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Commentary

Primary aldosteronism, diagnosed by the aldosterone to renin ratio, is a common cause of hypertension

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Blood pressure (BP) control in hypertensives in general remains suboptimal, with less than a quarter of those treated having controlled BP in western societies and even less in developing nations (Anonymous, 1997; Chamontin *et al*., 1998; Colhoun *et al*., 1998; Joffres *et al*., 1997; Marques-Vidal & Tuomilehto, 1997). It is thus unsurprising that a recent report suggested that hypertension remains a major modifiable risk factor worldwide contributing to global mortality (Ezzati *et al*., 2002). Importantly, it has been clearly shown that controlling BP offers significant benefits. A 5-mmHg reduction in the population diastolic BP over 5 years is associated with a reduction in strokes of about 40% and cardiac events by about a quarter, highlighting the need for adequate BP control (Collins *et al*., 1990; MacMahon *et al*., 1990). There are many potential reasons why BP control is poor in those diagnosed with the disease. This is not due to the lack of anti-hypertensive agents as we now have an ever expanding armamentarium of drugs that are better tolerated. We believe that one problem with the current practice in hypertension management is that hypertension treatment is empirical, that the choice of drugs is dictated more by large drug trials based on populations rather than based on the individuals. There is thus a dissociation between the underlying pathophysiology and drug therapy.

The heterogeneity of hypertension as a disease has been well demonstrated by Dickerson *et al*. (1999), who found that by a process of drug rotation through the four major classes of anti-hypertensive drugs (ACE inhibitors, β-blockers, calcium channel blockers and diuretics), they could adequately control 73% (n = 56, 161/98 mmHg to below 140/90 mmHg) of patients with mild hypertension with the 'best' monotherapy but only 39% when a random approach was adopted. Furthermore, it appeared that the plasma renin activity weakly but significantly predicted the response to ACE inhibitors and β-blockers, and that older patients responded better to calcium channel blockers and diuretics. This important study suggests that if a better BP control is to be achieved more widely, drug treatment should be tailored individually according to the prevailing haemodynamics or neurohormonal status.

This article will focus on a simple diagnostic test, the aldosterone-to-renin ratio (ARR) as a marker of inappropriate aldosterone activity in hypertensive patients. We believe that identifying such individuals allows tailoring of effective treatment targeted at the neurohormonal abnormality. In other words, these patients with a high ratio have a form of primary aldosteronism (PA) that responds well to aldosterone antagonists.

The ARR was first tested clinically by Hiramatsu *et al*. (1981). It was then adopted by the Brisbane group (Gordon, 1994) who suggested (controversially) that the prevalence of primary aldosteronism in hypertension could be much higher than previously suspected. Indeed, this group reported that, from 1987, when the test was first applied to normokalaemic patients, the cases of PA diagnosed at their centre rose exponentially from less than 10 per year to between 50 and 100 each year. Over the last 5 years, numerous other centres worldwide have also reported a much higher prevalence of PA of between 5% and 32% as compared to the traditional textbook PA prevalence of less than 1% (albeit using different methodologies; Stowasser, 2001).

Plasma renin activity and aldosterone levels each vary markedly with posture and salt status. In theory, the ratio between the two, the ARR, varies to a lesser extent. The ratio is derived by dividing the plasma aldosterone level by the plasma renin activity. This ratio capitalizes on the divergence between the two neurohormones. In patients with PA, the plasma aldosterone level is high and this, via a negative feedback system, suppresses renin production, the level of which provides the denominator of the ratio. Hence in PA the ratio puts into context any given aldosterone level. Thus the importance of a 'high normal' aldosterone is amplified by a low renin status. In contrast, subjects with a 'high normal' aldosterone and high renin are less likely to have PA, the changes in plasma aldosterone mirroring that of renin and producing a low ratio.

The ARR has been criticised by some who claim that the ratio is overly renin-dependent (Montori *et al*., 2001). This is because plasma renin activity cannot be accurately measured in many

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centres below a minimum value of 0·3 ng/ml/h. Some groups, including the Mayo Clinic group, have proposed interpreting the ARR in conjunction with a plasma aldosterone threshold to overcome this renin dependency (Young, 1999). Despite this more stringent definition of PA, the Mayo Clinic group have largely reproduced the Brisbane experience (Young, 2002).

