Influence of sleep stages on determining positional dependency in patients with obstructive sleep apnea

Somi Ryu¹, Seung Chan Kim², Rock Bum Kim³, Byechong Min Lee¹, Sang-Wook Park¹, Yung-Jin Jeon¹,⁵, Yeon-Hee Joo⁵,⁶,⁷, Hyun-Jin Cho¹,⁵, Sang-Wook Kim¹,⁵,⁷

¹Department of Otorhinolaryngology, Gyeongsang National University Hospital, Jinju; ²Department of Biostatistics, Clinical Trial Center, Biomedical Research Institute, Pusan National University Hospital, Pusan; ³Regional Cardiocerebrovascular Disease Centre, Gyeongsang National University Hospital, Jinju; ⁴Section of Hematology-Oncology, Baylor College of Medicine, Houston, Texas, United States; ⁵Institute of Medical Science, Gyeongsang National University, Jinju; ⁶Department of Otorhinolaryngology, Gyeongsang National University Changwon Hospital, Changwon; ⁷Department of Otorhinolaryngology, Gyeongsang National University College of Medicine, Jinju, Republic of Korea.

ORCID

Somi Ryu: 0000-0002-6528-736X
Seung Chan Kim: 0000-0002-9210-9040
Rock Bum Kin: 0000-0001-5868-0465
Byeong Min Lee: 0000-0002-1828-5855
Sang-Wook Park: 0000-0002-7579-2327
Yung-Jin Jeon: 0000-0002-0285-5534
Yeon-Hee Joo: 0000-0003-4011-3475
Hyun-Jin Cho: 0000-0002-6518-351X
Sang-Wook Kim: 0000-0002-1681-0556
Author contribution

Conceptualization and project administration: SWK

Formal analysis: SCK, RBK

Methodology: BML, SWP

Project administration: YJJ, YHJ, HJC

Writing - original draft: SR, SWK

Writing - review & editing: SWK, SCK, RBK, BML, SWP, YJJ, YHJ, HJC

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This work was supported by Biomedical Research Institute Fund (GNUHBRIF-2023-0012) from the Gyeongsang National University Hospital, and the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1A2C1013224).

Corresponding author: Sang-Wook Kim, MD, PhD

Department of Otorhinolaryngology, Gyeongsang National University Hospital, 79 Gangnam-ro, Jinju, Gyeongsangnam-do (52727), Republic of Korea

Tel. +82-55-750-8177; Fax. +82-55-759-0613

E-mail address: basilent@gnu.ac.kr

Running head: Influence of sleep stages on positional dependency

Key words: diagnosis; polysomnography; sleep apnea, obstructive; sleep stages; supine position.
Highlights

- The non-supine/supine apnea-hypopnea index (AHI) ratios during REM sleep, NREM sleep, and entire sleep showed poor agreement.
- Calculating a weighted non-supine/supine AHI ratio by multiplying the ratio during REM sleep and NREM sleep by their respective time proportions within the entire sleep revealed differences compared to the original non-supine/supine AHI ratio, which did not consider sleep stages. This difference was particularly pronounced in patients with mild obstructive sleep apnea (OSA).
- The weighted non-supine/supine AHI ratio appears to be a useful metric for accurately diagnosing positional dependency, especially in mild OSA patients.
Abstract

Objective: Supine sleep position and rapid eye movement (REM) stage are widely known to aggravate the severity of obstructive sleep apnea (OSA). In general, position-dependent OSA is defined as an apnea-hypopnea index (AHI) at least twice as high in the supine position as in other sleep positions, but it can be misdiagnosed if a certain sleep stage, REM or NREM, is dominant in a specific sleep position. In this study, we investigated the influences of the sleep stages on positional dependency.

Methods: The polysomnographic data from 111 OSA patients aged ≥ 18 years (AHI > five events/hour) who slept in both supine and non-supine positions (each ≥ 5% of the total sleep time) were retrospectively analyzed. The overall ratio of non-supine AHI/supine AHI (NS/S AHI ratio) during the entire sleep was compared between specific sleep stages, i.e., REM or NREM sleep. Additionally, the weighted NS/S AHI ratio reflecting the proportion of each sleep time was created and compared with the original NS/S AHI ratio.

