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MR-FLIP: A new method that combines FLIP with anatomical information for the spatial compliance assessment of the anal sphincter muscles

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EF, LB, RT, and TB designed the study. JH developed the MR sequences and TB recruited the volunteers. CG, DA, LB, RT, and TB performed the research. DA, LB, PB, PS, RT, and TB analyzed the data. DA and TB performed the statistical analysis and wrote the paper. JH, LB, PB, and PS participated in drafting the final version.

Conflicts of Interest

The authors declare no competing interest related to this study.

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Abstract

Introduction Continence results from a complex interplay between anal canal (AC) muscles and sensory-motor feedback mechanisms. The AC's passive ability to withstand opening pressure – its compliance – has recently been shown to correlate with continence. Functional lumen imaging probe (FLIP) is used to assess AC compliance, although it provides no anatomical information. Therefore, compliance assessment of specific anatomical structures has not been possible, and the anatomical position of critical functional zones remains unknown. In addition, FLIP assumes a circular orifice cross-section, which has not been shown for the AC. To address those shortcomings, a technique combining FLIP with a medical imaging modality is needed.

Method We implemented a new research method (MR-FLIP) that combines FLIP with MR-imaging. Twenty healthy volunteers underwent MR-FLIP and conventional FLIP assessment. MR-FLIP was validated by comparison with FLIP results. Anatomical markers were identified, and the cross-sectional shape of the orifice was investigated.

Results MR-FLIP provides compliance measurements identical to those obtained by conventional FLIP. Anatomical analysis revealed that the least compliant AC zone was located at the proximal end of the external anal sphincter. The AC cross-sectional shape was found to deviate only slightly from circularity in healthy volunteers.

Conclusion The proposed method was equivalent to classical FLIP. It establishes for the first time a direct mapping between local tissue compliance and anatomical structure, which is key for gaining novel insights into (in)continence. In addition, MR-FLIP provides a tool for better understanding conventional FLIP measurements in the AC by quantifying its limitations and assumptions.

What does this paper add to the literature?

This paper proposes a new method for direct mapping local tissue compliance in the anal canal to the precise anatomical location of the measurement in vivo. The correlation of anatomy and biomechanical tissue properties is key to understanding the causes of incontinence and improving the diagnostic methods used for its timely detection.

Introduction

Mechanically, the internal anal sphincter (IAS) and external anal sphincter (EAS) muscles are, together with the puborectalis muscle (PRM) and the hemorrhoidal cushion (HC) (Fig. 1), responsible for maintaining anal continence. Their dysfunction, or deficiencies in the sensory-motor feedback loops, might result in fecal incontinence (FI). In addition, stool consistency and rectal compliance influence the development of FI. The prevalence of FI is estimated to be between 11 % and 15 % in the adult population (1). This prevalence increases with age such that approximately one-third of the population in retirement homes is affected. However, due to underreporting, the prevalence is likely to be even higher (2). FI has a considerable economic impact (2) and severe consequences on the quality of life of the persons affected. Its social stigmatization (1) leads to exclusion and isolation.

The exact mechanisms leading to incontinence are not fully understood (2). ‘Passive incontinence’ refers to the unconscious loss of feces during rest. It is likely caused by malfunction of the smooth IAS muscle, which is responsible for 70-85 % of the anal canal (AC)’s closing pressure during rest (3). ‘Urge incontinence’ corresponds to the inability to defer defecation when feeling the urge and is associated with EAS weakness. Therefore, quantifying the competence of these muscles is important for diagnosis and treatment. Currently, anal manometry is the modality of choice in clinical practice to assess local pressures along the AC during rest and those resulting from voluntary EAS contraction. Nevertheless, no strong correlation has been found between these manometric measurements and the clinical manifestation of incontinence (4). It has been suggested that the ability of sphincter muscles to withstand distension is more important for continence than their contraction capabilities (5,6). Compliance, which describes the AC’s elasticity, is a promising parameter for predicting sphincter performance (7).

The functional lumen imaging probe (FLIP) has been proposed to measure the AC’s compliance by using an inflatable cylindrical balloon (8). In initial clinical studies (7,9–12), significantly higher compliance was found in patients suffering from FI compared to healthy volunteers (7,10). In addition, the spatial positioning of compliance features relative to the AC anatomy has been attempted. It has been proposed that the mid-AC is the least compliant segment, followed by the more distensible distal and proximal AC segments (9–11). However, this subdivision into three segments and their locations relative to the AC were not based on the specific anatomy of the patient because FLIP does not provide anatomical information. Another assumption underlying the FLIP measurements concerns the shape of the balloon during inflation. FLIP was predominantly used to assess the esophagus and has only recently been adopted for AC compliance measurements. The lower esophageal sphincter is thought to be circular, and FLIP operates on the assumption of a circular orifice cross-section. However, the validity of this assumption in the AC has not been tested.

The lack of direct anatomical information is a major shortcoming of the FLIP technique and prohibits the investigation of the biomechanical properties of specific AC structures. Consequently, the role of AC compliance in explaining continence is poorly reported, and the position of the lowest compliance along the AC is unknown. This paper proposes a new methodology (MR-FLIP), which combines classical FLIP with MR-imaging, to overcome this shortcoming and investigate the limitations and assumptions of conventional FLIP.

Methods

In a clinical study on senior healthy volunteers, which is the age group most affected by incontinence, a new research method (MR-FLIP) – combining FLIP with MR-imaging – was tested. First, MR-FLIP's ability to reproduce conventional FLIP measurements was verified. Then, the cross-sectional shape of the anal canal was investigated, and the anatomic location of the least compliant AC region was identified.

Clinical Study

A prospective, single-center, observational cross-sectional study was conducted. Exclusion criteria were age < 60 years, incontinence with a Wexner Score (13) > 0, constipation with a Longo's obstructed defecation syndrome (ODS) score > 0 (14), Body Mass Index (BMI) < 20 or > 30, history of diseases in the pelvic floor or anal region, and premenopausal state. The study was approved by the local ethical committee (KEK-BE: 048/14) and complied with the ethical principles defined in the Declaration of Helsinki II. It has been registered at ClincialTrials.gov (NCT02263170) and was carried out in the University Clinic for Visceral Surgery and Medicine at the University Hospital Bern (Switzerland).

