Published in final edited form as:

Neurogastroenterol Motil. 2011 September ; 23(9): e345–e355. doi:10.1111/j.1365-2982.2011.01739.x.

High-resolution spatial analysis of slow wave initiation and conduction in porcine gastric dysrhythmia

Gregory O'Grady^{1,2,*}, John U. Egbuji^{1,2,*}, Peng Du², Wim J.E.P. Lammers^{2,3}, Leo K. Cheng², John A. Windsor¹, and Andrew J. Pullan^{2,4,5}

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

Abstract

Background—The significance of gastric dysrhythmias remains uncertain. Progress requires a better understanding of dysrhythmic behaviors, including the slow wave patterns that accompany or promote them. The aim of this study was to use high-resolution (HR) spatiotemporal mapping to characterize and quantify the initiation and conduction of porcine gastric dysrhythmias.

Methods—HR mapping was performed on healthy fasted weaner pigs under general anesthesia. Recordings were made from the gastric serosa using flexible arrays (160–192 electrodes; 7.6mm spacing). Dysrhythmias were observed to occur in 14 of 97 individual recordings (from 8 out of 16 pigs), and these events were characterized, quantified and classified using isochronal mapping and animation.

Key Results—All observed dysrhythmias originated in the corpus and fundus. The range of dysrhythmias included incomplete conduction block (n=3 pigs; 3.9±0.5 cpm; normal range: 3.2±0.2 cpm) complete conduction block (n=3; 3.7±0.4 cpm), escape rhythm (n=5; 2.0±0.3 cpm), competing ectopic pacemakers (n=5, 3.7±0.1 cpm) and functional re-entry (n=3, 4.1±0.4 cpm). Incomplete conduction block was observed to self-perpetuate due to retrograde propagation of wave fragments. Functional re-entry occurred in the corpus around a line of unidirectional block. 'Double potentials' were observed in electrograms at sites of re-entry and at wave collisions.

Conclusions & Inferences—Intraoperative multi-electrode mapping of fasted weaner healthy pigs detected dysrhythmias in 15% of recordings (from 50% of animals), including patterns not previously reported. The techniques and findings described here offer new opportunities to understand the nature of human gastric dysrhythmias.

Keywords

Arrhythmia; bradygastria; conduction block; ectopic; re-entry; tachygastria

Address for Correspondence Dr Gregory O'Grady, Department of Surgery, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand., gog@ps.gen.nz.; Phone: 0064 21 448 523; Fax: 0064 9 377 9656.

*These authors contributed equally to this work.

Author contributions: GOG, JUE: study design, experiments and analysis, drafting of manuscript. PD, LKC: experiments and analysis, critical revision of manuscript. WJEPL, JAW, AJP: supervision of research, critical analysis and revision of manuscript.

Disclosures: No author has any conflict of interest to declare in relation to this work.

Introduction

Gastric dysrhythmias have been associated with several disorders of gastric motility, including gastroparesis, functional dyspepsia, and gastroesophageal reflux disease (1),(2),(3). However, the clinical significance of these associations remains uncertain, and current methods used to diagnose dysrhythmia continue to be of uncertain reliability (4), in turn impeding therapeutic advances.

An important barrier to clinical progress has been a limited understanding of the behavior of gastric dysrhythmia, including the slow wave propagation patterns that accompany, underlie or maintain them. A contributing factor to this poor understanding is that most previous studies of dysrhythmia have employed cutaneous electrogastrography (EGG) or sparse serosal or mucosal electrodes. While these tools have been usefully applied to define the deviations in frequency or rhythm that may accompany dysrhythmia (5), their lack of spatial resolution means that they cannot be reliably used to resolve, quantify or classify abnormal propagation patterns (6).

To overcome this problem, high-resolution (HR) multi-electrode mapping has recently been applied to study gastric dysrhythmia, whereby dense arrays of electrodes are placed over the tissue to track sequences of electrical activation in accurate spatiotemporal detail (6),(7). The utility of this approach was recently demonstrated in a study of canine antral tachygastric, in which new tissue-level mechanisms involving high spatial complexity were demonstrated to contribute to the dysrhythmias, including slow wave re-entry (6).

The aim of this study was to use HR mapping to characterize, quantify and classify several additional types of gastric dysrhythmia that were observed to occur spontaneously in the fundus and corpus during open-abdomen recording in healthy anaesthetized pigs. This work was motivated by the need to further establish an improved foundation for understanding the tissue-level mechanisms and behaviors of gastric dysrhythmia, in order to inform future clinical studies.

Materials and Methods

Animal Preparation

In-vivo HR mapping studies were performed on healthy white cross-breed weaner pigs of either sex and mean weight 37 ± 1 kg. Ethical approval was obtained from the University of Auckland animal ethics committee. Normal slow wave propagation data from these animals was described in another study, providing comparative data for the present work (8).

