

## Gastric myoelectrical activity in patients with inflammatory bowel disease

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Submitted April 25, 2015; accepted in final form June 23, 2015

### Abstract

**Aim:** Inflammatory bowel disease is characterized by the presence of gastrointestinal motility disturbances; however alterations in the gastric myoelectrical activity have not been characterized. In this study we have recorded the gastric myoelectrical activity in patients with ulcerative colitis (UC) and Crohn's disease (CD) during their clinical remission. **Materials and Methods:** Gastric activity was assessed using electrogastrography (EGG) in patients with UC ( $n = 60$ ), CD ( $n = 40$ ) and healthy controls ( $n = 40$ ). In each case, their response to water load test, as well as the dominant frequency (DF), dominant power (DP) and the power ratio (PR) of the electrical activity were recorded. **Results:** In healthy controls, the resting DF was  $2.57 \pm 1.05$  cycles per minute (cpm), which decreased after water ingestion ( $2.34 \pm 0.99$  cpm;  $P = 0.001$ ). Compared to healthy controls, patients with UC had low resting DF (bradygastria) ( $2.57 \pm 1.05$  vs.  $1.86 \pm 1.28$  cpm;  $P = 0.01$ ). The change in DF after water ingestion was insignificant in patients with UC and CD. Post-water ingestion, healthy controls exhibited an increase in the DP as compared to the resting state, ( $7.1 [2.93, 102.56]$  vs.  $15.94 [3.92, 133.41]$   $\mu V^2$ ;  $P = 0.02$ ). Patients with UC ( $1.26 [0.14, 9.83]$  vs.  $3.27 [0.61, 42.12]$   $\mu V^2$ ) and CD ( $2.54 [0.44, 47.06]$  vs.  $15.8 [0.1, 126.68]$   $\mu V^2$ ) also showed a significant increase in the DP post-water ingestion. **Conclusions:** Patients with ulcerative colitis have altered resting gastric myoelectrical activity during the remission phase of the disease.

**Key words:** Gastrointestinal motility, Crohn's disease, ulcerative colitis, smooth muscles, adults

Abbreviations used: CPM, Cycles per minute; CDAI, Crohn's disease activity index; CD, Crohn's disease; DF, Dominant frequency; DP, Dominant power; EGG, Electrogastrography; IBD, Inflammatory bowel disease; PR, Power ratio; UC, Ulcerative colitis.

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## Introduction

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Inflammatory bowel disease (IBD) comprises a group of diseases, such as ulcerative colitis (UC) and Crohn's disease (CD), and is characterized by the presence of ulcers in the digestive tract extending from the oral cavity to the anus. It is accompanied by abdominal pain, diarrhea, and blood in stools. Upper gastrointestinal symptoms such as nausea, vomiting, and anorexia are common in patients with lower gastrointestinal tract disease. Conceivably, gastric motility disturbances might play a pathophysiological role, but only a few studies have addressed gastric motility in CD and virtually none in UC. Available data suggest an altered gastric motility in response to solids in adults and children with CD (1, 2). Therefore, in the present paper, we report the gastric myoelectrical activity in a large group of adult patients with UC and CD, during the clinical remission phase of these diseases.

Electrogastrography (EGG) detects slow gastric activity (3) using non-invasive cutaneous electrodes and provides a record of the gastric myoelectrical activity which precedes contractions. The quantitative comparison of the EGG signal variability showed a 94% sensitivity and 79% specificity (4). EGG records the sinusoidal signals with a certain periodicity determined by the slow wave frequency [gastric electrical control activity (ECA)]. The dominant EGG frequency determines the frequency of stomach contraction (5). In humans, simultaneously recording the gastric myoelectrical activity from either the serosa or mucosa, together with recordings from cutaneous electrodes have shown that the EGG signals reflect the normal 3 cycles per minute (cpm) gastric slow waves and thus the slow wave frequency (6). Slow frequency is termed bradygastria (0–2.4 cpm) and abnormally high frequency is termed tachygastria (3.6–9.9 cpm). This has been accurately detected noninvasively by EGG and simultaneous serosal recording.

