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Mechanisms of Aerodigestive Symptoms in Infants with Varying Acid Reflux Index determined during Esophageal Manometry

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Abstract

Objective: To test whether symptom generation in infants is related to GERD severity determined by Acid Reflux Index (ARI), stimulus media, and stimulus volume during provocative esophageal manometry.

Study design: Symptomatic neonates (N=74) that were born at 28.9 (range: 23.4–39.4) weeks gestation were studied at 41.0 (range: 34.6–48.0) weeks post menstrual age using 24-hour pH-Impedance methods to determine ARI severity, followed by provocative esophageal manometry with graded mid-esophageal infusions (0.1 to 5.0 mL) of air, water, and apple juice. Peristaltic reflexes and symptom characteristics were compared for ARI severity using linear mixed models and generalized estimating equations.

Results: Effects of 2635 esophageal stimuli on reflexes and symptoms were analyzed. Peristaltic reflexes were present in 1880 (71%) infusions and symptoms (physical, cardiorespiratory, sensory) with 439 (17%) infusions. Symptom prevalence did not differ between ARI severities (ARI <3: 18%, ARI 3–7: 17%, ARI >7: 16%, $P = 1.0$). Symptom and peristaltic responses increased with incremental stimulus volumes (all media, $p < 0.001$).

Conclusions: Symptoms and peristaltic reflexes are manifestations of the recruitment of several neuro-sensory and neuro-motor pathways evoked upon mid-esophageal infusions. ARI severity grade plays no role in symptom generation, indicating that a GERD diagnosis or severity should not be assessed based on symptoms alone. An increase in symptom occurrence was noted with increasing stimulus volumes, thus providing more activation of receptors, afferents and efferents in evoking peristaltic clearance reflexes.

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Non-verbal neonates have few ways to express pain or discomfort other than crying and irritable behavior; thus, parents and caretakers must interpret symptoms and decide on further testing or empiric treatment. Troublesome problems such as excessive crying, irritability, and failure to thrive can be a consideration for gastroesophageal reflux (GER) disease (GERD).^{1, 2} Reflux-type of symptoms are prevalent in neonates with an estimated GERD diagnosis of 10.3% among premature NICU infants, thus extending their length of stay by 30 days and imposing an additional economic burden of \$70,000 per patient, per hospital stay.^{3, 4} However, making a true diagnosis based on non-specific symptoms alone can be challenging.^{2, 5} The exact definition of GERD across the pediatric age spectrum still remains an enigma. The working definition as “the passage of gastric contents into the esophagus causing troublesome symptoms and/or complications” has many caveats due to its symptom-based nature, and is considered controversial.^{2, 6, 7} Parental knowledge, symptom tolerance and caretaker perception combined with ambiguous definitions can lead to an erroneous diagnosis of GERD, inconsistent or inappropriate treatments, and/or persistent overuse of medical and surgical interventions.^{1-3, 8, 9}

Evaluating GERD symptoms in infants is difficult given the lack of clear symptom descriptions. Additionally, GER events are highly variable in frequency and composition, leading to a wide range in severity and symptoms.^{4, 9-13} GERD severity can be objectively quantified using Acid Reflux Index (ARI). Per NASPGHAN 2009 criteria, an ARI <3% is considered normal, 3–7% is indeterminate, and >7% is an indicator of severe acid-GERD.^{1, 2, 10} Though the 2018 NASPGHAN guidelines address some concerns related to pH-metry, the criteria for diagnosis has not been altered or updated in the new version, and is still ambiguous in infants.² Other factors that may affect the presence and type of symptoms include physical content of the refluxate (liquid, gas, mixed), volume of the refluxate, vigilance states (awake or sleep), maturation, and/or underlying illness.¹⁴⁻¹⁷ Due to the spontaneous nature of both symptoms and reflux events, it can be challenging to capture these events in real time and determine their true associations. Provocative esophageal manometry can be used to determine the impact of mid-esophageal stimulus on peristaltic reflexes and symptom generation mechanisms in neonates with GERD.¹⁸⁻²⁰ Infusions of air, water, and apple juice are used to stimulate mechano-receptors, osmo-receptors, and chemo-receptors, respectively.¹⁸⁻²¹

This study was undertaken to evaluate the mechanistic causes of GERD-type symptoms in NICU infants determined during provocative pharyngo-esophageal manometry with video recordings. Our objective was to test the hypothesis that symptoms are related to ARI severity, stimulus media, and stimulus volume.

