Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping

Gregory O’Grady,1,2 Peng Du,2 Leo K. Cheng,2 John U. Egbuji,1,2 Wim J. E. P. Lammers,2,3 John A. Windsor,1 and Andrew J. Pullan2,4,5

1Department of Surgery, 2Auckland Bioengineering Institute, and 4Department of Engineering Science, The University of Auckland, Auckland, New Zealand; 3Department of Physiology, United Arab Emirates University, Al Ain, United Arab Emirates; and 5Department of Surgery, Vanderbilt University, Nashville, Tennessee

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O’Grady G, Du P, Cheng LK, Egbuji JU, Lammers WJ, Windsor JA, Pullan AJ. Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping. Am J Physiol Gastrointest Liver Physiol 299: G585–G592, 2010. First published July 1, 2010; doi:10.1152/ajpgi.00125.2010.—Slow waves coordinate gastric motility, and abnormal slow-wave activity is thought to contribute to motility disorders. The current understanding of normal human gastric slow wave activity is based on extrapolation from data derived from sparse electrode recordings and is therefore potentially incomplete. This study employed high-resolution (HR) mapping to reevaluate human gastric slow-wave activity. HR mapping was performed in 12 patients with normal stomachs undergoing upper abdominal surgery, using flexible printed circuit board (PCB) arrays (interelectrode distance 7.6 mm). Up to six PCBs (192 electrodes; 93 cm²) were used simultaneously. Slow-wave activity was characterized by spatiotemporal mapping, and regional frequencies, amplitudes, and velocities were defined and compared. Slow-wave activity in the pacemaker region (mid to upper corpus, greater curvature) was of greater amplitude (mean 0.57 mV) and higher velocity (8.0 mm/s) than the corpus (0.25 mV, 3.0 mm/s) (P < 0.001) and displayed isotropic propagation. A marked transition to higher amplitude and velocity activity occurred in the antrum (0.52 mV, 5.9 mm/s) (P < 0.001). Multiple (3–4) wavefronts were found to propagate simultaneously in the organoaxial direction. Frequencies were consistent between regions (2.83 ± 0.35 cycles per min). HR mapping has provided a more complete understanding of normal human gastric slow-wave activity. The pacemaker region is associated with high-amplitude, high-velocity activity, and multiple wavefronts propagate simultaneously. These data provide a baseline for future HR mapping studies in disease states and will inform noninvasive diagnostic strategies.

SLOW WAVES ARE GENERATED AND propagated by interstitial cells of Cajal (ICC) in the stomach wall and confer a fundamental level of control over gastric motility by initiating and coordinating peristalsis (28). ICC loss and network degradation have been described in association with several gastrointestinal (GI) motility disorders, including diabetic gastroenteropathy (12, 24). Abnormal slow-wave activity has been implicated as a disease mechanism in several functional gastric disorders, notably gastroparesis and functional dyspepsia (20, 21).

A number of previous studies have contributed to the current understanding of the origin and propagation of normal slow-wave activity in the stomach (11, 13, 35). In humans, slow waves are understood to originate from a pacemaker region near the greater curvature of the mid to upper corpus and to propagate toward the pylorus with an increase in antral velocity and amplitude, at a frequency of approximately three cycles per min (cpm) (11, 22). The fundus is typically considered to be devoid of slow waves. It has often been assumed that each new wave begins in the corpus while the previous wave is terminating in the distal antrum, such that only one wave is usually propagating at any one time (2, 14).

All previous studies of normal human gastric slow-wave propagation have employed a limited number of recording electrodes (typically 4–8) sutured to the gastric serosa (10, 11, 22). Although these techniques have been instrumental in outlining the general pattern of gastric slow-wave activity, they also have some important limitations. In particular, extrapolating whole organ activity from a few samples at low spatial resolution requires significant assumptions to be made regarding what is occurring in the unmeasured areas. Therefore, the current understanding of human gastric slow-wave activity is potentially inaccurate and/or incomplete, which may prove to be a barrier to the development of effective treatments for gastric motility disorders.

In other fields of electrophysiology, notably cardiology, sparse electrode studies have been superseded by high-resolution (HR) mapping, whereby spatially dense arrays of multiple electrodes are used to simultaneously record from many sites over a defined field (31). Activation maps (graphic analyses of electrical propagation) can be derived from these recordings to quantify the characteristics and spread of electrical activation in much more accurate spatiotemporal detail than sparse electrode recordings can provide (6, 23). HR mapping of the GI tract was introduced by Lammers et al. (17) and has recently enabled valuable new insights into normal and dysrhythmic slow-wave propagation in the canine stomach (18, 19).

