Title: Studies in Patients with Low Anterior Resection Syndrome (LARS)

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Background of research

Colorectal Cancer is the commonest cancer diagnosed for both genders combined in Hong Kong. In 2015 16.6% of all new cancer cases registered on the Hong Kong registry were cancer of colon and rectum.[1] Distal colon cancer is more common than proximal colon cancer, with up to 38% of cancers being found in the rectum.[2] Curative surgical treatment option for rectal cancer involves excision of tumour with 5cm proximal and 2cm distal margin with its draining lymphatics. The level of anastomosis or need for temporary or permanent stoma will depend on the height of tumour from the anal verge, extent of local invasion, the sphincter function preoperatively, co-morbidity and whether they required preoperative chemoradiotherapy. With neoadjuvant chemoradiotherapy offering potential tumour shrinkage and improvements in surgical technique such as the transanal total mesorectal excision (TaTME) technique offering accurate distal resection margin, many patients are now receiving sphincter-preserving surgery with low colorectal or coloanal anastomosis to avoid permanent colostomy. Up to 80% of patients who has undergone low anterior resection (LAR) suffer from severe bowel dysfunction post operatively[3]. Patients symptoms typically fall into two categories: those with incontinence, frequency, and urgency, and those with constipation and feelings of incomplete emptying. However, some patients report features of both, either occurring simultaneously or fluctuating between these two groups of symptoms[4]. This combination of symptoms after LAR is referred to as Low Anterior Resection Syndrome (LARS) which is associated with negative impact on quality of life (QoL)[5].

Originally, it was thought that these symptoms were short-lived neorectal irritability in the postoperative period. However, many studies report that the majority (up to 90%) of patients experience long-term changes in quality of life after LAR[6]. Therefore, a large number of patients worldwide are suffering from unpredictable, poor bowel function postoperatively affecting their day-to-day activity and quality of life.

In a prospective study assessing consecutive patient's functional outcome post low anterior resection in our unit since January 2016, 34 patients have had their defunctioning stoma closed to date with 4 months follow up. 73.5% of our patients were experiencing major LARS. Approximately half of the patients had persistent symptoms at 2 years post stoma closure: 65.5% (19/29) and 46.2% (6/13) had major LARS at 12 and 24 months respectively. Hence, the figures from our unit correspond to reports from other centers Worldwide.

Unfortunately, there is no cure for LARS at present. Biofeedback treatment and nerve stimulation sacral nerve stimulation or tibial nerve stimulations with stimulators such as the Acutens seems to provide some symptomatic relief for some patients. The cause of LARS is thought to be multifactorial and difficult to define. Therefore, this trial is designed to use Fecobionics, a new Hong Kong based innovation, to provide new mechanistic insights regarding anorectal physiological function post low anterior resection. This will help us to understand the condition better and hopefully to improve their treatment options.

Technological background

In the proposed studies it is important to compare the new technology, Fecobionics, to current state-of-the-art reference technologies. We expect Fecobionics to provide data that cannot be obtained with current technology and to reduce variation in measured variables.

Reference testing techniques

Anorectal Manometry (ARM)[7] with balloon expulsion testing (BET)[8] will be conducted with a standard single-use 8ch anorectal catheter (G-90150, MMS, Enschede, Netherlands). The catheter will be inserted with the subjects lying inside position with bent hip and knees. The bag will be placed in the rectum and pressure will be measured at 0.5cm distance in the anal canal. The following parameters will be evaluated: resting anal pressure, maximum anal squeeze pressure, the recto-anal inhibitory reflex (RAIR), urge volume, maximum tolerable volume, and expulsion time for the 50ml balloon.

