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COMMENTARY

Mineralocorticoid receptor antagonism as an add-on treatment for resistant hypertension

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INTRODUCTION

Despite the availability of >100 antihypertensive drugs, which may be used as a monotherapy or as combination therapy, a substantial proportion of hypertensive patients continue to have blood pressure (BP) values that far exceed the desirable values, based on their levels of risk worldwide.[1] The hypertension community has recognized this considerable problem, which has been grown like a Hydra, and have therefore introduced the concept of refractory, or drug-resistant hypertension (RH), which is defined in Table 1.[2] Given the importance of salt and water retention and body fluid volume expansion as mechanisms of drug resistance, both the ESH/ESC Guidelines definition and the AHA Scientific Statement note the importance of including a diuretic in any drug cocktail. However, neither set of guidelines explicitly states that a mineralocorticoid receptor antagonist (MRA), a drug proven to be effective in correcting salt and water retention, should be an indispensable ingredient of this cocktail. Both clinical experience and evidence from clinical trials such as ASCOT and ASPIRANT have demonstrated that MRAs lowers BP in patients with RH.[3–5] Furthermore, when added to other antihypertensive drugs, spironolactone (25–100 mg per day) reduces BP.[6,7] Unfortunately, the majority of these studies were uncontrolled, nonrandomized and open-label investigations, and included poorly characterized patients. Moreover, in the only randomized, double-blinded, controlled study using 25 mg spironolactone, which documented a decrease of daytime ambulatory systolic BP of 5.4 mm Hg compared with the study's control group, 24% of patients with RH were found to have secondary forms of hypertension,[4] a substantial number of which were the result of primary aldosteronism (PA). This phenomenon may explain the effectiveness of MRAs in RH patients, which will be discussed in greater detail in this text. Undetected PA among RH patients may also account for the negative findings of a recently published trial involving similar patients, the SIMPLICITY-3 trial,[8] an investigation in which sympathetic renal denervation failed to demonstrate its superiority in lowering BP over a 'sham' procedure, as a higher proportion of patients in the denervated group were put on an MRA compared with the sham group (28% *vs.* 21%), a difference that most likely did not achieve statistical significance due to the lack of statistical power.

The following two questions have subsequently arisen: (1) why are MRAs effective in some patients with RH but not in others? (2) How do we identify those patients who are more likely to respond to treatment?

WHY ARE MRAs EFFECTIVE AGAINST RESISTANT HYPERTENSION?

The efficacy of MRAs in lowering BP in patients with RH may be explained based on several features of this drug class, features listed in Table 2. They include the targeting of pressor mechanisms, such as mineralocorticoid receptors and related pathways, which are not adequately antagonized by other classes of widely used antihypertensives, as well as a more complete blockade of Na^+ and water resorption by nephrons, as recently demonstrated.[6] Antagonism of secondary aldosteronism, which is triggered by diuretic-induced activation of the renin–angiotensin-aldosterone system, is an additional mechanism by which this class exerts its effects.[5] Furthermore, relative hyperaldosteronism exists in many patients, such as those with metabolic syndrome, most likely as a consequence of excess body fat deposition.[9] Additionally, mineralocorticoid receptors have extra-renal effects,[10] including activation of the sympathetic nervous system,[11] mediation of endothelial dysfunction[12] and vasoconstriction,[13] which occurs due to the activation of human vascular smooth muscle cells.[14] Finally, individual and racial differences in vasculature sensitivity to mineralocorticoid receptor activation exist: in fact, blacks exhibit lower plasma renin activity levels and plasma aldosterone levels than whites, their BPs correlate directly with plasma aldosterone concentrations and increase with the administration of 9-α fludrocortisone, an effect not observed in whites.[15]

However, perhaps the most important mechanism of BP responsiveness to MRAs in patients with RH is unrecognized PA,[16] a highly prevalent and generally overlooked cause of hypertension in patients referred to specialized hypertension centers,[17] particularly those who are 'resistant' to therapy. The under-diagnosis of PA is most likely a result of the difficulties encountered by clinicians in evaluating patients' endocrine and biochemical profiles, as patients with RH require multiple drugs, the majority of which profoundly affect the renin–angiotensin-aldosterone system,[18] thus impeding a 'clean' assessment of the aldosterone-to-renin ratio.

Shlomai[19] addressed the challenging task of treating RH with an MRA by undertaking a retrospective study of 48 hypertensive patients with overt signs of target organ damage. More than two-thirds (70.4%) of these patients had

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Table 1 Definitions of resistant hypertension according to major scientific societies

Society/year/ref	*Definition*
AHA scientific statement, 2008	'… blood pressure … above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic…'
	'… patients whose blood pressure is controlled but require 4 or more medications to do so …'.
Arterial hypertension ESH/ESC guidelines, 2013[2]	'… when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower SBP and DBP values to 140 and 90 mm Hg, respectively.'

