

New Insights on the Pathophysiology of Inspiratory Flow Limitation During Sleep

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Abstract

Introduction Inspiratory flow limitation (IFL) is defined as a “flattened shape” of inspiratory airflow contour detected by nasal cannula pressure during sleep and can indicate increased upper airway resistance especially in mild sleep-related breathing disorders (SRBD). The objective of this study was to investigate the association between upper airway abnormalities and IFL in patients with mild SRBD.

Methods This study was derived from a general population study consisting of selected individuals with apnea–hypopnea index (AHI) below 5 events/h of sleep, (“no obstructive sleep apnea” group) and individuals with AHI between 5 and 15 events/h (“mild obstructive sleep apnea” group). A total of 754 individuals were divided into four groups: group 1: AHI <5/h and <30 % of total sleep time (TST) with IFL (515 individuals), group 2: AHI <5/h and >30 % of TST with IFL (46 individuals), group 3: AHI: 5–15/h and <30 % of TST with

IFL (168 individuals), and group 4: AHI: 5–15/h and >30 % of TST with IFL (25 individuals).

Results Individuals with complains of oral breathing demonstrated a risk 2.7-fold larger of being group 4 compared with group 3. Abnormal nasal structure increased the chances of being in group 4 3.2-fold in comparison to group 1. Individuals with voluminous lateral wall demonstrated a risk 4.2-fold larger of being group 4 compared with group 3.

Conclusion More than 30 % of TST with IFL detected in sleep studies was associated with nasal and palatal anatomical abnormalities in mild SRBD patients.

Keywords Flow limitation · Nasal cannula · Sleep apnea · Upper airway

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Introduction

The diagnosis of sleep-related breathing disorders (SRBD) relies on a clinical history of snoring, gasping, non-restorative sleep, excessive daytime sleepiness, or fatigue associated with an objective analysis of the obstructive respiratory events during sleep through polysomnography [1]. A sleep study can document the presence and severity of SRBD by recognizing apnea, hypopnea, and respiratory event-related arousal (RERA) [1]. The physiological consequences of apnea and hypopnea are similar and were well studied during the past decades. Individuals with mild SRBD present with less frequent apneas and with more frequent periods of partial upper airway obstruction and increased upper airway resistance. More subtle respiratory parameters indicating mild upper airway obstruction should be studied in order to better define mild SRBD.

Inspiratory flow limitation (IFL) is a respiratory parameter that has been used to indicate increased upper airway resistance, based on flattening nasal cannula pressure signal [2]. IFL reflects upper airway collapsibility especially in mild SRBD. It is commonly caused by narrowing of a hypotonic upper airway in response to the negative intrathoracic pressure developed during inspiration [3]; however, the pathophysiology of IFL with no obstructive sleep apnea syndrome (OSAS) has not been described yet. Previous study has demonstrated that normal individuals can present up to 30 % of total sleep time (TST) with IFL [4].

The relationship between pharyngeal abnormalities and IFL seems complex, and the precise role played by these abnormalities in SRBD was not yet studied.

The objective of this study was to investigate the association between upper airway anatomical abnormalities and IFL in patients with mild SRBD.

Methods

The study protocol was approved by the Ethics Committee for Research of the Universidade Federal de Sao Paulo/Hospital Sao Paulo (CEP:0593/06), Clinical Trials: NCT:00596713.

This study was derived from a general population epidemiologic survey described in previous articles involving questionnaires, physical examination, and nocturnal polysomnography [5]. The cohort consisted of a representative sample of the inhabitants of Sao Paulo, Brazil according to gender, adult age (20–80 years old), and socioeconomic status, chosen with a three-stage cluster sampling technique. The sample consisted of 1101 individuals, which allowed for prevalence estimates with 3 % precision. Consenting subjects (1042 volunteers) underwent polysomnography. Methodological details of the Sao Paulo epidemiologic sleep study were described in previous studies [6].