Results: The mean value of the NS/S AHI ratio did not differ between the entire sleep and the specific sleep stages. However, those ratios in the individual patients showed poor agreement of the NS/S AHI ratios between the entire sleep and the specific sleep stages. The weighted NS/S AHI ratio also demonstrated poor agreement with the original NS/S AHI ratio, mainly due to the discrepancy in mild to moderate OSA patients.

Conclusion: The weighted NS/S AHI ratio might help assess precise positional dependency.
Introduction

Obstructive sleep apnea (OSA) is a representative disorder that disrupts normal sleep by causing repetitive collapse of the upper airway during sleep, leading to hypoxia and frequent awakenings. OSA not only impairs the quality of sleep but can also result in complications such as myocardial infarction, stroke, arrhythmias, and other cardiovascular diseases, necessitating active management. Polysomnography (PSG) is the standard diagnostic test for OSA, and if the apnea-hypopnea index (AHI) derived from PSG is five or higher, along with symptoms such as excessive daytime sleepiness, OSA can be diagnosed (1). The treatment for OSA depends on the severity, with moderate defined as an AHI of 15 or higher and severe defined as an AHI of 30 or higher (2, 3).

The severity of OSA is influenced by factors such as sleep position, sleep stage, body weight, alcohol, and drug use (4). In particular, it is well known that in the supine sleep position, the gravitational effect makes the upper airway collapse more likely, exacerbating the severity of OSA (5, 6). Patients who experience a significant increase in OSA severity in the supine sleep position are called to have a positional dependency (PD). Generally, PD is defined when the AHI measured in the supine position (supine AHI) is twice or higher than that measured in the non-supine position (non-supine AHI) (7). Another factor that significantly worsens OSA severity is REM sleep. Patients whose AHI worsens significantly during REM sleep compared to NREM sleep are referred to as REM-dependent OSA patients (8). Suppose REM sleep is distributed mainly in the non-supine position, and NREM sleep appears mainly in the supine position in a REM-dependent patient. In such a case, the supine AHI may be underestimated, whereas the non-supine AHI is exaggerated, making it appear as if there is no PD in a position-dependent OSA patient. Similarly, suppose REM sleep is concentrated only in the supine position. In that case, the supine AHI may be overestimated, and the non-supine
AHI may be underestimated, leading to the misdiagnosis of non-position-dependent OSA patients as position-dependent OSA patients. In the PSG report, the influence of the sleep stage is not generally reflected in calculating the PD-related parameters, which could lead to incorrect decisions regarding the application of positional therapy (7, 9, 10). Therefore, in the present study, the authors analyzed how often PD changes when considering the influence of sleep stage using data from patients who underwent PSG to diagnose OSA. We also developed the modified parameter that reflects the influence of the sleep stages.

**Materials and Methods**

We retrospectively analyzed data from adult patients aged 18 and above who underwent in-laboratory PSG (Grael 4K PSG; Compumedics, Melbourne, Australia) at [Gyeongsang National University Hospital] and were diagnosed with OSA with an AHI≥5. All the patients were instrumented with standard PSG recording sensors: nasal pressure transducer, oronasal thermistor, electroencephalography, left and right electrooculography, electrocardiography, submental and leg electromyography, pulse oximetry probe, and respiratory effort belts around the chest and abdomen. We excluded cases from the analysis where either the supine or non-supine positions accounted for less than 5% of the total sleep time, as it was deemed difficult to define PD in such cases (11). Consequently, the dataset included 111 patients (96 [86.5%] males; mean age of 46.6 years; mean body mass index [BMI] of 26.6 kg/m²; mean AHI of 32.0). Consistent with the conventional definition, we defined PD as a ratio of non-supine AHI to supine AHI (NS/S AHI ratio) of 0.5 or less. We calculated the overall NS/S AHI ratio during the entire sleep, *i.e.*, total sleep time, and that during REM sleep (NS/S AHI ratio in R) and during NREM sleep (NS/S AHI ratio in NR). For evaluating the agreement among these three NS/S AHI ratios, group-wise comparisons were performed between each
pair of ratios (i.e., overall NS/S AHI ratio vs. NS/S AHI ratio in R, overall NS/S AHI ratio vs. NS/S AHI ratio in NR, and NS/S AHI ratio in R vs. NS/S AHI ratio in NR). Furthermore, we calculated the weighted NS/S AHI ratio by multiplying the proportion of REM and NREM sleep during the total sleep time by the respective NS/S AHI ratios in each sleep stage, as shown below.

