REVIEW ARTICLE

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From the organ bath to the whole person: a review of human colonic motility

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Abstract

Motor function of the colon is essential for health. Our current understanding of the mechanisms that underlie colonic motility are based upon a range of experimental techniques, including molecular biology, single cell studies, recordings from muscle strips, analysis of part or whole organ *ex vivo* through to *in vivo* human recordings. For the surgeon involved in the clinical management of colonic conditions this amounts to a formidable volume of material. Here, we synthesize the key findings from these various experimental approaches so that surgeons can be better armed to deal with the complexities of the colon.

Introduction

A knowledge of gastrointestinal motility is a prerequisite to understanding motor patterns in health and disease. Much information can be gained from the study of animals, however there are significant inter-species differences in neuromuscular function. Thus, a focus on human studies is warranted.[1–4]

Measurement of colonic motility in humans extends from analysing the actions of nerves and muscles in strips of colonic muscle to studies of the whole organ *in situ*. Eliciting colonic motor patterns mediated by myogenic and neural mechanisms, strengthens such observations.[5] Segments of human colon are often resected for treatment of cancer, and these segments include a healthy margin of normal colon. With patient consent, these healthy sections can be studied, giving insights into the physiology of colon motility in a controlled *ex vivo* setting. *In vivo*, the colon and anorectum have motility patterns that can either be controlled voluntarily (squeeze of the external anal sphincter) or can be induced by physiological, chemical or mechanical stimulation.[6] This review provides an overview of the various experiments utilized to explore the physiology or pathophysiology of human colonic motility.

Smooth muscle

Colonic motility is mediated by contractility of smooth muscle cells, these cells have been extensively studied. For example, electrophysiological analysis of ion channel function has been performed in single human smooth muscle cells.[7] Colonic

smooth muscle cells have a membrane potential which oscillates several times per minute. These 'myogenic' oscillations (slow waves) are generated by a network of non-neuronal pacemaker cells, the Interstitial Cells of Cajal (ICC) which are connected by gap junctions to smooth muscle cells. ICC oscillations depolarize smooth muscle cells bringing them close to the threshold for generating action potentials that evoke contractions. Intracellular recordings from human colonic smooth muscle cells show two main sets of oscillations in membrane potential: the dominant slow waves at 2–8 cycles per minute (cpm) and a faster waves at 18 cpm.[8] A third type of cell, the PDGFR-alpha cells ('fibroblast-like-cells') make up the other major cell type in the so-called 'SIP syncytium' (Smooth muscle, ICC and PDGFR-alpha cell syncytium). The PDGFR-alpha cells are involved in mechanosensitivity and neuromuscular transmission.[9] Together, these three cell types orchestrate contractility that underlies human colonic motility.

Small muscle strips

Studies of single cells do not necessarily show how smooth muscle tissue works as an integrated network. A more in-depth insight can be gained from studying the mechanical activity of colonic smooth muscle in strips or segments. Since the 1950s, electrical stimulation of muscle strips has been used to activate the axons of excitatory and inhibitory enteric motor neurons.[10] Contractile activity is measured using force transducers. After surgical excision, the muscle strip needs to equilibrate (usually ~30 min) before consistent motor activity is observed. This is likely due to a temporary disruption of gap junction function caused by tissue trauma.[11] Damage to the gut causes prostaglandin release which suppresses contractility, whereas inhibition of prostaglandin production restores motility.[12,13] In human colonic muscle strips, electrical stimulation activates both excitatory and inhibitory motor neurons synchronously. This involves cholinergic and non-cholinergic excitatory motor neurons and non-adrenergic inhibitory motor neurons.[14] Pharmacological blockade of excitatory motor neurons (with hyoscine or atropine) reveals the actions of inhibitory motor neurons. Cholinergic antagonists do not entirely suppress stimulus-evoked contractions however, due to the presence of non-cholinergic excitatory transmitters including Substance P and other tachykinins. Conversely, pharmacological blockade of inhibitory transmission during electrical stimulations reveals the actions of excitatory motor neurons.[15,16] Inhibitory transmission can be blocked by nitrergic and purinergic antagonists such as L-NOARG & MRS2179[17,18] suggesting that inhibition is mediated by both nitric oxide and purines.