Defecography (fluoroscopy or MRI) will be used as a reference for Fecobionics. A water-soluble paste will be injected into the rectum and serial x-rays will be taken during defecation. Defecography will be used to study several anorectal characteristics. The height of the colorectal anastomosis, any abnormality at the anastomosis such as narrowing, orientation of neo-rectum will be assessed in addition to usual measurements of the anorectal angle and the position of the pelvic floor at rest or during Valsalva (perineal descent). The presence of rectocele, rectal intussusception, and the ability to expel rectal contents will be evaluated[9,10]. Balloon proctography can simplify the procedure of examining the ability to evacuate by providing a quick and clean test with minimal radiation[11].

New technology

Fecobionics[12,13] is a novel device, a simulated faeces, that we currently are testing in healthy subjects and in patients suffering from fecal incontinence and constipation (RGC funded proposal "Unraveling anorectal function and biomarker signatures in patients suffering from subtypes of defecatory disorders"). Fecobionics records pressures, orientation, bending, shape, and viscoelastic properties during defecation. It is made of a 10 cm long and 12 mm wide core of medical grade resin that contains multiple electronic sensors and circuit boards. A bag is mounted on the bendable core. Pressure transducers are placed at the front, rear and inside the bag, in addition to two gyroscopes for orientation and angle measurements. A novelty of Fecobionics is that it measures pressures in axial direction (in the direction of flow) in contrast to current technologies and that it integrates almost all current anorectal functional tests into a single test that only takes minutes to perform without the use of radiation or expensive equipment. Since the Fecobionics technology was developed by the PI Professor Hans Gregersen, we are currently the only clinical research group with access to the technology. This gives us a unique opportunity to becomes the leaders in the field.

Impact

Defecatory disorders affect 25% of the population with rising incidence. They pose a major health care

burden and are poorly recognized and treated. The need for better diagnostics and therapeutics is substantial. Constipation, a symptom of underlying disease, affects 12-19% of Americans[14,15] with expenditures on medication for constipation alone greater than $250 million per year[16]. Defecatory diseases are associated with diet, aging and a variety of underlying factors and diseases[17-20]. As described above LAR is associated with reduced quality of life and anorectal symptoms in the majority of patients.

Since the etiology is multifactorial, a significant problem is the lack of physiologically relevant and practical diagnostic tests for identifying the underlying mechanisms. Assessment begins with detailed questioning about symptoms. Digital rectal examination is done to assess tone, maximum anal squeeze with detection of sphincter defects, rectal prolapse, and abnormal perineal descent[17]. Current diagnostic tests such as Anorectal Manometry (ARM), Balloon Expulsion Test (BET) and defecography are surrogates for the act of defecation and provide incomplete and often conflicting information due to the static nature of the tests. Not surprisingly results of these tests correlate poorly with symptoms and treatment outcomes. The problem with most tests is that they do not reflect the dynamics of the defecation process and are far from representing physiological conditions[21-25]. Even defecography, regarded as the most physiological test, uses a liquid with mechanical properties quite different from the properties of faeces. The anorectal expulsion test suffers from the lack of physiological measurements such as pressure profiles, angling and geometric changes during anal passage. Hence, current paradigms for defecatory disorders need to be changed by approaches that can provide insight by simulating defecation physiologically and examining the mechanistic changes multidimensionally in terms of pressure profiles, deformability, and topographic changes. Based on promising new data using the Functional Luminal Imaging Probe (FLIP) in the anal canal[26-30], ARM[31], and Fecobionics[12,13], the goal is to use the novel integrated Fecobionics device (combined FLIP-ARM-BET-defecography-in-part) for functional studies in LAR patients. Fecobionics has been developed according to current safety standards for medical devices (ISO13485)[13] by the PI Professor Hans Gregersen and have been trialed with success in our patients with anorectal functional disorders based on GRF support. We are currently the only clinical research centre worldwide with access to the technology. This provides us with a unique opportunity to lead the field. The measurement variables include pressures, shape changes, the expulsion velocity and an “objective” anorectal angle (important for evaluation of several anorectal disorders). Hence, it will be feasible to describe objectively, without disturbing the defecation process, sensation, opening characteristics and geometric changes during initial entry from the neo-rectum into the relaxing anal canal.

