The relationship between esophageal acidity and symptom frequency in symptomatic nonerosive gastroesophageal reflux disease

Jerry D. Gardner

Abstract

The present paper examines the extent to which novel measures of esophageal acid exposure can elucidate possible relationships between symptom perception and esophageal acidity in subjects with nonerosive gastroesophageal reflux disease. Recordings of esophageal pH and symptom occurrence from 20 subjects with nonerosive gastroesophageal reflux disease were analyzed. Interval esophageal acid exposure was calculated in two different ways for the interval that preceded each symptom in each subject. Interval esophageal acidity was calculated as the time-weighted acid concentration for the interval. Interval esophageal acid exposure time was calculated as the percentage of the total recording time that esophageal pH was less than pH 4 for the interval. There was a negative relationship between the probability of a symptom and interval esophageal acid exposure indicating the paradoxical finding that the lower the value of esophageal acid exposure, the higher the probability of a symptom. The time courses of symptoms and cumulative esophageal acidity resolved this paradox by indicating that esophageal acid exposure oscillates between longer periods of low esophageal acid exposure with a high number of symptoms reflecting high esophageal acid sensitivity, and shorter periods of high esophageal acid exposure with fewer symptoms reflecting low esophageal acid sensitivity. Thus, the present analyses show how novel measures of acidity can identify and also resolve a previously unrecognized paradoxical relationship between esophageal acid exposure and symptom frequency in subjects with nonerosive gastroesophageal reflux disease.

Keywords

interval esophageal acid exposure time, interval esophageal acidity, nonerosive gastroesophageal reflux disease
1 | INTRODUCTION

Recently, the Lyon Consensus Conference (Gyawali et al., 2018) proposed criteria for the clinical diagnosis of gastroesophageal reflux disease (GERD) and commented that the association of esophageal acid exposure and symptoms of GERD is weak. Nearly, all previous analyses of relationships between GERD symptoms and esophageal acidity have used the symptom index (SI; Weiner et al., 1988), or the symptom association probability (SAP; Weusten et al., 1994), which assesses the relationship between symptoms and esophageal reflux episodes identified initially by a decrease in esophageal pH to below pH 4 or more recently, by a change in esophageal impedance (Kamal et al., 2020). The SI and SAP are standard measures of impedance-pH studies, and have been used clinically to identify different phenotypes of symptomatic GERD subjects (Gyawali et al., 2018).

For the present analyses, however, I was interested in possible relationships between esophageal acid exposure and symptom frequency in subjects with symptomatic nonerosive gastroesophageal reflux disease (NERD). I calculated interval esophageal acid exposure from the time of one symptom until the time of the next symptom using two different methods—interval esophageal acidity (Gardner et al., 2001) and interval esophageal acid exposure time (Gyawali et al., 2018). Thus, each symptom is associated with two particular values for esophageal acid exposure. The entire interval between symptoms instead of just a portion of it was chosen because there was no apparent reason to do otherwise. Also, previous analyses have found that there is a statistical association between sequential values of esophageal pH for up to 2 h in normal as well as GERD subjects (Gardner et al., 2005); therefore, it seemed appropriate to capture information from the entire inter-symptom interval.

2 | METHODS

Subjects were identified for the present analyses by interrogating the electronic database (January 2016–August 2019) at the Royal London Hospital GI Physiology Unit. All subjects in the Royal London Hospital database had undergone impedance–pH monitoring because the referring physician reported an unsatisfactory response to gastric antisecretory medication such as proton pump inhibitors (PPIs). No details regarding the unsatisfactory response were provided by the referring physician. Subjects were included in the database if they were over 16 years old and underwent upper gastrointestinal endoscopy, high-resolution manometry (HRM), and 24-h impedance–pH monitoring while not taking a PPI. Patients were excluded if they had (i) endoscopic esophagitis, Barrett’s esophagus, or eosinophilic esophagitis, (ii) HRM diagnosis of a major esophageal motility disorder, or (iii) belching as the main symptom.

