Effects of Epalrestat, an Aldose Reductase Inhibitor, on Diabetic Neuropathy and Gastroparesis

Hiroshi OKAMOTO, Masahiro NOMURA*, Yutaka NAKAYA**, Kohzou UEHARA*, Ken SAITO***, Masaru KIMURA, Kazumasa CHIKAMORI and Susumu ITO*

Abstract

Objective Diabetic patients with severe autonomic nervous disorder show delayed gastric emptying accompanied by diabetic gastroparesis, which decreases the electric activity of the stomach associated with gastric motility. It is reported that epalrestat, an aldose reductase inhibitor, is useful for treating diabetic neuropathy. Therefore, we evaluated whether this drug improves the decreased gastric motility in diabetic patients.

Methods The present study evaluated the electro-gastrograms (EGG) and autonomic nervous activity in 15 healthy volunteers (N group), and in 15 diabetic patients before and after the administration of epalrestat (DM group). Autonomic nervous activity was evaluated by spectral analysis of heart rate variability. The EGGs were recorded before and after oral administration of epalrestat (3 months or more) in the DM group.

Results The dominant frequency of EGG was 3 cycles/min (cpm) in the N group. However, these 3 cpm waves disappeared with bradygastria, and postprandial increases in the peak powers of EGG were not observed in the DM group. Both the amplitude of 3 cpm waves and the postprandial peak powers were significantly increased after the administration of epalrestat. The parameters of autonomic nervous activities (LF power, HF power, and the LF/HF ratio) were significantly lower in the DM group before the administration of epalrestat than in the N group. However, these parameters were improved after the administration of epalrestat.

Conclusion Since gastroparesis is a form of diabetic dysautonomia, complication by gastroparesis may influence blood sugar control and the absorbance of oral antidiabetics. Epalrestat significantly increased the amplitude of 3 cpm waves on EGG and improved the spectral analytical parameters of heart rate variability. These findings suggest that epalrestat is useful for the treatment of diabetic gastroparesis. (Internal Medicine 42: 655–664, 2003)

Key words: heart rate variability, electrogastrogram, autonomic nerves, diabetes mellitus

Introduction

Diabetic gastroparesis was first reported by Rundles (1) in 1945, and Kassander (2) named the condition gastroparesis diabeticorum in 1958. Diabetic patients with severe autonomic nervous disorder show delayed gastric emptying accompanied by gastroparesis, which decreases electric activities of the stomach associated with gastric motility (3). There have been many reports that epalrestat, an aldose reductase inhibitor, is useful for treating diabetic neuropathy (4, 5). However, the effect of epalrestat on gastric motility has not been studied extensively in diabetic patients. The present study evaluated the gastric motility and autonomic nervous activity using electrogastrography (EGG) and spectral analysis of heart rate variability before and after the administration of epalrestat.

Methods

Subjects

The subjects consisted of 15 healthy volunteers (N group: 8 men and 7 women; mean age, 56.3±6.5 years) and 15 patients with type 2 diabetes mellitus (DM group: 7 men and 8 women; mean age, 59.1±7.8 years). Subjects of the N group had no history of cardiac disorder, no physiological abnormalities, a systolic blood pressure of <140 mmHg, a diastolic blood pressure of <90 mmHg at rest, normal standard ECG,
Table 1. Patient Characteristics in DM Group before and after Administration of Epalrestat

<table>
<thead>
<tr>
<th></th>
<th>Before administration of epalrestat (n=15)</th>
<th>After administration of epalrestat (n=15)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>59.1±7.8</td>
<td></td>
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<tr>
<td>Sex (M/F)</td>
<td>7/8</td>
<td></td>
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<tr>
<td>Treatment (cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>13 (86.7%)</td>
<td></td>
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<tr>
<td>Insulin</td>
<td>2 (13.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from diagnosing DM (yr)</td>
<td>9.8±5.6</td>
<td>185±45</td>
<td>ns</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>198±52</td>
<td>185±45</td>
<td>ns</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.53±2.9</td>
<td>7.49±3.5</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetic dysautonomia</td>
<td>8 (53.3%)</td>
<td>5 (26.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Abdominal symptom</td>
<td>5 (26.7%)</td>
<td>2 (13.3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>(constipation and/or diarrhea)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.6±5.3</td>
<td>131.8±4.9</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.3±6.7</td>
<td>86.8±5.6</td>
<td>ns</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12 (80.0%)</td>
<td>10 (66.7%)</td>
<td>ns</td>
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</table>

Values are expressed as mean±SD. ns indicates non-significant; FBS: fasting blood sugar level, HbA1c: glycohemoglobin.

