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An ANMS-NASPGHAN consensus document on esophageal and antroduodenal manometry in children

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Abstract

Background—Upper gastrointestinal symptoms in children are common and motility disorders are considered in the differential diagnosis. High resolution esophageal manometry (HRM) has revolutionized the study of esophageal physiology, and the addition of impedance has provided new insights into esophageal function. Antroduodenal motility has provided insight into gastric and small bowel function.

Purpose—This review highlights some of the recent advances in pediatric esophageal and antroduodenal motility testing including indications, preparation, performance and interpretation of the tests. This update is the second part of a two part series on manometry studies in children (first part was on anorectal and colonic manometry [1]), and has been endorsed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the American Neurogastroenterology and Motility Society (ANMS).

Graphical Abstract

This review highlights some of the recent advances in pediatric esophageal and antroduodenal motility testing including indications, preparation, performance and interpretation of the tests. It has been endorsed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the American Neurogastroenterology and Motility Society (ANMS).

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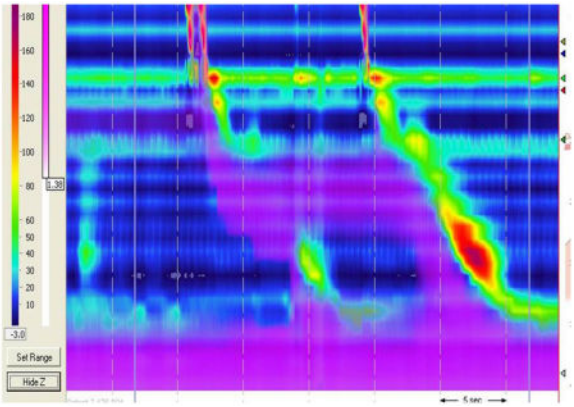

1. Introduction

Esophageal manometry is one of the most common procedures performed in pediatrics and the advent of high resolution manometry offers particular advantages for children because the study is easy to perform and provides unparalleled insight into esophageal physiology. With the addition of impedance to HRM, the clinical significance of motor abnormalities can be assessed in the context of effective or ineffective bolus clearance [2–5] (Figure 1).

While less commonly performed, the use of *antroduodenal manometry* (ADM) has become important in the diagnosis of gastroparesis and pseudobstruction in children presenting with upper tract symptoms [6, 7]. As with esophageal manometry, HRM technology has also been applied to ADM [8] (Figures 2 and 3), but its use has not yet become mainstream.

The present document highlights some of the recent advances in the study of upper gastrointestinal motility in pediatric patients.

2. Background

*Esophageal Manometry (*CPT Code 91010) is a diagnostic test performed to evaluate dysphagia, chest pain, and intractable regurgitation. High resolution manometry (24 or 36 sensors separated by 1 cm) has replaced standard manometry (4–8 pressure sensors spaced at 3–5-cm), as the gold standard test to assess esophageal function in children (Figure 1) [2, 4, 5, 9]. The increased number of HRM sensors allows for simultaneous measurement of pharynx, esophagus and stomach, without the need for repeated catheter adjustments required in standard manometry (Figure 1). When impedance sensors are added, the interrelationship between bolus flow, peristalsis and sphincter opening can be studied [2].

Antroduodenal manometry (2 separate CPT codes 91020 for gastric motility, 91022 for duodenal motility) can assess foregut motor function by recording intraluminal pressure in the antrum and the proximal small intestine. It has contributed to the understanding of the pathophysiology of neuromuscular disorders of the stomach and small bowel by assessing pressure amplitude and coordination [6, 7, 10, 11]. In most institutions, ADM is still performed using traditional perfused catheters (Figures 2 and 3) though high resolution catheters are now available (Figures 2 and 3) [8].

3. Indications

The current indications *for esophageal manometry* include:

1. To diagnose primary and secondary esophageal motor disorders
2. To diagnose motility abnormalities associated with symptoms including dysphagia, choking with feedings, globus sensation, vomiting, chest pain, refractory heartburn or regurgitation
3. To diagnose anatomic abnormalities such as a hiatal hernia and esophageal compression from rings
4. To evaluate for esophageal obstruction in post-fundoplication or other surgical patients
5. When associated with impedance, to evaluate the association between motility abnormalities and esophageal transit
6. To assess for motility abnormalities and esophageal stasis associated with signs such as pneumonia and aspiration
7. To evaluate esophageal function before therapeutic procedures
8. To diagnose rumination syndrome

Indications for *Antroduodenal manometry*

The most important contribution of ADM is to show normal physiology in patients with apparent intestinal failure, by differentiating true motility disorder from somatoform disorder or Munchausen by Proxy [6, 7, 12]. ADM manometry testing is warranted to:

1. To diagnose and classify types of pseudobstruction
2. To evaluate patients with severe nausea and retching
3. To evaluate patients with inability to tolerate enteral feedings
4. To distinguish between rumination and vomiting
5. To determine gastric and small bowel responsiveness to medications

4 How to perform the test?

4.1 Preparation

Esophageal manometry—Prokinetics, narcotics, and anticholinergics are typically stopped 48 hours prior to testing, unless the clinical question is related to the effect of the medication. Typically, acid suppression is continued unless the patient is more likely to experience symptoms during testing off therapy thus providing greater insight into the pathophysiology of symptoms [6, 7, 11, 13]. While other medications may have an effect on motility (e.g. baclofen, antipsychotic medications, attention deficit medications), stopping them prior to testing may not medically feasible. Similarly, while vagal nerve stimulators may have an impact on esophageal motility, the risk/benefit analysis for turning off the stimulator must be considered.

Guidelines for NPO status vary depending on whether sedation is used for the placement of the esophageal catheter. The length of NPO may vary depending on the sedation (or lack thereof) used and the suspected underlying problem. In patients at higher risk for aspiration (e.g. gastroparesis, EGJ obstruction), NPO times may need to be longer. Typically NPO periods for children range from 3–4 hours for a healthy patient to up to 8 hours if significant dysmotility is suspected and the planned sedation is deep.

Antroduodenal manometry—As with esophageal manometry, medications which affect motility typically need to be stopped 48–72 hours prior to testing [6]. NPO guidelines will vary according to the technique used. If upper endoscopy will be used to place the catheter, the NPO guidelines will be dictated by anesthesia. If the catheter is placed without sedation, experts recommend at least a 4 hour NPO period, though the NPO period for solids may need to be extended to 8 hours if there is suspicion is for gastroparesis.

With both ADM and esophageal manometry metabolic, endocrine and electrolyte disturbances should be corrected prior to testing and structural abnormalities should be excluded to prevent complications during testing or secondary impacts on motility [14].

4.2 Equipment

Esophageal manometry—Standard HRM catheters have 36 pressure transducers (circumferential or unidirectional) spaced by 1 cm increments. This spacing allows for precise mapping of the entire pediatric esophagus without motion or sensor artifacts that occurred with standard manometry [3]. The study can be performed with perfused or solid state catheters, although most institutions use solid state catheters. Recent advances include the addition of interspersed impedance sensors and small diameter pediatric catheters (6 French).

The measurements obtained with different vendors are not interchangeable, and even normal values vary between systems [3]. Vendor choice may vary depending on the desired catheter configuration, size and impedance capability.

Antroduodenal manometry—ADM can be performed with solid state or water perfused catheters, and the configuration depends on the size of the patient and the degree of precision needed to map an anatomic area of interest [7]. Typical perfused manometry uses 8 pressure sensors (Figures 2 and 3) where as high resolution catheters have 36 sensors (Figures 2 and 3) [8].

Water perfused: For standard manometry, the system is composed of small capillary tubes, a pneumohydraulic pump and external transducers. On the pediatric catheters, the proximal recording sensors for antral recording are usually spaced 0.5 to 1.5cm apart, while more distal ports for small intestine recording, are usually spaced 2 to 5cm apart for infants/toddlers and 5 to 10cm apart for older children [7]. Each capillary tube (0.35 mm diameter) is connected to an external transducer on the pneumohydraulic pump which provides constant flow rates. Perfusion rates vary from 0.1 to 0.4ml/min. These perfusion volumes can cause water overload in small children and successful adaptations to decrease the perfusion rate have been developed with perfusion rates as low as 0.02ml/min [7, 15].While

the catheters are perfused with distilled water in adults, many centers use 1/4 to 1/2 normal saline or oral hydration solutions to avoid hyponatremia in children [7].

