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A state-of-the-art summary

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REVIEW ARTICLE

Current and future perspectives on the utility of provocative tests of anal sphincter function: A state-of-the-art summary

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Abstract

Background: The maintenance of fecal continence depends upon coordinated interactions between the pelvic floor, anorectum, and anal sphincter complex orchestrated by central and peripheral neural activities. The current techniques to objectively measure anorectal function rely on fixed diameter catheters placed inside the anal canal with a rectal balloon to obtain measurements of anal resting and squeeze function, and rectal compliance. Until recently it had not been possible to measure the distensibility of the anal canal, or in other words its ability to resist opening against an increasing pressure, which has been proposed as the main determinant of a biological sphincter's function. Anal acoustic reflectometry (AAR) and the functional lumen imaging probe (FLIP) are two novel, provocative techniques that dynamically assess the anal sphincter complex under volume-controlled distension. In doing so, both provide information on the viscoelastic properties of the anal canal and offer new insights into its function.

Purpose: This review details the current and potential future applications of AAR and FLIP and highlights the unanswered questions relevant to these new technologies.

KEYWORDS

anal canal, continence, defecation, distensibility, fecal incontinence, proctology

1 | BACKGROUND AND AIMS

The maintenance of fecal continence depends upon coordinated interactions between the pelvic floor, anorectum, and anal sphincter complex orchestrated by central and peripheral neural activities.¹

Multiple techniques to objectively measure anorectal function have been described in the literature with anorectal manometry (ARM) commonly utilized to evaluate parameters of both anal and rectal function. Conventional ARM, which has become relatively obsolete in recent years, consisted of a limited number of water-perfused or

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solid-state pressure sensors along a fixed diameter catheter to record pressures generated by the anal canal during rest and voluntary squeeze.² Since the advent of high resolution anorectal manometry (HRAM) or three-dimensional high-definition anorectal manometry (3D HD-ARM), these modalities have become established as the investigations of choice, available in many centers for the assessment of the anorectal continence mechanism.³ These advanced tools are able to record information from at least eight or more tightly spaced pressure sensors to generate color-contoured topographical plots along the length of the anal canal and into the rectum.⁴ Despite the recent advances in this technology, all the devices rely on fixed diameter catheters placed inside the anal canal to obtain measurements, which will vary depending on the diameter of the catheter used. The length-tension relationship is used to describe the function of any muscle where tension increases as the muscle is stretched to an optimal length. Therefore, with an increasing diameter catheter, the active and passive properties of the structures surrounding it are stretched, increasing measurements of resting and squeeze pressures.⁵⁻⁷ Being fixed diameter, these catheters also open and distort the sphincter complex before measurements are taken. As a result, it is not possible to measure the distensibility of the anal canal, or in other words its ability to resist opening against an increasing pressure, which has been proposed as the main determinant of a biological sphincter's function.⁸

Anal acoustic reflectometry (AAR) and the functional lumen imaging probe (FLIP) are two techniques available that provide dynamic assessments of the opening and closing function of the anal sphincter complex during volume-controlled distension.^{9,10} Both tools are unique in their ability to measure the length-tension properties of the anal sphincter muscles as the anal canal opens and closes, unlike manometry, which obtains measurements at only one length.¹¹ These novel emerging techniques have the potential to improve our understanding of anal sphincter competence and may act as an additional diagnostic tool in the assessment and management of anorectal dysfunction. This review aims to summarize the current evidence on the use of these two techniques in their assessment of anal sphincter competence.

2 | RESISTANCE TO DISTENSION AS A DETERMINANT OF ANAL SPHINCTER COMPETENCE AND THE RATIONALE FOR PROVOCATIVE TESTING

The concept of resistance to distension, as opposed to resting sphincter tone, as the main determinant of a biological sphincter's function was first proposed by Harris and Pope in 1964.¹² In 1966 Harris et al. described, for the first time, the "yield pressure" of the anal canal by injecting small increments of water into a catheter system and identifying the pressure required to break the "seal" generated by the anal sphincter complex surrounding it.⁸ This technique was later adapted with the use of a balloon, which was gradually inflated in the anal canal and the yield pressure was

Key points

- Distensibility of the anal canal, or in other words its ability to resist opening against an increasing pressure, has been proposed as the main determinant of its function.
- Conventional manometric techniques rely on fixed diameter catheters to record the pressure generated by the anal canal during rest and voluntary squeeze.
- In contrast to manometry, anal acoustic reflectometry and the functional lumen imaging probe are two novel, provocative techniques that dynamically assess the anal sphincter complex under volume-controlled distension.

identified as the point where the pressure would plateau as the anal canal just started to open.^{13,14} Katz et al., using the same balloon technique, also described the "maximal sphincter pressure" defined as the maximum pressure achieved with voluntary contraction that no longer increased despite further volume increments of the balloon.¹⁵ These provocative tests of sphincter function, with controlled distension, allow an assessment of the mechanosensory and viscoelastic properties of the sphincter complex. The principles described in these early experiments demonstrated that assessing the ability of the anal canal to resist distension offered a useful method to study the anal sphincter complex and its role in maintaining continence. However, although balloon distension tools measuring pressure and volume are relatively low cost and easy to use, it is impossible to obtain data on the geometry or location of the balloon along the sphincter. As a result, due to the unknown deformation of the balloon, any calculated parameter such as tension or distensibility would be inaccurate and it is not possible to confirm the location of the balloon in relation to the area of maximum resistance to opening. Due to these limitations, it is necessary to combine pressure and volume measurements with a simultaneous geometric profile along the length of the sphincter.^{16,17} Finally, it is important to ensure the balloons did not resist inflation thereby affecting the results, leading to a move away from latex "balloons" to highly compliant "bags."¹⁶

3 | ANAL ACOUSTIC REFLECTOMETRY

3.1 | Development

AAR is a technique developed to assess the physiological profile of the anal canal during distension. The principles of acoustic reflectometry are derived from seismology and the study of reflected acoustic impulses¹⁸ which were initially used to determine the cross-sectional area (CSA) of the vocal tract at the lips.¹⁹ Klarskov et al. adapted this technique to measure both the CSA and pressure in the female urethra with the addition of a pressure transducer, a pump, and a thin inflatable polyurethane bag.²⁰ A digital

signal processor produces sound waves, which are transmitted into the bag before being reflected and recorded by a microphone to calculate the CSA. This technique, termed urethral pressure reflectometry, allows for the first time an assessment of the point of initial opening termed the "urethral opening pressure,"²⁰ which can discriminate between patients with stress urinary incontinence and healthy controls²¹ and assess the efficacy of drug therapy for urinary incontinence.^{22,23}