Diabetic patients who fulfilled the following inclusion criteria were diagnosed as having type 2 diabetes mellitus and enrolled in the DM group: those showing venous fasting plasma glucose levels ≥126 mg/dl, those showing plasma glucose levels ≥200 mg/dl at 2 hours after oral administration of 75 g of glucose (75 g OGTT), or those showing increased casual plasma glucose levels (≥200 mg/dl) on two or more occasions.

Table 1 shows the patient characteristics in DM group before and after administration of epalrestat. Among patients with diabetes mellitus (DM) treated at the outpatient or inpatient department of Tokushima University Hospital, we selected only those without organic gastrointestinal disorders as determined by gastrofiberscopy. In this group, 13 patients were receiving oral antidiabetics (sulfonylurea hypoglycemic agents), and the remaining 2 were receiving insulin therapy. DM patients treated with drugs containing vitamin B12, peripheral vasodilators, analgesics, antiepileptics, herbal medicine, or other vitamin preparations were excluded from the study. In addition, the dose of antidiabetics was fixed during the study period.

The mean duration of DM was 9.8±5.6 years, and the mean percentage of glycohemoglobin (HbA1c) was 7.53±2.9%. Since hypertension influences autonomic nervous activities, DM patients receiving hypotensive agents or those showing blood pressure of 140/90 mmHg or over were excluded. Eight DM patients (53.3%) had diabetic dysautonomia. In the present study, DM patients with various symptoms associated with autonomic disorders, such as dyshidrosis, vasomotor disorder, splanchic nervous disorder, impotence, or bladder disorder, or those who had a coefficient of variation of R-R intervals (CV_R_R) below the normal value for the respective age group, were diagnosed as having diabetic dysautonomia. Five DM patients (26.7%) complained of abdominal symptoms such as constipation or diarrhea.

On the night before the examination, all subjects fasted overnight after 21:00 and the studies were performed between 7:00 and 12:00 in the morning. The subjects ate breakfast at 10:00 in the morning. Holter’s ECG and percutaneous
Effects of Epalrestat on Gastroparesis

A. Fasting

4-channel EGG wave

<table>
<thead>
<tr>
<th>Channel</th>
<th>Voltage</th>
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<tbody>
<tr>
<td>1</td>
<td>500 μV</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>500 μV</td>
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<tr>
<td>4</td>
<td>500 μV</td>
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FFT

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<th>Power</th>
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<tbody>
<tr>
<td>1</td>
<td>0 μVpp</td>
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<tr>
<td>2</td>
<td>400 μVpp</td>
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B. 30 min after meal

4-channel EGG wave

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<tr>
<th>Channel</th>
<th>Voltage</th>
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<tbody>
<tr>
<td>1</td>
<td>500 μV</td>
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<td>1</td>
<td>0 μVpp</td>
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<td>2</td>
<td>400 μVpp</td>
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Figure 2. EGG waves and FFT analysis of the respective EGG waves obtained during fasting and 30 minutes after a meal in the N group. Panel A: EGG waves (left side) and FFT analysis (right side) of 4 channels during fasting. Panel B: EGG waves (left side) and FFT analysis (right side) of 4 channels 30 minutes after meal. EGG: electrogastrograhy, cpm: cycle per minute, FFT: fast Fourier transform, μVpp: microvolt peak to peak.

EGG were serially recorded. Before the examination, written informed consent was obtained from all subjects.

Percutaneous electrogastrography

The EGG was recorded using a portable electrogastrographic recorder (NIPRO EG; A&D, Tokyo, Japan). As shown in Fig. 1, 4 surface electrodes (CH1–CH4) were placed on the abdominal skin over the stomach, and the central electrode (N) was placed on the line between the navel and the processus xiphoideus, in the center. The EGG was recorded by bipolar leads from 1 central electrode and 4 surface electrodes. The EGG data were recorded at a sampling cycle of 1 second, with a sampling frequency of 2.1 to 6.0 cycle/min (cpm). Data recording was 13 bit, and the influence of respiration was completely removed using band-pass filter between 2.1 cpm (roll-off, 18 dB/octave) and 5.4 cpm (roll-off, 48 dB/octave). In addition, the influence of body movement was minimized using a linear phase filter to decrease the strain of EGG signals (6).

