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Nocturnal Gastroesophageal Reflux and Sleep Depth in Healthy Adults, as Measured by Portable High-Resolution Manometry, Esophageal pH, and Electroencephalography

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Background: The primary mechanism of diurnal gastroesophageal reflux (GER) is transient lower esophageal sphincter relaxation (TLESR) in both healthy persons and patients with gastroesophageal reflux disease (GERD). However, few studies have examined nocturnal GER. Using portable high-resolution manometry (HRM), esophageal pH, and electroencephalography (EEG), we investigated the association of onset of nocturnal GER with sleep depth in healthy Japanese adults.

Methods: We recruited ten healthy men (mean age 33.5 ± 4.2 years) with no reflux symptoms, no history of surgery, and no current medication use. HRM and an esophageal pH catheter were inserted in the evening. The participants returned home after consuming a test meal, and EEG was placed at home before bedtime to measure sleep depth.

Results: The main mechanism underlying nocturnal GER was TLESR (15/17 episodes: 88.2%). The rate of TLESR with nocturnal GER during sleep was high (51.9%, 27/52 episodes). Sleep depth during TLESR was 44.2% (23/52 times) awake and 34.6% (18/52 times) shallow sleep (N1-2). Sleep depth during TLESR with nocturnal GER was 74.0% (20/27 time) awake and 18.5% (5/27 times) shallow sleep (N1-2).

Conclusion: The primary mechanism underlying nocturnal GER was TLESR in healthy Japanese men. TLESR and TLESR with nocturnal GER were more frequent during awakenings and shallow sleep.

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Key words: high-resolution manometry, electroencephalograph, transient lower esophageal sphincter relaxation, nocturnal acid reflux

Introduction

The relationship between gastroesophageal reflux (GER) and sleep disorders is attracting increasing attention. Previous studies reported that the primary mechanism of diurnal GER is transient lower esophageal sphincter relaxation (TLESR) in healthy adults and patients with gastroesophageal reflux disease (GERD)[1–4]. TLESR is characterized by lower esophageal sphincter (LES) relaxation without swallowing and is the main mechanism responsible for acid reflux and belching. However, information on the mechanisms underlying nocturnal GER is limited, and only one such study has been conducted in Japan[5–7].

A study[5] using high-resolution manometry (HRM), esophageal pH, and polysomnography to evaluate nocturnal GER found that TLESR was mainly responsible for nocturnal GER in controls. However, GER was evaluated in a hospital setting, and in-hospital measurements may differ from those in a home setting. Therefore, the present study used portable HRM and electroencephalography (EEG), instead of HRM and polysomnography, to examine the mechanisms underlying nocturnal GER in a realistic home environment, and to evaluate the association of nocturnal GER with sleep depth in healthy Japanese.

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Materials and Methods

Study Design

The present study was conducted at Nippon Medical School Chiba Hokusoh Hospital between December 2015 and December 2016. It was approved by the Ethics Committee on Human Research of Nippon Medical School Chiba Hokusoh Hospital (approval number: 481) and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Participants

The participants were healthy men (age 33.2 ± 4.2 years) with no reflux symptoms, no history of surgery, and no current use of medication.

Study Protocol

On the day of the exam, participants were allowed to have breakfast but did not eat for 6 hours or drink fluids for 1 hour before the test. Participants were asked to come to the hospital at 6:00 p.m. The nasal cavity was locally anesthetized with xylocaine jelly, and the catheter was inserted at 7:00 p.m.

Before catheter insertion, an esophageal internal pressure catheter (Unisensor AG, Attikon, Switzerland) and an esophageal pH catheter (Synectics Medical Lda, Lisbon, Portugal) were ligated with a silicone tubular band. The distal pH sensor was positioned in Ch1 of the internal pressure catheter. The proximal pH sensor was placed 10 cm from the tip of the internal pressure catheter. After insertion, a proximal pH sensor (in the esophagus) was positioned 5 cm above the LES.

