Sleep Apnea, Aldosterone, and Resistant Hypertension

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Obstructive sleep apnea, aldosterone excess, and resistant hypertension are common comorbidities in obese patients. The mechanisms that link these conditions are not fully elucidated, but sympathetic nervous system activation, sodium retention, renin-angiotensin-aldosterone system stimulation, endothelial dysfunction, and increased production of reactive oxidative species may be contributing factors. Patients diagnosed with this triad should be treated with low-salt diet, weight-loss counseling, and continuous positive airway pressure, as well as aggressive antihypertensive therapy, usually with multiple agents, including a mineralocorticoid receptor antagonist. Patients with aldosterone-producing adenoma may require adrenalectomy.

Obstructive sleep apnea (OSA) is an independent risk factor for systemic hypertension.[1-3] Resistant hypertension (RH), defined as blood pressure (BP) that remains above goal despite the use of 3 antihypertensive medications in effective doses, ideally including a diuretic, is particularly common in patients with OSA.[4-6] The BP goal is less than 140/90 mm Hg in the general population of hypertensives and less than 130/80 mm Hg in high-risk hypertensive patients, including those with diabetes, chronic kidney disease, or coronary heart disease. Patients who are intolerant of diuretics and have uncontrolled BP on regimens of 3 drugs from other classes or who require 4 or more medications to control their BP are considered to have RH.

Primary aldosteronism (PA), a clinical condition in which aldosterone is produced in excess and renin is suppressed, is common in patients with RH,[7,8] and recent studies have suggested that aldosterone excess may play a pathophysiological role in the relation between hypertension and OSA.[9-11] Obesity is common in patients with OSA, aldosterone excess, and RH, and potentially links these conditions.

Epidemiology

Primary Aldosteronism

Primary aldosteronism has a prevalence of approximately 20% in patients with RH. In an evaluation of patients referred to our hypertension specialty clinic, we found that 18 (20%) of 88 consecutively evaluated patients with RH were diagnosed with PA based on a suppressed plasma renin activity (PRA; <1.0 ng/mL per hour) and a high 24-hour urinary aldosterone excretion (>12 μg/d) in the course of a high dietary sodium intake (>200 mEq/d).[7] A similar prevalence of PA in patients with RH has been reported in a number of distinct patient populations (Fig 1).

In a study conducted in Seattle, Washington, 90 patients with poorly controlled hypertension despite the use of multiple antihypertensive medications were screened for PA.[12] Primary aldosteronism was diagnosed in 17% of patients with RH based on a high (>100) plasma aldosterone concentration (PAC; in nanograms per deciliter) to PRA (in nanograms per milliliter per hour) ratio (ARR). Similarly, in an evaluation of 90 treatment-resistant hypertensive patients investigators in Oslo, Norway, found a prevalence of PA of 23% based on a high PAC (>400 pmol/L) and/or urinary aldosterone excretion (>50 nmol/d).[13] Lastly, investigators in Prague, Czech Republic, evaluated more than 400 patients with moderate/severe hypertension. Based on a high (≥50) ARR (PAC in nanograms per 100 milliliters/PRA in nanograms

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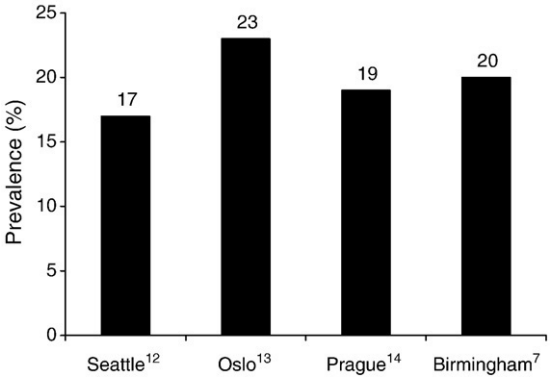

Fig 1. Prevalence of PA in patients with RH.