MATERIALS AND METHODS

Study participants presenting with GERD-like symptoms were evaluated by the Innovative Neonatal and Infant Feeding Disorders Research Program in the Neonatal ICU at Nationwide Children’s Hospital, Columbus Ohio, USA. Infants were included if they were between 34–60 weeks’ postmenstrual age (PMA) and enterally fed at the time of evaluation. Infants received 7–8 feeds over 24-hours per the subject’s feeding cues.²² Those with known genetic, metabolic, syndromic or neurological (congenital or Intraventricular Hemorrhage

Grade III) disease, gastro-intestinal malformations, or surgical conditions were excluded. Infants receiving acid suppressive treatment prior to or at the time of evaluation were also excluded. Informed parental consent was obtained prior to the study. Study protocol was approved by the Institutional Review Board at The Research Institute of Nationwide Children's Hospital, and Health Insurance Portability and Accountability Act guidelines were followed.

pH-Impedance Methods and Protocol

Subjects underwent 24-hour pH-impedance testing as previously published to objectively determine ARI and acid-GERD severity.^{4, 10, 11} Studies were performed with a single-use antimony pH-impedance probe (Greenfield MMS-Z1-I or ZandorPH MMS-6Z1P-I01, Laborie Medical Technologies, Mississauga, ON, Canada) connected to a portable recording device (Ohmega, Laborie Medical Technologies, Mississauga, ON, Canada). Both probe designs had seven impedance electrodes placed 1.5 cm apart to create 6 impedance channels, and one pH sensor located in the most distal channel. ARI was defined as the percent of time that acid was present in the esophagus, indicated by $\text{pH} < 4$.^{4, 10, 11} ARI severity was determined using the working NASPGHAN criteria as normal ($\text{ARI} < 3\%$), indeterminate ($\text{ARI} 3\text{--}7\%$), or abnormal ($\text{ARI} > 7\%$).^{1, 10} Meal times were excluded from ARI calculation. Bolus reflux events were determined as acidic ($\text{pH} < 4$) or non-acid ($\text{pH} \geq 4$).⁴ Symptoms were recorded by pressing event marker buttons on the portable recording device by a trained patient care assistant who was present at the bed side for the duration of the pH-impedance study.^{10, 23}

Video-Manometry Methods and Protocol

Concurrent pharyngo-esophageal manometry and mid-esophageal provocation testing was performed to simulate reflux events as previously described and validated.^{15, 18–21, 24–28} Briefly, a silicone catheter (Dentsleeve International, Mui Scientific, Mississauga, Ontario, Canada) with five ports (pharynx, proximal-, middle-, distal-esophagus, and stomach), two sleeves (upper and lower esophageal sphincters), and a mid-esophageal infusion port was connected to a water-perfused manometry system (Solar-2, Laborie Medical Technologies, Mississauga, ON, Canada). Infants with a nasal feeding tube at the time of manometric evaluation had their feeding tubes removed prior to catheter placement so as not to obstruct both nares. The catheter was zeroed prior to the study at the mid-axillary line of the patient, who was lying in supine position. Using the pull-through technique, the catheter was inserted nasally by a physician and positioned such that the two sleeves were properly in line with the upper esophageal sphincter (UES) and lower esophageal sphincter (LES).^{19, 20, 24, 27, 28}