In this study, HR mapping was employed to reevaluate the origin and propagation of slow-wave activity in the normal human stomach.

MATERIALS AND METHODS

Study population and preparation. All experiments were performed in vivo on patients in the operating room, after the abdominal incision had been made and prior to undertaking the planned elective surgery. Ethical approval was granted by the New Zealand Northern Regional Ethics Committee. Adult patients of either sex who were undergoing elective upper abdominal surgery at Auckland City Hospital were invited to participate, and all participating patients provided their informed consent.
Patients were excluded if they had a known gastric pathology or a condition in which dysrhythmic gastric activity has previously been described, including gastroparesis, diabetes mellitus, gastric tumors, pregnancy, anorexia nervosa, functional dyspepsia, atrophic gastritis, hyper- or hypothyroidism, or gastroesophageal reflux disease (14). Patients who had previous gastric surgery were also excluded. In addition, patients on gastric prokinetic agents or medications that are suspected to interfere with gastric electrical activity were further excluded, including progesterone, erythromycin, domperidone, metoclopramide, and imatinib (a tyrosine kinase inhibitor used in the treatment of ICC-related tumors).

No restrictions were placed on the anesthetic protocols used for the included patients. The effects of different anesthetic agents on GI slow waves have not been comprehensively evaluated in the intraoperative setting, although a number of studies investigating normal slow-wave behavior have previously been successfully performed in the anesthetized state in animal models (6, 16, 18). Existing descriptions of human gastric slow-wave propagation were also derived from studies performed under anesthesia (11).

All patients in this study received the following routine combinations of perioperative and anesthetic agents prior to the onset of mapping: 1) prophylactic antibiotics (typically cefoxitin), 2) a benzodiazepine premedication (midazolam), 3) an epidural anesthetic (typically ropivacaine or bupivacaine), 4) a short-acting intravenous opiate (typically fentanyl), 5) a muscle relaxant (typically suxamethonium or atracurium), 6) an anesthetic induction agent (propofol), and 7) an inhalational anesthetic agent (isoflurane or sevoflurane). Other commonly administered medications included dexamethasone and metaraminol (a sympathomimetic used to counter anesthesia-induced hypotension). Sporadic episodes of gastric tachyarrhythmias have previously been described during open abdominal mapping following the administration of fentanyl (19); however, opioids were not withheld in this study because of ethical considerations regarding their routine use to facilitate intubation and intraoperative anesthesia.

Methods of HR mapping. Flexible printed circuit board (PCB) multielectrode arrays were developed and validated for in vivo HR slow-wave mapping prior to this study (Fig. 1A) (6). These arrays consist of copper wires and gold contacts on a polyimide ribbon base. PCBs have a modestly lower recording quality than the resin-embedded arrays produced with high-fidelity at low cost, and therefore are also potentially used in the intraoperative setting, although a number of studies investigating normal slow-wave behavior have previously been successfully performed in the anesthetized state in animal models (6, 16, 18). Existing descriptions of human gastric slow-wave propagation were also derived from studies performed under anesthesia (11).

Fig. 1. A: flexible printed circuit board (PCB) electrode design used in this study. Each PCB has 32 electrodes per head (4 × 8 configuration; interelectrode distance 7.6 mm). B: multiple PCBs were arranged in parallel alignment before intraoperative mapping, and attached to ribbon cables that were stabilized against a ring retractor.
region could be assessed. Some regional velocity and amplitude data were noted to be moderately skewed, so this data was log-transformed for analysis and the backtransformed estimates were presented. Mean values and their 95% confidence intervals are given, based on the regression analyses.

RESULTS

Study population. Intraoperative HR mapping was performed on 12 patients (7 men and 5 women) of median age 50 (range 21–60) yr. These patients were undergoing pancreatic surgery (n = 6), esophageal surgery (n = 2), liver resections (n = 2), transduodenal excision of an ampullary mass (n = 1), or total gastrectomy (a prophylactic procedure in a patient with an E-cadherin mutation and no known gastric pathology) (n = 1). Five of these patients had previously completed various regimens of preoperative chemotherapy, and none had known metastatic disease. A total of 29 recordings were taken (mean 2.4 per patient) for a total duration of 135 min (mean 11.5 ± 3.9 min per patient).

