Hirschsprung's Disease and Anorectal Manometry

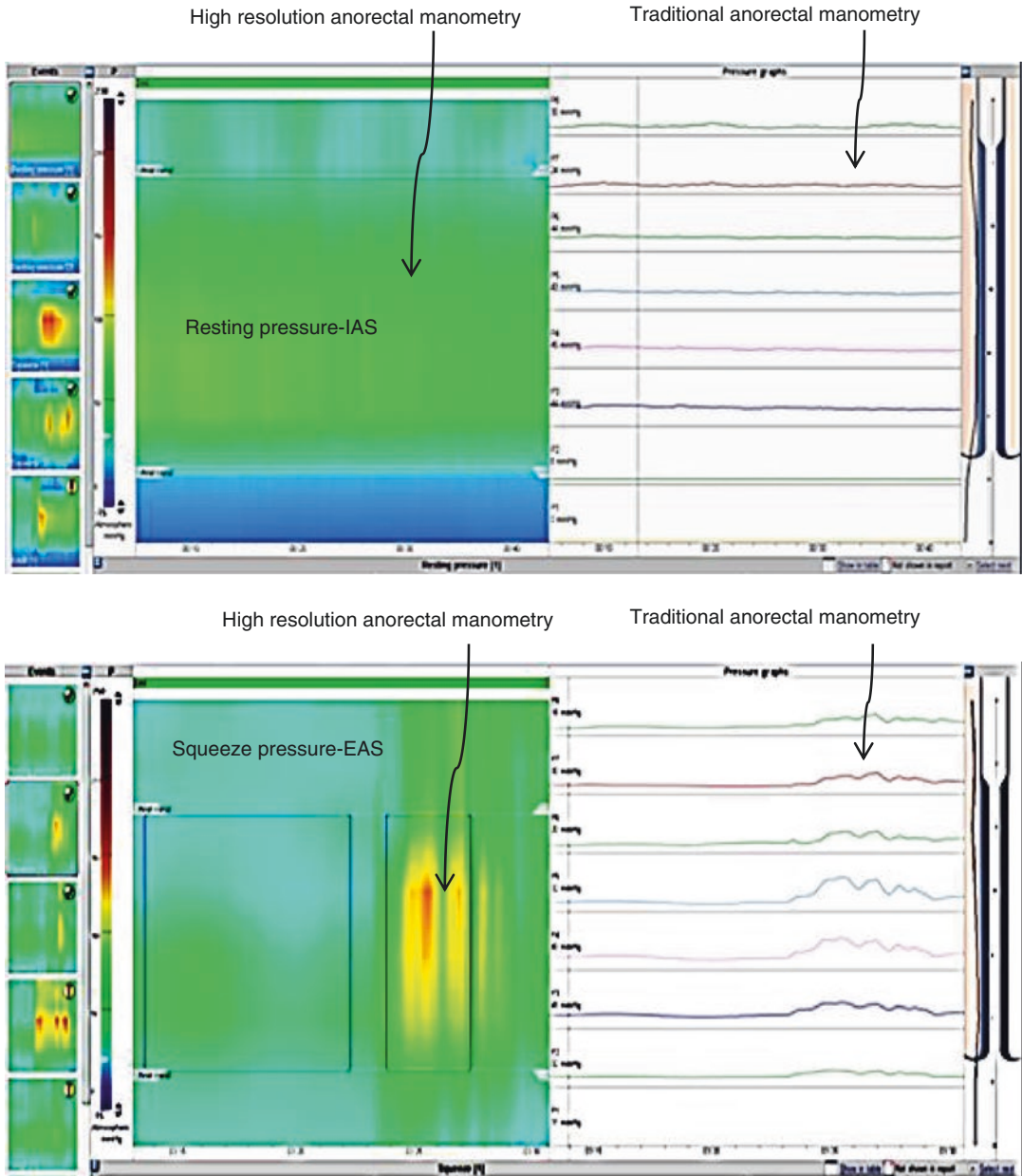Eleni Athanasakos and Stewart Cleeve

Contents

15.1 Normal Physiology of the Anorectum

Continence relies on a complex physiological interaction between motor and sensory function in the anorectum [1, 2]. An area of great growth in published work has been on sphincteric mechanisms. These consist of two muscular components: internal anal sphincter (IAS) and external anal sphincter (EAS) (Fig. 15.1). The IAS is responsible for about 85% of the total pressure of the anal canal at rest [3, 4]. The EAS is responsible for the increase in anal pressure when continence is challenged—such as when there is a rise in intrarectal/abdominal pressure [5, 6]. Dysfunction of the IAS results in decreased anorectal pressure, which is associated with passive faecal incontinence (FI): 'not [being] aware of defaecation' [7–10]. Dysfunction of the EAS leads to decreased squeeze anorectal pressures, which are associated with urge FI: 'the inability to hold on' [9, 11–13].