HRM and esophageal pH measurements were performed using a portable pocket monitor (Star Medical, Tokyo, Japan) capable of long-term measurements. After insertion, participants consumed a test meal (2 sandwiches, 1 Belgian waffle, 500 mL water; 900 kcal) in the laboratory by 8:00 p.m. and returned home. At 11:30 p.m., the electrodes of the portable EEG were placed on the forehead and behind the auricle, and the pocket monitor button (signal for bedtime) and EEG start button were pressed simultaneously. Participants woke at 6:00 a.m. the next morning, pressed the pocket monitor button (signal for waking up) and the EEG stop button, and removed the EEG electrodes. Participants were asked to come to the hospital during the day, and the catheter was removed by a physician.

The time deviation of the portable EEG was measured in advance to accurately adjust for bedtime. Since we noted the clock on the portable EEG advanced 1 second every 3 hours, we set the clock on the portable EEG to 18:00:00 at 18:00:02 before the examination; therefore, the actual time and the time on the portable EEG were set to coincide almost exactly at 0:00:02.

Data Analysis and Endpoint

Using Starlet analysis software (Star Medical, Tokyo, Japan), 2 authors (S.H. and K.I.) manually checked all data. Measurement criteria for the present study were as follows:

(1) Measurement time, Sleep time (Measurement time: interval from bedtime to waking up; Sleep time: interval from the first continuous 5 minutes of sleep to awakening);

(2) Frequency of nocturnal GER (pH <4 for longer than 4 seconds);

(3) Mechanisms underlying nocturnal GER (TLESR, free reflux [due to low LES pressure], strain reflux, and others);

(4) Frequency of TLESR during sleep;

(5) Complication rate of TLESR with nocturnal GER (pH <4 for longer than 4 seconds, or a pH decrease >1 unit);

(6) Sleep depth during TLESR and TLESR with nocturnal GER (awakening, rapid eye movement sleep, and non-rapid eye movement sleep [N1-2: shallow sleep, N3: deep sleep]).

With the advent of HRM, the definition of TLESR has been revised, and the new definition of TLESR by Roman et al.[8] was used in the present study, i.e., no swallowing within 4 seconds before and 2 seconds after the start of LES relaxation, LES relaxation longer than 10 seconds, and crural diaphragmatic inhibition.

Recording Methods

HRM was performed by connecting an internal pressure catheter with 36 solid-state sensors at 1-cm intervals to a portable pocket monitor capable of long-term measurements. Esophageal pH was assessed using a single-use pH catheter with an antimony electrode. pH measurements were corrected with a calibration solution (pH 4 and 7).

EEG was performed using Sleep Scope (Sleepwell Corporation, Osaka, Japan), a portable EEG measuring device. All data were digitally recorded in European Data Format. EEG was measured over time and analyzed by Sleepwell experts to assess sleep depth every 30 seconds, based on the Analysis System SEAS-G1.4. Sleep stages were scored according to the EEG criteria of the American Academy of Sleep Medicine's Manual for Scoring Sleep (2007). A previous study reported that the accuracy of this portable EEG was similar to that of polysomnog-

Table 1 Participant characteristics and sleep measurements

Factor	Group	Overall
n		10
Sex (%)	Male	10 (100.0)
Age		33.2 (4.2)
Total time in bed (min)		377.6 (45.2)
Sleep duration (min)		325.1 (62.3)
REM stage (%)		18.4 (9.3)
N1 and N2 stage (%)		61.6 (11.0)
N3 stage (%)		3.9 (6.5)
Total number of awakenings (times)		14.9 (6.7)
Total duration of awakenings (min)		47.7 (53.0)
GER events during sleep		1.7 (2.9)
TLESR events during sleep		5.2 (5.2)
TLESR events with GER during sleep		2.7 (3.3)

REM: rapid eye movement, GER: gastroesophageal reflux, TLESR: transient lower esophagealsphincter reflux. Values are means (SD).

raphy[9].