EGG data were transferred to a personal computer (Windows 2000) via RC232C, and 512 data sets were analyzed by fast Fourier transformation (FFT) using EG software (NIPRO ESC1; A&D, Tokyo, Japan). During the analysis of the EGG, mean values of dominant frequency and their peak amplitude (peak powers) were respectively obtained at each channel (CH1–CH4).
A. Fasting

4-channel EGG wave

FFT

B. 30 min after meal

4-channel EGG wave

FFT

Figure 3. EGG waves and FFT analysis of the respective EGG waves obtained during fasting and 30 minutes after a meal in the DM group before the administration of epalrestat. Panel A: EGG waves (left side) and FFT analysis (right side) of 4 channels during fasting. Panel B: EGG waves (left side) and FFT analysis (right side) of 4 channels 30 minutes after meal. EGG: electrogastrography, cpm: cycle per minute, FFT: fast Fourier transform, Vpp: microvolt peak to peak.

Percutaneous EGG was serially recorded from 1 hour before to 90 minutes after the meal. In the DM group, the EGG was recorded again more than 3 months (mean administration duration, 125.6±25.6 days) after the oral administration of epalrestat (150 mg/day) (Table 1).

Spectral analysis of heart rate variability

Simultaneous with the recording of percutaneous EGG, 2-channel Holter's ECGs (CM5 and CC5 leads) were recorded in the supine position to avoid the influence of positional changes using a Holter's ECG recorder (SM-50; Fukuda Denshi Co., Ltd., Tokyo, Japan). Holter’s ECGs recorded on magnetic tapes were analyzed using a Holter’s ECG analyzer (DMW-9000H), and the data on ECG R-R intervals were input to a personal computer (Windows 2000) via an RS232C cable and analyzed using time-series data-analysis software (Fukuda Denshi Co.).

During spectral analysis of heart rate variability, 512 heart rate data were analyzed based on low frequency components (LF power, 0.04–0.15 Hz), high frequency components (HF power, 0.15–0.40 Hz), and the LF/HF ratio. Extra and missing beats were excluded from analysis of the R-R intervals. We measured LF power, HF power and LF/HF ratio at 6 intervals every hour, and these three parameters were averaged.
B. Fasting

Figure 4. EGG waves and FFT analysis of the respective EGG waves obtained during fasting and 30 minutes after a meal in the DM group after the administration of epalrestat. Panel A: EGG waves (left side) and FFT analysis (right side) of 4 channels during fasting. Panel B: EGG waves (left side) and FFT analysis (right side) of 4 channels 30 minutes after meal. EGG: electrogastrography, cpm: cycle per minute, FFT: fast Fourier transform, Vpp: microvolt peak to peak.

Results

Glycohemoglobin level and abdominal symptom after administration of epalrestat

The mean HbA1c level decreased slightly, not significantly, to 7.49±3.5% in DM group 3 months after the administration of epalrestat. In addition, the numbers of patients with diabetic dysautonomia and those complaining of constipation or diarrhea decreased from 8 (53.5%) to 5 (26.7%), and from 5 (26.7%) to 2 (13.3%), respectively, after administration of epalrestat (Table 1).
**Bradygastria (<2.4 cycle/min)**  
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**Normogastria (2.4~3.6 cycle/min)**  
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<th>NDM-E</th>
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**Tachygastria (>3.6 cycle/min)**  
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<tr>
<th>NDM-E</th>
<th>DM</th>
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Means±SD

Figure 5. Comparison of peak power amplitudes by FFT analysis in the three frequency ranges in the N group and DM group before and after the administration of epalrestat: bradygastria (<2.4 cpm), normogastria (2.4~3.6 cpm), and tachygastria (>3.6 cpm). DM-E: DM group after the administration of epalrestat, DM: DM group before the administration of epalrestat. FFT: fast Fourier transform.

**EGG waves and FFT analysis in the N group**

Figure 2 shows the representative case of 4-channel EGG waves and the results of FFT analysis obtained during fasting and 30 minutes after a meal in the N group. Three cpm waves were observed on 4-channel EGG patterns over a 15-minute period both during fasting and 30 minutes after a meal.

FFT analysis of EGG waves showed a dominant frequency of 3.2 cpm and a mean peak power amplitude of about 230 μV during fasting. However, EGG waves at 30 minutes after a meal showed an increased amplitude compared to those obtained during fasting. FFT analysis demonstrated that the dominant frequency and mean peak power amplitude of EGG waves obtained 30 minutes after a meal (3.3 cpm and 300 μV, respectively) were larger than those obtained during fasting.

