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Pathophysiology of colonic causes of chronic constipation

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Abstract

Colonic sensorimotor dysfunction is recognized as the principal pathophysiological mechanism underpinning chronic constipation. This review addresses current understanding derived from both human and animal studies, with particular reference made to methods of investigation.

Keywords

colon; constipation; manometry; scintigraphy; marker studies

Introduction

Severe constipation is a chronic condition with major morbidity and health care burden. Billions of dollars are spent on its diagnosis and treatment,¹ yet one-third of patients will have an unsatisfactory response to therapy.² However, attempting to elucidate the pathophysiological mechanisms underlying chronic constipation is a not inconsiderable challenge, given the inaccessibility of the colon for study, and there remains a paucity of information on many aspects of function.

Measurement of Colonic Motor Activity: Human *In Vivo* Studies

Colonic motor activity comprises four main components: myoelectric activity, phasic contractile activity, tonic contractile activity and intraluminal transit. Specific methods are available for the assessment of each separate component,³ but no single investigation gives information regarding all four types of activity. In current clinical practice, evaluation of colonic motor function is almost exclusively limited to assessment of intra-luminal transit. Although the direct assessment of colonic contractile activity can be achieved through colonic manometry, this procedure is only slowly gaining clinical acceptance, notably in the paediatric field. Other novel methods are also available, and all are discussed below.

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Transit studies

Two techniques exist for the routine assessment of colonic (or whole gut) transit, both of which involve irradiation of the subjects: radio-opaque markers and radionuclide scintigraphy. Together with assessment of rectal evacuation and rectal sensation, studies of colonic transit should form the cornerstone of investigation in patients with chronic idiopathic constipation. These investigations have led to constipation being conceptualized in three broad and overlapping categories: normal transit constipation, slow transit constipation (STC), and evacuation disorders (ED).⁴ Transit studies *per se* primarily address the question: 'does the patient have normal or slow colonic transit'.

Radio-opaque marker studies—Available methods are based on a technique first described by Hinton *et al.* in 1969,⁵ and involve the ingestion of radio-opaque (e.g. barium-impregnated polyvinyl chloride) markers and assessing their movement through the GI tract by use of plain abdominal X-rays. Unfortunately, greater than 10 methods involving administration of a single set of markers, and at least five methods in which multiple sets of markers are ingested on subsequent days have been published, and thus no standardisation of the test exists. The two most widely accepted techniques in routine clinical practice are: (i) the 'simple' radio-opaque marker test, which involves swallowing a single gelatine capsule containing 20–50 markers on day 0, and taking an abdominal X-ray, to determine the number of markers remaining in the colon, on days 4⁶ or 5⁷; and (ii), the 'multiple marker' or 'segmental test', modified from that initially described by Metcalf *et al.* at the Mayo Clinic,⁸ in which three capsules, each containing markers of a different shape, are administered successively on days 0, 1 and 2, and plain abdominal X-rays are taken at days 4 and 7, or on day 5.⁹ The former (simple) method is used as a screening test to differentiate normal from slow colonic transit, whereas the latter method enables assessment of a numerical mouth-to-anus transit time, and also residence times of the markers within defined colonic regions (usually right side, left side and rectosigmoid).

Radionuclide scintigraphy—The progress of a radioisotopic chemical through the GI tract can be followed using a gamma camera, and this is recognised as the 'gold standard' method for assessing colonic transit in constipated patients. Based on the seminal study by Krevsky *et al.* in 1986,¹⁰ two methods have been popularised: (i) oral administration of ¹¹¹Indium, bound to diethylenetriaminepentaacetic acid (DTPA), with scans taken once or twice per day up to 72 or 96 h,^{6,11} and (ii) ¹¹¹Indium mixed with a slurry of activated charcoal within a methacrylate-coated capsule is ingested; the pH-sensitive coating breaks down in the mildly alkaline environment of the distal ileum, releasing the contents at the desired location and scans are taken at 4, 24, and 48 h.¹² Intraluminal movement is usually expressed by calculating the geometric centre of the isotope mass, which is a weighted average of radioactivity counts within various regions of the colon (typically, five or seven regions are delineated, including expelled faeces). A low value for geometric centre (toward 1) implies that the majority of the radionuclide marker is in the caecum and ascending colon, whereas a high geometric centre value indicates that the majority has been expelled. Time-activity curves can be constructed to show the progression of the geometric centre over the course of the study period. Further mathematical manipulation allows the residence of isotope in individual regions to be determined, and a composite value for colonic transit time can be calculated by linearising the time-activity curves.¹³

