

Aldosterone to Renin Ratios in the Evaluation of Primary Aldosteronism

P H K Eng,*^{MRCP (UK)}, K E K Tan,*^{MRCP (UK)}, D H C Khoo,**^{FAMS, M Med (Int Med), MRCP (UK)},

C E Tan,**^{FAMS, M Med (Int Med), PhD (Glas)}, H S Lim,***^{FAMS, M Med (Int Med)}, S C Lim,*^{MRCP (UK)},

L K H Koh,†^{M Med (Int Med), MRCP (UK)}, S C Ho,*^{M Med (Int Med), MRCP (UK)}, E S Tai,*^{MRCP (UK)},

A C K Fok,‡^{FAMS, M Med (Int Med), MRCP (UK)}

Abstract

Primary aldosteronism, though an uncommon cause of hypertension, causes significant morbidity, making it important to diagnose and treat this condition. Its evaluation requires complex and time consuming investigative procedures in order to confirm the diagnosis and to differentiate between the subtypes of aldosterone producing adenoma and idiopathic hyperaldosteronism. Often, the values of renin and aldosterone are equivocal, and the diagnosis of primary aldosteronism is in doubt. In this study, we examine the use of aldosterone to renin ratios in confirming the diagnosis of primary aldosteronism when the usual criteria of suppressed renin and elevated aldosterone are not met. We have found that an aldosterone to renin ratio of 50 has a 100% specificity and 92% sensitivity for detecting primary aldosteronism. Also, an aldosterone to renin ratio of >2000 is suggestive of an aldosterone producing adenoma.

Ann Acad Med Singapore 1997; 26:762-6

Key words: Adenoma, Hypertension, Idiopathic hyperaldosteronism

Introduction

Primary aldosteronism (PA) was first described in 1955 when Jerome Conn described a patient whose hypertension was cured by the removal of an adrenal adenoma.¹ Aldosterone producing adenomas (APAs) are now found to be just one subset of a spectrum of disorders encompassed by PA.² PA is an uncommon cause of hypertension and its prevalence is usually estimated at less than 1%.³ However, in certain selected groups of patients, there have been reports of prevalence rates of between 2% and 12%.^{4,5} Considering the last Singapore National Health Survey in 1992⁶ where the prevalence of hypertensives was 13.2% of the population, the number of patients with PA would not be insignificant. There are several reasons to recognise and diagnose PA. Firstly, it can present as severe and refractory hypertension with cardiovascular as well as renal complications.⁷ Secondly, in the case of APAs, there are potential for cures of between 35%⁸ and 50%⁹ in patients who undergo surgery. Thirdly, in the case of idiopathic hyperaldosteronism (IHA), the knowledge of this condition will lead to a more rational therapeutic approach in the management of hypertension.

PA remains a diagnostic and therapeutic challenge despite the array of tests. Unfortunately, the test results are often conflicting, making the diagnosis difficult at best. This is compounded by the more recent discoveries of different subtypes of PA. APAs represent about 60% and IHA represents about 30% of all cases of PA. The remaining 10% comprise the rarer subtypes. The treatment for APA is surgical and that for IHA is medical, and thus the differentiation of these subtypes is important.

We review 26 patients with PA managed by our Department. We describe the clinical and biochemical characteristics of the different subtypes and evaluate the usefulness of the investigative procedures, with particular emphasis on the use of aldosterone to renin ratios.

Materials and Methods

This study is a retrospective analysis of 26 patients with proven PA. A comparison was made with a group of 10 hypertensive controls who did not have PA. The criteria used for diagnosis of PA were:

- 1) hypertension,
- 2) hypokalaemia $K \leq 3.5$ mmol/L,
- 3) inappropriate kaliuresis >30 mmol/day,¹⁰ and

* Registrar

** Consultant

*** Senior Consultant

† Senior Registrar

‡ Senior Consultant and Head

Department of Endocrinology

Singapore General Hospital

Address for Reprints: Dr Peter Eng, Department of Endocrinology, Singapore General Hospital, Hospital Drive, Singapore 169608.