\[
\text{Weighted NS/S AHI Ratio} = \left( \frac{\text{Non-supine AHI during REM}}{\text{Supine AHI during REM}} \times \frac{\text{REM sleep time}}{\text{Total sleep time}} \right) + \left( \frac{\text{Non-supine AHI during NREM}}{\text{Supine AHI during NREM}} \times \frac{\text{NREM sleep time}}{\text{Total sleep time}} \right)
\]

We compared the difference between the weighted NS/S AHI ratio and the original overall NS/S AHI ratio. Statistical analyses were conducted with R software version ’4.1.2’ (R Core Team. R Foundation for Statistical Computing, Vienna, Austria, 2021). The paired t-test, Bland-Altman plot, and Lin’s concordance correlation coefficient (CCC) were employed to assess and quantify the agreement of the NS/S AHI ratios between entire sleep and REM sleep, entire sleep and NREM sleep, and original value and weighted value. The values of CCC were regarded as follows: < 0.90, poor; 0.90 to 0.95, moderate; 0.95 to 0.99, substantial; and > 0.99, almost perfect. A \( p \)-value<0.05 was considered statistically significant.

Results

Of the 111 patients, 75 (67.6%) were position dependent (65 [86.7%] males; mean age of 47.8 years; mean BMI of 25.7 kg/m²; mean AHI of 29.3) and 36 (32.4%) were non-position dependent (31 [86.1%] males; mean age of 44.1 years; mean BMI of 28.2 kg/m²; mean AHI of 45.8). The mean value of the overall NS/S AHI ratio was not significantly different from that during REM sleep (Fig. 1A), but the values in each patient showed poor agreement (CCC
When the difference between those two ratios was explored, there were 8 (7.2%) outliers beyond ±2S.D. from the mean (Fig. 1B). Among them, three (case numbers 1.1–1.3) were position-dependent during REM sleep. However, they were not position-dependent based on the overall NS/S AHI ratio. In contrast, two (case numbers 1.4–1.5) were not position-dependent during REM sleep but were position-dependent based on the overall NS/S AHI ratio. There were also considerable discrepancies between the two ratios in the remaining three (case numbers 1.6–1.8), although the status of PD by the definition of 0.5 did not change (Fig. 1C). In comparing the NS/S AHI ratios between the entire sleep and NREM sleep, the mean value of the overall NS/S AHI ratio was not significantly different from the NS/S AHI ratio during NREM sleep (Fig. 1D). However, the values in each patient also showed poor agreement (CCC = 0.81 [0.74-0.86]), although it was less poor than in the comparison between the entire sleep and REM sleep. When it comes to the difference between those two ratios, there were two (1.8%) outliers beyond ±2S.D. from the mean (Fig. 1E). One (case number 2.1) was position-dependent during NREM sleep but was not position-dependent based on the overall NS/S AHI ratio. In another one (case number 2.2), there were remarkable discrepancies between the two ratios, but the status of PD by the definition of 0.5 did not change (Fig. 1F). When those two outliers were excluded, the agreement of the NS/S AHI ratio between the entire sleep and NREM sleep became substantial (CCC = 0.96 [0.94-0.97]). Similarly, when the NS/S AHI ratios were compared during REM and NREM sleep, the mean values were not significantly different (Fig. 1G), but the values in each patient also showed poor agreement (CCC = 0.25 [0.06-0.43]). There were six (5.4%) outliers beyond ±2S.D. from the mean in the comparison of the NS/S AHI ratios.
between REM and NREM sleep (Fig. 1H). Among them, one (case number 3.1) was position-dependent during NREM sleep but not during REM sleep. On the contrary, another two (case numbers 3.2 and 3.3) were position-dependent during REM sleep but not during NREM sleep. The remaining three (case numbers 3.4–3.6) also showed considerable discrepancies between the two ratios, but the status of PD by the definition of 0.5 did not change (Fig. 1I).

