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Heart Rate Variability and Somatization in Adolescents With Irritable Bowel Syndrome

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Background/Aims

Changes in autonomic regulation and psychological distress play an important role in the pathobiology of irritable bowel syndrome (IBS). The aim of the current study is to evaluate the autonomic function and to link it to the levels of somatization in adolescents with IBS.

Methods

We enrolled 30 adolescents with various types of IBS and 35 healthy controls. Time and frequency domain indexes of heart rate variability (HRV) were measured in supine (baseline) and standing (orthostasis) positions using short-term electrocardiographic recordings. The somatic symptoms index was assessed with the modified Screening for Somatoform Symptoms questionnaire.

Results

Adolescents with IBS showed no differences of HRV parameters in the supine position compared to healthy control. In orthostasis, a decrease in the standard deviation of normal RR intervals as well as main spectral index total power (TP) were observed. The reduction of TP was attributed to the reduced activities of the high- and low frequency components. Increased somatic symptoms index in IBS patients negatively correlated with TP in orthostasis ($r = -0.485$, $P = 0.007$). A subgroup analysis revealed that adolescents with IBS with TP values either < 2500 msec^2 or > 5500 msec^2 in the supine position demonstrated significantly reduced activity of the low frequency component.

Conclusions

Adolescents with IBS showed signs of autonomic dysfunction only during the orthostatic test, which were associated with increased somatization scores. Further research is needed to establish the links between emotional wellbeing and autonomic function in this population.
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Key Words

Adolescent; Heart rate; Irritable bowel syndrome; Medically unexplained symptoms primary dysautonomias

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Introduction

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal pain or discomfort, stool irregularities and bloating.[1] IBS is one of the most common diseases of the pediatric population, where its prevalence ranges from 6% to 14% depending on the geographical region and age.[2,3] In the adolescent population from China the prevalence of IBS was reported to be as high as 21%, which was attributed to the higher levels of psycho-emotional distress.[3] Further increase in IBS cases is expected as the consequence of coronavirus disease 19 pandemic.

The Rome IV Consensus (2016) acknowledges the biopsychosocial model of IBS as the framework to understand its pathophysiology.[4] According to this model, an onset and persistence of symptoms are determined by the complex interactions between physiological, psychological and social factors.[5] Dysfunction of the autonomic nervous system (ANS) was proposed as an important pathogenetic mechanism in IBS largely due to its linking role between the brain and the gut.[6,7] It has been suggested that the development of autonomic imbalance in IBS may be triggered by the disorders of intestinal motility and production of the pro-inflammatory cytokines within the intestinal mucosa as well as changes in the regulation within the hypothalamic-pituitary-adrenal axis.[7]

Measurement of heart rate variability (HRV) is commonly used in research and clinical practice to evaluate autonomic function[8,9] and to test resilience against physical, psycho-emotional and metabolic stressors.[10,11] Based on the measurement of differences between successive heart beats, HRV links their rhythmic patterns with the activity of main regulatory subsystems which are responsible for the control of the heart rate.[8] Standard HRV metrics comprise of the time and frequency domain parameters, which reflect changes in the neurohumoral regulation in response to homeostatic shifts.[12] Commonly used frequency domain HRV indexes include high frequency (HF) and low frequency (LF). The HF component (power) is believed to be mainly defined by the activity of parasympathetic nervous system.[12] The LF component is linked primarily to the sympathetic activity, although this point is being debated and contribution of the parasympathetic nervous system cannot be excluded.[13]

In IBS changes of HRV have been well characterized in the adult population, which showed impaired parasympathetic functioning as demonstrated by a decrease in HF power, and abnormal sympathovagal balance.[14,15] The information about autonomic function in adolescents with IBS is rather limited. Researchers agree that during this period of life ANS undergoes progressive physiologic maturation.[16-18] The study by Chelimsky et al,[19] showed decreased cardiovagal modulation as seen from the reduced activity of HF component in a group of adolescents with functional gastrointestinal disorders (median age 17 years [range 11-21]). This study, however, did not focus exclusively on the population with IBS and did not evaluate other time and frequency domain and HRV indexes which are relevant for the characteristics of the neurohumoral regulation in IBS.

