Update on gastric dysrhythmia: pathophysiology, clinical significance and future horizons

Gregory O'Grady,[*,†] Tim Wang,[*] Peng Du,[†] Timothy R. Angeli,[†] Wim J.E.P. Lammers,[†,‡] and Leo K. Cheng[†,¶]

[*]*Department of Surgery, The University of Auckland, New Zealand,*
[†]*Auckland Bioengineering Institute, The University of Auckland, New Zealand,*
[‡]*Department of Physiology, UAE University, Al Ain, UAE,*
[¶]*Department of Surgery, Vanderbilt University, TN, USA*

Summary

Gastric dysrhythmia continues to be a clinical enigma 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 abnormalities are associated with motility disorders have reinvigorated gastric dysrhythmia research. Increasing evidence now suggests that ICC depletion and damage, network disruption and channelopathies may serve as causes of aberrant slow wave initiation and conduction. Histological and high-resolution (HR) electrical mapping studies have recently redefined the normal human 'gastric conduction system', providing an improved baseline for dysrhythmia research. Further, the application of HR mapping to dysrhythmia has generated important new insights into the spatiotemporal dynamics of dysrhythmia onset and maintenance, resulting in the emergence of new provisional classification schemes. 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 GI dysrhythmias. 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 dysrhythmogenesis also continue to be elucidated, and a deepening understanding of these mechanisms may open opportunities for drug design for treating dysrhythmia. However, for such translational goals, it remains to be seen whether dysrhythmia can be corrected in a way that improves organ function and symptoms in patients.

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 dysrhythmia.

The role of ICC

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 dysrhythmia research, and reinvigorate clinical interest in evaluating gastric electrical activity.

In the stomach, the strongest evidence for a pathophysiologic role for ICC is in gastroparesis.[6,7] While 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. ICC abnormalities are the most common histological finding in both idiopathic and diabetic gastroparesis,[6] and severity of ICC loss has been correlated with severity of gastric retention as well as electrogastrography (EGG) abnormalities.[9,10] Animal model research supports a pathophysiologic 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 dysrhythmia 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 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 dysrhythmias in a manner analogous to defined types of cardiac dysrhythmia.[15] Further research is needed to determine whether such mechanisms are also important in disorders such as functional dyspepsia.[16]

ICC also serve several other functions beside 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 dysrhythmia.[17]

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.[18] 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.[19,20] It is helpful to consider the pathogenesis of dysrhythmia mechanisms in terms of disruption to normal entrainment ('disorders of conduction') or to the intrinsic ICC frequencies ('disorders of initiation') (*e.g.* Figure 1), and each of these abnormalities may in turn promote secondary forms of dysrhythmia (*e.g.* Figure 2).

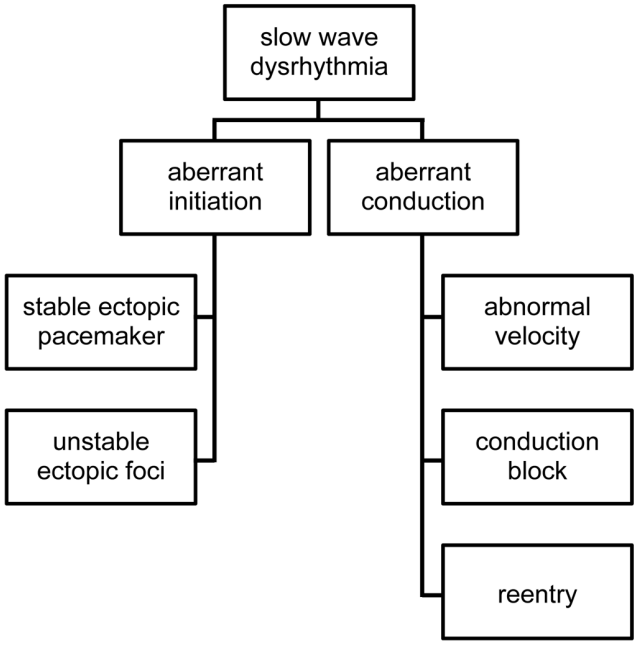

***Figure 1*. An example of the classification schemes for gastric dysrhythmia that are emerging.** *These are now being based on mechanisms and spatial patterns of slow wave activation. Aberrant initiation relates to abnormalities of intrinsic ICC frequencies, and example activities include stable ectopic 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.*

