Duration of respiratory events in obstructive sleep apnea: In search of paradoxical results

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Summary

Research related to the duration of respiratory events in obstructive sleep apnea (OSA) has been scarce, perhaps due to the dominant role played by the apnea-hypopnea index (AHI) in the diagnosis and severity estimation of OSA. Lately, however, researchers and clinicians have started to acknowledge the importance of this overlooked parameter. Intuitively, 40-seconds-long apnea events have more harmful physiological and health consequences than 10-seconds-long apnea events. But is this the case? Here, we review the research-based evidence showing physiological, hemodynamic, clinical, sleep quality, and health consequences of long vs. short respiratory events. Even though the literature related to these issues is limited, the results are of interest and in some cases paradoxical.

Keywords: Sleep**,** Sleep apnea**,** Obstructive sleep apnea**,** OSA, Apnea duration, Hypopnea duration, AHI, Apnea / hypopnea length, OSA phenotype, Personalize sleep medicine

Abbreviations:

AHI – apnea-hypopnea index

AHDI – apnea-hypopnea desaturation index

BP – blood pressure

BMI – body mass index

CBFV – cerebral blood flow velocity

COMISA – comorbid insomnia and OSA

HR - heart rate

ΔHR – percentage difference between the maximum and the minimum HR value

MAD – mean apnea duration

N2 – sleep stage 2

NREM - non-rapid eye movement

ODI – oxygen desaturation index

OSA – obstructive sleep apnea

PSG – polysomnography

REM – rapid eye movement

RR interval - the time elapsed between two successive R waves of the QRS signal on the electrocardiogram

TAHD% - total apnea-hypopnea duration as a percentage of TST

TAD% - total apnea duration as a percentage of TST

THD% - total hypopnea duration as a percentage of TST

TST – total sleep time

Introduction

Obstructive sleep apnea (OSA) is a chronic disorder characterized by recurrent apnea and hypopnea events during sleep causing several adverse health consequences – not only affecting sleep quality but also the overall well-being and quality of life [1]. The severity of OSA is defined by calculating the average number of apneas and hypopneas per hour of sleep i.e., the Apnea-Hypopnea Index (AHI). Accordingly, a patient having the AHI value between 5-15, 15-30, or >30 is considered to have mild, moderate, or severe OSA, respectively [2].

The AHI has been used for decades in the sleep medicine community and its contribution to understanding the degree of severity of this chronic disease has been noteworthy. The AHI is simple to calculate and interpret, and it is well known among all sleep clinicians and researchers, providing a common language for the evaluation and discussion of clinical investigations [3]. Nonetheless, if the severity of OSA is solely estimated based on the AHI, many characteristics of OSA severity are overlooked, particularly the duration of apnea and hypopnea events. It is surprising that until now the duration of these breathing abnormalities has been assessed only sporadically by sleep researchers and clinicians. It is intuitively evident that the effect of a 10-second-long apnea event is not the same as a 40-second-long apnea event. It is also logical to think that the hemodynamic responses, the physiological consequences, and the clinical implications of respiratory events having different durations probably differ as well. Since many patients have suffered from OSA for many years before receiving the diagnosis and treatment [4], the OSA-related health deterioration could be different at the time of the diagnosis, not only because of the difference in the number of events but also depending on respiratory event duration.

According to the AHI, a patient with a high number of short respiratory events will have a high AHI while a patient with a few long respiratory events will have a low AHI – assuming that

the total sleep time is similar. This leads to the question: who in fact has a more severe disease? Who is at the highest risk for adverse health consequences caused by sleep-related breathing abnormalities? Two patients may belong to the same OSA severity group based on the AHI, but the total duration of apnea and hypopnea events could be totally different and therefore, it is possible that the clinical severity and the health consequences in these two OSA patients could differ significantly [5, 6].

One dominant factor defining the duration, depth, and area of desaturation events is the duration of apnea and hypopnea events [7]. Thus, the OSA-related hypoxic burden, which has been linked to adverse cardiovascular consequences [8-10], is directly affected by the duration of the breathing abnormalities, a parameter which, as already mentioned, is neglected by the AHI. In general, OSA patients having long and deep desaturations (as a consequence of long apnea and hypopnea events) normally experience more deleterious physiological effects during sleep and thus, may have an increased risk for cardiovascular morbidity and mortality compared to patients with short apnea and hypopnea events and less severe desaturations (Figure 1) [8-10].