Measurement Protocol

All volunteers were assessed with FLIP and MR-FLIP. Both measurement series followed a step-distension protocol comparable to those used in earlier studies (7,9–12). First, the balloon was inflated once to 50 ml to ensure proper unfolding during the examination. Then, the probe was inserted gently into the AC and manually held in position. The balloon was inflated in 10-ml steps from 0 ml to 50 ml. Measurements were recorded at a constant volume between inflation steps. Patients were examined in the left lateral position (FLIP) and in the supine position with slight flexion in the hip and knee joints (MR-FLIP). The compliance of the tissue along the AC was assessed by inflating a water-filled balloon to multiple predefined volumes while measuring the intra-luminal pressure and AC cross-section.

FLIP measurements were acquired using an EndoFLIP® catheter EF-325N (Crospon Ltd, Galway, UK). The cross-sectional information (diameter) was extracted for 16 segments over a length of 80 mm (5 mm – 25 mm, ±1 mm), and intra-luminal pressure was measured directly in the catheter (0 mmHG - 150 mmHG, ± 1 mmHG). The catheter was composed of a 3-mm-diameter polyethylene tube on which a 120-mm-long inflatable non-compliant balloon was mounted. The pressure in the balloon and the balloon's diameter were constantly monitored and recorded.

MR-FLIP measurements relied on a custom-made MR-compatible version of the EndoFLIP® catheter EF-325N (Crospon Ltd, Galway, UK). The probe does not contain any integrated sensors for balloon diameter or pressure measurement. Instead, AC cross-sectional information was derived from MR images, and pressure was recorded outside the MR room using a Fluke 700GA4 (Fluke, Everett, USA) pressure sensor (tubing: 10 m long, inner diameter: 3 mm, outer diameter: 5 mm, stiffness: 75 ±5 Shore A). At each balloon volume, the pressure values were recorded, and a transverse T2-weighted MR image (TE=104 ms/TR=4170 ms) was acquired using a 3 Tesla Siemens Skyra system (Siemens, Erlangen, Germany). The MR images had a pixel size of 0.52 mm x 0.52 mm and an inter-slice distance of 3.3 mm, resulting in a total field of view of 180 mm x 180 mm x 95 mm (width x depth x height). The acquisition time was 5 min per image.

Data Acquisition and Analysis

To exclude transient viscoelastic effects in the pressure and diameter measurements, we allowed for muscle relaxation after each inflation step. Therefore, in both modalities, all computations were based on measurements taken at least 15 seconds after reaching the volume plateau (15).

The EndoFLIP system directly provides pressure and balloon diameter, but additional steps are needed to obtain these parameters for MR-FLIP. Cross-sectional information of the AC was obtained from the MR images. First, the FLIP balloon was segmented (Fig 1, A-D, hyper-intense). To prevent the distortion of the AC anatomy during image analysis, a cut perpendicular to the centerline of the segmented balloon represented the AC cross-section.

The cross sectional area (CSA) was computed from the orifice opening at 100 positions along the AC. Additionally, the circularity of the AC's cross-section was evaluated at each position by fitting an ellipse to the cross-sectional boundary. This analysis was carried out for all balloon volumes, always using the centerline obtained from the patient's 50-ml MR image.

Information about AC anatomy was also extracted from 50 ml MR images. The proximal end of the EAS was defined as the transition between EAS and PRM, as indicated by the ventral opening of the EAS (Fig. 1, A). The distal end of the EAS was defined as the position where at least one-third of the AC is surrounded by muscle tissue (Fig. 1, C). These anatomical positions (Fig. 1, A and C) were identified independently by five observers for each volunteer.

To validate the MR-FLIP technique, the pressure, CSA, and compliance were compared with the measurements obtained by the regular FLIP system. For pressure comparison, the zero-pressure offset of MR-FLIP measurements was adjusted to match the value of the respective FLIP measurements at 10 ml. The CSA and compliance were compared at the position of the minimum orifice opening, which represented the least compliant portion of the AC. Only orifice openings exceeding the measurement threshold diameter of 6 mm were included. Compliance was computed for each subject as the slope of a linear regression of orifice diameter as a function of intra-luminal pressure at multiple balloon volumes.

In addition, CSA was compared along the whole catheter. A two-step process was applied for aligning the opening profiles obtained by both techniques (Fig. 2). First, FLIP and MR-FLIP orifice opening measures were superimposed at the position of their minimum radii. Then, this initial alignment was optimized by minimizing the sum of the root mean square distances between the 16 FLIP and the corresponding MR-FLIP radii. The residual of the optimization function was used to quantify the overall comparability of the opening profiles.

The circularity of the AC cross-section was assessed over the length of the EAS in planes perpendicular to the AC centerline. An ellipse was fitted to each cross-section, and the ratio of minor to major half-axes was used to quantify circularity. A value equal to unity corresponds to a perfect circular shape, whereas values < 1 indicate deviation from circularity. Only positions where the estimated diameter exceeded 6 mm were considered.

Statistics

Data are presented as the mean ± standard deviation. Measurements were compared with paired t-tests when normally distributed. The Wilcoxon signed rank-sum test was used to compare non-normally distributed variables. P values were two-sided, and p = 0.05 was considered the threshold for statistical significance. Inter-observer reliability in identifying anatomical structures was assessed using the intra-class correlation coefficient (16).

Results

Twenty healthy Caucasian volunteers – 10 women and 10 men – were included in the study (Fig. 3). The volunteers had a mean age of 70 years (range: 63-85 years) and a mean BMI of 23.5 (range: 20.1-28.0). On average, women had 1.8 deliveries (range: 1-3).