A full-night, attended polysomnography was performed in each subject (EMBLA[®]S7000, Embla Systems, Inc., Broomfield, CO, USA) and sleep stages [7], arousals [8], and leg movements [8] were scored according to the standard criteria. OSAS was defined according to the International Classification of Sleep Disorders of the American Academy of Sleep Medicine criteria (2005) [9].

Apneas were scored following the recommended AASM rules [8]. Hypopneas were scored by the AASM “alternative” rules, i.e., when a >50 % reduction in airflow amplitude was observed on the nasal cannula signal lasting ≥ 10 s and accompanied by a decrease of ≥ 3 % in SpO₂ or an arousal [8]. We chose the alternative AASM rule in order to minimize the underestimation of obstructive sleep apnea (OSA) severity.

Inspiratory flow limitation was scored manually and visually identified as a “flattened shape” of the inspiratory airflow contour at nasal cannula pressure from Embla system (square root of the flow signal), with no filters applied. At least four consecutive breaths with “flattened shape” were required to score IFL events [4, 10]. Those events should not meet the criteria for hypopnea. The percent of total sleep time (TST) during which the IFL was calculated.

From the 1042 individuals of the epidemiologic sleep study [6], those selected were patients with apnea–hypopnea index (AHI) below 5 events/h of sleep, considered as “no OSA” group and individuals with apnea–hypopnea index between 5 and 15 events/h are considered as having mild OSA. Approximately 11 % of the polysomnographic records were excluded because their nasal cannula signal was not reliable. A total of 754 individuals were divided into four groups: group 1 (no OSA and no IFL group): AHI <5 events/h and <30 % of TST with IFL (515 individuals), group 2 (no OSA and with IFL group): AHI <5 events/h and >30 % of TST with IFL (46 individuals), group 3 (OSA and no IFL group): AHI: 5–15 events/h and <30 % of TST with IFL (168 individuals), and group 4 (OSA and with IFL group): AHI: 5–15 events/h and >30 % of TST with IFL (25 individuals).

Upper airway physical examination was performed by six trained ear–nose and throat physicians. Complaints were classified as present if individuals reported nasal obstruction, oral breathing, or habitual snoring.

Body mass index (BMI) and neck circumference (NC) were measured at physical examination. NC was measured at the level of the cricothyroid membrane and was considered high when ≥ 43 cm in men or ≥ 38 cm in women. Physical examination consisted of facial inspection, oral and oropharynx examination, and anterior rhinoscopy [11].

During facial inspection, individual was seated in a horizontal Frankfurt position and the distance between a virtual vertical line tangential to the outer edge of lower lip and the most anterior part of chin was measured. If the

anterior prominence of the chin was two or more millimeters behind the virtual vertical line, individual was considered to have mandibular retrusion [12].

Oral cavity was evaluated for the presence of high-arched palate and dental occlusions. Individuals were classified as class I (normal occlusion), class II (possibility of mandibular retrognathism), and class III (possibility of mandibular prognathism). Presence of class II dental occlusion, retrognathia, or high-arched palate was considered as unfavorable facial skeleton.

Nasal septal deviation was evaluated through anterior rhinoscopy examination and was classified as Grade I (deviation did not touch the sidewall), Grade II (deviation touched the inferior turbinate), and Grade III (deviation touched and compressed the sidewall). Inferior turbinate was considered hypertrophic if at least one of them appeared swollen and touched by the nasal septum, significantly obstructing the nose [13].

The nasal structure was considered abnormal if one of the following conditions was present: Grade II or III septal deviation; an association of Grade I septal deviation with inferior turbinate hypertrophy or complaints of nasal obstruction, and inferior turbinate hypertrophy with complaints of nasal obstruction [13].

Soft palate characteristics were classified into three categories: posteriorly placed, thick (when rounded in size and swollen), and webbed (webbed palate due to redundant posterior pillars). The tonsillar pillars were considered voluminous if they were close to the midline of the oropharynx (voluminous lateral wall). Uvula was considered thick when swollen. Long uvula was defined as one that approached the base of the tongue [14, 15].