Table 2 Possible mechanisms of BP-lowering with MRA in resistant hypertension patients

Targeting of pressor mechanisms not antagonized by other antihypertensive drugs
Counteraction of the secondary hyperaldosteronism triggered by medications (e.g., diuretics)
Decrease of vascular stiffness
Decrease of vascular tone
Improvement of endothelial function
More complete blockade of Na^+ reabsorption along the nephron (e.g., more effective natriuresis)
Individual and/or racial hypersensitivity to MRA
Relative hyperaldosteronism in patients with the metabolic syndrome (e.g., secondary to overweight-obesity)
Unidentified primary aldosteronism

Abbreviations: BP, blood pressure; MRA, mineralocorticoid receptor antagonist.

left ventricular hypertrophy, and almost one-third (30.8%) had microalbuminuria, both of which are typical findings in patients with RH who are known to be at increased cardiovascular risk. Spironolactone exhibited significant (−9 mm Hg) BP-lowering effects in these patients, which is not surprising given the well-known efficacy of MRAs in patients with RH.[4–7] The authors addressed these BP-lowering effects from a slightly different perspective, however, as they attempted to identify predictors of spironolactone responsiveness.

HOW DO WE IDENTIFY THOSE PATIENTS WHO ARE MORE LIKELY TO RESPOND TO MRA TREATMENT?

Shlomai[19] observed a heterogeneous BP response in their patients, which prompted them to investigate the patients who were more responsive to therapy. They defined a 'satisfactory' BP reduction as a percentage change of >10% compared with baseline values. They discovered that a baseline potassium level <4.5 mequiv. l^{-1} was a predictor of this 'satisfactory' BP response. Regression analysis revealed that for each 1 mequiv. l^{-1} decrease in serum K^+, a satisfactory decrease in BP was five times as likely to occur, a phenomenon that was independent of older age, BMI or high baseline systolic BP.

These observations are consistent with previous findings by the same group, who found that patients with essential hypertension and serum potassium levels were <4.0 mequiv. l^{-1} exhibited greater responsiveness to MRAs in terms of both systolic BP ($P=0.04$) and diastolic BP ($P=0.01$), than patients with serum potassium levels above this threshold.[20] The value of low serum K^+ level as a predictor of BP response also confirms data collected by Vaclavik *et al.*,[4] who reported that it was possible to predict the BP-lowering efficacy of MRAs by adding low serum K^+ to a high aldosterone–renin ratio (>7) and a low plasma renin activity value ($\leqslant$1.34 ng ml^{-1} h^{-1}), features suggestive of mild PA. Therefore, the authors concluded that their results support the practice of utilizing MRAs for patients with RH and serum K^+ levels <4.5 mequiv. l^{-1}, particularly if these patients are elderly and obese.[19]

STRENGTHS AND LIMITATIONS OF THIS STUDY

The authors should be commended for their attempts to identify predictors of MRA responsiveness in patients with RH, as well as for obtaining results that may be useful to physicians caring for these types of patients.

Some limitations of their study should be noted, however. These limitations include the study's retrospective design and small size, both of which allow for the possibility of selection bias and serendipitous results, as well as the study's lack of mechanistic information. Moreover, although the authors initially evaluated their patients for secondary hypertension according to 'standard clinical protocols', it is not entirely clear how they accomplished this task. The chances of detecting such disease processes, particularly PA,[17] are related to the diagnostic approaches utilized by investigators. As mentioned above, interpretation of the aldosterone–renin ratio is challenging in patients with RH who are being treated with multiple drugs. Patients with RH usually present either with evidence of target organ damage or with evidence of cardiovascular disease and are therefore at increased risk for cardiovascular events. Hence, it is usually not feasible to withdraw or down-titrate their medications. Therefore, one cannot be certain that these patients were excluded beforehand. The authors acknowledged this possibility when discussing their findings.

Moreover, even though the authors did not provide any data regarding differences in MRA dosing between patients with high baseline serum K^+ and patients with low baseline serum K^+, it is conceivable that the onset of hyperkalemia in patients with serum K^+ levels >4.5 mequiv. l^{-1} may have limited subsequent increase in MRA dosage, a crucial step in increasing the proportion of patients responsive to treatment.[10]

This study also falls short from a mechanistic standpoint, as it remains unclear whether the effectiveness of spironolactone is related to the favorable effects of MRAs on arterial stiffness, the attenuation of sympathetic tone or the improvement of endothelial function, all of which represent documented effects of MRAs.[11–13]

Uncertainty also remains regarding patients with RH in whom low serum K^+ levels were not reflective of an underlying pathophysiology, but rather, the concomitant administration of K^+ losing diuretics. This information may be important for framing their findings in the proper context.

Notwithstanding these limitations, this study is important in that it highlights the predictive role of serum K^+ level, a measurement that is inexpensive and widely available, but requires utmost attention to avoid haemolysis during blood drawing. Accordingly, serum K^+ levels may be used extensively to identify those patients in whom an MRA will be most effective.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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