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Recent progress in gastric arrhythmia: Pathophysiology, clinical significance and future horizons

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SUMMARY

Gastric arrhythmia continues to be of uncertain diagnostic and therapeutic significance. However, recent progress has been substantial, with technical advances, theoretical insights and experimental discoveries offering new translational opportunities. The discoveries that interstitial cells of Cajal (ICC) generate slow waves and that ICC defects are associated with dysmotility have reinvigorated gastric arrhythmia research. Increasing evidence now suggests that ICC depletion and damage, network disruption and channelopathies may lead to aberrant slow wave initiation and conduction. Histological and high-resolution (HR) electrical mapping studies have now redefined the human 'gastric conduction system', providing an improved baseline for arrhythmia research. The application of HR mapping to arrhythmia has also generated important new insights into the spatiotemporal dynamics of arrhythmia onset and maintenance, resulting in the emergence of new provisional classification schemes. Meanwhile, the strong associations between gastric functional disorders and electrogastrography (EGG) abnormalities (e.g. in gastroparesis, unexplained nausea and vomiting and functional dyspepsia) continue to motivate deeper inquiries into the nature and causes of gastrointestinal arrhythmias. In future, technical progress in EGG methods, new HR mapping devices and software, wireless slow wave acquisition systems and improved gastric pacing devices may achieve validated applications in clinical practice. Neurohormonal factors in arrhythmogenesis also continue to be elucidated and a deepening understanding of these mechanisms may open opportunities for drug design for treating arrhythmias. However, for all translational goals, it remains to be seen whether arrhythmia can be corrected in a way that meaningfully improves organ function and symptoms in patients.

Keywords

electrogastrography; gastric electrical activity; high-resolution mapping; interstitial cells of Cajal; tachygastria

INTRODUCTION

Almost a century has passed since the esteemed physiologist Alvarez made his 'little prophesy' that 'gastroenterologists would come to rely upon electrical measures for the

routine diagnosis of stomach disorders, just as the heart specialist [does]'.[1] Despite intensive investigations through the intervening years, Alvarez's prophesy remains unfulfilled. There continues to be little uptake of gastric electrical diagnostics beyond a few specialist research centres due to ongoing uncertainty regarding the reliability and value of current clinical tests.[2,3]

However, recent progress has been substantial, with technical advances, theoretical insights and experimental discoveries offering new translational opportunities in gastric electrophysiology. This update evaluates several of these advances and addresses future horizons in the basic and clinical science of gastric arrhythmia.

ROLE OF THE INTERSTITIAL CELLS OF CAJAL

It is now widely accepted that slow waves are generated and propagated by interstitial cells of Cajal (ICC) and this discovery has been accompanied by intense interest in what roles ICC defects may play in disease.[4,5] These advances have critically informed new directions in arrhythmia research and reinvigorate clinical interest in evaluating gastric electrical activity.

In the stomach, the strongest evidence for a pathophysiological role for ICC is in gastroparesis.[6,7] Although gastroparesis is multifactorial and also associated with autonomic, smooth muscle, enteric nervous system and immune cellular changes and fibrosis,[6,8] the ICC loss appears to be of particular significance. Abnormalities in ICC are the most common histological finding in both idiopathic and diabetic gastroparesis,[6] and the severity of ICC loss has been correlated with the severity of gastric retention, as well as electrogastrography (EGG) abnormalities.[9,10] Animal model research supports a pathophysiological role for ICC in gastroparesis; for example, induction of heme oxygenase-1, a cytoprotective molecule against oxidative stress, has been shown to both restore ICC and normalize gastric emptying in non-obese diabetic mice.[11]

Another emerging ICC research area with implications for arrhythmia is ion channel defects (channelopathies).[12] Early work in this area has linked mutations in the mechanosensitive Na(v)1.5 sodium channel, encoded by the sodium channel, voltage-gated, type V, alpha subunit (*SCN5A*) gene and found in human ICC and smooth muscle cells, with irritable bowel syndrome.[13] Channel defects of this type can substantially modify whole cell slow wave activation,[14] potentially inducing arrhythmias in a manner analogous to defined types of cardiac arrhythmia.[15] Further research is needed to determine whether such mechanisms are also important in disorders such as functional dyspepsia.[16] Another recent focus of substantial current interest in ICC are calcium-activated chloride channels, which likely play a key role in gastric excitability.[17,18]