This proposal will result in a new paradigm in evaluation of LARS. The simulated faeces technology will potentially replace current tests as it provides an integration of measurements from multiple tests of anorectal diagnostics. Our expected outcome is to characterize abnormal pressures, forces and topographic changes in the neo-rectum and anal canal during defecation in LARS patients, to help with understanding of the cause of their symptoms to guide and improve LARS management.

Objectives and specific aims

General Objective

Fecobionic will provide new mechanistic insights regarding anorectal physiology in LARS patients that is not obtainable with current technology.

Specific Aim 1: Anorectal pathophysiology of LARS patients

Objective: use fecobionics to obtain physiological and pathophysiological signatures of anorectal function in a heterogeneous group of LARS patients. Based on the epidemiology and symptomatology of LARS, it is expected that the heterogeneous group will contain an almost equal number of LARS patients with incontinence, frequency and urgency, and those primarily with constipation and feelings of incomplete emptying. Due to the spread (heterogeneity) in the patient group regarding symptoms, regression analysis will be the primary statistical tool to associate symptoms with experimental findings. We will also compare to age- and sex-matched healthy controls from already conducted studies.

Milestone: Describe the mechanosensory signature, variation of the measured variables, and computed endpoints in LARS patients.

Approach

Device Characteristics and human recordings. The integrated Fecobionics device is uniquely designed to improve diagnostics of anorectal disorders. The design integrates ARM, BET, defecography and FLIP[20-24,32-36]. The new design features of the integrated device are shown in Figure 1 and include the inner bendable core that contains the sensors and a bag for distension made of 25 micrometer polyurethane. The core is easily bendable and contains electronic components such as pressure transducers, gyroscopes, and impedance electrodes as well as circuit boards for the central processing unit (CPU). A tube is used for filling of the bag after the placement in rectum to the urge-to-defecate level. All materials in the device are medical grade. The core and the bag provide a double layer protection for the electronic components. Our institutional review board did not have any concerns about the risks and safety of the device.

Figure 1 shows the design of the Fecobionics device with the computer that also serves as a visual analog scale (VAS) for sensory evaluation in addition to displaying data. The core is made from medical grade resins and contains three pressure sensors placed at the front, rear and inside the bag. It also contains two gyroscopes used for determination of orientation and bending (the anorectal angle). Furthermore, eight pairs of electrodes that utilizes the FLIP principle to determine the geometry of the bag surround the core[26-30]. The core also contains the CPU, multiplexer, amplifiers, and batteries. A valve and bag filling tube system as well as a safety thread are attached in the front of the device (not shown).

Figure 2 shows schematics of novel analysis of the pressure signals from preliminary studies in healthy human subjects and patients with anorectal disorders. The left panel shows the front and rear pressure and the difference between them as function of time. Studies have demonstrated that defecation can be subdivided into five distinct phases[12,13]. The difference in the two axial pressures (pointing forward and

backward) during the expulsion indicate the usefulness of this kind of measurements. For example, the entrance of the device into the canal as well as the anal relaxation can be assessed. The right panel shows the front pressure as function of the rear pressure. This is a novel representation corresponding to the well-known preload-afterload analysis of cardiac function. Human data from our preliminary data are shown in figure 3.

Figure 3 shows data from a healthy subject (AB), a patient with fecal incontinence (CD) and chronic constipation (EF). The left panels are the pressure-time plots useful subdividing defecations into phases. The right panel is the front-pressure as function of the rear pressure. Both types of analysis show marked differences between the subjects. In general, the heathy subjects use a few pressure increases (abdominal contractions) to expel the device. The FI subject is characterized by a low anal sphincter pressure and the device pops out by itself. The constipation patient cannot expel the device despite many attempts. Other data (not shown) based on gyroscope data also demonstrate distinct differences between subjects.