The phenomenon of somatization denotes a tendency to experience personal psycho-emotional and social distress at a somatic level, namely, as increased perception, awareness, and/or pathological interpretation of unpleasant physiological sensations.[20] Frequent complaints related to somatization include abdominal distension, pain or bloating, which significantly impair quality of life and may require use of medications. In adult populations, persistent somatization itself was shown to be negatively associated with the vagally mediated HRV indices, suggesting involvement of ANS.[21] In another study involving adults with somatization disorder, autonomic dysfunction defined by impaired baroreflex sensitivity was reported in 62% of participants with no clear links between the severity of symptoms and somatization scores.[22] Children and adults with IBS were reported with higher somatization compared to the healthy controls.[23,24] However, in adolescents with IBS possible associations between the autonomic dysfunction and somatization were not studied and the role of autonomic changes in the diseases pathobiology remains to be unclear.

The aim of current study is to evaluate autonomic dysfunction and to link it with the somatic symptoms index in adolescents with IBS.

Materials and Methods

Study Design and Patients Population

This comparative, cross-sectional study prospectively recruited patients who were referred with gastroenterological complaints to Lviv Regional Children's Clinical Hospital "OHMATDYT" and were diagnosed with IBS using the Rome IV criteria.[25] Diagnosis of IBS was confirmed prior to enrollment with complex testing which included detailed medical history, physical examination, laboratory testing of blood, urine, stool. An abdominal ultrasound and endoscopic examinations were performed to exclude organic gastrointestinal pathology. Presence of any chronic medical or surgical diseases and/or history of previous abdominal surgery served as exclusion criteria. Participants were enrolled into the study upon stabilization of their clinical condition and just prior to discharge form the hospital. An age- and sex-compatible control group of healthy adolescents was recruited from the same geographical area. Study was approved by the Ethical Committee of Lviv National Medical University named after Danylo Halytsky (01 from 20.01.2014). Informed consent was obtained from all participants.

Study of Heart Rate Variability

The study of HRV was performed in a quiet room with a temperature of 20-22℃. Participants were instructed to breathe normally, avoid coughing and stay with eyes opened during the electrocardiographic (ECG) recording. Prior to recording, an ECG signal was monitored for 5-10 minutes to ensure stable condition. Subsequently, ECG was recorded for 5 minutes in the supine position and, subsequently, for 6 minutes in standing position (active orthostasis) with a computer electrocardiograph. Neurosoft software version 5.3.1.0 was used for the HRV analysis.

The time and spectral domain indexes were analyzed in both supine and standing positions in accordance with the current recommendations.[26] The time domain indices included standard deviation of normal RR intervals (SDNN, msec), square root of the mean squared differences of successive RR intervals (RMSSD, msec), percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds (pNN50, %) and the K30:15 coefficient, which represents the ratio between 15th and 30th RR interval measured after active standing. The spectral HRV analysis included assessment of total power (TP) and main frequency components such as very low frequency (VLF), LF, and HF power as well as the LF/HF ratio and the ratio between TP in supine and TP in orthostatic position (TPsup/TPortho) All HRV parameters used in this study and their interpretation are summarized in Table 1.[12,26-29]

Because values of HRV are known to show significant variability in young subjects, groups of both IBS patients and healthy controls were further divided into 3 subgroups based on the supine TP values as described previously.[27,30,31] The low resistance (LR) subgroup included individuals with absolute supine TP values < 2500 msec^2, the medium resistance (MR) subgroup individuals with TP from 2500 msec^2 to 5500 msec^2 and the high resistance (HR) subgroup with TP > 5500 msec^2.

Study of Somatization

The Ukrainian version of the Screening for Somatoform Symptoms questionnaire modified for adolescents[32] was given to the participants on the same day as HRV was measured. The questionnaire included 42 symptoms, which were assessed for the period of

Table 1. Heart Rate Variability Parameters, Which Were Used in This Study[12,26-29]

