Characterization of Patients With Obstructed Defecation and Slow Transit Constipation With a Simulated Stool

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INTRODUCTION: **Defecatory disorders including obstructed defecation (OD) are currently diagnosed using specialized investigations including anorectal manometry and the balloon expulsion test. Recently, we developed a simulated stool named Fecobionics that provides a novel type of pressure measurements and analysis. The aim was to study OD phenotypes compared with slow transit constipation (STC) patients and normal subjects (NS).**

METHODS: **Fecobionics expulsion parameters were assessed in an interventional study design. The Fecobionics device contained pressure sensors at the front, rear, and inside a bag. All constipation patients had colon transit study, defecography, anorectal manometry, and balloon expulsion test performed. The Fecobionics bag was distended in the rectum until desire-to-defecate in 26 OD compared with 8 STC patients and 10 NS. Rear-front pressures (preload-afterload parameters) and defecation indices (DIs) were compared between groups.**

RESULTS: **The Wexner constipation scoring system score was 13.8 ± 0.9 and 14.6 ± 1.5 in the OD and STC patients ($P > 0.5$). The median desire-to-defecate volume was 80 (quartiles 56–80), 60 (54–80), and 45 (23–60) mL in OD, STC, and NS, respectively ($P < 0.01$). The median expulsion duration was 37 (quartiles 15–120), 6 (3–11), and 11 (8–11) seconds for the 3 groups ($P < 0.03$). Fecobionics rear-front pressure diagrams demonstrated clockwise loops with distinct phenotype differences between OD and the other groups. Most DIs differed between OD and the other groups, especially those based on the anal afterload reflecting the nature of OD constipation. Several OD subtypes were identified.**

DISCUSSION: **Fecobionics obtained novel pressure phenotypes in OD patients. DIs showed pronounced differences between groups. Larger studies are needed on OD subtyping.**

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INTRODUCTION

Defecation is a complex physiological process through which stools are eliminated through the anus (1–3). The evacuation process may easily get disturbed, resulting in symptoms including fecal incontinence and constipation (4). Defecatory disorders affect 25% of the population with rising incidence (1,4). The disorders pose a major health care burden but are poorly recognized and treated (4). Chronic constipation (CC) affects 12%–19% of Americans (5,6) with US expenditures on laxatives alone being greater than $800 million per year (7). CC is associated with low fiber diet, aging, and a variety of underlying factors and diseases (8–10). The mechanisms of defecation and continence depends on colorectal motility, stool consistency, rectal capacity and compliance, anorectal sensitivity, and coordination of the pelvic floor muscles and anal sphincters.

Constipation refers to abnormally delayed or infrequent passage of usually dry, hardened feces and may be associated with pain during defecation. The Rome III and IV criteria are widely used to diagnose CC and are helpful in separating cases of chronic functional constipation (11,12). Constipation is a symptom with 3 major causes: obstructed defecation (OD), normal transit constipation, and colonic slow transit constipation (STC). About 50% of patients evaluated for constipation have OD (5). Management options for these patients are limited because of the multifactorial control of defecation and continence and because of difficulties in identifying the exact cause of CC with current diagnostics. Precise diagnosis is necessary to judge whether the patient is eligible for biofeedback treatment.

Constipation is a symptom where the degree often is assessed with constipation scores (13). Anorectal physiology and defecatory

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disorders can be assessed using specialized investigation including anorectal manometry (ARM), balloon expulsion test (BET), and defecography (14–18). Physiological evacuation phenomena such as the opening characteristics of the anal sphincter during defecation cannot be described in detail with current technology. For example, defecography does not measure anorectal pressures, BET does not assess geometry (15–17,19), and ARM is not performed during defecation. Considerable disagreement exists between the results of various anorectal tests, and they correlate poorly with symptoms and treatment outcomes (4,20). Therefore, the need for physiologically relevant and easy-to-use diagnostic tests for obtaining a mechanistic understanding of defecation and identifying underlying mechanisms is substantial.

Fecobionics is a novel simulated stool that integrates ARM-BET, and in some embodiments impedance planimetry and anorectal angle measurements, in a single examination (21–25). Fecobionics makes it possible to describe the opening characteristics during entry into the relaxing anal canal without disturbing the defecation process. Recently, technological validation (22) and studies on normal subjects (NS) (21,23) were published. It was demonstrated that rear-front pressure (so-called preload-afterload) analysis provided useful end points (23).

The aim was to evaluate the feasibility and performance of Fecobionics for assessment of defecation parameters in OD patients compared with patients with sexually transmitted disease and NS. We provide detailed descriptions of novel pressure signatures as the article will serve as a reference for future large-scale clinical studies of constipation subtypes. Expulsion characteristics are described with endpoints of physiological and clinical value. Furthermore, data obtained with current state-of-the-art technologies are described.

METHODS

Subjects

Twenty-six subjects with suspected OD and 10 patients with suspected STC attending the functional colorectal surgery clinic at Prince of Wales Hospital were invited to participate in this exploratory study. The Rome III criteria for constipation (11) were used. The primary selection criteria were symptoms of either STC or OD. All constipated patients included had colon transit study, defecography, ARM, and BET performed. The colon transit study used the standard criteria for the Sitz marker test (26). ARM and BET are described further in Procedures since they were performed on the same day as Fecobionics. The final decision on the type of constipation was based on a combined evaluation of symptoms and test results. The lower age limit was 18 years. No upper limit was imposed. Data were obtained on age, sex, body mass index, health status, symptoms, diseases, and previous treatments. Constipation questionnaires data were obtained using the Wexner constipation scoring system (13). The patient data were compared with an age- and sex-matched group of NS studied previously with Fecobionics, ARM-BET, and constipation symptom scores.

Before the functional testing, the subjects were asked to empty their rectum if they were able to. Enema was not used to make the test as natural as possible. Anorectal examination was performed before insertion of the Fecobionics to assess anal tone and verify that the lower rectum was empty. Experiments using Fecobionics and ARM-BET were performed randomized on the same day with appropriate time between the tests. All subjects had the tests completed. Constipation score <8 was considered normal (13).

