Resistant Hypertension and Obstructive Sleep Apnea
Is There a Specific Indication for Endovascular Renal Denervation?

Michel Azizi, Laurence Amar, Aurélien Lorthioir

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Despite current knowledge on the management of hypertension and the availability of multiple potent antihypertensive drugs, hypertension remains poorly controlled worldwide, and its prevalence is increasing because of the aging of populations and the obesity epidemic.[1] Part of the patients have resistant hypertension (RHTN) to at least a triple antihypertensive therapy including a diuretic.[2] Aging, male gender, black ethnicity, blood pressure (BP) at detection of hypertension, as well as obesity, diabetes mellitus, a Framingham 10-year coronary risk >20%, chronic kidney disease, and the presence of target organ damage are significantly associated with RHTN.[2] In addition, obstructive sleep apnea (OSA) often associated with hypertension particularly in obese patients, is about almost 4× more frequent in patients with RHTN.[2] Its pathophysiology includes sympathetic overdrive, aldosterone excess[3] as well as possible fluid retention and its nocturnal rostral redistribution from the legs, where it may narrow the upper airway and increase its collapsibility, predisposing to OSA during sleep.[4]

The treatment strategy in RHTN is based on antihypertensive drug escalation, including aldosterone antagonists as fourth line treatment,[5] which may expose to the risk of drug-related adverse events and of nonadherence to treatment. In this context, new device-based approaches aiming to modulate the sympathetic nervous tone including renal denervation (RDN) and baroreceptor stimulation are under development and may improve BP control as well as OSA.[6]

In this issue of the journal, Warchol-Celinska et al[7] suggest a possible interplay between the presence of OSA and the BP lowering response as well as improvement of the apnea/hypopnea index (AHI) after RDN in patients with RHTN. In this small multicenter, open-label, randomized proof-of-concept trial which compared radiofrequency-based RDN to no intervention, in 60 patients with true RHTN and moderate-to-severe OSA, results show a between-group difference in office systolic BP of −17 mm Hg (95% confidence interval, −27 to −6 mm Hg; P=0.002) and in 24-hour systolic BP of −9 mm Hg (95% confidence interval, −17 to −3 mm Hg; P=0.008) in favor of RDN at 3 months (primary end point). After adjustment on baseline values, between-group differences in AHI (secondary end point) and in mean oxygen saturation were significant, especially in patients not on continuous positive airway pressure (CPAP) treatment. However, there were no changes in the Epworth Sleepiness Scale score and no difference in the number of patients being on CPAP treatment after RDN. The precise pathophysiological mechanisms by which RDN may improve OSA remains hypothetical and may involve an RDN-induced decrease in extracellular fluid volumes and a reduction in rostral fluid shifts during sleep as reported for aldosterone antagonists or intensified diuretic therapy,[8] as suggested by the authors (Figure).[7] However, nighttime ambulatory BP values which may more reflect the effects of rostral fluid volume shift during sleep did not differ between the RDN and the control group in their trial.[7]

This is the first trial assessing the effect of RDN on OSA severity as a secondary end point in obese patients with RHTN and OSA. Up to now, the evidence was based on a pooled analysis of 5 small observational studies of 49 patients showing that RDN was associated with a reduction in mean AHI of ≈10 events/hour at 6 months.[9] However, as highlighted by the authors, their study may experience methodological issues including the open study design and the lack of antihypertensive treatment standardization.[6] Finally, the improvement in OSA severity with RDN may not have a clinical relevance: the difference between AHI values measured before and after RDN was small (≈8 events/hour) compared with what is reported with CPAP therapy. Indeed, compared with sham procedure, CPAP was associated with a larger reduction of AHI of ≈34 events/hour, however, with much smaller reduction in ambulatory systolic BP of ≈3 mm Hg than RDN.[10]

In conclusion, the results of this trial on the effects of RDN on OSA severity in patients with RHTN should be considered as preliminary. Additional sham-controlled trials of larger size are needed to further explore this issue. At this stage, RDN for reducing OSA should be still investigational. In the future, it may be complementary to other effective means to reduce severity of OSA, including lifestyle modification, reduction in alcohol consumption, weight loss, exercise, and the use of mandibular advancement devices or CPAP therapy in those with the severe forms of OSA.[10] Moreover, in addition to lifestyle measures and exercise, mandibular advancement devices or CPAP may also be of moderate benefit in terms of lowering BP.[10]

