

Assessment of parasympathetic autonomic functions in ulcerative colitis patients

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Summary:

Background: Ulcerative colitis has been reported to be associated with autonomic dysfunction, mainly of vagal involvement.

Objectives: To Determine whether there is a parasympathetic dysfunction in ulcerative colitis patients in remission state or not.

Materials and methods: Three standardized tests of parasympathetic function, based on heart rate variation in response to certain stimuli (heart rate response to Valsalva maneuver, to deep breathing and to standing from supine position) were used on 54 ulcerative colitis patients in remission, and 41 healthy volunteers as a control group.

Results: For all of the three tests, patients group gave significantly lower results ($P < 0.05$) which was the least level of significance.

Conclusion: Ulcerative colitis is associated with vagal dysfunction which could be a hidden cause for the underlying inflammatory status because of the recently established anti-inflammatory role of vagus nerve.

Key Words: Parasympathetic function tests, Ulcerative colitis, Vagus nerve.

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Introduction:

Ulcerative colitis (UC) is a common disorder; various factors contribute to its clinical manifestations including psychiatric and physical components. The etiology of the disease remains poorly understood. The pathological manifestations of UC are superficial ulcerations that involve the mucosa in a continuous pattern, usually affecting the distal colon particularly the rectum, but in more severe cases, ulceration can extend proximally [1]. Several studies have reported parasympathetic dysfunction in patients with UC [2, 3]. Parasympathetic nervous system represented by the vagus nerve, plays an important role in immunomodulation and several studies have demonstrated the anti-inflammatory role played by the vagus nerve [4, 5, 6, and 7]. In the present study we assessed the parasympathetic function in UC patients using simple non-invasive tests and our aim was to determine if there is vagal insufficiency in these patients or not.

Patients and Methods:

A total of 54 patients with ulcerative colitis were recruited for this study, (25 females/ 29 males) their age ranged between 22 and 60 years, with a mean of (43+/- 9.5 SD) years, and all of them were registered in the center of Liver

and gastrointestinal diseases in Bab Al Muadham, Baghdad. Their diagnosis with UC was established there by history, physical examination, endoscopic and histopathological findings. The duration of their disease ranged between 1 and 30 years. 12 patients had either proctitis or proctosigmoiditis, 34 had left sided colitis and only 8 patients with pancolitis, according to their endoscope reports. None of them was a smoker. All patients were in remission state confirmed by history, examination, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and Hemoglobin (Hb) level as laboratory markers of acute inflammation [8]. Patients suspected to have cardiovascular, pulmonary, thyroid diseases and diabetes mellitus, or patients using drugs that are known to interfere with autonomic function or patients with severe anemia or older than 60 years were excluded from the beginning. Patients of ulcerative colitis were subdivided according to their disease extent based on their endoscopical findings into three subgroups; proctitis or proctosigmoiditis, left sided colitis where the inflammation is limited to the splenic flexure of the colon, and pancolitis [3]. The proximal the inflammation extends the more severe the disease is considered [1]. The numbers and percentage of the subgroups are shown in (table 1). 41 healthy controls, 18 were females, their age ranged between 21 and 59 years with a mean of (40 +/- 10.7 SD) years, were selected from the medical and paramedical staff of the center and from