The protocol was approved by the Joint CUHK-NT East Cluster Clinical Research Ethics Committee (ref. no. 2017.122).

Fecobionics

The basic design of Fecobionics has been described (21–24) and is sketched in Figure 1. The probes were manufactured by Maxwell Electronic Technology Co (Chongqing, China). Fecobionics was 12-mm-OD, 10-cm-long and made of medical grade Silicone rubber (PS6600; Yipin Mould Material, Dongguan City, China). It contained pressure sensors and circuit boards including the Microprogrammed Control Unit. The miniature pressure sensors (MS5837-30BA; TE connectivity, Berwyn, PA) were embedded at the front, inside the bag, and at the rear of the core. The front and rear sensors pointed in the direction of the trajectory. Since the sensor measures absolute pressure, zero pressure reference adjustment at atmospheric pressure was performed before measurements.

A 30-μm-thick and 8-cm-long polyester-urethane bag spanned most of the core length. The spherically shaped bag contained up to 80-mL saline without being stretched and had a maximum diameter of 6 cm. The bag was connected through a thin tube extending from the front of Fecobionics to a syringe containing saline.

With the architecture, silicone hardness shore A5, and the bag, Fecobionics obtained consistency that corresponds approximately to type 4 (range 3–4) on the Bristol Stool Form Scale (27). The range from types 3–4 is found in +60% of healthy subjects (27). Four wires were threaded inside a thin tube extending from the front to the USB port of a computer for power supply and data transmission for real-time collection, computation, and display of data on the graphical user interface. Further processing was performed in MATLAB. Validation data for Fecobionics have been published (22).

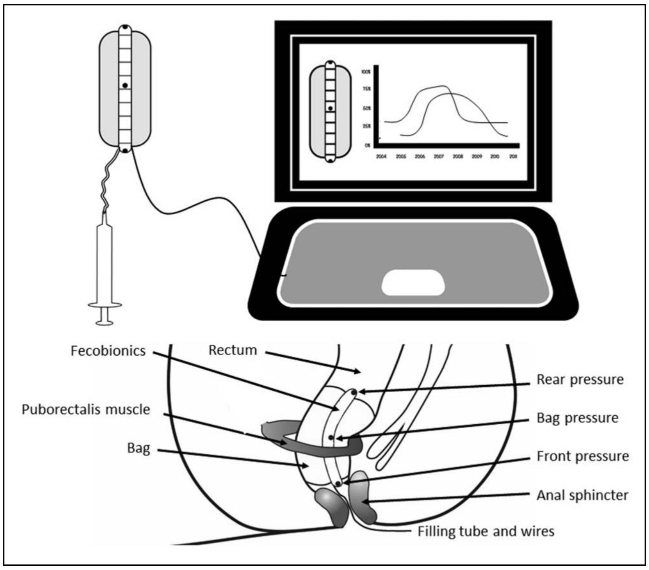

Figure 1. Sketches of Fecobionics. (Top) The system with the Fecobionics device, the syringe to fill the bag, and the computer for data transmission and power supply. (Bottom) Fecobionics inside the rectum with pressure sensors placed at the front, rear, and inside the bag. The front pressure sensor measures initially from the upper anal canal, whereas the bag and rear pressure sensors measure the rectal pressure.

Procedures

The experiments took place in a private room, and the investigators left the room during defecations. The Fecobionics test and ARM-BET were performed in random order, whatever was most convenient from a logistics point of view.

ARM with BET was conducted with a standard single-use 8ch anorectal catheter (G-90150; MMS, Enschede, the Netherlands). It was inserted with the subjects lying in left lateral position with bended hip and knees. The bag was placed in the rectum, and pressure was measured at 0.5-cm distance in the anal canal. Resting anal pressure, maximum anal squeeze pressure, the rectoanal inhibitory reflex (RAIR), urge volume, maximum tolerable volume, and expulsion duration for the 50-mL balloon were evaluated. BET was performed on the commode chair, and the investigators left the room during BET defecation.

Fecobionics was manually inserted in the rectum with the subjects in the same position as for ARM-BET. The subject changed from horizontal to sitting position and moved from the bed to the commode chair. After approximately 3 minutes of resting, the subjects were asked to squeeze the anal muscle twice and to cough twice to validate correct placement of Fecobionics, i.e., that the front sensor recorded pressure change on squeezing and coughing. Anal squeezes confirmed that the subjects were able to contract the anal sphincter. Afterward, the bag was distended to the desire-to-defecate level, where the volume was noted. The subjects were asked to evacuate Fecobionics after the investigators left the room. If the subject could not defecate the device in 2 minutes, the experiment was stopped and the device gently retracted.

Device safety was assessed during and after the procedures by feedback from the subjects studied as well as from the recorded data. The devices were inspected for leaks and damage or malfunction. Any safety issue and adverse effects were characterized and reported as unanticipated adverse device effects. The subjects were instructed in contacting a specific member of the research team if they experienced any problem after leaving the clinic.

Data analysis

Multiple parameters were calculated including the constipation score, duration of the whole experiment, expulsion duration, pressure amplitudes from the rear, bag and front sensors, and the difference between the rear and front pressure sensors.

Advanced parameters and analyses comprised preload-afterload (2,23,28,29) characteristics and computation of defecation indices (DIs). The front pressure was plotted as function of rear pressure as a proxy of preload-afterload conditions (2,23,28). The preload-afterload diagram is a new way to visualize Fecobionics data. The concept is adopted from cardiology where it has significant functional value (2,28). In cardiac physiology, preload is the end diastolic volume that stretches the ventricles to their greatest dimensions under variable physiologic demand. Afterload is the pressure against which the heart must work to eject blood during systole. The analogy for defecation is that rectum or abdominal muscle contractions generate the preload, whereas the afterload is due to anal resistance. Fecobionics measures the preload and afterload with the rear and front pressure sensors that are aligned with the defecatory trajectory.