Enteric nervous system

So far, we have concentrated on the effector tissue of motility—the smooth muscle SIP syncytium—but the patterning that is central to coordination is largely mediated by the enteric nervous system (ENS). This has been extensively studied at the cellular level. The ENS consists of three interconnected ganglionated plexuses—the myenteric (Auerbach's) plexus lying within the external smooth muscle and two plexuses in the submucosa—an outer (Meissner's) plexus (close to the epithelium) and an inner (Schabadasch's) plexus closer to the circular muscle. There is also an intermediate submucous plexus in humans.[19] Enteric neuron cell bodies lie within the ganglia of these plexuses and their axons project via inter-ganglionic 'internodal') strands to their targets. The ENS contains entire neural circuits that mediate simple reflexes and responses and is made up of populations of enteric sensory neurons, inhibitory and excitatory motor neurons many populations of interneurons with axons running up or down the bowel, secretomotor neurons and vasomotor neurons.

The ENS of the human colon has been studied, at a cellular level, using multi-labelling immunohistochemistry with neuronal tracing techniques.[20–22] Results show 15–30 different classes of enteric neuron in human colon and that their longest axonal projections are 40–80 mm along the gut wall. This indicates that the ENS controls moment-to-moment local control of motility, secretion and blood flow. Intracellular electrophysiological recordings from human myenteric neurons reveal that their electrical activity is similar to that of experimental animals.[23]

Most recently, single cell RNAseq techniques have been applied to human colonic ENS.[24,25] This latter technique defines the transcription of RNA of individual cells and has been applied to cells from the human smooth muscle/SIP syncytium.[26] Single cell RNAseq has enormous potential to identify new, cell-specific targets for targeted therapy or diagnosis of human colonic disorders and allows for clustering of cells into putative classes.

Larger *ex vivo* preparations

Muscle strips provide information about neuromuscular transmission but are too small to keep the functional neural circuits intact. However, larger preparations of intact human colon can also be studied *ex vivo*. Such preparations, 5 cm or larger in each dimension, can be stimulated with stretch, mimicking luminal distension, rather than relying on electrical stimulation. Thus, it can be shown that the ascending excitatory reflex, widely studied in animal specimens, is also present in human colon specimens.[27]

When a segment of colon is resected it can be studied *ex vivo* before it must be sent for pathological analysis.[28] Large preparations can be kept for several hours if adequately supported. In our institution, an organ bath 1.2 m in length (13 L volume), accommodates total colectomy specimens[28,29] and a smaller bath is used for anterior resection specimens (Fig. 1).[30,31] Specimens are maintained in warmed, oxygenated Kreb's solution (at body temperature) and recordings of wall tension can be performed using multiple force transducers. Alternatively, intraluminal pressure can be recorded using colonic manometry.[29,30] Compared to the full range of motor patterns that have been recorded and described *in vivo*[32] (see *in vivo* section), large *ex vivo* specimens typically show a restricted range of motor patterns.

Extrinsic autonomic innervation

Even large preparations studied *ex vivo* do not have the full complement of neural pathways because extrinsic autonomic neural pathways to the colon are inevitably disrupted. Extrinsic autonomic pathways play an important role in modulating ENS activity to meet physiological needs. During exercise or arousal, the sympathetic nervous system