Perfused systems have also been adapted for HRM, with 36 pressure ports, usually 2–3 cm apart, but the distal port can be spaced as necessary to span more of the small intestine.

Most ADM catheters have a built in central lumen that is used both for placement (utilizing glide wires), and to administer post-pyloric feedings in those patients unable to tolerate gastric feeds. Water perfused catheters are relatively inexpensive, widely available, and have flexible configurations.

Solid state: Solid state transducers are now used for most HRM studies. They include 36 pressure ports spaced by 2–3 cm in pediatrics, but the distal ports can be separated by longer segments, usually 5 cm. Most catheters also have a central lumen and diameters comparable to that of the water perfused manometric catheters and can produce pressure topography plots of gastric and small intestine pressure activity (Figures 2 and 3). While these catheters avoid the issues of electrolyte imbalances, their utility is limited by their high cost and the lack of standardized values in normal children.

4.3 Catheter placement and sedation

Esophageal manometry—The HRM catheter is introduced nasally and advanced into the stomach, which is identified by specific landmarks (see below). Having the patient flex their neck down towards the chest and asking them to swallow as the catheter is passed through the posterior oropharynx are helpful maneuvers to make passage of the catheter easier. After the catheter is in place it is important to secure it to the cheek with tape or tegaderm. Occasionally fluoroscopy guidance (or even rarer, endoscopic guidance) is needed for patients with complex anatomy. In very small babies, or patients with certain craniofacial malformations, the catheter may be introduced orally. A topical anesthetic (1–2 mL of viscous lidocaine, 2% lidocaine jelly, or 4% cocaine) may be applied into the nares, and may obviate the need for sedation.

If needed, however, oral, intranasal, or IV sedation can be used. Because the test requires some degree of cooperation and repeated crying and swallowing may make interpretation difficulty, sedation choices in pediatrics are important. Care should be taken to avoid deep sedation, as oral intake is critical to assess for intact swallowing and peristalsis, and may predispose the patients to aspiration when wet swallows are attempted. If necessary, oral midazolam has been shown to be an effective anxiolytic though in patients with esophageal obstruction, oral sedation may be ineffective as the medication may not reach the stomach for absorption. In those patients, intranasal or IV midazolam can be used. Most studies show no major effect of midazolam on esophageal function, although minor abnormalities have been described. In the only study of infants and children the IV administration of midazolam at 0.5 mg/kg did not have any effect on LES pressure or function [16]. In adults intravenous midazolam at doses of 5 and 10 mg have also been shown no to have an effect on esophageal manometry parameters [17], however higher doses of 20 mg produced a mild increase in LES pressure, that lasted up to 40 minutes. In another study it was suggested that midazolam at a

dose of 0.02 micrograms/kg in adults may reduce UES and mid-esophageal body pressures while mildly increasing LES residual pressures [18].

If the patient is still unable to tolerate catheter placement, the catheter can be placed using deeper sedation with ketamine, pentobarbital or propofol. However, it is important to recognize that deeper sedation may have a long lasting effect on motility, so it is necessary to avoid measurements until these effects have worn off. The exact mechanism on how anesthesia affects gastrointestinal motility is unknown [19, 20]. Experimental data suggest an inhibitory effect over smooth muscle cells via acetylcholine [20] and calcium channel pathways [21] while under anesthesia but the mechanisms of potential effects hours later are unknown [19, 22]. Pentobarbital does not seem to have any effect in animal models, but there are no human studies [23]. In limited studies ketamine does not seem to have a significant effect [24] but in animal models can increase LES basal pressures [23]. Propofol at a small dose (0.3 mg/kg) does not have an effect on LES pressure, while higher doses produced a pressure increase [22–25]. However propofol reduces UES pressures [25]. New agents like dexemedetomidine may reduce LES pressures [22]. Other anesthetics, opioids, and sedatives may have variable effects on sphincter and esophageal body motility [26] so interpretation of an abnormal study in patients who received these medications should be made with caution. The optimal time interval to begin studies after these medications are given has not been studied but typically clinicians wait 2–4 hours for the effects to have worn off and for the patient to be able to eat and drink safely. With placement under anesthesia, patients with significant dysmotility and/or obstruction will need airway protection with an endotracheal tube to avoid aspiration of retained food or liquids in the esophagus. Care should be given not to give opiates during the anesthesia, as they can affect motility.

Antroduodenal manometry—The performance requires the placement of a catheter either nasally or through gastrostomy or jejunostomy stomas. This is typically achieved with the use of fluoroscopy and/or endoscopy. Ideally the catheter is advanced beyond the ligament of Treitz. [6, 7, 15]. The minimum recommended recording ports include one in the antrum and three in small bowel [6, 7, 15]. More frequently the catheter is placed endoscopically under anesthesia. When anesthesia is used, pressure recording should not be started until the patient is fully awake and any potential anesthetic effects on motility have worn off. In most institutions, the study is performed the next day to avoid anesthesia effects, and there is preliminary evidence in pediatrics that anesthesia may adversely affect digestive motility [27].

In adults diazepam has been found no to have no major effect on interdigestive antroduodenal motility [28]. Studies in healthy controls undergoing elective surgery have found that all methods of general anesthesia studied (halothane, enflurane, pethidine and fentanyl) reduced the duration of the interdigestive motility complex, mainly by reducing phase II [28]. Halothane impeded the occurrence of antral contractions during phase II, decreased the frequency of antral contractions in the recovery period and decreased the amplitude and frequency of duodenal contractions during phase III [29]. Enflurane nearly abolished motility in the antrum but this was regained rapidly in the recovery period. It also decreased the frequency and amplitude of duodenal contraction during phase III, although

they seemed to last longer [30]. Fentanyl affected antral amplitude contractions in phase II while pethidine affected amplitude and frequency [31].

In cases in which there is a gastro-jejunal (G-J) or a jejunostomy tube in place, the tube can be exchanged for an AD catheter over a glide wire. In patients with a gastrostomy, a small Foley catheter is placed in the gastrostomy stoma alongside the AD catheter to allow for gastric venting and drainage, as well as medication and formula administration.

4.4 Study procedure

Esophageal manometry—Pediatric esophageal motility testing is usually performed in the semi-upright position typically at angles of 45–90 degrees which is in contrast to adult studies which are performed in the supine position [32]. The catheter is placed into the stomach, and positioned to record from the hypopharynx to the stomach. Positioning is confirmed by identifying the two high pressure zones that correspond to the UES and the LES. In patients where the anatomy is less clear, it is critical to map the esophagus and identify placement into the stomach by identifying the pressure inversion point (PIP) which becomes more evident when the patient takes a deep breath. The PIP is defined as the most distal site at which the inspiratory pressure was lower than the expiratory pressure [33]. A hiatal hernia, defined as a separation between pressure peaks of the crural diaphragm and LES and its relation to the PIP, is assessed between swallows when the patient is quiet [33]. A minimum of 10 liquid swallows are observed. Whenever possible, additional viscous and solid food swallows are also performed, because subtle motility abnormalities can be uncovered with different textures [34]. If high resolution esophageal manometry is being paired with impedance, all liquids and solids need to have ions to detect impedance changes so added salt or salt water may be required [35].

To assess swallowing function, the patient is given the liquid/viscous/solid swallows, spaced by a minimum of 30 seconds to allow for esophageal recovery, and avoid deglutitive inhibition. This can be challenging in young or uncooperative patients and care needs to be taken to ensure abnormal motility patterns are not diagnosed when closely repeated swallows are present. For each swallow, the patient is given 5 ml of liquid with some modification for infants or aspirating patients. *Because of a high rate of false positive testing when only dry swallows are used, the administration of liquid swallows is necessary, and should be considered in every manometry, even in patients with aspiration, or those with food aversion, to avoid over-diagnosing a motility disorder.* This is particularly critical if surgical or endoscopic interventions are being considered. Given the risk of aspiration, the administration of liquid swallows should be discussed on an individual basis between the provider and the patient/family in cases in which aspiration has been previously documented or is strongly suspected. Close monitoring is necessary during the administration of the liquid swallows in those patients, and if necessary the liquids can be thickened.