Validation of the MR-FLIP Method

The pressure, CSA and compliance measured using FLIP and MR-FLIP were compared for each volunteer. No statistically significant differences were found between the FLIP and MR-FLIP pressure measurements (Fig. 4, A) (n=19; 10 ml: p=1.00; 20 ml: p=0.37; 30 ml: p=0.24; 40 ml: p=0.71; 50 ml: p=0.64). A detailed analysis of CSA and compliance was performed at the position of the narrowest AC opening (Fig. 4, B). For balloon volumes below 30 ml, the canal opening was insufficient for measuring CSA. In a few volunteers, CSA was measurable at a 30-ml balloon volume, but for most volunteers, CSA could be assessed at higher balloon volumes (40 ml and 50 ml) (Fig. 3). Statistical evaluation revealed no significant differences between FLIP and MR-FLIP (40 ml: p=0.54, n=13; 50 ml: p=0.68, n=15).

Compliance was calculated for both modalities for volumes ≥ 30 ml, which provided sufficient AC opening (Fig. 4, C), i.e., an opening above the defined thresholds of 5.5 mm for the FLIP and 6 mm for the MR-FLIP. No significant difference was observed between modalities (p=0.97, n=12).

In addition, the AC orifice radii were compared over the entire probe length. Registration between both modalities relies on the AC distension profile, which is directly dependent on the balloon's volume (Fig. 2). The quality of the alignment was good for catheter volumes larger than 30 ml. The average error per electrode was comparable to the manufacturer-reported FLIP accuracy of 1 mm (30 ml: 1.2±0.6 mm, 40 ml: 0.8±0.6 mm, 50 ml: 0.9±0.5 mm).

MR-based Identification of AC Anatomy

MR images (50 ml) were analyzed to determine the proximal and distal ends of the EAS (Fig. 1, marker A and C) and the numerical uncertainty associated with the identified positions. Although the difference was not significant (p=0.14), the average EAS length was found to be shorter in women (24±4 mm) than in men (29±4 mm). Rater consistency was higher for men (ICC35=0.92, 95% CI: 0.75-0.99) than for women (ICC35=0.84, 95% CI: 0.52-0.97). This was also reflected in the pooled standard deviations across independent ratings and volunteers for these positions; the distal end of the EAS was determined with an uncertainty of ±1 mm in women and ±3 mm in men. For the proximal end of the EAS, these uncertainties were ±5 mm and ±3 mm, respectively.

A higher degree of balloon inflation increased the average circularity scores along the EAS (minor to major half-axes at 30 ml: 0.71±0.10, 40 ml: 0.77±0.08, 50 ml: 0.83±0.10). At the least compliant position of the EAS, the cross-section was smaller on average, and a significant increase in circularity was observed between 40 ml and 50 ml FLIP volume (minor to major half-axes at 30 ml: 0.75±0.19, 40 ml: 0.73±0.15, 50 ml: 0.83±0.07).

Additionally, the position of the proximal end of the EAS was compared to the position of narrowest AC opening. The results indicate that the narrowest opening (Fig. 2, dotted line) was, on average, located a few millimeters below the proximal end of the EAS muscle (Fig. 2, dashed line).

Discussion and Conclusion

In this study, we validated MR-FLIP as a new method for estimating the compliance of specific anatomical structures in the AC. The results showed that the proposed method provides the same mechanical information as a commercial FLIP system. Moreover, the measurements obtained from both MR-FLIP and FLIP at the least compliant location of the AC were comparable to the literature (10). Small differences from the literature might be explained by the higher age of our cohort (7).

The imaging information collected during MR-FLIP enables the identification of anatomical structures that are responsible for continence in women and men for the first time. Luft et al. attributes the least compliant position to the mid-AC, where EAS and IAS overlap (11). Using our approach, we identified this position to be at the transition from the mid to upper AC, where the EAS starts to overlap the IAS and PRM. Although there is no agreement on the exact muscle anatomy in the EAS/PRM transition region (17, 18) – also due to the high anatomical variation between individuals (17) – our finding indicates that the presence of pelvic floor muscles contributes to the reduced tissue compliance.

Additionally, MR-FLIP allows the quantification of the cross-sectional shape of the AC orifice. In our cohort, the cross-sectional shape along the EAS was well approximated by ellipses, with an average ratio of minor to major half-axis of approximately 3/4. This means that the opening cross-section is not strictly circular, as assumed by FLIP. Despite this non-circularity, the agreement between FLIP and MR-FLIP measurements indicates the correct CSA assessment by FLIP in healthy volunteers. Further studies should investigate the AC shape and its influence on conventional FLIP results in FI patients. We expect MR-FLIP to play an important role in such studies because it allows the detection of asymmetries in AC shape and muscle compliance, which may be present in patients.

To ensure reliable measurements, we assumed conservative thresholds in this study: for FLIP, a measurement threshold of 5.5 mm diameter was applied to reduce measurement fluctuations still present at the manufacturer-reported threshold of 5 mm. For MR-FLIP, a measurement threshold of 6 mm diameter was applied. Below this opening diameter, the balloon shapes were found to be very irregular and thus difficult to segment consistently.

Due to these limits, only small changes in CSA could be observed at the least compliant position for volumes below 30 ml. Balloons with larger opening capabilities would allow more precise measurements in low compliance regions and would reflect the AC behavior during defecation more accurately.

The study also revealed that the compliance measurement is not affected by the positioning of the patient. Both FLIP and MR-FLIP provided the same mechanical information, although FLIP was performed in the lateral position and MR-FLIP was acquired in the supine position.

Although a tendency towards higher compliance in women can be observed, no significant differences between genders could be determined. A reliable evaluation of gender differences in compliance was not possible due to the low number of suitable datasets from male volunteers (3). However, it would be of particular interest to determine whether gender differences influence the compliance or the anatomical position of the lowest compliance along the AC.

