

# Mineralocorticoid receptor antagonists, sleep apnea, and resistant hypertension: a consolidated relationship

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Mineralocorticoid receptor antagonists (MRAs) are a growing group of medicines, increasingly prescribed for cardiovascular disorders. There is clear evidence that they improve outcomes in patients with chronic heart failure (CHF) caused by left ventricular systolic dysfunction.<sup>1,2</sup> They have also proved beneficial in hypertensive patients and mainly in those with resistant arterial hypertension (RAH).<sup>3,4</sup> Major international guidelines recommend this group of drugs as therapy for both cardiovascular diseases.<sup>5,6</sup>

Obstructive sleep apnea (OSA) is frequently associated with CHF and RAH. It is commonly believed that more than half of all patients with severe OSA are hypertensive.<sup>5,7</sup> The disease has an obvious multifactorial pathogenesis, and the search for a more effective therapeutic approach to the problem shows a growing role of MRAs on top of many other groups of drugs used in these clinical settings. The rationale for this evidence is that blocking the mineralocorticoid receptor inhibits the deleterious mechanisms that cause cardiovascular and respiratory dysfunction and potential organ damage.<sup>4</sup>

OSA is defined as a momentary, often cyclical, cessation of breathing rhythm or momentary or sustained reductions in the breath amplitude, sufficient to cause significant arterial hypoxemia and hypercapnia.<sup>8,9</sup> These changes produce alterations in the basic mechanisms of neural and local control of vascular resistance. In the pathogenesis of OSA, simultaneously with mechanical and chemical changes in respiratory physiology, there is a significant activation of the renin-angiotensin-aldosterone system (RAAS), with a significant increase in plasma levels of aldosterone. It depends mainly on the magnitude of plasma oxygen changes produced by ventilatory disorders. In any case, the stimulation of the RAAS, and more specifically aldosterone, results in hyperactivation of the mineralocorticoid receptor,

which is a crucial factor in the pathogenesis of OSA in patients with RAH. In parallel, respiratory function disorders contribute to a negative feedback with vascular dysfunction. This scientific evidence is the basic rationale for the use of MRAs in this population of patients.<sup>9-11</sup>

In the current issue of the *Polish Archives of Internal Medicine (Pol Arch Med Wewn)*, Krasinska et al<sup>12</sup> published a very interesting article with a provocative title: “Effect of eplerenone on the severity of obstructive sleep apnea and arterial stiffness in patients with resistant arterial hypertension”. The study included 31 patients with RAH and OSA in whom other causes of this respiratory dysfunction were excluded. The patients received 50 mg of oral eplerenone daily, in addition to other drugs, and examinations were done before and after 3 months of MRA therapy. The authors used an accurate methodology that includes several tests evaluating cardiovascular and respiratory function. After a solid and detailed discussion, the authors concluded that the data provided another piece of evidence confirming the clinical significance of eplerenone not only as an antihypertensive agent, but also as a drug that may reduce the severity of OSA and arterial stiffness in patients with RAH and OSA.<sup>12</sup>

In addition to the references included in the article, the above findings were confirmed by a very recent meta-analysis published by Dahal et al.<sup>13</sup> The authors included 15 studies (3 randomized controlled trials, 1 nonrandomized comparative study, and 11 single-arm studies) with a total of 1204 patients. They concluded that aldosterone antagonists are a safe and effective therapy in patients with RAH.<sup>13</sup>

**Therapeutic tips** The therapeutic management of sleep disorders in patients with RAH includes a large number of tools. One approach focuses on the “ventilatory aspect” of the problem. Certainly,

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continuous positive airway pressure (CPAP) prevents airway obstruction in patients with OSA. The effects of CPAP treatment on nighttime blood pressure are also beneficial; however, the treatment is not well tolerated by all patients.<sup>8,9</sup> Alternatively, several drugs with serotonin influences have been studied in clinical trials. Both serotonergic and serotonin receptor antagonists have been tested for effectiveness in reducing OSA-disordered breathing, but none of the compounds have proved significant and widely effective. Pharmacologically induced stimulation of respiratory motor output via such agents as carbonic anhydrase inhibitors (hydroxytryptamine) have been also proposed.<sup>9</sup>

As for the cardiovascular aspect, many drugs have been used so far. Interventions in the RAAS are the first-line option. Among them, the growing role of MRAs has been observed.<sup>14,15</sup> As to the choice of drugs for individual patients, Iqbal et al<sup>4</sup> emphasized in their outstanding review that there is a paucity of direct comparative data for spironolactone and eplerenone. It may not be appropriate to compare trials using spironolactone or eplerenone in cardiovascular disorders directly due to vast differences in patient populations and trial designs. The choice of a specific agent could be based on clinical indications (such as the nature of heart failure), individual patient factors (such as sex, comorbidities, side effects), geographical licensing restrictions, and community-level cost-benefit analysis.<sup>4</sup> However, it should be also considered that many patients with RAH and OSA suffer from related clinical disorders. Obesity, dyslipidemia, and renal dysfunction are the most frequent and they must be taken into account in the management of such population. In particular, obesity has been clearly described as a negative factor influencing respiratory function and aggravating the full pathophysiology of patients with RAH and OSA.<sup>15,16</sup>

**Summary** In conclusion, there is clear evidence for the relationship between RAH and OSA. Many common pathways are described in the pathogenesis of both clinical conditions. The role of the mineralocorticoid receptor is very important, and the use of MRAs appears to be a therapeutic tool with growing beneficial effects in patients with concomitant RAH and OSA.

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