Duration of respiratory events in obstructive sleep apnea: Factors influencing the duration of respiratory events

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Short Title: Factors influencing the duration of respiratory events

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Summary

The duration of respiratory events during sleep in obstructive sleep apnea patients has recently become a parameter of interest as it appears to have important physiological and clinical consequences. For example, short apnea and hypopnea events are associated with all-cause mortality in men and women, and long respiratory events with adverse cardiovascular consequences. Moreover, respiratory event duration has been proposed to have heritable characteristics and in a Latino/Hispanic American community, a novel and specific genetic location for respiratory event duration has been identified. Therefore, respiratory event duration during sleep appears to represent a phenotype with heritable trait characteristics. In the present report, we will discuss the best-known factors that influence this important component of abnormal breathing events during sleep.

Keywords:

Sleep, Obstructive sleep apnea, OSA, Apnea duration, Hypopnea duration, Apnea/hypopnea length, AHI, Respiratory events.

Abbreviations:

AHI – apnea-hypopnea index

BMI – body mass index

N2 – sleep stage 2

N3 – sleep stage 3

NREM - non-rapid eye movement

NPP – non-positional patient

OSA – obstructive sleep apnea

PSG – polysomnographic

PP – positional patient

REM – rapid eye movement

UA – upper airway

Effect of sex on apnea and hypopnea event duration

Before describing the effect of sex on respiratory event duration, it should be mentioned that sex has a clear effect on the characteristics of obstructive sleep apnea (OSA); the prevalence of OSA is lower in women and women have a milder form of OSA compared to men [1-5]. Leech et al., 1988, [2] were perhaps the first ones to describe the differences in respiratory event duration between men and women in OSA patients. They assessed polysomnographic (PSG) data of 118 OSA patients with the apnea-hypopnea index (AHI) > 10 and hypersomnolence, and found that the proportion of hypopnea events from all apnea and hypopnea events was much higher in women compared to men. They also found that in women, the mean and maximum duration of apneas was shorter compared to men. In general, women had shorter respiratory events and lower AHI, and they suffered more often from insomnia compared to men [6]. Already in 2000 Ware et al. reported that apneas are significantly shorter (by an average of 3 seconds) in women compared to men during sleep stage 2 (N2) and rapid eye movement (REM) sleep [4]. In the same year, O'Connor et al. reported that despite of age or body mass index (BMI), women with OSA have a greater proportion of their respiratory events during REM sleep and that the REM-related OSA is more prevalent in women compared to men (62% in women vs. 24% in men) [7]. In addition, they showed that in REM sleep, women have shorter apnea events than men (17.3±0.5 sec vs. 21.2±0.3 sec, respectively) [7]. Thus, it appears that women have a more reactive upper airway (UA) (i.e. lower pharyngeal collapsibility) contributing to the occurrence of short apnea and hypopnea events leading to more fragmented sleep, and ultimately to a higher probability of insomnia [8, 9]. Findings by Leppänen et al., 2017 supported these findings by showing that among patients with moderate-to-severe OSA, women have shorter apnea and hypopnea events compared to men with similar AHI values [5]. Nevertheless, in mild OSA, which is a more common phenotype of OSA among women, hypopneas were longer and desaturation events more severe in women compared to men. In addition, desaturations following obstructive apneas lasting 30-45 seconds have been shown to be more severe in women compared to men [10]. Aline with these, Koo and Mansour, 2014 [11] showed that men had longer apneas than women, but their findings were not statistically significant. In addition, when OSA patients were divided into the groups based on apnea duration, women with short apneas were significantly younger and more obese than those with long apneas. Also men with short apneas were significantly younger than those with long apneas, however, no significant differences were observed in BMI. Accordingly, age appears to have an important role in the duration of respiratory events but the interaction between age and sex should not be ignored [11, 12]. In the study by Koo and Mansour, 2014 [11], the ratio of respiratory event-related arousal index to the AHI, which reflects the percentage of respiratory events that end with arousal, was significantly greater for OSA patients with long apneas than those with short apneas despite sex. However, for women the difference was greater and more evident. In other words, women had a higher tendency of arousal after apneas than men but mainly related to long respiratory events. As already mentioned, in general, women have more short events than men. Nevertheless, it appears that many of those short apnea events are not terminated by an arousal. Therefore, the higher prevalence of insomnia in women with OSA may not necessarily be a direct consequence of sleep fragmentation. This topic certainly requires further investigation.

