Management of resistant arterial hypertension: role of spironolactone versus double blockade of the renin–angiotensin–aldosterone system

Beatriz Alvarez-Alvarez[a], María Abad-Cardiel[b], Arturo Fernandez-Cruz[b] and Nieves Martell-Claros[b]

Background **Currently there is no consensus regarding which add-on therapy to use in resistant hypertension. This study was designed to compare two treatment options, spironolactone (SPR) versus dual blockade of the renin–angiotensin–aldosterone system (RAAS).**

Methods **Forty-two patients with true resistant hypertension were included in the study. An open-label prospective crossover design was used to add a second RAAS blocker to previous treatment and then SPR following 1 month of wash-out. BP was measured in the office and by ambulatory blood pressure monitoring (ABPM). Changes in laboratory tests were also studied for both treatments. The predictive values of aldosterone–renin ratio (ARR) and serum potassium of determining the antihypertensive response were analyzed for both arms.**

Results **Following the first stage of dual blockade, SBP dropped significantly both in office (reduction of 12.9 ± 19.2 mmHg)) and by ABPM (reduction of 7.1 ± 13.4 mmHg). Office DBP was unchanged but was significantly reduced as measured by ABPM (3.4 ± 6.2 mmHg). On SPR treatment, office BP was reduced 32.2 ± 20.6/10.9 ± 11.6 mmHg. By ABPM the reduction was 20.8 ± 14.6/8.8 ± 7.3 mmHg ($P < 0.001$). The BP control was achieved by 25.6% of patients in dual blockade and 53.8% in SPR with office blood pressure. By ABPM, 20.5% were controlled on dual blockade and up to 56.4% with SPR. Serum potassium was a weak inverse predictor of the blood pressure-lowering effect of SPR.**

Conclusion **SPR has a greater antihypertensive effect than dual blockade of the RAAS in resistant hypertension. SPR at daily doses of 25–50 mg shows a potent antihypertensive effect when added to prior regimes of single RAAS axis blockade in patients with resistant arterial hypertension.**
J Hypertens **28:2329–2335**

Journal of Hypertension 2010, **28**:2329–2335

Keywords: ambulatory blood pressure monitoring, potassium, renin–aldosterone ratio, renin–aldosterone axis dual blockade, resistant arterial hypertension, spironolactone

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACE-I, angiotensin-converting enzyme inhibitor; AHT, arterial hypertension; ARB, angiotensin receptor blockade; ARR, aldosterone–renin ratio; LVH, left ventricular hypertrophy; LVM, left ventricular mass; PAC, plasma aldosterone concentration; RAAS, renin–angiotensin–aldosterone system; RAH, resistant arterial hypertension; SPR, spironolactone

[a]CS Andrés Mellado and [b]Unidad de Hipertensión, Hospital Clínico San Carlos, Madrid, Spain

Correspondence to Professor Nieves Martell-Claros, PhD, Unidad de Hipertensión, Hospital Clínico San Carlos, C/ Martin Lagos s/n, 28040 Madrid, Spain
Tel: +34 913 303 395; e-mail: nmartellc@terra.es

Received 26 April 2010 **Revised** 9 June 2010
Accepted 17 June 2010

See editorial comment on page 2194

Introduction

Resistant arterial hypertension (RAH) is defined as the inability to reach adequate control of arterial blood pressure (BP) despite treatment with at least three drugs (including a diuretic) in adequate doses and after exclusion of spurious hypertension such as isolated office hypertension and failure to use large cuffs on large arms [1].

The prevalence of this phenomenon has not been well defined, because clinical trials designed to study 3 or more medications have not been performed. However, in large published studies, the need to make use of three antihypertensive medications has been shown to be necessary in around 25–30% of cases in order to reach adequate BP control as defined by international guidelines (<140/90 or 130/80 mmHg according to the patient's cardiovascular risk [2]. The diagnosis of RAH or true resistance is made having excluded other underlying factors that could explain or exacerbate poor control of the patient's BP; volume overload, drug interactions, sleep apnea, secondary causes, etc. It is also important to ensure that patient compliance is adequate.

The renin–angiotensin–aldosterone system (RAAS) plays a role which remains unclear in the genesis and maintenance of arterial hypertension (AHT). Various studies show that more than 10% of hypertensive patients have a ratio of aldosterone to renin at plasma levels higher than normal [3,4] without showing hyperaldosteronism. These patients frequently have poor BP control despite treatment with multiple antihypertensive agents, and it has been suggested that they are patients who would show a good response to spironolactone (SPR) [5].

