VECTION-INDUCED GASTRIC DYSRHYTHMIAS AND MOTION SICKNESS

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Abstract

Gastric responses to motion stimuli have been neglected since the 1940's. The overall objective of our three year proposal is to investigate gastric electrical and mechanical activity during vection-induced motion sickness. Specific aims during the first year were: (1) to measure simultaneously the contractile events of the gastric antrum and gastric myoelectric activity in healthy subjects exposed to vection; (2) to determine symptomatic and myoelectric responses of subjects with vagotomy and gastric resections during vection stimuli; and (3) to develop laboratory-based computer systems for analysis of the myoelectric signal. Gastric myoelectric activity was recorded from cutaneous electrodes, i.e. electrogastrograms (EGGs), and antral contractions were measured with intraluminal pressure transducers. Vection was induced by a rotating drum. Gastric electromechanical activity was recorded during three periods: 15 min baseline, 15 min drum rotation (vection), and 15-30 min recovery.

Fifteen healthy men were studied: seven subjects reported mild to severe nausea during vection. In 6 of 7 subjects (86%), nausea was associated with the onset of abnormally rapid EGG frequencies termed tachygastrias. The number of antral contractions did not change significantly during vection, although the trend was toward fewer contractions during vection and recovery. A burst of phasic duodenal contractions was recorded in one subject during severe nausea and retching during vection. Eight healthy subjects reported no symptoms during vection; 6 of the 8 (75%) maintained normal 3 cpm EGG patterns, 1 had respiratory artifact, and 1 had tachygastria. In these asymptomatic subjects, antral contractions did not change significantly during vection or recovery. Preliminary results showed that catecholamine responses in nauseated versus symptom-free subjects were divergent and pretreatment with metoclopramide HCl (Reglan) prevented vection-induced nausea and reduced tachygastrias in two previously symptomatic subjects.

Six subjects with previous vagotomy and various gastric resections were studied. Five of six postoperative subjects reported mild-moderate nausea during vection, and in 3 subjects the EGG frequency and amplitude increased during nausea. The EGG signal was unchanged in two subjects. Intraluminal pressures measured in three subjects were quiescent in all test periods. Only the subject with total gastrectomy was symptom-free during vection.

Running spectral analysis was accomplished with laboratory-based computer systems. The plots are presented herein.

We conclude: In subjects with intact stomachs - (1) Onset of tachygastria or maintenance of 3 cpm EGG patterns discriminates subjects with vection-induced nausea or no symptoms, respectively; (2) Antral contractility did not distinguish symptomatic from asymptomatic groups, but severe nausea and retching were associated with duodenal contractions; and in postoperative subjects - (1) All subjects with vagotomy and gastric remnants were susceptible to vection-induced nausea, indicating a role for non-vagal pathways or other neurohormonal fluxes in the genesis of motion sickness; (2) Total gastrectomy appeared protective, suggesting a gastric remnant was necessary for vection-induced nausea.

Gastric electromechanical events induced by vection represent brain-gut interactions which may be relevant to the pathophysiology and treatment of motion sickness and space adaptation syndrome.

II. Introduction

The following report presents accomplishments during the first year (May 1985 - April 1986) of our three year project entitled, "Vection-Induced Gastric Dysrhythmias and Motion Sickness" (NASA Grant NAG 9-118).

Objectives for the first year were:

(1) To measure electrical and mechanical (i.e. contractile) activity of the gastric antrum during vection in healthy subjects (Protocol A4, p. 22 of original proposal); (2) To examine symptomatic and gastric myoelectric responses of subjects with vagotomy and various gastric resections during vection stimuli (Protocol A3, p. 22 of original proposal); and, (3) To develop laboratory-based computer systems for analysis of the gastric myoelectric signals (p. 26 original protocol).

III. Background

As described in the original proposal, gastric responses to motion stimuli have been virtually ignored for the past 40 years. In the 1940's, several investigators described loss of gastric tone and peristaltic contractions in subjects who developed symptoms of motion sickness while positioned in various movement devices (1,2). Despite the fact that most individuals describe symptoms of motion sickness as vague epigastric discomfort and nausea, the relationship between stomach motility and motion sickness has been neglected.

The present investigators have reported that almost 2/3 of subjects who experience illusory self motion or vection develop sweating, epigastric distress and nausea, i.e. symptoms of motion sickness (3). Moreover, normal 3 cycle per minute (cpm) gastric slow wave frequency or "pacemaker" activity shifted to more rapid frequencies (i.e. 5-9 cpm) prior to or concomitantly with the onset of nausea during vection (3). (The 5-9 cpm frequencies, termed tachygastrias, have been previously described in patients with idiopathic nausea and vomiting (4) and gastroparesis (5)). Gastric slow wave frequencies recorded by mucosal or EGG electrodes are virtually identical (6,7). Furthermore, after drum rotation and vection stopped, the nausea resolved, the tachygastrias disappeared and the 3 cpm rhythm usually returned within 20 min in these healthy individuals (3). Thus, the central nervous system (CNS) responses elicited by visual-vestibular mismatch of vection induced symptoms of motion sickness and the objective finding of a shift from 3 cpm EGG activity to tachygastria. Equally important, other individuals remained asymptomatic and maintained a normal 3 cpm gastric rhythm. Thus, measurement of gastric electromechanical events during vection provides a unique setting to investigate brain-gut interactions during motion stimuli.

These findings may be particularly relevant to the space adaptation syndrome (SAS). Symptoms of SAS mimic motion sickness, and visual-vestibular-cerebellar interactions with altered otolithic function may have roles in the SAS (8). Moreover, a recent report indicated Space Lab I astronauts experienced an enhanced sense of vection in microgravity when compared with ground tests (9). Brain-gut interactions such as vection-induced tachygastria may be relevant to the physiology of and treatment approaches to SAS as well as earthly motion sickness.

The neurohormonal changes evoked during vection which disrupt normal 3 cpm gastric pacemaker function are unknown. Labyrinthine stimulation was associated with increased levels of plasma epinephrine and endorphins and with a delay in gastric emptying of a meal (i.e. decreased gastric contractility) (10). Infusion of glucagon disrupts normal gastric rhythms in man (6). Infusion of epinephrine, prostaglandin E_2, and glucagon in dog also causes a shift from normal pacemaker frequency of 5 cpm to canine tachygastrias of 12 cpm (11). The roles of parasympathetic and sympathetic nervous system responses in eliciting or preventing human tachygastria and symptoms of motion sickness during vection are unknown.

Our vection-gastric myoelectric data suggested three related hypotheses regarding the gastric responses to motion stimuli:

Hypothesis 1:
Visual-vestibular sensory mismatch, which occurs during vection, stimulates a "neuro-hormonal" response and outflow from the CNS which disrupts a peripheral physiologic process - normal 3 cpm gastric pacemaker activity. That is, in subjects who develop nausea the normal 3 cpm pattern is disrupted and shifts to tachygastrias. On the other hand, asymptomatic subjects may have different CNS neuro-hormonal outflow in response to vection, or they have "resistant" 3 cpm gastric pacemaker function.

Hypothesis 2:
Vection-induced gastric dysrhythmias are ultimately perceived as epigastric distress and nausea (possibly via vagal afferents) and reinforce or potentiate the ongoing visual-vestibular neural mismatch.

Hypothesis 3:
The preservation of normal 3 cpm gastric rhythm may prevent or diminish symptoms of motion sickness elicited by vection or other motion stimuli.

The studies performed during Year 1 provided data which was relevant to these underlying hypotheses.

IV. Plan of Research - Year 1

Two of the original ten protocols were funded for the first year. The methods and design of investigations are briefly reviewed below:

(1) Methods:

a) Vection - Vection was induced by rotating a drum (91.5 cm x 76.0 cm) around the subjects who were seated within. A chin rest was used to stabilize the head. The inner surface of the drum is covered with 48 alternating black and white vertical stripes, each black and white stripe subtending 15 degrees of the surface (Figure 1). The drum was rotated 60 degrees per second.

b) Electrogastrography - Gastric myoelectric activity was recorded from three electrodes in bipolar configuration positioned on the abdomen as shown in Figure 2. The resulting electrogastrograms or EGGs were recorded simultaneously on a rectilinear recorder (Beckman R612) and magnetic tape (Honeywell 101-1B tape recorder) for visual and computer analysis. The frequency of EGG waves is virtually identical to the frequency of gastric slow waves measured with mucosal electrodes (6,7). Normal slow wave frequency is 3 cpm; tachygastrias range from 4-9 cpm. Additional information concerning EGG recording techniques may be found in Reference (12).

c) Intraluminal pressures - Pressures were recorded from the gastric body and antrum with three solid-state pressure transducers located 5 cm apart on a 6 French flexible catheter (Figure 2). Catheter position within the stomach was verified by fluoroscopy.

d) Respiratory rate was recorded in all subjects with a bellows pneumograph.

e) Computer instrumentation and analysis in the EGG laboratory - The output of the Beckman polygraph was routed to a Sperry Model 500 Personal Computer for purposes of data analysis. The Sperry PC is equipped with a 10 megabyte fixed disk drive, 640 kilobytes of Random Access Memory (RAM), an Intel 8087 math co-processor chip, and a high resolution color monitor. Additional peripheral devices are a Variant Technologies Model VT-700, 26 megabyte streaming tape cartridge drive for mass storage of data; a Metrabyte Model Dash-16 analog to digital (A/D) conversion board which allows acquisition of up to 8 true differential channels of data as well as 4 channels for digital input and output which allow control of laboratory equipment; a Sperry Model 5 dot-matrix printer for rough copies of graphs and hard copies of data; an Everex expansion chassis which provides additional slots for the peripheral device controller cards; and a Hewlett-Packard Model HP7470A plotter for presentation quality and camera ready data plots.

From the polygraph or magnetic tapes, the EGG signal was channeled to the A/D conversion board where it was digitized into a series of discrete numerical voltage levels. Thus, the analog EGG signal was converted to a digital time series which can then be subjected to a wide range of analyses. The A/D conversion unit allowed sampling at a wide range of speeds and the EGG was sampled at a rate of 1 Hertz or once per second. This rate allowed definition of frequencies up to 30 cpm which was more than adequate for the EGG. Once the signal was digitized, it was stored first on disk and then transferred to magnetic tape for long term storage.

The analysis of the EGG signal: The digital signal was first zero centered and linearly detrended. In other words, a simple linear regression line was fitted to the time series and then subtracted. The zero centering procedure was conducted so the time series varies around the value zero which ensured that the time series fulfills the assumptions inherent in spectral analysis. The linear detrending removed

any remaining linear shifts in the signal. The time series may also be subjected to digital filtering to provide a "clearer" time series. That is, any remaining frequencies in the signal higher than those in the EGG may be removed. The time series was then Fourier transformed and the spectral density estimates were calculated. This spectral analysis provided information concerning the frequencies contained in the signal. The typical output of a spectral analysis is a graph showing the strength, or power, of the frequencies present in the original time series. Power may be considered an index of the amplitude of the sine waves of a particular frequency that would be required in order to recreate the original signal. The 0-1 cpm low frequency spectra are difficult to evaluate during the vection experiments because vigorous high amplitude EGG signal responses were often evoked during vection. Thus, if the recording pens "pegged out" for more than 20 s and created "flat" EGG signals, computer analysis showed high power 0-1 cpm activity. Therefore, 0-1 cpm activity is not described in detail. Changes in recording techniques are under study to limit the number of "flats" in the EGG signal.

Spectra are graphed in a pseudo 3-dimensional plot called a "running spectral plot". Such a graph was obtained by conducting spectral analyses on successive segments of the signal, each of which overlaps 75% with the preceeding and subsequent segments. Each separate spectrum represents 4 minutes of real time, with the first line showing the frequency spectrum of minutes 1-4, the second represents minutes 2-5 and so on. This procedure allows easy viewing of frequency changes as a function of time.

(2) Data Analysis

Visual analysis of EGG records was accomplished by counting the number of waves per minute in each test period. The EGG electrode lead with the clearest signal and least artifact was chosen for these analyses.

The same EGG channel was digitized and analyzed by FT (see above). The FT plots are described qualitatively in the report.

Intraluminal pressures were analyzed by counting the number of contractions, the amplitude of each contraction, and by determining a Motility Index (no. of contractions x amplitudes) for each test period. These data were subjected to statistical analysis (i.e. paired and unpaired t-tests). $P<0.05$ was considered significant.

(3) Design

All studies followed the "Protocol A" design shown in Figure 3. Each subject fasted at least four hours before testing. EGG, respiration and intraluminal pressures were simultaneously recorded during the baseline, drum rotation and recovery periods. The subjects indicated the intensity of nausea experienced during vection by marking a 300mm analog scale (0 = no symptoms; 300mm = severe nausea, almost vomited) after the recovery period.

In several subjects, peripheral venous blood samples were obtained af after a 30 min rest period (outside the drum), and then at the end of the 15 min baseline period, and 1, 10 and 20 minutes after drum rotation ceased (i.e. during the recovery period). The latter four samples, then, were drawn while the subject was within the drum. Also, two symptomatic subjects who had developed tachygastria returned 8-12 weeks after the first test and received metoclopramide (20 mg by mouth) before their second trial of vection.

V. Results

A. Vection Studies in Healthy Subjects:

1. Relationship of Antroduodenal Contractile Activity and Vection-Induced Gastric Dysrhythmias and Motion Sickness (Protocol A4).

Fifteen healthy men (ages 22 to 37, mean 26.5 yr) entered the vection protocol with EGG and intraluminal pressure recordings. Time to onset of vection averaged 1.6 min, range 1-2.5 min. Table I summarize the EGG frequency responses in these healthy subjects during the vection protocol. Baseline EGG patterns in the 7 subjects who subsequently developed nausea during vection showed low amplitude intermittent 3 cpm patterns (i.e. poor 3 cpm activity) or flatline in four subjects, clear 3 cpm pattern in one, tachygastria in one and respiratory artifact in one. During vection-induced nausea, tachygastrias were observed in six of the seven subjects; in the other subject, respiratory rhythms obscured the EGG activity. First report of nausea occurred after an average of 6.4 min of vection (range 2-11 min). During the recovery period, 3 cpm patterns returned in three subjects, but tachygastrias were clearly present in three other subjects and respiratory artifact continued to predominate in one. Nausea scores ranged from 29 to 290 indicating the spectrum of intensity of vection-induced nausea. Other symptoms reported by these subjects included warmth, sweating, slight headache, dizziness, faster respiration and "churning" in stomach. (See Appendix A for detailed report of the evolution of symptoms and EGG frequencies during vection.)

Eight subjects reported no nausea during vection and their EGG responses are also shown in Table I. Each subject had a clearly discernible 3 cpm pattern during baseline. During vection, the 3 cpm pattern was maintained in six of the eight subjects; in one subject, respiratory rhythms predominated (this subject reported "sweating"); and in the other subject, a 4-5 cpm tachygastria developed (this subject reported he was "dizzy"). During recovery, clear 3 cpm patterns were present in six subjects; a flatline EGG pattern was seen in one subject, and poor 3 cpm activity was noted in one subject. These latter two subjects were the ones with sweating and dizziness during vection.

Figure 4 shows the EGG recording from Subject (6, MD) who developed nausea during vection: the baseline shows a 3 cpm rhythm; whereas, during nausea the EGG signal contains narrow-based, sharp peaked waves with 7-8 cpm frequency. The 3 cpm pattern reappears during the recovery period as nausea disappears. Figure 5 shows the running spectral analysis (RSA) of the EGG signal from Subject (6, MD). During baseline peaks at 3 cpm are seen. After 3-4 min of drum rotation the subject reported nausea which increased in intensity at 8 to 11 minutes of rotation. Several tachygastria peaks are seen during these times. During the recovery phase the tachygastrias resolved; and little to no 3 cpm activity reappeared during recovery (Figure 5A). Low frequency components 0-1 cpm are seen throughout the recording and indicates both low frequency signals and flat portions of the raw signal.

Figure 6 shows EGG activity in Subject (7, JE) who reported no symptoms during vection. The EGG rhythm during baseline, vection and recovery periods remained clear at 3 cpm. Figure 7 shows the RSA of the entire vection study of Subject (7, JE). Prominent 3 cpm peaks are seen during baseline; the power at 3 cpm decreased slightly during vection but the frequency remained clearly 3 cpm. No tachygastrias developed. Also, fewer 0-1 cpm peaks are seen in Figure 7 reflecting fewer flat portions in the raw EGG signal.

Intraluminal pressure responses during vection studies in 12 healthy subjects are summarized in Table 2. Three of the 15 healthy subjects did not undergo gastric intubation. Thus, the pressure data from five subjects who developed nausea during vection and seven who did not are presented. The range of contractile events in the subjects who developed nausea was marked, ranging from 0 to 42 contractions during the 15 minute baseline period. During vection, the number of contractions decreased in two subjects, increased in one, and was unchanged in two. Compared with baseline the average motility index (MI), which takes into account the amplitude of the contractions, did not change significantly during vection. The mean number of contractions and MI during recovery were less than during baseline or vection, but none of the changes reached statistical significance.

Concerning the seven subjects who had no nausea during vection, the mean number of contractions and MI during baseline (4.1 and 1089.2, respectively) decreased during vection (0.9 and 48.3), but the differences were not significant. Again, the wide range of contractile events (0-12) and MIs (0-3555) among individual subjects was marked. Contractions and MI remained decreased during recovery, but the differences were not significant. Additional comparisons of MI in subjects with nausea versus those without nausea showed no differences at baseline or during vection. During the recovery period, the symptomatic group had a significantly larger MI than the asymptomatic group (710 vs. 35.8 $P<0.01$). These results must be interpreted cautiously because subject (1, SK) probably represents an "outlier" whose values have skewed the means. Despite Subject (1, SK), the trend is toward decreased number of contractions during vection, but more studies are needed to determine if the trend is significant.

In addition, although large changes in the amplitude of the EGG signal frequently occurred with tachygastria, no accompanying change in intraluminal pressures was detected as seen in Figure 4. Thus, the marked shifts in EGG frequency reflected changes in electrical pacemaker or slow wave frequencies and not mechanical events.