Abbreviation	Parameter	Physiological interpretation
Time domain parameters		
SDNN (msec)	Standard deviation of NN RR intervals	Effect of the sympathetic and parasympathetic nervous system
RMSSD (msec)	Square root of the mean squared differences of successive NN intervals	Mainly the activity of the parasympathetic nervous system
pNN50 (%)	Percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds	Mostly the activity of the parasympathetic nervous system
K30:15	Coefficient, which is measured as the ratio between of the 15th and 30th RR after standing	Reactivity of autonomic regulation with position change (from supine to standing)
Frequency domain parameters		
TP (msec^2)	Total power (0.01-0.4 Hz)	Reflects activity of all regulatory components
VLF (msec^2)	Very low frequency power (0.01-0.04 Hz)	Mainly the activity of the neurohumoral regulation, thermoregulation and cerebral ergotropic effects
LF (msec^2)	Low frequency power (0.04-0.15 Hz)	Predominantly sympathetic but also vagal activity, baroreflex sensitivity
HF (msec^2)	High frequency power (0.15-0.4 Hz)	Mainly the vagal activity
LF/HF	Ratio of LF to HF	Mix of sympathetic and vagal activity
TPsup/TPortho	Ratio of TP in supine position to TP during standing	Reactivity of the regulatory systems in response to the standing challenge

SDNN, standard deviation of normal RR intervals; NN, normal-to-normal; RMSSD, square root of mean squared differences of successive RR intervals; pNN50, the percentage of the differences between adjacent normal RR intervals exceeding 50 milliseconds; K30/15, the ratio between maximal and minimal heart rate during the first 30 heart cycles of the orthostatic test; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; TPsup/TPortho, ratio between TP in supine and orthostatic positions.

previous 2 years as a binary variable (1- “yes”, 2-”no”) to calculate the somatic symptoms index (SSI). Presence of 6 or more symptoms indicated of high levels of somatization. The questionnaire has demonstrated good test-retest reliability ($r = 0.86$) and internal consistency ($\alpha = 0.88$).[33,34]

Statistical Methods

Data were processed using Microsoft Excel 2016 and analysed with GraphPad (Prism 5.0; San Diego, CA, USA). The normal distribution of variables was determined by the Shapiro-Wilk normality test. The differences of mean values of HRV parameters in supine and orthostatic positions between the groups was tested with Mann-Whitney test and with Wilcoxon signed-ranks test for the within-group difference. The Spearman’s test was used to assess correlation between HRV parameters and SSI. The value of $P < 0.05$ was considered statistically significant.

Results

In the total thirty 12-18 years old IBS patients including 14 (46.7%) males and 16 (53.2%) females were enrolled. The constipation-predominant IBS subtype (IBS-C) was diagnosed in 10 participants (34.8%), diarrhea-predominant IBS (IBS-D) in 12 (39.1%) cases, and IBS with mixed stool pattern in 8 (26.1%) adolescents. An average duration of the disease was 3.6 ± 2.1 years. The control group included 35 healthy volunteers among which 17 (48.6%) males and 18 (51.4%) females.

The most frequent comorbidities identified in IBS group included functional dyspepsia 66.7%, functional nausea 33.3% and cyclic vomiting syndrome 26.7%. On average, there were 1.3 functional gastrointestinal symptoms reported per patient. Adolescents with IBS also frequently complained on light-headedness (43.3%), sleep disturbances (36.7%), and muscle pain (26.7%). The treat-

Table 2. Heart Rate Variability in Adolescents With Irritable Bowel Syndrome and Healthy Volunteers

Parameter	IBS, n = 30	Control, n = 35	*P*-value[a]
Supine position			
SDNN (msec)	64.4 ± 4.9	59.7 ± 2.8	0.713
RMSSD (msec)	65.4 ± 7.1	54.0 ± 3.4	0.257
pNN50 (%)	30.1 ± 3.9	29.8 ± 2.6	0.817
TP (msec^2)	4979 ± 695	4344 ± 382	0.967
VLF (msec^2)	1451± 201	1165 ± 147	0.156
LF (msec^2)	1401 ± 184	1399 ± 114	0.589
HF (msec^2)	2127 ± 40	1780 ± 188	0.836
LF/HF	0.85 ± 0.08	1.10 ± 0.15	0.605
Orthostatic position			
SDNN (msec)	55.8 ± 11.1	55.6 ± 2.8	0.042
RMSSD (msec)	40.5 ± 15.9	31.2 ± 3.2	0.065
pNN50 (%)	5.4 ± 1.6	5.1 ± 1.1	0.156
K30/15	1.3 ± 0.1	1.4 ± 0.1	0.002
TP (msec^2)	2952 ± 439	4390 ± 414	0.005
VLF (msec^2)	1324 ± 173	1522 ± 127	0.178
LF (msec^2)	1114 ± 206	2054 ± 221	< 0.001
HF (msec^2)	515 ± 121	814 ± 156	0.038
LF/HF	4.2 ± 0.7	4.5 ± 0.5	0.589

[a]*P*-values for between-group comparison.
SDNN, standard deviation of normal RR intervals; RMSSD, the square root of mean squared differences of successive RR intervals; pNN50, the percentage of the differences between adjacent normal RR intervals exceeding 50 milliseconds; K30/15, the ratio between maximal and minimal heart rate during the first 30 heart cycles of the orthostatic test; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF, autonomic balance.
Data are expressed as mean ± SEM.

