Oscillating Esophageal Acid Sensitivity in Symptomatic Reflux Hypersensitivity and Functional Heartburn

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1 Science for Organizations

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Abstract

Background In previous analyses of recordings of esophageal pH and symptom occurrence in subjects with nonerosive esophageal reflux disease, all of whom had increased esophageal exposure, I found that the lower the value of esophageal acid exposure, the higher the probability of a symptom. This finding could be explained by esophageal acid sensitivity oscillating between longer periods of high esophageal acid sensitivity, and shorter periods of low esophageal acid sensitivity. To examine whether these oscillations also occur in symptomatic subjects with normal esophageal acid exposure, I analyzed data from subjects with Reflux Hypersensitivity and subjects with Functional Heartburn, to examine relationships between esophageal acid exposure and the probability of symptoms.

Methods For each subject I calculated interval esophageal acidity that measures esophageal acid exposure that precedes each symptom and cumulative interval esophageal acidity.

Results In each group of subjects there was a negative relationship between the probability of a symptom and interval esophageal acid exposure indicating that the lower the value of esophageal acid exposure, the higher the probability of a symptom. The time course of symptoms and cumulative esophageal indicated that esophageal acid exposure oscillates between longer periods of high esophageal acid sensitivity, and shorter periods of low esophageal acid sensitivity.

Conclusions The present analyses of subjects with Reflux Hypersensitivity or Functional Heartburn in conjunction with previous analyses of subjects with nonerosive esophageal reflux indicate that oscillating esophageal acid sensitivity is a characteristic feature of symptomatic gastroesophageal reflux disease.

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Introduction

The Lyon Consensus Conference [1] proposed criteria for the clinical diagnosis of three different phenotypes of gastroesophageal reflux disease: nonerosive gastroesophageal reflux disease (NERD), Reflux Hypersensitivity, and Functional Heartburn. Using Lyon consensus thresholds, NERD subjects have increased esophageal acid exposure time (AET) (pH <4 for greater than 6% of a 24-hour esophageal pH recording). In contrast, both Reflux Hypersensitivity subjects and Functional Heartburn subjects have normal AET (pH <4 for less than 4% of a 24-hour esophageal pH recording). Reflux Hypersensitivity subjects have a positive association between symptoms and esophageal reflux episodes whereas Functional Heartburn subjects do not.

Previously [2], I analyzed recordings of esophageal pH and symptom occurrence from 20 subjects with NERD and found that the lower the value of esophageal acid exposure, the higher the probability of a symptom. This finding could be explained by esophageal acid sensitivity oscillating between longer periods of high esophageal acid sensitivity, and shorter periods of low esophageal acid sensitivity. Since NERD subjects have increased esophageal acid exposure, it is possible that this oscillating esophageal acid sensitivity is in some way a result of this increased esophageal acid exposure and will not occur in symptomatic GERD phenotypes with normal esophageal acid exposure. Thus, for the present report I analyzed data from subjects with Reflux Hypersensitivity or Functional Heartburn to compare relationships between esophageal acid exposure and the probability of symptoms with those observed previously in NERD subjects.

Subjects

Patients were identified by interrogating the electronic database (January 2016-August 2019) at the Royal London Hospital GI Physiology Unit that contains impedance-pH recordings from 542 patients with typical symptoms of gastroesophageal reflux. Of these patients, 300 had NERD, 116 had Reflux Hypersensitivity, and 126 had Functional Heartburn.

Using Lyon consensus thresholds for esophageal acid exposure time (AET)[1] I divided 40 subjects with normal esophageal pH (pH <4 for less than 4% of the 24-hour esophageal pH recording) into the Reflux Hypersensitivity group defined as AET <4% plus a positive SI [3] and a positive SAP [4] (20 subjects) or into the Functional Heartburn group defined as AET <4% plus a negative SI and a negative SAP (20 subjects). Reflux Hypersensitivity subjects (7 males; 13 females) ranged in age from 20 to 60 years, and Functional Heartburn subjects (7 males; 13 females) ranged in age from 17 to 68 years. All subjects had a normal upper gastrointestinal endoscopy and no biopsies were taken. Tables 1 and 2 in APPENDIX give traditional values for impedance-pH testing in the Reflux Hypersensitivity and Functional Heartburn subjects selected for analysis.