The ICC also serve several other functions in addition to slow wave pacemaking, including mediating neurotransmission, mechanotransduction and establishing smooth muscle resting membrane potential gradients.[4,5] Importantly, ICC pathologies will therefore impact on gastric motility by other pathways beyond just slow wave arrhythmia.[19]

THE GASTRIC CONDUCTION SYSTEM

In the normal stomach, ICC generate slow waves synchronously at a common frequency, achieved by their 'entrainment' to the highest frequency expressed in their syncytium within the gastric wall.[20] Entrainment is maintained by an underlying frequency gradient intrinsic to ICC, which declines in the aboral direction, as may be revealed by partitioning the stomach into isolated segments.[21,22] It is helpful to consider the pathogenesis of arrhythmia mechanisms in terms of disruption to normal entrainment ('disorders of conduction') or to the intrinsic ICC frequencies ('disorders of initiation'; Fig. 1) and each of these abnormalities may, in turn, promote secondary forms of arrhythmia (Fig. 2).

In the human stomach, an anastomosing network of ICC is distributed throughout the myenteric plexus (ICC-MP) and circular and longitudinal muscle layers (intramuscular ICC; ICC-IM).[23,24] The ICC-IM run parallel to the smooth muscle fibres within the muscle layers, forming a loosely connecting network, with a further anatomical subclass of ICC encasing and connecting bundles (ICC-SEP).[24] In animal models (but yet to be shown in humans), a decrease in ICC-MP within the pylorus functions as an electrical barrier, helping to isolate gastric and duodenal electrical events.[25]

Extracellular recordings remain the primary tool for evaluating in vivo gastric slow wave activation patterns over large tissue areas.[26] Classically, gastric slow wave propagation was studied using sparse arrangements of extracellular electrodes, typically up to eight, placed at regular intervals along the gastrointestinal (GI) tract. However, such results were incomplete due to the limitations of sparse sampling and could be misleading due to spatial aliasing. [27] Therefore, these limitations motivated the introduction of GI high-resolution (HR) electrical mapping by Lammers et al., whereby dense arrays of electrodes are applied to accurately track activation in spatiotemporal detail.[28,29] The analysis of gastric conduction patterns using HR mapping has now yielded a much more accurate description of the normal origin and propagation of gastric slow waves in large animal models and in humans,[27,30,31] serving as a reliable baseline for arrhythmia investigations.

GASTRIC ANISOTROPY

Velocity anisotropy has proved to be an important finding from HR mapping studies for arrhythmia interpretation, whereby extracellular slow waves in the region of the normal gastric pacemaker show a much higher velocity and amplitude activity than events in the surrounding corpus (~2.5-fold greater in humans).[27,30] The reason for the high velocity and amplitude pacemaker pattern was only recently resolved in a combined theoretical–experimental study,[32] aided by novel methods for analysing the spatial properties of slow wave activation.[33–35] The high local velocity is the consequence of the fact that the impulse propagates from the pacemaker area initially and predominantly in the circumferential direction.[32] In human stomach, propagation in the circumferential direction is approximately 2.5-fold faster than in the longitudinal direction (termed 'anisotropic' propagation). The accompanying increase in extracellular amplitudes is due to changes in current distribution associated with the higher impulse velocity.[32] However, by the time slow waves reach the mid to lower corpus they have formed into complete ring wavefronts, such that the rapid

circumferential conduction ceases and wavefronts propagate with slower antegrade activation towards the pylorus.[27,32]

Velocity anisotropy is critical to the interpretation of arrhythmic activity, because disorders of both initiation and conduction disrupt normal gastric ring wavefronts.[7,32] This allows 'ectopic circumferential propagation' to emerge, such that arrhythmias are characterized by high-velocity wavefronts and high-amplitude signals local to their source, which directly determines the patterns of arrhythmic activation. This anisotropy also plays a key role in the maintenance and stability of arrhythmic patterns, such as slow wave re-entry[36] (for a recent review, see Cheng, Du and O'Grady[37]).