- 4) suppressed plasma renin with an elevated serum aldosterone.

All the patients were investigated initially because of hypertension associated with hypokalaemia.

The criteria used for the diagnosis of APA were:

- 1) an adrenal tumour visualised on a computerised tomographic (CT) scan of the adrenals,
- 2) postural studies suggesting an adenoma,
- 3) lateralising values on adrenal venous sampling when 1) and 2) were conflicting, and
- 4) histological confirmation on surgery.

The criteria used for the diagnosis of IHA were:

- 1) normal looking adrenals or bilateral hyperplasia on CT scan,
- 2) postural studies suggesting hyperplasia, and
- 3) non lateralising values on adrenal venous sampling when 1) and 2) were conflicting.

Postural studies of supine and erect renin and aldosterone values were performed in all cases using standard guidelines.² Supine values were taken with the patient fasted at 8 am, after 10 hours of supine posture. Erect values were taken at noon, with the patients having stood or walked for four hours. Cortisol was taken concurrently with renin and aldosterone to ensure the validity of the erect values of aldosterone. Under normal circumstances, the level of cortisol would drop from 8 am to 12 pm, parallel to the drop in adrenocorticotrophic hormone (ACTH). If the level of cortisol at noon was higher than that at 8 am, this would invalidate the test. A postural study suggestive of an APA was defined by a fall in the erect aldosterone or a rise of not more than 30%.⁷ A postural study suggestive of IHA was defined as a rise of erect aldosterone of more than 30%. Aldosterone was assayed by radioimmunoassay (Coat-A-Count Aldosterone, Diagnostic Products Corporation, Los Angeles, California, USA). Aldosterone was measured in pmol/L. Plasma renin activity was assayed by radioim-

munoassay (Incstar GammaCoat 1251 Plasma Renin Activity Radioimmunoassay Kit, Incstar Corporation, Stillwater, Minnesota, USA). Plasma renin activity was measured in ng/ml/h. When renin levels were undetectable, a value of 0.018 ng/ml/h was assigned for the purpose of calculating the aldosterone to renin ratio as this was the lowest limit of detectability for the assay. To arrive at the aldosterone to renin ratio, aldosterone values had to be first divided by 27.75 to convert the aldosterone units from pmol/L to ng/dl. Cortisol was assayed by radioimmunoassay (Incstar GammaCoat 1251 Cortisol Radioimmunoassay kit, Incstar Corporation, Stillwater, Minnesota, USA). CT scans of the adrenals were performed for all patients using 3 mm interval cuts. Patients who had a diagnosis of APA had unilateral adrenalectomies. Patients who had diagnosis of IHA were treated with spironolactone. Statistical analysis was performed using the non-parametric Mann Whitney U test. A value of less than 0.05 was considered as significant.

Results

Clinical Features

The ages of the 26 patients in our series ranged from 30 to 74 years (mean 50 years). Systolic blood pressure whilst on medication ranged from 130 to 240 mmHg (mean 172 mmHg) and diastolic blood pressure ranged from 70 to 140 mmHg (mean 99 mmHg). The duration of hypertension ranged from 0 to 28 years (mean 9 years). Out of the 26 patients, 7 had cardiovascular complications, 4 had cerebral vascular accidents and 3 had hypertensive heart disease with congestive cardiac failure. Despite hypokalaemia in all patients, only 2 patients presented predominantly with myositis and paralysis.

Biochemistry

The difference in the routine biochemistry between APA and IHA was not statistically significant (Table I).