All subjects had undergone the following procedures. HRM (ManoScan, Medtronic) and impedance–pH monitoring (Sandhill Scientific) were performed after overnight fasting. Ambulatory impedance–pH monitoring was performed following HRM with gastric antisecretory agents having been discontinued for at least 7 days. The impedance–pH catheter was inserted with an esophageal pH sensor positioned 5 cm above the upper border of the lower esophageal sphincter, and a gastric pH sensor positioned 15 cm below the esophageal pH sensor. Six impedance channels were positioned 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter, respectively. The pH electrodes were calibrated following the instructions from the manufacturer and using their standard calibration solutions at pH 4 and pH 7. Because antimony electrodes, which are temperature sensitive, were used to record pH, the software provided by Sandhill to process pH recordings automatically adjusts all pH values for the difference between the calibration temperature 25°C and the recording temperature 37°C. Software provided by the manufacturer was also used to export pH data for every 4th second of the recording to a Microsoft Excel file. Values of pH below 0.5 were replaced with 0.5, and pH values above 7.5 were replaced with 7.5.

Subjects were instructed to follow their usual daily routines and meals, but to avoid carbonated or acidic beverages. Subjects pressed an event marker to signal the meal periods, recumbent period, and symptoms of heartburn, regurgitation, or chest pain.

Recordings from 20 subjects with NERD defined as acid exposure time >6% regardless of values for SI and SAP (Gyawali et al., 2018) were selected for analysis. Table A1 in Appendix gives traditional values for impedance–pH testing in the NERD subjects selected for analysis.

For this retrospective analysis of clinically indicated tests with no identifiable patient data, formal ethics approval was not deemed necessary.

Figure 1 illustrates a representative esophageal pH recording and the time at which each of 25 symptoms occurred. Symptoms appeared to occur in two different groups. One group of symptoms occurred during the first 6 h of the recording and the second group occurred during the last 5 h of the recording.

Esophageal acid exposure time measured as the percentage of total recording time that esophageal pH is less than pH 4 is what most investigators use to measure esophageal acid exposure (Gyawali et al., 2018; Table A1 in Appendix). Figure 2 illustrates that for each esophageal pH recording, interval esophageal acid exposure time was...
measured as the percentage of total recording time that esophageal pH was less than pH 4 and interval esophageal acidity (Gardner et al., 2001) was measured as the time-weighted acid concentration in mmol/L from the beginning of the recording until the time of the first symptom, from the time of the first symptom until the time of the second symptom and so on until the time of the last symptom. These procedures result in each symptom being associated with a specific value of interval esophageal acidity and interval esophageal acid exposure time.

Cumulative interval esophageal acidity and cumulative interval esophageal acid exposure time for the time course for each subject were calculated as the sum of sequential values of interval acidity and acid exposure time for each symptom until the time of the last symptom.

Curve fitting and statistical analyses were performed using GraphPad Prism software.

3 RESULTS

NERD subjects (9 males; 11 females) ranged in age from 22 to 74 years. The median number of symptoms was 24 with an interquartile range of 10 to 31. Symptom distribution was heartburn 426; regurgitation 35; and chest pain 15.

Table 1 gives the time of symptoms illustrated in Figure 1 as well as the duration of the time between sequential symptoms. Values for interval esophageal acid exposure time and interval esophageal acidity associated with each symptom are also given. There was a broad range for each set of values. The time between symptoms ranged from 0.01 to 10.59 h. Interval acid exposure time ranged from 0.00% to 1.64% and interval esophageal acidity ranged from 0.00001 to 1.24 mmol·h/L.

Twelve of the values for interval acid exposure time were zero indicating no values <pH 4 during the interval. Seven of these values occurred during the initial 6 h of the recording and five of these values occurred during the last 5 h of the recording. The duration of the interval during which no pH values were <pH 4 ranged from 0.01 to 1.22 h, and the accompanying value of interval esophageal acidity ranged from 0.00001 to 0.00148 mmol-hr/L.

Figure 3 illustrates that the lower the bin interval, the higher the percentage of values in the bin for both interval esophageal acidity and interval esophageal acid exposure time. Since each value of esophageal acidity and esophageal acid exposure time is associated with a symptom, the percentage of values in each bin gives the percentage of
total symptoms associated with that bin. Thus, Figure 3 illustrates the paradoxical finding that the lower the value of esophageal acid exposure, the higher the probability of a symptom.