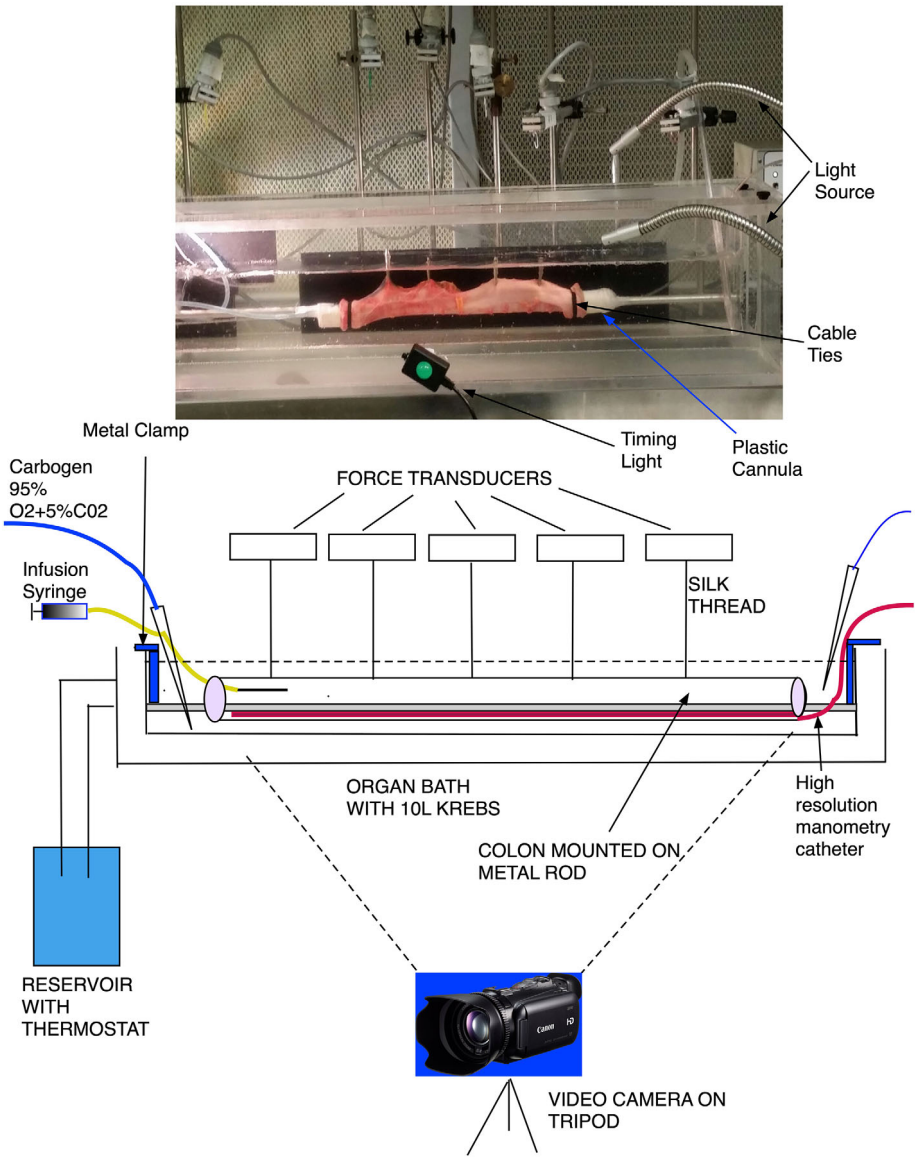

Fig. 1. Experimental setup for recording motility from an intact segment of human sigmoid colon. Motility is recorded from; (i) the force transducers (clips attached to the top of the specimen); (ii) the fibre-optic manometry catheter attached to rod inside the preparation; and (iii) the video that record wall motion.

is activated. Final sympathetic neurons ('post-ganglionic') have cell bodies in the prevertebral ganglia (coeliac, superior mesenteric, inferior mesenteric and pelvic/hypogastric ganglia). Their axons run via colonic nerves and enter the gut wall where they innervate the myenteric and submucous plexuses. Here they release noradrenaline as their major neurotransmitter which acts via alpha 2 receptors to inhibit release of neurotransmitters in the ENS, thus dampening down excitatory pathways and reducing motility and secretion.[33] Sympathetic neurons, with cell bodies in paravertebral ganglia, directly innervate blood vessels in the gut wall causing vasoconstriction. Thus, blood flow can be redirected to other body systems.

The human colon also receives a parasympathetic innervation via two pathways. Firstly, neurons in the dorsal motor nucleus of the medulla project via the vagus nerve to innervate the gut, from the stomach to the proximal two thirds of the colon. A second pathway originates via neurons in the sacral spinal cord which synapse in the hypogastric plexus where they activate cholinergic parasympathetic neurons which reach the distal colorectum via the rectal nerves. Parasympathetic axons primarily target the enteric plexuses, where they release acetylcholine and upregulate motility. This plays a key role in defaecatory activity and damage to this pathway can cause chronic constipation.[34] For surgeons, it is important to note that sacral parasympathetic pathways innervate the full extent of the rectum, sigmoid colon and descending colon, travelling in specialized intramural 'ascending nerves' which join with the myenteric plexus at multiple sites.[35] However, sacral parasympathetic axons appear to enter the bowel solely in the rectum. Low rectal resections may therefore interrupt sacral parasympathetic pathways before they enter the gut wall, contributing to Low Anterior Resection Syndrome (LARS).[36]

In vivo studies

The clinical assessment of functional colonic disorders begins with a history of a patient's symptoms. A validated questionnaire and bowel diary provide objective and quantified measures of bowel

function and symptoms. The location of pain, frequency and overall duration gives some potential clues of gut dysmotility but a direct relationship is hard to determine. Nevertheless, symptoms are the primary outcome measure for pre- and post-treatment assessments for functional bowel disorders.[37]

Scintigraphy and radiopaque marker studies are commonly used to distinguish between normal colonic transit, delayed colonic transit (slow-transit constipation), or a rectal evacuation disorder.[38] Transit could also be recorded with a wireless motility capsule[39] however, at the time of writing this review, the product had been removed from the market.