At the end of the single swallows, deglutitive inhibition is measured with the use of repetitive swallows, or with the use of the Rapid Drink Challenge, in which 100–200 ml of fluid are swallowed [34, 36, 37]. While there are no pediatric studies documenting normal esophageal and bolus pressures in children undergoing the rapid drink challenge, adults studies suggest it increases the sensitive to detect motility disorders, and do support its use to

unmask subtle abnormalities which may include abnormalities in pressurization in the esophageal body, elevations in intra-esophageal bolus pressures and elevations in the pressure gradient across the EGJ, all of which may explain the dysphagia [34, 36, 37]. At times it may also reveal better peristaltic activity [34, 36, 37]. Finally, when rumination is being considered, patients should also consume a symptom-evocative meal after which the patient is observed for 30 minutes to an hour for the development of symptoms [35] as 40% of rumination episodes are only seen after a meal [35]. There is no routine indication for provocative medications during esophageal manometry in children.

Antroduodenal manometry—Most pediatric studies are stationary and performed in a hospital setting. While ambulatory studies in adults have been proposed to improve accuracy of the test and reduce the intra-individual and inter-individual variability [6, 7, 38], frequently catheter migration may limit the usefulness of the ambulatory study, particularly in active children.

A physician, nurse or technician is typically present with the patient for the duration of the study, to assess for catheter migration and correlation with symptoms. It is common, especially with 8-port perfused catheters, for the catheter to migrate distally during fasting, or migrate backwards after a meal, which may result in the technical inability to assess the antrum or small bowel motility. Therefore the catheter may need to be readjusted during the study. If the location is unclear, catheter location may need confirmation using a plain abdominal X-ray or fluoroscopy. These technical difficulties are eliminated when HRM is used, because of the spacing of sensors.

Typically ADM studies last for 6–8 hours, although the optimum duration of the test is unknown. However it is critical to assess all of the phases of antral and small bowel motility.

I.- Fasting or interdigestive phase: Given the rare occurrence of the phase III of the MMC [7, 39], most centers record for at least 3 hours of fasting followed by at least 1 hour of postprandial recording [40], as recommended by the pediatric task force of the ANMS. The fasting phase can be shortened if at least two MMCs are seen [7].

II.- Feeding phase: The fed period follows the fasting period, as it disrupts the interdigestive motility. Ideally the meal will be taken orally, over 30 minutes or less, but in children that are g-tube dependent, or those that refuse to eat enough calories, the meal may be administered intragastrically (through the Foley described in section 3.3) or occasionally jejunally (if there is no gastric port). Gastric feedings may be given as a rapid bolus, or depending on the symptoms, over 30–60 minutes. Jejunal feedings are given as continuous feedings, usually over 60 minutes, to avoid unnecessary small bowel distention. When necessary a combination of oral and enteral are given to insure adequate caloric intake. The characteristics of the fed pattern vary based on the type, composition and amount of nutrients given. In adults, the meal has been standardized to be at least 400 kcal (with 20 to 25% fat, 20 to 25% protein, and 50 to 55% carbohydrate) to ensure a postprandial response of 2 hours duration [6, 41]. While there are no pediatric studies, the ANMS task force recommends that patients receive 5 to 10 mL/kg of a formula during testing or oral solid

food to try to achieve at least 10–20 cal/kg or 400 to 600 kcal with >30% of kcal from lipids [7].

III.- Provocative tests: If no spontaneous phase III activity is observed, intravenous erythromycin can be administered during fasting, usually at 1 or 3 mg/kg given over 30 minutes with lower doses associated with fewer side effects [6, 7, 42, 43], and less small bowel inhibition [7, 42]. Occasionally in non-cooperative children or in those at risk of removing the catheter prematurely, the fasting period may be aborted and erythromycin is given as soon as the test begins. When erythromycin is given after a meal, antral stimulation will occur but the response in the small bowel may vary from the expected phase III of the MMC, to no response to the drug. Other medications that induce phase III activity are azithromycin (only adult studies using 250 mg or 500 mg) [44, 45] and amoxicillin/clavulanate (20 mg/kg) [46] the latter of which was found to induce phase III-type activity in the small bowel, similar to those in the fasting state, but with no effect on antral activity [46].

Octreotide can also be administered and has been shown to induce phase III activity in the small bowel, including a variable inhibitory effect on antral activity. Phase III-type activity in small bowel induced by octreotide is usually of longer duration and greater propagation velocity than spontaneous phase III activity [40, 47, 48]. Octreotide is dosed at 1μcg/kg to a maximum of 50 mcg and is given subcutaneously.

It is recommended to observe for 1 to 1 ½ hours post-erythromycin and 30 minutes post octreotide before other interventions are done. At times there may be a high probability of catheter dislodgement from vomiting after a meal, so it may be necessary to administer provocative medications before the meal is given.

Neostigmine (1mg IV) has been found to increase both the amplitude and frequency of pressure waves in the antrum and small intestine though it is not routinely administered during testing [49]. Occasionally other drugs may be administered if it is necessary to determine their effects on motor activity.

5. Interpretation

Esophageal manometry

The method of interpretation of esophageal manometry has changed with the advent of HRM. Three functional regions of the esophagus are evaluated: the upper esophageal sphincter (UES), the esophageal body and the lower esophageal sphincter (LES) (figure 1).

New parameters to define motor abnormalities using HRM have resulted in the Chicago Classification (CC) [3], which consists of a hierarchical approach to HRM interpretation, focusing first on disorders of the esophagogastric junction (EGJ) outflow, then the diagnosis of major and minor peristaltic disorders [3]. A diagnosis based on the Chicago classification is then provided by combining the analysis obtained from the individual swallows.

To assess correct placement, the location of the two high pressure zones of the UES and LES are first identified. In patients in whom the sphincter anatomy is not clear particularly in the postoperative patient, deep breathing maneuvers (to identify the pressure inversion point

between the chest and abdomen), performance of swallows, and even the use of fluoroscopy may help clarify the catheter location. Once in place, the EGJ pressure is measured as an average of inspiratory and expiratory values for three normal respiratory cycles. The inspiratory EGJ pressure is the mean of maximal inspiratory EGJ pressures reached during inspiration, and the expiratory EGJ pressure is the average EGJ pressure midway between inspirations [3].

Even though the CC was developed in adults and its parameters have been applied to the pediatric population, there are very few studies validating the CC in children. While some of the key HRM measurements have changed over time, the integrated relaxation pressure (IRP; defined as the mean pressure during the 4 s of maximal deglutitive relaxation in the 10-s window beginning at UES relaxation), the distal contractile interval (DCI: a composite measurement quantifying the contractile pressures exceeding 20 mmHg) and the distal latency (DL: interval between UES relaxation and the contraction deceleration point) have endured [3]. The IRP, a more complex version of the residual LES pressures after swallowing measured using standard manometry, is used in pediatrics but the normal range of IRPs may vary based on age and size so the adult standards for elevations in the IRP (>15 mmHg) may not apply to all pediatric patients[4]. Similarly, small pediatric studies have shown that there may be age and height differences in DCI, distal latencies, and esophageal break size though further studies are needed to determine the clinical significance of some of these findings [4, 9]. Because of the differences in pediatric measurements, the use of CC diagnostic criteria should be used with caution to avoid incorrect diagnoses. In the only pediatric study available, 66% of children undergoing HRM had a definable motility disorder using the adult CC diagnostic criteria. When measurements were adjusted for age and size, the percentage of patients with a definable motility disorder dropped to 50% and 53% respectively, with the largest reduction being in the reclassification of IRP and DL dependent disorders, EGJ outflow obstruction and diffuse esophageal spasm (13% to 7% and 5% and 14% to 1 and 5%, respectively) [4]. This potential for incorrect diagnosis when applying the adult CC criteria to pediatric patients might strongly influence treatment choice. Studies have also shown that the interpretation of HRM is reproducible [50], but there are still some specific areas that may need more validation.

