

Effect of different body position on anorectal manometry for chronic constipation patients

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Abstract. – OBJECTIVE: To analyze the different influence of body position on wireless high-resolution anorectal manometry parameters and in classification for chronic constipation patients.

PATIENTS AND METHODS: Fifty consecutive patients with chronic constipation and 20 healthy volunteers were included in this study, all of whom accepted the Rome IV constipation questionnaires, underwent rectal balloon expulsion test and wireless high-resolution anorectal manometry. The wireless high-resolution anorectal manometry was performed in the left lateral, seated, and squatting positions for every study subject. The Statistical Product and Service Solutions (SPSS) 21.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

RESULTS: The anal sphincter resting pressure, anal sphincter squeezing pressure, and rectal internal pressure during the evacuation in the seated position and squatting position were significantly higher than those in the left lateral position in both the volunteer group and patient group, without a significant difference between the seated position and squatting position. The initial perception threshold was higher in the patient group than in the volunteer group. The wireless high-resolution anorectal manometry in different positions combined with the rectal balloon expulsion test mainly affects the diagnosis of the subtype of inadequate defecatory propulsion.

CONCLUSIONS: Compared with the left lateral position test, the wireless high-resolution anorectal manometry in the seated position and squatting positions is more consistent with the human physiological bowel condition, and the result of the test can be affected by the body position. The wireless high-resolution anorectal manometry can differentiate between subtypes during the diagnosis of inadequate defecatory propulsion.

Key Words:

Wireless, Anorectal manometry, Chronic constipation, Functional defecation disorders.

Introduction

Chronic constipation is one of the most common functional gastrointestinal diseases. It can be divided into¹ slow transit constipation (STC), outlet obstructive constipation (OOC), and mixed constipation (MC) according to pathophysiology. According to the Rome IV standard², it can be divided into functional constipation (FC), functional defecation disorder (FDD), and constipation-predominant irritable bowel syndrome (IBS-C). FDD is subdivided into dyssynergic defecation and inadequate defecatory propulsion. We chose different treatments according to the classification. For STC, the volumetric laxative is the better choice³, and biofeedback therapy is the preferable choice for OOC⁴. In chronic constipation patients, 20-81% present with FDD⁵⁻⁸, and the volunteers may also show FDD when they undergo anorectal manometry in left lateral position⁹.

To obtain the correct classification, related diagnostic tests are needed¹⁰. The rectal balloon expulsion test is a preliminary screening test for FDDs⁹, and the anorectal manometry and the perianal electromyography are the main procedures for the diagnosing of FDDs. The high-resolution anorectal manometry can provide more anatomical information² by simulating the change in anorectal pressure during defecation, which is very important for the diagnostic classification and treatment of defecation disorders. However, the anorectal manometry is traditionally performed in the left lateral position, which is not consistent with human physiological defecation and thus accounts for the high incidence of FDDs. The wireless high-resolution anorectal manometry provides us with the opportunity to perform the test in the seated and squatting positions

very conveniently. To analyze the diagnostic value of different body positions using the wireless high-resolution anorectal manometry for the classification of chronic constipation, 50 chronic constipation patients and 20 healthy volunteers were recruited for our study. All the study subjects underwent anorectal manometry in three different positions, namely, the left lateral position, the seated position and the squatting position, and the influence of each position on the results of parameters was observed. We also analyzed the effect of different body position on the classification of chronic constipation.

Patients and Methods

Patients

Fifty consecutive chronic constipation patients were recruited between June 2016 and April 2017, and 20 healthy volunteers were recruited. All chronic constipation patients complied with the Rome IV diagnostic criteria. All volunteers had no constipation symptoms. Both the chronic constipation patients and the volunteers met the following exclusion criteria: 1) anorectal disease confirmed by colonoscopy or lower digestive tract angiography, 2) diabetes mellitus, hyperthyroidism, hypothyroidism, and history of connective tissue disease, 3) abdominal, pelvic, and anorectal surgery history, 4) inability to make body position changes because of spinal joint disease, and 5) inability to cooperate because of mental neurosis diseases. This study was approved by the Ethics Committee of Capital Medical University Affiliated Beijing Shijitan Hospital. All volunteers and chronic constipation patients signed informed consent before the study.