0263-6352 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32833d4c99

In fact, the presence of a direct relationship between the ratio of aldosterone to plasma renin activity (ARR) and BP levels has been shown [6].

At the same time, the inadequate production of aldosterone in relation to renin levels is known to be due to the increase in activity of aldosterone synthase, the limiting enzyme in the final step of aldosterone biosynthesis [7].

Therapeutic options include inhibition of this system at two levels as a plausible objective in patient control.

In clinical practice, there are three pharmacological possibilities for acting on the RAAS; converting enzyme inhibitors (ACE-I), AT-1 receptor blockers of angiotensin II (ARB) and finally the possibility of acting on the final stage of the system, by blocking mineralocorticoid receptors with SPR.

Among the other options for the treatment of RAH there exists the combination of ACE-I and ARB, the antihypertensive efficacy of which has been demonstrated [8–10]. In patients with renal involvement, dual blockade reduces proteinuria and slows the development of terminal renal failure [11,12]. The other possibility is the addition of SPR, shown to be capable of reducing BP in hypertensive patients with or without hyperaldosteronism. Using doses of up to 50 mg significantly reduce BP in patients with RAH previously treated with three or more drugs [13]. In fact, UK hypertension guidelines [14] and other experts [15] include SPR as a fourth-line or fifth-line treatment when adequate patient control is not reached with three or four antihypertensive agents.

ARR has been reported as predictive of the hypertensive response to SPR [5] although this remains open to debate [13].

Our working hypothesis is based on the supposition that patients with RAH may show overactivation of the RAAS and therefore, in order to achieve an adequate reduction, more aggressive blockade is required (e.g. RAAS inhibition at two different points, in other words a double blockade of the system) or may have higher aldosterone production in relation to circulating renin, which would be as a result of increased aldosterone formation unstimulated by angiotensin II. To this end, we designed a study with the objective of being able to decide which treatment regime would be most effective for those patients with RAH, treated in our Hypertension Unit, that were already receiving prior treatment with at least a diuretic and calcium antagonist together with an ACE-I or ARB, proposing two possible regimes; double blockade of the system with an ACE-I and ARB at higher doses or blockade via ACE-I or ARB with low dose SPR.

Objectives

To study which of the two proposed treatments is the most appropriate as a fourth or fifth drug in patients with RAH.

Secondary objectives included to study whether there was a relationship between ARR and the antihypertensive response to either of the two treatment regimes and also whether the reduction in BP with these regimes showed an inverse relationship to serum potassium levels.

Patients and methods

The patients were selected from hypertensives followed for at least 1 year in the Hypertension Unit at the Hospital Clínico San Carlos in Madrid (Spain), and who had undergone exhaustive studies to reveal drug interactions, secondary causes or other reasons that could explain the refractive nature to treatment, including patient compliance.

The screening was carried out on 70 patients, classified initially as having refractory hypertension. 28 patients were excluded by the following causes: white coat, 12; hyperaldosteronism, 9; obstructive sleep apnea (OSA), 1; not agreeing to participate, 4; change of residence, 2.

Thus, forty-two patients with true resistant hypertension were enrolled in the study.

On entering the study, office BP measurement was performed in the out-patient clinic (in accordance with ESH-ESC guidelines of 2007) [1], together with a complete physical examination. Laboratory evaluation included serum lipids, glucose, electrolytes, creatinine and hs-CRP. A baseline creatinine level more than 1.5 mg/dl or potassium level more than 5.5 mEq/l was the exclusion criteria. In order to determine creatinina clearance, Na and K, 24-h urine was collected. Plasma aldosterone concentration (PAC), plasma renin activity were obtained; the ratio of these two were calculated (ARR). For calculation of ARR, plasma renin activity was corrected to 0.3 ng/ml per h when less than this value; consequently, no patients with PAC more than 15 ng/dl were considered to have an ARR at least 30. Patients with AAR at least 30, adrenal alterations in abdominal computed tomography scan and abnormal response of PAC after a saline infusion test were identified as having primary aldosteronism and were not included in this study. ECG, echocardiogram and 24-h ABPM were also performed.

In accordance with the Helsinki protocol guidelines, informed consent was given before taking part in the study, which was also approved by the hospital's ethics review committee.