The wide range of values for interval acidity and interval acid exposure time illustrated in Figure 3 suggests that there will not be a significant relationship between the total number of symptoms in a given subject and corresponding values for total esophageal acidity or total esophageal acid exposure time. Figure 4 examines this possibility.

Figure 4 shows that there is no significant relationship between total number of symptoms in a given subject and corresponding values for total esophageal acidity or total esophageal acid exposure time as would be expected from the wide range of values for interval esophageal acid exposure is illustrated in Figure 3.

Figure 5-left illustrates that the lower the bin interval, the higher the percentage of values in the bin for interval size. Since each value of interval size is associated with a symptom, the percentage of values in each bin gives the percentage of total symptoms associated with that bin. Thus, Figure 5-left illustrates that the lower the value of interval time, the higher the probability of a symptom, and the higher the value of interval time, the lower the probability of a symptom. Taken together, Figures 3 and 5-left illustrate that the shorter the interval between symptoms and the lower esophageal acid exposure during the interval, the higher the probability of a symptom, and the longer the interval between symptoms and the higher esophageal acid exposure during the interval, the lower the probability of a symptom.

Figure 5-right also illustrates a direct relationship between interval esophageal acidity and interval time and raises the possibility that the values for interval esophageal acidity are actually caused by the duration of the interval between symptoms. For example, during sleep, a subject might have ongoing esophageal acid exposure but no symptom so that the next symptom after the sleep period would have a high value for interval esophageal acidity.

### TABLE 1

| Symptom number | Symptom time (h) | Interval duration (h) | Interval AET (%) | Interval ESO acidity (mmol·h/L) |
|----------------|------------------|-----------------------|------------------|--------------------------------|
| 1              | 0.44             | 0.44                  | 0.00             | 0.00026                        |
| 2              | 0.47             | 0.03                  | 0.00             | 0.00001                        |
| 3              | 1.37             | 0.90                  | 0.48             | 0.55015                        |
| 4              | 1.98             | 0.61                  | 0.45             | 0.58619                        |
| 5              | 2.58             | 0.61                  | 0.65             | 0.39918                        |
| 6              | 2.85             | 0.26                  | 0.00             | 0.00004                        |
| 7              | 3.99             | 1.15                  | 0.72             | 0.08430                        |
| 8              | 4.00             | 0.01                  | 0.00             | 0.00001                        |
| 9              | 4.67             | 0.67                  | 0.30             | 0.02112                        |
| 10             | 4.68             | 0.01                  | 0.00             | 0.00001                        |
| 11             | 4.70             | 0.02                  | 0.00             | 0.00002                        |
| 12             | 5.12             | 0.41                  | 0.00             | 0.00012                        |
| 13             | 5.43             | 0.31                  | 0.17             | 0.01142                        |
| 14             | 5.97             | 0.54                  | 0.51             | 0.09085                        |
| 15             | 6.13             | 0.17                  | 0.04             | 0.01600                        |
| 16             | 16.72            | 10.59                 | 1.03             | 0.48270                        |
| 17             | 16.76            | 0.04                  | 0.00             | 0.00027                        |
| 18             | 17.32            | 0.55                  | 0.37             | 0.03409                        |
| 19             | 18.59            | 1.27                  | 1.65             | 1.23879                        |
| 20             | 19.34            | 0.76                  | 0.64             | 1.00073                        |
| 21             | 20.56            | 1.22                  | 0.00             | 0.00148                        |
| 22             | 21.30            | 0.74                  | 0.00             | 0.00047                        |
| 23             | 21.49            | 0.19                  | 0.00             | 0.00022                        |
| 24             | 21.57            | 0.08                  | 0.00             | 0.00001                        |
| 25             | 22.02            | 0.45                  | 0.17             | 0.01674                        |

Abbreviation: AET, esophageal acid exposure time.
On the other hand, ingestion of a meal or changing position might cause symptoms to occur close together in time and be associated with low values of interval esophageal acidity. To examine the possibility that values for interval esophageal acidity are actually determined by the duration of the interval between symptoms, I calculated interval esophageal acidity for a fixed, 60-s interval (15 pH values) before each of the 476 symptoms.

