J Neurogastroenterol Motil, Vol. 28 No. 4 October, 2022
pISSN: 2093-0879 eISSN: 2093-0887
https://doi.org/10.5056/jnm21137
Journal of Neurogastroenterology and Motility

Original Article

Predicting Responsiveness to Biofeedback Therapy Using High-resolution Anorectal Manometry With Integrated Pressurized Volume

Myeongsook Seo,[1] Jiyoung Yoon,[2] Kee Wook Jung,[3*] Segyeong Joo,[4*] Jungbok Lee,[5] Kyung Min Choi,[4] Hyo Jeong Lee,[6] In Ja Yoon,[3] Woojoo Noh,[3] So Young Seo,[3] Do Yeon Kim,[3] Sung Wook Hwang,[3] Sang Hyoung Park,[3] Dong-Hoon Yang,[3] Byong Duk Ye,[3] Jeong-Sik Byeon,[3] Suk-Kyun Yang,[3] and Seung-Jae Myung[3*]

[1]Department of Gastroenterology, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Gangwon-do, Korea; [2]Department of Gastroenterology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeoungbu, Gyeonggi-do, Korea; Departments of [3]Gastroenterology, [4]Biomedical Engineering, and [5]Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; and [6]Health Screening and Promotion Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background/Aims
Biofeedback therapy is widely used to treat patients with chronic constipation, especially those with dyssynergic defecation. Yet, the utility of high-resolution manometry with novel parameters in the prediction of biofeedback response has not been reported. Thus, we constructed a model for predicting biofeedback therapy responders by applying the concept of integrated pressurized volume in patients undergoing high-resolution anorectal manometry.

Methods
Seventy-one female patients (age: 48-68 years) with dyssynergic defecation who underwent initial high-resolution anorectal manometry and subsequent biofeedback therapy were enrolled. The manometry profiles were used to calculate the 3-dimensional integrated pressurized volumes by multiplying the distance, time, and amplitude during simulated evacuation. Partial least squares regression was performed to generate a predictive model for responders to biofeedback therapy by using the integrated pressurized volume parameters.

Results
Fifty-five (77.5%) patients responded to biofeedback therapy. The responders and non-responders did not show significant differences in the conventional manometric parameters. The partial least squares regression model used a linear combination of eight integrated pressurized volume parameters and generated an area under the curve of 0.84 (95% confidence interval: 0.76-0.95, $P < 0.01$), with 85.5% sensitivity and 62.1% specificity.

Conclusions
Integrated pressurized volume parameters were better than conventional parameters in predicting the responsiveness to biofeedback therapy, and the combination of these parameters and partial least squares regression was particularly promising. Integrated pressurized volume parameters can more effectively explain the physiology of the anorectal canal compared with conventional parameters.
(J Neurogastroenterol Motil 2022;28:608-617)

Key Words
Biofeedback; Constipation; Least-squares analysis; Manometry

Received: July 6, 2021 Revised: November 25, 2021 Accepted: March 13, 2022

*Correspondence: Kee Wook Jung, Segyeong Joo, and Seung-Jae Myung are equally responsible for this study.
Kee Wook Jung, MD, PhD
Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3900, Fax: +82-2-3010-6517, E-mail: jung.keewook30@gmail.com
Segyeong Joo, PhD
Department of Biomedical Engineering, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-5101, Fax: +82-2-2045-4133, E-mail: sgjoo@amc.seoul.kr
Seung-Jae Myung, MD, PhD
Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3917, Fax: +82-2-3010-0824, E-mail: sjmyung@amc.seoul.kr
Myeongsook Seo and Jiyoung Yoon contributed equally to this manuscript.

Introduction

Recent developments of high-resolution anorectal manometry (HRAM) have allowed for precise anorectal pressure measurements to be obtained using densely arranged catheter sensors.[1,2] HRAM is a basic technique used to diagnose constipation, but it is more advanced than conventional manometry. Conventional anorectal manometry has limitations involving data analysis and signal interpretation because it relies on linear waves emitted from single sensors that are intermittently spaced. HRAM provides color-contoured topographic plots based on the distance, time, and amplitude, whereas conventional manometry solely generates linear plots of amplitude signals. However, although HRAM provides a considerable amount of information, we still use the parameters from conventional manometry linear waves, which form the basis of the current diagnostic criteria.

In a previous study, we attempted to precisely measure anal canal muscular contractility using HRAM.[3-5] We reported the potential utility of integrated pressurized volume (IPV), which can be calculated by multiplying the distance, time, and amplitude. The IPV is the volume under the HRAM surface plot, and the IPV parameters and their combination through partial least squares regression (PLSR) could predict the results of delayed balloon expulsion (BE) tests.[4]

Biofeedback therapy (BFT) is commonly used for patients with chronic constipation, especially those with dyssynergic defecation (DD).[6] Three randomized controlled trials showed that BFT resulted in superior outcomes over other modes of therapy such as polyethylene glycol, diazepam, and sham feedback therapy, with a success rate of 70-81%.[7-9] Moreover, in our previous study, BFT showed long-term effectiveness in patients with dyssynergic defecation after a median follow-up of 44 months.[10] Despite these encouraging results, a considerable proportion of patients with DD do not respond to BFT, and there are conflicting reports regarding the parameters that can be used to predict the BFT success rate.[11-14] Moreover, no reports have been published describing the use of HRAM with spatiotemporal plotting. Thus, we aim to demonstrate the correlation between IPV and BFT responders during simulated evacuation (SE) and use IPV to generate a predictive model for the response to BFT.