The tongue was considered voluminous if it has impression of teeth in the lingual border [14, 15].

Modified Mallampati scoring was conducted with the patient seated and asked to open the mouth to its maximum width and to maintain the tongue relaxed inside the oral cavity. It was classified as class I (the entire oropharynx was visible, including the soft palate, tonsillar pillars, tonsils, and tip of the uvula), class II (the upper pole of the tonsils and the uvula were visible), class III (part of the soft palate and the uvula were visible), and class IV (only the hard palate and part of the soft palate were visible) [16].

The palatine tonsils were classified as Grade I (intravelar), Grade II (extending beyond the anterior tonsillar pillar), Grade III (extending up to three quarters toward the midline), Grade IV (completely blocking the throat), and Grade 0 in tonsillectomized individuals [14, 16].

An oropharynx with at least three of the following observations was considered unfavorable: Grade III or IV palatine tonsils, an abnormal uvula (long and/or thick), an abnormal palate (posterior and/or thick), a webbed palate, and a voluminous lateral wall [14].

Statistical Analysis

SPSS version 21.0 was used for the statistical analysis. Chi-squared tests (χ^2) were conducted to identify associations between mild SRBD with/without IFL and upper airway abnormalities. Multivariate logistic regression models were used to analyze the adjusted associations and interactions among the SRBD groups and those upper airway abnormalities (abnormal nasal structure, abnormal oropharynx, unfavorable facial skeleton). BMI was used as covariate during multivariate logistic regression analysis. The level of significance set was 5 % ($p < 0.05$).

Results

From the cohort of 1042 individuals, 754 were individuals with $AHI < 5$ events/h (“no OSA” group: 561 individuals) or mild OSA patients (193 individuals) that had the TST with IFL measured. There were 305 men (40.5 %) and 449 women (59.5 %). Mean age was 39.8 ± 13.4 years. Mean BMI was 26 ± 4.8 kg/m² and mean NC was 35.6 ± 5.6 cm.

There were 515 individuals (68.3 %) in group I (“no OSA” with < 30 % of TST with IFL), 46 individuals (6.1 %) in group 2 (“no OSA” with > 30 % of TST with IFL), 168 individuals (22.3 %) in group 3 (mild OSA with < 30 % of TST with IFL), and 25 individuals (3.3 %) in group 4 (mild OSA with > 30 % of TST with IFL). Multivariate logistic regression was used for upper airway abnormalities that had a significant statistical difference in the Chi-square test with adjusted residuals (Table 1 and 2).

Oral breathing was associated with mild OSA with > 30 % TST with IFL in comparison to mild OSA with < 30 % of TST with IFL ($p = 0.28$). Habitual snoring increased 1.83-fold the chances of having OSA with < 30 % of TST with IFL in comparison to normal group with < 30 % of TST with IFL ($p = 0.003$).

Abnormal nasal structure increased 3.2-fold the chances of having mild OSA with > 30 % of TST with IFL and 1.84-fold the chances of having mild OSA with < 30 % of TST with IFL in comparison to “no OSA” with < 30 % of TST with IFL ($p < 0.001$ and $p = 0.006$, respectively).

For those that had voluminous lateral wall, the odds of having mild OSA with > 30 % of TST with IFL was 4.2-fold larger than the odds of having mild OSA with < 30 % of TST with IFL ($p = 0.025$). Thick uvula increased 1.94-fold the chances of having mild OSA with < 30 % of TST with IFL in comparison to “no OSA” with < 30 % of TST with IFL ($p = 0.017$).

Discussion

For the best of our knowledge, this is the first study that investigates and demonstrates the role of nasal and palatal anatomical abnormalities in IFL during sleep in mild SRBD.