Table 3. Heart Rate Variability in Adolescents With Irritable Bowel Syndrome and Healthy Volunteers From the Low Resistance Subgroups

Parameter	IBS patients, n = 8	Control, n = 9	*P*-value[a]
Supine position			
SDNN (msec)	37.0 ± 3.6	39.7 ± 1.6	0.465
RMSSD (msec)	34.5 ± 7.1	32.8 ± 2.7	0.806
pNN50 (%)	12.8 ± 6.2	13.0± 3.0	0.955
TP (msec^2)	1573 ± 137	1897 ± 137	0.126
VLF (msec^2)	698 ± 115	552 ± 78	0.288
LF (msec^2)	342 ± 34	707 ± 104	0.013
HF (msec^2)	533 ± 93	638 ± 83	0.419
LF/HF	0.72 ± 0.09	1.47 ± 0.32	0.074
Orthostatic position			
SDNN (msec)	36.4 ± 6.6	50.7 ± 2.9	0.111
RMSSD (msec)	21.5 ± 8.9	28.9 ± 5.4	0.467
pNN50 (%)	1.3 ± 0.7	2.4 ± 0.6	0.193
K30/15	1.12 ± 0.1	1.39 ± 0.1	0.078
TP (msec^2)	1546 ± 274	3417 ± 723	0.057
VLF (msec^2)	768 ± 96	1155 ± 207	0.164
LF (msec^2)	593 ± 158	1440 ± 276	0.032
HF (msec^2)	184 ± 71	822 ± 410	0.227
LF/HF	4.53 ± 1.05	3.79 ± 0.74	0.559

[a]*P*-values for between-group comparison.
SDNN, standard deviation of normal RR intervals; RMSSD, the square root of mean squared differences of successive RR intervals; pNN50, the percentage of the differences between adjacent normal RR intervals exceeding 50 milliseconds; K30/15, the ratio between maximal and minimal heart rate during the first 30 heart cycles of the orthostatic test; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF, autonomic balance.
Data are expressed as mean ± SEM.

ment plans for the IBS patients included combinations of various medications (eg, spasmolytics, prokinetics, prebiotics, probiotics, laxatives, anti-diarrheal medications) with individualized scheme depending on the clinical presentation of the disease.

The indexes of HRV in supine position in IBS group did not differ from the control (Table 2). During active standing the study of HRV in IBS patients showed significant reduction in TP, which was attributed to the decrease in both LF and HF components (Table 2), suggesting lowering of sympathetic and parasympathetic activity in response to hemodynamic challenge. No significant differences in HRV parameters were observed during comparison between various clinical subtypes of IBS with IBS-D subjects only tending to have higher TP in the supine position comparing to individuals with other clinical subtypes (Supplementary Table).

The results of HRV study obtained in the subgroup analysis are presented on Tables 3-5. In supine position the patients with IBS from the LR subgroup had lower LF component (Table 3), while the analysing the percentage contribution of various regulatory components to the spectral structure demonstrated significant increase in VLF (43 ± 4% vs 29 ± 3% in control, $P = 0.011$) as well as reduction of LF (24 ± 2% vs 36 ± 4%, $P = 0.016$) power. During the orthostatic test, which reflects readiness of the regulatory components to maintain hemodynamics in response to a position change, reduction in absolute values of LF was observed in the LR IBS subgroup (Table 3). The percentage of LF was also significantly reduced (32 ± 3% vs 44 ± 3% in control, $P = 0.013$), while VLF percent contribution to TP increased excessively (54 ± 4% vs 38 ± 5% in control, $P = 0.016$) in the LR IBS subgroup. Additionally, in response to standing the values of TP did not change, while the TPsup/TPortho ratio was significantly increased in the LR control subgroup ($P = 0.041$, Fig. 1).

