Gastric and lower esophageal sphincter pressures during nausea: a study using visual motion-induced nausea and high-resolution manometry

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Schaub N, Ng K, Kuo P, Aziz Q, Sifrim D. Gastric and lower esophageal sphincter pressures during nausea; a study using visual motion-induced nausea and high-resolution manometry. Am J Physiol Gastrointest Liver Physiol 306: G741–G747, 2014. First published May 13, 2014; doi:10.1152/ajpgi.00412.2013.—Nausea is the subjective unpleasant sensation that immediately precedes vomiting. Studies using barostats suggest that gastric fundus and lower esophageal sphincter (LES) relaxation precede vomiting. Unlike barostat, high-resolution manometry allows less invasive, detailed measurements of fundus pressure (FP) and axial movement of the gastroesophageal junction (GEJ). Nausea was induced in 12 healthy volunteers by a motion video and rated on a visual analog scale. FP was measured as the mean value of the five pressure channels that were clearly positioned below the LES. After intubation, a baseline (BL) recording of 15 min was obtained. This was followed by presentation of the motion video (at least 10 min, maximum 20 min) followed by 30 min recovery recording. Throughout the experiment we recorded autonomic nervous system (ANS) parameters [blood pressure, heart rate (HR), and cardiac vagal tone (CVT), which reflects efferent vagal activity]. Ten out of 12 subjects showed a drop in FP during peak nausea compared with BL (−4.0 ± 0.8 mmHg; P = 0.005), and 8/10 subjects showed a drop in LES pressure (−8.8 ± 2.5 mmHg; P = 0.04). Peak nausea preceded peak fundus and LES pressure drop. Nausea was associated with configuration changes at the GEJ such as LES shortening and esophageal lengthening. During nausea we observed a significantly increased HR and decreased CVT. In conclusion, nausea is associated with a drop in fundus and LES pressure, configuration changes at the GEJ as well as changes in the ANS activity such as an increased sympathetic tone (increased HR) and decreased parasympathetic tone (decreased CVT).

Because nausea is a subjective feeling, it cannot be fully assessed in experimental animal studies. Behavioral reactions such as excessive salivation and swallowing have been used as surrogate markers for nausea. It is known that nausea in humans is associated with gastric arrhythmia (e.g., tachyarrhythmia) on electrogastrogram (18) and autonomic nervous system (ANS) changes such as increased sympathetic and decreased parasympathetic tone (7, 9, 12). Experimental animal and human studies using gastric barostats have suggested that nausea and/or vomiting are associated with gastric fundus and LES relaxation (5, 25–27). These studies could not clearly distinguish between changes induced by isolated nausea from those induced by vomiting. Furthermore, in human studies, nausea has been induced by intragastric lipid infusion and/or proemetic medication (e.g., apomorphine) that can “per se” induce gastric and LES pressure changes.

A better understanding of gastroesophageal changes during nausea requires a nonpharmacological nausea induction method and less invasive techniques to assess gastric and esophageal behavior. Nausea can be provoked effectively by viewing a motion video of a rotating and tilted landscape (3, 32). Unlike barostat, high-resolution manometry (HRM) allows minimal invasive, detailed measurements of fundus pressure (FP) and axial movement of the gastroesophageal junction (GEJ) (19, 20, 30). The relationship between nausea perception, gastric pressure changes, and ANS modifications is not clearly understood. It is well known that gastric fundus tone, LES pressure, and nausea are modulated by parasympathetic (vagal) and sympathetic activity, and transient lower esophageal sphincter relaxations (TLESRs) are vagally mediated. Meals are followed by a significant increase in the number of TLESRs and reflux episodes and a reduction in vagal activity (24). ANS changes can be recorded noninvasively with the NeuroScope, which provides real-time, beat-to-beat information on the systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiac vagal tone (CVT) that reflects efferent vagal activity, and cardiac sensitivity to baroreceptor reflex (CSB) that reflects afferent vagal activity (21, 22, 31, 33).

