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Baroreflex mechanisms in Irritable Bowel Syndrome: Part I. Traditional indices

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Abstract

Objective—This study was conducted to present evidence of differences in autonomic regulation of cardiovascular activity and its role in the severity of specific (disease-related) and non-specific (negative affect and chronic pain-related) symptoms in individuals with Irritable Bowel Syndrome (IBS).

Methods—Seventy-eight female patients with IBS and 27 healthy women age 18–62 years were assessed for IBS symptoms, negative affect, and baroreceptor sensitivity (BRS), blood pressure (BP), heart rate, and heart rate variability (HRV) at rest. Direct and indirect regression effects were examined with application of the bootstrap procedure to validate findings.

Results—IBS was reliably related to lower resting BRS, higher BP, and higher negative affect compared to healthy controls. Longer disease duration (chronicity) was related to BRS decrease coupled with systolic BP increase (95% CIs = -0.14 to -0.01). Three autonomic mechanisms associated with BRS decrease were found to further regulate severity of IBS symptoms. Lower BRS was related to higher IBS severity in general if the effect was transferred through the decrease of low frequency power of HRV (e.g., 95% CIs = -0.039 to -0.001 for abdominal pain severity). However, lower BRS was related to lower IBS severity in general if the effect was transferred through diastolic BP increase (95% CIs = 0.01 to 0.11 for abdominal pain severity). Lower BRS was related to higher abdominal pain severity coupled with high negative affect if the

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effect was transferred through the decrease of higher frequency power of HRV (95% CIs = -0.026 to -0.003).

Conclusions—These findings indicate that different cardiovascular mechanisms are associated with IBS development and the increase and decrease of severity of IBS symptoms. Their assessment suggests ways to personalize treatment of IBS.

Keywords

: baroreceptor sensitivity; systolic blood pressure; diastolic blood pressure; heart rate variability; Irritable Bowel Syndrome; negative affect; chronic pain severity

1. Introduction

The gastrointestinal (GI) tract is a complex organ with interacting neural and endocrine mechanisms that control its main functions: digestion and assimilation of nutrients and the transport and excretion of waste products. Visceral sensation involves a chain that conveys information from the GI tract to interceptive and affective centers in the brain. Alterations in bidirectional communication between the brain and the gut have been hypothesized to underlie symptoms of chronic visceral pain disorders such as Irritable Bowel Syndrome (IBS) and may in addition affect positive and negative emotions [1–3]. IBS is the most common of the functional GI disorders impacting 5-11% of the US population and leading to significant suffering and health care costs [4]. Given the critical role of the autonomic nervous system in GI function and brain-gut communications, disorders like IBS may be closely associated with altered central autonomic control, and specific IBS phenotypes (e.g. pain vs bloating symptoms) may be associated with specific autonomic patterns. Few definitive autonomic patterns have been found to be reliably associated with IBS phenotypes [4].

Studies evaluating autonomic function have found increased sympathetic activity and/or lower vagal tone during waking and/or sleep in IBS patients compared to healthy controls [5–10], and other studies have found no difference in autonomic activity between the groups [10–12]. Phenotype differences in IBS, severity of symptoms, or disease duration (chronicity) may be contributing to the inconsistency of findings [11,13–16]. This suggests that activity of both branches of the autonomic nervous system may serve as an index of symptom severity or a sense of discomfort in IBS [14,17,18]. However, further research is needed to improve the validity of autonomic measures for their translation to clinical practice [16].

Visceral afferent stimulation has been found to affect baroreflex activity that may play an important role in the pathophysiology of IBS [19]. For example, baroreceptor sensitivity (BRS) values at rest were found to be reduced in patients with IBS compared to a control group [18,20,21]. BRS is an autonomic measure of integrative sympathetic and parasympathetic regulation of cardiovascular processes assessed by blood pressure (BP) level and heart rate variability (HRV), and its resting values were found to be associated with mood regulation in our previous studies in healthy subjects and patients with major depression [22,23]. Since IBS was found to be associated with higher anxiety and depression

[12], the association between lower BRS and higher IBS severity may be mediated not only through a pathophysiological (peripheral somatosensory) but also through this psychopathological (central affective) mechanism.

The aim of the study was to confirm a hypothesis that IBS compared to a healthy condition is associated with lower BRS and to provide evidence that lower BRS is indirectly related to greater IBS severity and longer duration (chronicity) in patients. Indirect effects between BRS and IBS scores were expected to be mediated through negative affect (anxiety and depression) and autonomic measures (HRV and BP).

2. Methods

2.1 Subjects

Seventy-eight women age 18–62 years with IBS based on Rome III criteria [24] and symptoms lasting a minimum of 6 months (IBS group) and 27 healthy women age 19–54 years without IBS (control group) were recruited by community advertisement. IBS diagnosis, Rome III bowel habit predominance, and inclusion/exclusion status were determined by a physical examination by a physician or nurse practitioner experienced in functional GI disorders. Patients were excluded if they had undergone GI surgery, had an active organic GI disorder, had cardiovascular disorders or arrhythmias, had a severe psychiatric disorder, used warfarin or other blood-thinning drugs, were pregnant, or were using pain medications or beta-blockers. The University of California, Los Angeles, Institutional Review Board approved the study. All subjects provided signed informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki.

2.2 Symptoms and psychological instruments

Patients and control subjects answered self-report questions on age, ethnicity, smoking habit, caffeine and alcohol consumption, physical activity, and IBS chronicity (in years). Severity of usual IBS symptoms was assessed as mild, moderate, severe, or very severe (usual IBS severity), and current severity of IBS symptoms of pain, bloating and overall GI symptoms (current IBS severity) were assessed for the past week using 0-20 numeric rating scales (anchored by “none” and “most intense symptoms imaginable”) [25]. The Hospital Anxiety and Depression Scale (HADS) was administered as a self-report measure of current total affect (HADS-T), anxiety (HADS-A), and depression (HADS-D) symptoms validated for nonpsychiatric samples [26].

