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Impaired Gastric Slow Wave Rhythmicity in Patients After Bone Marrow or Stem Cell Transplant

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Patients after bone marrow or stem cell transplant often develop gastrointestinal symptoms. The aim of this study was to investigate possible impairment of gastric myoelectrical activity in these patients. The study was performed in 15 patients who had had bone marrow or stem cell transplant and 13 healthy subjects. Gastric myoelectrical activity was assessed using electrogastrography. The electrogastrogram (EGG) was made for 30 min in the fasting state and 60 min after a test meal (475 kcal; turkey sandwich). Overall and minute-by-minute spectral analyses were performed to derive various parameters of the EGG. Compared with the healthy controls, the patients showed a significantly higher percentage of arrhythmia (no obvious rhythmicity observed in the EGG) in both fasting (17.6 ± 3.8% vs 7.1 ± 2.17%, $P < 0.02$) and fed (11.4 ± 2.65% vs 4.19 ± 1.04%, $P < 0.02$) state. The patients showed a significantly higher instability coefficient of the dominant frequency in the fasting state than in the controls (0.51 ± 0.06 vs 0.29 ± 0.18, $P < 0.008$). The total average symptom score was 3.93 ± 0.84 in the patients and 0 in the controls, and a relatively weak but significant correlation was found between the symptom scores and the percentage of arrhythmia in the patients in fed state ($r = 0.69$, $P < 0.02$). It was concluded that patients with bone marrow or stem cell transplant have excessive arrhythmia that is correlated with their dyspeptic symptoms.

KEY WORDS: stem cell transplant; gastric myoelectrical activity; electrogastrography or electrogastrogram; gastric motility; gastrointestinal symptoms; gastric emptying.

Patients undergoing bone marrow or stem cell transplants for various diseases, both malignant and nonmalignant, suffer significant gastrointestinal complications. In patients developing graft-versus-host disease (GVHD), significant symptomatology attributable to the gastrointestinal tract may develop such as nausea, vomiting, abdominal cramping/pain, and diarrhea. Although GVHD typically occurs in the allogeneic transplant recipient, a GVHD-like syndrome has been described in patients after autologous stem cell transplantation. Some of these GVHD patients are plagued with abdominal complaints such as nausea, vomiting, cramping, early satiety, pain, or alternating constipation and diarrhea (1–3).

Gastric motility is regulated by gastric myoelectrical activity that is composed of gastric slow waves and spikes (4, 5). Previous studies have shown that abnormal gastric myoelectrical activity is associated with gastric motility disorders and gastrointestinal symptoms such as nausea, vomiting, abdominal pain, bloating, and early satiety (6–9). Those gastrointestinal symptoms are common in patients after bone marrow or stem cell transplant (1–3). Electrogastrography

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(EGG) is an accurate noninvasive technique of recording gastric slow waves (10–16). When appropriately recorded, the dominant frequency of the EGG accurately reflects the frequency of the gastric slow wave and the relative amplitude of the EGG dominant power is associated with gastric contractility (5, 11, 12, 14).

Numerous studies have been performed in patients with gastric motility disorders and/or gastrointestinal symptoms using electrogastrography (7–9, 17–32). However, it is still not clear whether patients after bone marrow or stem cell transplant who complain of gastrointestinal symptoms have impaired gastric myoelectrical activity. The aims of this study were therefore to study gastric myoelectrical activity by using the EGG in recipients of bone marrow or stem cell transplants, to compare results of EGG studies in transplant patients with various symptoms to historic normal controls, and to investigate possible correlation between the EGG parameters and gastrointestinal symptoms in symptomatic transplant patients.