We developed several DIs to make the pressure tracings including the preload-after load diagrams quantifiable. DIs-F was computed as the integration of the front pressure during the defecation attempt. DIs-F/s DIs-F was computed as the integration of the front pressure during the defecation attempt per time unit (seconds). The same type of DIs was computed for the rear pressure (DIs-R and DIs-R/s). Thus, these DIs expressed the preload and afterload during defecation with or without normalization for time. Based on these 4 measures, we computed 4 additional DIs that were multiplied with the volume at desire to defecate (named DIs-F * vol and so on). Furthermore, we computed the ratio between DIs-R * vol and DIs-F * vol, named DIs * vol (R/F ratio). This is a measure of the relative contribution of defecatory work load versus anorectal resistance. Hence, in total, we computed 9 DIs.

Statistics

The Shapiro-Wilk normality test was used to demonstrate whether the data were normal distributed or not. For parametric data, *t* test and ANOVA were used where appropriate and data are reported and plotted as mean $\pm$ SEM. For nonparametric data, the Kruskal-Wallis test and Mann-Whitney test were used, and data are reported and plotted as median and quartiles. In the box-whisker plot, all data are shown as median, quartiles, range, and outliers. The Pearson correlation was used for analysis of association of data obtained with the technologies used. Furthermore, Bland-Altman plots were generated to compare technologies (30). Results were considered statistically significant when $P < 0.05$ (2-tailed).

RESULTS

Exclusion of subjects

All subjects were Asians living in Hong Kong. Two suspected STC patients were excluded from analysis since they turned out to have mixed OD and STC. Hence, 26 OD patients (22F/4M, age 55.5 $\pm$ 3.1 years) and 8 STC patients (5F/3M, age 52.3 $\pm$ 5) were analyzed. Table 1 outlines relevant demographic data including clinical data. None of the parameters differed between the 3 groups except for the constipation score that was lowest in the NS group ($P < 0.05$). None from the NS group had constipation scores above 5, and 70% of the subjects had score 0–1.

Fecobionics data

None of the Fecobionics studies lasted more than 10 minutes, and no adverse effects were reported. Insertion typically took 10–30 seconds, movement to the commode chair and assessment of resting anal pressure and anal squeeze pressure took 4–5 minutes, distension of the bag 1 minute, and evacuation took up to the 2-minute limit (Figure 2).

Pre-evacuation Fecobionics data

The squeezes after insertion confirmed that the subjects from all groups were able to contract the anal sphincter in a controlled manner, i.e., the front pressure increased instantly. The median anal resting pressure was 43.5 (quartiles 36.0–56.7), 29.0 (24.8–44.0), and 32.5 (quartiles 21.7 and 42.1) cmH_2O in OD, STC, and NS, respectively ($\chi^2 = 2.7$, $P > 0.2$). The median anal squeeze pressure was 109.3 (quartiles 91.7–114.9), 81.5 (69.5–132.2), and 143.3 (132.3–164.0) cmH_2O in OD, STC, and NS, respectively ($\chi^2 = 10.8$, $P < 0.02$, see Figure 3 [left diagram] for comparison with ARM-BET data). Coughing induced simultaneous pressure increase in all channels in the range 100–150 cmH_2O.

The bag was slowly distended until the subjects felt desire to defecate. The slow distension resulted in variable bag pressure

Table 1. Comparison of demographic and clinical data between groups

	OD patients	STC patients	NS
Age (yr)	55.5 ± 3.1 yr	Age 52.3 ± 5	53.9 ± 4.1
Sex (female/male)	22/4	5/3	7/3
Weight (kg)	57.6 ± 190	52.9 ± 2.6	57.4 ± 3.4
BMI	23.0 ± 0.7	20.5 ± 0.6	21.5 ± 4.3
Wexner constipation scoring system score[13]	13.8 ± 0.9	14.6 ± 1.5	1.7 ± 0.7[a]
Duration of constipation (yr)	10.3 ± 1.5	13.3 ± 3.1	n/a
Previous abdominal surgery	0/26	0/8	n/a
Other symptoms and observations than constipation	Rectal bleeding 7/26 Straining to defecate 6/26 Incomplete emptying 3/26 Hemorrhoids 3/26 Open hemorrhoidectomy 3/26 Rectal intussusception 1/26	Hemorrhoids 2/8 Stapled hemorrhoidectomy 1/8 Tenesmus 1/8	n/a
Coexisting diseases	Dermatitis herpetiformis 1/26 Hyperlipidemia 1/26 Diabetes mellitus 1/26 Hypertension 1/26 Gastroesophageal reflux disease 1/26 Coronary artery disease 1/26	Dermatitis herpetiformis 1/8 Hypothyroidism 1/8 Diabetes mellitus 1/8 Hypertension 1/8	n/a
BET			
1-minute cutoff	50%	50%	6%
2-minute cutoff	50%	50%	0%
ARM			
Abnormal push procedure	80%	50%	50%
Rectal hyposensitivity	27%	13%	13%
Lack of RAIR	31%	13%	0%

Data are presented as mean and SEM or as percentage of the group size.
ARM, anorectal manometry; BET, balloon expulsion test; BMI, body mass index; OD, obstructed defecation; n/a, not available; NS, normal subjects; RAIR, rectoanal inhibitory reflex; STC, slow transit constipation.
[a]Statistical difference between healthy subjects and the patient groups for the constipation score ($P < 0.05$). No other statistical differences were noted.

increase and often minor anal sphincter relaxation. The median desire-to-defecate volume was 80 (quartiles 56–80), 60 (54–80), and 45 (23–60) mL in OD, STC, and NS, respectively ($P < 0.02$, see Figure 3 [left diagram] for comparison with ARM-BET data). Fourteen of the 26 OD patients (54%) reached the 80-mL maximum bag volume before feeling desire to defecate or even without feeling desire to defecate. Three of the 8 STC patients reached the 80-mL level (37%). For the NS, only 1 male subject reached the 80-mL level (10%).

Evacuation of Fecobionics

The subjects were asked to evacuate Fecobionics after the desire to defecate level or maximum volume was reached. None of the subjects (normal or with constipation symptoms) reported pain, discomfort, or bleeding from the anus during or after the experiments.

