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Woodley, Frederick W
Hayes, Don
Kopp, Benjamin T
et al.

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Title: Abnormal Spatial Patterns on Cutaneous High-Resolution Electrogastrogram Correlate with Symptom Severity in Functional Dyspepsia and Gastroparesis

Short title: Spatial HR-EGG Patterns Correlate with Symptoms

Authors:

Armen A. Gharibans, Ph.D. [1,2,3], Hayat Mousa M.D. [1,3,4], Todd P. Coleman, Ph.D. [1,2], and David C. Kunkel M.D. [1,5,*]

Affiliations:

1. GI Innovation Group, University of California-San Diego, La Jolla, CA, United States
2. Department of Bioengineering, University of California-San Diego, La Jolla, CA, United States
3. Department of Pediatrics, University of California-San Diego, La Jolla, CA, United States
4. Neurogastroenterology and Motility Center, Rady Children's Hospital, San Diego, CA, United States
5. GI Motility & Physiology Program, University of California-San Diego, La Jolla, CA, United States

*Corresponding Author:
David C. Kunkel
dkunkel@ucsd.edu
(858) 657-5088
9500 Gilman Drive, #0956
La Jolla, CA 92093

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Background: Invasive gastric electrical mapping has revealed spatial abnormalities of the slow wave are present among subjects with gastroparesis and functional gastrointestinal disorders. The cutaneous high resolution electrogastrogram (HR-EGG) can non-invasively detect spatial features of the gastric slow wave. In this study, we performed HR-EGG on subjects with gastroparesis and functional dyspepsia with normal gastric emptying, evaluating for associations between gastric myoelectric abnormalities, symptoms on a validated questionnaire, and gastric emptying.

Methods: HR-EGG was performed on 32 subjects (7 controls, 7 functional dyspepsia with normal gastric emptying, 18 gastroparesis). Subjects completed the PAGI-SYM questionnaire on foregut symptoms, which includes the Gastroparesis Cardinal Symptom Index (GCSI). Volume reconstruction of the torso and stomach from CT images was performed to guide accurate placement of the HR-EGG array.

Results: Spatial abnormalities were detected noninvasively in 44% of subjects with foregut symptoms. Moreover, subjects with a higher percentage of slow waves with abnormal propagation direction had a higher GCSI total score ($r = 0.56$, $p < .001$) and more severe abdominal pain ($r = 0.46$, $p = .009$). We found no significant correlation between symptoms and traditional EGG parameters.

Conclusions: The genesis of symptoms in functional dyspepsia and gastroparesis is likely multifactorial, including possible pathophysiologic contribution from gastric myoelectric dysfunction. We report here that abnormal spatial parameters on cutaneous HR-EGG correlated robustly with severity of upper gastrointestinal symptoms, regardless of gastric emptying. This noninvasive, repeatable approach will allow for assessment of slow wave dynamics across time, including symptom-association analyses and response to targeted therapies.

Introduction

Functional dyspepsia and gastroparesis are the two most common gastric neuromuscular disorders with a prevalence of 10% and 1.5-3%, respectively (1,2). Although delayed gastric emptying is the *sine qua non* of gastroparesis, symptoms show inconsistent correlation with emptying on scintigraphy or gastric transit time via the wireless motility capsule (3,4). Moreover, multiple medications improve symptoms but not gastric emptying and vice versa (5–7). It has been proposed that functional dyspepsia and gastroparesis should be subtyped for more specificity and targeted interventions (8,9). Specifically, impaired fundic accommodation, gastric myoelectric dysfunction, antral hypomotility, pylorospasm, autonomic dysfunction, visceral hypersensitivity, duodenal dysmotility, psychosocial stress, and central nervous system abnormalities, which can all lead to symptoms, may need to be differentiated to provide more tailored treatment strategies (9–11).

The electrogastrogram (EGG) is a technique for assessing gastric myoelectric activity using cutaneous electrodes (12). Although it is noninvasive and easy to administer, EGG has limitations that have prevented widespread uptake. While some studies have observed EGG abnormalities in patients with upper gastrointestinal symptoms (13–15), other studies have found no differences between dyspeptic patients and healthy volunteers (16,17). Moreover, its clinical usefulness has been questioned, due to insufficient correlation with diagnoses made via antroduodenal manometry (18) and gastric emptying tests (12). There remains an unmet need to objectively assess gastric neuromuscular function in a noninvasive manner that correlates with symptoms and can be easily used to guide targeted therapies.

High-resolution invasive electrical mapping allows for spatially detailed analysis of propagating slow wave patterns directly from the serosa of the stomach (19). Using this approach, abnormalities in slow wave initiation and propagation have been identified among subjects with gastroparesis and chronic unexplained nausea and vomiting (20,21). These findings indicate that the slow wave spatial electrical patterns may be associated with disease and symptom severity. As such, there is a unique opportunity to develop non-invasive means to detect this spatial electrical information and determine if these patterns show similar clinical associations.

The recently developed high-resolution electrogastrogram (HR-EGG) utilizes a cutaneous multielectrode array to estimate spatial parameters of slow wave propagation. This has been performed successfully in estimating the direction and speed of the gastric slow wave in healthy subjects (22). The objective of this study was to determine whether the HR-EGG, combined with methodological refinements consisting of enhanced artifact rejection technique and array placement (23), provides quantitative descriptions of the gastric slow wave that differentiate subjects with and without foregut symptoms. We also sought to evaluate associations between novel HR-EGG parameters, traditional EGG features, foregut symptoms on validated questionnaire, and gastric emptying.

