Functional Diagnosis in Upper and Lower Gastrointestinal Diseases: Relevance for Conservative, Interdisciplinary and Surgical Therapies

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Question 1: What are the most frequent reasons or indications for which you refer patients to the Neurogastroenterology and Motility Laboratory? What clinical question do you want answered ... or is it (almost) always 'just' to confirm your suspicion?

Heinrich: From the gastroenterologist's perspective, referrals to our Motility Laboratory are not restricted to the relatively clear-cut preoperative questions posed by upper and lower gastrointestinal (GI) surgeons, such as gastroesophageal reflux disease (GERD) and oesophageal motility disorders or faecal incontinence and obstructive defecation. Referring doctors request investigation of a wide range of symptoms such as unexplained epigastric pain, regurgitation, nausea and vomiting, as well as abdominal and anal pain. In many cases, a detailed history using a structured questionnaire can provide clues as to whether primary functional or organic pathology is present and, occasionally, point to the final diagnosis. However, upper and lower GI motility testing provides an objective description of pathophysiology of symptoms and can help diagnosing important conditions such as achalasia, GERD, rumination, and dyssynergic defecation.

Perretta: For foregut surgeons, the most frequent indications for referral to the Neurogastroenterology and Motility Laboratory are:

- 1) Preoperative workup for patients referred for surgical treatment of GERD. Reflux studies with combined pH-impedance monitoring is used to provide objective evidence of GERD based on acid exposure and number of reflux events and also to determine symptom association. Furthermore, manometry is

important to rule out severe dysmotility such as achalasia and other major motility disorders including severe, symptomatic ineffective oesophageal motility as seen in scleroderma, as well as, on occasion, individuals with very severe reflux disease.

- 2) Patients presenting with symptom recurrence or dysphagia after fundoplication. Upper GI motility testing with high-resolution manometry (HRM), especially if combined with solid swallows, can rule out 'outlet obstruction' at the esophagogastric junction (EGJ) due to a tight fundoplication, fundoplication slippage or migration, and hiatal hernia recurrence. Reflux studies can also provide objective evidence of persistent (or recurrent) reflux disease if the fundoplication is too loose or has dehisced.
- 3) Further assessment of patients with dysphagia and unexplained ('non-cardiac') chest pain to rule out achalasia, other motility disorders (e.g. hypercontractile motility), and reflux disease as a cause of symptoms.

Steinemann: As a colorectal surgeon, I mainly refer patients with symptoms of faecal incontinence and obstructed defecation to the Neurogastroenterology and Motility Laboratory. Moreover, I am interested in the anorectal function of patients with chronic pelvic pain.

Anorectal manometry is an important tool to confirm and objectify a clinical finding of a weak sphincter tone in anal sphincter injury. It is even more important in patients with symptoms of obstructed defecation to identify pelvic floor dyssynergia, where the appropriate treatment is physiotherapy with biofeedback, or, together with other tests of evacuation (e.g. defaecography), anatomical causes of symptoms (e.g. rectocele with intussusception).

Question 2: In your experience, how frequently do the results of physiological investigations establish the cause of symptoms and the diagnosis? To what extent is clinical diagnosis based on patient symptoms and to what extent on the results of these tests? In what cases do the results provide a 'stand-alone' diagnosis, and in what cases do the results contribute to the diagnosis? Please illustrate this response with examples from your own practice!

Heinrich: Oesophageal HRM and pH-impedance monitoring have greatly contributed to our understanding of oesophageal motility disorders, as pressure phenomena from the pharyngeal swallow, along the oesophagus, and through the EGJ (as well as oesophageal clearance if combined with impedance) can now be described in detail [1].

HRM metrics have been validated against independent measurements of oesophageal function and are utilized by the Chicago Classification system to diagnose motility disorders [2]. The system is hierarchical, which serves to focus attention on clinically relevant findings. Most important, abnormal EGJ function is considered first because failure of the EGJ to relax and/or open in achalasia and outflow obstruction has a greater effect on bolus transport than abnormal peristalsis such as spasm or aperistalsis. In addition, the Chicago Classification makes a clear distinction between major motility disorders, which are never observed in healthy individuals and are always associated with clinical disease, and minor abnormalities, which are 'outside the normal range' but can be observed in patients without dysphagia and, occasionally, in healthy individuals [2]. In the former group, there is a clear rationale for treatment directed at correcting the pathology. In the latter group, the association of minor motility disorders with patient symptoms is less certain, and other factors could also be involved (e.g. acid reflux, visceral hypersensitivity). In particular, HRM – in contrast to conventional manometry – has allowed a more objective and detailed classification of achalasia subtypes, which have been shown to react differently to treatment options [3, 4].