Eight OD patients could not expel Fecobionics within the 2-minute period. All STC patients and NS expelled Fecobionics within 1 minute. The median expulsion duration was 37 (quartiles 15–120), 6 (3–12), and 11 (8–11) seconds for OD, STC, and NS, respectively ($P < 0.01$, see Figure 3 [left] for comparison with ARM-BET data). The median number of contractions to expel Fecobionics was 4 (quartiles 2–10), 1 (1–3), and 2 (1–3) in OD, STC, and NS, respectively ($P < 0.03$). Some of the OD patients would use more than 30 contraction attempts before the end of the 2-minute defecation limit. Figure 2 shows representative pressure tracings during expulsion from all 3 groups. Tracings from an NS and an STC patient are shown in Figure 2a,b. The OD subjects showed very different patterns as illustrated in Figure 2c–h. Some had a defecation pattern similar to the normal and STC groups (Figure 2c), others displayed more complex defecation patterns, often with multiple contraction attempts and dyscoordinated anal relaxation. When the front pressure reached zero (atmospheric pressure), the front was outside anus. When the rear pressure reached the same point, the whole device was expelled.

The NS and the STC patients had many features in common. For the OD patients, we identified 5 distinct patterns:

1. Subjects (n = 6) who appeared normal (Figure 2c,k), i.e., with normal Fecobionics parameters including desire-to-defecate volume and expulsion duration. However, some were characterized as low-pressure defecation. ARM-BET and

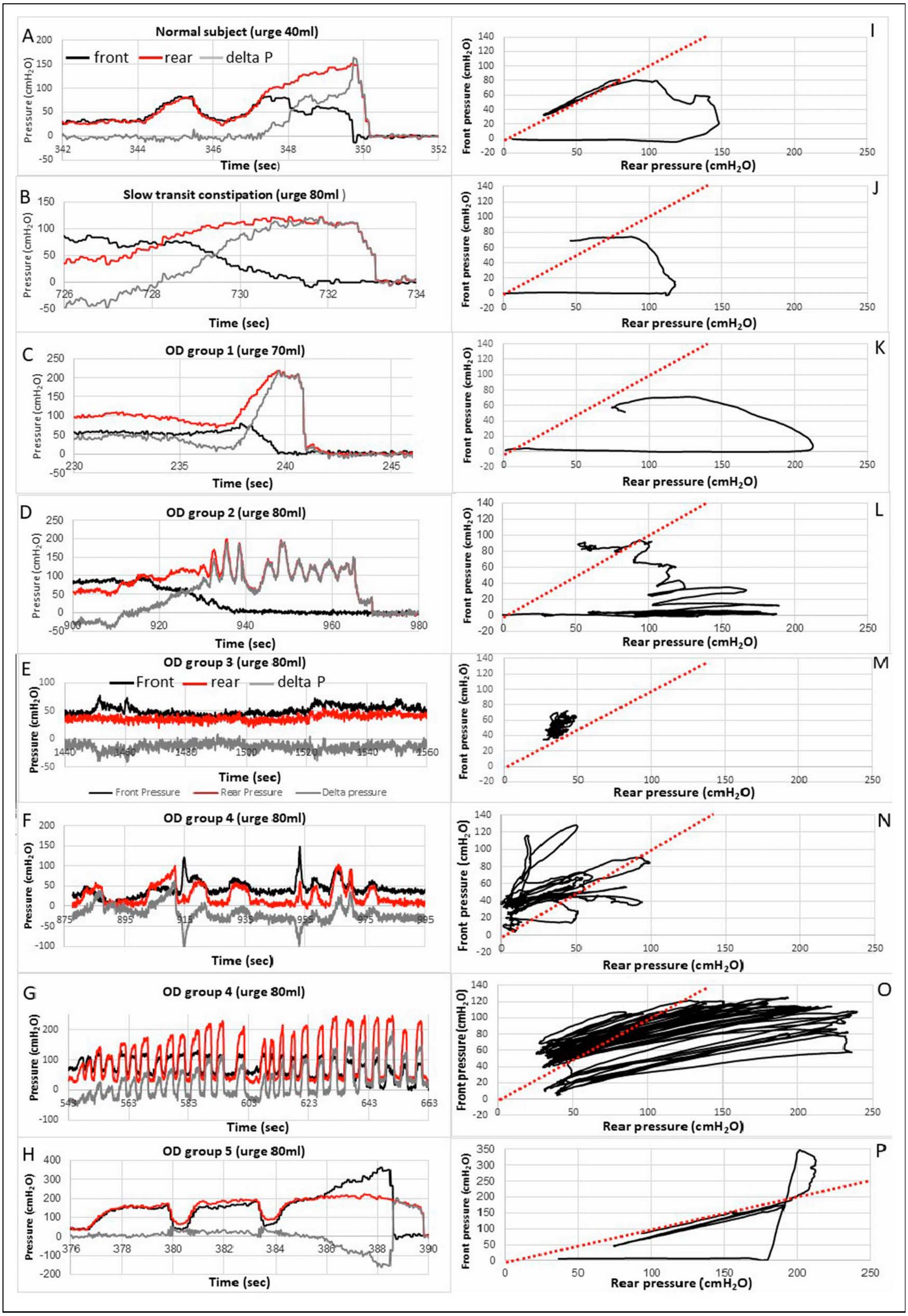

Figure 2. Representative examples of defecations from an NS (**a**) and patients with STC (**b**) and OD (**c**-**h**). The left diagrams illustrate the front (black) and rear (red) pressures and the delta pressure (gray) as function of time. The right diagrams (I-P) show the front pressure as function of the rear pressure. The stippled line is the line of unity. The NS and STC patients showed almost similar patterns, whereas the OD patients showed very variable patterns during defecation, indicating the existence of subtypes. See text for further information. Note that the axis scales differ between some of the diagrams. NS, normal subjects; OD, obstructed defecation; STC, slow transit constipation.