The mechanisms of upper airway obstruction in OSAS are commonly interpreted in terms of the Starling resistor model [17]. Accordingly, the upper airway has a compliant

wall that allows the air passage when the transmural pressure across the wall is positive. The intraluminal pressure must be greater than the external pressure to allow air passage. Inspiratory flow induces a negative intraluminal pressure. The degree of airway closure depends on the balance between the negative intraluminal pressure and the pressure at the external side of the airway wall. In patients with SRBD, the pressure applied by upper airway muscles is not sufficient to compensate the negative

Table 1 Symptoms related to upper airway and upper airway abnormalities associated with mild SRBD and IFL (according to the χ^2 test) ($p < 0.05$)

	“no OSA” with <30 % TST with IFL (%) (N = 515)	“no OSA” with >30 % TST with IFL (%) (N = 46)	OSA with <30 % TST with IFL (%) (N = 168)	OSA with >30 % TST with IFL (%) (N = 25)	<i>p</i>
Symptoms					
Nasal obstruction	29.3	41.3	28.5	48	0.097
Dryness in the nose/mouth	50.6	47.8	54.1	48	0.971
Habitual snoring	29.9	47.8	48.2	56	<0.001*
Oral breathing	35.1	47.8	26.7	56	0.004*
Upper airway abnormalities					
Retrognathia	14.5	13	10.1	24	0.248
High-arched palate	24.8	21.7	20.8	16	0.5
Class II dental occlusion	14.9	10.8	13.1	28	0.144
Unfavorable skeletal features	11.4	8.7	8.9	20	0.42
Septal deviation Grade II or III	24.4	28.2	31.5	44	0.096
Inferior turbinate hypertrophy	37.4	41.3	26.7	56	0.009*
Abnormal nasal structure	44.4	50	49.4	76	0.029*
Palate webbed	58.2	45.6	61.3	64	0.316
Palate posterior	24.4	23.9	29.7	32	0.544
Palate thick	13.9	17.4	26.2	40	<0.001*
Voluminous lateral wall	16.7	13	19	4	0.034*
Long uvula	23.5	21.7	30.9	40	0.106
Thick uvula	14.9	23.9	28.5	32	<0.001*
Palatine tonsils Grade III or IV	2.7	2.1	1.7	4	0.884
Mallampati score Grade III or IV	50.5	56.5	64.2	72	0.006*
Neck circumference	2.9	2.1	7.7	4	0.022*
Abnormal oropharynx	19.6	19.5	28.5	36	0.04*

OSA obstructive sleep apnea, TST total sleep time, IFL inspiratory flow limitation

* $p < 0.05$ (statistical significant)

Table 2 Multivariate logistic regression model for OSA with and without IFL adjusted for BMI

Symptoms and upper airway abnormalities	“no OSA” with <30 % TST with IFL or (95 % CI)	“no OSA” with >30 % TST with IFL or (95 % CI)	OSA with <30 % TST with IFL or (95 % CI)	OSA with >30 % TST with IFL or (95 % CI)
Oral breathing	1.61 (0.68–3.75)	0.96 (0.34–2.71)	2.74 (1.11–6.72)*	1 ^a
Habitual snoring	1.98 (0.85–4.61)	1.38 (0.49–3.88)	1.06 (0.44–2.58)	1 ^a
Neck circumference ^b	–	–	–	1 ^a
Inferior turbinate hypertrophy	0.98 (0.39–2.48)	1.02 (0.33–3.21)	2.18 (0.82–5.77)	1 ^a
Abnormal nasal structure	3.20 (1.10–9.26)	2.66 (0.75–9.39)	1.74 (0.58–5.21)	1 ^a
Palate thick	2.86 (0.93–8.73)	2.46 (0.58–10.39)	1.84 (0.57–5.94)	1 ^a
Voluminous lateral wall	2.55 (0.78–8.35)	4.4 (0.91–21.36)	4.25 (1.2–15.03)*	1 ^a
Thick uvula	1.54 (0.50–4.73)	0.72 (0.18–2.83)	0.79 (0.25–2.54)	1 ^a
Mallampati score Grade III–IV	1.74 (0.70–4.37)	1.57 (0.52–4.69)	1.29 (0.49–3.38)	1 ^a
Abnormal oropharynx	0.45 (0.10–1.89)	0.58 (0.10–3.36)	0.43 (0.09–1.95)	1 ^a

