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Impairment of gastrointestinal motility by nitrate administration: evaluation based on electrogastrographic changes and autonomic nerve activity

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SUMMARY

Background: Nitrates decrease the tone of the lower oesophageal sphincter, and may thus induce gastro-oesophageal reflux.

Aim: In the present study, we evaluated electrogastrographic changes and heart-rate variability before and after the administration of nitrates.

Methods: In 15 patients with chest pain treated with nitrates, electrocardiography and percutaneous electrogastrography were performed before and after administration of nitrates. Autonomic nervous system function was evaluated by spectral analysis of heart-rate variability and serial changes in low frequency and high frequency power, and the low frequency/high frequency ratio were compared. Electrogastrograms were analysed by obtaining peak power amplitudes and their dominant frequencies.

Results: After the administration of nitrates (isosorbide dinitrate), high frequency power, an index of parasympathetic nervous activity, was significantly decreased, whereas the low frequency/high frequency ratio, an index of sympathetic nervous activity, was significantly increased. The mean peak amplitude of the electrogastrogram significantly increased postprandially both before and after treatment. After isosorbide dinitrate treatment, however, mean peak amplitudes after a meal were significantly lower than those obtained before treatment. The mean dominant frequency of the electrogastrogram did not vary before and after treatment.

Conclusions: The present study suggests that nitrates inhibit gastrointestinal motility by decreasing autonomic nervous activity.

INTRODUCTION

Nitrates inhibits the gastric motility because they promote the sympathetic nervous activity and decrease the parasympathetic nervous activity. Moreover, nitrates may affect gastric motility by decreasing lower oesophageal sphincter (LES) pressure.[1] The aged frequently take medications known to decrease LES pressure, which may promote gastro-oesophageal reflux.[2, 3] Bult *et al.*[4] reported that the L-arginine–nitric oxide system is a nonadrenergic, noncholinergic nerve inhibitory neurotransmitter present in the peripheral nervous system of the gastrointestinal tract. Further, Tottrup *et al.*[5] reported that nitric oxide may be a nonadrenergic, noncholinergic nerve inhibitory neurotransmitter in the LES, while Preiksaitis *et al.*[6] reported that nitric oxide is involved in LES relaxation. In addition, nitric oxide induces gastric relaxation,[7] and the administration of exogenous nitric oxide may also decrease LES pressure and induce gastric relaxation.

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Patients with gastro-oesophageal reflux disease may exhibit chest pain, which is often mistakenly diagnosed as angina pectoris, thus possibly leading to unnecessary administration of nitric acid drugs. To our knowledge, however, no clinical studies have investigated the effect of nitrates on gastric motility. We therefore evaluated electrogastrograms and autonomic nervous activity in aged subjects treated with nitrates.

SUBJECTS AND METHODS

Subjects

The subjects were 15 elderly people >65 years old (mean age 72.4 ± 5.6 years) with no history of cardiopulmonary disease. All subjects were clinically diagnosed as healthy. They showed normal findings on physical examination and resting blood pressures of 140/90 mmHg or less. They showed no abnormalities on standard 12-lead electrocardiogram, chest X-ray, urinalysis, or haematological and biochemical examinations. In addition, no significant findings were obtained during upper gastrointestinal endoscopy. Although they had consulted our hospital with angina pectoris-like thoracic discomfort, no significant electrocardiogram changes were detected. During the interval between the initial consultation and further examinations of the heart, their clinical course was followed by applying an isosorbide dinitrate tape to their chest. Those with diabetes mellitus or hypertension and those receiving drugs affecting the autonomic nervous system were excluded from the study. Written informed consent was obtained from all subjects before examination.

Electrogastrograms (Nipro EG, Tokyo, Japan) were recorded before and after treatment with isosorbide dinitrate, and autonomic nervous activity was evaluated by electrogastrograms and spectral analysis of heart-rate variability.

