

A review of the medical treatment of primary aldosteronism

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Purpose: Use of the aldosterone-to-renin ratio (ARR) has suggested that at least one in 10 hypertensive subjects have primary aldosteronism (PA). There is thus a timely need to review the literature for effective drug therapies and to speculate on other therapeutic options by taking into account recent advances in understanding of the PA disease pathophysiological process.

Data source: A MEDLINE and EMBASE search of all articles published from the start of the databases until July 1999 and reviews of the bibliographies of textbooks.

Study selection: Primary research articles on the medical treatment of PA with emphasis on diagnosis, treatment option, drug dosage, therapeutic response and adverse drug effect.

Data extraction: Study design and quality were assessed. Relevant data on diagnostic methodology, drug usage and response were analysed and compared.

Data synthesis: A select number of subjects with aldosterone-producing adenoma (APA) can be expected to respond well to surgical treatment. For the majority of PA cases especially subjects with idiopathic hyperaldosteronism (IHA), long-term medical treatment is now safe and feasible although no randomized controlled trials have been carried out to date. The best therapeutic response is obtained by directly antagonizing aldosterone at the receptor level using medium to low dose

spironolactone and this response can be predicted by a raised ARR. The response to other potassium-sparing diuretics and calcium channel blockers are modest. IHA responds better than angiotensin II-unresponsive APA to angiotensin converting enzyme inhibitors and this may also be true with angiotensin II receptor blockers. The discovery of the aldosterone synthase gene opens up the possibility for gene therapy.

Conclusion: The diagnosis of PA allows appropriate management with resultant blood pressure control in many hypertensive subjects who otherwise have resistant hypertension despite multiple drug therapy. *J Hypertens* 19:353–361 © 2001 Lippincott Williams & Wilkins.

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Introduction

The diagnosis of hypertension usually means life-long medication, but in a significant proportion of patients, a distinct cause can be identified. Removing this cause may thus offer a cure. Primary aldosteronism (PA) due to an aldosterone-producing adenoma (APA) is one such example, where hypertension may be curable by surgery, hence the importance of making this diagnosis. However, favourable surgical outcome in APA depends on several factors which include age, duration of hypertension, concomitant essential hypertension, presence of renal impairment, and prior response to spironolactone. Inevitably, many patients will not be suitable for this treatment option. Surgery is also not without risks [1], making this option unattractive for many patients, especially as most cases can be treated successfully with long-term medical therapy [2,3]. Since Jerome Conn first described APA 46 years ago, medical treat-

ment of hypertension has improved. We now have many more antihypertensive agents with greater efficacy and better tolerability. More recently, the use of aldosterone-to-renin ratio (ARR) as a screening test has made PA due to unilateral APA and also that due to bilateral idiopathic hyperaldosteronism (IHA) increasingly diagnosed [4]. At least one in ten hypertension clinic patients [5] and a similar proportion of community-treated patients [6] appear to have PA. These patients with PA tended to have poorer blood pressure (BP) control than other hypertensives despite multiple drug therapy. Since medical treatment is the preferred option for older patients with APA and most if not all of those with IHA, the time is right to review this area and to speculate on the possible uses of new and emerging drugs that can be used to treat PA. Publications were identified by searching the medical databases of Medline (1966 to July 1999) and EMBASE

(1974 to July 1999), and from bibliography review of these papers.

Treatment rationale

There have been no placebo-controlled randomized trials evaluating the relative efficacy of drugs in the treatment of PA. This is not unexpected, given the rarity with which this diagnosis was made using previous diagnostic methodology. Previously the diagnosis required the presence of clinically resistant hypertension accompanied by 'frank' laboratory findings of hyperaldosteronism, which included hypokalaemic alkalosis, suppressed plasma renin activity and excessive aldosterone production. It is now clear that hyperaldosteronism can manifest without necessarily fulfilling all of these diagnostic criteria. The current 'gold standard' for confirming the diagnosis of PA is the failure of plasma aldosterone suppression in response to salt loading and/or fludrocortisone [7]. However, as will be discussed later, the ARR provides a reasonably robust screening test in clinical practice.

In order to treat the effects of aldosterone excess, an appreciation of how this condition leads to hypertension is essential. Early experiments involving administering aldosterone to normal volunteers or stopping treatment abruptly in patients with PA allowed the short-term changes in haemodynamics to be observed [8,9]. The initial blood pressure (BP) rise with aldosterone is due to fluid and sodium retention consistent with the anticipated effect of aldosterone working through the cytoplasmic mineralocorticoid receptor in the epithelial cells in the late distal tubules and collecting ducts. One effect of this is an overexpression of sodium channels in these cells thus promoting sodium reabsorption. The rise in BP allows a 'pressure natriuresis', which together with the release of natriuretic factors promotes the excretion of excess sodium and reduces the initially expanded fluid volume, despite on-going aldosterone excess. However, the rise in BP continues once plasma volume is restored and this correlates with a rise in systemic vascular resistance. One hypothesis suggests that aldosterone redistributes sodium into cells with the aid of circulating ouabain-like-factors (OLF) that inhibit the cellular sodium pumps [10]. The resultant increased intracellular sodium then alters the cellular calcium metabolism which increases the tonic contraction of vascular smooth muscles thus increasing the systemic vascular resistance [11]. Recent studies have also suggested that aldosterone excess sensitizes the peripheral vasculature to vasoconstrictors such as angiotensin II and norepinephrine via receptor upregulation [12]. Aldosterone has also been shown to directly increase intracellular cAMP via a calcium-dependent non-genomic process facilitating contraction in smooth muscle cells [13]. In addition, receptors for another potent vasoconstrictor, endothelin, have been found in

the zona glomerulosa layer of the adrenal gland where aldosterone is synthesised. These receptors are down-regulated in APA but not in IHA [14], where they are involved in a paracrine control of aldosterone production [15]. Another recent revelation is that there are extra-adrenal sources of aldosterone, produced locally in the heart as well as the vasculature [16] and that mineralocorticoid receptors are more widespread than previously thought. In IHA, the activity of aldosterone synthase, a rate-limiting enzyme involved in the synthesis of aldosterone is increased as well as the expression of mRNA for the gene for CYP11B2 in mononuclear leukocytes [17]. The same findings are apparent in resected APA specimens [18]. At least in IHA, early results have hinted that this maybe related to aldosterone synthase (CYP11B2) genetic polymorphism [19–22].