Esophagogastric junction obstruction—The diagnosis of esophageal obstruction is based on the IRP and is the first manometric parameter measured when analyzing HRM tracings. The differential diagnosis for pediatric patients with an elevated IRP includes achalasia or an obstructing fundoplication. As with adults, all three subtypes of achalasia (Types I, II and II) have been observed in pediatrics (Figure 4). Because of a lack of a validated normal IRP in pediatrics and because of variations in IRP values by age and size, as well as between vendors, the cut off value for the diagnosis of EGJ obstruction is not clear; in pediatric achalasia, IRPs as low as 10 mmHg have been reported [4], while IRPs higher than 15 mmHg have also been described in children with no evidence of GEJ obstruction or achalasia [4]. The significance of an isolated elevated IRP in pediatric patients, in the absence of symptoms or in a patient in whom the bolus, by impedance, passes easily through the area of increase pressure is unknown.

Peristaltic Assessment—The next step after analyzing the EGJ includes the assessment of the presence and quality of peristalsis which includes an assessment of the strength and the patterns of contractions. Assessment of peristalsis in children includes: 1) the presence or absence of antegrade peristaltic contractions; 2) the presence or absence of esophageal pressurization with or without intact peristalsis; 3) the presence or absence of long esophageal breaks; 4) the presence or absence of high pressure distal esophageal contractions, represented by an elevated DCI and 5) the ability of the peristaltic wave to clear a bolus, as measured by impedance. Whether the adult definitions of major motor disorders (absent contractions, distal esophageal spasm, and hypercontractile esophagus) [3] apply in children is not known. Therefore, the most critical questions to address in the assessment of major disorders of peristalsis in pediatrics are: 1) is achalasia present? ; 2) do the motor findings explain the patient's symptoms?and 3) do the motor patterns result in impaired bolus transit? Additional studies are needed to determine the cut-off values for abnormal DCI, abnormal length of esophageal breaks, abnormal cut-offs for esophageal pressurization and values for an abnormal distal latency.

Minor Motor Disorders—The significance of minor motor disorders (ineffective esophageal motility and fragmented peristalsis) [3] in pediatrics are even less clear than the major motor disorders. The key with these minor disturbances of pressure is to determine if there is incomplete bolus transit as determined by pairing impedance with pressure sensors. Abnormalities in esophageal peristalsis can be mimicked with poorly spaced swallows, dry swallows, double swallowing or even by change in consistency of the ingested liquids, or position of patient. There is no pediatric data on the frequency or the significance of these minor motor disturbances. *Finally any other abnormality seen during HRM that does not fulfill any of the above criteria, is considered normal esophageal motility in adults, and over interpretation of these findings in children needs to be avoided* [3].

Assessment of the UES—Very little has been published on UES dysfunction using HRM. UES abnormalities are not included in the CC. The main goal in the assessment of UES function is to assess for coordination of pharyngeal contractions with simultaneous UES relaxation, and their relationship to bolus transit. The presence of dyscoordination between pharyngeal contractions and UES relaxation as well as abnormalities in UES relaxation, including cricopharyngeal achalasia, can easily be assessed with the use of HRM. The addition of impedance to the UES motility parameters further allows assessing the risk of aspiration in children with upper esophageal dysfunction. In pediatrics, the interrelationship between the UES and bolus transit may predict aspiration risk and this may of particular importance in children with respiratory symptoms or oropharyngeal dysphagia. [51].

High resolution manometry with impedance (HRIM)

The addition of impedance provides the ability to establish if the peristaltic abnormalities seen are significantly impairing the bolus transit (Figures 1 and 5) [2, 51, 52]. This is particularly important to evaluate the significance of minor peristaltic abnormalities. While impedance is still not part of the CC, new objective parameters utilizing impedance have been proposed including the incorporation of pressure flow analysis (PFA) [53]. PFA has

been used to assess for UES dysfunction as well as to discriminate among patients with subtle motility abnormalities as well as to determine the degree of LES obstruction [2, 51, 52]. In addition the pairing of impedance and manometry into mathematical models has yielded the automated impedance manometry (AIM) analysis to predict dysphagia risk and the swallow risk index (SRI) to predict aspiration in adults and children [53]. Other parameters have been proposes such as the duration of the duration of bolus presence within the EGJ (BPT or bolus presence time), and the trans-EGJ-bolus flow time (BFT or bolus flow time) [54, 55] [56]. This ratio of BFT and BPT (BFT/BPT) can be used to define the effectiveness of trans-EGJ emptying relative to the period of bolus presence [54–56]. It has been shown that in patients these measurements also correlate with dysphagia severity, [54, 55] type of achalasia, and efficacies of therapies in treating EGJ obstruction. Similar findings have been described in children with achalasia [51,56]. In pediatrics, the automated impedance manometry analysis has also been able to discriminate causes of dysphagia in children [2], where it was shown to differentiate patients with dysphagia due to weak peristalsis and resultant poor bolus clearance from abnormal bolus flow resistance due to esophageal outflow obstruction. It has also been applied to children that underwent fundoplication to discriminate those children with and without postoperative dysphagia [57].

The following are other special pediatric conditions in which HRM, and HRIM hav e significantly changed clinical management:

Rumination—HRIM has been effectively used to diagnose rumination, and to differentiate subtypes of rumination [35]. Performance of HRM to diagnosis rumination syndrome offers significant advantages over the traditional ADM including: 1) the ability to perform the test without sedation; 2) the ability to assess for bolus flow following R waves; 3) the short test duration; and 4) the ability of the patient to choose a meal that triggers symptoms (Figure 6) [35].

Esophageal Atresia—The performance in this population may be particularly helpful in patients with recurrent dysphagia with or without a fundoplication in patients with recurrent respiratory infections. In patients with EA, performance of HRIM is critical in order to assess not only the strength of peristalsis but whether the peristalsis is able to clear the esophageal bolus [58, 59]. This latter point is critical in patients with recurrent respiratory symptoms as esophageal stasis can increase the risk for aspiration of esophageal contents. While several pediatric studies have documented near universal esophageal dysmotility in patients with EA, there are no published studies pairing HRM with impedance to document the physiologic consequences of dysmotility in these children [58, 59]. Current consensus guidelines recommend HRIM in children with EA with persistent symptoms including dysphagia [60, 61].

Fundoplication—Studies comparing High resolution esophageal manometry in preoperative patients with or without esophageal dysmotility have shown no difference in the prevalence of post-operative dysphagia [62]. However, in select patients at highest risk for postoperative dysphagia, preoperative HRM testing may be of value, particularly to determine if there is baseline bolus stasis even before the fundoplication; this may be particularly true of patients with esophageal atresia or scleroderma as severity of

preoperative dysmotility may be helpful to determine if a fundoplication is warranted or if a partial or complete wrap is warranted [63, 64]. Pediatric literature suggests that while standard HRM measurements can be normal, EGJ outflow obstruction, bolus stasis, and elevated intrabolus pressures can be seen in post-fundoplication patients and these results may be helpful to determine which patients may benefit from postoperative *BotulinumToxin* injection or dilation [57, 65].

Antroduodenal manometry

Interpretation of ADM in children has multiple challenges such as:

- **a.** There is lack of data establishing patterns in normal controls, as all normal values are derived from symptomatic children undergoing ADM but whose studies were felt to be normal [7, 11, 66].
- **b.** Some atypical manometric patterns can be present in healthy and asymptomatic adults [6, 67] making a precise definition of what constitutes significant abnormality a challenge. Therefore it is important to avoid over interpretation of the findings which can lead to unnecessary medical or surgical interventions [12, 68].
- **c.** Age needs to be taken in consideration as there are important manometric changes that occur as the infant enteric nervous system matures, evolving from frequent short clusters with lack of temporal association between antral and small bowel contractions to increase length of clusters and amount of quiescence [69, 70].
- **d.** Ensuring adequate caloric intake during testing to elicit a post-prandial response is challenging in some patients because of symptoms.
- **e.** Frequent artefacts from moving and straining, can make interpretation difficult.