It is not yet known which ICC network structures underlie the anisotropic properties outlined above. There are likely to be two complimentary gastric conduction pathways active, supporting circumferential conduction at high velocity and longitudinal conduction at low velocity.[38] For humans, it was recently proposed that within a bidirectionally coupled ICC system, the leading network may switch between ICC-MP (dominant during longitudinal conduction) and ICC-IM (dominant during circumferential conduction), depending on the presence or absence of complete gastric ring wavefronts.[32] This theory awaits validation, but could offer mechanistic insights into arrhythmogenesis. For example, slow wave frequencies are known to increase in ICC-IM at sites of sustained cholinergic stimulation,[39] which could then act as sites of arrhythmic initiation within a bidirectionally coupled system.

ELECTROGASTROGRAPHY AND ARRHYTHMIA

Much of what is known about gastric arrhythmia, particularly in human disease, continues to be derived from electrogastrography (EGG). Electrogastrography is a non-invasive test and is relatively simple to perform,[40] but the signals are currently difficult to relate to the underlying slow waves. In addition, EGG signals are of low amplitude and susceptible to motion artefacts induced by even fine patient movements, such that subjects must lie completely still during the recording period. Signal acquisition and processing for effective EGG generally requires the use of bipolar electrodes, tight band-pass filtering (e.g. 0.016–0.3 Hz), careful attention to noise discrimination and, ideally, concurrent respiratory motion sensing.[41]

Electrogastrography recordings are typically taken before and after a test meal and variables analysed include the dominant slow wave frequency and its consistency, dominant power (reflecting signal amplitude and regularity over time), the 'fasting–fed power ratio' (the dominant power increases after a test meal in normal subjects), as well as measures of signal instability.[3,40] Analysis of the EGG waveform morphology has no defined role, but EGG may also be applied to detect 'gastric uncoupling' (where discrete areas of the stomach are entrained to different sources and frequencies),[42] particularly using modern multichannel approaches (e.g. four bipolar electrodes).[43]

The normal frequency range defined by EGG is approximately 2.4–3.7 cycles/min, with frequency abnormalities outside this range classed as bradygastria, tachygastria or non-specific.[3,40] However, a limitation of this approach is that it is not yet certain how and from

where the gastric slow wave potentials actually summate to form the EGG signal, especially because it has now been shown that there may be three to five slow waves propagating at any time in the stomach.[27,30] This issue is even more problematic during arrhythmias, when different frequencies may be simultaneously active in multiple uncoupled gastric regions.[7,44]

Several decades of EGG investigations have produced an extensive literature associating electrical abnormalities with gastric disorders (Table 1). Multiple studies have also demonstrated that hyperglycaemia is associated with arrhythmia, possibly contributing to arrhythmia in diabetic gastroparesis,[45,46] leading to recommendations that blood glucose be tested and normalized prior to testing.[3] In addition, EGG abnormalities have been associated with chronic renal failure,[47] anorexia nervosa (after a prolonged period)[48] and chronic intestinal pseudo-obstruction.[49]

In terms of symptoms, the strongest association with EGG-diagnosed frequency abnormality is with nausea and vomiting.[71] Arrhythmia is common when vomiting is likely, as seen in chronic unexplained nausea and vomiting,[58,72] after chemotherapy,[73] in motion sickness[74] and in nausea of pregnancy.[75] Indeed, physiological evidence suggests that myoelectrical derangements may be part of the normal physiological sequence of vomiting.[76–78] However, some controversy remains as to whether arrhythmia is truly a cause of nausea and vomiting or merely an associated epiphenomenon. More research on this point is needed, but it is notable that gastric electrical pacing therapy may have potential to both revert arrhythmia and reduce nausea, suggesting arrhythmia does have a role in symptom genesis.[79] A pathogenic role for arrhythmia in the motion sickness induced by circular vection[80] has also been suggested by the fact that the rhythm disturbances arise 1–2 min before symptoms and their severity correlates with nausea intensity.[71] In addition, in patients with gastroparesis, the resolution of nausea and vomiting has been associated with improvements in EGG abnormalities.[50]

