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Autonomic nervous system dysregulation in irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a very common gastrointestinal disorder. Multiple factors may cause or exacerbate IBS symptoms. For example, stress and anxiety are two important factors. The Rome III criteria have been developed in order to help facilitate accurate diagnosis of IBS The autonomic nervous system (ANS) controls several basic bodily functions. These include heart rate, body temperature, breathing rate, digestion, and many other systems as well. The ANS dysregulation has been long linked to IBS.

Materials and methods: This study was designed to be a Case-control study. It included 20 patients with IBS and 20 healthy matched controls. All the studied cases were subjected to the following: Full medical history, Thorough clinical examination, Routine laboratory investigation, Holter ECG, All patients and controls are subjected to this questionnaire about anxiety and stress and a scale was calculated to measure them.

Results: there was a significant difference between studied groups as regards to erect systolic BP, erect diastolic BP, **with that** of IBS patients. **Also there is significant difference** between supine heart rate, **erect** heart rate with the heart rate of IBS patients ($P<0.001$). But there was no significant difference between the two groups as regards the 24h Holter results.

Conclusions: there was a significant autonomic nervous system dysregulation in IBS group as regards to; heart rate, which represent higher sympathetic. Holter ECG data regarding SDNN, SDANN and RMSSD has no value or benefit in recording autonomic dysregulation in IBS patients. Large scale multi-center studies with adequate design should be carefully planned to provide a more precise estimation of autonomic dysregulation in irritable bowel syndrome.

Keywords: IBS, Multiple factors, ANS, ECG, BP.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal tract defined as recurrent abdominal pain or discomfort at least three days per month in the last three months with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (1) The Rome III criteria have been developed in order to help facilitate accurate diagnosis of IBS (2) Subtypes of IBS have been defined as follows; IBS with constipation – IBS with constipation (IBS-C) is defined as the presence of hard or lumpy stools with ≥25 percent of bowel movements and loose or watery stools with <25 percent of bowel movements. IBS with diarrhea IBS with diarrhea (IBS-D) is defined as the presence of loose or watery stools with ≥25 percent of bowel movements and hard or lumpy stools with <25 percent of bowel movements. Mixed IBS – Mixed IBS (IBS-M) is defined as hard or lumpy stools with ≥25 percent of bowel movements and loose or watery stools with ≥25 percent of bowel movements. Unsubtyped IBS – IBS is termed unsubtyped if there is

insufficient abnormality in stool consistency to meet the above subtypes (3)

The causes (s) of IBS are not clear(4). Stress, altered gut bacteria, genetics, and food sensitivities may all be involved(5).

The pathophysiology of IBS remains uncertain(6). Although the symptoms of irritable bowel syndrome (IBS) have focused attention on colonic motility, no predominant pattern of motor activity has emerged as a marker for IBS (7)

Visceral hypersensitivity (increased sensation in response to stimuli) is a frequent finding in irritable bowel syndrome (IBS) patients (8)

Immunohistologic investigation has revealed mucosal immune system activation, in some patients with irritable bowel syndrome (IBS) particularly those with diarrhea-predominant IBS (9). An increased number of mast cells has been demonstrated in the terminal ileum, jejunum, and colon of IBS patients(10). In addition, elevated levels of plasma pro-inflammatory interleukins have been observed in patients with IBS(11). The increased risk of post infectious IBS is associated with bacterial, protozoan, helminthes infections, and viral infections (12). Emerging data suggest that the fecal microbiota in individuals with IBS differ from healthy controls and vary with the predominant symptom (13). Some patients with IBS report worsening of symptoms after eating and perceive certain foods (14). Familial studies suggest a modest contribution of genetics to the development of IBS(15, 16). Psychosocial factors may influence the expression of irritable bowel syndrome (IBS) (17).

Although, the incidence of lactose malabsorption is not higher in patients with IBS, patients with IBS and lactose intolerance have an exaggerated symptom response to lactose ingestion (18).