Materials and Methods

Study Population

In total, 104 female patients with constipation who underwent more than 3 sessions of BFT at Asan Medical Center from September 2011 to September 2015 were screened for this study. Elevation of the rectal pressure by > 1 standard deviation (SD) from the mean value and relaxation of the anal sphincter by > 20% of the baseline anal sphincter tone during SE was considered normal defecation.[15,16] Dyssynergia was diagnosed as ineffective rectal propulsion (< 1 SD from the mean value or < 25 mmHg [mean, 55.51 mmHg; SD, 30.53 mmHg in asymptomatic normal volunteers]) or paradoxical anal contraction during SE. These values were obtained from a previously published study involving a normal healthy population using a HRAM catheter in our center.[3,4,17,18] In Rao's study,[19] these patterns were classified as 4 abnormal patterns including paradoxical anal contraction with adequate propulsive force (type I) or without (type II), or incomplete anal relaxation with adequate propulsive force (type III) or without (type IV). We excluded 5 pa-

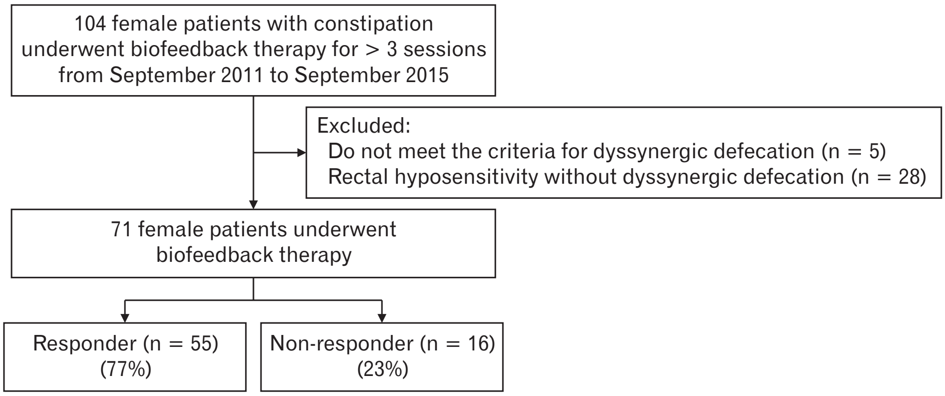

Figure 1. Flowchart of the study patient selection process. Five patients not satisfying the dyssynergic defecation (DD) criteria were excluded, as were 28 patients who presented with rectal hyposensitivity only. Finally, 71 female patients with DD were enrolled in this study.

tients whose medical records did not meet the criteria for DD. We also excluded 28 patients with rectal hyposensitivity without DD because the BF protocol was different. Finally, 71 female patients with DD (age: 48-68 years) were included in the study (Fig. 1). Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (Approval No. 2012-0082, 2013-1052, and 2014-0282).

Data Assessment and Study Protocol

Anorectal physiologic tests were conducted prior to BFT. All patients underwent HRAM and BE testing, and subsequently, BFT. Before and after BFT, all patients completed the Rome III criteria-based structured questionnaires composed of 6 aspects of constipation symptoms. The questionnaires evaluated stool frequency, hard stool frequency (Bristol stool form scales 1-2), the frequency of manual maneuvers for the facilitation of defecation, and severity using self-reported numeric scales (visual analog scales) for straining (0 = absent, 10 = severe), sensation of incomplete evacuation (0 = absent, 10 = severe), sensation of anorectal obstruction (0 = absent, 10 = severe), and global bowel satisfaction (GBS) (0 = dissatisfaction, 10 = satisfaction). By referring to a previous study,[10] we defined responders as those who showed a 3-point increase or higher in the GBS score after BFT or a 2-point increase if the baseline GBS score was higher than 6 points.

Anorectal Physiologic Tests

All patients underwent an initial HRAM using sensors with a length of 6 cm and 23 channels (Sandhill, Highland Ranch, CO, USA). All standard procedures were performed by a single experienced nurse. The procedural details are described in a paper published previously by our center.[4] With the patient assuming the left lateral decubitus position, the manometry catheter was inserted into the rectum. The catheter had a latex balloon on its tip, and the anal canal sensors and rectal pressure sensors were separated by 10 mm to measure the pressure of the anterior, posterior, right, and left quadrants. To calculate the mean sphincter pressure, the pressure values recorded by the anal sensors were averaged. The pressure values during resting, squeezing, and SE, as well as the minimal volumes for the first sensation, rectoanal gradient, rectoanal inhibitory reflex, desire to defecate, and urgency were reported.[20] The defecation index (DI) was calculated as the ratio of rectal pressure to anal residual pressure during straining.[15,19] A rectal BE test was performed, and an elapsed time < 1 minute was considered successful.

Biofeedback Therapy

Details of the BFT protocol have been published previously.[4,10] In brief, the BFT comprised a 40-60-minute session, performed once or twice a week, using electromyography (Orion Platinum; SRS Medical Systems, Redmond, WA, USA). An abdominal sensor probe was attached to the abdomen, and surface electromyography was performed in the anal canal during a sham defecation. The patient practiced increasing the voluntary strength of the external sphincter while looking at the graph of the electrical activity. Additionally, the protocol included an abdominal push effort with anal relaxation synchronized with strain, BE retraining, and rectal sensory retraining, while modifying inappropriate responses. An experienced therapist performed all of the BFT procedures.