3.2 | Practical aspects

Mitchell et al. applied the technique to the anal canal and termed it anal acoustic reflectometry.²⁴ Current ARM probes use a fixed diameter catheter, which distort the anal canal beyond its physiological resting state thereby overestimating its CSA and pressure.²⁵ By contrast, AAR has the advantage of a polyurethane bag 70 mm in length with a collapsed CSA of just 0.4 mm², which is considered negligible. The bag can be inflated to a maximum diameter of 5 mm (CSA: 16 mm²) and pressure measurements taken between 10 and 200 cmH₂O (Figure 1). The AAR protocol has been refined in recent years with the development of the "fast-fill" technique. This uses a handheld syringe to inflate and deflate the bag in the anal canal and allows continuous measurements of the CSA without the noise generated by the pump interfering with the microphone.²⁶ During one AAR measurement, the bag is inflated over seven seconds and deflated over seven seconds. This is repeated ten times at rest and five times during voluntary squeeze.²⁶ Parameters are calculated from the mean of rest cycles two to ten and from all five squeeze cycles. The measurements obtained from the first cycle at rest are significantly higher than the subsequent nine cycles because of tissue preconditioning and are, therefore, excluded with the first cycle instead used to ensure the bag is unfolded correctly.^{27,28} With the addition of a rectal balloon, AAR has been shown to have the ability to measure the recto-anal inhibitory reflex expanding its utility in the assessment of the anorectum.²⁸

AAR obtains both CSA and pressure measurements during inflation and deflation of the bag allowing the identification of the point of minimum measurable CSA, which represents the high-pressure zone (HPZ) (Figure 2). Physiologically, this is the point of most resistance to opening, and identifying the pressure at which the bag starts to open is considered the pressure providing continence.²⁹ The minimal distortion of the anal canal allows, for the first time, an assessment of the point of initial opening termed the "opening pressure."²⁹ During a cycle of inflation and deflation of the bag, or opening and closing of the anal canal, several parameters are calculated at the HPZ during rest including the opening pressure (Op), opening elastance (Oe), closing pressure (Cp), closing elastance (Ce), and hysteresis (Hys). During voluntary squeeze two additional parameters are calculated including squeeze opening pressure (SqOp) and squeeze opening elastance (SqOe) (Figure 3, Table 1).

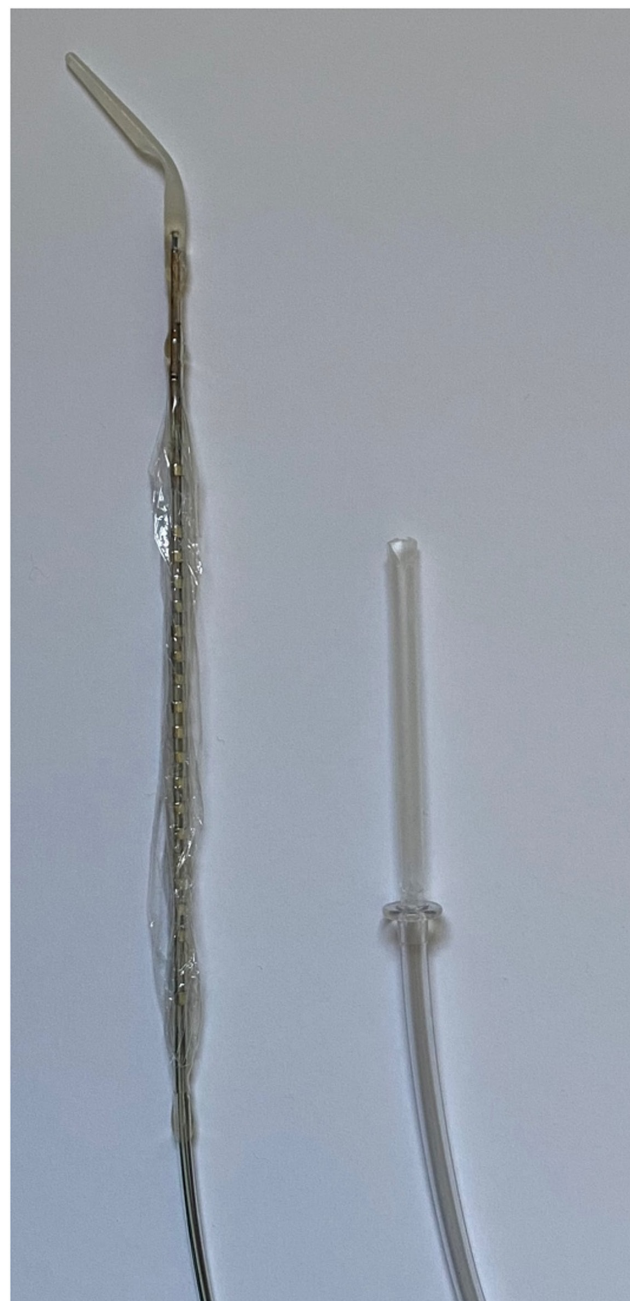


FIGURE 1 Anal acoustic reflectometry catheter (right) measuring 70 mm in length inflated to a maximum diameter of 5 mm (cross-sectional area 16 mm²). EndoFLIP® EF-325N catheter (left) consisting of a 12 cm highly compliant bag on the distal 14 cm of a catheter, 3 mm in diameter. The bag can reach a maximum diameter of 25 mm (cross-sectional area 490 mm²). There are 16 pairs of sensing electrodes calculating CSA at 5 mm intervals along 8 cm. The curved tip at the distal end is to allow nasal intubation (EF [EndoFLIP] - 3 [catheter diameter] 25 [bag diameter] N [nasal tip])

3.3 | Evidence base

AAR has been shown to be an easy to perform, reproducible tool with good repeatability to measure the physiological profile of the anal canal during distension.^{10,24} It offers a dynamic assessment

