Mapping and modelling human gastric slow wave activation in health and disease

G. O'Grady, P. Du and L.K. Cheng, Auckland Bioengineering Institute, University of Auckland, New Zealand.

Gastric contractions are coordinated by slow wave activity generated by interstitial cells of Cajal (ICC). Clinical interest in evaluating human slow wave activity is motivated by associations between slow wave dysrhythmias and motility disorders, such as gastroparesis.

Multielectrode mapping has recently been adapted for GI electrophysiology, and involves the use of dense electrode arrays to track electrical activation patterns in fine spatial detail. The recent advent of electrodes suited to intraoperative use has now enabled the first detailed studies of normal and abnormal human gastric activation (O'Grady *et al.*, 2010,2012a). Gastric conduction was found to be anisotropic (7.3 mm/s circumferential *vs* 2.9 mm/s longitudinal; P=0.002), with velocity being proportional to amplitude (O'Grady *et al.*, 2012b). The gastric pacemaker site was localized accurately for the first time, to the corpus greater curvature, and demonstrated rapid (~8 mm/s) high-amplitude activity, due to localized circumferential conduction. Activation then proceeds as ring wavefronts propagating longitudinally at ~3 mm/s, at ~6 cm intervals. A further velocity transition was found in the antrum to ~6 mm/s.

Patients with gastroparesis were enrolled to investigate human gastric dysrhythmia (n=12) (O'Grady *et al.*, 2012a). Full thickness biopsies showed low ICC counts compared to controls (2.3 *vs* 5.4 bodies/field; P<0.0001), and corpus slow wave amplitudes were reduced (170 *vs* 415 μV; P=0.002). Abnormalities of slow wave initiation and/or conduction occurred in 11/12 (*vs* 0/12 controls), and were classified by a new scheme. Initiation abnormalities (10/12) were classed as 'stable ectopic pacemakers' or 'diffuse focal events' (median 3.3 cycles/min, range 2.1–5.7), while conduction abnormalities (7/10) was classed as 'reduced velocity' or 'conduction blocks' (median 2.9 cycles/min; range 2.1–3.6). Circumferential conduction routinely emerged during dysrhythmias, due to ectopic activation amid resting tissue, or disruption of ring wavefronts, such that dysrhythmic wavefronts assumed elliptical configurations.

Multiscale modelling has emerged as a key strategy for quantitatively integrating physiological events across the vast spatial (10^{-9} to 10^{0} m) and temporal (10^{-6} to 10^{9} s) scales they encompass. Recently, gastric multiscale models have been developed and applied to investigate research questions relevant to humans that are difficult to address experimentally.

Human gastric multiscale modelling has now achieved mathematical integration of data from gastric mapping, computed tomography anatomical geometries, biophysically-based cell models, and multiple other experimentally-derived sources (Du *et al.*, 2010a). As well as presenting a unified conception of human whole-organ gastric electrophysiology, these models have also been applied in predictive *in silico* simulations of the sources of the cutaneous electrogastrogram. A further emerging application of gastric multiscale modeling is to quantify structure-function relationships. Predictive simulations of slow wave entrainment were performed on confocal images of ICC network geometries from wild-type and 5HT-2B knockout mice jejuna, and demonstrated lower current density output and reduced conduction velocity in ICC depletion (Du *et al.*, 2010b). These results are consistent with, and potentially explain, several outcomes of human gastroparesis mapping detailed above. Multiscale models are furthermore being applied to quantitatively investigate coupling between ICC populations, to investigate the mechanisms of anisotropic conductivity and the emergence of rapid circumferential propagation during dysrhythmia (O'Grady *et al.*, 2012b).

In summary, mapping and modelling are contributing to a time of rapid progress in human gastric electrophysiology. The next challenge will be to convert this progress into clinical benefit.

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