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Characterisation of patients with supine nighttime reflux: observations made with prolonged wireless oesophageal pH monitoring

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Summary

Background: Although nighttime reflux symptoms are common, the presence of nocturnal reflux is seldom confirmed with a standard 24 hours pH study.

Aim: To study patients with supine nighttime reflux symptoms using prolonged wireless pH monitoring.

Methods: In this retrospective study, patients with typical acid reflux symptoms were studied using 96-h pH monitoring. Patients with nighttime reflux symptoms were compared to those without. Night-to-night variability and diagnostic accuracy of 24-, 48- and 72-hours pH studies compared to the 96-hours "gold standard" were evaluated.

Results: Of the 105 included patients (61.9% females; mean age 46.8 ± 14.4 years), 86 (81.9%) reported nighttime reflux symptoms, of which 67.4% had pathological supine nocturnal acid exposure in at least one night. There was high variance in night-to-night acid exposure (94% [IQR0-144]), which was larger than the variance in upright acid exposure (58% [IQR32-88]; $P < 0.001$). When analysing the first 24 hours of the pH study, 32% of patients were diagnosed with pathological supine nighttime acid exposure versus 51% of patients based upon the 96-hours pH-test. The diagnostic accuracy and yield improved with study duration ($P < 0.001$). Reflux episodes with a lower nadir pH or longer acid clearance time were more prone to provoke nightly symptoms.

Conclusions: The majority of patients with nocturnal reflux symptoms had pathological acid exposure in at least one night of the prolonged pH recording. A high night-to-night variability in acid exposure reduces the clinical value and diagnostic yield of pH monitoring limited to 24 hours. Prolonged testing is a more appropriate diagnostic tool for patients with nocturnal reflux symptoms.

1 | INTRODUCTION

Nighttime reflux symptoms are common in the general population; it has been estimated that approximately 50% of individuals who suffer from generalised reflux symptoms, also experience nighttime symptoms, disturbing sleep and daytime functioning.[1-3] Conversely, poor sleep quality and arousal from sleep have been shown to evoke reflux as well, underlining the complex relationship between sleep and reflux.[4,5] Although the last years' progress has been made in our understanding of the pathogenesis of nocturnal reflux, several questions remain unanswered and patients with nocturnal reflux symptoms are still an underreported group in the current literature.[2,4,6]

In patients with nighttime reflux symptoms referred for ambulatory pH monitoring, the diagnosis of nocturnal reflux is seldom confirmed. One could argue, however, that a traditional 24-hour catheter-based system is not the appropriate diagnostic tool to identify nocturnal reflux. Gastro-oesophageal reflux occurs multiple times during the day, also in healthy subjects.[7,8] In patients with gastroesophageal reflux disease (GERD), the incidence of daytime reflux episodes is often increased and this usually causes multiple symptoms during the day. Nighttime reflux occurs less frequently, both in healthy asymptomatic subjects and in patients.[6,8,9] However, when nocturnal reflux does occur, these episodes are commonly associated with prolonged oesophageal acid exposure due to reduced acid clearing mechanisms at night, frequently resulting in mucosal damage such as reflux oesophagitis and severe symptoms leading to sleep arousal, poor sleep quality and excessive heartburn.[10] In other words, although a single nocturnal reflux episode can alter the clinical diagnosis of a 24-hour study, the likelihood of detecting it is low, which may result in a falsely negative study report in a substantial subset of patients. In addition, the very nature of catheter-based pH systems influences comfort and sleeping behaviour, which minimises the occurrence of nocturnal reflux.[11] We hypothesise that patients with nocturnal reflux symptoms may benefit from prolonged pH monitoring because of improved sensitivity. Wireless pH study uses a radio-telemetric capsule temporarily attached to the oesophageal mucosa. It allows for a prolonged recording and has been shown to be generally better tolerated by patients, thereby increasing sensitivity for detecting reflux events.[12-15] Intuitively, it is presumed that this improved sensitivity extends to nocturnal reflux. In this study, we aimed to explore this concept. Our primary objective was to evaluate the added diagnostic value and reproducibility of prolonged pH testing for the presence of nocturnal reflux. Our second objective was to study patients with nocturnal reflux, specifically prevalence, clinical characteristics and symptom perception.

