**Does Aldosterone-to-Renin Ratio Predict the Antihypertensive Effect of the Aldosterone Antagonist Spironolactone?**

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**Background:** The recognition that some 10% to 15% of the hypertensive population may have aldosterone excess has increased the frequency of measurement of the aldosterone-to-renin ratio (ARR) and the use of aldosterone antagonists. Whether this ratio will predict the blood pressure (BP) response to spironolactone is not clear.

**Methods:** We correlated the BP response to spironolactone 50 mg/day to baseline ARR in 69 hypertensive patients (mean ± SD age 57 ± 2 years, 65% male), consisting of 39 subjects with long-standing hypertension (4.0 ± 0.2 years) whose hypertension was uncontrolled on at least three antihypertensive medications and 30 previously untreated patients who were randomized in a crossover design to receive either spironolactone 50 mg/day or bendroflumethiazide 2.5 mg/day for 4 weeks.

**Results:** After 4 weeks of spironolactone, BP in patients with never-treated hypertension was reduced by 18 ± 3 / 11 ± 1 mm Hg. There was a highly significant correlation between log ARR and the fall in systolic BP (r = 0.69, P < .001) and diastolic BP (r = 0.45, P < .05).

Nine of ten patients with low renin activity (≤0.5 ng/mL/h) showed a >20–mm Hg fall in systolic BP. No such correlations were seen when BP was reduced by bendroflumethiazide 2.5 mg. For patients with resistant hypertension, despite a BP reduction of 28 ± 3 / 13 ± 2 mm Hg after 14 weeks of spironolactone, there was no relationship between the reduction in BP and the ARR; however, subjects with pretreatment potassium <4.0 mmol/L had a greater response than those with levels ≥4.0 mmol/L (34 ± 3 / 16 ± 2 v 20 ± 6 / 8 ± 3 mm Hg, P < .05).

**Conclusions:** Based on the study results, ARR and low renin activity may predict the response to spironolactone in never-treated hypertensive patients but not in patients taking antihypertensive drugs, possibly because of the effect of these agents on ARR. In such patients a trial of spironolactone is required to assess the BP response.

**Key Words:** Aldosterone, hypertension, aldosterone-to-renin ratio, spironolactone.

Until recently, primary hyperaldosteronism was thought to be an uncommon condition (<2% in the hypertensive population) characterized by hypokalemic alkalosis and suppressed plasma renin activity in most cases caused by excessive adenomatous aldosterone production. However a number of recent studies have suggested that based on a raised ambulant aldosterone-to-renin ratio (ARR), a marker of inappropriate aldosterone activity, the prevalence of primary hyperaldosteronism in the hypertensive population may be as high as 10% to 15%. Functional hyperaldosteronism in the absence of an adrenal adenoma may contribute to hypertension, and it has been suggested that these patients show a marked fall in blood pressure (BP), particularly systolic, with aldosterone antagonism using spironolactone. In addition, a subset of patients with resistant low-renin hypertension may show marked responsiveness to spironolactone. However these studies did not specifically relate drug response to baseline aldosterone and renin.

Interest in the contribution of aldosterone to hypertension has been rekindled by its possible role in the pathogenesis of vascular damage. There is evidence that aldosterone has a BP-independent effect on left ventricular structure, increasing collagen deposition and fibrosis, and on the development of diastolic and systolic dysfunction. Recently a significant correlation between the ARR, a marker of aldosterone activity, and arterial stiffness, a major determinant of cardiovascular risk in the hypertensive population, has been established. Patients with hyperaldosteronism have greater cardiovascular risk and
end-organ damage than matched subjects with essential hypertension and are more likely to have resistant hypertension than other hypertensive subjects.

Although some early studies have suggested that spironolactone is more effective in patients with low-renin hypertension, the hallmark of primary hyperaldosteronism, other studies did not confirm this observation. A recent study in treated patients with resistant hypertension using lower doses of spironolactone (≥50 mg/day) did not find any relationship among renin, aldosterone, or the ARR and the response in patients with resistant hypertension. Introduction of the ambulatory ARR overcame some of the problems associated with the influences of the time of day, dietary salt intake, and posture on both renin and aldosterone and is now an established technique for assessing relative aldosterone activity. We therefore determined the relationship between the ARR and the response to spironolactone in two groups of patients: 1) those with newly diagnosed, never-treated hypertension, and 2) those with established long-standing hypertension resistant to standard antihypertensive therapy.

