Impedance-pH monitoring Profile of Patients with Reflux and Obstructive Sleep Apnea Syndrome: A Controlled Study.

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Abstract

Objective: To study the profile of patients with obstructive sleep apnea syndrome (OSAS) and laryngopharyngeal reflux (LPR) at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) and to compare their reflux findings with LPR patients without OSAS. Design: Prospective controlled study. Methods: Patients with LPR and OSAS were prospectively recruited from Augustus 2019 to June 2020. The profile of hypopharyngeal reflux events (HRE) of patients was studied through a breakdown of the HEMII-pH findings over the 24-hour of testing. Reflux symptom score (RSS), gastrointestinal and HEMII-pH outcomes were compared between LPR patients and patients with LPR and OSAS. Multivariate analysis was used to study the relationship between reflux data and the following sleep outcomes: Apnea-Hypopnea Index, Epworth Slippiness Scale (ESS) and paradoxical sleep data. Results: A total of 89 patients completed the study. There were 45 patients with LPR and 44 subjects with both OSAS and LPR. The numbers of upright and daytime HREs and the otolaryngological RSS were significantly higher in patients with LPR compared with those with OSAS and LPR. There was a significant positive association between RSS quality of life score and ESS (p=0.001). The occurrence of HREs in the evening was associated with higher ESS (p=0.015). Patients with OSAS, LPR and GERD had higher number of nocturnal HREs compared with those without GERD (p=0.001). Conclusion: The presence of OSAS in LPR patients is associated with less severe HEMII-pH and ear, nose and throat symptoms. There may have different OSAS patient profiles according to the occurrence of GERD.

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was used to study the relationship between reflux data and the following sleep outcomes: Apnea-Hypopnea Index, Epworth Slippiness Scale (ESS) and paradoxical sleep data.

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Conclusion: The presence of OSAS in LPR patients is associated with less severe HEMII-pH and ear, nose and throat symptoms. There may have different OSAS patient profiles according to the occurrence of GERD.

Key words : Laryngopharyngeal; Reflux; Laryngitis; pH monitoring; impedance; Reflux episode; Pharyngeal; Sleep; Apnea; Obstructive; Profile; Polysomnography.**Introduction** :

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effect of gastroduodenal content reflux, which induces morphological changes in the upper aerodigestive tract.[1] Currently, the hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) is the best way to diagnose LPR through the identification of hypopharyngeal-esophageal reflux events (HRE).[2,3] Patients with LPR-related symptoms and findings mainly have upright and daytime HREs and only a low proportion of patients have nighttime and supine episodes.[4] The deposit of pepsin and other gastroduodenal enzymes into the respiratory tract leads to the development of an inflammatory reaction of the mucosa and respiratory symptoms. Many studies reported the coexistence between LPR and obstructive sleep apnea syndrome (OSAS) but the exact role of reflux in the pathogenesis of OSAS is still unclear.[5-7]

In this study, we explored the profile of patients with OSAS and LPR at the HEMII-pH and we compared the reflux features of patients with both LPR and OSAS with those with only LPR. Among patients with OSAS and LPR, we investigated the relationship between hypopharyngeal reflux events and the occurrence of arousals.

Methods :

Subjects and setting

Patients with sleep disturbances and LPR symptoms were prospectively recruited from Augustus 2019 to June 2020 from the Polyclinique Elsan (Poitiers, France) and CHU Saint-Pierre (Brussels, Belgium). The primary reason of patient consultation was sleep disturbance. We included those with both sleep disturbance and LPR symptoms. All patients underwent simultaneously 24-hour HEMII-pH (Versaflex Z®, Digitrapper pH-Z testing System, Medtronic, Europe) and polysomnography (Cidelec LXe, Loire, France). Only patients with confirmed diagnoses of LPR and OSAS were included. Gastrointestinal (GI) endoscopy was proposed to patients with GERD-related symptoms and elderly patients (>55 yo) who are known to less feel GERD-symptoms.[8] The following exclusion criteria were considered: smoker, alcohol dependence, use of anti-reflux treatment(s), neurological or psychiatric illness, head and neck malignancy, history of head and neck radiotherapy, active seasonal allergies and asthma. Symptoms of patients were evaluated with reflux symptom score (RSS).[9] A group of patients with LPR symptoms and positive HEMII-pH without sleep disturbances was composed throughout the same period respecting the same exclusion criteria. The IRB approved the study protocol (n°BE076201837630). The informed consent was obtained.

Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance-pH monitoring.

The HEMII-pH was composed of 8 impedance segments and 2 pH electrodes. Device details were available in previous publication.[4] Six impedance segments were placed along the esophagus zones (Z1 to Z6). The pharyngeal impedance segments were placed 1 and 2 cm above the cricopharyngeal sphincter. The pH

electrodes were placed 2 cm above LES and 1-2 cm below cricopharyngeal sphincter, respectively. HRE was defined as an episode reaching two hypopharyngeal impedance sensors. The LPR diagnosis was based on the occurrence of [?]1 acid or nonacid HRE.[10] Acid reflux episode was defined as an episode with pH[?]4.0. Nonacid reflux episode consisted of an episode with pH>4.0. Two senior physicians (FB and VM) analyzed the HEMII-pH tracing to isolate the HRE. Patients were invited to keep their daily life habits and diet the day of the testing.

Sleep Findings

Polysomnography (PSG) was performed during the 24-hour HEMII-pH period. Patients were invited to fulfill the French version of Epworth Slippiness Scale (ESS)[11] and the Pichot fatigue scale.[12] Regarding the PSG data, the following data were extracted by a board-certified sleep physician (GA) using the Cidelec v2.2.6. software (Cidelec, Loire, France): Apnea-Hypopnea Index (AHI); total number of arousals; number of arousals/hour; % of time with O_2 saturation level<90%; and the 4 sleep phases including the paradoxical sleep. OSAS status was retrieved from the home sleep study findings considering an AHI[?] 5 per hour as a positive OSAS diagnosis. OSAS severity was scored according to the report of the American Academy of Sleep Medicine based on the patient's AHI: mild (5-14 events/hour); moderate (15-30 events/hour); or severe (>30 events/hour).[13] Patients with AHI<5 were excluded.

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 22,0; IBM Corp, Armonk, NY, USA). The relationships between the demographic data, HEMII-pH, symptoms and sleep findings were investigated through multivariate analysis. The outcome comparison between patient groups (LPR + OSAS*versus* LPR) was performed through Mann-Whitney U Test. A level of significance of p<0.05 was used.

Results :

A total of 89 patients completed the study. There were 45 patients with LPR and 44 subjects with both OSAS and LPR. The demographic and epidemiological data of both groups are described in Table 1. Patients with OSAS and LPR had significant lower proportions of esophagitis, hiatal hernia and gastritis compared with LPR patients. OSAS individuals had higher BMI than patients without OSAS (p=0.001). Table 2 reports the clinical presentation of LPR of both groups. The following symptom scores of LPR patients with OSAS were significantly lower than the scores of those with LPR: dysphonia; throat pain; throat clearing; excess throat mucus and ear pressure/pain. Thus, otolaryngological RSS and related quality of life (QoL) RSS were lower in patients with OSAS and LPR compared with LPR patients.

The HEMII-pH profiles of patients are available in Tables 3 and 4. Irrespective to the daytime period, patients with LPR had significant higher number of acid and nonacid HREs than patients with OSAS and LPR. Both groups were comparable regarding the nighttime HREs and the GERD features.

The PSG features of patients with both OSAS and LPR are described in Table 5. There were 12 and 13 individuals with mild (AHI: 5-15) and moderate (AHI: 16-30) OSAS, respectively. Nineteen patients had severe OSAS according to the AHI (>30). There were significant associations between ESS, BMI (r_s=0.491; p=0.003), QoL RSS (r_s=0.549; p=0.001) and the number of HREs in the evening (r_s=0.415; p=0.015). The multivariate analysis revealed that patients with longer paradoxical sleep had higher RSS (r_s=0.399, p=0.009). There was no additional significant association in the OSAS population and in subgroups of patients regarding AHI categories. There was no significant association between the severity of OSAS and the severity of LPR in the cohort. The analysis of the occurrence of arousals and hypopharyngeal reflux events revealed that only 3 patients had nighttime HREs, and, among them, the HREs were not followed by arousals/awakenings.

Subgroup analysis reported that the presence of GERD at the HEMII-pH was associated with a high number of HREs in patients with OSAS, especially nighttime (Table 6). There was a statistical trend in the

association between DeMeester score and AHI (r_s=0.539; p=0.070). Sleep outcomes did not differ between OSAS patients regarding the presence of GERD.