This was an open-label prospective crossover study in which each patient underwent treatment with both regimes. In the first stage, patients were treated with one drug to inhibit the renin–angiotensin–aldosterone axis, using a different drug from the one they received previously; an ARB was added if they were taking an ACE-I or vice versa. This regime was maintained for a period of 12 weeks. At the end of this stage, the office

BP was again performed in out-patients, as well as a physical examination, blood tests and ABPM. Following a wash-out of the added drug for a period of 4 weeks, the patients then received a dose of 25 mg of SPR, increasing doses 4 weeks later if necessary. The patients maintained this regimen for a further 12 weeks, with BP control measurements and serum potassium levels at 4 and 8 weeks follow-up, ending with BP measurement in out-patients, ABPM and blood testing at 12 weeks.

Three patients were lost to follow-up, two due to poor tolerance of ACE-I (cough) in the first stage of dual therapy and one during mineralocorticoid-receptor blockade due to hyperkalemia.

Statistical analysis

Absolute and relative rates were studied in the form of percentage values for each of the qualitative variables.

In case of the quantitative variables, the normality of distribution was studied via the Kolmogorov–Smirnov test, the mean and median are both shown, and for statistical dispersion, the standard deviation and the first and third quartile are shown together with the respective mean and median values.

For comparison between treatments, for the quantitative variables, a Student *t*-test was used for paired samples if they followed a normal distribution and the Mann–Whitney *U* test when they did not show a tendency to Gaussian distribution. Variable correlation was determined using the Pearson test.

Results

Our study population was 50% male. Mean age was 66.8 ± 8.8 years, the majority with obesity (BMI 31.8 ± 3.9), mainly abdominal (abdominal circumference: 104.3 ± 8.6 cm). In Table 1 the anthropometrical characteristics of the patients are shown. A total of 10.3% of the group were smokers, 69.2% did physical exercise, 17.9% had a previous family history of early cardiovascular disease and 23.1% had a prior personal history of cardiovascular disease.

The mean number of antihypertensive medications received before entering the study was 4.1 ± 0.8 (range 3–5); 28.2% were taking three medications, 48.7% on four and 23.1% were being treated with five antihypertensive.

Out-patient BP levels were 158.4 ± 15.3 mmHg (SBP) and 80.4 ± 11.4 (DBP). Mean BP as measured by ABPM was $141.0 \pm 14.4/77.7 \pm 9.1$ mmHg, predominantly with a nondipping profile (89.8%).

Table 1 Baseline characteristics

	Mean ± SD
Age (years)	66.85 ± 8.76
Weight (kg)	81.21 ± 10.94
BMI (kg/m^2)	31.79 ± 3.94
Abdominal circumference (cm)	104.33 ± 8.59
Cholesterol total (mg/dl)	197.92 ± 34.68
Cholesterol LDL (mg/dl)	115.20 ± 27.41
Cholesterol HDL (mg/dl)	57.72 ± 16.77
Triglycerides (mg/dl)	130.10 ± 79.48
Apo A (mg/dl)	162.76 ± 35.54
Apo B (mg/dl)	97.96 ± 22.72
Fasting glucose (mg/dl)	115.38 ± 25.17
Fasting insulin (μl U/ml)	12.48 ± 6.32
HOMA index	3.58 ± 2.33
Highly sensitive CRP (mg/dl)	0.43 ± 0.57
Creatinine (mg/dl)	1.04 ± 0.22
Creatinine clearance (ml/min)	83.08 ± 22.81
Uric acid (mg/dl)	5.98 ± 1.39
Serum Na (mg/dl)	140.43 ± 2.21
Serum K (mg/dl)	4.08 ± 0.40
Albumin/creatinine excretion (mg/g)	79.48 ± 160.69

CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 1 shows the baseline anthropometrical characteristics and blood test results of these patients. Renal function was preserved in the majority with a mean serum creatinine of 1.03 ± 0.20 mg/dl and creatinine clearance of 84.6 ± 27.0 ml/min. A total of 94.6% of patients had LVH; 75.7% concentric hypertrophy, 13.5% remodeling and 5.4% eccentric hypertrophy. The group therefore was comprised of patients with resistant hypertension and at high or very high cardiovascular risk.

The ARR was found to be at 46.9 ± 56.2 pg/ml (range 1.2–232 pg/ml). Mean plasma potassium levels were within normal range at 4.08 ± 0.4 mmol/l.

