Inspiratory Flow Limitation in a Normal Population of Adults in São Paulo, Brazil

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Study Objectives: Inspiratory flow limitation (IFL) during sleep occurs when airflow remains constant despite an increase in respiratory effort. This respiratory event has been recognized as an important parameter for identifying sleep breathing disorders. The purpose of this study was to investigate how much IFL normal individuals can present during sleep.

Design: Cross-sectional study derived from a general population sample.

Setting: A “normal” asymptomatic sample derived from the epidemiological cohort of São Paulo.

Patients and Participants: This study was derived from a general population study involving questionnaires and nocturnal polysomnography of 1,042 individuals. A subgroup defined as a nonsymptomatic healthy group was used as the normal group.

Interventions: N/A.

Measurements and Results: All participants answered several questionnaires and underwent full nocturnal polysomnography. IFL was manually scored, and the percentage of IFL of total sleep time was considered for final analysis. The distribution of the percentage of IFL was analyzed, and associated factors (age, sex, and body mass index) were calculated. There were 95% of normal individuals who exhibited IFL during less than 30% of the total sleep time. Body mass index was positively associated with IFL.

Conclusions: Inspiratory flow limitation can be observed in the polysomnography of normal individuals, with an influence of body weight on percentage of inspiratory flow limitation. However, only 5% of asymptomatic individuals will have more than 30% of total sleep time with inspiratory flow limitation. This suggests that only levels of inspiratory flow limitation > 30% be considered in the process of diagnosing obstructive sleep apnea in the absence of an apnea-hypopnea index > 5 and that < 30% of inspiratory flow limitation may be a normal finding in many patients.

Keywords: Flow limitation, nasal pressure cannula, sleep, upper airway resistance, weight

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INTRODUCTION

The American Academy of Sleep Medicine (AASM) defines obstructive sleep apnea syndrome (OSAS) as the confluence of specific complaints and polysomnographic criteria. One respiratory criterion, the severity of upper airway obstruction, is characterized by recognizing obstructive respiratory events including apnea, hypopnea, and respiratory event related arousal (RERA).¹ In addition, it has been demonstrated that evidence of elevated upper airway resistance can be recognized non-invasively by identifying inspiratory flow limitation (IFL), or a flattened appearance of the flow curve detected by nasal cannula pressure during sleep.² However, the shape of the inspiratory flow as visualized during polysomnography (PSG) is only a surrogate measure of flow limitation, which is limited by its subjective definition,^{3,4} and the amount of flow limitation in normal populations is a matter of debate. Because true IFL is indicative of upper airway obstruction, its clinical significance was initially demonstrated in continuous positive airway pressure (CPAP) studies. During CPAP titration, studies have demonstrated that the correction of IFL, in addition to conventional

respiratory parameters, leads to an improvement in vigilance and cognitive function^{5,6} and elimination of periodic leg movement.⁷ Its detrimental effect has also been shown in sleep disorders when investigating fatigue in premenopausal women and older women⁸⁻¹⁰ and in association with sleepwalking in adults.¹¹ Presence of flow limitation was also shown to be associated with phases A2 and A3 of the cyclic alternating pattern scoring system.¹²⁻¹⁴

IFL is often associated with, but not synonymous with, increased respiratory effort, which is required to meet the definition of a RERA. However, there have been few normative data published on how much IFL can be considered “within normal range” as detected with a nasal cannula.^{2,15,16} Flow limitation, defined as a “flattened shape” of the inspiratory airflow contour, can be detected by visual inspection or by any of several proprietary automated algorithm (generally used in CPAP autotitration), but no uniform set of rules defining this appearance has been published.

The purpose of the current study was to evaluate the distribution of IFL during sleep in individuals without clinical complaints related to OSAS from a representative population sample based on a census of São Paulo, Brazil. Our goal was to define how much IFL is present in non-complaining individuals in the general population. We also compared IFL of the normal group with other groups of sleep disordered breathing (SDB). From these normative data, we propose a cutoff of the polysomnographic parameter given by the percentage of total sleep time spent in IFL, which can be used to help define the presence of the upper airway resistance syndrome or mild OSAS.

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METHODS

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

Sampling

The current study took advantage of an existing epidemiological cohort who had undergone full PSG to identify “normal” asymptomatic patients.