In patients with lower GI symptoms, diagnosis is based on all available information including symptoms, anorectal manometry and rectal studies, balloon expulsion tests, and defaecography (in patients with outlet obstruction) [5]. It is often possible to identify the causes of symptoms using this technology; however, in contrast to upper GI motility, a classification system for the diagnosis of anorectal disorders based on physiological testing is still lacking.

Perretta: Achalasia as well as oesophageal motility disorders are the best examples which manometry can reveal as the cause of upper GI symptoms in a significant proportion of patients when other tests such as endoscopy have failed to provide a diagnosis.

In our practice, we frequently rely on motility testing in patients presenting with symptoms such as epigastric pain and vomiting after bariatric surgery, especially sleeve gastrectomy. Here, motility testing including manometry and pH-impedance monitoring can detect dysmotility as well as GERD when other investigations, typically upper GI series and endoscopy, fail to provide an explanation for symptoms.

Steinemann: I refer patients with faecal incontinence for anorectal manometry before planning anorectal surgery including sacral nerve modulation, haemorrhoidectomy, or fistula surgery to make an objective measurement of sphincter pressures. Certainly, there is also a legal aspect to the use of manometry in these indications to 'document' sphincter insufficiency before performing the intervention.

However, lower GI motility testing can provide an explanation for symptoms in a relevant proportion of patients. This is illustrated well by the case of a patient with a history of extensive sphincterotomy performed for fistula-in-ano many years ago. He presented with large haemorrhoids, and closed haemorrhoidectomy was performed. The patient, who was clinical continent before, complained of severe urgency and incontinence after surgery. Unfortunately, anorectal investigations had not been performed before the operation. I suspected a weak and damaged sphincter; however, the manometry performed 3 months after surgery revealed a strong internal and external sphincter. Rectal sensation testing revealed marked rectal hypersensitivity, which no doubt contributed to the patient's urge faecal incontinence. He was referred for biofeedback therapy and recovered completely.

In patients with a complex dysfunction of the pelvic floor with outlet obstruction and/or incontinence, the diagnosis of the underlying causes is multifactorial, and anorectal manometry, rectal sensation testing, and, in many cases, defaecography are needed to provide a detailed understanding of the underlying pathophysiology to guide multidisciplinary treatment.

Question 3: To what extent have advances in technology, such as HRM, impacted on the clinical utility of tests? Have you noticed an increase in diagnostic yield or accuracy?

Heinrich: The yield for the diagnosis of upper GI motility disorders has increased with the advent of high-resolution technology. Prospective studies have established that HRM significantly improves interobserver agreement and increases diagnostic accuracy compared to 'conventional' manometry with line tracing from ≤ 8 sensors (conventional line tracing (CLT)) [6–8]. Direct comparison between the techniques showed that the odds of an incorrect oesophageal motility diagnosis were 3.3 times higher with CLT than with HRM assessment, and the odds of incorrect identification of a major motility disorder requiring specific management were 3.4 times higher with CLT than with HRM

[8]. Further, a randomized controlled trial reported a significantly increased diagnostic yield for major motility disorders with HRM compared to CLT, in particular for achalasia (26 vs. 12%) [9].

Additionally, the combination of manometry with intraluminal impedance enables simultaneous assessment of motility and bolus movement through the oesophagus [10]. A key insight from this work is that dysphagia and other symptoms are rarely caused by abnormal motility unless it is accompanied by impaired function such as bolus retention or reflux [11, 12]. This approach has been applied to assess oesophageal function during 'rapid drink challenge' and eating a solid test meal (STM) [13–15]. In serial diagnostic studies, this approach increased the diagnostic yield of HRM for major oesophageal motility disorders. Patient reports of symptoms during STM also established motility disorders as the cause of oesophageal symptoms [14]. The findings can also identify patients that profit from specific clinical management (e.g. outlet obstruction in patients with dysphagia after fundoplication [16]). Extending HRM observations after the meal can also be of interest in patients with therapy-resistant reflux and other postprandial symptoms. These observations can differentiate typical reflux events from behavioural disorders such as rumination syndrome [17].

For lower GI disorders, the yield of diagnosis based on anorectal manometry alone is low, in spite of high-resolution anorectal manometry (HR-ARM) having expanded our understanding of pressure changes at rest, during squeeze, and during simulated defecation [18]. Here, the yield of testing is greatly increased by a combination of tests including manometry, sensation and barostat testing, as well as tests of evacuation such as conventional or magnetic resonance defaecography [19].

Perretta: HRM had a positive impact in our practice on both diagnostic yield and accuracy. In my practice, this is especially valuable in patients with failed fundoplication presenting with dysphagia and/or recurrent GERD symptoms after anti-reflux and bariatric surgery to identify EGJ obstruction and to quantify reflux.

Steinemann: Findings of HR-ARM and defaecography often correlate. This is very valuable when it comes to determining the clinical significance of, e.g., mucosal prolapse or intussusception. The quality of manometry after introduction of the high-resolution technology has improved but recent advances in the assessment of rectal sensation, volume, and compliance have added substantive yield for diagnosis of faecal incontinence and pelvic floor disorders.