Discussion:

The relationship of LPR with and its potential role in the pathogenesis of OSAS have not been fully elucidated. The originality of the present study is the realization of both HEMII-pH and PSG in the same time in patients with untreated sleep and LPR findings. We found that patients with LPR and OSAS have different HEMII-pH and clinical patterns compared with LPR individuals without OSAS. Precisely, OSAS patients had a lower number of HREs and less severe otolaryngological symptoms compared with LPR patients. Moreover, there were no significant associations between nighttime HREs and PSG data and between the severity of LPR and OSAS. We only observed associations between ESS, RSS and the number of evening HREs, which supports potential relationship between both conditions without providing pathophysiological explanations. The association between pH-study and PSG findings was investigated in many studies,[14-20] which reported controversial results. Some authors observed that patients with severe OSAS had a significant higher number of nocturnal proximal or distal esophageal events compared with patients with mild OSAS,[14,16,17] while others did not find any association between reflux and OSAS findings.[15,18,19,21-23] The inconsistencies may result from methodological differences across studies.

Some authors used dual- or triple-probe pH monitoring to evaluate reflux events and did not consider nonacid HREs.[18,19] Others only included patients with GERD (distal probe findings)[14,20,23] or esophagitis.[21]Among studies reporting gastrointestinal findings, the prevalence of patients with GERD or GERD and LPR varied from 38.9% to 100% of cases.[14,15,18,20,21] From an epidemiological standpoint, the use of different inclusion criteria and diagnostic approaches may have a substantial impact on the results of the study.

First, LPR is defined by the occurrence of acid, weakly acid and nonacid HREs.[10] Nonacid HREs concern more than 50% of LPR patients and are not detected by pH monitoring without impedance.[4] The lack of consideration of nonacid/weakly HREs may lead to a bias selection through the exclusion of patients with nonacid/weakly LPR.

Second, it has been reported that patients with both GERD and LPR have different profile at the HEMII-pH with higher proportion of nocturnal and supine HREs in GERD patients.[4] Moreover, patients with GERD may have a significant higher probability to have acid LPR, while patients without GERD had equal proportions of acid, nonacid and weakly acid LPR.[4] In that respect, the consideration of GERD as a key inclusion criteria may lead to the introduction of an important bias because many patients with GERD have no LPR or *vice versa* .[1,4] To have a representative sample of LPR population, authors should use HEMII-pH that detects GERD, acid, weakly acid and nonacid HREs.

Third, the severity of LPR was evaluated through different patient-reported outcome questionnaires including GERD-related questionnaires,[5,7,15] reflux symptom index,[6,14,17,21,22] or LPR-health-related quality of life.[22] These patient-reported outcome questionnaires are all validated but do not include similar symptoms and rating approaches, yielding the comparison across studies difficult. According to these reasons, the comparison of our results with the literature remains limited. Only Xiao *et al* . used HEMII-pH monitoring to investigate the relationship between HREs and PSG findings,[15] and they did not find significant objective association, corroborating our observations. Our findings as well as the observations of Xiao *et al* . reinforce the controverse about the pathophysiological link between LPR and OSAS.

For a long time, it has been proposed that reflux is thought to be induced by decreasing intraesophageal pressure during obstructive sleep apnea, which causes a vacuum-like effect on the gastric contents. This theory was strengthened by the observation that during sleep, there would be a delay in the nocturnal acid clearance, facilitated by the suppression of salivation and esophageal peristalsis.[24] However, recent data supported that despite a decrease in esophageal body pressure during obstructive apnea events, compensatory changes in upper esophageal sphincter and gastroesophageal junction pressures prevent reflux.[25]The lack of significant association between HREs, AHI and arousal findings of the present study may strengthen these findings. According to our observations and those of studies using HEMII-pH or high-resolution pharyngeal

manometry,[25] we believe that there would exist several pathophysiological mechanisms depending on the lower and upper esophageal sphincter tonicity, the presence of GERD and the type of HREs (liquid *versus* gaseous). The investigation of the type of HREs makes particularly sense because the supine position would be more favorable for liquid reflux events that are more aggressive for the laryngopharyngeal mucosa because they contain more gastroduodenal enzymes.[4] In that way and according to our subgroup analysis, the correlation between reflux and OSAS severity could particularly concern patients with GERD and liquid HREs; the overweight being a favoring factor. Naturally, this hypothesis needs to be confirmed through future studies considering the type (liquid *versus* gaseous) and the nature of HRE (acid, weakly acid, nonacid) and the time of occurrence of HREs.