Subjects were given time to adapt to catheter placement before infusion protocol began. Abrupt graded mid-esophageal stimuli (in triplicate) of air (0.1, 0.5, 1.0, 2.0, 5.0 mL), water (0.1, 0.5, 1.0, 2.0 mL), and apple juice (0.1, 0.5, 1.0, 2.0 mL) were administered to test mechano-, osmo-, and chemo-sensitive receptors, respectively. Infusions were given in the same order to each patient, starting with air from smallest to largest dose, followed by water from smallest to largest dose, and lastly apple juice from smallest to largest dose. To ensure

patient safety, studies were performed at the crib-side while vital signs were continuously monitored by a registered nurse and physician.

Additionally, a video camera (Sony Handycam DCR-SX45, Sony, Minato, Tokyo, Japan) was mounted to the crib-side facing the patient, and video clips were recorded concurrently with esophageal manometry during provocations when feasible.

Symptom Recognition Methods

A registered nurse, blinded to stimuli (timing, infusion volume and media) identified symptom onset and type as they occurred. The symptoms were then documented by placing event markers on the motility study in real time. The following symptoms were defined during the manometry studies: *Movement/Arching/Irritability*: Infant arches the back while extending the head and neck; *Cough*: A forceful exhalation with an audible sound; *Gag*: A choke or retch when the infant thrusts their tongue forward; *Sneeze*: A forceful exhalation with a nasal clearance and audible sound; *Stridor*: Noisy breathing; *Gasp/Sigh*: A sharp inhalation (gasp), or a prolonged exhalation (sigh); *Apnea*: A cessation of rhythmic breathing with varying magnitude; *Bradycardia*: A decrease in heart rate below 80 beats per minute for longer than 20 seconds; *Desaturation*: A decrease in oxygen saturation below 80% for longer than 20 seconds; *Throat Clearing/Flushing*: An attempt to clear the throat associated with congested (red flush) face; *Startle*: Involuntary somatic response to sudden stimulus manifested as extension of arms, legs, and/or back arching; *Grimace*: A furrow in the brow; *Grunting*: A low, short guttural expiratory sound; *Mouthing*: Infant moves their mouth as in swallowing; *Yawning*: Deep inhalation through the mouth followed by short exhalation.

Data Analyses

Following the 24-hour pH-impedance test, the Fisher exact test was calculated using MMS analysis software (v. 9.5, Laborie Medical Technologies, Mississauga, ON, Canada) to determine symptom associated probabilities (SAP), symptom index (SI), and symptom sensitivity index (SSI) for pH (acid) and Impedance (bolus) positive events with each symptom.^{4, 10, 11, 23} Only symptoms that occurred ≥ 5 times were included, as these are considered troublesome.²⁹ SI $\geq 50\%$, SSI $\geq 10\%$, and SAP $\geq 95\%$ were considered abnormal.

Responses to mid-esophageal infusions were analyzed using MMS analysis software and were classified as 1 of the 4 possible scenarios: peristaltic response(s) only, determined by presence of Esophageal Deglutition Response (EDR) or Secondary Peristalsis (SP), symptom(s) only, combination of peristaltic response(s) and symptom(s), or no response. Both peristaltic and symptom responses must occur within 12 seconds of the infusion onset.^{18, 20, 21} *Peristaltic response prevalence*, %, was defined as the percent of infusions that resulted in the presence of EDR or SP, with or without a symptom, as previously published.^{18–21, 27} *Symptom prevalence*, %, was determined as the percent of infusions that resulted in at least one symptom, with or without a peristaltic response. Symptoms were classified into the following categories: a) physical: crying, irritability, body movement, postural adjustment, or back and neck arching; b) cardiorespiratory: cough, gag, sneeze, stridor, gasp, sigh, apnea, bradycardia, or desaturation; c) sensory: throat clearing, flushing, startle,

grimace, grunting, mouthing, or yawning.^{4, 10, 11} Examples of esophageal motility tracings and representative symptoms are shown (Figure 1).