Normal antroduodenal manometry has two distinct phases: a) a fasting or interdigestive phase, and b) a phase that occurs after feeding. During fasting, the gastrointestinal tract shows a cyclic pattern, known as the migrating motor complex (MMC) [39]. It is usually divided into three phases: Phase I is the quiescent phase with no contractions, phase II is characterized by random contractions that vary in amplitude and frequency, and phase III is characterized by the highest amplitude contractions, occurring in the antrum at a rate of 2 to 3 per minute for at least 2 minutes, and in the small bowel 11 to 12 per minute for at least 3 minutes. During phase III, contraction amplitudes average 75mmHg in the antrum and 33mmHg in the duodenum (Figure 2). The phase III contractions migrate distally in an organized fashion, with a variable velocity of propagation that decreases progressively from proximal duodenum to distal jejunum accompanied by a progressive increase in duration of phase III [39]. There is no exact consensus on the minimal distance that the contractile activity of phase III needs to advance. The distance will therefore depend on the length and position of the catheter. The phase III should span the length of the catheter. The duration of the cycle in adults is approximately 130 minutes and this may be shorter in children [39, 66, 71]. The mean interval between phase III cycles is 25–45 minutes in newborns, 60 minutes in toddlers, and approximately 100 minutes in older children [72]. Phase III occupies

3%, Phase I occupies 10% and Phase II occupies 87% of total recording time [73]. It has been shown that 95% of healthy children have phase III within a 3–4 hour fasting study.

Feeding interrupts the interdigestive pattern (Figure 3). Postprandial activity is characterized by irregular occurrence of contractions with varying amplitudes. After solid meals, strong, repetitive contractions are often induced in the antrum and the duodenal response looks similar to that of phase II but with greater amplitude and frequency of contractions [6, 7] (Figure 3). The fed period ends when phase III of the MMC returns and its duration is dependent on food calories and consistency.

Data analysis of ADM is usually performed by visual inspection [6, 7]. Quantitative analysis includes calculation of the motility index (MI), expressing the contractile activity as the natural logarithm of the area under the manometric pressure peaks above a threshold pressure with a normal antral contractility value being 13.67 to 15.65 (5^{th} to 95^{th} percentile) in adults [6, 7]. A normal motility pattern is defined as: 1) the presence of at least one MMC in 24 hours; 2) conversion to the fed pattern without return of MMC for at least 2 hours after a meal; 3) distal antral postprandial contractility; 4) antral contractions >40mmHg; 5) small intestinal contractions >20mmHg; and 6) absence of other abnormal findings [6, 7, 74]. When evaluating interobserver variability, ADM compares favorably with other standard medical assessments, and there is excellent inter-observer agreement for the number of phase III of the MMC in fasting and its measurement [11]. Antroduodenal manometry findings have been shown to be reproducible in adults [75], although there are no studies in children.

The following patterns are considered abnormal in children : 1) absence of phase III after a 4 h fast; 2) abnormal migration of phase III; 3) intervals < 30 minutes between MMCs; 4) persistent low amplitude contractions; 5) sustained tonic phasic contractions; 6) postprandial hypomotility; 7) high amplitude retrograde contractions; 8) inability to establish a fed pattern (Figure 6); and 9) presence of phase III like activity during the fed period if appropriate calories were administered [6, 7, 11, 38, 41, 66, 70]. Because 1/3 to ½ of the phase III activity can commence distal to the stomach, the absence of the antral component of phase III is not necessarily abnormal [6, 76]. Other abnormal contractions patterns that can be seen include : 1) discrete clustered contractions (DCC) composed of 3 to 10 pressure waves of slow frequency, that propagate aborally at a rate of 1–2 cm/s usually through 30 – 40cm (Figure 4) [77]; 2) bursts of contractions that can be short or sustained, the latter of which is abnormal [77] ; 3) the simultaneous increases in pressure throughout all the recording sensors (R wave), usually associated with regurgitation or frank emesis, that represent the manometry correlate of rumination syndrome [40].

Clinical Utility—Its main use has been in confirming (or excluding) the diagnosis of pseudo-obstruction or a motility disorder [78]. Most importantly, a normal study indicates that intestinal motor dysfunction likely is not the cause of the symptoms. [6, 7, 12, 41], so one of the most important contributions of the antroduodenal manometry is to show normal physiology in patients with apparent intestinal failure.

The presence of phase III activity is a marker of neuromuscular integrity,, while its abnormalities usually diagnose pseudobstruction.

The term pseudobstruction is used to denote the failure of propulsive forces of the intestinal peristalsis to overcome the natural resistance to flow, and it is characterized by severely abnormal bowel motility in combination with episodic or chronic signs of bowel obstruction in the absence of a mechanical obstruction. The diagnosis is mostly clinical. ADM is aimed at ruling out conditions that can mimic pseudobstruction (pain associated disability syndromes, medical child abuse, mechanical obstruction) as well as to classify the types of pseudobstruction as neuropathic or myopathic [7, 40]. A *neuropathic pattern* consists of normal amplitude contractions but the MMC is disorganized with abnormal propagation. There may also be intestinal bursts of phasic pressure activity sustained over 30 minutes, uncoordinated intestinal pressure activity or failure of the meal to produce a fed pattern.

A *myopathic pattern* consists of a preserved MMC but very low amplitude contractions (<20mmHg) (Figure 8) [40, 79]. However it is important to stress that low amplitudes might be a consequence of bowel dilatation [6, 41].

Therefore in addition to making a diagnosis of and predicting outcome of pseudobstruction [74, 80], ADM also helps to establish if the dysmotility has a neuropathic or myopathic etiology. It also predicts which children will have a poor response to enteral feedings or to prokinetics by showing absence of MMCs [81]. ADM is also indicated in patients with pseudo-obstruction being considered for intestinal transplant to confirm the primary diagnosis and may suggest an unexpected mechanical obstruction [7, 82]. Therefore AD manometry is useful in children with gut failure to clarify the pathogenesis, to optimize clinical management, to determine if intestinal transplantation is needed and, if so, what organs need to be transplanted [83].

In addition to the small bowel abnormalities mentioned above, several other diagnosis can be made using ADM:

Post prandial antral hypomotility—A reduced motility index of post-prandial distal antral contractions correlates with impaired gastric emptying of solids from the stomach (Figure 9) [6, 7, 40].

Mechanical obstruction—Multiple simultaneous giant contractions as well as the presence of non-propagated discrete clustered contractions in the postprandial period (> 30 minutes duration) are seen [40, 74, 82]. In neonates, presence of high amplitude retrograde prolonged contractions should raise the suspicion of mechanical obstruction [82].

Rumination—In vomiting, there are high amplitude (>30 mmHg) retrograde peristaltic contractions of small intestine from distal to proximal [6, 40], also associated with retching in which simultaneous contractions at all sensors are observed. In patients with rumination, the only identifiable waves are these simultaneous contractions which represent abdominal wall contractions but not intestinal contractions (Figure 10).

Additionally ADM [81] can be used to help decide if there is generalized dysmotility disorder in patients with dysmotility elsewhere (e.g., chronic constipation when surgery is

contemplated, severe reflux with evidence of distal dysmotility when a fundoplication is being considered, or after a failed fundoplication that requires reintervention) [84].

In patients with pain associated with feeding, a normal ADM is critical to redirect therapies towards neuromodulation and behavioral interventions. Antroduodenal manometry allows a better understanding of the basis of feeding intolerance in different populations including: developmentally delayed children [85], mitochondrial diseases [86], survivors of neonatal extracorporeal membrane oxygenation [70], celiac disease [87], refusal to eat in medically fragile toddlers [88], patients after fundoplication [84] or to diagnose rumination syndrome [6].

6. - Conclusions

Esophageal and antroduodenal manometry are useful tools to diagnose dysmotility of the upper gastrointestinal tract and while they are critical in understanding motility disorders, their results should always been taken in the context of the clinical picture and presenting symptoms.