Data Analysis

The MATLAB program (MathWorks, Natick, MA, USA) was used to analyze the HRAM profiles during SE. The pressure signals during SE from the rectum to the anus (6-cm and 1-cm from the distal tip of the catheter, respectively) were divided into five 1-cm-separated regions (Fig. 2A). The 5 regions' IPVs were

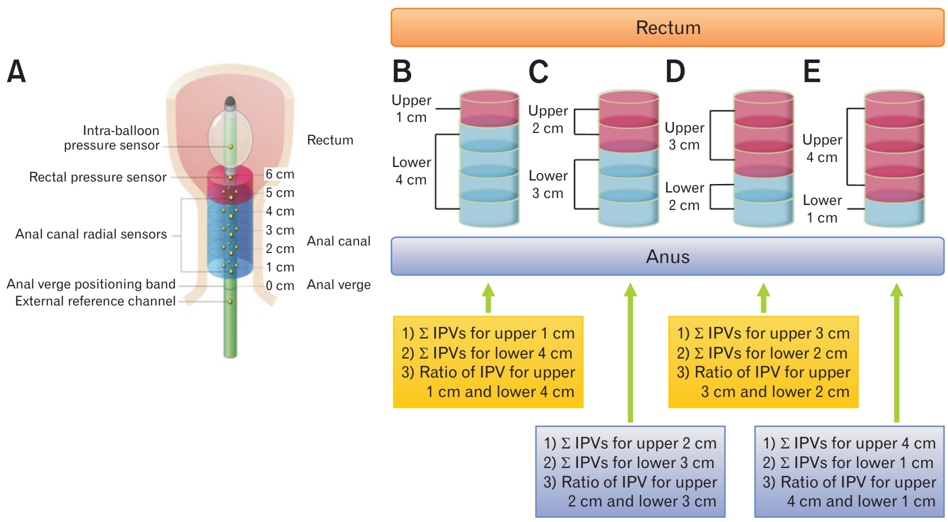

Figure 2. Four categories of integrated pressurized volumes (IPVs) from the rectum to the anal canal. (A) Categorization of the pressure signals during simulated evacuation from the rectum to the anus into 5 regions. (B-E) IPVs from the lower portion (blue), upper portion (red), and the IPV ratio.

calculated by multiplying the time, distance, and amplitude during SE. We recorded 4 types of IPV ratio: the IPV_{14} ratio (upper 1-cm to the lower 4-cm), the IPV_{23} ratio (upper 2-cm to the lower 3-cm), the IPV_{32} ratio (upper 3-cm to the lower 2-cm), and the IPV_{41} ratio (upper 4-cm to the lower 1-cm) (Fig. 2B-E). The IPV of each region and the IPV ratios were then compared in order to identify the values most closely associated with the response to BFT.

Statistical Methods

Categorical variables were analyzed using Fisher's exact test, and numeric values were compared using Mann–Whitney *U* test or Student's *t* test. Continuous variables are reported as median (interquartile range) or mean ± SD. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff values of significant parameters that maximize the specificity and sensitivity. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp, Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

PLSR is a recently developed technique similar to principal component analysis, and is able to generalize and combine features from multiple regression analysis and principal component analysis.[21,22] PLSR is useful for predicting a set of correlated variables from a large set of independent variables.[4] We applied the PLSR technique to predict BFT responders or non-responders based on the correlations between the IPVs and the anorectal parameters. We used numerous and collinear IPV parameters that represent the X and Y matrices of the BFT results, and applied the PLSR technique to calculate the linear decomposition of predictors (X) and responses (Y); X was calculated as TP' + E and Y was calculated as UQ' + E, where and P' and Q' are the matrices of the loadings and T and U are the matrices of the scores. Finally, PLSR was used to construct estimates of the linear regression between X and Y as Y = XW + E. The MATLAB toolbox (MathWorks USA) for the PLSR model was used to run the algorithm (Supplementary Fig. 1).

The leave-one-out cross-validation method was used to train and test the performance of the BFT responders' model.[23] The scheme selected 70 cases to train the model in each model training and testing iteration.

Results

Baseline Characteristics

Among the 71 patients, 55 (77.5%) showed responsiveness to BFT. The baseline clinical and conventional anorectal manometric parameters of the patients according to the response to BFT are shown in Tables 1 and 2. All patients had rectoanal inhibitory reflex for each rectal distension volume (10-20 mL), and there were no significant differences between the 2 groups in terms of age, body mass index, and underlying diseases (Table 1). The median durations of the constipation symptoms were 9 and 10 years among the responders and non-responders, respectively. Among the patients with DD who underwent a colonic transit time study, 14 (57.7%) had coexisting slow transit constipation. The baseline symptoms were not significantly different between the responders and non-responders. The GBS scores and all aspects of the constipation symptoms, except for the hard stools, improved after BFT (*P* <

Table 1. Comparison of the Baseline Clinical Characteristics Between the Responders to Biofeedback Therapy and Non-responders