2 | MATERIALS and METHODS

2.1 | Subjects

In this retrospective study, patients with daytime and/or supine nighttime reflux symptoms referred for prolonged wireless pH monitoring, primarily in the work-up of anti-reflux surgery, were studied at a tertiary referral centre (University College London, London) between January 2017 and December 2020. A requirement for inclusion was the presence of typical reflux symptoms (heartburn, regurgitation and/or chest pain) as a primary presenting complaint. A complete medical history was undertaken prior to the pH study in all patients. Patients with a history of oesophageal or gastric surgery or other known oesophageal diseases were excluded. Acid-suppressive medication and drugs that affected oesophageal motility (eg, prokinetics and sedatives) were discontinued for at least 7 days prior to all pH studies. Patients with a nocturnal work (or reversed sleep) pattern, a technical unsuccessful study or with capsule detachment prior to 72 hours, were excluded. The study protocol was submitted to the local Institutional Review Board and formal evaluation was waived (reference number W21_004 # 21.006).

2.2 | Prolonged wireless pH monitoring

A wireless pH system (Bravo, Medtronic) was calibrated and a radio-telemetry capsule was placed 6 cm proximal to the Z-line as described in the literature.[15] The capsule was attached while patients were under sedation during endoscopy as per standard protocol. Patients were instructed to press the event marker button on the pH data logger whenever they experienced a pre-assigned reflux symptom. Subjects were encouraged to maintain their normal daily activities, consume their usual meals and were asked to mark the period spent in the supine position. After 96 hours, patients returned the recording device for downloading of the data.

2.3 | Data analysis

We defined "night" "nighttime" or "nocturnal" as the (patient-reported) period of >3 continuous hours with an onset between 8 PM and 8 AM, spent in the supine position. Periods in the supine position during the day (ie, naps) were excluded from the analysis. Total acid exposure was considered pathological if it was found to be >6% and supine nocturnal acid exposure was defined as pathological if >1.5%.[16] Variance was calculated as the deviation of the 24-, 48- or 72-hour values from the overall 96-hour result and the coefficient of variation was calculated as the ratio of the standard deviation to the mean. The Symptom Index (SI) was calculated as the percentage of symptoms related to reflux (diagnostic cut-off >50%). For each patient, the acid exposure time (AET), the total number of acidic reflux events, SI, diagnostic accuracy and day-to-day variability were calculated cumulatively for the first 24-, 48-, 72- and entire 96 hours overall and for days and nights separately

2.4 | Statistical analysis

Descriptive statistics were presented as the percentage for categorical data and as mean with standard deviation (SD) or median with

interquartile range (IQR) for continuous variables. Mann–Whitney U or chi-squared tests were used to analyse variables between groups. Paired data were compared using the Wilcoxon signed-rank test, Friedman test and Cochran's Q test when appropriate. To explore factors associated with the occurrence of supine nocturnal reflux, logistic regression analysis was performed. SPSS Statistics (ver. 24; SPSS) was used for statistical analysis.

3 | RESULTS

3.1 | Study population

A total of 162 patients underwent wireless pH monitoring for their reflux symptoms. After an initial screening and the removal of duplicates, 130 eligible pH studies were assessed. Patients with incomplete or missing documentation (n = 19) or a history of oesophageal surgery (n = 6) were excluded (Figure 1). As a result, analysis was completed in 105 patients. All patients (61.9% females; mean age 46.8 ± 14.4 years) reported typical symptoms (heartburn, 84.8%; regurgitation, 65.7%; and/or chest pain, 31.4%) and a proportion reported additional atypical symptoms including cough (29.5%) and belching (24.8%). At upper endoscopy, reflux oesophagitis was found in 20 (19.0%) patients.

3.2 | Supine nocturnal gastro-oesophageal reflux

The median overall recording time of the pH studies was 80:09 hours (IQR 74:15-84:56), with a median nocturnal recording time of 31:16 hours (IQR 27:20-36:09) across 4 days. Complete recordings of four consecutive nights were available in the majority (78.1%) of patients. A total of 8591 acidic reflux episodes were manually detected and analysed. Of these, 917 (10.7%) occurred in the night and 7674 (89.3%) during the day. A median of 75 (35-111) acidic reflux episodes were found per patient, of which a small proportion (5 [1-12]) was supine nocturnal reflux episodes. Patients had a median AET of 5.6% (2.1-9.4), with 6.8% (2.4-13.3) during the day and 1.4% (0.0-5.0) during the night. Based upon the total recording, 49 patients (46.7%) had a pathological total acid exposure. In 53 (50.5%) patients, a pathological supine nighttime acid exposure over 96 hours was observed.