Slow-wave frequency and rhythm. The mean slow-wave frequency across the population sample was 2.83 ± 0.35 cpm. There was no difference between frequencies at the pacemaker region (2.85 ± 0.27 cpm), corpus (2.80 ± 0.34 cpm), and antrum (2.86 ± 0.41 cpm) (P = 0.3). No dysrhythmias were observed in any recording during the entire study, and no data from the different gastric regions are presented in Fig. 3. Gastric corpus. The corpus activity was continuous with the pacemaker activity. Aboral to the pacemaker area, the slow-wave activity organized into a circumferential band propagating in the organoaxial direction (down the longitudinal axis of the organ) toward the pylorus (Fig. 4). The box-plot diagram (Fig. 3) demonstrates the relatively lower amplitude and velocity of the corpus slow-wave activity compared with the activity in the pacemaker region. There were no differences in

![Fig. 2. A: activity at the human gastric pacemaker. i: Position of the electrodes during pacemaker mapping. ii: Activation map, corresponding to the mapped area outlined in yellow in i. Each black point represents an electrode and each isochronal color band demonstrates the area of slow-wave propagation per 1-s time step. Activity propagated for only a limited distance toward the fundus (30 mm) and cardia (30 mm) before terminating (blank area). iii: Velocity field map. Velocities were markedly greater in the pacemaker region than in the surrounding corpus (mean velocity for displayed field = 7.8 mm/s). iv: Pacemaker electrogams from 9 representative channels, corresponding to electrode positions 1–9 on the electrode diagram (i) and activation time map (ii). Activity in the pacemaker region is of higher amplitude than that of the surrounding corpus. B: a further example from a second subject. Slow waves propagated for a limited distance toward the fundus (30 mm) and cardia (30 mm) before terminating. Activity was consistently of higher velocity and amplitude in the pacemaker region compared with the corpus.](http://ajpgi.physiology.org/DownloadedFrom)
propagation velocities between the proximal corpus (mean 3.3 mm/s; CI: 2.7, 4.0), the mid corpus (mean 3.0 mm/s; CI: 2.5, 3.5), and the distal corpus (mean 3.1 mm/s; CI: 2.6, 3.7). Similarly, there were no differences in slow-wave amplitudes between the proximal corpus (mean 0.28 mV; CI: 0.23, 0.35), mid corpus (mean 0.24 mV; CI: 0.19, 0.29), and distal corpus (mean 0.25 mV; CI: 0.21, 0.31). Corpus slow waves were of longer duration and less steep morphology than pacemaker and antral waves (Fig. 4D), and sometimes showed two or more small negative deflections, rather than a single deflection, therefore being similar to the “fractionated” activity described in the heart and in the canine corpus (9, 18) (see Fig. 5).

More than two simultaneously propagating slow-wave events were always observed in the corpus recordings, at a spacing that was dependent on the slow-wave frequency and velocity. For example, in the sequences shown in Fig. 4, the slow-wave frequency was ~2.9 cpm (period 20.6 s) and the corpus velocity was 2.7 mm/s. Accordingly, the leading edges of active fronts of successive waves can be observed in the corpus of this subject at a separation of ~55 mm. Because of the presence of multiple simultaneous wavefronts, it would be difficult using a sparse-electrode (low resolution) approach to accurately determine which slow waves in consecutive channels belonged to the same propagation cycle, as demonstrated in Fig. 4F.

Fig. 4. A: position of the PCB electrodes during an episode of gastric corpus mapping. B: activation map of slow-wave propagation in the corpus, from the mapped area indicated in yellow in A, and for the wave sequence indicated by the arrow in D. The wavefront is organized as a band of excitation propagating in the aboral direction. C: conduction velocity was consistent within the corpus and was low compared with the velocities in other regions (mean velocity 2.7 mm/s for the presented cycle). D: corpus electrogram sequence from 18 representative electrodes of the 192 total, from the orientation shown in A and the specific configuration indicated in B. Corpus slow waves are of low amplitude compared with the activity in other regions. E: 3 different wave fronts (a, b, and c) are shown to be simultaneously propagating in the corpus over a 10-s time segment. F: a sparse electrode sample is mimicked from 3 selected channels from D. With sparse (low-resolution) electrode recordings, it is difficult to determine which waves in consecutive recordings in the corpus belong to the same cycle. For example, it may be assumed that the waves indicated by the solid line belong to a common cycle; however, as revealed by studying the higher-resolution electrograms in D, the dashed line indicates the correct sequence.
of three or more wavefronts propagating simultaneously in the organoaxial direction, and 3) a marked increase in amplitude and velocity in the antrum. These findings provide a substantially more complete understanding of human gastric slow-wave propagation, which is summarized in Fig. 7.