Continence is additionally maintained by the 'rectoanal inhibitory reflex' (RAIR), which refers to the relaxation of the caudal anus in response to rectal distension [14–16]. Gowers [17] was the first to describe the RAIR in 1877, and it was later confirmed by Denny-Brown and Robertson (1935) [18]. In a consensus statement on anorectal physiology (ARP), the RAIR has been described as 'the transient decrease in

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High resolution anorectal manometry   Traditional anorectal manometry

Resting pressure-IAS

High resolution anorectal manometry   Traditional anorectal manometry

Squeeze pressure-EAS

Fig. 15.1 Demonstration of the sphincteric mechanism (Source: Images are from the Children's Anorectal Physiology Service at the Royal London Hospital (MMS Ardmore Health)

resting anal pressure by ≥25% of basal pressure in response to rapid inflation of a rectal balloon with subsequent return to baseline' [19]. The RAIR is controlled by the sacral cord and myenteric neurons [20]. It has been suggested that the RAIR acts as a 'sampling reflex'—enabling the upper anal canal to discriminate between flatus and faeces [21, 22]. When the RAIR is absent,

it is then that HSCR can be suspected, as will be discussed in further detail in this chapter.

Individuals may present with bowel symptoms—including FI—even if they have an anatomically intact and normal functioning sphincter complex. This highlights the importance of other pathophysiological mechanisms, such as rectal sensation [13, 23–30]. Studies

have shown that stretch receptors located in the pelvic floor muscles, including the sphincteric complex, contribute to sensory discrimination [31]. Disruption of the afferent nerve pathway alters sensory perception, and this deficit has been associated with symptoms such as FI [24, 29]. The afferent pathway can be altered in multiple ways. An *elevated* sensory threshold will result in 'rectal *hypo*sensitivity'. Conversely, a *decreased* sensory threshold will result in 'rectal *hyper*sensitivity'.

Rectal hyposensitivity has been found in patients with functional constipation [32, 33]. Rectal hypersensitivity has been linked to autonomic neuropathy, congenital neurogenic anorectal malformation, spinal bifida, myelomeningocele, HSCR and functional and somatic alterations of the rectal reservoirs, such as megarectum and descending perineum syndrome [33]. Rectal hypersensitivity may underpin a heightened perception of rectal filling in FI [13, 34, 35], as well as the faecal urgency experienced by patients with 'urge' FI [9, 13, 34]. Disturbed sensory function has been reported in megarectum [24, 32, 36–38] and in children with idiopathic constipation [39].

15.2 ARP

ARP, also known as 'anorectal manometry', has been recognised for about 140 years. The first study of ARP was conducted by Gowers in 1877 [17]. Gowers demonstrated how to measure anal canal resting tone and RAIR. ARP provides an objective measurement of both motor and sensory functions—specifically pressures of the anal canal—for evaluation of the sphincteric mechanism in terms of contraction, relaxation and sensory rectal function [40, 41].

ARP has been considered the gold standard tool for [42] assessment of functional dysfunction in anal sphincter tone, [1] presence of the RAIR and [2] alteration of rectal sensory function. ARP is performed by placing a specifically designed catheter with a small balloon into the lower rectum and anal canal. The catheter is pressure-sensitive and is connected to a transducer, through which mechanical signals are converted into electronic signals that are recorded and displayed on a monitor.

Since Gower's initial work, there have been vast practical and technical advancements in the use of ARP, with high-resolution anorectal manometry (HRAM) becoming increasingly accepted worldwide [43–74]. Adult health services now perform HRAM to guide the management of bowel problems, such as constipation, FI, evacuation difficulties and dyssynergic defaecation. However, HRAM has yet to be fully recognised as a gold standard investigation in children. ARP for children is predominantly performed under sedation [48–55]—because the child is too young, insufficiently cooperative or being managed by clinicians who perceive ARP to be an invasive procedure [56, 57]. Traditional ARP in the awake child has been restricted to isolated research cases, or specific conditions such as HSCR [58–72]. Use of HRAM has been limited [73, 74].

Employment of ARP in both research and clinical practice remains hindered by a lack of uniformity among different institutions with regard to equipment, protocol and technique. Consequently, comparison of ARP data between centres is extremely limited, and it has been suggested in the literature that individual centre uses their own control values or, if using normative data from the literature, adopts a methodology similar to its author(s).

Despite variation among institutions, the use of ARP has revolutionised clinical practice in adult services. The authors hope that the service that is routinely available to adults will soon become routinely available to children.