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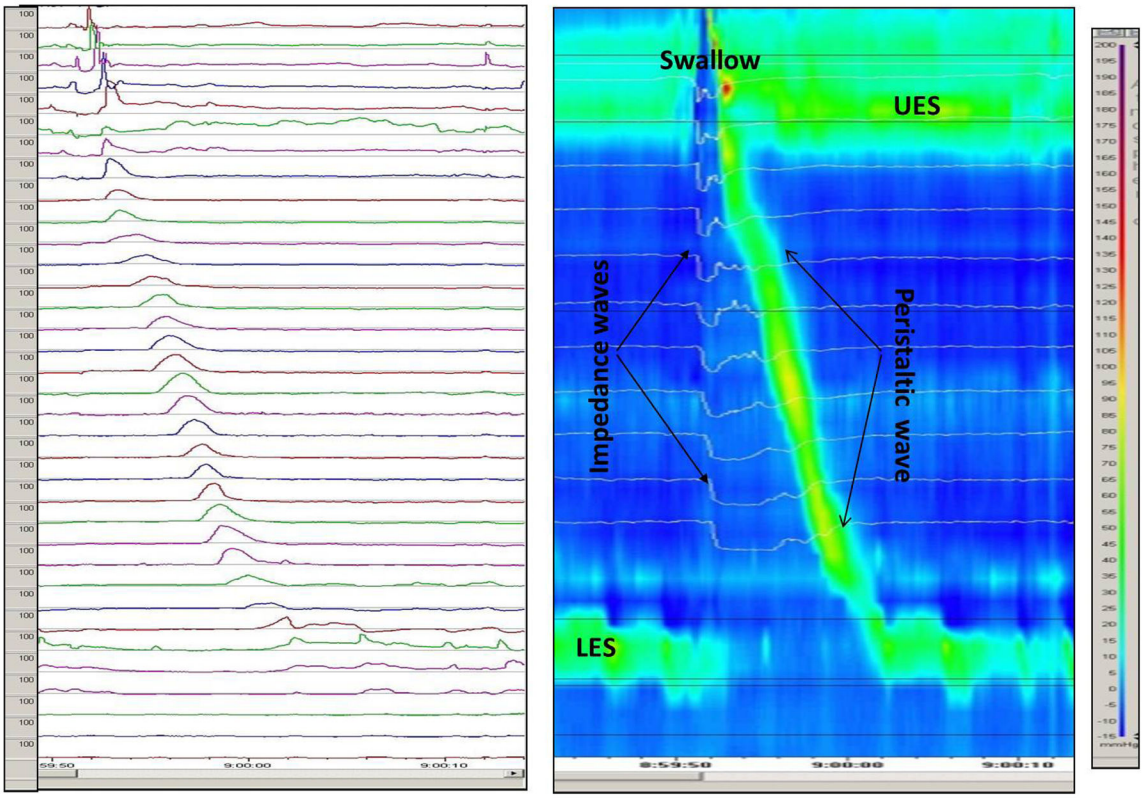

Figure 1.

Normal esophageal HRM with impedance. Normal sphincter relaxation and peristaltic wave can be observed. The impedance waves show normal bolus transit after a saline swallow. (LES; Lower esophageal sphincter; UES.- Upper esophageal sphincter)

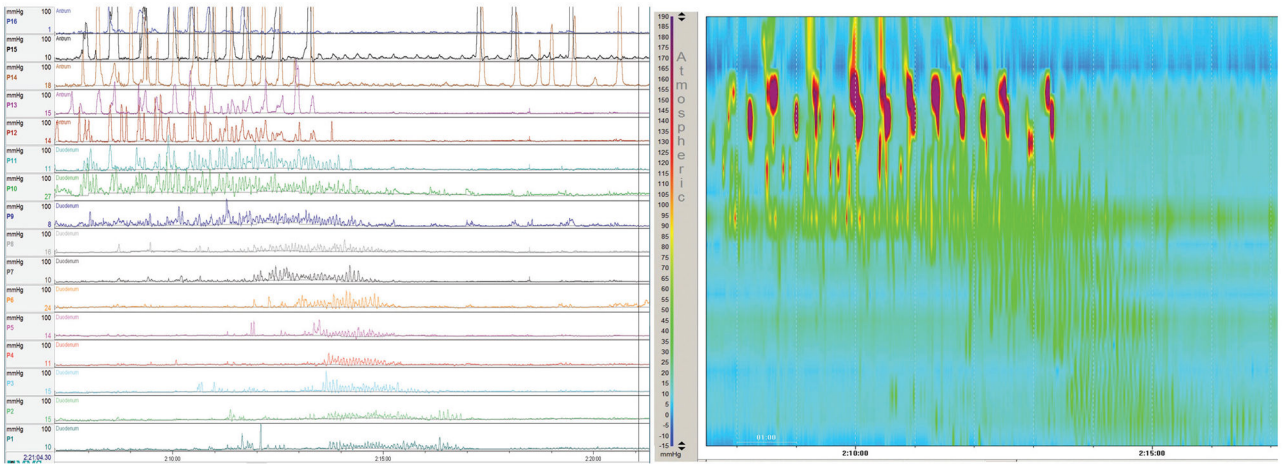

Figure 2.

Normal fasting antroduodenal manometry.- A spontaneous phase III MMC showing propagated antral contractions at 3 per minute and normal propagated small bowel contractions at 11–12 per minute can be seen both in a standard or a HRM tracing. In HRM the antrum (higher pressure in red) and small bowel (green/yellow) can easily be identified.

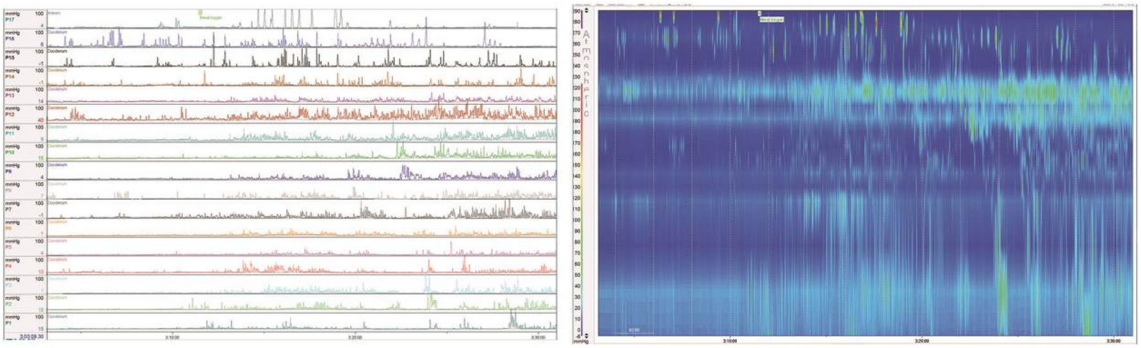

Figure 3.

Normal post-prandial antroduodenal manometry.- Normal response to a meal can be observed both in the antrum and the duodenum, both in a standard or HRM tracing.

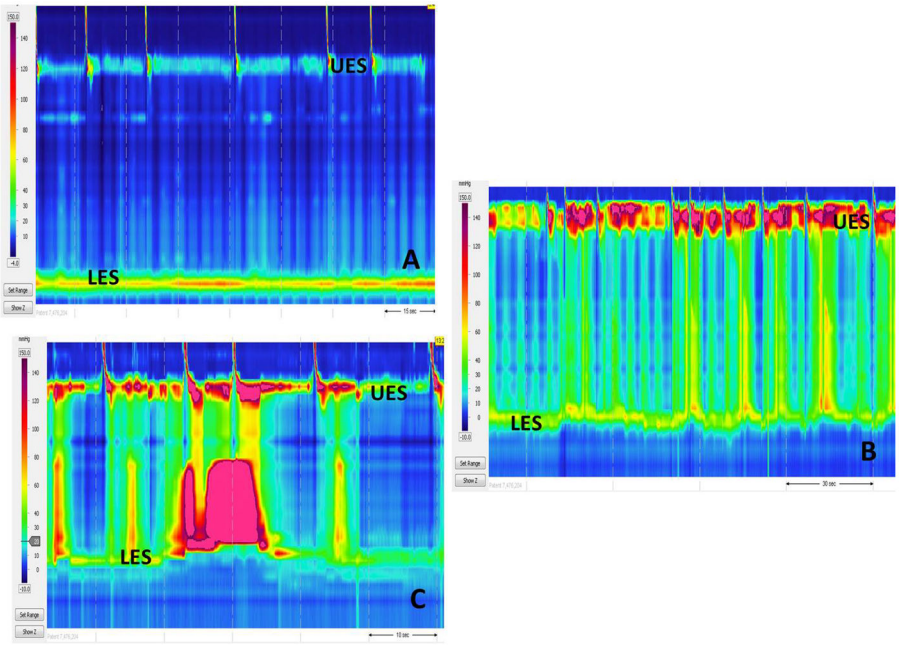

Figure 4.