Statistical Analysis

Statistical analysis was performed using SAS (v9.3, SAS Institute, Cary, North Carolina). Parametric and non-parametric tests were used to compare demographic characteristics between ARI severity groups. ANOVA and t-tests were used to compare pH-impedance metrics (SI, SSI, SAP) for acid and non-acid GER events. Generalized estimating equations (GEE) were used to compare symptom and peristaltic response prevalence by: (a) ARI severity (<3%, 3–7%, and >7%) (b) stimulus media (air, water, and apple juice) and (c) stimulus volume (0.1, 0.5, 1.0, 2.0 and 5.0mL for air only). Chi-square tests were used to assess concurrence in symptom detection by the diagnostic approaches (pH, impedance, and manometry).²³ Data are presented as mean $\pm$ SEM, median (IQR), or %. A p value <0.05 was considered significant.

RESULTS

Participant characteristics

A total of 74 neonates (43 male) born at 28.9 (23.4–39.4) weeks gestation were evaluated at a chronological age of 11.6 (1.0–21.0) weeks and a PMA of 41.0 (34.6–48.0) weeks. Based on 24-hour pH-impedance testing, 12 (16%) infants had a normal ARI, 21 (28%) had an indeterminate ARI, and 41 (56%) had an abnormal ARI. The duration between pH-impedance and manometry evaluations was 1 (1–2) days. Clinical characteristics grouped by ARI severity as determined by pH-impedance testing are shown (Table. 1).

pH-Impedance Results

Bolus reflux events were determined as acid (pH<4) or non-acid (pH $\geq$ 4). There were 1311 acid events, and 2867 non-acid events that occurred. A total of 8950 symptoms were recorded during the pH-impedance studies (5113 physical symptoms, 1879 cardiorespiratory symptoms, and 1958 sensory symptoms), with an average of 121 (24–339) symptoms per patient. All 74 infants had normal SI to acid, non-acid, or total reflux. On the other hand, 61 infants had an abnormal SSI for acid reflux, and 69 had an abnormal SSI to non-acid and total reflux. Alternatively, 20 subjects had an abnormal SAP to acid reflux, and 37 had an abnormal SAP to both non-acid and total reflux. SI (acid: 5.3 ± 0.6 , non-acid: 11.5 ± 0.8 ; $p < 0.01$) and SAP (acid: 57.8 ± 4.8 , nonacid: 76.4 ± 4.2 ; $p = 0.003$) were significantly different between acid and non-acid reflux events, and SSI was not (acid: 28.3 ± 2.3 , non-acid: 32.5 ± 1.8 ; $p = 0.09$).

Effect of esophageal stimulation

A total of 2870 infusions were administered during the manometry studies, of which 2635 (92%) had analyzable responses: 1481 (56%) resulted in peristaltic response(s) only, 40 (2%) resulted in symptom(s) only, 399 (15%) resulted in both peristaltic response(s) and symptom(s), and the remaining 715 (27%) infusions resulted in no response. From the 439 infusions resulting in symptoms, 287 (65%) resulted in a single symptom, and 152 (35%) resulted in more than one symptom for a total of 635 observed symptoms; 348 (79%)

infusions resulted in physical symptom(s), 132 (30%) resulted in cardiorespiratory symptom(s), and 130 (30%) resulted in sensory symptom(s). When both symptoms and peristaltic responses were present (n=399), the peristaltic response occurred prior to the symptom in 355 infusions (89%).

Effect of GERD Severity Determined by ARI

Symptom prevalence stratified by ARI was 69 (18%) for the normal ARI group, 130 (17%) for the indeterminate ARI group, and 240 (16%) for the abnormal ARI group ($p=1.0$). ARI severity did not affect motility characteristics (response vs no response for $ARI<3$: 73 vs 27; $ARI\ 3-7$: 73 vs 27; $ARI>7$: 73 vs 27, $p=0.8$). Presence of physical symptoms ($ARI<3$: 80%; $ARI\ 3-7$: 77%; $ARI>7$: 81%; $p=0.4$), cardiorespiratory symptoms ($ARI<3$: 27%; $ARI\ 3-7$: 40%; $ARI>7$: 26%; $p=0.4$), or sensory symptoms ($ARI<3$: 26%; $ARI\ 3-7$: 22%; $ARI>7$: 35%; $p=0.3$) were also not significantly different by ARI groups.