Significant understanding of gastric fundus and LES function during meals and gastroesophageal reflux allowed development of pharmacological strategies to modulate fundus relaxation in patients with dyspepsia (28, 39) and reduction of TLESRs in patients with gastroesophageal reflux disease (10, 15). Comparison of functional and anatomical changes of the fundus and GEJ during nausea with changes during meals and reflux can provide a better understanding of the pathophysiology of nausea and potential therapeutic pathways.

We aimed to assess gastroesophageal pressure and anatomical and ANS changes during visual motion-induced nausea using HRM.

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MATERIALS AND METHODS

Subjects. Studies were performed in 12 healthy volunteers (5 males, median age 23 yr) who all gave written informed consent. The study was approved by the Queen Mary University of London Research Ethics Committee. None of the healthy volunteers had symptoms or a history of gastrointestinal disease, other significant disease and/or psychological disorders, or were on any medication. The selected volunteers had previously been identified to be susceptible to the motion video [defined as reporting moderate to severe nausea on the visual analog scale (VAS)] (32).

Protocol. The experiments were performed after an overnight fast of at least 8 h. Subjects were studied in the sitting position. HRM and reflux monitoring catheters were inserted transnasally. The HRM catheter (Manoscan HRM System; Given Imaging) recorded pressures from the hypopharynx to the proximal stomach (assuring 5–8 internal gastric pressure sensors). Gastroesophageal reflux was measured with multichannel intraluminal impedance pH-metry using a Comfortec ZipH catheter and Sleuth recorder (Sandhill Scientific). After an initial 15-min lead-in phase, a 15-min baseline (BL) recording was obtained. This was followed by a 10- to 20-min projection of the nausea-inducing video and a 30-min recovery period (Fig. 1).

Motion video. Nausea was induced by watching a video of a rotating and tilted landscape through a pair of goggles (to limit the field of view) (32). During the video, volunteers were asked to rate their nausea and anxiety levels on a VAS scale (no-mild-moderate-severe/1-2-3-4) every minute and until complete recovery thereafter. The video was projected until at least moderate nausea was perceived (for a minimum of 10 min) or up to 20 min, whichever came first. To assess other dimensions of nausea we used a slightly modified version of the validated Motion Sickness Assessment Questionnaire (MSAQ) (11). Volunteers were asked to rate symptoms of gastrointestinal distress (nauseated, may vomit, sick to the stomach, queasy), central distress (faint-like, lightheaded, disoriented, dizzy, spinning), peripheral distress (sweaty, clammy, hot), and the sopite syndrome (anoyed, drowsy, tired, uneasy) on a VAS scale (not at all-somewhat-moderately so-very much so/1-2-3-4) before and 5 min after the end of the nausea video. The sums of the subscores were summed to get the total score. Together with the MSAQ, we asked about the subjective feeling of salivation before and 5 min after the end of the nausea video on a VAS scale ranging from 1-2-3-4 (not at all-somewhat-moderately so-very much so). Just before and just after the video, subjects completed the Spielberger State and Trait Anxiety Inventory (STAI).

Gastric fundus and GEJ pressure analysis with HRM. Recordings underwent thermal compensation and interpolated thermal compensation to overcome the thermal drift that had occurred as a result of the long duration of the study (35). The reported gastric fundus and LES pressures correspond to atmospheric pressures. Gastric FP was measured as the mean value of the first five pressure channels clearly positioned below the lower margin of LES and the diaphragmatic crura. Because the spacing between adjacent sensors was 1.0 cm on the HRM probe we used, we recorded the first 5 cm of pressure in the stomach. To account for movement artifacts as well as artifacts caused by coughing, sneezing, swallowing, and TLESRs, a moving median was calculated per channel from the original (median value over 1 min of the original data) as described by Janssen et al. (19, 20). Because of slight position change of the volunteers during the experiment, the sensing channel of the LES pressure had to be defined individually for each period. LES pressure was measured at every 1 min after the beginning of each time period by visually avoiding any swallows, TLESRs, and inspiratory periods. The reported LES pressure therefore corresponds to a mean expiratory pressure. LES length was measured from the upper to the lower border of the LES at every minute of the tracing. Esophageal length was measured from the lower border of the upper esophageal sphincter to the crura. To account for movement artifacts as well as artifacts caused by coughing, sneezing, swallowing, and TLESRs, a moving median was calculated per channel from the original (median value over 1 min of the original data) as described by Janssen et al. (19, 20). Because of slight position change of the volunteers during the experiment, the sensing channel of the LES pressure had to be defined individually for each period. LES pressure was measured at every minute of the tracing. Esophageal length was measured from the lower border of the upper esophageal sphincter to the upper border of the LES (Fig. 2). The number of reflux events (acidic, weakly acidic, weakly alkaline) and esophageal acid exposure was assessed during each period.