To summarize: the shifts in baseline EGG frequency to tachygastrias discriminated 6 of 7 subjects with vection-induced nausea; whereas, intraluminal pressure responses did not. Symptomatic subjects had weaker baseline 3 cpm patterns than the asymptomatic subjects. Maintenance of 3 cpm was associated with no symptoms during vection in 6 of 8 subjects; whereas, a wide range of contractile events was also recorded in these subjects. Thus, changes in gastric rhythms were more susceptible to vection than changes in gastric contractile events. EGG recordings were more sensitive than antral pressure recordings in detecting perturbations in gastric function during vection.

2. Duodenal Contractions and Gastric Dysrhythmias During Vection-Induced Nausea.

In one subject the distal pressure transducer inadvertently slipped into the duodenum during the baseline period. This subject subsequently developed severe nausea culminating in retching after only 4 minutes of vection. As shown in Figure 8A, a burst of contractions (approximately 10-11/min) is seen in duodenum (DI) at the time of severe nausea and retching. At the same time, EGG signal is temporarily lost. As duodenal contractions diminish in amplitude, 8-9 cpm tachygastria becomes apparent (Figure 8B). During recovery, 3 cpm activity reappears and intraluminal pressures are quiescent. Figure 9 is the RSA from this same subject. The 8-9 cpm peaks indicate tachygastrias while the peaks at 10 cpm appear to coincide with the duodenal contraction frequency of 10-11 per min. Respiratory peaks at 13-14/min are seen. These data indicate rhythmic duodenal contractions may occur during severe nausea and retching and the accompanying electrical activity may be detected by RSA of the EGG signal. Further studies are needed to examine the role of duodenal contractile activity in severe nausea induced by vection.

3. Vection-Induced Plasma Catecholamine Responses in Nauseated and Symptom-Free Subjects.

Plasma catecholamine levels were measured by radioenzymatic assay (13) in subjects who did and did not report nausea during vection; the EGG records and RSAs from these subjects are shown in Figures 4 and 5 and 6 and 7, respectively. Figure 10 shows the results of the catecholamine studies. In the subject who developed tachygastria and nausea, norepinephrine, epinephrine and dopamine were decreased immediately after vection and at a time when nausea and tachygastria were still present. The catechol levels returned toward baseline at 10 min and then "overshot" baseline levels by 44-118%.

The catecholamines also decreased in the asymptomatic subject who maintained 3 cpm activity; but, in contrast to the nauseated subject, the catechol levels remained suppressed during the 20 min recovery period. Although vection-induced motion sickness may be considered "stressful", classic sympathetic "fight or flight" mediators appear to be suppressed immediately after vection (see Discussion).

It should be pointed out that a catecholamine profile was also measured after a 30 min rest period in a chair before the subject entered the drum to begin the baseline period. From the rest period to the pre-rotation baseline period, the asymptomatic subject had a 95% and 177% increase in plasma norepinephrine and dopamine, respectively; whereas, the subject who developed nausea had a 67% and 0% increase in these two catechols. In other words, the asymptomatic subject appeared to muster a greater sympathetic nervous system response before vection than the symptomatic subject. On the other hand, the adrenal epinephrine response during this rest to baseline period was greater in the nauseated subject (980% increase) than in the symptom-free subject (800% increase in epinephrine). It is interesting to consider that these divergent catecholamine responses may have influenced the baseline EGG patterns (i.e. compare the baseline EGG activity in Figures 4 and 5 (the nauseated subject) versus the clear 3 cpm patterns in Figures 6 and 7 (the asymptomatic subject).

4. Effect of Metoclopramide HCl (Reglan) on Vection-Induced Tachygastria and Nausea.

Two symptomatic men who developed tachygastria returned for a second trial 8-12 weeks after the initial vection experiment. Thirty to 45 minutes before vection, 20 mg. of metoclopramide was given by mouth. With metoclopromide pretreatment, neither subject reported nausea during the vection period and tachygastrias were reduced. Figure 11 shows the gastric electromechanical responses to metoclopramide. Intraluminal pressures were increased during the baseline period (compare Figures 11 and 4; this is the same subject) but were again quiescent during the vection period. The EGG pattern showed a slightly stronger 3 cpm pattern during baseline; during vection the EGG configuration changed, but remained at the 3 cpm frequency, and the subject reported only slight dizziness. Low amplitude 3 cpm pattern was present during recovery. The post-metoclopramide RSA is shown in Figure 12 and may be compared with Figure 5: the number and power of tachygastrias are reduced.

B. Vection Studies in Subjects with Vagotomy and Gastric Resections:

1. Vection-induced motion sickness and gastric dysrhythmias in patients with vagotomy and various gastric resections.

Seven subjects (3 men and 4 women, ages 34 to 65, mean 50.3 yrs) were studied as described above. Intraluminal pressures in three subjects showed no change during vection; this finding, in addition to the negative results in the healthy subjects, resulted in a decision to discontinue intraluminal pressure recordings in the gastric resection

subjects. One subject failed to experience vection and is not reported. Of the six subjects who experienced vection, three had Roux-en-Y anastomoses (vagotomy plus antrectomy), two had vagotomy and pyloroplasty (V+P) and one had a total gastrectomy.

The symptoms and EGG frequency responses of the postoperative subjects to the vection protocols are listed in Table 3. Vection was reported within an average of 2.5 min of drum rotation. Only one of the six subjects had a predominant 3 cpm pattern during baseline; four subjects had flatline or 1 cpm pattern and one had an 11 cpm pattern. During vection all subjects, except the total gastrectomy patient, reported mild to moderate nausea 4-8 min after onset of vection. Three of these subjects had a shift to higher EGG frequencies at onset of symptoms: two had tachygastrias (one Roux-en-Y and one V+P) and one (Roux-en-Y) had a burst of 3 cpm activity. No obvious EGG changes occurred in the two other symptomatic subjects. During recovery, the baseline EGG pattern returned in two of the three symptomatic subjects and remained 5-6 cpm in one. The EGG patterns during recovery in the other 3 subjects were similar to their baseline patterns.

Figure 13 shows a composite of EGG segments and the RSA from subject (1, SM)'s vection experiment. Prominent 3 cpm peaks are seen during baseline and the inset A shows a sample of the actual EGG signal during this period. Moderate nausea began after about 4 min of vection and was associated with a shift to tachygastrias as shown in the RSA and EGG inset B. During recovery, the tachygastria resolved and 3 cpm patterns in RSA and EGG signal returned. This pattern in a nauseated postvagotomy subject was similar to EGG pattern seen in the nauseated subjects with intact stomachs.

Figure 14 shows the EGG signal from subject (2, MB) with Roux-en-Y before, during and after vection. Flat, low-frequency wave forms, presumably a result of the previous gastric surgeries, are seen during baseline. After approximately 5 min of vection the subject reported nausea; the EGG signal had shifted to narrow-based, high-amplitude waves at 8 cpm. The tachygastria continued until drum rotation stopped; during recovery the baseline EGG pattern was re-established. Figure 15 shows the RSA of the entire vection experiment of subject (2, MB). As described further in the figure legend, the computer analysis showed the predominance of 0-1 cpm frequencies during baseline (almost no 3 cpm peaks), an 8 cpm peak as well as 10-11 cpm peaks during vection, and resolution of tachygastrias and return of 1 cpm peaks during recovery.

The EGG signals and RSA from the subject with total gastrectomy (6, WC) are shown in Figures 16 and 17, respectively. No rhythmic pattern is discernible during the study periods: the signal is flat with intermittent low amplitude undulations at frequencies near the respiratory rate. The total gastrectomy patient was asymptomatic during vection. (This subject repeated the experiment 8 weeks later and again reported no symptoms.) The RSA (Figure 17) shows predominance of low frequency activity (0-1 cpm) although during vection 8 cpm and 15 cpm peaks emerge which probably represent jejunal electrical activity and respiratory rate, respectively.

Figure 18 shows the catechol responses from subject (2, MB) with Roux-en-Y who developed nausea and tachygastria (Figures 14 and 15) and from the total gastrectomy Subject (6, WC) who was symptom-free during vection (Figures 16 and 17). Plasma samples were obtained as described above. Immediately after vection, the nauseated subject had 365% and 355% increases in epinephrine and dopamine, respectively, and an 85% increase in norepinephrine. These findings are consistent with "fight or flight" sympathetic responses, but are distinctly different from the catecholamine responses of the subject with nausea and intact stomach (compare with Figure 10). Furthermore, the patient with total gastrectomy and no symptoms during vection had a persistent decrease in catecholamines, a pattern similar to the symptom-free subject with an intact stomach (compare with Figure 10).

Catecholamines were also measured after the 30 minute rest period before the subject entered the drum and these values were compared with the pre-drum rotation catechol measurements. The changes in epinephrine, norepinephrine and dopamine levels were +35%, -76% and 0%, respectively, in the Roux-en-Y subject who developed nausea during vection. The lack of anticipatory sympathetic activation (i.e. norepinephrine and dopamine) before vection is more pronounced than in the nauseated subject with normal stomach (see page 11). A 30 min rest period plasma sample was not obtained in the gastrectomy patient, so similar comparisons cannot be made.

VI. Discussion

The significant findings of the Year 1 studies are summarized and discussed below:

Eighty-six percent of the healthy subjects who reported nausea during vection developed tachygastrias, whereas most symptom free subjects (75%) maintained 3 cpm EGG patterns and/or did not develop tachygastrias. In contrast, contractile activity of the gastric antrum during vection did not distinguish symptomatic from asymptomatic subjects. A trend toward diminished contractility during vection was apparent, but the changes did not reach statistical significance. Nevertheless, the trend was consistent with earlier studies which showed loss of contractility or peristalses during motion sickness (1,2). More recent studies have shown loss of gastric muscle contraction during tachygastria (14). As shown in Figure 4, antral contractions were not seen during the tachygastrias.

No distinct intraluminal pressure changes were found in the symptom-free subjects, but low amplitude 3 per min contractions may escape detection by luminal catheter transducers (14). Nevertheless, the EGG pattern remained clearly 3 cpm in the symptom-free subjects, distinguishing the majority of them from those who developed nausea. These findings confirm our previous work (3) and indicate that vection stimuli primarily affect the pacemaker or slow wave activity of the stomach. Thus, shifts in pacemaker frequency (3 cpm to tachygastria) appear to be more sensitive indicators of vection-induced gastric dysfunction than antral contractility. (Please see Appendix A for additional discussion of symptoms of motion sickness and EGG changes.)

Duodenal motility, however, may have a role in the genesis of severe nausea and in the contractile events which produce retching and vomiting. Other studies have shown that duodenal contractions accompany nausea induced by labyrinthine stimulation (15,16). Recent studies in dog show that apomorphine and chemotherapeutic agents elicit a variety of duodenal and gastric electromechanical events, including reverse peristalsis which involves the duodenum (17). We observed rhythmic duodenal contractions at the onset of severe nausea and retching induced by vection, findings consistent with the previous studies in which nausea was induced by cold calorics or pharmacologic stimuli (15,17). Thus, vection also represents a potent nauseogenic CNS stimulus in certain individuals. These findings warrant further evaluation of duodenal contractile activity during vection.

To summarize: EGG patterns distinguish the majority of symptomatic from asymptomatic subjects during vection; whereas, antral contractions do not. Duodenal contractions, however, may indicate severe nausea and imminent vomiting.

Patients with vagotomy and various gastric resections uniformly experience nausea during vection, whereas the total gastrectomy patient was symptom-free during vection. The role of vagal efferent and afferent neural activity in human motion sickness is unknown. In that scopalamine is effective in treating symptoms of motion sickness, cholinergic activity in brain stem, vestibular

nuclei and vestibular sensory organs is considered relevant to the causes of motion sickness. It is possible that the parasympathetic cholinergic outflow from these CNS structures to the periphery may affect the gastric myoelectric activity (i.e. cause shifts to tachygastria and symptoms of epigastric distress, "queasiness", "churning" stomach, and nausea). As suggested in Hypothesis 2, if vagal efferent or afferent pathways were activated during vection or caused gastric dysrhythmias, then vagotomy should prevent these phenomena. Our studies show that vagotomy did not protect the subjects from symptoms of vection-induced motion sickness. These findings suggest non-vagal neural pathways or hormonal mechanisms may mediate the gastric dysrhythmias and motion sickness symptoms evoked during vection.

In dog and man, acute vagotomy disrupts normal gastric slow wave activity for several weeks (18,19). It was hypothesized, but never proven, that postvagotomy gastric dysrhythmias in man were due to "sympathetic dominance" (19). Interestingly, infusions of epinephrine, prostaglandin E_2 and glucagon cause tachygastrias in dog (11). In three of our postvagotomy subjects, shifts in EGG frequency coincided with onset of nausea and catecholamines (measured in one subject) were markedly elevated immediately after vection. Sympathetic pathways as well as hormonal responsiveness would remain intact in the postoperative stomach remnant. These preliminary findings suggest adrenal-sympathetic responses to vection may result in gastric dysrhythmias and motion sickness, at least in some postvagotomy subjects. In two symptomatic subjects, however, no detectable changes in EGG activity occurred, suggesting a nongastric locus of symptoms - perhaps jejunal or CNS. However, it appeared some gastric remnant was required for vection-induced nausea to occur because only the total gastrectomy patient was symptom-free during vection.

Do the symptoms of motion sickness in man arise from visual-vestibular-cerebellar axis activity within the central nervous system, from peripheral (i.e. stomach) dysfunction, or from both? If the stomach (or a remnant thereof) is a critical "target organ" which temporarily dysfunctions (i.e. shifts to tachygastria) in response to the CNS outflow resulting from vection, then the absence of that organ should protect the subject from motion sickness symptoms. Thus, the response of the total gastrectomy subject is intriguing because during two trials he remained symptom-free during vection. Does total gastrectomy protect against vection-induced motion sickness in man? Additional trials with total gastrectomy patients are needed to determine if symptom-free vection is a characteristic finding.

To summarize: Postvagotomy subjects experienced motion sickness, indicating vagal pathways do not mediate vection-induced nausea. Thus, the adrenal-sympathetic axis and/or other mediators (i.e. opioids or prostaglandins) may contribute to gastric dysrhythmias and vection-induced symptoms.

The preliminary catecholamine and metoclopramide results reported above relate to mechanisms and treatment of motion sickness and are discussed below:

The basic mechanisms which mediate the escalating symptoms of motion sickness remain unclear. A variety of hormones and neurotransmitters have been measured during motion stimuli (20-22); the motion stimuli used in these

studies, however, involved vigorous rotation or actual movement of the subjects, intense physical activities with their own "counterregulatory" responses. In contrast, the subject who experiences vection is stationary and comfortably seated; and, the physiologic changes which accompany "motion-sickness" are responses only to the relatively pure CNS stimulus of vection. Nevertheless, certain subjects progressively develop sweating, warmth, epigastric distress, and mild to severe nausea during vection; i.e., the range of symptoms experienced during motion sickness. Furthermore, the CNS circuitry which mediates vection may be relevant to space sickness, during which otolithic function is altered (8,9). Vection experiments have other desirable characteristics in that the subjects are safe, sensitive physiological signals such as the EGG may be measured, and blood samples may be obtained quickly and easily.

Because motion is a stressful stimulus for certain individuals, one might expect adrenal and sympathetic nervous system activation. Indeed, motion stimuli which increase G-forces result in abrupt increases in plasma epinephrine and norepinephrine in man (21). Gastric dysrhythmias after acute vagotomy have been attributed to sympathetic dominance (19). Moreover, intra-arterial infusions of epinephrine also caused canine tachygastrias (11). Thus, it is conceivable that gastric dysrhythmias and motion sickness may be mediated in part by catecholamine release. Other subjects, however, have no symptoms during vection; some describe vection as "exhilarating" (personal observation). Do these subjects, have a different catechol response to vection?

Catecholamine Responses in Healthy Subjects

Divergent plasma catecholamine responses to vection were found in symptomatic and asymptomatic healthy subjects. The preliminary results showed decreased catecholamines 1 min after vection in both the nauseated and the symptom-free subject. However, during the 20 minutes after vection, catecholamines rebounded in the nauseated subject; whereas, they remained suppressed in the symptom-free subject. These were unexpected findings which suggested that adrenal and sympathetic neural activity were suppressed during vection stimuli; this is the opposite sympathetic response measured during motion stimuli which produces G-forces (21). However, vection is a uniquely and purely a CNS "motion" stimulus in contrast to experiments in which the subjects are actually accelerating or moving. Moreover, the rebound catechol response in the nauseated subject clearly diverged from the sustained catechol suppression in the symptom-free subject, suggesting that in the symptom-free subject different neuro-hormonal mediators may have suppressed the adrenal-sympathetic axis. How decreased levels of norepinephrine, dopamine and epinephrine may affect gastric electrical rhythm is unclear; interestingly, in some patients with idiopathic nausea and vomiting symptoms improve after lidamidine HCL, an alpha$_2$ agonist (23).

In addition, the symptom-free subject with clear 3 cpm EGG baseline had "boosted" his pre-vection norepinephrine and dopamine levels 85% and 177%, respectively; whereas the nauseated subject with weaker 3 cpm baseline increased these two catechols 67% and 0%, respectively.

Are "anticipatory" boosts in catechols and enhanced 3 cpm EGG power related? Does an "unconscious" boost in certain catecholamines provide resistance to vection-induced nausea and tachygastria? Traditionally, sympathetic neural input to the gut is inhibitory. However, sympathetic cholinergic fibers also innervate the antrum: low level stimuli elicit gastric contractions; whereas, greater stimulation causes relaxation (24). Perhaps a specific blend of sympathetic and parasympathetic efferent input to the corpus-antrum may strengthen 3 cpm rhythms before vection. Then, as shown in the symptom-free subject (Figure 7), the power at 3 cpm may be decreased, but is not abolished during vection and tachygastrias do not develop.

The above findings are particularly interesting because amphetamine, a drug which releases norepinephrine, is effective in reducing motion sickness (25). The effect of amphetamine on gastric electromechanical activity is unknown. Interestingly, a recent report by Kohl indicates that a variety of sympathomimetic drugs are effective anti-motion sickness agents (26). These drugs may provide the boost in catecholamines (and 3 cpm EGG activity) which some subjects are unable to recruit naturally prior to motion stimuli. Additional studies are needed to confirm the differential "anticipatory and "post vection" catechol responses in healthy subjects.

