



Visceral and somatic hypersensitivity, autonomic cardiovascular dysfunction and low-grade inflammation in a subset of irritable bowel syndrome patients*

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Abstract: The pathophysiology of irritable bowel syndrome (IBS) is complex and not fully understood, so the aim of this study was to evaluate whether visceral and somatic hypersensitivity, autonomic cardiovascular dysfunction, and low-grade inflammation of the gut wall are associated with diarrhea-predominant IBS (D-IBS). Sixty-two patients with D-IBS and 20 control subjects participated in the study. Using the ascending method of limits (AML) protocol, we demonstrated that D-IBS patients had significantly lower sensory thresholds compared with healthy controls ($P < 0.001$). Using diverse methods, especially the ischemic sensitivity test, for the first time in China, we confirmed that D-IBS patients have somatic hypersensitivity. They had a significantly higher systolic blood pressure and heart rate after a cold stimulus, indicative of autonomic cardiovascular dysfunction. Compared with the control group, D-IBS patients had a significantly higher level of calprotectin ($P < 0.001$). We also found significant correlations between visceral and somatic hypersensitivity, visceral hypersensitivity and autonomic cardiovascular dysfunction, and somatic hypersensitivity and autonomic cardiovascular dysfunction. Our findings may provide valuable suggestions for the treatment of D-IBS.

Key words: Irritable bowel syndrome (IBS), Visceral hypersensitivity, Somatic hypersensitivity, Autonomic cardiovascular dysfunction, Low-grade inflammation

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1 Introduction

Irritable bowel syndrome (IBS) is one of the most common functional bowel disorders seen by gastroenterologists and is characterized by intermittent episodes of abdominal pain or/and distension, without any organic diseases (Liu *et al.*, 2014). IBS is

common in Western countries, where the incidence is up to 20%. In recent years, the morbidity in Asian countries has been rising year by year, and has now nearly reached that of Western countries (Zhong and Hou, 2012; Song *et al.*, 2012; Omagari *et al.*, 2013). Without biological markers, the diagnosis of IBS depends mainly on the patient's symptoms. According to Rome III criteria, IBS patients are subdivided into diarrhea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), mixed type IBS (M-IBS), and un-subtyped IBS (U-IBS). The pathophysiology of IBS is complex and not fully understood; a central-peripheral regulatory mechanism may be involved (Zhou *et al.*, 2010).

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Although the pathophysiology of IBS is unclear, visceral hypersensitivity is one of the accepted mechanisms, and may have some relationships with the severity of the symptoms (Zhou *et al.*, 2009). However, previous evaluations of visceral sensitivity have typically been based on “rapid phasic distension”, and Harraf *et al.* (1998) claimed that visceral hypersensitivity could not be induced by the “ascending method of limits (AML)” protocol. On the other hand, compared with normal controls, some IBS patients exhibit a high proportion of somatic hypersensitivity symptoms, such as migraine headaches, heartburn, back pain, and muscle pain. Most previous investigations of somatic hypersensitivity involved only a single stimulus method, and the conclusions were contradictory (Whitehead *et al.*, 1990; Zighelboim *et al.*, 1995). Whether autonomic cardiovascular dysfunction is involved in the pathological process of IBS is controversial (Elsenbruch and Orr, 2001; Tousignant-Laflamme *et al.*, 2006; Cheng *et al.*, 2013). Finally, a growing body of research evidence suggests that damage to the intestinal mucosal barrier and low-grade inflammation of the gut wall are related to the pathogenesis of IBS (Peuhkuri *et al.*, 2010; Snoek *et al.*, 2010; Liu *et al.*, 2012).

The aims of this study were: (1) to evaluate visceral sensitivity in IBS patients using the AML method and to explore patterns of stimulus in the evaluation of somatic sensitivity; (2) to determine whether IBS patients have autonomic cardiovascular dysfunction; (3) to verify if IBS patients have intestinal mucosal barrier damage and low-grade inflammation of the gut wall; and, (4) to identify relationships among visceral hypersensitivity, somatic hypersensitivity, autonomic cardiovascular dysfunction, intestinal mucosal barrier damage, and low-grade inflammation of the gut wall in IBS patients, and to determine if the related experimental parameters are correlated with the severity of symptoms.