Statistical Analysis

All statistical analyses were performed with EZR (version 1.54: Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria)[10]. The data obtained are shown as means and standard deviations unless otherwise noted.

Results

Characteristics of Healthy Participants

All 10 participants completed the planned protocol, and data were obtained. Two authors (S.H. and K.I.) verified and analyzed all cases. The characteristics of the participants and measurement results are shown in **Table 1**.

(1) Measurement Time and Sleep Time

The measurement time (interval from bedtime to awakening) was 377.6 ± 45.2 minutes, and sleep time (interval from falling asleep to awakening) was 325.1 ± 62.3 minutes.

(2, 3) Frequency of Nocturnal GER and Mechanisms Underlying Nocturnal GER

Nocturnal GER was detected 17 times, averaging 1.7 ± 2.9/5.4 hours. The main mechanism responsible for nocturnal GER was TLESR (15 of 17 episodes: 88.2%); strain reflux and multiple rapid swallows were observed once each during awakenings. These results are shown in **Figure 1**.

(4, 5) Frequency of TLESR during Sleep and the Complication Rate of TLESR with Nocturnal GER during Sleep

TLESR was detected 52 times during the measurement time, with a mean duration of 5.2 ± 5.2/5.4 hours. TLESR with nocturnal GER occurred 27 times, with a mean duration of 2.7 ± 3.3/5.4 hours. The complication rate of TLESR with nocturnal GER during sleep was 51.9% (27 of 52 episodes).

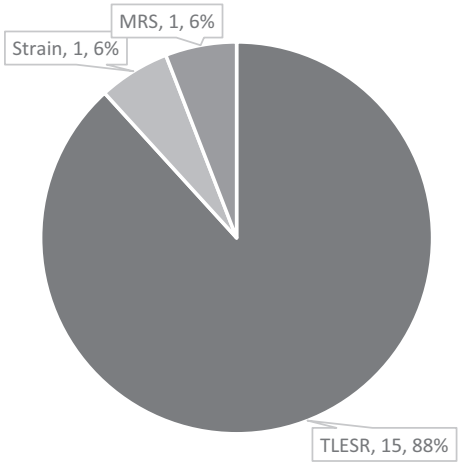

Fig. 1 Mechanisms underlying nocturnal GER
The main mechanism responsible for nocturnal GER was TLESR (15 of 17 episodes: 88.2%); mechanisms other than TLESR were strain reflux (n = 1) and multiple rapid swallows (MRS) (n = 1).

(6) Sleep Depth during TLESR and TLESR with Nocturnal GER

Sleep depth during TLESR was 44.2% (23/52 times) awake and 34.6% (18/52 times) shallow sleep. Sleep depth during TLESR with nocturnal GER was 74.0% (20/27 times) awake and 18.5% (5/27 times) shallow sleep. These results are shown in **Figure 2**.

