

# A study on aldosterone to renin ratio as a predictor of antihypertensive efficacy of spironolactone

Dr Rushil Donga<sup>1</sup>, Dr Yatin Prajapati<sup>2</sup>, Dr Utsav Patel<sup>3</sup>, Dr Arpit Goel<sup>4</sup>, Dr R K Samar<sup>5</sup>

<sup>1,2,3</sup>Post Graduate Student, <sup>4</sup>Senior Resident, <sup>5</sup>Associate Professor  
<sup>1,2,3,4,5</sup>Department of General Medicine, Pacific Institute of Medical Sciences, Udaipur  
Corresponding Author – Dr Rushil Donga

**Abstract : Aim - Aldosterone/renin ratio is an index for inappropriate aldosterone activity, and it is increasingly being used to screen for primary aldosteronism within the hypertensive population. This ratio can also be useful in predicting the effectiveness of spironolactone treatment for hypertension in patients with primary aldosteronism, which is characterized by excessive aldosterone production. To determine the impact of oral spironolactone on blood pressure in hypertensive patients with primary aldosteronism identified by an elevated aldosterone/renin ratio.**

**Method - A prospective cohort study was done of hypertensive patients with raised aldosterone/renin ratio, who failed to suppress plasma aldosterone with salt loading and fludrocortisone suppression test. spironolactone treatment was given and were followed-up for a period of up to 3 years.**

**Result - In this study, 28 participants (12 male) with an average age of 55 years (standard deviation of 10) were followed for an average of 12.9 months (standard deviation of 7). At the start of the study, the patients were taking an average of 2.1 (standard deviation of 1.2) antihypertensive drugs, but 16 out of 28 (57%) still had a diastolic blood pressure greater than 90 mmHg and 39% had a systolic blood pressure greater than 160 mmHg. After starting spironolactone treatment, three patients reported breast tenderness but continued treatment and one patient was unable to tolerate the medication and had to stop treatment. Of the remaining 27 patients, the average number of antihypertensive drugs taken decreased to spironolactone plus 0.7 (standard deviation of 0.9). All but one patient (96%) had a diastolic blood pressure less than or equal to 90 mmHg, and 78% had a systolic blood pressure less than or equal to 160 mmHg. A total of 48% had a blood pressure less than or equal to 140/90 mmHg, and 13 out of 27 (48%) were treated with spironolactone monotherapy. When only considering patients who were taking medication at the start of the study (n=24), spironolactone significantly reduced the number of antihypertensive drugs needed by 0.5 (confidence interval of 0.1 to 1.0, p=0.02) and also significantly reduced both systolic blood pressure by 15 mmHg (confidence interval of 5 to 25, p=0.007) and diastolic blood pressure by 8 mmHg (confidence interval of 4 to 13, p=0.001).**

**Conclusion - This study found that spironolactone was an effective treatment for hypertension in patients with high aldosterone/renin ratios. Since an elevated ratio is a strong indicator of primary aldosteronism, characterized by excessive aldosterone production, it may be worthwhile for hypertensive patients with high aldosterone/renin ratios to use spironolactone, as long as they have been ruled out for adrenal adenomas through imaging methods.**

**Keywords - aldosterone/renin ratio, hypertension, primary aldosteronism, spironolactone**

## INTRODUCTION

The prevalence of primary aldosteronism is uncertain, but it may be more common than previously believed, affecting up to 15% of people with hypertension seen in clinics. In a single primary care practice, the prevalence of primary aldosteronism may be similar. These studies used the aldosterone to plasma renin activity ratio (ARR) as a screening tool and found that 94% of individuals with an ARR of 750 or higher were unable to suppress their aldosterone levels with salt loading. The present study treated a group of these patients with oral spironolactone and reports the response to this treatment.

## METHOD

In this study, all hypertensive patients referred in the OPD were screened for primary aldosteronism using the ambulant plasma aldosterone to plasma renin activity ratio of 750 or higher as the selection criteria. Patients with an elevated aldosterone/renin ratio were admitted for a salt loading and fludrocortisone suppression test, and those with positive results (aldosterone levels that were not suppressible at 140 pmol/L or higher) underwent CT scans to look for adrenal adenomas. The study also screened for glucocorticoid suppressible hyperaldosteronism (GSH) in patients who had a decrease in plasma aldosterone at noon following salt loading, using genetic testing. Patients without an adrenal adenoma on CT scans and without GSH on genetic testing were included in the cohort for this follow-up study. Seated blood pressure measurements were carried out using standard mercury sphygmomanometer.

During the study, the usual antihypertensive medications were stopped for 7 to 10 days. None of the patients were taking oral spironolactone, which would have required a longer period of drug withdrawal. If necessary, an alpha-adrenergic blocker was prescribed to control blood pressure if the diastolic blood pressure was 110 mmHg or higher. All patients were given two tablets of potassium chloride daily to prevent hypokalemia. On day 1, each patient was given five tablets of sodium chloride at 6:00 PM and 10:00 PM, following baseline blood sampling in the supine position at 8:00 AM and ambulant sampling at noon. On day 2, each patient was given four tablets of sodium chloride with 0.5 mg of fludrocortisone at 8:00 AM, and five tablets of Sodium chloride at noon, four tablets at 6:00 PM, and four tablets at 10:00 PM. The same regimen was repeated on day 3. On day 4, the 8:00 AM regimen was given following supine blood sampling, and blood was sampled at noon following four hours of ambulation. In total,

48 tablets of sodium chloride with 1.5 mg of fludrocortisone were given over a four-day period. Blood pressure was carefully monitored throughout the study to identify any complications.