Autonomic dysfunction represents a loss of normal autonomic control of the cardiovascular system associated with both sympathetic nervous system overdrive and reduced efficacy of the parasympathetic nervous system (19)

Symptoms of autonomic dysfunction include dizziness and orthostatic hypotension, exercise intolerance, Sweating abnormalities, which could alternately be too much sweat or insufficient sweat (20). Digestion difficulties due to slow digestion. Urinary problems can include difficulty starting urination, incontinence, and incomplete emptying of the bladder.

Dysfunction of the autonomic nervous system (ANS) has been hypothesized to be involved in a number of functional diseases including irritable bowel syndrome (IBS), with evidence dating back to the beginning of the twentieth (21). ANS dysfunction appears to be involved in the pathophysiology of IBS and its assessment may open new perspectives for clinical management of patients suffering from IBS (22), showed that patients with IBS and a history of abuse had a significantly lower pain and urge thresholds and a greater tendency to report pain, as there are central mechanisms of pain amplification or regional brain activation at sites linked to affect and attention, resulting in heightened awareness to visceral and somatic symptoms, greater pain reports, and greater clinical behavioral responses to painful visceral stimuli(23)

There are higher levels of anxiety and stress with IBS than healthy controls, causing lower parasympathetic nervous system activity, which is supposed to alter autonomic nervous system input to the gastrointestinal system (autonomic dysregulation).

This study aimed to establishing the effect of the IBS on the ANS and if there is certain optimal measures that can be used to assess these autonomic dysregulation better than others.

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Patients and Methods

This study is a case-control study, conducted in Ain Shams University Hospitals outpatient clinic, on 40 patients divided into two groups, Group I including 20 patients with IBS, Group II including 20 healthy controls.

Inclusion criteria: Patients presenting with clinical picture of irritable bowel syndrome and fulfilling Rome III criteria of IBS.

Rome III criteria: Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following:

a. Improvement with defecation.
b. Onset associated with a change in frequency of stool.
c. Onset associated with a change in form (appearance) of stool.

- Patients with negative colonoscopy.

Exclusion Criteria:

Patients with the following conditions were excluded:

1. Presence of organic gastrointestinal diseases, cardiovascular, autoimmune and metabolic diseases, and psychiatric disorders.
2. Positive blood tests including ESR and high-sensitivity CRP (hsCRP).
3. Clinical autonomic dysfunction (e.g., peripheral neuropathy, vagotomy, amyloidosis).
4. Medical treatment modifying the ANS (e.g., anticholinergic, antiarrhythmic, beta blockers, antidepressants, SSRIs).
5. Pregnancy. None of the subjects included in the study were on any medication affecting ANS, nor reported either alcohol abuse or recreational drug use. All subjects were evaluated by a psychologist in order to exclude major psychopathologies.

Sample size determination: The sample size was calculated by Epi Info program (version 6.0) at 95% Confidence Limit, Power of the Test is 80%.

All the studied cases were subjected to the following: Full medical history, clinical examination including blood pressure and heart rate measured supine and then remeasured after patient stands for five minutes. Laboratory investigations include, Complete blood picture, C reactive protein and Erythrocyte Sedimentation Rate.

Holter ECG:

The recorded data was analysed by a special program from which these parameters were calculated [Standard deviation of the normal to normalinterval (SDNN)–Standard deviation of sequential 5-min RR interval means (SDANN) – Root mean square successive difference (RMSSD)]

Questionnaire:

All patients and controls are subjected to this questionnaire about anxiety and stress and a scale was calculated to measure them

1	No	Yes	Disturbed sleep pattern
2	No	Yes	I have some phobia in comparison to mates
3	No	Yes	At times experience lack of sleep
4	Nol	Yes	I think im more nervous than others
5	No	Yes	Rarely I experience night mares
6	No	Yes	Frequently I experience abdominal pain
7	No	Yes	Frequently I experience tremors
8	No	Yes	Frequently experience diarrhea
9	No	Yes	Work makes me stressed out
10	No	Yes	Frequently experience nausea
11	No	Yes	Most time Iam a worried person
12	No	Yes	Always I feel hunger
13	No	Yes	I feel very confident
14	no	Yes	I acclimatize quickly
15	No	Yes	When I await something I get frustrated
16	No	Yes	At time I feel restless that I even cannot sleep
17	No	Yes	Iam usually calm and nothing irritates me
18	No	Yes	sometimes I find myself so anxious I can get myself to sit on a chair for a long time
19	No	Yes	I am always happy in all situations
20	No	Yes	it is very hard for me to concentrate for a considerable duration in doing any work
21	No	Yes	Always I feel worried on something or someone
22	No	Yes	If I face anything difficult I avoid it
23	No	Yes	I want to feel happiness that other people experience
24	No	Yes	Mostly I find myself occupied by something
25	No	Yes	Sometimes I feel I am useless
26	No	Yes	AT times I feel bored and frustrated
27	No	Yes	I easily perspire even in cold weather