Methods

Participants

We enrolled 32 subjects in this study; age 21 to 85 years old, BMI 16 to 36 kg/m^2, 17F/15M. We divided subjects into three groups: healthy controls (n=7), functional dyspepsia as defined by Rome III criteria (24) with normal gastric emptying (n=7), and gastroparesis (n=18). A summary of detailed subject characteristics can be found in Table 1. Patients were recruited from a tertiary referral gastrointestinal motility program and provided their informed consent. We documented demographic data, disease etiology, medical histories, and body mass index for each subject. The study included subjects with any ethnic background older than 18 years of age who had a recent fasting abdominal computed tomography (CT) scan (i.e., within 3 years). Subjects with malignancy, primary eating disorder, pregnancy, or a history of skin allergies to adhesives or ECG electrodes were excluded. Subjects were also excluded if they had a disorder other than functional dyspepsia or gastroparesis that affects gastric motility, including rumination syndrome, cyclic vomiting syndrome, untreated *H. pylori* Infection, gastric outlet obstruction, small bowel motility problem, or uncontrolled thyroid disease.

Gastric Emptying Scintigraphy

Gastric emptying scintigraphy was completed at a single medical center, the UC San Diego Department of Nuclear Medicine. Patients were instructed to stop taking any medications that could affect motility (e.g., prokinetics, opioids, anti-cholinergics) for at least two days prior to the gastric emptying study. The blood glucose level in diabetic subjects were tested prior to the study to ensure it was below 250 mg/dL, as hyperglycemia has been shown to change gastric emptying (25). The study was performed according to the clinical guidelines using a technetium-99m labeled egg meal (26). Anterior and posterior images were obtained at 0, 1, 2, 3, and 4 hours after meal ingestion. Gastric retention of the meal was determined by calculating the geometric mean of the radioactivity, corrected for decay, within the stomach region of interest (27). We defined abnormal emptying as having gastric retention greater than 10% at 4 hours.

Abdominal CT Image Processing

We used recent abdominal CT scans to determine the location and geometry of each subject's stomach. A single operator manually drew a region of interest (ROI) outlining the stomach on each axial slice in OsiriX (28). We then performed a 3D volume reconstruction of the torso and stomach for each subject (see Supplemental Materials). We developed a custom routine to automatically calculate the medial line of the stomach using the manually drawn ROIs. The procedure was as follows: (i) the isolated stomach was exported as an STL file; (ii) the STL volume was converted to a binary 3D matrix (i.e., voxelized); (iii) using a thinning procedure (29), the stomach was skeletonized to reveal the medial line. We determined the 3D location of the pylorus by calculating the endpoint of the medial line and confirmed by identifying the pylorus in the CT images. We noted the position of the pylorus relative to the midpoint between the xiphoid and umbilicus, which is typically used for traditional EGG electrode placement. We used standard linear algebra methods to project the three-dimensional medial line onto the coronal plane to compute the stomach angle relative to the electrode array.

High-Resolution EGG

We recorded the high-resolution electrogastrogram (HR-EGG) as previously described, using a cutaneous array of 25 pregelled Ag-AgCl electrodes (measurement area 95 mm^2) arranged in a five-by-five grid with 2 cm center-to-center spacing (22). We performed all recordings in the morning after an overnight fast. Following the same protocol as the gastric emptying study, subjects were off medications that affect motility for at least two days and we ensured the blood glucose levels in diabetics was below 250 mg/dL. Prior to placing the electrode array, we removed excess hair and prepared the skin with NuPrep® to reduce skin impedance. We placed the array over the antrum by localizing the stomach relative to anatomical landmarks from the subject's anatomical CT scan. We placed reference and ground electrodes on the subject's right side outside of the array (Figure 1). We used the Brainamp 32ch EEG amplifier (Brain Products, Gilching, Germany) to collect unfiltered data at sampling rate of 250Hz. During the recording, subjects sat in a reclined position and were instructed to limit movement and talking. We captured 30 minutes preprandial and 60 minutes after a test meal that included a 250-kcal nutrient bar (CLIF Bar: 5 g fat, 45 g carbohydrate, 10 g protein, 7 g fiber) and 8 ounces of room temperature water. We had no adverse events during the recordings and the test was well tolerated by the subjects.

Prior to data analysis, we reduced the sampling rate of the recorded signals from each electrode to 5 Hz after low pass filtering the signal to lower computational time. We then filtered between 0.015 and 0.20 Hz (i.e., 1-20 cpm) to isolate the EGG frequency bands of interest. We removed any movement artifacts as described previously (23). In brief, we identified any artifact using linear minimum mean squared error (LMMSE) estimator and subsequently subtracted it from each individual waveform. This approach was fully automated and preserved the phase across electrodes because windows of time were not deleted. We have previously shown that this approach yields an improvement in the correlation of EGG with an invasive clinically indicated measure (i.e., manometry) (23).

We applied the HR-EGG analysis as described previously (22). In brief, the phase changes across the electrode array were calculated at every time point, from which the presence, direction, and speed of planar waves were automatically estimated. Prior to analysis, we used the average reference spatial filter instead of the surface Laplacian (30). We found it was more robust at high BMI since the surface Laplacian suppresses deep sources (31). Phase gradient directionality (PGD) is a measure between 0 and 1 indicating the degree of alignment of the phase gradients across the array. We defined a sustained wave as having a PGD greater than 0.5 for at least 10 seconds (22). We defined the anterograde (i.e., normal) direction of wave propagation along the mean angle of the stomach ± 60 degrees to account for J-shaped stomachs, inaccuracies due to the delay between CT imaging and recording, and changes in stomach shape after a meal. We defined the percent abnormal direction as the percentage of slow waves not propagating in the anterograde direction. We considered each spatial feature (e.g., percent abnormal direction and speed) to be abnormal if it was below 1.96 standard deviations of the mean pertaining to the control group data.