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In addition, one of the most detrimental effects of OSA is a decreased sleep quality due to severe sleep fragmentation, caused by arousals and awakenings related to apnea, hypopnea and flow limitation events. Sleep fragmentation should not be considered less important than the cardiovascular consequences of OSA, as it is most likely the main reason behind excessive daytime sleepiness; the most prevalent daytime symptom of OSA patients. Not only the fragmented sleep, but the chronicity of the hemodynamic reaction at the end of each apnea and hypopnea event, could

be a possible mechanism behind the fact that also patients with high AHI but short respiratory events are at high risk for harmful OSA-related health consequences [11].

OSA patients with long apnea and hypopnea events - what are the consequences?

One of the first studies considering the respiratory event duration during sleep assessed the effect of sleeping position on the severity of obstructive apnea events among 30 severe non-positional OSA patients [12]. Thirty apneas occurring in the supine position and thirty apneas in the lateral position were analyzed during sleep stage 2 (N2). They found that obstructive apneas occurring in the supine position were significantly longer and were associated with more severe physiological changes (i.e., deeper desaturations, greater changes in heart rate, increased snoring loudness, and longer arousal durations) compared to events occurring in the lateral position. Thus, sleeping position is an important factor affecting the duration of respiratory events and the associated physiological consequences during sleep [12].

In 2012 Muraja-Murro et al., introduced a novel parameter for the assessment of OSA severity: Total apnea-hypopnea duration (TAHD%) (as a percentage of total sleep time (TST)) and proposed a combined index incorporating the duration and the severity of apnea, hypopnea, and desaturation events (TAHD% × average desaturation depth) [5]. Interestingly, they found that total apnea duration as a percentage of TST (TAD%), total hypopnea duration as a percentage of TST (THD%), and total apnea/hypopnea duration as a percentage of TST (TAHD%) increased significantly as function of the severity of OSA. Moreover, the average duration of apneas increased significantly with increased OSA severity, when the severity was defined based on the AHI. However, the average duration of hypopneas was not significantly different between normal,

mild, and moderate OSA severity groups. Actually, among severe OSA patients, hypopneas were shorter on average compared to milder OSA severity groups. In addition, the average desaturation depth increased significantly as a function of the AHI. They concluded that the AHI explained 72% of the variation in the combined index (i.e. TAHD% × average desaturation depth). Interestingly, but not surprising, neither the AHI nor the above-mentioned novel parameters were correlated with self-reported daytime sleepiness. It is noteworthy that TAHD% was found to be over 30% in the severe OSA group and among the most severe cases, it exceeded 70% - in other words, patients with severe OSA can breathe without respiratory events only 30% of the TST. The authors concluded that these new severity indices (TAHD% and TAHD% × average desaturation depth) can provided more information about the severity of OSA than the AHI alone, but that should be confirmed by evaluating their connection to morbidity and mortality in follow-up studies.

Furthermore, in 2013, Muraja-Murro et al., introduced a new parameter, obstruction severity, defined as the sum of products of the duration of the respiratory event and the area of the related desaturation. They found that obstruction severity was related to an increased mortality rate in severe OSA patients [9]. The study was based on ambulatory polygraphic recordings of 1068 men with suspected OSA with over 16 years of follow-up. Among this population, the recordings of 113 deceased patients were compared to 113 living counterparts matched by the AHI, body mass index (BMI), age, and smoking habits. Deceased patients with severe OSA had higher obstruction severity values compared to their living counterparts, and in contrast to the AHI, obstruction severity was significantly associated with mortality. In addition, 59% of all deceased patients and 83% of deceased patients with severe OSA, had higher obstruction severity values compared to their living counterparts. Therefore, the authors concluded that the obstruction

severity parameter could provide valuable prognostic information supplementing the AHI. These authors have also shown that values of obstruction severity parameter can vary significantly between individuals with similar AHI and suggested that the use of this parameter could enable the separation of patients with increased mortality rates more accurately than the AHI alone [6].

These studies mentioned above corroborate the pioneering concept of Otero et al., 2012 who assessed the contribution of several indices to discriminate healthy subjects from OSA patients [13]. They analyzed 46,505 respiratory events from 274 polysomnographic (PSG) recordings, to find the best index/indexes to differentiate healthy individuals from OSA patients. They found that the apnea-hypopnea desaturation index (AHDI), which is the sum of percentages of apnea, hypopnea, and desaturation times from TST, was the best index to differentiate OSA patients from healthy subjects. The main advantage of this index is that, unlike the AHI, it takes the duration of the respiratory events into account.