3.3 | Clinical characteristics of subjects with self-reported nocturnal symptoms

Of the included patients, 86 (81.9%) reported nighttime reflux symptoms. Table 1 shows the clinical characteristics stratified for the presence of self-reported nocturnal reflux symptoms. Patients that explicitly reported nighttime symptoms were found to have both, greater supine nighttime acid exposure ($P < 0.01$) and increased number of acidic reflux episodes ($P < 0.01$). Moreover, nocturnal reflux symptoms were predominantly reported by male patients ($P < 0.030$). In patients with nocturnal symptoms, heartburn and chest pain were more frequently reported (both $P < 0.030$). Of the patients with self-reported nocturnal reflux symptoms, 74 (86.0%) patients had at least one reflux episode in at least one of the four nights, versus 10 (52.6%) of the patients without nighttime symptoms ($P < 0.001$). In 12 (14.0%) patients with nocturnal symptoms, no supine nighttime reflux events were identified for the entire recording. When assessing the first recorded night of patients with nocturnal symptoms, 43 (50.0%) patients had no supine nighttime reflux events at all, but in the majority

162 pH-studies

Screening

Excluded n = 32
  < 3 nights (n=20)
  Duplicates (n=10)
  Atypical sleeping pattern (n=2)

130 eligible pH-studies

Data extraction

Excluded n = 25
  No history available (n=19)
  History of anti-reflux surgery (n=6)
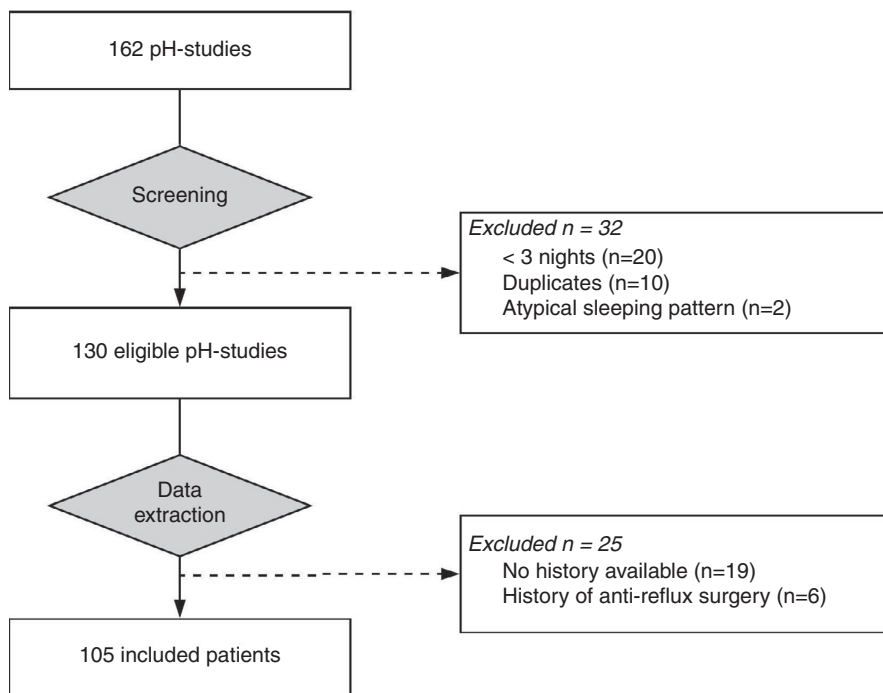
105 included patients

FIGURE 1 Flowchart of case finding

TABLE 1 Demographic and clinical characteristics of included patients stratified for the presence of nocturnal reflux symptoms

	Patients with nocturnal symptoms (n = 86), n (%)	Patients without nocturnal symptoms (n = 19), n (%)	P-value
Demography			
Sex			
Male	37 (43.0)	3 (15.8)	0.027[b]
Female	49 (57.0)	16 (84.2)	
Age, mean ± SD	45.9 ± 13.9	48.6 ± 16.6	0.400
Symptoms at presentation			
Heartburn	76 (88.4)	13 (68.4)	0.029[b]
Regurgitation	59 (68.6)	10 (52.6)	0.184
Chest pain	31 (36.0)	2 (10.5)	0.030[b]
Cough	24 (36.8)	7 (36.8)	0.440
Belching	22 (25.6)	4 (21.1)	0.679
Dysphagia	19 (22.1)	5 (26.3)	0.692
Throat pain	14 (16.3)	3 (15.8)	0.958
Hoarseness	6 (7.0)	2 (10.5)	0.598
Medical history			
Gastrointestinal comorbidities[a]	5 (5.8)	2 (10.5)	0.608
PPI-use	62 (72.1)	12 (63.2)	0.579
Endoscopic findings			
Gastritis	16 (18.6)	3 (15.8)	1.000
Schatzki ring	8 (9.3)	0 (0.0)	0.345
Reflux oesophagitis	18 (20.9)	2 (10.5)	0.296
Grade A	10	2	
Grade B	8	0	
pH study findings			
Nocturnal acid exposure, median [IQR]	2.3 [0.2-5.6]	0 [0-1.5]	0.002[a]
Number of nocturnal reflux episodes, median [IQR]	6 [1-12]	1 [0-6]	0.008[b]
Pathological nocturnal acid exposure (>1.5%)	48 (55.8)	5 (26.3)	0.020[b]
At least 1 nocturnal reflux episode	74 (86.0)	10 (52.2)	0.001[b]

IQR interquartile range; n, number of patients; PPI, proton pump inhibitor; SD, standard deviation.