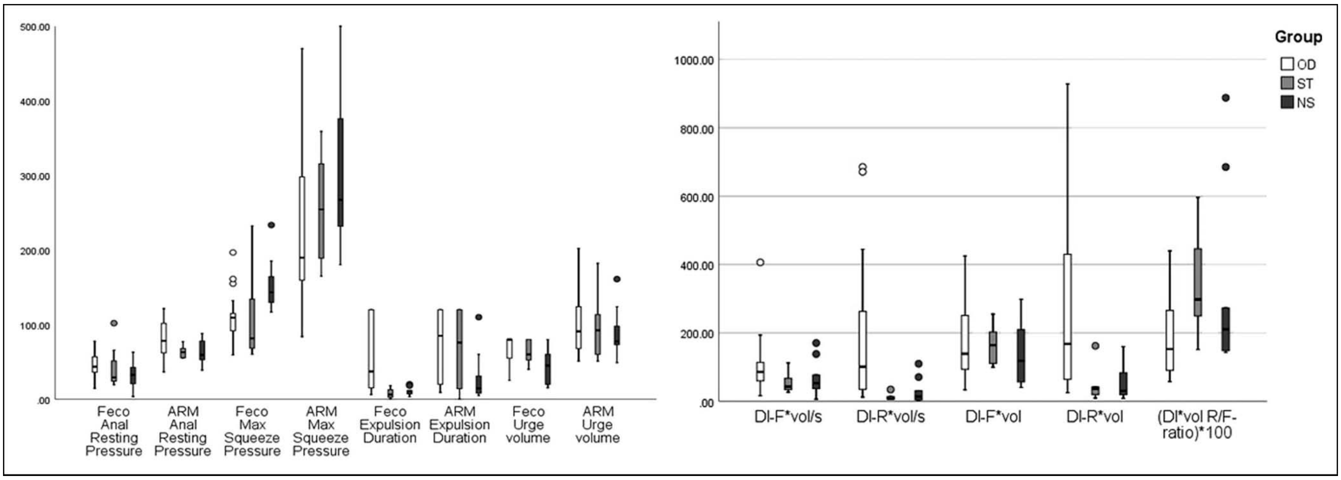

Figure 3. Box-whisker plots of comparative parameters obtained with ARM-BET and Fecobionics (left) and selected Fecobionics DI. For the comparative parameters (left), Fecobionics expulsion duration showed the most marked difference between groups. The DI differed between groups (right). OD patients clearly showed more variability than the 2 other groups. ARM, anorectal manometry; BET, balloon expulsion test; DI, defecation index; OD, obstructed defecation

defecography were normal for the 6 subjects. Constipation scores were in the range 6–15, except 22 for 1 subject. The clinical descriptions revealed that these were mild cases, often with bowel movement every third day, some feeling of obstruction, and passing hard stools.

2. Subjects (n = 5) who were not capable of fully expelling the device, i.e., it would hang with the front outside anus for 10–40 seconds before being finally expelled (Figure 2d,l). Two of the 5 subjects had the lowest bag volumes (40 mL) with Fecobionics. Constipation scores were in the range 8–17. Defecography showed largely normal defecations, although small anal diameter was noted in 2 subjects. All subjects had normal RAIR on ARM. Three of the subjects did not defecate BET within the 2-minute period. The clinical descriptions revealed that most subjects did moderate straining to defecate, bowel movement was less frequent compared with group 1, and often had minor bleeding during defecation.
3. Subjects (n = 4) characterized by low-amplitude sustained contraction, i.e., a pattern without the typical phasic defecatory attempts (Figure 2e,m). One patient seemed to fit both this group and group 2 above. Constipation scores were in the range 13, 15, and 27. Defecography gave indications of pelvic floor weakness in 3 patients, whereas the third had normal defecography. All had RAIR, but 3 of the 4 patients could not expel BET in 120 seconds. Clinical description was similar to group 2. The patients had bowel movements every 4–7 days.
4. Subjects (n = 3) with multiple simultaneous contractions. All had maximum expulsion duration of 120 seconds with Fecobionics, whereas 1 subject had lower than 120-second expulsion duration with ARM-BET. For Fecobionics, 2 subjects had low-amplitude contractions (Figure 2f,n), whereas the third subject had high-amplitude repetitive contractions (Figure 2g,o). Constipation scores were in the range 8–16. Defecography shows clear indication of functional outlet with delayed and incomplete evacuation in 1 subject, dyskinetic puborectalis muscle syndrome with anismus in the second patient, and excessive pelvic floor descent during evacuation with sluggish initiation and progress of evacuation with incomplete emptying of contrast in the third. All had absent RAIR with ARM. The clinical description revealed a highly variable pattern, e.g., the 3 patients had bowel movements every single, fourth or seventh day.
5. Subjects (n = 5) who showed paroxysmal anal contraction beyond what was observed in the other groups (Figure 2h,p). Three patients reached the maximum distension volume of 80 mL. Constipation scores were 8, 10, 13, 19, and 20 in 2 subjects. One patient had normal defecography except anterior rectocele. Three of the subjects defecated BET before the 2-minute limit, and 1 of the subjects had absence of RAIR on ARM. From the clinical descriptions, we noticed that several patients had no sensation of urge.

The remaining 2 patients did not fit these patterns. One dropped the device before asked to defecate it.

Fecobionics preload-afterload diagrams demonstrated clockwise loops that reflected the abdominal contractions and anal relaxation. Representative diagrams are shown in the right column of Figure 2. Most NS and STC patients defecated Fecobionics in 1–2 contractions, i.e., with only 1 or 2 loops (Figure 2a–d). The OD patients showed a variable pattern with some patients appearing normal, whereas others had multiple loops and could not defecate Fecobionics within the 2-minute limit. The patients had a variable pattern depending on the tentative subgroups defined above. Some showed uncoordinated patterns, whereas others slowly changed the loops downward. At some point, a cutoff was reached where the anal pressure dropped quickly followed by complete expulsion of the device.

All DIs differed between the groups except DIs-F and DIs-F/s. The most significant indices were those that were multiplied by the volume. Both preload and anal afterload were increased, reflecting that higher preload is needed to overcome the afterload ($P < 0.01$; Figure 3, right). The DIs * vol R/F ratio was computed as a proxy of the workload relative to anal resistance. The median ratio was 1.56 (quartiles 1.05–2.66), 2.98 (2.50–4.46), and 2.11 (1.50–2.71 for OD, STC, and NS, respectively). OD was different from STC (z-score −2.10, $P = 0.05$).