OSA obstructive sleep apnea, TST total sleep time, IFL inspiratory flow limitation

* $p < 0.05$ (statistical significant)

^a Variable used as reference (OSA with >30 % TST with IFL)

^b Some numbers of patients with some variables were too small. There was not possible to calculate Odds ratio for neck circumference

intraluminal pressure. Consequently, total occlusions (apnea) and/or partial collapse (hypopnea or IFL) of the upper airway occur [17].

It is important to perform a physical examination of the upper airway of patients with SRBD in order to detect areas that may collapse during sleep. The relationship between the nasal airway and the collapse of the upper airways is complex, and the precise role played by the nasal airway in SRBD is not yet completely known. But nasal obstruction forces the individual to breathe through the oral cavity. Oral breathing lengthens and narrows the upper airway and makes it more collapsible to inspiratory negative pressure [18].

IFL during sleep is a respiratory parameter that has been described and has been associated with consequences, however, the exact cut off point between healthy and disease is not well defined yet. Currently, AASM criteria considers IFL only if it is part of RERA event [8]. Isolated IFL is not recognized yet as an abnormal respiratory event. The clinical significance of IFL during sleep that includes insymptomatic (and non-symptomatic) individuals will be established after long-term studies associating different outcomes to this respiratory parameter. Palombini et al. [4] evaluated the distribution of IFL in a representative sample of the general population and found that normal individuals can present up to 30 % of the total sleep time with IFL. Some authors suggested that either isolated brief episodes or long periods of IFL can have clinical consequences [19, 20]. Calero et al. concluded after studying prolonged

periods of IFL (lasting more than 10 min) induced by suboptimal nasal continuous positive airway pressure (nCPAP), that they were associated with an increase in end tidal CO₂ and decrease in oxygen saturation [21].

Edwards et al. studied the presence of flow limitation in pre-eclamptic females and found that this respiratory parameter was common in this group of patients and that short-term relief of IFL by nCPAP was associated with a reduction in nocturnal blood pressure (BP) levels [22].

We found that complain of oral breathing and presence of voluminous lateral wall were more frequent in individuals with mild OSA with IFL than in those with OSA without IFL. Abnormal nasal structure increased the chances of having mild OSA with IFL in comparison to mild OSA without IFL. These findings show that individuals with mild SRBD with more than 30 % of TST with IFL might have some upper airway anatomical differences in comparison to those without IFL.

Our study demonstrates that IFL in OSA and non-OSA individuals is associated with nasal and palatal abnormalities. This could indicate that having IFL as part of polysomnographic criterion in SRBD is associated with more significant disease. It could be suggested that as part of the treatment of these sleep breathing disorders, it should be aimed to decrease time with IFL, besides normalizing AHI.

This study had some limitations. One of them is the fact that physical examination is a subjective task. The six otolaryngologists that evaluated the patients were well

trained, but we did not analyze their intra- and inter-rater agreement.

The shape of the IFL as visualized during polysomnography is also subjective. Analyzing IFL using pneumotachograph flow measurement and esophageal manometry could solve this study limitation. However, Ayappa et al. showed that IFL, RERAs, and similar subtle respiratory events could be detected indirectly through the shape of the inspiratory flow curve on a nasal pressure cannula in place of esophageal manometry [23]. The nasal cannula is the most used tool for measuring airflow in sleep studies and is not invasive as esophageal manometry is, which is an important characteristic that allows its widespread clinical usage.

Further studies addressing upper airway resistance of individuals with mild SRBD should be performed in order to better define the complete pathophysiology of IFL in this group with mild disease as well as the impact of these findings in clinical outcomes.

Conclusion

More than 30 % of TST (total sleep time) with IFL is associated with nasal and palatal anatomical abnormalities in mild SRBD patients.

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Conflict of interest None.

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