Based on the above-described PA pathophysiology, there are several therapeutic targets. The most obvious strategy is to antagonize aldosterone at the receptor level, using spironolactone, its metabolite potassium canrenoate or eplerenone, an as yet unlicensed drug which has less anti-androgenic and anti-progestational effects than spironolactone. The next option is to block the sodium epithelial channels directly using potassium-sparing diuretics such as amiloride or triamterene. Since calcium may be involved in maintaining a raised systemic vascular resistance and is involved as a cellular messenger in the adrenal synthesis and secretion of aldosterone [23], calcium channel blockers should be effective. Angiotensin converting enzyme inhibitors (ACEI) which reduce circulating angiotensin II may also be useful, especially in IHA as the adrenal glands in these patients have heightened angiotensin II stimulated aldosterone release [24]. Similarly, blocking angiotensin II at the receptor level may be equally efficacious using specific angiotensin II receptor blockers (ARB). Finally, interrupting the adrenal synthesis of aldosterone may be a viable approach whether by aldosterone synthesis antagonist or inhibiting aldosterone synthase using drugs or gene therapy. Importantly, since the effects of aldosterone are salt-dependent, reducing salt intake will aid the management of patients with PA [25]. Treatments are currently instituted empirically in practice and we now review the efficacy of these drugs where data are available.

Mineralocorticoid receptor antagonists

Spironolactone

Most studies in the past used doses of 400–800 mg daily of spironolactone to treat PA. Spironolactone directly antagonizes aldosterone at the mineralocorticoid receptor level. The BP-lowering efficacy in PA has been impressive in small uncontrolled studies, with BP falls of 40–60 mmHg systolic and 10–20 mmHg diastolic not uncommonly reported. Ferriss and colleagues

[26] treated 95 patients with PA using spironolactone 50–400 mg per day for between 1 and 96 months. A mean fall in BP from 189/122 to 148/97 mmHg was observed. Exchangeable sodium was also reduced with correction of all electrolyte abnormalities. Others have reported similar results (see Table 1) [27–31]. Brown and colleagues [27] reported that the response to spironolactone predicted the subsequent response to adrenal surgery, an important observation that has clinical relevance in identifying patients who might be suitable candidates for surgery. Crane and Harris [31] also treated patients with hypertension stratified by their stimulated renin levels [low renin 43, normal renin 24 and high renin 13] as well as 10 patients with PA using 100 mg spironolactone four times daily. Mean BP falls in the four groups after 3 weeks treatment were; 53/21 mmHg in the PA group, 45/22 mmHg in the low renin group, 29/13 mmHg in the normal renin group and 25/8 mmHg in the high renin group, respectively. Hence, renin suppression may be an indicator of response to an aldosterone antagonist. Kremer and colleagues [32] extended this observation by treating with spironolactone (50 to 400 mg daily, > 4 weeks) 67 subjects with low plasma renin activity and high plasma aldosterone concentration (> 500 pmol/l). Mean BP fell from 201/122 to 149/97 mmHg and mean serum potassium rose from 3.1 to 4.5 mmol/l. Of these subjects, 38 had adrenals explored of which 23 had adenomas and 15 had hyperplasia. Another approach to predicting the response to spironolactone was to assess the suppressibility of aldosterone production with salt loading in hypertensives. Wambach and colleagues [33] studied ten hypertensive patients who had high aldosterone excretion despite a high-salt diet and compared these with 16 hypertensive who had suppressed aldosterone secretion on a high-salt diet. They found that treatment with 200 mg spironolactone a day caused a greater fall

in mean BP in the former compared to the latter group (22 versus 9 mmHg), and that the fall in BP was correlated with aldosterone excretion on a salt-rich diet.

The presence of inappropriate aldosterone activity can be more easily assessed using the random and ambulant ARR derived from blood sampling done in the out-patient department. Lim and colleagues [35] treated with spironolactone a cohort of 28 (12 males) hypertensive subjects with a mean age of 55 ± 10 years and ARR greater than 750 (pmol/l per ng/ml per h) who failed to suppress their plasma aldosterone concentration in response to salt loading. These subjects were followed up for a mean period of 12.9 ± 7 months. Spironolactone in doses of 25 to 50 mg daily significantly reduced the need for antihypertensive drugs by -0.5 (2.3 to 1.8) drugs (CI 0.1 to 1.0), $P = 0.02$, as well as reducing systolic BP -15 (161 to 146) mmHg (CI 5 to 25, $P = 0.007$) and diastolic BP -8 (91 to 83) mmHg (CI 4 to 13, $P = 0.001$); 48% of the subjects achieved a BP $\leq 140/90$ mmHg and about half of the study subjects were managed with spironolactone monotherapy. More than half of these patients were previously treated with thiazide diuretics without adequate BP control suggesting that the effect of spironolactone in this patient cohort was likely to be over and above its diuretic effect, an experience shared by others [36].

Spironolactone has also been widely used in mainland Europe as an antihypertensive agent for treating essential hypertension. In an early randomized double-blind study in essential hypertension, Wolf and colleagues [37] found that 100 mg spironolactone was as effective as 200 mg but more effective than 25 mg. BP falls of 20/7 mmHg were achieved confirming that spironolactone is a good antihypertensive drug. In a database with over 20 000 hypertensive patients on this treatment followed up over a 10 year period, the antihypertensive effect of spironolactone as monotherapy in 182 patients was found to plateau above the dose of 100 mg. Furthermore, the incidence of gynaecomastia in 699 patients was found to relate to the dose used; 6.9% (< 50 mg) and 52% (> 150 mg) [38]. The spironolactone doses commonly used in the past to treat PA were thus probably unnecessarily high. There is a theoretical risk of breast carcinoma with the use of this agent because of the effects on oestrogen receptor [39]. However, this theoretical risk has not been translated into an excess of breast carcinoma in practice [38].

