Hypertension Society recommendation to use spironolactone.[29] The value of adding spironolactone was equally great whether or not patients were receiving a thiazide diuretic, but formal, comparative studies are now in progress to determine in

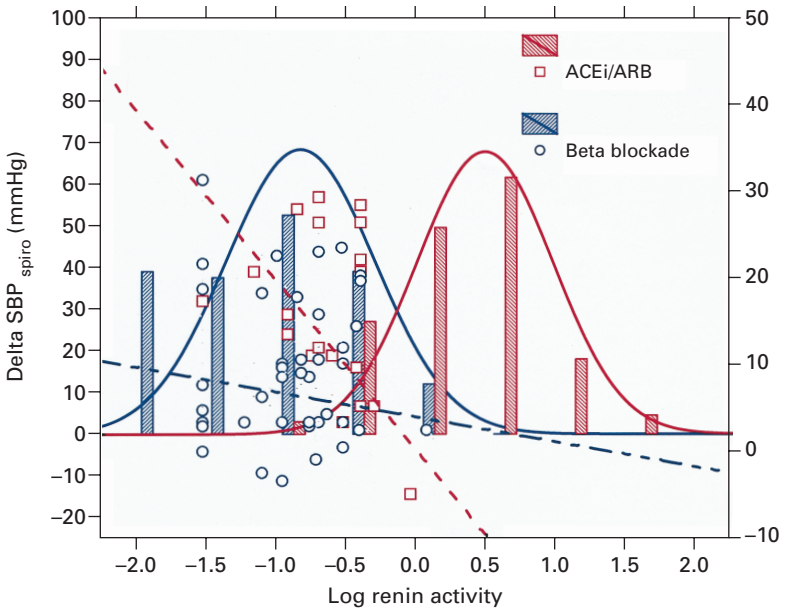

Fig 3. Prediction of blood pressure response to spironolactone by plasma renin, and influence of current drug treatment. The distribution of plasma renin is shown separately for patients receiving ACEi/ARB (right-hand histogram) or β blockade as monotherapy (left-hand histogram). Superimposed on the histograms is a scattergram of the systolic blood pressure response to spironolactone upon plasma renin (ΔSBP_{spiro}), shown only for the patients on ACEi/ARB (squares), or β blockade (circles). Patients with an ARR >400 received spironolactone 50 mg for one month. The figure illustrates how the ARR cut-off selected patients on ACEi/ARB at the left of their plasma renin distribution, whereas among β-blocker-treated patients the ARR cut-off of 400 was not discriminatory. The curved lines show the regression of ΔSBP_{spiro} upon renin, which was steeper for ACEi/ARB (right-hand side, r = –0.32) than for β blockade (left-hand side, r = –0.12).

how many patients spironolactone is superior to a thiazide in achieving blood pressure control. The success of spironolactone even in patients who previously had a two-week trial of high-dose bendrofluazide suggests that, within the pool of low-renin patients, there is a subset in whom aldosterone plays a role in treatment resistance.

It might be argued that there is a continuous spectrum of aldosterone/renin ratio, with one extreme being the hypokalaemic, classical PHA patient in whom spironolactone would be expected to reduce blood pressure by twice as much as our cut-off of 20 mmHg.[30] However, we identified a practical benefit of separating the normokalaemic, high ARR from the classical PHA patient. This benefit is the ability of plasma renin measurement alone to predict the blood pressure response to spironolactone. The direct Nichols Advantage assay is a two-site immunochemiluminometric assay employing separate capture and detection monoclonal antibodies. It permits high throughput assay of some 80 samples an hour, and at about £12 per sample costs about the same as a month's average treatment for hypertension. The immunochemiluminometric assay reduces the detection limit for renin by about four-fold; this increased sensitivity permitted its quantification in most patients, and served to emphasise the degree to which renin secretion is normally suppressed by β blockade. Nevertheless, sensitivity was still insufficient to identify the 'true' (salt-suppressed) low-renin patients among those on a β blocker. We therefore recommend substitution of an ACE inhibitor (or angiotensin blocker) before measuring plasma renin; where a β blocker cannot be withdrawn, we found that the opposing effects of ACEi and β blockade on the renin distribution are effectively cancelled out when the two drugs are combined.

In summary, measurement of renin and aldosterone identified a subset of previously uncontrolled patients whose hypertension responds to spironolactone, but did not unmask a missing cohort of curable adenomas. Secondary analyses suggest that the same information can be obtained from renin measurements alone, and that these could be extended from untreated patients[31] to treated patients with resistant hypertension when selecting appropriate treatment. Whereas ACE inhibition and β blockade might be regarded as interchangeable in the treatment of high-renin hypertension,[32] the former should be substituted for β blockade in the diagnosis of low-renin hypertension.

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