Electrogastrogram analysis

As shown in Figure 1, four surface probe electrodes (CH1–CH4) were placed around the stomach, and a central electrode (C) was placed equidistant between the umbilicus and xiphoid process. The electrogastrogram then was recorded by bipolar leads between N and each of the four surface probe electrodes. Electrogastrogram waveforms in the frequency band-pass between 2.1 and 6.0 cycles/min were measured at a sampling cycle of 1 s. Data was recorded at a 13-bit sample rate, and the influence of respiration was completely removed using a 10th filter. In addition, using a linear phase filter, the influence of body movement was minimized to reduce artefacts in the electrogastrogram signals. Data recorded with a ambulatory electrogastrogram apparatus (weight 300 g) were transferred to a personal computer (Windows 2000) via a RC232C cable, and fast Fourier transformation analysis was performed at 512 points using specialized software for electrogastrogram analysis (Nipro ESC1, A & D, Tokyo), during which mean dominant frequencies of the 4-channel electrogastrogram and their peak amplitudes (peak powers) were calculated.

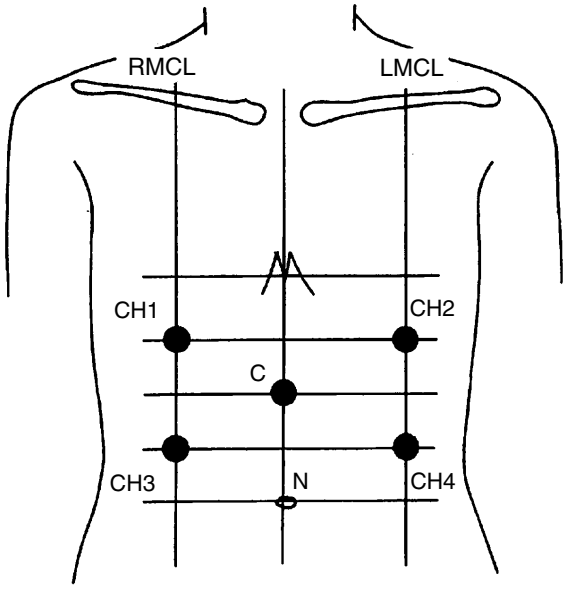

Figure 1. Electrode positions for recording the electrogastrogram. RMCL, right mid-clavicular line; LMCL, left mid-clavicular line; N, navel; CH1, channel 1; CH2, channel 2; CH3, channel 3; CH4, channel 4; C, central terminal electrode. Four surface electrodes (CH1–CH4) are placed on the abdominal skin over the stomach, and the central electrode (C) is placed on the centre of the line between the navel and the processus xiphoideus. The electrogastrogram was recorded by bipolar leads from one central electrode and four surface electrodes.

Spectral analysis of heart-rate variability

Holter electrocardiogram data recorded on magnetic tape were analysed using a Holter electrocardiogram analyser (DMW-9000H). R–R interval data were input

into a personal computer (Windows 2000) via a RS232C cable for analysis using time series data analysis software (Fukuda Denshi Co., Tokyo, Japan). With regard to spectral analysis of heart-rate variability, data for 256 heartbeats were analysed to obtain the low frequency (0.04–0.15 Hz) and high frequency power (0.15–0.40 Hz), and the low frequency/high frequency ratio. R–R intervals obtained during any onset of arrhythmia were excluded from analysis.

Statistical analysis

All values are expressed as mean ± SD Statistical analysis was performed using paired and unpaired Student's *t*-test, ANOVA, and χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Electrogastrogram and spectral analysis before and after treatment with isosorbide dinitrate

Figure 2 shows the electrogastrogram and results of spectral analysis during fasting (upper panel) and 1 h after a meal (lower panel) in an 85-year-old woman before treatment with isosorbide dinitrate. Approximately 3-cycles/min electrogastrogram waveforms were observed at both time points, and mean amplitude of the electrogastrogram obtained 1 h postprandially was greater than that during fasting. Spectral analysis of these electrogastrogram waveforms revealed that the mean peak amplitude obtained during fasting (51.5 mV) increased (to 87.3 mV) 1 h postprandially. However, mean dominant frequency during fasting (3.3 cycles/min) did not significantly differ from that 1 h postprandially (3.4 cycles/min).