[a] Inflammatory bowel disease (n = 4), coeliac disease (n = 1), eosinophillic enterocolitis (n = 1), superior mesenteric artery (SMA) syndrome (n = 1).

[b] $P < 0.001$.

(51.2%) of these patients, reflux eventually occurred at a later moment during the 96-hour recording. As for the presence of pathological supine nighttime acid exposure (>1.5%), 58 (67.4%) patients with nocturnal symptoms had an abnormal acid exposure in at least one of the nights. Of these patients, only nine (15.1%) had a pathological acid exposure for all nights, while in the majority of patients pathological acid exposure was present for just one or two nights during the 96-hour recording (21 [36.2%] and 17 [29.3%], respectively).

3.4 | Night-to-night diagnostic variability of AET

Figures 2A,B show the oesophageal acid exposure and the proportion of patients with a pathological supine nighttime acid exposure for the total study population for each day and night separately. There was no overall change in supine nocturnal acid exposure over time (all $P > 0.1$). Night-to-night variance in oesophageal acid exposure, reflected by the coefficient of variation, was high (median 94% [IQR 0-144]) and significantly higher than variance in diurnal acid exposure (58% [IQR 32-88], $P < 0.001$). Variance in supine nocturnal acid exposure values compared to the 96-hour average, reduced with increasing length of recording, from 73% (IQR 0-100) in the first 24 hours, to 40% (IQR 0-75) and 13% (IQR 0-29) after 48 and 72 hours respectively, $P < 0.001$. The proportion of patients with a pathological acid exposure for all nights was significantly lower than the proportion of patients with a pathological acid exposure based on worst-night analysis 9/105 (8.6%) versus 63/105 (60.0%), respectively, ($P < 0.001$). Forty-one (39.0%) patients had a consistent diagnosis for all four nights, whereas the vast majority would end up with different diagnoses when the nights were to be assessed separately (Figure 3A). A diagnosis consistent with that
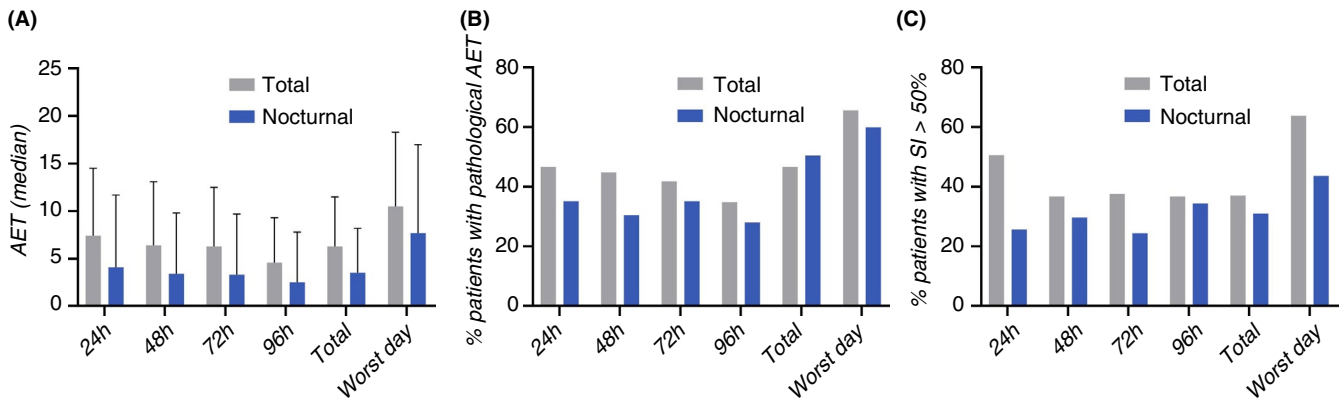
FIGURE 2 A, Median oesophageal acid exposure time; B, the proportion of patients with a pathological supine nocturnal acid exposure and C, the proportion of patients with SI > 50% for each day and night separately
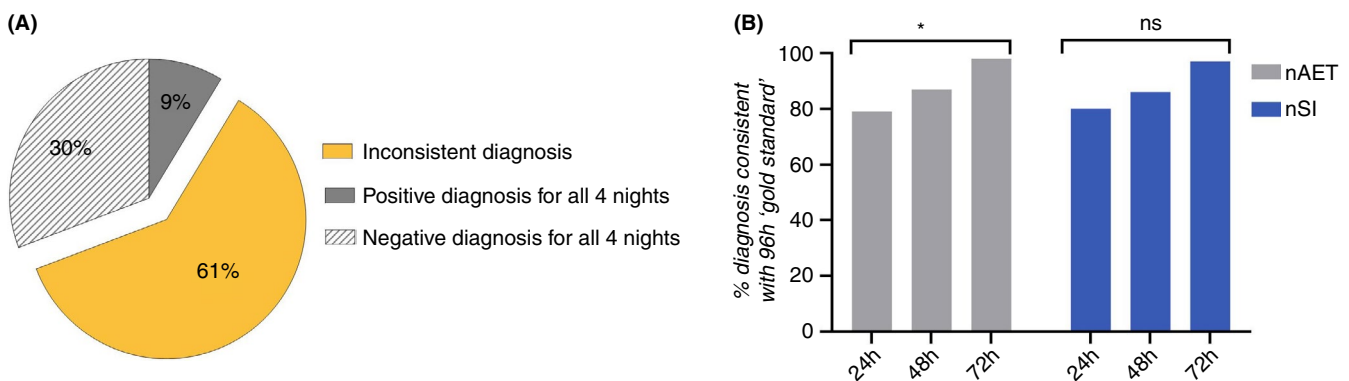