For this retrospective analysis of clinically indicated tests with no identifiable patient data, the Stanford University Institutional Review Board determined that this research does not involve human subjects as defined in 45 CFR 46.102(f) or 21 CFR 50.3 (g) [5].

Methods

All pH recordings for each subject were processed as described in detail previously[2]. Interval acidity was measured for each pH recording from the beginning of the recording until the time of the 1st symptom, from the time of the 1st symptom until the time of the 2nd symptom and so on until the time of the last symptom. Fixed interval acidity was calculated as interval acidity during the 60-second period that preceded each symptom. Cumulative interval acidity was calculated as the sum of sequential values of interval acidity until the time of the last symptom with each value expressed as a percentage of total acidity [2].

Curve fitting and statistical analyses were performed using GraphPad Prism 9.4.1 software.

Results

The frequency distributions in Figure 1 illustrate that the lower the bin interval, the higher the percentage of values in the bin for both Reflux Hypersensitivity and Functional Heartburn. In agreement with a previous report based on subjects with NERD [2], interval esophageal acid exposure time gave results like those in Figure 1 (not shown). Since each value of interval esophageal acidity is associated with a symptom, the percentage of values in each bin gives the percentage of total symptoms associated with that bin. Thus, Figure 1 illustrates the paradoxical finding that the lower the value of esophageal acid exposure, the higher the probability of a symptom.

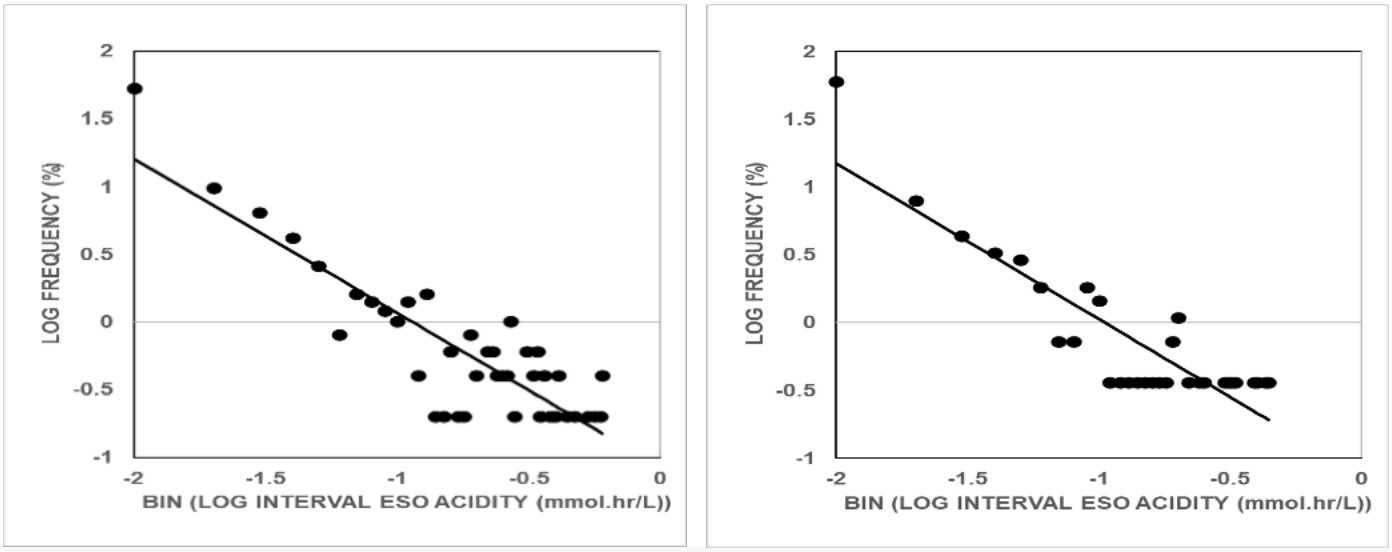

Figure 1. Distribution of values for interval esophageal acidity in Reflux Hypersensitivity (left panel) and in Functional Heartburn (right panel). Each distribution used a bin width of 0.5 and values given on the x-axis are for the lower boundary of the bin. Values are for 499 symptoms from 20 Reflux Hypersensitivity subjects and for 276 symptoms from 20 Functional Heartburn subjects. Every subject reported at least 3 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

The frequency distributions in Figure 2 illustrate that the lower the interval size, the higher the percentage of values in the bin for interval size for both Reflux Hypersensitivity and Functional Heartburn. Taken together, Figures 1 and 2 illustrate that the shorter the interval between symptoms and the lower esophageal acid exposure during the interval, the higher the probability of a symptom.