2 Materials and methods

2.1 Participants

This study was carried out from September 2013 to May 2014 in the Gastroenterology Kinetic Laboratory of the China-Japan Friendship Hospital, Beijing, China. Sixty-two patients with D-IBS and 20 control

subjects participated in the study. IBS patients were recruited at the endoscopy center or the outpatient clinic, and control subjects were via advertisements. The participants gave their written informed consent prior to data collection. The study was approved by the Ethics Committee of the China-Japan Friendship Hospital, China. The diagnosis of all IBS patients was made by the same doctor and was based on the Rome III criteria, with normal colonoscopy examination. None of the controls had organic gastrointestinal disorder, abnormal laboratory findings, weight loss, anemia, bloody stools, family history of cancer, or other alarming signs, and those who were pregnant or had previously undergone gastrointestinal surgery were excluded from the study. None of the participants had taken serotonin antagonists, tricyclic antidepressants, pain medications, proton pump inhibitors, or serotonin uptake inhibitors for at least three weeks prior to the study.

All sessions were conducted between 8:00 am and 6:00 pm to avoid circadian rhythm effects. Demographics, such as the gender, age, height, weight, resting heart rate, and blood pressure, of all subjects were recorded. A research coordinator provided detailed information to the subjects about how to collect stool and urine specimens (for the purpose of gut wall inflammation and intestinal mucosal barrier function tests). Specimens were temporarily stored in a fridge at -80°C for enzyme-linked immunosorbent assay (ELISA) testing. Fig. 1 shows the experimental process.

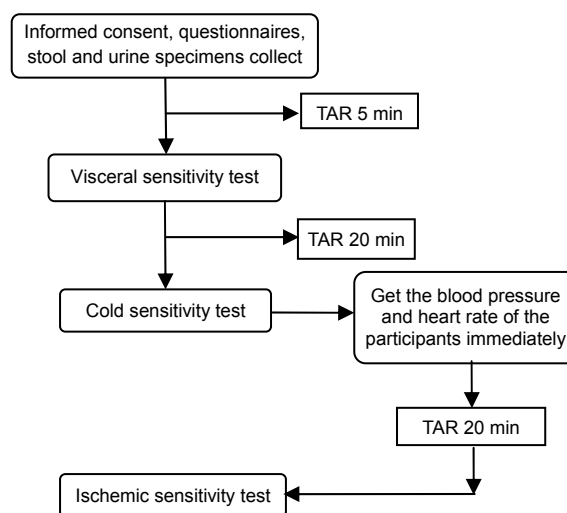


Fig. 1 Experimental process

TAR: take a rest

2.2 Measures

2.2.1 Hospital anxiety and depression scale (HADS)

HADS is commonly used for estimating emotional disorders, and can be divided into anxiety (HAD-A) and depression (HAD-D) subscales (Dong *et al.*, 2013). For each subscale, there are seven questions. A total score of 0–7 is classed as normal, 8–10 as borderline, and >11 as severe.

2.2.2 “Severity of IBS” questionnaire

The IBS severity questionnaire, which includes five items, was used to assess the severity of symptoms. Each item has a 100-point scale and the final score is the sum of scores from the five items. Patients were defined as having mild IBS with the score of 75–175, moderately severe IBS with the score 175–300, or severe IBS of the score >300 (Francis *et al.*, 1997; Singh *et al.*, 2012).

2.2.3 Visceral sensitivity test (AML protocol)

A barostat (G&J Electronics Inc., Willowdale, Ontario, Canada) was used for this test. All subjects were placed in the left lateral decubitus position in a hospital bed. A lubricated polyethylene balloon (with a maximum volume of 600 ml) secured to a rectal catheter was inserted into the rectum such that the distal attachment site was 4 cm from the anal verge. The barostat was used to inflate the balloon. Distensions of 30-s duration were followed by 30-s rest intervals, starting at the operating pressure and progressively increasing in 1-mmHg steps. In the process of the test, patients were asked to report on sensory thresholds: initial feeling (IF), initial defecate feeling (IDF), embarrassment of defecation (EOD), and maximum of tolerance (MOT). If the MOT or the maximum pressure (50 mmHg) was reached, the balloon was deflated automatically. All subjects were examined by the same physician.