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## Materials and Methods

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### Subjects

The study was carried out on patients with UC ( $n = 60$ ) and CD ( $n = 40$ ) and healthy controls ( $n = 40$ ). All the patients selected were in the clinical remission phase of the disease, to avoid confounding the results due to processes associated with active inflammation such as glucocorticoid release, cytokine production, pain etc. Demographic and clinical data of all the study participants were collected using a proforma specially prepared for the study. All patients were referred from the Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, India. The assessment of the EGG recordings was carried out in the Department of Physiology, AIIMS, New Delhi, India. Forty healthy volunteers (28 males and 12 females, mean age:  $31 \pm 8$  years) were recruited for the study after explaining the study and taking written informed consent. They had no prior medical history of heart, lung, or digestive diseases and were diagnosed to be healthy.

The diagnosis of UC was established on the basis of clinical evidence of large bowel diarrhea, hematochezia and tenesmus; endoscopic evidence of diffuse pattern of involvement of the gastrointestinal mucosa characterized by loss of vascular pattern, erythema, friability or ulcerations; and histological evidence. The diagnosis of CD was established on the basis of the presence of characteristic clinical manifestations (chronic diarrhea, hematochezia, abdominal pain, and intestinal obstructive manifestations), endoscopic features (skip lesion, asymmetrical involvement, deep ulcers, ileocecal valve involvement, and terminal ileum involvement), together with histological evidence (acute or chronic colitis, presence of inflammation extending beyond muscularis mucosa, lymphoid follicles, and noncaseating granulomas). The involvement of the small intestine was assessed by a barium meal follow-through, a small bowel enema, and/or retrograde ileoscopy.

Inclusion criteria were (a) patients ranging between 16–60 years of age and (b) patients in the remission phase of the disease. The activity of UC and CD was assessed using True Love and Witts criteria (7) and Crohn's Disease Activity Index (CDAI) (8), respectively. Patients with a CDAI score  $\leq 150$  were included in the study. The inclusion criteria for UC patients were (a) one or two stools a day without blood, (b) no fever, (c) no tachycardia, (d) hemoglobin normal or returning towards normal, (e) erythrocyte sedimentation rate (ESR) normal or returning towards normal.

Exclusion criteria were (a) IBD patients with other chronic diseases like diabetes mellitus, hypertension, cardiovascular diseases, (b) any condition known to affect the cardiovascular autonomic functions such as chronic alcoholism or smoking (c) patients who have undergone any surgical intervention for IBD (d) pregnant women, (e) patients on any drug regime affecting autonomic functions, and (f) those on psychiatric medication. The ethical committee of AIIMS, New Delhi for human studies approved the protocol (Reference #: A-66/9.8.2006) of the study.

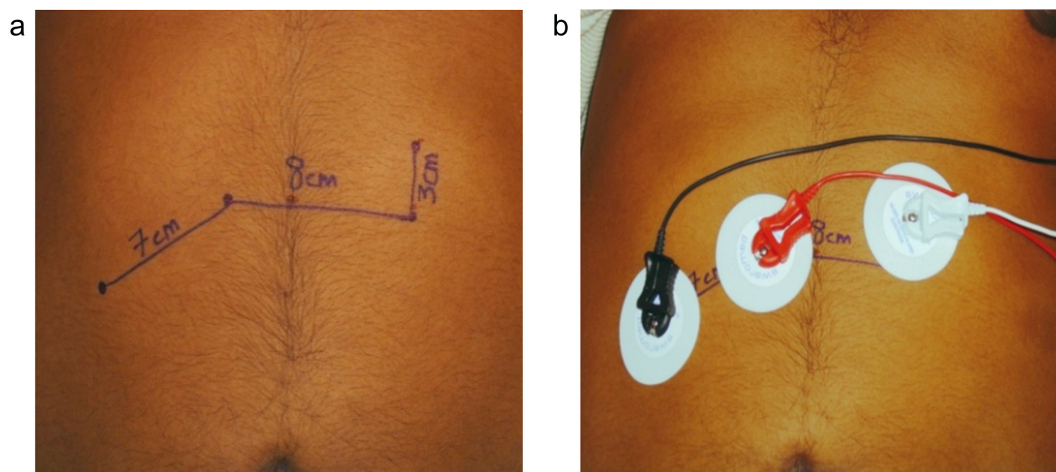
### ***Gastric myoelectrical activity evaluation by EGG***