Alternatively, actual renin concentration can be measured directly using immunoreactive techniques. However, at present there are no good published data on ARR using such total renin rather than plasma renin activity so the jury is out for now. Nevetheless, the predictive value of ARR used to signal PA is dependent on the threshold used; the higher is the ratio, the more likely that PA is present. We now know from the PHarst study (Hood *et al*., 2001) that β-blockers (by suppressing renin) elevate the ratio and that ACEI (by stimulating renin) suppress it. So a marginally high ARR in a patient taking a β-blocker should be viewed with caution but a marginally high ARR in a patient taking an ACEI is likely to be diagnostic. Calcium blockers and diuretics do not appear to interfere with the ratio (Lim *et al*., 2002a).

Whether it is worthwhile looking for PA amongst hypertensives, first and foremost it has to be demonstrated that such patients can be effectively treated. We have reported that in hypertensive patients with a raised ARR alone, monotherapy with the aldosterone antagonist spironolactone (low dose, 25–50 mg daily) can effectively control BP in nearly half of those who previously had resistant hypertension or needed multiple drugs for effective BP control (Lim *et al*., 1999). This observational study involved 28 hypertensive patients with a raised ARR ≥ 750 and poorly controlled BP despite being on multiple drug therapy. Spironolactone was added to their existing treatment regimen and they were followed up over a mean period 12·9 months. Spironolactone significantly reduced the need for antihypertensive drugs by a mean of 0·5, as well as reducing the mean BP by 15/8 mmHg. Hence spironolactone improved BP control and at the same time also reduced the need for polypharmacy in these patients. The Cambridge group led by Morris Brown extended our observation that ARR could predict response to spironolactone treatment. They conducted a large community-based study involving 529 unselected hypertensive patients and found that 12·3% of the study population had ARR > 800 (PHarst study). Consistent with what we have found, 70% of these patients with a raised ARR responded (as defined by a BP fall of ≥ 20 mmHg) favourably to 50 mg spironolactone treatment with a mean BP reduction of 32·3/12·7 mmHg. Whereas of those with an ARR of 400–800, only 40% dropped their BP ≥ 20 mmHg with spironolactone treatment. This is strong evidence that the ARR could be used as a guide for drug therapy in hypertension. A recent literature review that we have conducted found that in patients with demonstrable PA on dynamic tests, spironolactone reduced BP by 16–32%/17–31% (systolic/diastolic) and that this drug was well tolerated even in the long-term in patients with or without an adenoma (Lim *et al*., 2001). Although we and others have compelling clinical experience as to the efficacy of spironolactone in patients with a raised ARR, as yet we do not have any properly randomized study to support our claim. There are, however, two ongoing randomized drug trials, one in Scotland and one in Cambridge assessing whether spironolactone offers superior BP control over other diuretics in patients with a raised ARR.

The use of ARR in hypertension management has raised many more questions about the 'apparent' epidemic of PA or those with inappropriately increased aldosterone activity. Some authorities use the ARR as the first step in a diagnostic pathway (Young, 2002). Until such time that we have clear support from randomized drug trials, this whole area remains speculative except that the data from the PHarst study are quite convincing. Nevertheless, the next step would obviously be to explore the origin of this inappropriate aldosterone activity, whether there is a genetic component and if there is an interaction with environmental factors. These are important questions, especially when one considers that at least 10% of hypertensives have a degree of inappropriate aldosterone production.

