

Sleep disorders and the prevalence of asymptomatic nocturnal acid and non-acid reflux

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Abstract

Background Nocturnal acid reflux is associated with symptomatic and asymptomatic sleep arousals, leading to fragmented sleep. The frequency and influence of acid reflux in patients with various forms of insomnia has not been reported. The aim of this study was to quantify nocturnal acid and nonacid reflux in patients with primary sleep disorders as previously diagnosed by polysomnography.

Methods Thirty one subjects were studied: (A) 9 subjects with a polysomnographically diagnosed sleep disorder (1 with restless legs syndrome, 4 with narcolepsy, 4 with periodic limb movement disorder); (B) 12 subjects with primary insomnia (PI) and unrevealing polysomnography; and (C) 10 controls without disturbed sleep. All subjects underwent a physical examination and 24 h transnasal pH and impedance monitoring to detect acid and non-acid reflux.

Results The 21 subjects with fragmented sleep due to a primary sleep disorder had significantly more recumbent acid exposure (>1.2% of time) as compared with control subjects (33% versus 0%). When fragmented sleep subjects were divided into two groups, 17% of PI subjects and 55% of subjects with a diagnosed sleep disorder had significant recumbent acid exposure (P=0.009). Likewise, the median recumbent nonacid events were increased in the sleep disordered group (P=0.011).

Conclusions This study indicates that patients with primary sleep disorders have prominent nocturnal acid reflux without symptoms of daytime acid reflux. Acid reflux is most prominent in patients with polysomnographic findings of disturbed sleep as compared to patients with PI; while non acid reflux is increased minimally in these patients.

Keywords Gastro-esophageal reflux, nocturnal acid reflux, non-acid reflux, sleep disorders, insomnia

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Introduction

Nocturnal acid reflux is associated with symptomatic and asymptomatic sleep arousals, leading to disordered sleep and

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complaints of insomnia. Increased nocturnal acid exposure time may also lead to esophageal damage in the form of esophagitis, Barrett's esophagus, and adenocarcinoma at a higher rate than daytime acid reflux [1,2]. Insomnia is a common complaint that affects 30% of the population in the United States and more than 50% of the population over age 65. Insomnia is defined as a difficulty in initiating, difficulty maintaining sleep, or the sensation of nonrestorative sleep in the context of adequate opportunity to sleep [3]. Impaired sleep is associated with impaired daytime function, decreased quality of life, and reduction in work productivity and leads to the use of hypnotics in over 15% of adult patients [4,5].

The relationship between gastroesophageal reflux and sleep is quite complex. Based on prior research, a gastroesophageal reflux event is temporally associated with an arousal or awakening [6-8]. Although the relationship between these two events is not known, the arousal is presumed to be a consequence of the reflux event. The arousal, in turn, is thought to trigger a swallow leading to esophageal acid clearance. This sequence of events, especially in gastroesophageal reflux

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disease (GERD) patients, may lead to disordered sleep, feelings of fatigue, daytime sleepiness, and decreased quality of life [6-10]. Prior studies have focused on gastroesophageal reflux and its effect on impaired sleep using questionnaire analysis [10,11]. The use of proton pump inhibitors has been noted to decrease gastroesophageal acid reflux and thus to improve disordered sleep [1,7,8]. Inversely, central nervous system depressing hypnotic medications such as zolpidem have been shown to increase nocturnal acid exposure time by blunting the arousal and protective swallow reflex which occur after esophageal acid exposure [12].

