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Determinants of Unintentional Leaks During CPAP Treatment in OSA

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BACKGROUND: Unintentional leakage from the mouth or around the mask may lead to cessation of CPAP treatment; however, the causes of unintentional leaks are poorly understood. The objectives of this study were (1) to identify determining factors of unintentional leakage and (2) to determine the effect of the type of mask (nasal/oronasal) used on unintentional leakage.

METHODS: Seventy-four polysomnograms from patients with OSA syndrome treated with auto-CPAP were analyzed (23 women; 56 $\pm$ 13 years; BMI, 32.9 kg/m^2 (range, 29.0-38.0 kg/m^2). Polysomnographic recordings were obtained under auto-CPAP, and mandibular behavior was measured with a magnetic sensor. After sleep and respiratory scoring, polysomnographic signals were computed as mean values over nonoverlapping 10-s intervals. The presence/absence of unintentional leakage was dichotomized for each 10-s interval (yes/no). Univariate and multivariate conditional regression models estimated the risk of unintentional leaks during an interval "T" based on the explanatory variables from the previous interval "T-1." A sensitivity analysis for the type of mask was then conducted.

RESULTS: The univariate analysis showed that mandibular lowering (mouth opening), a high level of CPAP, body position (other than supine), and rapid eye movement (REM) sleep increased the risk of unintentional leaks and microarousal decreased it. In the multivariate analysis, the same variables remained independently associated with an increased risk of unintentional leakage. The sensitivity analysis showed that oronasal masks reduced the risk of unintentional leaks in cases of mouth opening and REM sleep.

CONCLUSIONS: Mouth opening, CPAP level, sleep position, and REM sleep independently contribute to unintentional leakage. These results provide a strong rationale for the definition of phenotypes and the individual management of leaks during CPAP treatment.

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KEY WORDS: CPAP; mask; polysomnography; sleep apnea; unintentional leakage

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ABBREVIATIONS: AHI = apnea hypoxia index; PSG = polysomnography

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CPAP is the first-line treatment for moderate to severe OSA syndrome.[1] Although adherence to CPAP is crucial to improve symptoms[2] and prevent cardiometabolic consequences,[3-5] > 50% of patients discontinue or comply poorly with the treatment over the long term (< 4 h/night).[6,7] Although the causes of CPAP cessation are multifactorial,[8,9] unintentional leakage from the mouth or around the mask is common with CPAP therapy and may contribute to nonadherence to treatment.[10,11] However, the causes of unintentional leaks are poorly understood.

Technological innovations are constantly being developed to improve the sealing of interfaces (eg, shape of mask, different breathing routes, materials, ergonomic straps, rotating elbows, lighter masks) to reduce unintentional leakage. Likewise, accessories such as chin straps and heated humidification systems have also been reported to limit the magnitude of unintentional leakage[12,13] and its consequences.[14,15] However, some unexpected effects have been found. For instance, oronasal masks are usually proposed to reduce mouth-related leakage[16]; however, they have paradoxically been found to be associated with a higher magnitude of unintentional leakage than found with nasal masks.[17] Thus technological improvements may not actually overcome the problem of unintentional leakage. Robust methods to identify the determining factors of unintentional leakage are required before taking any action.

The determining factors of an unintentional leak can be split into two categories: (1) patient-related factors, such as facial or pharyngeal anatomy,[18] age,[13,19] BMI,[20,21] and concomitant comorbidities (eg, COPD)[22] that cannot be changed and (2) factors that evolve overnight such as sleep stage, body position, and mouth opening, which can be altered. The frequent loss of tonic activity of the masseters[23,24] contributes to a progressive increase in mouth opening while sleep deepens,[25,26] favoring unintentional leaks during CPAP. Although there are no robust data to demonstrate that sleep position affects mouth opening,[26,27] different body positions might impact unintentional leakage by displacing the mask and changing upper airway resistance.

The aim of this study was to identify the determining factors of unintentional leakage throughout a whole night of CPAP treatment. We used objective measurements of unintentional leakage and mandibular movement to phenotype unintentional leaks using an innovative data analysis. The secondary aim was to investigate whether the type of mask (nasal vs oronasal) influences the determining factors.