Instrument

An eight-channel wireless high-resolution anorectal manometry catheter produced by Zhejiang Ningbo Maida Medical Device Inc. (Ningbo, China) was used. The data analysis was carried out by a computer expert diagnostic system.

Procedure

Each subject's medical history was collected by the same trained specialists and the Rome IV constipation questionnaires were completed at the same time. Each subject underwent feces evacuation with a glycerin enema 30 minutes before the examination. All the study subjects underwent anorectal manometry in three different positions: left lateral position, seated position, and squatting position. All subjects underwent rectal balloon expulsion in a seated position.

Statistical Analysis

The SPSS (Statistical Product and Service Solutions) 21.0 software (IBM, Armonk, NY, USA) was used for the statistical analysis. The general characteristics of each subject were analyzed by the *t*-test. The parameters of anorectal manometry in different body positions were analyzed by single factor analysis of variance. The classification of chronic constipation conducted by anorectal manometry in different body positions was analyzed by the Chi-square test. The rectal perceptual function of different groups in chronic constipation was analyzed by an independent sample *t*-test. The statistical significance was defined as $p < 0.05$.

Results

Subject Characteristics

Age, height, weight, and body mass index (BMI) showed no significant differences in either the volunteer group or the patient group, $p > 0.05$ (Table I).

Comparison of the Parameters of the Wireless High-Resolution Anorectal Manometry in Different Body Positions in the Volunteer Group

There was a significant difference in the anal sphincter resting pressure, the anal sphincter squeezing pressure, and rectal internal pressure during evacuation among the three testing positions, $p < 0.05$ (Table II, Figure 1). The anal

Table I. Subject's characteristics.

	Sex (male; female)	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
Volunteer	10:10	46.65 ± 12.02	166.60 ± 6.52	64.40 ± 7.01	23.17 ± 1.75
Patient	13:37	50.42 ± 16.10	164.04 ± 6.61	61.74 ± 8.16	22.94 ± 2.75
<i>p</i> -value		0.072	0.877	0.469	0.137

Table II. Comparison of parameters in different positions in volunteer group.

	Anal sphincter resting pressure (mmHg)	Anal sphincter squeezing pressure (mmHg)	Rectal internal pressure during evacuation (mmHg)	Sphincter residual pressure during evacuation (mmHg)
Left Lateral	37.05 ± 8.33	112.00 ± 14.36	58.25 ± 12.38	24.25 ± 10.04
Seated	43.65 ± 6.21	127.75 ± 19.36	70.00 ± 9.46	22.50 ± 6.18
Squatting	41.00 ± 5.98	120.75 ± 18.01	72.30 ± 8.30	22.10 ± 5.69
Compared with each other	<i>p</i> -values are 0.004, 0.076, and 0.231, respectively	<i>p</i> -values are 0.006, 0.117, and 0.208, respectively	<i>p</i> -values are 0.001, 0.000, and 0.478, respectively	<i>p</i> -values are 0.467, 0.372, and 0.868, respectively

sphincter resting pressure and the anal sphincter squeezing pressure in the seated position were significantly higher than those in the left lateral position ($p < 0.05$), which was also higher than that in the squatting position without significant

difference. The rectal internal pressure during evacuation in the seated position and squatting position were significantly higher than that in the left lateral position, $p < 0.05$. The rectal internal pressure during the evacuation in the squatting