Previous studies examining the relationship between GERD and sleep have excluded patients with a polysomnographically diagnosed sleep disorder in order to diminish the potential impact of these disorders on sleep and GERD. Thus, the effects of primary sleep disorders on gastroesophageal reflux have not been studied. Sleep disorders are often classified into eight different categories [3]. One of these categories is sleep-related movement disorders, which includes two disorders, restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). RLS is the spontaneous, continuous leg movements associated with unpleasant paresthesias. The symptoms are temporarily relieved by movement [13]. The polysomnographic findings can include prolonged sleep onset latencies, shorter total sleep time, lower sleep efficiency, more arousals, higher number of stage shifts, and longer rapid eye movement (REM) sleep latency [14]. PLMD is characterized as repetitive bursts of electromyographic activity in the lower extremities, which usually correspond to sudden muscle "jerks." They can occur in isolation, or in conjunction with the complaint of restless legs. The movements are repetitive, stereotyped and typically involve extension of the big toe with partial flexion of the ankle, knee, and sometimes hip. The patient is often unaware of these movements, yet often complains of incomplete or disturbed sleep or daytime somnolence due to frequent arousals and fragmented sleep. The polysomnographic findings includes, repetitive movements that are 0.5 to 5 sec in duration, typically separated by an interval of 20 to 40 sec (maximum 90 sec) and, more than 15 periodic limb movements per hour of sleep time [3,15].

Narcolepsy is a less common, but debilitating neurological sleep disorder. It is defined as a hypersomnia of central origin which presents as daytime sleepiness with hypnagogic hallucinations, sleep paralysis, disturbed nocturnal sleep, and cataplexy [16]. The diagnosis is based on nocturnal polysomnographic findings and daytime multiple sleep latency testing (MSLT). The polysomnographic findings exclude other sleep disorders such as obstructive sleep apnea (OSA) and sleep deprivation, whereas the MSLT demonstrates a mean sleep latency of less than or equal to 8 min with REM sleep evident on at least 2 of the 5 MSLT nap opportunities.

The frequency of nocturnal acid reflux in patients without heartburn or GERD symptoms but with various types of primary sleep disorders [RLS, narcolepsy, PLMD, primary insomnia (PI)] has not been reported. The aim of this pilot study was to quantify nocturnal acid and nonacid reflux in patients with previously diagnosed sleep disturbance.

Materials and methods

Study population

Thirty one subjects were included in this study. Twenty one subjects were recruited from the Jefferson Sleep Disorders Center based on results of prior polysomnographic evaluations. Chart review identified two groups of subjects. The first group had a polysomnographically diagnosed sleep disorder: one subject with RLS, four with narcolepsy, and four with PLMD. The second group had PI which consisted of twelve subjects with difficulty falling asleep or staying asleep in association with daytime sleepiness and a non-diagnostic polysomnography (PSG). This group included subjects who fit American Academy of Sleep Medicine diagnostic criteria for insomnia based on subjective complaints, and other diagnostic categories were excluded [3]. Ten control subjects were recruited by local advertisement. No subjects had complaints of GERD.

Subjects were eligible for the study if they were 18 years of age or older, and had a documented polysomnogram prior to enrollment. Subjects were eligible for enrollment as a subject in the polysomnographically diagnosed sleep disorder group if they had RLS, PLMD, or narcolepsy. Subjects were eligible for inclusion in the PI group if they had a previous unrevealing polysomnogram and complaints of falling asleep or staying asleep in association with daytime sleepiness or other daytime impairments attributable to insomnia. Possible polysomnographic findings in this group included poor sleep efficiency, reduced or prolonged REM sleep, and frequent arousals, yet specific PSG criteria were not utilized for study inclusion. Exclusion criteria included a history of GERD, heartburn, current or past use of acid suppressive medication. Subjects were also excluded if they had been polysomnographically diagnosed with sleep apnea syndrome, or were using any sleep aids including hypnotic medications over the course of the one month. Subjects with a prior history of esophagogastric surgery or currently pregnancy were excluded. Controls were held to the same exclusion criteria and did not have any complaints of sleep disturbance.

Protocol

Full approval was obtained from the University's institutional review board. On the basis of the chart review of all patients with polysomnographic studies completed within 3 years before the data collection period, inclusion and exclusion criteria, eligible subjects were contacted via phone. If subjects were interested in participating and met initial criteria for study entry, the study was further explained and the subject was provided with a consent form.