Methods

Centralized analysis of polysomnographic recordings was performed during auto-CPAP with a magnetic movement sensor to measure mandibular behavior. The study was approved by the local ethical committee (Institutional Review Board No. 00004890).

Data Collection

Between July 2015 and October 2015, consecutive adult patients diagnosed with moderate to severe OSA syndrome (apnea-hypopnea index [AHI] > 15/h) who attended in-laboratory polysomnography (PSG) under CPAP were included (Saint Elisabeth Namur clinic, Liège Belgium). In Belgium, after OSA syndrome is diagnosed, in-laboratory PSG during CPAP is required to demonstrate treatment efficacy in order for the social security system to reimburse the treatment. In practice, patients who are prescribed CPAP are initiated with auto-CPAP devices at home a few weeks before in-laboratory PSG under CPAP.

Medical history, anthropometric data, and OSA syndrome severity were collected from patients' medical charts at the time of diagnosis of OSA syndrome. The Epworth Sleepiness Scale and a self-reported evaluation of nasal obstruction and mouth dryness (visual numeric scale: 1 = absence of symptoms to 5 =severe symptoms) were performed prior to the in-laboratory PSG under CPAP. The type of mask used during CPAP titration was documented.

Raw polysomnographic data under auto-CPAP were extracted in a European Data File format for subsequent transformation and analysis (see details further on and Fig 1).

Polysomnographic Features

PSG (B3iP, Medatec) was performed with the same auto-CPAP (S9 Autoset, RESMED). During PSG, patients used their own masks (nasal or oronasal mask). The parameters monitored included electroencephalography (Fz-A+,Cz-A+, Pz-A+), right and left electrooculography, submental electromyography, tibial electromyography, and chest and abdominal wall motion by respiratory inductance plethysmography (SleepSense S.L.P. Inc.); airflow, CPAP level, and unintentional leakage were obtained from the CPAP device; and arterial oxygen saturation was measured by a digital oximeter that displayed the pulse waveform (Nonin, Nonin Medical).

A midsagittal mandibular magnetic movement sensor (Brizzy Nomics) was used to measure the distance in millimeters between two parallel coupled resonant circuits placed on the forehead and the chin (Fig 1).[28] The transmitter generates a pulsed magnetic wave of low energy at 10 Hz. The change in the magnetic field is inversely related to the cube of the distance between the chin and forehead probes. The resolution of the measurement was 0.1 mm. This mandibular movement sensor was connected to an electronic module before being transmitted to the polysomnographic record.

The mandibular movement signal was automatically analyzed using mathematical morphology to identify oscillations relating to