Effect of mid-esophageal stimulus volume and media

Responses to 989 air, 814 water, and 832 apple juice infusions were analyzed. Motility characteristics did not differ by media type (response vs no response, air: 79 vs 21, water: 71 vs 29, 68 vs 32, $p=0.4$). As the infusion volume increases, presence of both symptoms ($p<0.001$) and peristaltic responses ($p<0.0001$) increase for air, water, and apple juice (Figure 3, A and B). The prevalence of symptoms for water and apple juice infusions is higher when compared with air at 2.0 mL only ($p=0.005$ for water, $p=0.03$ for apple juice). The presence of peristaltic responses is decreased with apple juice infusions vs air infusions at 0.1 mL only ($p=0.001$) (Figure 3, B).

The types of symptoms that occurred are also impacted by both stimulus volume and media. Physical symptoms increased from 71% at 0.1 mL to 84% at 5.0 mL for all media ($p<0.0001$) and sensory symptoms increased from 30% at 0.1 mL to 35% at 5.0 mL for all media ($p=0.03$). The occurrence of cardiorespiratory symptoms differs by media (air: 21%, water: 41%, apple juice: 36%, $p=0.02$ overall, $p<0.05$ for water and apple juice vs air); other symptom group were not affected by media. Additionally, the odds ratio of a cardiorespiratory symptom is 2.37 (95% CI, 1.35–4.18) with water and 2.27 (95% CI, 1.28–4.02) with apple juice infusions, both compared with air ($p<0.05$).

Symptom detection

Symptoms were identified in 73 (99%) of observed infants by at least one of the diagnostic methods. SAP was selected as a measure of symptom association in the Ph-impedance tests.²³ For symptom types, agreement of symptoms detected by manometry and impedance was 33%, and for manometry and pH was 26%, with no significant difference in the overlap by group ($p=0.5$). Figure 2 indicates that in 17 infants (23%), there is an overlap in symptom detection across all three diagnostic methods (manometry, impedance, and pH-metry).³⁰

DISCUSSION

The true definition of GERD in the pediatric age-spectrum and the pathophysiological mechanistic basis for symptoms is not known.^{1, 2} However, the prevalence of empiric acid

suppressive therapies or feeding modification strategies remain high, despite the presence of short-term and long-term consequences.^{3, 8} In this study, we found that provocative stimulus volume is the strongest determinant of symptom prevalence regardless of ARI severity or the composition of the stimulus, which likely activates supra-esophageal and extra-esophageal reflexes. Cardiorespiratory symptoms are more likely to occur with both pH-neutral (water) infusions and acidic (apple juice) than air, and symptoms are indicators of esophageal dysmotility and maladaptive aerodigestive protective mechanisms. In this study we characterized the connectivity-links between direct esophageal provocation induced peristaltic reflexes and the multi-systemic symptom reflexes.

Our study is unique in that we carefully classified subjects based on GERD severity as determined by ARI criteria, per most recent working definitions, and further examined using provocative manometry methods. Because GER events are not predictable and generally occur at a lower frequency (2–5/hr)^{10, 11}, we simulated reflux by stimulating the mid-esophagus with known media and volumes during esophageal quiescence using provocative manometry techniques. We also note similarities with symptoms and peristaltic reflex response trends between the media (Figure 3, A and B); this suggests that heightened awareness or desensitization as a result of our current investigation protocol is not a concern. In this way, we defined the neurosensory and neuromotor mechanisms involved with esophageal reflexes facilitating clearance, in addition to characterizing the origin of symptoms as they occurred in real time. Additionally, we compared symptom detection of 3 diagnostic methods: manometry, impedance, and pH-metry. To our knowledge, this is the first study that has systematically investigated the mechanisms of purported GERD-like troublesome symptoms, regardless of the age-spectrum, and explained the clinical reasoning for the basis of symptoms.