Each subject underwent esophageal pH and impedance monitoring at the Thomas Jefferson University Hospital Motility Laboratory. Subjects arrived at the clinic in the morning where a physical exam was performed. The subjects completed questionnaires including Flinders Fatigue Scale,

Epworth Sleepiness Scale, Insomnia Severity Scale, and Reflux Disease Questionnaire [17-20]. An esophageal pH catheter was placed transnasally in standard fashion. The pH catheter had a built-in reference electrode and was calibrated at pH 7 and 1 with a buffer solution. The catheter was positioned 5 cm above the lower esophageal sphincter. A monitoring unit was attached to the subject and the subject left the clinic. The subjects were instructed on use of the unit and recording information pertaining to when they were awake in the supine position or asleep in the recumbent position. The subject returned to the clinic the following day, the catheter was removed and the data was downloaded.

pH and impedance measurements

The total time the pH of the distal esophagus was less than 4.0 in both the upright and recumbent positions was calculated. If the subject's esophageal pH was less than 4.0 for greater than 6.3 percent of the study period in the upright position, it was considered abnormal. If the percent time was greater than 1.2% in the recumbent position it was considered abnormal. If the esophageal pH was less than 4.0 for greater than 4.2% of the total observed time, this was considered abnormal. The mean acid clearance time was calculated in both the upright and recumbent position. A DeMeester score was calculated in traditional fashion with a normal score being less than 14.7. Reflux episodes in both the upright and recumbent positions were recorded using the impedance data. Reflux episodes were detected by impedance and categorized as acid and nonacid by pH. Less than 73 total reflux episodes were considered within normal range. All data were recorded and read in a blinded fashion. Blinding was not broken until all studies were completed.

Data analysis

All esophageal pH and impedance data were reviewed. The distributions of the variables of interest with regard to sleep disorder group -- Acid (recumbent), Non-acid (recumbent), total reflux episodes, percent time (recumbent), total acid exposure time -- were examined using box plots and percentile descriptive statistics (median, 25th and 50th percentiles) for each of the sleep disorder groups. Non-parametric tests were used to compare the scores between groups. When all three of the sleep disorder groups were tested, the Kruskal-Wallis test was used to test an overall hypothesis of any difference. The abnormal reflux groups were tested using the Wilcoxon test.

Results

A total of 31 subjects were enrolled in the study. Nine subjects had a polysomnographically diagnosed sleep disorder: one with RLS, four with narcolepsy, and four with PLMD.

Table 1 Summary of subjects' characteristics (N=31)

	Normal controls (N=10)	Primary insomnia (N=12)	Diagnosed sleep disorder (N=8)
Age (years), median (min, max)	26.5 (24, 29)	32 (24, 72)	41 (22, 64)
Sex, n			
Female	6	9	8
Male	4	3	1
Race, n			
White	7	8	5
Black	0	2	4
Asian	1	2	0
Latino	2	0	0
BMI, median (min, max)	20.9 (20.2, 31.8)	29 (16.6, 49.5)	25.6 (20.8, 31)
Tobacco Use, n	0	1	2
Medical history, n			
Anemia	0	0	1
Asthma	1	0	1
Inflammatory bowel disease	1	0	1
Irritable bowel syndrome	0	1	1
Diabetes	0	0	1
Hypertension	0	1	1
Depression	1	2	2
Migraines	0	1	0

There were twelve subjects with PI. Ten control subjects had no complaints of insomnia and no symptoms of GERD. A summary of the subjects' characteristics can be found in Table 1.

Daytime reflux

The median daytime acid exposure time was 0.7% in the control group, 0.9% in the PI group, and 1.9% in the sleep disordered group with a normal value being less than 6.3%. Thus daytime acid exposure time was normal in all groups of subjects. The median number of acid and nonacid reflux events was 9 and 12, respectively, in the control group, 10 and 15 in the PI group and 15 and 16 in the sleep disordered group.