The association between hemodynamic changes and apnea duration has also been investigated. Alex et al., 2014 divided 309 apnea events from nine OSA patients based on their duration [14]. They showed that the change in arterial blood pressure (BP) and cerebral blood flow velocity (CBFV) were greater after longer apnea events compared to shorter ones [14]. For example, when the apnea duration increased from 10-sec to > 30-sec, the apnea event-related change in BP increased from 14% to 26% and the change in CBFV increased from 22% to 42%. These results suggest that the magnitude of the apnea-induced changes in BP and CBFV is associated with the duration of apnea events. In support of these findings, Wu et al., 2016 showed in a group of 596 OSA patients that mean apnea duration (MAD) is significantly associated with moderate-to-severe hypertension even after adjusting for age, sex, BMI, history of current smoking, alcohol usage, AHI, and lowest oxygen desaturation [15]. They speculated that this

association could be due to worse hypoxemia and hypercapnia as well as disturbed sleep architecture related to longer respiratory events.

Sola-Soler et al., 2017 studied the relationship between apnea-related ΔHR (percentage difference between the maximum and the minimum heart rate (HR) values associated with obstructive apnea events) and apnea duration [16]. They analyzed 1454 obstructive apnea events from eight patients with severe OSA and showed that the average change in HR associated with ≥ 30-sec apneas was significantly greater compared to the average change in HR caused by < 30-sec apneas. They also observed that patients with identical AHI values can have remarkably different distributions of ΔHR and apnea duration and that patients with high AHI do not necessarily have high average ΔHR. They concluded that the apnea-related change in HR (heart rate excursion) could be partially explained by the duration of apnea events, and thus, apnea duration may be a simple measure of the cardiovascular stress associated with OSA that is not expressed in the AHI.

The same group also evaluated the effect of respiratory event type and duration on the severity of oxygen desaturations by analyzing the desaturation depth, duration, and area. They utilized 2022 apnea and hypopnea events from the same eight severe OSA patients [17]. The authors found that the duration of desaturation events was directly proportional to the duration of the respiratory events and that this association was similar for apneas and hypopneas, as was also shown by Kulkas et al., 2017 [7] (Figure 2). In addition, the depth of oxygen desaturations was also directly proportional to the respiratory event duration [17], and similarly to the results by Kulkas et al., 2017 [7] the desaturations were deeper when related to apneas compared to hypopneas. Accordingly, the depth of oxygen desaturations was dependent on event type and duration, however, remarkable variability was found between subjects.

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Furthermore, patients with long (≥ 20-sec) apneas have been shown to snore louder, complain of morning tiredness more often, and be at a higher risk for hypertension compared to patients with short apneas (< 20-sec) [18]. Also, according to this study, patients with long apneas had significantly higher AHI, less total wake time, lower percentages of N1 and N3 sleep, and lower mean oxygen saturation. Consequently, in patients with longer average apnea duration, OSA is associated with poorer sleep quality, poorer quality of life, and more severe health consequences compared to the patients with shorter average apnea duration. As longer apnea events usually lead to deeper desaturations [7] (Figure 1) and the longer mean apnea-hypopnea duration has been linked to low blood oxygen saturation levels [19], these findings could explain the association between respiratory event duration and cardiovascular consequences, thus, providing evidence that long respiratory events have detrimental health effects.

Recently, Karhu et al., 2021 showed that mild OSA patients with long and deep desaturations are at higher risk for worsening of OSA over time than patients with short and shallow desaturations [20]. Thus, mild OSA patients should be treated, or at least should be followed on a regular basis to avoid the harmful consequences of the disease [20]. This study also showed that the severity of desaturation events can increase progressively over time in mild OSA patients without a change in oxygen desaturation index (ODI) values. These results suggest that among mild OSA patients, the morphology of the desaturation events is more sensitive to estimate OSA progression compared to the ODI that only quantifies the number of desaturation events. It is of interest to evaluate if this worsening in the severity of desaturations with time is unique to mild OSA or if the same phenomenon is also observed in moderate and severe OSA patients. The

effect of age, sex, BMI, sleep stages, and body posture on this time-related worsening of desaturation events also needs to be further investigated.

To summarize, the above-mentioned studies have provided clear evidence that the duration of apnea and hypopnea events is a parameter to consider when estimating the severity of OSA – the number of the events is not enough. The results of these former studies support the idea that longer respiratory events have more severe physiological and clinical consequences than shorter events and therefore, the duration of the respiratory events should be quantified in the diagnostic assessment of OSA patients.