The current cohort consisted of a representative sample of the inhabitants of São Paulo, Brazil according to sex, adult age (20–80 y), and socioeconomic status, chosen with a three-stage cluster sampling technique.^{17,18} The sample consisted of 1,101 individuals, which allowed for prevalence estimates with 3% precision.¹⁹ Consenting individuals (1,042 volunteers) underwent PSG (refusal rate of 5.4%). Methodological details of the São Paulo Epidemiologic Sleep Study are described in previous studies.²⁰ Individuals had physical examination and questionnaires: Epworth Sleepiness Scale (ESS),²¹ Chalder Fatigue Scale,²² Pittsburgh Sleep Quality Index,²³ UNIFESP (Universidade Federal de São Paulo) Sleep Questionnaire,²⁴ and the World Health Organization Quality of Life quality of life assessment (WHOQOL-BREF)²⁵ before PSG.

Pulmonary disease symptoms were evaluated by a validated respiratory questionnaire.²⁶

A full-night attended PSG was performed in each patient (EMBLA®S7000, Embla Systems, Inc., Broomfield, CO, USA). Sleep stages,²⁷ arousals,¹ and leg movements¹ were scored according to the standard criteria.

Apneas were scored following the recommended AASM rules. Hypopneas were scored by the AASM “alternative” rules, i.e., when a greater than 50% reduction in airflow amplitude was observed on the nasal cannula signal lasting 10 seconds or longer and accompanied by a decrease of $\geq 3\%$ in oxyhemoglobin saturation (SpO_2) or an arousal.¹

Scoring of IFL was manually (visually) performed. Flow signal used to score flow limitation was derived from nasal pressure cannula from the Embla system (square root of the flow signal), with no filters applied. By analogy to the AASM rules for scoring periodic limb movements, periods tabulated as showing IFL required the presence of at least four consecutive breaths showing inspiratory flattening of the airflow curve^{17,28} that did not meet the criteria for hypopnea. The percent of total sleep time during which there was IFL was calculated, but, to avoid doubling their effect, breaths showing flow limitation that were within a scored hypopnea were not included in this count. To validate the scoring of percentage of IFL (% IFL), three scorers scored 20 studies and % IFL marked by each scorer for each patient was compared. The inter-rater agreement for % IFL was 0.950 ($P < 0.001$).

From the initial sample of 1,042 patients with polysomnographic results, moderate to severe OSAS was defined as an apnea-hypopnea index (AHI) of ≥ 15 events/h, and these patients with moderate to severe OSAS were excluded from the current analysis. The rationale for this was that the elevated number of apneas/hypopneas sufficed to make the diagnosis of OSAS; furthermore, it has been our experience that IFL may be completely absent in patients with severe obstructive sleep apnea (OSA) when apnea alone predominates. We also

excluded all patients with any significant primary lung disease as evidenced by responses to a validated respiratory questionnaire²⁶ or PSG showing baseline oxygen saturation below 92%.

The remaining patients with AHI < 15 events/h (“group AHI < 15 events/h”) ($n = 755$) were considered the group of interest, where OSA was not definite and where the presence of IFL was a candidate to explain symptoms when present. These patients’ PSGs were analyzed for the presence and amount of flow limitation. All 755 sleep studies had the percentage of IFL scored by one same scorer. Furthermore, from these patients, we identified a “normal group” to be used for defining the distribution of “normal” amounts of IFL. The goal was to establish a 95% confidence interval for this parameter that could establish a value below which percentage of IFL was not sufficient to differentiate normal patients from those with a diagnosis of OSA. This normal group was chosen by the following criteria:

1. No known diagnosis of a sleep disorder or sleep complaints (i.e., no chronic health complaint, no complaint related to sleep problems and scores on specific questionnaires used in the field of sleep disorders considered as normal such as the ESS < 10 , eliminating daytime sleepiness, a Chalder Fatigue Scale score ≤ 4 , eliminating the presence of fatigue, and no witnessed apneas.
2. No OSAS according to International Classification of Sleep Disorders (ICSD-2) criteria,²⁹ i.e., AHI < 5 .
3. No significant primary lung disease as evidenced by responses at the validated respiratory questionnaire.²⁶

The percentage of IFL was analyzed according to age groups (20–39, 40–59, and 60–80 y). Patients were classified according to their body mass index (BMI) as eutrophic (18–24.99 kg/m²), overweight (25–30 kg/m²), and obese (BMI ≥ 30 kg/m²).

As a final analysis, after excluding those within the group with AHI < 15 with evidence of obstructive lung disease or a known sleep disorder other than OSAS, we compared IFL in those classified as “normal” to the IFL in those having an AHI 5–15 and symptoms of excessive daytime sleepiness (EDS)/chronic fatigue and with AHI 5–15 with no symptoms.