Another documented EGG abnormality is the loss of normal power increase after a test meal observed in gastroparetic patients.[54] The EGG signal is considered summative of slow wave activity and smooth muscle potentials and/or contractions.[81] Therefore, the normal postprandial power increase may reflect increased electromechanical activity and/or perhaps gastric distension, [82,83] whereas its loss in gastroparesis may reflect reduced electromechanical activity,[83] potentially related to hypomotility or reduced current density output caused by ICC loss.[84] Consistent with this latter hypothesis, a recent extracellular study has shown reduced serosal slow wave amplitudes in patients with gastroparesis.[7]

Despite the many studies showing the potential value of EGG, clinical adoption remains weak. In addition to the limitations outlined above, EGG is perceived as having incomplete sensitivity and specificity and inconsistent associations with symptoms, and there are uncertainties regarding its functional significance and role in management.[2,3] The positive predictive value of EGG for normal gastric emptying ranges from 65% to 100% in published studies (average 85%) and from 50% to 81% for predicting abnormal gastric emptying (average 65%).[3] However, it should be noted that EGG and gastric emptying tests likely reflect and characterize different patient subgroups. More significantly, additional work is needed to define validated roles for EGG in therapeutic algorithms.[3] There is also

considerable scope to further refine the principles and practice of EGG, through biophysical modelling, technical advances and basic experimental studies.[85]

NEW INSIGHTS INTO ARRHYTHMIA FROM HR MAPPING

The advent of HR mapping has been a major advance in gastric arrhythmia research. The first HR analyses of slow wave arrhythmias were performed in dogs in 2008, reporting novel abnormalities of both initiation (e.g. focal or ectopic activities) and conduction (e.g. re-entrant propagations) as mechanisms of antral tachygastrias.[44] These concepts were extended in a subsequent porcine study, demonstrating that complex slow wave abnormalities also underlie tachygastria in the corpus, including re-entry, self-perpetuating conduction block and ectopic initiation and showing 'escape rhythms' in bradygastria.[86] These two studies are representative of a new era for gastric arrhythmia, in which modern methods of cardiac rhythm analysis are brought to bear to achieve accurate analyses of arrhythmic onset and maintenance. [87]

Clinical translation of HR mapping was recently achieved in a study of patients with idiopathic and diabetic gastroparesis, providing the first spatially detailed description of human arrhythmic patterns.[7] Whereas previous studies had focused almost exclusively on human abnormalities of slow wave initiation (e.g. ectopic activity), that study demonstrated that conduction abnormalities (e.g. slow conduction and conduction blocks) were also prevalent in gastroparesis.[7] These conduction abnormalities could be a consequence of ICC loss, which results in network remodelling and haphazard or delayed conduction.[84,88] The complex arrhythmic propagation patterns described in that recent study[7] also have pathophysiological implications, because disorganized patterns, such as competing pacemakers, colliding wavefronts, retrograde propagation and uncoupling, must be highly disruptive to gastric mixing and motility, in a manner akin to cardiac fibrillation disrupting cardiac contractility and output. This notion is supported by canine studies that show slow wave arrhythmia impairs gastric contractions and induces hypomotility. [89,90]

With a range of abnormalities now being discovered and examined by HR mapping, early attempts are being made to classify these arrhythmias. In their canine study, Lammers et al.[44] proposed a first classification mostly based on rate and rhythm, very similar to what is used in cardiac arrhythmias.[91] In contrast, in the human gastroparesis mapping study,[7] the changes in rate were less dramatic and arrhythmias were classified in patterns of propagation, as elucidated by HR mapping (e.g. Fig. 1). The limited alterations in slow wave rate during human arrhythmia is important, because it means that many such abnormalities could be missed by tests relying predominantly on frequency analysis, perhaps partly explaining the limited sensitivity of EGG.

Given that the HR mapping analysis of arrhythmias has only recently begun, there may well be additional types of arrhythmias to be discovered and analysed and it therefore seems premature at present to suggest a complete or comprehensive classification system. Furthermore, future classifications could also be based directly on the mechanisms of these arrhythmias, as is starting to occur in the nascent field of small intestine arrhythmias.[36,92]

Despite its advantages, a major limitation of HR mapping is that all studies to date have been performed in fasted anaesthetized subjects subjected to laparotomy. Although routine anaesthesia is substantially unlikely to alter slow wave activity,[29] this research context is limiting because mechanical and nutrient factors are likely to be significant in slow wave arrhythmogenesis. For example, balloon distension of the antrum can provoke arrhythmias,[93] as can duodenal perfusion with lipid- and protein-rich solutions,[71] suggesting that it would also be productive to evaluate arrhythmias in the post-prandial period, as occurs with EGG. Major technical advances would be required to achieve multi-electrode mapping in fed, awake subjects (discussed below).