MATERIALS AND METHODS

Subjects

The study was performed in 15 patients (9 women, 6 men, age: 19–53 years, mean: 39.1 years), who had had bone marrow or stem cell transplant 23.1 ± 4.6 months ago, and 13 healthy subjects (7 women, 6 men, age: 23–41 years, mean: 31.0 years). All patients were clinically confirmed with a prior history of bone marrow or stem cell transplant and were consecutively included in the study according to their scheduled follow-up visit. Patients with unstable medical conditions or previous gastrointestinal surgery or significant ascites or inability to be taken off medication including anticholinergics, potassium supplements, reserpine, H_2 antagonists, sucralfate, and proton pump inhibitors during the period of two weeks prior to the study were excluded. The selection of patients was based on the following eligibility criteria: Patients must have prior history of bone marrow or stem cell transplant and be older than 18 years. Patients must not be on prokinetic (metoclopramide, cisapride, erythromycin) drugs for at least one week prior to the study. Patients must not be on interferon for the last four months prior to the study. Patients were queried about gastrointestinal symptoms, and each patient's symptom score was graded according to a modified gastrointestinal symptom scale prior to the initial baseline recording of gastric myoelectrical activity. Each of the following symptoms was graded from 0 to 4 (0: none; 1: mild; 2: moderate; 3: severe; 4: extremely severe): nausea, vomiting, diarrhea, abdominal pain, anorexia, heartburn, and bloating. The clinical details of the patients are shown in Table 1. The healthy subjects had no history of gastrointestinal diseases and were free of gastrointestinal symptoms. The protocol was approved by the institutional review board at the Integris Baptist Medical Center of Oklahoma, and the written consent form was signed by all subjects prior to the study.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH BONE MARROW OR STEM CELL TRANSPLANT

Patient	*Age (Yr)*	*Sex*	*Symptom scores*	*Diagnosis**
1	47	F	4	CML
2	43	F	7	CML
3	34	F	4	CML
4	30	F	11	CML
5	39	M	3	CML
6	46	M	9	AML
7	53	F	2	AML
8	52	F	7	CLL
9	34	M	1	CML
10	38	M	3	NHL
11	27	F	3	EWING
12	30	F	5	CML
13	19	M	0	ALL
14	48	F	0	AML
15	46	M	0	AML

*CML: chronic myeloid leukemia; AML: acute myelocytic leukemia; ALL: acute lymphocytic leukemia; NHL: nodular histiocytic lymphoma.

Electrogastrogram

Surface electrogastrography was applied to measure gastric myoelectrical activity. Before the placement of electrodes, the abdominal surface where the electrodes were to be put was shaved, if hairy, and cleaned with sandy skin prep jelly (Omni Prep, Weaver and Aurora, Colorado, USA) to reduce the impedance. The skin was rubbed with sandy skin-prep jelly until pinkish. Three silver–silver chloride ECG electrodes (Red Dot, 3M Health Care, St. Paul, Minnesota, USA) were placed on the abdominal skin as shown in Figure 1. Two epigastric electrodes were connected to yield a bipolar EGG signal. The other electrode was used as a reference. The bipolar EGG signal was derived from electrodes 1 and 2 and was amplified using a portable EGG recorder (Digitrapper EGG, Medtronic-

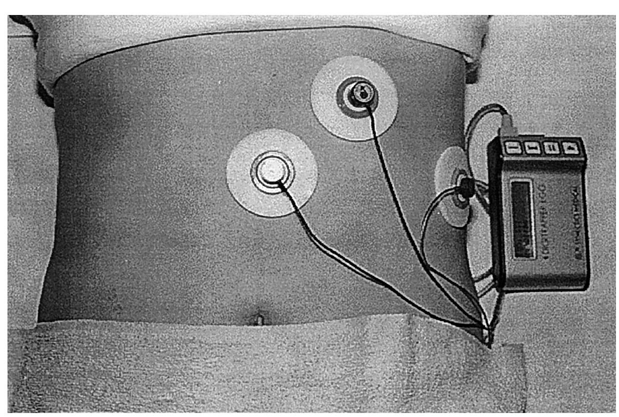

Fig 1. Placement of electrodes. Two epigastric electrodes were connected to generate a bipolar electrogastrogram (EGG) signal. The other electrode in the lower quadrant close to the left costal margin was used as a ground.

Synectics, Shoreview, Minnesota, USA) with low and high cutoff frequencies of 1 and 18 cpm, respectively. On-line digitization with a sampling frequency of 1 Hz was performed using a built-in 8-bit analog-to-digital converter and digitized samples were stored on the recorder.

Study Protocol

After a fast of 6 hr or more, the EGG recording of each subject was made for 30 min in the fasting state in a supine position. Then the subject sat up and consumed a standard test meal of turkey sandwich (475 calories: fat 32.4%, protein 17.5%, carbohydrate 50.1%) within 10 min. A 60-min recording of the EGG was made after the meal in the same supine position. The subjects were allowed to watch regular TV and were asked to stay awake, not to talk and read, and to remain as still as possible during the whole recording period to avoid motion artifacts.

Data Analysis

The EGG data stored on the recorder were downloaded to an IBM 486 personal computer and subjected to computerized spectral analysis using a program previously developed by one of the authors in our laboratory (33). The following parameters were calculated from the EGG.