15.3 ARP in Hirschsprung's Disease (HSCR)

15.3.1 Diagnostic Tests

ARP has been used in the diagnosis of HSCR, although there remain discrepancies concerning its accuracy and uncertainty, as to when it should be performed and whether it should be performed alongside other diagnostic tests. A 30-year retrospective study undertaken by [75]

showed that the mean age at HSCR diagnosis could be decreased to 2.6 months through use of ARP, increased clinician awareness and early rectal suction biopsy.

HSCR must be distinguished in the neonate from other causes of intestinal obstruction. Later in development, HSCR must be further distinguished from idiopathic constipation or megacolon secondary to anal stenosis or stricture. HSCR predominately presents at birth and in males, with well-recognised signs of bilious vomiting, lack of passage of meconium or abdominal distension. Delayed passage of meconium can be an important early sign of HSCR [76, 77]. In rare cases, HSCR can be diagnosed later in life, in early childhood. According to the national institute for health and care excellence (NICE) guidelines (2004), constipation affects 5–30% of children in the United Kingdom [78]. In light of these figures, it is vital that idiopathic constipation is differentiated from HSCR in clinical practice.

Diagnostic tools used to diagnose HSCR include:

- *Barium enema* to locate the transition zone
- *Rectal suction biopsy* to confirm the absence of ganglion cells in the myenteric and subcutaneous plexi
- *Acetylcholinesterase (AChE) histochemistry* to show increased AChE activity
- *ARP* to establish the absence of the RAIR

A perfect investigation for the diagnosis of HSCR does not exist. The use of barium enema has been plagued with inaccuracies and technical difficulties, especially in the neonate. For example, the HSCR transition zone, which has been traditionally used as the hallmark for radiological diagnosis, has been shown to be falsely positive in 43% of infants [79]. There has been concern regarding the inadequacy of sampling at rectal biopsy, which had led to routine haemotoxylin and eosin (H&E) preparation which has shown imperfection with failure to reveal ganglion cells in 39% of patients without HSCR. AChE measurements were thought to improve the reliability of the rectal biopsy, but false-negative results have been demonstrated [80] in up to 29% in patients

with HSCR. This error has been attributed to factors such as inhomogeneity, highly short-segment HSCR and incorrect sitting or sampling of rectal biopsy [81, 82]. Thus, only an increase in AChE activity contributes to the diagnosis of HSCR. The disease can be definitively excluded by the demonstration of ganglion cells histologically following conventional full-thickness rectal biopsy [83], but it depends on the adequacy of the sample.

In summary, an accurate diagnosis of HSCR is based on rectal biopsy [84, 85]—yet it is not necessarily needed to confirm the diagnosis of HSCR [86, 87]. The following section will discuss the diagnostic value and accuracy of ARP, with particular reference to the RAIR.

15.3.2 RAIR

The various reported applications of ARP in HSCR are listed in Table 15.1. As discussed previously, the diagnosis of HSCR on ARP is established by an absence of the reflex relaxation of the IAS (i.e. the RAIR) in response to rectal distention seen in the normal population (Fig. 15.2) [107, 108] (Fig. 15.3). The RAIR is induced by rapidly instilling air into a balloon in the rectum and studying the characteristics of the subsequent IAS relaxation. Air is withdrawn within 3–5 s of inflation [109]. The recommended maximum inflation volume for obtaining RAIR is 30 mL for infants, 60 mL for older children and more in patients with a megarectum [57].

Unfortunately, the accuracy of ARP has not been uniform, varying from 75% in neonates [110] to 90% [83] or close to 100% in children [110, 111]. One explanation for the variation in infant could be due to the technical difficulties in neonatal ARP due to the immaturity of the ganglion cells [110, 112, 113], particularly in premature and/or low birth weight babies [113, 114]. Yet other studies have been able to use ARP to diagnose HSCR in neonates with 90–92% accuracy [83, 88, 90, 115–117]. Low et al. [83] demonstrated that the accuracy of ARP was similar in neonates, infants and older children, and it was suggested that ARP should be done under sedation under the age of 4 years or older children