Catecholamine Responses in Postoperative Subjects

Differential catecholamine responses to vection were also found in symptom-free and nauseated postoperative subjects. After vection, the symptom-free total gastrectomy subject had persistently decreased catecholamine levels, a pattern similar to the symptom-free healthy subject. In contrast, the Roux-en-Y (antrectomy plus vagotomy) subject with vection-induced nausea had marked increases in catecholamines one and ten minutes after vection; and, the epinephrine increase was sustained at 20 minutes post vection. Thus vection-induced catechol responses in the total gastrectomy subject were the opposite of responses in the Roux-en-Y subject. Both subjects had vagotomy. These data imply that some contribution of sympathetic efferent or afferent neural input to and/or from the stomach remnant modified the catechol response in the Roux patient. In any case, only the Roux subject had a "fight or flight" sympathetic response to vection.

Also, the catechol surge in the Roux subject was immediate; whereas, the surge was delayed in the nauseated subject with intact stomach, suggesting that the intact vagus and/or antrum may have modified the catecholamine response to vection. The circuitry is complex; more studies are necessary before conclusions can be drawn.

Metoclopramide and Vection-Induced Nausea

Pretreatment with metoclopramide, a drug which stimulates gastric contractility, prevented vection-induced nausea, stimulated 3 cpm activity, and reduced but did not eliminate tachygastrias. These preliminary results support our hypothesis (number 3) that maintenance of 3 cpm activity (and prevention of tachygastria) may prevent or diminish symptoms of motion sickness. It is unknown if larger doses of drug could completely abolish tachygastrias. Metoclopramide increases gastric contractility and decreases nausea and vomiting in diabetics with gastroparesis (27), but it has not been

systematically studied as an antimotion sickness agent. Anecdotal reports indicate metoclopramide diminished the symptom of space sickness and stimulated bowel sounds (28). Metoclopramide is a dopamine antagonist with indirect cholinomimetic effect (29). A recent review suggests metoclopramide is a prejunctional agonist at alpha$_2$ adrenergic or 5-hydroxtryptamine receptors (30). Does metoclopramide provide a blend of adrenergic and cholinergic activity needed to increase 3 cpm EGG activity and to resist vection-induced dysrhythmia? Control of gastric dysrhythmias with prokinetic agents represents a novel approach to the treatment of motion sickness.

Furthermore, metoclopramide crosses the blood-brain barrier, but investigational gastroprokinetic agents, domperidone and cisapride (31), act predominantly on the gastrointestinal tract. The effect of these latter drugs on vection- induced nausea and tachygastria may provide important data concerning the origins of motion sickness symptoms: central nervous system versus stomach.

VII. Summary

Responses to vection separated healthy subjects into two groups - those who experienced nausea and those who remained symptom-free. The symptomatic group was objectively identified by the onset of tachygastrias. Duodenal contractions may correlate with severe nausea and retching, but antral contractions did not distinguish symptomatic from asymptomatic subjects. In preliminary work, catecholamine responses of symptomatic and asymptomatic subjects were divergent, indicating differential sympathetic nervous system responses in the two groups. Catecholamine responses, particularly "anticipatory" responses, to vection may be relevant to basic mechanisms of motion sickness. Metoclopramide reduced tachygastrias and prevented nausea. Pharmacologic control of gastric dysrhythmias with gastroprokinetic drugs provides a novel rationale and offers multiple therapeutic approaches to the treatment of motion sickness.

Vagotomy subjects with gastric remnants were uniformly susceptible to vection-induced nausea, indicating that vagal pathways do not mediate the symptoms of motion sickness in these subjects. To the contrary, vagotomy and/or antrectomy appeared to increase the likelihood of motion sickness. The only operated subject who had no symptoms during vection had a total gastrectomy. Thus, it appears that the sympathetic nervous system or other neurohormonal circuits may mediate the gastric dysrhythmias and symptoms evoked by vection. Preliminary studies in a vagotomy-antrectomy subject showed marked increases in catecholamines after vection; in contrast, the total gastrectomy subject had catechol responses similar to the healthy asymptomatic subject. Thus, vagotomy and/or partial gastrectomy appears to alter the catecholamine response to vection. Further studies in additional subjects are needed.

Gastric electromechanical responses to vection are relatively "pure" brain-gut interactions which provide new insights into the gastric component of motion sickness. The underlying mechanisms which mediate susceptibility to or resistance to vection-induced nausea may be relevant to the pathophysiology of motion sickness. A better understanding of these mechanisms will allow more rational treatment approaches to symptoms arising from a variety of motion stimuli.

VIII. References

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FIGURE 1

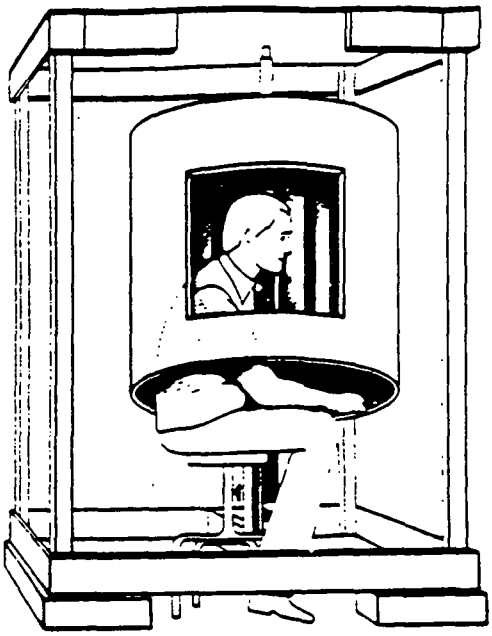


FIGURE 1. Illustration of a subject seated within the rotating drum.

FIGURE 2

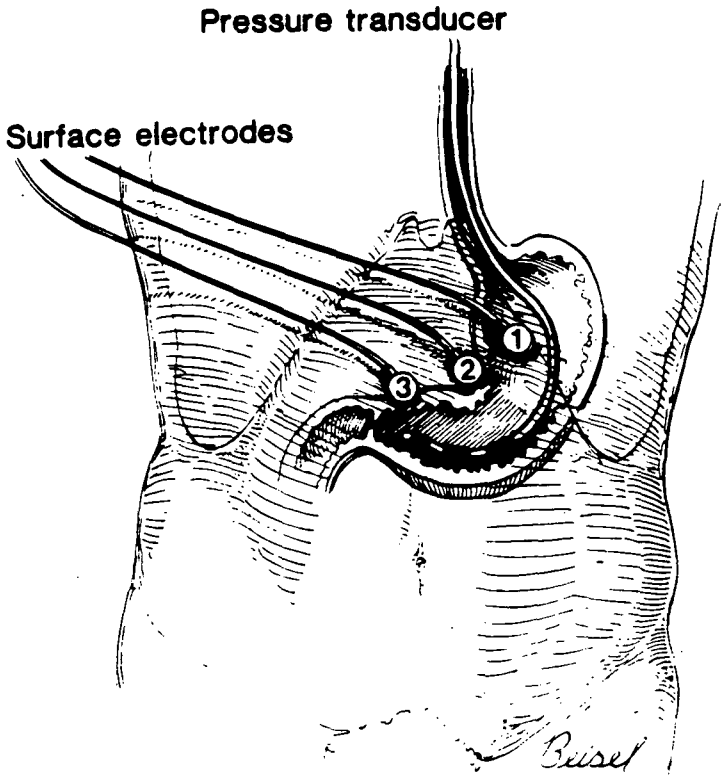


FIGURE 2. Illustration of electrode placement. Electrode 1 is over the proximal or orad gastric body; Electrode 3 is over the distal antrum. Reference electrode is not shown. A catheter with three solid state pressure transducers is positioned in the distal body and antrum for simultaneous measure of gastric electromechanical activity.

FIGURE 3.

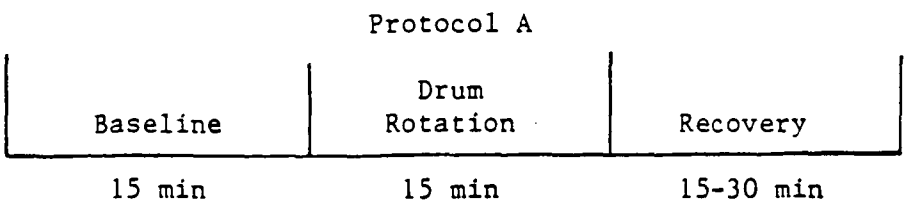


TABLE I

Symptoms and Electrogastrogram (EGG) Frequency Responses in Healthy Subjects With and Without Vection-Induced Nausea

Subjects w. nausea	EGG Frequencies (cpm) Baseline	Vection	Recovery	Nausea Score*
1. SK	3 (poor+)	5-7	5-7	29
2. RS	Resp.[a] only	Resp. only	Resp. only	169
3. MF	5-7	5-7	5-7	95
4. SH	Flatline	8-10	8-10	73
5. BT	3 (poor)	6-7	3	253
6. MD	3	6-8	3	210
7. KK	3 (poor)	6-8	3	290
Subjects w/o nausea				
1. DJ	3	3	3	0
2. MH	3	3	3	0
3. DS	3	3	3	0
4. BR	3	3	3	0
5. MB	3	3	3	0
6. DW	3	Resp. only	Flatline	0[b]
7. JE	3	3	3	0
8. PD-A	3	4-5	3 (poor)	0[c]

*Indicates mm from 0 (no nausea) along a 300 mm line (300 mm = severe nausea, near vomiting) and reflects intensity of nausea during vection.
+Poor indicates low amplitude or intermittent 3 cpm pattern
[a]Resp = respiration [b]"sweating" [c]"dizzy"

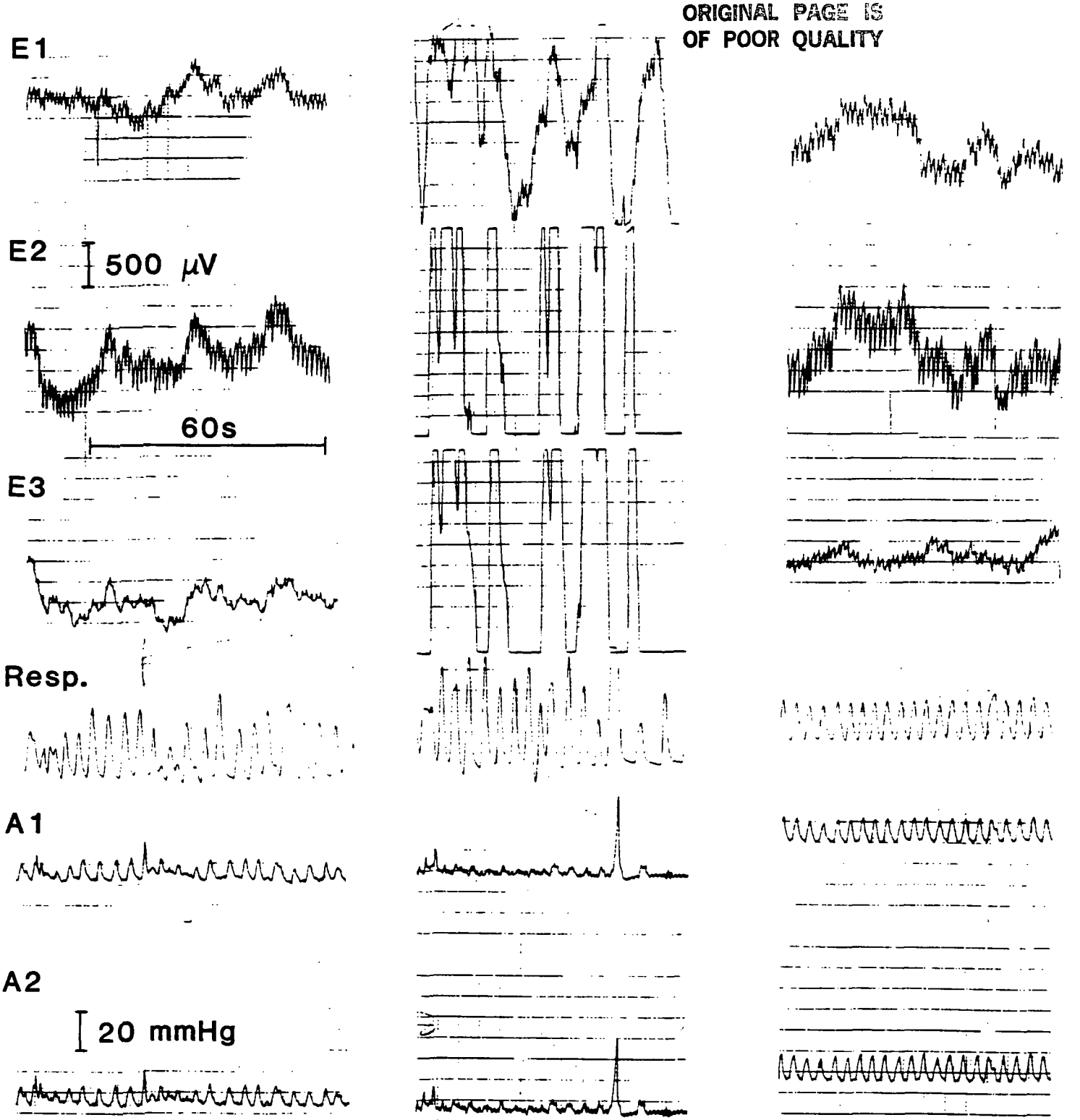


FIGURE 4. GASTRIC ELECTROMECHANICAL ACTIVITY IN A HEALTHY SUBJECT WHO DEVELOPED NAUSEA DURING VECTION. E1, E2 and E3 indicate EGG signals simultaneously recorded from electrodes E1-E3. Minute and electrical standards are shown. The fourth panel is Respiration (Resp). A1 and A2 indicate intraluminal pressures in the antrum recorded from the distal two pressure transducers. Figures 6, 8 and 11 are set up in similar fashion.

During Baseline, 3 cpm EGG pattern is seen, particularly at E2 and E3. Intraluminal pressure is quiescent and shows only respiratory artifact. At six minutes of Vection, the EGG waves are narrow-based with increased amplitude, the frequency is approximately 6 cpm (i.e. tachygastria), intraluminal pressure is unchanged, and the subject reported nausea. Ten minutes into the Recovery period, low amplitude 3 cpm activity is best seen at E3: intraluminal pressures remain quiescent. Nausea resolved.

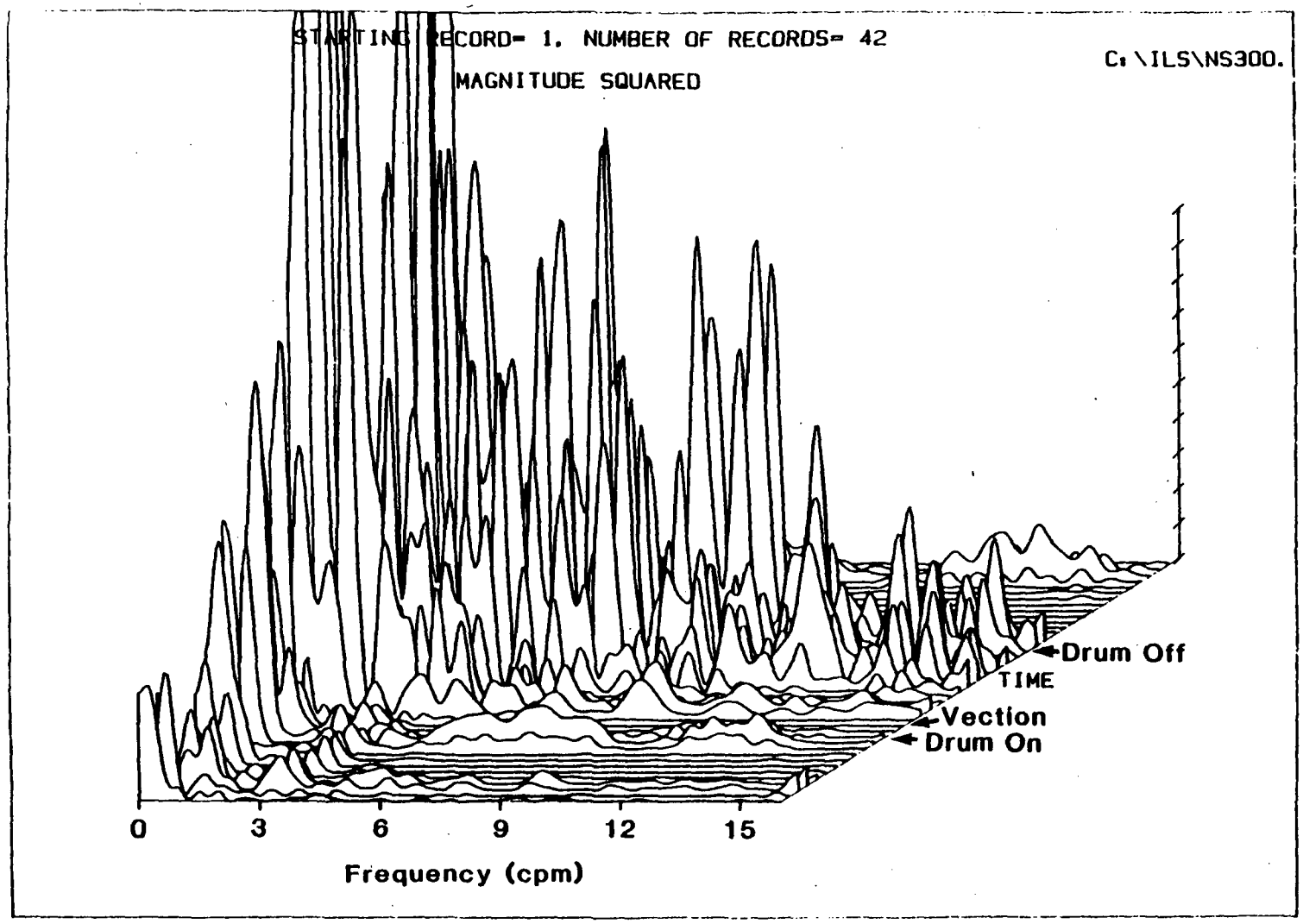
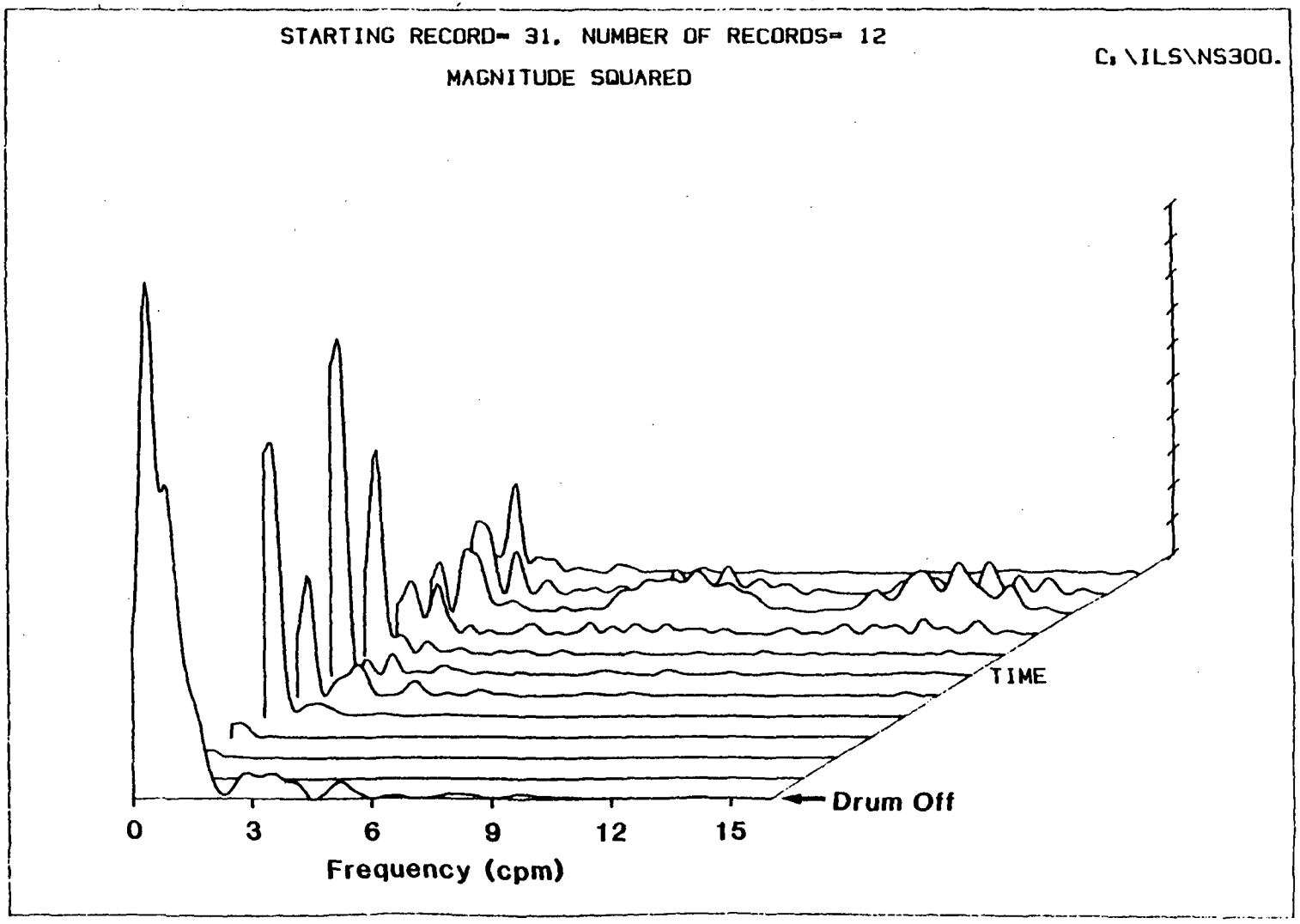


