4. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev* 2014;94:265–301.
5. Ständer S, Yosipovitch G. Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus. *Br J Dermatol* 2019; 181:932–938.
6. Mutolo D, Bongianni F, Fontana GA, Pantaleo T. The role of excitatory amino acids and Substance P in the mediation of the cough reflex within the nucleus tractus solitarii of the rabbit. *Brain Res Bull* 2007;74: 284–293.
7. Mazzone SB, Mori N, Canning BJ. Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. *J Physiol* 2005;569:559–573.
8. Hope-Gill BDM, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:995–1002.
9. Fahy JV, Wong HH, Geppetti P, Reis JM, Harris SC, Maclean DB, *et al*. Effect of an NK1 receptor antagonist (CP-99,994) on hypertonic saline–induced bronchoconstriction and cough in male asthmatic subjects. *Am J Respir Crit Care Med* 1995;152:879–884.
10. Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, *et al*. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *J Allergy Clin Immunol* 2014;134:56–62.
11. Pascoe S, Knight H, Chung K. DNK333 a dual NK1/NK2 receptor antagonist does not inhibit cough in COPD [abstract]. *Am J Respir Crit Care Med* 2007;175:A451. [Published retraction appears in *Am J Respir Crit Care Med* 2011;183:418].
12. Smith J, Allman D, Badri H, Miller R, Morris J, Satia I, *et al*. The neurokinin-1 receptor antagonist orvepitant is a novel antitussive therapy for chronic refractory cough: results from a phase 2 pilot study (VOLCANO-1). *Chest* 2020;157:111–118.
13. Smith J, Ballantyne E, Kerr M, Mcgarvey L, Morice A, Sher M, *et al*. Late breaking abstract: the neurokinin-1 receptor antagonist orvepitant improves chronic cough symptoms—results from a phase 2b trial [abstract]. *Eur Respir J* 2019;54:PA600.
14. Menlo Therapeutics Inc. Study of the efficacy, safety, and tolerability of serlopitant for the treatment of refractory chronic cough. Bethesda, MD: U.S. National Library of Medicine, NIH; 2020 [accessed 2020 Sep 27]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03282591.
15. Ratti E, Bettica P, Alexander R, Archer G, Carpenter D, Evoniuk G, *et al*. Full central neurokinin-1 receptor blockade is required for efficacy in depression: evidence from orvepitant clinical studies. *J Psychopharmacol* 2013;27:424–434.

Endotyping in Patients with Obstructive Sleep Apnea and Hypoglossal Nerve Stimulation

The Golden Goal to a Successful Treatment?

In this issue of the *Journal*, Op de Beeck and colleagues (pp. 746–755) report about the different endotypes in patients with obstructive sleep apnea (OSA) and which of these factors have influence on outcomes for hypoglossal nerve stimulation (HGNS) (1). The authors' tremendous work will help future patient selection to be more precise regarding various treatment options. HGNS for patients who are noncompliant with the standard treatment of continuous positive airway pressure (CPAP) therapy has rapidly emerged in the foundational clinical routine in Western industrialized countries (2, 3). Nonetheless, approximately one-third of the patients are incomplete responders, fueling the need for more discerning selection criteria. Op de Beeck and colleagues used polysomnographic data from the STAR trial to assess the pathophysiological mechanisms, namely, arousal threshold, loop gain, collapsibility, and muscle compensation (4). The authors demonstrated that all four key traits were associated with clinical outcomes in HGNS therapy. Somewhat paradoxically, collapsibility was more severe in responders versus nonresponders and arousal threshold higher in patients who responded to HGNS therapy. These results are striking and provide novel insights into the mechanism of HGNS in patients with OSA. Most notably, a high arousal threshold showed a significantly favorable effect on outcomes, which is really surprising, because one would normally expect that a higher arousal threshold is associated with poorer sleep quality and that patients who receive HGNS would complain more about disturbing stimulations during sleep at night. The authors found that a higher arousal threshold at baseline corresponded with a larger therapeutic window for HGNS. However, a plausible, mechanistic explanation of this phenomenon remains elusive. Regarding the critical closing pressure (Pcrit), another interesting point arose. Measuring Pcrit is the gold standard to measure the pharyngeal airway collapsibility (5). As Pcrit increases, the more collapsible the upper airway seems to be. In clinical trials, the Pcrit was associated with therapeutic CPAP pressures (6). Patients with modest collapsibility of the upper airway (lower Pcrit) had a lower therapeutic CPAP level (7). One would also expect that patients with a lower Pcrit would be easier to treat with HGNS. The reverse was, in fact, true. Op de Beeck and colleagues explain this phenomenon by elucidating that lower pharyngeal collapsibility is associated with more nonanatomical deficits underlying the OSA etiology (high loop gain, low arousal threshold). Although compelling, the relatively modest number of patients with severe collapsibility available for this analysis was too low to draw conclusions, and further clinical trials are merited.

Next, a higher loop gain was associated with lower HGNS response, which makes sense, in that a more severe loop gain indicates a more central-OSA phenotype (8). Anatomical factors, which are contributing to OSA in patients with HGNS therapy, are easier to treat versus attempts to solve a hypersensitive ventilatory control.