per milliliter per hour) and failure to suppress PAC with saline infusion, 19% of the patients were found to have PA.[14] Primary aldosteronism is less common in unselected patients with general hypertension. In the Primary Aldosteronism Prevalence in Hypertensives Study, 126 (11.2%) of 1125 of newly diagnosed hypertensive patients had PA.[15]

Obstructive Sleep Apnea

Obstructive sleep apnea is a strong and independent risk factor for the presence and future development of hypertension.[1,2,16,17] A cross-sectional evaluation of 1190 consecutive patients referred for evaluation of possible sleep-disordered breathing demonstrated a positive linear association between the respiratory disturbance index and BP.[1] The relative risk of hypertension increased as the respiratory disturbance index increased, suggesting that OSA is related to hypertension. In the Wisconsin Sleep Cohort Study, 709 participants were followed for 4 years after polysomnography (PSG).[2] The authors found a dose-response association between sleep-disordered breathing at baseline and the presence of hypertension 4 years later that was independent of known confounding factors for hypertension. Cross-sectional studies indicate that the severity of OSA is related to BP and that hypertension occurring in patients with OSA is more likely severe and treatment resistant.[1,4] In 42 patients with RH referred to a university center, Logan et al[5] found that 83% of patients had unsuspected OSA (apnea-hypopnea index [AHI], ≥10/h). In our population, 85% of patients with RH had OSA (AHI, ≥5/h).[11]

The prevalence of OSA is approximately 20% in the general population and ranges from 23% to 35% in an unselected hypertensive population.[18-21] Recognizing that OSA and hyperaldosteronism are both highly prevalent in patients with RH, studies have shown that the 2 conditions are related and may interact on a pathophysiological basis. We previously reported that OSA is related to aldosterone excess.[10,11] Of 114 patients referred to our clinic for RH, those at high risk for OSA were almost twice as likely to have PA, tended to have lower PRA, and had significantly greater 24-hour urinary aldosterone excretion compared with subjects at low risk of OSA. We subsequently reported a significant correlation between aldosterone levels and OSA severity in patients with RH.[11] The PAC was positively and significantly correlated with AHI in

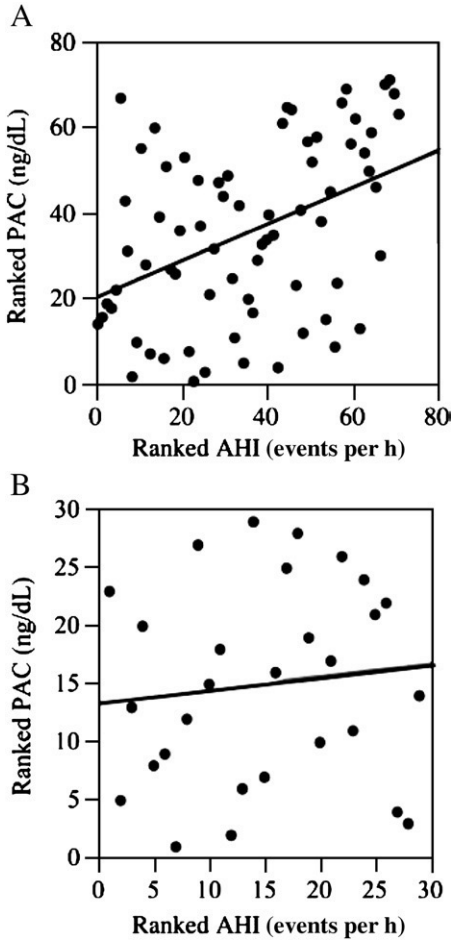

Fig 2. The AHI correlates with plasma aldosterone in patients with RH (ρ = 0.44, ρ = .0002; A), but not in normotensive or controlled hypertensive subjects (ρ = 0.12, ρ = .52; B). Reprinted from Pratt-Ubunama et al.[11]