NEUROHORMONAL INFLUENCES AND THERAPIES

Multiple neurohormonal factors have shown potential to induce gastric arrhythmias, some of which are discussed here. Hormonal factors that may affect slow wave rhythms include insulin, cholecystokinin, pentagastrin and glucagon.[71] Administration of progesterone and oestrogen to non-pregnant women, in levels equivalent to that occurring in the pregnant state, can also induce gastric arrhythmia and nausea,[94] and adrenaline and noradrenaline have also been shown to be arrhythmogenic in susceptible individuals and animals.[71,90] In general, however, the clinical significance of these associations remains quite uncertain. For example, although female sex steroids can induce arrhythmias and arrhythmias are associated with nausea and vomiting in pregnancy,[75] proof of causality within this chain of events is lacking.

Neural influences may also promote or suppress arrhythmia. As discussed above, cholinergic stimulation may modulate intrinsic ICC frequencies, potentially inducing arrhythmias.[39] In addition, anticholinergic agents, such as atropine and scopolamine, can inhibit tachygastria and reduce nausea during circular vection, implying a cholinergic influence, which is likely to be centrally mediated.[74,95] Phentolamine has also been shown to blunt nausea and tachygastria induced by circular vection and ephedrine infusion, implying that α-adrenoceptor pathways are also involved.[71,74] In contrast, arrhythmias induced by gastric antral distension cannot be inhibited by anticholinergic administration, [93] and other influences could also be active in this context, such as mechanosensitive ion channels within the ICC network.[96]

The exact pathways by which neural influences may mediate arrhythmias remain incompletely understood. In general, ICC show extensive innervation, having synapse-like contacts with enteric nervous system (ENS) varicosities, such that ENS motor neurons may impact directly on ICC excitability and frequency and ICC also show anatomical associations with vagal fibres.[5,97] Through these connections, ICC likely play a mediating role in nitrergic and cholinergic modulation of gut smooth muscle function, whereas purinergic and peptidergic innervation appear to act via direct neurotransmitter diffusion, such that parallel influences are ultimately integrated in smooth muscle function.[5]

Paracrine factors are also known to induce gastric arrhythmias, such as the endogenous prostaglandin E_2,[98] which may act through prostanoid EP_3 receptors with chronotropic responses mediated by inositol 1,4,5-trisphosphate (IP_3) generation.[99] Indomethacin has been shown to reduce arrhythmia in hyperglycaemia, among other conditions,[100] but the

clinical applicability and safety of prostaglandin synthesis inhibitors in arrhythmia management currently remain uncertain.

Finally, dopamine and serotonin pathways have also been associated with gastric arrhythmia pathogenesis. Domperidone, cisapride and ondansetron are all known to stabilize gastric rhythm; however, it is unclear whether these are simply associations or pharmacological mechanisms of action.[71] Interestingly, ginger has similar effects, mediated by unknown means.[101]

ADVANCES IN GASTRIC ARRHYTHMIA MONITORING DEVICES

Future advances in gastric arrhythmia research will continue to be underpinned by technical advances and some of these opportunities are addressed here. To date, human HR mapping studies have been facilitated by a flexible printed circuit board (PCB) electrode platform.[102] In addition to being flexible, these arrays are cheap to mass produce, are readily sterilized and potentially disposable. However, their relatively low signal-to-noise ratio (SNR) can make signal interpretation problematic in the electrically noisy clinical environment, and further refinements to human serosal mapping arrays will be important.