The precision of the anatomical analysis associated with the MR-FLIP method depends on the MR image quality. In this study, transverse MR images were acquired with a small in-plane pixel size and a relatively large inter-slice distance. This protocol proved sufficient data to investigate the EAS. It could be easily adapted to fulfill other requirements concerning the identification of further anatomical structures. Sagittal and coronal images could be included to improve the identification of sphincter muscles along the AC. The MR protocol is limited by the acquisition time and potential motion artifacts. For this reason, MR-FLIP is restricted to step-distention protocols for the assessment of passive (in)continence. The imaging speed of the MRI is not sufficient to track the three-dimensional opening of the AC during dynamic procedures for investigating urge (in)continence such as ramp distention or squeeze maneuvers. Three-dimensional ultrasound (3D US) could potentially track such events while providing anatomical information. Using transvaginal US assessment, Jung et al. (19) found that the least compliant zone is where the IAS, EAS, and PRM overlap. While transvaginal US is restricted to women, trans-perineal volumetric US has been shown to allow for length and surface measurements (20) and has the advantage of being applicable to men and women. Mounting the FLIP balloon directly on a 3D US probe might be an option in the future, but it would require further miniaturization of the US probe.

The clinical study was performed on healthy volunteers whose AC orifice was expected to be regular and approximately circular. This controlled configuration was well suited for the validation study. The collected data provide baseline information for a healthy cohort that matches the typical age of the population that is most affected by FI. A similar study on FI patients could reveal potential differences in the position of the least compliant zone and AC circularity compared to the healthy population. It could also confirm whether the minimum

AC compliance correlates with clinical symptoms of incontinence.

The proposed MR-based method is costly and therefore unlikely to replace classical FLIP. Instead, MR-FLIP is aimed at research applications, with the primary goal of transferring the insights gained from MR-FLIP studies to classical FLIP.

In conclusion, this study is the first to propose and validate a method for assigning FLIP-based mechanical properties to specific AC anatomical structures. The application of this technique to healthy volunteers revealed the least compliant section to be located at the level of the HC, where the EAS starts overlapping with the IAS and PRM. This finding suggests that the superior segment of the AC is responsible for the mechanics of passive (in)continence. In this context, the innovative technique presented here could provide the basis for identifying mechanical markers for early FI diagnosis and thus support clinical decision making.

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Figure 1: Sagittal sketch of the continence organ with FLIP catheter and corresponding MR-images in transversal plane. The anatomical overview of the continence organ (left) shows the external anal sphincter (EAS), the internal anal sphincter (IAS), the puborectalis muscle (PRM), the hemorrhoidal cushion (HC), and the filled FLIP catheter. MR images A-D (right) show the FLIP catheter (hyper-intense, center), EAS and IAS muscles (hypo-intense), fatty tissue (semi hyper-intense) and the HC (A and B, semi hypo-intense, between FLIP balloon and EAS) at different heights of the anal canal (AC). Boundaries of the EAS muscle are indicated by dashed white lines. Marker (B) depicts the position where the FLIP cross-sectional area (CSA) is minimal, and (D) is located at the height of the anal verge where the FLIP catheter is almost completely surrounded by the fat body of the ischioanal fossa.

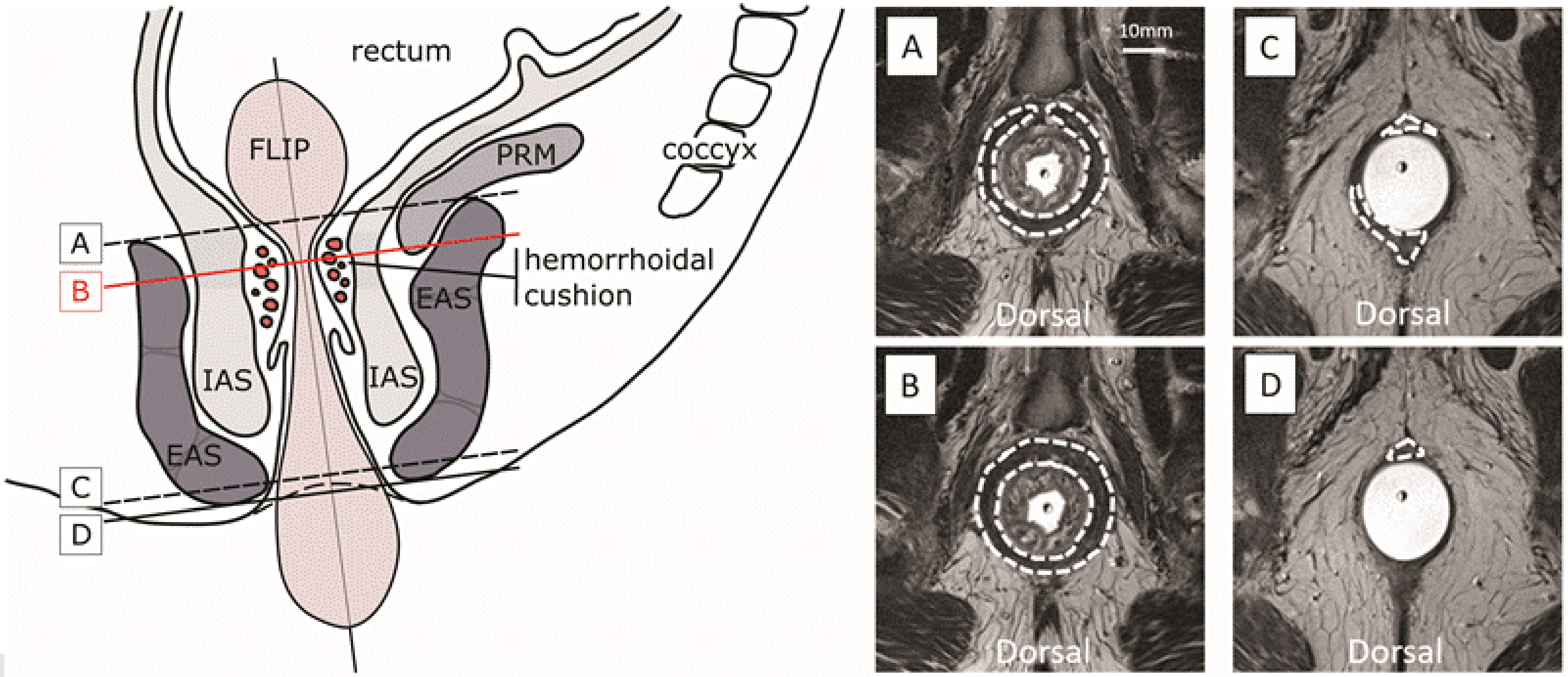


Figure 2: Radius profiles of inflated FLIP and MR-FLIP. Radius of FLIP balloon assuming circular cross-section, shown from caudal (15 mm) to cranial (75 mm) end of AC for FLIP (stars) and MR-FLIP measurement (solid lines). Measurements are reported for catheter volumes of 30 ml (black), 40 ml (red) and 50 ml (blue). Anatomical information - EAS proximal (A, dashed line), narrowest AC opening (B, dotted line), and EAS distal (C, dashed line) - is obtained from MR-imaging at 50 ml balloon volume.