The animals were fasted overnight, then subjected to general anesthesia with Zoletil (tiletamine HCl 50 mg/ml and zolazepam HCl 50 mg/ml), and isoflurane (2.5 – 5% with an oxygen flow of 400 ml within a closed circuit anesthetic system). Opiates were not used. Vital signs including heart rate and blood pressure were continuously monitored and maintained, and rectal and intra-abdominal temperatures were kept within the normal range at all times with the aid of a heating pad and a lamp. Either a midline or bilateral subcostal laparotomy was performed. At the conclusion of the experiments, the animals were euthanized with a bolus injection of 50 ml of magnesium sulfate.

Recording Methods

HR mapping was performed using validated flexible printed-circuit-board (PCB) multi-electrode arrays (9). Each PCB contained 32 individual gold electrodes spaced at 7.6 mm intervals in a 4×8 configuration (refer (9) for full details of this design). Between five and

six PCBs were used in each recording, and these were joined together with waterproof adhesive in precise adjacent configurations (160–192 electrodes; 78–93 cm²).

The abdominal walls were retracted, and the assembled PCBs were gently positioned over sequential regions of the serosa to map the whole gastric surface, as previously described (8). The PCBs were kept in place by gentle packing with warmed (39°C) saline-soaked gauze, and the wound edges were approximated during recordings to prevent serosal drying and gastric cooling.

Signal Acquisition and Processing

All signals were acquired using an ActiveTwo System (Biosemi, Amsterdam, The Netherlands) that was modified for passive electrode recordings. The reference Ag/AgCl body surface electrode (common mode sense) was placed on the left lower abdomen. Each PCB was connected via a 1.5 m 68-way ribbon cable to the ActiveTwo System, which was in turn connected to a notebook computer via a fibre-optic cable. Customised acquisition software was written in LabView v8.2 (National Instruments, TX, USA) and the recording frequency was 512 Hz.

Recordings were filtered using a Butterworth filter with a band pass between 1 and 60 cpm. Analyses were performed using two software platforms: SmoothMap v3.02 (10) and the Gastric Electrical Mapping Suite (GEMS, Auckland University, New Zealand) v0.6 (11). In SmoothMap, slow wave activation times were manually identified at the point of maximum negative gradient, as previously described (8). In GEMS, activation times were automatically detected using the recently validated 'falling-edge variable threshold' (FEVT) algorithm (12), followed by manual review and correction. The marked events were then grouped into discrete wavefronts (cycles) in GEMS using the recently validated REGROUPS algorithm (13), also with careful manual review and correction.

Isochronal maps were generated according to a validated 'spatial interpolation and visualisation' algorithm (SIV) (13). Where data points on the map were interpolated, a red circle is used to represent the electrode (13). When activation block was found, manual correction of the maps was undertaken to eliminate 'isochronal crowding' (misleading stacking of isochronal bars due to automated interpolation across the blocks) (14). Animation sequences were also created for selected cycles according to our described methods (11).

Frequencies were determined by measuring and averaging the cycle-to-cycle intervals of successive slow waves in several consecutive electrodes. Data is presented as means $\pm$ standard deviation (s.d.) or standard error of the mean (sem) as appropriate, and Student's t-test was used to test statistical differences. A p-value of less than 0.05 was deemed significant.

Identification and Classification of Dysrhythmic Events

Porcine gastric slow waves normally arise from a pacemaker region near the greater curvature of the lower fundus (pigs have a large fundus and small antrum, with the gastro-esophageal junction lying near the mid-point of the lesser curvature) (8). Dysrhythmia was defined as any deviation from an organised regular slow wave propagation from fundus to antrum, including all abnormalities of propagation direction, frequency, or pattern compared to normal porcine reference data (8). For reference, the normal porcine gastric slow wave frequency is 3.2 ± 0.2 cpm (8). All recordings were screened for the presence of dysrhythmias by evaluating several rows and columns of electrograms from each cycle, and by reviewing the animation sequences of each recording. If a dysrhythmia was identified, a

detailed spatiotemporal analysis of the whole recording was performed, in order to reconstruct the origin and evolution of the abnormal behaviour within the mapped field.

Results

Dysrhythmias were found to occur in 14 out of 97 total recordings (from 8 out of 16 animals), for a combined duration of 129 minutes. All of these dysrhythmias were analysed in detail.

Classification of Dysrhythmias

Abnormalities of both impulse conduction and impulse formation were observed, and these were described as: conduction blocks, escape rhythms, ectopic events, and re-entrant activities (refer glossary in Table 1). Burst sequences, premature slow waves, and single aberrant slow waves, which have previously been described during HR mapping in the canine antrum (6) (defined in Table 1), were not observed in this study. All dysrhythmias were observed to originate in the corpus or fundus.

The relative frequency and mean recorded duration of each class of dysrhythmia is reported in Table 2, noting that different types of dysrhythmias often occurred in the same animal and in combination. The frequency range across the classes of dysrhythmia was 2.0 – 4.1 cpm (Table 2), with the lowest frequency associated with escape rhythm and the highest frequencies associated with instances of re-entry (4.1 ± 0.4 cpm).