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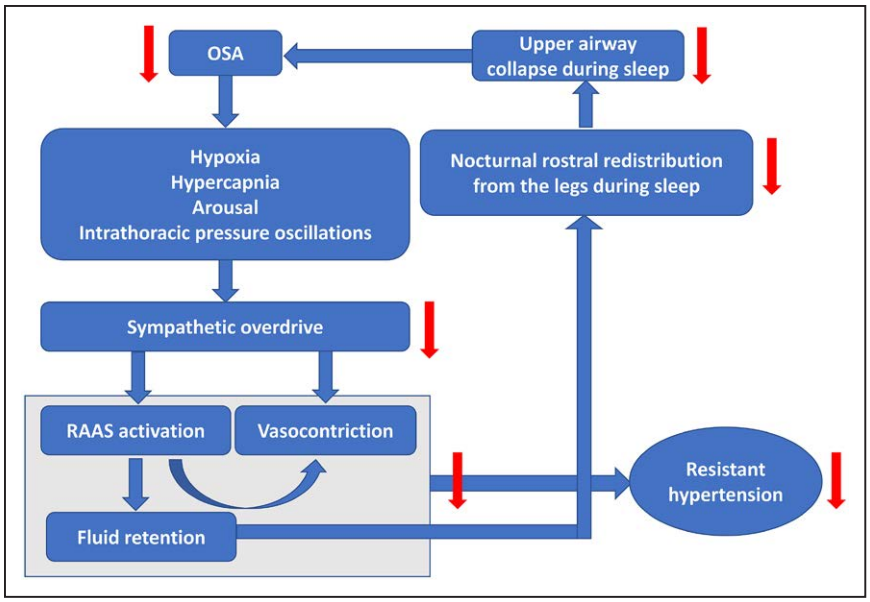

Figure. Obstructive sleep apnea (OSA) is associated with hypoxia, hypercapnia, arousal, and fluctuations of intrathoracic pressure which all contribute to the sympathetic overdrive. Sympathetic activation contributes to vasoconstriction effect and activation of the renin-angiotensin-aldosterone system (RAAS) which induces fluid retention. All these mechanisms participate to resistant hypertension. Fluid retention and its nocturnal rostral redistribution from the legs, where it may narrow the upper airway and increase its collapsibility, predispose to or aggravate OSA during sleep. By modulating the sympathetic drive, renal denervation not only decreases BP in patients with resistant hypertension and OSA but may also decrease extracellular fluid volumes and reduce rostral fluid shifts during sleep (arrows).

Disclosures

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References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–223. doi: 10.1016/S0140-6736(05)17741-1.
2. Bobrie G, Amar L, Faucon AL, Madjalian AM, Azizi M. Resistant hypertension. In: Bakris GL, Sorrentino MJ, eds. *Hypertension: A Companion to Braunwald's Heart Disease*. Philadelphia, PA: Elsevier; 2018:398–408.
3. Dudenbostel T, Calhoun DA. Resistant hypertension, obstructive sleep apnoea and aldosterone. *J Hum Hypertens*. 2012;26:281–287. doi: 10.1038/jhh.2011.47.
4. White LH, Bradley TD, Logan AG. Pathogenesis of obstructive sleep apnoea in hypertensive patients: role of fluid retention and nocturnal rostral fluid shift. *J Hum Hypertens*. 2015;29:342–350. doi: 10.1038/jhh.2014.94.
5. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC 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). *Eur Heart J*. 2013;34:2159–2219. doi: 10.1093/eurheartj/eht151.
6. Mahfoud F, Schmieder RE, Azizi M, et al. Proceedings from the 2nd European clinical consensus conference for device-based therapies for hypertension: state of the art and considerations for the future. *Eur Heart J*. 2017;38:3272–3281. doi: 10.1093/eurheartj/ehx215.
7. Warchol-Celinska E, Prejbisz A, Kadziela J, et al. Renal denervation in resistant hypertension and obstructive sleep apnea: randomized proof-of-concept phase II trial. *Hypertension*. 2018;72:381–390. doi: 10.1161/HYPERTENSIONAHA.118.11180.
8. Kasai T, Bradley TD, Friedman O, Logan AG. Effect of intensified diuretic therapy on overnight rostral fluid shift and obstructive sleep apnoea in patients with uncontrolled hypertension. *J Hypertens*. 2014;32:673–680. doi: 10.1097/HJH.0000000000000047.
9. Shantha GP, Pancholy SB. Effect of renal sympathetic denervation on apnea-hypopnea index in patients with obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath*. 2015;19:29–34. doi: 10.1007/s11325-014-0991-z.
10. Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, Lux L, Harris RP. Screening for obstructive sleep apnea in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;317:415–433. doi: 10.1001/jama.2016.19635.

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