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colleagues and relatives, all of them were checked carefully for any medical problem, and none of them was on treatment that might interfere with the autonomic function. A sphygmomanometer was used to measure the arterial blood pressure (BP), an electrocardiograph (ECG) (Medifix model M102C) with paper speed set on 25 millimeter per second was used to monitor heart rate (HR), and lead II was recorded in all the tests. The parasympathetic cardiovascular reflex tests used can be summarized as follows; the first test is based on measuring the heart rate response to Valsalva maneuver, where the subject abruptly blows into a mouthpiece attached to a sphygmomanometer at 40 mmHg for 15 seconds, then releases the strain also abruptly. During the strain and release periods; ECG is recorded to monitor the Heart rate changes which are expressed as Valsalva ratio. The ratio is calculated by dividing the widest R-R interval during the release period, by the shortest R-R interval during the straining period [9], a ratio less than 1.2 is abnormal [10]. The second test is based on measuring the heart rate variation during deep breathing or what is called respiratory sinus arrhythmia, where the subject is asked to breathe deeply, slowly and steadily at a rate of 6 breaths per minute for one minute while ECG is recording. The inspiratory- expiratory difference is calculated by taking the mean of the difference between heart rate during inspiration (maximum) and heart rate during expiration (minimum) in the six respiratory cycles [9], a difference less than 10 beat per minute is abnormal [10]. The third test is based on heart rate changes in response to standing from supine position. This test was performed by asking the subject to stand up from resting supine position, quickly within 3-4 seconds, during this time ECG is recording few seconds before he stands up and for about 60 seconds after standing up. The HR response is expressed as 30/15 ratio, which is calculated by dividing the R- R interval of the thirtieth heart beat by the R- R interval of the fifteenth heart beat. Counting the beats can be made easy by observing the skeletal muscle artifacts in the ECG. The time period of supine rest before standing can affect the 30/15 ratio, and it should be at least 20 minutes. These 20 minutes can be spent performing the first two tests as the subjects need few minutes to recover from them [9], a ratio less than 1 is abnormal [10]. SPSS version 17 was used in all of our statistical analysis, Student t-test was used to compare means, Pearson Chi-Square Test was used to compare the gender distribution among patients and controls and ANOVA test was used to compare between patients subgroups. Pearson correlation test was used to test the relation between various parameters. P value of less than 0.05 was considered the least significant level.

Results:

The mean age and mean body mass index of patients and controls did not show a significant difference (table 1), and there was no significant difference in gender distribution among patients and controls (table 1).

(Table 1) age, gender and BMI compared between patients and controls. Disease duration and extent are also shown in this table.

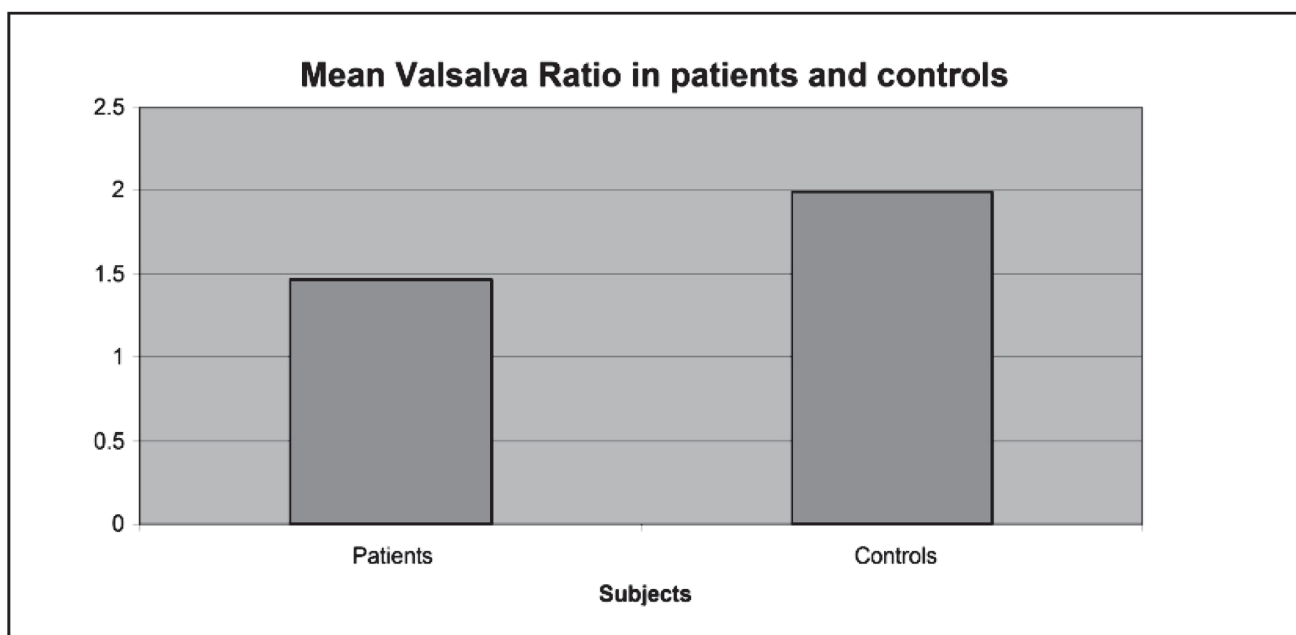
		Patients	Controls	P value
Number		54	41	
Age (years)	mean +/- SD	43 +/- 9.5	40 +/- 10.7	P> 0.05
Gender	males	55.60%	56.10%	P> 0.05
	females	44.40%	43.90%	
BMI*	mean +/- SD	27 +/- 3	26 +/- 4	P> 0.05
Disease duration (years)	mean +/- SD	9.4 +/- 8	-	-
Extent** (within the colon)	proctitis or procto-sigmoiditis	12 (22.2%)	-	-
	left sided colitis	34 (63.0%)	-	-
	pancolitis	8 (14.8%)	-	-
* body mass index				
** extent is demonstrated in number and percentage				
SD: standard deviation				