TABLE I: BIOCHEMISTRY OF ALDOSTERONE PRODUCING ADENOMAS (APA) AND IDIOPATHIC HYPERALDOSTERONISM (IHA)

	APA		IHA		P value*	Hypertensive controls		P value#
	Mean	SD	Mean	SD		Mean	SD	
Serum potassium (mmol/L)	2.6	0.6	2.9	0.6	ns	3.9	0.4	0.002
Serum sodium (mmol/L)	141	2.9	141	2.2	ns	138	1.5	ns
Serum bicarbonate (mmol/L)	30.8	3.1	29.7	2.4	ns	26.8	2.3	ns
Supine aldosterone (pmol/L)	1381	876	682	295	0.021	422	214	0.01
Erect aldosterone (pmol/L)	1083	724	1168	451	ns	774	358	0.03
Supine renin (ng/ml/h)	0.15	0.24	0.27	0.19	ns	1.44	1.02	0.01
Erect renin (ng/ml/h)	0.49	1.18	0.42	0.32	ns	2.68	0.96	0.02
Supine aldosterone to renin ratio	1530	1845	314	605	0.006	12	2.8	0.002
Erect aldosterone to renin ratio	774	1350	384	607	ns	11	4.2	0.012

SD: standard deviation; ns: not significant

* Difference between APA and IHA

Difference between PA and hypertensive controls

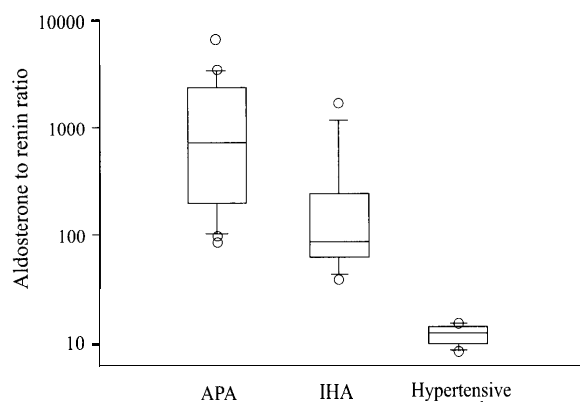


Fig. 1. Supine aldosterone to renin ratios in patients with APA and IHA compared to hypertensive controls.

The supine aldosterone to renin ratios, however, were significantly different. The aldosterone to renin ratio was higher in APA, ($P = 0.006$, 95% CI 65 to 2194). A supine aldosterone to renin ratio of ≥ 2000 was found only in APA (Fig. 1). The serum potassium, supine and erect aldosterone, supine and erect renin and the aldosterone to renin ratios were significantly different between patients with PA and the normal hypertensive controls. Of note, the aldosterone to renin ratios were very much higher in patients with PA compared with the hypertensive controls.

Postural Studies

All patients who had a fall (or rise of $<30\%$) in aldosterone with the erect posture were eventually diagnosed to have APA. Only one patient with an APA had a rise in aldosterone with posture. This gives the postural study 100% specificity and 94% sensitivity for diagnosing APA. The converse is true for the test to diagnose IHA, where it gave a specificity of 94% and a sensitivity of 100%.

Imaging

All patients had CT scans of their adrenal glands. The CT scans of 2 patients who were eventually diagnosed to have IHA initially showed adrenal tumours. The initial CT scan of a third patient localised the adenoma to the wrong side. For identifying APA, a CT scan was 94% sensitive and 82% specific.

Venous Sampling

Adrenal venous sampling was performed in 6 patients. Sampling was done when there were conflicting results between the postural studies and the CT scans. In 2 patients the right adrenal vein was not entered, giving a cannulation success rate of 60%. Sampling lateralised the aldosterone secretion in 2 patients and confirmed bilateral aldosterone secretion in 2 other patients. In the 2 patients who had unsuccessful cannulation of their right adrenal veins, based on the ratio of the aldosterone level between the left adrenal vein and the inferior vena

cava,¹⁰ a right-sided APA was correctly predicted in 1 case and the diagnosis of IHA was made in the other.

Histology

Based on the postural studies, CT scans and venous sampling, an APA was predicted in 17 patients. Of these, 15 agreed to surgery. Two patients declined surgery at present although a clear-cut diagnosis of an adenoma was made based on the postural study and CT scan. All 15 patients had unilateral adrenalectomies of the adrenal with the suspected APA. Of these, 11 had single adenomas which were classically well-circumscribed yellow nodules, and which ranged from 1.5 cm to 2.5 cm in diameter. In the remaining 4 patients, in addition to the main adenoma, there were additional smaller nodules.