Both the gastric mechanical and electrical activities were recorded non-invasively by using electrodes on the upper abdominal skin. This technique is known as EGG (9). The EGG recording was carried out after ingestion of a light meal at least 2-hrs prior to the recording. Patients with IBD were not on any medication that might modify gastric motility (e.g., prokinetic, anti-emetic agents, narcotic analgesics, anti-cholinergic, and non-steroidal anti-inflammatory agents). The subjects were asked to void the bladder before commencement of the recording to minimize the need for interruption of the test and to eliminate any motion artifact which might develop as a consequence of urinary or faecal urgency. The EGG recording was carried out in the supine position, in a sound proof room and the subjects were requested to lie quietly and not to sleep during the recording. The EGG was recorded using cutaneous bipolar Ag/AgCl electrodes positioned on the abdomen wall over the abdomen. Before the placement of the electrodes, the epigastric skin where the electrodes were to be positioned was shaved (to remove hair), cleaned properly with an abrasive sponge and sandy skin preparation jelly to reduce impedance. The EGG electrodes were not placed on the ribs, as this can increase respiratory artifacts in the recorded signal.

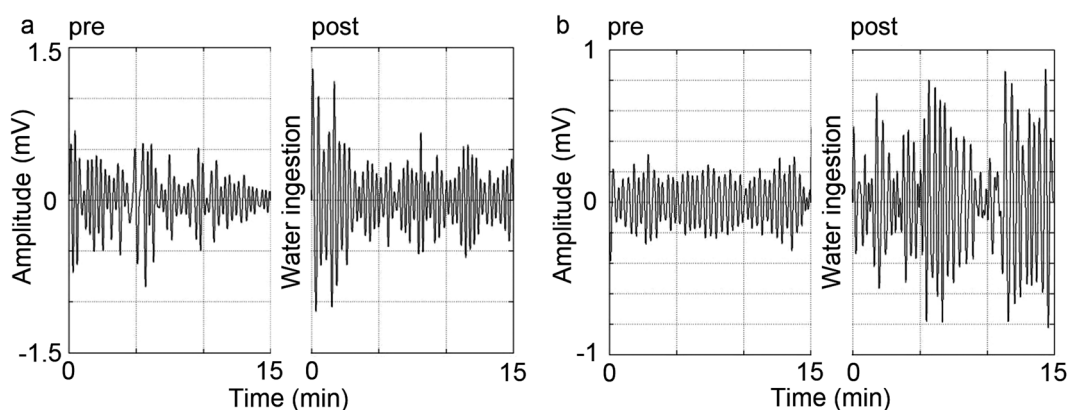
After the skin preparation, the electrodes were placed on the abdominal surface overlying the pyloric antrum and the greater curvature of stomach. Two active electrodes and one reference electrode were placed as depicted in Fig. 1. The first active electrode was positioned at 3 cm away towards the right of the midpoint between the xiphoid process and the umbilicus. The second active electrode was placed 8 cm to the left and cephalic to the first active electrode, at least 2 cm below the rib cage, and in the mid-clavicular line. The reference electrode was placed 7 cm away from the first electrode in the lower quadrant.

