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Prospective Cohort Studies of Major Disorders Can Facilitate Phenotyping for Sleep Apnea

A few decades ago, several prospective cohort studies were initiated with the support of epidemiologists and often focused on a specific disorder or risk factors (1). One example of such a cohort study is MESA (Multi-Ethnic Study of Artherosclerosis), which was designed to investigate risk factors for cardiovascular diseases (2). Assessments of cardiovascular disease, including severity, risk factors, and comorbidities, were carefully chosen according to the methodology and physiological knowledge available 20 years ago. The hypotheses in the studies begun decades ago are borne out by the results that have been published more recently (3). However, sleep recording was not part of the original methodology. Today, however, this information can be added, as was done in the study by Borker and colleagues (pp. 1173–1182) in this issue of the *Journal* (4); this addition offers new insights on the meaning of sleep apnea in medicine.

Today, it is increasingly recognized that sleep apnea is more than a diagnostic entity; it has been found to be a contributor to many cardiovascular, respiratory, and metabolic disorders (5). And vice versa: sleep medicine also views cardiovascular, respiratory, and metabolic disorders as contributors to sleep apnea. Respiratory events during sleep such as obstructive, mixed, or central apneas and obstructive and central hypopneas, or even less well-defined events such as respiratory-related arousal or airflow flattening, are carefully scored in sleep centers and then counted and used as metrics for sleep apnea severity. It is now recognized that apnea–hypopnea index is not an adequate measure of severity. Counting oxygen desaturations and calculating the oxygen desaturation index is not much better, but instead distracts from the core problem of pathophysiological mechanisms.

Sleep apnea, as defined by apnea–hypopnea index (or oxygen desaturation index), is heterogenous. Sleep apnea may be the cause of cardiovascular, respiratory, or metabolic disorders, or it may be the consequence of these. For an appropriate treatment, this does not matter much. However, for an understanding of pathophysiological pathways, and thus for prevention, this is important. The assessment of sleep apnea can be regarded as being similar to that used for high blood pressure. It is a sign, and a finding, that a basic physiological regulation (of blood pressure or, respectively, of respiratory stability during sleep) is losing its physiological boundaries. Different parameters are used to characterize the regulation. All these parameters are recorded by polysomnography and can be analyzed by exploiting the recordings more (6). Not only the number, but also the duration, of respiratory events is important for phenotyping patients (7). Analyzing subgroups related to event duration may provide surprising results (8). Event duration may even allow a prediction of mortality, as recently reported based on a sleep cohort study (9).

To change the perspective on sleep-disordered breathing and change the view on the pathophysiology of sleep apnea, it is valuable

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to approach existing prospective cohort studies focused on other disorders (such as cardiovascular disease), like the MESA study, and add a sleep apnea assessment module (4). In this study designed to investigate outcomes of atherosclerosis in relation to age, race, obesity, and other factors, sleep apnea assessment was added during the fifth examination of subjects; this is exactly the right step forward. We, as sleep researchers, need to approach steering committees of prospective studies on disorders that we regard as important comorbidities and convince them to add a sleep apnea assessment module now or during one of the upcoming exams. This does not apply only to established comorbidities but also to more recently identified ones, such as cancer and dementia (10, 11). These more recent comorbidities are specific targets worthwhile to approach in registries or prospective studies. Only then will we be able to identify more pathophysiological parameters, which may help to determine how sleep apnea affects other diseases.

In the study by Borker and colleagues, this exact step—adding a sleep exam at a later examination stage—had been taken (4). A sleep apnea assessment module with in-home polysomnography was used to assess all currently known aspects of sleep apnea. This study confirmed that event duration is very important and allows us to discriminate between groups and possibly phenotypes. In this way, it is possible to increase our understanding of sleep apnea pathophysiology. Surprising results found in previous studies could be confirmed (8). Furthermore, big data analysis and machine learning techniques can help to manage the large amounts of data obtained by sleep studies, and may help identify novel parameters that we do not consider today (12).

Currently, prevention of sleep apnea, prevention of sleep apnea progression, and prevention of associated comorbidities such as atherosclerosis are becoming the next research targets. Studies focused on finding a high prevalence of sleep apnea in certain disorders, although reassuring the importance of sleep apnea medicine, are no longer a priority.

There is another dimension in the activity of sleep medicine expertise—approaching and adding to existing large prospective cohort studies. We need to raise awareness of sleep in other medical fields (cardiac, respiratory, and metabolic) about the important comorbidity "sleep apnea" and that the assessment of sleep-disordered breathing can help to better characterize their patients and develop better preventive, precision, tailored therapies. In clinical practice, this may be as simple as finding out which particular patients with the underlying disorder (here, atherosclerosis) might benefit more from continuous positive airway pressure therapy in terms of slowing the progression of the underlying disorder (atherosclerosis). Generally speaking, patients in all medical fields could benefit from this approach of combining pathophysiological knowledge to derive preventive actions and find the optimal treatment including comorbidities. ■

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