In our study, we observed significant association between the number of HREs in the evening, RSS and ESS score. The occurrence of evening HREs and the deposit of gastroduodenal enzymes into the laryngopharyngeal mucosa could be associated with the development of a more significant inflammatory reaction before sleep and related sleep (ESS) disorders. This hypothesis cannot be confirmed with our data but our findings support the need to consider daytime and nighttime periods of occurrence of HREs and not only the nighttime reflux events. Moreover, the measurement of pepsin saliva in the morning could provide additional useful analysis in the understanding of the mechanisms underlying the association between LPR and OSAS.[6]

With regard to the clinical presentation of patients with OSAS and LPR, our observations supported that OSAS patients may have less severe clinical picture than LPR patients. To the best of our knowledge, only Teklu *et al* . specifically investigated the symptom profile of LPR patients with or without OSAS, reporting that patients with OSAS had worse symptoms as measured by RSI.[7] As above-mentioned, the inclusion of a high number of patients with GERD in the study of Tekly *et al* . makes the comparison difficult. Another finding highlighted in the present study is the higher proportion of hiatal hernia and potential related esophagitis in LPR group compared with patients with LPR and OSAS. In the LPR general population, esophagitis and hiatal hernia concern 20% to 30% of patients.[1] According to our observations, patients with LPR and OSAS may have a lower proportion and the potential mechanisms are still unknown.

In this study, we tried to explore the relationship between the occurrence of arousals/awakenings and HREs. However, we only had 3 patients with nighttime HREs and among them, the sleep events were not associated with HREs. The low number of patients with nighttime HREs is not surprising regarding previous data.[4] The lack of association between sleep and reflux events corroborates the findings of a previous study where authors observed that 82% of reflux events occurred during a PSG epoch that was classified as wake.[26] Authors also reported that arousals/awakenings preceded almost all reflux events, whereas fewer had an arousal/awakening after the event.[26]

The primary limitations of our study are the low number of patients and the lack of investigation of laryngopharyngeal signs. In practice, many patients did not accept to benefit from HEMII-pH and PSG in the same time and declined one of two examinations. However, the realization of both examinations in the same period is important to study the relationship between both conditions. To date, only a few studies prospectively investigated the relationship between LPR and OSAS through simultaneous pH-study and PSG.[15,16,18,21] This methodological point is particularly important because the reproducibility of the HEMII-pH results from one day to the other is not guaranteed. The number of HREs may depend on the patient diet,[4] or, hypothetically, on the patient stress the day of the testing that may be both associated with esophageal sphincter relaxations.[1] The primary strengths of the study are the prospective design and the use of HEMII-pH for the diagnosis. The consideration of acid, nonacid and weakly acid HREs led us to include all patients with LPR and not only a subgroup of individuals (acid LPR). Moreover, in this study we deliberately use the full and not the short version of RSS (RSS-12) because the consideration of otolaryngological, digestive and respiratory symptoms makes sense in patients with OSAS that commonly includes respiratory and, in some GERD patients, digestive symptoms.

Conclusion

The clinical profile of LPR patients may vary regarding the occurrence of OSAS but the relationship between

OSAS and LPR is still unclear. The findings of the present study support a potential relationship between some subjective evaluations of both conditions without identifying objective links. Patients with LPR and OSAS could have less HREs compared with those with LPR only, which may be clinically observed by less otolaryngological symptoms. However, there may have different profiles of OSAS patient according to the occurrence of GERD.

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Summary/Key points

-The clinical profile of LPR patients may vary regarding the occurrence of OSAS. The presence of OSAS in LPR patients may result with fewer LPR-related symptoms, while LPR patients without OSAS had a higher number of HREs than patients with LPR and OSAS. Moreover, OSAS patients has a lower proportion of hiatal hernia and esophagitis than classical LPR patients.

-The occurrence of HREs in the evening was associated with a more severe ESS; the severity of subjective OSAS symptoms being associated with the severity of LPR according to RSS quality of life score.

-Patients with OSAS, LPR and GERD had higher number of nocturnal HREs compared with those without GERD but there was no temporal relationship between nocturnal HRE and the occurrence of awakenings/arousals.

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Table 1: Characteristics of Patients.