Research Design and Methods

The overall goal of this proposal is outlined in the specific aims section. Specifically, we will target anorectal diagnostics of LARS patients to be conducted in the Department of Surgery at Prince of Wales Hospital in Hong Kong. In both studies listed below, we aim to recruit a heterogeneous group of patients to allow us to assess the effect of several underlying risk factors. In both studies, we will study the patients after closure of defunctioning stoma as we deem it impossible to carry out anorectal functional studies in patients with low rectal cancer before their rectal cancer surgery and assessing anorectal function post LAR before defunctioning stoma closure will produce unreliable, irrelevant data.

Study Protocol:

Following ethics approval, patients will be assessed for their eligibility to participate in the trial. The PI and collaborators who are Good Clinical Practice (GCP) trained will recruit patients who are eligible for the study. Information sheet will be given to the patient in the surgical clinic, and written consent will be obtained at the next hospital visit. Ethics approval for this study will be granted prior to the start of the trial. The trial will be compliance with the Declaration of Helsinki. The trial will be registered in www.clinicaltrials.gov.

Data collection:

Patients will be assessed at baseline and following will be recorded for all patients:

- Demographic data
- Body Mass Index (BMI)
- Significant Past Medical and Surgical History
- Obstetric History (female patients only)
- Rectal Cancer stage: TNM staging, location of tumour from anal verge on preop image

- Rectal Cancer treatment
  - o Neoadjuvant chemoradiotherapy/radiotherapy/chemotherapy
  - o Surgery – Open/Laparoscopic/Robotic/TaTME, level of anastomosis
  - o Post-operative complications
  - o Postop chemotherapy / radiotherapy
  - o Timing of defunctioning stoma (ileostomy / colostomy) closure
- LARS questionnaires: to assess Quality of life associated with LARS (Figure 4)[37,38]

All patients will undergo the following tests:

- Integrated Fecobionics anorectal test (see clinical workflow below)
- High Resolution Anorectal Manometry (ARM) to assess resting and squeeze pressures, sensitivity, rectal capacity and recto-anal inhibitory reflex.
- Conventional balloon expulsion test
- Defaecography

Clinical data will be recorded and stored electronically in the hospital server. Completed questionnaires will be recorded and entered into database software and stored in the hospital server.

Clinical Work Flow for the integrated device.

This section pertains to the procedures related to use of Fecobionics. All tests prior to Fecobionics are done per department standards. The patient is instructed about the tests. The integrated device is calibrated in a one-step procedure. Similar to the conventional expulsion test, the device is placed in the rectum by manual insertion with the person lying on the side. The bag is distended with simultaneous recording of symptom level until urge to defecate. Volume is recorded. When the urge level is reached, the patient will move to the toilet chair for attempting to expel it. The patient will report sensory data. Most patients who do not suffer from constipation will be able to expel it within 1-2 minutes. If the patient fails to expel the device by himself, the physician or nurse can, if deemed necessary, pull it out by traction of a tiny thread attached to the front end (like the thread used for tampons). The thread is 50 cm long so even if the device relocates to the left side of the colon, it can still gently be pulled out. In the worst case, an endoscope can be used to pull it out.

Study design related to specific *Aim 1*: Anorectal pathophysiology of LARS patients

Studies are planned to include a heterogeneous group of LARS patients with a broad scale of symptoms. We will study 30 patients recruited from a pool of postoperative patients who are under the care of our Department. The department has a large cohort of patients with LARS and it is anticipated that it will be easy to recruit the patients.

Inclusion Criteria:

1. Patients 18 years of age or older with history of LARS over 3 months.

2. Informed, written consent by the patient

Exclusion Criteria:

1. Patients who are not willing to undergo the specified tests in this study
2. Pregnant women

The studies on LARS patients will focus on pathophysiological studies where we describe the expulsion characteristics, with focus on anal canal opening related to rectal mechanosensory data and to changes in the anorectal angle during defaecation. We will study expulsions at the urge-to-defecate level for the patients and we will correlate to data obtained by conventional technologies and to patient characteristics such as age, and symptoms as well as to risk factors. The study subjects will also be tested with conventional expulsion testing, defecography, rectal bag distension, and ARM[20-24,32-35,39]. The studies will determine endpoints of clinical value such as expulsion time and velocity, maximum angle difference, pressure signatures and geometry changes.