Potassium canreonate

Potassium canreonate is converted to canrenone, an active metabolite of spironolactone with a half-life of about 16.5 h. Experience with this agent in treating PA is limited. This drug is not available in the USA and in the UK, only a parenteral form is available. Studies from Italy have suggested that this agent is effective

Table 1. Spironolactone: observational studies

Study	Year	Type	Dose (mg)	% fall in BP
Crane and Harris [31]	1970	10 APA	400	28/20
		43 IHA	400	22/18
Brown [27]	1972	38 APA	50–400	21/17
		29 IHA		
Kremer [32]	1973	23 APA	50–400	26/20
		15 IHA		
Ganguly [28]	1976	9 APA	50–400	32/21
		7 IHA	50–400	32/31
Ferriss [26]	1978	95 PA	400	22/20
Wambach [33]	1980	6 APA	200	16 MAP
		10 IHA	200	16 MAP
Helber [34]	1980	9 IHA	200	15 MAP
		8 APA	200	16 MAP
Kater [30]	1983	15 APA	100–300	19 MAP
		9 IHA	100–300	17 MAP
Ghose [2]*	1999	24 APA	100–200	26/25

*Eight patients were treated with drugs other than potassium-sparing diuretics. APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism; MAP, mean arterial pressure.

[40,41]. Patients who developed gynaecomastia on spironolactone have been treated with potassium canreonate with resolution of this adverse effect [42]. In addition, potassium canreonate can be given intravenously with normalization of BP within 7 days in some patients with PA [43].

Eplerenone

Eplerenone (SC-66110) is a new steroid nucleus-based anti-mineralocorticoid, which acts as a competitive and selective aldosterone receptor antagonist. The 9,11-epoxide group in eplerenone results in a significant reduction of the molecule's progestational and anti-androgenic actions compared to spironolactone; eplerenone has 0.1% of the binding affinity to androgen receptors and < 1% of the binding affinity to progesterone receptors compared to spironolactone [44]. Eplerenone is extensively metabolized by the liver and excreted in the urine and faeces as metabolites. The effectiveness of eplerenone in the treatment of mild to moderate essential hypertension in 417 patients has been demonstrated [45]. The doses used ranged from 50 to 400 mg per day. Eplerenone was well tolerated with the incidence of adverse events similar to placebo. Potency studies with eplerenone show either equal or 25% less mg per mg potency when compared to spironolactone (data on file with Searle pharmaceuticals). Eplerenone may be a superior drug if it is shown to be as effective as spironolactone for treatment of mineralocorticoid-dependent hypertension and if it lacks the limiting anti-androgen side effects of spironolactone. A multicentre randomized double-blind controlled trial comparing spironolactone and eplerenone in treating patients with hyperaldosteronism is currently underway.

Epithelial sodium channel blockers

Amiloride

The use of amiloride in treating PA is associated with BP falls of 20–30 mmHg systolic and 10–15 mmHg diastolic for treatment periods of between 6 weeks to 6 months (see Table 2) [26,32,46–49]. Unlike spironolactone, where nearly 50% of patients can be maintained on monotherapy [3,35], about 75% of patients on amiloride needed additional antihypertensive agents to achieve BP control [47]. In a non-randomized crossover study involving ten patients with PA, Hoefnagels and colleagues [50] reported that 400 mg per day spironolactone reduced mean arterial BP by 20.5% after 6 weeks' treatment. In comparison, a mean arterial BP reduction of 10.4% was achieved using 40 mg amiloride per day for a similar length of time following a washout period of 4 weeks. In 10 patients with essential hypertension, the mean arterial BP reductions were 7.4 versus 6.5%, respectively. Hence, spironolactone was more efficacious than amiloride in the presence of hyperaldosteronism. Others have also suggested this

Table 2 Potassium-sparing diuretics: observational studies

Study	Year	Type	Drug/Dose (mg)	% fall in BP
Kremer [32]	1973	5 IHA	Amiloride 40	14/14
Kremer [46]	1977	8 APA, 11 IHA	Amiloride 40	15/13
Ferriss [26]	1978	18 IHA	Amiloride 40	18/11
Griffing [47]	1982	4 APA, 8 IHA	Amiloride 10–40	12/10
Ganguly [48]	1981	5 APA, 3 GRA	Triamterene + Thiazide	23/17

GRA, glucocorticoid remediable aldosteronism; APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism.

[26] although these studies were not randomized and the washout periods might not have been sufficiently long [51].

Triamterene

The efficacy of a thiazide–triamterene (hydrochlorothiazide 25 mg and triamterene 50 mg) combination has been investigated in eight patients with hyperaldosteronism (five APA, three with glucocorticoid-remediable hyperaldosteronism) [48]. BP fell from 168/101 to 130/84 mmHg with treatment. Serum potassium rose in six out of eight patients. Renin rose only in two patients indicating that continuing excess aldosterone activity sufficient to cause renin suppression was probably present in the other patients.

Calcium channel blockers

Calcium channel blockers lower BP independent of their effect on aldosterone secretion in patients with essential hypertension, an action that is similarly applicable in patients with PA. This group of drugs, however, could also reduce aldosterone secretion in some cases of PA as a mode of BP reduction. The calcium ion may be the final common intracellular messenger of most aldosterone secretagogues including angiotensin II, corticotrophin and potassium [52]. Hence, on this basis, by blocking the influx of calcium ions into the adrenal glomerulosa cells, calcium channel blockers may reduce aldosterone secretion and thus BP in patients with PA (see Table 3). A single sublingual dose of 20 mg nifedipine when given to 10 patients with PA reduced plasma aldosterone from 612 to 167 pmol/l within an hour without affecting plasma renin activity in one study [53]. In six patients, nifedipine therapy was continued for 4 weeks. Plasma aldosterone suppression was not sustained, rising to 556 pmol/l although BP fell from a mean of 162/102 to 134/85 mmHg (a fall of 28/17 mmHg). In a separate study reported by Carpenne and colleagues [54], neither acute nor chronic nifedipine administration in 15 PA patients [seven IHA, eight APA] reduced plasma aldosterone significantly, although BP fell from 174/106 to 147/84 mmHg over 90 days with 20 mg nifedipine twice per day. When compared with spironolactone, in an open non-randomized