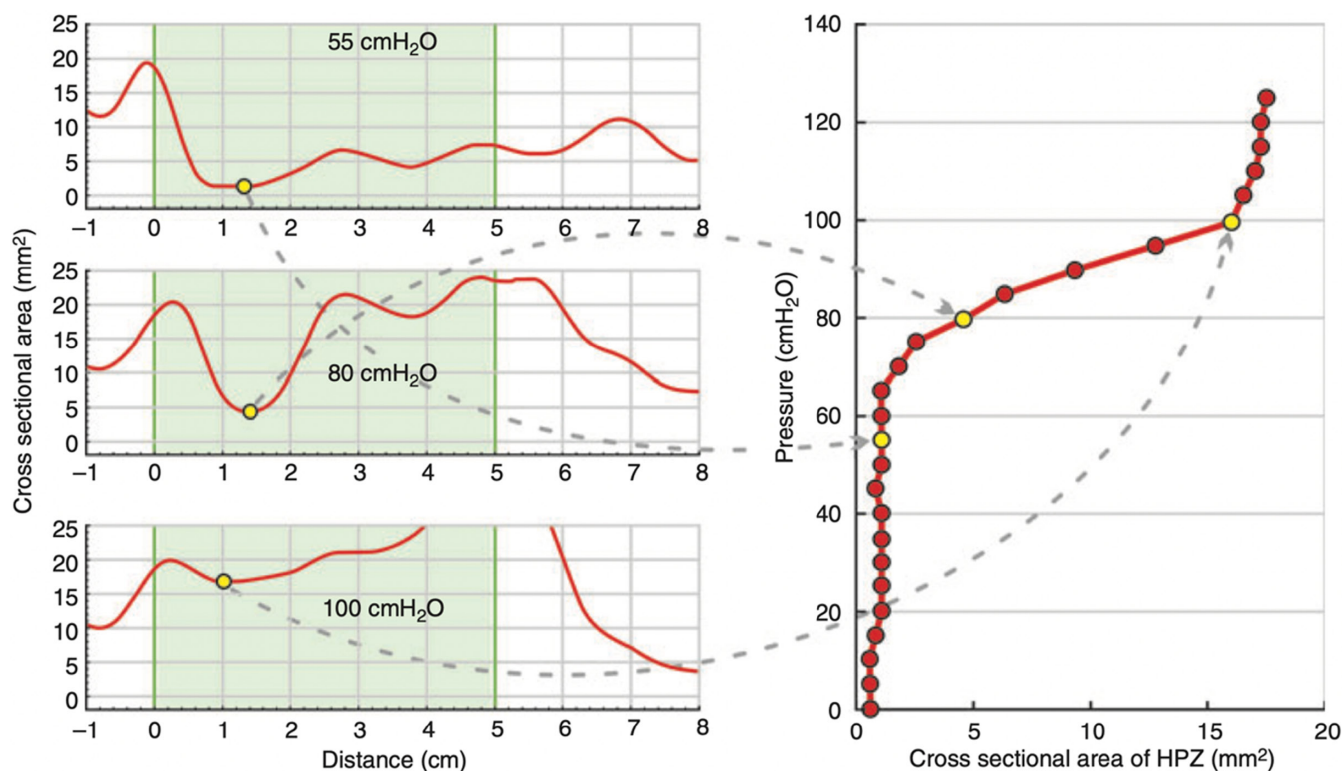


FIGURE 2 Minimum cross-sectional area values, representing the high-pressure zone, identified at 55, 80, and 100 cmH₂O used to plot a cross-sectional area/pressure curve during inflation of the bag at rest. The same process is repeated during deflation of the bag at rest, and during inflation of the bag during squeeze to calculate the anal acoustic reflectometry parameters. (Reproduced with permission from Mitchell et al.²⁴ © John Wiley & Sons Ltd Publishing License No 5380740440148)

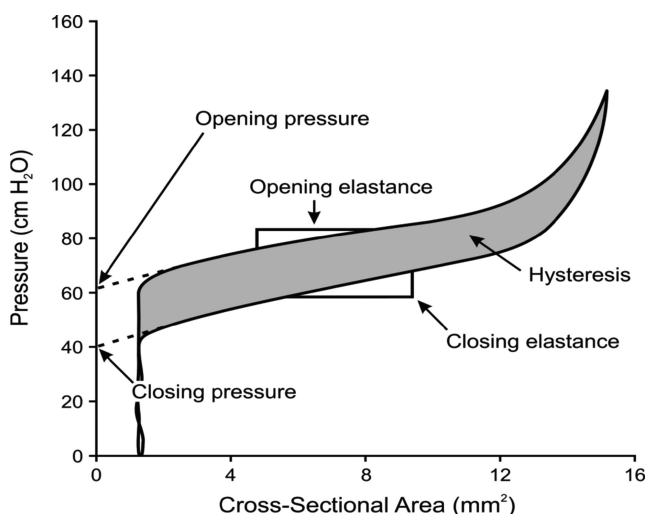


FIGURE 3 Graph of cross-sectional area and pressure at the high-pressure zone produced by one cycle of inflation and deflation of the polyurethane bag with anal acoustic reflectometry. The calculated physiological parameters are highlighted on the graph. (Reproduced with permission from Mitchell et al.¹⁰ © Wolters Kluwer Health, Inc. Publishing License No 5380741033645)

of the opening and closing function of the anal canal, representing conditions akin to defecation, whereas manometry records resting and squeeze pressures around a fixed diameter catheter. In a

study of 100 age and sex matched individuals, 50 continent and 50 incontinent, Mitchell et al. demonstrated AAR was superior to conventional manometry in distinguishing between continent and incontinent individuals, and that four of the resting AAR parameters, opening pressure (Op), closing pressure (Cp), closing elastance (Ce), Hysteresis (Hys), and both squeeze parameters were reduced in fecal incontinence (FI) (Table 1). In addition, when the patients were classified according to the FI subgroups of urge, passive or mixed, the same parameters were significantly different between the groups, a finding not replicated with manometry. In a further study of 81 continent subjects, squeeze opening pressure (SqOp) and squeeze opening elastance (SqOe) were significantly higher in males, likely representing the increased volume of the external anal sphincter (EAS),³⁰ whilst no difference was found in the resting AAR parameters between sexes. With advancing age, a significant negative correlation was found with Op and Cp.¹⁰

In a larger study of 100 incontinent females, Hornung et al. identified that, unlike conventional manometry, the AAR parameters of Op, Oe, Cp and SqOp correlated with symptom severity assessed with the Vaizey score. Furthermore, as with earlier work, AAR was able to distinguish between FI subgroups.³¹ Op was significantly reduced in patients with passive FI whilst SqOp was significantly reduced in the urge group. It was suggested that this is consistent with the understanding that urge incontinence is due to EAS dysfunction, and passive to internal anal sphincter (IAS) dysfunction.