Characteristics	BFT responders (n = 55)	BFT non–responders (n = 16)	*P*-value
Age (yr)	58 (48-68)	56 (44-70)	0.910
BMI (kg/m^2)	21.4 (19.6-24.8)	24.1 (21.3-26.4)	0.100
Underlying disease			
Diabetes mellitus	6 (10.9)	4 (25.0)	0.220
Parkinson's disease	2 (3.6)	1 (6.3)	0.540
Cerebral infarction	1 (1.8)	1 (6.3)	0.400
Lower abdominopelvic surgery	5 (9.1)	2 (12.5)	0.650
Spinal surgery	5 (9.1)	3 (18.8)	0.370
Hysterectomy	5 (9.1)	3 (18.8)	0.370
Hemorrhoidectomy	8 (14.5)	3 (18.8)	0.700
Use of laxative	10 (18.2)	3 (18.8)	> 0.999
Symptom duration (yr)	9 (2-20)	10 (2-28)	0.410
Number of BFT sessions	4 (3-4)	4 (4-5)	0.120
Baseline symptoms			
Bowel movements < 3/wk	21 (38.2)	8 (50.0)	0.400
Hard stool ≥ 25%	20 (36.4)	3 (18.8)	0.190
Manual maneuvers to facilitate defecation ≥ 25%	12 (21.8)	2 (12.5)	0.500
Straining, VAS[a]	8 (5-10)	7 (5-10)	0.520
Sensation of incomplete evacuation, VAS[a]	5 (3-8)	5 (4-9)	0.860
Sensation of anorectal obstruction, VAS[a]	3 (0-9)	6 (5-9)	0.090
GBS[b]	3 (0-5)	5 (1-6)	0.050
Symptoms immediately after BFT			
Bowel movements < 3/wk	4 (7.3)	6 (37.5)	0.010
Hard stool ≥ 25%	2 (3.6)	0 (0.0)	> 0.999
Manual maneuvers to facilitate defecation ≥ 25%	2 (3.6)	1 (6.3)	0.540
Straining, VAS[a]	5 (4-6)	7 (5-10)	0.030
Sensation of incomplete evacuation, VAS[a]	2 (0-4)	5 (4-8)	< 0.01
Sensation of anorectal obstruction, VAS[a]	0 (0-0)	5 (0-7)	< 0.01
GBS[b]	8 (6-8)	5 (1-7)	< 0.01
Willingness to participate	7 (5-8)	6 (5-8)	0.240
Slow transit constipation	33 (60.0)	8 (50.0)	0.720
Balloon expulsion time (sec)	15 (6-300)	31 (11-300)	0.150
Delayed balloon expulsion	19 (34.5)	7 (43.8)	0.500

[a]0: absent, 10: severe.
[b]0: dissatisfaction, 10: satisfaction.
BMI, body mass index; BFT, biofeedback therapy; VAS, visual analog scale; GBS, global bowel satisfaction.
Data are presented as median (interquartile range) or n (%).

0.01). Additionally, 18.0% of the responders used laxatives at baseline, and the use of laxatives did not differ before and after BFT. Other conventional manometric findings were comparable between the groups (Table 2). Conventional manometric findings were compared between BFT responders and non-responders according to dyssynergia type. We found that the most common type is type I dyssynergia in BFT responders (50.9%) and type II dyssynergia in BFT non-responders (43.8%) without significant differences between groups (P = 0.550). Regarding to defecation index, significant differences were not observed between 2 groups without balloon distension (P =0.090) and with balloon distension (P = 0.980).

Novel Manometric Parameters

Figure 3 shows the representative images of the patients who failed the BE test before BFT, and those for whom the BE test was successful after BFT. Figures 3A and 3C present 3-dimensional surface plots of the pressure data used to calculate the IPVs. Figures 3B and 3D present the representative manometric cylinder plots.

When the new manometric parameters were compared, the

Table 2. Comparison of the Conventional Manometric Parameters Between the Responders and Non-responders

Variables	BFT responders (n = 55)			BFT non-responders (n = 16)			P- value
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	
Anal resting pressure (mmHg)	28.00	24.00	38.00	30.50	26.25	38.45	0.240
Anal squeezing pressure (mmHg)	67.00	47.00	86.00	74.00	61.75	97.75	0.110
Minimal sense (mL)	20.00	10.00	30.00	15.00	10.00	20.00	0.250
Desire to defecate (mL)	60.00	50.00	90.00	60.00	60.00	67.50	0.760
Urge sense (mL)	110.00	100.00	150.00	100.00	82.50	120.00	0.130
Maximal volume of tolerance (mL)	160.00	130.00	210.00	120.00	105.00	177.50	0.030
Compliance	5.00	2.75	8.00	5.00	3.25	11.75	0.670
Simulated evacuation without balloon distension							
Maximal rectal pressure (mmHg)	47.30	34.10	60.40	44.75	28.50	66.65	0.800
Residual anal pressure (mmHg)	24.40	9.20	40.20	37.80	13.75	48.48	0.210
Defecation index	1.70	1.02	6.40	1.25	0.74	1.98	0.090
Rectoanal gradient (mmHg)	14.90	1.20	42.40	12.05	−12.93	28.73	0.290
Simulated evacuation with balloon distension							
Maximal rectal pressure (mmHg)	47.4	29.3	63.9	47.10	33.80	62.38	0.650
Residual anal pressure (mmHg)	19.80	10.90	37.40	20.50	15.95	40.18	0.800
Defecation index	1.90	1.03	6.00	1.85	1.17	4.68	0.980
Rectoanal gradient (mmHg)	17.60	1.60	41.10	25.25	5.05	43.28	0.690
Dyssynergia							0.550
Type I dyssynergia		28 (50.9)			6 (37.5)		
Type II dyssynergia		14 (25.5)			7 (43.8)		
Type III dyssynergia		9 (16.4)			3 (18.8)		
Type IV dyssynergia		2 (3.6)			0 (0.0)		
Unclassified dyssynergia (delayed relaxation)		2 (3.6)			0 (0.0)		

BFT, biofeedback therapy.
Data are presented as median (interquartile range) or n (%).

responders had significantly lower values of the IPVs (upper 1-cm, upper 2-cm, and upper 3-cm portions) and the IPV_{14} and IPV_{23} ratios with balloon distension compared with the non-responders (Table 3). ROC curve analysis showed that the IPVs of the upper 1-cm portion showed the best performance for predicting responders (area under the curve [AUC], 0.74; 95% confidence interval [CI], 0.63-0.80; $P < 0.01$) (Fig. 4A). At the optimal cutoff value, the sensitivity and specificity were 74.6% and 75.0%, respectively.