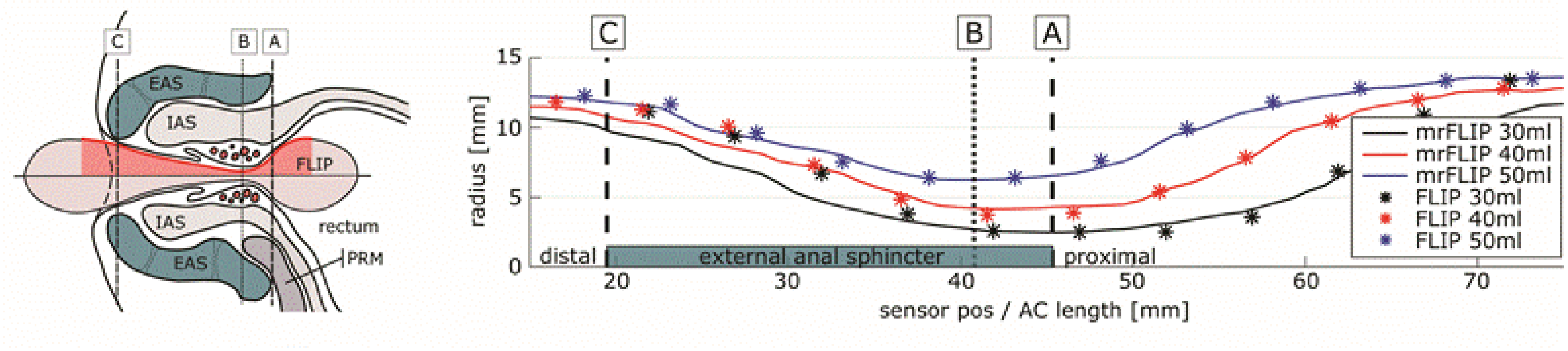


Figure 3: CONSORT flow diagram of healthy volunteer recruitment and study analysis.