OSA patients with short apnea or hypopnea events - what are the consequences?

In an important study, Butler et al., 2019 investigated the relationship between respiratory event duration and mortality risk using data from the sleep heart health study (SHHS) [11]. The mean age of patients was 63 years, and they had a mean AHI of 13.8 events/hour; 35%, 20%, and 12% of the patients had mild, moderate, and severe OSA respectively, and the remaining 33% were diagnosed to have no OSA. They found that short respiratory events were associated with an increased risk for mortality, even when the effect of the AHI, age, sex, hypertension, diabetes, and cardiovascular disease were considered. Female sex, younger age, African American race, current smoking status, higher BMI, lower AHI, and higher minimum oxygen saturation were also associated with shorter respiratory events. It is remarkable, surprising and even paradoxical, that in mild OSA patients, among which lower AHI is related with short respiratory events, could have a notable result; i.e. to be associated with an increased risk of mortality. Respiratory event duration was assessed in quartiles, and among patients with the shortest event duration (i.e. Q4), the

mortality rate was 20% higher compared with those patients with the longest event duration (i.e. Q1). After adjusting for the AHI, hypertension, diabetes, and cardiovascular disease, the results were even stronger. Although respiratory events tended to be longer in rapid eye movement (REM) sleep compared to non-REM sleep (NREM), a separate analysis of REM vs. NREM sleep did not change the conclusion: short respiratory events were associated with increased mortality risk, especially in the moderate OSA group. However, as acknowledged by the authors [11], only 5% of the patients had an average duration of respiratory events over 30 seconds, therefore it is unclear whether these results can be generalized to those patients with very long respiratory events. Butler et al., also mentioned that the results of their study are different from previous results on the effect of long respiratory events and the characteristic hypoxic burden on cardiovascular health [6, 9]. However, it may be speculated that OSA characterized by long respiratory events and OSA characterized by short events may represent different phenotypes of OSA, both of which may contribute to increased risk for mortality but by independent pathophysiological pathways. Clearly, these results provide an important message for sleep clinicians and researchers: it is time to pay much more attention to mild OSA patients.

Butler et al., 2019 also suggested that the OSA phenotype characterized by short respiratory events could be associated with sleep fragmentation and elevated sympathetic tone [11] and thus, explaining why several OSA patients also suffer from comorbid insomnia (COMISA) [21]. This could be especially relevant for women as among them OSA is more often associated with insomnia and sleep fragmentation compared to men [22]. Furthermore, as the AHI has not been found to be associated with mortality in women [23], it appears that the duration of the respiratory events should be considered especially in women when estimating the severity of OSA and related health consequences. Definitely, this is a topic for further investigation since there are no data

available supporting this hypothesis, and the mechanism behind the association between short respiratory events and sleep fragmentation is not yet fully understood. However, it has been proposed that short respiratory events during sleep could be due to the low arousal threshold that terminates respiratory events in their early stage, preventing long events to occur [24]. Thus, a low arousal threshold will lead to short events and a high arousal threshold for long ones. The arousal related to respiratory events have chemical (chemoreceptors) and mechanical (mechanoreceptors) components. The interaction of the chemical drive (hypoxia/hypercapnia) and the respiratory effort (respiratory muscles) will determine the occurrence of an arousal. It should be mentioned that sleep stage (REM or NREM), sleep fragmentation, sleep deprivation, and time of the night (circadian modulation) are factors that may also influence the arousal threshold. In addition, as mentioned previously, sleeping position is another factor that affects the arousal threshold and the duration of respiratory events [12].

Recently, Borker et al., 2021 evaluated how durations of apneas and hypopneas during NREM sleep vary between demographic groups and quantified their association with different physiological traits i.e., loop gain, arousal threshold, circulatory delay, and pharyngeal collapsibility [25]. They analyzed sleep data from 1546 participants and found that shorter respiratory events were more common among women, African Americans, younger participants, and individuals with higher BMI. Shorter events were also associated with lower arousal threshold, shorter circulatory delay, increased loop gain, and less severe pharyngeal collapsibility. However, the association between the event duration and demographic factors diminished when controlling for these physiological traits. Therefore, it seems that the variation in respiratory event duration is mostly explained by measurements that are reflecting chemoreflex, arousal threshold, and pharyngeal collapsibility. Furthermore, it has been also shown that respiratory event duration may

be a genetically encoded feature of OSA [26] as a genetic locus associated with respiratory event duration in Latin/Hispanic Americans has been identified [27]. As mentioned by the authors, this supports the idea that respiratory event duration appears to be an independent, inherited trait and could help explain differences between OSA phenotypes.