28	No	Yes	Life for me is considered stressful and exhausting
29	No	Yes	I am always busy and wandering that something negative would happen
30	No	Yes	Usually I feel shy and shameful of myself
31	No	Yes	Occasionally I feel strong heart beats and chest pain
32	No	Yes	I have emotional lability
33	No	Yes	Sometimes iam scared from things or people
34	No	Yes	At all times I feel burden and worried
35	No	Yes	I frequently experience headache
36	No	Yes	Something Iam busy with issues of no importance
37	No	Yes	I cannot put my mind to concentrate on one thing only
38	No	Yes	I easily panic or get confused
39	No	Yes	At times I feel hopeless
40	No	Yes	Iam a very strong person
41	No	Yes	At times when I panic I sweat and this disturbs me
42	No	Yes	I never feel shy
43	No	Yes	Iam sensitive in comparison with other people
44	No	Yes	I never experience flushing in certain situation
45	No	Yes	I couldnt get over them ,sometimes I feel that problems and hardships accumulate
46	No	Yes	Whenever I perform work it creates burden on me
47	No	Yes	Most cases I dream about thing I don't prefer to share with anyone
48	No	yes	I don't feel self confident
49	No	Yes	rarley I have bouts of troublesome constipation

Results of the questionnaire were categorised in four categories:

Less than 16 → No.
17 – 25 → Mild.
25 - 36 → Moderate.
36 - 49 →Severe.

Statistical Methodology

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 14 (MedCalc© Software bvba, Ostend, Belgium). Normality of numerical data distribution was examined with the D'Agostino-Pearson test. All data were normally distributed and were presented as mean ± SD.

Degree of change (Delta) of BP and heart rate was calculated by the following equation:

$$\text{Delta (\%)} = ((\text{Erect} - \text{Supine}) / \text{Supine}) \times 100$$

Comparison between quantitative data was done using unpaired sample t test, while paired data were compared using Paired t test. Qualitative data were compared using chi-square (X2), or Fisher-exact test. Analysis of age as a co-variant was done using ANCOVA analysis. Data were tabulated and graphically illustrated.

Results

Our study was carried on 20 IBS patients (90% females) and 20 healthy controls (70% females), there was no significant difference between IBS patients and control could be elicited as regards to sex ($P > 0.05$), but it revealed that IBS is more common in females.

The mean age of the studied IBS group was 32.2± 8.1 (mean ± SD) while 20 controls with mean age of 31.1± 10.4 (mean± SD) which showed no significant difference between studied groups as regards the mean age ($P>0.05$).

In our study the Holter data of IBS patients and controls shows no significant difference as regards to SDNN ($P=0.371$), SDANN ($P=0.286$) and RMSSD ($P=0.837$).

In our study a significant difference between studied groups as regards to erect systolic BP, erect diastolic BP ($P<0.001$) of IBS patients which shows that there is orthostatic changes of arterial blood pressure in IBS patients from supine to erect position more than that occur in controls patients.

In our study the difference between mean supine systolic BP (117.3 mmHg) and mean erect systolic BP (105.0 mmHg) is less than 20 mmHg, and the difference between mean supine diastolic BP (77.5 mmHg) and mean erect diastolic BP (70.8 mmHg) is less than10 mmHg in IBS patients, so there is no orthostatic hypotension.

Our study shows a significant difference between IBS patients and controls as regards to supine HR and erect HR (P<0.001).