Figure 3 shows the electrogastrogram and results of spectral analysis during fasting (upper panel) and 1 h after a meal (lower panel) from the same woman 1 week after treatment with the isosorbide dinitrate tape. Although approximately 3-cycles/min electrogastrogram waveforms were again observed at both time points, mean amplitude of the electrogastrogram obtained after treatment with isosorbide dinitrate was smaller than that before treatment. In addition, postprandial increases in electrogastrogram amplitude after treatment were smaller than those before. Spectral analysis revealed that the mean peak amplitude during fasting (26.5 mV) increased to 46.3 mV 1 h postprandially. However, the mean dominant frequency during fasting (3.3 cycles/min) only slightly increased to 3.5 cycles/min at 1 h after a meal.

Figure 4 shows a comparison of pre- and postprandial peak amplitude (Figure 4a) and the dominant frequency of the electrogastrogram (Figure 4b) before and after treatment with isosorbide dinitrate. The mean peak amplitude significantly increased postprandially both before and after treatment. After treatment, however, mean peak amplitudes of electrogastrogram obtained during fasting and up to 90 min after a meal were significantly lower than those obtained before treatment. The mean dominant frequency did not significantly vary before and after treatment.

Changes in autonomic nervous activity before and after treatment with isosorbide dinitrate assessed by spectral analysis of heart-rate variability

Figure 5 shows the representative cases of l spectral analysis of heart-rate variabilities in over a 24-h period before and after treatment with isosorbide dinitrate. Before treatment with isosorbide dinitrate, bimodal peaks were observed at 0.04–0.15 Hz (low frequency power zone) and 0.15–0.40 Hz (high frequency power zone). After treatment with isosorbide dinitrate, the high frequency power decreased and low frequency/high frequency ratio increased.

Figure 6 shows a comparison of mean low frequency and high frequency powers and low frequency/high frequency ratios over a 24-h period before and after treatment with isosorbide dinitrate, as assessed by spectral analysis of heart-rate variability. The mean low frequency power did not significantly vary before and after treatment. After treatment, however, mean high frequency power was significantly decreased ($P < 0.05$) and the mean low frequency/high frequency ratio was significantly increased ($P < 0.01$).

DISCUSSION

In the present study, spectral analysis of heart-rate variability showed that oral administration of isosorbide dinitrate increased sympathetic nervous activity and decreased parasympathetic activity. To our knowledge, this study is the first to clinically demonstrate using electrogastrogram that nitrates decrease gastric motility, which may result in relaxation of gastric smooth muscle.