Comparison of radiological methods—When performed in tandem, radio-opaque markers progress slightly more quickly than a radioisotopic substance, although diagnostic capability for assessing slow transit is equivalent.¹⁴ Radio-opaque markers have the advantage over scintigraphic methods of being cheap, simple to perform and widely available. Though more expensive and restricted to specialist centres, radioisotopic methods allow for more

precise quantification and are more physiological. Nevertheless, analysis is substantially more complex and labour intensive.

Alternative techniques—To overcome the fundamental limitation of irradiation of the subject under study, several alternative methods, based on the transit of an indigestible solid through the GI tract, have recently been developed. These include wireless (telemetric) motility capsules,^{15,16} and magnetic markers.¹⁷ Further validation of these tools is required before being incorporated into general clinical practice.

Clinical utility: defining subtypes in chronic constipation based on patterns of intraluminal movement—Using a simple radio-opaque marker study, colonic transit delay is defined when >20% of markers are retained at the time of the abdominal X-ray.⁵ Similarly, when three sets of markers are ingested on consecutive days, retention of >20% of markers at 120 h defines slow transit.⁹ In several published studies, the mean diagnostic yield of radio-opaque marker studies in identifying patients with delayed colonic transit is around 44% (range 13–68%: data from 12 studies, with >30 subjects recruited; references omitted for brevity); that is, approximately half of patients presenting with chronic and intractable symptoms have evidence of STC. In the adult population, STC is an almost exclusively female disorder,¹⁸ whereas in children, the prevalence is more similar between males and females.¹⁹ When transit times are taken into account, the upper limit of normal is considered to be around 70 h (in 18 published studies, 12 showed an upper limit of normal between 66 and 75 h, median 72 h; references omitted for brevity, but available on request). The diagnostic yield of this method for detecting slow transit constipation is approximately 49% (range 16–80%; data from 10 studies, with >30 subjects recruited; references again omitted for brevity). Patterns of slow transit, typically characterised as: (i) colonic inertia (delay throughout the colon), (ii) left-sided or ‘hindgut’ delay, or (iii) a rectosigmoid delay have been reported; the latter is believed by some to be synonymous with an ED, though this has never been satisfactorily substantiated.

For scintigraphic studies, diagnosis of delayed colonic transit is determined by the geometric centre of isotope mass (GCI) at given time points. For the Mayo Clinic method (methacrylate-coated capsule; five anatomical regions of interest delineated), slow colonic transit is defined as a GCI <1.7 at 24 h. With orally administered ¹¹¹Indium[DTPA] (7 regions of interest delineated), a GCI of <3.6⁶ or <4.1 at 48 h²⁰ indicates a delay in transit. As with radio-opaque marker studies, different patterns of colonic transit delay have also been reported, although the cut-off values used vary: diffuse slow transit has been defined as a GCI <3.51 at 24 h²¹ or <3.6 at 48 h,⁶ whilst patients with a GCI ≥3.51 at 24 h,²¹ or a GCI between 4.1 and 6.4 at 48 h, with significant retention at 72 h,²⁰ are believed to have a functional rectosigmoid obstruction. Other studies have delineated right-sided, left-sided and rectosigmoid holdup. Whether the latter represents a ‘primary’ site-specific delay within the very distal colon, or is secondary to ED is unclear. It also remains unproven whether knowledge of varying patterns of colonic transit delay informs better therapeutic intervention.