Discussion

This is the first local series of patients with PA. The proportion of APA (65%) and that of IHA (35%) corresponds to reported distribution of subsets.² All the patients had mild to severe hypertension in association with hypokalaemia. Although malignant hypertension was initially thought not to occur in PA,¹¹ subsequent reports have shown this to be false.^{12,13} In our series, 4 patients had cerebral vascular accidents, and an acute haemorrhagic stroke was the presenting problem in 3 of these patients. Three other patients had hypertensive heart disease with congestive cardiac failure. It can be seen that there was significant morbidity among patients with PA. The majority of our patients were asymptomatic for symptoms of hypokalaemia, with only 2 patients presenting predominantly with myositis and weakness. This is in contrast with Ma's finding that periodic paralysis was common in Orientals with PA.¹⁴ A major difficulty in the diagnosis of PA is the choice and interpretation of screening tests. The usual tests are serum potassium, plasma renin, plasma aldosterone and the aldosterone to renin ratio. Hypokalaemia as an initial screening test provides an important clue to the presence of PA. It has however been reported that serum potassium is normal in between 7% and 38% of cases of PA.¹⁵⁻¹⁷ Thus, relying only on hypokalaemia as the sole initial screening test will miss a substantial number of patients who have PA. It is also known that 4% of essential hypertensives have a serum potassium of less than 3.5 mmol/L.⁴ Suppressed plasma renin is also clue to PA. This, however, is complicated by the fact that these patients may overlap with about 35% of essential hypertensives who have low plasma renin activity.⁷ Plasma aldosterone is also not an ideal test to screen for PA as 39% of patients with PA will have aldosterone values that fall within the range for essential hypertension.⁹ It is said that in a hypertensive patient with hypokalaemia, the finding of an elevated serum aldosterone with a suppressed plasma renin makes the diag-

nosis of PA unequivocal. Often however, either the renin or the aldosterone will fall within the normal range, making the diagnosis of PA questionable. In our series, we have found this to be a common occurrence. Using supine values, it occurred in 42% of the patients, and using erect values, occurred in 35% of the patients. In 3 patients both the supine as well as the erect values failed to meet the criteria of both an elevated aldosterone with suppressed renin. Traditionally, these patients would be excluded from the diagnosis of PA, but as the clinical suspicion of PA was high, they were further investigated. The ratio of serum aldosterone to plasma renin has been proposed¹⁸⁻²⁰ as a more accurate screening test to identify patients with PA. With plasma aldosterone expressed in ng/dl and plasma renin activity in ng/ml/h, ratios of between 25 and 50 have been proposed to differentiate PA from other forms of hypertension. The conditions for measurement of the ratio are not standardised, however, McKenna et al²⁰ have shown that although the values of renin and aldosterone vary depending on posture and salt status, the ratio of aldosterone to renin remains essentially unchanged, indicating that the ratio may be a fairly robust index. It has been reported that any ratio more than 25 is suspicious and a ratio of more than 50 is diagnostic for PA.² In contrast, essential hypertensives have an aldosterone to renin ratio that is less than 25.¹⁸ From our study, 100% of our patients had supine ratios of more than 25, and 92% of the patients had supine ratios of more than 50 (Fig. 2). The erect ratios gave similar results. In contrast, our group of hypertensive controls who did not have PA had ratios ranging from 7 to 15. We thus believe that using the aldosterone to renin ratio is of considerable help, not just for screening purposes but also in confirming the diagnosis of PA. We felt that the higher ratio of 50 should be used for confirming the diagnosis of PA, as it is both very specific (100%) as well as sensitive (92%). Confirmation of autonomous aldosterone secretion should