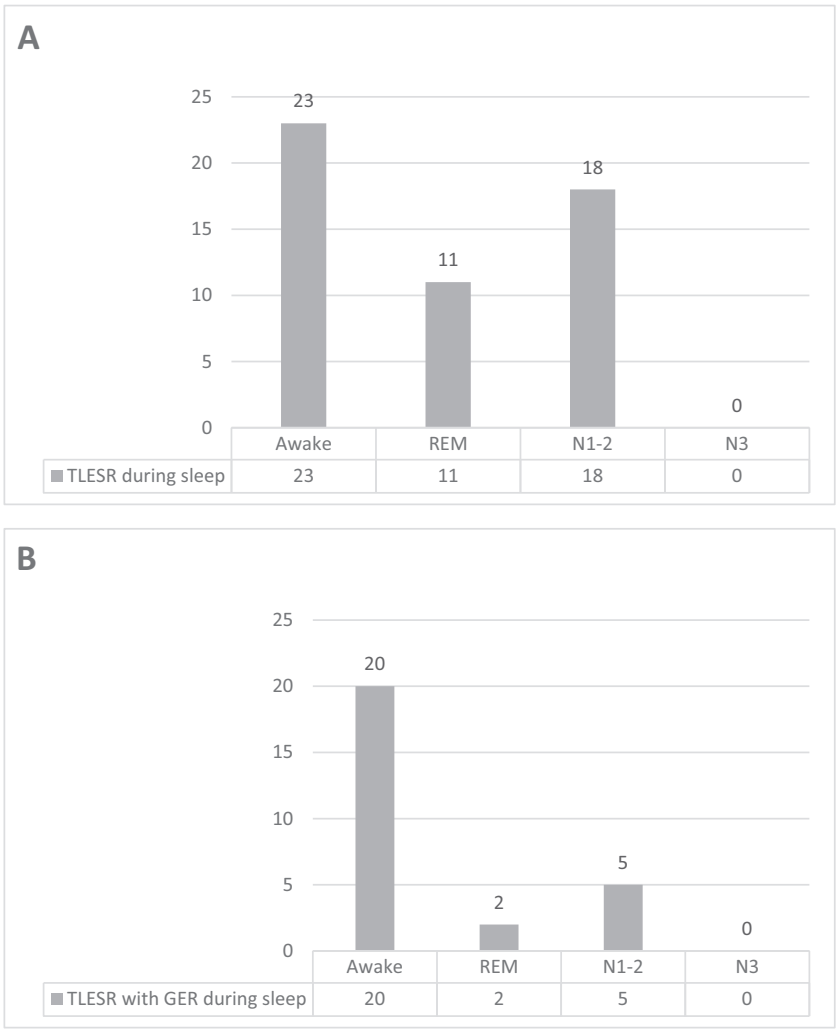

Fig. 2 Sleep depth during TLESR and TLESR with nocturnal GER
(A) Sleep depth during TLESR was 44.2% (23/52 times) awake and 34.6% (18/52 times) shallow sleep (N1-2). (B) Sleep depth during TLESR with nocturnal GER was 74.0% (20/27 times) awake and 18.5% (5/27 times) shallow sleep (N1-2).

Discussion

In the present study, nocturnal GER occurred 17 times during measurement, averaging 1.7 ± 2.9/5.4 hours. A US study reported nocturnal GER 184 times in healthy participants (9 participants were tested twice each), with a mean of 0.9 ± 0.6/hour[6]. Kuribayashi et al.[5] examined Japanese controls during sleep and detected nocturnal GER 10 times (mean 1.3 ± 0.5/5.2 hours). These findings are consistent with the present results.

The main mechanism responsible for nocturnal GER was TLESR (15 of 17 episodes: 88.2%), as shown in **Figure 1**, which is in accordance with the findings of 2 previous studies identifying TLESR as the mechanism responsible for nocturnal GER in 98% and 100% of cases[6,7]. Data on nocturnal GER in healthy adults are limited. Kuribayashi et al.[5] examined control participants (patients presenting with snoring or suspected apnea, with no esophagitis on esophagogastroduodenoscopy, and not satisfying the criteria for apnea). Therefore, this is the first study to examine nocturnal GER in healthy Japanese adults. We confirmed that the primary mechanism underlying nocturnal GER was TLESR in healthy Japanese.

TLESR was observed 52 times, with a mean of 5.2 ± 5.2/5.4 hours. A previous study detected TLESR 445 times in healthy participants during sleep, with a mean of 1.78/hour[6]. TLESR with nocturnal GER occurred 27 times, with a mean of 2.7 ± 3.3/5.4 hours. The complication rate of TLESR with nocturnal GER during sleep was 51.9% (27 out of 52 episodes), which is consistent with previous studies reporting a complication rate of 69%[6].