Conduction Block

Conduction blocks were classified as incomplete (Figure 1) (observed in 3 animals) or complete (Figure 2) (4 animals). Incomplete conduction block was defined when part of the normal antegrade wavefront was blocked within the mapped field, compared to total cessation of the antegrade propagating wavefront in complete conduction block. Conduction blocks were found to typically occur when slow wave frequencies were higher than normal, and there was no difference in frequency between incomplete and complete block (3.9 ± 0.5 cpm vs 3.7 ± 0.4 cpm; $p=0.77$) (Table 2).

Incomplete Conduction Block and Wavelet Rotation—A typical example of an incomplete block is presented in Figure 1 (and animation Figure1.avi; supplementary material). In this case, a portion of the mapped wavefront continued to propagate antegrade (a 'broken wavefront'), whereas the area immediately distal to the line of block initially remained unexcited. A 'wavelet' (i.e., a wave fragment that separates from a main wave and propagates independently) then routinely emerged from the broken wavefront, and rotated to propagate circumferentially and / or retrograde into the initially unexcited region. In this example, the mean slow wave frequency was high (4.2 ± 0.3 cpm), and substantial variability in wave intervals was also noted over the 12 minute recorded duration (interval range: 12 – 16 s; s.d 1.0 s).

As shown in Figure 1 (and Figure1.avi; supplementary material), wavelet rotation could result in self-perpetuation of the incomplete conduction block. This occurred because the subsequent antegrade wavefronts collided with the abnormally propagating wavelet (Figure 1C). These self-perpetuating states of stable incomplete block were observed to last up to 132 s (9 cycles) before they either spontaneously resolved or the recording had ended.

Complete Conduction Block and Escape—Complete conduction block was routinely accompanied by escape events, whereby delayed activation of the distal field, caused by a premature wavefront termination, allowed distal break-out of ectopic slow-wave activity. An

example of this sequence is presented in Figure 2 (and animation Figure2.avi; supplementary material). As demonstrated in Figure 2C, the propagation pattern was often unstable in complete block because of variance in the site of both the block and the escape from cycle to cycle.

Across all four animals showing conduction block, the frequency of the escape activity was lower than that of the antegrade activity occurring before the block (2.0 ± 0.3 vs 3.7 ± 0.4 cpm; $p < 0.001$; Table 2). However, as demonstrated in Figure 2, these frequency differences could also be relatively slight (4.3 ± 0.1 vs 3.7 ± 0.2 cpm; $p < 0.01$).

Functional Re-entry

Re-entrant slow wave activity occurred in the corpus of three animals, with wavefront rotation around a line of unidirectional block oriented in the longitudinal organ axis. In all cases, normal antegrade wavefronts were observed to propagate through the area in which reentry had occurred. In other words, these regions were anatomically normal but functionally discontinuous at the time of the re-entry. All events were therefore classified as 'functional' re-entry (15). Functional re-entry was observed in association with episodes of incomplete conduction block (2 cases), and multiple competing ectopic events (1 case). As demonstrated in Figure 1C, incomplete conduction block routinely provided opportunities for the initiation of re-entry, because the resultant wavelet rotation generated unidirectional wavefront loops around lines of functional block.

Functional re-entry could be stable over several minutes, with a mean recorded duration of 7 ± 5 cycles. An example of stable re-entry, occurring over the greater curvature of the corpus, is presented in Figure 3 (and animation Figure3.avi; supplementary material). Figure 3 also demonstrates simultaneous re-entry and normal antegrade activity, resulting in complex patterns of competing, colliding and merging wavefronts.

'Double potentials' were recorded from the electrodes located close to the functional block at the centre of re-entrant circuits (Figure 3C). The two deflections of the double potential corresponded with the antegrade and retrograde propagating arms of the circuit (from opposite sides of the block line), and could occur several seconds apart (Figure 3D).

Ectopic Events

Ectopic events were observed in 4 animals, characterized by the spontaneous initiation of one or more wavefronts from sites different to the normal pacemaker region. Once initiated, these ectopic events dynamically competed with each other and / or with normal wavefronts, resulting in complex patterns of propagation.

An example of multiple competing ectopic events, generating persistent, irregular and unsynchronised activity, is shown in Figure 4 (and animation Figure4.avi; supplementary material). The high frequency of the ectopic events in this example (range: 3.5 – 4.1 cpm) suggested a generalised hyperexcitability of wave initiation in the upper stomach. In this and all other instances, ectopics events were generated only in the proximal stomach, with a relative sparing of the distal porcine stomach.

Figure 5 (and animation Figure5.avi; supplementary material) presents a further example of competing pacemakers, and demonstrates that the patterns generated could be sustained over several cycles. In this example, two pacemaker sites were observed, one ectopic pacemaker from an area high in the fundus that could normally be expected to be quiescent (8), and one from around the region of the normal pacemaker site (8),(16),(17). Wavefronts from these sites repeatedly terminated in each others' refractory tails. Double potentials (Figure 5B) were observed in the region of the wavefront collision.