Transit studies: limitations and future directions—As with most available tests of gastrointestinal function, transit studies are not standardised. As a consequence, normative ranges are severely lacking; by way of example, the cut-off of >20% for an abnormal study, using the multiple marker method with X-ray at 120 h was based on only 43 subjects, of whom only 19 were female!⁹ The largest study to date enrolled 192 healthy subjects,²² and employed the Metcalf method⁸ (see above). The upper limit of normal from this study was 71 h. Bouchoucha *et al.* enrolled 148 healthy volunteers, and used a method by which sets of markers were ingested on six successive days, with a single X-ray taken at day 7.²³ They reported very wide ranges for normal transit time of 44 ± 29 h in males, and 68 ± 54 h in females. Another fundamental issue, that is almost universally disregarded, is that unless the marker of interest (radio-opaque or radionuclide) is delivered to the ileum or caecum, the measurement yielded

is *mouth-to-anus* transit time, and *not* colonic transit time, as so frequently reported. This is a substantial concern; transit to the ileo-caecal region after oral administration takes around 6 h in most subjects, but can be considerably longer; this indicates that true colonic transit time is regularly underestimated, and the magnitude of that underestimation is rarely known. Reproducibility of studies of colonic transit have been reported to be only reasonable in both health¹¹ and in constipated subjects,²⁴ indicating that there is a wide biological variability. Study conditions must also be taken into account: transit correlates with stool form²⁵ and is faster in men than women.^{8,11} The influence of the menstrual cycle remains uncertain.²⁶ Finally, the recognition of scintigraphy as the gold standard method for assessing colonic transit is flawed, given that there is no other final diagnostic technique to compare it to.

A better critical examination of the diagnostic yield and accuracy of current (and emerging) investigations is needed, and this is only feasible through large, well-designed prospective studies. Such an approach would enable the refinement of existing techniques, both in terms of test performance, indications for use and data interpretation.

Colonic manometry

Although transit studies probably provide the best ‘functional’ appreciation of colonic motility (i.e. movement of intracolonic contents), they do not provide data on actual colonic motor patterns. Recording colonic contractility can be achieved with colonic manometry. One of the recommended indications for this test is to assess severely constipated patients (both adult and paediatric) who are unresponsive to medical therapy, and have evidence of slow colonic transit in the absence of an ED;⁴ indeed, the paediatric literature suggests that colonic manometry may guide clinical decision making.²⁷ However, in adult practice, data to support this rationale are fundamentally lacking.

In patients with constipation, the first attempts to record true colonic (as opposed to anorectal) motility were published in 1988,²⁸ and there have been approximately 20 studies in adults (and less in the paediatric population) published since. As with measurement of colonic transit, there is very little standardisation of colonic manometry techniques (Table 1). Colonic pressures can be recorded with water-perfused or solid-state catheters which are introduced via a nasocolonic route or with the aid of a colonoscope. The number of sensors contained within the catheter varies (typically 4–16), as does the spatial resolution (distance between recording sites of 1–15 cm), the duration of the recording (2–24 h), and the colonic regions from which the data are recorded. The interpretation of data and resultant definition of identified motor patterns thus varies greatly amongst studies. Indeed there is no *standard* measure for defining colonic motility, with different groups using: motility index (MI); area under the curve (AUC); propagating sequences (PS: also called propagating contractions) or high amplitude propagating sequences (HAPS: also called high amplitude propagating contractions); isolated pressure waves; or non-propagating pressure waves to describe colonic activity (Table 1). Finally the majority of studies contain small sample sizes and the normal ranges are wide. Collectively all of these factors will potentially impact upon recorded data and make comparison between studies difficult.³ Yet, despite such lack of standardisation, a number of observations have been made, and these are discussed below.

High amplitude propagating sequences—In patients with slow transit constipation, a consistent finding is a reduced frequency of HAPS^{28–32} These motor patterns are associated with both luminal transit³³ and defaecation,³⁴ and their reduced frequency in patients is implicated as a potential cause of retarded colonic transit. In contrast, manometric studies in children with STC have demonstrated a normal HAPS frequency, suggesting that children with slow transit constipation may have a different clinical identity from the adult STC population.