In addition, it has been proposed that by combining information on pulmonary function with polysomnographic parameters it is possible to predict the development of hypertension in OSA patients by utilizing machine learning [28]. This novel combination of parameters predicted the incidence of hypertension better than the AHI alone. Shorter respiratory events were associated with an increased risk of hypertension, corroborating previous results showing an association between short respiratory events and higher mortality risk [11, 25]. However, these results are contrary to previously published results showing that longer respiratory events were associated with more detrimental cardiovascular outcomes than shorter ones [9] and therefore with a higher risk of hypertension. It is well known that arousals and awakenings cause a sudden increase in BP and HR [29]. Since patients with many short respiratory events typically have a high number of arousals and awakenings, the chronicity of several rapid increases in BP, inducing sympathetic hyperactivity, could be one explanation for the higher risk of hypertension, leading to an increased risk of cardiovascular morbidity and mortality. Nevertheless, long apneas and hypopneas generate a significantly greater increase in BP compared to shorter events [14] and as a result, long respiratory events may also increase the risk for hypertension. Therefore, the question is whether several small increases in BP after short respiratory events are more detrimental to the cardiovascular system than a lower number of greater increases in BP after long respiratory events. Perhaps both are damaging the cardiovascular system through different pathways and the timing

for the functional cardiovascular deterioration is different. This topic clearly requires further investigation.

The hemodynamic changes between short and long apneas among severe OSA patients have also been investigated [30]. The authors divided apneas into short (< 20-sec) and long (> 27-sec) ones based on their previous study showing that the median duration of apneas in severe OSA patients is 22-sec [31]. They found that BP increased after both short and long apnea events, but after long apneas, the systolic BP was significantly higher than after short apneas. In addition, during long apneas, a gradual increase in BP was observed whereas a small decline in BP occurred during short apneas. Diastolic BP followed the systolic BP pattern. In addition, it has been shown that HR increases and RR intervals shorten after respiratory events but these changes are greater in relation to longer respiratory events [30, 32]. However, a significant decrease in peripheral resistance has been observed only in relation to short apneas and regardless of the duration, apneas cause acute and pronounced peri-apneic hemodynamic alterations [30]. These are significant findings showing that short apneas (not only long apneas) have an important influence on hemodynamic changes and therefore may also have a role in cardiovascular deterioration.

The relative few but highly qualified studies mentioned above provide clear evidence that short apnea and hypopnea events have a deleterious effect on sleep, as well as on physiological and clinical aspects of OSA. The high risk for all-cause mortality associated also with short respiratory events is a serious concern and further research should address the imperious need of identification and treatment of OSA patients whose OSA is characterized by short respiratory events.

What are the mechanisms controlling the duration of respiratory events?

Probably the most critical factor affecting the respiratory event duration is the level of arousability; high arousability (i.e. low arousal threshold) will terminate the respiratory event earlier leading to the occurrence of short respiratory events and resulting in sleep fragmentation. Short respiratory events are probably also associated with a sensitive upper airway (with high arousability) that is highly responsive to chemical (hypoxia and/or hypercapnia) and/or mechanical input. Kimoff et al., 1994 showed that the arousal response and apnea termination are mediated mainly by feedback from mechanoreceptors in the respiratory system, most likely from respiratory muscles, as well as indirect stimuli from chemoreceptors through ventilatory effort [24]. Therefore, mechanoreceptors may also have a dominant role in the upper airway resistance syndrome , which by definition is a pattern of highly fragmented sleep with a high number of arousals without desaturations (and a clinical history suggestive of OSA) [33].

Already in 1981, Lavie et al. showed that the duration of apnea events increases across the night during N2 sleep [34]. They suggested that this increase in apnea duration results from a progressive increase in the arousal threshold due to a deepening of sleep or due to a progressive change in chemoreceptor sensitivity. Since this increase in apnea duration was not found in REM sleep, they argued that the apnea termination during REM sleep is mediated by a different mechanism than in NREM sleep [34]. Several years later, these results were confirmed by several authors [35-37]. In addition, Charbonneau et al., 1994 found that in spite of the increase in the duration of apneas across the night and decrease in ODI, the severity of apnea-related desaturation did not change. They also found that the time spent in apnea increased as the night progressed due to three components: the increased apnea duration across the night, the increased amount of REM