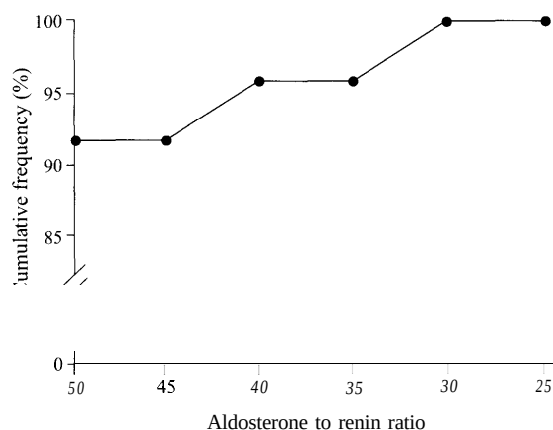


Fig. 2. Supine aldosterone to renin ratios in patients with PA

also be done by measuring urinary aldosterone following salt loading. This has been recently introduced and we are evaluating its use. The next step is to differentiate between APAs and IHA. Most studies have shown that the biochemistry does not reliably differentiate between them. We found this to be true with the exception of the supine aldosterone to renin ratio. For IHA, the upper limit of the supine aldosterone to renin ratio was 2000. Values above these limits suggest APA, and if obtained, time-consuming postural studies could be bypassed, and one could proceed directly to a CT scan of the adrenals. Posture studies were among the first tests devised to differentiate between these two subgroups.²¹ APAs are supposed to produce an anomalous fall (or a rise of <30%) in aldosterone at the end of the postural test, paralleling the dip in the circadian rhythm of ACTH, as APAs are more responsive to the stimulus of ACTH and less responsive to the renin-angiotensin system. IHA on the other hand showed a rise in aldosterone of >30% as they tend to be exquisitely sensitive to the rise in the renin and angiotensin in response to upright posture. We found that the postural study had 100% specificity and 94% sensitivity for diagnosing APAs, with the converse being true for diagnosing IHA, where it gave a specificity of 94% and a sensitivity of 100%. Overall these values compare very favourably with reported values of sensitivity and specificity of the postural test of between 80% and 85%.² The other differentiating test we used was a CT scan of the adrenals. In our series, CT scan of the adrenals was 94% sensitive and 82% specific for the diagnosis of APAs. The sensitivity of the CT scans in identifying adenomas approaches 90% in most studies.^{22,23} In equivocal cases, we proceeded to adrenal venous sampling, which is considered as the gold standard for localising the source of aldosterone secretion, with an accuracy of between 95% and 100%.²⁴ The procedure is unfortunately invasive and technically demanding. Often the right adrenal vein is not cannulated as it is technically more difficult. Our cannulation success rate was 60%, with most studies reporting success rates of 33.5% to 80%. All patients who were diagnosed to have adenomas were sent for adrenalectomy except two patients who are still considering surgery. Our overall surgical cure rate was 46%. Usually reported cure rates range from 35%⁸ to 50%.⁹ Spironolactone was used for patients with IHA in doses of between 50 mg and 200 mg per day. Overall, over 90% of patients had improvement in blood pressure with treatment.

Conclusion

We concluded that, in the event of normal aldosterone or renin values, a supine aldosterone to renin ratio of 50 is confirmatory of PA, and will detect 92% of patients with PA. Also, a supine aldosterone to renin ratio of more than 2000 suggests an APA.