Partial Least Square Regression Models Using Novel Manometric Parameters

By using the MATLAB program, we selected 24 novel IPV parameters for maximizing the AUC. By using these parameters, the PLSR model showed an AUC of 0.94 (95% CI, 0.86-1.00; $P < 0.01$), with a sensitivity of 90.1% and specificity of 87.5%. To select the variables that most contributed to each component, the PLSR method was used. To maximize the performance, manual selection procedures were employed for selecting the variables. Figure 4B illustrates the ROC curves according to the number of IPV parameters using the PLSR model. We were able to achieve the best prediction (AUC, 0.84; 95% CI, 0.76-0.95; $P < 0.01$) when the following 8 parameters were used: the IPV of the upper 1-cm portion, IPV_{14} ratio, IPV_{23} ratio, and IPV_{32} ratio, all with or without balloon distension. At the optimal cutoff value, the sensitivity was 85.5% and the specificity was 62.1%. When using a cutoff value of 0.44, the positive predictive value was 88.7% and the negative predictive value was 55.6%. The predicted probabilities for the responders are described in Supplementary Figure 1. We also performed a leave-one-out cross-validation test. The data were divided into a training set and a test set, and the performance was averaged out; consequently, we achieved 79.0% sensitivity and 69.0% specificity (Supplementary Fig. 2).

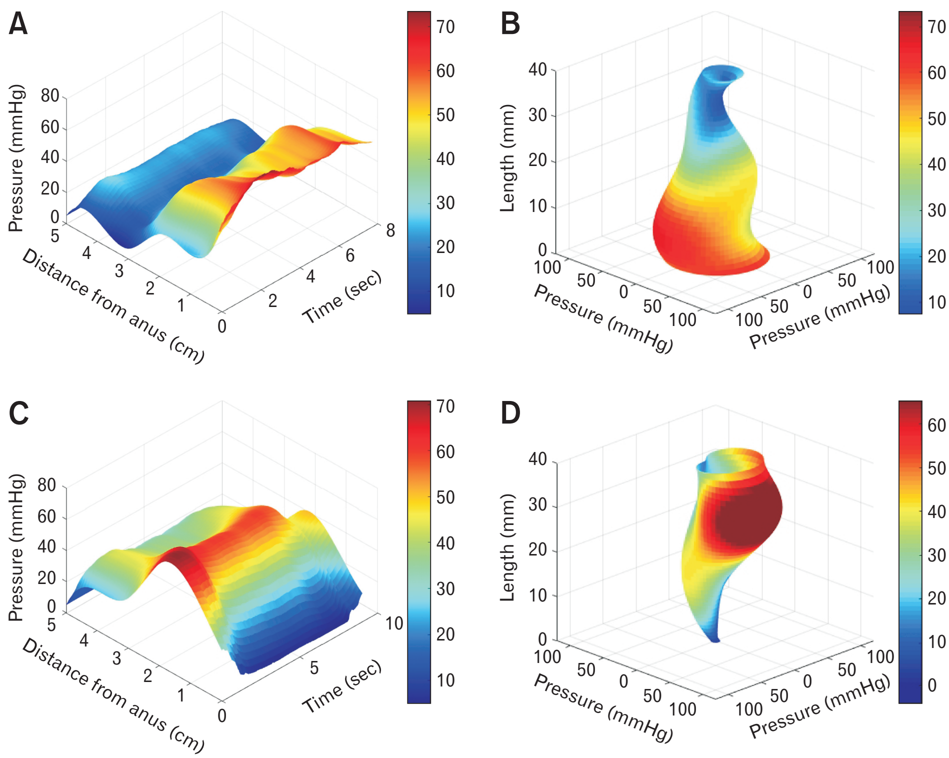

Figure 3. Three-dimensional (3D) representative manometric traces from a patient during simulated evacuation before/after the biofeedback therapy (BFT). (A) Pre-BFT surface plot of pressures in patients who failed the balloon expulsion test. (B) Pre-BFT 3D pressure cylinder manometric traces in patients who failed the balloon expulsion test. (C) Post-BFT surface plot of pressures in patients who passed the balloon expulsion test. (D) Post-BFT 3D pressure cylinder manometric traces obtained from a patient who passed the balloon expulsion test. (A, C) X-axis, Y-axis, and Z-axis depict the time (seconds), distance from the anus (cm), and pressure (mmHg), respectively. (B, D) X-axis and Y-axis represent the pressure (mmHg) along the 4 cardinal directions (north, south, east, and west), and the Z-axis represents the distance from the anus (cm).