Statistical Analysis

The percentage of IFL in our “normal” group was not normally distributed (Figure 1). The percentage of IFL was described using median, mean, standard deviation, and percentiles in the normal group and in the total group of 755 with < 15 events/h. Spearman rank correlation coefficient was calculated for nonnormally distributed variables. IFL was compared between eutrophic, overweight, and obese individuals and between age groups with one-way analysis of variance and between sexes with chi-square tests. The Kruskal-Wallis test was chosen as the nonparametric test for nonnormally distributed variables.

A linear regression analysis was performed to evaluate effects of age, sex, and BMI in % IFL.

RESULTS

A total of 171 individuals (16.6% of the original population) met the criteria for inclusion in the normal group. The mean age of this group was 36.0 ± 12.7 y, the mean BMI was 25.3 ± 4.9 kg/m², and the group consisted of 86 men and 85 women. After excluding eight individuals who had nasal

cannula signal with artifact, we ended with a group of 163 individuals for the normal group.

In this group, the distribution of the % IFL was not normally distributed (Figure 1).

The values for % IFL observed were as follows: mean 8.8 ± 10.4 %, median of 5. 1% with a minimum of 0 and a maximum of 56.1%. The 95th percentile for % IFL was 31% (Table 1). Only 10 of 163 patients had % IFL > 30% and only 4 of 163 had % IFL > 40%.

Polysomnographic parameters for the normal group are described in Table 2. Overall, the mean polysomnographic values for this group were within the normal range.

In the normal group, the % IFL was lower in women than in men (8.7 ± 10.8 % versus 9.8 ± 11.85 %, $P < 0.05$). Additionally, the % IFL did not show a clear correlation with an increase in age (Table 3).

In the normal group, IFL was significantly correlated with BMI ($r = 0.422$, $P < 0.01$). Other anthropometric variables (waist-hip ratio, neck circumference, hip circumference, and waist circumference) did not show a correlation with IFL.

The normal group showed a significant correlation between IFL and BMI in the young and middle-aged patients (younger than 60 y) and disappeared in the older age group (60-80 y) (Figure 2).

Finally, we constructed a linear regression model to evaluate the association of IFL with anthropometric variables and PSG parameters in the larger group of all patients with AHI < 15. BMI was the only factor significantly predictive of IFL. Other anthropometric and polysomnographic parameters were not significant (Table 4).

In our final analysis we compared IFL in those patients classified as normal versus IFL in patients having an AHI of 5-15 and symptoms of EDS/chronic fatigue (mild OSA) and patients with AHI 5-15 with no symptoms (possible abnormality). The results demonstrated that there is a progressive increase in percentage of flow limitation from normal (median 5%) to AHI 5-15 with no symptoms (median 6.1%) and from

Table 1—Percentage of total sleep time with inspiratory flow limitation of the normal group

Mean (%)	8.31
Median (%)	5.09
Standard Deviation (%)	10.45
Confidence Interval	6.47-10.53
Minimum (%)	0.00
Maximum (%)	56.13
Percentiles	
5	0.00
15	0.00
50	5.09
75	12.85
95	31.02
Total (N)	163

Table 2—Polysomnographic variables of the normal group

	Mean $\pm$ SD	Min	Max
SL (min)	17.1 ± 20.7	0	168
REMSL (min)	100.8 ± 47.2	40.5	331
TST (min)	336 ± 79.9	49	569.5
Stage 1 (%)	4.4 ± 4.3	3	37.8
Stage 2 (%)	53.9 ± 8.8	22.4	88.1
SWS (%)	23.0 ± 7.3	0	42.1
REM sleep (%)	18.5 ± 6.5	0	38.4
Arousal index (events/h)	11.1 ± 6.7	2.1	42.1
AHI (events/h)	1.2 ± 1.3	1.2	1.3
Mean SpO ₂ (%)	96.4 ± 1.2	90.4	98.1
Lowest SpO ₂ (%)	91.4 ± 2.7	78	96

AHI, apnea-hypopnea index; REM, rapid eye movement; REMSL, rapid eye movement sleep latency; SL, sleep latency; SpO₂, oxyhemoglobin saturation; SWS, slow wave sleep; TST, total sleep time.