**EGG waves and FFT analysis in the DM group**

Figure 3 shows the representative case of EGG waves and the results of FFT analysis obtained during fasting and 30 minutes after a meal in the diabetic patients. The regularity of the 3 cpm waves observed in healthy subjects was disturbed in the EGG waves obtained both during fasting and postprandially in the diabetic patients. FFT analysis demonstrated a decreased peak power amplitude of 3 cpm waves during fasting, in addition to the presence of peak waves at a frequency below 2.4 cpm. The postprandial EGG patterns showed an increase in the amplitude of 3 cpm waves compared to those obtained during fasting. FFT analysis also demonstrated that the peak amplitude of 3 cpm waves obtained postprandially tended to be higher than during fasting. However, EGG waves of 2.4 cpm or below were still observed in FFT analysis.

Figure 4 shows the EGG waves and the results of FFT analysis obtained during fasting after 4 months of treatment with epalrestat (150 mg/day, oral administration), and 30 minutes after a meal in the same patients as in Fig. 3. Regular 3 cpm EGG waves were more clearly observed both during fasting and after a meal than at baseline. Thus, FFT analysis demonstrated an increase in the amplitude of 3 cpm waves and the amplitude of EGG waves with a low frequency (<2.4 cpm) was markedly decreased. EGG waves after a meal and FFT analysis demonstrated that the mean power amplitude of the 3 cpm waves was increased to 75μV.

**Comparison of FFT analysis on EGG waves between the N and DM groups before and after the administration of epalrestat**

Figure 5 shows the comparison of peak power amplitudes obtained by FFT analysis of three frequency ranges, bradygastria (<2.4 cpm), normogastria (2.4~3.6 cpm), and tachygastria (>3.6 cpm), in the N and DM groups before and after the administration of epalrestat. Although the peak power amplitude did not significantly increase during tachygastria, the peak power amplitude during normogastria (2.4~3.6 cpm) was significantly lower in the DM group before epalrestat administration than in the N group. Moreover, the peak power amplitude during bradygastria (<2.4 cpm) was decreased after the administration of epalrestat in the DM group.

Figure 6 shows the comparison of 3 cpm peak power amplitudes between the N and DM groups before and after a meal. The peak power amplitudes were significantly increased in the N group after a meal, but not in the DM group. However, postprandial increases in peak power amplitudes were observed in the DM group after the administration of epalrestat.
Effects of Epalrestat on Gastroparesis

Comparison of spectral analysis of heart rate variability between the N and DM groups before and after the administration of epalrestat

Figure 7 shows two representative cases of the circadian rhythms of autonomic nervous activity in the N (panel A) and DM (panels B and C) groups. In the case of a healthy volunteer, HF power, an index of parasympathetic nervous function, was higher during the night than during the day. In addition, changes in LF power almost mirrored the patterns of HF power. In the case of a diabetic patient, however, the HF and LF powers decreased (panel B) and the normal circadian rhythms of autonomic nervous activity observed in the healthy volunteer, did not appear. However, the normal circadian rhythms of autonomic nervous activity did appear in this diabetic patient after the administration of epalrestat, in addition to increased HF and LF powers (panel C).

Figure 8 shows the comparison of the LF power, HF power and LF/HF ratio between the N and DM groups before and after the administration of epalrestat. Before the administration of epalrestat, both the LF and HF powers were significantly lower in the DM group than in the N group, and these powers significantly increased after the administration of epalrestat.

Correlation between spectral analysis of heart rate variability and EGG waves

The relationship between autonomic nervous functions and gastric motility was evaluated based on the correlation between 3 parameters of autonomic nervous functions obtained by spectral analysis of heart rate variability and EGG parameters in the N and DM groups before the administration of epalrestat. HF power was positively correlated with normogastria (r=+0.56, p<0.05), and negatively correlated with bradygastria (r=-0.63, p<0.05) (Fig. 9). However, there were no significant correlations among LF power, the LF/HF ratio, and the respective EGG parameters.

Discussion

Gastroparesis is a form of diabetic dysautonomia that occurs in 20–50% of diabetic patients (7, 8). Patients with gastroparesis are often asymptomatic, but diabetic gastroparesis may influence the absorption of oral antidiabetics and glycemic control. Although aldose reductase inhibitors have been reported to be useful for treating diabetic neuropathy, few studies have evaluated their effects on diabetic...
gastroparesis. In the present study, epalrestat, an aldose reductase inhibitor, significantly increased the number of 3 cpm waves on EGG and improved the spectral analytical parameters of heart rate variability, suggesting that epalrestat may be useful for the treatment of diabetic gastroparesis.