In 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).[21,22] 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).[22] 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.[23]

Extracellular recordings remain the primary tool for evaluating *in vivo* gastric slow wave activation patterns over large tissue areas.[24] Classically, gastric slow wave propagation was studied using sparse arrangements of extracellular electrodes, typically up to eight, placed at regular intervals along the GI tract. However, such results were incomplete due to the limitations of sparse sampling, and could be misleading due to spatial aliasing.[25] These limitations therefore motivated the introduction of GI high-resolution (HR) electrical mapping by Lammers *et al.*, whereby dense arrays of electrodes were applied to accurately track activation in spatiotemporal detail.[26,27] 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,[25,28,29] serving as a reliable baseline for dysrhythmia investigations.

Gastric anisotropy

Velocity anisotropy has proven to be an important finding from HR mapping studies for dysrhythmia 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× in humans).[25,28] The reason for the high velocity and amplitude pacemaker pattern was only recently resolved in a combined theoretical-experimental study,[30] aided by novel methods for analysing the spatial properties of slow wave activation.[31,32,33] 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.[30] In human stomach, propagation in the circumferential direction is ~2.5× 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.[30] By the time slow waves reach the mid to lower corpus, however, they have formed into complete ring wavefronts, such that the rapid circumferential conduction ceases, and wavefronts propagate with slower antegrade activation towards the pylorus.[25,30]

Velocity anisotropy is critical to the interpretation of dysrhythmic activity, because disorders of both initiation and conduction disrupt normal gastric ring wavefronts.[7,30] This allows 'ectopic circumferential propagation' to emerge, such that dysrhythmias are characterized by high-velocity wavefronts and high-amplitude signals local to their source, which directly determines the patterns of dysrhythmic activation. This anisotropy also plays a key role in the maintenance and stability of dysrhythmic patterns, such as slow wave re-entry[34] (recently reviewed by