We have looked at a large cohort of hypertensives with regard to aldosterone synthase genetic variation and how this relates to the ARR (Lim *et al*., 2002b). Aldosterone synthase is the rate-limiting enzyme in the production of aldosterone. The gene (CYP11B2) which encodes for this enzyme has a couple of genetic variants that have been reported to influence the activity of the enzyme. One polymorphism affects a putative steroidogenic factor-1 binding site(-344 T/C) in the 5′-regulatory region, whereas the other marker reflects replacement of the intron-2 from CYP11B2 with that from the neighbouring gene encoding 11 β-hydroxylase (CYP11B1; wild-type/conversion). We found significant excesses of the SF-1 T and intron-2 conversion alleles in patients with a raised ARR. Interestingly, we also found an association between the number of such 'deleterious' alleles present in each individual with the likelihood that a raised ARR was present (see Fig. 1). Furthermore, this risk of a raised ARR appeared to increase with age in individuals homozygous for such alleles. This raises the possibility that some individuals might have genetic susceptibility to develop inappropriate aldosterone activity but that they require an environmental stimulus to express this. Thus PA may be acquired in genetically susceptible individuals (Lim *et al*., 2002c).

In our PA case series (Lim *et al*., 2000), those without an adrenal adenoma on CT scanning predominated and indeed with the use of ARR as a screening tool, the traditional ratio of three adenomas to one idiopathic hyperaldosteronism (IHA) for PA is reversed. In our experience therefore most patients with PA diagnosed using the ARR have IHA. These are older patients with high plasma aldosterone level but not as high as can be found in patients with an adenoma, who are usually younger. We propose

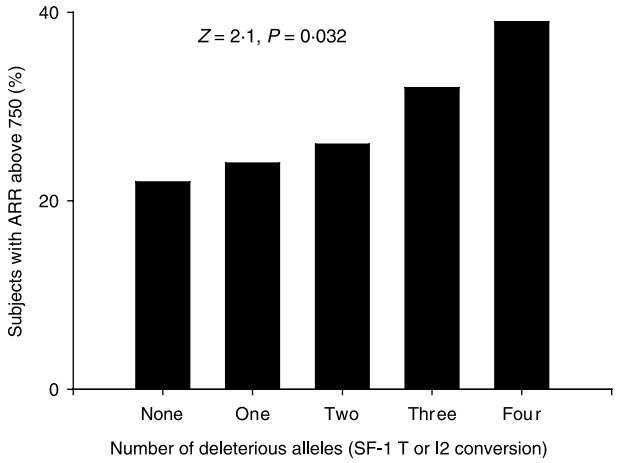

Fig. 1 The relationship between the number of deleterious alleles and a raised aldosterone to renin ratio.

that IHA as a cause of PA is an acquired disease in genetically susceptible subjects. It is possible that neurohormonally, such patients pass through a low renin stage having had essential hypertension for a number of years with increasing adrenal sensitivity to angiotensin II (Lim *et al*., 2002c). Eventually, the adrenal glands of these individuals become hypersensitive to angiotensin II stimulation such that aldosterone secretion appears autonomous, synonymous with tertiary hyperparathyroidism seen in chronic renal failure, hence, 'tertiary hyperaldosteronism' (Lim *et al*., 2002).

In conclusion, we believe that primary aldosteronism is probably a common form of hypertension. Such hypertension appears aldosterone-driven, is identified quite easily by the ARR and is effectively managed with appropriate treatment. There are theoretical reasons as to why a relative excess of aldosterone in itself may be deleterious (Rocha & Funder, 2002) but the most compelling reason for appropriate management of this form of hypertension is the much improved BP control achieved using spironolactone in this subgroup of hypertensive patients who have been difficult previously to control.

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References

Anonymous (1997) The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Archives of International Medicine*, **157**, 2413–2446.

Chamontin, B., Poggi, L., Lang, T., Menard, J., Chevalier, H., Gallois, H. & Cremier, O. (1998) Prevalence, treatment, and control of hypertension in the French population: data from a survey on high blood pressure in general practice, 1994. *American Journal of Hypertension*, **11**, 759–762.

Colhoun, H.M., Dong, W. & Poulter, N.R. (1998) Blood pressure screening, management and control in England: results from the health survey for England 1994. *Journal of Hypertension*, **16**, 747–752.

Collins, R., Peto, R., MacMahon, S., Hebert, P., Fiebach, N.H., Eberlein, K.A., Godwin, J., Qizilbash, N., Taylor, J.O. & Hennekens, C.H. (1990) Blood pressure, stroke, and coronary heart disease. Part 2: Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*, **335**, 827–838.