Regarding the heart rate based parasympathetic tests it was observed that the patients group had significantly lower results in all of the three above mentioned tests (P< 0.05). Tests results of both groups are shown in (table 2) and (figure 1, 2, and 3).

(Table 2) heart rate based tests (Valsalva ratio, inspiratory-expiratory difference of heart rate, 30/15 ratio)

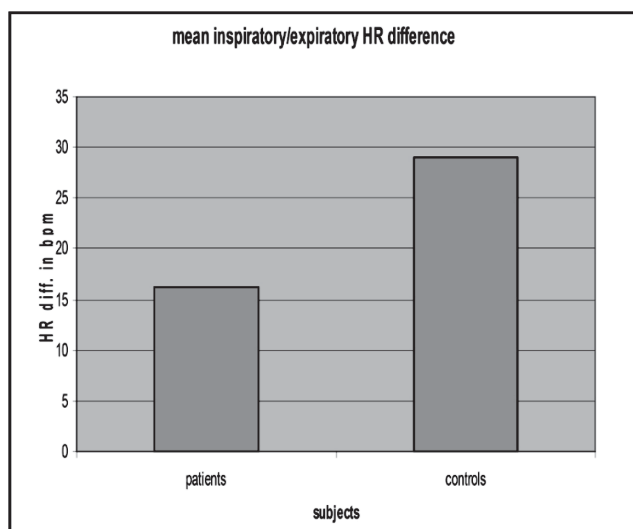
		Patients	Controls	
Number		54	41	
Valsalva Ratio*		1.46 +/- 0.45	1.99 +/- 0.19	P< 0.05
Inspiration/ Expiration difference in HR*		16 +/- 10	29 +/- 8	P< 0.05
30/15 ratio*		1.23 +/- 0.15	1.31 +/- 0.11	P< 0.05

*results are expressed in mean +/- standard deviation

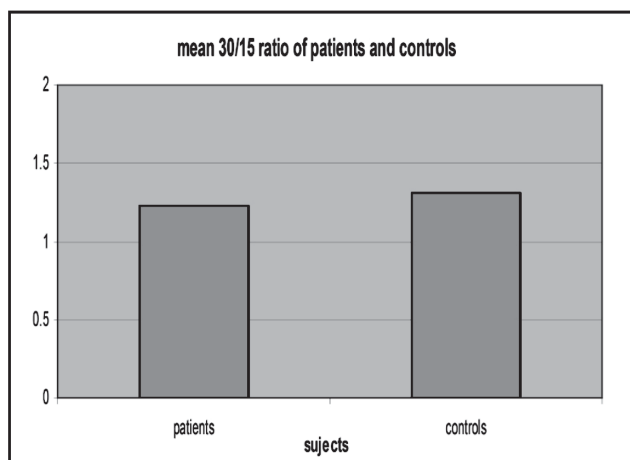


(Figure 1) mean Valsalva ratio in patients and controls.

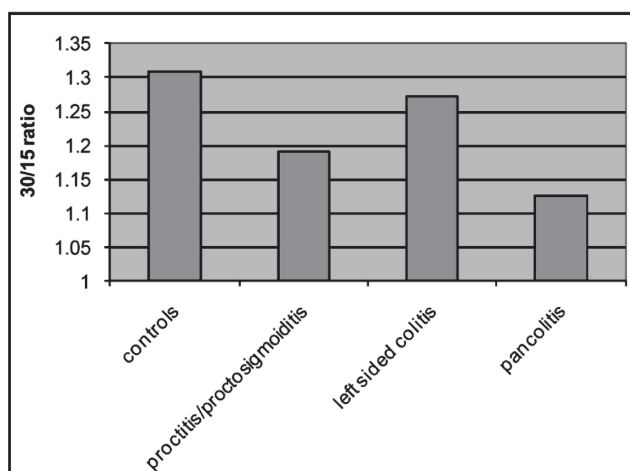
When compared, patient subgroups did not show any difference in autonomic function tests, except for the heart rate response to standing (30/15 ratio), where the pancolitis group had the lowest ratio, while the left sided colitis had the highest ratio ($P < 0.05$), while there was no significant difference between the proctitis group with neither left sided and pancolitis, (figure 4).