Dominant Frequency and Power of Slow Waves. The frequency at which the power spectrum of an entire recording had a peak power in the range of 0.5–9.0 cpm was defined as the dominant frequency. The power corresponding to the dominant frequency in the power spectrum was defined as the dominant power. Decibel units were used to represent the power of the gastric slow wave. The relationship of the power P in decibels and power P' in the linear scale is as follows: $P = 10 \log_{10} (P')$. A negative value in the power reflects a power between 0 and 1 in the linear scale.

Percentage of Normal Slow Waves. This parameter specifies the regularity of gastric slow waves and was computed using adaptive running spectral analysis method (10). In this method, the gastric myoelectrical recording was divided into 1-min segments and the power spectrum of each 1-min recording was derived using the previously validated adaptive spectral analysis method (5, 10). The 1-min segment of the recording was defined as normal if its power spectrum had a clear peak in the 2- to 4-cpm frequency range. Otherwise it was defined as dysrhythmia. The percentage of normal gastric slow waves was determined by computing the ratio between the number of normal segments and the total number of segments.

Percentage of Gastric Dysrhythmia. The percentage of gastric dysrhythmia was defined as the percentage of time during which gastric dysrhythmia was present in the EGG. Gastric dysrhythmia includes bradygastria, tachygastria, and arrhythmia. This parameter reflects the abnormalities of gastric slow waves. It was computed in a similar way for the calculation of the percentage of normal gastric slow waves. Bradygastria was defined if the peak power of the 1-min EGG segment was within the range of 0.5–2 cpm, tachygastria if the peak power was within the range of 4–9 cpm, and arrhythmia if there was no dominant peak in the range of 0.5–9 cpm (10).

Instability Coefficient of Dominant Frequency. The instability coefficient (IC) of dominant frequency was used to measure the stability of the dominant frequency. The IC was defined as the ratio between the standard deviation and the mean of dominant frequency IC: = SD/Mean. The IC reflects the variation of the EGG-dominant frequency over the whole recording period and is not subject-dependent (10).

Symptom Scores

Seven symptoms were scored, including nausea, vomiting, diarrhea, abdominal pain, anorexia, heartburn, and bloating, based on information obtained before the baseline recording. Each symptom was graded from 0 to 4 (0: none; 1: mild; 2: moderate; 3: severe; 4: extremely severe) and a total symptom score was computed for each patient. Then an average total symptom score was calculated.

Statistical Analysis

All data were presented as mean ± SE. The unpaired t test was used to investigate the difference of the EGG parameters between the patients with bone marrow or stem cell transplant and the normal controls. Correlations between the gastrointestinal symptom scores and the gastric myoelectrical activity parameters in the symptomatic patients after bone marrow or stem cell transplant were assessed by using Spearman rank order correlation test. The results were regarded as significant at $P < 0.05$.

RESULTS

Dominant Frequency and Power of Slow Waves. Both the healthy controls and the patients showed a normal response to the test meal: a significant postprandial increase in the dominant frequency and power. The postprandial dominant frequency in the controls increased from 2.93 ± 0.04 cpm to 3.17 ± 0.07 cpm ($P < 0.04$) after the meal. The patients showed a similar postprandial increase in the dominant frequency (2.80 ± 0.09 cpm to 3.05 ± 0.11 cpm, $P < 0.004$). The net change of dominant EGG frequency from the fasting state to the postprandial state was 0.24 cpm for the control group and 0.25 cpm for the patient group. There was no significant difference on the net changes of dominant frequency from the fasting state to the postprandial state between two groups ($P > 0.05$). The pre- and postprandial dominant EGG powers were 28.5 ± 1.43 dB and 31.8 ± 1.14 dB ($P < 0.05$) in the patients and 30.32 ± 1.27 dB and 32.56 ± 0.85 dB ($P < 0.02$) in the controls. The net change of dominant EGG power from the fasting state to the postprandial state was 3.3 dB for the control group and 2.24 dB for the patient group. There was no significant difference on the net changes of dominant power from the fasting state to the postprandial state between two groups ($P > 0.05$).