TABLE 1 A summary of anal AAR measured at the high-pressure zone.

AAR parameter	Description
Opening Pressure (Op) cmH ₂ O	The pressure at which the anal canal just starts to open at rest. This functionally represents the ability of the anal canal to remain closed in response to an increasing pressure. It is considered to represent a measurement of all the closing forces generated by the tissues and structures surrounding the anal; however, it is mainly a measure of IAS function. ⁶⁹ In patients with fecal incontinence, Op is significantly reduced ²⁹ and has been shown to be an independent predictor of success for peripheral nerve evaluation in the treatment of FI. ³²
Opening Elastance (Oe) cmH ₂ O/mm ²	Is calculated from the gradient of the opening curve representing the resistance of the anal canal to dilatation after just starting to open. The lower the Oe the less resistant the anal canal is to further dilatation once the Op is reached. Oe is thought to represent resistance from the connective tissue of the anal canal and lengthening of the muscles. Mitchell et al. found no difference in Oe between continent and incontinent individuals suggesting that once the anal canal starts to open, after the Op is reached, further resistance to distension is no different between the two groups. ²⁹
Closing Pressure (Cp) cmH ₂ O	The pressure at which the anal canal just starts to close following an episode of dilatation. As with opening pressure, Cp is significantly reduced in patients with FI. ²⁹
Closing Elastance (Ce) cmH ₂ O/mm ²	Calculated from the gradient of the closing curve during deflation of the AAR polyurethane bag, Ce represents the ability of the anal canal to close during an assessment at rest.
Hysteresis (Hys) %	A measurement of the amount of energy dissipated during inflation and deflation of the polyurethane bag in the anal canal. Given each tissue type surrounding the anal canal has its own hysteresis, the overall measurement is the sum of the composition of these tissues, which includes muscle fibers and connective tissue. It is calculated from the difference between the area below the inflation and deflation curves and given as a percentage in relation to the inflation curve (Hysteresis, % = [Op at 10mm ² - Cp at 10mm ²]/Op at 10mm ² × 100). Hysteresis is significantly higher in patients with FI when compared to healthy controls. ²⁹ This is thought to be due to a higher proportion of collagen fibers, which have a higher hysteresis than muscle fibers, and is consistent with histological studies. ⁷⁰
Squeeze Opening Pressure (SqOp) cmH ₂ O	The pressure at which during squeeze the HPZ of the anal canal just starts to open. This represents the maximum closing force that a patient can generate and is thought to be a measure of EAS function. SqOp is significantly reduced in patients with FI ²⁹
Squeeze Opening Elastance (SqOp) cmH ₂ O/mm ²	Using the gradient of the opening curve generated during voluntary squeeze, just as during rest, the SqOe can be calculated. As with SqOp this is felt to be a measure of EAS function, but its clinical significance is unclear

In contrast to many other physiological tests, AAR has been shown to be able to predict the outcomes of interventions for FI. Sacral Nerve Stimulation (SNS), whilst an established treatment option for severe FI, is both expensive and invasive. In a study of 52 patients, conventional ARM and AAR were performed prior to a two-week trial period of percutaneous nerve evaluation (PNE). The trial of PNE was considered a success if the patient demonstrated a 70% reduction in weekly FI episodes or symptom severity assessed by Vaizey score. Hornung identified that an Op of greater than 18.4cmH₂O at AAR could predict the success of PNE with a sensitivity of 0.81 and specificity of 0.61.³² This is in contrast to many other physiological tests, including manometry, which have so far been unable to predict the outcome of this treatment.³³

3.4 | Utility

AAR has demonstrated its ability to provide valuable physiological data on the opening and closing function of the anal canal and has potential applications in the diagnosis and management of FI. It remains the only catheter-free technique to investigate the anal canal sphincter complex without distorting the canal at rest. Despite this, it has yet to find a role outside of the research setting. Only three AAR or UPR devices are in existence, studied in two university hospital research

units in England and Denmark, with no commercially available devices. Therefore, the findings from AAR studies whilst informative and encouraging, cannot yet be translated into routine clinical practice.

4 | FUNCTIONAL LUMEN IMAGING PROBE

4.1 | Development

The functional lumen imaging probe (FLIP) is a commercially available product marketed as the **Endolumenal Functional Lumen Imaging Probe**, EndoFLIP® (Medtronic®, MN, USA). The device uses impedance planimetry (IP) technology during volume-controlled distension of a highly compliant cylindrical bag to calculate CSA along the length of a biological sphincter. When used in the anal canal, in combination with a pressure measurement, it can assess the geometric and mechanical properties of the anal sphincter complex at rest and during squeeze. The development and commercialization of this device has led to a renewed interest in the concepts first described by Harris and Pope that resistance to distension is the primary determinant of sphincter competence.¹⁷ Unlike AAR, which is not yet commercially available, FLIP has the potential for widespread use as an investigation of anal sphincter competence.

Using electrical measurements to calculate CSA led to the term "impedance planimetry" first appearing in publications from 1991.³⁴ To calculate CSA, the bag surrounding the catheter is filled with a solution of known conductivity and a constant current is passed through it from an excitation electrode at each end. Between these excitation electrodes are several pairs of detection electrodes. Using Ohm's law the CSA is calculated at each detection electrode pair as it is inversely proportional to the voltage recorded across them, multiplied by a calibration constant.³⁴ A solid-state pressure transducer in the bag at its distal end is used in combination with the CSA measurements to generate a CSA-pressure profile of the sphincter. The diameters along the sphincter can be estimated from the CSA measurements by assuming the cross-section of the sphincter is circular, a finding confirmed in healthy volunteers.³⁵