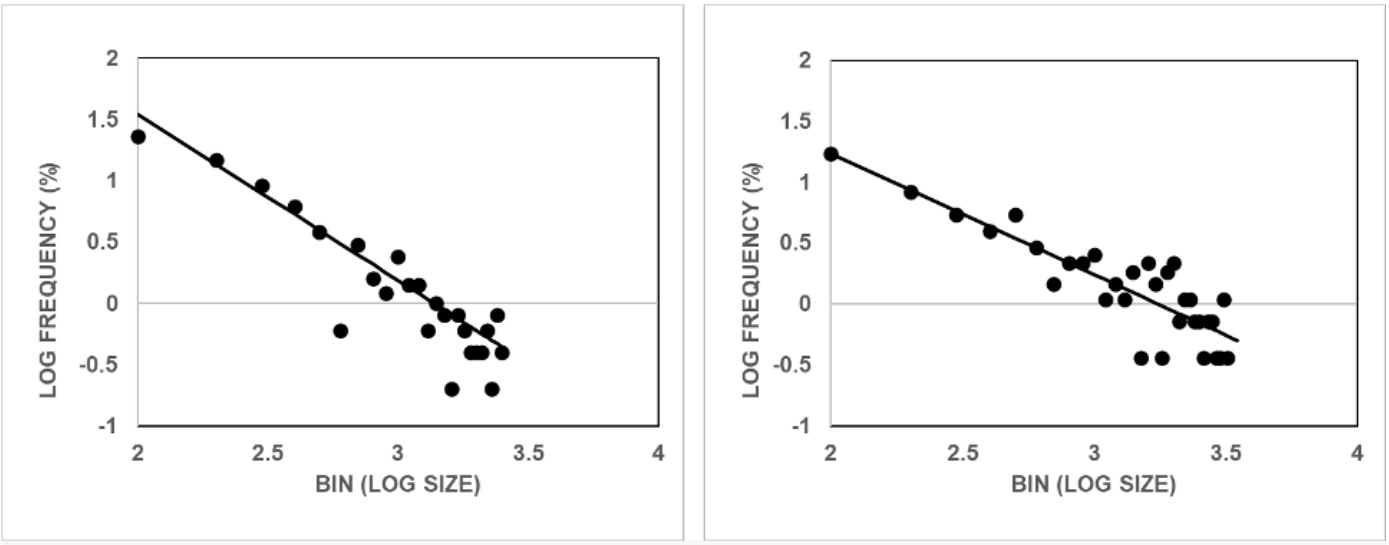

Figure 2. Distribution of values for interval size corresponding to values for interval esophageal acidity in Reflux Hypersensitivity (left panel) and in Functional Heartburn (right panel). Each distribution used a bin width of 0.5 and values given on the x-axis are for the lower boundary of the bin. Values are for 499 symptoms from 20 Reflux Hypersensitivity and for 276 symptoms from 20 Functional Heartburn subjects. Every subject reported at least 3 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

To examine the possibility that values for interval esophageal acidity are determined by the duration of the interval between symptoms, I calculated interval esophageal acidity for a fixed, 60-second interval (15 pH values) before each symptom in Reflux Hypersensitivity and Functional Heartburn subjects.