FIGURE 3 A, Diagnostic agreement (nocturnal acid exposure >1.5%) between the different nights and B, diagnostic consistency between the first 24-, 48- and 72 h with the 96-h "gold standard" for pathological supine nocturnal acid exposure (nAET >1.5%) and symptom index (nSI >50%)

of the 96-hour "gold standard" was present in 83 (79.0%), 91 (86.7%), and 98 (93.3%) patients for 24-, 48-, and 72-hour test periods, respectively, with a significant improvement in diagnostic consistency with duration of pH recording (P < 0.001)) (Figure 3B).

3.5 | Night-to-night variability of symptom association

A median of 18 (IQR 10-61) typical reflux symptoms were recorded per patient during the 96-hour reflux measurement period. Eight (7.6%) patients remained entirely symptom-free during the prolonged monitoring period. Combining all typical reflux symptoms recorded during the wireless pH study, 36 of the 105 (34.3%) patients had a positive SI overall. As expected, the frequency of nocturnal symptoms was significantly lower compared to the number of diurnal symptoms (P < 0.001). Figure 2C presents the proportion of patients with SI > 50% for each day and night separately. There was no overall change in symptom frequency and association over time (both P > 0.5). Worst-night analysis showed a positive SI in 31 of the 105 (29.5%) patients. The frequency of symptoms during the nights was low (median

2 [0-6]) and varied substantially. In just one patient, a positive SI for every night of the 96-hour recording could be calculated. Variance in nocturnal SI compared to the 96-hour average, reduced with the increasing length of recording (P < 0.001). A diagnosis consistent with that of the 96-hour "gold standard" was present in 35/44 (79.5%), 48/56 (85.7%) and 62/64 (96.9%) patients for 24-, 48- and 72-hour test periods, respectively (Figure 3B). However, the increase in the diagnostic agreement was not statistically significant (p > 0.5).

3.6 | Added diagnostic yield of prolonged pH monitoring

The diagnostic yield and parameters of diagnostic performance for the detection of pathological supine nocturnal acid exposure were calculated for the first 24-, 48-, 72-hours and worst night and compared to the complete four-night recording as "gold standard" (Table 2). The proportion of patients with a pathological supine nighttime acid exposure during the first night (24 hours) was significantly lower than the proportion of patients diagnosed based upon the complete 96-hour recording (32.4% vs 50.5% P < 0.001). If this

TABLE 2 Diagnostic performance for the detection of supine nocturnal reflux of the first night, first two nights, first three nights and the worst night compared to the gold standard (complete 96 h recording)