Traditional EGG

We computed short-time Fourier transform spectrograms for each electrode pair by dividing the time domain into consecutive four-minute windows with 75% overlap. We calculated traditional EGG parameters from the electrode pair with the highest signal-to-noise ratio (SNR), which we defined as the average 2-4 cpm power (in dB) subtracted from the average power in all other frequencies between 1 and 9 cpm (23). Consistent with traditional EGG practice (32), we defined: (i) postprandial power change as the difference of the mean power in the 2-4 cpm frequency band before and after the meal (in dB); (ii) dominant frequency in each time window as the frequency with the highest spectral power; (iii) percentage of normal, bradygastria, and tachygastria activity as the fraction of the recording with the highest power in the 2-4 cpm, 1-2 cpm, and 4-9 cpm frequency band, respectively.

Symptom Assessment

We assessed symptom severity in subjects with the Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) questionnaire prior to recordings (33). The PAGI-SYM captures 20 symptoms on a 0-5 scale experienced by the subjects within the previous two weeks. It also contains the Gastroparesis Cardinal Symptom Index (GCSI), which combines the individual symptom scores into three subscales: nausea/vomiting, postprandial fullness/early satiety, and bloating/distension (34).

Statistical Analysis

Data are presented as numbers with percentages for categorical variables and mean ± standard deviation for continuous variables. Results were divided into three groups: control, functional dyspepsia with normal gastric emptying, and gastroparesis. For the categorical variables, we employed Fisher's exact test to determine independence of observed frequencies in the contingency tables. We used one-way analysis of variance (ANOVA) for continuous variables to test the null hypothesis that the three groups have the same population mean. Prior to ANOVA, we confirmed that samples within groups belonged to a normal distribution using D'Agostino's K^2 test, and used Bartlett's test to verify that the distributions from each group had equal variances. For variables with statistically significant differences in means between groups identified by ANOVA, we did pairwise comparisons between individual groups using a two-sided unpaired t-test and reported the p values with no correction. We determined the associations between all the study variables (e.g., subject characteristics, EGG, symptoms) by calculating the Pearson's correlation coefficient, a measure of the linear correlation between two variables. We reported statistically significant correlations after Benjamini-Hochberg correction (family-wise error rate alpha = 0.05) for all variables to avoid Type-I errors and reduce the false discovery rate (35).

Results

Subject Characteristics

Demographic and relevant medical information are included in Table 1 for the three groups in this study; controls, functional dyspepsia with normal gastric emptying, and gastroparesis. The groups were age, sex, and BMI matched, and the ethnicity of the subjects in this study were representative of the San Diego area. There were no significant differences in the subject characteristics between the three groups, with the exception of opioid use and diabetes, that were more common in the subjects with gastroparesis. There were a wide range of etiologies for gastroparesis and all except one of the subjects with gastroparesis also fit the Rome III criteria for functional dyspepsia. One of the subjects in the study had a gastric surgery, fundoplication, which can affect gastric emptying and function (36).

Anatomical Variability

Since previous studies have shown that stomach localization can greatly improve EGG signal quality (23,37), we evaluated the stomach location relative to traditional EGG electrode placement to determine variability across subjects. Specifically, for each subject, we plotted the location of the pylorus on a coronal and sagittal views of a representative torso relative to the midpoint of the xiphoid and umbilicus, which is where traditional EGG electrodes are placed (Figure 2). We found the most variability along the inferior-superior axis. The mean location of the pylorus relative to the midpoint of the xiphoid and umbilicus was -3.1 ± 1.9 cm (range: -6.7 to 1.7 cm) in the right-left direction, 1.3 ± 3.9 cm (range: -5.8 - 8.4 cm) in the inferior-superior direction, and 7.4 ± 3.0 cm (range: 1.7 - 14.3 cm) anterior-posterior direction. The mean fasting stomach volume determined from the abdominal CT images was 309 ± 176 cm^3 (range 132 - 740 cm^3) and the mean stomach angle was 202 ± 13 degrees (range: 180 - 233 degrees) across all subjects. Besides the significant variability in stomach location between subjects, there were also a wide range of stomach shapes (e.g., steer-horn, cascade, J-shape, hourglass) (see Figure 3 for volumetric stomach reconstructions; Supplemental Materials includes all subjects).

Traditional EGG

We observed a clear EGG signal in most subjects in this study; percent 2-4 cpm activity was 95 ± 6 % (range 83 - 100 %) for all subjects. Only four subjects (2/7 functional dyspepsia and 2/18 gastroparesis) had a low amplitude EGG signal that was near the background noise level (see Supplemental Materials for spectrograms for each subject). The slow wave frequency was 0.053 ± 0.005 Hz (range: 0.044 - 0.066 Hz) and the postprandial power change was 2.7 ± 4.0 dB (range: -3.5 - 14.4 dB) for all subjects. Six subjects (1/7 functional dyspepsia and 5/18 gastroparesis) did not have an increase in EGG power after the meal. There were no significant differences between groups for any of the traditional EGG parameters (Table 2).

High-Resolution EGG

We conducted HR-EGG recordings in the morning after an overnight fast; the mean start time was 10:34 AM ± 1:09. From the imaging, we computed the direction of the stomach projected onto the plane of the electrode array (see Methods). This direction was used to define a subject-specific window (mean angle ± 60 degrees); slow wave propagation direction within this window was considered normal (Figure 3; see green region on polar histogram). The mean time between abdominal CT imaging and the HR-EGG recordings was 1.6 ± 1.3 years.

The control group had the majority of slow waves propagating within the CT-defined normal axis of the stomach. We detected abnormalities in the propagation direction (i.e., greater than 45% abnormal direction) or speed (i.e., mean less than 5 mm/s) in 14 subjects (6/7 functional dyspepsia and 8/18 gastroparesis). Of the 14 subjects with spatial abnormalities, five had both speed and direction abnormalities, five only had slow propagation speed, and four had abnormal propagation direction with normal speeds. Of the nine subjects with direction abnormalities, six had a combination of anterograde and retrograde propagation, while the remaining three had chaotic propagation patterns (see Figure 3 for representative patterns; Supplemental Materials includes results for each subject). Most of these spatial abnormalities occurred at the normal EGG frequency. The one subject in this study with previous fundoplication surgery had slow wave propagation abnormalities. There were no significant associations for drug use, gastroparesis etiology, diabetes type or demographics differentiating those with slow wave spatial abnormalities. The percentage of sustained slow waves along with its speed were significantly higher in the controls compared to functional dyspepsia and gastroparesis (Table 2). The HR-EGG parameters were not statistically different between the functional dyspepsia and gastroparesis groups.