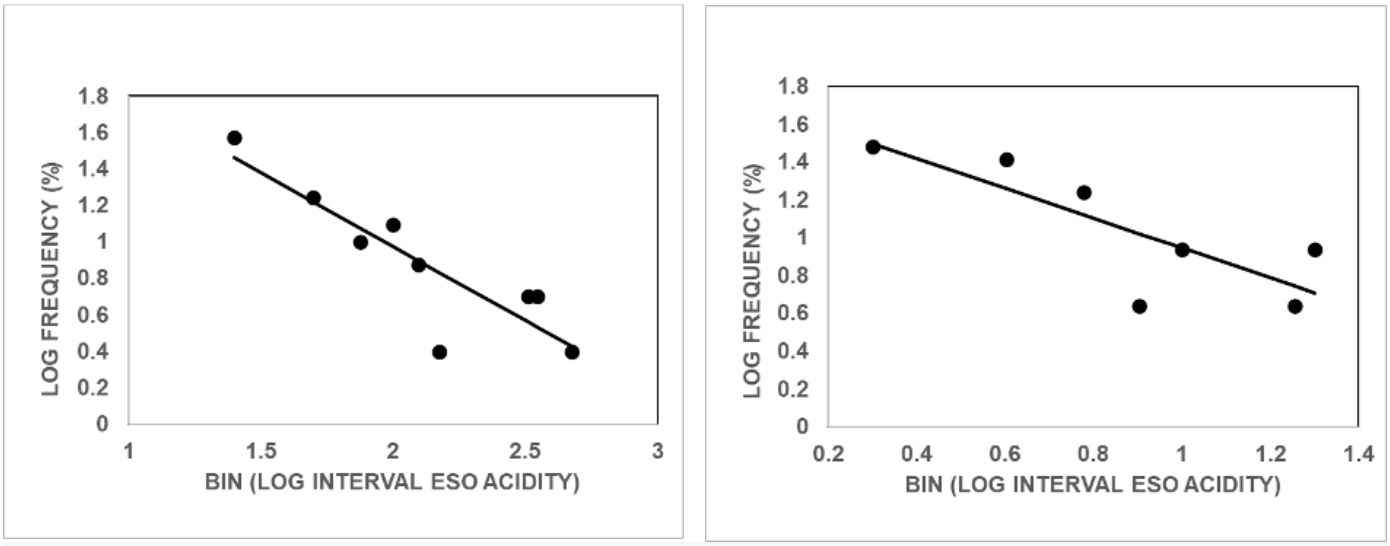

Figure 3. Distribution of values for interval esophageal acidity during a 60-second interval preceding each of 499 symptoms in Reflux Hypersensitivity (left panel) and each of 276 symptoms in Functional Heartburn (right panel). The solid line in each panel is the linear, least-squares fit of the data and was significantly different from zero by an F test: P=0.0017 for Reflux Hypersensitivity and P=0.0281 for Functional Heartburn

Figure 3 illustrates that the distributions of values of fixed interval esophageal acidity in Reflux Hypersensitivity subjects and Functional Heartburn subjects are like those for interval esophageal acidity shown in Figure 1 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.

Previously [2] I showed that plotting cumulative interval esophageal acidity as a function of 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 is a measure of esophageal acid exposure for the symptoms in that series (referred to as a segment), in that the steeper the slope, the higher the esophageal acid exposure.

Figure 4 illustrates that all Reflux Hypersensitivity subjects and all Functional Heartburn subjects except two 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).