Achalasia subtypes. A.- Achalasia type I, B.- Achalasia type II, C.- Achalasia type III. Type I achalasia defined as a mean IRP > upper limit of normal (usually > 15 mmHg) with 100% failed peristalsis, (DCI < 100 mmHg.s.cm); 2) Type II achalasia defined as a mean IRP > upper limit of normal (usually > 15 mmHg), absent peristalsis, and panesophageal pressurization seen in more than 20% of swallows; and 3) Type III achalasia defined as a mean IRP > upper limit of normal (usually > 15 mmHg), absent peristalsis, premature (spastic) contractions with DCI >450 mmHg_s_cm with ≥ 20% of swallows.[3].

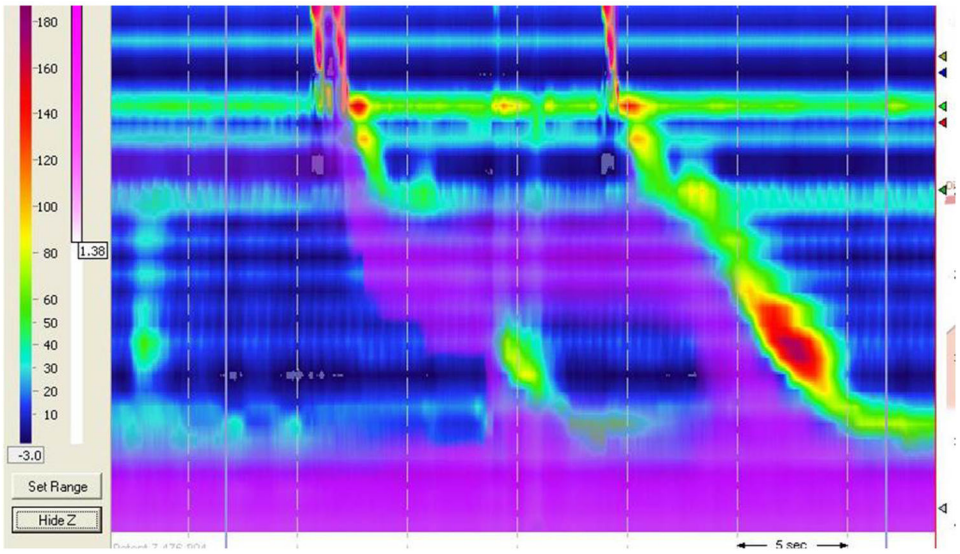

Figure 5.

Esophageal HRIM showing an abnormal peristaltic wave associated with the retention of the bolus (as show by purple in the mid esophagus even after the initial swallow). The bolus is cleared on the next swallow.

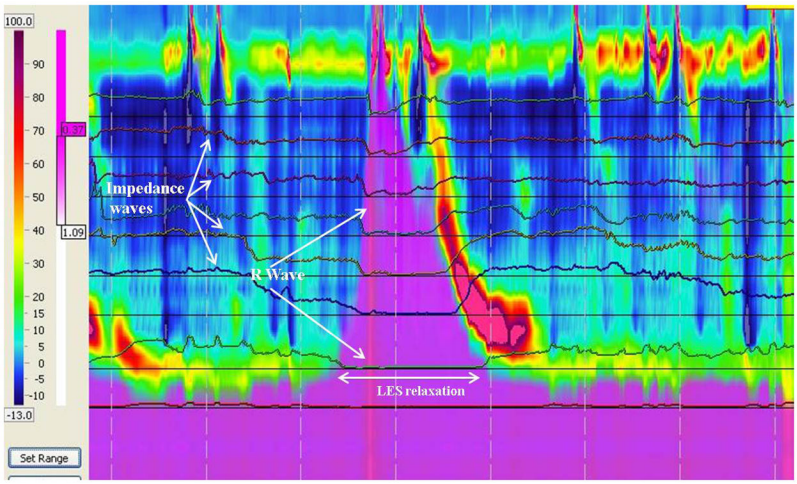

Figure 6.

Rumination-. An example of secondary rumination with the use of HRIM is shown. There is LES relaxation with retrograde flow before the R wave. Adapted from Rosen at al [35].

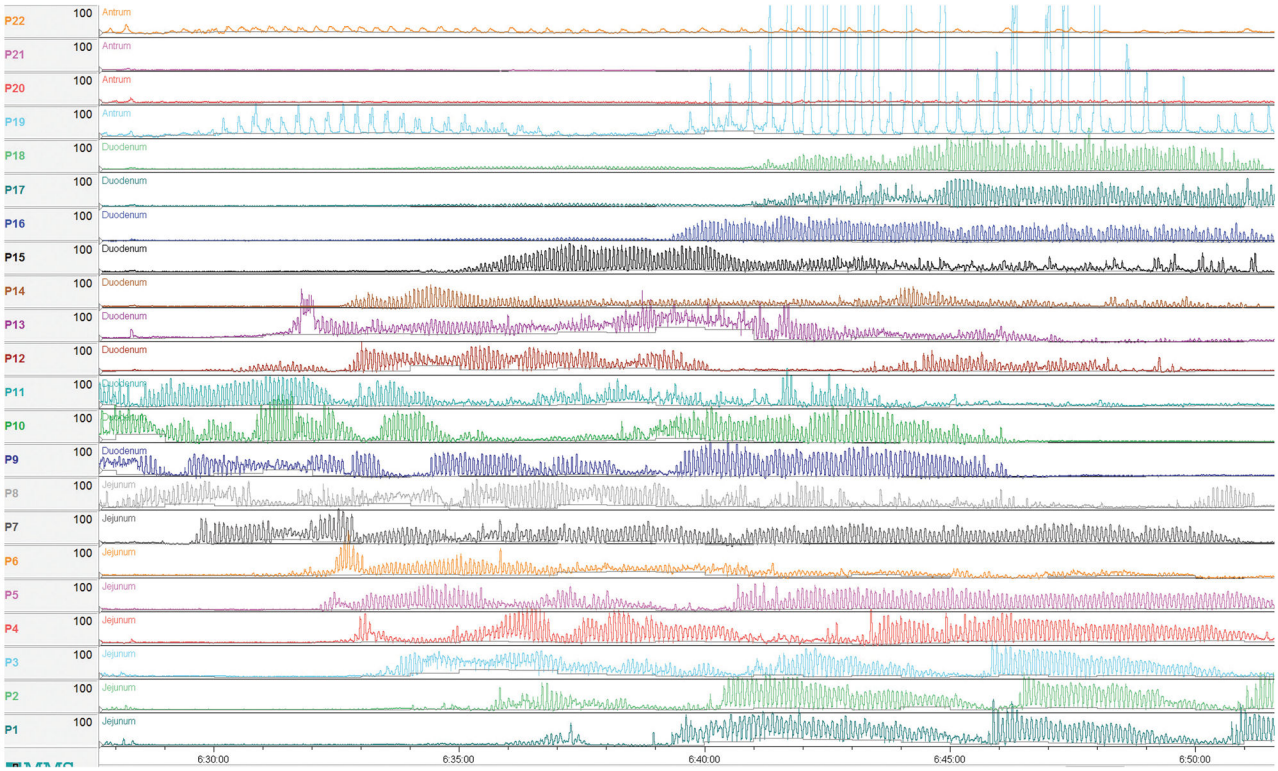

Figure 7.

Neuropathic pseudobstruction. ADM tracing showing an abnormal Phase III of MMC, with retrograde propagation, alternating amplitudes and elevation of baseline can be seen.