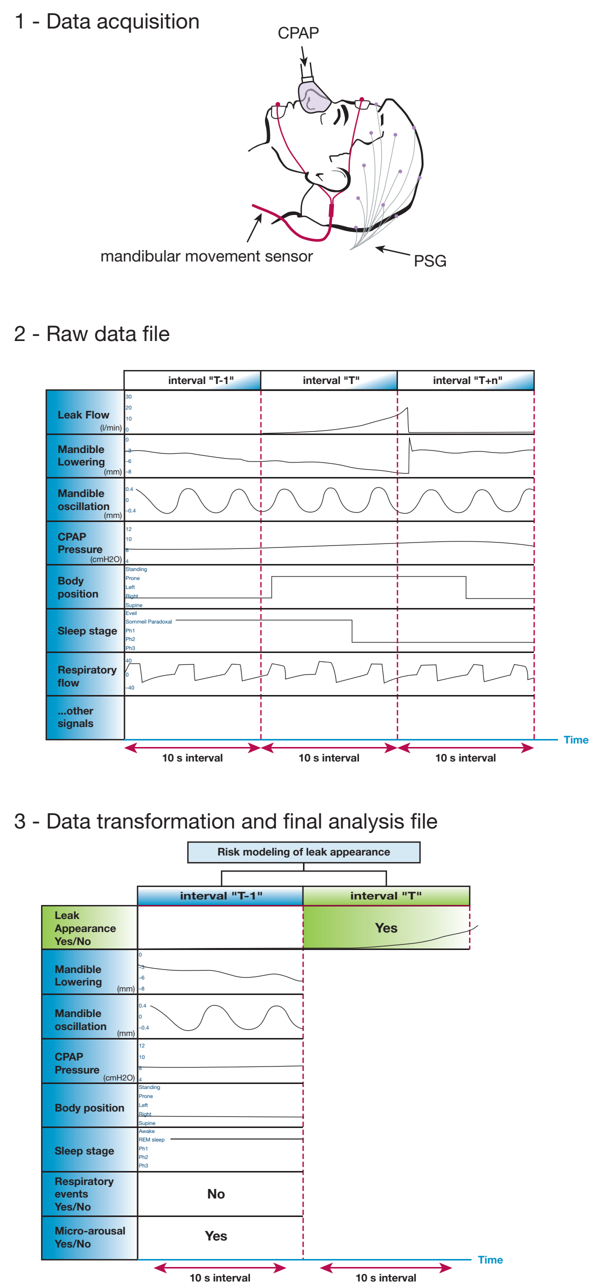

Figure 1 – *Methods. PSG = polysomnography.*

respiration (0.15-0.5Hz). The inspiratory and expiratory peaks were identified, and the corresponding lower and upper envelope signals were constructed by joining these peaks using linear interpolation (e-Fig 1). The difference between these two envelope signals defined the peak-to-peak amplitude of the oscillations. Mandibular oscillations have been shown to be a reliable marker of respiratory effort.[29] The sum of the two envelope signals divided by two (ie, the mean values of corresponding upper and lower envelope samples) defined the baseline of the signal, which constituted the mandibular lowering: the more negative the signal, the lower the mandibular position and the greater the mouth opening.

PSG scoring was performed manually by two readers (S. D., V. C.) according to standard criteria.[30] A minimum 4-hour duration with a good quality signal was required.

Signal Processing and Data Management

Figure 1 shows the procedure for signal processing and analysis. Continuous signals (mouth opening, mandibular oscillations, unintentional leakage, and CPAP level) were down-sampled from 500 to 10 samples/s using a 4.4-Hz frequency cutoff low-pass anti-aliasing finite impulse response filter. They were then computed as mean values over nonoverlapping 10-s intervals. Categorical data (sleep position and sleep stage), as well as dichotomous data (presence of respiratory events or microarousals, or both: yes/no), were also reported for intervals of 10 s. Finally, for each patient, PSG recordings were summarized in a data file that included eight variables of interest (1) mouth opening, (2) mandibular oscillations, (3) unintentional leakage, (4) CPAP level, (5) body position, (6) sleep stage, (7) occurrence of respiratory events (yes/no), and (8) microarousals (yes/no); a single value was analyzed for each variable for every consecutive 10-s interval. Each mandibular movement signal was inspected visually to remove false or noncontributive information. The main reasons for discarding signals were awake period, sleep without CPAP, and aberrant mandibular movements owing to sensor misplacement. These periods of sleep were removed from the final file before the statistical analysis.

Statistical Analysis

Data were analyzed using SAS software, version 9.4 (SAS Institute). Continuous data were expressed as means (SD) when normally distributed and medians (interquartile range) when not normally distributed; categorical data were expressed as percentages.

First Study Objective

Univariate conditional regression models (one strata per patient) were used to estimate the risk of leakage during a “T interval” using the following variables predefined from the previous interval (“T-1”): mouth opening (mandibular lowering), mandibular oscillations, CPAP level, body position, sleep stage, respiratory event and microarousal (Fig 1). Since there are no reports of a clinically significant threshold of unintentional leakage in the literature, the presence of unintentional leakage in an interval was classified in a dichotomous manner (yes or no: > 0 L/min or = 0 L/min). A subanalysis was also carried out using the thresholds recommended by the manufacturer for unintentional leaks (≥ 24 L/min or < 24 L/min for nasal masks and ≥ 36 L/min or < 36 L/min for oronasal masks).[31] Continuous variables were dichotomized to the median values (median values were individualized for every patient), except mandibular oscillation for which a threshold value of 0.3 mm was chosen.[29] All variables that were significant in the univariate analysis were then entered into a multivariate conditional regression model.