At the end of the first stage of treatment with dual blockade, that is to say with ACE-I and ARB, SBP dropped significantly both office BP (145.5 ± 24.3 mmHg, reduction of 12.9 ± 19.2 mmHg) and ABPM (133.8 ± 14.8 mmHg, reduction of 7.1 ± 13.4 mmHg) (Table 2), whilst office measured DBP was unchanged, but with a significant reduction in ABPM measured levels (74.3 ± 8.1 mmHg, reduction of 3.4 ± 6.2 mmHg). mmHg). With regards to metabolic parameters, no great change was observed except a significant reduction in Apo B (Table 3).

Table 2 Changes in blood pressure with dual blockade and spironolactone plus single blockade

	Office BP		ABPM 24 h		ABPM day		ABPM night	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Baseline	158.4 ± 15.3	80.4 ± 11.4	141.0 ± 14.4	77.7 ± 9.1	142.1 ± 16.0	79.9 ± 9.2	136.5 ± 18.7	73.9 ± 16.7
Dual blockade	145.5 ± 29.3	78.2 ± 13.9	133.9 ± 14.8	74.3 ± 8.1	136.0 ± 14.6	77.4 ± 9.2	129.4 ± 17.2	69.2 ± 9.5
SPR + SB	126.2 ± 19.0	69.5 ± 11.7	120.2 ± 15.4	68.9 ± 9.7	122.1 ± 15.9	71.4 ± 10.1	117.1 ± 17.1	64.8 ± 10.7

ABPM, ambulatory blood pressure monitoring; SPR + SB, spironolactone plus double blockade; SPR, spironolactone.

Table 3 Changes in lipid, glycaemic profiles and renal function according to treatment arm

Metabolic parameter	Baseline	Dual blockade	Spironolactone	P1	P2	P3
Apo A (mg/dl)	163.70 ± 35.49	163.84 ± 33.74	154.45 ± 29.33	NS	0.014	0.001
Apo B (mg/dl)	98.07 ± 23.12	89.89 ± 24.01	90.30 ± 18.45	0.047	0.025	NS
HDL cholesterol (mg/dl)	57.72 ± 16.77	56.64 ± 16.75	54.97 ± 15.03	NS	0.016	NS
Insulin (μl U/ml)	12.48 ± 6.32	12.27 ± 7.14	14.51 ± 7.90	NS	0.047	0.023
Creatinine (ml/min)	1.04 ± 0.22	1.05 ± 0.24	1.19 ± 0.30	NS	0.0001	0.0001
Serum Na (mg/dl)	140.4 ± 32.21	140.38 ± 2.62	139.28 ± 3.70	NS	0.031	0.032
Serum K (mg/dl)	4.08 ± 0.40	4.17 ± 0.51	4.61 ± 0.56	NS	0.0001	0.0001
Uric acid (mg/dl)	5.98 ± 1.39	6.00 ± 1.51	6.37 ± 1.45	NS	0.052	NS
Creatinine clearance (mg/dl)	84.58 ± 27.03	90.08 ± 27.16	79.25 ± 25.50	NS	NS	0.020

HDL, high-density lipoprotein; P1, dual blockade versus baseline; P2, spironolactone versus baseline; P3, spironolactone versus dual blockade; NS, not significant.

In the second stage of treatment with SPR, BP dropped to 126.2 ± 19.0/69.5 ± 11.7 mmHg in office BP readings (reduction of 32.2 ± 20.6/10.9 ± 11.6 mmHg). As measured by ABPM, levels of 120.1 ± 15.4/68.9 ± 9.7 mmHg were achieved (reduction of 20.8 ± 14.6/8.8 ± 7.3 mmHg). All BP reductions were statistically significant ($P < 0.001$) (Table 2).

Comparing BP at the end of both treatment regimes, statistically significant differences were found in antihypertensive efficacy favoring SPR, both on office BP measurements and by ABPM ($P < 0.0001$) (Table 2).

The drop in 24-h pulse pressure as measured by ABPM was of a greater magnitude following treatment with SPR (12 ± 8.5 mmHg) than with dual blockade with ACE-I + ARB (3.7 ± 9.0 mmHg) ($P < 0.0001$) (Fig. 1).

Office BP control (<140 and <90 mmHg) was achieved in 25.6% of patients with dual blockade and in 53.8% of those on SPR. As measured by ABPM, control was achieved in 20.5% of those with dual blockade and in 56.4% of those receiving SPR (Fig. 2).

Despite this improvement in BP control, the percentage of nondipping patients remained unchanged in both treatment groups.