Relationships with Symptoms

As expected, subjects with functional dyspepsia and/or gastroparesis had more severe symptoms compared to controls (Table 2). The mean GCSI score, particularly the nausea-vomiting subtype, was higher in gastroparesis compared to functional dyspepsia with normal gastric emptying.

Statistically significant correlations between study variables are displayed in a circular plot in Figure 4 (see Supplementary Figure 1 for all correlation coefficients). Anthropomorphic characteristics (e.g., BMI, age, or stomach volume) were not significantly correlated with any patient-reported or objective measures in the study. Gastric retention at 4 hours was measured on symptomatic subjects ($n = 25$) and correlated with only two of the symptoms: unable to finish normal-sized meal ($p = .009$) and upper abdominal discomfort ($p = .01$). Despite CT-guided localization of the array and motion artifact rejection, traditional EGG parameters failed to associate with any clinical symptom.

All three spatial features of the HR-EGG predicted the quantity and intensity of foregut symptoms. Specifically, abnormalities in slow wave propagation direction correlated with the overall GCSI score ($p < .001$), bloating/distension ($p = .003$), fullness/early satiety ($p < .001$), abdominal discomfort (lower: $p = 0.01$; upper: $p < .018$), and lower abdominal pain ($p = .009$). Globally, subjects without anterograde propagation of their slow wave, regardless of gastric emptying status, reported the most severe symptoms (see Figure 5).

Discussion

In this manuscript, we presented data from 32 healthy controls and well-characterized patients with active foregut symptoms. We applied recently developed approaches to noninvasively characterize gastric myoelectrical activity in high spatiotemporal detail. We accounted for differences in gastric anatomy by generating subject-specific volumetric torso reconstructions from CT imaging.

Using data from an appropriately placed cutaneous electrode array, we automatically rejected movement artifacts (23) and estimated features of slow wave propagation (22) in addition to traditional EGG parameters. These methodological improvements resulted in a robust acquisition of the gastric slow wave in subjects with BMI up to 36. Moreover, we observed abnormal slow wave propagation in subjects with functional dyspepsia and/or gastroparesis compared to healthy controls. The key finding of this study was a statistically significant correlation between the percentage of slow waves with abnormal propagation direction and overall foregut symptom severity, regardless of gastric emptying.

Even though traditional EGG studies considered greater than 70% of the recording with 3 cpm activity to be normal (12), fewer rhythm disruptions have been observed on serosal measurements (38,39). By guiding electrode array placement with CT imaging and automatically suppressing artifacts, we observed 3 cpm activity in most subjects, including those with impaired gastric emptying. We have previously shown that these methodological refinements resulted in an improved correlation of EGG amplitude with motility index on antroduodenal manometry (23). These findings are also consistent with other studies that demonstrated electrode placement guided by stomach localization significantly improved EGG signal quality (37,40). Although we did not find a difference in traditional EGG parameters between groups, future studies with longer recordings (e.g., ambulatory monitoring) may be able to identify spectral features that correspond with abnormalities.

Multichannel EGG measurements (i.e., typically up to 4 channels) have been carried out previously (41). Although aboral slow wave propagation was observed in patients with foregut symptoms (42), the only reproducible parameter was found to be the average percentage of slow wave coupling, which compares spectral features between channels (43). We believe this is due to sensitivity of multichannel EGG to electrode placement; if the reference electrode is placed near the antrum, a phase delay will not be observed between channels (41). Our method captures wave propagation information (i.e., not frequency-based coupling) and is not dependent on placement of the reference electrode. This is important, since there is a significant amount of anatomical variability between subjects in both the location and shape of the human stomach (see Figure 2 and Supplemental Materials).

High-resolution electrical mapping of the gastric serosa in humans has shown that spatial slow wave abnormalities are present in patients with gastroparesis and chronic unexplained nausea and vomiting (20,21). These included conduction blocks, aberrant initiation, and abnormal conduction velocity, which often occurred at the normal 3 cpm frequency. Our results are consistent with those studies. Similar to their findings in fasting subjects under anesthesia, we observed both fasting and postprandial spatial disruption in slow wave direction and speed in awake subjects. These abnormalities would go undetected by single channel EGG measurements, since most occurred at the normal 3 cpm frequency. Both slow wave speed and percentage of sustained waves were reduced in functional dyspepsia and gastroparesis compared to controls, and abnormalities in the direction of slow wave propagation correlated with a variety of important symptoms.

Although multiple simultaneous wavefronts exist on the stomach surface (19), we hypothesize that the HR-EGG findings in this study reflect slow wave propagation through the antrum, due to the higher amplitude of antral slow waves and their proximity to the electrode array (44). It should be noted that the estimated slow wave speed for controls was higher than reported in our previous study (22). This is because we used a different spatial filter (i.e., average reference instead of surface Laplacian), which we found to be more robust at high BMI. Additional theoretical and experimental validation is necessary to determine the relationship between the estimated cutaneous HR-EGG speed and the actual serosal slow wave speed. It also remains to be seen how the retrograde and chaotic propagation abnormalities observed with HR-EGG are related to those measured on the serosa (e.g., conduction block, abnormal initiation).