Discussion

This study has characterized and classified several gastric slow wave dysrhythmias recorded in HR in anaesthetized pigs. Dysrhythmias were detected in 14% of recordings (in 50% of animals). Several novel insights and tissue-level mechanisms of dysrhythmia are reported, including the spatiotemporal dynamics of incomplete conduction block, complete block with escape, re-entrant activity in the corpus, and competing ectopic pacemakers. The new finding of double potentials in the GI tract is also reported.

The evolution and maintenance of incomplete gastric conduction block is described here for the first time. A complex sequence of incomplete conduction block, broken wavefront propagation, and aberrant wavelet propagation was revealed to occur, which could induce prolonged periods of stable, self-perpetuating corpus dysrhythmia at near-normal frequencies.

Conduction blocks were associated with higher than normal frequency pacemaking, which may have been a consequence of the neurohormonal stress of laparotomy, prostaglandin release, and/or anesthesia (18), (19), (20). Normally, successive corpus wavefronts propagate close to the refractory tails of the previous impulses (16),(17). With increased frequency, or with lengthening of the refractory period, the distance between waves narrows and successive wavefronts may run into the refractory tail of the previous wave and terminate prematurely, resulting in conduction block. A similar sequence of events has been previously shown to occur in the feline small intestine (21). Heterogeneities in wave propagation, spacing and refractorytail length may then determine whether a block becomes complete or incomplete.

The occurrence of 'escape' slow wave activity distal to a complete conduction block is well known. Classic studies undertaken in the 1970s showed that if the gastric muscle layers are surgically divided, slow wave escape would subsequently occur within distal regions at reduced frequencies (22),(23). Distal slow wave pacemakers have also been shown to emerge following disruption to normal pacemaking following the induction of hypoxia (24), cooling (25) or ischaemia (26). These previously latent pacemaker sites are normally overridden, because intact ICC networks hierarchically entrain to the site of highest frequency and there is a decrease in ICC intrinsic frequency toward the distal stomach (27). The present study demonstrates how escape can occur inconsistently and at variable sites in the absence of entrainment following complete block, and how this can lead to retrograde propagation and competing wavefronts.

This study expands on the recent finding by Lammers et al that slow wave re-entry is an important mechanism of high-frequency gastric dysrhythmias (6). The previously described re-entrant activities occurred during canine antral tachygastria (6), whereas in this study the re-entry occurred in the corpus and at frequencies closer to the normal range (8). The lower frequency of re-entry was because the recurring wavefronts had to travel for longer distances around functionally-determined lines of block, which is required due to the long duration of the corpus refractory period. Accordingly, the 'excitable gap' for corpus re-entry to occur is relatively small. Functional re-entry around lines of conduction block is a well known phenomenon in the myocardium, where it contributes to lethal tachyarrhythmias (15). Whether or not functional re-entry is also of pathophysiological and clinical significance in human gastric motility disorders is now an important question.

'Uncoupling' of adjacent gastric regions has been described for many years in association with dysrhythmias (1),(2). This study demonstrates that competing ectopic pacemakers may be a cause of this uncoupling, and shows that ectopic events can be stable or unstable, few or multiple, and can occur at high frequencies across a large area of the stomach. Highly

complex propagation patterns can result, involving dynamic wave collisions, merging wavefronts and conduction blocks.

This study has documented for the first time in electrical recordings of the GI tract a clear association between 'double potentials' and functional block, as occurred in re-entry or wavefront collisions, when two distinct activation events occur in close spatial proximity. Double potentials are well known to occur in cardiac conduction block, where they are routinely observed in extracellular recordings at the centre of functional re-entrant circuits in both the atria and ventricles (28), (29). Each deflection corresponds to an activation from an opposite side of the region of functional block (29), (30), and since unipolar electrodes detect electrical activity from adjacent tissue as well as the tissue with which they are in direct contact, both events are detected (31),(32). Double potentials are therefore different to other previously described repetitive slow wave patterns, such as 'doublets', or 'triplets', in which the same patch of tissue is activated repeatedly in quick succession, for example in burst and tachygastric re-entry (6),(33), (34). The finding of GI double potentials means that caution is warranted when interpreting a rapid sequence of slow waves recorded from sparse unipolar electrodes as 'tachygastric', because the true slow wave frequency may in fact be half of what has been measured. This point further reinforces the fact that frequencies alone are insufficient to characterize gastric dysrhythmias. Of relevance and clinical interest, Bortolotti et al previously documented the 'duplication' of potentials in slow wave recordings from patients with idiopathic gastroparesis, but could not determine their source because of low resolution sampling (1). With HR spatial mapping, it is now possible to better understand the significance of isolated recordings and their potential importance in individual patients.