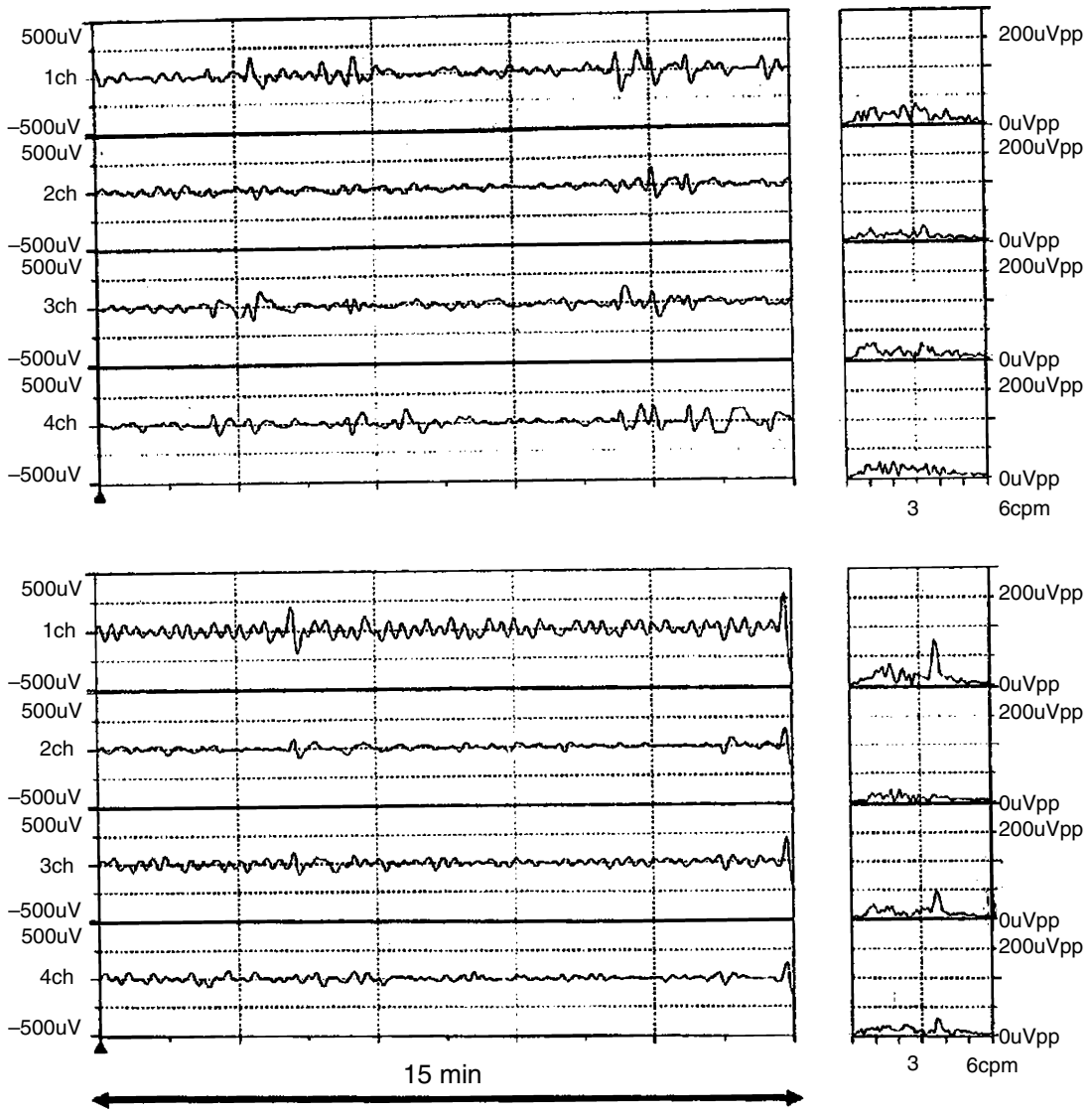

Figure 2. Electrogastrogram and spectral analysis during fasting and 1 h after a meal before treatment with isosorbide dinitrate in an 85-year-old woman. Spectral analysis of these electrogastrogram waveforms reveal that the mean peak amplitude obtained during fasting (51.5 mV) increased to 87.3 mV 1 h postprandially.

Relationship between isosorbide dinitrate and autonomic nervous activity

It was difficult to measure the respective levels of sympathetic and parasympathetic nervous activities. Recently, however, novel procedures using heart-rate intervals have been applied to evaluate autonomic nervous activity. As heart-rate intervals are minutely controlled by both sympathetic and parasympathetic nerves, the level of contribution of the two systems can be serially estimated by heart-rate variability analysis. Heart-rate intervals (R–R intervals) are not uniform, and vary at each heartbeat. The autonomic nervous system minutely controls the sinus rhythm, resulting in heart-rate fluctuation.