2.2.4 Cold sensitivity test and autonomic cardiovascular reaction

A cold pain test is commonly used to evaluate somatic sensitivity (Whitehead *et al.*, 1990; Zighelboim *et al.*, 1995). In this study, all subjects were asked to immerse their feet in water at 4 °C (the volume of cold water was such that the temperature change was not obvious in a short time). Subjects

were instructed to keep their feet in the water for up to 5 min or until the pain became intolerable. The cold pain threshold (CPT_h) was recorded as the time when the subjects first felt pain and the cold pain tolerance (CPT_o) was recorded as the time when they removed their feet from the cold water. An automatic blood pressure monitor (Andon Health Co., Ltd., Tianjin, China) was then used immediately to record the systolic blood pressure (SBP) and heart rate (HR) of the participants.

2.2.5 Ischemic sensitivity test

A sphygmomanometer (Liankang Co., Ltd., Shanghai, China) was used for the ischemic sensitivity test. The right arm of the patient was elevated above heart level for 1 min, after which the blood flow was occluded with a blood pressure cuff. The cuff was inflated to 240 mmHg and kept at that level. Participants were told to perform 20 hand grip exercises (50% of maximum grip strength) with 2-s duration and 4-s rest interval. The ischemic pain threshold (IPT_h) was recorded as the time when they first felt pain, and their ischemic pain tolerance (IPT_o) was recorded when the pain was intolerable or when 15 min had elapsed (Zhou *et al.*, 2010).

2.2.6 Gut wall low-grade inflammation and intestinal mucosal barrier function

The ELISA test (double antibody sandwich method) was used to quantify the level of calprotectin in stool specimens, and the levels of intestinal fatty acid binding protein (I-FABP), intestinal bile acid binding protein (I-BABP), and liver fatty acid binding protein (L-FABP) in urine specimens. Calprotectin results are expressed as mg/kg, and urine specimen results are expressed as ng/ml. The ELISA procedures were followed according to the recommendations of the manufacturer (Beijing Xinfangcheng Biotechnology Co., Ltd., China).

2.3 Statistical analysis

Statistical analysis was performed using SPSS Version 19.0 (IBM, USA). Distributions of demographic characteristics were analyzed by Pearson's χ^2 or Fisher's exact test. Student's *t*-test was used to compare group differences between continuous variables. Data are presented as mean±standard deviation (SD). Pearson's correlation coefficients among

visceral hypersensitivity, somatic hypersensitivity, autonomic cardiovascular dysfunction, mucous membrane barrier damage, and low-grade inflammation of the gut wall were determined. Spearman's correlations were used to determine the relationships between experimental parameters and the severity of symptoms for IBS patients. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Demographic characteristics of participants

All participants completed the study. The demographic characteristics of participants are listed in Table 1. The gender distribution, height, weight, HAD-A, and HAD-D were similar between the D-IBS and control groups ($P > 0.05$). D-IBS patients were much older on average than the healthy controls. Of the 62 D-IBS patients, 42 had moderately severe IBS, 20 had severe IBS, and none had mild IBS.

3.2 Visceral sensitivity test

In the D-IBS group, the four kinds of sensory

thresholds (IF, IDF, EOD, and MOT) were significantly lower than in healthy controls ($P < 0.001$; Table 2). There was no gender difference among the four kinds of sensory thresholds in the D-IBS group.

3.3 Somatic sensitivity test

With the cold sensitivity test, D-IBS patients took a shorter time to reach both the CPT_h and CPT_o ($P < 0.001$; Table 3). Likewise, the time to reach both the IPT_h and IPT_o was much shorter in the D-IBS group ($P < 0.001$; Table 3). No gender difference was found in somatic sensitivity among D-IBS patients.

3.4 Autonomic cardiovascular reaction

There were no significant differences in the SBP or HR in the resting state between the two groups ($P > 0.05$; Table 4). However, the SBP and HR after the cold sensitivity test were much higher in D-IBS patients ($P < 0.001$; Table 4).