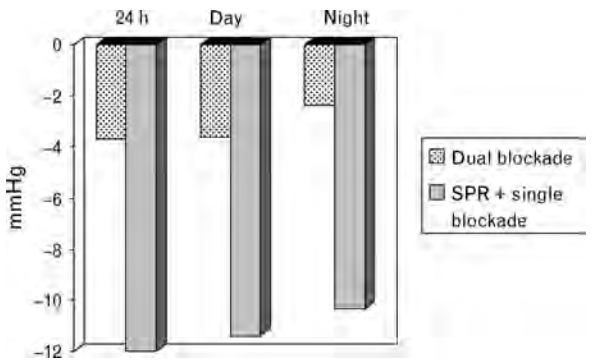
Throughout the antimineralocorticoid-receptor blocker treatment phase, there were a greater number of changes in metabolic profile and renal function compared to the dual blockade phase. We found significant rises in creatinine and serum potassium levels and reduction in serum sodium. Other metabolic changes included higher insulin levels and reduction in HDL cholesterol and Apo A and B (Table 3).

In this study the relationship between serum potassium levels, ARR and the BP-lowering effect at the end of treatment did not reach statistical significance. This was also true for LV telediastolic volume or left ventricle mass index (measured by echocardiogram) and the reduction in BP levels. There was a generalized tendency seen, albeit at the limit of statistical significance, of higher ARR on entry into the study producing a greater reduction in BP at the end. Likewise a higher potassium and left ventricle volume at baseline were associated with a lesser reduction in BP; lower levels of potassium at the beginning of the study could predict a greater response to SPR ($P < 0.079$) (Table 4).

Discussion

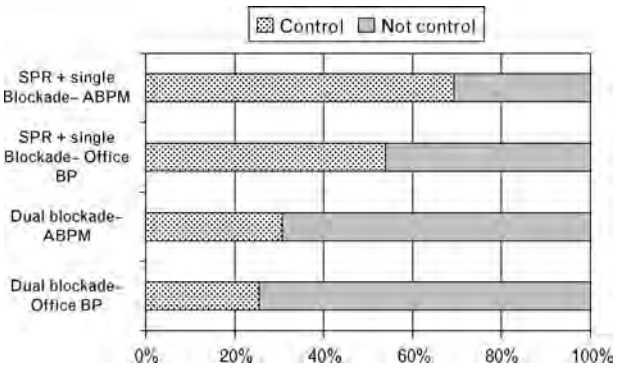
Our study clearly shows the superiority of low-dose SPR on BP levels in patients with resistant hypertension and

Fig. 1



Difference in pulse pressure reduction (measured by ambulatory blood pressure monitoring) between dual blockade and spironolactone. ABPM, ambulatory blood pressure monitoring.

Fig. 2



Percentage of hypertensive patients controlled by dual blockade and spironolactone (in office and by ambulatory blood pressure monitoring). ABPM, ambulatory blood pressure monitoring.

Table 4 Relationship between baseline levels of the PRA/ALD, serum K, LVD and the antihypertensive response in both treatment arms

	Reduction in SBP		Reduction in DBP	
	r Pearson	*P*	*r* Pearson	*P*
End of treatment				
ARR	0.239	0.143	0.046	0.779
Serum K	−0.140	0.395	−0.049	0.768
LVD	−0.026	0.876	0.036	0.828
Dual blockade				
ARR	0.225	0.168	0.049	0.765
Serum K	−0.026	0.875	0.040	0.810
LVD	0.082	0.626	0.173	0.299
Spironolactone				
ARR	0.148	0.370	0.018	0.914
Serum K	−0.284	0.079	−0.170	0.302
LVD	−0.215	0.196	−0.207	0.212

ARR, aldosterone–renin ratio; LVD, left ventricle diameter.

normal renal function versus dual blockade of the RAA axis. These results support the choice of SPR as a fourth or fifth drug because of its greater antihypertensive effect compared to that of double blockade of the RAAS via ACE-I and ARB.

This data is similar to that described by other authors in prospective studies. Ouzan *et al.* [16] obtain a similar reduction in BP by ABPM in hypertensive patients not controlled with two or more drugs and with normal renal function, and with similar doses to those we have used. The reduction in office SBP in our study (−32.16/−10.94) was greater than that obtained by Nishizaka *et al.* [17] with a mean daily SPR dose of 30 mg (−26/11 mmHg) in younger patients (58 years) and with similar BMI (32.4 kg/m^2).