2.3 Physiological measures

Before the physiological session, after the participant was seated for 5 min, three casual blood pressure (BP) readings were taken using standard methods. Continuous measures of electrocardiogram (ECG), beat-to-beat BP, and respiration were recorded during the laboratory session using Biopac MP 100 hardware and Acq- Knowledge 3.8.2 software (Biopac, Goleta, California). A standard electrode configuration (right clavicle and precordial site V6) with three disposable Ag-AgCl electrodes (ConMed Corp.) was used to record the ECG. The signal was digitized at 2000 Hz, and RR-interval (RRI) series were

derived using a QRS complex template detection algorithm to obtain R-peak localization as the apex of the interpolating parabolas. Beat-to-beat BP was measured non-invasively using a Finapres Continuous NIBP Monitor (Ohmeda, Englewood, Colorado) via a finger cuff attached to the third finger of the non-dominant hand and digitized at 2000 Hz with 12-bit resolution. The Finapres has been shown to be a suitable tool for reliable tracking of changes in BP [27]. Systolic (SBP) and diastolic (DBP) points were derived using two different template detection algorithms. All recordings were automatically and visually examined to verify ECG and BP wave classification and to correct for artifacts. Further details on the methods and algorithms can be found elsewhere [22,23,28]. Respiration was recorded with the Biopac Respiratory Effort Transducer (Biopac, Goleta, California), a belt placed around the lower rib cage measuring changes in chest circumference.

2.4 Baroreflex sensitivity and heart rate variability

We measured BRS by the sequence method [22,23]. SBP and RR interval (RRI) time series were scanned by custom software (see below) to identify sequences during which SBP and associated RRI both increased ("up" [+] sequences) or both decreased ("down" [−] sequences) successively in parallel over three or more beats (SBP and RRI ramps). We required a minimum change of 1 mmHg for SBP and 3 ms for RRI per beat and a minimum correlation of 0.80 between the parallel values to accept the pairs for calculating BRS (gain of baroreceptor sensitivity, ms/mmHg) as means of least squares linear regression slopes with lag 0, 1, and 2 [22,23].

Multistage band-pass linear filtering was adopted to suppress extraneous sources of RRI variation [22,28,29]. This method is comparable to the Porges-Bohrer moving polynomial filter method of the assessment of respiratory sinus arrhythmia (HF-HRV) [30,31], but extended the filtering procedure also to lower frequencies like the Traube-Hering-Mayer wave (LF-HRV). In this method, the RRI variances of residual time series (the filtered waveform) after a bandpass smoothing FIR (finite impulse response) filtering for alien frequencies and baseline trend are used to calculate HRV (RRI variability, ms^2) in the low frequency power band (LF-HRV; 0.075–0.125 Hz) and the high frequency power band (HF-HRV; 0.125–0.50 Hz). These bands of frequencies were selected to optimally adapt mathematical properties of the filtering method to the properties of the particular physiological processes [30-32]. As the distributions of the HRV measures were skewed, natural logarithms (ln) of the LF and HF measures were used. Data processing for R-peak and BP-peak detection, artifact search, and baroreflex sequences was performed off-line using a custom computer program written by DMD using the Spike2 system (Cambridge Electronic Design, Cambridge, England).

2.5 Laboratory procedure

The protocol included a 10-minute resting baseline during which the subjects were comfortably seated in a chair and instructed to minimize movement and to rest. Subjects were monitored via a video feed.

2.6 Statistical analysis

Descriptive and inferential analyses were performed with SPSS (SPSS Science, Chicago, IL) software using General Linear Models by the Type III method (GLM), SPSS built-in bootstrapping option for computing confidence intervals for regression estimates in GLM, and the SPSS macro command set 'PROCESS' to evaluate the significance of mediation effects [33]. Values of $p < 0.05$ were regarded as statistically significant in parametric analyses. Bias-corrected and accelerated (BCa) bootstrap procedure with 5000 bootstrap samples was used to generate non-parametric 95% confidence intervals (CIs) of regression coefficients from empirical sampling distribution. The bootstrap procedure was suggested as a robust alternative to inference based on parametric assumptions (such as normally distributed errors) to confirm findings obtained by parametric analyses and is recommended for reporting inferences in scientific reports [34,35]. All parameter estimates were expressed as non-standardized (B) regression coefficients and their standard errors (SE) in the text. Where necessary, a partial η^2 was reported as a measure of strength of association (effect size). Demographic variables (age and body mass index) were included in those analyseswhere they had significant ($p < 0.05$) correlations with dependent variables to control for their probable effects as confounders or covariates. According to these correlations age (natural log(ln)-transformed value) was included in all models, but body mass index was only included in the analyses of BP.

To confirm the main hypothesis that the autonomic nervous system is impaired in patients with IBS, the first group of GLM analyses with multivariate and univariate models (Pillai's Trace and regression statistics) was conducted to test the Group (IBS vs Healthy Control) main effect on cardiovascular (CV) variables. A second group of the same GLM analyses tested that symptom severity, chronicity, and negative affect of IBS patients would be significantly associated with differences in CV measures. Additional analyses with the bootstrap non-parametric procedure were used in the first and the second groups of analyses to inspect and confirm (validate) those main effects that were found significant or with a tendency to be significant by the parametric procedures. Final inferences of significance of the effects and relationships were based on results of the bootstrap non-parametric procedure.