Gastric contractions are initiated and coordinated by slow-wave activity, and the results from this study are generally consistent with existing descriptions of human gastric motility. MRI studies of contraction wave propagation in healthy stomachs have demonstrated a contractile displacement rate of ~2.5 mm/s (15, 26, 30), which is similar to the corpus velocities described in this study. The presence of two or more simultaneously propagating contraction waves has been described (30), and Pal et al. (26) have previously quantified their spacing at ~60 mm, which is again in accordance with the electrophysiology data presented in this study. A relatively sudden transition to more rapid propagation within the antrum has not been reported in previous gastric MRI studies to our knowledge; however, as pointed out by Carlson et al. (4), it is possible that this acceleration in antral slow-wave velocity actually serves to induce a nearly simultaneous contraction of the distal stomach. It may be difficult to observe a transition from peristalsis to simultaneous contraction over a relatively short gastric segment on MRI, and it would be of interest to study this phenomenon further.

The present study was performed on fasted patients undergoing surgery, and it is possible that differences in activity may occur in the awake fed state, particularly as a consequence of neurohormonal influences. For example, Sarna et al. (29) showed that slow waves were not usually recorded near the lesser curvature of the corpus in the dog, but that the administration of acetylcholine could induce them. However, the concordance in timing between the slow-wave data and awake MRI contraction dynamics, as discussed above, provides reassurance that preoperative fasting and anesthesia are unlikely to have had any significant effects on the general patterns of slow-wave activity, and the results from this study are generally consistent with existing descriptions of human gastric motility. MRI studies of contraction wave propagation in healthy stomachs have demonstrated a contractile displacement rate of ~2.5 mm/s (15, 26, 30), which is similar to the corpus velocities described in this study. The presence of two or more simultaneously propagating contraction waves has been described (30), and Pal et al. (26) have previously quantified their spacing at ~60 mm, which is again in accordance with the electrophysiology data presented in this study. A relatively sudden transition to more rapid propagation within the antrum has not been reported in previous gastric MRI studies to our knowledge; however, as pointed out by Carlson et al. (4), it is possible that this acceleration in antral slow-wave velocity actually serves to induce a nearly simultaneous contraction of the distal stomach. It may be difficult to observe a transition from peristalsis to simultaneous contraction over a relatively short gastric segment on MRI, and it would be of interest to study this phenomenon further.

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slow-wave propagation described here. Whereas opioids have previously been associated with gastric tachyarrhythmias in canines (19), no dysrhythmias were observed in any patient in this study despite the routine use of rapid-acting opioids, possibly because these agents were systemically cleared prior to the onset of mapping.

In contrast to animal studies, this HR mapping study on human subjects is constrained by the reduced recording time per subject and the modestly inferior signal quality of the PCB arrays (6). Despite this, the results are consistent with the HR description of canine gastric slow-wave activity recently presented by Lammers et al. (18). Both studies show high-amplitude and high-velocity activity in association with the pacemaker region, a marked transition in activity in the antrum, and multiple simultaneously propagating wavefronts. The mechanisms underlying these regional differences are yet to be fully determined. Fractionated slow-wave activity was also observed in both human and canine corpus mapping, and is also evident in the corpus electrograms shown in earlier human studies (11); however, its significance remains uncertain.

Spike activity (smooth muscle action potentials) was not observed in this study. As pointed out by Sanders (27), it is likely that the role of spikes in gastric motility has been overstated in previous years, partly owing to outdated terminology referring to slow waves as “electrical control activity” and spikes as “electrical response activity.” In vitro studies have since demonstrated that slow waves alone can induce excitation-contraction coupling in the stomach (25). Nevertheless, spike activity is well known to be associated with gastric contractions, having been most consistently described in the distal antrum (4, 34). It is possible that spikes were not observed in this study because of the gastric quiescence induced by fasting and surgery.