(Figure 2) mean inspiratory- expiratory HR variation in patients and controls.



(Figure 3) mean 30/15 ratio in patients and controls.



(Figure 4) 30/15 ratio in patients subgroups and controls.

Discussion:

It has been noticed that aging is accompanied with a generalized decline in autonomic function. Age related changes of autonomic function parameters were observed by Cowan et. al [11]. These workers and many others recommended selecting age matched groups of healthy controls in order to eliminate the effect of age factor on the results. In the present study, although there was an inverse correlation with age, statistical analysis of the age factor in both groups (patients and controls) revealed no statistically significant difference among them indicating age matched controls were selected.

Gender variation in autonomic function tests were also reported by authors like Cowan et. al [11]. Differences were owed to greater muscular mass in males compared to females, and relatively greater susceptibility to stress and anxiety in females compared to males. In the present study there was no statistically significant difference between patients and controls regarding gender distribution, this indicates a gender matched control group was selected. Body mass index (BMI) is believed to affect the autonomic function test results [10]. After comparing the BMI of the patients and controls group, no statistically significant difference was found, indicating a height and weight matching control group was selected. Data obtained from patients and controls of each one of the three autonomic tests, were compared and it was interesting to note that these comparisons gave similar results for the three tests (table 2), the patient group had statistically significant lower results than the control group. These results provide good evidence for the presence of autonomic dysfunction involving the parasympathetic regulation of cardiac function in patients group. Our results conform to those reported by other investigators [2, 3] where they demonstrated similar results of parasympathetic or cardiac vagal dysfunction in patients with ulcerative colitis compared to controls or to Crohn's disease patients.

In the present study the extent of the disease did not seem to be of statistical significance regarding the severity of the autonomic dysfunction except for the 30/15 ratio where the patients with pancolitis had the lowest ratio, which conforms with the idea that the proximal the inflammation proceeds, the more severe the disease gets, but this is not the case in patients with proctitis or proctosigmoiditis, where they had unexpectedly lower 30/15 ratio than the relatively proximally diseased patients with left sided colitis. This is expected because not all patients had the same degree of inflammation and tissue damage or the same relapsing frequency or the same disease management and control.

Also the fact that only one of three tests was of significance, increases the doubt that the disease extent correlates with the severity of autonomic dysfunction. The site of the lesion was not the primary interest of the present study and the tests used in this study measure the overall autonomic cardiovascular reflex function but can not localize the site of the lesion. Many workers Oliveira et al. [12] and Gondim et al. [13] have demonstrated peripheral neuropathy in patients with ulcerative colitis, among them small fiber neuropathy, from which the ANS is mostly comprised, this small fiber affection might become extended to involve the autonomic fibers leading to peripheral autonomic neuropathy [14]. Others have demonstrated evidence of central demyelination in patients with ulcerative colitis [15, 16] Straub et al. in two separate studies, demonstrated both pupillary autonomic neuropathy and pupillary autonomic hyperreflexia respectively in patients with UC. These evidences suggest a potential central affection of autonomic centers in the brain stem or higher centers [17, 18]. Recent studies indicate that the vagus nerve represents a physiological target for pharmacological anti-inflammatory compounds [19]. Electrical stimulation of the cervical vagus nerve in rodents attenuates levels of TNF in serum, liver, lung and heart [20]. In conclusion, ulcerative colitis is associated with parasympathetic dysfunction regardless the disease extent. This autonomic dysfunction carries an additional burden on the clinical state of these patients. In the light of the role of vagus nerve in immunomodulation, vagal dysfunction found in ulcerative colitis patients may have a direct influence on the disease activity and the maintenance of a chronic inflammatory process even in the clinically remittent patients. Knowing these facts can bear a lot of therapeutic potentials. Studies directed on utilizing pharmacological and non-pharmacological modalities aiming to modulate immune reaction by manipulating the autonomic nervous system especially the vagus nerve, to create new therapies that replace or at least assist the conventional ones to reach a better control of the disease and hopefully to prevent future complications.

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