Consistent with other studies, we found a weak correlation of symptoms and EGG parameters with gastric emptying. We observed slow wave abnormalities in symptomatic subjects with both normal and abnormal gastric emptying. Unlike the gastric emptying results, HR-EGG abnormalities correlated with a variety of symptoms. For example, the degree of abnormal slow wave direction was associated with abdominal pain and discomfort, which is not a cardinal symptom in gastroparesis but a predominant one in functional dyspepsia (24). Collectively, these findings suggest the HR-EGG may be particularly attractive within the context of functional dyspepsia, irrespective of gastric motor function. Abnormal spatial slow wave propagation did not explain all symptoms, though; there was a subset of symptomatic subjects (i.e., 11/25 subjects) with normal slow wave propagation. Therefore, we hypothesize that HR-EGG may identify the subset of patients with functional dyspepsia and gastroparesis for whom gastric myoelectric dysfunction is an important pathophysiologic contributor to their condition.

Loss of interstitial cells of Cajal (ICC) has been identified as an potential biomarker in the pathogenesis of gastroparesis (45). It has been associated with gastric emptying (46) as well as gastric dysrhythmias measured from both the serosal (20) and cutaneous (47) surfaces. Loss of ICC has also been observed in chronic unexplained nausea and vomiting with normal gastric emptying, albeit to a lesser degree than in gastroparesis (21). Histological studies combined with HR-EGG can aid in determining the causality of symptoms and inform future therapies.

One limitation of our study was that the CT imaging was not performed at the time of electrode placement. We used scans from within three years of the recording, so changes in body composition may have occurred. Also, the images were in the fasting state; the stomach position and angle can change after a meal. To account for this variability, we defined a 120-degree window for normal slow wave propagation direction. Other localization approaches can be used in subsequent studies (e.g., ultrasound) that do not result in radiation exposure and provide measurements at the time of array placement. Another limitation of our study was that the gastric emptying test was not performed at the time of the HR-EGG recording and symptom assessment. Symptoms are dynamic and there is longitudinal variability in gastric emptying (48–50); a stronger correlation between gastric emptying and EGG has been previously reported when conducted simultaneously (51). We did not conduct HR-EGG measurements during the gastric emptying study because our recording equipment did now allow patients to move between images. Simultaneous measurements could be made in future studies using a recently developed wireless bioamplifier system (52).

In conclusion, HR-EGG has the potential to address several unmet needs in clinical gastroenterology. As an objective measure that correlates with symptoms, HR-EGG can be used to quantify improvement and guide therapies. The ability to subtype problems with gastric function beyond gastric emptying in both gastroparesis and functional dyspepsia can enable optimal targeted interventions, such as electrical pacing to normalize the gastric slow wave (53,54). As a noninvasive measure, HR-EGG can be easily repeated for multiple meals to account for inconsistencies in gastric emptying from day to day, which can be up to 31% (48–50). Also, our methodological refinements pave the way for ambulatory monitoring that can be repeated *ad infinitum* (23), which leads to observations outside of the clinic under a variety of conditions, including sleep. When combined with digital symptom annotation using smartphone technology, it can also create unique opportunities for prospective symptom-association analyses, addressing challenges with symptom recall (55). Continuing advances in establishing the pathophysiological basis for symptoms in gastroparesis and functional dyspepsia will enable increasing levels of precision in treating these common disorders.

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Ethics Statement

This study was carried out at the University of California, San Diego and all study protocols and consent documents were approved by the institutional review board on June 19, 2014. We obtained informed consent from all subjects who participated in this study and methods were performed in accordance with relevant regulations and guidelines.

Data Availability

Data were analyzed using in-house code developed in Python v3.6.3 using Jupyter Notebook with the following modules: Numpy v1.13.3, Scipy v0.19.1, Pandas v0.20.3, Matplotlib v2.1.0 and Seaborn v0.8. All figures were made in Python v3.6.3 and formatted using Adobe Photoshop CC 2018. The datasets generated and analysed during the current study are included in the supplemental materials and are available from the corresponding author on reasonable request.

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Conflict of Interest

Guarantor of the article: David C. Kunkel, M.D.
Specific author contributions: Armen A. Gharibans: study design, subject recruitment, data collection, data analysis, statistical analysis, manuscript preparation; Hayat Mousa: contribution to manuscript preparation; Todd P. Coleman: study design, data analysis, contribution to manuscript preparation; David C. Kunkel: study design, subject recruitment, data analysis, contribution to manuscript preparation. All authors have read and approved the final manuscript.
Financial support: None
Potential competing interests: None.

Study Highlights

The items under each heading should be bullet points that are very short, i.e., up to about 15 words.

1. WHAT IS CURRENT KNOWLEDGE
    - The link between foregut symptoms and gastric emptying is controversial.
    - Subtyping the specific pathophysiologic contributors to functional dyspepsia and gastroparesis can lead to targeted therapies.
    - Serosal electrical mapping has shown that spatial slow wave abnormalities are present in gastroparesis and functional gastrointestinal disorders.

2. WHAT IS NEW HERE
    - We detected spatial abnormalities of the slow wave noninvasively in gastroparesis and functional dyspepsia.
    - Abnormal slow wave direction correlated significantly with clinical symptom severity, regardless of gastric emptying status.
    - We propose that spatial parameters of the gastric slow wave be given important consideration in the evaluation of patients with functional dyspepsia and gastroparesis.

Figures and Tables

Table 1. Characteristics for control, functional dyspepsia, and gastroparesis subjects.