FIGURE 5. RUNNING SPECTRAL ANALYSIS OF EGG SIGNALS FROM SUBJECT WITH VECTION-INDUCED NAUSEA. (Same subject as in Figure 4). Horizontal axis indicates EGG frequency in cpm; vertical axis indicates the power (arbitrary units) of the EGG signal at the various frequencies; time indicates 4 min of EGG signal - 64_s of new data added to the previous three minutes of data. Similar format used in Figures 7, 9, 15 and 17.

Baseline period before Drum On shows regular 3 cpm peaks and 0-1 cpm activity. During the Vection period (between Drum On and Drum Off) a wide variety of frequency peaks emerge with particularly high power peaks at approximately 6 and 9-10 cpm and 13-15 cpm, frequencies representing gastric dysrhythmias and respiratory rates, respectively. Recovery period (between Drum Off and end of the plot) shows resolution of high power frequencies, although frequency peaks > 12 cpm persist. Inspection of recovery period is impaired because of the high peaks during vection. Minimal 3 cpm activity returned during recovery as shown in Figure 5A, a supplementary plot of the 15 min recovery period only.

FIGURE 5A. RUNNING SPECTRAL ANALYSIS OF THE RECOVERY PERIOD ONLY FROM FIGURE 5.



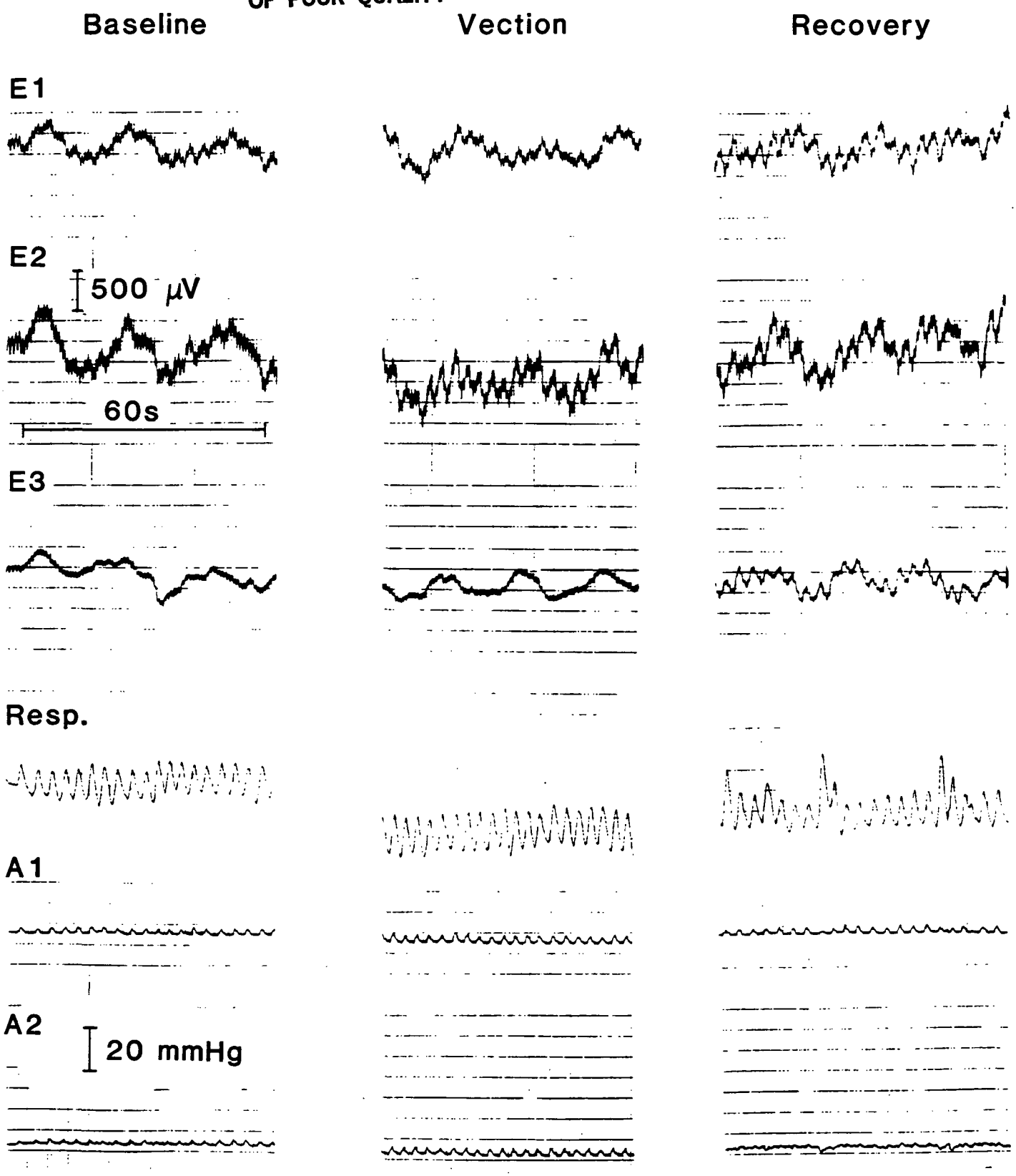


FIGURE 6. GASTRIC ELECTROMECHANICAL ACTIVITY IN A HEALTHY SUBJECT WHO REMAINED SYMPTOM FREE DURING VECTION. During Baseline, clear 3 cpm EGG signals are seen; intraluminal pressures are quiescent. During Vection the 3 cpm EGG pattern remains clear; 3 cpm pattern is also seen during Recovery, although more respiratory artifact is apparent. Pressures during vection and recovery were quiescent.

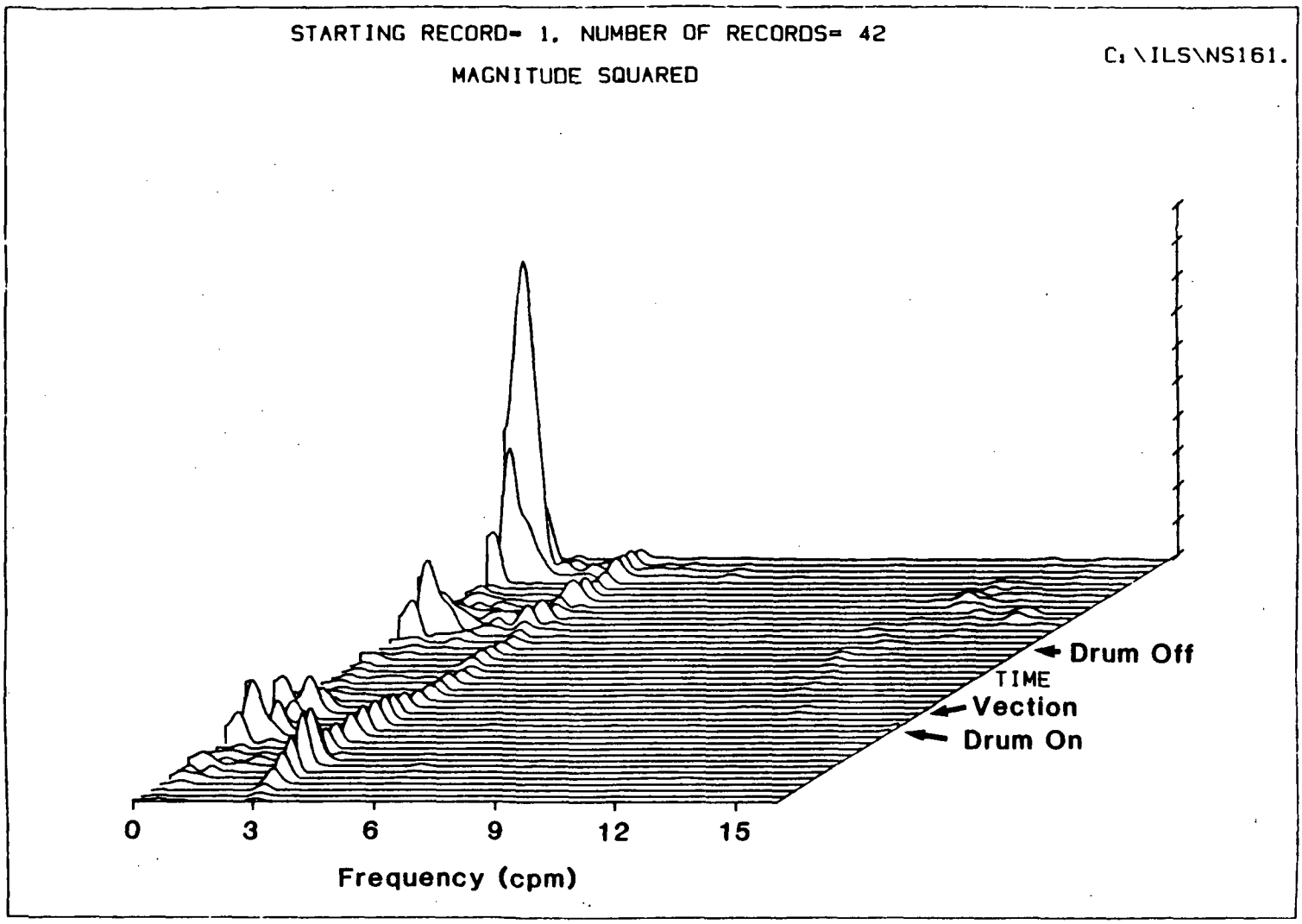


FIGURE 7. RUNNING SPECTRAL ANALYSIS OF EGG SIGNAL FROM A HEALTHY SUBJECT WHO REMAINED SYMPTOM-FREE DURING VECTION (same subject as in Figure 6). Before onset of drum rotation, an increasingly strong 3 cpm peak is seen; during Vection, the 3 cpm peak remains clear but decreases in power and no tachygastrias are seen. Also, at the onset and offset of drum rotation bursts of low frequency ($\sim$ 1 cpm) EGG activity are seen. During the Recovery period, the power at 3 cpm again increases slightly.

TABLE 2

Antral Motility Respones in Healthy
Subjects With and Without Vection-Induced Nausea

Subjects w. Nausea		Baseline Contractions	Baseline MI	Vection Contractions	Vection MI	Recovery Contractions	Recovery MI	Nausea Score*
1. SK		42	42,630	42	43,890	5	800	29
2. SH		6	390	13	910	12	1,020	73
3. BT		4	460	1	50	4	1,020	253
4. KK		0	0	0	0	0	0	290
5. MD		6	780	0	0	0	0	210
	Mean	11.6	11,065.0	11.2	11,212	4.2	710.0	
	±SEM	7.7	10,522.0	8.0	10,894	2.2	242.3	
Subjects w/o Nausea								
1. DJ		10	850	1	5	0	0	0
2. MH		2	30	0	0	0	0	0
3. DS		0	0	0	0	0	0	0
4. BR		12	2,100	5	275	0	0	0
5. MB		0	0	0	0	1	5	0
6. DW		9	3,555	1	10	3	195	0[a]
7. JE		0	0	0	0	0	0	0
	Mean	4.1	1,089.2	0.9	48.3	0.6	35.8	
	±SEM	1.9	595.9	0.6	45.4	0.4	31.9	

*MI (Motiity Index) = Number of contractions x sum of amplitudes
+Indicates mm from 0 (no nausea) along a 300 mm line
(300 mm = severe nausea, near vomiting) and reflects intensity of nausea during vection.
[a]"Sweating"

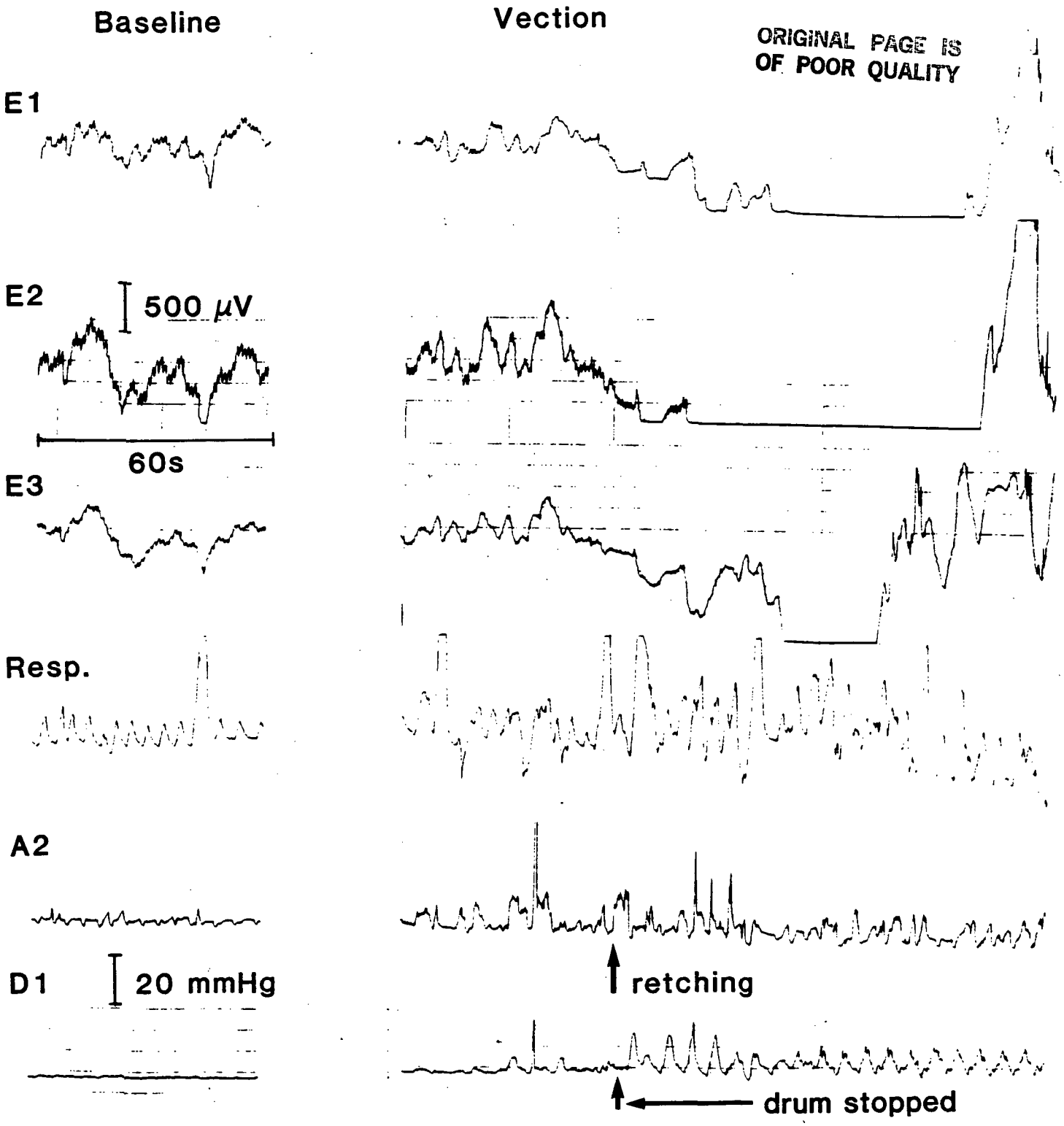


FIGURE 8A. EGG AND ANTRODUODENAL CONTRACTILE RESPONSES TO VECTION IN A HEALTHY SUBJECT. D1 indicates duodenal pressure; A2 indicates distal antral pressure. During Baseline, intermittent 3 cpm EGG activity was present (see E2) and intraluminal pressures were quiet. After 4 min. of Vection this subject experienced severe nausea and an episode of retching; the drum was stopped. Irregular EGG activity is temporarily lost as a rhythmic 11-12 per min burst of 10-15 mmHg duodenal contractions begin at D1. The irregular waves at A2 are respiratory. EGG signal returns with a large amplitude wave (i.e., E1 and E2).