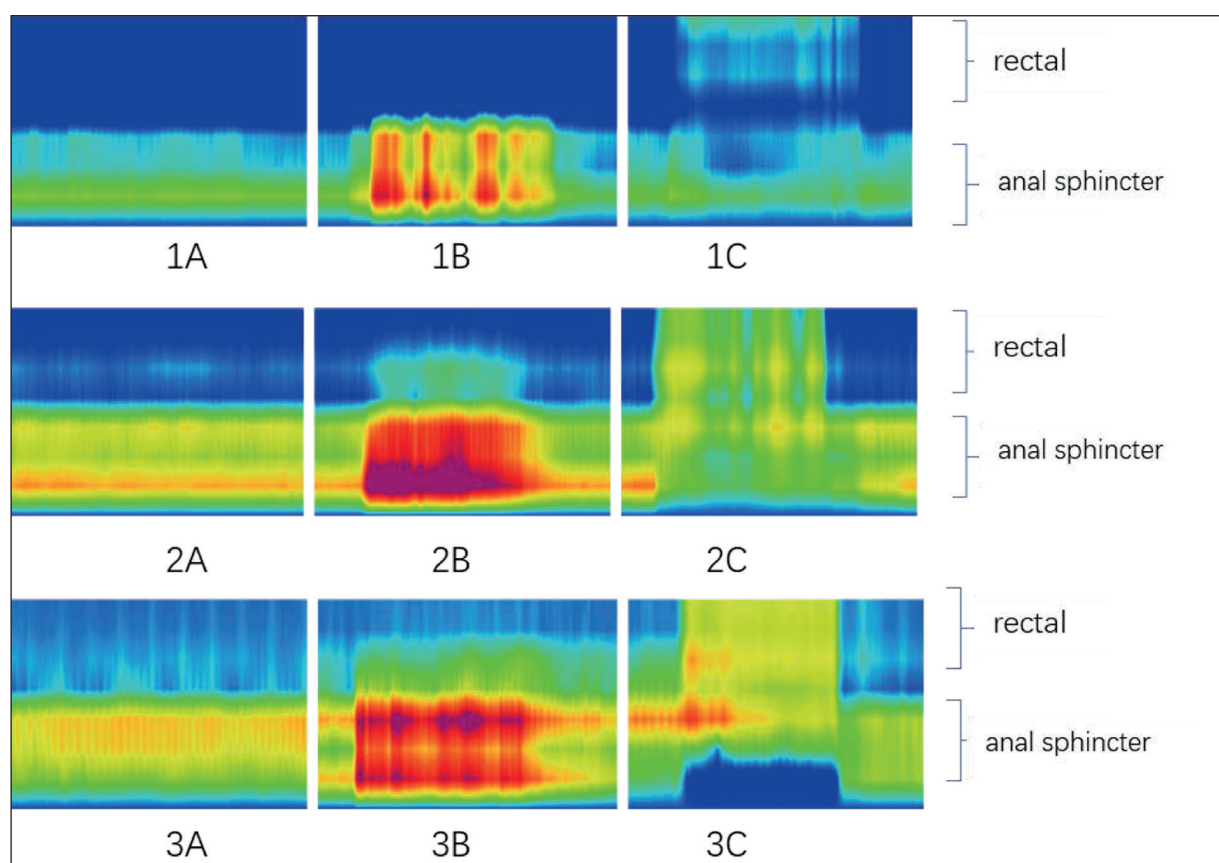


Figure 1. Comparison of the parameters of the wireless high-resolution anorectal manometry in different body positions in the volunteer. **1A, 2A, 3A** show the anal sphincter resting pressure in left lateral position, seated position, squatting position. **1B, 2B, 3B** show the anal sphincter squeezing pressure in left lateral position, seated position, squatting position. **1C, 2C, 3C** show the anal sphincter resting pressure and rectal internal pressure during evacuation in the left lateral position, seated position, squatting position. The anal sphincter resting pressure and the anal sphincter squeezing pressure in the seated position were significantly higher than those in the left lateral position. The rectal internal pressure during evacuation in the seated position and squatting position were significantly higher than that in the left lateral position.

position was higher than that in the seated position, but there was no significant difference between the two positions, $p>0.05$. The anal sphincter residual pressure during evacuation showed no significant difference among the three positions.