In the present study, spectral analysis of heart-rate variability was used to evaluate changes in autonomic nervous activity before and after treatment with isosorbide dinitrate. In this analysis, low frequency power around 0.10 Hz and high frequency power corresponding to a respiratory frequency between 0.2 and 0.4 Hz were observed. From the results of

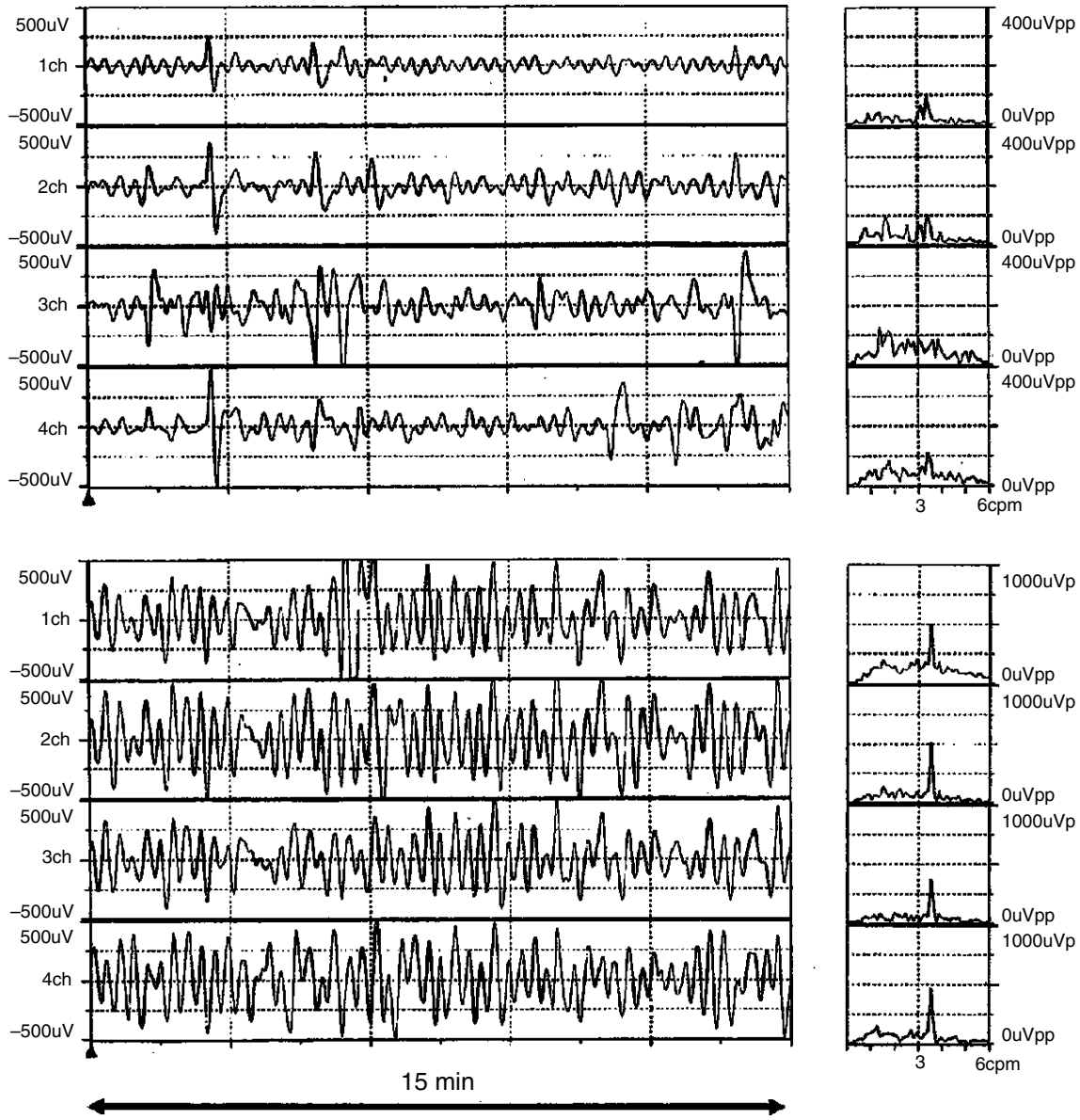

Figure 3. Electrogastrogram and spectral analysis during fasting and 1 h after a meal after 1 week's treatment with isosorbide dinitrate tape in the same subject as in Figure 2. Spectral analysis reveal that the mean peak amplitude during fasting (26.5 mV) increased to 46.3 mV 1 h postprandially. Postprandial increases in electrogastrogram amplitude after are smaller than those before treatment.

pharmacological blocking of sympathetic/parasympathetic nerves and experiments using ganglionectomized animals, low and high frequency power are known to reflect sympathetic nervous activity, mainly modified by parasympathetic nervous activity, and parasympathetic nervous activity, respectively.[8] Furthermore, the low frequency/high frequency ratio may reflect sympathetic nervous activity. The magnitude of these powers may also express autonomic nervous activity.

Pagani *et al.*[9] reported that administration of nitroglycerine compensatively increased sympathetic nervous activity against vasodilative hypotension. We also reported that the intravenous administration of isosorbide dinitrate increased both the low frequency power and the low frequency/high frequency ratio.[10] In the present study, changes in autonomic nervous activity after treatment with isosorbide dinitrate were evaluated by spectral analysis of heart-rate variability, and