Retrospective studies have also shown the potent BP-lowering effect of SPR. Sharabi *et al.* [18] reported a drop of 23.3/12.5 mmHg and Lane *et al.* [19] using SPR as additional therapy as part of routine clinical practice achieved a reduction in BP of 21.7/8.5 mmHg. Chapman *et al.* [20], in a retrospective study of 1411 participants in the ASCOT study describe the use of SPR as a fourth drug (between 25 and 50 mg) when BP control is not achieved after an average of 3.2 years of randomization and with 2.9 antihypertensive drugs, with this treatment producing a reduction in BP of 21.9/9.5 mmHg without relationship to age, sex, smoking or the presence of diabetes mellitus.

Although dual blockade reduces BP, it is not to the same magnitude as SPR. Dual therapy with ACE-I and ARB reduces the office SBP less than half than that seen with SPR and two-thirds less in ABPM. It also does not affect office DBP and only reduces DBP measured by ABPM half as well as the antimineralocorticoid-receptor treatment.

The BP-lowering effect of this combination has been shown in other studies [21], but its usefulness to reduce cardiovascular morbid-mortality in high-risk patients has not been shown [22]. Although dual blockade has been proposed as a possible therapeutic option in resistant hypertension, at present some experts warn against this combination in essential hypertension [23,24]. For this reason, recommendation of double blockade of the RAA axis as fourth or fifth option in patients with resistant hypertension and normal renal function is not advisable.

Aldosterone is involved in the genesis and maintenance of arterial hypertension, and therefore an overproduction of this hormone could contribute to the pathogenesis of resistant hypertension [25]. This could also be the explanation behind the partial failure in BP control of some conventional antihypertensive therapies in patients with high levels of aldosterone. Some studies have shown that high circulating levels of aldosterone increase the risk of poor arterial hypertension control, despite the lack of underlying hyperaldosteronism [26].

Eide *et al.* [27] found an association between low levels of renin and resistance to antihypertensive treatments in two-thirds of patients studied with resistant hypertension. In these patients with low renin, SPR produced a greater reduction in BP.

The Laragh hypothesis [28,29] describes SPR as a diuretic with specific and vascular effects, independent of its action on electrolyte and water balance. It also has an inhibitory effect on cardiovascular reaction to the adrenergic system and the RAAS activation [30]. This effect is longer-lasting than that produced by ACE-Is due to the escape phenomenon that occurs with these drugs, which is not seen with SPR [31].

Whether the greater BP-lowering effect of SPR is due to a more complete mineralocorticoid-receptor blockade or rather due to a more powerful diuretic and anti-adrenergic effect when compared to dual therapy is a question that needs to be answered in future studies.

The use of low-dose SPR has been shown to be safe as well as being potent at lowering BP. In our study, the number of side-effects, mostly hyperkalaemia, resulting in treatment withdrawal was minimal (2.6%). Studies referred to above have also shown this treatment to be safe. In the Chapman study, only 6% of cases resulted in treatment withdrawal due to adverse reactions. In these patients, as seen with ours, there are ionic and creatinine changes without clinical relevance. This data has also been seen in the Lane *et al.* study [19]. On the contrary, our study does not concur with the glycaemic and lipid changes that were also seen.

Clear risk factors for a resistant state were seen in this group of patients with resistant hypertension; advanced age, obesity, high prevalence of LVH, insulin resistance and metabolic syndrome, as our group has shown in a previous study [32]. Some of these factors are not easily modified, and achieving therapeutic targets is made that much more difficult.

The main limitation of this work is that the study is not randomized, with no placebo group and with a small number of patients. On the positive side, it was a cross-over study and that patients had well-defined true resistant hypertension.

In some studies a direct relationship between ARR and BP levels has been shown [6,28]. If the BP-lowering effect of SPR is related to underlying levels of aldosterone, or reduced levels of renin, then ARR would be a good predictor of response to treatment. This currently remains controversial because the results in studies do not always coincide; Pratt-Ubunama *et al.* [13] did not show the predictive value of ARR in BP-lowering response. But on the contrary, Lim *et al.* [5] showed that a raised ARR predicted a good response to SPR. In our study a higher ratio did not significantly predict a more marked BP-lowering effect with SPR, although a tendency was seen.

In our study, all the patients except one, presented overweight/obesity, this could explain the good antihypertensive response to SPR. It is well known that overweight and obesity are conditions that stimulate adrenal production of aldosterone. Human adipocytes produce an as-yet unidentified mineralocorticoid-releasing factor that stimulates adrenal aldosterone production by means of paracrine or endocrine mechanisms [33,34]. Weight reduction decreases plasma aldosterone levels and improves insulin sensitivity in both normotensive and hypertensive patients [35,36], which is further evidence of the interrelationship between excess aldosterone and fat tissue. Collectively, these effects suggest that obesity is associated with increased aldosterone production.