Nocturnal reflux

Nocturnal reflux was defined as recumbent pH <4 for greater than 1.2% of the recording time. The median nocturnal acid exposure time in the control group, PI group, and sleep disordered group was 0%, 0.1%, and 3.2% (P=0.009). The 21 subjects with disturbed sleep (PI and polysomnographically diagnosed sleep disorder) had significant recumbent acid exposure as compared with control subjects (33% versus 0%). There were no subjects in the control group with significant

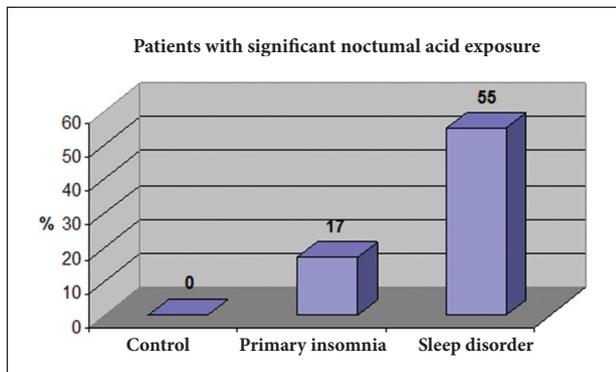


Figure 1 There were no subjects in the control group with significant nocturnal reflux, 17% of those subjects with primary insomnia and 55% of the subjects with a diagnosed sleep disorder had significant nocturnal reflux. Significant nocturnal reflux was defined as an esophageal pH <4.0 for more than 1.2% of time

nocturnal reflux. Seventeen percent of those subjects with PI had significant nocturnal reflux and 55% of the subjects with a diagnosed sleep disorder had significant nocturnal reflux (Fig. 1).

Table 2 shows the medians and interquartile ranges for the acid, non-acid and total reflux events in each group. Controls had nearly all zeroes (8 out of 10 measurements) for acid events, primary insomniacs had a median of 2 and sleep disorder subjects had a median of 5, with a Kruskal-Wallis P-value of 0.003 suggesting a significant difference in medians between these groups. When the PI group and sleep disordered group were combined and tested against the controls, the difference remained significant (P=0.004). Likewise, the median nonacid events were 0.5 in the control group, 0 in the PI group, and 3 in the sleep disordered group with a Kruskal-Wallis P-value of 0.011 suggesting a significant difference in medians between these groups.

Table 3 compares nocturnal acid exposure time and total

acid exposure time between the three groups. In all cases, the sleep disorder subjects tended to have the highest acid exposure times, primary insomniacs the next highest, and controls the lowest. All Kruskal-Wallis tests were significant.

Discussion

It has been well established in epidemiologic studies that patients with known GERD often experience nocturnal reflux symptoms and sleep disturbance [11,21-23]. Most studies which have examined the effect of GERD symptoms on sleep have done so using questionnaire analysis [11,22]. Over subjective studies, patients describe the effect acid suppressive treatment has on the sleep quality and time [7,11,24,25]. These studies have helped elucidate the relationship of sleep disturbance and acid reflux but at the same time the association appears more complex than originally believed. During sleep, an acid reflux event triggers a sleep arousal and swallow induced esophageal acid clearance. More frequent or prolonged nocturnal reflux events are associated with a longer acid clearance time and higher grades of esophagitis and Barrett’s esophagus [24,25]. One can only speculate about the causality between sleep disorders and GERD. As seen in prior study, treatment of reflux with a proton pump inhibitor improves sleep parameters in patients with PI and minimal heartburn symptoms [7,26].

In addition to disturbed sleep in known GERD patients, our group, Orr, and others, have identified a subset of patients with disturbed sleep that experience nocturnal acid reflux and prolonged acid exposure without daytime heartburn symptoms or diagnosed GERD [6,7,26]. Only a few studies have objectively evaluated the sleep parameters of patients who are without heartburn symptoms but who are experiencing sleep disturbance [26]. Using objective analysis, it has been suggested that in perhaps 25-35% of