**Figure 6** illustrates that the distribution of values of fixed interval esophageal acidity is similar to that for

---

**FIGURE 3** Distribution of values for interval esophageal acidity (left panel) and interval esophageal exposure time (right panel). Each distribution used a bin width of 0.5 and values given on the x-axis are for the lower boundary of the bin. Values are for 476 symptoms from 20 nonerosive gastroesophageal reflux disease subjects. Every subject reported at least three symptoms during the pH recording. The solid line in each panel is the linear, least-squares fit of the data and was significantly different from zero \( p < 0.0001 \) by an \( F \) test.

**FIGURE 4** Value for total number of symptoms versus corresponding value of total esophageal acidity (left panel) and total esophageal acid exposure time (right panel). Values are from 20 nonerosive gastroesophageal reflux disease subjects. The solid line in each panel is the linear, least-squares fit of the data and was not significantly different from zero by an \( F \) test (left panel; \( p = 0.9336 \); right panel; \( p = 0.3225 \)).
interval esophageal acidity shown in Figure 3 in that the lower the value of fixed interval esophageal acidity, the higher the probability of a symptom. These results also indicate that interval time is not an important determinant of the frequency distribution, and that when time is held constant the lower the value of fixed interval esophageal acidity, the higher the probability of a symptom.

Plotting cumulative esophageal acidity over time makes it possible to illustrate the increase in esophageal acid exposure with each successive symptom. The slope of the line that characterizes a series of symptoms (referred to as a segment) is a measure of esophageal acid exposure for the symptoms in that series, in that the steeper the slope, the higher the esophageal acid exposure. Figure 7 shows that for the NERD subject's pH recording illustrated in Figure 1, with both measures of esophageal acid exposure, there is an initial segment with a steep slope, followed by a segment with a shallow slope, followed by a segment with a steep slope, and finally followed by a segment with a shallow slope. Thus, this subject's symptoms occur in segments that are associated with alternating periods of high esophageal acid exposure and low esophageal acid exposure. Figure 8 illustrates that all NERD subjects except one showed a series of symptoms that occurred in periods of low esophageal acid exposure alternating with periods of high esophageal acid exposure. Similar results occurred with data for esophageal acid exposure time (not shown).

4 | DISCUSSION

Nearly all previous analyses of relationships between GERD symptoms and esophageal acidity have used the SI or the SAP, which are limited to symptoms that are associated with esophageal reflux episodes (Gyawali et al., 2018; Kamal et al., 2020; Weiner et al., 1988; Weusten et al., 1994). Calculating esophageal acid exposure over the entire interval that precedes a symptom results in every symptom in every subject being associated with distinct values of interval esophageal acid exposure.

The present analyses using interval esophageal acidity and interval esophageal acid exposure time provide novel information regarding relationships between esophageal acidity and symptom frequency in symptomatic NERD subjects. Frequency distributions of values for interval esophageal acidity as well as interval esophageal exposure time showed a paradoxical relationship between the
probability of a symptom and the value of interval esophageal acid exposure in that the lower the value of interval acidity the higher the probability of a symptom. This paradox of less esophageal acid and more symptoms was unanticipated, because nearly all published literature in the GERD field specifies or implies a direct relationship between esophageal acid and symptoms. For example, the occurrence of GERD symptoms has been reported to be associated with increased esophageal acid exposure time during the time before the symptom (Beedassy et al., 2000; Bredenoord et al., 2006) and reductions in esophageal acidity with gastric antisecretory agents such as PPIs reduce the occurrence of symptoms (Gyawali et al., 2018). The present findings indicate that it is unlikely that values for total esophageal acid exposure will provide meaningful information regarding symptom frequency in NERD subjects because some symptoms will be preceded by low values of esophageal acid and other symptoms will be preceded by high values of esophageal acid.