Comparison of the Parameters of the Wireless High-Resolution Anorectal Manometry in Different Body Positions in the Chronic Constipation Group

There was a significant difference in the anal sphincter resting pressure and rectal internal pressure during evacuation among the three testing positions, $p<0.05$ (Table III, Figure 2). The anal sphincter resting pressure and the rectal internal pressure during evacuation in the seated position and squatting position were significantly higher than that in the left lateral position, $p<0.05$. The anal sphincter resting pressure and the rectal internal pressure during the evacuation in the squatting position were higher than in the seated position, but there was no significant difference between the two positions, $p>0.05$. The anal sphincter squeezing pressure and the residual sphincter pressure during evacuation were not significantly different between the three body positions ($p>0.05$).

Comparison of Rectal Perception Function Between Chronic Constipation Group and Volunteer Group

There is no significant difference in the rectal anal inhibitory reflex, the threshold of defecation, and the maximum tolerance threshold between the chronic constipation group and the volunteer group, $p>0.05$ (Table IV). The initial perception threshold of the patient group was significantly higher than that in the volunteer group ($p<0.05$).

The Value of Different Body Position in the Diagnosis and Clinical Classification of Chronic Constipation

The patients were classified into FC and FDD by using wireless high-resolution anorectal manometry in different positions combined with the rectal balloon expulsion test (Table V). There was no significant difference among the left lateral position, seated position, and squatting position ($p>0.05$). Then, the FDD was subdivided into dyssynergic defecation and inadequate defecatory propulsion. We observed a difference when we used the wireless high-resolution anorectal manometry in different positions combined with rectal balloon expulsion test to subdivide the FDD group (Table VI). There was a significant difference between the seated position and the left lateral position, and between the squatting position and the left lateral position, but there was no significant difference between the seated position and the squatting position.

Discussion

Eighty-five percent of the anal-rectal resting pressure is produced by the internal anal sphincter, and the 15% is produced by the external anal sphincter. The anal sphincter squeezing pressure is primarily produced by the external anal sphincter and musculus puborectalis. Normal evacuation requires adequate rectal internal propulsion, which is more than 45 mmHg, with the anal sphincter 20% more relaxed than the resting state. In this study, in the volunteer group, the anal sphincter resting pressure and the anal sphincter squeezing pressure in the left lateral position were the lowest, and they were highest in the seated position. The anal sphincter squeezing pressure was 2 times higher than the anal sphincter resting pressure. The rectal internal pressure

Table III. Comparison of parameters in different positions in chronic constipation group.

	Anal sphincter resting pressure (mmHg)	Anal sphincter squeezing pressure (mmHg)	Rectal internal pressure during evacuation (mmHg)	Sphincter residual pressure during evacuation (mmHg)
Left Lateral	33.88 ± 14.08	90.08 ± 27.89	28.02 ± 16.68	31.10 ± 22.95
Seated	43.52 ± 18.99	93.40 ± 29.97	40.04 ± 16.97	42.24 ± 25.96
Squatting	43.90 ± 16.70	95.20 ± 30.02	45.50 ± 20.78	40.30 ± 28.06
Compared with each other	p -values are 0.005, 0.003, and 0.910, respectively	p -values are 0.572, 0.384, and 0.759, respectively	p -values are 0.001, 0.000, and 0.137, respectively	p -values are 0.032, 0.076, and 0.707, respectively

