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Comment

Sleep disorders and cardiovascular risk: Focusing on sleep fragmentation

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In this comment, we explored the link between sleep fragmentation and the cardiovascular risk, considering various sleep disorders and methodologies for assessing sleep fragmentation.

It is generally known that sleep deprivation increases the cardiovascular (CV) and metabolic risk. Additionally, some data indicates that prolonged sleep is also associated with such risk.[1] In addition to sleep duration, sleep quality is also essential in the assessment of the CV risk. The continuity of sleep is one of its crucial features that contributes to effective rest and refreshment. Sleep may be interrupted by arousals and awakenings, which can result in prolonged wakefulness after sleep onset (WASO). Therefore, it is important to determine the threshold for the number of arousals and awakenings during sleep to consider them a normal phenomenon. According to the American Academy of Sleep Medicine (AASM) definition, an arousal is an abrupt shift in electroencephalography (EEG) frequencies, including alpha, theta and/or frequencies greater than 16 Hz (but not spindles), that lasts at least 3 s, with at least 10 s of stable sleep preceding the change.[2] The scoring of arousals during rapid eye movement (REM) sleep requires a concurrent increase in the submental electromyography (EMG) lasting at least 1 s.[2] Arousals, which can be accompanied by respiratory events, periodic limb movements in sleep (PLMS) or sleep bruxism events, are usually followed by autonomic activation, resulting in increased heart rate and blood pressure. Nevertheless, they can also occur spontaneously or be elicited by pain, light, noise, or a change in temperature. The arousal index (ArI), counted as the number of arousals per sleep hour, is frequently considered to quantify sleep fragmentation.[3] Sleep fragmentation, characterized by repetitive interruptions of sleep, is one of the factors contributing to excessive daytime sleepiness.

The apnea–hypopnea index (AHI) is generally considered an imperfect indicator of obstructive sleep apnea (OSA) severity. It is strongly believed that oxygen saturation parameters (i.e., the mean oxygen saturation, the oxygen desaturation index (ODI), the nadir oxygen saturation, and the percentage of sleep with oxygen saturation <90%) are more effective predictors of CV complications than the index of respiratory events.[4] It is worth noting that

if the duration of apneas is long, the AHI values decrease, leading to an underestimation of OSA severity. Recent studies have also emphasized the importance of sleep fragmentation. Shahrbabaki et al. showed sleep fragmentation to be a long-term risk factor for all-cause and CV mortality, indicating that the association between mortality and sleep fragmentation was more pronounced in women than in men.[5] Interestingly, women usually report a significantly worse sleep quality as compared to men.[6] Repetitive arousals disrupt the circadian rhythm of the CV system through the modification of blood pressure patterns. The physiological "deeper" pattern measured in ambulatory blood pressure monitoring (ABPM) shifts to the "non-deeper" or "reverse deeper" pattern due to the lack of physiological decreases in blood pressure or due to increases in blood pressure during sleep, respectively.[1] Among the main consequences of sleep fragmentation there are insulin resistance, lipid profile dysregulation and the overdrive of the sympathetic system, leading to a sustained increase in daytime blood pressure. Sleep fragmentation is a pivotal stimulus to sympathetic activation, resulting in ArI being correlated with the sympathetic overdrive much closer than AHI.[7] This crucial observation may explain the increased CV and metabolic risk in patients with sleep fragmentation. Another mechanism may involve endothelium dysfunction leading to an increase in blood pressure. Indeed, recent studies have shown a link between sleep fragmentation and hypertension.[8] Consequently, a high ArI and a low percentage of time spent in stage 3 non-rapid eye movement (NREM) sleep (N3) are associated with a greater coronary artery calcification burden.[9] Zhang et al. showed that a high ArI is a risk factor for increases in the left atrial diameter and correlates with cardiac remodeling.[10] Recently, it has been found that sleep fragmentation can increase QT interval variability during arousal, which is associated with an increased all-cause and CV mortality.[11]

The current issue to be dealt with is defining the cut-off value that leads to an increase in the CV risk. The task has been extremely difficult due to the lack of sufficient data until now. The cut-off point for a normal arousal is fluid and depends on age.[12,13] An ArI of >32 events/h was reported to increase the risk of coronary plaque development as compared to controls (ArI < 32 events/h).[14] However, more studies on sleep fragmentation are needed to effectively determine the cut-off point for ArI in relation to the CV risk.