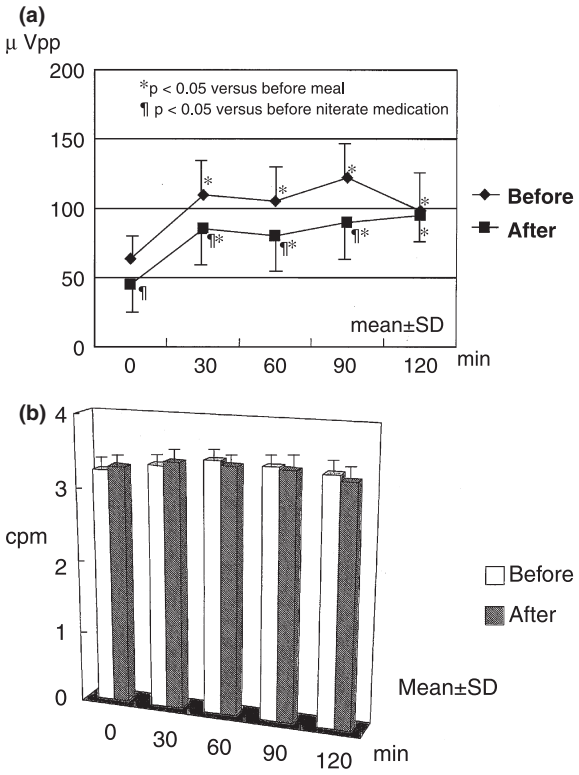

Figure 4. Comparison of pre- and post-prandial peak amplitude (a) and dominant frequency of electrogastrogram (b) before and after treatment with isosorbide dinitrate. The mean peak amplitude significantly increased postprandially both before and after treatment. Dominant frequency of the electrogastrogram did not significantly vary before and after treatment.

decreased high frequency power (an index of parasympathetic nervous activity) and increased low frequency/high frequency ratio (an index of sympathetic nervous activity) were detected.

Parasympathetic nervous activity is closely associated with gastric motility via the hypothalamus and medullary nuclei. Decreased parasympathetic nervous activity is reported to be associated with decreased gastric motility and LES relaxation.[11–14] It has also been reported that gastric motility and emptying are affected by proximal gastric vagotomy.[15] Furthermore, parasympathetic nervous activity is associated with gastric motility, as stimulation of parasympathetic nerves releases various neurotransmitters.[16–20]

Based on these results, we consider that the increased sympathetic nervous activity and decreased parasympathetic nervous activity as detected by spectral analysis of heart-rate variability after treatment with isosorbide dinitrate may induce a functional decrease in gastric motility. The use of nitrates may therefore be closely associated with the occurrence and exacerbation of GERD.