The indexes of HRV measured in supine position in adolescents from the MR IBS subgroup did not differ significantly from corresponding control (Table 4). However, during orthostatic test

Table 4. Heart Rate Variability in Adolescents With Irritable Bowel Syndrome and Healthy Volunteers From the Medium Resistance Subgroups

Parameter	IBS, n = 14	Control, n = 17	P-value[a]
Supine position			
SDNN (msec)	60.0 ± 2.8	59.2 ± 1.4	0.786
RMSSD (msec)	58.5 ± 5.1	52.5 ± 2.1	0.249
pNN50 (%)	29.0 ± 4.5	30.7 ± 2.5	0.734
TP (msec^2)	3884 ± 224	4109 ± 210	0.472
VLF (msec^2)	1141 ± 132	1021 ± 154	0.569
LF (msec^2)	1182 ± 82	1447 ± 142	0.136
HF (msec^2)	1562 ± 216	1641 ± 138	0.751
LF/HF	0.97 ± 0.14	1.12 ± 0.25	0.637
Orthostatic position			
SDNN (msec)	44.5 ± 5.0	51.5 ± 3.8	0.452
RMSSD (msec)	26.7 ± 7.1	26.9 ± 4.6	0.323
pNN50 (%)	5.5 ± 2.6	4.75 ± 1.7	0.811
K30/15	1.5 ± 0.2	1.43 ± 0.1	0.879
TP (msec^2)	2843 ± 567	3805 ± 506	0.215
VLF (msec^2)	1298 ± 249	1558 ± 208	0.424
LF (msec^2)	1006 ± 197	1710 ± 258	0.043
HF (msec^2)	539 ± 190	536 ± 136	0.991
LF/HF	4.71 ± 1.3	4.96 ± 0.84	0.868

[a]P-values for between-group comparison.
SDNN, standard deviation of normal RR intervals; RMSSD, the square root of mean squared differences of successive RR intervals; pNN50, the percentage of the differences between adjacent normal RR intervals exceeding 50 milliseconds; K30/15, the ratio between maximal and minimal heart rate during the first 30 heart cycles of the orthostatic test; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF, autonomic balance.
Data are expressed as mean ± SEM.

Table 5. Heart Rate Variability in Adolescents With Irritable Bowel Syndrome and Healthy Volunteers From the High Resistance Subgroups

Parameter	IBS, n = 8	Control, n = 9	P-value[a]
Supine position			
SDNN (msec)	99.4 ± 7.2	82.5 ± 2.8	0.026
RMSSD (msec)	108.5 ± 15.0	79.3 ± 5.3	0.052
pNN50 (%)	49.2 ± 5.4	46.5 ± 3.4	0.666
TP (msec^2)	10 299 ± 1152	7377 ± 599	0.076
VLF (msec^2)	2746 ± 460	2055 ± 342	0.235
LF (msec^2)	2844 ± 184	2081 ± 149	0.005
HF (msec^2)	4710 ± 995	3241 ± 289	0.342
LF/HF	0.78 ± 0.14	0.66 ± 0.04	0.366
Orthostatic position			
SDNN (msec)	54.6 ± 7.7	67.5 ± 4.5	0.145
RMSSD, msec	29.0 ± 6.4	40.2 ± 6.6	0.333
pNN50 (%)	9.4 ± 3.6	8.4 ± 2.6	0.257
K30/15	1.15 ± 0.09	1.41 ± 0.1	0.076
TP (msec^2)	4551 ± 1107	6354 ± 789	0.190
VLF (msec^2)	1924 ± 396	1866 ± 213	0.892
LF (msec^2)	1823 ± 628	3255 ± 482	0.052
HF (msec^2)	804 ± 279	1233 ± 260	0.201
LF/HF	3.04 ± 0.59	4.52 ± 1.32	0.710

[a]P-values for between-group comparison.
SDNN, standard deviation of normal RR intervals; RMSSD, the square root of mean squared differences of successive RR intervals; pNN50, the percentage of the differences between adjacent normal RR intervals exceeding 50 milliseconds; K30/15, the ratio between maximal and minimal heart rate during the first 30 heart cycles of the orthostatic test; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; LF/HF, autonomic balance.
Data are expressed as mean ± SEM.