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Low amplitude propagating sequences—In comparison to HAPS characteristics, very few authors have reported the frequency of low amplitude PS. In patients with STC, low amplitude PS are reported as being reduced^{29,35} or of similar frequency to healthy controls.³⁶ Some have identified regional differences in the PS frequency, with one study demonstrating a diminished frequency in the transverse colon³⁷ and another an increased frequency in the descending colon.³⁸ The implications of such findings remain unknown.

Meal response—Studies in healthy control subjects have demonstrated an increase in the MI, AUC, or HAPS frequency in response to a meal.^{39,40} In patients with constipation, a diminished or absent meal response is reported by most;^{29,31,32,41} this has been proposed as an indicator of an intrinsic neuropathy/mesenchymopathy.^{29,42}

Diurnal variation/morning waking—In health, both propagating and nonpropagating motor activity of the colon is suppressed at night.^{29,40} In constipated patients a similar decrease in activity has been noted by some,^{29,30,35} whilst others have demonstrated a notable absence of the normal nocturnal suppression.^{37,38} Morning waking induces an increase in colonic activity in health,^{29,40} and this has also been shown in some patients with constipation;^{38,43} others, however,^{29,35} have demonstrated that this response may be diminished or absent compared to controls. It is likely the diurnal variation in motor function is mediated by the central nervous system, and an attenuated response to sleep or morning waking may support a neuropathic cause in such patients.²⁹

Response to chemical stimuli (also see colonic reflexes)—In healthy controls, rectal or colonic infusion of bisacodyl⁴¹ or chenodeoxycholic acid⁴⁴ induces an increase in PS and HAPS frequency. Similar responses have been reported with intravenous injections of the cholinergic agonist edrophonium chloride.⁴⁵ In patients with constipation, bisacodyl has also been shown to induce an increase in PS/HAPS frequency^{41,46,47} although the response may be blunted in comparison to health.^{32,41} In contrast, an intravenous injection of edrophonium chloride or rectal infusion of chenodeoxycholic acid has been shown to have a minimal effect in the colon of constipated patients,^{44,45} which may indicate an abnormality within the myenteric plexus,⁴⁸ cholinergic pathways⁴⁵ or recto-colonic neural pathways.⁴⁴

Spatiotemporal patterning of colonic propagating sequences—Recently, studies have been published that examine the relationships that may exist between sequential propulsive motor events. In healthy controls, it has been shown that PS are linked in an organised spatio-temporal manner,⁴⁹ manifest as series' of three or more consecutive PS originating in either a more proximal or distal colonic location. Thus, while most single PS do not span the length the colon, collectively a series of linked PS do. This 'regional linkage' is largely absent in constipated patients, and may be among the hallmarks that will help define colonic dysmotility in severe constipation.⁴⁹

Differentiating constipation subtypes based upon colonic motility studies—Few studies have attempted to distinguish types of constipation based upon colonic manometry. O'Brien *et al.* compared colonic motor patterns of patients with an ED and STC, and concluded that intraluminal measurements alone do not discriminate between these subgroups of chronic constipation.⁵⁰ Furthermore Bassotti *et al.* noted that no colonic motor patterns were able to differentiate constipated patients with and without delayed transit.⁵¹

Colonic manometry: limitations and future directions—Based upon the data described above, a recent consensus paper⁴ published by the American Neurogastroenterology and Motility Society concluded that: 'There are no published quantitative data of phasic contractility that unequivocally differentiate normal colonic function from colonic inertia'.

This may suggest that the *a priori* assumption that colonic motor patterns in constipation are distinguishable from healthy control is wrong. A more likely explanation, however, is that current recording techniques are simply inadequate. Several limitations are evident: (i) although many studies describe 'colonic manometry', in the majority data have been recorded from the distal two-thirds or distal third of the colon only. This is particularly important, given that PS and HAPS are not distributed evenly throughout the colon, with the majority of these motor patterns originating in the ascending and proximal transverse colon.⁴⁰ (ii) As discussed above, recent studies have shown organisation between PS originating throughout *all* regions of the colon, and this organisation is dysregulated in constipation.⁴⁹ Therefore, to gain a realistic impression of colonic motility/dysmotility, true pan-colonic manometry must be performed. (iii) Using 'traditional' catheter design (sensor spacing of >7 cm), a significant proportion of propagating activity is missed, given that such motor patterns may only extend over distances as short as 2 cm⁴¹ (see Chapter 2). Spatial resolution must be increased to appreciate the full spectrum of colonic contractile activities. (iv) The effect of bowel preparation undoubtedly disturbs basal physiology; this must be taken into account in studies where cleansing of the colon is undertaken.