Table 3—Frequency of percentage of inspiratory flow limitation by age groups in the normal group

Age groups (y)	N	Mean $\pm$ SD (%)	Median	CI
20-39	80	8.1 ± 9.8	4.1	5.9-10.3
40-59	49	11.5 ± 14.2	6.3	7.4-15.6
60-80	11	9.4 ± 11.6	8.7	3.7-16.7

$P = 0.086$. One-way analysis of variance. CI, confidence interval; SD, standard deviation.

the group of AHI 5-15 and no symptoms to the group of AHI 5-15 with symptoms (median 8.3%). Also, % IFL in the normal group is significantly different than in the other two groups of AHI 5-15 (with and without symptoms: $F = 4.71$, $P < 0.00$)

DISCUSSION

Our study is the first to evaluate the distribution of IFL in a representative sample of the general population. In the normal patients who did not meet the stringent minimal

polysomnographic definition of OSA (AHI > 5), the 95th percentile value of % IFL was ~30% of the total sleep time. This value is significantly higher than prior anecdotal reports suggesting that any flow limitation might be abnormal, and suggests to us that only values above 30% be used to support a diagnosis of OSA. In fact, the maximum value of % IFL in our apparently normal patients was 56%, emphasizing that, *per se*, an elevated % IFL is not an absolute measure of abnormality (as is currently assumed for an elevated AHI). However, for both statistical and

Figure 2—Correlation between percentage of total sleep time with inspiratory flow limitation (IFL) and body mass index (BMI) according to age groups.

Table 4—Regression model for inspiratory flow limitation and anthropomorphic and PSG variables

	Unstandardized Coefficients		Standardized Coefficients	
	B	Std. Error	Beta	Sig.
1 (Constant)	-145.596	119.616		0.229
BMI	0.686	0.309	0.315	0.031
Age	-0.040	0.149	-0.048	0.788
Arousal index	0.138	0.205	0.112	0.505
Sleep efficiency	-0.020	0.173	-0.023	0.909
PLM index	1.293	1.057	0.178	0.227
SWS	0.215	0.233	0.159	0.361
Stage REM	0.021	0.291	0.012	0.943
AHI	-0.553	1.115	-0.068	0.622
Desaturation index	-0.311	0.520	-0.078	0.553
% time SpO ₂ < 90%	-0.237	0.481	-0.066	0.624
Lowest SpO ₂	1.113	1.051	0.174	0.295
Mean SpO ₂	0.331	1.418	0.037	0.816

AHI, apnea-hypopnea index; BMI, body mass index; PLM, periodic limb movement; REM, rapid eye movement; SpO₂, oxyhemoglobin saturation; SWS, slow wave sleep.

epidemiological reasons, we propose that the 30% value for % IFL be considered a statistical upper bound for “normal” in the absence of other markers of OSA on a PSG. Follow-up studies and studies assessing whether there are significant clinical outcomes associated with IFL above 30% will need to be done to establish clinical significance, if any, of the higher levels of IFL.

It has been previously suggested in several studies that IFL during sleep should be considered an abnormality just because of its presence, as it is an indirect indication of increased upper airway resistance.^{3,4,30} However, the frequency and amount of IFL in nonsymptomatic populations has not previously been reported. Our data in the current study show that some IFL is frequently present in patients without other evidence of sleep disorders. Thus, our normative data provide a statistical approach to identifying a lower threshold for % IFL that can be used to indicate an abnormality such as mild OSA or upper airway resistance syndrome (UARS). Because values up to 30% of IFL are found in 95% of asymptomatic patients, this does not meet the criteria of being “ab-normal.” There is a need to further evaluate the % IFL and long-term consequences in other populations with reference to such a statistically defined “norm” in order to judge the clinical significance of finding IFL in symptomatic individuals and attributing their symptoms to IFL.

Directly measured IFL (using pneumotachograph flow measurement and esophageal manometry) defines collapsibility of the upper airway, and it is almost always associated with increased upper airway resistance.^{2,15,31} The AASM definition of a RERA event was based on esophageal manometry indicating increased respiratory effort leading to an arousal. However, it has been shown that IFL, indirectly indicated through the shape of the inspiratory flow curve on a nasal pressure cannula, can also be used to identify RERAs and similar subtle respiratory events in place of esophageal manometry.³² It needs to be considered that IFL determined by nasal cannula pressure does not directly indicate respiratory effort. Furthermore, the severity of the increase in respiratory effort, which is thought to be important in determining the sleep fragmentation related to SDB,³³ cannot be clearly quantified by the shape of the flattening of the inspiratory airflow. This lack of sensitivity of flow limitation to indicate the degree of respiratory effort may cause some limitations in the detection of PSG events characterized mainly by abnormal respiratory effort during sleep. The nasal cannula remains, however, the most widely used tool for measuring airflow in the clinical arena. Thus, we think that analyzing the statistical distribution of the noninvasive measure of IFL (flattening on the inspiratory airflow curve) has practical value and was the subject of our study, in contrast to a focus on true physiologic IFL (dissociation of inspiratory flow from effort on esophageal manometry), which is an invasive method that is not in widespread clinical usage.