Another question is whether the significance of different arousals is equal. Most studies do not consider different polysomnographic types of arousals (Fig. 1), as such polysomnography assessment is difficult and time-consuming. Respiratory arousals following respiratory events in sleep-disordered breathing patients are most commonly studied. Unfortunately, the data concerning arousals evoked by PLMS or sleep bruxism is limited. In a study by Kanclerska et al., it was observed that the PLMS index was increased in hypertensive patients as compared to normotensive controls, but the ArI related to PLMS was

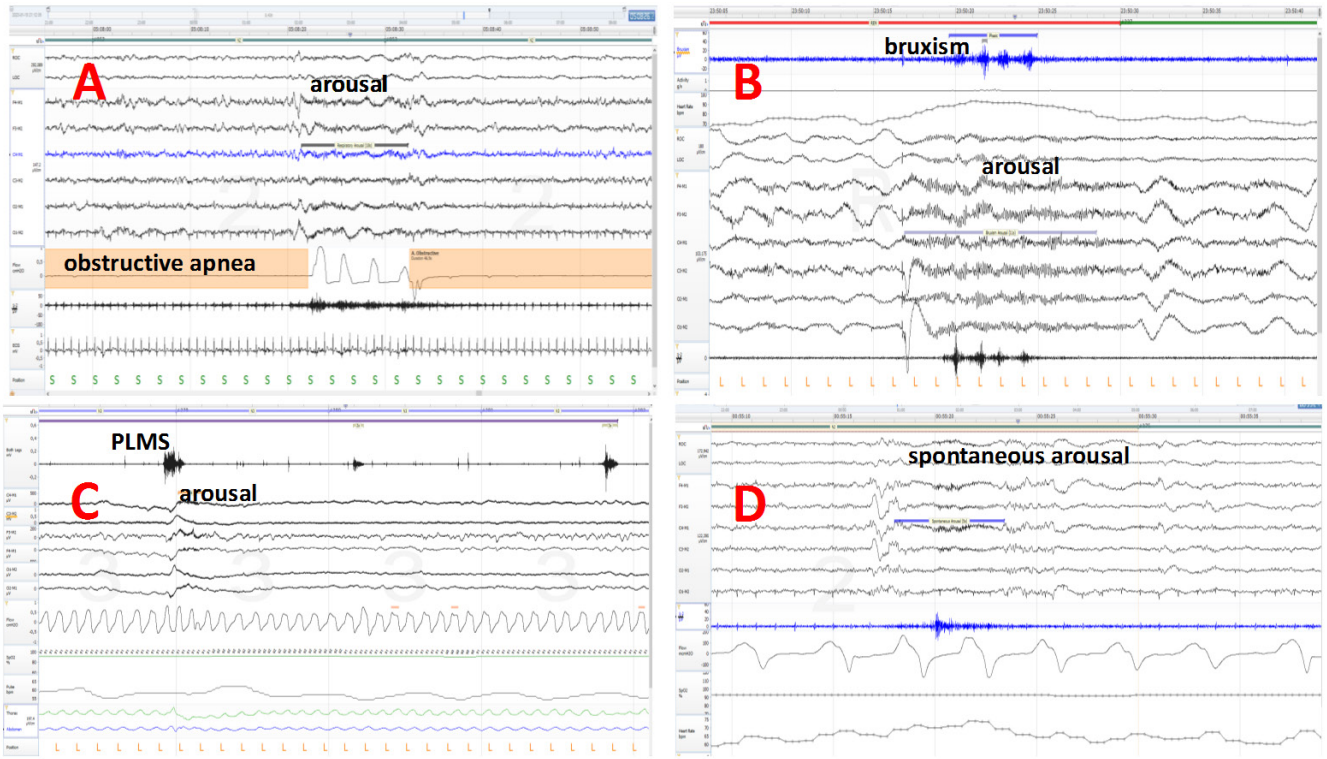

Fig. 1. Arousals in polysomnography

A – respiratory arousal; B – sleep bruxism arousal; C – periodic limb movements in sleep (PLMS) arousal; D – spontaneous arousal.

similar in normotensive and hypertensive patients, suggesting no significant sleep fragmentation due to PLMS in hypertensives; on the other hand, the ArI related to sleep bruxism was decreased in hypertensive patients as compared to normotensive controls.[15] Sleep bruxism is considered a physiological phenomenon; however, in some cases, it can be associated with systemic inflammation and excessive daytime sleepiness.[16] An increased frequency of arousals was demonstrated in repetitive sleep bruxism.[17] Although the treatment of bruxism is still not fully effective,[18] pharmacological therapy with sleep-promoting drugs, such as opipramol, may decrease ArI in patients with sleep bruxism.[19]

The last but not least issue is the quantification of sleep fragmentation. Sleep fragmentation can be determined with the sleep fragmentation index (SFI), calculated as the total number of awakenings and shifts to stage 1 NREM sleep (N1) divided by the total sleep time (TST). The most commonly used parameter is ArI, defined as the number of arousals per hour of sleep. However, both SFI and ArI do not consider arousal duration, unlike a new parameter called the arousal burden (AB), indicating the cumulative duration of all arousals relative to TST.[5] Unfortunately, none of these parameters includes all awakenings ("long arousals" lasting >15 s, which are also related to excessive daytime sleepiness).[20] Finally, the definitions of arousals include only EEG disruption (and additionally an increase in the EMG tone during REM sleep), but not autonomic activation, such as increases in the heart rate or blood pressure.

The current paper has addressed the important link between the CV risk and sleep fragmentation. In this context, the number of gaps and missing data was also revealed. Sleep fragmentation may represent a promising marker in identifying subjects at risk; however, new data on sleep fragmentation parameters, cut-off points, as well as larger data sets from clinical trials, are needed.

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