Originally Published in Press as DOI: 10.1164/rccm.202010-3897ED on November 10, 2020

Regarding the muscular compensation of the upper airway, which is mainly mediated by the genioglossus muscle group, a greater response was found in patients with high muscle compensation (9). From extant studies we know that upper airway muscle activity vis-à-vis OSA is a highly complex process with phenotypic variability. Not only the anatomy and function of the muscles play crucial roles; furthermore, neurological processes can undergird much of the pathophysiology (7). All the more striking were these findings on muscle compensation, and the authors are correspondingly positing the hypothesis that patients with a low muscle compensation cannot transfer the electrical impulse from the HGNS successfully toward dilating upper airway muscles.

Making this groundbreaking analysis even more remarkable, and quite possibly representing a major milestone for further treatment decisions, is the fact that with oral appliances similar characteristics in responders' rates have been detected (10). For both treatment options, the combination of low loop gain, moderate collapsibility, and higher arousal thresholds seems to portend greater likelihood of therapeutic efficacy. Using a cross-validated model and adding these endotypic mechanisms holds promise to improve the outcome parameters.

One major limitation of this study is its retrospective design. The next step to incorporate these findings into clinical routine will be a randomized trial that includes endotyped versus nonendotyped patients with the prevailing (i.e., U.S. Food and Drug Administration–indicated/CE mark) inclusion criteria.

This study raises many important questions. How can we implement measuring these endotypic traits for patient selection in the future? Much careful work will be needed to measure these parameters during polysomnography. Determining which patient-related outcome parameters are relevant should play an increasingly important role in the treatment of patients with OSA.

There is no doubt that we still have much to learn especially about the pathophysiology of OSA and which patients are suitable for which treatment option. Until then, studies such as this one from Op de Beeck and colleagues will continue to add pieces to this puzzle. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Clemens Heiser, M.D., Ph.D., M.H.B.A.
Klinikum rechts der Isar
Technical University of Munich
Munich, Germany

ORCID ID: 0000-0001-6301-2891 (C.H.).

References

1. Op de Beeck S, Wellman A, Dieltjens M, Strohl KP, Willemen M, Van de Heyning PH, *et al*.; STAR Trial Investigators. Endotypic mechanisms of successful hypoglossal nerve stimulation for obstructive sleep apnea. *Am J Respir Crit Care Med* 2021;203: 746–755.
2. Heiser C, Steffen A, Boon M, Hofauer B, Doghramji K, Maurer JT, *et al*.; ADHERE registry investigators. Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. *Eur Respir J* 2019;53:1801405.
3. Thaler E, Schwab R, Maurer J, Soose R, Larsen C, Stevens S, *et al*. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. *Laryngoscope* 2020;130:1333–1338.
4. Woodson BT, Strohl KP, Soose RJ, Gillespie MB, Maurer JT, de Vries N, *et al*. Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. *Otolaryngol Head Neck Surg* 2018;159:194–202.
5. Carberry JC, Jordan AS, White DP, Wellman A, Eckert DJ. Upper airway collapsibility (Pcrit) and pharyngeal dilator muscle activity are sleep stage dependent. *Sleep (Basel)* 2016;39:511–521.
6. Landry SA, Joosten SA, Eckert DJ, Jordan AS, Sands SA, White DP, *et al*. Therapeutic CPAP level predicts upper airway collapsibility in patients with obstructive sleep apnea. *Sleep* 2017;40:zsx056.
7. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - new pathways for targeted therapy. *Sleep Med Rev* 2018;37:45–59.
8. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. *Respirology* 2017;22:43–52.
9. Carberry JC, Hensen H, Fisher LP, Saboisky JP, Butler JE, Gandevia SC, *et al*. Mechanisms contributing to the response of upper-airway muscles to changes in airway pressure. *J Appl Physiol (1985)* 2015; 118:1221–1228.
10. Bamagoos AA, Cistulli PA, Sutherland K, Madronio M, Eckert DJ, Hess L, *et al*. Polysomnographic endotyping to select patients with obstructive sleep apnea for oral appliances. *Ann Am Thorac Soc* 2019;16:1422–1431.

Risk Stratification in Pulmonary Arterial Hypertension: Do Not Forget the Patient Perspective

Pulmonary arterial hypertension (PAH) is a cardiopulmonary condition associated with significant morbidity and mortality despite current advances in therapies (1). Health-related quality of life (HRQoL) in PAH has been found to be severely impaired at similar levels as those experienced by patients with debilitating illnesses such as interstitial lung disease, spinal cord injury, and treatment-resistant cancer (2). Despite the major impact of PAH on the physical, functional, emotional, and social domains of our patients' lives, physicians and clinical trials have traditionally focused on objective functional endpoints, such as the 6-minute-walk distance. In the sixth World Symposium on Pulmonary Hypertension (Nice 2018), a session devoted to "Patient Perspectives in Pulmonary

Originally Published in Press as DOI: 10.1164/rccm.202012-4350ED on December 24, 2020