Table 15.1 Literature review of anorectal physiology in children

Author	Year	Sample	Healthy children	Traditional ARP	HRAM ARP	Diagnosis	Post-operative assessment
Boston et al. [88]	1976	63 HSCR neonates		√		√	
Zaslavsky et al. [63]	2003	35 HSCR children		√		√	√
Martins et al. [89]	2009	42 HSCR children		√			
Noviello et al. [68]	2010	185 suspected HSCR		√		√	
Low et al. [83]	1989	50 constipated children		√		√	
Boston et al. [90]	1977	101 HSCR neonates		√		√	
Demirbag et al. [64]	2012	18 HSCR children		√			√
Lanfranchi et al. [91]	1984	34 suspected HSCR		√		√	
Nagasaki et al. [92]	1980	30 healthy children 22 HSCR children	√	√			√
Iwai et al. [93]	1979	9 HSCR children 10 idiopathic constipation		√		√	
Bigelli et al. [94]	2005	20 constipation children		√			
Ambartsumyan et al. [73]	2012	30 constipation children			√		
de Lorijn et al. [77]	2003	16 healthy neonates	√	√		√	
Nagasaki et al. [95]	1989	48 HSCR children 61 healthy children	√	√		√	
Keshtgar et al. [60]	2003	16 HSCR children		√			√
Kumar et al. [96]	2009	90 healthy children	√	√			
Fathy et al. [70]	2013	150 constipated children 50 healthy children	√	√			
van Ginkel et al. [97]	2001	212 constipated children		√			
Morikawa et al. [98]	1989	82 HSCR children		√			√
Chiarioni et al. [52]	2005	15 constipated children 12 healthy children	√	√			
Yokoyama et al. [99]	1989	268 constipated children 95 HSCR children		√		√	
Benninga et al. [100]	2001	22 healthy neonates	√	√			
Hsu et al. [101]	1999	35 HSCR children		√			√
Bjornland et al. [102]	1998	48 HSCR children		√			√
Tang et al. [74]	2014	180. asymptomatic newborns, 181. 16 newborns suspicious of HSCR			√	√	
Iwai et al. [103]	1988	79 constipated children		√		√	
Jarvi et al. [52]	2009	81 suspected HSCR 33 HSCR children 48 healthy children	√	√		√	
Stensrud et al. [104]	2015	52 HSCR children		√			√
Banasiuk et al. [105]	2016	14 HSCR children			√		√
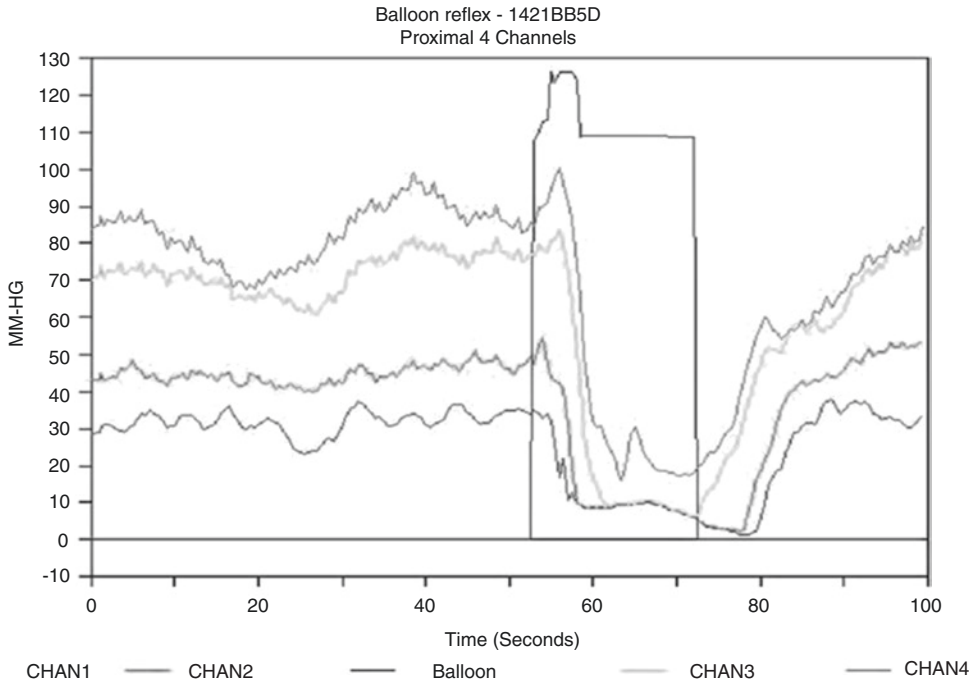
Fig. 15.2 Presence of RAIR [106]. (Source: Images are from the Children's Anorectal Physiology Service at the Royal London Hospital (MMS Ardmore Health)
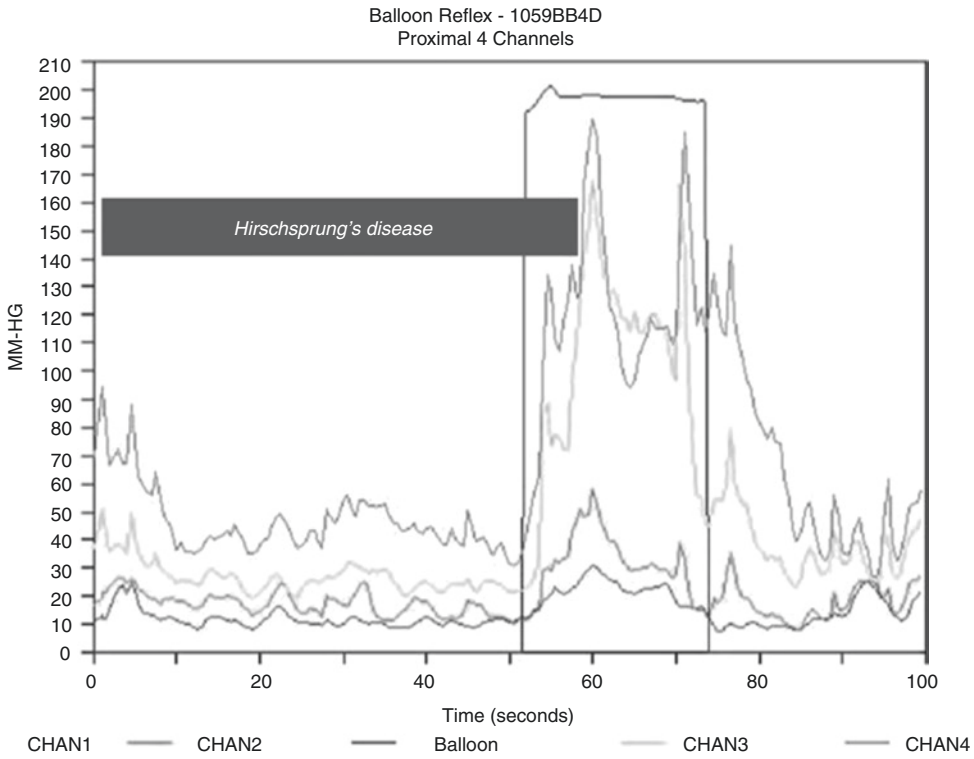
Fig. 15.3 Absence of RAIR in Hirschsprung's disease. (Source: Images are from the Children's Anorectal Physiology Service at the Royal London Hospital (MMS Ardmore Health)