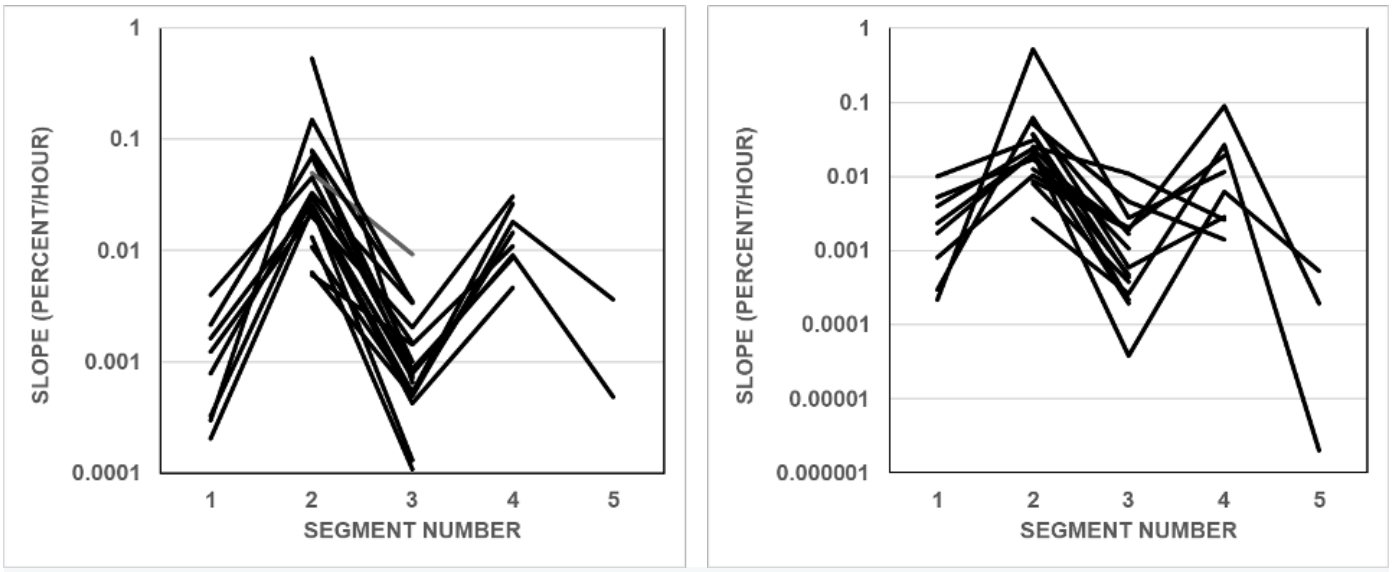

Figure 4. Slope patterns for cumulative interval esophageal acidity from 20 Reflux Hypersensitivity subjects (left panel) and 18 Functional Heartburn subjects (right panel). Slopes were calculated using piecewise linear regression for each segment. Data from two Functional Heartburn subjects are omitted because these subjects had a single slope for the entire time-course. If the pattern for a given subject began with a series of symptoms with a high slope, that subject's data were shifted to begin at the next segment

To examine a possible relationship between esophageal acid sensitivity and the number of sequential symptoms, I plotted the number of symptoms in each segment as a function of the magnitude of the slope of cumulative interval acidity for that segment. Figure 5 shows that for both Reflux Hypersensitivity subjects and Functional Heartburn subjects, the lower the slope and the higher the esophageal acid sensitivity, the higher the number of sequential symptoms.

In Figure 5, the slope of the linear, least-squares line for Reflux Hypersensitivity was not significantly different from that for Functional Heartburn by an F-test (P=0.2759). On the other hand, the Y-intercept of the linear, least-squares line for Reflux Hypersensitivity was significantly higher than that for Functional Heartburn by an F-test (P=0.0007) indicating that for a given value of esophageal acid sensitivity, Reflux Hypersensitivity subjects have significantly more sequential symptoms associated with this sensitivity than do Functional Heartburn subjects.

