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. ■

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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

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Table 1. Heath-related Quality-of-Life Instruments Used in PAH

Instrument	Domains	Number of Items	Comments
Generic			
SF-36	**Eight domains:** physical functioning, physical role limitations, bodily pain, general health perceptions, energy/vitality, social functioning, emotional role limitations, and mental health	36	• Used previously in PAH trials • No validation in PAH
SF-12	Same domains as the SF-36	12	• Used previously in PAH trials • No validation in PAH
EQ-5D	**Five domains:** mobility, self-care, usual activities, pain, and anxiety/depression	51	• Used previously in PAH trials • No validation in PAH
NHP	**Six domains:** physical mobility, social isolation, emotional reactions, pain, sleep, and energy	38	• Used previously in PAH trials • No validation in PAH
Pulmonary hypertension specific			
CAMPHOR	**Three domains:** symptoms, functioning, and quality of life	65	• First patient-reported outcome instrument validated for PAH • Predictive of clinical deterioration
LPH	**Two domains:** physical and emotional	21	• Validated for PAH • Adapted from the Minnesota Living with Heart Failure Questionnaire
emPHasis-10	**Unidimensional**	10	• Validated for PAH • Predictive of survival • Correlates with risk assessment
PAH-SYMPACT	**Two symptoms and two impact domains*:** cardiopulmonary symptoms, cardiovascular symptoms, physical impacts, and cognitive/emotional impacts	11	• Validated for PAH • Correlates with WHO FC

Definition of abbreviations: CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; EQ-5D = EuroQol Group Five-Dimension Self-Report Questionnaire; LPH = Living with Pulmonary Hypertension Questionnaire; NHP = Nottingham Health Profile; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension Symptoms and Impact Questionnaire; SF-12 = Medical Outcomes Study 12-item Short Form; SF-36 = Medical Outcomes Study 36-item Short Form; WHO FC = World Health Organization functional class.
*Symptom domain scores are recorded over the past week, and means are calculated by the sum of the past 7 days divided by the number of days with nonmissing data.

Hypertension" was championed for the very first time (3). In this session, disease-specific measures of HRQoL were highlighted as relevant and important endpoints in clinical trials, and these measures should also be integrated into daily clinical practice. Recently, PAH-specific HRQoL measures such as emPHasis-10 (4) and PAH Symptoms and Impact Questionnaire (PAH-SYMPACT) (5) have been developed as easy-to-administer instruments that can be embedded into routine care, registries, and clinical trials (Table 1).

In this issue of the *Journal*, the study by Min and colleagues (pp. 761–764) is timely, as it examines the important relationships between PAH risk assessment with HRQoL and hospitalizations (6). Risk assessment is recommended by current guidelines to stratify the risk of future mortality at the time of diagnosis and subsequent follow-up assessment. Although a number of PAH risk assessment tools have been proposed for use in clinical practice (7–11), they all demonstrate the ability to discriminate patients into low-, intermediate-, and high-risk groups. Accordingly, therapy can be tailored to the risk status of the patient, with escalation of therapy if low-risk status is not achieved (12). Risk assessment tools have also been shown to be dynamic and sensitive to the effects of PAH therapies (13).

What is unclear is whether risk assessment tools can predict patient-reported outcomes and future hospitalizations. It is this important question that Min and colleagues (6) address in their study of 869 patients with PAH who were prospectively enrolled in the Pulmonary Hypertension Association Registry. Two HRQoL instruments (Medical Outcomes Study Short Form-12 [SF-12] and emPHasis-10) were administered at baseline and follow-up visits. Risk assessment was conducted using the European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification instrument (with the approach used in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension [COMPERA] and the Swedish Registry) (8, 9, 14) and the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 score (11). For both ESC/ERS and REVEAL 2.0 risk models, there were clear correlations between low-, intermediate-, and high-risk groups with HRQoL scores, with the highest-risk group demonstrating the poorest HRQoL. Importantly, there was a much larger relative

difference in the emPHasis-10 scores compared with SF-12 scores across each risk stratum, suggesting that a disease-specific tool such as emPHasis-10 is more sensitive to the differences in the risk status. The minimally important difference of emPHasis-10 has been suggested to be ∼6.0 points (15), and it is worth highlighting that the low- and high-risk groups' scores differed by ∼10 points in this study. These findings are mirrored by a recent U.K. multicenter study that showed that the emPHasis-10 score predicted survival in PAH (16). This suggests that the emPHasis-10 score has the ability to integrate traditional clinical variables that are prognostic in PAH. Indeed, emPHasis-10 has been shown to correlate with World Health Organization functional class and 6-minute-walk distance (15, 16).

An additional finding of the present study is that higher-risk strata (using the ESC/ERS and REVEAL 2.0 models) were associated with higher risk of incident hospitalizations. The prognostic impact of hospitalization on future mortality has already been highlighted by the GRIPHON (Prostacyclin Receptor Agonist in Pulmonary Arterial Hypertension) trial, which observed a marked increased risk of death (hazard ratio, 6.55; 95% confidence interval, 4.02–10.67) among patients who experienced hospitalization for worsening of PAH within 3 months of enrollment (17). Thus, it is not surprising that risk assessment, hospitalization, and mortality are all linked. In fact, one of the main changes of the REVEAL 2.0 score from original REVEAL score was the addition of "hospitalization in the past 6 months" into the risk assessment algorithm (11).

The authors are to be congratulated on advancing patient-reported outcome research in PAH. It is time to embrace a patient-centered approach to the care of this vulnerable population and recognize that what is important to the clinician does not necessarily align with our patients' expectations. ■

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