who are uncooperative. Sedation does not appear to have any effect on the RAIR [95, 111, 118, 119]. Nagasaki et al. [95] suggested that indistinct reflexes often occur in neonates, possibly due to the weak constriction of the anal canal, and that using prostaglandin F2 alpha, electrical stimulation or cold water could improve the reliability of conventional ARP.

Variability in the accuracy of conventional ARP might also be attributed to other sources of variation, such as the volume of air required to elicit the RAIR [83, 111]. The literature is divided on the resting anal pressure in HSCR. Slightly higher resting pressures have been observed in patients with HSCR, yet these values do not differ markedly to individuals with a normal RAIR [115] and pronounced IAS contraction [93]. Indeed, some studies have found a lower anal resting pressure in patients with HSCR [91] and others no difference in anal resting pressures [95].

Further technical factors known to influence ARP results are incorrect positioning of the catheter, air leak in the circuit and performance of the test during faecal impaction. The pressure exerted by a solid mass of faeces can give false readings of inflation volume and increase the time needed to elicit the RAIR. Steyern et al. [93] used ARP in a group of 95 patients without signs of HSCR and reported the RAIR to be inconclusive or absent in 16 patients. The authors ventured several explanations for this finding, including difficulty in inducing the RAIR due to severe constipation, colitis and motility disorders and limitations in their broader methodology, which involved modified contrast enema supplemented with injections of cold agent in the rectum.

Reflecting on the literature, it appears that in patients with a neonatal onset of constipation and related symptoms, a rectal suction biopsy is the superior diagnostic tool. As discussed earlier in this chapter, it is vital for neonatal surgeons to detect HSCR. However, in the context of the high incidence of constipation in children, the balance of probability and specificity of symptoms shift massively in childhood [78]. Clearly it would be preferable to avoid exposing constipated children who do not have HSCR, the vast majority, to rectal biopsy. It is clear that ARP is a non-invasive screen test for the diagnosis of HSCR, especially when sedation is

not necessary. Ultimately, as HSCR is a histological diagnosis, rectal biopsy is necessarily the clinician's final arbiter in the diagnostic process.

It is important to adjust for the presence of a megarectum in estimating the likelihood of HSCR in a constipated patient. In patients with a megarectum, regardless of the cause of the rectal distention, the RAIR is not always seen. The larger rectum, understandably, requires larger volumes to trigger the sphincter response [108, 120]. The recommended volumes for eliciting this response are 50–80 cc in a megarectum patient [106].

While the RAIR is normally reported as 'present' or 'absent', it may be of some use to describe the various characteristics of the RAIR, such as its latency, duration and amplitude at both the proximal and distal ends of the sphincter [106, 121, 122]. The amplitude and duration of the RAIR is influenced by the frequency and volume of rectal distention: with increasing rectal volumes, the RAIR residual pressure will decrease, and its duration will increase [123, 124]. Limited publications feature an analysis of these different phases of the RAIR. Zbar et al. [120] separated the RAIR into different sphincter segments in normal controls, constipated patients and patients with FI. They revealed significant linear trends for most parameters at each sphincter level. Recovery time and area under the inhibitory curve differed between the sphincter levels and patient groups, with the most rapid recovery occurring in the distal sphincter of incontinent patients ($P < 0.001$).

