disease in patients with a specific OSA phenotype of high PWAD index, which is essential for the individualized management of OSA.

However, there are still some issues that deserve further discussion. Excessive daytime sleepiness (EDS) is the main clinical manifestation of OSA. A higher risk of cardiovascular death has been reported in patients with EDS compared with nonsleepy patients with OSA (3). In the study by Solelhac and colleagues, patients with EDS were excluded from the ISAACC (Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome: Effect of Intervention with CPAP) cohort, and low numbers of patients with EDS were included in the HypnoLaus and Pays-de-la-Loire cohorts (7), which may have excluded many patients with moderate to severe disease, resulting in an underestimation of cardiovascular risk in patients with OSA. Another issue that needs to be further explored is that, in the HypnoLaus and ISAACC cohorts, the baseline mean PWAD index was higher in patients with OSA than in those without OSA (7). The possible reason is that the PWAD index is increased in patients with OSA with obstructive respiratory events causing sympathetic activation. As the course of OSA progresses, respiratory events have a sustained effect on autonomic reactivity and endothelial function, resulting in a decrease in the PWAD index. In other words, without good treatment, repeated respiratory events and hypoxia in patients with OSA can lead to an accumulation and increase in the risk of adverse events over time. Therefore, it is reasonable to suspect that the PWAD index seems to be related to the course of OSA, not only to the apnea–hypopnea index. We suggest that the authors perform a longitudinal prospective study to correct for these confounding factors using time variation as a covariate.

In conclusion, despite some limitations of the study, the work of Solelhac and colleagues has made a valuable contribution to the identification and management of OSA-related cardiovascular events. Unfortunately, the course of OSA appears to have received little attention in current studies, and the relationship between PWAD and the course of OSA needs to be explored more deeply in the future. Patients with a low PWAD index are at higher risk of cardiovascular events and should be considered for management with other therapies. ■

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References

1. Salari N, Khazaie H, Abolfathi M, Ghasemi H, Shabani S, Rasoulpoor S, *et al.* The effect of obstructive sleep apnea on the increased risk of cardiovascular disease: a systematic review and meta-analysis. *Neurol Sci* 2022;43:219–231.
2. Labarca G, Dreyse J, Drake L, Jorquera J, Barbe F. Efficacy of continuous positive airway pressure (CPAP) in the prevention of cardiovascular events in patients with obstructive sleep apnea: systematic review and meta-analysis. *Sleep Med Rev* 2020;52:101312.
3. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019;200:493–506.
4. Maierean AD, Vulturar DM, Chetan IM, Todea DA. Is CPAP therapy improving the cardiovascular outcome in patients with obstructive sleep apnea? [abstract] *Eur Respir J* 2022;2150:60–66.
5. Arnaud C, Bochaton T, Pépin JL, Belaidi E. Obstructive sleep apnoea and cardiovascular consequences: pathophysiological mechanisms. *Arch Cardiovasc Dis* 2020;113:350–358.
6. Strassberger C, Zou D, Penzel T, Fietze I, Hedner J, Ficker JH, *et al.* Beyond the AHI-pulse wave analysis during sleep for recognition of cardiovascular risk in sleep apnea patients. *J Sleep Res* 2021;30:e13364.
7. Solelhac G, Sánchez-de-la-Torre M, Blanchard M, Berger M, Hirotsu C, Imler T, *et al.* Pulse wave amplitude drops index: a biomarker of cardiovascular risk in obstructive sleep apnea. *Am J Respir Crit Care Med* 2023;207:1620–1632.

Reply to Chen *et al.*

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From the Authors:

We thank Chen and colleagues for their comments on our article (1). They mention that excessive daytime sleepiness in obstructive sleep apnea (OSA) is associated with a higher risk of cardiovascular death, which has indeed been reported in some (2) but not all studies (3). They suggest that there may have been an underrepresentation of moderate-to-severe disease in our analysis, which might have induced an underestimation of cardiovascular risk. As mentioned in the methods, patients with OSA and severe sleepiness were excluded from the ISAACC (Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome). Effect of intervention with CPAP study represented only 11.5% of men and 4.8% of women in the HypnoLaus study (4), which is expected in a general population sample. In the PLSC (Pays de le Loire Sleep Cohort) study, the proportion of patients with an Epworth sleepiness scale score >10 was 53.4% in the entire OSA population and 54.1% in patients treated with continuous positive airway pressure, which is in accordance with previous findings in clinic-based cohorts (5). Furthermore, the aim of our analysis was not to determine the incidence of cardiovascular events but rather to assess the association between pulse wave amplitude drop index and the incidence of cardiovascular events in cohorts including different types of participants. The fact that this association was significant in samples with higher and lower degrees of sleepiness is probably one of the strengths of this analysis.

When a clinician diagnoses OSA, it is indeed difficult to determine when the disease started and what impact it has on the patient's cardiovascular system. We strongly agree with Chen and colleagues that a low pulse wave amplitude drop index might be useful in this regard, as it could reflect the duration of exposure to OSA, with progressive blunting of the autonomic nervous system and vascular reactivity over time. The longitudinal study they suggest that takes into account the duration of the disease would be interesting and could confirm this hypothesis. Unfortunately, the time of onset of the disease would be very difficult to determine and would require repeated sleep recordings in a general population sample over a long period of time, which is difficult to achieve. ■

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References

1. Solelhac G, Sánchez-de-la-Torre M, Blanchard M, Berger M, Hirotsu C, Imler T, *et al.* Pulse wave amplitude drops index: a biomarker of cardiovascular risk in obstructive sleep apnea. *Am J Respir Crit Care Med* 2023;207:1620–1632.
2. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019;200:493–506.
3. Trzepizur W, Blanchard M, Ganem T, Balusson F, Feuilloy M, Girault JM, *et al.* Sleep apnea-specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *Am J Respir Crit Care Med* 2022;205:108–117.
4. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, *et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310–318.
5. Roure N, Gomez S, Mediano O, Duran J, Peña MdeL, Capote F, *et al.* Daytime sleepiness and polysomnography in obstructive sleep apnea patients. *Sleep Med* 2008;9:727–731.

Electrical Impedance Tomography and Optimal Positive End-Expiratory Pressure: Uncovering Latent Heterogeneity of Treatment Effect

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To the Editor:

We read with great interest the study by Jonkman and colleagues (1), who performed a multicenter observational trial in coronavirus disease (COVID-19) patients with acute respiratory distress syndrome (ARDS) using electrical impedance tomography (EIT) to assess lung recruitability and select an optimal positive end-expiratory pressure (PEEP) by identifying the overdistension and collapse intercept (ODCL) at which lung overdistension and collapse are minimized (2). The authors found different levels of optimal PEEP in 81% of study subjects when comparing EIT-determined PEEP with PEEP determined by the maximal compliance method. In study subjects deemed recruitable (approximately two-thirds), the EIT-determined PEEP was slightly higher than the compliance-determined PEEP, but they did not differ in patients determined not to be recruitable.

Previously, three randomized controlled trials assessed the use of EIT for PEEP titration in ARDS. Hsu and colleagues demonstrated improved lung mechanics and survival with PEEP selection based on EIT versus pressure–volume curves (3). EIT led to the use of a lower PEEP, suggesting that the benefit was driven by decreased overdistension. Similarly, in a crossover physiological trial involving mainly patients with COVID-19 and ARDS, we found that EIT-guided PEEP titration resulted in a lower level of PEEP administration than that determined by a conventional high-PEEP table, with a concomitant decrease in mechanical power, a likely determinant of patient outcome (4). However, a study by He and colleagues found no difference in PEEP determined by EIT and the

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