Another tool capable of detailing transit is the 3D transit system. This consists of an electromagnetic capsule which can be tracked in real-time through the digestive tract. The capsule detects slow waves and their frequency (~3 cpm in stomach; 10–14 cpm in the small bowel and 2–8 cpm in the colon) and regional transit times can be assessed. This capsule can provide an accurate picture of pan-colonic or regional colonic delay.[39] Currently this device is limited to use in research studies only.

Real-time recordings of colonic motor patterns can be performed using high-resolution manometry. These catheters, placed into the colon with the aid of a colonoscope, contain multiple, closely-spaced pressure sensors. Depending upon the number of sensors and spacing, these catheters can span varying lengths of the colon.[32] Manometry recordings have identified several distinct motor patterns. The most recognizable is the high-amplitude propagating contraction (HAPC). These relatively infrequent motor patterns are associated with defaecation and the mass movement of colonic content.[6] In patients with slow transit constipation, these motor patterns are absent or diminished.

While the HAPCs stand out in a manometry recording, the most common activity seen is the cyclic motor pattern. This consists of pressure waves that occur at 2–8 cpm and propagate in retrograde or antegrade direction (Fig. 2). They dominate rectosigmoid motility, and may act as a rectosigmoid brake, helping to control rectal filling and thus maintain faecal continence.[40] Synchronous colonic pressurization (an increase in pressure across all colonic sensors) has also been described and associated with the passage of gas.[32] More recently, MRI has been used to detail colonic wall motion in the human colon.[41] However, as given images can only be captured for 20 s periods, the clinical worth is yet to be determined.

For rectal evacuation disorders and/or faecal incontinence, a range of clinical tests exist. Anorectal manometry tests the resting and squeeze pressures of the anal sphincter.[42] In general terms, a low resting pressure can indicate a weak or damaged internal anal sphincter, while a low squeeze pressure can indicate damage to the external anal sphincter. Rectal sensitivity can be tested with a balloon inflated in the rectum.[43] Tests of evacuation disorders commonly use the balloon expulsion test or defaecography. The former requires the patient to expel a fluid-filled balloon placed within the rectum. However, this does not provide any detail of structural anomalies. Defaecography can provide further evaluation of the pelvic floor during attempted defaecation. Barium paste is inserted into the rectum and the patient expels the paste during fluoroscopic or MRI imaging. This provides a dynamic structural assessment of rectal prolapse, rectoanal intussusception and rectocoele.[44]

Sensation

Recording of sensation from the gut is often under-rated. A powerful trigger of visceral pain is ischaemia (and low pH is used experimentally to activate sensory impulses).[45] Humans can report visceral sensation whereas in animals it has to be measured indirectly by observing visceromotor reflexes. The intensity of such sensation may be quantified by the patient's analgesic requirements and visual analogue scales.

The perception of visceral pain begins with nerve endings in the bowel wall and is transmitted via mostly unmyelinated nerve fibres to