### Patients and Methods

A total of 69 patients of white ethnicity (45 men and 24 women, mean (±SEM) age 57 ± 2 years) with essential hypertension (clinic BP >140/90 mm Hg on three occasions and ambulatory daytime BP >135/85 mm Hg were studied. One group (n = 30, 18 women and 12 men) comprised of patients who 1) had never received antihypertensive treatment, 2) were not on any prescribed diet or agents that interfered with BP control, salt, or potassium balance, and 3) had no concomitant medication or illnesses (fasting glucose 5.5 ± 0.6 mmol/L, creatinine 84 ± 12 μmol/L and potassium 4.2 ± 0.2 mmol/L). Patients were screened to exclude possible secondary causes of hypertension, including urinary catecholamines and magnetic resonance angiography of renal arteries when appropriate. These patients were randomized to receive either spironolactone 50 mg/day or bendroflumethiazide 2.5 mg/day in a cross-over design for 4 weeks with an intervening 4-week washout period. Blood pressure was measured in the morning in each patient, after a supine rest of 15 min, by an independent observer using an oscillometric device (Omron HEM 705 CP) before and after 4 weeks of therapy, in triplicate, and was averaged. The study was approved by the Institutional Review Board.

The second group comprised of 39 treated patients (27 men and 12 women) who were drawn from a Hypertension Clinic and had an inadequate BP response to standard antihypertensive treatment and BP >140/90 mm Hg on two consecutive clinic visits, despite administration of three or more antihypertensive agents in therapeutic doses. The mean duration of hypertension was 4.0 ± 0.4 years, and in approximately 30% of cases these patients had received a fourth antihypertensive drug. Four had type 2 diabetes and three had previous myocardial infarction. The mean creatinine was 94 ± 3 μmol/L and potassium 3.7 ± 0.1 mmol/L. Concomitant medication included β-blockers (n = 32), angiotensin-converting enzyme (ACE) inhibitors (n = 29), diuretics (n = 27), calcium channel blockers (n = 20), angiotensin receptor antagonists (ARB) (n = 9), α-blockers (n = 4), and methyldopa (n = 1). Eleven were taking aspirin and eight were taking statins. These patients were administered spironolactone 50 mg/day and reviewed at the clinic 3 to 4 months later. A single measurement of BP was made in the morning in the sitting position using a mercury sphygmomanometer by an independent observer who was unaware of any biochemical data.

Aldosterone (pmol/mL) and plasma renin activity (ng/mL/h) were measured by radioimmunoassay (Adaltis Italia Inc, Bologna, Italy) from samples drawn in the morning, with the patients ambulant and having fasted overnight and rested in seated position for 10 min.

Statistical analysis was performed with JMP Version 3.01 (SAS for Windows; SAS Institute, Cary, NC) using nonparametric methods, as the data were not normally distributed. The ARR was transformed to log ARR. Relationships between different parameters were analyzed using Spearman ρ correlations, and the change in biochemical and hemodynamic parameters was analyzed with the Wilcoxon signed rank sum test. The relationship between ARR and reductions in BP was adjusted for age using a stepwise regression model, taking changes in BP as the independent variable and both age and log ARR as dependent variables. All results are expressed as mean ± SEM. Values of P < .05 were considered to be significant.

### Results

The mean values for plasma aldosterone, plasma renin activity and the ARR were 680 ± 62 pmol/mL, 1.48 ± 0.2 ng/mL/h and 891 ± 142 respectively in the untreated and 634 ± 37,1.4 ± 0.7 and 1972 ± 231 in the treated patients. The number of patients with low renin (<0.5 ng/mL/h) was 10 in the untreated group and 24 in the treated group. Ten patients in the untreated group had a raised ARR (>800), whereas in the treated group 29 patients had an elevated ARR.

In the patients with newly diagnosed hypertension, spironolactone 50 mg reduced systolic BP by 18 ± 3 mm Hg and diastolic BP by 11 ± 1 mm Hg. There were no adverse reactions to therapy. There was a highly significant correlation between log ARR and the fall in systolic BP (r = 0.69, P < .001) and diastolic BP (r = 0.45, P < .05) (Fig. 1). For plasma renin activity alone the correlations were r = −0.58, P < .01 and r = −0.36, P < .05 respectively. There was a significant correlation between age and the fall in systolic BP (r = 0.39, P < .05) but not diastolic BP (r = 0.05, NS). However the correlation between log ARR and fall in systolic BP remained significant after correction for age (r = 0.63, P < .001). There was no relationship between the degree of fall in BP and...
the plasma aldosterone or potassium levels. Four patients with a plasma aldosterone level <400 pmol/mL, had a reduction in systolic BP of >20 mm Hg.

For patients (n = 8) with ARR >800 and aldosterone > 400 pmol/mL the fall in BP exceeded that of the other 22 (27 ± 16 ± 13 ± 3/10 ± 2 mm Hg, P < .05), and for six of these patients the fall in systolic BP was ≥20 mm Hg, which is regarded as a positive response to spironolactone. Among patients with ARR <400 (n = 8), only one had a fall of ≥20 mm Hg. Among patients (n = 10) with low renin activity (≤0.5 ng/mL/h), the systolic BP fall was ≥20 mm Hg in nine. No such relationships were seen between ARR or renin subgroups and BP reduction after bendroflumethiazide.