The actual recording was started after a baseline recording of gastric activity for 5 min to allow the jelly to settle on the body and also to make the subject acquainted with the procedure. Two blocks of gastric myoelectrical activity data were recorded. First, a 15-min baseline (pre-water ingestion) was recorded after which the subjects were asked to drink 200 ml of water at room temperature (in sitting position). Thereafter, a second 15-min recording was started in the supine position. The water load test is a standardized test to induce gastric distension and to evoke gastric motility responses without the complex hormonal responses of a caloric test meal. Recording an EGG during a water load test has been validated as reliable and reproducible (10).

The recordings were made at sampling frequencies of 500 Hz. The high- and low- pass filters were set at 0.005 and 0.1 Hz, respectively. After the measurement, the EGG data were digitized and analyzed by computer using a software program. The electrodes were connected to the EGG amplifier of the Biopac MP 150 recorder



**Fig. 1.** The epigastric skin preparation (a) and the electrode placement for EGG (b). First electrode (red) was placed 3 cm right to the mid-point of the line joining umbilicus and xiphoid process. The second electrode (white) was placed 8 cm to the left and above the first electrode. Reference electrode (black) was placed on the right side of the abdomen keeping a distance of 7 cm from the first electrode.



**Fig. 2.** Representative EGG traces of pre and post water ingestion in a normal subject (a) and in a patient with CD (b).

(Biopac, USA). Representative EGG tracings in both a normal subject (Fig. 2a) and a patient with CD (Fig. 2b) are shown. The acquired raw EGG signals were analyzed using a custom graphical user interface (GUI) developed in MATLAB v6.5 (MathWorks Inc., Japan). The high- and low- pass digital filters allowed suppression of unwanted interferences while enhancing the gastric myoelectrical activities. Thereby, the data were partitioned into baseline, pre- and post-water ingestion to further perform the spectral analysis. Power spectral density estimates using FFT and Thomson's multitapered approach were computed to determine the dominant frequencies, the power at the dominant frequency and to compute the relative power ratio associated with the alteration in gastric contractions.

### Parameters studied

**(a) Dominant frequency (DF):** defined as the dominant frequency during the pre-water and post-water ingestion period. The normal gastric frequency in healthy humans is approximately 3 cpm ranging from narrow 2.5 to 3.75 cpm (11), bradygastric waves (slow frequency) (0.0 to 2.4 cpm), and tachygastric waves (high frequency) (3.6 to 9.9 cpm).

**Table 1.** Demographic and clinical characteristics of patients with ulcerative colitis and Crohn's disease

	Healthy controls ( <i>n</i> = 40)	Ulcerative colitis ( <i>n</i> = 60)	Crohn's disease ( <i>n</i> = 40)
Age (years)	31 ± 8	34.7 ± 11.25	34.8 ± 10.53
Male : Female	28:12	35:16	21:19
BMI (kg/m <sup>2</sup> )	22.45 ± 3.82	22.06 ± 3.86	22.49 ± 5.05
Duration of disease (months) median (Inter quartile range)	–	36 (21, 114)	60 (30, 108)
Extent of diseases	–	Proctitis: 5 Proctosigmoiditis: 20 Left side colitis: 15 Pancolitis: 20	Small intestine (L1): 9 Large intestine (L2): 13 Small and large intestine (L3): 14

**(b) Dominant power (DP):** defined as the mean power in the power spectrum of the EGG recording during the pre-water and post-water ingestion period. The power of the gastric peak was determined by the absolute peak value, and the mean power was computed by averaging the individual spectrum.

**(c) Power ratio (PR):** defined as the relative change of gastric power before and after water ingestion and is commonly used parameter that is associated with alteration in gastric contractions. The PR is used since the absolute values of EGG power are influenced by several factors (distance between the electrodes and the wall of the stomach, skin conductance, and variable shape of the stomach). Thus, the EGG power can only be evaluated as ration of postprandial to fasting EGG power values. A ratio of < 1 reflects a decrease in gastric contractility, whereas a ratio of > 1 reflects an increase in gastric contractility.

### Statistical analysis

Parameters recorded in EGG were statistically analyzed by the analysis of variance (ANOVA), using statistical software package SPSS version 15.0 (SPSS, Chicago, IL, USA). Data are expressed as the mean ± S.D. and a *P*-value < 0.05 was considered to be statistically significant.