Expected Results and Milestones: The expected outcome is that the device will perform as shown in the previous human experiments (n>60) where no adverse effects have been recorded. We anticipate successful access in LARS patients with no device-related adverse events or device malfunctions. Completion of the study is expected to derive outcome measures reflecting the defecatory function as the major impact.

Potential Pitfalls and Alternative Strategies: According to the ISO 13485 standard, the device is an insertable low risk device since it will reside inside the body for less than one hour and there is no radiation exposure. All materials are medical grade and the design and mechanical properties chosen after input from KOLs in USA and Europe. Assessment for safety in the above reported preliminary studies and in testing during the developments will not fully recapitulate all the conditions in LARS patients. We will ask the investigators to be alert and retract the device instantly if it suddenly stops working as "alarmed" by the device, which could be indicative of a short circuit. We will work with safety experts to fully mitigate any issues as we have done with other projects. Another concern relates to retraction of the device if it cannot be defecated. To avoid the need for endoscopy, the device will have a thin string attached in the anal end. The string will be the same thin soft type as used in tampons to avoid interference with the mechanosensory properties of the anorectum. If enrollment is slower than expected, we will make an extra effort to recruit patients, but this is hardly to be anticipated considering the high incidence of LARS in our cohort of patients.

Data analysis including statistics and sample size determination.

A number of biomechanical parameters will be computed from the recorded data. These parameters include but are not limited to:

- Pressure difference between the rear and front ends (a measure of anal sphincter relaxation and key to the determination of phases of the defecatory process)
- Orientation and bending of Fecobionics for assessment of the anorectal angle

- Velocity of expulsion (as measured from the time difference between sensor data)
- Tension
- Strain (deformation) and displacement

Definitions of tension, strain and displacements can be found in the two books by the Professor Hans Gregersen[17,19]. Sensory measures and clinical data will be related statistically to the mechanical measures. Endpoint data will be expressed as mean±SD if they can be considered normally distributed. Significance of the differences between two methods will be evaluated by ANOVA where appropriate and by multiple and single regression analysis. The results will be considered statistically significant when $p<0.05$ (2-tailed). Multiple regressions will be used to evaluate risk factors using causal and predictive analysis. Repeatability and distribution will be determined based on coefficient of variation (SD/mean) and used to evaluate accuracy.

The projected number of subjects, n, required to test a null hypothesis is given by the following equation:

$$n > \left[\frac{\left[Z_{2\alpha} + Z_{2\beta} \right] \sigma}{\delta} \right]^2$$ where α is the required probability of a Type I error, β is the required probability of a Type II error, δ, is the estimated difference between the means of two comparison groups, and σ is the estimated standard deviation of the means in each of the two comparison groups. We assume $2a<0.05$ ($Z2a=1.96$) and $2b<0.10$ ($Z2b=0.84$). We assume the values of mean difference, d, and standard deviation, s, from previous experience in the clinical laboratory and from reported data in the literature on the involved patient groups and the sensitivity and specificity of current tests. An alternative method is to use sample size estimation based on the Altman-Bland analysis (http://wwwusers.york.ac.uk/~mb55/meas/sizemeth.htm). Preliminary data on expulsion time using BET and Fecobionics were used in the sample size analysis. Data variation (SD, SE) was computed for preliminary data. The confidence interval for the 95% limits of agreement was computed and n was determined. For both analyses, given the exploratory nature of the study, we consider a heterogeneous group of patients and that 80% of operated patients will develop LARS. Using these boundaries and criteria, we arrived at a sample size of 30 in the Aim 1 study for evaluation of statistical significance, association and risks. Though the material may be too small to account for confounders, we will obtain clear indications of risks and causes. For the comparison with previously studied subjects, we have a pool of 35 healthy asymptomatic subjects, 20 patients with FI and 15 patients with constipation to compare with.