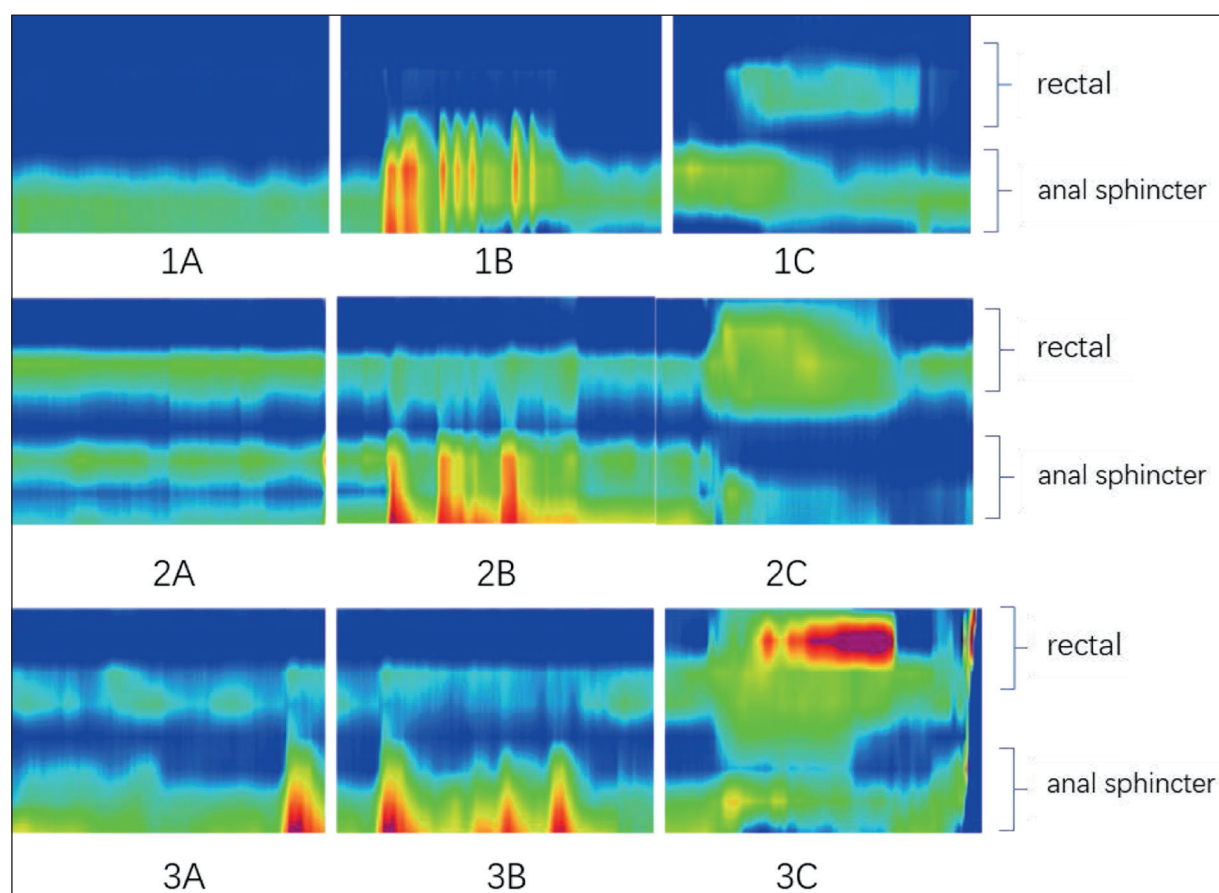


Figure 2. This figure shows the parameters of the wireless high-resolution anorectal manometry in different body positions in one chronic constipation patient. **1A, 2A, 3A** show the anal sphincter resting pressure in left lateral position, seated position, squatting position. **1B, 2B, 3B** show the anal sphincter squeezing pressure in left lateral position, seated position, squatting position. **1C, 2C, 3C** show the anal sphincter resting pressure and rectal internal pressure during evacuation in left lateral position, seated position, squatting position. The anal sphincter resting pressure and the rectal internal pressure during the evacuation in the seated position and squatting position were significantly higher than that in the left lateral position.

Table IV. Comparison of rectal perception function.

	N	RAIR (mL)	Initial perception threshold (mL)	Defecation threshold (mL)	Maximum tolerance threshold (mL)
Control	20	14.50 ± 5.10	31.50 ± 7.80	72.75 ± 15.34	123.25 ± 23.97
Constipation	50	13.00 ± 5.80	41.90 ± 20.18	83.00 ± 36.32	122.40 ± 51.73
<i>p</i> -value		0.316	0.003	0.102	0.926

RAIR: rectal anal inhibitory reflex.