Lastly, the weighted NS/S AHI ratio did not significantly differ from the overall NS/S AHI ratio (Fig. 2A), but those two measures in each patient showed poor agreement (CCC = 0.86 [0.80-0.90]). When it comes to the difference between those two ratios, there were three (2.7%) outliers beyond ±2S.D. from the mean (Fig. 2B). None of them was position-dependent based on the overall NS/S AHI ratio. When the weighted NS/S AHI ratio was applied, one (case number 4.1) was revealed to have PD. The other two also showed noticeable changes in the values, but the status of PD by the definition of 0.5 did not change (Fig. 2C). All three outliers exhibited mild or moderate severity (AHI of 9.7, 5.5, and 24.0 for case numbers 4.1, 4.2, and 4.3, respectively). When those three outliers were excluded, the agreement between the overall and weighted NS/S AHI ratios became substantial (CCC = 0.98 [0.97-0.98]). When the degree of agreement between the overall NS/S AHI ratios and weighted NS/S AHI ratios was compared according to OSA severity, a poor agreement was identified in mild to moderate OSA patients (n = 49; CCC = 0.69 [0.52-0.81]; Fig. 3A), while a substantial agreement was exhibited in severe OSA patients (n = 62; CCC = 0.99 [0.98-0.99]; Fig. 3B).

Discussion

Positive airway pressure (PAP) therapy is considered the cornerstone treatment for patients
with moderate to severe OSA in terms of safety and efficacy (12). Since patients not only seek OSA treatment but also desire comfortable sleep, however, the inconvenience of using a mask device during sleep and the additional effort required for equipment cleansing leads to a low long-term compliance rate, reaching around 50% (13). In other words, over time, nearly half of OSA patients may end up untreated and left with similar outcomes to those who receive no treatment at all. Therefore, the clinical need for alternative non-PAP therapies is significant. Options such as mandibular advancement device (MAD) or hypoglossal nerve stimulation can be considered among these treatment methods (14). Similarly, for positional OSA patients, various positional therapies, from using a tennis ball to more advanced methods including vibratory or auditory alarms or vests, can be explored as alternatives to PAP therapy (15).

The prevalence of position-dependent OSA is known as 23%–63% (16, 17). The possibility of positional therapy arises from the past pioneering study by Cartwright, which reported that many OSA patients exhibit an AHI in the supine sleep position that is twice as high as the AHI in the side sleep position. In that study, such a trend was inversely proportional to obesity. Thus, positional therapy was suggested as a potential treatment option for OSA patients with a normal body weight who exhibit PD. Furthermore, 20.8% (= 5/24) of the patients having PD achieved an AHI < 5 in the side sleep position (7). In that study, it was mentioned that the changes in AHI by switching the sleep position might be influenced by the sleep stage. Nevertheless, it was presumed that sleep position-dependent changes in AHI might be independent of the alteration of sleep stage, as the AHI ratio between supine and non-supine sleep positions remained stable despite significant variations in the proportion of each sleep position over the total sleep time among individuals (7). However, given the findings of the present study, which indicate a poor agreement between the NS/S AHI ratio during REM and NREM sleep (Figs. 1G and 1H), it is deemed that such an assumption may not be valid. Moreover, the individuals'
NS/S AHI ratio varied significantly during REM and NREM sleep. In some patients, the NS/S AHI ratio during REM sleep was small, but that during NREM sleep significantly increased; in others, the opposite result was exhibited (Fig. 1G). The reasons for these contrasting characteristics in patients could not be ascertained, and it seems necessary to conduct further in-depth studies to explore the mechanisms or risk factors that may lead to such contrasting tendencies among patients. The significant discrepancy in the NS/S AHI ratio between the entire sleep and NREM sleep was noted only in a few patients (Figs. 1E and 1F). Therefore, the actual clinical impact of this difference may not be substantial. In fact, when two outliers were excluded, the agreement of the NS/S AHI ratio between the entire sleep and NREM sleep improved significantly (the values of CCC from 0.81 [0.74-0.86] to 0.96 [0.94-0.97]). Similarly, in comparison between the overall and the weighted NS/S AHI ratio, the values of CCC became substantial after excluding the outliers (from 0.86 [0.80-0.90] to 0.98 [0.97-0.98]). Nevertheless, since there are at least some OSA patients who can benefit solely from positional therapy, a reliable indicator to accurately determine PD would be clinically valuable.

