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Journal

Digestive Diseases and Sciences, 67(7)

Authors

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Publication Date

2022-07-01

DOI

10.1007/s10620-022-07496-7

Peer reviewed



Published in final edited form as:

Dig Dis Sci. 2022 July ; 67(7): 2730–2738. doi:10.1007/s10620-022-07496-7.

Factors that Impact the Variability of Day-to-Day Esophageal Acid Reflux Exposure and its Diagnostic Significance for Gastroesophageal Reflux Disease

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Abstract

Gastroesophageal reflux disease (GERD) is a common disease affecting a significant number of adults both globally and in the United States. GERD is clinically diagnosed based on patient-reported symptoms and the gold standard for diagnosis is ambulatory reflux monitoring, a tool particularly utilized in the common scenario of non-response to therapy or atypical features. Over the past 20 years there has been a shift towards extending the duration of reflux monitoring, initially from 24-hours to 48 hours and more recently to 96 hours, primarily based on a demonstrated increase in diagnostic yield. Further, multiple studies demonstrate clinically relevant variability in day-to-day acid exposure levels in nearly 30% of ambulatory reflux monitoring studies. For these reasons an ongoing clinical dilemma relates to the optimal activities that patients should engage in during prolonged reflux monitoring. Thus, the aims of this review are to detail what is known about variability in daily acid exposure, discuss factors that are known to influence this day-to-day variability (i.e., sleep patterns, dietary/eating habits, stress, and exercise), and finally provide suggestions for patient education and general GERD management to reduce variation in esophageal acid exposure levels.

Keywords

ambulatory reflux monitoring; sleep; diet; stress; exercise

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Conflicts of Interests:

SM: None

VP: None

RY: Consultant for Medtronic, Phathom Pharmaceuticals, StatLinkMD; Research Support: Ironwood Pharmaceuticals; Advisory Board with Stock Options: RJS Mediagnostix

Writing Assistance: None

INTRODUCTION

Gastroesophageal reflux disease (GERD) is extremely common in the United States, affecting up to 30% of adults and accounting for over 7 million ambulatory visits annually^[1, 2]. GERD is primarily a clinical diagnosis based on patient reports of typical symptoms such as heartburn or regurgitation, atypical symptoms such as non-cardiac chest pain, or extra-esophageal symptoms including chronic cough, dysphonia or globus sensation. First-line diagnosis and management typically involve an empiric trial of proton pump inhibitor (PPI) therapy^[3]. Despite this, approximately 50% of patients on PPI therapy do not achieve symptomatic relief^[1, 4].

Current guidelines recommend the use of ambulatory reflux monitoring off antisecretory therapy over patient-reported symptoms, GERD questionnaires, PPI trial, and endoscopy alone for definitive diagnosis of GERD^[5]. Studies have shown that patient-reported symptoms or response to PPI therapy do not necessarily correlate with reflux burden on ambulatory reflux monitoring^[6]. This is important to acknowledge as patients with pathologic reflux on ambulatory reflux monitoring (i.e. those with abnormal acid exposure time) tend to have improved rates of response to antireflux therapy^[7].

A prominent question in the field relates to whether 24 hours of acid exposure monitoring is sufficient for a diagnosis of GERD. This stems from the fact that day-to-day variability of esophageal acid exposure is seen on ambulatory reflux monitoring^[8–10], as well as multiple studies that highlight increased diagnostic yield of GERD with prolonged pH monitoring^[11–13]. In this review, we will discuss the day-to-day variability seen with esophageal acid exposure time (AET) and explore factors such as sleep, diet and eating habits, stress, and exercise that may modulate acid exposure throughout the day to account for this variability.

DAY-TO-DAY ACID REFLUX EXPOSURE VARIABILITY

Esophageal pH monitoring measures multiple metrics related to acidic gastro-esophageal reflux. One of the most reliable and reproducible parameters in diagnosing GERD is measuring the acid exposure time (AET)^[14], which is defined as the percent time esophageal pH is less than 4.0^[15]. According to the Lyon Consensus, patients with AET less than 4.0% is considered normal/physiologic, AET greater than 6.0% is considered definitively abnormal, and AET between 4.0–6.0% being inconclusive^[16]. Various studies have shown that the 95th percentile of normal AET ranged from 4.4% to 5.3%^[17, 18].