Relationship between nitrates and gastric motility

Any evidences for relaxation of LES due to nitrates were not demonstrated in the present study, as LES function could not be evaluated by electrogastroram. It has been reported that nitrites, calcium antagonists, anticholinergic agents, prostaglandin and thophylline, all of which are more likely to be administered to elderly rather than young patients, decrease LES pressure.[2, 3] Some cases of GERD show an atypical clinical picture and GERD patients frequently complain of non-cardiac chest pain. Calcium antagonists and nitrites are sometimes used to treat cardiac chest pain in these patients, but may in fact exacerbate symptoms if the chest pain is caused by gastro-oesophageal reflux. The results of the present study indicate that cardiac chest pain should be differentiated from chest pain caused by GERD, because the therapeutic approaches to the two conditions are fundamentally different.

In the present study, the mean peak electrogastrogram amplitude of 3 cycles/min was significantly increased postprandially both before and after treatment with isosorbide dinitrate. However, the mean postprandial

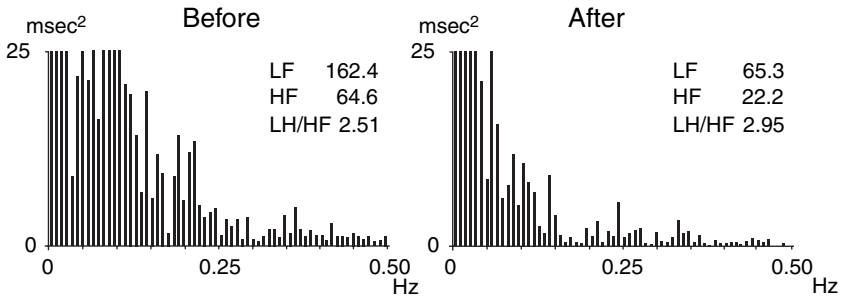

Figure 5. Representative cases of spectral analysis of heart-rate variabilities over a 24-h period before and after treatment with isosorbide dinitrate. After treatment with isosorbide dinitrate, the high frequency power decreased and low frequency/high frequency ratio increased compared with before treatment.

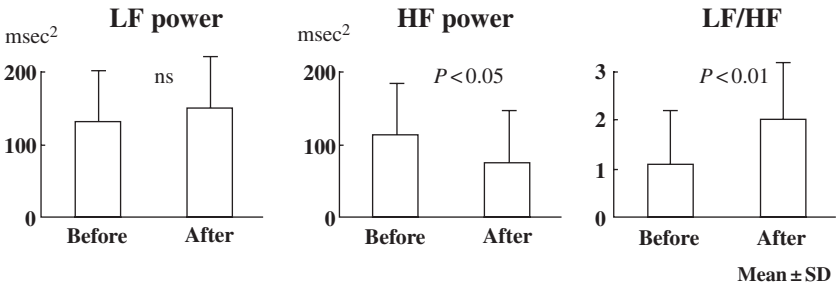

Figure 6. Comparison of mean low frequency and high frequency power and low frequency/high frequency ratio over a 24-h period before and after treatment with isosorbide dinitrate. After treatment with isosorbide dinitrate, high frequency power is significantly decreased and low frequency/high frequency ratio is significantly increased.

peak amplitude obtained after treatment with isosorbide dinitrate was significantly lower than that before treatment. Although the electrogastrogram does not directly reflect gastric motility, the decrease in mean peak amplitude of 3 cycles/min after treatment with isosorbide dinitrate suggests the inhibition of gastric motility.

Nitrates are sometimes administered to elderly patients with non-cardiac chest pain. In the present study, treatment with isosorbide dinitrate inhibited gastrointestinal motility by changing autonomic nervous activity, and may have exacerbated GERD.

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