PD not only impacts the choice of positional therapy but also affects the treatment outcomes of other OSA therapies. For instance, a study demonstrated that the effectiveness of the MAD was more significant in patients with supine-dependent OSA (median 41 to 5.9) compared to non-supine-dependent OSA (median 44 to 21) (18). Therefore, patients with PD will also likely benefit from MAD treatment, although caution is needed in interpreting the results of this study, as the definition of PD was inconsistent with the general “twice as high” rule. Based on the fact that the treatment success criteria for MAD were regarded as AHI < 10, the position-dependent OSA was defined as a supine AHI ≥ 10 and a non-supine AHI < 10.

It is essential to establish a consensus on the definition of PD to guide proper treatment selection. The “twice as high” rule, supine AHI being more than twice that of non-supine
AHI, has been commonly used to define PD since its introduction (7, 19, 20). Some studies have added additional conditions, such as requiring non-supine AHI to be below five, to define position-dependent OSA more precisely (10). When applying this criterion, 27.4% of all OSA patients were classified as having PD. Specifically, 50% of mild OSA patients were identified as having PD, whereas only 20% and 6.5% of moderate or severe OSA patients, respectively, fell into the position-dependent OSA category. This demonstrates that positional therapy is likely a significant treatment approach, particularly for patients with mild OSA. Given that, it is notable that two out of the three outliers with discrepant results between the overall and weighted NS/S AHI ratios in the present study were mild OSA patients.

Furthermore, in the present study, the weighted NS/S AHI ratio showed poor agreement with the overall NS/S AHI ratio in mild to moderate OSA patients, while it exhibited substantial agreement in severe OSA patients (Fig. 3). According to a previous study, as OSA severity increases, sleep stage shifts occur more frequently, implying reduced sleep stability (21). Therefore, it might be expected that the overall NS/S AHI ratio significantly differs from the weighted NS/S AHI ratio in severe OSA. However, the results were the opposite. This could be due to the diminishing trend of PD and the proportion of REM sleep within total sleep time with increasing OSA severity (10, 22). Consequently, the identification of PD in severe OSA patients remained accurate even in the absence of employing a precise formula to mitigate the influence of sleep stage shifts. Therefore, it can be assumed that using the weighted NS/S AHI ratio can be clinically valuable, especially in mild OSA patients where accurately diagnosing PD is crucial.

In another study, PD was defined differently: overall AHI ≥ 15, having a sleep duration of 20 minutes or more in all sleep positions, and supine AHI ≥ twice the non-supine AHI while maintaining non-supine AHI < 15 (23). This lack of consistency in defining PD across different studies is evident. In a study conducted by an expert group meeting, the additional
criteria were included: having each sleep position for 10% or more of the total sleep time, an overall AHI ≥ 40/h, and a reduction of AHI by 25% or more in the non-supine position. The point was that the aim of determining PD is to identify patients suitable for positional therapy (24). In another study, the "modified Cartwright index" was proposed as a measure for PD based on the wide variation in the proportion of each sleep position among patients (6).

Specifically, the modified index was calculated by multiplying the proportion of time spent in the supine position (time in supine position/total sleep time) by a ratio of supine AHI to total AHI (supine AHI/total AHI). Also, the index was defined only in patients with an overall AHI ≥ 15, indicating at least moderate severity. In that paper, it was also noted that the classic Cartwright index based on the “twice as high” rule does not predict the success of non-PAP therapies such as upper airway surgeries (25). Nevertheless, an alternative cut-off ratio was not suggested.