Although the thresholds for AET are defined, day-to-day variability in AET over multiple days of recording poses a diagnostic dilemma. Prior studies have shown that symptomatic patients undergoing 48 hours wireless pH monitoring may have normal esophageal acid exposure values on either day 1 or day 2 of recordings^[17]. In fact, Ayazi et al. demonstrated a 27% discordance between the first and second day of recording in patients with suspected GERD^[18]. Another study also showed that sensitivity and detection accuracy can increase up to 22% if at least two days of testing were completed compared to just a single 24-hour

period^[19]. For these reasons, the duration of monitoring was extended from 24 hours to 48 hours in the early 2000s.

In more recent years, investigators demonstrate the added utility of extending monitoring to 96 hours. A study performed by Patel et al. highlights the suboptimal diagnostic accuracy of acid exposure over the first 24 hours of monitoring. This group of investigators demonstrated that extending recording times to 96 hours allowed for the confident diagnosis of GERD in an additional 22% of patients^[20]. Another study by Hasak et al. also highlights the advantage of prolonged pH monitoring up to 96 hours being beneficial, particularly in the 35.9% of their patients with discordant/borderline acid exposure metrics during the first 48 hours of monitoring^[21]. A unique study examined trajectory modeling to examine patterns of acid exposure burden over 96 hours, highlighting that an assessment of acid exposure trajectory (low, mid, or high) may better categorize severity of acid burden and improve the diagnostic yield of GERD^[22]. As such, current guidelines recommend prolonged, ranging anywhere from 48 to 96 hours, recording times as it increases diagnostic yield for identification of abnormal/pathologic reflux burden^[23].

In order to further improve our framework in GERD diagnosis, the underlying factors that can modulate and affect day-to-day variability must also be explored.

FACTORS ASSOCIATED WITH DAY-TO-DAY ACID REFLUX VARIABILITY

Factor 1: Sleep

Sleep is a quintessential part of survival in which humans devote approximately one third of their lifetime. However, approximately 1 in 3 American adults sleep less than 7 hours each night; this timeframe of sleep deprivation is where physiologic and neurobehavioral deficits begin to manifest and worsen with further deprivation^[24], including GERD. Sleep and GERD share a bidirectional relationship with one another. First, GERD may be promoted during sleep as a result of slowed gastric emptying^[25], reduced swallowing and salivary secretion^[26, 27], and reduced occurrence of esophageal peristalsis^[28]. Nocturnal reflux in itself is clinically significant as it has been associated with more severe GERD symptoms and complications such as strictures, Barrett's esophagus, and esophageal adenocarcinoma^[29]. At the same time, GERD can lead to impaired sleep through two mechanisms: 1) nocturnal heartburn symptoms awakening patients leading to reports of sleep deprivation, and 2) through multiple short, amnesic arousals causing sleep fragmentation^[30]. Sleep deprivation in turn can lead to somatic hyperalgesia^[31, 32].

In a first of its kind study, Schey et al. assessed 10 patients with erosive GERD and 10 healthy controls who were randomized into sleep deprivation or sufficient sleep with crossover to the other arm after a washout period. Stimulus-response function testing to esophageal acid perfusion was conducted after their respective sleep protocol where a nasoesophageal catheter was placed with infusion of hydrochloric acid to the mid-esophagus to stimulate acid reflux. Amongst GERD patients, 9 of 10 experienced statistically significant worsening of all stimulus-response functions after sleep deprivation characterized by shortened lag time to symptom report, increased sensory intensity rating, and increased acid perfusion sensitivity; healthy controls did not have significant results regardless of

sleep deprivation^[33]. GERD patients with sufficient sleep tended to have reduced values in stimulus-response testing, thus highlighting the vicious cycle of GERD during sleep resulting in progressive sleep deprivation and subsequently worsening GERD^[34–36].