ANS recordings. Signals from the finger blood pressure and electrocardiogram were fed into the NeuroScope system, which calculates real-time, beat-to-beat information on the R-R interval, SBP, DBP, CVT, and CSB. CVT is a measure of cardiac parasympathetic efferent vagal activity and CSB of parasympathetic afferent vagal activity (21, 22, 31, 33). Data were recorded and calculated by the software VaguSoft (Meditf Instruments, London, UK). To compensate for interindividual HR variability, the whole dataset was converted into mean values for every minute of the recording.

Statistical analysis. Continuous variables are presented as means ± SE and categorical variables as numbers and percentages. Comparisons between groups were made using the chi square method for categorical and Mann-Whitney U-test for continuous variables, and with repeated-measures ANOVA followed by a Bonferroni posttest for multiple comparisons (P < 0.05 was considered significant). All statistical analyses were performed using GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, CA).

RESULTS

All 12 subjects completed the study and tolerated the procedures without vomiting. None of the healthy volunteers had hiatus hernia on HRM. The reported results correspond to measurements at BL (middle 5 min of the 15-min BL recording), peak nausea (period of highest VAS rating), early recovery (first 5 min of the recovery period), and late recovery (last 5 min of the 30-min recovery period).

Nausea ratings. The mean nausea rating during the motion video was VAS 2.4 ± 0.3, suggesting that the motion video was successful in inducing nausea. Ten out of 12 subjects reported moderate or severe nausea during the motion video, and the remaining 2 subjects reported only mild nausea. Those two subjects were still included in the analysis. Total MSAQ score was significantly higher after the nausea video compared with before the video (41.8 ± 15.1 vs. 24.4 ± 12.0, P < 0.0001). There was no significant difference in the MSAQ subscores of peripheral distress symptoms and the sopite syndrome. STAI state after the nausea video was significantly higher compared with before the video (55.9 ± 3.3 vs. 45.1 ± 4.0, P = 0.009).

Gastric FP changes. Nausea was associated with a reduction of gastric FP. Mean FP was 4.8 ± 1.1 mmHg during BL, 0.8 ±
1.2 mmHg during peak nausea, and 4.8 ± 1.3 mmHg during late recovery. Ten out of 12 subjects showed a significant drop in FP during peak nausea compared with BL (P < 0.05) with 7 out of those 10 subjects showing a partial or complete FP return to BL during late recovery (P < 0.05). Mean difference between FP during peak nausea and BL was −4.0 ± 0.8 mmHg (Fig. 3A). For the following results we will only report the 10 subjects who showed a FP drop during nausea.

**LES pressure changes.** Mean LES pressure was 24.2 ± 4.7 mmHg during BL, 15.3 ± 3.6 mmHg during peak nausea, and 19.6 ± 3.8 mmHg during late recovery. Eight out of 10 subjects showed a significant drop in LES pressure during peak nausea compared with BL (P < 0.05). Eight out of 10 subjects showed partial or complete LES pressure return to BL during late recovery. Mean difference between LES pressure during peak nausea and BL was −8.8 ± 2.5 mmHg. The reduction in LES pressure at peak nausea was relatively small compared with nadir LES pressures observed during swallows (15.3 ± 3.6 vs. 8.5 ± 0.5 mmHg) (Fig. 3B).

There was no significant difference in the relationship between gastric FP and LES pressures during the four time periods (BL −19.3 ± 4.1 mmHg, peak nausea −14.5 ± 3.7 mmHg, early recovery −14.8 ± 4.0 mmHg, and late recovery −15.3 ± 3.7 mmHg).