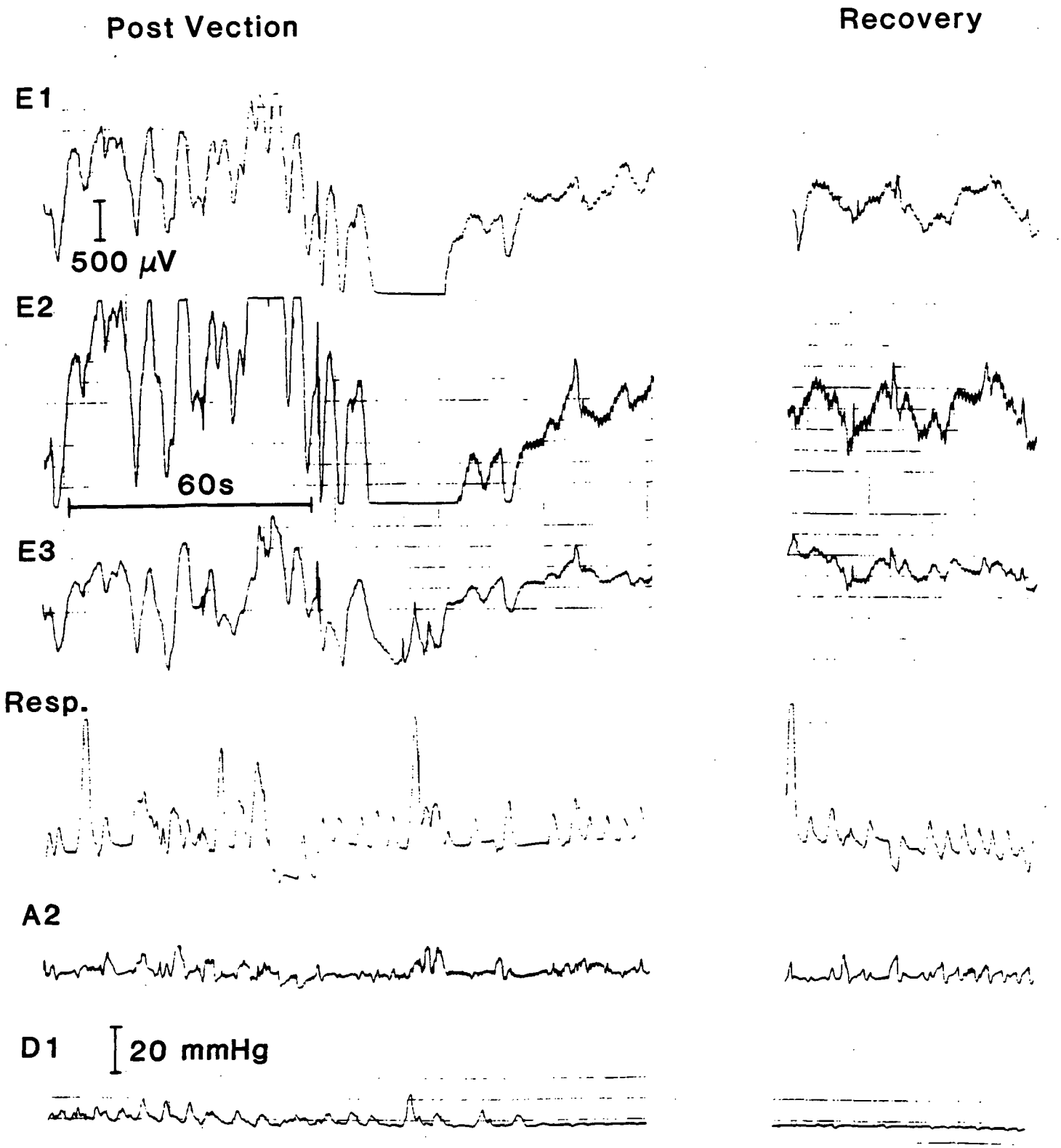


FIGURE 8B. This figure is a continuation of the previous tracing, (8A). In this immediate post drum rotation period of Recovery, the EGG now shows high-amplitude, narrow-based signals at 8-10 cpm (i.e. tachygastrias). Duodenal contractions are diminishing; tachygastria and nausea are also resolving. By the 12th minute of Recovery, the 3 cpm pattern is apparent (particularly at E1 and E2), and duodenal pressures are quiescent. Nausea has resolved.

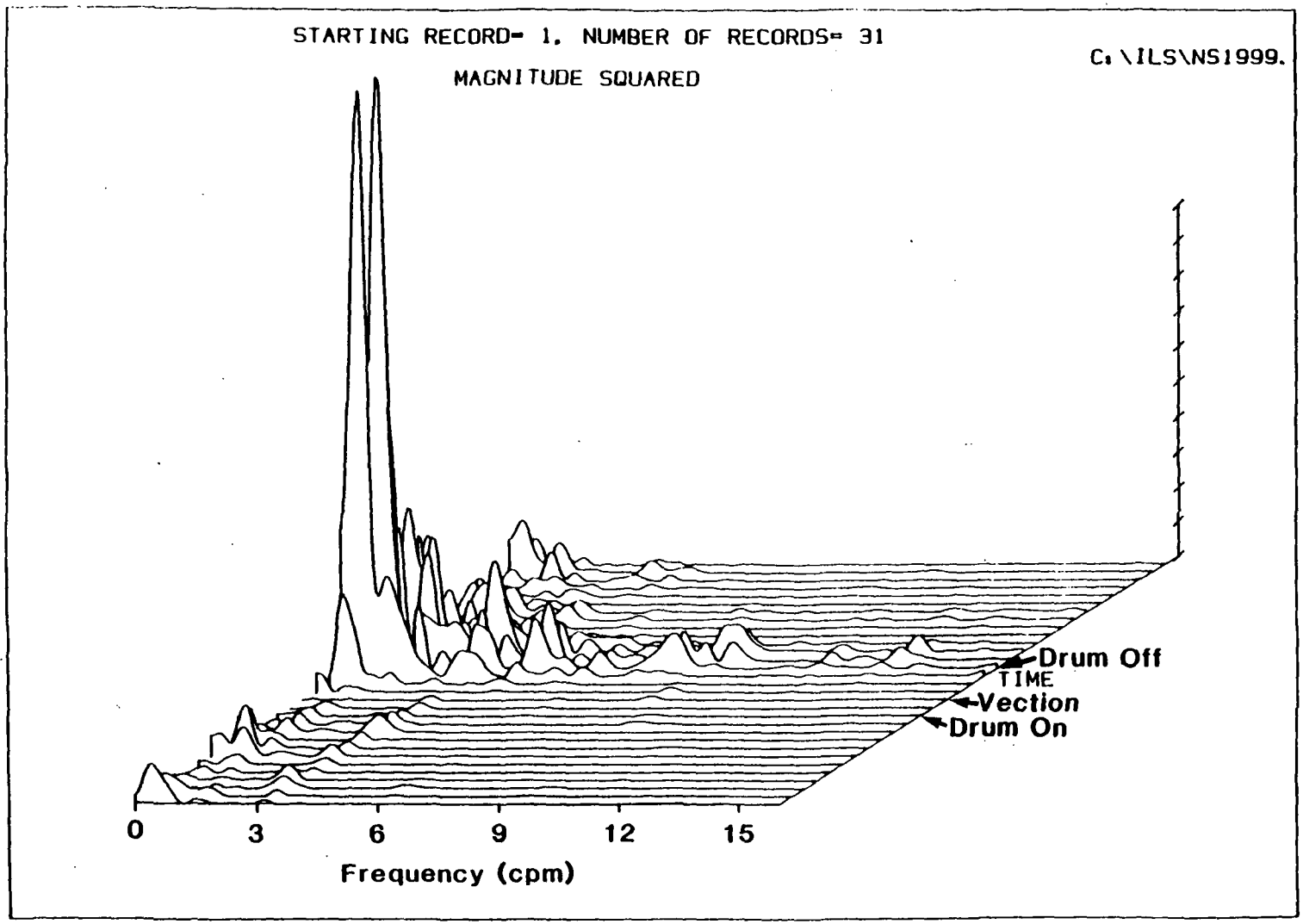


FIGURE 9. RUNNING SPECTRAL ANALYSIS OF EGG RECORDING FROM SUBJECT WITH SEVERE NAUSEA AND RETCHING (same subject as Figure 8A and B). Baseline period before Drum On shows low power peaks at 3 cpm. Three cpm peaks are suppressed after onset of vection. Vection lasted only 4 min; the drug was stopped at the time of retching. During the latter minutes of vection, new frequency peaks at 4, and 8-9 cpm are seen and represent tachygastrias. The peaks at 10 cpm probably represent duodenal frequency; the 13-14 cpm peaks represent respiratory rate. During Recovery the tachygastria peaks resolve and at the end of recovery, low power peaks at 3 cpm are seen.

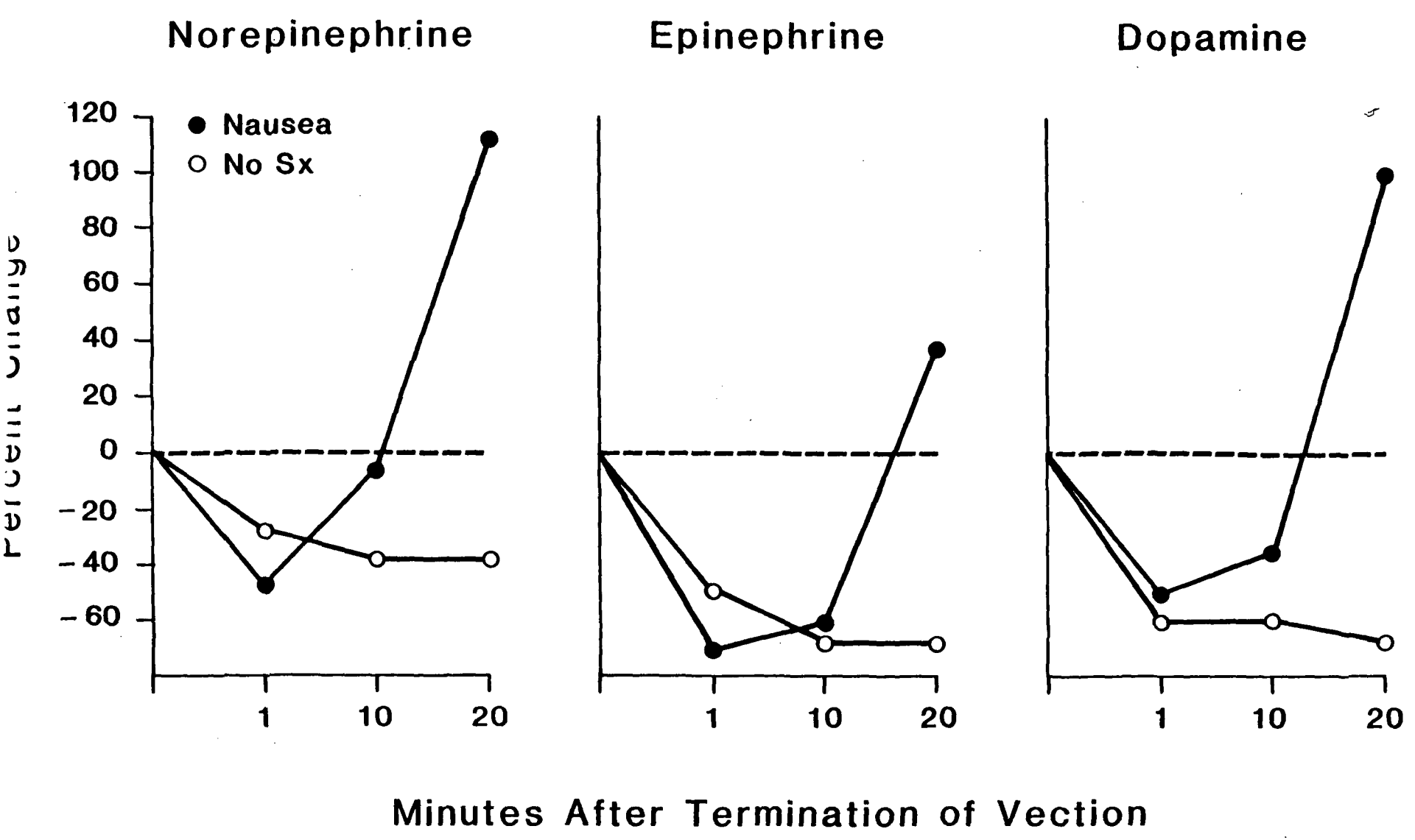


FIGURE 10. PLASMA CATECHOLAMINE RESPONSES TO VECTION IN HEALTHY SUBJECTS WITH AND WITHOUT NAUSEA. Percent change in catecholamine levels from baseline to 1, 10 and 20 minutes after vection are presented. One minute after vection, norepinephrine, epinephrine and dopamine are suppressed in both subjects. However, in the subject with no symptoms (No Sx), catechols remain suppressed (See Figures 6 and 7 for this subject's EGG and RSA patterns). In contrast, catechols rebound above baseline levels in the subject who had nausea during vection. (See Figures 4 and 5 for this subject's EGG and RSA).

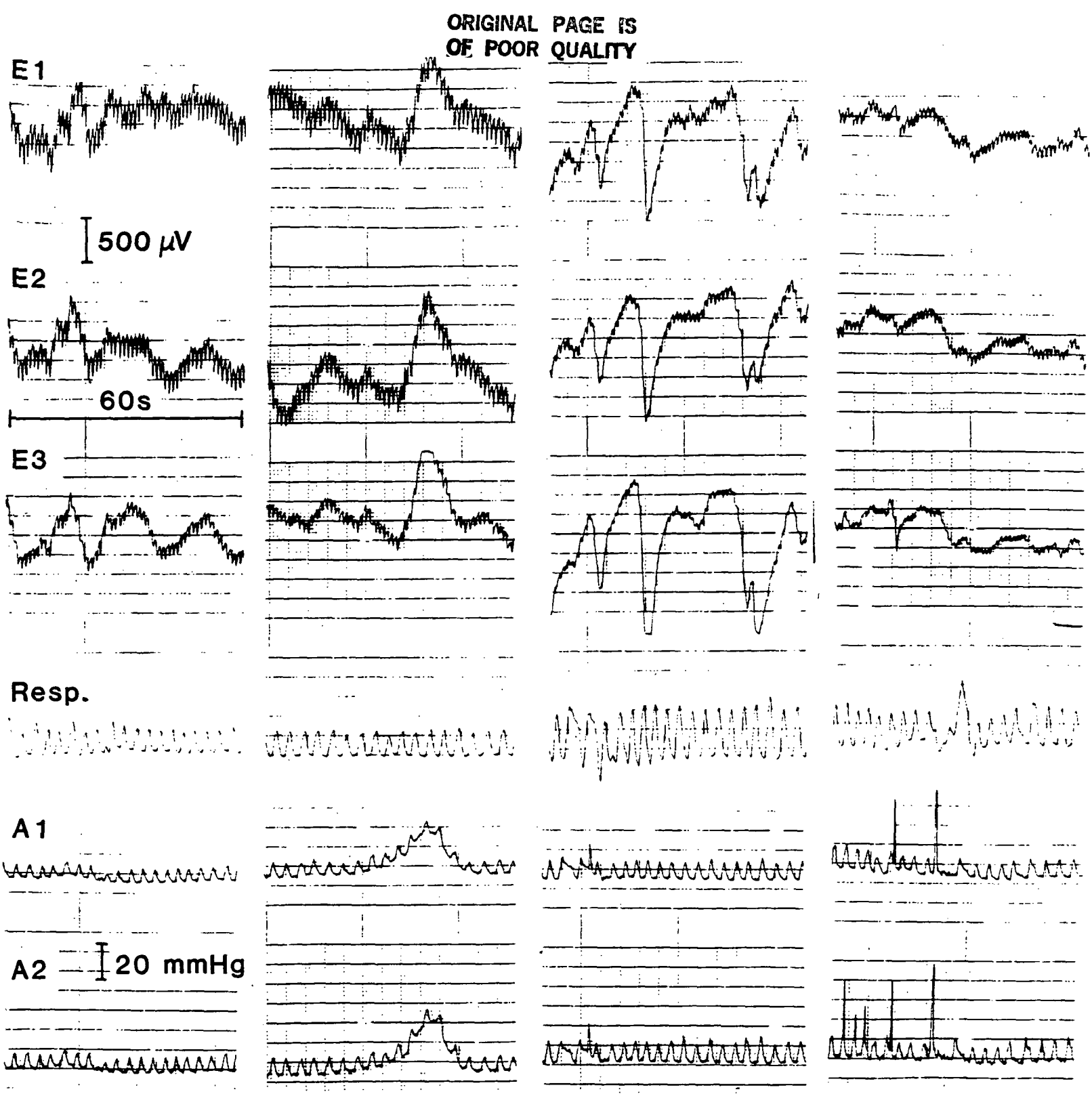


FIGURE 11. EFFECT OF METOCLOPRAMIDE HCL ON GASTRIC ELECTROMECHANICAL ACTIVITY DURING VECTION. (Same patient as in Figure 4). The panels are set up as before. Baseline I is from 10 min after 20 mg of metoclopramide: 3 cpm EGG activity is clearly seen at E2 and E3. Thirty min after metoclopramide (Baseline II), a 25 mmHg antral contraction is seen which correlates with the high amplitude, broad-based EGG wave. During the sixth min. of Vection, the EGG signal has a different configuration but the frequency remains approximately 3 cpm; intraluminal pressures are quiescent, and subject reported slight dizziness but no nausea. During Recovery period, weak 3 cpm EGG pattern is seen (E1) and antral pressures reflect respiration. No nausea during vection or recovery.