A third group of analyses inspected the relationships between CV measures, negative affect (anxiety and depression), and IBS severity and chronicity for possible mediation mechanisms to combine and explain GLM simple effects. All mediation effects were evaluated for significance by the BCa bootstrap procedure included in the 'PROCESS' macro command set as the bootstrapping technique more accurately captures the shape of the sampling distribution and therefore has greater power to detect mediation [36].

Number of individuals varied between different analyses due to missing or incomplete data of some CV, clinical (complaints), and personality variables in some subjects (between 4 and 9 subjects).

3. Results

3.1 Differences in demographic, medical, and psychological characteristics

Table 1 shows the demographic, medical, and psychological characteristics of the IBS and healthy samples. No differences between groups were found in ethnicity, age, body mass index, caffeine, and alcohol consumption (*ps* > 0.15 for all comparisons). Bowel habit subgroups did not differ in symptom severity and chronicity. The control group had significantly lower smoking habit, HADS-A and HADS-T symptoms (see Table 1). Usual severity of IBS symptoms was equally associated with 3 other subjective IBS measures assessing severity during the past week (Table 2). Main findings in IBS patients were similar with respect to all negative affect measures (HADS-A, HADS-D, and HADS-T) and therefore are only presented for HADS-T.

3.2 Main findings

3.2.1 GLM analyses—BRS and office (casual) SBP and DBP values were found to be statistically significant indicators of physiological difference between the IBS and control groups (Bs[SE] = 3.26[1.26], -9.53[3.23], and -6.65[2.34], ts[p] = 2.60[0.010], -2.95[0.004], -2.84[0.006], η^2 = 0.07, 0.09, and 0.09; confirmed by bootstrap 95% CIs: 0.35 to 6.25, -14.75 to -4.07, -10.06 to -2.90). BRS was lower and office SBP and DBP were higher in the IBS group compared to the control (Table 3).

Lower BRS was found to be significantly associated with higher office and laboratory BP levels and lower lnLF- and lnHF-HRV values in IBS patients (Pillai's Traces = .26 and .36, F = 5.56 and 18.92, p < 0.001, for four aggregated BP levels and for two HRV values, respectively). Higher negative affect was significantly associated with lower BRS and lnHF-HRV in IBS patients (Bs[SE] = -0.15[0.07] and -0.04[0.01], ts[p] = -2.13[0.037] and -2.95[0.004], η^2 = 0.06 and 0.11; confirmed by bootstrap 95% CIs: -0.28 to -0.02 and -0.06 to -0.01, respectively).

Higher usual severity of IBS symptoms was significantly associated with lower lnLF-HRV and lnHF-HRV in IBS patients (Bs[SE] = -0.31[0.15] and -0.38[0.14], ts[p] = -2.12[0.038] and -2.65[0.010], η^2 = 0.06 and 0.09; confirmed by bootstrap 95% CIs: -0.67 to -0.01 and -0.70 to -0.06). Higher negative affect was significantly associated with higher usual IBS severity and current abdominal pain severity in IBS patients (Bs[SE] = 0.04[0.01] and 0.13[0.06], ts[p] = 4.16[0.000] and 2.08[0.041], η^2 = 0.19 and 0.06; confirmed by bootstrap 95% CIs: 0.02 to 0.06 and 0.02 to 0.24, respectively).

3.2.2 Mediation analyses—Mediation analyses indicated that the absence of a direct relationship of symptom severity to the baroreflex measure may be explained by its linking to two opposite impairment and protection mechanisms. One mediation analysis found that lower BRS determined the increase in subjective sensation of usual IBS severity coupled with the increase of current severity of IBS symptoms by triggering a lnLF-HRV decrease (e.g., BRS->LF-HRV->usual IBS severity->current abdominal pain severity; B[SE] = -0.024[0.02], 95% CIs = -0.090 to -0.001). However, another mediation analysis found that lower BRS determined the decrease of usual IBS severity coupled with the decrease of

current severity of IBS symptoms by triggering a DBP increase (e.g., BRS->office DBP->usual IBS severity-> current abdominal pain severity; B[SE] = 0.04[0.02], 95% CIs = 0.01 to 011).[1] Additional mediation analysis found that the decrease in BRS transferred its effect through lower lnHF-HRV to both higher usual IBS severity and current severity of abdominal pain by triggering the increase of negative affect (BRS->HF-HRV->HADS-T->IBS severity; Bs[S]E = -0.012[0.006] and -0.047[0.031], 95% CIs = -0.026 to -0.003 and -0.131 to -0.004, respectively). Greater BRS decrease in IBS patients, in turn, was found to be determined by longer disease duration (chronicity) through higher SBP increase (chronicity-> office & lab SBP->BRS; Bs[S]E = -0.06[0.03] and -0.03[0.02], 95% CIs = -0.14 to -0.01 and -0.086 to -0.001).[2] No moderation effect of bowel habits on the relationships between IBS severity and CV variables was found in IBS patients.

4. Discussion

Findings confirm the prediction that patients with IBS in general have significantly lower resting baroreceptor sensitivity compared to healthy controls [18,20]. Higher scores of blood pressure[3] and negative affect were also attributed to IBS patients. Further analysis in IBS patients found that four mechanisms may combine them causally. (i) Chronicity of the disease determined the decrease of baroreceptor sensitivity through its adapting to the increased systolic blood pressure. In turn, the decrease of baroreceptor sensitivity determined (ii) the increase of IBS severity in general including abdominal pain through the mechanism associated with the decrease of low frequency power of heart rate variability and (iii) the increase of mainly abdominal pain severity through the negative affect associated with the decrease of high frequency power of heart rate variability. At the same time, (iv) the decrease of baroreceptor sensitivity determined the decrease of IBS severity in general through increasing diastolic blood pressure level. Negative and positive effects of baroreceptor sensitivity on disease severity can cancel each other out and explain the absence of a significant direct relationship between them if they are equal in size as in the present study. The mediation analysis showed that current IBS sensations (e.g., severity of abdominal pain) were related to physiological measures if their variation corresponded with the variation of usual IBS severity, i.e., physiological activity was associated with the stable or trait component of IBS symptoms.