**Configuration changes of the GEJ and esophagus.** We observed changes in LES length and total esophageal length. At peak nausea, there was a significant decrease in LES length (−0.7 ± 0.3 cm; P < 0.05) (Table 1) with consequent increase in esophageal body length (+0.8 ± 0.2 cm; P < 0.001). This effect was slowly reversed during recovery, and at late recovery the esophageal body was slightly shortened (−0.6 ± 0.2 cm; P < 0.01) (Table 1).

**Correlation between intensity of nausea and pressure changes.** The FP change from BL showed a weak but significant negative correlation with the intensity of the subjective nausea feeling on the VAS scale (r² = 0.205; P < 0.0001) (Fig. 4A). Also, LES pressure change from BL showed significant negative correlation with nausea ratings (r² = 0.030; P < 0.05) (Fig. 4B).

**Timing of pressure and configuration changes in relation to nausea.** To assess the timing of the pressure changes in relation to nausea we looked at the maximal pressure/configuration changes.
changes from BL throughout the whole experiment in relation to the beginning of the peak nausea period. Eight out of 10 volunteers showed a maximal FP drop after peak nausea (+4.0 ± 0.8 min), whereas the FP drop preceded peak nausea in 2/10 volunteers (by −6 and −8 min, respectively). Similarly, the maximal LES pressure drop occurred after peak nausea in 8/10 volunteers (+9.0 ± 0.8 min) and before peak nausea in 2/10 volunteers (−1 and −12 min, respectively). Overall, peak nausea preceded both pressure (FP drop: +2.4 ± 1.4 min, LES pressure drop: +8.0 ± 2.7 min) and configuration (LES shortening: +2.1 ± 2.8 min) changes. Figure 5 shows a typical example of the timing of the pressure changes and nausea ratings in one subject.

Number of swallows and TLESRs and reflux. There was no significant difference in the subjective salivation score before and after the nausea video (2.4 ± 1.2 vs. 2.8 ± 1.2, P = 0.18) as well as no significant difference between the number of swallows per minute during the BL, nausea, and recovery periods (2.0 ± 1.6, 2.0 ± 1.5, 1.8 ± 1.6). As expected in the fasting state, the number of TLESRs during BL was low (n = 0–2). During the nausea video only one subject experienced 1 TLESR, whereas all other subjects did not show any TLESRs. During the 30-min recovery period there was an increase in the number of TLESRs (1.5 ± 1.0, range 0–3, P = 0.01).

Esophageal acid exposure was normal in all subjects. The total number of reflux episodes throughout the study was low in all subjects (0.4 ± 0.2 reflux episodes) and comparable between the BL, nausea, and recovery periods. The recorded reflux episodes were either weakly acidic or weakly alkaline.

ANS recordings. There was a significant increase in HR during the nausea period compared with BL (77 ± 5 vs. 65 ± 3.4 beats/min, P < 0.01). CVT could not be analyzed in one volunteer because of artifacts in the tracing. CVT was significantly lower during the nausea period compared with BL (8.1 ± 1.5 vs. 11.5 ± 1.6 in linear vagal scale, P < 0.05) and showed a partial recovery during the recovery period (Table 1). There was no significant difference in blood pressures (SBP, DBP) and CSB during BL, nausea, and recovery. Nine out of 10 volunteers showed a significant positive correlation between nausea ratings and HR, but only 4/10 between nausea and CVT.

DISCUSSION

In this study we aimed to examine the physiological gastro-esophageal pressure and configuration changes during visual motion-induced nausea in 12 healthy fasting volunteers. We report four major findings: 1) nausea is associated with a significant drop in gastric fundus and LES pressure; 2) nausea is associated with configuration changes at the GEJ such as LES shortening and esophageal lengthening; 3) both pressure and configuration changes are preceded by the subjective nausea feeling; and 4) nausea is associated with increased sympathetic tone (increased HR) and decreased parasympathetic tone (decreased CVT).