Secondary Study Objective

The secondary objective was to investigate if the mask type influenced the risk of unintentional leakage. A sensitivity analysis was performed on the type of mask in the first multivariate model (with a threshold of leakage: yes or no, > 0 L/min or = 0L/min).

Finally a Mann-Whitney test was used to compare the proportion of time spent with unintentional leaks during the night between both interfaces.

Sample Size Estimation

No previous data from which sample size could be calculated were found. We therefore aimed to include 15 to 20 patients with oronasal masks (sample size equivalent to previous studies comparing different types of masks[17]). Considering that about

25% of patients use oronasal masks[9], we estimated that at least 70 consecutive patients would need to be included in the analysis.

Other Analyses

The characteristics of the patients with nasal masks vs those with oronasal masks (Tables 1 and 2) as well as the characteristics of the patients with a high percentage of sleep time with unintentional leakage vs a low percentage of sleep time with unintentional leakage (e-Table 1) were compared using a Student unpaired *t* test for continuous variables with a normal distribution, a Mann-Whitney *U* test for other continuous variables, and a χ^2 test for discrete variables (or a Fisher exact test when expected counts were greater than five).

Results

Over a 4-month period, 89 consecutive adult patients underwent full in-laboratory PSG under auto-CPAP. Ten recordings could not be used because of technical problems (eight due to failure of the mandibular signal and two due to failure of electroencephalography), four polysomnographic studies were carried out under fixed pressure and one was carried out in a bilevel mode; thus 74 polysomnographic recordings were analyzed.

Patient Characteristics and Treatment Parameters

Patient characteristics are presented in Table 1 and treatment parameters during the PSG can be seen in Table 2. The sample studied was representative of usual OSA syndrome groups treated with auto-CPAP.

Variables Associated With Unintentional Leak

Table 3 shows the factors associated with the presence of unintentional leakage during sleep in the univariate analysis. Mouth opening, CPAP level, body position, and rapid eye movement (REM) sleep were significantly associated with an increased risk of unintentional leakage during sleep. Microarousals were associated with a decreased risk of unintentional leakage. In the multivariate analysis (Table 4), the same variables remained independently associated with an increased risk of unintentional leakage. Microarousals were independently associated with a decreased risk of unintentional leakage.

Comparison of the main characteristics of the patients who had a high vs low percentage of sleep time with unintentional leakage (defined as ≥ 53.9% or < 53.9%, respectively, corresponding to the median percentage of sleep time with unintentional leaks) revealed that patients with a higher percentage of sleep time with unintentional leakage were older. No other factors differed between these two groups (e-Table 1).

The results of the subanalyses based on the manufacturer's recommended thresholds for unintentional leakage are shown in e-Tables 2 and 3.

TABLE 1] Patient Characteristics

Variable	All Patients (N = 74)[a]	Oronasal Mask Group (n = 14)	Nasal Mask Group (n = 58)	*P* Value
Anthropometric data				
Age, y	55.8 ± 13.0	51.7 ± 13.3	56.9 ± 13.3	.20
Sex, female, %	31	50	28	.11
BMI, kg/m²	32.9 (29.0-38.0)	37.8 (32.9-4.3)	32.5 (28.4-37.3)	.016
Current smoker or ex-smoker, %	8	0	10	.57
Sleep apnea severity at diagnosis				
AHI (No./h) at diagnosis	44.3 (25.9-61.8)	45.7 (24.9-63.8)	44.4 (29.4-6.2)	.80
Epworth Sleepiness Scale, 1-24	12 ± 5	13 ± 5	12 ± 5	.50
Nasal obstruction, 1-5	2 (1-3)	3 (2-5)	2 (1-3)	.042
Mouth dryness, 1-5	2 (1-3)	2 (2-4)	2 (1-3)	.20
Comorbidity				
Treated for hypertension, %	41	58	36	.15
Treated for diabetes, %	14	33	9	.05
Treated for hypercholesterolemia, %	33	50	27	.17
Treated with inhaled pulmonary drugs agents, %	9	25	4	.06
Treated with psychoactive drugs, %	24	25	24	.99

Means ± SD are provided for normally distributed variables; Medians (quartile 1-quartile 3) are provided for variables that are not normally distributed.
[a]Mask type from two patients was missing.