Performing ARR and the withdrawal of antihypertensive medication is controversial. Davidson [37] and Schwartz and Turner [38] showed the usefulness of ARR without drug withdrawal. Mahmud *et al.* [39] showed that the predictive value of the ratio and response to SPR depends on whether patients received prior treatment or not; in those patients who had not received prior antihypertensive treatment then an elevated ratio was predictive of the BP-lowering effect, but this was not true of patients having been treated with other drugs. These contrasting results may be due to patients being treated with antihypertensive that confound ARR, but it would not be ethical for these high-risk patients to undergo wash-out to perform a more realistic ratio.

The relationship between serum potassium levels and the response to SPR remains controversial. In the work done by Sharabi *et al.* [18], low potassium levels (<4 mmol/l) were associated with a greater reduction in BP. In this group, patients who improved with SPR had lower baseline potassium levels, higher LVM, and a slightly more severe grade of AHT. In our study, lower baseline potassium levels show a tendency ($P < 0.07$), although nonsignificant, to a better BP-lowering response to SPR. We did not find a relationship between LVM and LV volume, possibly because the overwhelming majority of our patients already had baseline LVH.

In conclusion, SPR has a greater BP-lowering effect than dual RAAS blockade in resistant hypertension.

SPR at a daily dose of 25–50 mg shows a potent BP-lowering effect when added to prior regimes with single blockade of the RAA axis in patients with resistant hypertension and normal renal function. Furthermore, the prevalence of side-effects is low.

Our study supports the hypothesis recommended by other authors of SPR as fourth-line or fifth-line treatment added to a regime of single RAAS blockade, compared to double blockade with ACE-I and ARB.

In our resistant patients on multiple antihypertensive medications, levels of circulating aldosterone and renin, as well as serum potassium, were shown not to be of clinical use to predict antihypertensive response to either of the treatment regimes used.

Acknowledgements

There are no conflicts of interest.

References

1 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**:1105–1187.

2 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2003; **288**: 2981–2997.

3 Lim PO, Dow E, Brennan G, Jung RT, McDonald TM. High prevalence of primary aldosteronism in the Tayside hypertensive clinic population. *J Hum Hypertens* 2000; **14**:311–315.

4 Lim PO, Rodgers P, Cardale K, Watson AD, McDonald TM. Potentially high prevalence of primary aldosteronism in a primary-care population. *Lancet* 1999; **353**:40.

5 Lim PO, Jung RT, MacDonald TM. Raised aldosterone to renin ratio predicts antihypertensive efficacy of spironolactone: a prospective cohort follow-up study. *Br J Clin Pharmacol* 1999; **48**:756–760.

6 Newton-Cheh Ch, Guo ChY, Gona P, Larson MG, Benjamin EJ, Wang TJ, *et al.* Clinical and genetical correlates of aldosterone-to-renin ratio and relations to blood pressure in a community sample. *Hypertension* 2007; **49**:846–856.

7 Takeda Y, Furukawa K, Inaba S, Miyamori I, Mabuchi H. Genetic análisis of aldoterone synthase in patients with idiopathic aldosteronism. *J Clin Endocrinol Metab* 1999; **84**:1633–1637.

8 Stergiou GS, Skeva II, Baibas NM, Roussias LG, Kalkana CB, Achimastos AD, Mountokalakis TD. Additive hypotensive effect of angiotensin-converting enzyme inhibition and angiotensin-receptor antagonism in essential hypertension. *J Cardiovasc Pharmacol* 2000; **35**:937–941.

9 Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper IME. Randomised controlled trial of dual blockade of renin–angiotensin system in patients with hypertension, microalbuminuria, and noninsulin dependent diabetes: the Candesartan and Lisinopril Microalbuminuria (CALM) Study. *BMJ* 2000; **321**:1440–1444.

10 Moser M, Setaro JF. Resistant or difficult to control hypertension. *N Engl J Med* 2006; **355**:385–394.

11 Nakao N, Seno H, Kasuga H, Toriyama T, Kawahara H, Fukugawa M. Effects of combination treatment with Losartan and Trandolapril on office and ambulatory blood pressures in non-diabetic renal disease: a COOPERATE-ABP substudy. *Am J Nephrol* 2004; **24**:543–548.