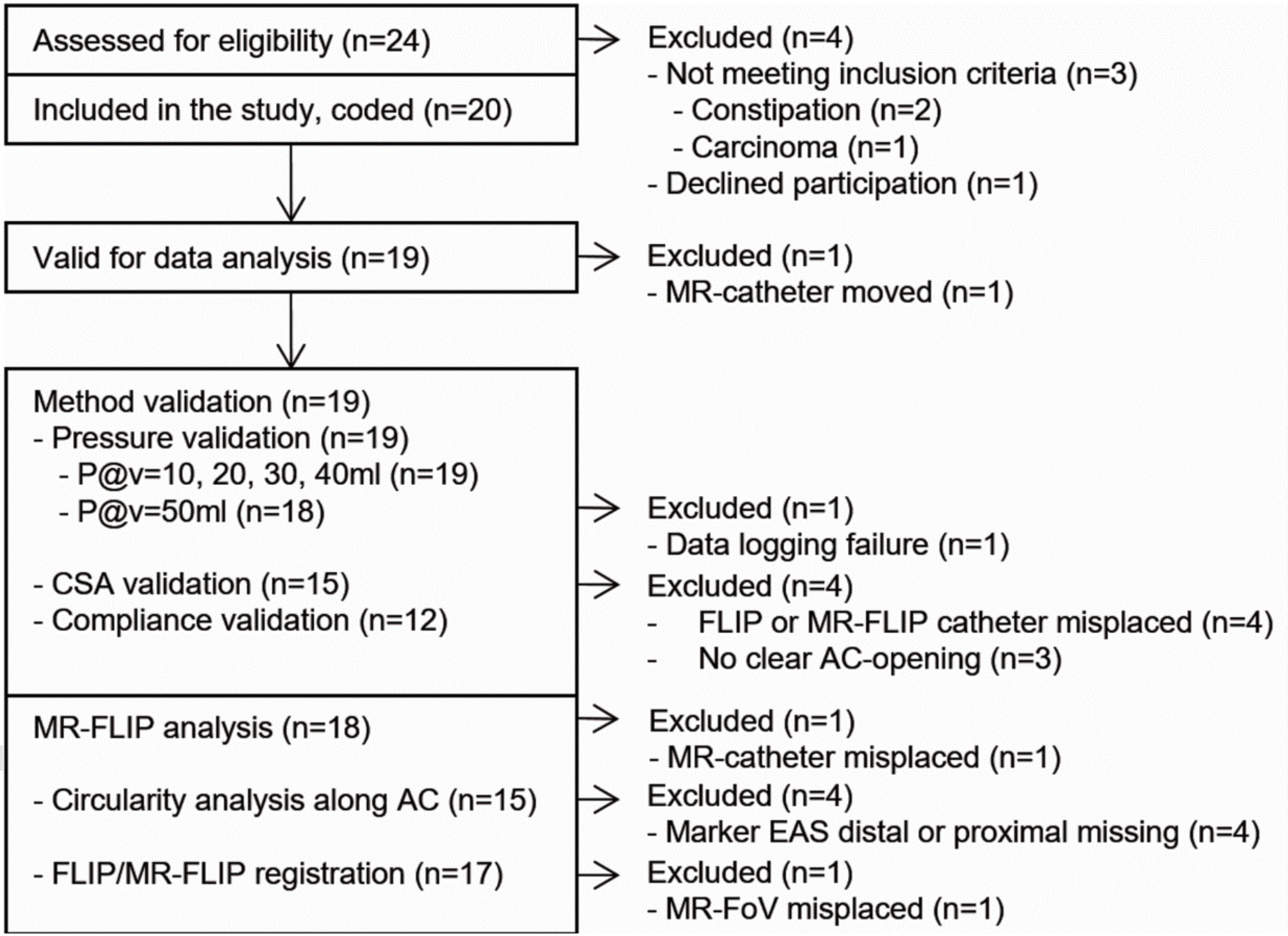
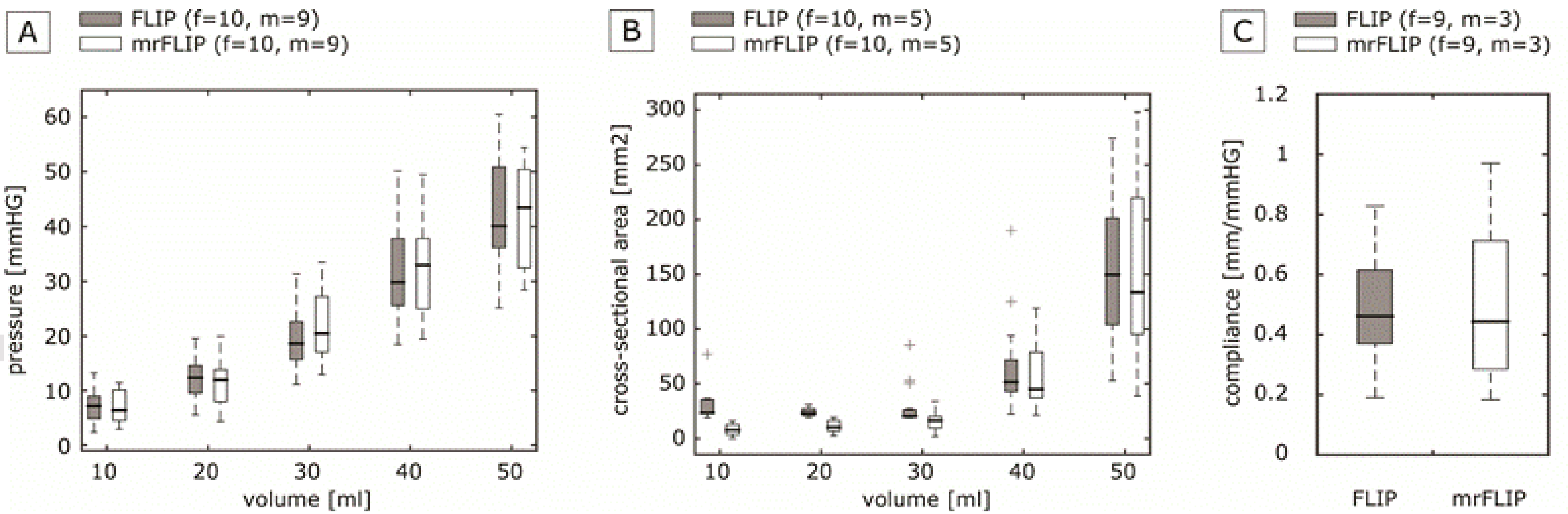
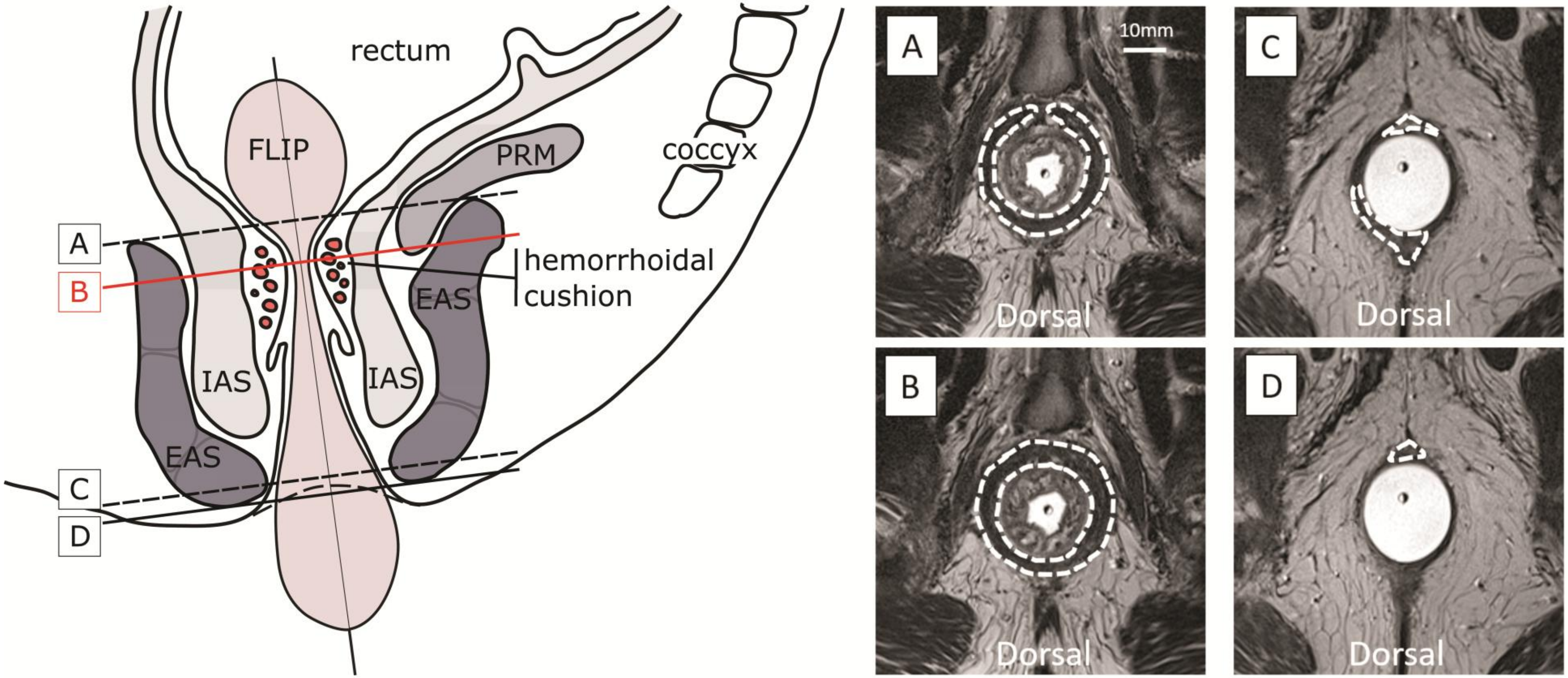