In that study, a modified indicator for REM dependency was also proposed with a similar principle to that for PD: the ratio of REM AHI over total AHI (REM AHI/total AHI) multiplied by the proportion of time spent in REM sleep during the total sleep time (time in REM sleep/total sleep time). However, that study did not consider the potential influence of sleep stage distribution on determining PD. On the contrary, the impact of sleep stage on PD was tested in the present study by comparing the weighted NS/S AHI ratios with the conventional ones. Consequently, 2.7% (= 3/111) of the data showed remarkable differences. When the “twice as high” rule was applied, the presence of PD was changed in only 0.9% (= 1/111) of the patients. Nevertheless, it should be noted that the “twice as high” rule is a conventional rule, not a gold standard based on strong scientific evidence. The present study at least showed the need for a discussion on developing the modified ratio for PD.
This study has several limitations, including its retrospective nature and the relatively small sample size of 111 patients. The potential for significant differences between the weighted NS/S AHI ratio and the conventional overall NS/S AHI ratio in only a minority of patients may limit its clinical impact. However, considering the importance of accurately diagnosing PD for determining the applicability of positional therapy, the modified value proposed by the authors could still hold value, even if only a small number of patients benefit from it. Of course, to prove the clinical utility of the weighted NS/S AHI ratio, further prospective studies must show that selecting patients for positional therapy based on this value results in a higher success rate than patient selection based on the conventional overall NS/S AHI ratio. Lastly, the present study is based on a single-night PSG test that was conducted in an unfamiliar sleep environment. Thus, the influence of night-to-night variation on the accuracy of the weighted NS/S AHI ratio was not evaluated. Since night-to-night variation exists distinctly enough to change the patient's OSA severity (26), further multi-night studies are needed to assess whether the weighted NS/S AHI ratio has clear advantages over the conventional overall NS/S AHI ratio, especially in mild to moderate OSA patients.
References


14. Nelson B, Wiles A. A more expansive approach to obstructive sleep apnea: Multiple studies have linked poor sleep to cancer and other negative health outcomes; in Part 2 of a 2-part series, we explore how sleep apnea diagnosti cs and interventions have expanded to include more patients and new treatment options.: Multiple studies have linked poor sleep to cancer and other negative health outcomes; in Part 2 of a 2-part series, we explore how sleep apnea diagnosti cs and interventions have expanded to include more patients and new treatment options. Cancer Cytopathol. 2022 Mar;130(3):168-9.

15. AS AL, Turnbull CD, Morrell MJ, Kelly JL. Efficacy of vibrotactile positional therapy devices on patients with positional obstructive sleep apnoea: a systematic


Figure legends

Figure 1. Comparison of the NS/S AHI ratio during the entire sleep, REM and NREM sleep. The mean value of the NS/S AHI ratio during entire sleep was not different from that during REM sleep (A), but the values in each patient showed poor agreement (CCC = 0.43 [0.26-0.57]). There were eight (7.2%) outliers beyond ±2S.D. from the mean of the difference between those two ratios (B and C). The mean value of the NS/S AHI ratio during entire sleep was not different from that during NREM sleep either (D), but the values in each patient also showed poor agreement (CCC = 0.81 [0.74-0.86]). There were two (1.8%) outliers beyond ±2S.D. from the mean of the difference between those two ratios (E and F). Similarly, the mean values of the NS/S AHI ratio were not different during REM and NREM sleep (G), but the values in each patient also showed poor agreement (CCC = 0.25 [0.06-0.43]). There were six (5.4%) outliers beyond ±2S.D. from the mean of the difference between those two ratios (H and I). CCC, Lin’s concordance correlation coefficient; NS/S AHI ratio, a ratio of an apnea-hypopnea index on the non-supine over the supine position; REM, rapid eye movement; NREM, non-rapid eye movement; R, REM sleep; NR, NREM sleep.

Figure 2. Comparison between the overall and weighted NS/S AHI ratios. The mean value of the weighted NS/S AHI ratio was not different from the overall one (A). However, there were three (2.7%) outliers beyond ±2S.D. from the mean of the difference between those two ratios (B and C). None of them was position-dependent based on the overall NS/S AHI ratio. When the weighted NS/S AHI ratio was applied, one (case number 4.1) was revealed to have positional dependency. The other two also showed noticeable changes in the
values, but the status of a positional dependency by the definition of 0.5 did not change (C).

NS/S AHI ratio, a ratio of an apnea-hypopnea index on the non-supine over the supine position.

Figure 3. Agreement between the overall and weighted NS/S AHI ratios according to the severity of obstructive sleep apnea. A poor agreement was identified in mild to moderate obstructive sleep apnea patients (n = 49; CCC = 0.69 [0.52-0.81]; A). On the contrary, a substantial agreement was exhibited in severe obstructive sleep apnea patients (n = 62; CCC = 0.99 [0.98-0.99]; B). NS/S AHI ratio, a ratio of an apnea-hypopnea index on the non-supine over the supine position.
Figure 1.
Figure 2.

Figure 3.