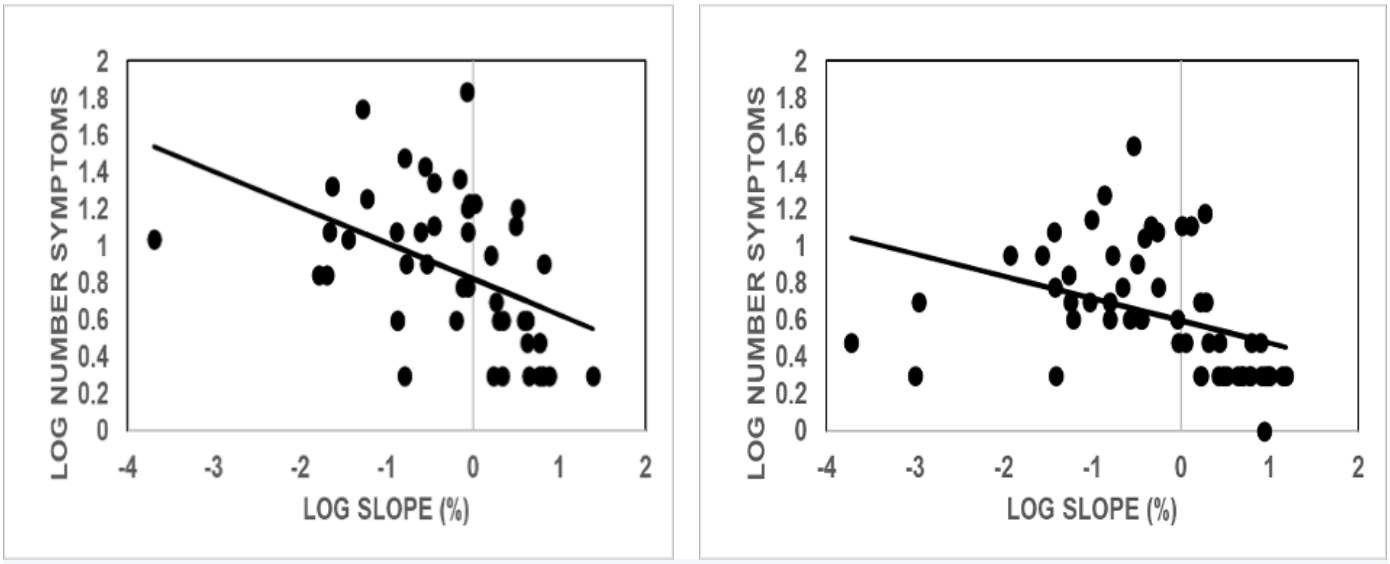

Figure 5. Relationship between the value of the slope for cumulative interval esophageal acidity and the number of symptoms associated with the corresponding slope for Reflux Hypersensitivity (left panel) and Functional Heartburn (right panel). The solid line in each panel is the linear, least-squares fit of the data and was significantly different from zero by an F test: P=0.0014 for Reflux Hypersensitivity and P=0.0032 for Functional Heartburn

The data in Figures 4 and 5 can account for the data in Figure 1 in that the lower the value of interval esophageal acidity the higher the probability of a symptom occurring because more sequential symptoms occur in segments of cumulative esophageal acidity with a low slope and a high esophageal acid sensitivity.

Discussion

The present results show that in both Reflux Hypersensitivity subjects and Functional Heartburn subjects, the lower the value of esophageal acid exposure the higher the probability of a symptom. A previous report found a similar relationship in NERD subjects [2] indicating that this relationship between lower esophageal acid exposure and the higher probability of a symptom is a general property of all three phenotypes of symptomatic GERD. As was the case for NERD subjects [2], calculating cumulative esophageal acidity for sequential symptoms indicated that esophageal acid sensitivity oscillates between periods of high and low esophageal acid sensitivity, and that more symptoms occur during periods with high esophageal acid sensitivity and low esophageal acid exposure than during periods with low esophageal acid sensitivity and high esophageal acid exposure. Thus, oscillation of esophageal acid sensitivity between periods of low sensitivity and high sensitivity is a general property of all three phenotypes of symptomatic GERD.

Oscillations are ubiquitous in biological systems [6]; however, the general principles that underlie the cellular organization that supports these oscillations are not clearly established [6][7]. What is clear, however, is that the complex behavior related to oscillations results from the architecture of the biological system rather than the properties of the individual components [7]. Many studies relate to the potential physiological roles of oscillating systems [6][7] and in some instances how disrupting oscillations is accompanied by pathology [8][9]. In terms of the present findings that in symptomatic GERD phenotypes, esophageal acid sensitivity oscillates between a state of high sensitivity and one of low sensitivity, it is not clear that this

oscillation involves an alteration of an existing oscillating system. Instead, this may involve the *de novo* emergence of an oscillating system similar to what has been proposed for tinnitus, an auditory sensation that appears without the presence of an external stimulus. Some patients with tinnitus have abnormal oscillatory brain activity and the tinnitus disappears after modifying the oscillatory brain activity by biofeedback training [10].

GERD subjects have been found to have increased sensitivity to both chemical and mechanical stimuli[11][12][13][14][15][16]. It may be that the sensitivity of GERD subjects to chemical or mechanical stimuli represents a setpoint around which esophageal acid sensitivity oscillates. Evidence for this in the present analyses is that although both Reflux Hypersensitivity subjects and Functional Heartburn subjects show oscillation of esophageal acid sensitivity, for a given value of esophageal acid sensitivity, Reflux Hypersensitivity subjects have significantly more sequential symptoms than Functional Heartburn subjects.