In our study the different laboratory investigations are within normal ranges in IBS patients and controls which exclude presence of any infectious or inflammatory disorders in the studied groups which may affect on the results of our study giving false positive or false negative results.

Our study shows that IBS patients have higher grades of anxiety and stress than controls (p<0.001).10% of IBS patients, 70% of controls have minimal grades of anxiety and stress, 80% of IBS patients, 30% of controls patients have mild grades of anxiety and stress.5% of IBS patients have moderate grades and the other 5% have severe grades.

Our study shows that no significant difference between IBS patients and control could be elicited as regards to correlation between Supine HR, Erect HR and Holter data (SDNN, SDANN, RMSSD), but it shows significant difference within IBS patients as regards to correlation between Supine HR, SDNN, SDANN and RMSSD, and correlation between Erect HR,SDNN and RMSSD. Also our study shows significant difference within IBS patients as regards correlation between SDANN and Erect systolic BP.

Table (1): Comparison between the two studied groups as regards to Demographic data (Age and Sex):

		Group				P Value
		IBS		Control		
		Mean	± SD	Mean	± SD	
Age (Years)		32.2	8.1	31.1	10.4	0392
Gender	Female	18 (90%)		14 (70%)		0.235
	Male	2 (10%)		6 (30%)		

Table 1 showed that no significant difference between IBS patients and control could be elicited as regards to sex (P > 0.05), and shows also no significant difference between studied groups as regards to Age (P >0.05).

Table (2): Comparison between the studied groups as regards Holter data:

	Group				P Value
	IBS		Control		
	Mean	± SD	Mean	± SD	
SDNN (ms)	147.3	57.3	131.6	51.9	0.371
SDANN (ms)	109.3	17.7	98.0	42.8	0.286
RMSSD (ms)	83.0	95.1	77.6	65.8	0.837

Table 2 showed that no significant difference between IBS patients and control could be elicited as regards to SDNN, SDAN and RMSSD.

Table 3 showed that no significant difference between IBS patients and control could be elicited as regards to supine systolic BP, supine diastolic BP and systolic BP of control, heart rate of the control (P > 0.05), but shows a significant difference between studied groups as regards to erect systolic BP, erect diastolic BP, systolic and diastolic BP of IBS patients, supine heart rate, diastolic heart rate and heart rate of IBS patients and diastolic BP of control (P<0.001).

Table 4 showed that no significant difference between IBS patients and control could be elicited as regards to correlation between Supine HR, Erect HR and Holter data (SDNN, SDANN, RMSSD), but it shows significant difference within IBS patients as regards to correlation between Supine HR, SDNN, SDANN and RMSSD, and correlation between Erect HR, SDNN and RMSSD (P<0.001).

Table (3): Comparison between the two groups regarding Orthostatic BP and Heart rate Changes:

		Group				P Value
		IBS		Control		
		Mean	± SD	Mean	± SD	
Systolic BP	Supine	117.3	6.0	120.3	9.9	0.254
	Erect	105.0	7.6	119.0	9.1	< 0.001
P Value		< 0.001		0.056		
Diastolic BP	Supine	77.5	4.4	80.3	7.0	0.145
	Erect	70.8	6.5	78.8	6.7	< 0.001
P Value		< 0.001		0.03		
Heart rate	Supine	68.8 ± 2.04		64.94 ± 2.8		< 0.001
	Erect	72.2 ± 1.96		65.04 ± 2.8		< 0.001
P Value		< 0.001		0.33		