Subjects with elevated ARR and positive results on the salt loading and fludrocortisone suppression test were given oral spironolactone (50 mg per day) in addition to their usual antihypertensive treatment. The first clinic visit was one month after starting treatment, and subsequent visits occurred at intervals of 4 to 12 weeks, as determined by the clinicians based on blood pressure responses and potential adverse effects. If blood pressure was 150/90 mmHg or lower after adding spironolactone, the usual antihypertensive drug treatment was discontinued. If adverse effects occurred or blood pressure normalized with a 50 mg dose of spironolactone, the dose was reduced to 25 mg.

Data are presented as mean (s.d.). Paired Student's t-test was used to assess the effect of spironolactone on the number of drugs used as well as its blood pressure lowering efficacy during follow-up. Statistical significance was defined at a P value of 0.05.

### **RESULT**

In this prospective cohort study, 28 subjects (12 males, mean age 55 years, standard deviation of 10) were followed for an average of 12.9 months (range of 3 to 35 months). Before starting spironolactone, the average number of medications the patients were taking was 2.1 (standard deviation of 1.2), but 16 out of 28 (57%) had a diastolic blood pressure greater than 90 mmHg and 39% had a systolic blood pressure greater than 160 mmHg. One patient was unable to tolerate spironolactone and had to stop treatment after four months (experiencing nonspecific illness). Of the remaining 27 patients, the average number of antihypertensive drugs required decreased to spironolactone plus 0.7 (standard deviation of 0.9). All but one patient (96%) had a diastolic blood pressure less than or equal to 90 mmHg and 78% had a systolic blood pressure less than or equal to 160 mmHg. In total, 48% had a blood pressure less than or equal to 140/90 mmHg and 13 out of 27 (48%) needed only spironolactone therapy.

### **DISCUSSION**

The favorable blood pressure-lowering response to spironolactone in this group of patients suggests that an elevated ARR is a useful indicator for identifying patients who may benefit from this type of treatment. Approximately 60% of these patients were taking non-spironolactone diuretics at the start of the study, and most of the remaining patients had tried diuretics at some point. Despite this, blood pressure control remained suboptimal, suggesting that the positive blood pressure response to spironolactone in this study was not solely due to its diuretic effect.

There are similarities between our study and previous studies that found a favorable response to spironolactone in subjects with low "stimulated" renin hypertension [6-8]. However, other small studies have shown that other hypotensive agents, such as methylopa [9] and thiazide diuretics [10, 11], were just as effective in patients with low renin hypertension, and the blood pressure-lowering effects were not dependent on renin status [12] (thiazide diuretics, nifedipine, and methylopa). In our opinion, using the ARR is more specific than using "stimulated" renin for identifying primary aldosteronism, which is a significant contributor to mineralocorticoid-related hypertension. We have previously reported that the frusemide stimulation test, a commonly used method for evaluating renin responsiveness, has a poor negative predictive value for identifying subjects with possible primary aldosteronism. In other words, many subjects with primary aldosteronism maintain renin responsiveness. In contrast, a raised ARR in our center predicted primary aldosteronism in 94% of subjects [3]. The finding of hypertensive subjects with low renin and nonsuppressible serum aldosterone is not new and was described about 20 years ago. In our experience, this test is reasonably specific for primary aldosteronism if a ratio of 750 or higher is used.

The use of spironolactone to treat "essential" hypertension was largely discontinued in Britain following the 1988 report by the Committee on Safety of Medicines (CSM) stating that it was associated with monomyelocytic leukemia in rats. However, spironolactone has been used in humans for more than 30 years without any reported risk of cancer, with the exception of five cases of breast carcinoma in women. This potential link is not considered significant, given the high prevalence of this type of cancer in the female population. In contrast to studies conducted in the late 1960s and early 1970s, we used lower doses of spironolactone, which may explain the relatively low incidence of adverse effects and small dropout rate in our cohort.

According to our results, we believe that the ARR may be a useful way to identify hypertensive subjects who will respond to spironolactone, as this group represents a significant proportion of the hypertensive population. We believe that there is now sufficient evidence to conduct a randomized trial comparing spironolactone to other therapies in this group of patients. If our results are generalizable and confirmed by further studies, our treatment approach could have a significant impact on the management of hypertension, particularly since it is estimated that up to 10% of hypertensives may fall into this subcategory.

### **LIMITATION**

It is unlikely that "regression to the mean" explains the results of our study. Before being labeled as hypertensive, the blood pressure of our patients was measured for 3-6 months by their general practitioners, and they were then referred to our hypertension clinic for evaluation. Additionally, the response to spironolactone was significant, as almost half of the patients only needed spironolactone to control their hypertension, even though many of these patients had previously required three or more drugs to achieve blood pressure control. However, we do recognize that in 6 out of the 27 patients who continued to take spironolactone, either systolic or diastolic blood pressure or both were higher at the follow-up, indicating that this treatment is not uniformly effective in all subjects.

Our study is subject to the inherent biases of an uncontrolled, nonrandomized design and blood pressure measurements were conducted by multiple individuals. However, the strength of our study is that it was conducted as part of routine clinical practice, making it relevant to the daily care of hypertensive patients. Our results suggest the need for a randomized controlled study to evaluate the response to spironolactone in this subgroup of hypertensive patients.

### **CONCLUSION**

Low-dose spironolactone was found to be highly effective in reducing blood pressure in hypertensive patients with nonadenomatous primary aldosteronism identified by a raised aldosterone to renin ratio. Treatment with spironolactone also significantly reduced the need for other antihypertensive medications.

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