Characteristics	OSAS & LPR	LPR	p-value
Age (m ± SD)	53.4 ± 12.2	51.1 ± 14.8	NS
BMI (m ± SD)	29.2 ± 5.6	26.1 ± 7.0	0.001
Gender			
Male	19	15	NS
Female	25	30	-
Gastrointestinal endoscopy (N, %)	27 (61.4)	32 (71.1)	
Normal	9 (33.3)	10 (31.3)	NS
Esophagitis (LA Grading system)	3 (11.1)	7 (21.9)	0.022
Hiatal hernia	3 (11.1)	10 (31.3)	0.004
LES insufficiency	11 (40.7)	14 (43.8)	NS
Gastritis	1 (3.7)	9 (28.1)	0.001

Table 1 footnotes : Abbreviations: BMI= body mass index; LA= Los Angeles; LES= lower esophageal sphincter; LPR=laryngopharyngeal reflux; m=mean; N=number; NS=not significant; OSAS=obstructive sleep apnea syndrome; SD= standard deviation.

Table 2: Clinical differences between patient groups .

LPR Symptoms	OSAS & LPR	LPR	p-value
Ear, nose and throat symptoms			
1. Voice disorder	1.80 ± 5.42	2.96 ± 4.64	0.011
2. Throat pain	3.39 ± 6.81	7.07 ± 8.11	0.001
3. Pain during swallowing time	2.61 ± 5.51	2.42 ± 5.02	NS
4. Dysphagia	2.68 ± 5.13	3.09 ± 4.94	NS
5. Throat clearing	4.30 ± 5.46	9.48 ± 7.56	0.001
6. Globus sensation	6.25 ± 8.45	7.64 ± 7.75	NS
7. Excess throat mucus	6.36 ± 7.08	13.33 ± 9.74	0.001
8. Ear pressure/pain	1.64 ± 3.88	4.38 ± 7.04	0.003
9. Tongue burning	1.27 ± 3.56	2.87 ± 6.63	NS
Ear, nose and throat total score	31.61 ± 35.58	53.33 ± 37.90	0.001
Digestive symptoms			
1. Heartburn	9.86 ± 7.89	3.83 ± 7.40	NS
2. Regurgitations or burps	4.11 ± 4.90	2.57 ± 6.09	NS
3. Abdominal pain	2.75 ± 4.49	2.74 ± 5.31	NS
4. Diarrheas	2.57 ± 5.15	0.13 ± 0.34	NS
5. Constipation	2.23 ± 4.20	3.70 ± 6.14	NS
6. Indigestion	2.55 ± 5.33	1.52 ± 5.45	NS
7. Abdominal distension/flatus	5.48 ± 6.76	4.61 ± 7.86	NS
8. Halitosis	4.89 ± 6.85	2.78 ± 7.12	NS
9. Nausea	2.14 ± 4.55	1.74 ± 4.73	NS
Digestive total score	37.14 ± 29.39	35.87 ± 30.90	NS

LPR Symptoms	OSAS & LPR	LPR	p-value
Respiratory symptoms			
1. Cough after eating/lying down	3.98 ± 6.72	6.13 ± 8.34	NS
2. Cough	3.82 ± 6.38	5.02 ± 6.78	NS
3. Breathing difficulties	1.95 ± 4.05	1.96 ± 4.45	NS
4. Chest pain	4.75± 6.88	3.02 ± 5.81	NS
Respiratory total score	15.84 ± 17.13	16.13 ± 18.49	NS
RSS - score total	84.59 ± 65.02	105.33 ± 69.79	NS
Quality of Life Score	22.80 ± 15.79	30.4 ± 17.79	0.031
Ear, nose and throat QoL	7.58 ± 7.32	14.24 ± 9.47	0.001
Digestive QoL	11.12 ± 7.83	10.91 ± 8.41	NS
Respiratory QoL	4.63 ± 4.80	4.24 ± 4.58	NS

Table 2 footnotes : Abbreviations: LPR=laryngopharyngeal reflux; m=mean; NS: not significant; OSAS=obstructive sleep apnea syndrome: QoL=quality of life; RSS=reflux symptom score.

Table 3: HEMII-pH Characteristics of Patient Groups.