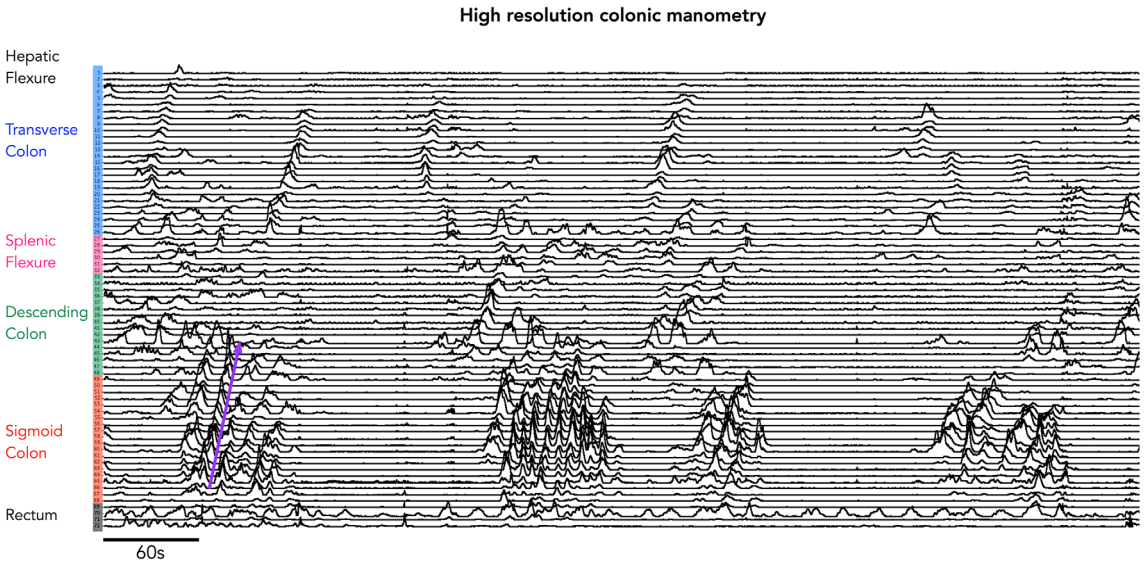

Fig. 2. A high resolution manometry catheter recording of activity in the human colon. Retrograde propagating contracts can be seen in the sigmoid colon (purple arrow).

the spinal cord (the cell bodies are in the dorsal root ganglia). Action potentials in sensory nerves can be recorded *ex vivo* (these nerve bundles also contain sympathetic and viscerofugal nerve fibres). Recordings have been made from human bowel resections, showing these nerves are activated by stretch, probing and bradykinins.[46,47]

There is a big gap in our understanding before the next level of reported sensory activity. Functional MRI (fMRI) scanning of the brain relies on increased neural activity in the sensory cortex causing an increased blood flow. In patients with irritable bowel syndrome or functional constipation, studies with fMRI have reported several alterations in brain function associated with pain, when compared to healthy adults.[48,49]

Implications for clinicians

Normally gut motility functions silently and unheralded. Local pathways ensure that even when a resection and anastomosis is performed the gut continues to function. There are several scenarios where gut motility is disrupted.

Postoperative ileus

A common problem of arrest of gut motility following surgery. Mast cell activation (due to handling) causes sympathetic activation and an overall dysfunction of coordinated gut motor activity.[50] Extensive animal studies have led to clinical trials, with prostaglandin inhibition showing some benefit, but definitive, effective treatments remain elusive.[51]

Low anterior resection syndrome

This is a chief cause of morbidity after rectal resection. Potentially relevant is the removal of the rectosigmoid brake as well as lack of a rectal reservoir.[52] possibly exacerbated by interruption of the pelvic nerve inflow via the rectum.

Faecal incontinence

Studies to date focus on anal sphincter integrity but colonic motor patterns may well contribute.[53]

Irritable bowel syndrome (IBS)

There are multiple potential causes of IBS, and symptoms may be confused with surgical diseases,[54] however as IBS is associated with constipation and/or diarrhoea, colonic motor abnormalities are likely to be associated.

Pseudo-obstruction (acute and chronic)

These are often treated surgically, as the symptoms are similar to a mechanical bowel obstruction. In chronic cases, intestinal biopsy may clarify whether there is a myopathy, neuropathy or a cause such as lymphocytic infiltration.[55,56]

Hirschprung's disease

This is an archetypal neural condition (absent enteric nerve cells) of the colon affecting about 1 out of 5000 newborns. Motility problems may persist after resection of the aganglionic bowel, suggesting that there can be wider problems of enteric neural formation from the neural crest.[57]

Conclusion

Evaluation of colonic motor activity continues to evolve. Organ bath studies can lead to wider conclusions of motility and enable drugs to be evaluated in small specimens. Integrating the results from colonic specimens ranging from single cells to the intact human subject will improve our knowledge of the pathophysiology of this organ and aid surgeons and physicians in their practice.

Conflicts of interest

None declared.

Author Contributions

David Wattchow: Conceptualization; writing – original draft; writing – review and editing. **Simon Brookes:** Conceptualization; writing – original draft; writing – review and editing. **Nick Spencer:** Writing – review and editing. **Paul Thomas Heitmann:** Writing – review and editing. **Roberto De Giorgio:** Writing – review and editing. **Marcello Costa:** Writing – review and editing. **Phil Dinning:** Conceptualization; writing – original draft; writing – review and editing.

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