Recognizing the influence of sleep on GERD, variation in daily sleep quantity and quality likely contributes to day-to-day variability seen on prolonged pH monitoring. Thus, in an ideal standardized scenario, patients should optimize sleep habits during pH monitoring and in management of their GERD. Outside of invasive devices such as pH-impedance or wireless pH monitoring placement, there are limited validated and noninvasive biodevices for use of measuring GERD parameters overnight. There is certainly potential in future investigation of wearable biodevices such as wrist actigraphy, which has been shown as a reliable, noninvasive, and wearable biodevice to monitor sleep parameters^[37–40]. These sleep parameters can be coupled with reflux monitoring to examine the relationships between sleep quality and quantity and esophageal acid exposure on a day-to-day basis.

Factor 2: Diet and Eating Habits

Diet and eating habits have been long postulated to play a significant role in the pathogenesis, course, and day-to-day variability observed with GERD and esophageal acid reflux exposure. In terms of eating habits, certain practices such as eating too quickly, having an irregular eating schedule, eating a larger meal, and/or eating before bed are recognized as exacerbating factors for esophageal acid reflux and GERD symptoms. Unfortunately, there is conflicting data to support particular lifestyle regimens^[41–46]; the American Gastroenterology Association (AGA) and American College of Gastroenterology (ACG) generally recommend empiric lifestyle/behavioral interventions such as avoiding late night meals and recumbency 2–3 hours after eating, particularly for patients with nocturnal symptoms^[3, 47].

Similar to eating habits, the relationship between diet and GERD in various studies have generally been inconsistent with conflicting findings regarding specific diets and their influence on exacerbating esophageal acid exposure/GERD-related symptoms^[48]. Theoretically, food products such as carbonated/cafeinated beverages, citric/acidic products, spicy foods, and chocolate have been cited to cause transient lower esophageal sphincter relaxations (TLESRs) or reduce lower esophageal sphincter (LES) pressures^[49–54]. Likewise, patients are generally advised to avoid fatty meals due to observational studies citing how it can lower LES pressure and exacerbate esophageal acid reflux^[55, 56]. A study conducted by Fox et al. attempts to further elucidate the relationship between dietary fat, calorie density, and esophageal acid exposure. Through this study, they found how dietary fat can increase visceral sensitivity to reflux events and how high-calorie diets can significantly increase duration of GERD episodes, thus suggesting a potential relationship between high-caloric meals, delayed gastric emptying, and increased acid reflux^[57]. However, other studies on fat intake and GERD-symptoms have shown conflicting results^[58].

Despite multiple studies supporting food avoidance to reduce esophageal reflux exposure, the data to support this in a clinically meaningful context is not available and patients should generally only be advised to limit certain types of food that are known to specifically trigger

their symptoms. Diet and eating habits can vary drastically from person-to-person due to a wide-range of factors such as culture, ethnicity, finances, and personal views. As such, diet and eating habits can also significantly vary day-by-day and modulate the variability seen on esophageal pH monitoring as patients change their daily dietary/eating habits based on current events and preferences.

Factor 3: Stress

Stress is a universal condition, both physical and/or psychological, that affects individuals in different ways. Recent studies have improved our understanding about the ways stress affect the pathogenesis of gastrointestinal diseases, including its effect on gastric secretion, gut motility, mucosal permeability, visceral sensitivity, gut microbiota, and mucosal blood flow^[59]. The communication between the brain and gut as well as the gut response to said stress is termed the brain-gut axis (BGA)^[60].

In regards to esophageal acid reflux, stress can exacerbate GERD-related symptoms by lowering LES pressure and increasing hypersensitivity of esophageal mucosa to acid exposure^[59]. Acute stress and induction of anxiety seem to be associated with decreased gastric compliance, inhibition of meal-induced accommodation, and increased symptoms^[61]. An animal model study completed by Farre et al. shows how acute stress can increase mucosal permeability and dilation of intercellular space in esophageal mucosa which could account for the above findings^[62]. Although there are conflicting studies that show an increase in GERD symptoms without a change in number of acid reflux events^[59, 63], other studies highlight the ways that amplified psychosocial stress increases severity of reported reflux symptoms^[63], amplifies gastric acid output^[64], and correlates with worsened severity of reflux esophagitis^[65].