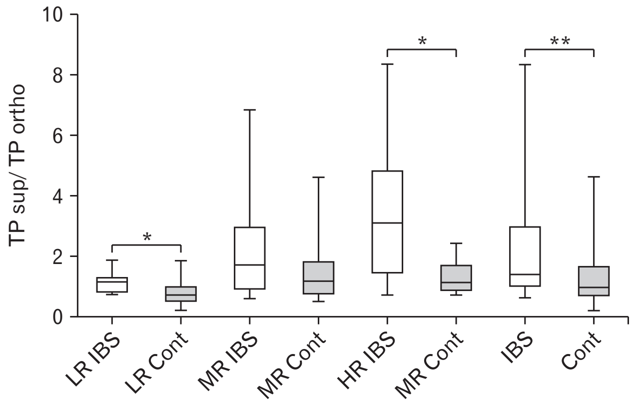

Figure 1. Changes in the ratio between total power in supine and orthostatic positions (TPsup/TPortho) in patients with irritable bowel syndrome (IBS) and control (Cont) from various subgroups. LR, low resistance; MR, medium resistance; HR, high resistance. $^*P < 0.05$, $^{**}P < 0.01$.

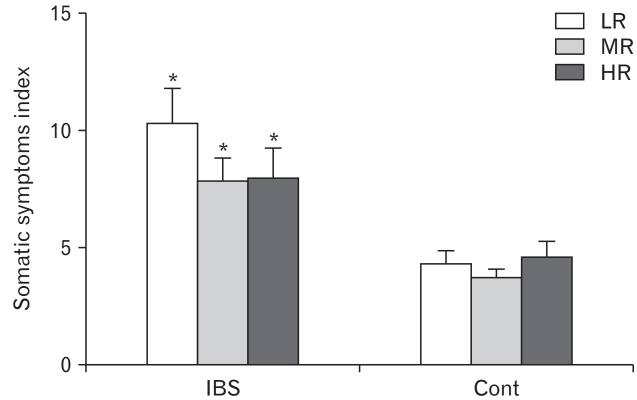

Figure 2. Somatic symptoms index in adolescent with irritable bowel syndrome (IBS) and healthy controls from the low resistant (LR), medium resistant (MR), and high resistant (HR) subgroups. $^*P < 0.05$ compared with the values in corresponding control group.

reduction of TP comparing to the TP values in supine position ($P = 0.072$) was observed in this subgroup of IBS patients. Similar to the LR IBS subgroup, patients from the MR IBS subgroup showed significant decrease in the LF power during orthostatic test (Table 4). The percent contribution of various spectral components in orthostasis did not differ significantly between MR IBS and control subgroups with VLF being 48 ± 4% in IBS vs 43 ± 3% in control ($P = 0.341$), LF 37 ± 3% in IBS vs 45 ± 3% in control ($P = 0.075$) and HF 15 ± 3% in IBS vs 13 ± 2% ($P = 0.515$) in control.

The subgroup of adolescents with IBS with TP > 5500 msec^2 in supine position (HR IBS subgroup) tended to have higher TP as well as significantly higher values of the time domain parameter SDNN, which is largely influenced by the vagal activity, and values of LF, which reflects mainly sympathetic and, to some degree, parasympathetic activity. Together with tendential increase in the time domain index RMSSD, such HRV profile may be suggestive about parasympathetic predominance in the HR IBS subgroup in supine position (Table 5). This was not confirmed by the analysis of percent contribution of various spectral components, which showed relatively similar values for VLF (28 ± 4% in IBS comparing to 27 ± 4% in control), LF (29 ± 2% in IBS vs 29 ± 2% in control), and HF (43 ± 5% in IBS versus 44 ± 2% in control) components in the HR control subgroups.

Standing caused two-fold decline of TPsup/TPortho ratio in the HR IBS subgroup (Fig. 1). A prominent reduction of the TP was accompanied by downregulation of absolute values of all spectral components in this IBS subgroup (Table 5). However, the percent contribution of various HRV components to the spectrum structure in IBS patients showed upregulation of VLF (49 ± 6% vs 31 ± 3% in control, $P = 0.011$) and significant decrease in LF (35 ± 5% vs 51 ± 3% in control, $P = 0.016$) components with almost unchanged values of HF (15 ± 4% vs 18 ± 3% in control, $P = 0.587$) during the orthostatic test. A decrease in TP during orthostatic test in the comparable HR control subgroup was less pronounced, which indicates better compensation response to standing challenge and, thus, better adaptive potential (Table 5).