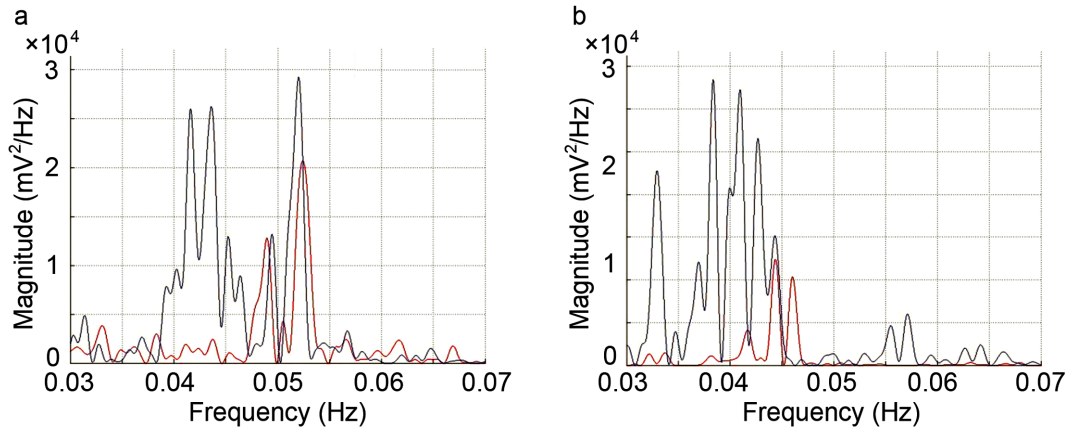
## Results

The clinical characteristics of the patients are presented in Table 1. All the patients were in the clinical remission phase of the disease. A representative record of gastric myoelectrical activity in a healthy subject and a patient with CD is shown in Fig. 3.

**(a) Dominant frequency (DF):** As compared to the normal subjects, low resting gastric myoelectrical activity was observed in patients with UC (*P* = 0.01) (Table 2). There was no significant difference in resting gastric myoelectrical activity in patients with CD and normal subjects (Table 2). In normal subjects, after ingestion of water there was a significant decrease in gastric DF (*P* = 0.001) (Table 2). However, in patients with UC and CD, there was no significant lowering of DF observed after ingestion of water (Table 2).

**(b) Dominant power (DP):** Normal subjects exhibited an increase in the DP after water ingestion, compared with the fasting state (*P* = 0.02) (Table 2). Similarly, in comparison with the fasting state, the patients with UC and CD showed an overall increase in the DP after water ingestion. No such relationship was observed among the UC subtypes on the EGG data. Power ratio (PR) was > 1 in the normal subjects, and patients with UC and CD (Table 2).





**Fig. 3.** Representative power spectral density of EGG in a normal subject (a) and in a patient with CD (b). Red and black curves represent the data before and after water ingestion, respectively.

**Table 2.** Results of gastric myoelectrical activity in healthy controls, patients with ulcerative colitis and Crohn’s disease

Variables	Healthy controls		Ulcerative colitis (UC)		Crohn’s disease (CD)	
	Pre-water ingestion	Post-water ingestion	Pre-water ingestion	Post-water ingestion	Pre-water ingestion	Post-water ingestion
Dominant frequency (cpm) (mean ± S.D.)	2.57 ± 1.05	2.34 ± 0.99*	1.86 ± 1.28**	2.06 ± 1.17	2.07 ± 1.27	1.98 ± 1.27
Dominant power ( $\mu V^2/Hz$ )	7.1 (2.93, 102.56)	15.94 (3.92, 133.41)*	1.26 (0.14, 9.83)**	3.27 (0.61, 42.12)*	2.54 (0.44, 47.06)	15.8 (0.1, 126.68)*
Power ratio (PR)	1.29 (0.61, 2.24)		2.55 (1.01, 6.66)		1.43 (0.50, 3.55)	

\*  $P \leq 0.05$  compared to pre-water ingestion values; \*\* $P \leq 0.05$  compared to healthy controls. The values are presented as median (inter quartile range). CPM, cycles per minute.