Clinical Assessments of device safety: Fecobionics have now been used in more than 70 human studies without any incidents or adverse effects. In addition, a safety study has been performed in 12 pigs without any device related issues or damage to anorectal mucosa (yet unpublished data). Since Fecobionics is still an experimental device, we will pay attention to safety. If any safety issue occurs, it will be characterized and reported. Additional data obtained will include procedural duration, sensation

including pain, inspection of the anus after the expulsion in addition to any adverse events that may occur. Follow-up physician interviews will obtain qualitative measures of device performance and utility. Unanticipated adverse device effects **(UADE)** are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. The procedure for reporting any adverse event (whether device-related or not) is to fill in all sections of an adverse event case report form. Details and symptoms associated with the event will be reported in the narrative section on the Narrative/Notes CRF. It will be the responsibility of the clinical study investigator to inform the IRB of adverse events (whether device related or not) according to their requirements.

Location of study

The studies will be conducted in the Department of Surgery at Prince of Wales Hospital,
Shatin, Hong Kong.

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Figure 1: The design of the integrated Fecobionics device and system.

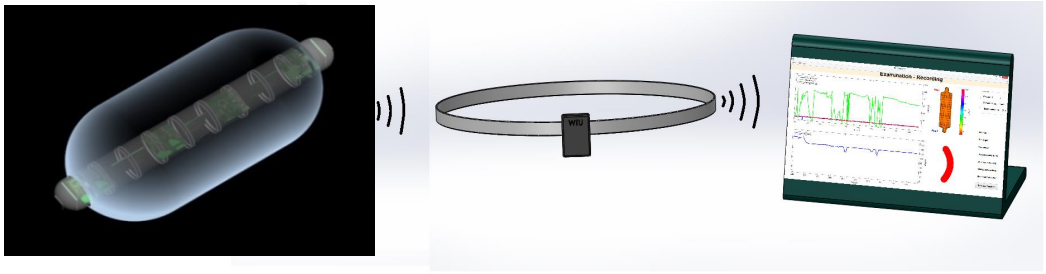

Figure 2: Schematic representation of novel advanced analysis of pressure signals

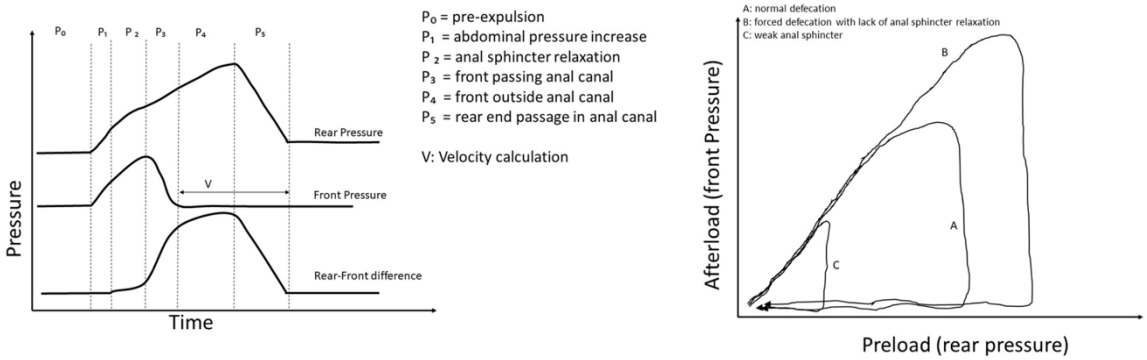

Figure 3: Pressure signatures of healthy subject (AB), FI patient (CD) and CC patient (EF) during defecation of the device