Data management remains a major technical challenge in HR mapping research, with vast volumes of electrograms being recorded in each study. This problem has been partly overcome through a recent series of signal processing advances, which have generated an efficient data analysis package (i.e. the Gastrointestinal Electrical Mapping Suite or 'GEMS') that is largely automated when data quality is sufficient.[103] The back end of this analysis package is supported by a number of signal processing algorithms specifically developed for slow wave identification; these include validated algorithms for filtering,[104] identifying slow wave activation times,[105] grouping and mapping propagation cycles,[106] and mapping amplitude and velocity fields.[33,34] Efforts are also underway to apply similar methods in real time, allowing live mapping during experiments or clinical studies.[107]

To progress the goal of HR mapping arrhythmias in conscious, fed patients, Farajidavar et al.[108] recently presented the first telemetric platform for wireless slow wave data acquisition and transmission. In future, wireless transmission could be coupled with secure mucosal recording methods,[109] allowing detailed clinical studies to be performed over several days and in the awake state.

Gastric pacing (i.e. low-frequency stimulation to entrain slow waves) has shown potential to revert arrhythmias, modulate symptoms and accelerate gastric emptying,[79] and continues to be explored as a treatment modality. In a recent porcine study, HR mapping was applied to evaluate the effects of gastric pacing on slow wave entrainment in spatiotemporal detail,[110] and it would be valuable to reproduce this work in humans. An endoscopically implantable gastric stimulation device was recently proposed that could reduce invasiveness.[111]

Another critical advance will be development of effective devices for endoscopic HR mapping, which holds the potential for a routinely deployable diagnostic device. This task is complicated by the high impedance of the gastric mucosa, which attenuates signals that are already low in amplitude. However, past efforts at mucosal recordings in humans show that

the approach is feasible[109,112] and we anticipate that endoscopic prototypes will be proposed within the coming years. Laparoscopic approaches are also being developed, which could be usefully applied to investigate the consequences of operative procedures on slow wave activity.[113]

CONCLUDING REMARKS

Despite substantial recent progress, gastric arrhythmia remains a clinical enigma, with uncertain pathogenesis, pathophysiology and therapeutic implications. Many lines of enquiry must be further developed before we will know the full potential of Alvarez's ‘little prophesy’ that ‘gastroenterologists would come to rely upon electrical measures for the routine diagnosis of stomach disorders’. However, like Alvarez, we continue to see significant unmet potential in this field. The ultimate test will be to show that arrhythmias can be reversed in a way that meaningfully improves organ function and symptoms for the benefit of patients. In light of the many advances discussed here, such a goal may finally be within reach.

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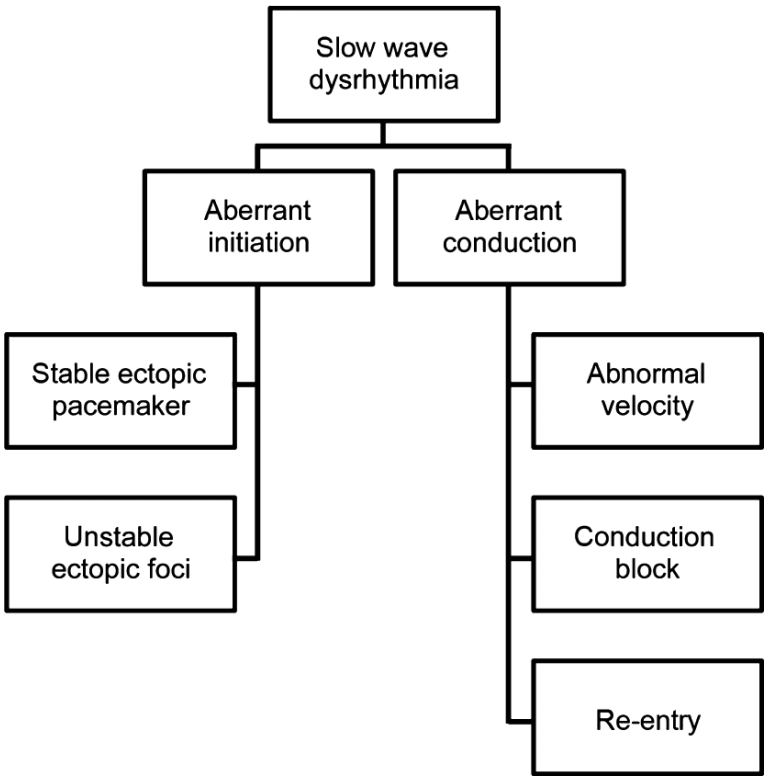

Figure 1.