Characteristic	Diagnostic yield[a] n/N	Patient missed, n	Sensitivity	Specificity	Accuracy[b]	PPV	NPV
96 h (4 nights) "gold standard"	53/105	0	—	—	—	—	—
72 h (3 nights)	48/105	5	90.6 (79.3-96.9)	96.2 (86.8-99.5)	93.3 (86.8-97.3)	96.0 (86.0-98.9)	90.9 (81.3-95.9)
48 h (2 nights)	42/105	11	79.3 (65.9-89.2)	94.2 (84.1-98.8)	86.7 (78.6-92.5)	93.3 (2.2-97.7)	81.7 (72.4-88.3)
24 h (1 night)	34/105	19	64.2 (49.8-76.9)	94.2 (84.1-98.8)	79.1 (70.0-86.4)	91.9 (78.8-97.2)	72.1 (64.1-78.8)
Worst night	63/105	0	100.0 (93.3-100.0)	80.8 (67.5-90.4)	90.5 (83.2-95.3)	84.1 (75.2-90.2)	100.00%

Values are presented as percentages with 95% confidence interval, CI, confidence interval; n, number of identified supine nocturnal GERD cases; N, number of the study sample; NPV, negative predictive values; PPV, positive predictive value.

[a]The diagnostic yield was defined as the proportion of patients in whom prolonged pH monitoring yielded a pathological nighttime acid exposure out of the total number of patients analysed.

[b]Overall diagnostic accuracy, expressed as a proportion of correctly classified subjects (true positives and true negatives) amongst all subjects was calculated.

study population had undergone only one night of pH monitoring, 19 (18.1%) patients would have been missed. If the first two or three nights were taken into account, the diagnostic yield increased to 40.0% and 45.7%; and 11 and 5 patients would have been missed, respectively. The negative predictive value of a reflux-free first night was 72.1%. The diagnostic yield, sensitivity, specificity and positive predictive values all increased with the duration of the pH study. Worst night analysis resulted in 10 more pathological supine nighttime acid exposure diagnoses compared to the gold standard and had the highest sensitivity, but lowest specificity for the detection of pathological supine nighttime acid exposure.

3.7 | Characteristics of subjects with pathological supine nighttime acid exposure

Patients were stratified for the presence of pathological supine nighttime acid exposure. The presence of cough and reflux oesophagitis was more frequently found in patients with abnormal supine nighttime acid exposure (P < 0.05). The median time interval from the last meal until the supine period was 2 hours and 41 minutes (IQR 1:39-3:23) but there was no difference in length between the two groups (P > 0.060). To further explore predictive factors for nocturnal reflux, we performed a logistic regression analysis with pathological supine nocturnal acid exposure as a dependent variable (Table 3). In accordance with the sub-analysis, univariate logistic regression identified the symptoms of coughing, endoscopic reflux oesophagitis and presence of pathological daytime acid exposure as predictive factors for nocturnal reflux diagnosis (all P < 0.05). Subsequently, in multivariate logistic regression modelling, only the presence of endoscopic reflux oesophagitis (OR 3.98; 95% CI 1.15-13.81), P < 0.05) was identified as an independent predictor. Of the 53 patients with a pathological supine nocturnal supine acid exposure, 26 (49.1%) had a normal upright acid exposure while in 50.1% an increased bi-positional acid exposure was observed. In patients with pure supine reflux

and with bi-positional reflux, the occurrence of reflux was spread more evenly throughout the night and the acid clearance time was longer, compared to the groups of patients with a normal supine nocturnal acid exposure (both P < 0.001) (Table 4).

3.8 | Determinants of supine nocturnal reflux perception

To further assess the characteristics of supine nocturnal reflux, we manually examined a total of 917 supine nocturnal acidic reflux events, of which 857 occurred in the first 8 hours of the supine nocturnal period. The number of reflux episodes was highest in the first hours and significantly decreased thereafter (P < 0.015) (Figure 4). The occurrence of early reflux was not associated with shorter meal-bedtime interval (P > 0.05). Finally, we wanted to look for specific determinants of supine nocturnal reflux perception. In Table 4, the characteristics of the reflux episodes which were associated with symptoms were compared with those which were not. In total, 107 reflux episodes were followed by a symptom within 2 minutes, while 810 reflux episodes were not. The nadir pH was significantly lower in the symptom-associated reflux episodes (P < 0.001). In addition, we found that the acid clearance time was significantly longer in the symptom-associated reflux episodes compared with the non-associated episodes (P = 0.02). No significant differences were found for the baseline pH and the magnitude of the pH drop.

