**High-resolution analysis of human gastrointestinal motor patterns and the clinical applications**

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**Introduction.** More than a century has passed since Canon’s pioneering studies, and a vast literature now underpins the field of gut motility (Szurszewski 1998). However, it must be concluded that clinical translation has lagged. Many clinical disorders of gut motility are still poorly defined, and there remains a lack of reliable tools to guide diagnosis, with few therapies that effectively address root causes.

One area of success has been in oesophageal motility, where the direct, high-resolution (HR) analysis of motility patterns now allows the comprehensive classification of disease states (Kahrilas et al., 2015). However, throughout the remainder of the gut, from stomach to the rectum, clinical tools for reliably analysing motor patterns remain limited. Consequently, diagnostic classification schemes for abnormal motor patterns in the stomach, small intestine, colon and rectum and have remained embryonic. In recent years, however, translational progress in HR motility diagnostics has begun to advance (Dinning et al., 2010; Cheng et al., 2013). We describe two areas of significant current progress: HR electrical mapping and HR colonic manometry, with a specific focus on recent translational applications. HR electrical mapping is a technique adapted from modern methods in cardiac electrophysiology, involving the use of finely-spaced arrays of electrodes to track electrical propagation sequences in fine spatiotemporal detail (Du et al., 2009; O’Grady et al., 2013). This method was pioneered in the GI tract by Lammers et al., who custom-built silver wire arrays and applied them in multiple innovative studies describing the motility patterns of the GI tracts of animal models (Lammers, 2015a, 2015b).

Clinical methods for the translation of GI HR mapping are now emerging. The principle device applied to date in human studies has been a flexible printed circuit (FPC) array, employing regular arrays of gold contacts (Du et al., 2009). The advantages of these arrays are that they can be mass-produced and easily sterilised, but with a trade-off in signal quality, and they can only be applied at invasive surgery. A vast volume of data is retrieved, which is processed through semi-automated software algorithms to enable efficient processing (Yassi et al., 2012).

The FPC arrays have enabled the first reliable studies of human gastric slow wave activation, including pacemaker behaviour and regional variations in activity (O’Grady et al., 2010a). More recently, the arrays have also been applied to study the specific physiology of the terminal gastric antrum, where a sudden acceleration of slow waves occurs prior to the pylorus, contributing to effective trituration (Berry et al., 2016). In addition, the FPC device is also being applied in studies defining patterns of gastric dysrhythmia in patients with motility disorders, including studies into gastroparesis and chronic unexplained nausea and vomiting (CUNV) (O’Grady et al., 2012; Angeli et al., 2015). Results from these studies have enabled a provisional classification scheme of human gastric dysrhythmias, with distinction between ‘disorders of slow wave initiation’ and ‘disorders of slow wave conduction’ (O’Grady et al., 2014). The figure shows an example of the classification schemes for gastric dysrhythmia that are emerging, 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 (Reproduced with permission from O’Grady et al., 2014). More work is required to validate this scheme and assess its utility in diagnosis and practice, but it is already proving useful in research.

The crucial next step for HR gastric electrical mapping will be to develop non-invasive devices to expand clinical investigations. Minimally-invasive (laparoscopic) devices have been proposed (O’Grady et al., 2009; Berry et al., 2016), but an endoscopic device is critically needed, to enable routine studies of gastric dysrhythmia during upper GI endoscopy. Significant progress towards this goal has been presented in preliminary form (Angeli et al., 2016b) and human studies are now awaited. In addition, while gastric dysrhythmias have been strongly implicated in generating nausea and vomiting (Koch 2014; Owyang & Hasler 2002), their significance in the overall symptom profile and diagnosis and management of motility disorders still needs to be defined (O’Grady et al., 2014).

Another important and emerging area of clinical interest is the application of HR electrical mapping to cases of gut dysmotility arising after surgical manipulations (Du et al., 2015). An example application is in patients after sleeve gastrectomy, where the native gastric pacemaker is resected (O’Grady et al., 2016). The same HR mapping techniques could also be applied to surgical manipulations in the small intestine, colon and rectum (Lammers 2015b),(Lammers 2013), although translational work in these areas has not yet significantly progressed.
New therapeutic directions are also needed for applications in conjunction with HR mapping, as has been successfully achieved for many years in cardiology (Tse et al., 2016). Electrical stimulation using the only currently-approved device (Enterra®, Medtronic) does not modify gastric dysrhythmias (Angeli et al., 2016), and attention is returning to the use of long-pulse (high-energy) gastric pacing in conjunction with HR mapping (O’Grady et al., 2010, Lin et al., 1998). Whether this approach will be successful in patients with gastroparesis and CUNV, where ICC networks are depleted and damaged awaits to be seen. Another interesting proposal is the emerging concept of using targeted ablation therapy to eliminate aberrant sources of gastric slow wave initiation (Angeli et al., 2016c).

In summary, the evolution and continued application of HR gastric mapping holds promise to finally resolve longstanding questions about the clinical significance and therapeutic importance of gastric dysrhythmias. However, work is still needed to show the clinical importance of this new technology.

High-resolution colonic manometry is a second prominent emerging technique with potential to critically advance translational GI motility (Dinning et al., 2010). A key advance enabling HR colonic studies has been the development of fibre-optic catheters by Arkwright et al., which apply a fibre-Bragg grating method to achieve multi-point recordings at resolutions of 1 cm over long distances (Arkwright et al., 2009).

To date, the main group publishing HR colonic manometry work has been Dinning and colleagues in Australia (Bampton & Dinning 2013), although publications are now also emerging from groups in New Zealand and Europe (Vather et al., 2016; Corsetti et al., 2016). An important step has been to present a comprehensive description of normal baseline activity in the human colon (Dinning et al., 2014). A particularly interesting result of this work has been to reveal the prominence of lower-amplitude propagating patterns, which could not be adequately resolved with lower-resolution methods (Dinning et al., 2013).

In particular, a cyclic activity in the distal colon and rectum has now been shown to be the most active motility pattern in the post-prandial state, which often propagates in the retrograde direction, and which may play a role in limiting rectal filling. This pattern has potential clinical implications, as it appears to be enhanced by sacral nerve stimulation, pointing to a possible mechanism of action for this therapy in faecal incontinence (Patton et al., 2013). In addition, this pattern is diminished in slow transit constipation, with patients lacking the normal post-prandial activity increase, pointing to underlying neuromuscular dysfunction (Dinning et al., 2015).

Another emerging area of interest is again post-operative states of dysmotility. Vather et al recently performed HR colonic manometry in patients with normal bowel function following anterior resection, and showed that by one-year post-operatively, distal colonic motility had recovered (Vather et al., 2016). This recovery included restoration of the normal post-prandial increase in cyclic activity, as well as the ability of activity sequences to freely propagate across sites of healed anastomosis, implying regeneration of neuromuscular cellular elements through scar. Comparison studies are now awaited from patients with anterior resection syndrome, where bowel function has not recovered after surgery.

In summary, the continued application of HR colonic manometry holds promise to resolve longstanding questions about the role of dysmotility in common disease states such as severe constipation, irritable bowel syndrome, faecal incontinence and anterior resection syndrome. However, much work is still needed to determine if this technique will become a routine clinical tool.

Conclusions. It is clear that a key element to progress in clinical motility disorders will be through
improved understanding of the underlying abnormal motility patterns. Towards this end, translational tools for HR motility analysis have emerged, in the form of HR electrical mapping and HR colonic manometry. Early progress in applying these tools has been encouraging, and as a result, the coming decade may prove a particularly productive period for the field of translational GI motility.