One possible explanation for the relationship between symptoms and low values of interval esophageal acid exposure is that “something else” besides esophageal acid, such as bile or pepsin, is responsible for the symptoms. Although perfusion of bile salts into the esophagus can induce heartburn in subjects with functional heartburn or normal subjects (Siddiqui et al., 2005), the presence of bile in the esophagus is associated with only a small percentage of symptoms in GERD subjects (Bredenoord, 2012). Pepsin can cause damage to esophageal mucosa in experimental settings (Bredenoord, 2012); however, there is no good evidence that pepsin is involved with symptoms in GERD subjects (Bredenoord, 2012). The presence of gas in reflux material (Bredenoord, 2012) as well as reflux material that reaches the upper esophagus can enhance the perception of GERD symptoms (Bredenoord, 2012). Neither of these phenomena, however, would be expected to occur with sufficient frequency to account for low values for interval esophageal acidity being associated with a high probability of GERD symptoms. It is also known that psychological factors can modify symptom perception in symptomatic GERD (Rubenstein et al., 2021), and possibly psychological factors amplify the esophageal sensitivity to low values of esophageal acid exposure.

Another possible explanation for the paradoxical finding is that the lower the value of esophageal acid exposure the higher the probability of symptoms comes from analyses of the time course of interval esophageal acidity in individual subjects. In individuals with symptomatic NERD, values for interval esophageal acidity tended to occur in clusters and in oscillating sequences of high and low interval acid exposure. Thus, a sequence of symptoms with low interval acid exposure could reflect high esophageal acid sensitivity, and the high acid exposure might reflect low esophageal acid sensitivity. The neurochemical mediators of symptoms produced by esophageal acid exposure have not been clearly established; however, the acid-sensitive, transient receptor potential cation channel that is associated with the capsaicin or vanilloid receptor (TRPV1) is a possible candidate (Ang et al., 2008). Protein kinase C and nerve growth factor are both capable of sensitizing TRPV1 by lowering the
activation threshold to hydrogen ions (Koivistö et al., 2022). Once activated, TRPV1 can undergo reversible desensitization (Koivistö et al., 2022). In addition, acid-sensing ion channels are members of the voltage-insensitive, amiloride-sensitive degenerin family of cation channels that can be activated by protons (Waldmann & Lazdunski, 1998). These channels are upregulated in the esophageal mucosa from GERD patients and increased expression of ASCI correlated positively with symptom severity in GERD (Han et al., 2022). Studies in rats implicate ASCIs in visceral hypersensitivity mediated by vagal afferents in GERD (Han et al., 2022; Lennerz et al., 2007). Thus, it seems likely that neurons in esophageal mucosa play an important role in determining esophageal acid sensitivity. It is conceivable that with low esophageal acid exposure, nociceptive neurons in esophageal mucosa become sensitized to luminal acid. This sensitization is then followed by reversible desensitization of the neurons that, in turn, results in higher esophageal acid exposure being necessary to elicit symptoms. Since the desensitization is reversible, it eventually wanes or is overcome by renewed sensitization and the cycle repeats itself.

The association of symptoms with oscillating esophageal acid exposure might influence the response of symptoms in NERD subjects to gastric antisecretory agents such as PPIs. For example, if symptoms associated with low values of esophageal acid exposure are actually caused by “something else”, these symptoms might not be affected by a gastric antisecretory agent. Furthermore, if all symptoms are caused by esophageal acid exposure, symptoms associated with high values of esophageal acid might be less likely to be affected by a gastric antisecretory agent than symptoms associated with low values of esophageal acid.

NERD subjects have been found to have increased sensitivity to both chemical and mechanical stimuli (Bhalla et al., 2004; Howard et al., 1991; Rodriguez-Stanley et al., 1999; Smith et al., 1989; Trimble et al., 1995). The present results indicate that NERD subjects may also have increased sensitivity to endogenous esophageal acid, and that this sensitivity oscillates.