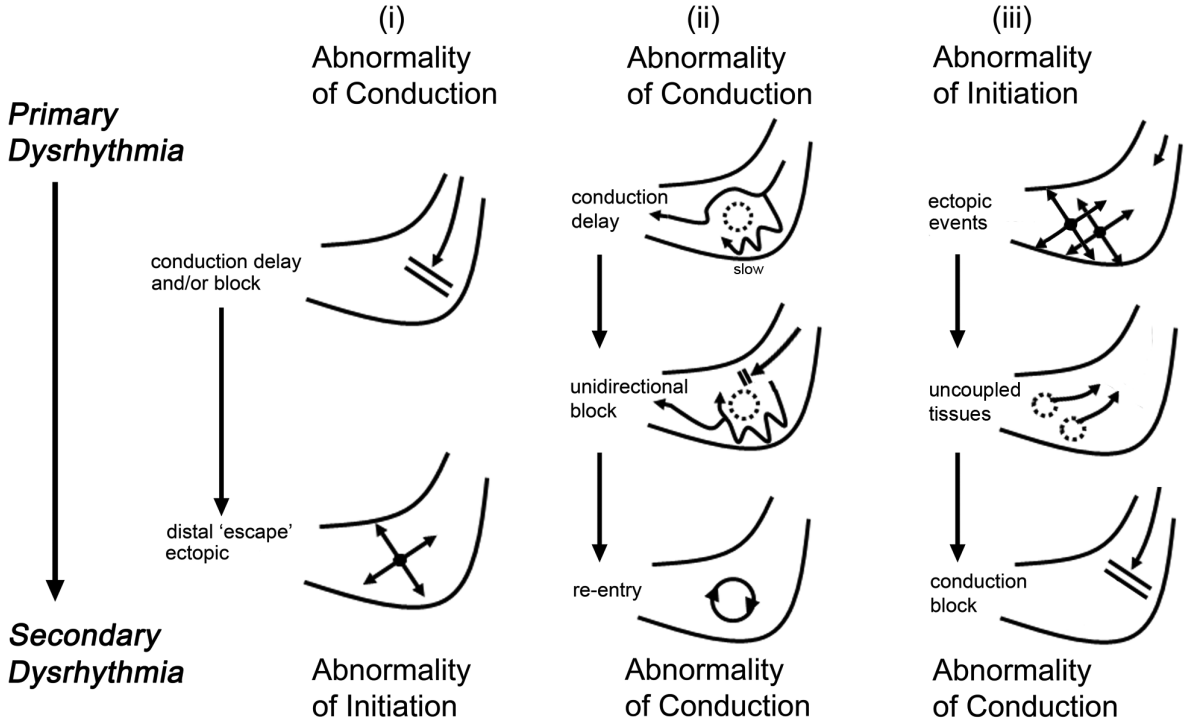

Figure 2. Examples of secondary gastric dysrhythmia mechanisms. *These were observed during multi-electrode (high-resolution) mapping, whereby one class of dysrhythmia may induce secondary dysrhythmic events. (i) Conduction delay or block may give rise to distal 'escape' events, due to the inherent automaticity of distal ICC;[7,66] (ii) Conduction inhomogeneity, in the presence of unidirectional block, may give rise to re-entrant slow wave activity;[34,42,66] (iii) Ectopic events in the distal stomach may cause uncoupled areas of tissue, resulting in block of the normal antegrade wavefronts.[7,42,66]*

Cheng *et al.*, 2013[35]).

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.[36] For humans, it was recently proposed that within a bidirectionally-coupled ICC system, the leading network might 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.[30] This theory awaits validation, but could offer mechanistic insights into dysrhythmogenesis. For example, slow wave frequencies are known to increase in ICC-IM at sites of sustained cholinergic stimulation,[37] which could then act as sites of dysrhythmic initiation within a bidirectionally-coupled system.

Electrogastrography and dysrhythmia

Much of what is known about gastric dysrhythmia, particularly in human disease, continues to be derived from electrogastrography (EGG). EGG is a non-invasive test and is relatively simple to perform,[38] 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 artifacts, necessitating use of bipolar electrodes, tight band-pass filtering (*e.g.* 0.016 - 0.3 Hz), careful attention to noise discrimination, and ideally, concurrent motion sensing.[39]

EGG recordings are typically taken before and after a test meal, and analysed variables 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.[3,38] 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),[40] particularly using modern multichannel approaches (*e.g.* four bipolar electrodes).[41]

The normal frequency range defined by EGG is around 2.4 – 3.7 cycles/min, with frequency abnormalities outside this range classed as bradygastria, tachygastria, or non-specific.[3,38] 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 since it has now been shown that there may be 3-5 slow waves propagating at any time in the stomach.[25,28] This issue is even more problematic during dysrhythmias, when different frequencies may be

simultaneously active in multiple uncoupled gastric regions.[7,42]

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 dysrhythmia, possibly contributing to dysrhythmia in diabetic gastroparesis,[43,44] leading to recommendations that blood glucose be tested and normalized prior to testing.[3] EGG abnormalities have also been associated with chronic renal failure,[45] *anorexia nervosa* (after a prolonged period),[46] and chronic intestinal pseudo-obstruction.[47]

In terms of symptoms, the strongest association with EGG-diagnosed frequency abnormality is with nausea and vomiting.[48] Dysrhythmia is common when vomiting is likely, as seen in chronic unexplained nausea and vomiting,[49,50] after chemotherapy,[51] in motion sickness,[52] and in nausea of pregnancy.[53] Indeed, physiological evidence suggests that myoelectrical derangements may be part of the normal physiological sequence of vomiting.[54,55,56] Some controversy remains, however, as to whether dysrhythmia 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 dysrhythmia and reduce nausea, suggesting dysrhythmia does have a role in symptom genesis.[57] A pathogenic role for dysrhythmia in the motion sickness induced by circular vection,[58] has also been suggested by the fact that the rhythm disturbances arise 1-2 minute before symptoms, and their severity correlates with nausea intensity.[48] Additionally, in patients with gastroparesis, the resolution of nausea and vomiting has been associated with improvements in EGG abnormalities.[59]