However, as with endoanal ultrasound, the quality of functional testing and its interpretation is highly dependent on the skills and experience of the investigator. As a surgeon, I value direct discussion of results with the involved gastroenterologist, and in our hospital, management of patients with complex pelvic floor dysfunction usually is multidisciplinary.

Question 4: How often do the results of physiological investigations alter your management of patients? Please illustrate this response with examples from your own practice! To what extent is a definitive diagnosis therapeutic in and of itself?

Heinrich: One example for change in management based on physiological measurements is the diagnosis of rumination. In clinical practice, repeated regurgitation or belching are often interpreted as 'volume reflux' or 'vomiting', whereas investigation using oesophageal HRM with observations during and after a test meal can reveal a characteristic pressure profile associated with typical symptoms. Similarly, the appearance of repeated intake and expulsion of air into and out of the oesophagus during ambulatory pH-impedance monitoring is diagnostic of supragastric belching.

While the diagnosis of dyssynergic defecation and anismus is crucial in obstructive defecation, diagnosis solely based on HR-ARM is controversial as manometric patterns typical for dyssynergia can also be seen in health [20, 21]. In our practice, impaired balloon expulsion is required before the diagnosis of dyssynergia is made, and a further test of evacuation (defaecography) is performed if any doubt remains to ensure a valid diagnosis.

Perretta: Most of our patients are referred for surgery with an established diagnosis. Nevertheless, the results of physiological investigations may change the indication for surgical treatment of GERD in patients with a negative preoperative pH study off proton pump inhibitors and/or a negative or poor symptom association. For patients presenting with suspected atypical or laryngo-pharyngeal reflux symptoms, results of physiological investigations are very important before proceeding to a surgical treatment because only a minority have clear evidence of GERD on testing.

In patients presenting with dysphagia after failed fundoplication, the motility of the oesophagus together with its diameter and emptying time are important indicators to tailor the operative strategy in order to build a new anti-reflux mechanism that would match the residual peristaltic activity. If oesophageal dilation, delayed emptying and/or ineffective motility are present, we would typically opt for a partial fundoplication instead of a 360° wrap.

Another category of patients in whom we now run routine manometry are candidates for bariatric surgery. In our unit, a low EJJ basal pressure and/or a hiatal hernia >2 cm are considered a contraindication for sleeve gastrectomy due to the high risk of postoperative GERD development, even in the presence of normal upper GI contrast study.

Steinemann: In obstructed defecation syndrome, it is quite difficult to clinically distinguish anatomic outlet obstruction from functional outlet obstruction. Even if there is an intussusception in defaecography, its clinical significance is not obvious until pelvic floor dyssynergia has been ruled out by manometry. We usually refrain from surgery for obstructed defecation when akinesia or paradoxical contraction of the sphincter ('anismus') is present.

These individuals are referred for pelvic floor therapy before re-evaluating surgery. In our experience, this is very important to improve the functional results of pelvic floor surgery.

Question 5: What further advance(s) in the functional diagnosis in GI diseases would most help you in your management of patients? What would you like to be able to measure that, at present, you cannot measure and how would this impact on practice (visceral sensitivity, intraoperative monitoring, etc.)?

Heinrich: For the gastroenterologist, the combination of wearable technology and mobile apps that monitor GI function and symptoms over prolonged periods will expand our knowledge of how GI events cause symptoms in functional and organic GI disorders.

In lower GI physiology, the development of comprehensive metrics based on physiological measurements of anal pressure, distensibility, rectal sensation, compliance, and capacity that predict outcomes for conservative treatment and surgery, such as sacral neurostimulation, rectocele, and even rectal carcinoma surgery, are the way ahead.

Perretta: Oesophageal functional testing such as HRM is limited by its ability to only capture a brief moment and by its relative invasiveness. Wireless systems capable of prolonged monitoring of motility and pH (BRAVO capsule) are not widely available. Validated and standardized paperless monitoring and symptoms in the form of smartphone apps will be a useful tool in the future.

In addition, present technologies do not allow measuring gut motility from top to bottom. Current monitoring systems are or-

gan-based using a purely anatomical segmentation of the GI tract, which does not always correspond to the actual physiological behaviour. A system assessing oesophageal, gastric, and duodenal motility at the same time would allow a better understanding of motility in patients with normal and surgically altered anatomy.

Steinemann: In sacral neuromodulation for faecal incontinence, the influence of this therapy on rectal sensibility is assumed but still not very well investigated. Pre- and postoperative measurement and follow-up studies are needed to better understand the changes in sensibility and anorectal function. Furthermore, it would be desirable to measure the change in rectal sensation and reactivity during the placement of the electrode intraoperatively.

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