A study conducted by McDonald-Haile et al. provides further insight into the effect of psychosocial stress/anxiety on esophageal acid reflux and efficacy of relaxation techniques to combat exacerbation of symptoms. Their study not only showed that relaxation techniques helped reduce GERD-related symptoms, but also significantly decreased esophageal acid exposure secondary to a decrease in number of reflux episodes on esophageal pH-monitoring^[66]. Thus, psychosocial factors can play an important role to account for variability seen on prolonged pH monitoring.

Factor 4: Exercise

Regular exercise has long been regarded as an important lifestyle activity with significant health benefits, including but not limited to reducing risks for the development of cardiovascular diseases^[67], combating components of metabolic syndrome^[68], and improving psychiatric disorders such as anxiety and depression^[69]. The benefits of exercise on the gastrointestinal system is less defined. Although there is evidence that exercise provides benefits for patients with inflammatory bowel disease and lowers relative risk of colon cancer^[70], it has been associated with increased GERD-related symptoms such as heartburn, chest pain, or abdominal fullness in up to 45% to 90% of athletes^[71].

There appears to be a relationship between type of exercise, body movement, and fasting/post-prandial state in exacerbation of esophageal acid reflux and GERD-related symptoms.

A study conducted by Clark et al. enrolled 12 asymptomatic patients and revealed that runners had the most amount of reflux frequency/duration (both fasting and worse post-prandial) on 24-hour esophageal pH-monitoring; they were followed by weight trainers and lastly cyclists, who have lower degree of body movement/agitation with their physical activity^[72]. This finding was subsequently supported by a study by Yazaki et al. where healthy adults experienced increased esophageal acid reflux on esophageal pH-monitoring with running and rowing, more so after a meal^[73].

The main mechanism in which exercise is thought to exacerbate esophageal acid reflux is through TLESRs as seen in 82% of episodes in a study by Schoeman et al. where LES pressures were measured in ambulatory healthy subjects during a standardized exercise program involving cycling and moderate/fast walking^[73]. A more recent study by Herregods et al. further supports this finding where the effects of running was studied in 10 healthy participants via a combination of both pH-impedance monitoring and prolonged high-resolution manometry. Not only did this novel study show that exercise led to a significantly higher esophageal AET and frequency/duration of acid reflux episodes, but also revealed all but one reflux episode was associated with TLESRs^[74]. In fact, exercise resulted in significantly increased frequency of TLESRs, in conjuncture with increased abdominal pressure and decreased duration/contractility of peristaltic contractions^[74].

The majority of the studies exploring the effects of exercise and acid reflux were completed with healthy, asymptomatic volunteers or athletes, so concerns on whether the above data can be extrapolated to patients with symptoms exist. Regardless, it is important to acknowledge that exercise in numerous forms can increase both TLESRs and esophageal acid exposure even in healthy patients, which can subsequently modulate day-to-day esophageal acid reflux and contribute to the variability seen on esophageal pH-monitoring testing.

SUMMARY OF SUGGESTIONS TO REDUCE VARIABILITY IN ACID EXPOSURE

In summary, GERD is an incredibly common gastrointestinal disorder for which the gold standard for diagnosis is ambulatory reflux monitoring, with a preference towards prolonged wireless pH monitoring when available. However, day-to-day variability with pH-monitoring has been observed and established in prior studies^[17-19]. A multitude of environmental, psychosocial, and physical factors can modulate day-to-day esophageal acid exposure, with significant impacts on diagnostic interpretation. Thus, optimal acid exposure management should be recommended during reflux monitoring, which includes optimizing long-term sleep hygiene, dietary/eating habits, exercise (type and frequency), and stress reduction. Future areas of interest include methods to improve biowearable devices to measure these components of stress, sleep, exercise, and their relationship to an individual patient's esophageal acid burden and symptoms. Incorporating these measured parameters into mobile apps for easy monitoring could also be developed. Doing this would allow patients suffering from GERD to better target and monitor specific factors affecting their GERD so that they can improve their overall health and wellness.