**EGG waves in patients with diabetic gastroparesis and the effects of epalrestat**

Since the gastric pacesetter potential is disturbed by an autonomic nervous disorder, diabetic patients complicated by dysautonomia frequently complain of nausea, epigastric fullness, regurgitation, and bloating, in addition to hyperglycemia and delayed gastric emptying (9). However, it has been reported that examination of autonomic nervous functions and glycosylated hemoglobin are not useful for predicting the occurrence of diabetic gastroparesis (10–12), and that the manifestation of subjective symptoms is not significantly correlated with the severity of visceral neuropathy. Other studies, however, have reported that the occurrence of diabetic gastroparesis was closely related to the results of heart rate variability analysis (13, 14). These findings suggest that the treatment of diabetic gastroparesis should be initiated from the early stage and before the appearance of subjective symptoms, based on the results of an easy and simple assessment of gastrointestinal motility.

Previously, nuclear scintigraphy, the gastric tube method,
Heart rate variability is a useful index for evaluating the nervous activity (24-30).

In 1922, Alvarez et al first reported the EGG technique, which facilitates percutaneous recording of electric activities of the stomach associated with gastric motility (21). Since recent advances in computer technology and digital filters have facilitated stable recording of EGG, many studies have reported the clinical usefulness of this method. The EGG is able to reflect both the electrical control activity and electrical response activity of the gastric smooth muscle. The electrical control activity is a spontaneous action potential generated from a gastric motility pacemaker located in the upper gastric body near the greater curvature, and is transferred to the pylorus at a frequency of 3 cpm (3). Although the electrical control activity regulates gastric motility, it is not associated with gastric motility. However, the electrical response activity is induced by gastric contraction. Experimentally, it has been demonstrated that EGG patterns are similar to electrical activities and motion patterns directly recorded on the mucosal or serous surface of the stomach.

A decrease in the amplitude of 3 cpm waves and an increase in the size of spectral components of bradygastria and tachygastria by EGG have been reported in patients with diabetic gastroparesis (23). In the present study, the DM group showed a decrease in the amplitude of 3 cpm waves and a significant increase in the amplitude of abnormal spectral components of bradygastria before the administration of epalrestat, resulting in the observation of a bimodal FFT wave. However, the spectra of normogastricia around 3 cpm increased after the administration of epalrestat, suggesting the improvement of diabetic gastroparesis.

Increased polyol metabolism is likely to be involved in the development of diabetic neuropathy. Since it inhibits polyol metabolism, epalrestat has been reported to be useful for relieving numbness, pain, abnormal paresthesia, and abnormal heart rate variability induced by diabetic neuropathy (5). Though there have been no previous studies on the efficacy of epalrestat for diabetic gastroparesis, the present results suggest that epalrestat should also be useful for treatment of this condition.

**Effects of epalrestat on spectral analytical parameters of heart rate variability**

Heart rate variability is a useful index for evaluating the influence of the autonomic nervous system on cardiac rhythm. And in recent years, the spectral analysis of heart rate variability has been greatly facilitated by the advances in personal computers. Spectral analyses of heart rate variability have revealed two peaks: LF power (0.04–0.15 Hz) and HF power (0.15–0.40 Hz). LF power reflects sympathetic nervous activity modified by parasympathetic nerves, while HF power reflects parasympathetic nervous activity. In addition, the LF/HF ratio may reflect the balance of sympathetic nervous activity (24–30).

In a study by Howorka et al (31), spectral analysis of heart rate variability in diabetic patients revealed decreases in the power spectra. In the present study, spectral analysis of heart rate variability before the administration of epalrestat showed decreased LF and HF powers, which were improved after the administration of epalrestat.

Strict blood sugar control is important in patients with diabetic dysautonomia. However, previous studies have confirmed that epalrestat is useful for improving or preventing the development of diabetic cardiac dysautonomia, because epalrestat inhibits polyol metabolism.

**Correlation between spectral analysis of heart rate variability and gastric motility**

It has been reported that diabetic gastroparesis is not associated with indices of diabetic dysautonomia. However, Nakamura et al (13) reported that coefficients of variation (CV\textsubscript{r.r}) obtained by time-domain analysis of heart rate variability were closely correlated with gastric motility evaluated by the acetoaminophen and isotope methods. Furthermore, Ziegler et al (14) reported that gastric motility evaluated by the [13C]octanoic acid breath test was correlated with dysautonomia evaluated by CV\textsubscript{r.r}. However, few studies have reported on the relationship between the spectral analytical parameters of heart rate variability and gastric motility. In the present study, HF power, an index of parasympathetic nerve functions, was significantly correlated with peak power values of EGG and gastric motility at a frequency between 2.4 and 3.6 cpm. Patients with diabetic gastroparesis are often asymptomatic during the early stage.

**References**

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