Dickerson, J.E., Hingorani, A.D., Ashby, M.J., Palmer, C.R. & Brown, M.J. (1999) Optimisation of antihypertensive treatment by cross-over rotation of four major classes. *Lancet*, **353**, 2008–2013.

Ezzati, M., Lopez, A.D., Rodgers, A., Vander Hoorn, S. & Murray, C.J. (2002) Selected major risk factors and global and regional burden of disease. *Lancet*, **360**, 1347–1360.

Gordon, R.D. (1994) Mineralocorticoid hypertension. *Lancet*, **344**, 240–243.

Hiramatsu, K., Yamada, T., Yukimura, Y., Komiya, I., Ichikawa, K., Ishihara, M., Nagata, H. & Izumiyama, T. (1981) A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity. Results in hypertensive patients. *Archives of International Mediciney*, **141**, 1589–1593.

Hood, S., Cannon, J.C., Scanlon, M.J. & Brown, M.J. (2001) Results from the Prevalence of Primary Hyperaldosteronism Measured by Aldosterone to Renin Ratio and Spironolactone Testing (PHArst) Study. 55th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research, Chicago.

Joffres, M.R., Ghadirian, P., Fodor, J.G., Petrasovits, A., Chockalingam, A. & Hamet, P. (1997) Awareness, treatment, and control of hypertension in Canada. *American Journal of Hypertension*, **10**, 1097–1102.

Lim, P.O., Dow, E., Brennan, G., Jung, R.T. & MacDonald, T.M. (2000) High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *Journal of Human Hypertension*, **14**, 311–315.

Lim, P.O., Jung, R.T. & MacDonald, T.M. (1999) Raised aldosterone to renin ratio predicts anti-hypertensive efficacy of spironolactone. A prospective cohort follow-up study. *British Journal of Clinical Pharmacology*, **48**, 756–760.

Lim, P.O., Jung, R.T. & MacDonald, T.M. (2002) Is aldosterone the missing link in refractory hypertension?: aldosterone-to-renin ratio as a marker of inappropriate aldosterone activity. *Journal of Human Hypertension*, **16**, 153–158.

Lim, P.O., MacDonald, T.M., Holloway, C., Friel, E., Anderson, N.H., Dow, E., Jung, R.T., Davies, E., Fraser, R. & Connell, J.M. (2002) Variation at the aldosterone synthase (CYP11B2) locus contributes to hypertension in subjects with a raised aldosterone-to-renin ratio. *Journal of Clinical Endocrinology and Metabolism*, **87**, 4398–4402.

Lim, P.O., Struthers, A.D. & MacDonald, T.M. (2002) The neurohormonal natural history of essential hypertension: towards primary or tertiary aldosteronism? *Journal of Hypertension*, **20**, 11–15.

Lim, P.O., Young, W.F.J. & MacDonald, T.M. (2001) A review of the medical treatment of primary aldosteronism. *Journal of Hypertension*, **19**, 353–361.

MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., Abbott, R., Godwin, J., Dyer, A. & Stamler, J. (1990) Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*, **335**, 765–774.

Marques-Vidal, P. & Tuomilehto, J. (1997) Hypertension awareness, treatment and control in the community: is the 'rule of halves' still valid? *Journal of Human Hypertension*, **11**, 213–220.

Montori, V.M., Schwartz, G.L., Chapman, A.B., Boerwinkle, E. & Turner, S.T. (2001) Validity of the aldosterone-renin ratio used to screen for primary aldosteronism. *Mayo Clinical Proceedings*, **76**, 877–882.

Rocha, R. & Funder, J.W. (2002) The pathophysiology of aldosterone in the cardiovascular system. *Annals of New York Academy of Science*, **970**, 89–100.

Stowasser, M. (2001) Primary aldosteronism: revival of a syndrome. *Journal of Hypertension*, **19**, 363–366.

Young, W.F. Jr (1999) Primary aldosteronism: a common and curable form of hypertension. *Cardiological Review*, **7**, 207–214.

Young, W.F. Jr (2002) Primary aldosteronism: management issues. *Annals of New York Academy of Science*, **970**, 61–76.