Based on the principles first described by Harris & Pope,¹² the technology was developed as a tool to assess distensibility and to measure the mechanosensory and viscoelastic properties of a biological sphincter. The combined CSA and pressure data is commonly used to calculate the distensibility index (DI), defined as the minimum CSA divided by the pressure at a constant bag volume and reflects a simple to use assessment of distensibility at the point of greatest resistance to opening.^{36–39} The DI at the minimum CSA is displayed on the FLIP device along with the sphincter diameter, CSA, bag pressure, and compliance measurements, which are routinely reported in the literature to describe the distensibility of gastrointestinal tract with FLIP. These parameters have been used in physiological studies of the gastrointestinal tract, particularly in the assessment of the esophagus and the esophagogastric junction (EGJ) sphincter.¹⁷ EGJ compliance and distensibility has been shown to be of use in conditions such as achalasia and eosinophilic esophagitis, characterized by reduced distensibility, and gastroesophageal reflux disease where an abnormally distensible EGJ has been identified.⁴⁰ In a recent review for the American Gastroenterological Association, FLIP was highlighted as a complimentary tool to assess EGJ opening dynamics and esophageal wall stiffness, but more work was needed to standardize protocols and data analysis before widespread adoption.⁴¹

4.2 | Practical aspects

Several FLIP catheters are available, which were originally designed for EGJ distensibility measurements; however, the catheter used in the anal canal is the EF-325 device. It consists of a 12 cm highly compliant bag mounted on the distal 14 cm of a catheter, which is 3 mm in diameter (Figure 1). The bag can be inflated with 50 ml of conductive solution, to a maximum diameter of 25 mm (CSA: 490 mm²). There are 16 pairs of sensing electrodes calculating CSA at 5 mm intervals along an 8 cm length providing a detailed geometric profile of the anal sphincter.³⁷ The inflation and deflation of the bag can be manually controlled or pre-programmed offering bespoke bag volumes, filling rates and hold times. Data can then be recorded or downloaded for post-acquisition processing using specialized programs such as MATLAB™ subroutines to generate several measurable

parameters⁴¹ (Table 2). As a result, and in a similar fashion to manometry assessments, it is possible to create innumerable protocols and observed parameters, which makes direct comparison between institutions difficult.^{41,42}

There is no clear consensus on the protocols, observed parameters or normal ranges measured with FLIP limiting its widespread adoption into clinical practice at this stage. However, literature exists evaluating the resistance of the anal canal to distension in patients with FI^{38,39,43–46} and a limited number of healthy volunteers^{9,11,47} during rest and voluntary squeeze, and using different measured parameters (Table 2). FLIP has also been compared against HRAM to establish its clinical utility in the evaluation of FI,^{38,39,45} and used to observe the effects of neuromodulation,⁴⁸ biofeedback,⁴⁹ Naloxegol administration,⁵⁰ the STARR procedure,⁵¹ and neoadjuvant chemoradiotherapy treatment for rectal⁵² or anal cancer.⁵³ In all studies, the catheter was purged and calibrated at atmospheric pressure and the individual placed in the left lateral position with the lubricated catheter inserted into the anal canal such that only two detection electrodes were visible at the anal verge.

The two distension protocols commonly described in the literature are the "stepped"^{11,35,38,39,45,46,54} and "ramp"^{9,43,44,47,48,50,52,53} protocols (Figure 4). With the stepped protocol, the bag is inflated from 0 to 50 ml in increments of 10 ml. At each step there is a pause for approximately 30 s after which time the resting parameters are observed before the patient is asked to perform a voluntary squeeze. With the ramp distension protocol, the bag is inflated to 10 ml twice to unfold the bag, then to 20, 30, 40 and 50 ml, but between each volume the bag is deflated and reinflated. The same resting and squeeze parameters can be calculated at each bag volume but in addition, during inflation and deflation of the bag, the continuous opening and closing of the anal canal can be observed. This is not possible with a stepwise approach due to the non-uniform bag filling with 10 ml increments. By observing the opening and closing of the anal canal, the resistance to distension can be calculated using the opening and closing pressure and measures of elastance or compliance. In studies with EndoFLIP using the ramp distension models the opening pressure is typically referred to as the "yield pressure."^{48,52,53}

4.3 | Evidence base

Using the stepped protocol, FLIP has been compared with HRAM in the evaluation of FI. In a study of 40 healthy volunteers and 34 patients with FI, Gourcerol et al. identified a higher DI (indicating less resistance to opening) in the FI group at 30, 40 and 50 ml during rest and squeeze. A high DI at rest and during squeeze correlated with low resting and squeeze pressures with HRAM, respectively. In addition, at 40 ml, the DI at rest ($\geq 1 \text{ mm}^2/\text{mmHg}$) and during voluntary squeeze ($\geq 0.5 \text{ mm}^2/\text{mmHg}$) was better able to discriminate between normal and FI and had a more significant correlation with FI severity when compared to HRAM parameters.³⁸ However, the same authors in later work with an analysis of 83 FI patients using the same

TABLE 2 A summary of measured FLIP parameters.

FLIP parameter	Description
Cross-Sectional Area (CSA) mm ²	The cross-sectional area measured at 5 mm intervals over a length of 8 cm providing a total of 16 measurements.
Diameter (Dest) mm	The diameter calculated from the CSA measurements assuming the anal canal is circular.
Pressure mmHg	The pressure inside the bag recorded from the single solid-state pressure sensor at the distal end.
Bag Volume ml	The volume of conductive solution in the bag.
Distensibility Index (DI) mm ² /mmHg	A measure of the distensibility of the anal canal calculated as "minimum CSA / pressure" observed at rest or during voluntary squeeze. A high DI has been found in patients with FI and the DI at rest at 40ml bag volume has been found to better discriminate between FI and continent subjects. ³⁸
Compliance mm/mmHg	A measure of stiffness where the lower the compliance the greater the stiffness. It is the inverse measure of elastance and is calculated in the area immediately around the minimum CSA. In the proximal anal canal, where the sphincter complex is thicker the compliance is lower. ³⁵
Opening/Yield Pressure ^a mmHg	The pressure required to open the narrowest point of the anal canal. This pressure is lower in patients treated with neoadjuvant therapy for rectal ⁵² or anal ⁵³ cancer and higher following treatment with neuromodulation. ⁴⁸
Functional Anal Canal Sphincter Length ^a mm	Given CSA can be measured at 0.5 cm intervals along an 8 cm length it is possible to calculate the functional length of the anal canal sphincter complex at rest when the bag is inflated. It is also possible to calculate changes in sphincter length during squeeze and with increasing bag distensions although the clinical significance of this is unclear. ⁴⁷
Pressure-Strain Elastic Modulus (Ep) ^a kPa	A measure of stiffness of the anal canal and defined as the change in the anal canal diameter to the change in the bag pressure relative to a reference diameter. A low Ep in the middle and distal part of the anal canal has been found in patients with FI, but Ep as a parameter was not superior to standard anal manometry in discriminating between FI and continent subjects. ⁴⁴ A trend towards increased Ep after sacral nerve modulation has been observed but this was not statistically significant. ⁴⁸
Tension ^a N/m	Calculated according to Laplace's law ($T = P.r$) where P is the distension pressure recorded with FLIP and r is the measured radius. This has been used to display area-tension loop analysis of the anal sphincters with differences in the magnitude of the displacement of the loops, as the bag volume increases, in FI compared with healthy volunteers. ^{11,46}