TABLE 2] Sleep and Treatment Parameters

Variable	All Patients (N = 74)[a]	Oronasal Mask Group (n =14)	Nasal Mask Group (n = 58)	*P* Value
TST, min	433.6 ± 96.6	440.7 ± 59.0	434.1 ± 104.8	.75
Stages 1 and 2, % TST	58.3 ± 14.7	59.8 ± 12.5	58.0 ± 15.1	.68
Stages 3 and 4, % TST	24.1 ± 11.7	20.9 ± 10.5	24.6 ± 11.9	.29
REM, % TST	17.6 ± 7.9	19.3 ± 6.7	17.4 ± 8.2	.42
Arousal index, n/h	24.3 (15.4-35.1)	23.7 (16.9-32.4)	24.3 (14.3-38.5)	.99
AHI, events/h	11.5 (5.0-19.2)	17.5 (8.7-22.2)	10.3 (4.5-16.7)	.19
Supine position, % TST	66.7 (39.5-95.5)	63.6 (36.7-81.3)	67.5 (40.4-96.6)	.59
Mean CPAP pressure, cm H_2O	8.5 ± 2.6	8.9 ± 2.8	8.5 ± 2.6	.65
Unintentional leakage, median/patient, L/min	0.5 (0.0-4.2)	0.6 (0.0-2.9)	0.5 (0.0-4.9)	.89
Mouth opening (mm) median/patient	−13.1 (−16.9 to 8.3)	−16.3 (−18.7 to14.2)	−11.3 (−16.2 to 6.7)	.04

Means ± SD are provided for normally distributed variables; Medians (quartile 1; quartile 3) are provided for variables that did not have a normal distribution. AHI = apnea-hypopnea index; REM = rapid eye movement; TST = total sleep time.
[a]Mask type from two patients was missing.

Mouth opening, CPAP pressure, and REM sleep remained significantly associated with an increased risk of unintentional leakage using these thresholds. Microarousals were associated with a decreased risk of unintentional leakage. In contrast, the presence of a residual event at T-1 became associated with an increased risk of unintentional leakage. Mandibular oscillation (≥ 0.3 mm) was associated with a reduced risk of unintentional leakage. Time spent with unintentional leakage due to mouth opening using the thresholds of 24 L/min and 36 L/min for nasal and oronasal masks, respectively, are shown in e-Figure 2.

Impact of the Type of Mask on Unintentional Leakage

Figure 2 shows the distribution of time spent with unintentional leakage during sleep according to the type of mask. Of the total group, 28.4% had a low percentage of sleep time with unintentional leakage (0%-24% of total sleep time), and 29.7% had a high percentage of sleep time with unintentional leakage (75%-100% of total sleep time). The time spent with unintentional leakage did not differ between the two mask types (P = .67). Figure 2B depicts the time spent with unintentional leakage with respect to mouth opening for each type of mask.

Figure 3 displays the sensitivity analysis performed in the multivariate model for the type of mask (nasal and oronasal). Oronasal masks were associated with a lower risk of unintentional leakage in cases of mouth opening (mandibular lowering less than or equal to median value per patient) and REM sleep compared with nasal masks.