Percentage of Normal Slow Waves. Compared with healthy controls, the patients showed a lower percent-

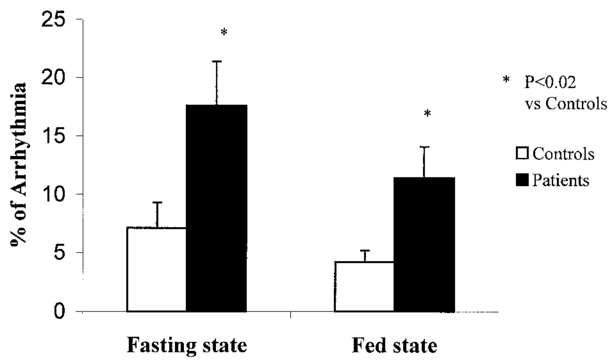

Fig 2. Percentage of arrhythmia in patients and healthy controls in both fasting state and fed state. Compared with controls, the percentage of arrhythmia in patients was significantly higher in both states ($P < 0.02$).

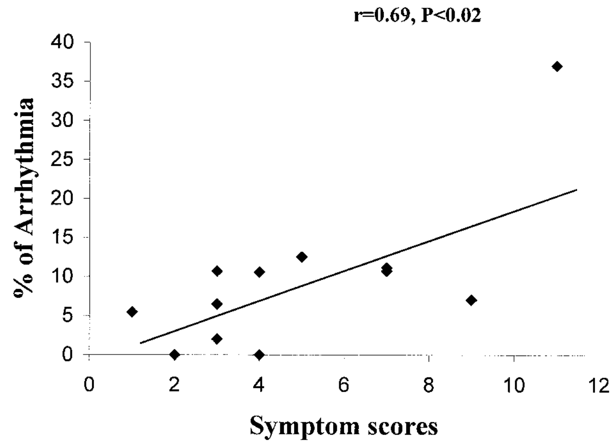

Fig 4. Correlation between the symptom score and the percentage of arrhythmia in symptomatic patients in the fed state. A significant positive correlation was present. ($r = 0.69$, $P < 0.02$).

age of normal 2 to 4-cpm slow waves in both fasting state and fed state. However, the difference was not statistically significant (fasting state: 68.81 ± 5.27% vs 79.45 ± 4.01%, $P = 0.07$; fed state: 79.58 ± 4.31% vs 85.72 ± 1.59%, $P = 0.1$).

Percentage of Gastric Arrhythmia. Compared with the healthy controls, the patients showed a significantly higher percentage of arrhythmia (no obvious rhythmicity observed in the EGG) in both fasting and fed state (Figure 2). The percentage of arrhythmia in the fasting state was 7.1 ± 2.2% for the control group and 17.6 ± 3.8% for the patient group ($P < 0.02$). The percentage of arrhythmia in the postprandial state was 4.2 ± 1.0% for the control group and 11.4 ± 2.7% for the patient group ($P < 0.02$).

Instability Coefficient of Dominant Frequency. In addition, the patients showed a significantly higher instability coefficient of the dominant frequency in the fasting state than in the controls (Figure 3), but not in the fed state. The instability coefficient of the dominant frequency in the fasting state was 0.29 ± 0.18 for the control group and 0.51 ± 0.06 for the patient group ($P < 0.0008$). The instability coefficient of the dominant frequency in the postprandial state was 0.27 ± 0.02 for the control group and 0.33 ± 0.05 for the patient group. No significant difference was found in the postprandial state between two groups ($P > 0.05$).

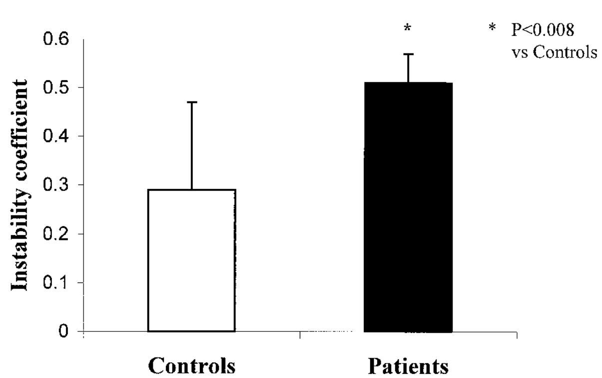

Fig 3. Instability coefficient of dominant frequency in the fasting state in patients and controls. The instability coefficient was significantly higher in patients compared with healthy controls ($P < 0.008$).

Symptom Scores. The average total symptom score was 3.93 ± 0.84 for the patients and 0 for the healthy controls. Twelve of the 15 patients (80%) had various gastrointestinal symptoms. The correlation of the total symptom score and each of the EGG parameters was computed in these 12 symptomatic patients. A relatively weak but significant correlation between the total symptom score and the percentage of arrhythmia in the symptomatic patients was found in fed state ($r = 0.69$, $P < 0.02$; Figure 4), but not in fasting state. There was no correlation between the symptom score and any of other EGG parameters.