The relative lack of antral tachygastric in the pig (including burst, regular and irregular tachygastric) in this study was notable. The episodes of high frequency that did occur were still relatively close to the normal range (maximally 4.3 ± 0.1 cpm compared to 3.2 ± 0.2 cpm (8)). This finding is consistent with an earlier report by Roze et al, who reported no sequences of spontaneous tachygastric in 22 conscious miniature pigs studied with chronically-implanted sparse electrodes (35). They speculated that differences in antral excitability may have been responsible for the lack of tachygastric, a theory that is consistent with another recent study showing that pigs lack the increase in antral slow wave amplitude and velocity observed in humans and canines (8). It is also possible that differences in ICC network structure or function may account for these inter-species differences.

The findings from this study have several implications for the potential clinical translation of HR mapping techniques. Dysrhythmias were observed in these pigs with normal stomachs when exposed to anaesthesia, laparotomy and gastric handling, indicating that caution will be needed when interpreting the pathophysiological significance of dysrhythmias detected by similar methods in patients. However, it is encouraging that no dysrhythmias were detected in any of 12 normal human subjects recently evaluated by the same technique (17). Therefore, weaner pigs may be more prone to induced dysrhythmias. Nevertheless, the potential to induce dysrhythmia during the measurement process, and the invasiveness of these current methods should motivate efforts to develop less invasive mapping strategies for clinical use. Recent advances in minimally invasive slow wave recording techniques provide encouragement that such an aim may be achievable (36),(37).

The functional consequences of the dysrhythmias described here are currently unknown, however it is plausible that the retrograde propagation induced might be expected to compromise normal gastric function (38). Chronic awake studies would be useful to analyze these functional consequences, however further development of miniature implantable HR arrays will first be required (39). It is also possible that some or all of the described patterns

may be incidental findings, or part of the normal repertoire of gastric function, rather than pathophysiological.

A number of limitations need to be acknowledged with this study. Firstly, this was a study of normal pigs and it is likely that other arrhythmias will also be described in the context of various human motility disorders and disease states. Secondly, the serosal coverage was not complete. A maximum of one quarter of the whole gastric surface area was mapped at any one time, meaning that activities of interest in the unmapped area may have been missed.

Together with another recent HR study into tachygastria (6), this work provides a substantially improved foundation for understanding gastric dysrhythmias and their mechanisms at the tissue-level. The technique and findings described here will now be applied in clinical studies, offering new opportunities to understand the nature of human gastric dysrhythmias. It may then be possible to more rationally design and apply potential therapies, such as gastric pacing guided by HR mapping (7).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Linley Nisbet for her expert technical assistance, Dr Rita Yassi and Dr Jon Erickson for their assistance with the analysis methods, and Dr Ian LeGrice and Mr Tim Angeli for their help and advice. This work and / or the authors are supported by grants from the American Neurogastroenterology & Motility Society (ANMS), the New Zealand Health Research Council, and the NIH (R01 DK64775).

References

1. Bortolotti M, Sarti P, Barara L, Brunelli F. Gastric myoelectrical activity in patients with chronic idiopathic gastroparesis. *J Gastroint Motil.* 1990; 2:104–108.
2. Leahy A, Besherdas K, Clayman C, Mason I, Epstein O. Abnormalities of the electrogastrogram in functional gastrointestinal disorders. *Am J Gastroenterol.* 1999; 94:1023–1028. [PubMed: 10201477]
3. Leahy A, Besherdas K, Clayman C, Mason I, Epstein O. Gastric dysrhythmias occur in gastro-oesophageal reflux disease complicated by food regurgitation but not in uncomplicated reflux. *Gut.* 2001; 48:212–215. [PubMed: 11156642]
4. Parkman HP, Hasler WL, Barnett JL, Eaker EY. Electrogastrography: a document prepared by the gastric section of the American Motility Society Clinical GI Motility Testing Task Force. *Neurogastroenterol Motil.* 2003; 2003:89–102. [PubMed: 12680908]
5. Smout AJPM, Van der schree EJ, Grashuis JL. What is measured in electrogastrography? *Dig Dis Sci.* 1980; 25:179–187. [PubMed: 7371462]
6. Lammers WJEP, Ver Donck L, Stephen B, Smets D, Schuurkes JAJ. Focal activities and re-entrant propagations as mechanisms of gastric tachyarrhythmias. *Gastroenterology.* 2008; 135:1601–1611. [PubMed: 18713627]
7. O'Grady G, Du P, Lammers WJ, et al. High-resolution entrainment mapping for gastric pacing: a new analytic tool. *Am J Physiol Gastrointest Liver Physiol.* 2010; 298:314–321.10.1152/ajpgi.00389.2009
8. Egbuji JU, O'Grady G, Du P, et al. Origin, propagation and regional characteristics of porcine gastric slow wave activity determined by high-resolution mapping. *Neurogastroenterol Motil.* 2010; 22:e292–300. [PubMed: 20618830]
9. Du P, O'Grady G, Egbuji JU, et al. High-resolution mapping of in vivo gastrointestinal slow wave activity using flexible printed circuit board electrodes: methodology and validation. *Ann Biomed Eng.* 2009; 37:839–846. [PubMed: 19224368]