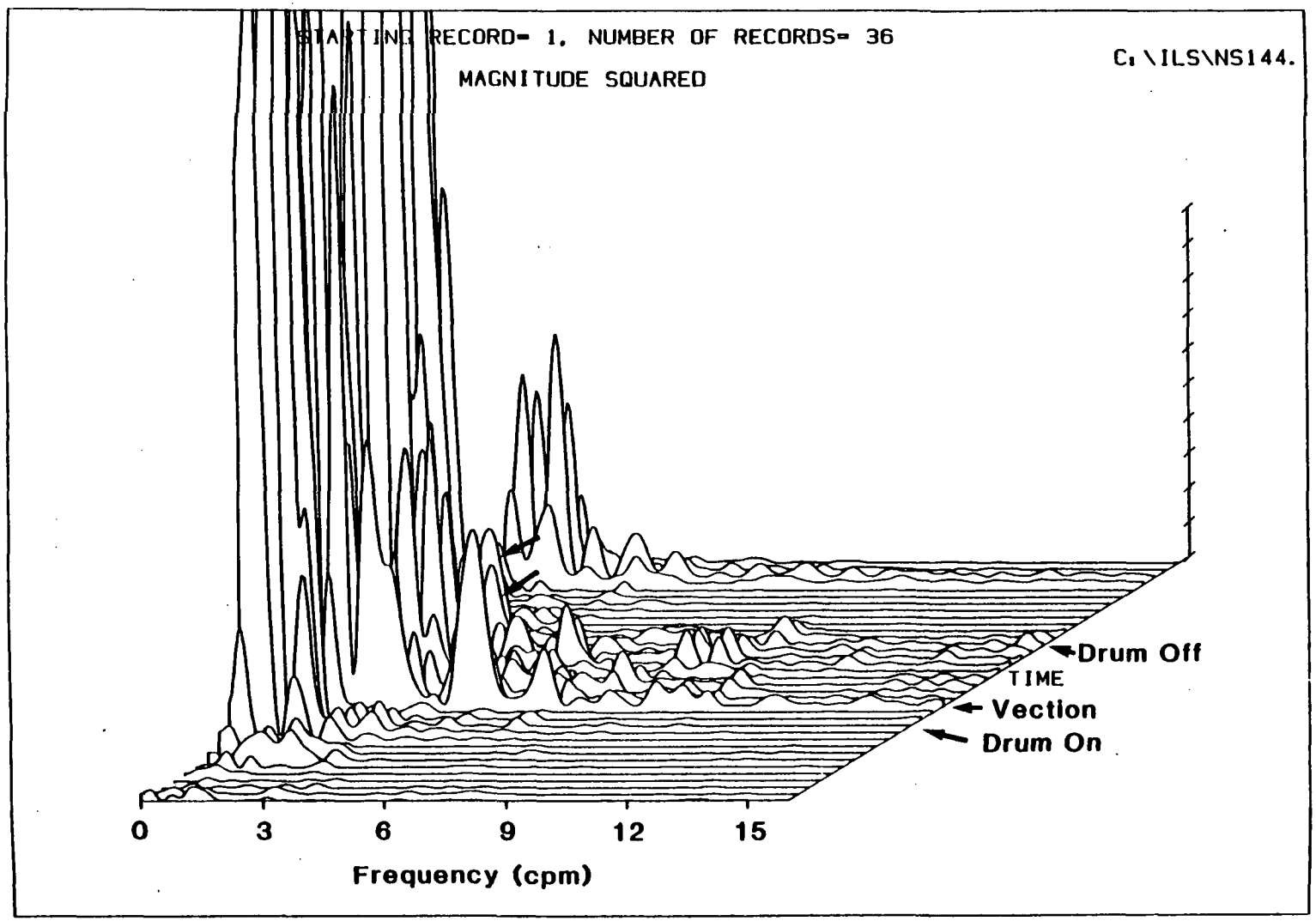


FIGURE 12. RUNNING SPECTRAL ANALYSIS OF EGG RECORDING FROM SUBJECT PRETREATED WITH METOCLOPRAMIDE BEFORE VECTION (same subject as shown in Figures 4, 5 and 11).

During Baseline low power 3 cpm peaks are seen. As drum rotation and Vection begin, a prominent 4 cpm peak occurs and is followed by prominent 3 cpm peaks (arrows). Lower power tachygastrias (5 and 8-9 cpm) are seen. Subject reported he was "dizzy; not queasy" 2 min before Drum Off. During early Recovery, 3 cpm peaks are suppressed but 3 cpm peaks become more prominent in the late Recovery period.

TABLE 3

Symptoms and Electrogastrogram (EGG)
Frequency Responses in
Postoperative Subjects During Vection Protocols

		EGG Frequencies (cpm)*			
	Subject	Baseline	Vection	Recovery	Sx +
1.	V + P (SM)	3	6	3	mod nausea, sweating
2.	Roux (MB)	1-3	5-7	1-3	mod nausea, hot
3.	Roux (CT)	flatline	3	5-6	mod nausea, belching
4.	Roux (LR)	11	11	11	mild nausea, sweating
5.	V + P (LB)	flatline	flatline	13	mild nausea, sweating
6.	Gastrectomy (WC)	flatline	flatline	10-11	No Sx

*cpm = cyles per min
+Sx = symptoms; subjective estimate of intensity during vection; mod = moderate
V+P = vagotomy and pyloroplasty
Roux = Roux-en-Y

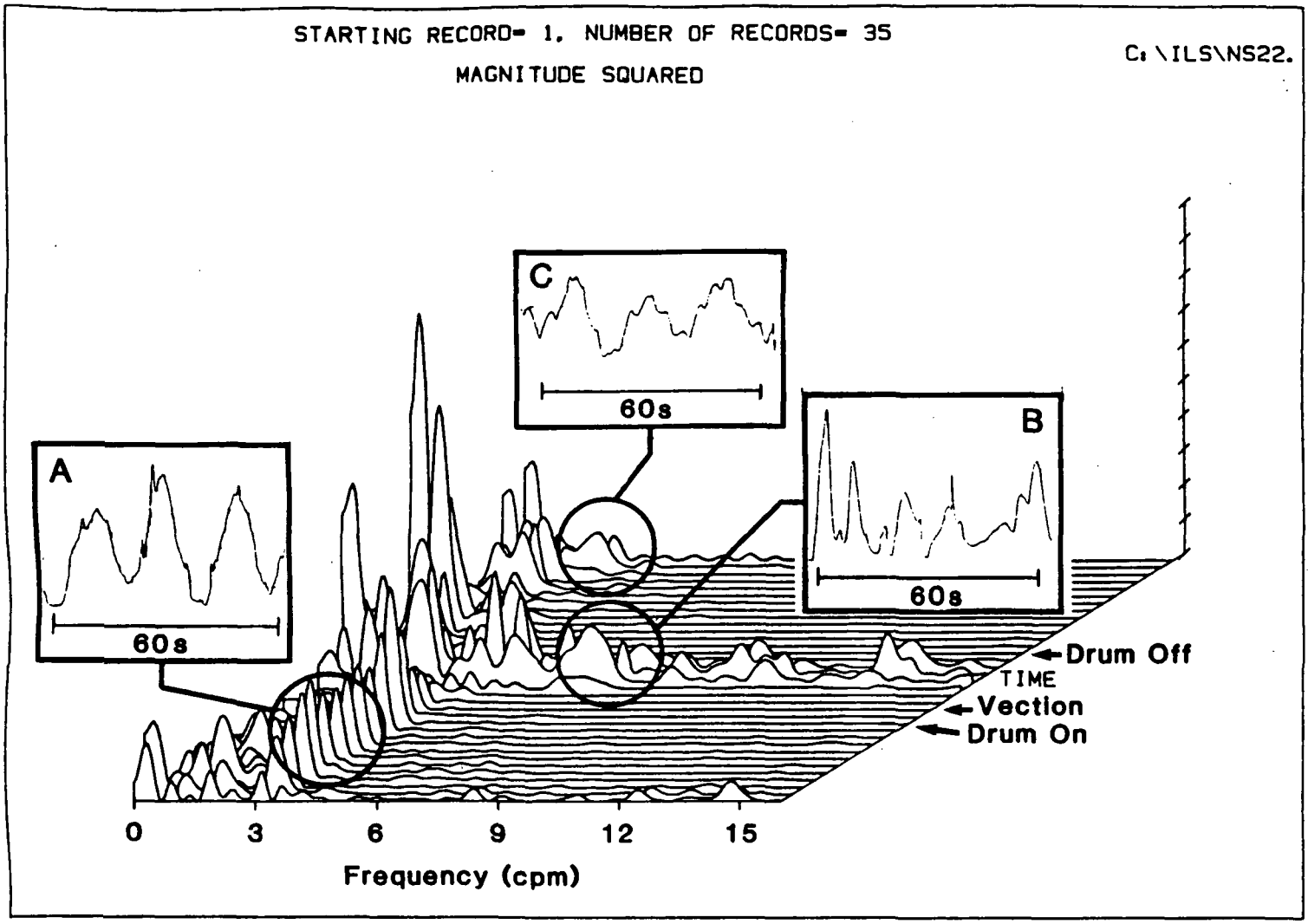


FIGURE 13. COMPOSITE EGG AND RUNNING SPECTRAL ANALYSIS (RSA) FROM A POST VAGOTOMY AND PYLOROPLASTY SUBJECT. RSA shows strong 3 cpm peaks during baseline. Actual EGG signal also shows strong 3 cpm pattern (see insert A). Subject developed moderate nausea after 6 min. of Vection with onset of tachygastria as shown in EGG signal (insert B) and the loss of 3 cpm peak in RSA with onset of a spectrum of tachygastria peaks (predominantly 6-7 cpm and 9-10 cpm). Late in the Recovery period the RSA 3 cpm peak returns; 3 cpm pattern is also seen in the actual EGG signal (insert C). Nausea has resolved.

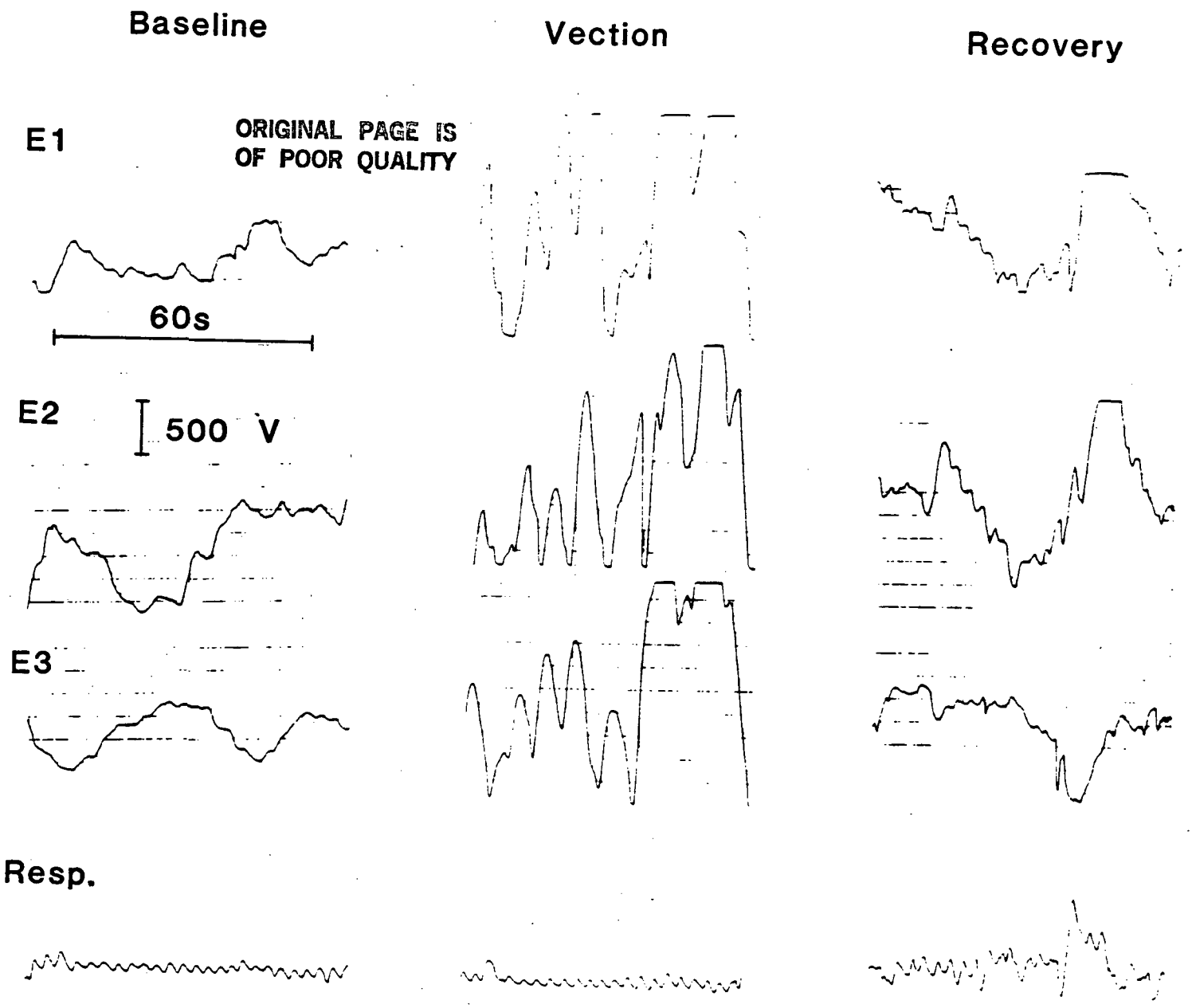


FIGURE 14. VECTION-INDUCED NAUSEA AND GASTRIC MYOELECTRIC RESPONSE TO VECTION IN A SUBJECT WITH VAGOTOMY AND ANTRECTOMY (Roux-en-Y). Baseline EGG shows low frequency wave forms; during Vection (min 8 is shown). High-amplitude, narrow-based waves (approximately 8 cpm) are seen and the subject reported nausea. Tachygastria continued until drum rotation was stopped. During Recovery, nausea resolved and low frequency waves of higher amplitude than baseline returned. Respiratory rate is 18-20/min during each period.

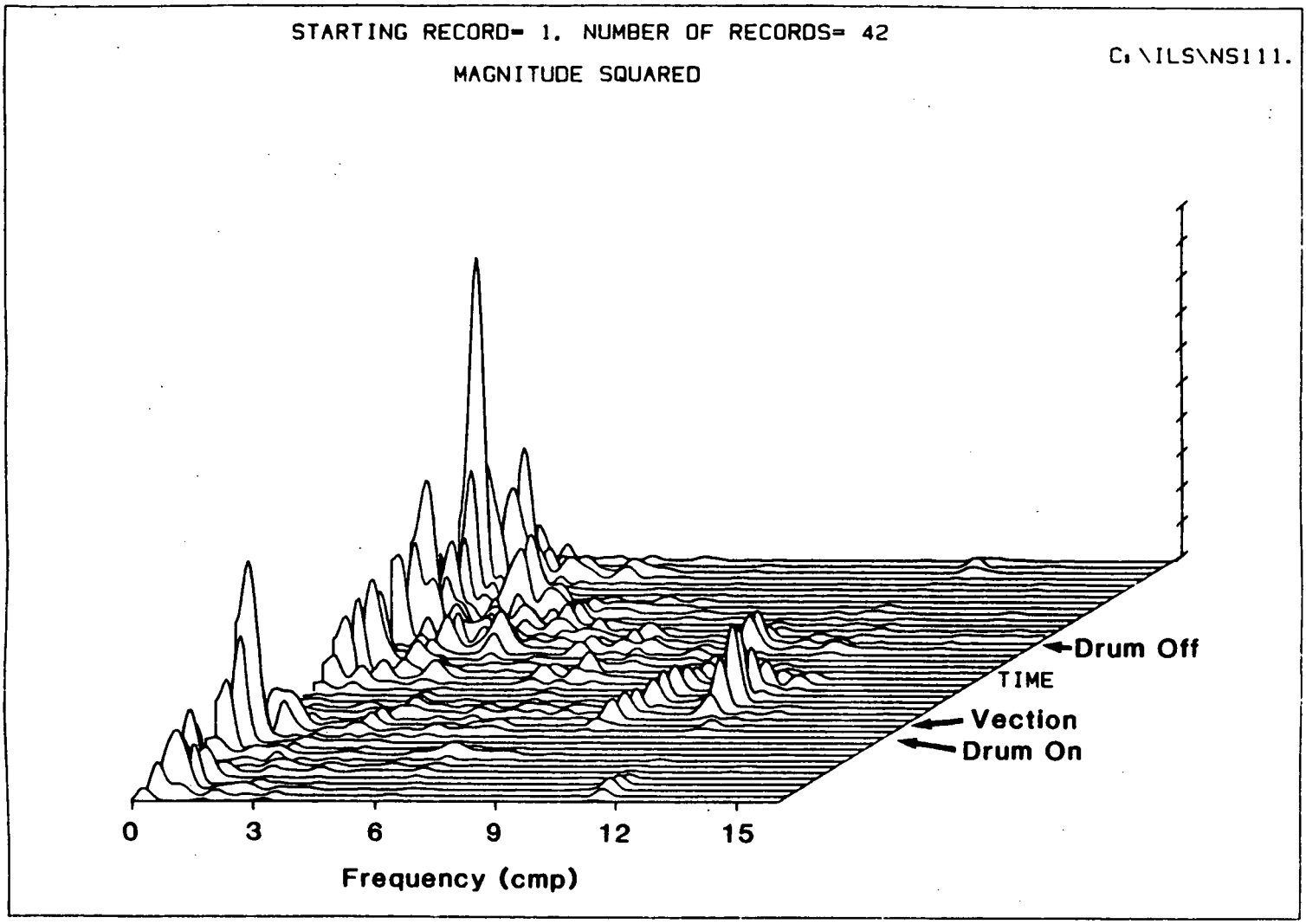


FIGURE 15. RUNNING SPECTRAL ANALYSIS OF EGG SIGNAL IN A SYMPTOMATIC SUBJECT WITH VAGOTOMY AND ANTRECTOMY (same subject as in Figure 14). Baseline period before "Drum On" shows predominant power at low frequencies (approximately 1 cpm). During Vection an 8 cpm peak develops and with onset of nausea (approximately min 8) a 10-11 cpm peak temporarily emerges. The 8 cpm peak persists until drum is turned off. During Recovery, the low frequency peaks again predominate. No 3 cpm peaks are seen.