In a previous report on the relationship between symptoms and esophageal acidity in NERD subjects[2], I considered several possible alternative explanations besides oscillating esophageal acid sensitivity that might account for the present results. One possible explanation was that the relationship between esophageal acid exposure and symptoms was determined by the duration of the interval between symptoms with short intervals resulting in low esophageal acid exposure and long intervals resulting in high esophageal acid exposure. Measuring the relationship between the probability of a symptom and interval esophageal acidity during a fixed 60-second period before each symptom showed that interval esophageal acidity but not interval time is the important determinant of the probability of a symptom. I was unable to identify alternatives such as bile, pepsin, or gas in reflux material that might occur with sufficient frequency to account for the present results [2]. A possibility that I did not consider previously is that there might be an inverse relationship between interval esophageal acidity and the proximal extent of reflux liquid such that the lower the value of interval acidity the greater the proximal esophageal liquid exposure. The result could be that with low values of interval esophageal acidity, the total esophageal acid exposure is approximately the same as with high values of interval acidity with limited proximal esophageal liquid exposure.

In my previous report[2], I also mentioned that the neurochemical mediators of symptoms produced by esophageal acid exposure have not been clearly established; however, the acid-sensitive, transient receptor potential cation channel (TRPV1) that is associated with the capsaicin or vanilloid receptor [17][18] as well as acid-sensing ion channels (ASICs) are members of the voltage-insensitive, amiloride-sensitive degenerin family of cation channels that can be activated by protons [18][19] are possible candidates.

It is conceivable, for example, that with high esophageal acid exposure, nociceptive neurons in esophageal mucosa become sensitized to luminal acid that elicits symptoms. 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 and the cycle repeats itself. It is also possible that different types of neuronal mechanisms are involved in different GERD phenotypes. For example, different neuronal mechanisms might account for a given value of esophageal acid sensitivity in Reflux Hypersensitivity subjects having significantly more sequential symptoms associated with this sensitivity compared to Functional Heartburn subjects.

There are some limitations to the present analyses that were also present in my previous analyses of data from NERD subjects [2]. A major limitation is the lack of a causal explanation for the oscillating esophageal acid sensitivity in all three phenotypes of symptomatic GERD subjects. I also have no explanation for the occurrence of GERD symptoms in Reflux

Hypersensitivity subjects or Functional Heartburn subjects that are associated with normal esophageal acid exposure. There are other limitations that may have influenced important relationships between esophageal acidity and symptoms such as impedance-pH recordings beginning at different times during the day and meals that were not standardized with respect to time of the day or composition. The recumbent periods were also not standardized.

Tables

Supplemental Table 1. Standard Values From Impedance and PH Monitoring for Reflux Hypersensitivity Subjects in the Present Study.

	S2	S4	S9	S10	S11	S13	S15	S16	S22	S24	S25	S28	S30	S33	S35	S37	S40	S47	S51	S56
DURATION (HR:MIN)																				
Upright	16:43	11:27	10:57	9:47	8:26	12:27	16:29	10:47	11:55	11:32	11:42	8:20	14:36	11:47	12:26	15:13	15:06	10:16	11:04	9:26
Recumbent	7:06	9:37	10:59	11:28	10:45	9:29	8:13	8:57	8:20	7:40	8:59	14:09	8.:18	10:00	8:53	5:10	7:41	9:27	9:38	11:06
Total	23:49	21:05	21:56	21:14	19:10	21:56	24:42	19:44	20:15	19:12	20:41	22:30	22:54	21:47	21:20	20:23	22:46	19:43	20:42	20:32
ACID EXPOSURE (%)																				
Upright	2.9	4.9	1.3	1.3	1.5	3.8	3.5	2.7	3.6	3.8	3.7	0.8	4.8	13	3.3	0.2	2.8	4.3	1.0	3.8
Recumbent	0.2	0.0	0.2	0.6	0.3	0.2	0.0	0.7	0.4	0.0	0.0	0.8	0.0	0.2	0.0	0.0	0.6	0.4	3.8	0.1
Total	2.1	2.6	0.8	0.9	0.8	2.2	2.3	1.8	2.3	2.3	2.1	0.8	3.1	0.8	1.9	0.2	2.1	2.5	2.3	1.8
REFLUX EPISODES (#)																				
Acid	18	24	39	22	14	80	43	45	50	7	29	26	13	37	29	8	47	29	33	11
Non-Acid	7	9	38	17	50	30	26	28	31	6	16	57	8	12	11	48	17	3	31	27
Total	25	33	77	39	64	110	69	73	81	13	45	83	21	49	40	56	64	32	64	38
SYMPTOM INDEX (%)																				
Hrtburn	67	67	94	67	40	91	77		86	11	87	60	60	89	80	50	71	73	62	33
Regurg			100	30	50	65	93	75		67	80	0	0			100	100	88	86	83
Chest Pain					33							0	0	30						
SYMPTOM ASSN PROB (%)																				
Hrtburn	100	100	100	100	99	100	100		100	0	100	99	99	100	100	100	98	100	100	100
Regurg			100	98	99	97	100	100		100	100	0	0			100	100	100	100	100
Chest Pain					54							0	0	100						