Effect of obesity on apnea and hypopnea event duration

Obesity is the most dominant risk factor for OSA. The effect of weight on the development and worsening of OSA is noteworthy. Increase in weight in healthy subjects may lead to OSA and increase in weight in OSA patients usually lead to a worsening in OSA severity [13-15]. On the contrary, weight loss is often associated with an improvement in OSA severity and in some cases even with the elimination of the disease [16, 17]. In addition, women patients with OSA are much more obese than men with OSA. For example, in the Wisconsin Sleep Study Cohort, in every OSA severity level, women had a higher BMI than men [18].

The effect of obesity on respiratory event duration is somewhat paradoxical. It is known that obesity increases the severity of OSA through different pathways; for example, the increase in the amount of adipose tissue on UA affects the patency and collapsibility of the UA, and an increase in body weight, mainly central obesity, reduces the lung volume which increases pharyngeal collapsibility [19, 20]. Intuitively, these changes should make the UA more difficult to reopen after the collapse, suggesting that obese OSA patients should have longer respiratory events compared to non-obese OSA patients. Nevertheless, Leppänen et al., 2019 showed that an increase in BMI led to a decrease in the median duration of apneas, hypopneas, and desaturations in all OSA severity categories [15]. These findings are consistent with earlier results showing that weight reduction decreases, and weight gain increases, the number of shorter respiratory events, whereas the number of longer respiratory events tended to remain unchanged [21, 22]. Also, when OSA patients were divided into the groups based on the event duration (i.e. short apneas vs. long apneas), women with shorts apneas had a significantly higher BMI than those with long apneas. However, when OSA patients with short and long apnea events were compared, BMI was not found to be significantly different in men [11]. Thus, according to this study, sex appears to modulate the effect of weight change on the duration of respiratory events. The results by Butler et al., 2019 [23] are in line with these previous results, as they found a negative association between respiratory event duration and BMI [15]. Nonetheless, it should be noted that the effect of BMI on event duration were found to diminish after adjusting for circulatory delay and loop gain, which suggests that higher BMI appears to affect partially the functioning of respiratory chemoreceptors, possibly altering ventilation stability. Therefore, an increase in BMI increases the AHI (i.e. the severity of OSA) especially by increasing the number of short respiratory events and is associated with an increased risk of all-cause of mortality in men and women [23].

Effect of age on apnea and hypopnea event duration

Increasing age is associated with a higher prevalence of OSA in both men and women. Increased prevalence of OSA with age is suggested to be the result of complex pathophysiological mechanisms. However, it is evident that the increase in body weight associated with the aging process is one of the dominant factors influencing the increased prevalence of OSA as people ages [24].

Leech et al., 1988 [2] were perhaps the first ones to investigate the effect of age on the duration of apneas and hypopneas in men and women. They found that irrespective of the age (older vs. younger than 42 years, the breaking point of menopause in women in their study population), women had a significantly shorter maximum durations of apneas than men. It is important to note that in this study, neither age, nor AHI differ between age groups or between men and women. This study further indicated that menopause had no effect on apnea duration. The minimal effect of menopause on other characteristics of OSA has also been reported [7, 25].

Later, Ware et al., 2000 reported that the duration of apnea events increases with age regardless of sex in N2 and REM sleep [4]. Koo and Mansour, 2014 studied the correlation between apnea duration and several demographic and PSG parameters among 140 OSA patients and found that long apnea events occurred more frequently in older patients compared to younger ones regardless of sex [11]. In support of these findings, event duration has been found to be longer in older adults compared to younger ones indicating that the predominant mechanism explaining this phenomenon could be the increased circulatory delay due to age-related blunting of chemoreflex [26, 27]. In addition, Leppänen et al., 2017 found that the AHI and durations of apnea, hypopnea, and desaturation events increase with age after adjusting for BMI, sex, smoking, daytime sleepiness, snoring, hypertension, heart failure, and supine sleep time [12]. However, in a more detailed analysis, the AHI increased with age only in the moderate OSA severity category. Instead, the apnea event duration increased in mild and severe OSA categories, hypopnea event duration increased in mild and moderate OSA severity groups, and desaturation event duration increased in all OSA severity categories [12]. They concluded that OSA may progress over time by increasing the number and/or the severity of the individual respiratory and desaturation events.

Effect of sleep stages on apnea and hypopnea event duration

REM and non-REM (NREM) sleep are two states of sleep with different anatomical and physiological basis and are organized in a distinctly cyclic fashion across the night. During these two types of sleep, different characteristics in several physiological processes like brain activity, heart rate, blood pressure, sympathetic activity, blood flow activity, muscle activity, temperature control, airway resistance, and respiratory function can be seen [28]. Therefore, it is not surprising that not only the frequency but also the duration of respiratory events may differ in these two sleep states.