3.5 Low-grade inflammation of the gut wall and intestinal mucosal barrier function tests

Stool calprotectin was higher in D-IBS patients. Compared with the healthy controls, the D-IBS

Table 1 Demographic characteristics of participants

Group	Male/female	Height (m)	Weight (kg)	Age (year)	HAD-A	HAD-D
D-IBS ($n=62$)	35/27	1.68±0.08	66.5±14.9	38.4±10.1	3.53±3.30	3.74±3.55
Control ($n=20$)	12/8	1.69±0.07	62.8±10.4	27.9±3.4	3.25±2.47	2.20±2.09
<i>P</i> -value	0.826	0.442	0.306	<0.001	0.726	0.070

HAD-A: the hospital anxiety and depression scale-anxiety; HAD-D: the hospital anxiety and depression scale-depression. Data are presented as mean±SD

Table 2 Results of visceral sensitivity tests

Group	IF (mmHg)	IDF (mmHg)	EOD (mmHg)	MOT (mmHg)
D-IBS ($n=62$)	5.21±2.20	8.97±2.81	12.63±3.66	16.75±4.59
Control ($n=20$)	8.97±1.93	13.11±1.97	17.93±2.45	23.04±3.38
<i>P</i> -value	<0.001	<0.001	<0.001	<0.001

IF: initial feeling; IDF: initial defecate feeling; EOD: embarrassment of defecation; MOT: maximum of tolerance. Data are presented as mean±SD

Table 3 Results of somatic sensitivity tests

Group	CPT _h (s)	CPT _o (s)	IPT _h (s)	IPT _o (s)
D-IBS ($n=62$)	21.97±9.75	61.00±42.78	77.21±40.85	188.36±73.74
Control ($n=20$)	44.79±14.35	128.93±49.73	171.79±46.48	414.39±79.09
<i>P</i> -value	<0.001	<0.001	<0.001	<0.001

CPT_h: cold pain threshold; CPT_o: cold pain tolerance; IPT_h: ischemic pain threshold; IPT_o: ischemic pain tolerance. Data are presented as mean±SD

patients also showed elevated levels of I-FABP, I-BABP, and L-FABP, but these differences were not statistically significant ($P>0.05$; Table 5).

3.6 Pearson's and Spearman's correlations for IBS patients

For D-IBS patients, significant correlations were found between visceral and somatic hypersensitivity, and visceral hypersensitivity and autonomic cardiovascular dysfunction ($P<0.001$; Table 6). Similarly, somatic hypersensitivity and autonomic cardiovascular dysfunction had a significant negative correlation ($P<0.001$; Table 7). Finally, except for weak significant correlations with HAD-A ($r=0.225$; $P<0.001$), HAD-D ($r=0.302$; $P<0.001$), and CPT_H ($r=-0.345$; $P<0.001$), we found no significant correlations between the severity of symptoms and experimental parameters.

4 Discussion

Unlike most previous studies, in this study, we used the AML method and demonstrated that compared with healthy controls, D-IBS patients had significantly lower sensory thresholds, i.e., they had visceral hypersensitivity. Harraf *et al.* (1998) claimed that visceral hypersensitivity could not be induced by the AML protocol. Compared with "rapid phasic distension", which mainly stimulates the intestinal serosa receptors, the main effect of AML is through

the stimulation of the intestinal mucosa and submucosa receptors. These receptors are involved in different nerve conduction pathways while also participating in intestinal perception (Mertz *et al.*, 1995; Dorn *et al.*, 2007). Visceral hypersensitivity is a biological marker in some IBS cases, especially D-IBS patients. In contrast to Posserud *et al.* (2007), we found no gender difference in the visceral hypersensitivity. Gender distribution was balanced in our IBS group, while Posserud *et al.* (2007)'s group was composed of almost all women. This may have caused a gender bias, and so comparisons with our study may be inappropriate.

Many IBS patients exhibit a variety of somatic symptoms, such as migraine headaches, heartburn, back pain, and muscle pain. In this study, we confirmed that D-IBS patients have somatic hypersensitivity using both cold and ischemic sensitivity tests. Our results were similar to those of previous studies (Zhou *et al.*, 2009; 2010). To our knowledge, our work is the first study to use diverse methods, especially the ischemic sensitivity test, to examine somatic sensitivity in China. Unlike the cold sensitivity test which activates superficial A δ fibers in the skin, the ischemic sensitivity test stimulates a large number of thick C-fibers in muscle and produces a deep and diffuse pain (Zuo *et al.*, 2006; Zhou *et al.*, 2010). In view of the above features, the ischemic sensitivity test may be more accurate for the evaluation of somatic sensitivity.