We analyzed how the DIs distributed for the 5 groups defined above. Data are provided in Figure 4. The most noticeable results were that all patients in (i) group 1 had lower DIs-F * vol and DIs-R * vol, (ii) group 2 had lower DIs-F*vol/s, and (iii) group 4 had higher DIs-F * vol and DIs-R * vol and lower DIs * vol R/F ratio.

Group/DI parameter	DI-F*vol/s	DI-F*vol	DI-R*vol/s	DI-R/vol	DI*vol R/F ratio
Group 1	↔↓↓↑↓↓	↓↓↓↓↓↓	↔↔↔↑↓↑	↓↓↓↓↓↓	↔↔↑↑↑↑
Group 2	↓↓↓↓↓	↓↑↓↓↑	↓↑↓↓↔	↓↑↓↓↑	↑↑↑↓↑
Group 3	↑↑↓↓	↑↑↓↓	↓↓↓↑	↑↑↓↑	↓↓↓↑
Group 4	↔↔↑	↑↑↑	↓↓↑	↑↑↑	↓↓↓
Group 5	↑↔↑↓↓	↑↓↓↓↓	↑↑↑↓↑	↔↔↑↓↑	↓↑↓↑↓

Figure 4. Distribution of 5 DI relative to the median for the OD patients. Notes: The arrows indicate whether a subject was higher, lower, or similar to the median of the whole group of OD patients. The fields shaded with gray color indicate that all patients in the group showed identical behavior. DI, defecation indices; F, front; OD, obstructed defecation; R, rear; vol, volume.

The 5 OD patients with absence of RAIR on ARM had high desire-to-defecate volumes (n = 1 for 70 mL and n = 4 for 80 mL). Only other characteristics for these 5 patients was that all had lower than average DIs-F * vol.

Reference recordings

ARM-BET showed absence of RAIR in 8 OD patients and in 1 STC patient. All NS had RAIR. The median resting anal pressure was 78.3 (quartiles 62.8–101.3), 63.0 (55.8–67.5), and 59.4 (54.5–79.3) mm Hg in the OD, STC, and normal groups, respectively ($P < 0.05$). The median squeeze pressure was 189.8 (164.2–297.0), 254.5 (192.5–311.3), and 235.0 (222.3–355.8) mm Hg in the 3 groups ($P > 0.1$, Figure 3 [left]).

Thirteen of 26 OD (50%) and 4 of 8 STC (50%) patients could not expel BET within the 2-minute limit, whereas all NS expelled BET within 110 seconds (Table 1). The median expulsion duration for BET was 85 (20.5–120.0), 76.0 (18.5–120.0), and 18.5 (9.5–26.0) seconds for OD, STC, and NS, respectively ($P < 0.05$). The median urge volume was 91.0 (70.0–121.8), 92.5 (62.5–112.3), and 77.5 (75.3–114.8) mL for OD, STC, and NS, respectively ($P > 0.5$). The maximum tolerable volume was 128.5 (96.5–192.3), 130.0 (100.5–150.5), and 126.0 (111.5–176.3) mL for OD, STC, and NS, respectively ($P > 0.5$). Figure 3 [left] show parameters that were obtainable with both Fecobionics and ARM-BET (anal resting and squeeze pressures, desire to defecate volume, and expulsion duration). The most notable difference between OD and the 2 other groups was found for Fecobionics expulsion duration, whereas the other parameters show a great deal of overlap. Figure 5 compares abovementioned 4 parameters using Bland-Altman plots. For all 4 parameters, the ARM-BET data differed significantly from Fecobionics data. Correlation between tests was poor with the R^2 between 0.08 and 0.30.

DISCUSSION

This feasibility study demonstrated significant differences between patients with OD and STC when studied with Fecobionics. STC patients had similar defecation patterns as NS. Novel phenotypes and DIs were demonstrated. Although not a primary aim of this study, we succeeded in identifying distinct subtypes of OD. ARM-BET failed to show similar differences, and in general, ARM-BET data differed from Fecobionics data.

Fecobionics concept, methodological aspects, and limitations of study

As often encountered in anorectal testing, disagreement may exist between tests and between test results and symptoms (20,31,32). This was also the case in this study, e.g., half of the OD patients evacuated BET within 2 minutes, the normal range (Table 1). BET data of more than 1- or 2-minute duration are by many considered abnormal. However, the test had considerable numbers of false positive and false negative (33) and should be used in conjunction with other anatomic and functional testing to confirm the diagnosis of evacuation disorder (34). The final categorization between OD and STC was based on symptoms and the results of the 4 tests. However, the test results did not make us reclassify patients in any of the cases. Two suspected STC patients were excluded from analysis since they turned out to have mixed OD and STC. Suspected OD patients who turned out also to have slow transit were not excluded.

This study was performed in an Asian population. Only sparse literature exist on differences in GI function between races. Although significant differences are not to be expected, it is a limitation that only 1 population was studied at a single site. Furthermore, the OD group turned out to have a higher percentage of women. However, this is unlikely to affect the findings, especially on the OD subtypes.

Fecobionics provides a new bionics concept for assessment of anorectal physiology and diagnostics by integrating several current tests. Compared with the descriptive data presented previously, this study is the first quantitative study conducted in a patient cohort. Technological and methodological aspects including providing measurement during defecation and the advantage of measuring axial (front and rear in the direction of the trajectory) pressures during defecation have been discussed (23). This is a key design feature distinctly different from ARM that measure radial pressures (16). The anal pressure measured by Fecobionics was lower than the pressure measured by ARM. The likely explanation is that ARM provides a stationary measure along the entire anal canal length, whereas Fecobionics measures in the proximal part of the sphincter and likely displaced in rectal direction during anal squeeze. Although not a primary aim of this study to compare ARM-BET and Fecobionics, we noted differences in almost all parameters. This is likely due to differences in device design, bag/balloon behavior during distension, and placement of the probe, e.g., ARM-BET likely distends the bag more proximal in rectum. The differences between technologies are not surprising since each technology has limitations, and previous reports have shown low specificity, considerable disagreement between the results of anorectal tests for diagnosing constipation, which correlate poorly with symptoms and treatment outcomes (20). New test standards are needed (20). This is a critical problem in the anorectal clinics that impacts patient management and care. Improved test devices for integrated anorectal function studies are warranted to improve diagnostics and therapeutics such as biofeedback treatment (35). In addition to the data presented in this study, we consider it favorable that the Fecobionics test takes less than 10 minutes compared with