Lammers et al. (18) localized the gastric pacemaker site in the canine to the high greater curvature and reported that a small area of the adjacent fundus was activated by slow waves. Another recent high-resolution study by Egbruji et al. (8) has also located the porcine pacemaker in the fundus, near the greater curvature. The present study, however, supports the established sparse-electrode description by Hinder and Kelly (11) that the human gastric pacemaker is normally located at the greater curvature of the mid to upper corpus.

There have been variable findings from sparse-electrode studies regarding the existence of slow-wave activity in the human fundus. Hinder and Kelly (11) reported in a series of 26 patients that slow-wave activity could never be recorded in the fundus or cardia. Halpern et al. (10) reported that low-amplitude fundal activity could be detected in 4 of 138 recordings from 18 patients (3 of the fundal recordings being from the same patient), whereas Waldhausen et al. (34) reported that fundal slow waves were found in 87–94% of patients. Our data support the finding that the fundus is usually devoid of slow waves, and it may be that only a small percentage of the population have fundal slow-wave activity. More sensitive recording arrays would be required to exclude the possibility that very-low-amplitude fundal activity is present more often.

The finding of multiple simultaneous propagating slow-wave fronts was noteworthy, since it is often still assumed that only one electrical wavefront is usually propagating at a time (e.g., Refs. 2, 14), despite the contrary existing evidence from imaging studies. Verhagen et al. (33) have previously pointed
out that two to three waves are likely to be simultaneously present, and this study finds that up to three to four waves occur at once. This finding is relevant to attempts to interpret electrogastrography (EGG), where a frequent assumption has been that the EGG can conveniently be related back to a single electrophysiological source (wavefront), as is the case for the interpretation of the normal electrocardiogram (ECG) (2, 14). This erroneous assumption has perhaps arisen from an understandable tendency to alias the signals generated from sparse-electrode recordings, particularly when taken from the corpus, as was demonstrated in Fig. 4F. The results of this study will help to inform a more definitive understanding of the electrophysiological basis of the EGG and therefore may help improve its clinical application.

The finding of multiple simultaneous propagating wavefronts also presents a challenge for researchers of magnetogastrography (MGG), a diagnostic approach that attempts to use magnetometers to noninvasively evaluate gastric electrical disorders (1). Previously, model-based inverse approaches have relied on simple dipole methods to define the relationship between MGG far-field measurements and slow-wave activity, again assuming a single source, in a strategy adapted from cardiac research (3, 5). The results of this study indicate that using dipole methods to accurately track the gastric sources would be problematic, and other approaches to informing MGG analysis should therefore be considered.

Technical advances may assist in further refining this description of human gastric slow-wave activity. Ultimately, it would be preferable to map the anterior and posterior gastric surfaces at the pacemaker region simultaneously, with more exact anatomical registration (e.g., with concurrent imaging) and at higher spatial resolutions. Technical advances in anatomical registration and electrode design could also be applied to determine the exact location and width of the transition zone occurring within the antrum. Qualitatively, the results of this study suggest that this electrophysiological transition site may be somewhat distal to the traditionally recognized anatomical site of the corpus-antrum border (e.g., Fig. 6), and a formal study of this matter would therefore be of interest.

The normal human data presented in this study, enabled by the development of new recording technologies, have paved the way for comparative studies of slow-wave activity in disease states. A principal limiting factor to the more widespread use of HR mapping in clinical practice is the invasive nature of recording; however, some opportunities do currently exist to clinically apply MGG to determine the exact location and width of the transition zone occurring within the stomach. Qualitatively, the results of this study suggest that this electrophysiological transition site may be somewhat distal to the traditionally recognized anatomical site of the corpus-antrum border (e.g., Fig. 6), and a formal study of this matter would therefore be of interest.

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Technical advances may assist in further refining this description of human gastric slow-wave activity. Ultimately, it would be preferable to map the anterior and posterior gastric surfaces at the pacemaker region simultaneously, with more exact anatomical registration (e.g., with concurrent imaging) and at higher spatial resolutions. Technical advances in anatomical registration and electrode design could also be applied to determine the exact location and width of the transition zone occurring within the antrum. Qualitatively, the results of this study suggest that this electrophysiological transition site may be somewhat distal to the traditionally recognized anatomical site of the corpus-antrum border (e.g., Fig. 6), and a formal study of this matter would therefore be of interest.

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