DISCUSSION

In this study, we have found that the patients after bone marrow or stem cell transplant showed an excessive amount of arrhythmia that was correlated with gastrointestinal symptoms in symptomatic patients. In addition, there was an increased variation in the frequency of the gastric slow wave.

A significantly higher percentage of arrhythmia was found in the patients with bone marrow or stem cell transplantation. In addition, the normal percentage of normal 2 to 4-cpm slow waves was also lower in the patients, although the difference did not reach statistical significance. A recent study by DiBaise et al studied the effect of stem cell transplantation on gastric myoelectrical activity (34). Instead of comparing the patients after stem cell transplantation with healthy controls, they studied the difference before and after stem cell transplantation. Gastric dysrhythmia was reported at baseline. Normalization of dysrhythmia was noted immediately after the transplantation. The patients were followed for 28 days. In this study, however, gastric myoelectrical activity was recorded at about 23 months after the transplantation.

The EGG pattern in healthy subjects has been reported in numerous previous studies (10, 11, 16, 27). In these studies, the percentage of 2- to 4-cpm slow waves in healthy subjects was above 70% in both fasting state and fed state, and there was a significant postprandial increase in dominant frequency and dominant power in healthy subjects. An EGG was defined as abnormal if the percentage of 2- to 4-cpm slow waves was below 70% in either fasting state or fed state or a postprandial increase in dominant power was less than 0 dB (20, 21, 25, 26). Using this definition, we found 8 of the 15 patients (53%) had abnormal EGG in the fasting state and 4 of the 15 patients (27%) had abnormal EGG in the fed state. The response to the test meal in the patients was, however, normal, similar to the controls: there was a significant postprandial increase in the dominant frequency and dominant power.

Compared with the controls, the patients in this study showed a significantly higher instability coefficient of gastric slow wave frequency in the fasting state. Since the instability coefficient reflects the minute-by-minute variation of slow wave frequency, a higher value represents more unstable gastric slow wave frequency. Unstable slow wave frequencies or high instability coefficients have been previously reported in various patient groups with gastric motor disorders. Lin et al reported that patients with functional dyspepsia showed a higher value of the instability coefficient in both fasting state and fed state (27). Riezzo et al found that the coefficient of variation of gastric frequency during pregnancy was significantly higher than after voluntary interruption of pregnancy (19). Chen et al reported that the instability coefficient in pediatric patients with functional dyspepsia was significantly higher in comparison with healthy controls in both fasting state and fed state (9). Geldof et al reported that instability of the gastric pacemaker frequency was present in patients with unexplained nausea and vomiting (31). In patients with cervical spinal cord injury, however, Lu et al reported that the pre- and postprandial instability coefficient of the dominant slow wave frequency was not significantly different from the healthy controls (24).

In this study a weak but significant correlation was found between the percentage of arrhythmia and dyspeptic symptoms in fed state. A similar correlation was reported in the literature, although there has been a lack of consistency (23, 27, 30–32, 35–37). Dyspeptic symptoms were reported to be correlated with the postprandial dominant power change of the EGG (9, 30), the percentage of normal slow waves (31), or the percentage of tachygastria (36). There were also a number of studies suggesting disassociation of dyspeptic symptoms with any of the EGG parameters (23, 27, 32), although it has been well accepted that gastric dysrhythmia is associated with gastric motor disorders (11, 31, 38).

Although significant, the disturbance (a higher percentage of arrhythmia) observed in gastric slow waves was not substantial. The percentage of normal slow waves was marginally decreased ($P = 0.07$) in comparison with the controls in the fasting state and the difference was even smaller in the fed state. We believe that the abnormalities observed in these patients were attributed to their dyspeptic symptoms, rather than the transplantation itself. Actually, DiBaise et al studied the effect of transplantation (they recorded the EGG right before and after transplantation) on the EGG and showed a negative result, although abnormalities were noted in the baseline recording before the transplantation (34). However, the correlation of the EGG abnormalities with dyspeptic symptoms observed in this study suggests that the EGG may be used in clinical gastroenterology as a noninvasive tool to identify gastric motility disorder in patients after bone marrow or stem cell transplantation and thus to treat symptomatic patients with prokinetic agents.

In conclusion, patients with bone marrow or stem cell transplant have impaired gastric myoelectrical activity, including a higher prevalence of gastric dysrhythmia and less unstable gastric slow wave frequency.

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