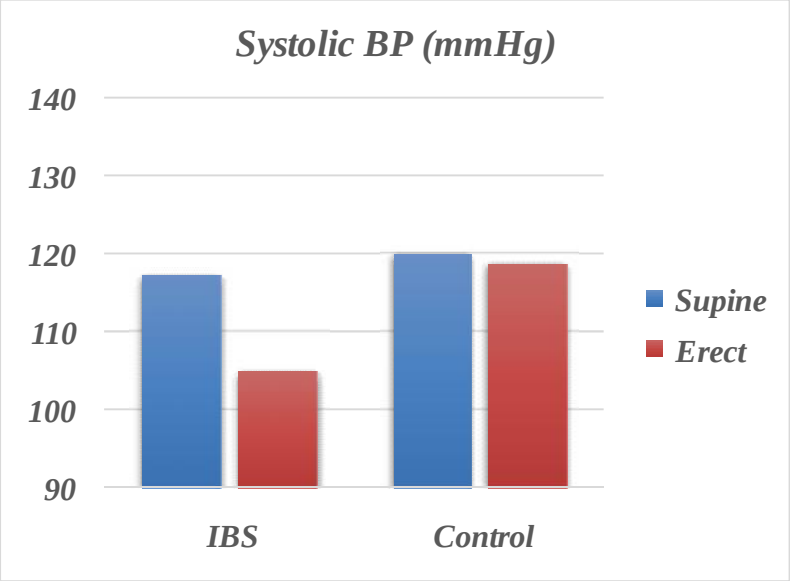

Fig (1):Systolic BP of the two studied groups.

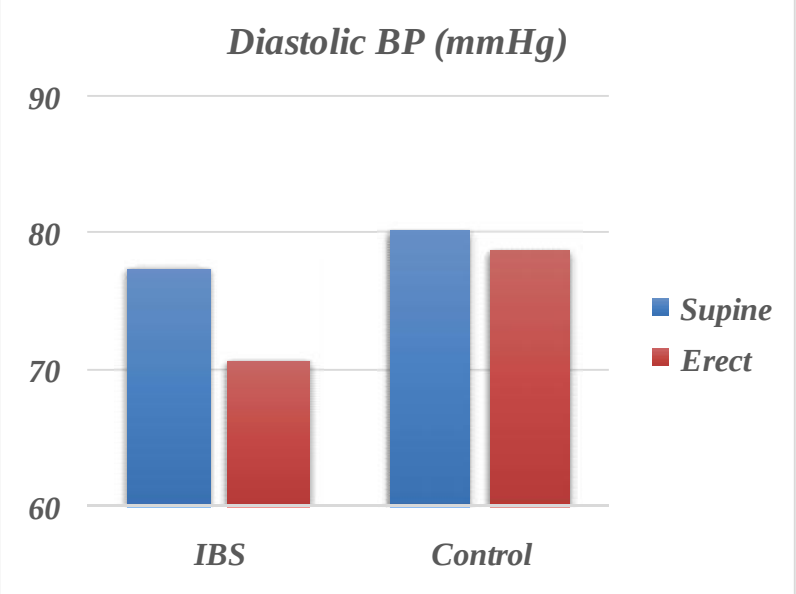

Fig (2): Diastolic BP of the two studied groups.

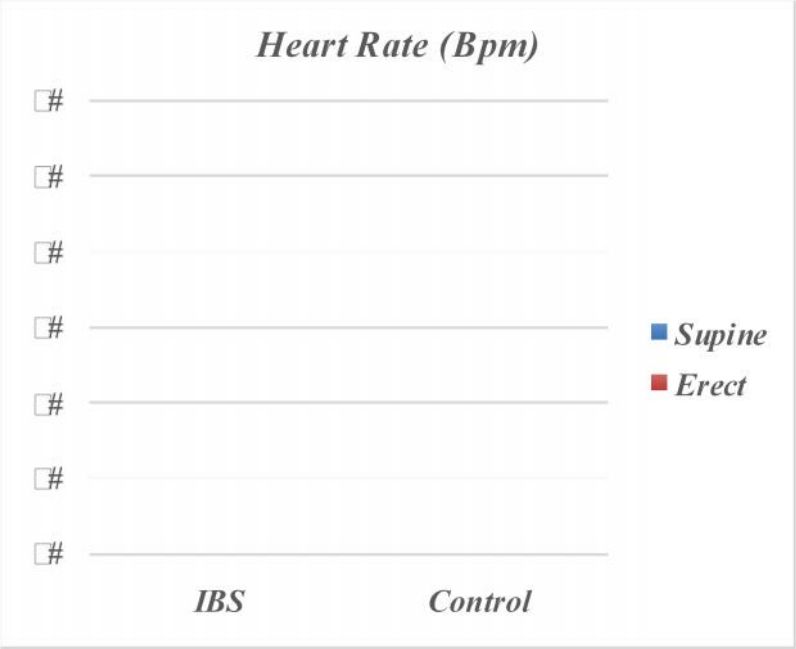

Fig (3): Supine and Erect heart rate of the studied groups.