Table V. Comparison of the classification of chronic constipation between the left lateral position and seated position/squatting position.

BE + LL ARM	BE + seated ARM		BE + squatting ARM	
	FC	FDD	FC	FDD
FC	19	1	19	1
FDD	1	29	4	26

LL: left lateral, ARM: anal rectal manometry, BE: balloon expulsion.

Table VI. Comparison of the classification of functional defecation disorder between the left lateral position and seated position/squatting position.

BE + LL ARM	BE + seated ARM		BE + squatting ARM	
	Dyssynergic defecation	Inadequate defecatory propulsion	Dyssynergic defecation	Inadequate defecatory propulsion
Dyssynergic defecation	7	0	5	0
Inadequate defecatory propulsion	8	14	10	11

during evacuation is the lowest in the left lateral position and highest in the squatting position, with all the results over 45 mmHg in the three positions. The relaxation percentage of anal sphincter is more than 20%. This process is accompanied by physiological defecation. The results are consistent with the previously reported results in healthy volunteers¹¹⁻¹⁴, which also verified the practicability of the high-resolution wireless pressure measuring instrument¹⁵. In this study, the rectal internal pressure during evacuation and the relaxation percentage of the anal sphincter in the chronic constipation patient group are inadequate, which indicates that chronic constipation patients may suffer from defecation disorders^{16,17}. The rectal perception function indicated that the initial rectal perception threshold in the patient group was higher than that in the volunteer group, which is consistent with a previous report¹⁸, indicating a reduction in rectal sensitivity in the patient group.

Anorectal manometry is traditionally performed in the left lateral position due to the previous instruments. However, the physical defecation position is the seated position or the squatting position, which can be timesaving and power saving as concluded from previous questionnaires¹⁹ on healthy volunteers. It is related to the contraction direction of the anorectal and the surrounding muscles when evacuating in different positions. The anorectal angle is approximately 80-90° in the seated position and approximately 100-110° in the squatting position. The greater the anorectal angle, the straighter the rectum is, and the easier the defecation is. We can also see an expanding trend of the anorectal angle from the seated position to the squatting position when taking X-ray defecography, which makes the defecation more feasible. The wireless high-resolution anorectal manometry instrument can be flexibly operated in the seated and squatting position, and the quality and inspection results are reliable and consis-

tent with the previously reported results carried out by water-perfused catheter and solid-state high-resolution anorectal manometry (3D) in volunteers and chronic constipation patients^{11,13-15}.

We recognized that there are 4 types of anorectal pressure changes during defecation^{2,20} as follows: a normal pattern is characterized by increased intrarectal pressure associated with anal relaxation. Type I is characterized by an increased intrarectal pressure (≥ 45 mmHg) and increased anal pressure, reflecting the contraction of the anal sphincter. Type III is characterized by an increased intrarectal pressure (≥ 45 mmHg) with absent or insufficient ($< 20\%$) relaxation of the anal sphincter. The type II pattern reflects inadequate propulsion (intrarectal pressure < 45 mmHg) with insufficient relaxation or contraction of the anal sphincter. The type IV pattern describes inadequate propulsion (intrarectal pressure < 45 mmHg) with adequate relaxation ($> 20\%$) of anal sphincter pressure. Types I and III describe dyssynergic defecation, and types II and IV describe inadequate propulsion. When performing biofeedback training⁴, we should emphasize rectal internal propulsion training for type II and IV, training for relaxation of the anal sphincter for types I and III. In this study, we found that the different positions mainly affect the rectal internal pressure, and the rectal internal pressure in the left lateral position of some chronic constipation patients can be enhanced when switching to a seated or squatting position, which can influence the subdivision of the FDD, from inadequate defecatory propulsion to dyssynergic defecation or normal. Therefore, the results of this study suggest that when patients were diagnosed with FDD in the left lateral position, they should repeat the test in the sitting or squatting position. In addition, they should consider the clinical assessment of chronic constipation and conduct an appropriate biofeedback training plan.