15.3.3 Contemporary Use of Anorectal Physiology in Infants and Children Older Than Six Months

Clinicians are referred patients with constipation, painful or difficult defaecation and withholding. Eighty-five percent of patients with HSCR will have been diagnosed before 6 months of age. Therefore, the pretest probability of a patient older than 6 months having HSCR is approximately 1 in 20,000, or 0.005%. [Assuming [42] incidence of HSCR is 1 in 3000 and [1] 85% of children with HSCR are diagnosed in the first

6 months of life.] The incidence of constipation in children is 5–30% (NICE) [78]. Using this data, a child's constipation is 1000 times more likely to be idiopathic in origin than attributable to HSCR.

We acknowledge that a degree of filtering by referring general practitioners, paediatricians, and paediatric gastroenterologists will occur. It is indisputable that the prevalence of idiopathic constipation is much greater than HSCR in infants over 6 months. ARP may be the investigation of choice for severe idiopathic constipation. The authors suggest that ARP may assist in screening which patients ultimately will need a rectal biopsy, thus increasing the pretest probability of the procedure in children older than 6 months and decreasing the number of normal rectal biopsies performed. The authors acknowledge that rectal biopsy is useful in diagnosing rare forms of dysganglionosis (e.g. hypoganglionosis, hyperganglionsis, intestinal neuronal dysplasia, immature ganglion cells, ganglioneuromata associated with neurofibromatosis and multiple endocrine neoplasia type 2B (MEN 2B)).

15.3.4 A Post-Surgical Role for ARP in HSCR

Studies of patients with HSCR have investigated changes in ARP following surgery.

Research has demonstrated that a RAIR can develop in children after a pull-through operation for HSCR [92, 98, 125, 126]—particularly following transanal procedures [127]. Morikawa et al. [98] demonstrated the presence of a RAIR in 39% of patients with HSCR after the Soave-Denda technique. A relationship has been identified in patients with HSCR between specific operative techniques and post-surgical changes in resting pressure [128]. Resting pressures have been found to be lower than normal in patients who undergo the Duhamel technique. Lower resting pressures can be explained by the IAS myotomy performed during the pull-through procedure when the septum between the rectum and the ganglionic segment is resected and partly by the anal dilation performed during the procedure [102].

Other authors contend that the majority of patients with HSCR continue to have an abnormal RAIR and a non-relaxing IAS after surgery [63, 102, 116, 128–132]. Zaslavsky et al. [63] studied 35 patients after corrective surgery for HSCR, and of the 16 who received ARP, all had persistent absence of RAIR, regardless of surgical technique. In fact, there was no difference found in anal resting pressure between patients with or without sphincterotomy. Thus, Zaslavsky et al. concluded that propulsive waves were not a prognostic indicator for achieving bowel control. Questions have been raised regarding the necessity of performing post-surgical ARP in HSCR, as normal findings are returned in many patients [63, 89, 127, 133] who have persistent symptoms of FI [64, 102, 104, 134, 135]. Stensrud et al. [104] reported no association between IAS defects in HSCR and low resting pressures on ARP after endorectal pull-through surgical approach, contrary to the findings of a comparable study, where IAS disruption was shown to correlate with low resting pressure after a Duhamel procedure [102].

Studies that have shown association between anal resting pressure and FI after different types of surgical procedures for HSCR have frequently used sedation when performing ARP. [60, 130]. Several studies have demonstrated the usefulness of ARP as an indicator of bowel function (particularly FI) after surgery for HSCR [60, 101, 114, 125, 128, 136–139]. Persistent symptoms in HSCR have been attributed to abnormalities of the enteric plexus, which may be associated with a diverse range of pathologies, including impaired colonic propulsive forces (or anorectal dyssynergia), [60, 64] anal stenosis, an enlarged Duhamel pouch, residual aganglionic segment or intestinal neuronal dysplasia [1, 128, 138, 140].