## Discussion

According to the findings of the present study, patients with UC showed lower resting DF and insignificant changes after water ingestion, as compared to normal subjects. The stomach muscle has a myogenic mechanism that modulates its motility. The DF reflects the regularity of gastric myoelectrical activity. These results highlight that the patients with UC have dysrhythmic gastric movements. In patients with CD, delayed gastric emptying has been related to gastric arrhythmias and antral hypomotility. Kohno et al. (1) using EGG observed that the patients with CD have a functional abnormality, not only in the small intestine, but also in the stomach (1). Bracci et al. (2) in a cross-sectional study observed disturbances in the gastric myoelectrical activity in children with CD (2). On the other hand, asymptomatic antral dysmotility has been documented by gastroduodenal manometry in patients with CD (12). A slower mouth-to-cecum transit has also been reported in patients with UC although gastric emptying was normal in them (13). In this study, we have for the first time reported that the patients with UC also exhibit dysrhythmic gastric movements during the remission phase of the disease. Changes in gastric emptying and oro-caecal transit time in patients with UC suggest that disturbances in gastro-

intestinal tract motility may not be restricted to inflamed regions of the gut. In experimental models of colitis, ultrastructural changes in mitochondria, endoplasmic reticulum (ER), and golgi apparatus have been observed in inflamed and noninflamed ileum in smooth muscle cells and mucosal epithelial cells. Furthermore, the ER is also an important source of intracellular  $\text{Ca}^{2+}$  for muscle contraction which is reduced in an inflamed colon. We predict that ER structural changes may, partly, be responsible for motility alterations in IBD (14).

The DP reflects the amplitude of gastric myoelectrical activity and the PR is believed to be associated with gastric contractility; the increase in the EGG PR observed in this study reflected an increase in gastric contractions. The EGG DP and PR both increased in the patients with UC and CD after water ingestion. This data suggests that the gastric contractile activity was increased after water ingestion. However, they were not rhythmic, as reflected by the lack of changes in the DF.

The autonomic nervous system plays an important role in gastric myoelectrical activity. Receptive relaxation of the fundus is believed to facilitate retention of the gastric contents. Gastric receptive relaxation occurs when the fundus relaxes in response to stimulation during the passage of food. Stimulation of the vagus nerve induces relaxation of the fundus. Water ingestion did not show a significant difference in high frequency (HF) of heart rate variability but demonstrated that changes of EGG PR correlated well with the changes of cardiac vagal nervous activity (15). Imai and colleagues (16, 17) conducted EGG's in healthy volunteers after administration of intravenous atropine sulphate, and observed that normal gastric motility was almost completely abolished, with clearly reduced waveform amplitude in all subjects. Geldof and colleagues (18) reported highly selective vagotomy is associated with abnormalities in gastric myoelectrical activity. Autonomic dysfunctions have been reported earlier in patients with IBD, characterized by low vagal tone (19), increased sympathetic activity (20). Therefore, we can speculate that autonomic imbalance in patients with UC and CD may have an adverse effect on the gastric myoelectrical activity.

In summary, patients with UC have altered resting gastric myoelectrical activity during the remission phase of the disease. These gastric myoelectrical dysfunctions in patients with inflammatory disease may have a bearing on the clinical symptoms.

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## Acknowledgments

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The authors are grateful to the Central Council for Research in Yoga and Naturopathy (CCRYN) for providing financial support for this study; to Mr. Rajendra Kumar for providing general technical assistance.

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## Conflict of interest

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The authors have no conflicts of interest.

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## Authors' contributions

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PS, KKD and GM designed the research. PS performed the research. PS, SND analyzed the data. GM screened the patients. RY developed the algorithms and software for the analysis of gastric motility data. PS, GM, RY and KKD drafted the manuscript.

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