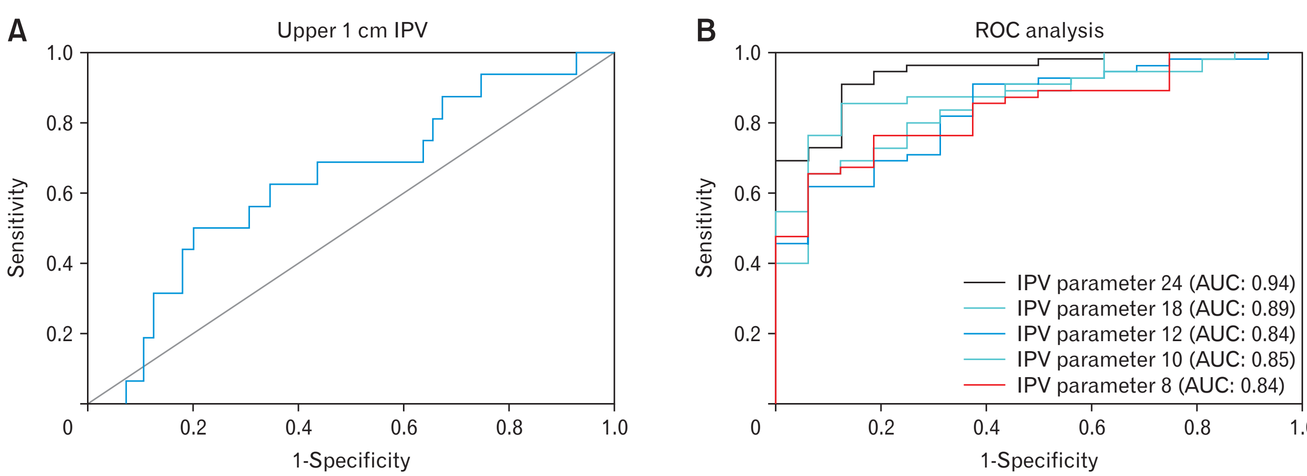

Figure 4. Receiver operating characteristic (ROC) curve analysis of the integrated pressurized volumes (IPV). (A) ROC curve of the IPV of the upper 1-cm portion with balloon distension. (B) The ROC curve according to the number of IPV parameters using a partial least squares regression model. AUC, area under the curve.

Table 3. Comparison of the New Manometric Parameters Between the Responders and Non-responders

Variables	BFT responder (n = 55)			BFT non-responder (n = 16)			*P*-value
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	
Simulated evacuation without balloon distension							
Upper 1-cm IPV (mmHg·sec·cm)	174.90	103.44	235.33	239.10	140.01	316.53	0.100
Lower 4-cm IPV (mmHg·sec·cm)	292.14	226.51	373.62	354.17	268.05	429.00	0.090
Upper 1-cm vs lower 4-cm ratio of IPV	0.59	0.41	0.86	0.64	0.54	0.76	0.500
Upper 2-cm IPV (mmHg·sec·cm)	190.83	155.06	289.34	243.11	169.98	354.38	0.150
Lower 3-cm IPV (mmHg·sec·cm)	312.64	246.70	409.84	387.80	306.34	473.64	0.070
Upper 2-cm vs lower 3-cm ratio of IPV	0.67	0.50	0.88	0.72	0.52	0.87	0.660
Upper 3-cm IPV (mmHg·sec·cm)	223.60	180.71	323.38	279.07	205.49	389.92	0.110
Lower 2-cm IPV (mmHg·sec·cm)	327.00	248.36	462.56	397.08	344.80	482.40	0.080
Upper 3-cm vs lower 2-cm ratio of IPV	0.71	0.52	0.93	0.73	0.61	0.93	0.460
Upper 4-cm IPV (mmHg·sec·cm)	261.07	201.95	338.97	301.19	242.58	401.05	0.120
Lower 1-cm IPV (mmHg·sec·cm)	333.57	221.97	445.83	421.22	286.69	507.97	0.100
Upper 4-cm vs lower 1-cm ratio of IPV	0.79	0.62	1.00	0.79	0.67	0.94	0.860
Duration of simulated evacuation	7.30	6.50	8.20	7.15	5.90	7.95	0.480
Simulated evacuation with balloon distension							
Upper 1-cm IPV (mmHg·sec·cm)	189.19	99.57	255.44	267.32	240.23	369.14	< 0.01
Lower 4-cm IPV (mmHg·sec·cm)	285.17	219.46	391.53	359.74	257.49	402.33	0.150
Upper 1-cm vs lower 4-cm ratio of IPV	0.64	0.41	0.89	0.80	0.63	1.02	0.050
Upper 2-cm IPV (mmHg·sec·cm)	209.99	143.10	334.90	302.35	239.05	377.81	0.020
Lower 3-cm IPV (mmHg·sec·cm)	303.15	227.91	418.03	362.98	248.77	433.30	0.330
Upper 2-cm vs lower 3-cm ratio of IPV	0.68	0.51	0.90	0.84	0.74	1.15	0.020
Upper 3-cm IPV (mmHg·sec·cm)	229.05	166.37	361.15	312.14	244.40	390.77	0.040
Lower 2-cm IPV (mmHg·sec·cm)	303.17	233.95	422.06	366.24	253.46	467.72	0.390
Upper 3-cm vs lower 2-cm ratio of IPV	0.74	0.57	0.97	0.85	0.71	1.24	0.090
Upper 4-cm IPV (mmHg·sec·cm)	247.11	198.32	358.13	312.92	273.32	375.24	0.060
Lower 1-cm IPV (mmHg·sec·cm)	299.66	217.38	410.41	331.83	239.87	538.63	0.360
Upper 4-cm vs lower 1-cm ratio of IPV	0.81	0.60	1.12	0.89	0.67	1.26	0.460
Duration of simulated evacuation	8.10	7.10	9.20	8.00	7.03	9.60	0.900

BFT, biofeedback therapy; IPV, integrated pressurized volume.

Discussion

In our study, the BFT responders and non-responders did not show significant differences in the conventional manometric parameters. However, our results show that the IPV parameters can predict responsiveness to BFT better than the conventional parameters. Therefore, the combination of the IPV parameters obtained using PLSR is a promising predictive method.