Table 2 Nocturnal acid, non-acid and total reflux episodes

	Controls (n=10)		Primary insomniacs (n=12)		Sleep disorders (n=9)		P-value
	Median	IQR	Median	IQR	Median	IQR	
Acid recumbent	0.0	(0.0, 0.0)	2.0	(0.0, 3.5)	5.0	(1.0, 9.0)	0.003
Non-acid recumbent	0.5	(0.0, 2.0)	0.0	(0.0, 0.0)	3.0	(1.0, 11.0)	0.011
Total reflux episodes	25.5	(11.0, 39.0)	31.5	(21.5, 37.0)	37.0	(24.0, 58.0)	0.370

IQR, interquartile range

Table 3 Acid exposure time

	Controls (n=10)		Primary insomniacs (n=12)		Sleep disorders (n=9)		P-value
	Median	IQR	Median	IQR	Median	IQR	
Nocturnal % time	0.0	(0.0, 0.0)	0.1	(0.0, 0.7)	3.2	(0.2, 9.3)	0.009
Total % time	0.4	(0.1, 0.5)	0.9	(0.3, 3.7)	2.6	(1.3, 5.1)	0.029

IQR, interquartile range

patients with disturbed sleep, and without known GERD or daytime heartburn symptoms, the etiology of the sleep disturbance may be gastroesophageal acid reflux [7,26]. Treatment with acid suppressive medications usually results in improvement, or resolution of poor sleep in such patients. It is in this subgroup of insomnia patients with silent GERD that hypnotic use without acid suppressive treatment may be especially damaging [12]. In addition, since these patients are without daytime heartburn symptoms, but clearly have GERD-associated sleep disturbance, the study of such patients using questionnaire analysis is difficult.

All prior studies evaluating nocturnal acid reflux in sleep disturbed patients with a polysomnographically diagnosed sleep disorder have been excluded from analysis based on the hypothesis that these subjects have a medical reason for sleep disturbance. This is the first reported study which suggests that subjects with a polysomnographically diagnosed sleep disorder including narcolepsy, RLS, and PLMD also experience significant nocturnal acid reflux. The fact that 9 of 17 patients (55%) with a primary sleep disorder have abnormal and therefore undiagnosed GERD, may have important clinical relevance regarding risk for future complicated disease without recognition and acid suppressive treatment. Patients with PI also experience significant nocturnal acid reflux but to a lesser extent. Acid suppression may improve sleep parameters in these patients with a diagnosed sleep disorder and should be an area of future research. This is also the first report of the frequency of non-acid reflux in a population of patients with diagnosed sleep disturbances. Non-acid reflux is minimally increased in the primary sleep disorder patients and the significance of this increase is uncertain without further study.

One limitation to this study is a small sample size. Recruitment was quite difficult given the rigorous exclusion criteria. Many subjects with primary sleep disorder were excluded based on the use of a sleep aid or a prior diagnosis of obstructive sleep apnea. The frequent use of sleep aids and prior history of obstructive sleep apnea patients are commonly found in a tertiary sleep referral center, both important exclusion criteria for our study. All PSGs over a 4-year period were evaluated from approximately 2600 patients and only 100 subjects that met the inclusion and exclusion criteria based on chart review. Another limitation to the study was the non-concomitant use of PSG and pH/impedance testing. Future research can focus on correlating sleep arousal with reflux events in such subjects.

In conclusion, this study indicates that patients with a polysomnographically diagnosed sleep disorder such as RLS, PLMD disorder, and narcolepsy, experience significant nocturnal acid reflux. Acid suppression may be necessary in patients with a sleep disorder in order to prevent the sequelae of uncontrolled acid reflux and this is an important finding in this study. The role of sleep disturbance in GERD remains quite complex and requires further investigation. Further studies should include those patients with a diagnosed sleep disorder since this group may be experiencing significant reflux often in the absence of daytime symptoms.

Summary Box

What is already known:

- In 25-35% of patients with disturbed sleep and without known gastroesophageal acid reflux disease (GERD), the etiology of the sleep disturbance may be secondary to GERD-induced arousal or awakening

What the new findings are:

- Patients who suffer from primary sleep disorders have an increased incidence of asymptomatic GERD and experience significant nocturnal acid reflux
- Acid suppression may be necessary in patients with primary sleep disorders in order to prevent the sequelae of uncontrolled GERD

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