Table (4): Correlation between Holter data and heart rate:

All Patients (40)						
	SDNN (ms)		SDANN (ms)		RMSSD (ms)	
	R	P Value	R	P Value	R	P Value
Supine HR (BPM)	-0.20	0.22	-0.02	0.90	-0.25	0.12
Erect HR (BPM)	-0.06	0.72	0.07	0.65	-0.15	0.36
Delta HR	0.18	0.26	0.18	0.26	0.08	0.61
IBS (20)						
Supine HR (BPM)	-.666**	< 0.001	-.536*	0.01	-.553*	0.01
Erect HR (BPM)	-.538*	0.01	-0.33	0.15	-.463*	0.04
Delta HR	0.19	0.42	0.25	0.30	0.14	0.55
Control (20)						
Supine HR (BPM)	-0.16	0.50	-0.06	0.79	-0.18	0.44
Erect HR (BPM)	-0.19	0.43	-0.07	0.76	-0.22	0.36
Delta HR	-0.18	0.44	-0.06	0.79	-0.22	0.35

Table (5): correlation between Holter data and BP:

	SDNN (ms)		SDANN (ms)		RMSSD (ms)	
All Patients (40)	**R**	**P Value**	**r**	**P Value**	**R**	**P Value**
Supine Systolic BP	-0.15	0.36	-0.31	0.05	0.04	0.81
Supine Diastolic BP	-0.12	0.45	-0.18	0.25	-0.02	0.89
Erect Systolic BP	-0.23	0.15	-.395*	0.01	0.00	0.98
Erect Diastolic BP	-0.21	0.19	-0.19	0.25	-0.13	0.42
Delta SysBp	-0.17	0.29	-0.22	0.18	-0.05	0.77
Delta DiastBp	-0.22	0.18	-0.07	0.67	-0.22	0.18
IBS (20)						
Supine Systolic BP	-0.09	0.69	0.12	0.62	-0.09	0.69
Supine Diastolic BP	-0.17	0.47	0.30	0.20	-0.26	0.27
Erect Systolic BP	-0.21	0.37	-0.35	0.13	-0.09	0.70
Erect Diastolic BP	-0.22	0.36	0.20	0.39	-0.29	0.22
Delta SysBp	-0.16	0.51	-0.42	0.07	-0.04	0.85
Delta DiastBp	-0.20	0.40	0.05	0.84	-0.23	0.32
Control (20)						
Supine Systolic BP	-0.15	0.52	-0.39	0.09	0.18	0.45
Supine Diastolic BP	-0.04	0.86	-0.27	0.25	0.21	0.37
Erect Systolic BP	-0.16	0.51	-0.41	0.07	0.19	0.42
Erect Diastolic BP	-0.10	0.69	-0.25	0.28	0.08	0.74
Delta SysBp	0.05	0.82	0.04	0.85	0.01	0.97
Delta DiastBp	-0.11	0.66	0.08	0.73	-0.31	0.19

Table 5 showed significant difference within IBS patients as regards correlation between SDANN and Erect systolic BP (P<0.01).

Table (6): Laboratory investigations of the studied groups.

	Group				P Value
	IBS		Control		
	Mean	± SD	Mean	± SD	
hsCRP (mg/l)	3.8	1.1	3.9	1.0	0.881
ESR (mm/hr)	9.6	1.7	10.7	3.3	0.192
WBCs ($x10^3$/mm)	7.0	1.8	7.0	1.9	0.953
HGB (gm/dl)	13.1	0.9	12.3	1.1	0.017
	254.5	59.3	240.0	71.2	0.488

Table 6 showed a significant difference between IBS patients and control as regards to HGB (P < 0.001), but no significant difference between the studied groups regarding other parameters could be elicited (P > 0.05).