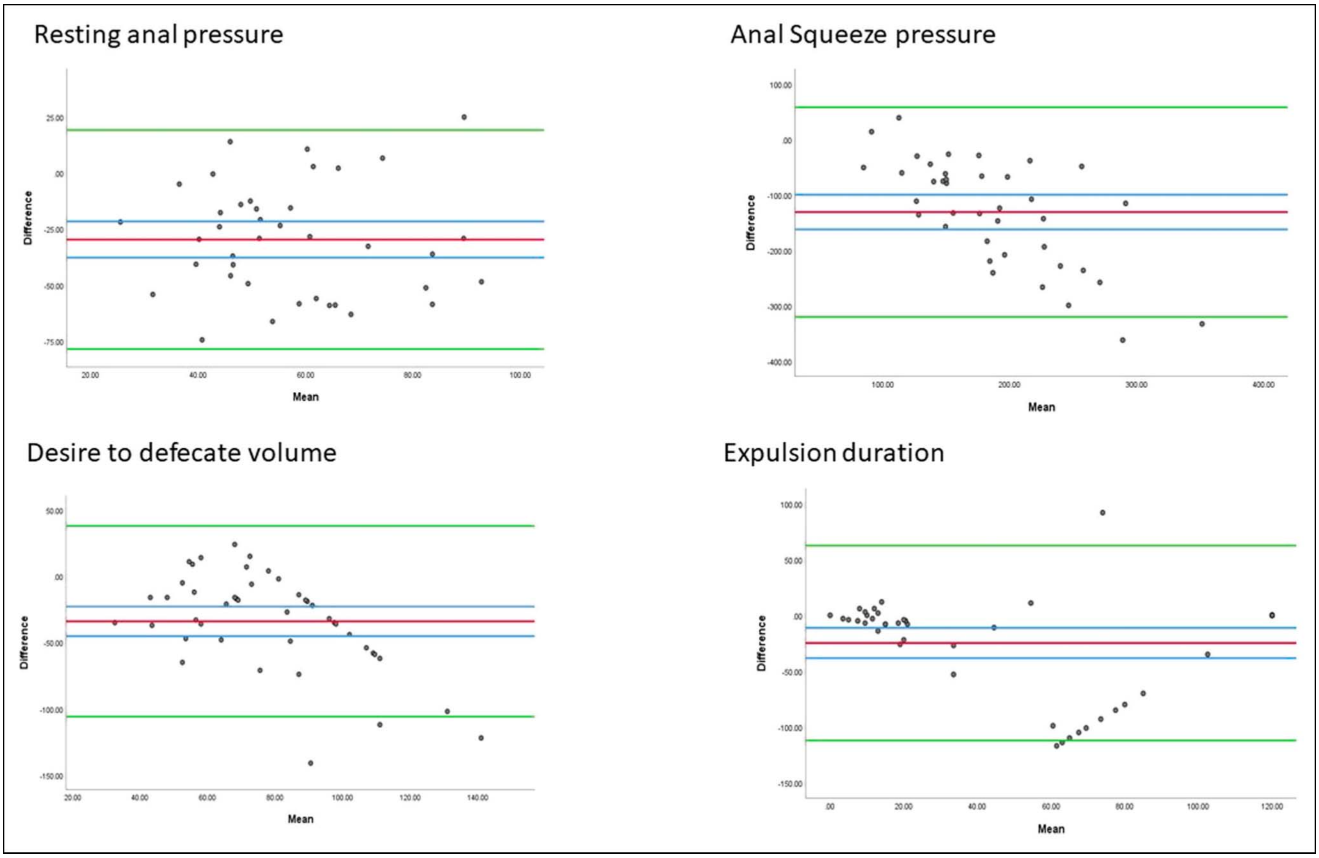

Figure 5. Bland-Altman plots demonstrating difference for 4 comparative parameters obtained by Fecobionics and ARM-BET. The red, green, and blue lines are the average, confidence intervals, and 2 SD. In all cases, the bias was larger than the confidence intervals and the 2 methods differed. ARM, anorectal manometry; BET, balloon expulsion test.

40–45 minutes for ARM-BET. Unfortunately, our ARM system did not allow reliable recordings of the 4 subtypes of dyssynergia (4,36). It would have been of interest to compare these subtypes with Fecobionics results in light of the subtypes identified in this study with Fecobionics (see below). It would also have been of interest to study in more detail the association between technologies and symptoms. However, we found that the OD patients had little span in constipation scores (most were between 11 and 15), hampering correlation analysis.

This feasibility study demonstrated successful access in all subjects with no device-related adverse events or device malfunctions. Fecobionics provided data for novel analysis of preload-afterload loops. Rectum or abdominal muscle contractions generate the preload, and the afterload reflects anal resistance. The preload must exceed the afterload before evacuation can take place since feces movement cannot occur against an anorectal pressure gradient. Fecobionics (and feces) will be expelled when the rectoanal pressure gradient is large enough to overcome the frictional force between the surface and mucosa. In the real situation with feces, the size and hardness of feces, as well as the anorectal angle, is important for the frictional force. For the pressure gradient, measurement of axial pressures and at front, rear, and inside the bag is essential in this regard. The value of the loop diagram is convincingly illustrated in Figure 2. Pressure tracings including preload-afterload diagrams need to be quantifiable. Hence, 9 DIs were developed. Clearly, that many indices may not be necessary as well as they may need refinement in future studies.

This study only used data from the pressure sensors in Fecobionics as this is the most developed and validated feature of the device. Future studies may include electronic measurement of the anorectal angle during defecation (22,23). Fecobionics can be developed further to encompass impedance planimetry that will allow for measurement of shape changes during defecation and better estimates of the preload-after load properties and stress-strain properties (2,29). For example, preload is better estimated as rectal diameter than rectal pressure. Developments are also ongoing for making Fecobionics wireless and battery-powered. Furthermore, the tube for filling the bag can be detached to avoid tethering after bag filling, and the bending rigidity of the device (stool consistency) can be changed by using a different resin to construct the core. Making the device stiffer may be an advantage for studying constipation patients with hard stools.