10. SmoothMap [Computer Program]. Version 3.05. Wim Lammers, Al Ain: United Arab Emirates; 2009. [url: <http://www.smoothmap.org>]
11. The Gastrointestinal Electrical Mapping Suite (GEMS) [Computer Program]. Version 0.6. Auckland University; Auckland, New Zealand: 2011. [url: <http://sites.google.com/site/gimappingsuite>]
12. Erickson JC, O'Grady G, Du P, et al. Falling-edge, variable threshold (FEVT) method for the automated detection of gastric slow wave events in serosal high-resolution electrical recordings. *Ann Biomed Eng.* 2010; 38:1511–1529. [PubMed: 20024624]
13. Erickson JC, O'Grady G, Du P, Egbuji JU, Pullan AJ, Cheng LK. Automated cycle partitioning and visualization of high-resolution activation time maps of gastric slow wave recordings: the Region Growing Using Polynomial Surface-estimate stabilization (REGROUPS) Algorithm. *Ann Biomed Eng.* 2011; 39:469–483. [PubMed: 20927594]
14. Potse M, Linnenbank AC, Grimbergen CA. Automated generation of isochronal maps in the presence of activation block. *Int J Bioelectromagnetism.* 2002; 4:115–116.
15. Jalife, K.; Delmar, M.; Anumonwo, J.; Berenfeld, O.; Kalifa, J. Basic Cardiac Electrophysiology for the Clinician. 2. Oxford, UK: Blackwell Publishing; 2009. Basic Mechanisms of Cardiac Arrhythmias.
16. Lammers WJ, Ver Donck L, Stephen B, Smets D, Schuurkes JA. Origin and propagation of the slow wave in the canine stomach: the outlines of a gastric conduction system. *Am J Physiol Gastrointest Liver Physiol.* 2009; 296:1200–1210.
17. O'Grady G, Du P, Cheng LK, et al. The origin and propagation of human gastric slow wave activity defined by high-resolution mapping. *Am J Physiol Gastrointest Liver Physiol.* 2010; 299:585–592.
18. Hotokezaka M, Mentis EP, Patel SP, Combs MJ, Teates CD, Schirmer BD. Recovery of gastrointestinal tract motility and myoelectric activity change after abdominal surgery. *Arch Surg.* 1997; 132:410–417. [PubMed: 9108763]
19. Forrest AS, Hennig GW, Jokela-Willis S, Park CD, Sanders KM. Prostaglandin regulation of gastric slow waves and peristalsis. *Am J Physiol Gastrointest Liver Physiol.* 2009; 296:G1180–90. [PubMed: 19359421]
20. Kim CH, Zinsmeister AR, Malagelada JR. Mechanisms of canine gastric dysrhythmia. *Gastroenterology.* 1987; 92:993–999. [PubMed: 3557006]
21. Lammers WJ, Stephen B. Origin and propagation of individual slow waves along the intact feline small intestine. *Exp Physiol.* 2008; 93:334–346. [PubMed: 18156170]
22. Kelly KA, Code CF. Canine gastric pacemaker. *Am J Physiol.* 1971; 220:112–118. [PubMed: 5538644]
23. Weber J, Kohatsu S. Pacemaker localization and electrical conduction patterns in the canine stomach. *Gastroenterology.* 1970; 59:717–726. [PubMed: 5475131]
24. Szurszewski J, Steggerda FR. The effect of hypoxia on the electrical slow wave of the canine small intestine. *Am J Dig Dis.* 1968; 13:168–177. [PubMed: 5639549]
25. Hasselbrack R, Thomas JE. Control of intestinal rhythmic contractions by a duodenal pacemaker. *Am J Physiol.* 1961; 201:955–960. [PubMed: 13905266]
26. Lammers WJ, el-Kays A, Manefield GW, Arafat K, el-Sharkawy TY. Disturbances in the propagation of the slow wave during acute local ischaemia in the feline small intestine. *Eur J Gastroenterol Hepatol.* 1997; 9:381–388. [PubMed: 9160202]
27. van Helden DF, Laver DR, Holdsworth J, Imtiaz MS. The generation and propagation of gastric slow waves. *Clin Exp Pharmacol Physiol.* 2010; 37:516–524. [PubMed: 19930430]
28. Cosio FG, Arribas F, Barbero JM, Kallmeyer C, Goicolea A. Validation of double-spike electrograms as markers of conduction delay or block in atrial flutter. *Am J Cardiol.* 1988; 61:775–780. [PubMed: 3354440]
29. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. *Circulation.* 1997; 95:1231–1241. [PubMed: 9054854]