Findley et al., 1985 were most probably the first ones who quantified the differences in apnea event duration and desaturation event severity between REM and NREM sleep [29]. They found among 12 OSA patients that apneas were longer and desaturations deeper in REM compared to NREM sleep. Krieger et al., 1997 confirmed these findings by showing that apneas are significantly longer in REM sleep compared to NREM sleep [30]. They also demonstrated that the respiratory effort is lower in REM sleep compared to NREM sleep and respiratory effort decreases with increasing age. Therefore, lowered respiratory effort could partially explain why apneas are longer during REM sleep and why the duration of apneas increases with age [30].

It should be noted that the way the UA responds to the increased airflow resistance is different between OSA patients and healthy individuals. This is, when healthy individuals are put under the inspiratory resistive load, the time it takes to arouse from sleep is significantly shorter during REM sleep compared to that during N2 or sleep stage 3 (N3) [31]. However, this is the opposite in OSA patients; arousals related to spontaneous UA occlusions occurred faster in NREM than in REM sleep [32]. Therefore, these differences may explain, at least partially, why the duration of apnea and hypopnea events is longer during REM in OSA patients. It appears that the chronic occurrence of respiratory events night after night during REM sleep leads to a gradual deterioration of protective mechanisms of the UA, which further may explain why respiratory events are longer in REM compared to NREM sleep.

Even though several studies have shown that the duration of apnea events is longer in REM sleep compared to NREM sleep [4, 11, 29, 30, 33] conflicting results also exist. For example, Guilleminault and Rosekind, 1981 reported no significant difference in the apnea event duration between REM sleep and NREM sleep in young patients with mild OSA, and speculated that longer apnea events during REM sleep could be related to age, obesity, and the number of apnea events [34]. However, they found that an increased number of arousals and greater sleep deprivation are associated with a greater increase in apnea duration in REM compared to in NREM sleep, and thought that this could be due to an increase in sleepiness-induced sleep pressure in older OSA patients [34]. Furthermore, even though Butler et al., 2019 showed that respiratory event duration predicts mortality in men and women and although respiratory events tend to be longer during REM sleep than in NREM sleep, a separate analysis of events in REM vs. NREM had only a minimal effect on the risk of mortality [23].

The duration of respiratory events has also been found to be modulated within REM and NREM sleep by the number of arousals, the magnitude of sleep deprivation, sleeping position, and body weight [35]. Non-positional OSA patients (NPPs) were found to have significantly longer total hypopnea time and total apnea-hypopnea time compared to positional patients (PPs) during REM sleep [35]. In addition, obese patients were found to have longer total hypopnea time and total apnea-hypopnea time during REM sleep but shorter respiratory events during NREM sleep compared with normal-weight patients [35].

Based on the previously published research, it seems to be well acknowledged that in general, apnea events are longer in REM sleep compared to NREM sleep. This phenomenon is modulated by the effect of age, weight, sex, sleeping position, and perhaps also by other factors that are not fully investigated yet. Although the mechanism underlying these differences, and the factors affecting them are not completely understood, it has been proposed that one of the main component is the greater pharyngeal muscle relaxation during REM sleep [36, 37].

Effect of sleeping position on apnea and hypopnea event duration

The important effect of sleeping position on snoring [38] and on the frequency of breathing abnormalities during sleep [39] has been recognized many years ago. OSA patients can be divided into positional and non-positional patients based on the worsening effect that the supine position has on the frequency of apneas and hypopneas [40]. Even thought, positional therapy – a behavioral therapeutic option for avoiding the supine position during sleep – has a long history [41], the effect of sleeping position on the duration of apnea and hypopnea events was described much later.

Oksenberg et al., 2000 studied the effect of the sleeping position on the duration of apneas in the supine and lateral positions [42] and found that apneas occurring in the supine position were significantly longer than those in the lateral position. Also, several physiological parameters associated with apnea duration were significantly more severe in the supine position: desaturations were deeper, changes in heart rate greater, snoring at the end of the respiratory event was louder, and arousals longer. Thus, they concluded that not only the AHI increases in the supine position but also the characteristics of apneas and physiological changes associated with them get worse.

The effect of sleeping position on PSG findings between patients with REM–related OSA and NREM–related OSA was evaluated by Oksenberg et al., 2010 among 100 consecutively diagnosed OSA patients [43]. They found that the average duration of apnea and hypopnea events during REM sleep was similar in the supine and lateral positions in both patient groups. Therefore, in patients with REM-related OSA the supine position seems to be associated with an increased frequency of respiratory events [40] but not with an increased duration of apneas and hypopneas during REM sleep.