Overall, BFT improved the DD symptoms in approximately 70-80% of the included patients. Our current results are in line with those of several other previously published studies.[7-9,24] Although BFT is safe and effective, it is also labor-intensive and requires patient prioritization. Several predictive factors of the success rate have been described for DD, including older age, patient motivation, stool consistency, pelvic floor dysfunction, inability to evacuate a 40-mL balloon, presence of dyssynergia with the absence of abdominal pain, > 5 BFT sessions, and low DI during straining.[6,11,12] However, the results of these previous studies are inconsistent, and the discordant results hinder clinicians from determining which patients are most likely to show desired outcomes after BFT. Also, these parameters are based on the previously used linear wave signals from manometry sensors. Therefore, we used a new technology (MATLAB) to postulate or assess the factors that would result in favorable BFT outcomes using HRAM based on spatiotemporal plots.

Using HRAM, we determined which factors are important for predicting BFT outcomes for female patients with chronic constipation and DD. We demonstrated that IPV parameters can be used to predict the responsiveness of women with DD to BFT. IPV parameters are superior to conventional parameters more effectively explaining the physiology of the anorectal canal.[4,5] For the first time in the literature, we showed that the IPV of the upper 1-cm portion was associated with successful BFT outcomes. Compared with non-responders, the BFT responders had significantly lower values of IPVs of the upper 2- and 3-cm portions as well as the IPV_{14} and IPV_{23} ratios with balloon distension. The IPVs of the upper 1-, 2-, and 3-cm portions represent the rectal pressure better than the conventional manometric parameters. In our previous study, the IPV was found to represent the muscular contractility of the entire anal canal; this is especially relevant for the IPV_{14} ratio, which may be useful as a marker of the rectoaxial force.[3,4] The IPV_{14} and IPV_{23} ratios during SE can explain the rectoaxial force more precisely than the previously used DI, which is based on the linear wave signals at a given time during SE. Consequently, low IPVs of the upper 1-, 2-, and 3-cm portions, and low IPV_{14} and IPV_{23} ratios are features of DD. In this study, the previously meaningful parameter (the IPV_{14} ratio) used during SE with balloon distension showed a marginal significance between the BFT responders and non-responders ($P = 0.050$) (Table 3). However, it failed to show statistical significance, which we believe may have been due to the small sample size.

Considering that the IPV is a quantitative measurement based on HRAM spatiotemporal plots, this model allows easy comprehension and identification of abnormalities compared to the previous model. Moreover, the combination of 8 IPV parameters (IPV of the upper 1-cm portion, and the IPV_{14}, IPV_{23}, and IPV_{32} ratios with and without balloon distension) can improve the prediction of BFT responders using PLSR analysis. The development of the equation only required a few seconds in the MATLAB program.

Conventional anorectal parameters have the following limitations. First, these parameters are not always correlate with patients' symptoms. One study showed that predictions about patient continence cannot be made with conventional resting and squeezing pressures.[25] Second, the novel parameters, including the HRAM squeeze profile and HRAM resting integral, detected anal hypocontractility better than the conventional parameters; this significantly increased the diagnostic accuracy for discriminating between 403 patients with fecal incontinence and 85 healthy control subjects.[26] In our previous study, the IPV_{14} ratio and PLSR method significantly discriminated between the symptoms of hard stools and anorectal obstruction sensation for > 25% of the bowel movements.[4] The conventional parameter is based on a linear waveform and may not be reflective of the patients' symptoms, whereas IPV is better at predicting BFT responders because it conveys the symptoms well. We believe that these novel parameters explain the anorectal pathophysiology better than conventional parameters.

This study has some limitations. A previous study demonstrated a significant improvement in DD, a higher rectal pressure, and a lower anal sphincter residual pressure than the baseline values with follow-up anorectal manometry.[27] However, our study did not show these improvements using the IPV parameters with follow-up manometry due to the high number of patients lost to follow-up. Nevertheless, some of these patients showed improvements with the new IPV parameters, but not with the conventional parameters (Fig. 3). In addition, this study had limitations inherent to the nature of a retrospective, single-center study. Exclusion of patients made the sample size small. A large-scale, prospective study is needed to confirm these findings.

This study shows clinically meaningful results. IPV parameters can be used to predict responsiveness to BFT better than conventional parameters, especially for female patients with DD. A combination of IPV parameters using PLSR was superior to conventional parameters in predicting the BFT responsiveness and explaining the physiology of the anorectal canal. The current data and the predictive model may be useful for clinicians in prioritizing patients for treatment with anorectal BFT.

Supplementary Materials

Note: To access the supplementary figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm21137.

Financial support: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2021R1G1A100831) and the Korean Society of Neurogastroenterology and Motility (KSNM-12-012, KSNM-20-02).

Conflicts of interest: None.

Author contributions: Myeongsook Seo and Jiyoung Yoon collected and analyzed the data, and drafted the manuscript; Kee Wook Jung and Seung-Jae Myung were involved in the study design, supervision, and critical revision of the study; Segyeong Joo and Kyung Min Choi prepared the MATLAB formula and analyzed the manometric data; Jungbok Lee supervised the research and contributed to the analysis; In Ja Yoon, Woojoo Noh, So

Young Seo, and Do Yeon Kim performed all the tests; Hyo Jeong Lee, Sung Wook Hwang, Sang Hyoung Park, Dong-Hoon Yang, Byong Duk Ye, Jeong-Sik Byeon, and Suk-Kyun Yang supervised the study and provided important intellectual contributions; and the guarantors of the article are Kee Wook Jung, Segyeong Joo, and Seung-Jae Myung; and all authors approved the final version.