^aDenotes parameter requires calculation in post-acquisition analysis.

discriminatory DI values at 40ml concluded the two modalities were largely in agreement in the diagnosis of FI. They suggest that FLIP should be considered complimentary to HRAM, as two patients had abnormal DI but normal HRAM results, and that further research is required to identify a role for FLIP in the diagnosis and management of FI.⁴⁵ No correlation could be identified in these studies between DI and age, BMI, parity, or menopausal status.^{38,45}

Brusa et al. used a bespoke MRI compatible FLIP catheter to obtain simultaneous stepped distension FLIP measurements with MRI images in healthy volunteers. They confirmed the least compliant portion of the anal canal was at the proximal end of the EAS, where it overlaps the IAS and puborectalis, highlighting this area's role in the maintenance of continence.³⁵ This area also demonstrated the maximal orifice closing function during voluntary squeeze, with the thickness of the EAS correlating with the change in orifice radius during contraction.⁵⁴

Using the stepped distension protocol in reverse, starting from the maximum volume, loop analyses with area-tension and area-pressure plots during voluntary squeeze have been used to describe external anal sphincter and puborectalis function in patients with FI compared to healthy volunteers. At each distension volume the patient was asked to perform a maximal voluntary squeeze

generating area-pressure and area-tension loops from resting to maximum squeeze, and back to resting. Authors reported significant differences in the shift of the loops to the right (increase in CSA) between FI and healthy controls. In addition, the shift of these loops correlated with the degree of muscle damage identified on endo-anal ultrasound, highlighting this as a useful tool for clinicians.^{11,46} The length-tension properties of a muscle described with these loop analyses have been proposed as a tool to describe dysfunction of the anal sphincter in patients with FI, advancing age, and anal sphincter injuries.⁵⁵⁻⁵⁷ They have also been used in experimental studies to describe changes in the function of the external anal sphincter.^{58,59}

With the use of a ramp distension protocol, it is possible to obtain data in addition to that obtained from a stepped protocol. It allows for an accurate assessment of the opening and closing of the anal canal and its resistance to distension, like AAR (Figure 5). First reported in 2012, this protocol has demonstrated a non-uniform opening pattern of the anal canal. During a ramp distension to 50ml Luft et al. observed the proximal anal canal opened first, shortly followed by the distal anal canal whilst the mid portion was last to open and, therefore, least compliant.⁹ This contrasts with Brusa et al. in their study with simultaneous MRI imaging and a bespoke FLIP catheter where

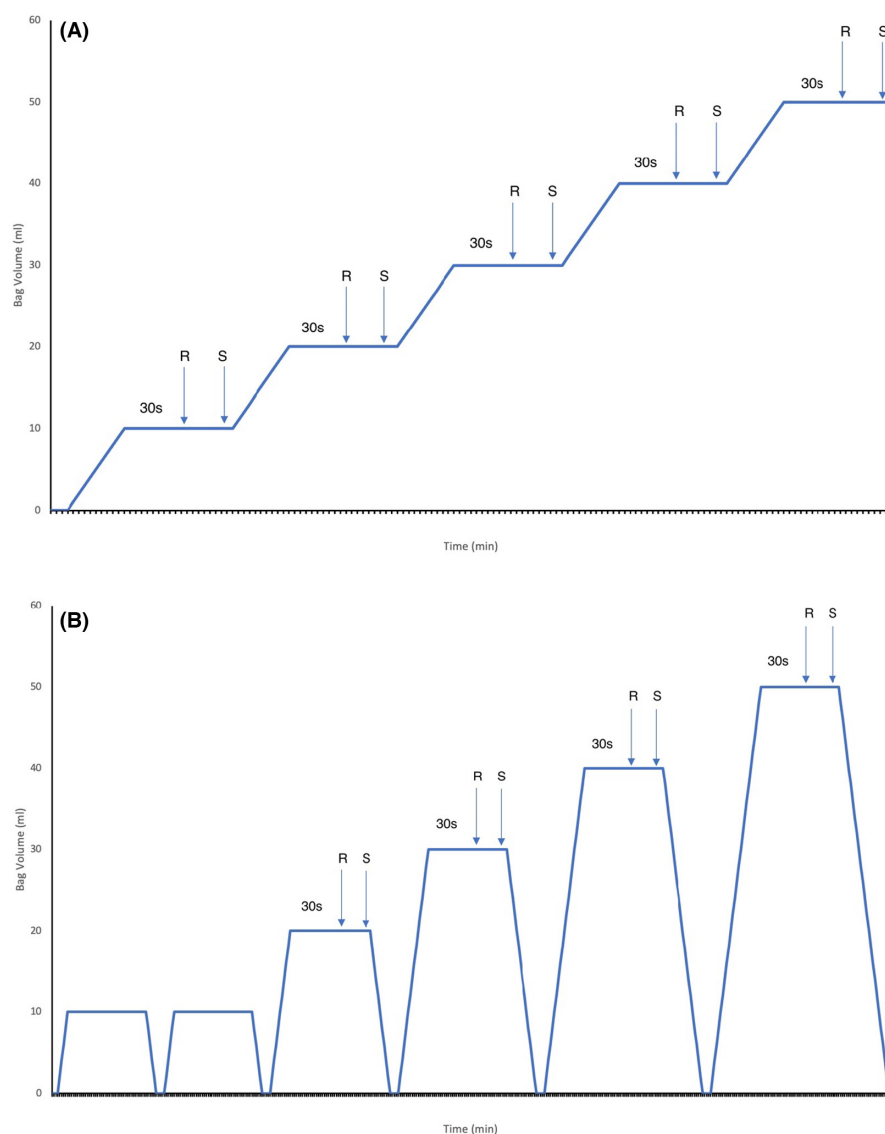


FIGURE 4 Two graphs demonstrating the two FLIP distension protocols (A: Stepwise, B: Ramp). At each inflation volume there is a 30sec resting period before resting parameters are measured (R) followed by squeeze parameters (S).