In our study, we defined acid GER events as those with pH<4.0, and non-acid reflux with pH ≥ 4.0. To assess symptom association of both acid and non-acid events, we used accepted metrics of SI, SSI and SAP. Across all three metrics, symptom association was higher with non-acid events compared with acid events; this aligns with manometry findings that symptoms are not strongly associated with acid-reflux. SI, signifying the attribution of symptoms with GER event as a proportion of total symptoms, was significantly more with non-acid reflux (vs. acid events). Similar trends were seen with SAP for non-acid reflux as well, supporting the plausibility of GER in contributing to the symptoms. In contrast, SSI, i.e., the number of symptoms due to GER as a proportion of total GER events was similar between acid and non-acid events, suggesting that the clearance mechanisms may be operational to minimize generation of symptoms with either chemical types of reflux. The non-acid nature of gastric contents is generally seen after feeds, and it is likely that the greater refluxed volumes may be contributory to the symptom sensitivity. However, there are no methods to ascertain the volume of actual refluxed material. Hence, we tested using volume escalation protocol, to determine if known volumes increased the recruitment of reflexes and symptoms.

Although there is increasing emphasis on not using acid-suppressive measures in convalescing premature infants^{1, 2, 31}, there is little evidence to clarify why the troublesome symptoms occur. The pathophysiology of these troublesome symptoms remain to be

completely understood in the settings of infants who are at-risk of chronic lung disease and neuropathology. Such cluster of symptoms/signs interpreted as ‘troublesome symptoms of GERD’ are likely to be cumulative mechanisms of aerodigestive vigilance, clearance and protection.^{18, 21, 25, 26, 32} This clinical reasoning stems from the proof of concept (Figure 3) that increasing stimulus volume likely activates esophageal, supra-esophageal and extra-esophageal reflexes, and therefore the occurrence of symptoms. Further studies are needed to clarify the pathophysiology in the context of chronic lung disease or neuropathology, both of which are uniquely common in preterm-born infants.

The variety of symptoms and symptom categories also suggests recruitment of multiple neural pathways, including respiratory regulation or autonomic systems.^{33–37} For example, changes in cardiac rhythm are suggestive of linking esophageal stimulus with influences of autonomic cardiac rhythms. Changes in respiratory rhythm may be a normal respiratory adaptation as it happens during safe swallowing, in that, deglutition apnea results or respiratory rhythm slows or changes in air flow in favor of expiratory flow occurs.^{15, 25, 26, 38, 39} In some situations, cough, gasp (prolonged inhalation) or sigh (active exhalation) ensue; these signs may also be defensive, in that, they facilitate maintenance of adequate lung volume before swallowing, increase airway vigilance, enhance airway clearance, increase pharyngeal tone, and facilitate swallowing. All of these aerodigestive mechanisms and patterns, when coupled with terminal peristalsis and restoration of respiratory normalcy, may be normal ways of adaptation. However, these signs, if associated with other systemic signs, can also be an exaggerated airway-sensory-pain response suggesting recruitment of more neural pathways and its effects on different muscular (somatic and esophageal) functions such as may happen during persistent cough.^{16, 24–26, 32}

We noted that provocative stimulus volume is the strongest determinant of symptom prevalence as well as peristaltic reflex frequency-recruitment, irrespective of ARI severity or the composition of the stimulus (Figure 3, A and B). This finding supports that the mechano-, osmo- or chemo- sensitivity (determined using air insufflation, water infusion and apple juice infusion, respectively) of the esophageal mucosa or esophageal muscles is increasingly activated with stimulus volume increments, regardless of the ARI severity categories. There was no effect of ARI on symptom prevalence or the odds of types of specific symptoms. Instead, we noted that physical symptoms are more seen with pH-neutral (water) and mechanosensitive (air) stimuli, although not statistically significant. Cardiorespiratory symptoms have higher odds of occurring with liquids compared with air. Further studies are needed to understand the pathophysiological basis for aerodigestive symptoms in at-risk infants such as those with bronchopulmonary dysplasia and or neuropathology.