It is well known that during food intake the proximal stomach relaxes to provide a reservoir and to avoid an increase in gastric pressure. This so called gastric accommodation is vagally mediated and associated with a release of nitric oxide. After meals, there is a significant increase in the frequency of TLESRs. TLESRs are triggered by gastric distension and involve a complex sequence of actions that includes vagally mediated LES relaxation, relaxation of the crural diaphragm, decreased esophageal peristalsis, and esophageal shortening (mediated by constriction of the longitudinal muscle of the esophagus) (23). In a recent study, we assessed ANS activity during meals and TLESRs. We found a significant reduction of the CVT (compatible with an increase in parasympathetic tone) after the meal that remained below BL during the first three postprandial hours with a strong positive correlation of CVT with the number of TLESRs and reflux episodes (24).

It has been proposed that TLESRs are not only the main mechanism for reflux but also an important mechanism for vomiting. Vomiting is associated with marked esophageal shortening and eventually complete opening of the LES for expulsion of the gastric content (26). Vomiting is normally preceded by nausea, but the physiological changes during nausea are incompletely understood. In our study, nausea was not associated with complete LES relaxation, esophageal shortening, or increased TLESRs. It is important to note that we studied visual motion-induced nausea with subjects in the fasting state. It is possible that nausea occurring during a period of gastric fullness (postprandial or secondary to duodenogastric reflux) is associated with different pressure patterns facilitating vomiting. Despite sometimes reporting severe nausea, none of our fasting volunteers vomited. It may be that gastric or duodenal contents are needed for the complete LES relaxation and esophageal shortening seen with vomiting. Mean FP drop during peak nausea compared with BL was −4.0 ± 0.8 mmHg in our study, which is comparable to the FP drop seen during nutrient drink infusion/drinking (19, 20). To
our knowledge, gastric FPs after a solid meal have not been assessed by HRM so far.

There were hardly any TLESRs during the nausea video, but in our fasting volunteers the number of TLESRs increased slightly during the recovery period (n = 1.5 ± 1.0, range 0–3). The average number of TLESRs in the first hour after a meal is around n = 5 (36). In general, TLESRs are triggered by gastric distension, which is associated with gastric relaxation. Most volunteers showed the maximal FP drop during the early recovery period, which may explain the increased TLESR rate during recovery. Gastric or duodenal contents may be needed as an additional factor to induce TLESRs when gastric relaxation is not enough. This may explain the lack of TLESRs during nausea despite FP drop and the low number of TLESRs in the recovery period compared with a postprandial state. Overall, the recovery period of 30 min is probably too short to make a sound statement about the frequency of TLESRs.

The configuration changes of LES shortening and esophageal lengthening during nausea are most likely secondary to anatomical changes occurring with gastric accommodation. The configuration changes subsided with the recovery of the gastric FP.

Hypersalivation and subsequent excessive swallowing has been reported as a typical symptom of the nausea syndrome, but there are also publications that suggest the opposite (14). To assure that the decrease in LES pressure during nausea was not caused by an increase in the swallow frequency we calculated the swallow rate per minute, which was comparable during the BL, nausea, and recovery periods and is in line other publications. Also, there was no difference in the VAS scale of the subjective salivation rate before and after the nausea video. Dry mouth may be a reflection of the reduced parasympathetic tone that we observed during motion-induced nausea.

We did not see an increased rate of reflux episodes during the nausea or recovery period. This can be explained by the low number of TLESRs and incomplete pressure drop of the LES (mean LES pressure 15.3 ± 3.6 mmHg during peak nausea and 19.6 ± 3.8 mmHg during late recovery) as well as the lack of any significant gastroesophageal pressure gradient during nausea and the recovery period.

Nausea is a subjective feeling, and its assessment can therefore be difficult and imprecise. To not only rely on the subjective nausea feeling we used the validated MSAQ, which assesses several other dimensions of the nausea syndrome. In line with the nausea rating, the total MSAQ score was significantly higher after the nausea video compared with before the video.

Anxiety is an important part of a general stress response and was increased after the motion video (STAI state after the nausea video 55.9 ± 3.3 vs. 45.1 ± 4.0 before the video, P = 0.009). From our results we cannot tell if the ANS changes are specific to motion-induced nausea or simply a result of a general stress response.