12 MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; **48**:8–20.
13 Pratt-Ubunama MN, Nishizaka MK, Calhoun DA. Aldosterone antagonism: an emerging strategy for effective blood pressure lowering. *Curr Hyperten Rep* 2005; **7**:186–192.
14 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, *et al.* Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society. *J Hum Hypertens* 2004; **18**:139–185.
15 Berecek KH, Farag A, Bahtiyar G, Rothman J, McFarlane SI. Adding low-dose spironolactone to multidrug regimens for resistant hypertension. *Curr Hypertens Rep* 2004; **6**:211–212.
16 Ouzan J, Perault C, Lincoff AM, Carré E, Mertes M. The role of spironolactone in the treatment of patients with resistant hypertension. *Am J Hypertens* 2002; **15**:333–339.
17 Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003; **16**:925–930.
18 Sharabi Y, Adler E, Shamis A, Nussinovitch N, Markovitz A, Grossman E. Efficacy of add-on aldosterone receptor blocker in uncontrolled hypertension. *Am J Hypertens* 2006; **19**:750–755.
19 Lane DA, Shah S, Beevers DG. Low-dose spironolactone in the management of resistant hypertension: a surveillance study. *J Hypertens* 2007; **25**:891–894.
20 Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR, on behalf of the Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007; **49**:839–845.
21 Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, *et al.* Resistant hypertension: diagnosis, evaluation and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; **51**:1403–1419.
22 ONTARGET investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Degenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**: 1547–1559.
23 Messerli FH. The sudden demise of dual renin–angiotensin system blockade or the soft science of the surrogate end point. *J Am Coll Cardiol* 2009; **53**:468–470.
24 2009 CHEP Recommendations for the Management of Hypertension. http://hypertension.ca/chep.
25 Tamargo J, López-Sendón J. Rationale and clinical evidence for the effects of new pharmacological treatments for heart failure. *Rev Esp Cardiol* 2004; **57**:447–464.
26 Sartori M, Calò LA, Mascagna V, Realdi A, Macchini L, Ciccariello L, *et al.* Aldosterone and refractory hypertension: a prospective cohort study. *Am J Hypertens* 2006; **19**:373–379.
27 Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP. Low-renin status in therapy-resistant hypertension a clue to efficient treatment. *J Hypertens* 2004; **22**:2217–2226.
28 Laragh JH. Laragh's lessons for treating hypertension. *Am J Hypertens* 2001; **14**:84–89.
29 Laragh JH, Sealey JE. Relevance of the plasma renin hormonal control system that regulates blood pressure and sodium balance for correctly treating hypertension and for evaluating ALLHAT. *Am J Hypertens* 2003; **16**:407–415.
30 Schohn DC, Jahn HA, Pelletier BC. Dose-related cardiovascular effects of spironolactone. *Am J Cardiol* 1993; **71**:40A–45A.
31 Staessen J, Lijnen P, Fagard R, Verschuren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol* 1981; **91**:457–465.
32 Martell N, Rodriguez-Cerrillo M, Grobbee DE, Lopez-Eady MD, Fernandez-Pinilla C, Avila M, *et al.* High prevalence of secondary hypertension and insulin resistance in patients with refractory hypertension. *Blood Pressure* 2003; **12**:149–154.
33 Lamounier-Zepter V, Ehrhart-Bornstein M. Fat tissue metabolism and adrenal steroid secretion. *Curr Hypertens Rep* 2006; **8**:30–34.
34 Goodfriend TL, Ball DL, Egan BM, Campbell WB, Nithipatikom K. Epoxy-keto derivative of linoleic acid stimulates aldosterone secretion. *Hypertension* 2004; **43**:358–363.
35 Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. *N Engl J Med* 1981; **304**:930–933.
36 Dall'Asta C, Vedani P, Manunta P, Pizzocri P, Marchi M, Paganelli M, *et al.* Effect of weight loss through laparoscopic gastric banding on blood pressure, plasma renin activity and aldosterone levels in morbid obesity. *Nutr Metab Cardiovasc Dis* 2009; **19**:110–114.
37 Davidson RC. Discontinuation on antihypertensives unnecessary before aldosterone screening. *Am J Kidney Dis* 2001; **37**:699–705.
38 Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of the plasma aldosterone concentration to plasma renin activity. *Clin Chem* 2005; **51**:386–394.
39 Mahmud A, Mahgoub M, Hall M, Feely J. Does aldosterone-to-renin ratio predict the antihypertensive effect of the aldosterone antagonist spironolactone? *Am J Hypertens* 2005; **18**:1631–1635.