In the meantime, patients can be recommended to avoid exercise after eating. Performing relaxation techniques have also been shown to reduce stress, esophageal acid exposure, and number of acid reflux events^[66] which could subsequently influence day-to-day variability in acid reflux patterns. Likewise, diet restriction, inspiratory muscle training, and abdominal/diaphragmatic breathing exercises have been shown to reduce day-to-day variability in pH composite score^[75], improve esophagogastric junction pressure^[76], and subsequently reduce the number of postprandial acid reflux events^[77, 78]. These lifestyle modifications can not only improve diagnostic yield by reducing variable/confounding factors that affect interpretation of prolonged esophageal pH monitoring, but also assist in long-term symptom management.

Funding Support:

RY is supported by NIH K23 DK125266 (PI: Yadlapati).

Abbreviations:

AET	Acid exposure time
ACG	American College of Gastroenterology
AGA	American Gastroenterology Association
BGA	brain-gut axis
GERD	gastroesophageal reflux disease
LES	loweresophageal sphincter
PPI	proton pump inhibitor
TLESR	transient lower esophageal sphincter relaxation

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GOT GASTROESOPHAGEAL REFLUX DISEASE (GERD)?

The following lifestyle factors have been associated with worsening acid reflux and GERD-related symptoms. These are things you can do at home outside of taking medications that can help manage and optimize your GERD.



SLEEP DEPRIVATION

- Optimize your long-term sleeping habits ("sleep hygiene")
- Cognitive behavioral therapy for insomnia (CBT-i) may be helpful for some



DIETARY/EATING HABITS

- Avoid known food or eating habit triggers. This will differ for each individual!
- Keeping a food-symptom diary can help figure out your triggers



STRESS

- Practice relaxation techniques such as meditation, yoga, aromatherapy, etc. Whatever works best for you, your interests, and your schedule!



EXERCISE

- Avoid high-intensity exercises like running or weight lifting immediately after eating to prevent acid reflux/regurgitation
- "Diaphragmatic breathing exercises" can help as well

QUESTIONS? CONTACT YOUR PRIMARY CARE PHYSICIAN OR GASTROENTEROLOGIST FOR MORE INFORMATION!

Figure 1.
: Educational infographic for GERD patients and/or those undergoing ambulatory pH monitoring with recommendations for optimization of GERD-related symptoms and esophageal acid reflux levels

Table 1:

Factors associated with day-to-day esophageal acid reflux variability

Factor	Mechanism	Intervention/Management
Sleep	Sleep deprivation → sleep fragmentation → nocturnal reflux → slowed gastric emptying, reduced swallowing/salivary secretions, reduced esophageal peristalsis, heightened hyperalgesia/hypersensitivity	<ul style="list-style-type: none"> • Optimize long-term sleep hygiene • Cognitive Behavioral Therapy for Insomnia (CBT-I)
Dietary and Eating Habits	Certain food triggers/eating habits → increased transient lower esophageal sphincter relaxations (TLESRs) and/or reduced LES pressures	<ul style="list-style-type: none"> • Avoiding known food or eating habit triggers (patient-dependent)
Stress	Acute/chronic stress → reduced LES pressure, heightened hypersensitivity, increased gastric acid output, decreased gastric compliance	<ul style="list-style-type: none"> • Relaxation techniques such as meditation • Exercise/yoga
Exercise	High intensity exercise → increased abdominal pressure, decreased duration/contractility of peristaltic contractions, increased TLESRs	<ul style="list-style-type: none"> • Inspiratory muscle training • Abdominal/diaphragmatic breathing exercises • Avoiding exercise immediately after eating