Table 3 Calcium channel blockers: observational studies

Study	Year	Type	Drug/Dose (mg)	% fall in BP
Nadler [53]	1985	3 APA, 3 IHA	Nifedipine 20	17/17
Bravo [55]	1986	6 APA	Nifedipine 40	9 MAP
Opocher [58]	1987	5 IHA 6 APA	Verapamil 40, IV	9 MAP 7 MAP
Stimpel [56]	1989	3 IHA, 3 APA	Nitrendipine 60	6/8
Carpene [54]	1989	8 APA, 7 IHA	Nifedipine 40	16/21
Veglio [57]	1990	6 IHA, 2 GRA	Nicardipine 80	25 MAP

GRA, glucocorticoid remediable aldosteronism; APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism; MAP, mean arterial pressure.

study reported by Bravo and colleagues [55], nifedipine in doses of 30–80 mg per day reduced mean arterial BP to 116 mmHg from a baseline of 127 mmHg in six patients with APA. In contrast, spironolactone in monotherapy doses of 100–200 mg per day reduced the mean arterial BP to 92 mmHg. The combination of nifedipine and spironolactone offered no additional benefit compared to spironolactone alone.

Other calcium channel blockers similarly have had variable effects on plasma aldosterone while having little effect on plasma renin activity in patients with PA. Nitrendipine in one report did not alter plasma aldosterone [59] while in another, plasma aldosterone was increased [56]. Nicardipine [57] may reduce plasma aldosterone, and in one case report, amlodipine [60] masked the diagnosis of APA in a 30-year woman by suppressing aldosterone secretion. Verapamil when given intravenously selectively reduced plasma aldosterone in patients with IHA but not in those with APA [58].

Angiotensin converting enzyme inhibitors

ACEIs by inhibiting angiotensin II generation may preferentially reduce BP in patients with IHA since these patients have enhanced adrenal sensitivity to angiotensin II in secreting aldosterone (see Table 4) [24]. This is reflected by the rise in plasma aldosterone concentrations in response to the erect posture in patients with IHA; not seen in patients with Conn's adenoma or angiotensin II-unresponsive APA. Mantero and colleagues [61] gave 75 mg captopril per day to six APA patients and five subjects with IHA. The mean arterial BP fell 13% (NS) in the APA group (from 152 to 147 mmHg) but fell 20% (from 139 to 120 mmHg, $P < 0.01$) in the IHA group with a slight decrease in plasma aldosterone in the latter group. A similar level of BP reduction was observed in four patients with IHA given 80 mg enalapril per day [62] with an associated significant reduction in aldosterone secretion. The BP-lowering effect of ACEIs in patients with PA is therefore modest. This may relate to the fact that plasma

Table 4 Inhibitors: observational studies

Study	Year	Type	Drug/Dose (mg)	% fall in MAP
Mantero [61]	1981	6 APA 5 IHA	Captopril 75	13 (NS) 20
Griffing [62]	1985	4 IHA	Enalapril 80	16 in 3 and 12 in 1

NS, not statistically significant; APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism; MAP, mean arterial pressure.

renin activity in these patients is already generally suppressed, hence the low baseline levels of circulating angiotensin II. In addition, ACEIs may not completely suppress continuing angiotensin II formation by non-ACE pathways. Spironolactone can stimulate this suppressed renin–angiotensin system in PA by blocking the usual negative feedback responsible for renin suppression. This rarely can result in resistant hypertension probably due to an increase in angiotensin II. Interestingly, this may then be responsive to ACEIs [63,64]. Nonetheless, with regard to angiotensin II-sensitive PA, the contribution of tissue ACE-dependent and -independent pathways of angiotensin II generation on aldosterone secretion is currently not well delineated.

Aldosterone synthesis inhibitors and other drugs affecting aldosterone secretion

Aldosterone synthesis inhibitors reduce plasma aldosterone but their BP-lowering efficacy is generally disappointing. Trilostane [65] and metyrapone [66] have both been used in hyperaldosteronism. Trilostane appears to be effective in the short term but not in the long term [67].

Heparin [68,69] and low-molecular-weight heparin [70,71] both suppress aldosterone secretion. However, since they are given by injection, their use as antihypertensive agents seems limited. Dopamine agonists suppress aldosterone release and dopamine antagonists stimulate aldosterone release from the adrenal glands [72]. In addition, cisapride, a 5-HT₄ receptor agonist increases plasma aldosterone [73] although the clinical relevance of this is uncertain. This drug has recently been withdrawn by the manufacturer because of its potential pro-arrhythmic effect.

Emerging therapies for primary aldosteronism

Drugs which specifically block the angiotensin II type I receptor (e.g. losartan, valsartan, irbesartan, candesartan, telmisartan, etc) are now available. At least in theory, these drugs should be effective in lowering BP in patients with PA caused by IHA. Anecdotally, we successfully treated a patient with ARR > 1000 and multiple drug intolerance with valsartan 160 mg monotherapy. No doubt, with the adoption of ARR as a screening test, more patients with PA will be identified

to allow formal trials to be carried out to assess the efficacy of these drugs.

Other areas of potential research involve the development of drugs which can effectively inhibit the actions of aldosterone synthase, thus reduce the production of aldosterone. This is the key enzyme that has been shown to be overexpressed in patients with PA. Also, the gene for aldosterone synthase (CYP11B2) has now been identified. It may be possible in the near future to develop gene therapy to reduce the expression of or to inhibit the action of mRNA of this gene at the cellular level [74]. Even more exciting, is the prospect that patients or normotensive individuals with aldosterone synthase genetic polymorphisms that predispose to inappropriate aldosterone activity may be identifiable by genetic testing, so that preventative measures can be undertaken either to treat the associated hypertension at an earlier stage or to avoid the development of hypertension [19]. Importantly, actions which abolish the inappropriate aldosterone activity whether in PA or other disease states such as heart failure may improve survival through non-BP-dependent means since aldosterone is involved in many adverse processes, including promoting fibrosis in the heart and the vasculature [75].