Table 4 Autonomic cardiovascular reaction after cold sensitivity test

Group	Resting state		After cold sensitivity test	
	SBP (mmHg)	HR (time/min)	SBP (mmHg)	HR (time/min)
D-IBS ($n=62$)	115.96 \pm 10.95	72.08 \pm 4.96	138.40 \pm 11.47	92.03 \pm 8.60
Control ($n=20$)	112.93 \pm 4.96	73.00 \pm 5.75	119.04 \pm 6.09	77.50 \pm 6.84
<i>P</i> -value	0.160	0.411	<0.001	<0.001

SBP: systolic blood pressure; HR: heart rate. Data are presented as mean \pm SD

Table 5 Results of stool and urine specimens

Group	Calprotection (mg/kg)	I-FABP (ng/ml)	I-BABP (ng/ml)	L-FABP (ng/ml)
D-IBS ($n=62$)	55.70 \pm 10.13	1475.10 \pm 281.02	1011.87 \pm 223.20	762.45 \pm 174.08
Control ($n=20$)	45.72 \pm 5.67	1425.62 \pm 300.66	955.99 \pm 180.00	705.30 \pm 166.44
<i>P</i> -value	<0.001	0.503	0.312	0.201

I-FABP: intestinal fatty acid binding protein; I-BABP: intestinal bile acid binding protein; L-FABP: liver fatty acid binding protein. Data are presented as mean \pm SD

Table 6 Pearson's correlation coefficients for D-IBS patients between visceral hypersensitivity and somatic hypersensitivity, and visceral hypersensitivity and autonomic cardiovascular dysfunction

Parameter	Pearson's correlation coefficient			
	IF	IDF	EOD	MOT
IPTh	0.519	0.497	0.523	0.537
IPTo	0.582	0.577	0.591	0.602
CPTTh	0.658	0.549	0.518	0.512
HR after cold sensitivity test	-0.523	-0.566	-0.559	-0.629

IF: initial feeling; IDF: initial defecate feeling; EOD: embarrassment of defecation; MOT: maximum of tolerance; IPTh: ischemic pain threshold; IPTo: ischemic pain tolerance; CPTTh: cold pain threshold; HR: heart rate. Data are presented as mean±SD. All $P < 0.001$

Table 7 Pearson's correlation coefficients for D-IBS patients between somatic hypersensitivity and autonomic cardiovascular dysfunction

Parameter	Pearson's correlation coefficient	
	SBP after cold sensitivity test	HR after cold sensitivity test
IPTh	-0.642	-0.683
IPTo	-0.661	-0.727

IPTh: ischemic pain threshold; IPTo: ischemic pain tolerance; SBP: systolic blood pressure; HR: heart rate. All $P < 0.001$

In our study, we found that compared with the control group, D-IBS patients had a significantly higher SBP and HR after cold stimulus, indicating the presence of autonomic cardiovascular dysfunction in the IBS group. Few studies have found autonomic nervous system (ANS) dysfunction in response to a painful somatic stimulus, but our results suggest that when exposed to an external stimulus, such as cold water, the regulation of the ANS was in an abnormal state in IBS patients. This phenomenon suggests that the dysfunction of central-peripheral nerve regulation mechanisms may be involved in the pathogenesis of IBS.

A number of IBS, especially D-IBS, patients have a history of acute gastroenteritis (Zhong and Hou, 2012; Liu *et al.*, 2012). Inflammation, even low-grade, can send many systemic and local signals, which may cause changes in the intestine (such as the dysfunction of digestion and absorption). Calprotectin, which is a protein released by white blood cells and stable in faeces, can indicate inflammation wherever it occurs in the digestive tract (Derikx *et al.*,

2010). In this study, compared with the healthy group, D-IBS patients had a significantly higher level of calprotectin. Some studies have found that faeces calprotectin was not higher in IBS patients. The recruitment of only D-IBS patients and the relatively large sample size in our study may explain this discrepancy. Three isoforms of FABP (I-FABP, I-BABP, and L-FABP) are present in the intestinal villus (Derikx *et al.*, 2010). The urinary concentration of FABP is a useful marker for evaluating intestinal mucosal barrier function. In our results, the concentrations of the three isoforms of FABP were all higher in D-IBS patients than those in the control group, but the differences were not statistically significant. We speculate that if the sample size had been larger, a significant difference may have been found.