Thus, longer disease duration determines hypertension associated with lower baroreceptor sensitivity in IBS patients which is further transferred either to more affective (decreased mood) or to more somatic (impaired heart rate regulation) mechanisms of disease aggravation. The findings confirmed the negative affect path between baroreceptor sensitivity measure and IBS severity but not as the only mechanism. Other mechanisms were independent of affect. A finding of higher systolic blood pressure level in this sample of IBS patients is consistent with other studies that found that a systolic blood pressure

[1]DBP above 70 mmHg determined the switching of autonomic regulation to the significant reduction of disease severity in patients (obtained using Akaike Information Criterion [AIC] for the best-fitting model; data not shown).
[2]Disease duration after 9 months and after 15 months determined the switching of autonomic regulation to significantly higher SBP and to significantly lower BRS, respectively, compared with the control (obtained by AIC; data not shown).
[3]Blood pressure levels of IBS patients and control subjects in the study in general were within normal limits or below high blood pressure threshold as defined by clinical recommendations [50] and therefore findings and discussions of higher and lower values of blood pressure in the paper should be accepted respectively.

increase in response to rectal pain stimulation was greater and prolonged in patients with IBS compared to healthy controls and that chronic pain is a significant predictor of increased blood pressure beyond the effects of traditional demographic risk [18,19,37]. Sustained increase of blood pressure level is considered to be an indicator of a pain regulation ('pain killer') mechanism [38–40]. In the present study, this pain alleviating mechanism associated with a diastolic blood pressure increase was affirmed and supported a recent finding of the impact of baroreflex function on endogenous control of acute pain coupled mainly with a diastolic blood pressure increase [41].

These findings correspond with studies demonstrating that increased nociceptive activity alters the sensitivity of the nucleus tractus solitarii to the neural impulses originating from the carotid baroreceptors that changes the baroreceptor sensitivity and the SBP operating point and thus determines the interaction between pain and blood pressure regulation [42]. In the present study, this mechanism was found to be related to disease chronicity (more chronic disease -> higher SBP level -> lower baroreceptor sensitivity) and to disease severity (lower baroreceptor sensitivity -> higher DBP level -> lower disease severity). Thus, chronic pain may initiate a central resetting of the baroreflex mechanism accounting for a sustained increase of arterial pressure and the pain-killing (anti-nociceptive) effect. This mechanism should be associated with greater activation of descending pain inhibitory processes by enhanced noradrenergic activity and may be relevant for producing pain relief in patients with chronic pain syndromes [43–48]. From an evolutionary viewpoint, this adaptation 'blood pressure' mechanism may help alleviate a recovery of physical functioning after impairments. Difference in effect size with respect to blood pressure measures obtained in office and laboratory may be explained by either the moderation effect of arousal variations between different settings [23,40,49,50] or worse accuracy of non-invasive beat-to-beat monitors in measuring absolute levels of blood pressure [51].

Findings in IBS patients showed that greater usual severity of IBS symptoms together with the current severity of abdominal pain were related to decreased power of both low and high frequency bands of heart rate variability at rest. However, only decreased power of the high frequency band of heart rate variability mediated the relationship between diminished baroreceptor sensitivity and higher usual severity of IBS symptoms through negative affect. This effect was mainly associated with the current severity of abdominal pain. It corresponds with the findings indicating association of reduced heart rate variability with both severe abdominal pain [14] and higher negative affect [11] in women with IBS. These findings in IBS patients also correspond with other studies of chronic pain that showed that an experimental chronic pain and a chronic pain syndrome (e.g., fibromyalgia) determines a coupled decrease of baroreceptor sensitivity and the power in the high or in all frequency bands of heart rate variability [47,52]. The causality of the mediation chain is supported by other findings that indicate that chronic baroreflex activation leads to increased heart rate variability in dogs and patients [53]. An evolutionary role of this 'negative affect' mechanism of illness severity induction could be to provide a coping behavior [54–57].

Thus, the study shows that the presence of IBS in general is reliably indicated by low resting baroreceptor sensitivity in general and its reduction is increased with disease duration. Other physiological indicators can specify pathophysiological mechanisms of IBS development

and this can improve and personalize treatment of the disease. Reduced baroreflex sensitivity may be coupled with the reduction in different bands of heart rate variability associated with either physical sensations (a sensation component of the disease) or affective behavior (an affective component or affective comorbidity of the disease). These findings confirm the notion that baroreflex modulates both the sensory and affective components of pain [58]. Coupling of reduced baroreflex sensitivity with hypertension is associated with the process of adaptation to chronic pain (an antinociceptive component or somatic comorbidity of the disease). Thus, these three different mechanisms associated with IBS severity suggest that three different targets of interventions may be specified to personalize the selection of a treatment strategy in patients depending on a predominant one through regulating, respectively: ascending nociceptive pathways at different stages from down to top (e.g., by probiotics or opioids, respectively), negative affect (e.g., by GABAergic sedatives) or descending analgesic pathways from top to down (e.g., by adren- or serotonin-ergic stimulants, respectively), in addition to the selection of treatment strategy by using a simple symptomatological approach (e.g. constipation or diarrhea).