the proximal anal canal was least compliant, likely representing different interpretation of the data obtained without the aid of MRI imaging.⁵⁴ It is possible to calculate the yield pressure of the anal canal with the ramp distension protocol, defined as the point at which the narrowest CSA just starts to increase in size.⁴⁷ This was unexpectedly found to be higher in healthy females than in males⁴⁷ but reduced in patients treated with radiotherapy for anal cancer⁵³ or chemoradiotherapy for rectal cancer.⁵² Importantly, it was increased after a three-week period of SNS in a pilot study of 10 women.⁴⁸ This highlights that FLIP, measuring the resistance to distension, could offer a measurable parameter of clinical utility in the field of neuromodulation. As with the parameters Oe and Ce measured with AAR, the stiffness of the anal canal to opening has been calculated with FLIP using the “pressure-strain elastic modulus” (Ep) defined as the change in the anal canal diameter for a change in the bag pressure relative to a reference diameter.⁴⁴ In a study of 22 patients with FI and 21 healthy controls, Ep was higher and, therefore, the anal canal stiffer, in the healthy controls compared the patients with FI. Additionally, the Ep also varied along the length of the anal canal with the highest value

identified in the mid part of the anal canal. However, Ep was not superior to standard pull-through manometry in discriminating between FI and healthy volunteers and Ep was unchanged following SNS treatment and after chemoradiotherapy for rectal cancer.^{48,52}

These two protocols have never been compared directly to each other limiting the ability to compare results between these studies. With either protocol, however, FLIP provides a detailed geometric profile of the whole anal canal. This data can be used to estimate the functional length of the anal canal and identify the area last to open during distension from which the opening pressure can be calculated.⁶⁰ With increasing bag volumes, or during voluntary contraction, it is also possible to observe changes in this functional length.⁴⁷

4.4 | Utility

Regardless of the endpoint used, FLIP has demonstrated potential to deepen our understanding of the anorectal continence mechanism through volume-controlled distension. It offers additional benefits

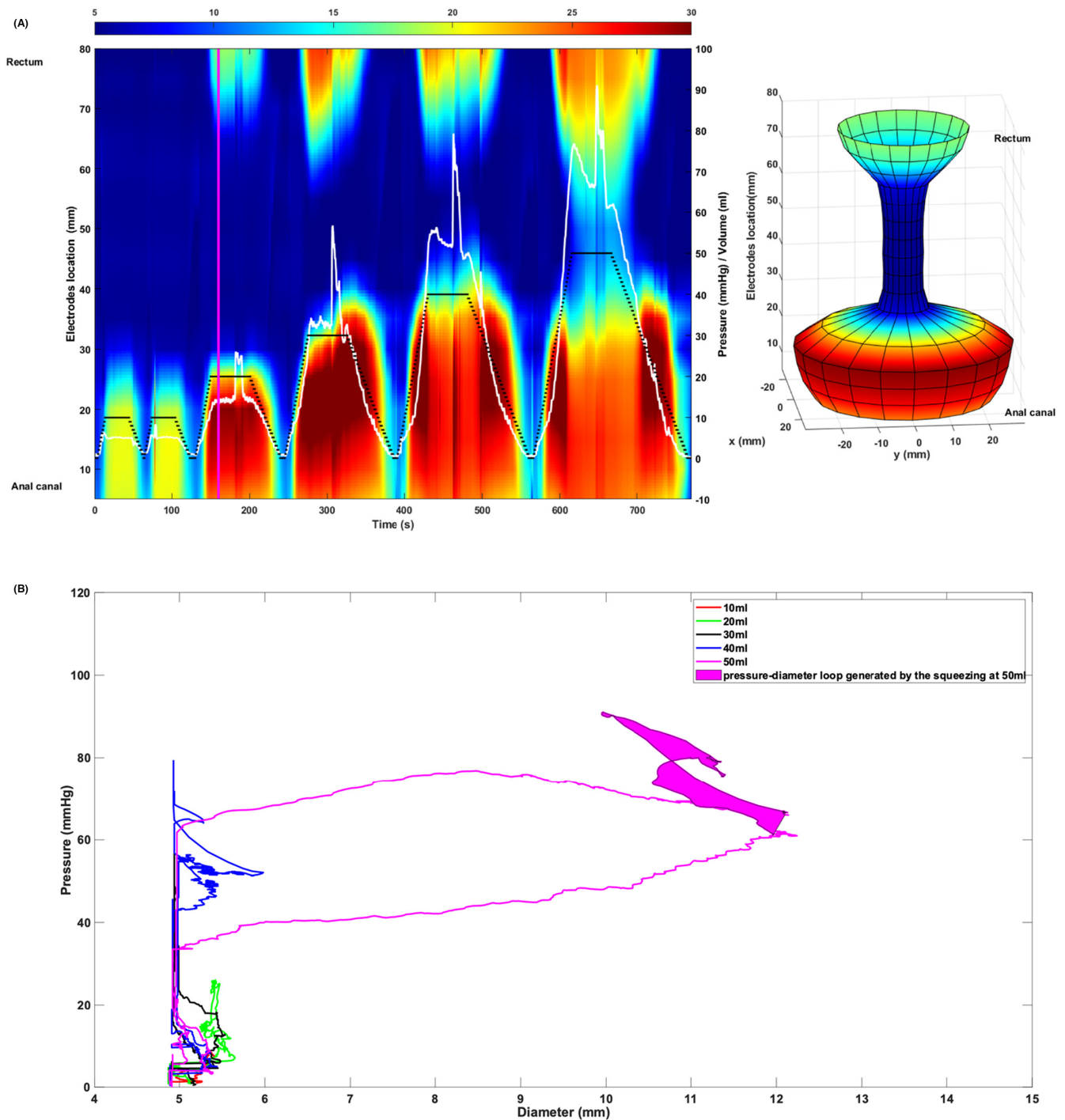


FIGURE 5 Representative spatiotemporal diameter map of the anal canal from a single subject measured with the “ramp” distension technique (A: left). The changing colors from blue to red indicate an increasing diameter. Each column represents the configuration of the anal canal at a particular time point, and each row the change in diameter over time, along the 8 cm measurable length of the FLIP catheter. The vertical axis on the right represents pressure in mmHg (white line) and bag volume (heavy black dotted line). 3D configuration of the anal canal at time = 160s (the vertical magenta line in right panel) is shown (A: right). Data obtained during an inflation, squeezing, and deflation cycle of the bag can be used to calculate the opening, closing, and squeezing function of the anal canal at each bag volume. In this subject the anal canal only yielded during inflation to 50 ml (B).