In summary, due to limitations in both study design and recording tools available, we still have only a rudimentary and simplistic (though growing) understanding of normal colonic physiology and of the pathophysiology of colonic motor function in constipation. Only through device development and the acquisition of large data sets, both in healthy subjects and constipated patients, can manometric (and also transit) biomarkers be determined that may help define constipation sub-types and ultimately guide treatment.

Relationship between pressure and flow

Simultaneous assessment of intraluminal pressure changes by manometry and colonic transit provides a powerful combination to assess the functional significance of colonic pressure events or motility patterns.^{33,52,53} Further integrated studies of this nature are required, both in health and chronically constipated patients.

Colonic barostat

Prolonged recordings of colonic tone, phasic contractile events and compliance are feasible using an oversized, infinitely-compliant bag attached to a barostat.^{50,54,55} Intracolonic placement of the barostat bag into the prepared bowel is favoured,⁴ although an antegrade (per oral) approach has also been employed.⁵⁵ Few data are available in constipation, and the clinical relevance of data attained is as yet unknown.⁵⁰

Sensory function—An intracolonic barostat also enables the assessment of parameters of visceral sensation.⁵⁶ Again, data in both severe constipation, and health, are grossly lacking,⁵⁰ with interpretation confounded by lack of standardisation of methodologies. Nevertheless, this is an important area for research, given the growing awareness of the impact of colorectal sensory dysfunction (both hypersensitivity⁵⁷ and hyposensitivity⁵⁸ in functional gastrointestinal disorders.

Colonic reflexes

One fundamental question that remains unanswered is whether any derangements of colonic motor function recorded (altered transit, or quantitative changes in contractile activities) are due to a primary (neuromuscular) colonic dysmotility, or are secondary to distal colorectal distension or obstruction (i.e. an ED). Mechanical rectal stimulation has been shown to inhibit motor activity from the stomach⁵⁹ to the proximal colon,⁶⁰ left hemi-colon⁶¹ and sigmoid colon.⁶² A classic study by Klauser *et al*, showed that voluntary suppression of defaecation resulted in prolongation of total and regional colonic transit times, as measured by radio-opaque

markers, indicating that a 'functional' ED has an effect on the right colon.⁶³ All of these studies provide evidence for the existence of a substantial network of recto-enteric/intestino-intestinal reflex pathways.

Results concerning whether a delay in transit through the rectosigmoid area may be secondary to an ED are conflicting. Some studies show a reasonable correlation between an ED (as defined using evacuation proctography) and distal colonic transit delay,⁶⁴ and on this basis, the Rome III criteria state that '*retention of markers in the proximal or transverse colon suggests colonic dysfunction, and retention in the rectosigmoid area suggests obstructed defecation*'.⁶⁵ However, recent work from Zarate *et al*⁶⁶ has challenged this assumption, by showing that colonic scintigraphic time-activity curves are equivalent in groups of patients with or without a severe ED. This finding supports other scintigraphic studies in small numbers of patients with STC but without ED, who nevertheless had a rectosigmoid hold-up of isotope.^{6,14} It is probable that an ED leads to colonic dysfunction in only a minority of patients. This issues certainly warrants further investigation, as the differentiation between 'pure' slow transit constipation, an isolated ED, and coexistent STC and ED (of varying degrees) remains the basis of management in patients with chronic idiopathic constipation.

Pathophysiology of Chronic Idiopathic Constipation: Lessons from Animal Models

The underlying causes of altered motor function identified in human studies of constipation have not been clearly elucidated. A full review of the pathoetiology of (colonic causes) of constipation is clearly beyond the scope of this review. Nevertheless, both classic historical studies and more contemporary use of animal models have greatly enhanced our understanding.

