Title

The Baby, the Bathwater, and the Polysomnogram

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The Baby, the Bathwater, and the Polysomnogram

Donovan and Patel make some important points regarding the utility of the polysomnogram (PSG) (1). We are also strong believers in technological innovation and that optimizing patient care in obstructive sleep apnea (OSA) will require approaches that are portable, scalable, and cost effective. However, we offer several counter arguments to our colleagues for consideration:

1. Although the PSG currently serves primarily to yield an apnea–hypopnea index (AHI), the rich data available from these recordings are largely ignored (2). We agree that if the only goal is to obtain an AHI, this goal could probably be achieved with home sleep testing or wearable technology. By analogy, if the only information gleaned from an ECG were a heart rate, the ECG would disappear as an antiquated instrument. However, we and others have done extensive processing of PSG signals and have developed robust methods to assess endotypes (mechanisms) underlying OSA (3) and to define better the heterogeneity underlying disease (4, 5). Furthermore, research into more advanced PSG metric parameters to characterize better individual patients (6, 7) and to prognosticate long-term outcomes (e.g., hypoxic burden [8]) is rapidly progressing. These approaches will likely help us move past the current "one size fits all" strategy, which is typically employed, and toward a more precision medicine approach (9). The abandonment of PSGs would yield a situation in which the recent progress and eventual clinical uptake may well be compromised.
2. The authors emphasize the importance of patient-reported outcomes, with which we concur (10). However, we would offer several situations in which the patient voice must be heard but objective data are crucial. For example, we commonly see patients who have a vested interest in obtaining an OSA diagnosis (e.g., government employees or military) because they may then qualify for service-related disability (11). In this context, we frequently observe very high prevalence rates of snoring and sleepiness ostensibly because patients are motivated to obtain an OSA diagnosis. In contrast, in some occupational medicine settings, based on human nature, patients may try to avoid an OSA diagnosis and minimize self-reported sleepiness and snoring (12). We estimate currently at University of California San Diego that roughly 30–40% of our patients fall into a category in which self-report may be unreliable. As such, objective data are critical in many cases to complement the patient voice (13).

Another example of when patient-reported outcomes may be complicated is in the follow-up of patients on continuous positive airway pressure therapy. In many cases, we see patients who report feeling well with treatment but have a high residual AHI. In such cases, we feel strongly that the underlying apnea needs to be addressed rather than just declaring victory based on improved symptoms. Clinically, we have seen the effectiveness of in-laboratory titration to assess these patients with residual apnea on positive airway pressure therapy. An extreme analogy might be giving a patient stimulants for untreated OSA; this action may be to the patient's short-term satisfaction but likely to their long-term detriment. Thus, again, we view patient-reported symptoms as helpful but not definitive data.

3. The authors appropriately emphasize the importance of OSA given the global prevalence of disease, estimated to be up to 1 billion people (14). However, we would argue that many other sleep conditions, including periodic limb movements, narcolepsy, insomnia, hypoventilation, and parasomnias, exist and need to be addressed. In many cases, home testing is not adequate to make these diagnoses, and PSG is quite helpful. Even in patients with OSA, comorbid conditions can frequently complicate therapy and interpretation of diagnostic information. For example, Gooneratne and colleagues (15) have reported high percentages of OSA with comorbid insomnia in the elderly, a situation in which home sleep testing (without any sleep assessment) may be complicated if not misleading.

We welcome a discussion regarding the optimal strategy to diagnose the major burden of sleep disorders in general and agree that implementation of technological solutions may be accelerated by the coronavirus disease (COVID-19) pandemic. However, we are reluctant to discard an important test until alternative strategies have been rigorously tested and proven effective. ■

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References

1. Donovan LM, Patel SR. The COVID-19 pandemic presents an opportunity to reassess the value of polysomnography [editorial]. *Am J Repir Crit Care Med* 2020;202:309–310.
2. Lim DC, Mazzotti DR, Sutherland K, Mindel JW, Kim J, Cistulli PA, *et al*.; SAGIC Investigators. Reinventing polysomnography in the age of precision medicine. *Sleep Med Rev* 2020;52:101313.
3. Sands SA, Edwards BA, Terrill PI, Taranto-Montemurro L, Azarbarzin A, Marques M, *et al*. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2018;197:1187–1197.