There are some limitations to the present analyses. A major limitation is the lack of a causal explanation for the oscillating esophageal acid sensitivity in NERD subjects. I realize that no set of analyses can address all relevant questions, and others have pointed out that it may not be possible to correlate the behavior of each specific detail of a time series with a particular event (Fossion et al., 2020). It seems to me, however, that future attempts to identify the basis for the oscillating esophageal acid sensitivity in NERD subjects should have a high priority. There were also other limitations such as no standardized definition of a subject’s unsatisfactory response to a gastric antisecretory agent. The impedance–pH recordings began at different times during the day and meals were not standardized with respect to time of the day or composition. The recurrent periods were not standardized. These features may have influenced important relationships among esophageal acidity and symptom frequency. Also, symptom severity was not assessed making it impossible to examine possible relationships between interval acidity or symptom frequency and symptom severity.

ACKNOWLEDGMENT
I am grateful to Dr. Daniel Sifrim, Director of Upper GI Physiology Unit, Royal London Hospital, for providing the impedance–pH records and for stimulating, helpful discussions.

CONFLICT OF INTEREST
Nothing to disclose.

ORCID
Jerry D. Gardner © https://orcid.org/0000-0001-9642-864X

REFERENCES
Ang, D., Sifrim, D., & Tack, J. (2008). Mechanisms of heartburn. *Nature Clinical Practice Gastroenterology and Hepatology, 5*, 383–391.

Beedassy, A., Katz, P. O., Gruber, A., Peghini, P. L., & Castell, D. O. (2000). Prior sensitization of esophageal mucosa by acid reflux predisposes to reflux-induced chest pain. *Journal of Clinical Gastroenterology, 31*, 121–124.

Bhalla, V., Liu, J., Puckett, J. L., & Mittal, R. K. (2004). Symptom hypersensitivity to acid infusion is associated with hypersensitivity of esophageal contractility. *American Journal of Physiology. Gastrointestinal and Liver Physiology, 287*, G65–G71.

Bredenoord, A. J. (2012). Mechanisms of reflux perception in gastro-esophageal reflux disease: A review. *The American Journal of Gastroenterology, 107*, 8–15.

Bredenoord, A. J., Weusten, B. L. A. M., Curvers, W. L., Timmer, R., & Smout, A. J. P. M. (2006). Determinants of perception of heartburn and regurgitation. *Gut, 55*, 313–318.

Fossion, R., Saenz-Burrola, A., & Zapata-Fonseca, L. (2020). On the stability and adaptability of human physiology: Gaussians meet heavy-tailed distributions. *Inter Disciplina, 8*, 55–81.

Gardner, J. D., Rodriguez-Stanley, S., & Robinson, M. (2001). Integrated acidity and the pathophysiology of GERD. *The American Journal of Gastroenterology, 96*, 1363–1370.

Gardner, J. D., Young, W., Sloan, S., Robinson, M., & Miner, P. B., Jr. (2005). The fractal nature of human gastro-oesophageal disease. *Alimentary Pharmacology & Therapeutics, 22*, 823–830.

Gyawali, C. P., Kahrilas, P. J., Savarino, E., Zerbib, F., Mion, F., Smout, A. J. P. M., Vaezi, M., Sifrim, D., Fox, M. R., Vela, M. F., Tutuian, R., Tack, J., Bredenoord, A. J., Pandolfino, J., & Roman, S. (2018). Modern diagnosis of GERD: The Lyon consensus. *Gut, 67*, 1351–1362.

Han, X., Zhang, Y., Lee, A., Li, Z., Gao, J., Wu, X., Zhao, J., Wang, H., Chen, D., Zou, D., & Owyang, C. (2022). Upregulation of acid sensing ion channels is associated with esophageal hypersensitivity in GERD. *The FASEB Journal, 36*, e22083.
Symptomatic gastroesophageal reflux, abnormal oesophageal acid exposure, and mucosal acid sensitivity are three separate, though related aspects of gastro-oesophageal reflux disease. Gut, 32, 128–132.

Kamal, A. N., Clarke, J. O., Oors, J. M., Smout, A. J., & Bredenoord, A. J. (2020). The role of symptom association analysis in gastroesophageal reflux testing. The American Journal of Gastroenterology, 115, 1950–1959.