Figure 4: Comparison of FLIP and MR-FLIP measurements. Pressure (A) and cross-sectional area (B) are dependent on the balloon volume. Pressure (A) does not differ significantly between the two measurement approaches. In (B) all measurement values are shown and it can be observed that MR-FLIP has the potential to detect smaller AC openings. No statistical difference in CSA could be found between modalities for balloon volumes of 40 and 50 ml. However, measurements at smaller balloon volumes suffered from low reproducibility; detection thresholds were introduced (see Material and Methods, section Data Acquisition and Analysis) to exclude measurements below a minimum diameter from further analysis. The compliance (C) of the AC was calculated for both measurement techniques. Again, no statistically significant difference was found between FLIP and MR-FLIP.

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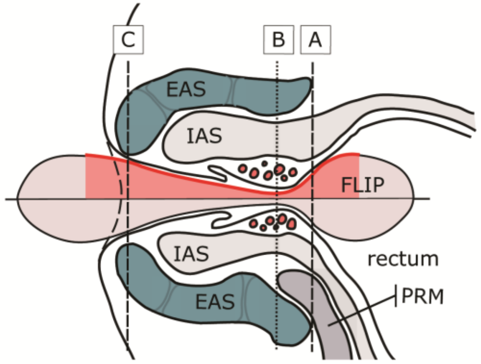
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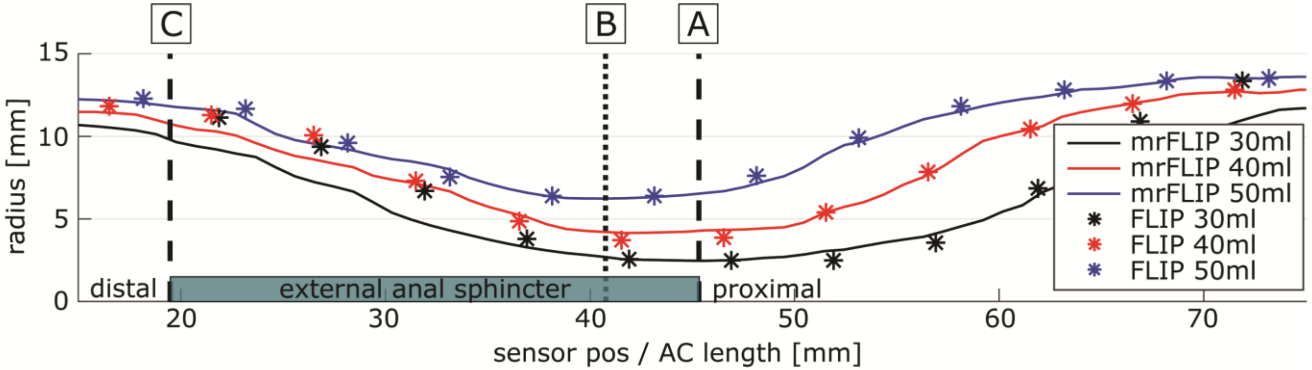
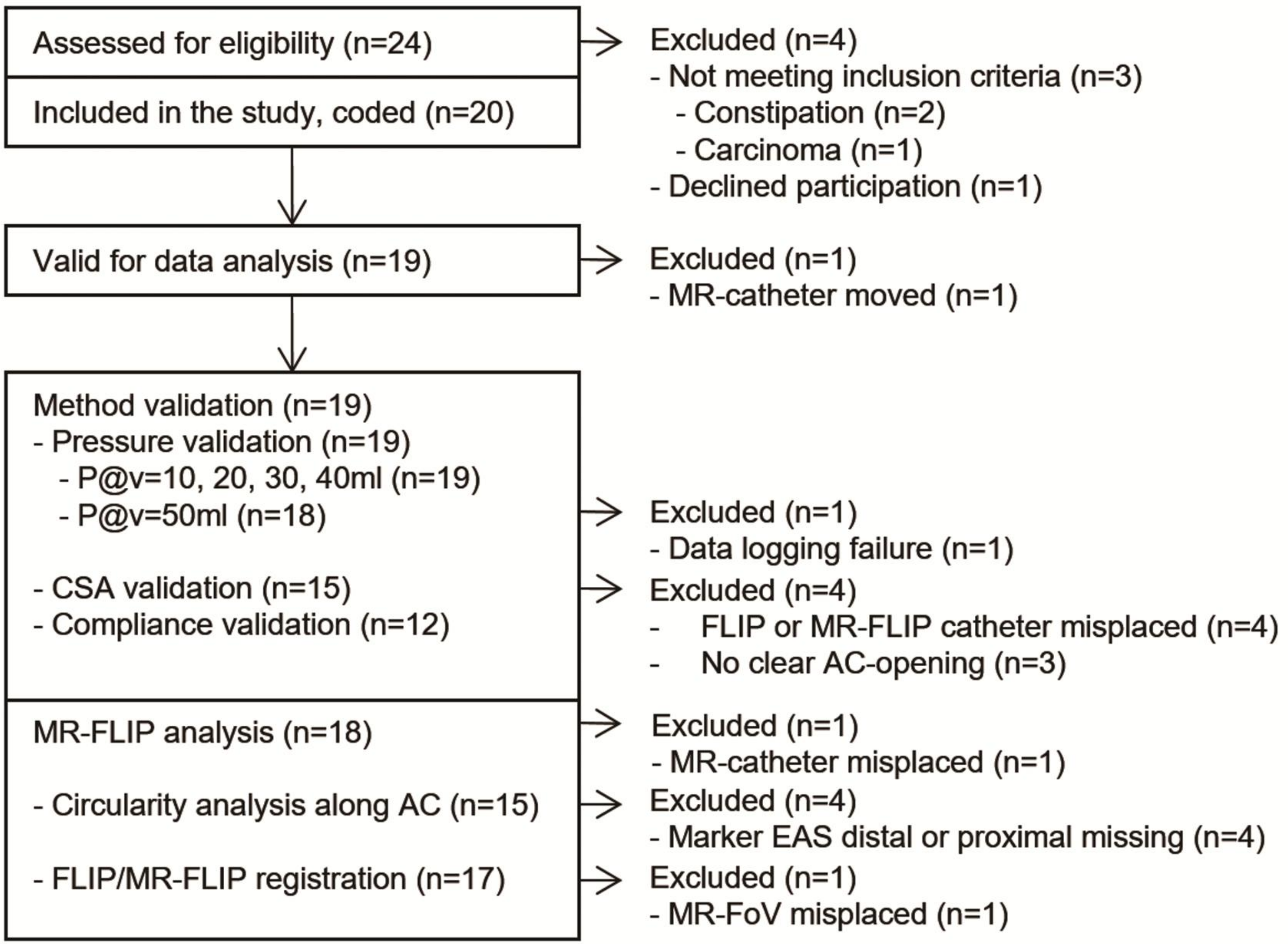
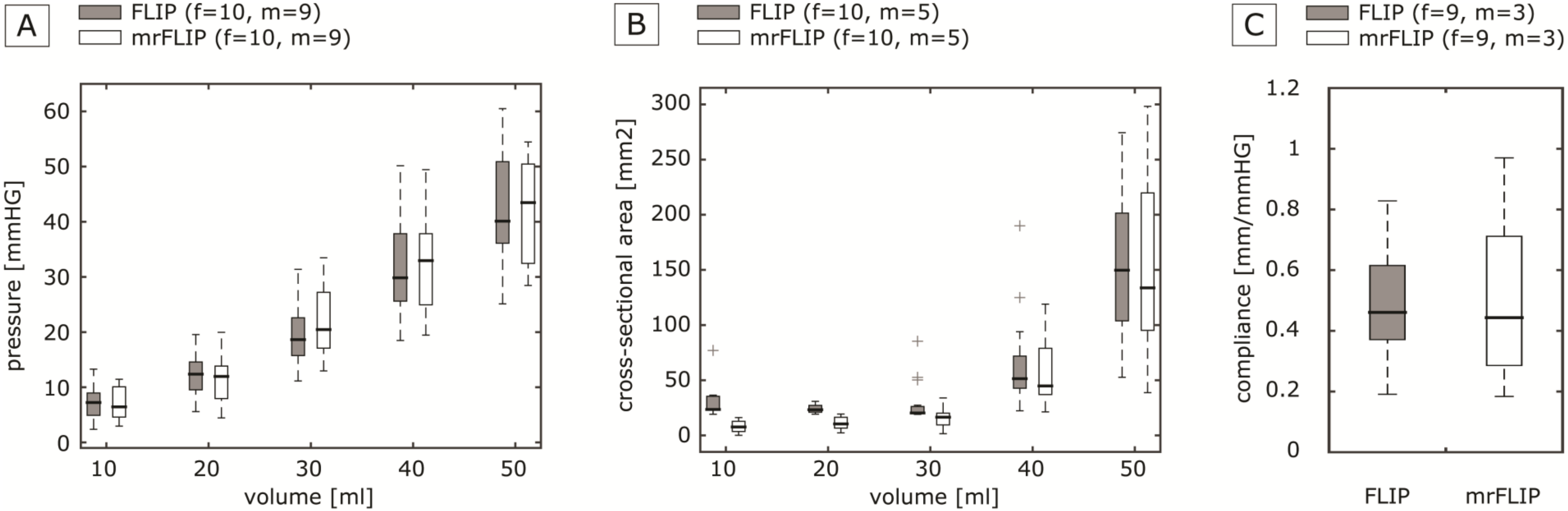
rectum
PRM