Table (7): Comparison between the studied groups as regardsAnxiety and Stress:

		Groups		P Value
		IBS	Control	
Anxiety and stress	Minimal	2 (10%)	14 (70%)	< 0.001
	Mild	16 (80%)	6 (30%)	
	Moderate	1 (5%)	0	
	Severe	1 (5%)	0	

Table 7 showed significant difference between IBS patients and control could be elicited as regards to Anxiety and Stress ($P < 0.001$).

Discussion

IBS is a common disorder, up to 20% of the general population are affected. IBS was more common in females in this study (90% of the IBS cases). This agrees by the fact that IBS prevalence in females is more than males in the general population in some areas, where female prevalence ranged from 7-24%, compared to male prevalence 5-19% in United Kingdom and United States (24-26) but not in South Korea were gender prevalence was the same (27). This could be explained by the link between the emotional state of the female patients and their vagal activity (28).

In this study anxiety tends to be more severe in patients with IBS than controls where the minimal anxiety is 10% versus 70%, mild anxiety is 80% versus 30%, and moderate to severe anxiety is 10% versus 0%, respectively. This agrees with a study done that showed that IBS patients are more prone to anxiety than the controls (29). In many studies anxiety has been connected to the increased HR and BP, either this stress and anxiety lead to change in the ANS of the patient and consequently cause a gastrointestinal functional disease with a decreased threshold of pain or that IBS is the cause of the stress from the start; where pain can cause induction of stress, both scenarios tends to complete each other in this vicious circle (30). Consequently, to that effect; a recent systematic review showed that there was a positive effect of relaxation therapy on IBS, however the authors recommended caution in interpretation of the results because both groups showed similar anxiety and quality of life and the overall small number of the patients studied (26).

Parameters for measuring autonomic dysregulation in IBS have been many including; the cutaneous thermal stimulation (30), colonic motility (31), the orthostatic blood pressure variability, heart rate and catecholamine level variability with stress (19, 22). They all revolve around the idea that pain will increase the sympathetic stimulation and cause imbalance between sympathetic and parasympathetic systems (30). In this study we concentrated on the effect of IBS on the HR either related to posture or monitored by 24 hours Holter, associated with the blood pressure changes with posture. Although the BP variability with posture was significantly higher in IBS patients than in controls, they still lie in the normal acceptable range, which is below 10mmHg change, so it is not specifically orthostatic hypotension, but this difference shows that indeed the ANS is affected. Also the HRV with posture was more significant in the IBS group, with higher mean HR than the control group, which could be explained by the higher sympathetic activity in this group (32).

Holter is used as a measure for sympathetic and parasympathetic system dysregulation, SDNN and RMSSD tends to be lower with lower parasympathetic activity. In this study there was no difference between the two groups regarding the SDANN, SDNN and RMSSD. Which was in accordance to multiple studies concerning the HRV in IBS (33-35). On the other hand, this is in contrary with a previous study which showed significant impairment in SDNN and RMSSD in the IBS group (36). This could be explained by the fact that the heart rate variability in the studies are related to multiple confounders including; pain severity, bowel discomfort, IBS pattern, sleep pattern, or emotional stress or depression which were not assessed in our study (28, 36). So while, our results agree with a previous study done on children with IBS and functional bowel disorder, which found no difference between the IBS and controls regarding the 24 hours Holter (28). On the other hand, one study used the Holter to monitor only 12 hours by night in the IBS patients, and found a link between the decreased vagal HRV and sleep pattern (29).

IBS is a functional disorder, but it might be expected to cause mild change in the inflammatory markers, although there is heterogeneity among the markers used for example IL-10 and calprotectin (37, 38). In our study there was no difference between the two groups regarding the CBC and metabolic profile, except for the hemoglobin, which showed difference between the two groups, which could be explained by the small sample of the study.

Conclusion

Non invasive methods of assessing functional disorders like IBS, could be benefit in assessing the treatment plan of the patient. Life style modification, anti stress aimed therapy, and medications that control the sympathetic over-activity might ameliorate the condition but wide scale studies are needed to assess the actual benefit/harm balance to IBS patients.

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