The findings of this study challenge the rationale for instituting anti-GERD therapies among neonates either based on ‘symptoms alone’ or ‘the existing acid-reflux indices or pH-impedance metrics’. Perceived troublesome symptoms can be the sign of constellation-patterns of multiple reflexes that may indeed be protective and facilitate aerodigestive vigilance and clearance. These may be normal reflex responses resulting from multi-neural systemic connectivity. Further testing is needed to identify which symptoms or combination of symptoms are truly correlated with acid-GERD and should indeed be considered

‘troublesome’. It is well known that bedside nurses and parents are often the first responders, and are the biggest drivers of reflux-type of symptoms; as a result, symptom-based management approaches are therefore widely prevalent. Providing bio-feedback to the bedside providers and parents can be helpful in ensuring when and whether certain symptoms and motility patterns are associated with reflux or not.

Despite our findings, there are some limitations to consider. The definition of GERD and GERD-like symptoms in this critical NICU population remain controversial, with no gold standard diagnostic methods. Given these shortcomings, we synthesized information from clinical practice, NASPGHAN guidelines, and scientific literature to determine ARI criteria as a widely accepted practice for diagnosing acid exposure severity. The study results are limited to infants seen within the NICU setting, and cannot be generalized to all infants. Comparing esophageal manometry to pH-impedance data comes with the limitations of three different techniques answering different questions separately; however, the strength lies in the scientific corroboration and interpretation. Further studies are needed while incorporating the pH-impedance data and examining specific reflux types (gas, liquid, mixed) and specific symptoms with larger samples. Finally, we are limited by video storage space and can currently only record video clips during infusions. Continuous video recording is an option in future studies, so as to understand the basis of infusion-induced symptoms to those that occur spontaneously.

In conclusion, we found that the provocative stimulus volume is the strongest determinant of symptom prevalence regardless of ARI severity or the composition of the stimulus, and GERD severity plays no role in the generation of symptoms. Symptoms resulting from increasing stimulus volume exposure likely activate supra-esophageal and extra-esophageal reflexes. Symptoms are indicators of esophageal dysmotility and maladaptive aerodigestive protective mechanisms.

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ABBREVIATIONS:

ARI	Acid Reflux Index
EDR	Esophageal Deglutition Response
GER	Gastroesophageal Reflux
GERD	Gastroesophageal Reflux Disease
SAP	Symptom Association Probability
SI	Symptom Index

SSI

Symptom Sensitivity Index

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Figure 1. Relationships between Peristaltic Responses and representative symptoms.

The relationship between peristaltic response and presence of symptoms has four potential scenarios: normal peristalsis with no symptoms, peristalsis followed by symptom, symptom with no peristalsis, or symptom followed by peristalsis. Grey shaded boxes denote the symptom duration, dashed line denotes infusion onset, arrows indicate direction of peristalsis. PR: Peristaltic Response; UES: Upper Esophageal Sphincter; LES: Lower Esophageal Sphincter; P-Eso: Proximal Esophagus; M-Eso: Mid Esophagus; D-Eso: Distal Esophagus; STO: Stomach; MA: Movement and Arching; G: Gasp; C: Cough. A) (0.5 mL air infusion) PR: A solitary PR without symptoms is shown in the form of esophageal deglutition response (noted by pharyngeal peak, esophageal body contraction, and relaxation of both the UES and LES). Also note the brief deglutition apnea in the nasal airflow channel. B) (1.0 mL air infusion) PR→S: A PR in the form of a secondary peristalsis (identified by UES increase, esophageal body contraction, LES decrease, and lack of pharyngeal peak) is followed by 2 failed pharyngeal swallows, and movement and arching, indicated by the mirrored signals in all channels, including the stomach. C) (0.1 mL apple juice infusion) S: A solitary gasp is shown, identified by a sharp increase in the respiratory channels, simultaneous with an increase in the UES and decrease in esophageal body channels. D) (1.0 mL air infusion) S→PR: Multiple coughing events are followed by an esophageal deglutition response which restores breathing and esophageal body quiescence. Prolonged apnea is also noted.