5. Conclusion

Severity of disorders with pain syndromes can be determined by different pathological mechanisms and are more thoroughly assessed by a combination of objective and self-report measures. Therefore, objective markers are needed when assessing severity and treating patients with these syndromes to avoid their maltreatment. This study shows that measures of baroreflex regulation of cardiovascular activity can be utilized in clinical settings to more accurately assess severity of Irritable Bowel Syndrome as a disorder associated with chronic pain, and as such, can specify its pathophysiological mechanisms, which can then be used to personalize its treatment.

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References

1. Tougas G. The autonomic nervous system in functional bowel disorders. Can J Gastroenterol. 1999; 13 Suppl A:15A–17A.
2. Farmer AD, Randall HA, Aziz Q. It's a Gut Feeling - how the gut microbiota affects the state of mind. J Physiol. 2014; 592:2981–8.10.1113/jphysiol.2013.270389 [PubMed: 24665099]
3. Chang MC, Shapiro D, Joshi A, Shahabi L, Tan S, Smith S, et al. Stress reactivity in traditional Chinese medicine-based subgroups of patients with irritable bowel syndrome. J Altern Complement Med. 2014; 20:276–83.10.1089/acm.2013.0197 [PubMed: 24256027]
4. Camilleri M. Physiological underpinnings of irritable bowel syndrome: neurohormonal mechanisms. J Physiol. 2014; 592:2967–80.10.1113/jphysiol.2014.270892 [PubMed: 24665101]
5. Smart HL, Atkinson M. Abnormal vagal function in irritable bowel syndrome. Lancet. 1987; 2:475–8. [PubMed: 2887777]
6. Heitkemper M, Burr RL, Jarrett M, Hertig V, Lustyk MK, Bond EF. Evidence for autonomic nervous system imbalance in women with irritable bowel syndrome. Dig Dis Sci. 1998; 43:2093–8. [PubMed: 9753278]

7. Waring WS, Chui M, Japp A, Nicol EF, Ford MJ. Autonomic cardiovascular responses are impaired in women with irritable bowel syndrome. J Clin Gastroenterol. 2004; 38:658–63. [PubMed: 15319647]
8. Manabe N, Tanaka T, Hata J, Kusunoki H, Haruma K. Pathophysiology underlying irritable bowel syndrome--from the viewpoint of dysfunction of autonomic nervous system activity. J Smooth Muscle Res. 2009; 45:15–23. [PubMed: 19377269]
9. Orr WC, Elsenbruch S, Harnish MJ. Autonomic regulation of cardiac function during sleep in patients with irritable bowel syndrome. Am J Gastroenterol. 2000; 95:2865–71.10.1111/j.1572-0241.2000.02318.x [PubMed: 11051361]
10. Lee CT, Chuang TY, Lu CL, Chen CY, Chang FY, Lee SD. Abnormal vagal cholinergic function and psychological behaviors in irritable bowel syndrome patients: a hospital-based Oriental study. Dig Dis Sci. 1998; 43:1794–1799. [PubMed: 9724171]
11. Jarrett M, Heitkemper M, Czyzewski D, Zeltzer L, Shulman RJ. Autonomic nervous system function in young children with functional abdominal pain or irritable bowel syndrome. J Pain. 2012; 13:477–84.10.1016/j.jpain.2012.02.007 [PubMed: 22520688]
12. Camilleri M, McKinzie S, Busciglio I, Low PA, Sweetser S, Burton D, et al. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2008; 6:772–81.10.1016/j.cgh.2008.02.060 [PubMed: 18456567]
13. Heitkemper M, Jarrett M, Cain KC, Burr R, Levy RL, Feld A, et al. Autonomic nervous system function in women with irritable bowel syndrome. Dig Dis Sci. 2001; 46:1276–84. [PubMed: 11414305]
14. Burr RL, Heitkemper M, Jarrett M, Cain KC. Comparison of autonomic nervous system indices based on abdominal pain reports in women with irritable bowel syndrome. Biol Res Nurs. 2000; 2:97–106. [PubMed: 11337820]
15. Cheng P, Shih W, Alberto M, Presson AP, Licudine A, Mayer EA, et al. Autonomic response to a visceral stressor is dysregulated in irritable bowel syndrome and correlates with duration of disease. Neurogastroenterol Motil. 2013; 25:e650–9.10.1111/nmo.12177 [PubMed: 23822743]
16. Mazurak N, Seredyuk N, Sauer H, Teufel M, Enck P. Heart rate variability in the irritable bowel syndrome: a review of the literature. Neurogastroenterol Motil. 2012; 24:206–16.10.1111/j.1365-2982.2011.01866.x [PubMed: 22256893]
17. Iovino P, Azpiroz F, Domingo E, Malagelada JR. The sympathetic nervous system modulates perception and reflex responses to gut distention in humans. Gastroenterology. 1995; 108:680–6. [PubMed: 7875470]
18. Spaziani R, Bayati A, Redmond K, Bajaj H, Mazzadi S, Bienenstock J, et al. Vagal dysfunction in irritable bowel syndrome assessed by rectal distension and baroreceptor sensitivity. Neurogastroenterol Motil. 2008; 20:336–42.10.1111/j.1365-2982.2007.01042.x [PubMed: 18179607]
19. van der Veek PPJ, Swenne CA, van de Vooren H, Schoneveld AL, Maestri R, Masclee AAM. Viscerosensory-cardiovascular reflexes: altered baroreflex sensitivity in irritable bowel syndrome. Am J Physiol Regul Integr Comp Physiol. 2005; 289:R970–R976.10.1152/ajpregu.00607.2004 [PubMed: 15919731]
20. Pytrus T, Iwanczak B, Iwanczak F. Baroreflex sensitivity in children with functional gastrointestinal disorders, insulin-dependent Diabetes Mellitus and in normal controls. J Pediatr Gastroenterol Nutr. 2004; 39:S442.
21. Gunterberg V, Strid H, Tygesen H, Osika W, Friberg P, Simren M. Autonomic nervous function assessed by two complementary methods - baroreceptor sensitivity and heart rate variability - in patients with irritable bowel syndrome (IBS). 19th United Eur Gastroenterol Week. 2011:220.
22. Davydov DM, Shapiro D, Cook IA, Goldstein I. Baroreflex mechanisms in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2007; 31:164–177.10.1016/j.pnpbp.2006.08.015 [PubMed: 17011098]
23. Davydov DM, Shapiro D, Goldstein IB. Relationship of resting baroreflex activity to 24-hour blood pressure and mood in healthy people. J Psychophysiol. 2010; 24:149–160.10.1027/0269-8803/a000012

24. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006; 130:1480–91.10.1053/j.gastro.2005.11.061 [PubMed: 16678561]
25. Spiegel B, Strickland A, Naliboff BD, Mayer EA, Chang L. Predictors of patient-assessed illness severity in irritable bowel syndrome. Am J Gastroenterol. 2008; 103:2536–43.10.1111/j.1572-0241.2008.01997.x [PubMed: 18637089]
26. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. J Psychosom Res. 1997; 42:17–41. [PubMed: 9055211]
27. Imholz B. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. Cardiovasc Res. 1998; 38:605–616.10.1016/S0008-6363(98)00067-4 [PubMed: 9747429]
28. Shapiro D, Cook IA, Davydov DM, Ottaviani C, Leuchter AF, Abrams M. Yoga as a complementary treatment of depression: effects of traits and moods on treatment outcome. Evidence-Based Complement Altern Med. 2007; 4:493–502.
29. Ottaviani C, Shapiro D, Davydov DM, Goldstein IB, Mills PJ. The autonomic phenotype of rumination. Int J Psychophysiol. 2009; 72:267–275.10.1016/j.ijpsycho.2008.12.014 [PubMed: 19272312]
30. Denver JW, Reed SF, Porges SW. Methodological issues in the quantification of respiratory sinus arrhythmia. Biol Psychol. 2007; 74:286–294.10.1016/j.biopsycho.2005.09.005 [PubMed: 17067734]
31. Lewis GF, Furman SA, McCool MF, Porges SW. Statistical strategies to quantify respiratory sinus arrhythmia: are commonly used metrics equivalent? Biol Psychol. 2012; 89:349–64.10.1016/j.biopsycho.2011.11.009 [PubMed: 22138367]
32. Morris KF, Nuding SC, Segers LS, Baekey DM, Shannon R, Lindsey BG, et al. Respiratory and Mayer wave-related discharge patterns of raphé and pontine neurons change with vagotomy. J Appl Physiol. 2010; 109:189–202.10.1152/japplphysiol.01324.2009 [PubMed: 20360432]
33. Hayes, AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. Guilford Press; New York, New York: 2013.
34. Calmettes G, Drummond GB, Vowler SL. Making do with what we have: use your bootstraps. J Physiol. 2012; 590:3403–6.10.1113/jphysiol.2012.239376 [PubMed: 22855048]
35. Davydov DM, Zhdanov RI, Dvoenosov VG, Kravtsova OA, Voronina EN, Filipenko ML. Resilience to orthostasis and haemorrhage: A pilot study of common genetic and conditioning mechanisms. Sci Rep. 2015; 5:10703.10.1038/srep10703 [PubMed: 26024428]
36. Fairchild AJ, McQuillin SD. Evaluating mediation and moderation effects in school psychology: a presentation of methods and review of current practice. J Sch Psychol. 2010; 48:53–84.10.1016/j.jsp.2009.09.001 [PubMed: 20006988]
37. Olsen RB, Bruehl S, Nielsen CS, Rosseland LA, Eggen AE, Stubhaug A. Hypertension prevalence and diminished blood pressure-related hypoalgesia in individuals reporting chronic pain in a general population: The Tromsø study. Pain. 2013; 154:257–262.10.1016/j.pain.2012.10.020 [PubMed: 23245863]
38. Bruehl S, Chung OY, Ward P, Johnson B, McCubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. Pain. 2002; 100:191–201. [PubMed: 12435472]
39. Drouin S, McGrath JJ. Blood pressure and pain sensitivity in children and adolescents. Psychophysiology. 2013; 50:513–520.10.1111/psyp.12036 [PubMed: 23517306]
40. Davydov DM, Perlo S. Cardiovascular activity and chronic pain severity. Physiol Behav. 2015; 152:203–216.10.1016/j.physbeh.2015.09.029 [PubMed: 26434786]
41. Lautenschläger G, Habig K, Best C, Kaps M, Elam M, Birklein F, et al. The impact of baroreflex function on endogenous pain control - a microneurography study. Eur J Neurosci. 2015; 42:2996–3003.10.1111/ejn.13096 [PubMed: 26454007]
42. Boscan P, Pickering AE, Paton JFR. The nucleus of the solitary tract: an integrating station for nociceptive and cardiorespiratory afferents. Exp Physiol. 2002; 87:259–266. [PubMed: 11856972]

