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Searching for a Vulnerable Cardiovascular Endotype in Obstructive Sleep Apnea: Is the Humble Pulse Wave a Useful Biomarker?

Clinical and community cohort studies have widely used the apnea–hypopnea index (AHI) to establish a clear link between obstructive sleep apnea (OSA) and increased risk for incident cardiovascular events (1–3). However, despite this risk, several recent randomized trials encompassing ∼1–5 years of follow-up have failed to demonstrate a reduction in cardiovascular events with continuous positive airway pressure (CPAP) treatment (4–6). This has been attributed to poor CPAP adherence in nonsleepy populations with established cardiovascular disease (CVD), in which it may be too late to reduce subsequent cardiovascular events (7). Part of the answer may lie in primary prevention trials that target sleepy, otherwise healthy patients with OSA with a high hypoxic burden but without established CVD (8). Such trials will need to be large, with long follow-up periods, that potentially incorporate adaptive designs (9) with individualized therapies to maximally alleviate OSA. In the interim, research must continue to better define vulnerable endotypes through the identification of specific biomarkers. One recently discovered biomarker is the pulse wave amplitude drop (PWAD) index, automatically detected (10) from changes in the amplitudes of photoplethysmographic waves, captured from pulse oximeters. Previous studies have shown that analysis of the timing and contour of these waveforms provides surrogate measures of vasomotor responsiveness, endothelial function, and arterial stiffness (11), which have been linked to increased cardiovascular risk in vulnerable populations, including in OSA (12).

In this issue of the *Journal*, Solelhac and colleagues (pp. 1620–1632) analyze data from a community cohort, a clinical cohort, and a randomized controlled trial to assess the association between PWAD index and incident cardiovascular events (13). The Swiss HypnoLaus community cohort (14) used unattended full polysomnography to identify participants with and without OSA who had no histories of CVD. Participants (35% with OSA) were followed over a mean of ∼49 months for incident fatal and nonfatal cardiovascular events. The French PLSC (Pays de la Loire Sleep Cohort) used data linkage with their health system to find people with OSA diagnosed by full polysomnography or type 3 polygraphy. Participants (∼57% with OSA) free of CVD were followed over a mean of ∼72 months for incident major adverse cardiovascular events. The Spanish ISAACC (Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome: Effect of Intervention with CPAP) clinical cohort (6) followed clinical trial participants with nonsleepy OSA and acute coronary syndrome who were randomized to CPAP plus usual care or usual care alone for a median of ∼3.35 years (∼40 mo) for incident composite fatal or nonfatal cardiovascular events. Patients without OSA ($n = 164$) but with acute coronary syndrome were included as a reference group. In the cardiovascular risk analyses, the authors used an AHI of ⩾15 events/h to classify OSA. Given the between-study differences (populations, AHI definition, cardiovascular endpoints), the study-specific attributable risks were calculated separately.

The key data of interest show that in those with OSA, every 10-unit increase in the PWAD index was associated with 15%, 9%, and 6% reduced hazard ratios of the risk for incident cardiovascular events in HypnoLaus, PLSC, and ISAACC, respectively. In the HypnoLaus and PLSC cohorts, the fully adjusted models showed that a low PWAD index (vs. high) was associated with a 2.16- and a 1.36-fold increased risk of a major cardiovascular event, respectively. Although nonsignificant, the associations in ISAACC were still consistent with the other cohorts (Figure 7C, right panel). This finding across three cohorts with different study features demonstrates the promise of this approach. Overall, it tells a consistent story: the PWAD index does provide additional prognostic information, albeit somewhat subtle.

Previous cross-sectional studies in OSA have revealed an association between photoplethysmographic features, including pulse amplitude attenuations and cardiovascular risk (12), but they do not demonstrate causality. By contrast, the study by Solelhac and colleagues (13), which prospectively linked high and low PWAD index stratified by OSA with hard cardiovascular events, provides stronger evidence supporting the involvement of both OSA and PWAD index in the causal pathway to CVD. However, there appear to be important caveats that need to be considered when interpreting the study findings. The HypnoLaus and PLSC analyses may suggest

Originally Published in Press as DOI: 10.1164/rccm.202304-0739ED on May 4, 2023

that the combination of OSA and a lower PWAD index only increases the risk of a cardiovascular event in people who have never had prior events (Figures 3B, 5, and 7, right panel). In the ISAACC study, in which people did have prior events, this finding, albeit not statistically significant, is still broadly consistent with the other cohorts. Nevertheless, in the original ISAACC trial, CPAP treatment (irrespective of adherence) did not reduce incident cardiovascular events (6), and in the present analysis (Figure 4), a high or low PWAD index does not appear to alter this risk in CPAP users. In contrast, good CPAP adherence in the PLSC cohort was associated with reduced major adverse cardiovascular events in people with high PWAD indexes (Figure 6). Could the presence or absence of prior events be an important factor?

The authors cite mechanistic evidence to support their hypothesis that in OSA, a low PWAD index could reflect impaired autonomic activity (involving decreased baroreceptor sensitivity) and endothelial dysfunction, which together dampen the PWAD response to apneas. It follows that in the longer term, CVD may develop. However, although it seems logical that a high PWAD index, present in newly developed OSA, may transition to a low PWAD index with protracted OSA over many years, the authors do not explain why the PWAD index can be high or low in people without OSA. A more in-depth analysis of PWAD events in each subgroup from the three cohorts that quantifies events related to OSA versus those that were spontaneous may clarify some of the mechanistic underpinnings.

Although the authors propose that the heterogeneity in the three studies was a limitation, the testing of a single hypothesis using the same analysis method across three diverse studies simultaneously is a strength. In contrast, the primary analyses dichotomized both PWAD and AHI, which is well known to cause a loss of statistical power, although it does allow the authors to demonstrate variation in risk using survival curves. Nevertheless, the authors need to be commended for their sensitivity analyses investigating both key metrics as continuous variables and their interactions. These latter analyses suggest that there may be some interesting nonlinear associations between both variables and cardiovascular risk that warrant further investigation. As with all cohort studies, there is potential for residual confounding from nonadjustment of other important risk factors (e.g., blood pressure and lipids), which are important pathophysiological mechanisms linking OSA with CVD (2, 15).

The study by Solelhac and colleagues (13) has uncovered a simple, yet potentially valuable prognostic tool: the humble photoplethysmographic pulse wave, which is readily available from most oximeter devices routinely used during polysomnography to diagnose OSA. We would recommend that the recording of this signal for further endotyping research of cardiovascular risk in patients with OSA be undertaken. ■

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

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