For patients previously on treatment the reduction in BP after spironolactone 50 mg for mean duration of 3.7 ± 0.4 months was 28 ± 3/13 ± 2 mm Hg from 167 ± 3/95 ± 2 to 139 ± 3/82 ± 2 mm Hg (P < .01). There were no significant correlations between the reduction in either systolic or diastolic BP and log ARR or renin activity. A high ARR (>800) did not predict responsiveness. Patients with pretreatment potassium levels <4.0 mmol/L (n = 26) had a greater reduction in BP (34 ± 3/16 ± 2 v 20 ± 6 / 8 ± 3 mm Hg, P < .05) than those with levels ≥4.0 mmol/L (n = 13). Treatment was associated with a significant increase (P < .01) in plasma potassium (3.7 ± 0.07 to 4.2 ± 0.09 mmol/L) and creatinine (93 ± 3 to 101 ± 4 μmol/L) and a nonsignificant fall in sodium (139 ± 0.4 to 138 ± 0.4 mmol/L). Two patients, both taking ACE inhibitors, developed hyperkalemia (5.2 and 5.5 mmol/L), and five (18.5% of men) developed gynecomastia.

**Discussion**

These data suggest that the antihypertensive effect of the aldosterone antagonist, spironolactone, is related to activity of the renin-angiotensin-aldosterone system. In untreated patients, there was a significant positive correlation between the degree of fall in BP and the ARR, a marker of aldosterone activity. However this relationship was not found in patients taking multiple antihypertensive agents.

This apparent discrepancy may in part be explained by concomitant use of medications. Antihypertensive agents may significantly alter both plasma renin activity and, to a lesser extent, aldosterone concentrations. Mulatto et al screened 230 treated patients for primary aldosteronism but excluded patients with resistant hypertension. After a 1-month washout from previous therapies, the subjects were allocated to treatment with single antihypertensive drugs. It was noted that the ARR was changed significantly more by the β-blocker atenolol (increased by 62% ± 82%) than by any other agent. Both ACE inhibition with lisinopril and angiotensin receptor blockade with irbesartan decreased the ratio by 30% ± 22% and 43% ± 27% respectively, whereas α-blockade with doxazosin decreased the ratio by 5% ± 6% and calcium channel blockade with amlodipine decreased the ratio by 17% ± 32%. The use of a ratio may, however, mask the divergent effects on individual components. For example, renin was reduced by atenolol but was raised by lisinopril, amlodipine, and irbesartan, whereas aldosterone was reduced by atenolol, lisinopril, amlodipine, and irbesartan. Given the considerable variation in these drug effects on both renin and aldosterone with no way of predicting the possibly synergistic or antagonistic effect of multiple agents used simultaneously, withdrawal of therapy or possibly the use of α-blockade as monotherapy seems the practical solution if ARR is to be of use in detecting primary aldosteronism. In addition aldosterone and renin do not always move in a parallel interdependent fashion, and potassium is a major determinant of aldosterone secretion. The fact that it was relatively low (3.7 mmol/L), possibly because of longstanding use of diuretics in resistant treated hypertensive patients compared with untreated (4.2 mmol/L) patients may also be a factor influencing both ARR and BP response to a potassium-sparing diuretic that increased potassium by 0.5 mmol/L. Indeed the pretreatment potassium levels predicted the extent of BP fall with a 80% greater
Aldosterone, or the ARR did not predict the antihypertensive response.14

We believe that our results are clinically relevant although we must be cautious because the numbers are relatively small. For untreated patients, although the study was short-term it was randomized and controlled. We believe that it helps to identify patients who are likely to have a good response to spironolactone (>20 mm Hg fall in systolic BP), as seen in six of eight patients with ARR >800 and elevated aldosterone (>400 pmol/mL), equivalent to a ratio of almost 30 and plasma aldosterone >15 ng/dL in conventional units, and those unlikely to respond (ie, those with ARR <400, of whom only one of eight responded). Indeed although the relationship, when considered as a continuous variable to BP response, was of lesser significance than for ARR, plasma renin activity is perhaps more predictive in that nine of 10 subjects with low levels (≤0.5 ng/mL/h) were good responders. This may in part be caused by the lack of a relationship with aldosterone, as some subjects with low levels appeared to be good responders. The question as to whether some of the patients with high ARR had primary aldosteronism cannot be answered with certainty, as formal suppression testing was not carried out.

The study of patients with resistant hypertension, although uncontrolled, was single blind. Such patients were taking a variety of medicines, and one third had previously tried on a fourth agent with an inadequate BP response. The relatively late review at 3 to 4 months reflects normal clinic practice. It is in this group of patients that the risk of hyperkalemia is greatest.

Taken in conjunction with our data, studies suggest that for the lower doses of spironolactone currently used, and possibly also for eplerenone, low renin status or a raised aldosterone-to-renin ratio may be predictive of the antihypertensive response to aldosterone antagonism as monotherapy. However for patients with chronic therapy and resistant hypertension, presumably because of the interaction between other antihypertensive agents with both aldosterone and renin, the ARR is not predictive of the extent of BP response to aldosterone antagonism. Nonetheless such patients, particularly those with low potassium values, often respond well to spironolactone; however the decision to use this agent would need to take into account the potential for adverse effects such as gynecomastia, hyperkalemia and azotemia.

References