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4. Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, Kehlmann G, *et al*. Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2014;190: 1293–1300.
5. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014;383:736–747.
6. Dres M, Younes M, Rittayamai N, Kendzerska T, Telias I, Grieco DL, *et al*. Sleep and pathological wakefulness at the time of liberation from mechanical ventilation (SLEEWE): a prospective multicenter physiological study. *Am J Respir Crit Care Med* 2019;199: 1106–1115.
7. Amatoury J, Azarbarzin A, Younes M, Jordan AS, Wellman A, Eckert DJ. Arousal intensity is a distinct pathophysiological trait in obstructive sleep apnea. *Sleep (Basel)* 2016;39:2091–2100.
8. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, *et al*. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the osteoporotic fractures in men study and the Sleep Heart Health Study. *Eur Heart J* 2019;40:1149–1157.
9. Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. *Am J Respir Crit Care Med* 2019;200:691–703.
10. Malhotra A, Nokes B, DeYoung P, Owens R. Why do we sometimes ignore the chief complaint in patients evaluated for obstructive sleep apnea? *J Clin Sleep Med* 2020;16:657–659.
11. Veterans Health Administration. Opportunities missed to contain spending on sleep apnea devices and improve veterans' outcomes [accessed 2020 Jun 29]. https://www.va.gov/oig/pubs/VAOIG-19-00021-41.pdf.
12. Federal Motor Carrier Safety Administration. Driving when you have sleep apnea [accessed 2020 May 21]. Available from: https://www.fmcsa.dot.gov/driver-safety/sleep-apnea/driving-when-you-have-sleep-apnea.
13. Deyoung PN, Bakker JP, Sands SA, Batool-Anwar S, Connolly JG, Butler JP, *et al*. Acoustic pharyngometry measurement of minimal cross-sectional airway area is a significant independent predictor of moderate-to-severe obstructive sleep apnea. *J Clin Sleep Med* 2013; 9:1161–1164.
14. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, *et al*. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7: 687–698.
15. Gooneratne NS, Gehrman PR, Nkwuo JE, Bellamy SL, Schutte-Rodin S, Dinges DF, *et al*. Consequences of comorbid insomnia symptoms and sleep-related breathing disorder in elderly subjects. *Arch Intern Med* 2006;166:1732–1738.

Vitamin D Deficiency in Asthma and Chronic Obstructive Pulmonary Disease

A Chicken-or-Egg Story

Whereas, traditionally, vitamin D has been considered as a main regulator of calcium and phosphate homeostasis, it has become increasingly clear that vitamin D is also an important regulator of immunity and host defense against infections in various tissues, including the lung (1–3). Asthma and chronic obstructive pulmonary disease (COPD) are both characterized by chronic inflammation, and exacerbations of these diseases are associated with respiratory infections. Therefore, the growing interest in the role of vitamin D in asthma and COPD is well justified. Patients with (severe) asthma and COPD are characterized by low circulating levels of 25-hydroxyvitamin D (25[OH]D), the main circulating but inactive form of vitamin D (3–6). However, the most important question that remains to be answered is the chicken and egg question: does vitamin D deficiency contribute to the development of asthma and COPD and their exacerbations, or is it solely a consequence of the disease (reverse causality)?

In this issue of the *Journal*, Jolliffe and coworkers (pp. 371–382) shed light on this issue through the study of vitamin D metabolism in patients with asthma and COPD as compared with healthy control subjects (7). The metabolism of vitamin D is complex, with enzymes regulating the formation of the active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), and various enzymes being involved in its catabolism. Two cytochrome P450 (CYP) enzymes take center stage in the balance between 25(OH)D and $1,25(OH)_2D$: CYP24A1 catabolizes both 25(OH)D and $1,25(OH)_2D$, whereas CYP27B1 is crucial for the generation of $1,25(OH)_2D$ through its 1-hydroxylase activity (8). Whereas these enzymes were initially considered to be mainly expressed in the liver and kidney, also cells of the immune system, and, for example, airway epithelial cells express these enzymes where they may contribute to local vitamin D metabolism (8, 9). Importantly, mechanistic studies have indicated that inflammatory mediators may increase activity of CYP24A1 and CYP27B1, which may result in lower local 25(OH)D concentrations (10–12).

The authors used samples collected in three clinical trials in which patients with asthma or COPD, or healthy control subjects, received high-dose vitamin D_3 supplementation every two months (7). They used serum samples obtained at baseline, after 2 months, and after 12 months for a detailed analysis of vitamin D_3, 25(OH)D_3, and the vitamin D metabolites $1,25(OH)_2D_3$, $24R,25(OH)_2D_3$, and $4\beta,25(OH)_2D_3$. They assessed a panel of 19 SNPs in DNA extracted from whole blood that may help to explain differences in serum 25(OH)D levels. They combined this analysis with that of available gene expression in 14 data sets from seven different studies to assess expression of vitamin D pathway genes in tissue from the respiratory tract and blood from patients with asthma and COPD, and control subjects.

The authors present interesting and sometimes unexpected findings. First, they observed that vitamin D_3

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