The SSI values were significantly increased in adolescents with IBS comparing to healthy volunteers (8.0 ± 0.6 vs 4.1 ± 0.2, $P = 0.001$). Twenty IBS patients (66.7%) were classified as having high somatization and 10 (33.3%) as having low somatization. Majority of subjects in the control group (n = 29) had low somatization scores (SSI < 6). We analyzed the SSI values in the LR, MR, and HR subgroups. The highest value, however, not statistically significant, was found in the LR IBS subgroup (10.4 ± 1.5) while SSI scores in the MR and HR IBS subgroups were relatively similar (Fig. 2). Correlation analysis demonstrated significant negative correlation between SSI and multiple time domain (SDNN $r = -0.555$, $P = 0.001$; RMSSD $r = -0.491$, $P = 0.006$; pNN50 $r = -0.402$, $P = 0.028$) and frequency domain (TP $r = -0.485$, $P = 0.007$; VLF $r = -0.437$; $P = 0.02$; HF $r = -0.434$, $P = 0.02$) HRV parameters measured in orthostasis in adolescents with IBS. No significant correlations between SSI and HRV indices in supine position were noticed. In the control group no significant correlations between SSI and HRV were observed.

Discussion

Sympathetic and parasympathetic branches of ANS are important parts of bidirectional gut-brain communication. ANS is involved in regulation of multiple gastrointestinal functions as well as local immune response. In patients with IBS autonomic imbalance has been recognized as an important contributor to the pathobiology and clinical presentation of the disease.[6,28,35] In experimental and clinical settings analysis of HRV is used to assess autonomic regulation, with higher HRV generally reflecting better functional state.[9,29] Moreover, parasympathetic withdrawal suggested by decrease in HF, was shown to be related to the mental stress and depression[36] as well as to the persistent somatization.[21] Therefore, HRV may be viewed as a tool to assess not only autonomic balance but also other complex pathogenetic mechanisms potentially involved in the development and persistence of IBS.

Multiple studies conducted in the adult population with various clinical subtypes of IBS confirmed changes of autonomic functions defined as a decrease the HF power in HRV spectrum.[14,15,37] At the same time, research on HRV changes in adolescents with IBS is rather limited. In the study by Chelimsky et al[19] involving adolescents with various functional gastrointestinal disorders and using comparable methodology to one applied in the present study, reduced activity of HF and LF components measured in supine position was observed. This contrasts with our results which did not demonstrate significant differences of HRV indexes between the IBS and controls groups in the supine position (Table 2). Chelimsky et al[19] also tested HRV during active standing which is viewed as a physiological stressor used to further characterize reactivity of neurohormonal regulation. Similar to our study, it was shown that standing triggered significant decrease in the LF and HF in patients with IBS. In addition, we also observed reduction in TP as well as other time domain indexes during the orthostatic test (Fig. 1). It is worth noting that the value of orthostatic response during the HRV measurement is often underestimated by the researchers, while, in fact, its monitoring can provide information about the functional reserves and reactivity of ANS. Significant shifts in the TPsup/TPortho ratio reflect maladaptive autonomic response and are important to be taken into consideration in the standard HRV profile for the short-term ECG recordings.

Analysis in the subgroups demonstrated downregulation of the LF component in supine position both in the HR and LR IBS subgroups. Furthermore, marked reduction of absolute values of LF was observed in all IBS subgroups during standing. The LF component has been initially characterized as a biomarker reflecting the activity of the sympathetic nervous system within HRV spectrum.[26] In the recent years this concept has been increasingly criticized and contribution of parasympathetic nervous system though the mechanisms of baroreflex sensitivity was suggested also to be reflected by the LF values, especially when the techniques of controlled breathing are used during ECG recording.[12,38] In this study spontaneous breathing was asked during ECG monitoring which allows to interpret the LF component as largely reflecting the activity of sympathetic regulation. Evidence suggests that sufficient sympathetic activity is a necessary prerequisite for an effective response to any stressors, including diseases[10,39,40] and, thus, downregulation of LF component can be viewed as a sign of autonomic dysfunction in the studied population.

During the analysis of percent contribution of the various spectral components to the main HRV index TP, a significant increase in VLF activity during orthostatic challenge was observed in the LR and HR IBS subgroups. Within the HRV spectrum the VLF band is relatively poorly understood with some evidence suggesting its dependence on the metabolic regulation, hormones and activity of the autonomic centres in the brain.[12,37] On top of TP reduction during the orthostatic test, upregulation of the VLF component may be suggestive of the insufficient neurohumoral response requiring recruitment of the other stress response systems in the studied IBS subgroups.