Chronic constipation requires a comprehensive therapy^{3,21-24}, retraining the physiology of defecation, improving the education of physiological defecation, establishing a balanced diet (such as increasing dietary fiber consumption and drinking more water), and exercising regularly. We should pay attention to the effect and safety as well as drug dependence when selecting drugs for patients with FC. Volumetric laxative, such as polyethylene glycol electrolytes, is a better choice because there is no intestinal absorption, less adverse effects, an increase in the frequency of defecation, and improvement of the fecal character^{25,26}. For STC, prodynamics, such as cisapride or mosapride, and 5-HT₄ receptor agonists, such as prucalopride, can be added to the treatment of severe chronic constipation to improve intestinal function and relieve constipation symptoms²⁷⁻³⁰. Biofeedback therapy is the preferable choice for FDD⁴. The therapist guidance and patient compliance will be the key factors for successful treatment. Psychotherapy plays a vital role in the treatment of patients with severe chronic constipation. Surgical treatment should be considered carefully, and the evaluation for serious psychological disorders or other gastrointestinal diseases, except colonic disease, should be considered before surgery.

Conclusions

In summary, the position of anorectal manometry mainly affects the subdivision of FDD because the body position mainly affects the rectal internal pressure during evacuation. Therefore, for chronic constipation patients, when they show inadequate propulsion in the left lateral position testing with the traditional instruments, it is recommended that the patient change to the seated or squatting position and repeat the test using the wireless high-resolution anorectal manometry instrument and make a preferable biofeedback treatment program based on the results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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References

- 1) CERESOLA ER, FERRARESE R, PRETI A, CANDUCCI F. Targeting patients' microbiota with probiotics and natural fibers in adults and children with constipation. *Eur Rev Med Pharmacol Sci* 2018; 22: 7045-7057.
- 2) DROSSMAN DA, HASLER WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. *Gastroenterology* 2016; 150: 1257-1261.
- 3) BOVE A, BELLINI M, BATTAGLIA E, BOCCHINI R, GAMBACCIANI D, BOVE V, PUCCIANI F, ALTOMARE DF, DODI G, SCIAUDONE G, FALLETTO E, PILONI V. Consensus statement AIGO/SICCR diagnosis and treatment of chronic constipation and obstructed defecation (part II: treatment). *World J Gastroenterol* 2012; 18: 4994-5013.
- 4) WALD A. Outlet dysfunction constipation. *Curr Treat Options Gastroenterol* 2001; 4: 293-297.
- 5) KUIJPERS HC. Application of the colorectal laboratory in diagnosis and treatment of functional constipation. *Dis Colon Rectum* 1990; 33: 35-39.
- 6) SURRENTI E, RATH DM, PEMBERTON JH, CAMILLERI M. Audit of constipation in a tertiary referral gastroenterology practice. *Am J Gastroenterol* 1995; 90: 1471-1475.
- 7) WALD A, CARUANA BJ, FREIMANIS MG, BAUMAN DH, HINDS JP. Contributions of evacuation proctography and anorectal manometry to evaluation of adults with constipation and defecatory difficulty. *Dig Dis Sci* 1990; 35: 481-487.
- 8) NULLENS S, NELSEN T, CAMILLERI M, BURTON D, ECKERT D, ITURRINO J, VAZQUEZ-ROOUE M, ZINSMEISTER AR. Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut* 2012; 61: 1132-1139.
- 9) RAO SS, KAVLOCK R, RAO S. Influence of body position and stool characteristics on defecation in humans. *Am J Gastroenterol* 2006; 101: 2790-2796.
- 10) RAO SS, OZTURK R, LAINE L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. *Am J Gastroenterol* 2005; 100: 1605-1615.
- 11) 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.
- 12) PILIPENKO VI, TEPLIUK DA, SHAKHOVSKAIA AK, ISAKOV VA. [Normal values for high-resolution anorectal manometry in a healthy women: effects of age and maternity]. *Eksp Klin Gastroenterol* 2014; 55-58.
- 13) LEE HJ, JUNG KW, HAN S, KIM JW, PARK SK, YOON IJ, KOO HS, SEO SY, YANG DH, KIM KJ, YE BD, BYEON JS, YANG SK, KIM JH, MYUNG SJ. 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.
- 14) CARRINGTON EV, GROSSI U, KNOWLES CH, SCOTT SM. Normal values for high-resolution anorectal ma-