over AAR in its ability to characterize the opening and closing pattern of the whole anal sphincter complex. Whilst this could provide useful clinical information, the EndoFLIP catheter is 3 mm in diameter with a minimum measurable diameter of 5 mm once sufficient

conducting solution fills the bag. As a result, in common with other catheter-based measurements, the anal canal is open and distorted past its physiological resting state by a minimum of 5 mm before measurements are obtained, which may influence subsequent

measurements.⁶¹ Whilst this means the “true” opening pressure cannot be elucidated with FLIP, due to the nature of its catheter-based design, at present it is the only commercially available tool to assess the opening and closing of the anal canal gathering similar data to AAR.

5 | FUTURE CONSIDERATIONS

These emerging provocative tests of anal sphincter function have demonstrated potential to add to our understanding of the sphincter's role in the maintenance of continence. They not only provide information about the sphincter complex at rest and during voluntary squeeze, but also offer additional assessments of the mechanosensory and viscoelastic properties of the anal canal during volume-controlled distension. Both tools are also unique in their ability to measure the length-tension function of the anal sphincter muscles with measurements of pressure and geometry. Given FLIP is widely commercially available, it has been studied in several centers internationally leading to a variation in distension protocols and measured parameters reported.^{38,48} Due to this lack of standardization, there is a risk that as with manometry, it becomes impossible to compare results between institutions.⁶² This would limit the ability to generalize the findings and define a role for FLIP in the assessment of continence. Almost all authors report measurements obtained at increments of 10 ml distension up to 50 ml, but some deflate and reinflate the bag between each increment. Given measurements obtained during this dynamic assessment have provided clinically relevant results in studies with both AAR and FLIP, it would seem essential not to ignore the potential to collect these data.^{31,44} Directly comparing the stepped and ramp distension techniques could confirm if comparable results are obtained at each 10 ml volume increment between the two study protocols allowing comparison of the results between these studies. Additionally, comparing AAR with FLIP could be used to establish if findings from AAR studies are applicable to FLIP measurements.

In recent years, HRAM has become established as the investigation of choice to objectively assess anal sphincter function and rectal sensation and is used to understand pathophysiology and guide treatment. Given the multifactorial nature of these conditions, HRAM results in isolation may be insufficient and are often used in combination with other investigative tools.⁶³ The results of HRAM may not correlate with symptoms reported by patients and cannot always predict the success of interventions.^{64–67} For these new provocative tests of anal sphincter function to gain widespread use they must be compared against HRAM to establish their diagnostic accuracy and ability to influence management decisions for patients. FLIP has been compared against HRAM with results suggesting the tests are complimentary to each other in the evaluation of FI, but this study relied on the “stepwise” bag inflation protocol, which does not offer an assessment of the opening or closing function of the anal canal.³⁹ Using the dynamic parameters of opening and closing pressure and elastance, AAR has shown an improved diagnostic

ability, better correlation with symptom severity and the ability to distinguish between the FI subtypes of urge, passive, and mixed when compared to standard manometry.³¹ In predicting the success of neuromodulation for FI, the opening pressure measured with AAR was identified as an independent predictor with a sensitivity of 0.81 and specificity of 0.60. This should prompt exploration of a similar finding using the commercially available equipment to further define its role in the management of FI. A pilot study has already identified that the opening pressure measured with FLIP is increased after 3 weeks of neuromodulation, making this an interesting target for future research.⁴⁸ Further work with FLIP is clearly required to appreciate its role amongst the other available, and more established, anorectal investigations.

Finally, it is pertinent to consider the catheter design and how it may affect the measurement of the anorectum. The FLIP catheter used in the anal canal is the EF-325 device, which was designed for measurements of the upper gastrointestinal tract.³⁷ Given only two detection electrodes are visible outside the anal verge, up to 9.5 cm of the catheter and bag will lie in the anal canal and lower rectum. It has yet to be established if this has the potential to induce the recto-anal inhibitory reflex when filling, or how it may affect measurements in patients with rectal sensory dysfunction. Indeed, with the absence of a dedicated rectal balloon, determining if rectal sensory dysfunction is contributing to disordered continence is not possible with FLIP.⁶⁸ Another limitation of the device is in the single pressure sensor. When the bag is divided into two compartments by a tight sphincter the pressure will only be measured in the distal compartment.⁶⁰ It may, therefore, be advantageous to establish if the length of the bag has an impact on the measurements of the anal sphincter, or to develop a catheter dedicated to anorectal testing with a rectal balloon and two pressure sensors.

6 | CONCLUSION

Provocative tests of anal sphincter function have the potential to find a role in the assessment and management of FI. Work with AAR and FLIP has demonstrated the importance of measuring parameters during volume-controlled distension as the anal canal opens and closes. The promising development of AAR both in this field and in the urinary tract has been limited by the lack of commercial investment. Future work should aim to standardize the measurement protocol with FLIP and compare the results to those of the current investigation of choice, HRAM. Finally, a dedicated anorectal FLIP catheter could offer further utility with the assessment of rectal sensory parameters.

AUTHOR CONTRIBUTIONS

Alexander O'Connor and Caroline M. Byrne identified and summarized the literature. Alexander O'Connor, Caroline M. Byrne, Dipesh H. Vasant, Abhiram Sharma, and Edward S. Kiff wrote the manuscript. Donghua Liao created Figure 5 and assisted in writing the functional lumen imaging probe aspects of the paper. Niels Klarskov

assisted in writing the anal acoustic reflectometry aspects of the paper. Karen Telford supervised the preparation of the paper. All authors edited and approved the final version of the manuscript.

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