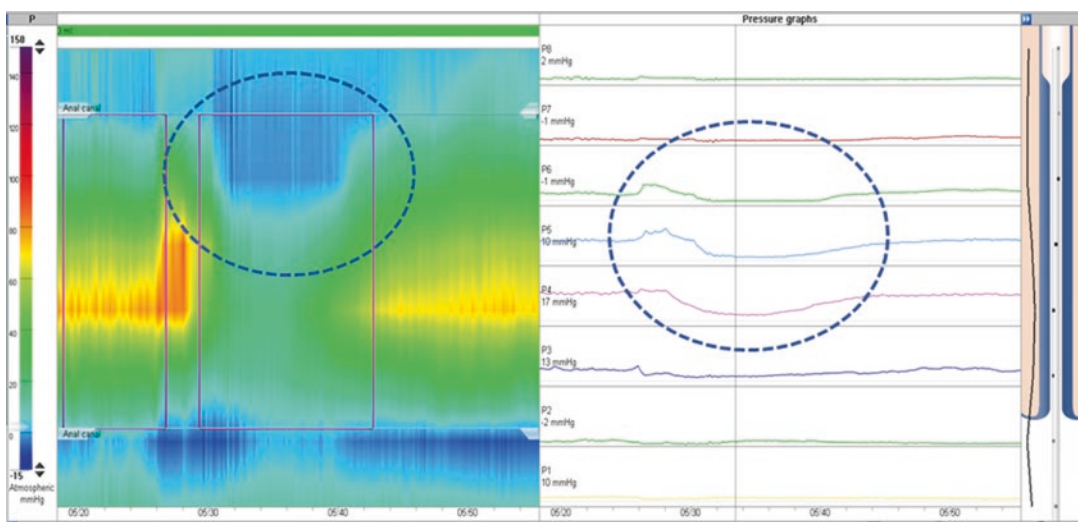## 15.4 HRAM and Hirschsprung's Disease

HRAM is a novel technique for assessing motor and sensory function in the anorectum, with several potential advantages over traditional ARP. The primary advantage of HRAM is that HRAM allows computerised data acquisition and display-utilised colour-coded amplitude

depiction, enabling enhanced visual and analytic assessment of the sphincter complex [141]. HRAM provides a better understanding of pressure profiles and synchronised events over time than can be derived from the traditional line traces seen on ARP [142, 143]. Moreover, HRAM can use either solid or water-perfused systems and two-dimensional or three-dimensional—albeit with limited guidance from the literature as to which is superior, due to limited studies. There has been a preference for solid-state catheters in HRAM. It has been suggested that traditional ARP method were cumbersome and required the placement of the recording sensors precisely within the anal sphincter for accurate diagnosis, as catheter movement with anorectal manoeuvres could confound the values.

Studies have demonstrated the efficacy of using HRAM to diagnose HSCR [74]. A few authors maintain that the RAIR cannot be elicited in newborns less than 1-week-old on account of their immature anorectum [77, 100], yet numerous studies [97, 144] have demonstrated that this can be done using HRAM with high sensitivity (89%) and specificity (83%). However, we face the same dilemma as we did with traditional ARP: there is variation in technique between centres, and an absence of robust normative data within paediatrics.

At the Royal London Hospital, Barts Health NHS (London, UK), the Children's Anorectal Physiology Service (CAPS) was established in August 2016. The service uses a combination of HRAM (2D) water-perfused ARP and complementary investigations including endoanal ultrasound, colonic transit study and proctogram. The service has seen 135 children suffering from chronic constipation with or without FI, HSCR or anorectal malformations, for both diagnostic and management purposes. Most investigations are performed when children are awake (90%) with a small number done under sedation (ketamine). All patients are discussed at a multidisciplinary team meeting with input from up to seven specialists: paediatric surgeon, paediatric gastroenterologist, clinical nurse specialist, health play specialist, clinical psychologist, paediatric radiologist and paediatric clinical scientist. Investigations are used to direct management, taking into consideration information from validated bowel assessment, psychological evaluation and medical history. The service believes in using both scientific diagnostic evidence and multi-professional input to manage these patients. The RAIR is measured in all patients using a 2D HRAM water-perfused machine (Figs. 15.4 and 15.5). Out of 135 patients seen at CAPS, 10 (7%) had HSCR, and ARP was performed in each to assess sphincteric

Fig. 15.4 Presence of RAIR in a symptomatic patient. (Source: Images are from the Children's Anorectal Physiology Service at the Royal London Hospital (MMS Ardmore Health)
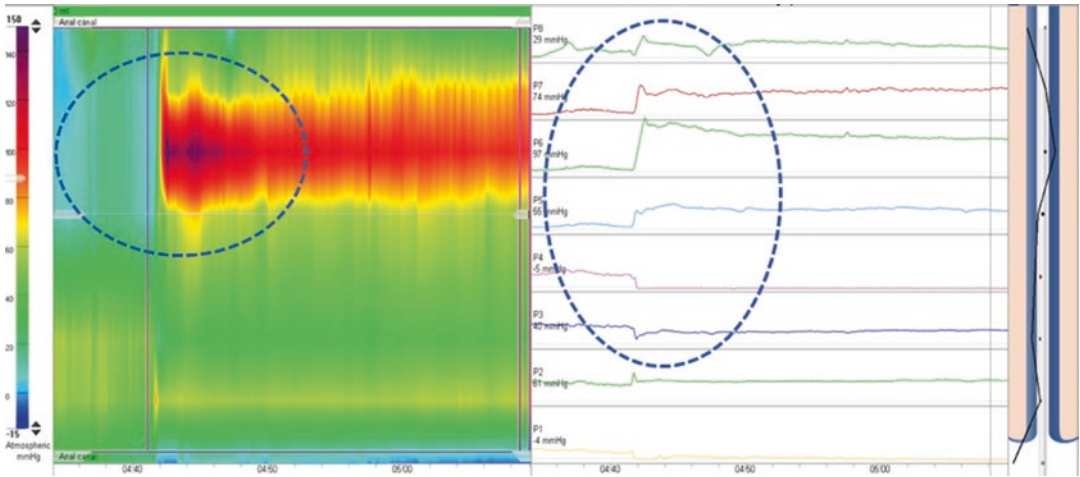
Fig. 15.5 Absence of RAIR in Hirschsprung's disease patient. (Source: Images are from the Children's Anorectal Physiology Service at the Royal London Hospital (MMS Ardmore Health)