REFERENCES

1. Conn J W. Primary aldosteronism. A new clinical syndrome. *J Lab Clin Med* 1955; 45:3-15.
2. Litchfield W R. Primary aldosteronism. *Endocrinol Clin North Am* 1995; 24:593-612.
3. Berglund G, Andersson O, Wilhelmsen L. Prevalence of primary and secondary hypertension: Studies in a random population sample. *BMJ* 1976; 2:554-6.
4. Streeton D H I, Thomycz N, Anderson G H. Reliability of screening methods for the diagnosis of primary aldosteronism. *Am J Med* 1979; 67:403-13.
5. Grimm C E, Weinberger M H, Higgins J T, Kramer N J. Diagnosis of secondary forms of hypertension. *JAMA* 1977; 237:1331-5.
6. Emmanuel S C. National Health Survey. Singapore: Ministry of Health, Singapore, 1992.
7. Bravo E L. Primary aldosteronism. *Urol Clin North Am* 1989; 16:481-6.
8. Blumenfeld J D, Sealey J E, Schluskel Y, Vaughn E D, Sos T A, Atlas S A, et al. Diagnosis and treatment of primary hyperaldosteronism. *Ann Intern Med* 1994; 121:877-85.
9. Bravo E L. Primary aldosteronism. Issues in diagnosis and management. *Endocrinol Clin North Am* 1994; 23:271-83.
10. Edwards C R W. Primary mineralocorticoid excess syndromes. In: Groot L J D, editor. *Endocrinology*. 3rd ed. Philadelphia: W B Saunders, 1995:1175-99.
11. Conn J W. Clinical characteristics of primary aldosteronism from an analysis of 145 cases. *Am J Surg* 1964; 107:159-72.
12. Ferriss J B, Brown J J, Fraser R. Primary hyperaldosteronism. *Clin Endocrinol Metab* 1981; 10:419-52.
13. Murphy B F, Whitworth J A, Kinkaid-Smith P. Malignant hypertension due to an aldosterone producing adenoma. *Clin Exp Hypertens A* 1985; 7:939-50.
14. Ma J T C, Wang C, Lam K S L, Yeung R T, Chan F L, Boey J, et al. Fifty cases of primary hyperaldosteronism in Hong Kong Chinese with a high frequency of periodic paralysis. Evaluation of techniques of tumour localisation. *Q J Med* 1981; 235:1021-37.
15. Bravo E L, Tarazi R C, Dustan H I, Fouad F M, Textor S C, Gifford R W, et al. The changing clinical spectrum of primary aldosteronism. *Am J Med* 1983; 74:641-50.
16. Conn J W. The evaluation of primary aldosteronism: 1954-1967. *Harvey Lect* 1967; 62:257.
17. Ferriss J B, Beevers D G, Brown J J, Davis D L, Fraser R, Lever A F, et al. Clinical, biochemical, and pathological features of low renin ("primary") hyperaldosteronism. *Am Heart J* 1978a; 95:375.
18. Hiramatsu K, Yamada T, Yukimura Y, Komiya I, Ichikawa K, Ishihara M, et al. A screening test to identify aldosterone producing adenoma by measuring plasma renin activity. *Arch Intern Med* 1981; 141:1589-93.
19. Hamlet S M, Tunny T J, Woodland E, Gordon R D. Is aldosterone/renin ratio useful to screen a hypertensive population for primary aldosteronism? *Clin Exp Pharmacol Physiol* 1985; 12:249-52.
20. McKenna T J, Sequeira S J, Heffernan A, Chambers J, Cunningham S. Diagnosis under random conditions of all disorders of renin-angiotensin-aldosterone axis, including primary aldosteronism. *J Clin Endocrinol Metab* 1991; 73:952-7.
21. Ganguly A, Dowdy A J, Luetscher J A, Melada G A. Anomalous postural response to plasma aldosterone concentration in patients with aldosterone producing adenoma. *J Clin Endocrinol Metab* 1973; 36:401-4.
22. Young W F Jr, Hogan M J, Klee G G, Grant C S, van Heerden J A. Primary aldosteronism: diagnosis and treatment. *Mayo Clin Proc* 1990; 65:96-110.
23. Ikeda D M, Francis I R, Glazer G M, Amendola M A, Gross M D, Aisen A M. The detection of adrenal tumours and hyperplasia in patients with primary aldosteronism: Comparison of scintigraphy, CT and MR imaging. *Am J Roentgenol* 1989; 153:301-6.
24. Miller D L. Endocrine angiography and venous sampling. *Radio1 Clin North Am* 1993; 5:1051-65.