Discussion

The issue of unintentional leakage during CPAP treatment has mainly been considered as a technological challenge to be resolved. This study is original because it involved the objective measurement of determining

TABLE 3] Univariate Conditional Regression Analysis

Predictive Variables From Interval T-1	OR	95% CI	*P* Value
Mouth opening[a] ≤ median vs > median/patient, mm	1.46	1.42-1.49	< .0001
Mean CPAP pressure, ≥ median vs < median/patient, cm H_2O	2.41	2.35-2.47	< .0001
Body position during sleep, other vs supine	1.28	1.24-1.32	< .0001
Sleep stage, REM vs other	2.83	2.74-2.93	< .0001
Microarousal, yes vs no	0.68	0.65-0.71	< .0001
Mandibular oscillation, ≥ 0.3 vs < 0.3, mm	0.99	0.96-1.03	.71
Respiratory event, yes vs no	1.01	0.96-1.07	.65

[a]Mandibular lowering.

TABLE 4] Multivariate Conditional Regression Analysis

Predictive Variables From Interval T-1	OR	95% CI	*P* Value
Mouth opening,[a] ≤ median vs > median/patient, mm	1.41	1.38-1.45	< .0001
Mean CPAP pressure, ≥ median vs < median/patient, cm H_2O	2.21	2.15-2.27	< .0001
Body position during sleep, other vs supine	1.50	1.45-1.55	< .0001
Sleep stage, REM vs other	2.23	2.15-2.30	< .0001
Microarousal, yes vs no	0.67	0.64-0.7	< .0001

[a]Mandibular lowering.

factors of unintentional leakage. The strengths of the study are the use of a novel methodology to characterize and analyze the overnight determinants of unintentional leakage. The results identified mouth opening, CPAP level, nonsupine position, and REM sleep as determining factors. This is the first study, to our knowledge, to identify the specific situations during which unintentional leakage was reduced by use of an oronasal mask (ie, mouth opening and REM sleep). These results will be useful for clinicians to propose individualized management strategies to reduce this frequent adverse effect of CPAP, which should improve adherence to treatment.

Mouth opening is widely identified by clinicians as a cause of unintentional leakage. Mouth opening can be associated with a loss of tonic activity of the masseter muscles from sleep onset to deep sleep ("passive phenomenon"),[23,24] but it can also be triggered by persistent inspiratory resistance during obstructive events.[32,33] During an obstructive event, it is likely that the suprahyoid muscles (mylohyoid and geniohyoid)[26,33] are recruited, leading to progressive mouth opening. We expected that an increase in respiratory effort would increase the risk of unintentional leakage; however, the results did not demonstrate any association between mandibular oscillations > 0.3 mm (a surrogate marker of increased respiratory effort) and unintentional leakage. The 0.3-mm threshold has mainly been reported for children and during diagnostic sleep studies; however, it may be not sensitive enough in adult patients using CPAP.[29] However, microarousal, which is mainly a consequence of persistent respiratory effort,[34,35] reduced the risk of unintentional leakage when upper airway resistance was normalized. It could