30. Olshansky B, Moriera A, Waldo AL. Characterization of double potentials during ventricular tachycardia. Studies during transient entrainment. *Circulation*. 1993; 87:373–381. [PubMed: 8425286]
31. Ideker RE, Smith WM, Blanchard SM, et al. The assumptions of isochronal cardiac mapping. *Pacing Clin Electrophysiol*. 1989; 12:456–478. [PubMed: 2466272]
32. de Bakker JM, Wittkampf FH. The pathophysiologic basis of fractionated and complex electrograms and the impact of recording techniques on their detection and interpretation. *Circ Arrhythm Electrophysiol*. 2010; 3:204–213. [PubMed: 20407105]
33. Code CF, Marlett JA. Canine tachygastria. *Mayo Clin Proc*. 1974; 49:325–332. [PubMed: 4829263]
34. Gullikson GW, Okuda H, Shimizu M, Bass P. Electrical arrhythmias in gastric antrum of the dog. *Am J Physiol*. 1980; 239:G59–68. [PubMed: 7396005]
35. Roze C, Couturier D, Debray C. Patterns of gastric electrical and motor activity in miniature pigs. *Can J Physiol Pharmacol*. 1976; 54:764–773. [PubMed: 1033025]
36. O'Grady G, Du P, Egbuji JU, et al. A novel laparoscopic device for measuring gastrointestinal slow-wave activity. *Surg Endosc*. 2009; 23:2842–2848.
37. Coleski R, Hasler WL. Coupling and propagation of normal and dysrhythmic gastric slow waves during acute hyperglycaemia in healthy humans. *Neurogastroenterol Motil*. 2009; 21:492–9. e1–2. [PubMed: 19309443]
38. Yao S, Ke M, Wang Z, Xu D, Zhang Y, Chen JD. Retrograde gastric pacing reduces food intake and delays gastric emptying in humans: a potential therapy for obesity? *Dig Dis Sci*. 2005; 50:1569–1575. [PubMed: 16133953]
39. Ver Donck L, Lammers WJ, Moreaux B, et al. Mapping slow waves and spikes in chronically instrumented conscious dogs: implantation techniques and recordings. *Med Biol Eng Comput*. 2006; 44:170–178. [PubMed: 16937158]

Figure 1.

Incomplete conduction block and wavelet rotation. **A.** Position diagram showing the PCB array over the greater curvature of the distal antrum and corpus (12×16 electrodes; inter-electrode spacing 7.6 mm; area 96 cm²). **B.** Electrogram sequence from eight electrodes positioned as shown in C, over 150 s. The dashed line shows onset of retrograde propagation in the displayed electrograms. **C.** Spatiotemporal maps relating to mapped area shown by the red rectangle in A, and the wavefronts *a-d* shown in B. The isochronal interval is 1 s. A normal wavefront (*a*) was followed by an incomplete conduction block (*b*), inducing a wavelet that rotated and subsequently activated the region distal the block. A self-sustaining cycle was then established, whereby the subsequent antegrade propagating collided with the retrograde propagating wavelet, inducing further incomplete blocks and wavelet rotations (*c*). After an initial unstable period of approximately 50 s, a relatively stable pattern was established (*d*) that continued for the remainder of the 150 s period, as shown in the electrograms in (B). (See also: animation Figure1.avi (supplementary material) of the same data. In the animation, successive wavefronts are colored red and blue to aid visualisation.)

Figure 2.

Complete conduction block and escape. **A.** Position diagram showing the PCB array on the porcine fundus and upper corpus (12×16 electrodes; inter-electrode spacing 7.6 mm, 96 cm²). **B.** Electrogram sequence for 10 electrodes from the positions shown in C, over 250 s. The initial slow wave frequency was high at 4.3 ± 0.1 cpm. **C.** Spatiotemporal maps from the position indicated by the red rectangle in A and for the wavefronts *a* - *j* in B. The isochronal interval is 1 s. Cycles of normal activity are shown in *a*, *c*, *d* and *e*. Cycles *b*, *f*, and *h* show complete conduction block with a marked reduction in the activated area. In map *g*, an escape event occurred within a part of the field that was not activated in cycle *f* (local activation delay of 36 s). Similarly, map *i* shows retrograde propagation from an escape event arising distal to the mapped area, in a region not activated in cycle *h*, which collides with the antegrade wavefront (the dashed line indicates wavefront collision). In map (*j*), the retrograde activity is shown to entrain the entire mapped region, and this pattern was sustained for the remainder of the recording at frequency 3.7 ± 0.2 cpm. (See also: animation Figure2.avi (supplementary material) of the same data. In the animation, the normal antegrade wavefronts are colored blue and the ectopic events are coloured red.)

Figure 3.