Kulkas et al., 2015, assessed the clinical consequences of apnea and hypopnea events occurring in the supine position by conducting a retrospective analysis of ambulatory polygraphic recordings of 793 patients, with a median follow-up time of 195 months [44]. They compared risk ratios of morbidity and mortality between PPs and NPPs and found that PPs having most of the obstruction events in the supine position, had significantly higher mortality and morbidity risk ratios in the severe OSA category compared to NPPs. As apneas and hypopneas are longer in severe OSA patients in the supine position than in the lateral position [42], it is possible that the increased morbidity and mortality risk is related to the increased severity of respiratory events occurring in this sleep posture. This idea was also supported by the findings of Leppänen et al., 2016 [45]. They found that apneas were 6.3%, 12.5%, and 11.1% longer in the supine position compared to lateral positions in mild, moderate, and severe OSA categories, respectively. Most probably due to the increase in apnea event duration, the desaturation areas were 5.7% and 25.5% larger for moderate and severe OSA patients in the supine position compared to the lateral position. As deeper and longer desaturation events have been linked to adverse health consequences more strongly than shorter and shallower ones [46-50], these results demonstrate that the supine sleep posture has adverse health consequences through the worsening effect on respiratory event characteristics regardless the severity of OSA. These results have clear clinical implications, especially for positional patients if treated efficiently with positional therapy: avoiding the supine position during sleep can effectively decrease the severity of OSA but also the severity of the respiratory and desaturation events, and therefore reduce the risk for severe health consequences.

Summary and conclusion

Based on the existing research evidence, it is clear that there are multiple factors influencing the duration of respiratory events during sleep. Sex, degree of obesity, age, sleep stage, and sleeping position are most probably the best-known factors that affect the duration of apnea and hypopnea events in OSA patients. However, the effect of these factors on respiratory events duration is complex; in general, most of these factors interact with each other affecting the duration of sleep-related respiratory events. Thus, the characteristic of respiratory events is the result of a complex interaction between several factors. Nevertheless, it is most probable that a number of other parameters not included in this analysis also play a key role in the determination of respiratory event duration during sleep. For example, sleep deprivation and the degree of sleep fragmentation, different drugs, co-morbidities (e.g. heart failure), alcohol consumption, the chronicity of the disease, as well as ethnic and genetic components, are also other elements that most probably influence the duration of respiratory events.

Moreover, several physiological components such as circulatory delay, arousal threshold, pharyngeal collapsibility, and the sensitivity of the ventilatory control system (loop gain) [26] are most probably factors that have also a crucial effect on respiratory event duration during sleep. However, the current data on whether and how these factors influence the duration of respiratory events is limited.

Given the current trend of emphasizing the importance of personalized sleep medicine, it is clear that the AHI alone is insufficient to explain the multifactorial nature of OSA, determine the severity of OSA, or estimate the risk for OSA-related health consequences. That is, at least the characteristics of apnea and hypopnea events (duration and type) and the number, duration, and depth of desaturation events should be considered while diagnosing and estimating the severity of OSA (Figure 1). In addition, it is important to consider also the known factors affecting the duration of respiratory events, e.g. sleep stage, age, sex, sleeping position, and body weight, to obtain as much patient-specific information as possible. Only by determining individually the accurate phenotype of each OSA patient, it is possible to provide tailored and the most effective treatment.

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Practice Points:

- The duration of individual apnea and hypopnea events has long been widely overlooked parameter in clinical practice. A short apnea and a long apnea are not similar even though they are treated as such in the apnea-hypopnea index.
- Several factors, such as; age, sex, body weight, and sleeping position affect the duration of abnormal respiratory events in adult OSA patients.
- The physiological response to respiratory events varies depending on the duration of respiratory events. This includes the magnitude of the changes in heart rate and blood pressure, the severity of desaturations, and the duration of arousals, among others.
- The duration of respiratory events should be taken into account when estimating the risk for OSA-related co-morbidities.

Research Agenda:

- The duration of respiratory events can modulate the risk for OSA-related co-morbidities through different pathways. Thus, it would be important to understand the mechanisms and causes for different OSA manifestations.
- As several factors can affect the duration of respiratory events, better understanding on the combined effect of these factors on respiratory event duration would enhance the tailored treatment planning.
- This study described the effect of the most common factors that affect the duration of respiratory events in adult OSA, however, future investigations should assess the effect of many other factors such as sleep deprivation, alcohol, oxygen therapy, drugs, smoking, and the effect of diseases such chronic obstructive pulmonary disease, asthma, and cardiovascular disorders have on the duration of abnormal breathing events during sleep.
- This study included only data from adult patients with OSA. Therefore, how the duration of respiratory events is modulated by different factors in children with OSA should be investigated.

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