The IFL criterion to differentiate normal individuals from individuals with SDB was previously undetermined. Currently, IFL is only recognized by AASM as part of RERA. Few studies have used the duration of time with IFL as a respiratory parameter,^{9,14,34} and the best criteria and analysis method to evaluate IFL have not previously been defined. There may be other ways

to better describe the effect of IFL, such as the association of IFL with other PSG variables, e.g., electroencephalographic abnormalities.^{11,12,14}

One limitation of this study was related to the manual scoring of IFL, which was performed by visual analysis and is subject to human error, supporting our “statistical” treatment of this variable. However, high interscorer reliability for visual scoring of IFL was observed in our subset of the dataset where multiple scorers were used, and has also been shown in other studies.³⁴ We used a rule for counting periods of IFL that required a minimum of four consecutive breaths to start a period of IFL in analogy to the approach used for other intermittent events as defined by the 2007 AASM Scoring Manual. For example, periodic limb movements are only counted when they occur repetitively in series of five, and Cheyne-Stokes events are tabulated only when three repetitive cycles occur.^{35,36}

It has been suggested that isolated, brief episodes of IFL can have clinical consequences. Several studies suggested also that sustained increases in respiratory effort³⁷ and long periods of IFL^{9,10,14,38} may have clinically important consequences and may be associated with significant outcomes. In one prior study, prolonged periods of IFL (lasting more than 10 min), induced by suboptimal CPAP pressures, were associated with an increase in end-tidal carbon dioxide and systolic blood pressure fluctuations.³⁸ In another study,⁷ IFL was associated with persistence of leg movements. Follow-up studies are still needed to demonstrate long-term consequences of IFL during sleep in individuals without OSAS, as our data show that up IFL up to 30% of total sleep time can be found in all but 5% of the asymptomatic population.

In our study, BMI was correlated with % IFL. IFL reflects upper airway collapsibility³⁹ in a similar mechanism to AHI. It is well known that weight is one of the major risk factors for OSAS.⁴⁰ It would be expected that weight and the enlarged abdomen related to pregnancy⁹ influences IFL to some degree. However, the pathophysiology of IFL has not been well demonstrated, and it may differ from AHI in some aspects. Our study suggests that weight is at least part of the mechanism for IFL. Other aspects that influence critical pressure, and are likely to be associated with IFL, are age, sex,⁴¹ and craniofacial anatomy.⁸ However, in our study, these factors were not significantly associated with IFL. Other factors that could influence IFL, such as nasal problems, should be investigated in future studies.

Our study demonstrated an interesting result: that there is a different association between IFL and BMI according to age groups. Older individuals did not demonstrate a significant association of IFL with BMI, whereas the younger groups did demonstrate this association. These results reinforce the idea that the pathophysiology of SDB may be different in elderly compared with younger individuals.⁴² It may be suggested that certain aspects may be more important in older individuals, such as decrease tone in upper airway muscles contributing to SDB, which causes weight to become a secondary risk factor.

Our results demonstrated that some IFL is common in normal individuals. It is well known that even normal individuals can present a rise in upper airway resistance when their state changes from awake to asleep.⁴³ When normal individuals are compared with patients with UARS, they also have “resistive events”. Although the periods of IFL are associated with

sleep fragmentation in patients with UARS, the resistive events in normal individuals were associated with fewer arousals and less negative pleural pressure.³⁸ Our study demonstrated that a certain amount of IFL is present in normal individuals, indicating that IFL can be part of breathing physiology during sleep, or may be related to an acute event (such as mild nasal allergy) but most likely not enough to lead to chronic consequences in sleep quality and consequent daytime complaints.

In summary, our study demonstrated that only 5% of normal individuals present with > 30% of the total sleep time with IFL, establishing a value for IFL below which one statistically cannot invoke OSA in otherwise healthy individuals. Despite the observation that some individuals of the “normal” group presented up to 56% of IFL, the 95th percentile of a distribution (e.g., 30% for % IFL) is conventionally used to statistically establish a likely boundary between health and disease. This is further supported by the increase in % IFL found in patients with mild OSA (AHI 5-15 and no symptoms) and OSAS (AHI 5-15 with clinical symptoms). Thus, values of up to 30% of IFL should be considered “within normal limits” and only values > 30% can support the likely presence of abnormality. However, studies of clinical outcomes related to the % IFL need to be done to confirm these findings.

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