Koivisto, A.-P., Belvisi, M. C., Gaudet, R., & Szallasi, A. (2022). Advances in TRP channel drug discovery: From target validation to clinical studies. Nature Reviews Drug Discovery, 21, 41–59.

Lennerz, J. K. M., Dentsch, C., Bernardini, N., Hummel, T., Neuhuber, W. L., & Reeh, P. W. (2007). Electrophysiological characterization of vagal afferents relevant to mucosal nociception in the rat upper oesophagus. The Journal of Physiology, 582, 229–242.

Rodriguez-Stanley, S., Robinson, M., Earnest, D. L., Greenwood-Van Meerveld, B., & Miner, P. B., Jr. (1999). Esophageal hypersensitivity may be a major cause of heartburn. The American Journal of Gastroenterology, 94, 628–631.

Rubenstein, J. H., Jianh, L., Kurlander, J. E., Chen, J., Metko, V., Khodadost, M., Nozf, K., & Raghunathan, T. (2021). Incomplete response of gastroesophageal reflux symptoms poorly predicts erosive esophagitis or Barrett’s esophagus. Gastroenterology, 19, 2284–2292.

Siddiqui, A., Rodriguez-Stanley, S., Zubaidi, S., & Miner, P. B., Jr. (2005). Esophageal visceral sensitivity to bile salts inpatients with functional heartburn and in healthy control subjects. Digestive Diseases and Sciences, 50, 81–85.

Smith, J. L., Opekun, A. R., Larkai, E., & Graham, D. Y. (1989). Sensitivity of the esophageal mucosa to pH in gastroesophageal reflux disease. Gastroenterology, 96, 683–689.

Trimble, K. C., Pryde, A., & Heading, R. C. (1995). Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux. Evidence for a spectrum of visceral sensitivity in GORD. Gut, 37, 7–12.

Waldmann, R., & Lazdunski, M. (1998). H(+)–gated cation channels: Neuronal acid sensors in the NaC/DEG family of ion channels. Current Opinion in Neurobiology, 8, 418–424.

Weiner, G. J., Richter, J. E., Copper, J. B., Wu, W. C., & Castell, D. O. (1988). The symptom index: A clinically important parameter of 24-hour esophageal pH monitoring. The American Journal of Gastroenterology, 83, 358–361.

Wu, T., Oefele, J. M., Akkermans, L. M., Van Berge-Henegouwen, G. P., & Smout, A. J. (1994). The symptom-association probability: An improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology, 107, 1741–1745.

How to cite this article: Gardner, J. D. (2022). The relationship between esophageal acidity and symptom frequency in symptomatic nonerosive gastroesophageal reflux disease. Physiological Reports, 10, e15442. https://doi.org/10.14814/phy2.15442
# APPENDIX

## TABLE A1  Standard values from impedance and pH monitoring for subjects in the present study

|       | S6 | S7 | S8 | S12 | S17 | S19 | S20 | S29 | S36 | S39 |
|-------|----|----|----|-----|-----|-----|-----|-----|-----|-----|
| Gender | F  | M  | F  | F   | M   | F   | M   | M   | M   | M   |
| Age (year) | 74 | 23 | 56 | 52   | 53  | 22  | 73  | 33  | 30  | 32  |
| Duration (h:min) | | | | | | | | | | |
| Upright | 12:42 | 8:54 | 16:57 | 10:26 | 10:22 | 11:36 | 10:50 | 15:50 | 13:32 | 10:34 |
| Recumbent | 6:48 | 10:22 | 8:38 | 9:49 | 9:45 | 7:59 | 10:17 | 9:01 | 9:53 | 12:33 |
| Total | 19:31 | 19:16 | 25:35 | 20:16 | 20:07 | 19:35 | 21:07 | 24:52 | 23:25 | 23:07 |
| Acid exposure (%) | | | | | | | | | | |
| Upright | 14.6 | 9.5 | 11.0 | 12.7 | 11.3 | 8.6 | 2.1 | 10.1 | 19.9 | 24.6 |
| Recumbent | 1.4 | 4.5 | 30.8 | 0.0 | 3.2 | 8.8 | 22.8 | 0.2 | 19.5 | 29.5 |
| Total | 10.0 | 6.8 | 17.7 | 6.6 | 7.4 | 8.7 | 12.1 | 6.5 | 19.7 | 27.3 |
| Reflux episodes (#) | | | | | | | | | | |
| Acid | 41 | 103 | 70 | 25 | 36 | 58 | 18 | 65 | 101 | 145 |
| Non-acid | 9 | 29 | 18 | 6 | 15 | 10 | 7 | 24 | 4 | 38 |
| Total | 50 | 132 | 88 | 31 | 51 | 68 | 25 | 89 | 105 | 183 |
| Symptom index (%) | | | | | | | | | | |
| Hrtburn | 80 | 65 | 76 | 80 | 83 | 76 | 40 | 78 | 80 | 72 |
| Regurg | 100 | 78 | 100 | 83 | 100 | 100 | 0 | 100 | 0 | 100 |
| Chest pain | 100 | 100 | 100 | 100 | 100 | 100 | 83 | 100 | 100 | 100 |
| Symptom association probability (%) | | | | | | | | | | |
| Hrtburn | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Regurg | 100 | 100 | 99 | 100 | 0 | 0 | 0 | 78 | 0 | 78 |
| Chest pain | 92 | 83 | 88 | 88 | 100 | 100 | 0 | 0 | 0 | 0 |

