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COMMENTARY

Resistant Hypertension and Untreated Severe Sleep Apnea: Slowly Gaining Insight

Commentary on Walia et al. Association of severe obstructive sleep apnea and elevated blood pressure despite antihypertensive medication use. J Clin Sleep Med 2014;10:835-843.

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Thirty years ago, Kales et al. noted the potential association between hypertension (HTN) and untreated sleep apnea, with HTN patients having a 30% prevalence of sleep apnea, much higher than in age- and sex-matched controls.[1] Then, the Wisconsin Sleep Cohort Study reported that incident HTN was associated with sleep apnea severity, which was further verified by the Zaragoza Sleep Cohort Study in Spain.[2,3] The Zaragoza Study also noted that CPAP therapy lowered the rate of incident HTN.[3] Other CPAP therapy intervention studies and meta-analyses show that CPAP modestly reduces mean blood pressure (BP) with greater effects noted in patients with higher CPAP adherence, blood pressure measurements, and sleep apnea severity, and in those with daytime sleepiness.[4,5] Since, even mild reductions in BP can significantly reduce cardiovascular risk, this finding is significant.

In this issue, Dr. Walia and colleagues report their baseline data from the Heart Biomarker Evaluation in Apnea (Heart BEAT) Study, hypothesizing that severe obstructive sleep apnea (OSA) is associated with persistent elevations of BP, despite medical BP management, in patients with high cardiovascular disease (CVD) risk.[6] This study examined patients with established stable coronary artery disease, or patients having three or more CVD risk factors. Exclusion criteria included heart failure (EF < 30% or NYHA classification > 2), poorly controlled hypertension or diabetes, prior stroke, and absence of HTN. Participants underwent type III sleep testing, and those with an AHI of 15-50 events/hour were included in the study (unless significant oxygen desaturation or central apnea was present). Results show an association between untreated resistant or difficult-to-treat HTN and OSA severity. Participants with severe OSA, compared to those with moderate OSA, had a higher likelihood of having an elevated BP despite being on ≥ 3 BP medicines, including a diuretic (p = 0.01). Those with severe OSA on multiple BP medications had an odds ratio of 4.1 (95% CI, 1.7-10.2) for having elevated BP, a finding not reproduced in participants not on ≥ 3 antihypertensive medications (including a diuretic).[6]

By definition, resistant HTN consists of patients whose HTN is uncontrolled (BP > 140/90 mm Hg) while on 3 or more medications and occurs in approximately 10% to 15% of all hypertensive patients.[7] There is a very high prevalence of OSA in patients with resistant HTN. Logan et al. noted that 96% of men and 65% of women with resistant HTN had AHI ≥ 10 events/hour.[8] Our laboratory at the University of Alabama at Birmingham noted that 90% of men and 77% of women with resistant HTN had an AHI ≥ 5 events/hour.[9]

Since even mild reductions in BP significantly reduce cardiovascular risk, patients with resistant HTN and severe OSA may represent a key population to target with aggressive OSA treatment interventions.[10] Martinez-Garcia et al. examined 194 patients with resistant HTN having an AHI ≥ 15/hour who were randomized to 12 weeks of CPAP or no CPAP.[11] The CPAP group had a 3.1 mm Hg reduction in 24-hour mean BP (p = 0.02) and a 3.2 mm Hg reduction in 24-hour diastolic BP (p = 0.005), without significant changes in 24-hour systolic BP. Also, 35.9% of the CPAP patients had return of the normal nocturnal BP dipper pattern, compared to 21.6% of the patients who did not receive CPAP (p = 0.02; adjusted odds ratio 2.4 [95% CI, 1.2-5.0]).[11] These BP outcomes have the potential to significantly reduce the risk of future cardiovascular events.

Proposed mechanisms whereby severe OSA impacts BP control include endothelial dysfunction (driven by intermittent hypoxia), increased sympathetic activity, hyperaldosteronism, poor medication adherence, and pharmacokinetic alterations or chronic therapeutic effects from untreated OSA.[6]

There is also the possibility that underlying mechanisms associated with resistant HTN could worsen OSA, so that the relationship could be bi-directional, such that treatment of HTN could improve OSA severity. Aldosterone excess is a common cause of resistant HTN, and 20% of our resistant HTN population has biochemical evidence of primary aldosteronism.[12] Interestingly, aldosteronism blockade with spironolactone significantly reduced BP in a small cohort of resistant HTN patients, including in those without biochemical aldosterone excess.[13] It is notable that in Walia's cohort, none of the 28 subjects with elevated BP despite an intensive BP regimen were on an aldosterone blocker.[6] This could partially explain the correlation between uncontrolled BP, despite an intensive BP regimen and OSA severity. Our laboratory has noted a correlation between plasma aldosterone levels and OSA severity in resistant HTN patients.[14] We also observed that spironolactone reduced OSA severity in these patients, despite remaining on a thiazide diuretic.[15] Aldosterone excess mediates chronic fluid retention, so our data support the hypothesis

that aldosterone-mediated chronic fluid retention could impact (worsen) OSA severity.[15] We also noted that increased dietary sodium correlated with OSA severity in patients with resistant HTN and hyperaldosteronism.[16] Although this finding needs to be verified in a randomized controlled trial, we postulate that this aldosterone-induced worsening of OSA may be mediated through increased fluid retention in the surrounding soft tissues of the upper airway.

Friedman et al. noted that a significant spontaneous fluid shift going from the legs to the neck occurs during sleep time in patients with drug-resistant HTN.[17] The AHI strongly correlated with the amount of leg fluid volume displaced.[17] Thus, fluid accumulation in the soft tissues of the upper airway in the neck may partly explain the higher OSA severity in patients with resistant HTN.

In conclusion, OSA severity correlates with poor BP control in patients with significant cardiovascular risk factors and resistant or difficult-to-control HTN.[6] Twelve weeks of CPAP therapy may result in a mild reduction in mean 24-hour BP (3.1 mm Hg) in patients with resistant HTN and an AHI > 15/hour, which has the potential to reduce CVD risk.[9] Mechanisms of the association between resistant HTN and OSA severity are still being elucidated and may be bi-directional.[15] Since spironolactone has the potential to improve BP control and AHI in patients with resistant HTN, spironolactone should be considered, along with CPAP therapy, in these patients.[15,18,19] Future research will define the best management strategies for OSA patients with resistant hypertension; hopefully it will not take another thirty years.

CITATION

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