Another documented EGG abnormality is the loss of normal power increase after a test meal observed in gastroparetic patients.[60] The EGG signal is considered summative of slow wave activity and smooth muscle potentials and/or contractions.[61] The normal post-prandial power increase may therefore reflect increased electromechanical activity, and/or perhaps gastric distension,[62,63] while its loss in gastroparesis may reflect reduced electromechanical activity,[63] potentially related to hypomotility or reduced current density output caused by ICC loss.[64] 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, 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 65-100% in published studies (average 85%), and from 50-81% for predicting abnormal gastric emptying (average 65%).[3] But 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.[65]

New insights into dysrhythmia from HR mapping

The advent of HR mapping has been a major advance in gastric dysrhythmia research. The first HR analyses of slow wave dysrhythmias 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.[42] 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.[66] These two studies are representative of a new era for gastric dysrhythmia, in which modern methods of cardiac rhythm analysis are brought to bear to achieve accurate analyses of dysrhythmic onset and maintenance.[67]

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 dysrhythmic patterns.[7] Whereas previous studies had focused almost exclusively on human abnormalities of slow wave initiation (*e.g.* ectopic activity), this study demonstrated that conduction abnormalities (*e.g.* slow conduction and conduction blocks) were also prevalent in gastroparesis. These conduction abnormalities could be a consequence of ICC loss, which results in network remodelling and haphazard or delayed conduction.[64,68] The complex dysrhythmic propagation patterns described in this recent study also have pathophysiologic implications, because disorganised 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 dysrhythmia impairs gastric contractions and induces hypomotility.[69,70]

With a range of abnormalities now being discovered and examined by HR mapping, early attempts are being made to classify these dysrhythmias. In their canine study,[42] Lammers *et al.* proposed a first classification mostly based on rate and rhythm, very similar to what is used in cardiac arrhythmias.[71] In contrast, in the human gastroparesis mapping study,[7] the changes in rate were less dramatic, and dysrhythmias were classified in patterns of propagation, as elucidated by HR mapping (*e.g.* Figure 1). The limited alterations in slow wave rate during human dysrhythmia 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 dysrhythmias

Table 1. *Published associations between electrogastrography measures and gastric disorders.*

Disorder	Refs	EGG Measure	Prevalence of Abnormalities	Comments
Gastroparesis	59	Any abnormality	6/6 patients	Dysrhythmias variably reported to be frequent or rare in gastroparesis by serosal or mucosal recording,[95,96,97] while HR mapping showed a high rate.[7]
	60	Any abnormality	72%	
	93	Dysrhythmia; pooled analysis	Increased	
	94	Any abnormality	75% *vs* 0% controls	
Chronic unexplained nausea and vomiting	98	Dysrhythmia by cutaneous EGG	Undefined	High dysrhythmia rate also described in direct organ recording studies[49,99]
		Dysrhythmia by serosal recording	95%	
Functional dyspepsia	100	Dysrhythmias	36% *vs* 7% controls	Dysrhythmias increased post-prandially;[103] and higher in patients also having delayed gastric emptying.[104] Increased detection using multichannel EGG.[105]
	101	Dysrhythmias; Any abnormality	33% *vs* 0% controls 66% *vs* 0% controls	
	102	Multichannel; any abnormality	83%; (tachy 36%; brady 15%)	
	103	Post-prandial dysrhythmias	43% *vs* 0% controls	
Gastro-oesophageal reflux disease (GORD)	100	Dysrhythmias	10% *vs* 7% controls	Dysrhythmia only significantly present in GORD patient subsets with regurgitation,[100] delayed gastric emptying,[107] and dyspepsia symptoms[108]
	106	Dysrhythmias	50% of GORD patients with food regurgitation	
	107	Dysrhythmias	22-24% *vs* 10% controls	
	108	Dysrhythmias	75% GORD with dyspepsia symptoms *vs* 11% GORD alone	
Cyclic vomiting syndrome	109	Tachygastria	5/8 symptomatic children pre-prandially; 8/8 post-prandially	High dysrhythmia rate observed when patients symptomatic.
Ischaemic gastropathy	110	Dysrhythmias	2/2 patients (case report)	Resolved after revascularisation

has only recently begun, there may well be additional types of dysrhythmias 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 dysrhythmias, as is starting to occur in the nascent field of small intestine dysrhythmias.[34,72]