4 | DISCUSSION

Nocturnal reflux symptoms are common, however, their aetiology and underlying mechanisms are less well studied and remain incompletely understood. Therefore, the appropriate diagnostic and therapeutic strategy to tackle nocturnal reflux might very well differ from standard management of daytime reflux symptoms. For example, it is well known that proton-pump inhibitor (PPIs) have less efficacy for nighttime reflux

TABLE 3 Logistic regression analysis for identifying predictive factors for pathological supine nighttime acid exposure

Possible risk factor	Univariate model			Multivariate model		
	OR	95% CI	P-value	OR	95% CI	P-value
Age[a]	1.01	0.98-1.04	0.437			
Gender						
Female	0.54	0.23-1.23	0.128			
Male	Ref.					
Symptoms of heartburn						
Present	1.83	0.61-5.53	0.279			
Absent	Ref.					
Symptoms of chest pain						
Present	2.47	1.00-6.09	0.070			
Absent	Ref.					
Symptoms of regurgitation						
Present	2.26	0.97-5.27	0.088			
Absent	Ref.					
Symptoms of coughing						
Present	0.42	0.18-1.00	0.049[a]	0.43	0.17-1.10	0.077
Absent	Ref.					
Endoscopic reflux oesophagitis						
Present	7.52	1.51-16.31	0.006[a]	3.98	1.15-13.81	0.029[a]
Absent	Ref.					
Night-meal interval						
Present	1.00	1.00-1.00	0.058			
Absent						
Pathological daytime acid exposure						
Present	3.12	1.36-7.12	0.007[a]	2.33	0.96-5.66	0.063
Absent	Ref.					

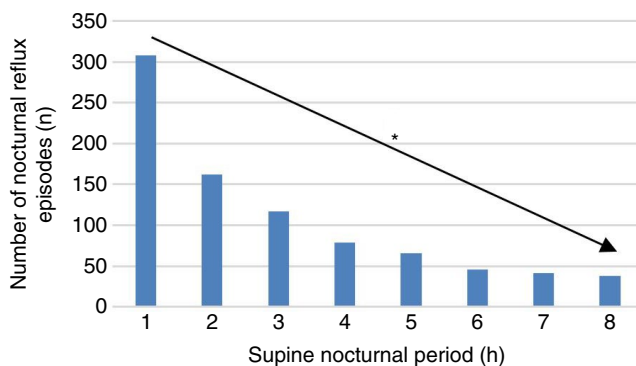Abbreviations: CI, confidence interval; OR, odds ratio.

[a] $P < 0.05$.

FIGURE 4 Total number of reflux episodes per hour. The incidence of nocturnal reflux episodes was highest in the first hour of the nocturnal period and decreased thereafter *$P < 0.015$

symptoms compared to daytime symptoms.[17] This is the first study that specifically focused on supine nocturnal reflux and nighttime symptoms using prolonged wireless pH monitoring. We demonstrated that just one or two nights with supine nocturnal reflux may cause bothersome nighttime symptoms. We showed that variance, and in particular, night-to-night variability in wireless pH monitoring is high. As a result, increasing the duration of a pH study from 24 to 72 hours or 96 hours, progressively improved the diagnostic yield and diagnostic accuracy for nocturnal reflux diagnosis. The infrequent occurrence of reflux in the night in combination with high night-to-night variability, can lead to missed (false-negative) diagnoses when based upon 24-hour testing. This study suggests that prolonged pH monitoring is preferred over a standard 24-hour pH study in the assessment of patients that report nocturnal reflux symptoms.

This study confirms that objective evidence of reflux at night is commonly found in those who complain of nighttime reflux symptoms. Of the group of patients that explicitly reported nighttime symptoms, 67% had pathological nocturnal acid exposure in at least one night. However, in most patients (65%), acid exposure was abnormal in just one or two nights of the total 96-hour recording. This implies that even the sporadic occurrence of reflux at night can lead to bothersome symptoms; however, due to its high variability, nocturnal reflux is easily missed if

TABLE 4 Characteristics of supine nocturnal reflux episodes stratified for the presence of symptom association

	Associated reflux episodes (n = 107)	Non-associated reflux episodes (n = 810)	P-value
Acid clearance time (s)	240 (76-912)	133 (57-233)	0.019[a]
Baseline pH	6.1 (5.6-7.2)	6.6 (5.9-6.9)	0.261
Nadir pH	2.3 (1.7-2.6)	2.8 (2.4-3.1)	<0.001[a]
pH drop	4.0 (3.1-4.9)	3.8 (3.1-4.2)	0.090

Abbreviations: N, number of patients; s, seconds.