Notably, among participants with IBS and healthy controls approximately 25% had rather high HRV values (TP > 5500 msec^2) in supine position. It seems that high HRV indexes indicate a fairly strong functional and metabolic reserve and high stress resistance in both study subgroups. However, to meet this assumption similar TP values during orthostatic test could have been expected with the TPsup/TPortho ratio values falling within 0.5-1.5 range. A significant reduction of TP (more than 2 times) and high K30/15 coefficient in orthostasis in the HR IBS subgroup may be suggestive about reduced stress resistance caused by insufficient autonomic activation in response to disturbances in homeostasis, despite high HRV values at rest. To add, such functional state with relatively high resting HRV values, which fails to be maintained during orthotasis, is frequently observed in overtrained athletes who struggle to improve their sports performance.[30] Monitoring of HRV in the supine position followed by active standing can identify such impaired functional state.

Our study revealed that adolescents with IBS had high levels of somatization, which negatively correlated with several time and frequency domain HRV parameters during standing. Compared to the literature data, adolescents with IBS enrolled in this study were found with same values of SSI as adult population with IBS.[41] A possible connection between somatization and ANS dysfunction can be explained by alexithymia, which is usually characterized by difficulties in understanding own feelings and emotions and their verbal expression.[42,43] Any emotion involves interaction of 3 areas in the brain, namely, activation of the limbic system ("emotional brain" itself) is channeled to the prefrontal areas of the cortex, which support awareness of an emotion and its expression in a symbolic verbal form (cognitive-rational level), and to the hypothalamus, which supports autonomic component of emotions (change in skin color, heart rate, blood pressure, sweating, etc). If the active synapses that connect the limbic system to the prefrontal cortex are supressed, processing of emotions at the cognitive level is compromised, which promotes excessive activation of ANS, potentially leading to the autonomic dysfunction.[43,44] Thus, higher somatization levels observed in adolescents with IBS may be partially responsible for the development of autonomic dysfunction.

In addition to the increased somatization, other pathogenetic mechanisms such oxidative stress and subclinical inflammation in the intestines were shown to influence the activity of hypothalamic-pituitary-adrenal axis and cause autonomic dysfunction in IBS patients.[45-47] Although we did not evaluate oxidative stress and inflammation in this research, in our previous studies involving subjects with various functional and pathological conditions the links between oxidative stress and changes of HRV biomarkers were shown[10,27,31,48,49] which may further support the value of HRV as a relevant diagnostic tool in IBS.

Use of medications to control IBS symptoms could have had an influence on the HRV indexes in this study. However, individualised approach to treatment and to small sample size do not allow analyze possible impact of the drug therapy on HRV indices in this study. Relatively small sample size could also be a reason why no differences between various IBS subtypes was found. To our knowledge changes of autonomic function assessed by HRV in adolescents with IBS according to predominant bowel pattern were not studied. Data obtained in adult population are controversial with some studies reporting vagal withdrawal and sympathetic predominance in IBS-C patients compared to IBS-D subtype,[50,51] while the other reporting same pattern of autonomic activity in IBS-D and IBS-C patients.[52] At the same time, in IBS-D patients measurements of HRV performed during sleep showed increase in HF power and reduction in LF/HF ratio,[53] while assessment of HRV after the meal reveled increased in LF/HF ratio and decrease in HF power compared to other IBS subtypes and healthy controls.[54] Further studies are needed to clarify characteristics of autonomic dysfunction in various IBS subtypes.

To summarize, in this study, adolescents with various types of IBS were found with the signs of autonomic dysfunction manifesting by decrease of multiple time and frequency domain HRV indexes only in response to standing. Moreover, increased levels of somatization observed in the IBS patients strongly correlated with reduced HRV during orthostatic test, which may be suggestive of some links between the changes in the psychoemotional state and autonomic regulation in IBS patients. Measurement of HRV not only in the supine position but also during to the orthostatic test allows to reflect better complex mechanisms of heart rate regulation and to reveal early signs of autonomic dysfunction, which gives important information about the interactions in the gut-brain axis.

Supplementary Material

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm22019.

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