sleep towards the morning, and the increased frequency of apnea events [35]. In addition, Monserrat et al., 1996 measured trans-diaphragmatic pressure and determined the diaphragm tension-time index during PSG studies in seven severe OSA patients [38]. They found that at the end of an apnea event just before an arousal, the values of these parameters were significantly higher at the end of the night compared to the beginning of the night. Thus, these findings suggest that across the night, there is a deterioration of the arousal response to neural stimuli that may weaken the arousal response and lead to an increase in the duration of respiratory events towards the morning [38]. Furthermore, Cala et al., 1996 reported that topical upper airway anesthesia increases the apnea duration at the beginning of the night but not at the end of the night [39]. These results suggest that upper airway sensory receptors may have a role in apnea termination at the beginning of the night, but as the night goes on the contribution of these receptors to the mechanism of apnea termination diminishes. Therefore, at the end of the night, a greater respiratory effort may be required to trigger arousal leading to apnea termination, which could explain why the duration of apneas increases across the night.

To investigate whether the increase in the apnea duration across the night is related to the sleeping position, Oksenberg et al., 1996 compared apneas occurring in the lateral position to apneas occurring in the supine position in N2 sleep within the early, middle, and late periods of night [36]. They found that apneas in the supine position were longer than those in the lateral position and that the duration of apneas increased across the night in both sleeping positions. Thus, they concluded that among severe OSA patients the sleep position does not have a significant effect on the increase in the apnea duration towards the morning during N2 sleep. The authors also hypothesized that sleep-dependent mechanisms (homeostatic and circadian) could participate in the determination of apnea characteristics across the night [36].

Later, Butler et al., 2015 demonstrated that the circadian system (an endogenous clock in the hypothalamus controlling most daily rhythms in physiology and behavior) is strongly associated with the increase in the duration of respiratory events during NREM sleep across the night. It has been estimated that the circadian system may explain >50% of the increase in the duration of respiratory events towards the morning [40]. In other words, at least two components appear to be involved in the lengthening of apneas across the night: the effect of the central circadian system and the weakening of the arousal response towards the morning. It is important to remember that the recurrent vibrations caused by loud and continuous snoring and by repetitive apneas and hypopneas can lead to injuries in the upper airways. These lesions can cause inflammatory changes and edema as well as damage nerves and muscles of the upper airway soft tissue, which may also partially explain the blunting in the arousal response and thus, the increase in the duration of apneas across the night [41].

Summary and conclusion

The duration of apnea and hypopnea events has different physiological and clinical implications. It appears that the importance of the respiratory event duration has been overlooked for many years by researchers and clinicians probably due to the widespread use of the AHI. Fortunately, this has changed in the last few years; more research has been conducted related to the respiratory event duration and clinicians have started to pay attention to this parameter too. The available evidence supports the fact that longer respiratory events have more detrimental effects on health compared to shorter events, as hemodynamic changes and cardiovascular stress (mainly due to the hypoxic burden related to these respiratory events) associated with OSA are higher in relation to longer respiratory events.

Nevertheless, recent well-qualified studies also provide strong evidence that OSA patients with short respiratory events have a significantly elevated risk of all-cause mortality, possibly because of more unstable ventilation and increased autonomic nervous system activity. Therefore, it seems that two distinct OSA phenotypes related to the duration of respiratory events exist and both have several adverse health effects. However, since the data available are limited, the respiratory scoring criteria may differ, and the results obtained so far are somewhat controversial, more research is required to fully understand the prognostic value of respiratory event duration, particularly in the era of personalized sleep medicine.

Practice Points:

- The apnea-hypopnea index does not take in account the duration of respiratory events even though the duration has physiological and clinical implications.
- Long respiratory events during sleep appear to have worse physiological and clinical consequences compared to short respiratory events.
- The most recent studies have also shown that short respiratory events increase significantly the risk of all-cause mortality in OSA patients.
- The duration of respiratory events should be considered in order to understand the severity of OSA more accurately.

Research Agenda:

- Large studies should evaluate the clinical consequence of long vs. short respiratory events in OSA patients.
- The night-to-night variability of respiratory events duration should be investigated.
- It would be important to understand the main pathways through which the respiratory event duration is associated with clinical consequence. It should be investigated whether this is through the desaturation or arousal events accompanied by the respiratory events, or whether there are another important factors (e.g. changes in heart rate and blood pressure) linking the respiratory event duration to adverse health consequences.

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