It is well accepted that vagal neurocircuits play a pivotal role in the development and mediation of nausea and vomiting. Vagal afferents are initiated by activation of mechano-, osmo-, and chemoreceptors in the gut. These signals are conducted to the nucleus tractus solitarius (NTS), which has connections with several other brain structures such as the hypothalamus, limbic system cortex, cerebellum, and vestibular nucleus and coordinates the complex actions (gastric contraction, relaxation

Fig. 4. Correlations of pressure changes and subjective nausea ratings. Correlation of mean change of gastric fundus pressure (A) and LES pressure (B) from BL and subjective nausea ratings on the visual analog scale (VAS) (1–4, no-mild-moderate-severe).

Fig. 5. Timing of pressure changes and nausea ratings. Graph of a representative volunteer showing the timing of the pressure changes (gastric fundus and LES) from BL during the nausea and recovery period and its correlation with the subjective nausea rating (VAS 1–4, no-mild-moderate-severe).
of the LES, contraction of the abdominal muscles, etc.) needed for nausea/vomiting via the efferent vagus (2). Visually induced motion sickness results from the mismatch of information from the vestibular, visual, and visceral sensory systems and also involves activation of the NTS. The fact that in our study nausea peaked before changes in gastric and LES pressures could suggest that centrally induced nausea may trigger efferent signaling via the vagus nerve, resulting in the pressure changes observed. It is possible that peripherally induced nausea (e.g., by ingestion of a lipid meal) induces both afferent and efferent signaling and that the physiological changes could therefore be very different.

The pharmacological treatment of nausea includes prokinetics (metoclopramide, domperidone), drugs acting on the vomiting center (prochlorperazine, haloperidole), antihistamines, and 5-HT3 receptor antagonists (ondansetron). The antiemetic mechanism of ondansetron is not completely understood, but antagonism on the peripheral (on the afferent vagus) and central 5-HT3 receptors is likely to be involved. The main finding of our study is that nausea is associated with a significant FP drop. However, antagonism of 5-HT3 receptors does not influence fundus tone in humans (41). It has been shown that 5-HT1 receptor agonists, such as sumatriptan and buspirone, are able to induce a relaxation of the proximal stomach in humans through a nitric pathway (38). We could speculate that 5-HT1 receptor antagonists may prevent the FP drop associated with nausea. Erythromycin and other motilin agonists enhance gastric emptying and increase fundus tone and are used in patients with gastroparesis and functional dyspepsia with varying success (6, 8, 29, 40).

Apart from pharmacologically modifying gastric fundus tone and LES pressure directly, modulation of the ANS may be a possible therapeutic target in nausea. It has been shown that “deep breathing” maneuvers increase parasympathetic tone (CVT), and this has been associated with a reduction in sensitization of the esophagus to electrical stimulation (4). Of course this option is speculative, and future studies will have to explore the cause and effect relationship between ANS activity, gastric FP, LES pressure, and the subjective nausea feeling. Considering treatment options, it is very important to acknowledge that motion-induced nausea is mainly centrally mediated and, as shown in our study, precedes the physiological gastrointestinal changes so that drugs acting peripherally on the gastrointestinal tract may show limited efficacy.

Potential limitations of the current study merit consideration. Most importantly, we were studying visual motion-induced nausea, and the physiological changes seen may be different from nausea originating in the gastrointestinal tract. We were only including subjects who have previously been identified as being susceptible to nausea. Therefore, the physiological changes seen with nausea might be much more subtle in a less specific cohort of healthy volunteers.

In conclusion, nausea is associated with a drop in gastric fundus and LES pressure as well as an increased sympathetic tone (increased HR) and decreased parasympathetic tone (decreased CVT). The configuration changes of esophageal lengthening and LES shortening during nausea are likely secondary to anatomical changes occurring with gastric fundus relaxation. The subjective feeling of nausea precedes these physiological changes.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
Author contributions: N.S., K.N., P.K., Q.A., and D.S. conception and design of research; N.S. and K.N. performed experiments; N.S., P.K., and D.S. analyzed data; N.S., P.K., Q.A., and D.S. interpreted results of experiments; N.S. drafted manuscript; N.S., P.K., Q.A., and D.S. edited and revised manuscript; N.S., K.N., P.K., Q.A., and D.S. approved final version of manuscript.

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