Figure 2: Symptom detection by manometry, impedance, and pH monitoring.

Individual percentages represent the prevalence of symptom detection by the specific testing method: impedance only (55.5%), pH only (37.9%) or Manometry (94.7%). Symptoms were considered present for manometry if they occurred as a response to mid-esophageal infusions, and for impedance and pH if there were at least 5 occurrences and the SAP value was $\geq 95\%$. We included only liquids (water and acidic infusions) as provocative media in the genesis of symptoms during manometry and for pH-Impedance methods. The Venn-Diagram was adapted from Shay & Richter (2005).³⁰

Figure 3: Effect of Stimulus Volume and Media.

*Volume increase $p < 0.0001$ † $p < 0.05$ vs air at specified volume **A)** Symptom prevalence during esophageal stimuli: As the stimulus volume increases the symptom prevalence increases across all media ($p < 0.001$). Media impact overall is significant but only evident at 2.0 mL ($p = 0.02$ overall). **B)** Peristaltic Response prevalence during esophageal stimuli: As the stimulus volume increases the peristaltic prevalence increases across all media ($p < 0.0001$). Effect of media is only evident at 0.1 mL ($p = 0.0006$ overall).

Table 1.

Clinical Characteristics of Infants with varying Esophageal Acid Reflux Index (ARI)

Characteristics	ARI <3 (N=12)	ARI 3–7 (N=21)	ARI >7 (N=41)	P-Value
Comorbidities				
Preterm, %	10 (83)	18 (86)	37 (90)	0.8
Bronchopulmonary dysplasia, %	7 (58)	8 (38)	24 (58)	0.3
Neuropathology, %	4 (33)	4 (19)	11 (27)	0.6
Cardiac pathology, %	7 (58)	7 (33)	9 (22) [†]	0.05
Congenital Anomalies, %	2 (17)	0	1 (2)	0.06
At Manometry Evaluation				
Chronological Age, weeks	12 (7.9 – 16.9)	9.3 (6.4 – 12.4)	12.3 (9.0 – 15.1) [*]	0.1
Post-menstrual age, weeks	43.4 (40.8 – 45.1)	41.4 (39.7 – 42.3)	41.7 (40 – 42.9)	0.1
Oxygen Support, %	4 (33)	3 (14)	16 (39) [*]	0.1
Feeding Method, Gavage:Transitional:Oral, %	8: 25: 67	0: 52: 48	2: 42: 56	0.4
At Discharge				
Length of Hospital Stay, days	99 (16 – 142)	79 (67 – 118)	117 (93 – 141) [*]	0.03
Oxygen Support, %	3 (25)	1 (5)	14 (34) [*]	0.04
Feeding Method, Gavage:Transitional:Oral, %	0: 0: 100	5: 19: 76	2: 20: 78	0.4

Data presented as median (IQR) or n (%). Statistical methods were ANOVA and pairwise testing.

^{*} p<0.05 vs ARI 3–7;[†] p<0.05 vs ARI <3. All gavage and transitional feeds at evaluation were via nasogastric tubes, and at discharge were via gastrostomy tubes. Neuropathology include IVH Grades I and II; Cardiac comorbidities include Pulmonary Hypertension, Tetralogy of Fallot, Patent Ductus Arteriosus, and Patent Foramen Ovale.