Functional re-entry with double potentials. **A.** Position diagram showing the PCB array on the greater curvature of the fundus and corpus (12x16 electrodes; inter-electrode spacing 7.6 mm, 96 cm²). **B.** Electrogram sequence for 8 electrodes from the positions shown in D(a). Electrogram 1 is repeated below electrogram 8 to demonstrate continuity in propagation during the re-entrant cycle. **C.** Electrograms from another set of 5 electrodes from the positions shown in D(b), demonstrating double potentials. The two deflections corresponded to the antegrade and retrograde arms of re-entry occurring on opposite sides of the block line (line and dashed line). **D.** Spatiotemporal maps from the position indicated by the red rectangle A, and corresponding to the overlapping time periods (a-d) indicated in B. The isochronal interval is 1 s. Stable re-entry (4.1 ± 0.2 cpm) occurred around a line of functional block for several cycles, and competed with continuing antegrade wavefronts entering the top of the mapped field, causing collisions or merging. The re-entry spontaneously terminated 62 s into the recording, with reversion to normal antegrade activity. (See also: animation Figure3.avi (supplementary material) of the same data. In the animation, the normal antegrade wavefronts are colored blue and the re-entrant activities are coloured red.)

Figure 4.

Multiple competing ectopic wavefronts. **A.** Position diagram showing the PCB array on the anterior serosal surface (8×20 electrodes; inter-electrode distance 7.6 mm; 77 cm^2). **B,C.** Electrograms corresponding to 100 s of recordings from the 6 electrodes shown in D(a) and the subsequent 200 s from the 8 electrodes shown in D(g). **D.** Spatiotemporal maps for wave sequences a-j from B and C. The isochronal interval is 2 s. Sporadic, high-frequency (3.5 to 4.1 cpm) wavefront initiation from 1–3 ectopic pacemaker sites caused abnormal and irregular activity, including retrograde propagation (e.g., maps d,e), wavefront collisions (a-g and i), merging wavefronts (a-g and i) and conduction blocks (d-g). Map h also shows a single escape activity, which followed a quiescent interval of 26 s. See also: animation Figure4.avi (supplementary material) of time period 0–120s from the same data.

Figure 5.

Stable colliding wavefronts from competing ectopic events. **A.** Position diagram showing the PCB array on the upper anterior serosa (8×20 electrodes; inter-electrode distance 7.6 mm; area 77 cm^2). **B.** Electrograms corresponding to the 8 electrodes positioned as shown in **C.** Spatiotemporal maps showing four cycles of wave collision. The isochronal interval is 2 s. The two panels (1–2) in each box (*a–d*) show alternate activation of the mapped field from the two distinct initiation sites. Each wave collides with the refractory tail of the previous event, causing a repeating pattern of abnormal propagation. Double potentials are evident in electrodes 4–5, corresponding to the boundary zone between the two colliding wavefronts, suggesting an irregular and heterogeneous area of tissue activation occurred in this region. (See also: animation Figure5.avi (supplementary material) of the same data. In the animation, the wavefronts emerging from the two distinct pacemaker sites are colored separately.)

Table 1

Glossary of terms used previously (6) and in the current study to describe gastric dysrhythmias in spatiotemporal detail. Several cardiac terms have been adapted for gastric use (15). The terms 'tachygastria' and 'bradygastria' are also broadly used to describe fast or slow rhythms in general.

Terminology Used	Definition
1. <i>Focal event or ectopic focus</i>	Slow wave/s arising from a site different to the normal pacemaker region.
2. <i>Conduction block</i>	Premature termination of a propagating wavefront, for example when refractory tissue is encountered.
3. <i>Re-entrant wavefront</i>	A wavefront that travels in a loop, and re-excites tissue that had been activated in the previous loop
4. <i>Escape activity</i>	An ectopic focus arising after a delay in excitation, due to failure of initiation or conduction of the normal wavefront.
5. <i>Wavelet (wave fragment)</i>	A fragment of a wave that separates from a main wave and propagates independently.
6. <i>Premature slow wave</i>	A single slow wave occurring before a regular slow wave period had been completed.
7. <i>Aberrant slow wave</i>	An abnormal pattern of propagation of a slow wave occurring at a normal interval.
8. <i>Burst</i>	A period of tachygastria with short slow-wave intervals, lasting <1 minute.
9. <i>Regular tachygastria</i>	Tachygastria lasting > 1 minute with a constant rapid rhythm and a stable propagation sequence.
10. <i>Irregular tachygastria</i>	Tachygastria lasting > 1 minute with an irregular rhythm and abnormal propagation.

Frequencies and average mapped durations of the dysrhythmias. The normal porcine gastric slow wave frequency is 3.2 ± 0.2 cpm (8).

Table 2

	Incomplete Conduction Block	Complete Conduction Block	Escape Rhythm	Competing Ectopic Events	Functional Re-entry
Frequency (cpm)	3.9 ± 0.5	3.7 ± 0.4	2.0 ± 0.3	3.7 ± 0.1	4.1 ± 0.4
# of pigs	3	4	5	5	3
Average mapped duration (s) *	113 ± 23	35 ± 30	184 ± 154	185 ± 67	96 ± 33

* mean $\pm$ s.d; each type often occurred recurrently in the same animal, and more than one type also often occurred in the same animal.