Historical studies

Various seminal articles describing the effect of nerve section/stimulation on colonic motility in animals have shown the parasympathetic outflow to be primarily excitatory and the sympathetic outflow to be inhibitory.⁶⁷ In terms of physiological effects, bilateral pelvic nerve section effects a fall in colonic tone and a decrease in spontaneous motor activity, while sympathetic nerve section causes an increase in colonic motility. In dogs, HAPS are abolished following bilateral pelvic nerve section and mass defaecation is lost, to be replaced by the passage of pellet-like stools.⁶⁸ Conversely, stimulation of the pelvic nerves causes contractions of the colon powerful enough to expel the entire luminal contents, whereas stimulation of pre- and postganglionic extrinsic sympathetic nerve fibres (lumbar splanchnics and lumbar colonics) inhibits spontaneous contractions. Notably, the stimulatory response to pelvic nerve stimulation is reduced or blocked by lumbar colonic nerve stimulation, indicating that sympathetic nerves mainly exert their inhibitory influence on the colon by suppressing the parasympathetic nerve-derived excitatory drive.

Colonic elongation

Novel studies have shown that changes in the length of the colon can have marked effects on colonic motility and may underlie or compound motor abnormalities displayed in constipation. The enteric nervous system in the large bowel contains intrinsic neural circuits that initiate peristaltic and secretomotor reflexes, triggered by luminal distension or mucosal stimulation.⁶⁹ In the isolated guinea-pig colon, the presence of intraluminal content may be associated with a significant increase in the colonic length, and with increasing length comes a significant reduction in transit speed.⁷⁰ Colonic elongation (longitudinal stretch) activates mechanosensory, myenteric descending neuronal nitric oxide synthase (nNOS) positive interneurons that release nitric oxide. This inhibits action potential firing in other myenteric sensory neurons driving peristaltic nerve circuits, and hence contractile activity is inhibited.

^{70,71} This inhibitory reflex is referred to as the 'occult' reflex, as it doesn't produce a direct output to the muscle, like the peristaltic reflex,⁷² but suppresses activity in other enteric sensory neurons.⁷¹ The presence of the occult reflex in the human colon and its possible role in constipation remains to be determined.

Other animal models

Adenosine receptor model—Adenosine, which is derived from ATP, acts through one of the four G protein-coupled receptors: A1, A2A, A2B, or A3. Among the adenosine receptors, A2BAR, which is linked to nitrergic signalling, has the highest expression in the colon, where it is expressed on both epithelial cells and enteric neurons.⁷³ The A2BAR knockout (A2BAR^{-/-}) mouse may prove an interesting model of constipation as it displays increased stool retention, decreased stool frequency, delayed colonic emptying and decreased nitrergic relaxation of circular muscle.⁷⁴ In addition, the stool water content is reduced in these mice, suggesting that the receptor also has a role in chloride secretion.

Aging models—In humans, constipation increases with age.⁷⁵ In the rat and murine gastrointestinal tract, the largest age-related decreases in neuronal populations within the myenteric and submucous plexus appear to occur in the colon. However, the age-related decline in specific functional classes of enteric neurons is unclear. Using NADPH-diaphorase as a marker for nitrergic neurons it has been shown that 100% of neurons in the aged rat proximal colon were positively stained. In contrast, others have shown, using specific antibodies to myenteric nNOS neurons, that the number of nitrergic neurons per ganglion are decreased (>50%) in the aged rat large bowel (4 vs 26 months).⁷⁶ Whereas intrinsic primary afferent (sensory) neurons (IPANs) in the submucosal ganglia decrease with age, IPANs in the myenteric plexus appear to increase.⁷⁷ Functional studies have demonstrated that electrically stimulated contractions are reduced in aged rats, as is the propulsion and the number of excreted faecal pellets.⁷⁷