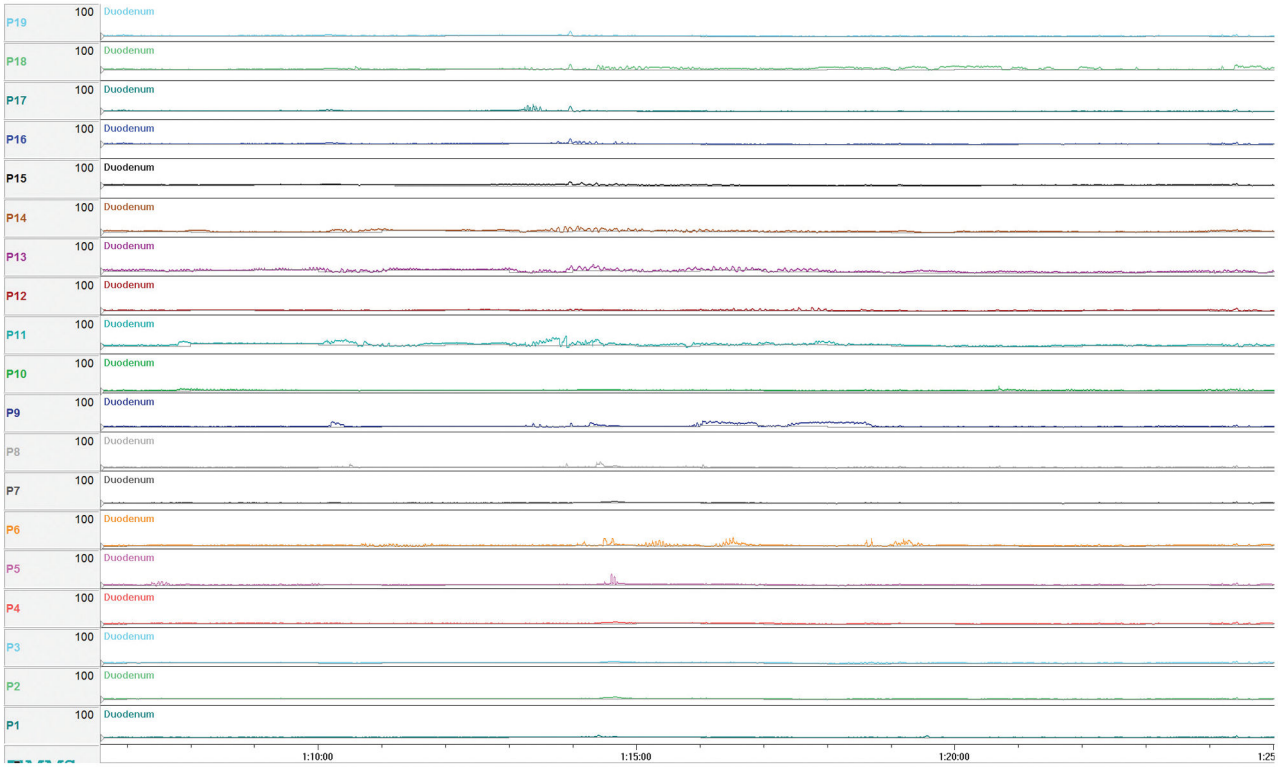

Figure 8.

Myopathic pseudobstruction. ADM tracing showing a normal interdigestive phase can be observed with low amplitudes.

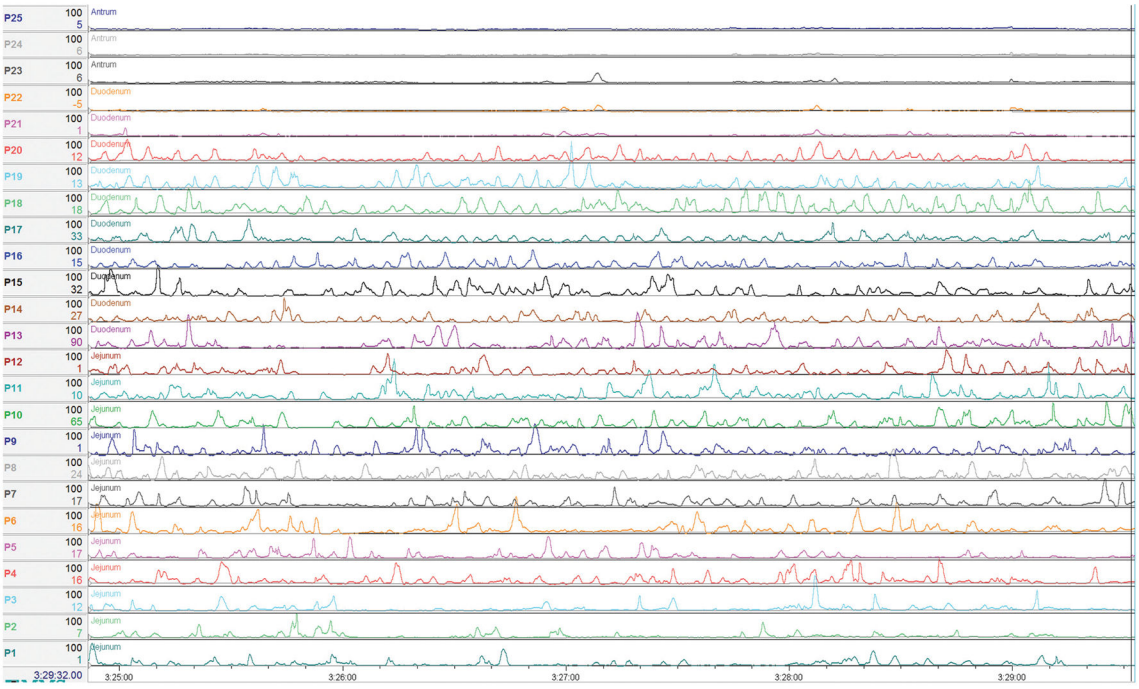

Figure 9.

Postprandial antral hypomotility.- ADM tracing showing a normal fed pattern in the small bowel and minimal to no antral response to a meal.

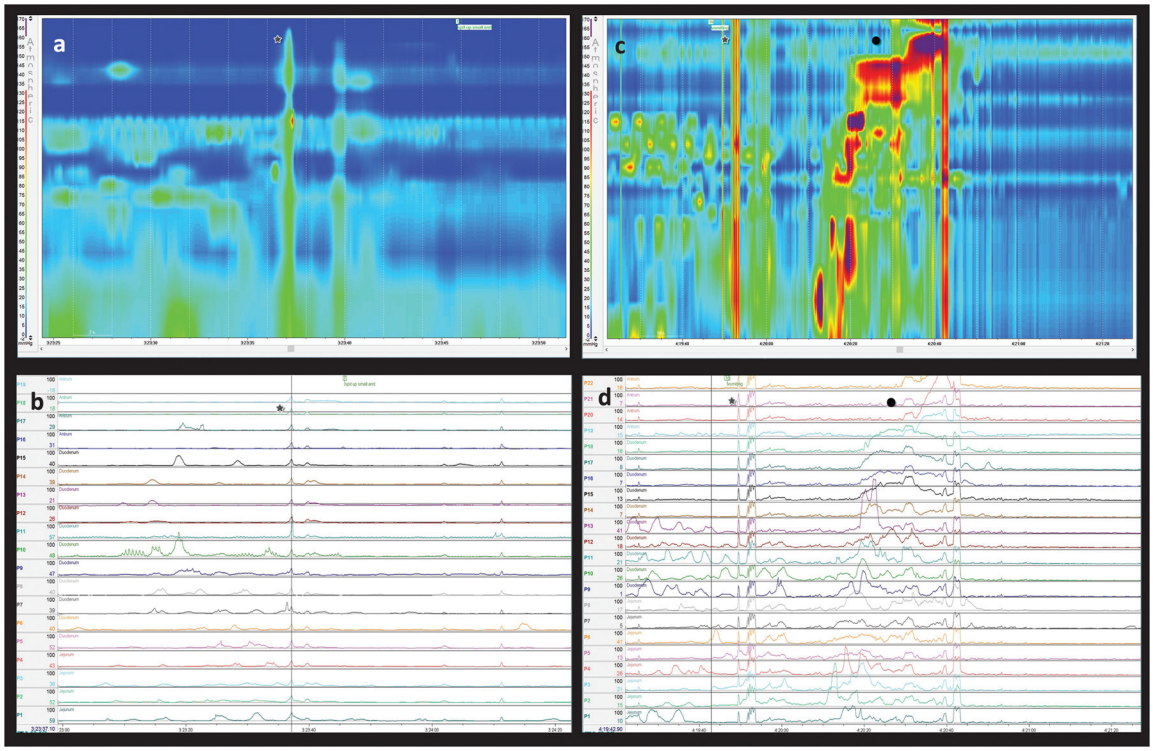

Figure 10.

Comparison of rumination vs vomiting during antroduodenal manometry. a) Contour plot showing R waves (star) caused by increase in intraabdominal pressure in a patient with rumination. b) Same tracing shown in standard pressure waves. c) Contour plot of patient with vomiting showing retching, followed by retrograde peristalsis at the time of the vomiting d) Same tracing shown in standard pressure waves.