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EDITORIAL COMMENT

Impact of Lifestyle on Sleep

Can We Alter Cardiovascular Risk?*

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In this issue of the *Journal*, Huang et al. (1) report on actigraphy-measured sleep regularity as novel risk factor for incident cardiovascular disease (CVD) based on a study with solid methodology and a sufficiently large cohort of patients.

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But where do we start when talking about the association between sleep and CVDs?

Sleeping for 6 to 8 h a day is an important component of a healthy lifestyle, as recently endorsed by the American College of Cardiology/American Heart Association guideline on the primary prevention of CVD (2). Getting sufficient sleep with good sleep architecture is important for key metabolic processes, such as the regulation of appetite, immune system function, and neurohormonal and sympathovagal balance (2–4). Sleep architecture refers to the physiology of good sleep in which healthy humans pass through a specific pattern of increasingly slow waves followed by rapid eye movement sleep. Healthy sleep is characterized not only by sufficient sleep quantity, but also by good objective sleep quality (defined as repetition of 5 to 7 of such sleep cycles) (3–5). In modern society, both the quantity and quality of sleep are negatively influenced by factors such as longer hours of work, more shift work, artificial light and cell phones, all leading to self-reported daytime symptoms such as fatigue, tiredness, and sleepiness (3).

Previous studies have already linked short sleep duration and poor sleep quality, in particular, to increased risk of major CVD and fatal cardiovascular outcomes (3–5). However, none of those published studies to date have assessed the potential association between circadian rhythms (i.e., high day-to-day variability in sleep duration or timing) and the incidence of CVD. Therefore, Huang et al. (1) are to be commended for the originality of their study and the quality of their findings.

Not only did they elegantly identify irregular sleep duration and timing as novel risk factors for CVD, but they also showed that impaired individual circadian rhythm as a novel CVD risk factor might be independent of traditional CVD risk factors and sleep quantity and/or quality (1). This is a particularly striking finding because impaired circadian rhythm is likely to be much more prevalent than the extreme example of shift work. This makes it appear that dysfunctional sleep might be at least 1 of the mechanisms underlying associations between modern lifestyles and poor cardiovascular outcomes.

But what are we really getting at when talking about circadian rhythm and its association with CVD?

Current pathophysiological understanding of most CVD and heart failure (HF), in particular, is based on neurohumoral and sympathovagal imbalance, which can be improved by current guideline-recommended therapies (2,3). Deep and/or slow-wave sleep itself is known to be associated with a decrease in sympathetic nerve activity (4). This supports the notion that

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abnormal sleep duration, quality and complaints, and abnormal circadian rhythm of sleep may all exert their detrimental effects through increasing sympathetic nerve activity and/or neurohormonal derangement (3,5).

However, before declaring the association between sleep and CVD as crystal clear and causal in nature, we need to be sure that other potential confounders have been meticulously adjusted for. One of the most important confounders of impaired sleep is sleep-disordered breathing (SDB) (3–7). A valid pathophysiological standpoint is that obstructive sleep apnea (OSA) reduces sleep quality and increases sympathetic nerve activity in patients with CVD (3,5). It is important to acknowledge that a line of well-conducted research supports the notion that OSA is linked with impaired sleep quality not only via negative intrathoracic pressure and a broad spectrum of pathological systemic events, but also directly via intermittent hypoxic stress (8). In particular, the fact that time spent with oxygen saturation below 90% independently influences cardiovascular mortality and that cardiovascular deaths occur in the morning, especially in patients with comorbid OSA, further reinforces this notion (9–11). Notably, there is also controversial data to support the notion that central sleep apnea (CSA) increases sympathetic nerve activity, worsens sleep quality, and therefore independently increases cardiovascular mortality (3,5,6). Conversely, it has been highlighted that CSA is not strictly restricted to sleep but rather a marker of altered central chemosensitivity that is also evident in the form of central apneas during daytime (7,12). Although Huang et al. (1) should therefore be congratulated for adjusting for the apnea-hypopnea index as a confounding factor in the association between sleep, circadian rhythm, and CVD, it would also have been interesting to adjust for nocturnal hypoxia and to have distinguished between OSA and CSA. Similarly, prognostic studies such as that by Huang et al. (1) need to include adjustment for underlying chronic diseases, including HF, pulmonary hypertension, arrhythmias, and chronic obstructive pulmonary disease because these have all been shown to directly affect sleep (3). To adjust for such comorbid conditions, the final models could have been adjusted for spirometry findings, electrocardiography, and blood sample–derived levels of amino terminal pro-brain natriuretic peptide (an easy to obtain marker of HF). At the same time, it should be acknowledged that it is hard to adjust for all confounding factors in such large cohort studies; the investigators honestly acknowledged this in the study limitations section.

The critical question arises as to how we can make further progress into our understanding of a potentially causal link between sleep and circadian rhythm, in particular, and CVD.

We believe that 3 avenues should be explored further. First, analysis of big data could facilitate understanding of the association between sleep (in duration, quality, and circadian rhythm) and CVD. Relatively recent availability of technology such as sleep trackers incorporated into smart watches may facilitate the collection of such data (3). It is particularly interesting to see that some of the largest randomized controlled trials that investigated the effects of mask-based treatment on SDB (e.g., SERVE-HF [Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure], SAVE [Sleep Apnea Cardiovascular Endpoints]) were not designed to investigate the effects of SDB or its treatment on sympathovagal balance (e.g., based on heart rate variability analyses) and sleep (based on polysomnography or actigraphy), with only a few investigator-initiated trials addressing this issue to date (13,14). Second, any future demonstration that conservative measures, such as teaching sleep hygiene or using behavioral therapy, could improve sleep quality (and potentially even sympathovagal balance and daytime functional status) in patients with CVD would be an important breakthrough (3). Third, the contribution of translational medicine to our understanding of circadian rhythm should not be forgotten. It was basic science that helped us to identify the clock genes and clock proteins (e.g., *clock*, *per2*, and *bmal1*) and to understand that the circadian clock is a transcriptionally based cell autonomous mechanism (15). Therefore, more than ever, it is now mandatory to test whether experimental data support the hypothesis that altered circadian rhythms would translate into unfavorable changes in 24-h sympathovagal and neurohormonal balance, and ultimately, CVD (e.g., arterial hypertension, pulmonary hypertension, HF, and arrhythmias). Similarly, most previous studies that addressed these associations were clinical and cross-sectional rather than experimental and longitudinal in nature, yet made it hard to judge whether the associations seen between CVD and sleep were correlative or causal (3).

Dysfunctional sleep likely is by far the most prevalent comorbidity in CVD. This makes it essential to explore the nature of sleep, but this is reliant on the enthusiasm of clinician scientists. The study by Huang et al. (1) is undoubtedly a crucial step in this process. It will, and should, stimulate much needed

additional research on the association between sleep and CVD that may offer novel approaches to help improve the prognosis and daily symptom burden of patients with CVD, and might make sleep itself a therapeutic target in CVD.

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