43. Bulls H, Goodin B. The association of elevated resting blood pressure with greater conditioned pain modulation is present for men but not women. J Pain. 2013; 14:S46.10.1016/j.jpain.2013.01.522
44. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care. 2014; 8:143–51.10.1097/SPC.0000000000000055 [PubMed: 24752199]
45. Marks DM, Shah MJ, Patkar AA, Masand PS, Park GY, Pae CU. Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. Curr Neuropharmacol. 2009; 7:331–6.10.2174/157015909790031201 [PubMed: 20514212]
46. Adeyemo MA, Chang L. New treatments for irritable bowel syndrome in women. Women's Heal. 2008; 4:605–623.10.2217/17455057.4.6.605
47. Oliveira LR, de Melo VU, Macedo FN, Barreto AS, Badaue-Passos D, Viana dos Santos MR, et al. Induction of chronic non-inflammatory widespread pain increases cardiac sympathetic modulation in rats. Auton Neurosci Basic Clin. 2012; 167:45–49.10.1016/j.autneu.2011.12.004
48. Furlan R, Colombo S, Perego F, Atzeni F, Diana A, Barbic F, et al. Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. J Rheumatol. 2005; 32:1787–1793. [PubMed: 16142879]
49. Davydov DM, Stewart R, Ritchie K, Chaudieu I. Depressed mood and blood pressure: The moderating effect of situation-specific arousal levels. Int J Psychophysiol. 2012; 85:212–223. doi:http://dx.doi.org/10.1016/j.ijpsycho.2012.04.011. [PubMed: 22561512]
50. Davydov DM, Shapiro D. Hypertension: Psychosocial Aspects. Int Encycl Soc Behav Sci. 2015; 11:453–457.10.1016/B978-0-08-097086-8.14104-2
51. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Cou. Circulation. 2005; 111:697–716.10.1161/01.CIR.0000154900.76284.F6 [PubMed: 15699287]
52. Reyes Del Paso GA, Garrido S, Pulgar A, Martín-Vázquez M, Duschek S. Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. Psychosom Med. 2010; 72:462–70.10.1097/PSY.0b013e3181da91f1 [PubMed: 20467004]
53. Lohmeier TE, Iliescu R. Chronic lowering of blood pressure by carotid baroreflex activation: mechanisms and potential for hypertension therapy. Hypertension. 2011; 57:880–6.10.1161/HYPERTENSIONAHA.108.119859 [PubMed: 21357283]
54. Davydov DM, Shapiro D, Goldstein IB, Chicz-DeMet A. Moods in everyday situations:effects of menstrual cycle, work, and stress hormones. J Psychosom Res. 2005; 58:343–349.10.1016/j.jpsychores.2004.11.003 [PubMed: 15992570]
55. Davydov DM, Shapiro D, Goldstein IB, Chicz-De Met A. Moods in everyday situations: effects of combinations of different arousal-related factors. J Psychosom Res. 2007; 62:321–329.10.1016/j.jpsychores.2006.10.021 [PubMed: 17324683]
56. Davydov DM, Zech E, Luminet O. Affective context of sadness and physiological response patterns. J Psychophysiol. 2011; 25:67–80.10.1027/0269-8803/a000031
57. Davydov DM, Luminet O, Zech E. An externally oriented style of thinking as a moderator of responses to affective films in women. Int J Psychophysiol. 2013; 87:152–164.10.1016/j.ijpsycho.2012.12.003 [PubMed: 23266659]
58. King JW, Bair E, Duggan D, Maixner W, Khan AA. The relationship between resting arterial blood pressure and acute postoperative pain in endodontic patients. J Orofac Pain. 2012; 26:321–327. [PubMed: 23110272]

Highlights

- IBS is associated with lower baroreceptor sensitivity compared to healthy controls
- IBS is associated with higher blood pressure (BP) compared to healthy controls
- IBS chronicity is associated with lower baroreceptor sensitivity through higher BP
- Lower baroreceptor sensitivity through lower HRV determines higher IBS severity
- Lower baroreceptor sensitivity through higher BP determines lower IBS severity

Table 1

Demographic, clinical, and psychological characteristics of the samples[1]

Groups:	Irritable Bowel Syndrome (IBS)					Healthy Control
	All IBS	Bowel Habits				
Subgroups:		Constipation	Diarrhea	Mixed	Unspecified	
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of subjects	78	21	24	20	13	27
Ethnicity:						
African Americans	9	4	2	2	1	4
Asian Americans	9	2	4	2	1	3
Caucasians	43	12	14	10	7	13
Hawaiian Americans	3	0	0	2	1	0
Hispanic Americans	13	3	4	4	2	6
Unspecified	1	0	0	0	1	1
Age (year)	35.3 (12.8)	35.4 (13.3)	33.7 (12.8)	37.8 (11.6)	34.4 (14.3)	33.3 (11.7)
BMI	23.6 (4.9)	22.3 (2.9)	22.4 (3.5)	25.8 (7.2)	25.2 (4.5)	24.2 (4.4)
Smoke (Yes/No)	13/65$^{\surd h}$	5/16$^{\surd u}$	3/21$^{\surd u}$	5/15$^{\surd u}$	0/13	1/26
Caffeine (Yes/No)	53/25	18/3	15/9	12/8	8/5	21/6
Alcohol (Yes/No)	51/27	17/4	13/11	12/8	9/4	16/11
Exercise (Yes/No)	50/28	13/8	16/8	10/10$^{\surd u}$	11/2	20/7
HADS-A	8.4 (4.7)$^{\surd h}$	7.9 (4.9)	7.2 (3.0)$^{\surd m}$	10.2 (5.0)	8.5 (6.1)	6.6 (4.0)
HADS-D	4.1 (3.3)	4.5 (3.3)	2.5 (2.5)$^{\surd m}$	5.3 (3.4)	4.5 (3.6)	2.7 (3.5)
HADS-T	12.4 (7.3)$^{\surd h}$	12.4 (7.9)	9.8 (3.9)$^{\surd m}$	15.4 (7.6)	13.0 (9.2)	9.3 (6.9)
GI (7d)	11.1 (3.8)*	11.9 (3.9)	10.4 (3.0)	11.9 (4.6)	10.5 (3.6)	1.5 (2.7)
Bloating (7d)	12.1 (5.1)*	13.8 (3.8)	10.7 (5.7)	11.6 (5.8)	13.0 (3.8)	0.1 (0.4)
Pain (7d)	10.6 (4.2)*	9.8 (4.6)	10.2 (3.4)	11.6 (4.8)	11.2 (3.7)	0.1 (0.4)
Severity (usual)	3.2 (0.7)*	3.2 (0.7)	2.9 (0.6)	3.3 (0.8)	3.3 (0.8)	0.2 (0.5)
Chronicity (years)	13.7 (11.2)*	13.0 (12.3)	13.4 (12.6)	15.7 (9.9)	12.6 (8.3)	1.7 (6.6)