The medical management of hyperaldosteronism

Despite the availability of an armamentarium of drugs which work at different parts of the BP regulatory system, the current management of hypertension is still empirical, based on guidelines derived from large treatment trials where patients were assumed to have homogeneous pathophysiology [76]. This non-specific approach [77] may partly underly the lack of success in controlling BP on a population level [78]. Attempts are being made to treat hypertensive patients on an individual basis, but this is more related to choosing drugs which potentially can treat a comorbid condition, such as recommending ACEI therapy to diabetic hypertensive individuals with microalbuminuria. Brown and colleagues [77] have tried to identify a 'best' antihypertensive drug on an individual basis using a systematic rotation of drugs on a 4-monthly basis of four drug classes which included ACEI, β -blocker, calcium channel blocker and diuretic. They were able to increase success of monotherapy (BP \leq 140/90 mmHg) from 22/56 (39%) to 41/56 (73%), comparing randomly assigned first drug and the best drug. This study further highlights the heterogeneity of the hypertension pathophysiology but the application of this complicated treatment methodology is likely to be limited in clinical practice.

Previous attempts to use renin profiling to guide treatment, i.e., treating low-renin individuals with diuretics and high-renin individuals with ACEIs and β -

blockers have not been translated into routine practice. This is probably due to a lack of standardization of the renin status and correlation with aldosterone secretion. Should it be based on random blood samples or following stimulatory manoeuvres? There are also a multitude of methodologies for defining renin status including the need for diuretic challenge, dietary salt manipulation or linkage with 24 h urinary sodium excretion. These cumbersome methodologies are clearly not practical. Furthermore, we have shown that the 'stimulated' renin, i.e., the renin level following oral frusemide pre-treatment, though specific, lacks sensitivity in detecting hyperaldosteronism [79].

We believe that the ARR may serve as a guide for targeting drug therapy, at least if applied to patients with resistant hypertension or those requiring more than two antihypertensive agents for BP control. Non-potassium-sparing diuretics should perhaps be avoided as first-line therapy in patients with a raised ARR since this may lead to hypokalaemic arrhythmic death in the presence of hyperaldosteronism [80,81]. A recent re-analysis of the Systolic Hypertension in the Elderly Program (SHEP) study data [82] suggested that even low-dose diuretic was associated with a 7.2% one-year incidence of hypokalaemia compared to 1% in the placebo-treatment group. Of further concern, those who developed hypokalaemia in this study did not derive any cardiovascular mortality benefits. It is conceivable that subjects prone to diuretic-induced hypokalaemia may also be those with undiagnosed hyperaldosteronism. Hence in patients with a raised ARR, spironolactone 25–50 mg daily can be given concurrently with other already-prescribed antihypertensive agents. The BP can then be observed over the next 3 to 6 months. If the BP response is good then the other agents can be downtitrated or even stopped. Otherwise, spironolactone can be co-prescribed with additional antihypertensive agents such as diuretics, ACEIs and calcium channel blockers as appropriate.

The role of surgery

The role of surgery in the treatment of PA is dependent on the subtype, patient comorbidities, and factors that predict surgical cure. APA (30 to 60% of PA cases) and unilateral adrenal hyperplasia (uncommon) are potentially biochemically correctable with unilateral adrenalectomy; whereas, IHA should be treated medically. Factors predicting cure of hypertension following adrenalectomy have not been described consistently in relatively small studies [83–86]. Sawka and colleagues [87] reported that in 97 patients with PA treated with adrenalectomy (56 laparoscopic), hypertension at a median follow-up period of 29 months was improved in 95% (decrease \geq 1 stage using JNC VI classification and/or fewer antihypertensives taken) or cured in 32%

of patients (BP < 140/90 mmHg without antihypertensives). Cure of hypertension was independently predicted by: family history of hypertension in ≤ 1 first-degree relatives, use of ≤ 2 antihypertensives preoperatively, systolic BP < 140 mmHg at postoperative dismissal and preoperative ARR > 2220. With appropriate surgical expertise, laparoscopic adrenalectomy is associated with a considerably shorter hospitalisation, lower pain medication requirements, a more rapid return to normal activities, and a decrease in late morbidity. Thus, laparoscopic adrenalectomy is the surgical treatment of choice for PA due to APA. However, many APAs are less than 1 cm in diameter, which is beyond the limit of CT scan resolution and would hence be missed unless more invasive techniques such as adrenal venous sampling are carried out. One approach is to treat all CT-scan-negative patients with a raised ARR medically and another approach is to exclude the presence of APA systematically for possible surgical intervention. It is unclear at present which is the better option with regard to long-term outcome. More research is clearly needed to outline a rational diagnostic pathway for these patients so that the most appropriate treatment can be instituted.

Conclusion

PA is being increasingly diagnosed, and may account for 10% or more of the hypertensive population. Appropriate medical treatment should thus be targeted at this significant subgroup of patients for optimum BP control. Long-term medical treatment has been shown to be both safe and feasible. Although no randomised controlled trial has been carried out to date, the best therapeutic response can be expected by directly antagonising aldosterone at the receptor level using medium-to-low dose spironolactone and this response can potentially be predicted by a raised ARR. Eplerenone, a new and better-tolerated specific mineralocorticoid receptor blocker is currently being assessed for the treatment of PA. The response to other potassium-sparing diuretics and calcium channel blockers are modest. IHA responds better than angiotensin II-unresponsive APA to ACEIs and this may also be true with ARBs. This may be due to the fact that subjects with IHA have enhanced adrenal sensitivity to angiotensin II. The discovery of the aldosterone synthase gene opens up the possibility for future gene therapy.