To our surprise, in this study, we showed significant correlations between visceral and somatic hypersensitivity, visceral hypersensitivity and autonomic cardiovascular dysfunction, and somatic hypersensitivity and autonomic cardiovascular dysfunction, which have not been found before to our knowledge. Our results also suggest recommendations for the treatment of IBS. Previously, too much attention has been given to only intestinal symptoms. At present, the conventional drugs used in the treatment of IBS include: laxatives, antidiarrheals, prokinetics, probiotics, and antispasmodics. The role of these drugs is mainly to relieve the patient's gastrointestinal symptoms, but the curative effects have been disappointing (Rahimi and Abdollahi, 2012). The possible reason is that many patients with IBS also exhibit a wide variety of extra-intestinal symptoms. From our results, individualized treatments (such as cognitive behavioral therapy, hypnotherapy, dietotherapy, relaxation, and stress management in improving the function of the ANS, and traditional Chinese medicine and acupuncture to relieve somatic hypersensitivity) are recommended to alleviate the extra-intestinal symptoms (Rahimi and Abdollahi, 2012; Wilkins *et al.*, 2012; Chang, 2014). According to our data, the remission of extra-intestinal symptoms may be associated with the alleviation of gastrointestinal symptoms in D-IBS patients.

Unlike previous studies, no strong correlations between the severity of symptoms and experimental parameters were found in our study (Zhou *et al.*, 2009), indicating that the mechanisms involved in the

expression of symptoms are still complicated and inadequately understood.

A strength of our study was that our analysis excluded the confounding effects of mental factors. However, some limitations should be considered. First, the survey was restricted to D-IBS, so the findings may not be generally applicable to other subtypes. Second, based on the current research, we could not explain the results in terms of molecular mechanisms, a future area of research focus. Third, there were age differences between the IBS and control groups. Sometimes, this is unavoidable in real-life clinical research, but no significant effects of gender were found in our two groups. Furthermore, age difference is not an influential factor in the evaluation of experimental parameters such as visceral hypersensitivity (Posserud *et al.*, 2007).

In summary, our results showed that patients with D-IBS showed evidences of visceral hypersensitivity, somatic hypersensitivity, autonomic cardiovascular dysfunction, and low-grade inflammation in the digestive tract. We also found significant correlations between visceral and somatic hypersensitivity, visceral hypersensitivity and autonomic cardiovascular dysfunction, and somatic hypersensitivity and autonomic cardiovascular dysfunction, which may provide valuable suggestions for the treatment of D-IBS.

Compliance with ethics guidelines

Liang LIU, Bei-ni LIU, Shuo CHEN, Miao WANG, Yang LIU, Yan-li ZHANG, and Shu-kun YAO declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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中文概要:

本文题目: 肠易激综合征亚型患者具有肠道和躯体高敏感, 自主心血管功能紊乱以及肠道低浓度炎症
Visceral and somatic hypersensitivity, autonomic cardiovascular dysfunction and low-grade inflammation in a subset of irritable bowel syndrome patients

研究目的: 明确腹泻型肠易激综合征患者是否具有肠道和躯体高敏感、自主心血管功能紊乱以及肠道低浓度炎症。

创新要点: 发现腹泻型肠易激综合征患者具有自主心血管功能紊乱和肠道低浓度炎症(这两方面在之前研究中尚存争议)。此外, 发现腹泻型肠易激综合征患者的肠道高敏感和躯体高敏感、肠道高敏感和自主心血管功能紊乱、躯体高敏感和自主心血管紊乱之间存在相关性, 为患者的治疗提供参考。

研究方法: 2013年9月至2014年5月, 62名腹泻型肠易激综合征患者和20名健康志愿者参与到了本研究。所有受试者接受并顺利完成了相关检查和问卷填写。利用恒压器(渐至极限值)检查我们发现腹泻型肠易激综合征患者具有肠道高敏感。同时, 采用冷水刺激法和缺血刺激法探明腹泻型肠易激综合征患者具有躯体高敏感。

重要结论: 腹泻型肠易激综合征患者具有肠道和躯体高敏感、自主心血管功能紊乱以及肠道低浓度炎症。肠道高敏感和躯体高敏感、肠道高敏感和自主心血管功能紊乱、躯体高敏感和自主心血管紊乱之间存在相关性。

关键词组: 肠易激综合征 (IBS); 肠道高敏感; 躯体高敏感; 自主心血管功能紊乱; 低浓度炎症