C
B
A
15
10
5
0
radius [mm]
distal
external anal sphincter
proximal
20
30
40
50
60
70
sensor pos / AC length [mm]
mrFLIP 30ml
mrFLIP 40ml
mrFLIP 50ml
FLIP 30ml
FLIP 40ml
FLIP 50ml


Assessed for eligibility (n=24)
Included in the study, coded (n=20)
Excluded (n=4)
- Not meeting inclusion criteria (n=3)
- Constipation (n=2)
- Carcinoma (n=1)
- Declined participation (n=1)
Valid for data analysis (n=19)
Excluded (n=1)
- MR-catheter moved (n=1)
Method validation (n=19)
- Pressure validation (n=19)
- P@v=10, 20, 30, 40ml (n=19)
- P@v=50ml (n=18)
Excluded (n=1)
- Data logging failure (n=1)
- CSA validation (n=15)
- Compliance validation (n=12)
Excluded (n=4)
- FLIP or MR-FLIP catheter misplaced (n=4)
- No clear AC-opening (n=3)
MR-FLIP analysis (n=18)
Excluded (n=1)
- MR-catheter misplaced (n=1)
- Circularity analysis along AC (n=15)
Excluded (n=4)
- Marker EAS distal or proximal missing (n=4)
- FLIP/MR-FLIP registration (n=17)
Excluded (n=1)
- MR-FoV misplaced (n=1)


A
FLIP (f=10, m=9)
mrFLIP (f=10, m=9)
pressure [mmHG]
volume [ml]
B
FLIP (f=10, m=5)
mrFLIP (f=10, m=5)
cross-sectional area [mm2]
volume [ml]
C
FLIP (f=9, m=3)
mrFLIP (f=9, m=3)
compliance [mm/mmHG]
FLIP
mrFLIP