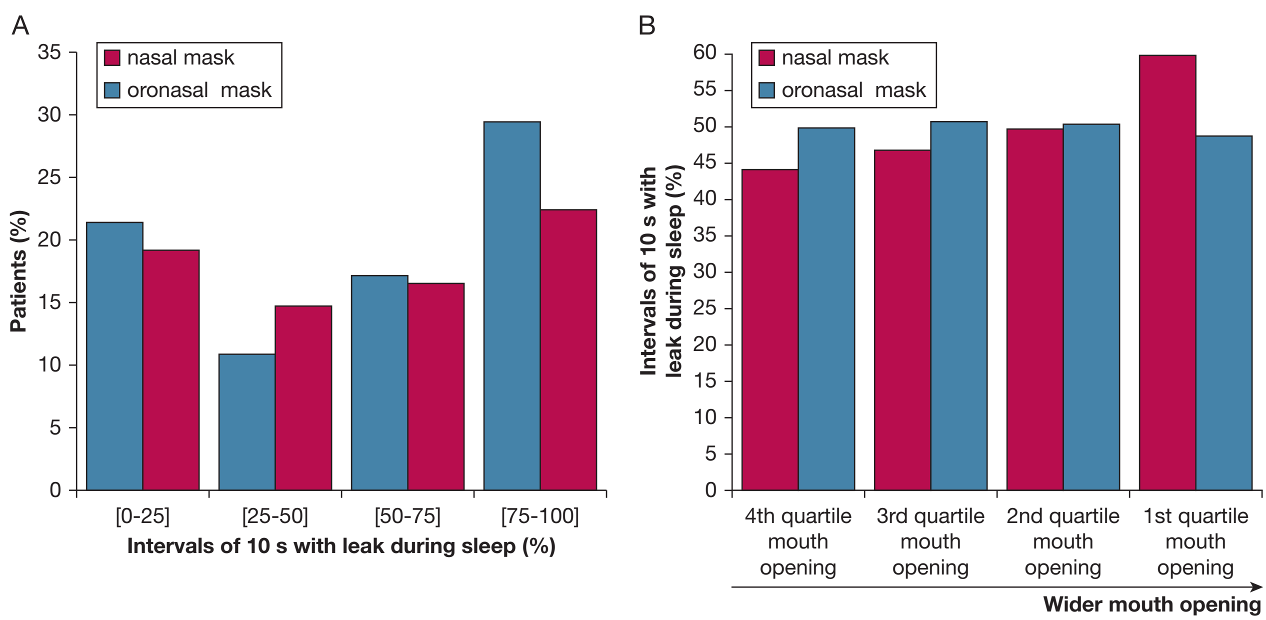

Figure 2 – *A, Sleep time spent with leakage for each type of mask (P = .67). B, Time spent with unintentional leakage related to mouth opening for each mask (expressed in quartiles). The first quartile represents the largest opening and the fourth quartile represents the smallest.*

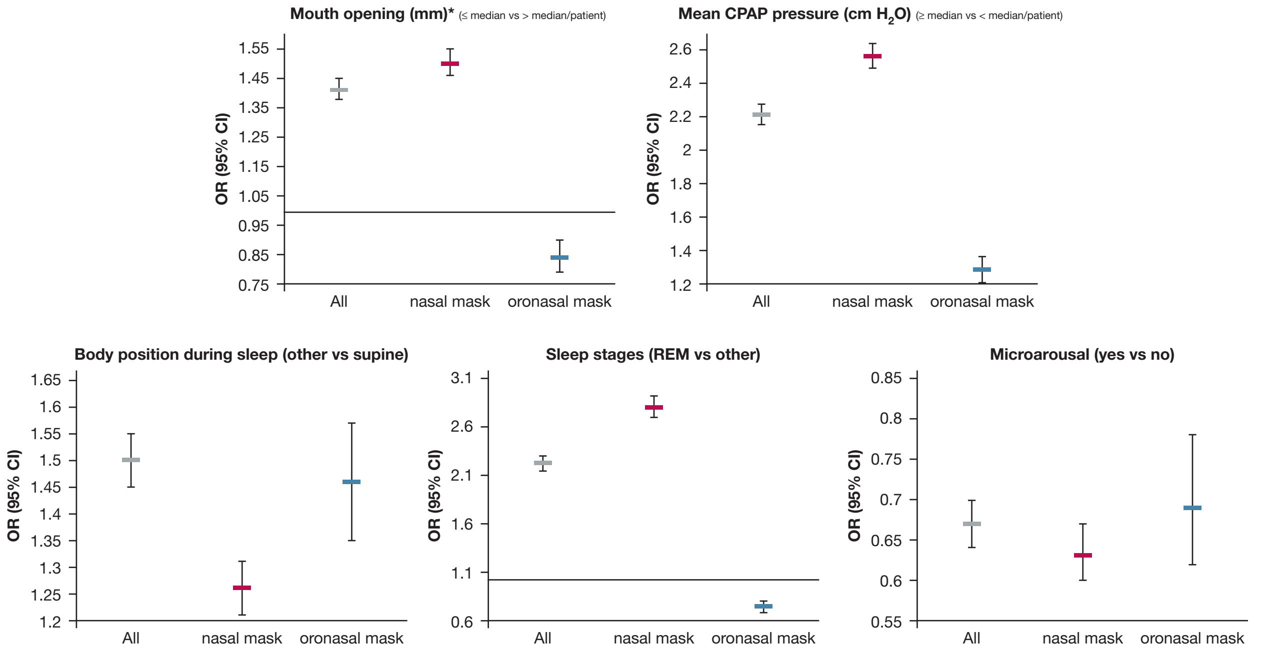

Figure 3 – *Sensitivity analysis for the type of mask (nasal vs oronasal) on the seven determining factors of unintentional leakage (with a threshold of leakage > 0 L/min or = 0 L/min). *Mandibular lowering. REM = rapid eye movement.*