[a] $P < 0.001$.

recordings consist of just one night. Previous studies evaluating pH test reproducibility already showed that the variability for AET and GERD diagnosis is high.[7,18] We showed a similarly high variance for the occurrence of reflux. The night-to-night variance was even higher than the diurnal variance. By extending the recording time of the pH test, there was improved detection of abnormal acid exposure and increased sensitivity for the diagnosis of nocturnal reflux. Of note, repeating or extending the duration of any diagnostic test, increases the probability of observing a positive test result, both true-positives and false-positives. Although we did not observe this effect in our data (probably as a result of the used 96 hours result as "gold standard"), it is important to bear in mind that an increased sensitivity might come at the cost of reduced specificity. Nevertheless, in the context of patients with reflux symptoms under evaluation for anti-reflux surgery, increased sensitivity is preferred over an increased specificity, as it is clinically more relevant to "rule out" than "rule in" in these cases.

The benefit of prolonged recording for the purpose of the symptom-reflux association is less certain. Although the variance in nocturnal symptom association did reduce with increasing length of recording, we did not find any improvement in diagnostic yield. This is in contrast to previous studies.[18,19] Of note, symptom reporting is not likely to be comparable to the daytime as, by its very nature, patients are commonly asleep. This consequently impairs the calculation of symptom association scores and likely explains the lack of added diagnostic value of prolonged recording for nocturnal symptom association in this study.

The finding of a high number of reflux episodes at the beginning of the nocturnal period is consistent with previous studies.[20] Interestingly, in patients with pure supine or bi-positional reflux, reflux episodes were spread more evenly throughout the night and the acid clearance time was longer, whereas reflux in patients with a normal supine nocturnal acid exposure mainly occurred in the first hours of the night and are shorter in general. Although it has been suggested that the consumption of a late evening meal evokes the occurrence of early nocturnal reflux,[21] we did not find a significant relation between the length of meal-night interval with the occurrence of early reflux, suggesting that early nighttime reflux is not simply a postprandial phenomenon, but that other factors most likely play a role. In healthy subjects, nocturnal acid reflux is very rare and occurs primarily during transient lower oesophageal sphincter relaxations (TLESRs).[9] TLESRs do only occur during awake periods or transient arousals from sleep, which might explain that in patients with physiological nocturnal acid exposure, reflux occurs mainly through TLESRs at the beginning of the recumbent period, while still being awake. In contrast, reflux as a result of poor motility or

hypotensive LES, which is more common in (bi-positional and supine) reflux patients,[22] will occur more consistently throughout the night.

We assessed why some reflux episodes trigger nocturnal symptoms and others do not. Not surprisingly, nightly reflux episodes with a lower nadir pH or longer acid clearance time were more prone to evoke symptoms. This supports the hypothesis that despite the infrequent occurrence of nighttime reflux, one acidic reflux episode with long acid contact time can still cause bothersome nocturnal symptoms. Previous studies that assessed reflux episodes, in general, have made clear that the acidity of the refluxate is an important determinant of perception of typical reflux symptoms.[23] In contrast to these studies, we did not find a significant difference when evaluating the size of the pH drop.

Some limitations must be acknowledged. First, in the absence of more advanced techniques such as sleep polysomnography, the difference between the recumbent-awake and the recumbent-asleep period and consequently, the effect of sleep itself on reflux was not taken into account. In line with this, we equated the patient-reported supine period as "nocturnal" or "nighttime," which potentially could have introduced bias. Second, normative nocturnal reflux data is currently lacking for wireless pH systems. Therefore, we had to rely on catheter-based studies to define our diagnostic threshold for pathological nocturnal acid exposure. Last, Bravo capsule placement was performed under sedation, which might have affected oesophageal motility and potentially nocturnal reflux on the first recording day. However, the AET and the number of reflux episodes recorded on the first day and night did not significantly differ compared to any of the other days and nights.

5 | CONCLUSION

We demonstrated that the majority of patients with nocturnal reflux symptoms had pathological supine nighttime acid exposure in at least one night of the prolonged pH recording. An observed high night-to-night variability in acid exposure and infrequent symptom reporting reduces the clinical value and diagnostic yield of pH monitoring limited to 24 hours. Prolonged reflux monitoring is a more appropriate diagnostic tool for patients with nocturnal reflux symptoms.

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AUTHORSHIP

Guarantor of the article: Renske A.B. Oude Nijhuis, MD.

Author contributions: RON, RS and AB played a role in planning of the study. RON, RS and AB had a role in conducting the study. RS and HAR were involved in the acquisition of data. RON, RS, HAR, RR, TW, JS, JO and AB had a role in collecting and/or interpreting data. RON played a role in drafting the manuscript. RS, JS, JO, RR, TW, AS and AB played a role in reviewing and revising the manuscript for important intellectual content. All authors had access to the study data and reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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