References

- Rutheford JC, Taylor WL, Rossetti TR. Surgical treatment of primary aldosteronism: evolution and evaluation [abstract]. In: *Primary aldosteronism and adrenal incidentaloma*. Couran Cove Resort, South Stradbroke Island, Queensland, Australia.; 1999. p. 30.
- Ghose RP, Hall PM, Bravo EL. Medical management of aldosterone-producing adenomas. *Ann Intern Med* 1999; **131**:105–108.
- Mantero F, Opocher G, Rocco S, Carpena G, Armanini D. Long-term treatment of mineralocorticoid excess syndromes. *Steroids* 1995; **60**: 81–86.
- Gordon RD. Mineralocorticoid hypertension. *Lancet* 1994; **344**:240–243.
- Lim PO, Dow E, Brennan G, Jung RT, MacDonald TM. High prevalence of primary aldosteronism in the Tayside hypertensive clinic population. *J Hum Hypertens* 2000; **14**:311–315.
- Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM. Potentially high prevalence of primary aldosteronism in a primary-care population. *Lancet* 1999; **353**:40.
- Gordon RD, Stowasser M, Klemm SA, Tunny TJ. Primary aldosteronism and other forms of mineralocorticoid hypertension. In: Swales J, (editor): *Textbook of hypertension*. Oxford: Blackwell Scientific, 1994, pp. 865–92.
- Wenting GJ, Man in 't Veld AJ, Derckx FH, Schalekamp MADH. Recurrence of hypertension in primary aldosteronism after discontinuation of spironolactone. Time course of changes in cardiac output and body fluid volumes. *Clin Exp Hypertens [A]* 1982; **4**:1727–1748.
- Wenting GJ, Man in 't Veld AJ, Verhoeven RP, Derckx FHM, Schalekamp MADH. Volume-pressure relationships during development of mineralocorticoid hypertension in man. *Circ Res* 1977; **40**(5):1163–1170.
- Haddy F, Pamnani M, Clough D. The sodium-potassium pump in volume expanded hypertension. *Clin Exp Hypertens* 1978; **1**:295–336.
- Blaustein MP, Hamlyn JM. Sodium transport inhibition, cell calcium, and hypertension. The natriuretic hormone/Na⁺-Ca²⁺ exchange/hypertension hypothesis. *Am J Med* 1984; **77**:45–59.
- Ullian ME. The role of corticosteroids in the regulation of vascular tone. *Cardiovasc Res* 1999; **41**:55–64.
- Christ M, Gunther A, Heck M, Schidt BM, Falckner E, Wehling M. Aldosterone, not estradiol, is the physiological agonist for rapid increases in cAMP in vascular smooth muscle cells. *Circulation* 1999; **99**:1485–1491.
- Tang X, Zeng Z, Zhang R. Endothelin-1 receptors of the normal adrenal gland and adrenal tumors in human. *Chung Hua Nei Ko Tsa Chih* 1996; **35**:462–465.
- Nussdorfer GG, Rossi GP, Belloni AS. The role of endothelins in the paracrine control of the secretion and growth of the adrenal cortex. *Int Rev Cytol* 1997; **171**:267–308.
- Slight SH, Joseph J, Ganjam VK, Weber KT. Extra-adrenal mineralocorticoids and cardiovascular tissue. *J Mol Cell Cardiol* 1999; **31**:1175–1184.
- Takeda Y, Furukawa K, Inaba S, Miyamori, Mabuchi H. Genetic analysis of aldosterone synthase in patients with idiopathic hyperaldosteronism. *J Clin Endocrinol Metab* 1999; **84**:1633–1637.
- Arnaldi G, Constantini C, Giacchetti G. Specific overexpression of ACTH-receptor mRNA and aldosterone synthase mRNA in aldosterone-producing adenoma [abstract]. In: *Primary aldosteronism and adrenal incidentaloma 1999*, Couran Cove Resort, South Stradbroke Island, Queensland, Australia 1999. p. 33.
- Tamaki S, Iwai N, Tsujita Y, Kinoshita M. Genetic polymorphism of CYP11B2 gene and hypertension in Japanese. *Hypertension* 1999; **33**:266–270.
- Giacchetti G, Lucarelli G, Ronconi V, et al. Aldosterone synthase gene polymorphism in idiopathic hyperaldosteronism and essential hypertension [abstract]. In: *Primary aldosteronism and adrenal incidentaloma 1999*, Couran Cove Resort, South Stradbroke Island, Queensland, Australia 1999. p. 25.
- Mulatero P, Schiavone D, Fallo F, Rabbia F, Pilon C, Chianci L. CYP11B2 gene polymorphisms in idiopathic hyperaldosteronism. *Hypertension* 2000; **35**:694–698.
- Komiya I, Yamada T, Takara M, Asawara T, Shimabukuro M, Nishimori T, et al. Lys(173)Arg and -344T/C variants of CYP11B2 in Japanese patients with low-renin hypertension. *Hypertension* 2000; **35**:699–703.
- Cherradi N, Brandenburger Y, Rossier MF, Capponi AM. Regulation of mineralocorticoid biosynthesis by calcium and the StAR protein. *Endocr Res* 1998; **24**:355–362.
- Wisgerhof M, Carpenter PC, Brown RD. Increased adrenal sensitivity to angiotensin II in idiopathic hyperaldosteronism. *J Clin Endocrinol Metab* 1978; **47**:938–943.
- Bravo EL, Dustan HP, Tarazi RC. Spironolactone as a nonspecific treatment for primary aldosteronism. *Circulation* 1973; **XLVIII**:491–498.
- Ferriss JB, Beevers DG, Boddy K, Brown JJ, Davies DL, Fraser R, et al. The treatment of low-renin ('primary') hyperaldosteronism. *Am Heart J* 1978; **96**:97–109.
- Brown JJ, Davies DL, Ferriss JB, Fraser R, Haywood E, et al. Comparison of surgery and prolonged spironolactone therapy in patients with hypertension, aldosterone excess, and low plasma renin. *BMJ* 1972; **2**:729–734.
- Ganguly A, Luetscher JA. Spironolactone therapy in primary aldosteronism: diagnostic and therapeutic implications. In: Sambhi MP (editor): *Systemic effects of antihypertensive agents*. New York: Stratton; 1976, pp. 383–392.
- Mantero F, Armanini D, Urbani S. Antihypertensive effect of spironolactone in essential, renal and mineralocorticoid hypertension. *Clin Sci Mol Med Suppl* 1973; **45** (suppl 1):219–224.
- Kater CE, Biglieri EG, Schambelan M, Arteaga E. Studies of impaired