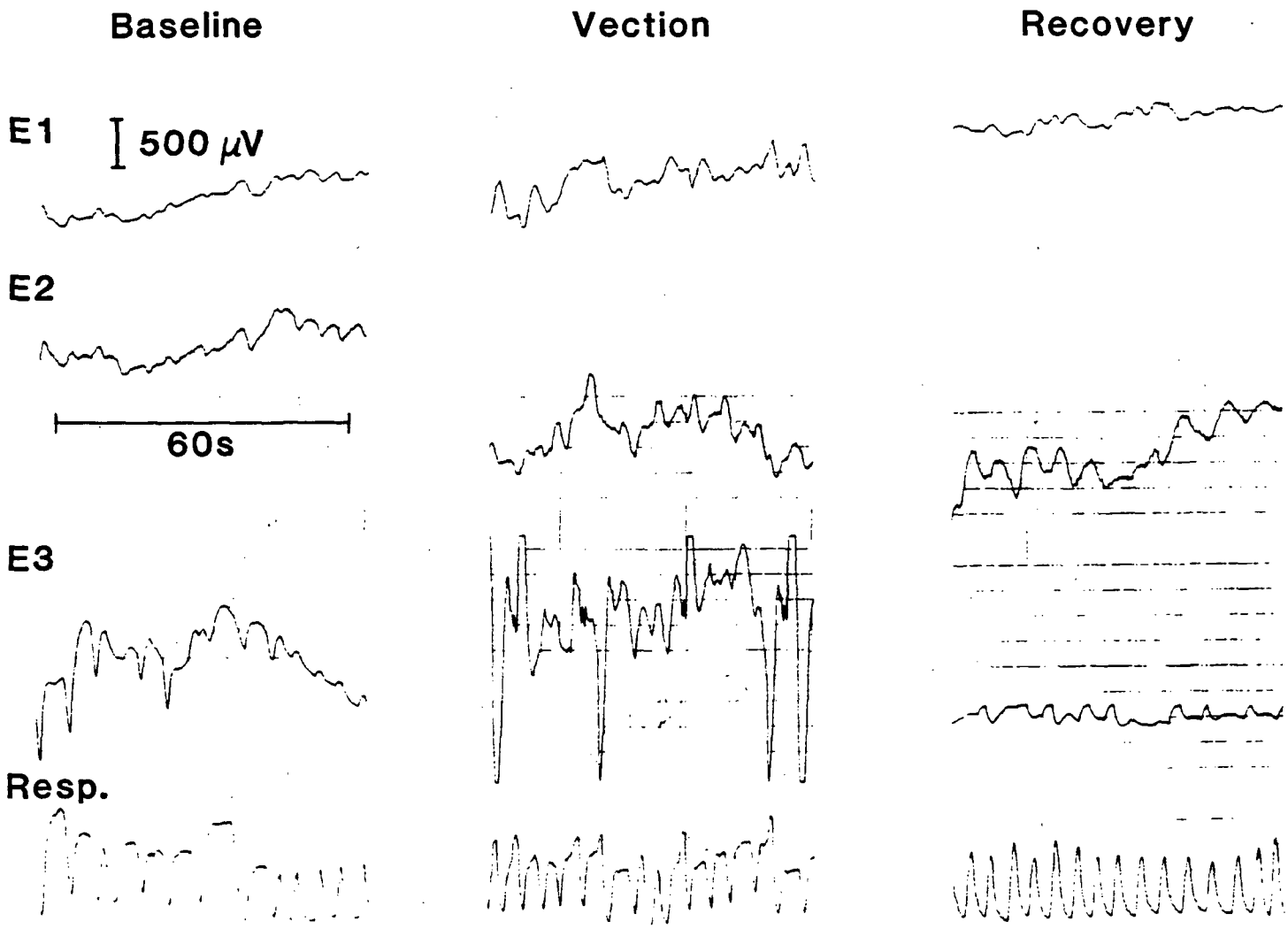


FIGURE 16. VECTION-INDUCED GASTRIC MYOELECTRIC ACTIVITY IN A SYMPTOM-FREE SUBJECT WITH TOTAL GASTRECTOMY. During Baseline, EGG shows a flat line with some respiratory artifact. During Vection (min 6 is shown), the subject has no symptoms and the EGG signal continues to reflect respiration (approximately 15 cpm). During recovery (min 12 is shown), at 9 cpm pattern presumably from jejunum is seen in E2; the subject remains symptom-free.

FIGURE 17

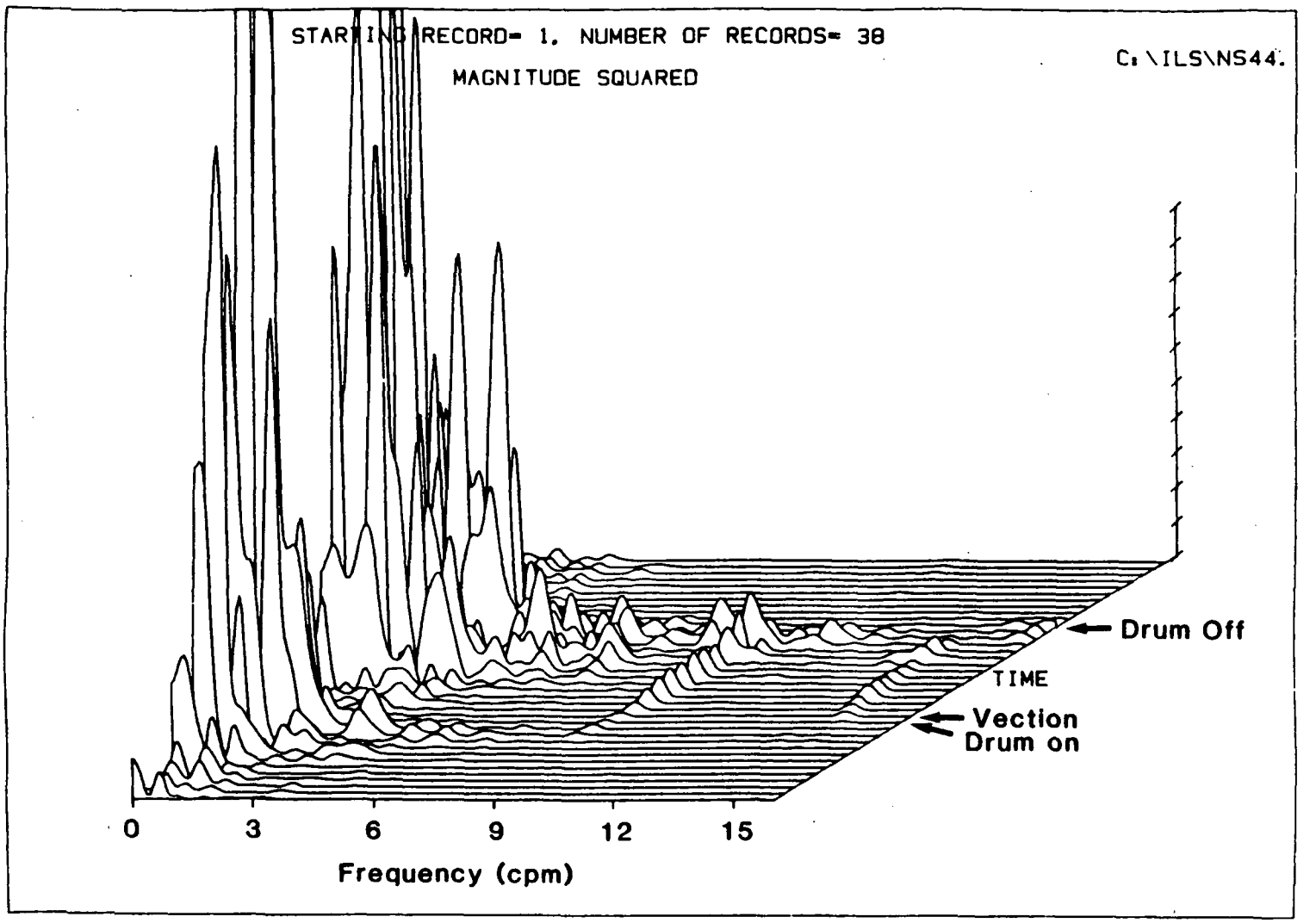


FIGURE 17. RUNNING SPECTRAL ANALYSIS OF EGG SIGNAL FROM SUBJECT WITH TOTAL GASTRECTOMY (same subject as in Figure 16). During Baseline, Vection and Recovery, low frequency 1-2 cpm peaks predominate and reflect the relatively flat EGG signal shown in Figure 16. During Vection, however, 9 cpm peaks and 15 cpm peaks emerge, probably reflecting jejunal activity and respiration, respectively. During Recovery, very little cyclical activity is present.

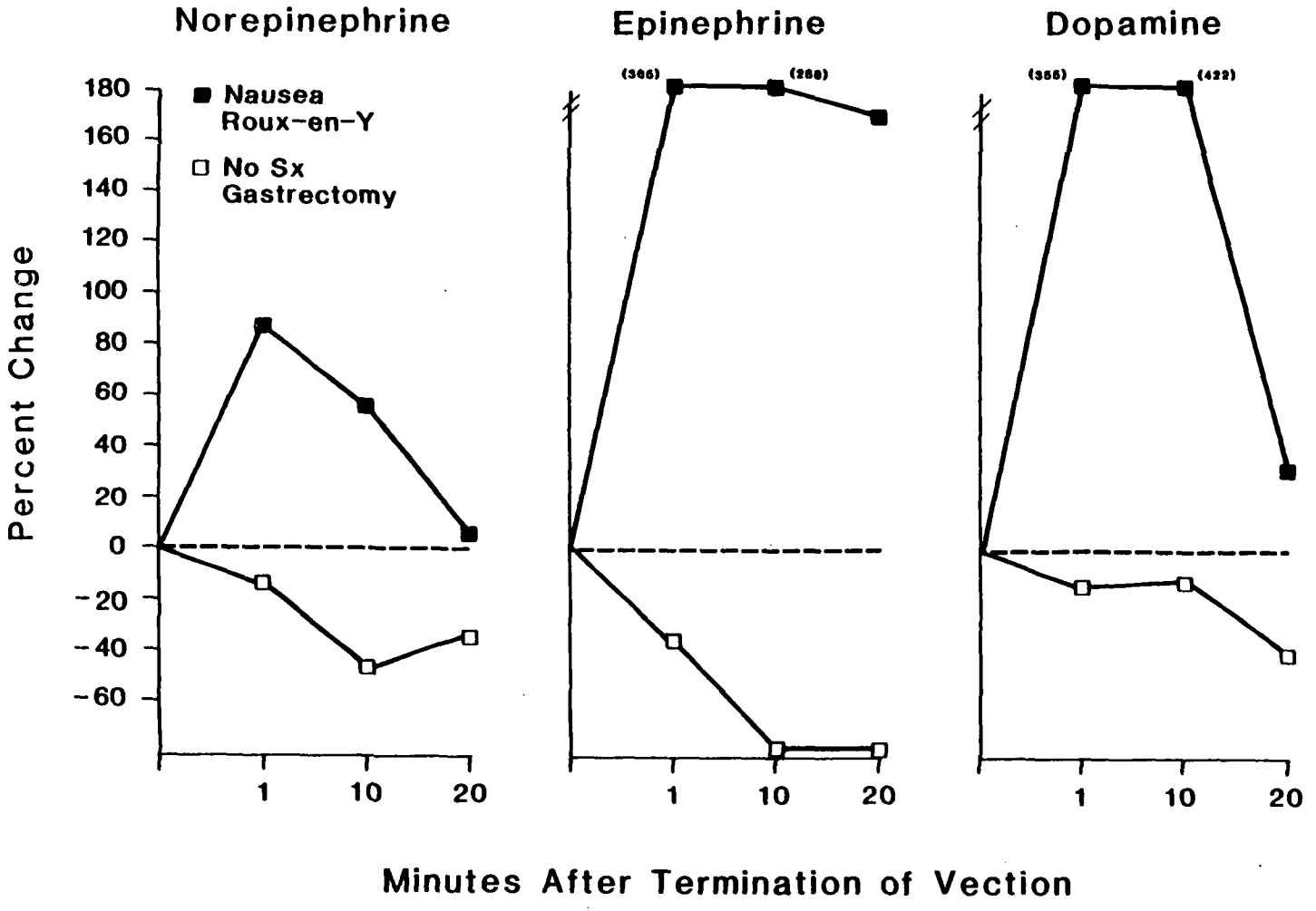


FIGURE 18. PLASMA CATECHOLAMINE RESPONSES TO VECTION IN SUBJECTS WITH ROUX-EN-Y AND TOTAL GASTRECTOMY. Percent change in catecholamine values from baseline to post vection time points are presented as in Figure 10. One minute after vection the catecholamines are markedly increased in the Roux-en-Y subject with vection-induced nausea, (see Figures 14 and 15 for this subject's EGG and RSA); whereas, catecholamines were persistently suppressed in the gastrectomy subject who reported no symptoms during vection (see Figure 16 and 17 for this subject's EGG and RSA).

X. Publications Resulting From NASA Support.

Please see Appendix A. Stern, R.M., Koch, K.L., Stewart, W.R. and Lindblad, I.M. Spectral analysis of tachygastria recorded during motion sickness. (Submitted to Gastroenterology.)

Spectral Analysis of Tachygastria Recorded During Motion Sickness

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Running Head: Tachygastria and Motion Sickness

Keywords: Tachygastria; Motion Sickness; Electrogastrogram; Gastric Myoelectric Activity; Visual-Vestibular Mismatch; Running Spectral Analysis.

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Abstract

The purpose of the present experiment was to study frequency changes in gastric myoelectric activity of healthy human subjects as a function of motion sickness brought about by vection or illusory self-motion. Fifteen fasted healthy human subjects were seated inside a circular vection drum, the rotation of which produces visual signals of self-motion which are in conflict with vestibular signals (i.e., mismatched sensory input). An electrogastrogram was obtained for three 15 min periods: baseline, rotation, and after drum rotation stopped. Respiration, symptoms volunteered by subjects, and a continuous measure of intensity of symptoms were recorded. Five subjects showed a continuation of normal 3 cpm activity during drum rotation and reported no symptoms of motion sickness. Ten subjects showed a shift of their dominant gastric frequency from 3 cpm to 5-8 cpm during drum rotation and reported symptoms of motion sickness. Running spectral analysis revealed a close correspondence over time between tachygastria and reports of symptoms of motion sickness.

Keywords: Tachygastria; Motion Sickness; Electrogastrogram; Gastric Myoelectric Activity; Visual-Vestibular Mismatch; Running Spectral Analysis.

Spontaneous tachygastria was first observed in dogs (1,2) in the 1970s and in humans (3) shortly thereafter. Subsequently, tachygastria has been related to gastric retention (4) and nausea and vomiting (5,6). Tachygastria has also been observed in healthy fasted subjects (7) and following ingestion of barium sulfate (8). Abell and Malagelada (9) evoked tachygastria in healthy human subjects by intravenously infusing glucagon. In this later study and in other human experiments (6,7,9,10) gastric myoelectric activity was recorded with mucosal and cutaneous electrodes and frequency analysis showed good correspondence between the mucosal and cutaneous signals (electrogastrogram or EGG).

Although most individuals who experience motion sickness describe symptoms of vague epigastric discomfort and nausea, the relationship between these symptoms and gastric motility has been neglected for almost 40 years. Two early reports (11,12) demonstrated that decreased gastric contractions and tone were associated with motion sickness. A more recent study (13) showed that the stress of the cold-pressor procedure caused decreased antral contractions and delayed gastric emptying of a standard meal.

In a preliminary study by the present authors (14) it was shown that circular vection, i.e., the sense of self-motion in a stationary subject, produced symptoms of motion sickness in 14 of 21 subjects and in each of the 14 the EGG frequency shifted from the normal 3 cpm to tachygastria with frequencies of 5-8 cpm. However, it should be pointed out that in recent studies of cutaneously-recorded tachygastria (9,14) dysrhythmias were identified by visual inspection.

The twofold purpose of the present study was to investigate further the relationship between onset of tachygastria and onset of the symptoms of motion sickness and to apply a relatively new method of quantifying gastric dysrhythmias, running spectral analysis, to the EGG signal.

Materials and Methods

Volunteers

Fifteen college students were used as subjects, 8 men and 7 women. They were between 18 and 23 years old and reported no central nervous system or gastrointestinal diseases or symptoms. Subjects were fasted at least 4 hours before the experiment. The procedure used was approved by the Penn State Committee on Use of Human Subjects and informed consent was obtained from each subject.

Electrogastrographic Method

EGG was recorded from cutaneous bipolar electrodes positioned on the abdominal wall over the antrum. The approximate position of the electrodes relative to the umbilicus was as follows: 10 cm cephalad from the umbilicus and 6 cm left, and 4 cm cephalad on the midline of the abdomen. Electrodes were connected to a Beckman R611 recorder (SensorMedics, Anaheim, Ca.) with a time constant of 10 sec., high frequency cutoff of .08 Hz, and a paper speed of 1 mm/sec. Respiration was recorded with a strain-gauge transducer which was placed around the subject's chest and connected to the Beckman recorder.

Circular Vection Apparatus

Testing was carried out using a circular vection drum. The drum consisted of a metal cylinder 91.5 cm in height and 76 cm in diameter, the interior of which was covered with alternating 3.8 cm (5.7 deg.) black and

6.2 cm (9.3 deg.) white vertical stripes. The drum could be rotated clockwise or counterclockwise about its vertical axis at various speeds resulting in illusory self-motion. At the beginning of the experiment, subjects were seated inside the stationary drum with their heads positioned in the center of the drum and aligned with the vertical axis. Head position was maintained throughout the experiment by means of a chinrest.