HEMII-pH findings	**OSAS & LPR**	**LPR**	**p-value**
Proximal acid reflux episodes	6.77 ± 7.59	16.0 ± 18.0	0.001
Proximal nonacid reflux episodes	5.30 ± 8.84	15.30 ± 18.25	0.001
Total number of proximal reflux episodes	12.07 ± 11.72	31.18 ± 26.40	0.001
Proximal reflux episodes by period of the day			
Post-breakfast hour	1.27 ± 1.77	4.02 ± 4.92	0.001
Post-breakfast hour to the lunch	3.23 ± 4.89	10.80 ± 14.60	0.003
Post-lunch hour	2.77 ± 6.26	4.42 ± 3.64	0.001
Post-lunch hour to the dinner	8.30 ± 12.80	17.51 ± 15.51	0.001
Post-dinner hour	2.64 ± 2.22	4.20 ± 3.36	0.022
Post-dinner hour to the bedtime	5.86 ± 6.19	11.60 ± 13.56	0.019
Nighttime	1.95 ± 2.45	4.11 ± 7.83	NS
GERD (N, %)	12 (26.7)	16 (36.4)	NS
Percentage of time with distal pH<4	3.04 ± 4.00	5.29 ± 8.33	NS
DeMeester score	11.07 ± 14.13	22.09 ± 36.02	NS

Table 3 footnotes: Abbreviations: GERD=gastroesophageal reflux disease; LPR=laryngopharyngeal reflux; NS: not significant; OSAS=obstructive sleep apnea syndrome

Table 4: Percentages of Hypopharyngeal Reflux Events over the 24-hour period of testing.

HEMII-pH	**OSAS & LPR**	**LPR**
Proximal Acid reflux episodes by period of the day		
Post-breakfast hour	5.75%	7.37%
Post-breakfast hour to the lunch	12.14%	15.97%
Post-lunch hour	9.93%	8.95%
Post-lunch hour to the dinner	29.68%	33.38%
Post-dinner hour	11.55%	8.94%
Post-dinner hour to the bedtime	22.37%	20.51%
Nighttime	8.58%	4.89%
Total	100%	100%

Table 4 footnotes: Abbreviations: HEMII-pH = hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring; LPR=laryngopharyngeal reflux; OSAS=obstructive sleep apnea syndrome.

Table 5: Polysomnography Features of Patients with SOAS.

Sleep outcomes	**Mean ± SD**	**Range**
AHI	29.17 ± 19.59	5 - 75
Sleep phases (min)		
Phase 1	43.15 ± 224.18	7 - 161
Phase 2	224.18 ± 79.30	104 - 453
Phase 3	88.35 ± 45.83	0 - 216
Paradoxal sleep	72.21 ± 35.51	0 - 151
Arousal data		
Arousal (tot N)	192.33 ± 136.48	54 - 625
Arousal (N/hour)	27.45 ± 18.82	7.7 - 83
Episodes of saturation <90%	3.84 ± 7.69	0 - 44.3
ESS	9.24 ± 4.84	0 - 19
Pichot Score	13.63 ± 9.13	0 - 32

Table 5 footnotes : Abbreviations: AHI=apnea-hyponea index; ESS=Epworth Sleepiness Scale; N=not significant; SD=standard deviation.

Table 6: HEMII-pH profile of patients with LPR and OSAS according to the presence of GERD.

	OSAS	**patients**	
HEMII-pH findings	GERD & LPR	LPR	p-value
Proximal acid reflux episodes	12.83 ± 8.05	4.54 ± 6.02	0.001
Proximal nonacid reflux episodes	8.08 ± 9.44	4.27 ± 5.31	NS
Total number of proximal reflux episodes	20.83 ± 15.66	8.85 ± 7.80	0.010
Proximal reflux episodes by period of the day			
Post-breakfast hour	2.67 ± 2.81	0.79 ± 0.74	0.006
Post-breakfast hour to the lunch	6.75 ± 8.27	2.12 ± 1.95	0.018
Post-lunch hour	5.08 ± 11.12	2.03 ± 2.80	NS
Post-lunch hour to the dinner	14.25 ± 21.84	6.21 ± 6.21	NS
Post-dinner hour	4.08 ± 2.50	2.24 ± 2.03	0.009
Post-dinner hour to the bedtime	10.08 ± 8.55	4.58 ± 4.46	0.009
Nighttime	3.83 ± 3.19	1.21 ± 1.67	0.007

Table 6 footnotes : Abbreviations: GERD=gastroesophageal reflux disease; LPR=laryngopharyngeal reflux; NS: not significant; OSAS=obstructive sleep apnea syndrome