- aldosterone response to spironolactone-induced renin and potassium elevations in adenomatous but not hyperplastic primary aldosteronism. *Hypertension* 1983; **5**:115–121.
- 31 Crane MG, Harris JJ. Effect of spironolactone in hypertensive patients. *Am J Med Sci* 1970; **260**:311–30.
 - 32 Kremer D, Beevers DG, Brown JJ, Davies DL, Ferriss JB, et al. Spironolactone and amiloride in the treatment of low renin hyperaldosteronism and related syndromes. *Clin Sci Mol Med Suppl* 1973; **45** (suppl 1):213–218.
 - 33 Wambach G, Helber A, Bonner G, Hummerich W, Meurer KA, Kaufmann W. Spironolactone in essential hypertension associated with abnormal aldosterone regulation and in Conn's syndrome. *Dtsch Med Wochenschr* 1980; **105**:647–651.
 - 34 Helber A, Wambach G, Hummerich W, Bonner G, Meurer KA, Kaufmann W. Evidence for a subgroup of essential hypertensives with non-suppressible excretion of aldosterone during sodium loading. *Klin Wochenschr* 1980; **58**:439–447.
 - 35 Lim PO, Jung RT, MacDonald TM. Raised aldosterone to renin ratio predicts anti-hypertensive efficacy of spironolactone. A prospective cohort follow-up study. *Br J Clin Pharmacol* 1999; **48**:756–760.
 - 36 Gwinup G, Steinberg T. Differential response to thiazides and spironolactone in primary aldosteronism. *Arch Intern Med* 1967; **120**:436–443.
 - 37 Wolf RL, Mendlowitz M, Roboz J, Styan GP, Kornfeld P, Weigl A. Treatment of hypertension with spironolactone. Double-blind study. *JAMA* 1966; **198**:1143–1149.
 - 38 Jeunemaitre X, Chatellier G, Kreft-Jais C, Charru A, DeVries C, Plouin PF, et al. Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol* 1987; **60**:820–825.
 - 39 Anonymous. Spironolactone: no longer for hypertension. *Drug Ther Bull* 1988; **26**:88.
 - 40 Tartagni F, Pasetti L, Ambrosioni E, Magnani B. Effectiveness of K canrenoate in the treatment of secondary hyperaldosteronism. *G Clin Med* 1979; **60**:196–206.
 - 41 Scaroni C, Armanini D, Fallo F, Opocher G, Boscaro M, Mantero F. Treatment of primary aldosteronism with oral potassium canrenoate. *Riv It Biol Med* 1981; **1**:239–243.
 - 42 Dupont A. Disappearance of spironolactone-induced gynaecomastia during treatment with potassium canrenoate. *Lancet* 1985; **2**:731.
 - 43 Mantero F, Armanini D, Opocher G. Effect of spironolactone and potassium canrenoate on plasma renin and plasma and urinary aldosterone in primary aldosteronism. In: *Aldosterone antagonists in clinical medicine*, Searle Symposium Nice: April 1978. pp. 428–437.
 - 44 de Gasparo M, Joss U, Ramjouw HP, Whitebread SE, Haenni H, Schenkel L, et al. Three new epoxy-spirolactone derivatives: characterization in vivo and in vitro. *J Pharmacol Exp Ther* 1987; **240**:650–656.
 - 45 Epstein M, Menard J, Alexander JC, Roniker B. Eplerenone, a novel and selective aldosterone receptor antagonist: efficacy in patients with mild to moderate hypertension. *Circulation* 2000; **98** (suppl):198–199.
 - 46 Kremer D, Boddy K, Brown JJ, Davies DL, Fraser R, Lever AF, et al. Amiloride in the treatment of primary hyperaldosteronism and essential hypertension. *Clin Endocrinol (Oxf)* 1977; **7**:151–157.
 - 47 Griffing GT, Cole AG, Aurecchia SA, Sindler BH, et al. Amiloride in primary hyperaldosteronism. *Clin Pharmacol Ther* 1982; **31**:56–61.
 - 48 Ganguly A, Weinberger MH. Triamterene-thiazide combination: alternative therapy for primary aldosteronism. *Clin Pharmacol Ther* 1981; **30**:246–250.
 - 49 Griffing GT, Melby JC. The therapeutic use of a new potassium-sparing diuretic, amiloride, and a converting enzyme inhibitor, MK-421, in preventing hypokalemia associated with primary and secondary hyperaldosteronism. *Clin Exp Hypertens [A]* 1983; **5**:779–801.
 - 50 Hoefnagels WH, Drayer JI, Smals AG, Kloppenborg PW. Spironolactone and amiloride in hypertensive patients with and without aldosterone excess. *Clin Pharmacol Ther* 1980; **27**:317–323.
 - 51 Lowder SC, Liddle GW. Prolonged alteration of renin responsiveness after spironolactone therapy. A cause of false-negative testing for low-renin hypertension. *N Engl J Med* 1974; **291**:1243–244.
 - 52 Schiffrin EL, Lis M, Gutkowska J, Genest J. Role of Ca²⁺ in response of adrenal glomerulosa cells to angiotensin II, ACTH, K⁺, and ouabain. *Am J Physiol* 1981; **241**:E42–E46.
 - 53 Nadler JL, Hsueh W, Horton R. Therapeutic effect of calcium channel blockade in primary aldosteronism. *J Clin Endocrinol Metab* 1985; **60**:896–899.
 - 54 Carpena G, Rocco S, Opocher G, Mantero F. Acute and chronic effect of nifedipine in primary aldosteronism. *Clin Exp Hypertens [A]* 1989; **11**:1263–1272.
 - 55 Bravo EL, Fouad FM, Tarazi RC. Calcium channel blockade with nifedipine in primary aldosteronism. *Hypertension* 1986; **8** (suppl. 1):191–194.
 - 56 Stimpel M, Ivens K, Volkmann HP, Wambach G, Kaufmann W. Therapeutic value of calcium antagonists in autonomous hyperaldosteronism. *Klin Wochenschr* 1989; **67**:248–252.
 - 57 Veglio F, Pinna G, Bisbocci D, Rabbia F, Piras D, Chiandussi L. Efficacy of nicardipine slow release (SR) on hypertension, potassium balance and plasma aldosterone in idiopathic aldosteronism. *J Hum Hypertens* 1990; **4**:579–582.
 - 58 Opocher G, Rocco S, Murgia A, Mantero F. Effect of verapamil on aldosterone secretion in primary aldosteronism. *J Endocrinol Invest* 1987; **10**:491–494.
 - 59 Stimpel M, Ivens K, Wambach G, Kaufmann W. Are calcium antagonists helpful in the management of primary aldosteronism? *J Cardiovasc Pharmacol* 1988; **12**:S131–134.
 - 60 Brown MJ, Hopper RV. Calcium-channel blockade can mask the diagnosis of Conn's syndrome. *Postgrad Med J* 1999; **75**:235–236.
 - 61 Mantero F, Fallo F, Opocher G, Armanini D, Boscaro M, Scaroni C. Effect of angiotensin II and converting enzyme inhibitor (captopril) on blood pressure, plasma renin activity and aldosterone in primary aldosteronism. *Clin Sci* 1981; **61** (suppl 7):289s–293s.
 - 62 Griffing GT, Melby JC. The therapeutic effect of a new angiotensin-converting enzyme inhibitor, enalapril maleate, in idiopathic hyperaldosteronism. *J Clin Hypertens* 1985; **1**:265–276.
 - 63 Atkinson AB, Brown JJ, Davies DL, Lever AF, Robertson JL. Combined captopril and spironolactone treatment in Conn's syndrome with renal impairment and refractory hypertension. *Clin Endocrinol* 1981; **14**:105–108.
 - 64 Stimpel M, Vetter W, Groth H, Germinger P, Vetter H. Captopril before and after spironolactone therapy in primary aldosteronism. Pathogenetic and therapeutic aspects. *Klin Wochenschr* 1985; **63**:361–363.
 - 65 Nomura K, Demura H, Horiba N, et al. Long-term treatment of idiopathic hyperaldosteronism using trilostane. *Acta Endocrinol* 1986; **113**:104–110.
 - 66 Sonino N, Levine LS, New MI. Mineralocorticoid and metabolic response to metyrapone on normotensive children and children with dexamethasone-suppressible and primary hyperaldosteronism. *Acta Endocrinol* 1981; **98**:87–94.
 - 67 Galy CI. Trilostane for long term treatment of primary aldosteronism. Comparison with spironolactone and amiloride. (abstract) *Kidney Int* 1984; **26**:497.
 - 68 Ford HC, Bailey RE. The effect of heparin on aldosterone secretion and metabolism in primary aldosteronism. *Steroids* 1966; **7**:30–40.
 - 69 Conn JW, Rovner DR, Cohen EL, Anderson JE Jr. Inhibition by heparinoid of aldosterone biosynthesis in man. *J Clin Endocrinol Metab* 1966; **26**:527–532.
 - 70 Levesque H, Verdier S, Cailleux N, Elie-Legrand MC, Gancel A, Basuyau JP, et al. Low molecular weight heparins and hypoaldosteronism. *BMJ* 1990; **300**:1437–1438.
 - 71 Cailleux N, Moore N, Levesque H, Courtois H, Godin M. A low molecular weight heparin decreases plasma aldosterone in patients with primary hyperaldosteronism. *Eur J Clin Pharmacol* 1992; **43**:185–187.
 - 72 Veglio F, Pinna G, Rabbia F, Panarelli M, Bisbocci D, Melchio R, et al. Dopaminergic regulation of aldosterone secretion: assessment in different subtypes of primary aldosteronism and in essential hypertension. *J Int Med Res* 1991; **19**:44–49.
 - 73 Lefebvre H, Heron F, Contesse V, Delarue C, Caudry H, Kuhn JM. Effect of the serotonin4 receptor agonist cisapride on plasma aldosterone levels in cirrhotic patients with secondary hyperaldosteronism [letter]. *Eur J Clin Pharmacol* 1998; **53**:479–480.
 - 74 Raizada MK, Francis SC, Wang H, Gelband CH, Reaves PY, Katovich MJ. Targeting of the renin-angiotensin system by antisense gene therapy: a possible strategy for the long-term control of hypertension. *J Hypertens* 2000; **18**:353–362.
 - 75 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**:709–717.
 - 76 Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med* 1993; **328**:914–921.
 - 77 Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999; **353**:2008–2013.
 - 78 Klungel OH, Kaplan RC, Heckbert SR, Smith NL, Lemaitre RN, Longstreth WT Jr. Control of blood pressure and risk of stroke among pharmacologically treated hypertensive patients. *Stroke* 2000; **31**:420–424.
 - 79 Lim PO, Brennan GM, Jung RT, MacDonald TM. Diagnosing primary