Numbers at top of each column are subject numbers. "Hrtburn" is abbreviation for heartburn and "Regurg" is abbreviation for regurgitation.

Supplemental Table 2. Standard Values From Impedance and PH Monitoring for Functional Heartburn Subjects in the Present Study.

	S1	S3	S5	S14	S18	S21	S23	S26	S27	S31	S32	S34	S38	S41	S42	S43	S45	S48	S49	S52
DURATION (HR:MIN)																				
Upright	4:25	7:18	11:43	7:05	13:54	18:37	7:58	11:55	12:03	13:49	16:30	10:27	17:11	10:12	11:01	15:53	10:49	11:01	12:13	11:25
Recumbent	13:13	12:40	8:40	13:13	7:17	0:00	12:37	8:42	10:01	6:47	6:26	10.01	8:58	11:53	10:38	4:12	7:03	10:24	7:59	8:26
Total	17:38	19:57	20:23	20:17	21:11	18:37	20:36	20:37	22:04	20:36	22:56	20:28	26:09	21:39	21:39	20:05	17:52	21:25	20:08	17:51
ACID EXPOSURE (%)																				
Upright	4.3	0.7	0.4	0.9	2.7	0.0	0.6	0.4	0.1	1.4	0.1	1.6	1.6	1.3	4.7	0.3	0.0	2.3	0.6	5.4
Recumbent	1.3	4.3	0.0	0.0	2.0	0.0	0.0	0.0	0.1	0.0	0.0	0.7	0.0	1.1	0.1	0.0	0.0	0.3	0.0	0.0
Total	2.0	3.0	0.2	0.3	2.4	0.0	0.2	0.2	0.1	1.1	0.1	1.1	1.1	1.2	2.4	0.2	0.0	1.3	0.4	3.1
REFLUX EPISODES (#)																				
Acid	14	13	16	6	38	2	12	4	2	10	4	16	14	14	35	9	0	25	9	5
Non-Acid	5	9	68	8	32	13	14	0	81	1	12	8	17	11	7	30	33	17	6	5
Total	19	22	84	14	70	15	26	4	83	11	16	24	31	25	42	39	33	42	15	10
SYMPTOM INDEX (%)																				
Hrtburn	38		20	0	86	0		0	22	21	0			13	33	9	17	43	0	0
Regurg				33		0										32		44	0	
Chest Pain		33					0	17		0		0	38	14		20				
SYMPTOM ASSN PROB (%)																				
Hrtburn	95		0	0	100	0		0	32	86	0			75	89	0	0	64	0	0
Regurg				93		0										97		90	0	
Chest Pain		71					0	91		0		0	73	78		33				

Numbers at top of each column are subject numbers. "Hrtburn" is abbreviation for heartburn and "Regurg" is abbreviation for regurgitation.

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Conflict of Interest Statement: Dr. Gardner is President of Science for Organizations (www.scifororg.com), a company that provides consulting services to biotechnology and pharmaceutical companies. These activities have no conflict of interest with

the analyses in the present paper.

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