References

1. Lee YY, Erdogan A, Rao SS. High resolution and high definition anorectal manometry and pressure topography: diagnostic advance or a new kid on the block? Curr Gastroenterol Rep 2013;15:360.
2. Ratuapli SK, Bharucha AE, Noelting J, Harvey DM, Zinsmeister AR. Phenotypic identification and classification of functional defecatory disorders using high-resolution anorectal manometry. Gastroenterology 2013;144:314-322, e2.
3. Jung KW, Joo S, Yang DH, et al. A novel high-resolution anorectal manometry parameter based on a three-dimensional integrated pressurized volume of a spatiotemporal plot, for predicting balloon expulsion in asymptomatic normal individuals. Neurogastroenterol Motil 2014;26:937-949.
4. Seo M, Joo S, Jung KW, et al. A high-resolution anorectal manometry parameter based on integrated pressurized volume: a study based on 204 male patients with constipation and 26 controls. Neurogastroenterol Motil 2018;30:e13376.
5. Seo M, Joo S, Jung KW, Song EM, Rao SSC, Myung SJ. New metrics in high-resolution and high-definition anorectal manometry. Curr Gastroenterol Rep 2018;20:57.
6. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology 2005;129:86-97.
7. Rao SS, Seaton K, Miller M, et al. Randomized controlled trial of biofeedback, sham feedback, and standard therapy for dyssynergic defecation. Clin Gastroenterol Hepatol 2007;5:331-338.
8. Heymen S, Scarlett Y, Jones K, Ringel Y, Drossman D, Whitehead WE. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. Dis Colon Rectum 2007;50:428-441.
9. Chiarioni G, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology 2006;130:657-664.
10. Lee HJ, Boo SJ, Jung KW, et al. Long-term efficacy of biofeedback therapy in patients with dyssynergic defecation: results of a median 44 months follow-up. Neurogastroenterol Motil 2015;27:787-795.
11. Gilliland R, Heymen S, Altomare DF, Park UC, Vickers D, Wexner SD. Outcome and predictors of success of biofeedback for constipation. Br J Surg 1997;84:1123-1126.
12. Fernández-Fraga X, Azpiroz F, Casaus M, Aparici A, Malagelada JR. Responses of anal constipation to biofeedback treatment. Scand J Gastroenterol 2005;40:20-27.
13. Shin JK, Cheon JH, Kim ES, et al. Predictive capability of anorectal physiologic tests for unfavorable outcomes following biofeedback therapy in dyssynergic defecation. J Korean Med Sci 2010;25:1060-1065.
14. Shim LS, Jones M, Prott GM, Morris LI, Kellow JE, Malcolm A. Predictors of outcome of anorectal biofeedback therapy in patients with constipation. Aliment Pharmacol Ther 2011;33:1245-1251.
15. Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol 1998;93:1042-1050.
16. Rao SS, Hatfield R, Soffer E, Rao S, Beaty J, Conklin JL. Manometric tests of anorectal function in healthy adults. Am J Gastroenterol 1999;94:773-783.
17. Lee HJ, Jung KW, Han S, et al. Normal values for high-resolution anorectal manometry/topography in a healthy Korean population and the effects of gender and body mass index. Neurogastroenterol Motil 2014;26:529-537.
18. Soh JS, Lee HJ, Jung KW, et al. The diagnostic value of a digital rectal examination compared with high-resolution anorectal manometry in patients with chronic constipation and fecal incontinence. Am J Gastroenterol 2015;110:1197-1204.
19. Rao SS. Dyssynergic defecation and biofeedback therapy. Gastroenterol Clin North Am 2008;37:569-586, viii.
20. Noelting J, Ratuapli SK, Bharucha AE, Harvey DM, Ravi K, Zinsmeister AR. Normal values for high-resolution anorectal manometry in healthy women: effects of age and significance of rectoanal gradient. Am J Gastroenterol 2012;107:1530-1536.
21. Chun H, Keleş S. Sparse partial least squares regression for simultaneous dimension reduction and variable selection. J R Stat Soc Series B Stat Methodol 2010;72:3-25.
22. Wold S, Sjöström M, Eriksson L. PLS-regression: a basic tool of chemometrics. Chemometr Intell Lab Syst 2001;58:109-130.
23. Li Q, Doi K. Reduction of bias and variance for evaluation of computer-aided diagnostic schemes. Med Phys 2006;33:868-875.
24. Rao SS, Valestin J, Brown CK, Zimmerman B, Schulze K. Long-term efficacy of biofeedback therapy for dyssynergic defecation: randomized controlled trial. Am J Gastroenterol 2010;105:890-896.
25. Felt-Bersma RJ, Klinkenberg-Knol EC, Meuwissen SG. Anorectal function investigations in incontinent and continent patients. Differences and discriminatory value. Dis Colon Rectum 1990;33:479-485; discussion 485-476.
26. Carrington EV, Knowles CH, Grossi U, Scott SM. High-resolution anorectal manometry measures are more accurate than conventional measures in detecting anal hypocontractility in women with fecal incontinence. Clin Gastroenterol Hepatol 2019;17:477-485, e9.
27. Patcharatrakul T, Valestin J, Schmeltz A, Schulze K, Rao SSC. Factors associated with response to biofeedback therapy for dyssynergic defecation. Clin Gastroenterol Hepatol 2018;16:715-721.