be hypothesized that a significant respiratory effort would progressively open the mouth, creating unintentional leakage and that the subsequent effort-related microarousal would promptly reduce unintentional leakage as a result of mouth closure.[29]

Previous investigations have studied the relationship between mouth opening and body position, showing that mouth opening was influenced more by sleep stage than by body position.[26-28] In the present study, lateral and prone positions were found to increase the risk of unintentional leakage, probably because of mask displacement or traction on the CPAP tube in these positions. Nasal obstruction may also be an independent determining factor of mouth opening[36] that can lead to the use of an oronasal mask. In the present study, nasal obstruction (assessed using a visual numeric scale) and mouth opening were significantly greater in patients who used an oronasal mask. Moreover, the oronasal mask itself may promote mouth opening by displacing the jaw backward and downward.[37]

The specific indications for oronasal masks are still debated.[9,17,37-40] The present study showed an overall equivalence between oronasal and nasal masks except for the specific situations of mouth opening and REM sleep, in which the sensitivity analysis demonstrated fewer leaks with oronasal interfaces. This suggests that oronasal masks could be an effective solution to reduce unintentional leaks in such cases.

This study has several limitations. First, unintentional leakage was dichotomized as yes or no over 10-s intervals, with no consideration of leak severity. The cutoff (> 0 L/min) to define air leakage was arbitrary. It could be argued that a leak of 40 L/min is clinically different from one of 3 L/min; however, a valid threshold above which leak becomes clinically relevant has not yet been determined.[17,31] Repeating the analysis using the manufacturer's recommended thresholds, only a subgroup of patients have been included in the analyses: 36 patients had unintentional leakage values greater than these thresholds. The results were concordant with the analysis using a threshold ≥ 0 L/min for mouth opening, CPAP pressure, REM sleep, and microarousals. However, the presence of a residual event at T-1 became associated with an increased risk of unintentional leakage. This could be explained by the fact that during an obstructive event, the mouth opens progressively.[26,28,41] Mandibular oscillation (≥ 0.3 mm) was associated with a reduced risk of unintentional leakage. As already discussed, the threshold may not be sensitive enough and needs to be investigated. These exploratory analyses and results should therefore be interpreted with caution and eventually revised when a clinically relevant leakage threshold is clearly identified by the community of physicians and researchers. Second, the magnitude of leakage was directly obtained from the CPAP device; however, the error in leak estimation by CPAP devices is currently not known.[40] This may have led to some false-positive and false-negative 10-s intervals.

Third, leakage from the mouth can occur through a very small opening, whereas no leakage may occur with a widely open mouth. In addition, air leaks often come from the mask itself, particularly an oronasal mask. The lack of a direct measurement of oral flow prevented any distinction being made between leakage from the mouth and leakage from the mask. However, as is very obvious in Figure 2B, the greater the mouth opening with a nasal mask, the higher the percentage of sleep time with unintentional leakage.

Finally, older age was the only factor associated with a higher percentage of sleep time with unintentional leakage. The present data do not allow a "phenotype of patients at risk of unintentional leakage" to be clearly identified; specific studies including larger samples are needed to address this important issue.[17]

Conclusions

This study provides an innovative method for characterizing the determining factors of unintentional leakage in patients with OSA syndrome treated with CPAP. Systematic measurement of mandibular movements during sleep studies using CPAP could identify the specific factors responsible for unintentional leakage in each individual patient, thus allowing appropriate corrective measures to be proposed. Further studies are needed to prospectively validate this model. Interventional trials are also necessary to validate the clinical relevance of individualized management of unintentional leaks based on this model.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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