Despite its advantages, a major limitation of HR mapping is that all studies to date have been performed in fasted anaesthetised subjects subjected to laparotomy. While routine anaesthesia is substantially unlikely to alter slow wave activity (reviewed by O'Grady *et al.*, 2013[27]), this research context is limiting because mechanical and nutrient factors are likely to be significant in slow wave dysrhythmogenesis. For example, balloon distension of the antrum can provoke dysrhythmias,[73] as can duodenal perfusion with lipid and protein rich solutions,[48] suggesting that it would also be productive to evaluate dysrhythmias 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 dysrhythmias, some of which are discussed here. Hormonal factors that may affect slow wave rhythms include insulin, cholecystokinin, pentagastrin, and glucagon.[48] Administration of progesterone and estrogen to non-pregnant women, in levels equivalent to that occurring in the pregnant state, can also induce gastric dysrhythmia and nausea,[74] and adrenalin and noradrenalin have also been shown to be dysrhythmogenic in susceptible individuals and animals.[48,70] In general, however, the clinical significance of these associations remains quite uncertain. For example, while female sex steroids can induce dysrhythmias, and dysrhythmias are associated with nausea and vomiting in

pregnancy,[53] proof of causality within this chain of events is lacking.

Neural influences may also promote or suppress dysrhythmia. As discussed above, cholinergic stimulation may modulate intrinsic ICC frequencies, potentially inducing dysrhythmias.[37] Additionally, 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.[52,75] Phentolamine has also been shown to blunt nausea and tachygastria induced by circular vection and ephedrine infusion, implying that α-adrenergic pathways are also involved.[48,52] Dysrhythmias induced by gastric antral distension, by contrast, cannot be inhibited by anticholinergic administration,[73] and other influences could also be active in this context, such as mechanosensitive ion channels within the ICC network.[76]

Paracrine factors are also known to induce gastric dysrhythmias, such as the endogenous prostaglandin E2,[77] which may act through EP3 receptors with chronotropic responses mediated by IP3 generation.[78] Indomethacin has been shown to reduce dysrhythmia in hyperglycaemia, among other conditions,[79] but the clinical applicability and safety of prostaglandin synthesis inhibitors in dysrhythmia management currently remains uncertain.

Finally, dopamine and serotonin pathways have also been associated with gastric dysrhythmia pathogenesis. Domperidone, cisapride and ondansetron are all known to stabilize gastric rhythm; however, it is unclear whether these are simply associations or pharmacologic mechanisms of action.[48] Interestingly, ginger has similar effects, mediated by unknown means.[80]

Advances in gastric dysrhythmia monitoring devices

Future advances in gastric dysrhythmia 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.[81] Besides being flexible, these arrays are cheap to mass-produce, are readily sterilized and potentially disposable. However, their relatively low 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 ('GEMS') that is largely automated when data quality is sufficient.[82] The backend 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,[83] identifying slow wave activation times,[84] grouping and mapping propagation cycles,[85] and mapping amplitude and velocity fields.[31,32] Efforts are also underway to apply similar methods in real-time, allowing live mapping during experiments or clinical studies.[86]

To progress the goal of HR mapping dysrhythmias in conscious fed patients, Farajadivar *et al.* recently presented the first telemetric platform for wireless slow wave data acquisition and transmission.[87] In future, wireless transmission could be coupled with secure mucosal recording methods (*e.g.* Coleski & Hasler, 2009[88]), 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 dysrhythmias, modulate symptoms, and accelerate gastric emptying,[57] 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,[89] and it would be valuable to reproduce this work in humans. An endoscopically-implantable gastric stimulation device was recently proposed that could reduce invasiveness.[90]

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 (*e.g.* Coleski & Hasler, 2009;[88] Monges & Salducci, 1970[91]), 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.[92]

Concluding remarks

Despite substantial recent progress, gastric dysrhythmia 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 dysrhythmias 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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Author for correspondence:

Dr Gregory O'Grady,
Department of Surgery,
The University of Auckland,
Private Bag 92019,
Auckland 1142, New Zealand.

Tel: +64 21 448 523
Fax: +64 9 377 9656
E-mail: ogrady.greg@gmail.com