Serotonin model—Serotonergic (5-hydroxytryptamine-5-HT) signalling abnormalities have also been implicated in the pathogenesis of functional bowel diseases.⁷⁸ Serotonin is an important regulator of peristalsis. It is released from enterochromaffin cells in the mucosa where it activates 5-HT₃ and 5-HT_{1P} receptors on the sensory processes of intrinsic primary afferent neurons (AH neurons) and is also released from interneurons to activate inhibitory motor neurons.⁷⁹ Serotonin is inactivated by the serotonin reuptake transporter (SERT)-mediated uptake into enterocytes or neurons. The abilities of selective 5-HT₃ receptor antagonists (e.g. granisetron) to evoke constipation have been examined in conscious guinea-pigs.⁸⁰ Following injection with 5-HT₃ receptor antagonists, guinea-pigs excreted a reduced number of faecal pellets, which was similar to the effects of these drugs in *in vitro* preparations of isolated distal colon.

Models of neurological disorders—Constipation is a recognised symptom of many neurological conditions. Several animal models have been developed to better examine these conditions, including those for: diabetes;⁸¹ Hirschsprung's disease;⁸² muscular dystrophy;⁸³ Parkinson's disease;⁸⁴ and spinal cord injury.⁸⁵ and they have shed light upon pathways that innervate colonic function. Full descriptions are outside the scope of this chapter.

Animal models: limitations and future directions

The obvious limitation of animal models is that findings will not necessarily translate to humans. Nevertheless, it is clear that animal models have aided not only our understanding of normal physiology, but have also helped elucidate pathophysiological mechanisms that might underlie some forms of constipation. Novel animal models that need to be further developed

are the nNOS knockout mouse model,⁸⁶ the outlet obstruction model⁸⁷ and transgenic mouse models where specific ICC and ion channels are knocked out.⁸⁸

Conclusions

With advances in diagnostic technology, it is now accepted that in the field of functional bowel disorders, symptom-based assessment, although important, is unsatisfactory as the sole means of directing therapy. A robust classification based on underlying pathophysiology has thus been suggested, highlighting a crucial role for physiological testing in clinical practice. Nevertheless, judicious use of these tests is recommended. The major caveat is that there is no uniform standardisation of tests, and thus results between centres are often difficult to compare. In addition, robust normative data for all measures of function remain inadequate, particularly with regard to age and gender stratification. Furthermore, there is currently a broad gap between *in vivo* research performed in human and *in vitro* work carried out in animal models. Recorded motor activity identified from human studies needs to be better integrated with findings in animals.

Areas for Future Research

1. Large sample size studies of colonic transit in healthy, predominantly female controls, using both traditional (radio-opaque markers and scintigraphy) and novel methodologies (ingestible telemetric capsules) are essential to firmly establish normal ranges. This can only be achieved through a global standardisation of techniques. Further validation of newer techniques^{14–16} is also required.
2. ‘Defined’ patterns of colonic transit delay. Are these real or artificial?
3. Is a distal colonic hold-up/delay truly secondary to an ED? Conversely, does an ED lead to colonic dysmotility?
4. Are slow transit constipation and colonic inertia separate conditions?
5. High-resolution pancolonic manometry needs to be performed in a large sample size of healthy controls to establish normal ranges of colonic motor patterns. Studies should be of sufficient duration to record the colonic response to standardised meal, sleep and morning waking.
6. Such studies also need to be performed in a large number of constipated patients to establish if there are biomarkers that can distinguish existing (largely predetermined) constipation subtypes (i.e. STC, ED etc.), or if they aid a more contemporary classification.
7. Animal models are needed in which we can recreate, inhibit and augment a range of similar motor patterns to those identified in humans.