	Control (n=7) No. (%)	Functional Dyspepsia[a] (n=7) No. (%)	Gastroparesis (n=18) No. (%)	p value[b]
Sex				
Female	3 (43)	4 (57)	10 (56)	.89
Male	4 (57)	3 (43)	8 (44)	
Age (years)				
Mean ± SD	48 ± 28	60 ± 14	54 ± 16	.45
18-30	3 (43)	0 (0)	1 (6)	
30-60	1 (14)	4 (57)	11 (61)	
60+	3 (43)	3 (43)	6 (33)	
Body Mass Index (BMI) (kg/m^2)				
Mean ± SD	24 ± 4	25 ± 5	26 ± 5	.58
Underweight (< 18.5)	0 (0)	1 (14)	1 (6)	
Normal (18.5 - 24.9)	4 (57)	2 (29)	6 (33)	
Overweight (25 - 29.9)	2 (29)	3 (43)	7 (39)	
Obese (> 30)	1 (14)	1 (14)	4 (22)	
Ethnicity				
Non-Hispanic White	4 (57)	6 (86)	13 (72)	.14
Hispanic	2 (29)	0 (0)	5 (28)	
Asian	1 (14)	0 (0)	0 (0)	
Black	0 (0)	1 (14)	0 (0)	
Martial Status				
Single	3 (43)	1 (14)	8 (44)	.49
Married	4 (57)	6 (86)	10 (56)	
Employment Status				
Employed	3 (43)	1 (14)	1 (6)	.06
Unemployed	4 (57)	6 (86)	17 (94)	
Previous Surgery				
Appendectomy	1 (14)	0 (0)	3 (17)	.79
Hysterectomy	0 (0)	0 (0)	2 (11)	1.0
Cholecystectomy	1 (14)	0 (0)	4 (22)	.58
Gastric/Esophageal	0 (0)	0 (0)	1 (6)	1.0
Abdominal/Bowel	0 (0)	2 (29)	6 (33)	.29
Current Drug Use				
Prokinetics	0 (0)	2 (29)	7 (39)	.22
Opioids	0 (0)	2 (29)	9 (50)	.05*
Cannabis	1 (14)	2 (29)	5 (28)	.87
None	6 (86)	3 (43)	6 (33)	.07
Diabetes				
Yes	0 (0)	0 (0)	7 (39)	.05*
Type I	n/a	n/a	3 (17)	
Type II	n/a	n/a	4 (22)	
Rome III				
Functional Dyspepsia	0 (0)	7 (100)	17 (94)	<.001*
Etiology of Gastroparesis				
Diabetes	n/a	n/a	7 (39)	
Idiopathic	n/a	n/a	4 (22)	
Postviral	n/a	n/a	2 (11)	
Scleroderma	n/a	n/a	2 (11)	
Postsurgical	n/a	n/a	1 (6)	
Sarcoidosis	n/a	n/a	1 (6)	
Parkinson's	n/a	n/a	1 (6)	

[a] Functional dyspepsia group meets Rome III criteria with normal gastric emptying.
[b] P values are from Fisher's exact test for categorial variables and one-way analysis of variance (ANOVA) for continous variables.

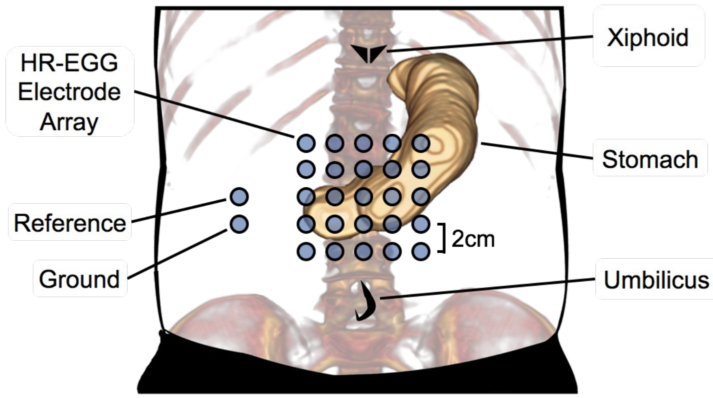

Fig 1. A cutaneous HR-EGG electrode array (25 channels with 2cm electrode spacing) placed over the antrum, which is identified from the subject’s abdominal CT scan. The reference and ground electrodes are on the subject’s right side.

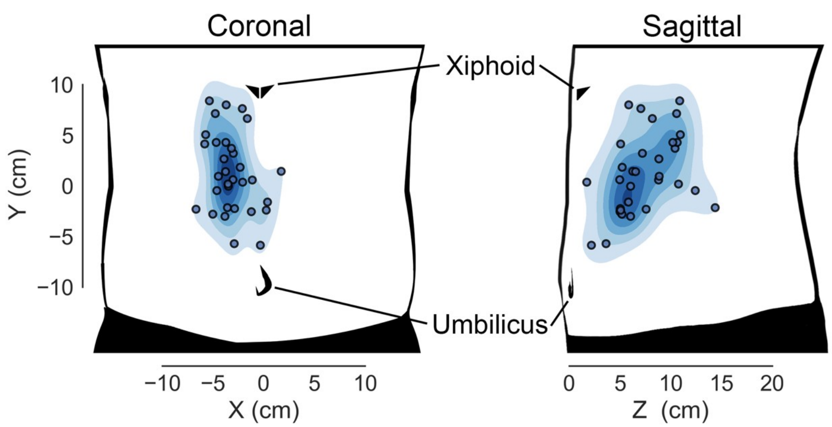

Fig 2. Anatomical variation in the location of the pylorus determined from cross-sectional imaging across 32 subjects. The reference point is halfway between the xiphoid and umbilicus.