|       | S44 | S46 | S50 | S53 | S54 | S55 | S57 | S58 | S59 | S60 |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gender | F  | M  | F  | F   | F   | F   | M   | F   | M   | F   |
| Age (year) | 63 | 60 | 53 | 39   | 32  | 44  | 54  | 31  | 68  | 45  |
| Duration (h:min) | | | | | | | | | | |
| Upright | 10:50 | 9:59 | 7:13 | 9:26 | 6:39 | 16:41 | 11:48 | 11:40 | 12:29 | 14:52 |
| Recumbent | 10:12 | 8:25 | 11:41 | 10:44 | 11:27 | 4:53 | 8:34 | 9:14 | 9:01 | 6:08 |
| Total | 21:02 | 18:24 | 18:54 | 20:10 | 18:06 | 21:34 | 20:22 | 20:54 | 21:31 | 21:00 |
| Acid exposure (%) | | | | | | | | | | |
| Upright | 37.2 | 3.1 | 28.2 | 38.7 | 1.4 | 13.8 | 11.5 | 4.2 | 2.8 | 13.2 |
| Recumbent | 47.9 | 46.1 | 40.8 | 17.0 | 12.2 | 0.0 | 0.5 | 10.8 | 12.3 | 15.6 |
| Total | 42.4 | 22.8 | 36.0 | 27.2 | 8.2 | 10.7 | 6.9 | 7.2 | 6.8 | 13.9 |
| Reflux episodes (#) | | | | | | | | | | |
| Acid | 122 | 34 | 77 | 117 | 9 | 86 | 27 | 58 | 38 | 57 |
| Non-acid | 32 | 4 | 8 | 12 | 12 | 9 | 27 | 2 | 35 | 60 |
| Total | 154 | 38 | 85 | 129 | 21 | 95 | 54 | 60 | 73 | 117 |
| Symptom index (%) | | | | | | | | | | |
| Hrtburn | 89 | 93 | 100 | 89 | 58 | 97 | 38 | 0 | 50 | 55 |
| Regurg | 90 | 100 | 100 | 0 | 50 | 50 | 0 | 100 | 0 | 100 |
| Chest pain | 0 | 100 | 100 | 0 | 100 | 100 | 0 | 100 | 0 | 100 |
| Symptom association probability (%) | | | | | | | | | | |
| Hrtburn | 100 | 100 | 100 | 100 | 100 | 100 | 87 | 0 | 88 | 100 |
| Regurg | 99 | 93 | 98 | 0 | 0 | 0 | 0 | 0 | 0 | 97 |
| Chest pain | 0 | 97 | 55 | 0 | 0 | 0 | 0 | 0 | 0 | 100 |

**Note:** Numbers at top of each column are subject numbers.

**Abbreviations:** Hrtburn, heartburn; Regurg, regurgitation.