[1] means and comparisons (Chi-square test, Mann-Whitney test, and one-way analysis of variance) presented for raw (not transformed and not adjusted) data

[√] $p < 0.05$;

[*] $p < 0.001$;

letters ([h, m, u]) point on a group of comparison (healthy, mixed or undefined, respectively)

Abbreviations: BMI = body mass index; HADS-T, -A, and -D = Total, Anxiety, and Depression subscales of Hospital Anxiety and Depression Scale; GI (7d), Bloating (7d), Pain (7d), Severity (usual) = intensity or severity of overall GI symptoms during the past week, intensity or severity of bloating symptom during the past week, intensity or severity of abdominal pain during the past week, and usual intensity or severity of IBS symptoms; Chronicity (years) = Irritable Bowel Syndrome chronicity in years

Table 2
Correlations between severity of IBS symptoms and disease duration (chronicity)

Variables	Pain (7d)	GI (7d)	Severity (usual)	Chronicity
Bloating (7d)	0.502**	0.636**	0.327*	0.210
Pain (7d)		0.812**	0.332*	0.235√
GI (7d)			0.364**	0.239√
Severity (usual)				0.142

√ $p < 0.05$.

* $p < 0.005$.

** $p < 0.001$.

GI (7d), Bloating (7d), Pain (7d), Severity (usual) = intensity or severity of overall GI symptoms during the past week, intensity or severity of bloating symptom during the past week, intensity or severity of abdominal pain during the past week, and usual intensity or severity of IBS symptoms

Table 3

Physiological characteristics of the samples[1]

Groups:	Irritable Bowel Syndrome (IBS)					Healthy Control
	All IBS	Bowel Habits				
Subgroups:		Constipation	Diarrhea	Mixed	Unspecified	
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SBPoff	115.0 (12.1)^{*h}	114.0 (12.7)	114.7 (9.0)	115.7 (13.6)	116.7 (14.6)	106.6 (8.8)
DBPoff	74.9 (9.1)$^{\surd h}$	72.9 (9.9)	76.5 (7.9)	75.1 (9.3)	74.4 (9.8)	69.4 (5.8)
HRoff	68.3 (9.8)	65.5 (9.4)	68.7 (9.3)	70.3 (10.3)	69.5 (10.7)	66.6 (10.7)
SBPlab	123.9 (20.5)	123.9 (20.6)	121.3 (17.1)	125.0 (19.1)	126.7 (28.8)	123.2 (17.1)
DBPlab	66.6 (12.4)	67.6 (12.8)	65.9 (9.7)	66.7 (13.7)	65.8 (15.2)	65.9 (10.6)
HRlab	71.4 (9.4)	65.1 (8.8)	74.5 (7.1)^{**c}	74.6 (11.1)^{*c}	71.2 (6.7)$^{\surd c}$	69.0 (10.4)
BRS	10.3 (4.9)$^{\surd h}$	11.6 (5.6)	10.5 (3.5)	8.9 (4.9)	10.4 (6.0)	13.1 (7.6)
LF-HRV	2383.6 (2605.6)	1570.1 (1472.6)	3872.7 (3786.2)	1612.3 (1167.9)	2135.5 (1913.4)	2425.7 (2427.0)
lnLF-HRV	7.31 (1.01)	7.03 (0.84)$^{\surd d}$	7.81 (1.09)	7.07 (0.89)$^{\surd d}$	7.25 (1.04)	7.23 (1.18)
HF-HRV	1076.2 (1085.5)	832.9 (719.1)	1370.8 (1159.9)	760.3 (769.2)	1411.4 (1618.3)	1119 (1004.6)
lnHF-HRV	6.50 (1.05)	6.35 (0.97)	6.83 (0.97)	6.22 (0.93)	6.53 (1.39)	6.66 (0.91)

[1] mean (raw data) and comparisons (analysis of covariance with Bonferroni correction presented for data adjusted to body mass index and/or age.

$^{\surd}$ $p < 0.05$.

* $p < 0.005$.

** $p < 0.001$.

letters ($^{h, d, c, m}$) point on a group of comparison (healthy, diarrhea, constipation, or mixed, respectively)

Abbreviations: SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate; off - obtained in office; lab -obtained in laboratory; BRS = regression slopes (ms/mmHg) between changes of R-R intervals and changes of associated beat-to-beat SBP, averaged for increased (“+”, “up”) or decreased (“-”, “down”) sequences, a measure of baroreflex sensitivity; (ln)LF-HRV and (ln)HF-HRV - natural log-transformed and non-transformed (ms^2) low and high frequency heart rate variability power bands