pressures (IAS/EAS), RAIR, enhanced squeeze, cough reflex, defaecatory function ('push') and rectal sensation (unpublished work). RAIR was absent in all known patients with HSCR.

Banasiuk et al. [105] have argued that 3D HRAM is the most precise method for assessment of anal sphincter function and may help to direct surgical procedures. It was suggested from Banasiuk et al. that using 3D HRAM gives the opportunity to assess the anal sphincter both longitudinally and circumferentially; however, there is limited understanding of how such measurements are practical in understanding further the pathophysiological role and characteristics in patients with bowel dysfunction and HSCR.

The main limitation with using HRAM in children is the lack of normative data available in the professional literature—unlike in adults, for whom we have normal values to compare patients to, despite wide variation in technique, protocol and manometric equipment [43, 44].

15.5 Concluding Remarks

This chapter has discussed ARP as one of multiple ways to investigate HSCR. There has been considerable debate as to which diagnostic tool is the most appropriate and accurate, as is often the case when the perfect investigation does not exist. Rectal suction biopsy and ARP are gen-

erally considered to be the most accurate tests [52, 145].

ARP has been demonstrated in the literature to be a reliable, cost-effective and non-invasive scientific tool for the diagnosis of HSCR [68, 91, 95, 99, 103, 116]. Nevertheless, it is clear that rectal biopsy is the investigation of choice in neonates. It has been proposed that in children under the age of 1 year, HSCR is very unlikely in the presence of a RAIR. Based on the specificity and positive predictive value of ARP for the diagnosis of HSCR, it remains inferior to other diagnostic tools (i.e. rectal suction biopsy) and should not be used solely [52, 84]. Guidelines must be developed to overcome the variability and discrepancies found when using ARP in patients with HSCR—both diagnostically and post-operatively. While there may be clear understanding of the various ways to diagnose HSCR among clinicians, there exists no definitive pathway for the integration of ARP in this process.

Post-operatively, a number of patients with HSCR will present with short- and long-term bowel problems, including constipation, FI, anorectal dyssynergia and intestinal motility disturbances [125, 128, 136, 137]. It is unclear whether ARP is necessary for such patients: their sphincter function can be normal, as made evident in recent research. Significant discussion has been devoted in this chapter to the presence or absence

of the RAIR post-operatively in patients with HSCR, yet understanding about the other parameters of the RAIR remains rudimentary—limiting the extent to which it may be used to predict functional outcome.

It is clear that there are obstacles which need to be confronted to gain uniformity in the use of ARP, for HSCR or other bowel conditions. In adults [40, 43, 146, 147], there is no standardisation in ARP for either protocol or equipment—this is also the case within paediatrics. Furthermore, there is a lack of normative data for scientific comparison of findings within paediatrics, as every institution performs the investigation on children differently (whether it be awake or under sedation), and there remains variation in ARP protocol and catheter use (solid/liquid, 2D/3D), making it impossible for scientific comparisons. It is important to keep in mind that, when comparing results, ARP should be performed with identical techniques in the same institution.

ARP is a useful tool for identifying the pathophysiology of a patient's anorectal dysfunction, which may be complex and multifactorial. Specifically, in the age of HRAM, we have the ability to assess the coordination of pelvic floor mechanisms, observing for dysfunction both when the patient is asked to squeeze and when they are asked to 'push' as a demonstration of their muscle activity during defaecation. Information gained from these observations can be used to direct biofeedback management. In conclusion, ARP does improve understanding of the pathophysiological mechanisms involved in HSCR. The primary ambition should be the establishment of an internationally agreed paediatric standardised protocol using uniform equipment. Future research will then be universally comparable and can proceed to improvements in investigation and, most importantly, outcomes for children and adults with HSCR.

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