Pathophysiological aspects

The diagnosis of constipation is essentially made from the patient's description of the symptoms, physical examination by rectal exploration, and various tests. Of the 3 major types of CC, OD is the most challenging and often associated with dyssynergia (4,31). Dyssynergic defecation is believed to be the result of pelvic floor dysfunction. Effective treatment requires determination of the cause and identification of the components in the defecatory mechanism that fail. Improved integrated diagnostics may aid individualized treatment of subtyped patients, define those who may benefit from biofeedback training, and define the specific component of the continence mechanism to target with different biofeedback modes such as correcting the neuromuscular dysfunction including relaxing the anal sphincter and straightening the anorectal angle in patients with dyssynergia, or enhance rectal sensory perception in patients with impaired rectal sensation (4,37,38). However, technologies such as ARM have provided many parameters that did not significantly change the biofeedback field. It remains to be shown if Fecobionics, when fully developed, will facilitate development of new biofeedback protocols and improve biofeedback efficacy.

In the anorectal clinic, the first clinical challenge is to distinguish OD from STC. Transit time studies with ingestible markers and defecography are useful in this regard (14–16,39–41). In this study, we found Fecobionics was useful in distinguishing these patient groups too. If we disregard the first OD subtype group, OD patients clearly had different pressure signatures, preload-afterload plots, and DIs compared with STC patients. Especially the DIs reflecting preload and anal afterload dysfunction were different. It is of interest to notice that the STC patients defecate similar to NS. In fact, they seem to have even more efficient defecation with slightly faster defecation and fewer contractions. This may be due to various reasons, i.e., since they feel constipated, they voluntarily or involuntarily created higher expulsion pressures. ARM-BET largely failed in distinguishing the 2 constipation groups.

The clinical challenge is to determine the subtype of OD patient. Rao et al. worked out a classification for dyssynergia where 4 subtypes of pelvic floor dyssynergic defecation based on ARM were proposed. This 2 × 2 square classification is based on whether the patient can generate adequate expulsion force and relaxation of the anal sphincter (36,38). However, the classification has been disputed since up to 90% of NS show sign of dyssynergia (31,32), which we also confirmed in a previous study (23). In this study, it was not a primary aim to subgroup OD patients. On the other hand, wide variability was noted, and the pressure phenotypes appeared to fall into 5 subgroups. Unfortunately, some subgroups only had 3-4 patients; therefore, much larger clinical trials are needed. However, this study provides a good starting point for follow-up clinical trials. Based on our study, the 2 × 2 dyssynergia classification may be too simple. It is difficult to translate the phenotypes in this study to the original dyssynergia classification. The first subtype group has pressure signatures like NS and only presented mild constipation symptoms. The second group was not capable of fully defecating the device at once, perhaps because of lack of sensation and lack of anal relaxation. It is probably closest to the Rao subtype III. Our group 3 had long low pressure rectal pressure contraction. Some patients had indication of weak pelvic floor on defecography and may overlap with Rao Subtype IV, whereas the last would be subtype II. Group 4 in this study was clearly the one with most severe neuromuscular dysfunction. Contractions were simultaneous, i.e., there would be paroxysmal anal contractions, which largely correspond to Rao subtype I for some patients and subtype 2 for others. Our subtype group 5 is also consistent with Rao subtype I or II. Most subtypes in this study had characteristics patterns for the DIs (Figure 4). Much larger scale studies are needed to shed light on this matter.

CONCLUSIONS AND FUTURE ASPECTS

We demonstrated successful application of Fecobionics in a cohort of constipation subjects. Fecobionics made it possible to evaluate conventional measures as well as novel DIs. Fecobionics provides several improvements to current anorectal functional assessment technologies, including mechanical properties that mimic stool and pressure measurements in the direction of the trajectory. This study suggests that the device is safe and useful for assessment of anorectal physiology and evacuatory efficacy.

We demonstrated significant differences between OD and STC patients and were able to define subtypes. Well-designed large-scale anorectal clinical trials are required to evaluate the clinical potential, especially for patients with constipation, which likely is the primary indication for Fecobionics. Future studies will provide a larger cohort for subtyping and will be useful for evaluation against the Rao subtyping classification. Our data as well as literature point to that a new gold standard is needed (36,38).

The potential translational outcome of future studies is a bionics platform for anorectal functional studies based on simulated defecations. This study establishes the foundation for future use of Fecobionics for dyssynergia diagnostics and as a potential biofeedback tool, where patients based on the signatures visualized on the graphical user interface can learn to control the muscles and correct the neuromuscular dysfunction.

CONFLICTS OF INTEREST

Guarantor of the article: Hans Gregersen, MD, PhD, AGAF.
Specific author contributions: H.G., K.F., T.M., and S.N. designed the study and advised the experimental work during the study period. S.C., C.W., K.F., W.L., and H.G. conducted the experiments. Data analysis was conducted by S.C., D.M., and H.G. and interpreted by all authors. All authors had access to the data, revised the manuscript, and approved the final version for submission.
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Potential competing interests: H.G. has filed patent applications but has no ownership in the manufacturing company. No other conflicts of interest noted.
Clinical trial registration: www.clinicaltrials.gov Identifier: NCT03317938.

Study Highlights

WHAT IS KNOWN

- ✓ The pathophysiology of defecation disorders has been described in numerous studies.
- ✓ Disagreement exists between results of anorectal tests, and they correlate poorly with symptoms.

WHAT IS NEW HERE

- ✓ We used the novel Fecobionics in 2 groups of constipated patients and compared with a cohort of normal subjects.
- ✓ Novel defecatory pressure signatures and defecation indices are presented beyond what is possible with conventional technology.
- ✓ The signatures and defecation indices differed between groups and showed large variation in obstructed defecators, indicating subtypes.

TRANSLATIONAL IMPACT

- ✓ The analysis proved important for subtyping of patients with anorectal disorders, which is a prerequisite for optimal treatment.

FUNCTIONAL GI DISORDERS

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