- aldosteronism with frusemide stimulation test in hypertensive patients with raised aldosterone to renin ratio. *Med Biochem* 1999; **1**:225–231.
- 80 Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X, *et al.* Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994; **330**:1852–1857.
- 81 Hoes AW, Grobbee DE, Lubsen J, Man in't Veld A, van der Does E, Hofman A. Diuretics, beta-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995; **123**:481–487.
- 82 Franse LV, Pahor M, Di Bari M, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *Hypertension* 2000; **35**:1025–1030.
- 83 Celen O, O'Brien MJ, Melby JC, Beazley RM. Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg* 1996; **131**:646–650.
- 84 Lo CY, Tam PC, Kung AW, Lam KS, Wong J. Primary aldosteronism. Results of surgical treatment. *Ann Surg* 1996; **224**:125–130.
- 85 Favia G, Lumanchi F, Scarpa V, D'Amico DF. Adrenalectomy in primary aldosteronism: a long-term follow-up study in 52 patients. *World J Surg* 1992; **16**:680–684.
- 86 Stowasser M, Klemm SA, Tunny TJ, Storie WJ, Rutherford JC, Gordon RD. Response to unilateral adrenalectomy for aldosterone-producing adenoma: effect of potassium levels and angiotensin responsiveness. *Clin Exp Pharmacol Physiol* 1994; **21**:319–322.
- 87 Sawka AM, van Heerden JA, Farley DR. Adrenalectomy for primary aldosteronism: factors predicting cure of hypertension. In: *82nd Annual Meeting of the Endocrine Society* [abstract] 2000. p. 2262.