- nometry: a time for consensus and collaboration. *Neurogastroenterol Motil* 2014; 26: 1356-1357.
- 15) WU GJ, XU F, LIN L, PASRICHA PJ, CHEN JDZ. Anorectal manometry: should it be performed in a seated position? *Neurogastroenterol Motil* 2017; 2. doi: 10.1111/nmo.12997.
 - 16) MION F, GARROS A, BROCHARD C, VITTON V, ROBERT A, BOUVIER M, DAMON H, SIPROUDHIS L, ROMAN S. 3D high-definition anorectal manometry: values obtained in asymptomatic volunteers, fecal incontinence and chronic constipation. results of a prospective multicenter study (NOMAD). *Neurogastroenterol Motil* 2017; 29. doi: 10.1111/nmo.13049.
 - 17) 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.
 - 18) LIU TT, CHEN CL, YI CH. Anorectal manometry in patients with chronic constipation: a single-center experience. *Hepatogastroenterology* 2008; 55: 426-429.
 - 19) SIKIROV D. Comparison of straining during defecation in three positions: results and implications for human health. *Dig Dis Sci* 2003; 48: 1201-1205.
 - 20) RAO SS, PATCHARATRAKUL T. Diagnosis and treatment of dyssynergic defecation. *J Neurogastroenterol Motil* 2016; 22: 423-435.
 - 21) DiPALMA JA. Current treatment options for chronic constipation. *Rev Gastroenterol Disord* 2004; 4 Suppl 2: S34-S42.
 - 22) LIU LW. Chronic constipation: current treatment options. *Can J Gastroenterol* 2011; 25 Suppl B: 22B-28B.
 - 23) MÜLLER-LISSNER S, TACK J, FENG Y, SCHENCK F, SPECHT GRYP R. Levels of satisfaction with current chronic constipation treatment options in Europe - an internet survey. *Aliment Pharmacol Ther* 2013; 37: 137-145.
 - 24) COSTILLA VC, FOXX-ORENSTEIN AE. Constipation: understanding mechanisms and management. *Clin Geriatr Med* 2014; 30: 107-115.
 - 25) AMERICAN COLLEGE OF GASTROENTEROLOGY CHRONIC CONSTIPATION TASK FORCE. An evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol* 2005; 100 Suppl 1: S1-S4.
 - 26) TACK J, MÜLLER-LISSNER S, STANGHELLINI V, BOECKXSTAENS G, KAMM MA, SIMREN M, GALMICHE JP, FRIED M. Diagnosis and treatment of chronic constipation--a European perspective. *Neurogastroenterol Motil* 2011; 23: 697-710.
 - 27) COREMANS G, KERSTENS R, DE PAUW M, STEVENS M. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. *Digestion* 2003; 67: 82-89.
 - 28) CAMILLERI M, KERSTENS R, RYKX A, VANDEPLASSCHE L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008; 358: 2344-2354.
 - 29) PIESSEVAUX H, CORAZZIARI E, REY E, SIMREN M, WIECHOWSKA-KOZLOWSKA A, KERSTENS R, COOLS M, BARRETT K, LEVINE A. A randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of long-term treatment with prucalopride. *Neurogastroenterol Motil* 2015; 27: 805-815.
 - 30) YIANNAKOU Y, PIESSEVAUX H, BOUCHOUCHA M, SCHIEFKE I, FILIP R, GABALEC L, DINA I, STEPHENSON D, KERSTENS R, ETHERSON K, LEVINE A. A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy, safety, and tolerability of prucalopride in men with chronic constipation. *Am J Gastroenterol* 2015; 110: 741-748.