Sleep depth during TLESR was 44.2% (23/52 times) awake and 34.6% (18/52 times) shallow sleep (N1-2). Sleep depth during TLESR with nocturnal GER was 74.0% (20/27 times) awake and 18.5% (5/27 times) shal-

low sleep (N1-2), as shown in **Figure 2**. Kuribayashi et al.[5] reported that sleep depth during TLESR in controls was 77.5% (62/80 times) awake and 22.5% (18/80 times) shallow sleep (S1-2) and that TLESR did not occur during rapid eye movement sleep or deep sleep (S3-4). Fujiwara et al.[11] also showed that nocturnal GER in 12 patients with NERD and 5 with GERD mainly occurred during awakening (67.2%) and shallow sleep (20.3%) and only rarely during deep sleep (1.6%). These findings suggest that TLESR and TLESR with nocturnal GER are more likely to occur during awakening or shallow sleep.

In the previous study by Mittal et al.[1], the frequency of acid reflux and TLESR (acid reflux, 9.3 times/4 hours; TLESR, 251 episodes, 24.8 ± 2.6/4 hours) in GERD patients and healthy participants during the daytime was higher than in the present study. They identified the mechanism responsible for acid reflux during the daytime as TLESR (93 of 93 episodes, 100%); the rate of complication with acid reflux was low, at 36.9%.

We used portable HRM, esophageal pH, and EEG in a home setting to investigate the mechanisms underlying nocturnal GER and its association with sleep depth in healthy Japanese adults. The results suggest that the main mechanism responsible for nocturnal GER was TLESR, even in a home setting, and that most TLESR and TLESR with nocturnal GER occurred during awakening or shallow sleep.

Study Limitations

The limitations of the present study are its small sample size and bias in the age and sex of the participants examined. However, using portable equipment we found that the results in a home setting were equivalent to those in a hospital setting[5–7]. Thus, the present results support the use of more-convenient home measurement in future research. The accuracy of GER data during sleep can be improved by increasing the number of cases, eliminating age and sex biases, and including GERD patients in future studies.

Conclusion

The primary mechanism underlying nocturnal GER was TLESR in healthy Japanese adults. TLESR and TLESR with nocturnal GER were more frequent during awakening and shallow sleep.

Contributions: Shintaro Hoshino submitted the ethics review, acquired and analyzed data, and wrote the manuscript. Noriyuki Kawami, Eri Momma, Mai Koeda, and Yoshimasa Hoshikawa edited the manuscript. Katsuhiko Iwakiri acquired and analyzed the data and managed the overall study.

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References

1. Mittal RK, McCallum RW. Characteristics and frequency of transient relaxations of the lower esophageal sphincter in patients with reflux esophagitis. Gastroenterology. 1988 Sep;95(3):593–9.
2. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol. 2001 Sep;96(9):2569–74.
3. Iwakiri K, Hayashi Y, Kotoyori M, et al. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. Dig Dis Sci. 2005 Jun;50(6):1072–7.
4. Iwakiri K, Kawami N, Sano H, et al. Mechanisms of excessive esophageal acid exposure in patients with reflux esophagitis. Dig Dis Sci. 2009 Aug;54(8):1686–92.
5. Kuribayashi S, Kusano M, Kawamura O, et al. Mechanism of gastroesophageal reflux in patients with obstructive sleep apnea syndrome. Neurogastroenterol Motil. 2010 Jun;22(6):611–e172.
6. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest. 1980 Feb;65(2):256–67.
7. Freidin N, Fisher MJ, Taylor W, et al. Sleep and nocturnal acid reflux in normal subjects and patients with reflux oesophagitis. Gut. 1991 Nov;32(11):1275–9.
8. Roman S, Holloway R, Keller J, et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neurogastroenterol Motil. 2017 Feb;29(2).
9. Kawamura A, Yoshiike T, Matsuo M, et al. Comparison of the usability of an automatic sleep staging program via portable 1-channel electroencephalograph and manual sleep staging with traditional polysomnography. Sleep Biol Rhythms. 2022 Aug;21(1):85–95.
10. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013 Mar;48(3):452–8.
11. Fujiwara Y, Kohata Y, Nakahara K, et al. Characteristics of nighttime reflux assessed using multichannel intraluminal impedance pH monitoring and a portable electroencephalograph. Dis Esophagus. 2016 Apr;29(3):278–84.

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