An example of the classification schemes for gastric arrhythmia that are emerging, which are now being based on mechanisms and spatial patterns of slow wave activation. Aberrant initiation relates to abnormalities of intrinsic interstitial cells of Cajal frequencies and example activities include stable ectopic pacemakers and unstable regions of ectopic foci. Aberrant conduction involves disruption of the normal slow wave entrainment and examples include abnormal velocities, conduction blocks and re-entrant activities.

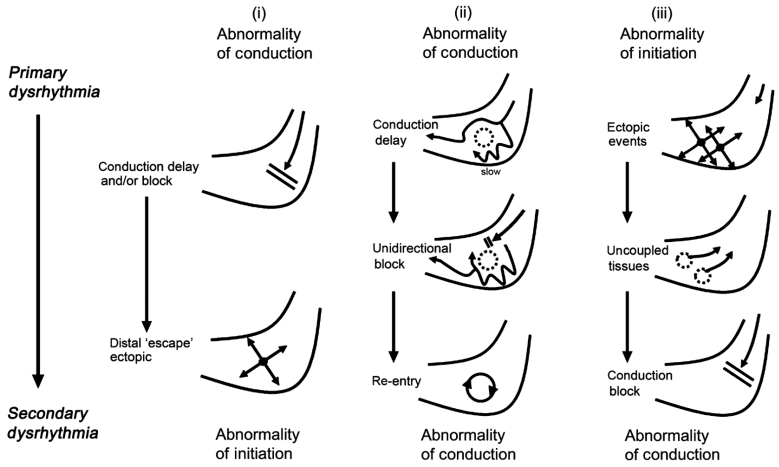

Figure 2.

Examples of secondary gastric arrhythmia mechanisms, as observed during multi-electrode (high-resolution) mapping, whereby one class of arrhythmia may induce secondary arrhythmic events. (i) Conduction delay or block may give rise to distal 'escape' events, due to the inherent automaticity of distal interstitial cells of Cajal;[7,86] (ii) conduction inhomogeneity, in the presence of unidirectional block, may give rise to re-entrant slow wave activity;[36,44,86] and (iii) ectopic events in the distal stomach may cause uncoupled areas of tissue, resulting in block of the normal antegrade wavefronts.[7,44,86]

Table 1

Published associations between electrogastrography measures and gastric disorders. EGG (electrogastrography), HR mapping (high-resolution mapping), GORD (gastro-oesophageal reflux disease).

Disorder	Reference	EGG Measure	Prevalence of Abnormalities	Comments
Gastroparesis	50	Any abnormality	6/6 patients	Arrhythmias variably reported to be frequent or rare in gastroparesis by serosal or mucosal recording,[51–53] whereas HR mapping showed a high rate[7]
	54	Any abnormality	72%	
	55	Arrhythmia; pooled analysis	Increased	
	56	Any abnormality	75% vs 0% controls	
Chronic unexplained nausea and vomiting	57	Arrhythmia by cutaneous EGG	Undefined	High arrhythmia rate also described in direct organ recording studies[58,59]
	57	Arrhythmia by serosal recording	95%	
Functional dyspepsia	60	Arrhythmias	36% vs 7% controls	Arrhythmias increased postprandially[61] and were higher in patients also having delayed gastric emptying[62]
	63	Arrhythmias	33% vs 0% controls	Increased detection using multichannel EGG[64]
	63	Any abnormality	66% vs 0% controls	
	65	Multichannel; any abnormality	83%; (tachygastria 36%; bradygastria 15%)	
	61	Post-prandial arrhythmias	43% vs 0% controls	
Gastro-oesophageal Reflux Disease	60	Arrhythmias	10% vs 7% controls	Arrhythmia only significantly present in GORD patient subsets with regurgitation,[60] delayed gastric emptying[66] and dyspepsia symptoms[67]
	68	Arrhythmias	50% of GORD patients with food regurgitation	
	66	Arrhythmias	22–24% vs 10% controls	
	67	Arrhythmias	75% GORD with dyspepsia symptoms vs 11% GORD alone	
Cyclic Vomiting Syndrome	69	Tachygastria	5/8 symptomatic children preprandially; 8/8 post-prandially	High arrhythmia rate observed when patients symptomatic
Ischaemic gastropathy	70	Arrhythmias	2/2 patients (case report)	Resolved after revascularization