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Table 1

Variations in colonic manometry recordings

Reference.	Sample size H:C	Patient population	Adult/child	Catheter	Placement technique	Manometric technique/duration	No. of sensors	Spacing (cm)	Colonic regions [§]	Measurements	Meal response (Y/N)	Diurnal variation (Y/N)	Waking response (Y/N)	Chemical stimuli (Y/N)	Defaecation (Y/N)
28	18/14	IC	Adult	WP	CS	Static (24 h)	8	12	HF-R	HAPS	N	Y	Y	N	N
53	12/16	IC	Adult	WP	CS	Static (~3 h)	4	15	HF-R	MI, HAPS, PS	Y	N	N	N	N
89	0/23	ED (11); other* (12)	Child	WP	CS	Static (4 h)	8	10–15	MT-R	HAPS, MI	Y	N	N	N	Y
90	29/15	STC	Adult	WP	CS	Static (~5 h)	8	12	HF-R	MI, PS, HAPS	Y	N	N	N	N
91	0/5	IC	Adult	WP	CS	Static (~2 h)	8	10	SF-R	PS	N	N	N	Y	Y
45	8/14	IC	Adult	WP	CS	Static (~2 h)	8	12	SF-R	ME	N	N	N	Y	N
45	18/25	NTC (9); STC (16)	Adult	WP	CS	Static (24 h)	9	12	SF-R	HAPC	N	N	N	N	N
50	15/40	NTC(12); STC (15); ED (13)	Adult	WP	CS	Static (~3 h)	5	5	SF-R	MI, HAPS	Y	N	N	N	N
43	12/12	STC	Adult	WP	CS	Static (~1–2 h)	8	12	SF-R	MI	N	N	Y	N	N
47	0/25	STC	Adult	WP	CS	Static (~2 h)	8	12	SF-R	HAPS	N	N	N	Y	N
92	5/7	Prolapse	Adult	WP	CS	Static (24 h)	8	12	MT-R	AUC, HAPS, MI	Y	N	N	N	N
32	5/7	IC (7); other [†] (7)	Adult	WP	CS	Static (24 h)	8	12	HF-R	AUC, HAPS	Y	N	Y	Y	N
30	10/8	STC	Adult	ss	NC/CS	Ambulatory (24 h)	10	15	C-R	HAPS, MI	Y	Y	N	N	N
36	16/29	STC	Adult	WP	CS	Static (24 h)	8	12	HF-R	PS, HAPS	N	N	N	N	N
93	14/45	STC (35); C-IBS (10)	Adult	WP	CS	Static (24 h)	8	12	MT-R	HAPS, PS	Y	N	N	N	N
94	0/26	STC	Adult	WP	CS	Static (24 h)	8	12	MT-R	Cyclic activity	Y	Y	N	N	N
41	10/10	STC	Adult	WP	CS	Static (6 h)	12	1–10	MT-R	HAPS, AUC	Y	N	N	Y	N
38	16/11	ED	Adult	WP	A	Static (24 h)	16	7.5	C-R	PS, HAPS, AUC	Y	Y	N	X	Y
31	20/40	STC	Adult	WP	CS	Static (24 h)	12	10	MT-R	HAPS, AUC	Y	N	N	Y	N
29	20/21	STC	Adult	ss	CS	Ambulatory (24 h)	6	7–15	MT-R	HAPS, AUC	Y	Y	Y	N	Y
42	0/32	IC (13); other [‡] ; (19)	Child	WP	CS	Static (3 h)	8	10–15	C-R	HAPS	Y	N	N	Y	N
35	16/26	STC (18); NTC/ED (8)	Child/adult	WP	NC/A	Static (24 h)	8	7.5	C-R	PS, HAPS	Y	Y	Y	N	Y
37	9/16	STC	Adult	WP	CS	Static (24 h)	16	7.5	C-R	HAPS, PS	Y	Y	Y	N	Y

* On the basis of histopathological and manometric studies of the upper gastrointestinal tract, 10 patients had a diagnosis of gastrointestinal neuropathy and two had a diagnosis of myopathy.

[†] Constipation secondary to antidepressants.

[‡] Hirschsprung's disease (2); cerebral palsy (1); imperforate anus (6); spinal abnormality (12).

[§] Where the majority of recording were taken from.

A, appendicostomy placement; AUC, area under curve; C, caecum; CS, colonoscopic placement; ED, evacuation disorder; HAPS, high amplitude propagating sequence/contraction; H.C, Health;Constipation; HF, hepatic flexure; IC, idiopathic constipation; MI, motility index; MT, mid-transverse; NC, nasocolonic; PS, propagating sequence/contraction; R, rectum; SS, solid state; SF, splenic flexure; STC, slow transit constipation; WP, water-perfused.