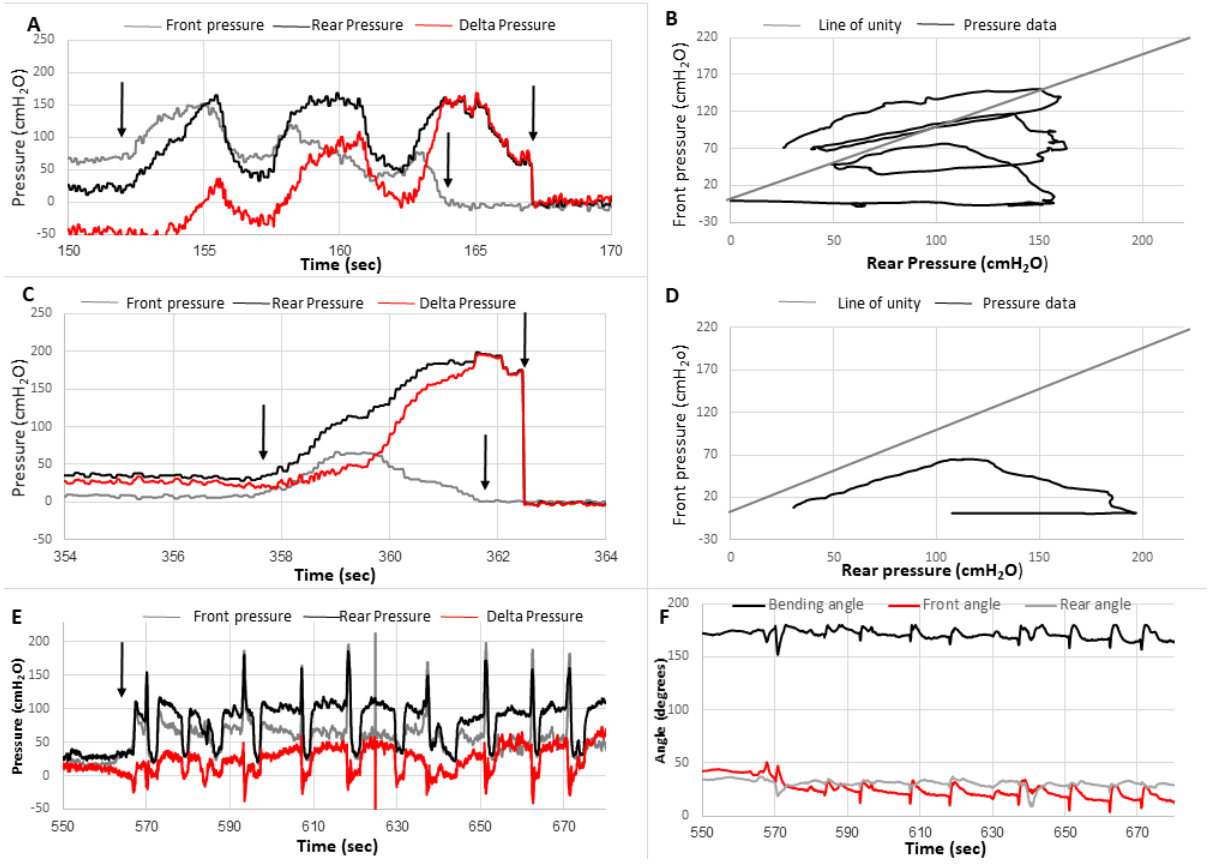

Figure 4: LARS Questionnaire

Do you ever have occasions when you cannot control your flatus (wind)?

	No, never	0
	Yes, less than once per week	4
	Yes, at least once per week	7

Do you ever have any accidental leakage of liquid stool?

	No, never	0
	Yes, less than once per week	3
	Yes, at least once per week	3

How often do you open your bowels?

	More than 7 times per day (24 hours)	4
	4–7 times per day (24 hours)	2
	1–3 times per day (24 hours)	0
	4–7 times per day (24 hours)	5

Do you ever have to open your bowels again within one hour of the last bowel opening?

	No, never	0
	Yes, less than once per week	9
	Yes, at least once per week	11

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

	No, never	0
	Yes, less than once per week	11
	Yes, at least once per week	16

Total Score:

Interpretation:
0–20: No LARS
21–29: Minor LARS
30–42: Major LARS