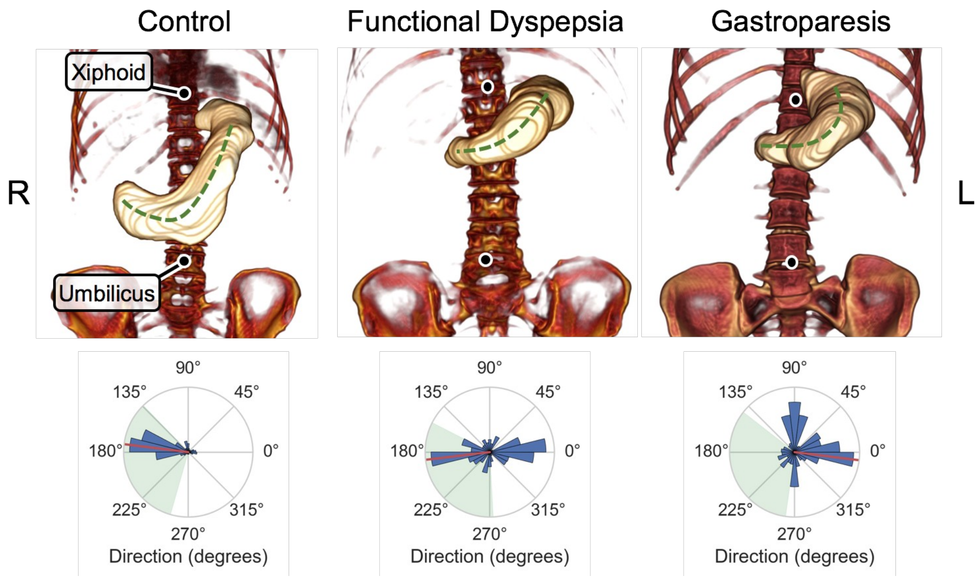

Fig 3. Coronal view of volumetric CT reconstructions for three representative subjects (top). The dotted blue line indicates the coronal projection of the medial axis of the stomach. Polar histograms of HR-EGG estimated slow wave direction throughout the recording (bottom). The green region indicates mean stomach angle ± 60 degrees and the red line is the most frequent slow wave direction.

Table 2. Descriptive statistics of study variables comparing the control, functional dyspepsia, and gastroparesis groups.

	Control (n=7) Mean ± SD	Functional Dyspepsia[a] (n=7) Mean ± SD	Gastroparesis (n=18) Mean ± SD	Overall (p value)[b]	Pairwise Comparisons (p value)[c]		
					C vs. FD	C vs. GP	FD vs. GP
Traditional EGG							
2-4 cpm Activity (%)	97 ± 5	92 ± 6	95 ± 6	.24			
Bradygastria (%)	0.6 ± 1.0	0.3 ± 0.9	0.1 ± 0.4	.31			
Tachygastria (%)	2.5 ± 3.8	7.6 ± 5.6	4.4 ± 5.4	.19			
Slow Wave Frequency (Hz)	0.053 ± 0.004	0.055 ± 0.007	0.053 ± 0.005	.74			
Postprandial Power Change (dB)	3.5 ± 4.0	3.3 ± 4.3	2.3 ± 4.1	.75			
High-Resolution EGG							
Abnormal Direction (%)	29 ± 8	39 ± 14	39 ± 15	.25			
Sustained Waves (%)	72 ± 17	47 ± 24	50 ± 21	.04*	.04*	.02*	.74
Speed (mm/s)	5.8 ± 0.4	4.9 ± 0.7	5.3 ± 0.7	.02*	.008*	.03*	.25
Symptoms							
Nausea-Vomiting Subtype	0.0 ± 0.0	0.8 ± 1.0	1.9 ± 1.3	.002*	0.07	.001*	.05*
Fullness-Early Satiety Subtype	0.1 ± 0.3	2.2 ± 0.8	3.1 ± 1.1	<.001*	<.001*	<.001*	.07
Bloating-Distension Subtype	0.6 ± 1.5	2.7 ± 1.0	2.8 ± 1.5	.005*	.01*	.004*	.95
Mean GCSI Score	0.2 ± 0.3	1.8 ± 0.6	2.6 ± 0.9	<.001*	<.001*	<.001*	.05*
Mean PAGI-SYM	0.1 ± 0.2	1.6 ± 0.8	2.3 ± 0.9	<.001*	<.001*	<.001*	.06

GCSI: Gastroparesis Cardinal Symptom Index, PAGI-SYM: Patient Assessment of Upper Gastrointestinal Disorders - Symptoms Severity Index

[a] Functional Dyspepia group meets Rome III criteria with normal gastric emptying.

[b] Overall p values are from one-way analysis of variance (ANOVA).

[c] P values for pairwise comparisons are from two-sided unpaired t-tests with no correction.

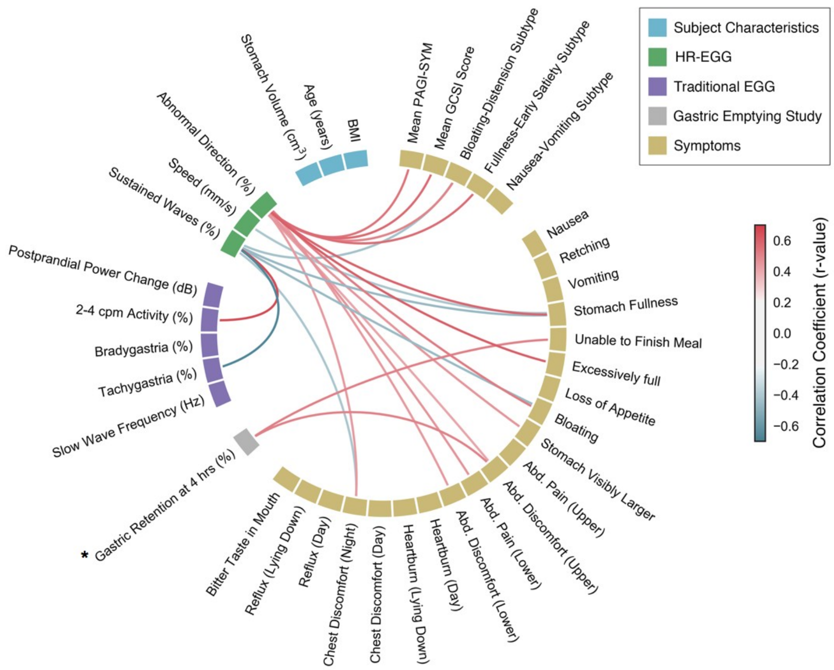

Fig 4. Circular plot showing robust correlation between HR-EGG parameters (e.g., abnormal slow wave direction, speed, and percentage of sustained waves) with bloating/distension/fullness, abdominal discomfort/pain and overall GSCI score across all subjects (n = 32). Consistent with other findings, gastric emptying showed few associations with symptoms and traditional EGG parameters had none. Measures from similar categories are grouped and only statistically significant correlations between categories are shown (after Benjamini-Hochberg correction). *Correlations with gastric emptying scintigraphy do not include the control group (n = 25).

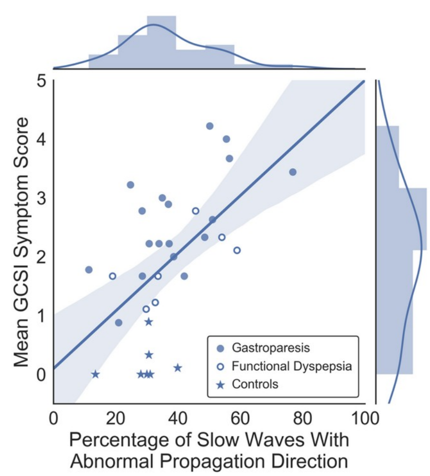

Fig 5. Scatter plot of percentage slow waves with abnormal propagation direction estimated with HR-EGG and overall Gastroparesis Cardinal Symptom Index (GCSI) symptom score for all subjects. Solid circle indicates gastroparesis (n = 18), hollow circles represent functional dyspepsia with normal gastric emptying (n = 7), and stars represent healthy controls (n = 7). The blue line is a linear least-squares regression and the light blue shading is the corresponding 95% confidence interval (n = 32, r = 0.57, p < .001).

Cover Letter

July 24, 2018

Dear Editors,

Please find our manuscript entitled, "Abnormal Spatial Patterns on Cutaneous High-Resolution Electrogastrogram Correlates with Symptom Severity in Functional Dyspepsia and Gastroparesis" that we are submitting for consideration for publication in the *American Journal of Gastroenterology*.

Background and Results: Our team has pioneered the cutaneous high-resolution electrogastrogram (HR-EGG), which addresses the shortcomings of single and multi-channel EGG measurements of the past. In previous publications, we showed that HR-EGG along with methodological refinements (e.g., artifact removal, array placement) yield significantly improved correlation with gastric manometry and can noninvasively measure slow wave propagation direction and speed. In this manuscript, we present our application of these techniques, for the first time, in a population with functional dyspepsia and gastroparesis. Our key finding was that unlike traditional EGG measures and gastric emptying, the degree of spatial slow wave abnormalities measured by HR-EGG exhibited statistically significant correlation with numerous clinical symptoms (e.g., overall GCSI score, bloating, early satiety, pain). Moreover, despite improved methodological refinements, the traditional EGG features did not have any statistically correlation with any symptom.

Significance and Impact: HR-EGG has the potential to address several unmet needs in clinical gastroenterology. As an objective measure that correlates with symptoms, HR-EGG can be used to quantify improvement and guide therapies. The ability to subtype problems with gastric function beyond gastric emptying in both gastroparesis and functional dyspepsia can enable targeted interventions, such as electrical pacing to normalize the gastric slow wave. As a noninvasive measure, HR-EGG can be easily repeated for multiple meals to account for inconsistencies in gastric emptying from day to day, which can be up to 31%. Also, our methodological refinements pave the way for ambulatory monitoring that can be repeated *ad infinitum*, which leads to observations outside of the clinic under a variety of conditions including sleep. When combined with digital symptom annotation using smartphone technology, it can also create unique opportunities for prospective symptom-association analyses, addressing challenges with symptom recall.

We believe these findings will renew interest in advancing noninvasive gastrointestinal measurements to establish clinical utility. Continuing advances in establishing the pathophysiological basis for symptoms in gastroparesis and functional dyspepsia will enable increasing levels of precision in treating these common disorders.

Given their relevant expertise, we suggest the following individuals for consideration as reviewers of the manuscript:

- Linda Nguyen, MD (Stanford) nguyenlb@stanford.edu
- John Clarke, MD (Stanford) jclarke2@stanford.edu
- Lin Chang, MD (UCLA) linchang@mednet.ucla.edu
- Thomas L. Abell, MD (University of Louisville) thomas.abell@louisville.edu
- Gregory O'Grady, MBChB, PhD (University of Auckland) greg.ogrady@auckland.ac.nz
- Adil E. Bharucha, MD, MBBS (Mayo Clinic, Rochester) bharucha.adil@mayo.edu
- Jan Tack, MD, PhD (KU Leuven, Belgium) jan.tack@kuleuven.be
- Bruno Chumpitazi, MD (Texas Children's Hospital) chumpita@bcm.edu
- Robert J. Shulman, MD (Texas Children's Hospital) rshulman@bcm.edu
- Gisela G. Chelimsky, MD (Children's Hospital of Wisconsin) gchelimsky@mcw.edu

Due to a conflict of interest potentially affecting impartiality, we respectfully request that Kenton Sanders, MD (University of Nevada, Reno) and Kenneth L. Koch, MD (Wake Forest University) NOT be considered as reviewers.

This manuscript has not been published previously and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. As corresponding author, I have obtained permission from all co-authors for submission of this manuscript.
Thank you for considering our manuscript for publication in *American Journal of Gastroenterology*.

Sincerely,

DAVID C. KUNKEL, MD
Assistant Clinical Professor of Medicine
Co-Director, GI Motility & Physiology Program
Division of Gastroenterology
University of California, San Diego
9500 Gilman Drive, #0956

La Jolla, CA 92093-0956