Procedure

The baseline frequency of the EGG was established during an initial 15-min period while the subject sat within the stationary drum. Following this baseline period, the drum was rotated at a speed of 60°/s around the stationary subject for a maximum of 15 min. The EGG and respiration were recorded continuously during rotation. Subjects were asked to report when they experienced a sensation of self-motion (circular vection) in response to the motion of the drum surface and any symptoms of motion sickness. In addition, the subjects turned a knob attached to a potentiometer to indicate the intensity of their symptoms (0--no symptoms to 7--near vomiting). One channel of the Beckman polygraph was used to record the output of the potentiometer. Drum rotation was stopped at the subject's request if at any point motion sickness symptoms became uncomfortably intense. Finally, with the subject remaining in the drum, the EGG was recorded an additional 15 min after the drum was stopped. The EGG signal was simultaneously recorded on the Beckman and on a Honeywell 5600C FM tape recorder (Honeywell, Denver, Col.) and was later digitized at a rate of 1 Hz by a DEC PDP 11/34 computer (Digital Equipment Corp., Maynard, Mass.) The digitized signal was transmitted to an IBM 370/3381 (IBM, White Plains, NY) for spectral analysis.

Spectral Analysis

In a general sense, spectral analysis is a method by which a signal such as the EGG is decomposed into a sum of sinusoidal components. The spectral analyses shown below were obtained using the BMDP statistical program P1T (15). Each line represents the spectral density function for a 256 s section of the EGG signal. The data window for each subsequent spectral density function included the final 75% or 192 s of the preceeding window as well as the next 64 s of digitized signal yielding a "running spectral plot" in which each consecutive line contains 64 s of new information.

Prior to analysis the entire series for each subject was linearly detrended and mean centered to zero. The first and last 5% of data in each 256 s epoch were tapered using a weighting function. These 256 point series were then fourier transformed and periodograms formed from the fourier coefficients. Spectral density estimates were formed from an average of adjacent periodograms within a bandwidth of .0195 Hz. To summarize, the pseudo 3-D plots displayed below show the spectral density at frequencies from 0 to 15 cycles per minute. Frequency is plotted on the horizontal axis, time on the vertical axis, and spectral density on the axis which appears to rise from the surface of the paper.

Results

Effects of Circular Vection on Gastric Electrical Activity

Five of the 15 subjects showed a decrease in power at 3 cpm during drum rotation but no tachygastria and reported no symptoms of motion sickness.

The running spectral analysis of the EGG recorded from one of these subjects is shown in Figure 1. Prior to drum rotation the dominant frequency of gastric electrical activity was 3 cpm. With the onset of drum rotation there was attenuation of 3 cpm activity; initially 1 cpm activity was observed but 3 cpm peaks dominate the vection period. After drum rotation stopped 1 cpm activity increased briefly, followed by the return of 3 cpm to the level of activity seen prior to drum rotation.

The remaining 10 subjects also showed a dominant frequency of 3 cpm prior to drum rotation, but all 10 developed tachygastria and symptoms of motion sickness during drum rotation. Figure 2 shows the running spectral analysis from a subject who developed tachygastria approximately 5 min after drum rotation began. This particular subject continued to show tachygastria 5 min after drum offset. Normal 3 cpm activity returned during the final few minutes of the session. Figure 3 shows a running spectral analysis from a subject who developed tachygastria after approximately 8 min of drum rotation. The tachygastria continued for approximately 6 min after the drum was stopped and was followed by the return of weak 3 cpm activity. The final example, Figure 4, shows the running spectral analysis from a subject who developed tachygastria as drum rotation was prematurely stopped at Min. 7 because of intense symptoms. The tachygastria continued for approximately 8 min with very weak 3 cpm returning at the end of the session.

Effects of Circular Vection on Symptoms of Motion Sickness

The effects of circular vection on electrogastrographic activity and symptoms of motion sickness are summarized in Table 1. Five of the subjects reported no symptoms of motion sickness, the same five who maintained 3 cpm

peaks and failed to develop tachygastria. One of these subjects, Subject No. 4, did indicate an intensity of symptoms of 2 (maximum 7) during drum rotation, but when questioned at the end of the session she reported no symptoms (see Figure 1). The remaining 10 subjects all reported symptoms of motion sickness including sweating, salivation, dizziness, headache, nausea, and stomachache and all 10 developed tachygastria.

Correspondence Between Electrogastrographic Frequency Shifts and Symptoms

As indicated above, 5 subjects reported no symptoms of motion sickness and maintained 3 cpm activity. The remaining 10 subjects reported symptoms of motion sickness and developed tachygastria. A correspondence between the onset of tachygastria and the first reports of symptoms is suggested. Of the 10 subjects who reported symptoms, in 7 cases the onset of tachygastria and the first report of symptoms came within 2 min. A very strong temporal correspondence between onset and resolution of tachygastria and increasing and decreasing symptoms can be seen in Figures 2-4. For example, in Figure 2, the subject indicated the start of symptoms at Min. 5 of drum rotation and the first peaks of tachygastria frequencies began at the same time. In Figure 3, the subject reported the first symptom, "suddenly felt sick in stomach," at Min. 8 of drum rotation, the same time that tachygastria became evident. Because of intense symptoms the subject asked that drum rotation be stopped at Min. 10. In Figure 4, the subject started to report symptoms as soon as drum rotation started and indicated that they became most intense at Min. 7 at which point she asked that drum rotation be stopped and manifested tachygastria.

Discussion

The present studies provide new information regarding gastric rhythm disturbances and motion-sickness symptoms induced by circular vection. Onset of symptoms during vection was associated with a diminution of 3 cpm activity and the emergence of tachygastrias ranging from 4-9 cpm. Asymptomatic subjects may temporarily shift to lower amplitude 3 cpm activity but do not develop tachygastrias. These results, which were derived from prospective rating of symptoms during vection and from objective analysis of the EGG waveforms, confirm and extend previous work (14) linking tachygastria and symptoms of motion sickness.

Gastric slow waves (also termed electrical control activity) oscillate at a frequency approximating 3 cpm in man and 5 cpm in dog. Previously, it was believed that the 3 cpm frequency was omnipresent, but recent work in healthy subjects revealed spontaneous (7) and glucagon-induced tachygastrias (9) which were recorded with equal fidelity by cutaneous and mucosal electrodes. Together with the present studies, these data suggest that slow wave activity in healthy individuals may intermittently shift into the tachygastria frequency ranges of 4-9 cpm.

Tachygastrias were originally described in patients with nausea and vomiting (5,6). The stimulus and cause of the tachygastrias in these patients are unknown. Nausea and epigastric distress are well-known and prominent symptoms of motion sickness. Circular vection created a sense of illusory self-motion in all our subjects. During vection the sensory input from the visual and vestibular systems is "mismatched," (i.e., visual input indicates motion; whereas, vestibular input indicates no motion), a circumstance which leads to symptoms of motion sickness in susceptible subjects (16). Previous

studies (11,12) have correlated decreased gastric contractility and tone and motion sickness. Tachygastrias have been associated with decreased contractility in dogs (1,2,17) and with delayed gastric emptying in a human subject (4). Thus, the emergence of tachygastria with onset of motion sickness is consistent with previous literature.

The integration of visual and vestibular sensory signals in brain stem nuclei is presumably important in the symptomatic outcome in susceptible individuals. Some healthy individuals experience pleasant sensations, i.e., exhilaration, during vection while the majority experience nausea and tachygastria. The neurohumoral mechanisms which mediate tachygastria are unknown. Sympathetic dominance has been hypothesized to account for gastric dysrhythmias in man and dog after gastric surgery (3,8). Infusion of catecholamines including dopamine induce antral dysrhythmias in dog (17,19,20). Thus, it is possible that the "stress" of the visual-vestibular mismatch results in catecholamine release, a response which temporarily suppresses gastric vagal input and precipitates tachygastrias. Consistent with these findings is the report by Stanghellini et al. (21) who observed that cold caloric vestibular stimulation caused nausea, decreased antral contractility and a delay in gastric emptying of a meal. The decrease in gastric motility caused by vestibular stimulation correlated with increased levels of plama nonepinephrine and beta-endorphin. Release of such sympathetic neurotransmitters may also influence gastric electrical rhythm during vection. The present results show several distinct EGG frequency peaks during motion sickness symptoms indicating the instability of the slow wave pacemaker and suggesting the possibility of several and/or wandering pacemaker foci.

Of interest, also, are the subjects who do not develop motion sickness during vection. Does vection elicit minimal activity of sympathetic or humoral pathways which might disturb slow wave rhythm? Or, in these asymptomatic subjects, do parasympathetic vagal influences resist shifts in gastric frequency? in the symptomatic subjects, the 3 cpm EGG pattern gradually was re-established after the stress of vection ceased, suggesting the return of baseline conditions, i.e., parasympathetic predominance. Our studies suggest that strengthening or maintaining 3 cpm EGG patterns may retard/decrease the onset of tachygastria and motion sickness, a hypothesis with therapeutic implications.

The methods used in the present study have certain advantages over those previously used to induce and measure tachygastria and motion sickness. The circular vection drum described in this report is safe, since the subject remains stationary, and reliably evokes both tachygastria and symptoms of motion sickness in approximately 66% of healthy human subjects. The frequency of tachygastria as measured with the non-invasive EGG, has been shown to be identical to the frequency recorded with mucosal electrodes (7). Furthermore, running spectral analysis of EGG recordings together with the continuous measure of symptom intensity allows for the comprehensive visual displays shown in Figures 1-4.

In summary, 15 healthy human subjects were exposed to circular vection and the non-invasive EGG was used to monitor changes in gastric basic electrical rhythm. Vection produced tachygastria and symptoms of motion sickness in 10 individuals. Running spectral analysis and the continuous measure of intensity of symptoms revealed a close correspondence over time between tachygastria and reports of symptoms of motion sickness.

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Table 1. Summary of the Electrogastrographic Activity and Reports of Symptoms of Motion Sickness in Response to Circular Vection

Subject Number	Sex	Onset of Tachygastria*	First Report of Symptoms*	Description of Symptoms
1	F	12	3	Sweating, dizzy, salivating
2	F	--	--	None
3	M	7	6	Dizzy, feeling of loss of control
4	F	8	8	Suddenly felt sick in stomach
5	F	--	--	None
6	F	4	7	Headache, queasy stomach
7	F	7	1	Sweating, chills, drowsy, headache, stomachache
8	M	6	5	Sweating, queasy stomach, dizzy
9	M	3	1	Nausea at beginning of rotation
10	M	7	6	Chills, dizzy, queasy stomach
11	M	3	3	Sweating, headache, stomachache
12	M	--	--	None
13	M	--	--	None
14	M	--	--	None
15	F	3	3	Headache, stomachache

*In minutes from start of drum rotation

Figure Legends

Figure 1. Running spectral analysis of the EGG of a subject who reported no specific symptoms of motion sickness. Note strong 3 cpm activity prior to drum rotation, attenuation during rotation but no tachygastria, and a return to strong 3 cpm after rotation. As can be seen on the right hand side of the figure, this subject did report a low level of symptom intensity (2 out of a possible maximum of 7) but at the completion of the session denied experiencing any specific symptoms.

Figure 2. Running spectral analysis of the EGG of a subject who reported that during rotation he was sweating, dizzy and had a queasy stomach. Whereas 3 and 1 cpm activity dominate the spectral analysis prior to drum rotation, 6 minutes after the onset of rotation spectral density showed a peak at 6 cpm with additional activity in the tachygastria range (5-9 cpm). At approximately this same point in time the subject reported his first symptoms of motion sickness.

Figure 3. A clear peak of activity at 3 cpm can be seen in the running spectral analysis of the EGG of this subject prior to drum rotation. With the onset of rotation there was attenuation of the 3 cpm activity until Min 8 at which time tachygastria began and the subject suddenly felt sick in the stomach. The subject requested that rotation be stopped at Min 10. Tachygastria continued for approximately 6 minutes after drum offset and was followed by a return of weak 3 cpm activity.

Figure 4. Running spectral analysis of the EGG of a subject who showed a peak of activity at 3 cpm prior to drum rotation and for 6 minutes after the onset of rotation. At Min 7 the subject reported the intensity of her symptoms at 6 (out of 7) and asked that rotation be stopped. Tachygastria appeared at this point and continued for approximately 6 minutes. Weak 3 cpm activity can be seen at the end of the session.

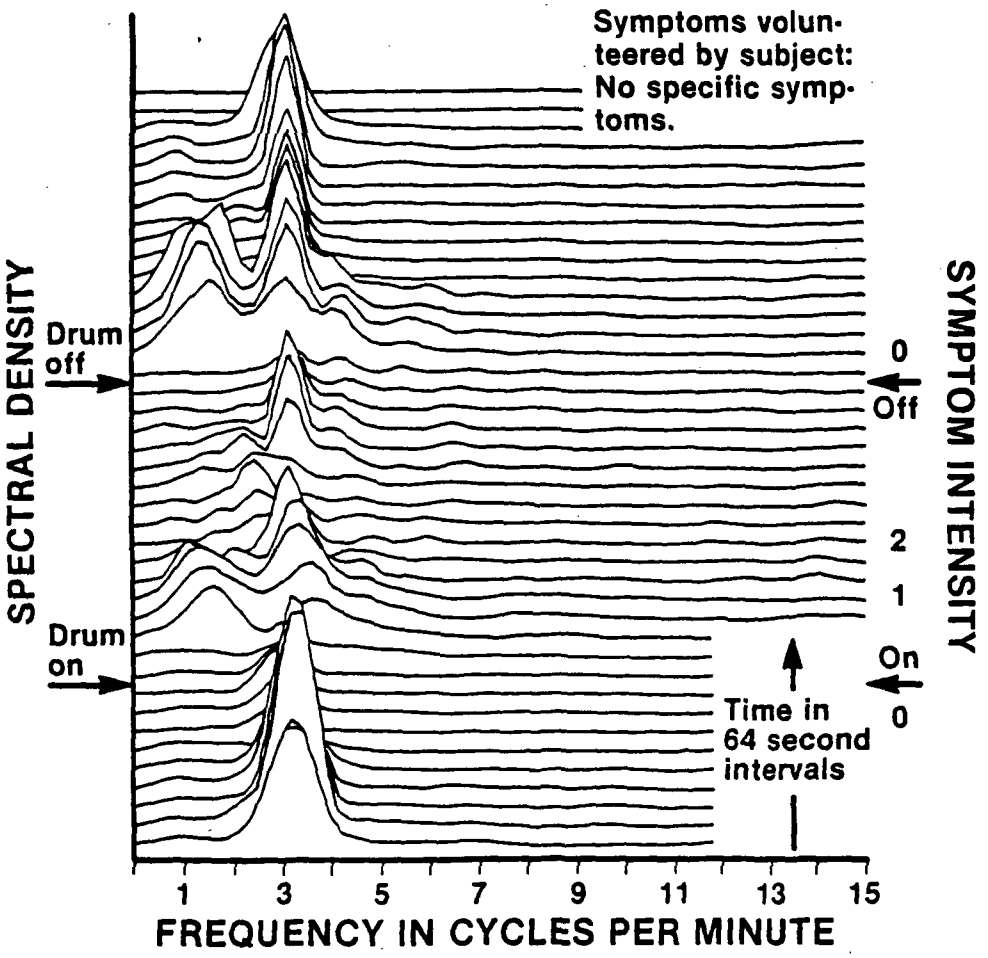
Symptoms volunteered by subject: No specific symptoms.
SPECTRAL DENSITY
Drum off
Drum on
SYMPTOM INTENSITY
0
Off
2
1
On
0
Time in 64 second intervals
1
3
5
7
9
11
13
15
FREQUENCY IN CYCLES PER MINUTE

Fig-1

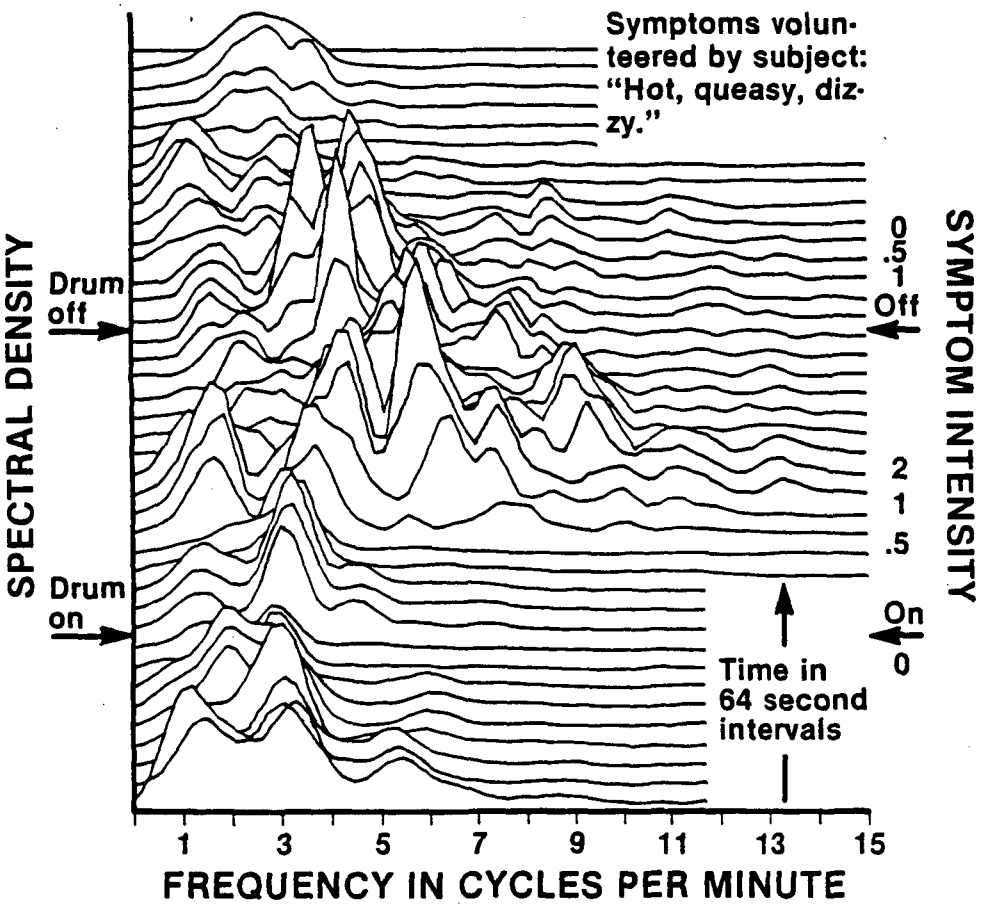
Symptoms volunteered by subject: "Hot, queasy, dizzy."
SPECTRAL DENSITY
Drum off
Drum on
SYMPTOM INTENSITY
0
.5
1
Off
2
1
.5
On
0
Time in 64 second intervals
1
3
5
7
9
11
13
15
FREQUENCY IN CYCLES PER MINUTE

Fig. 2

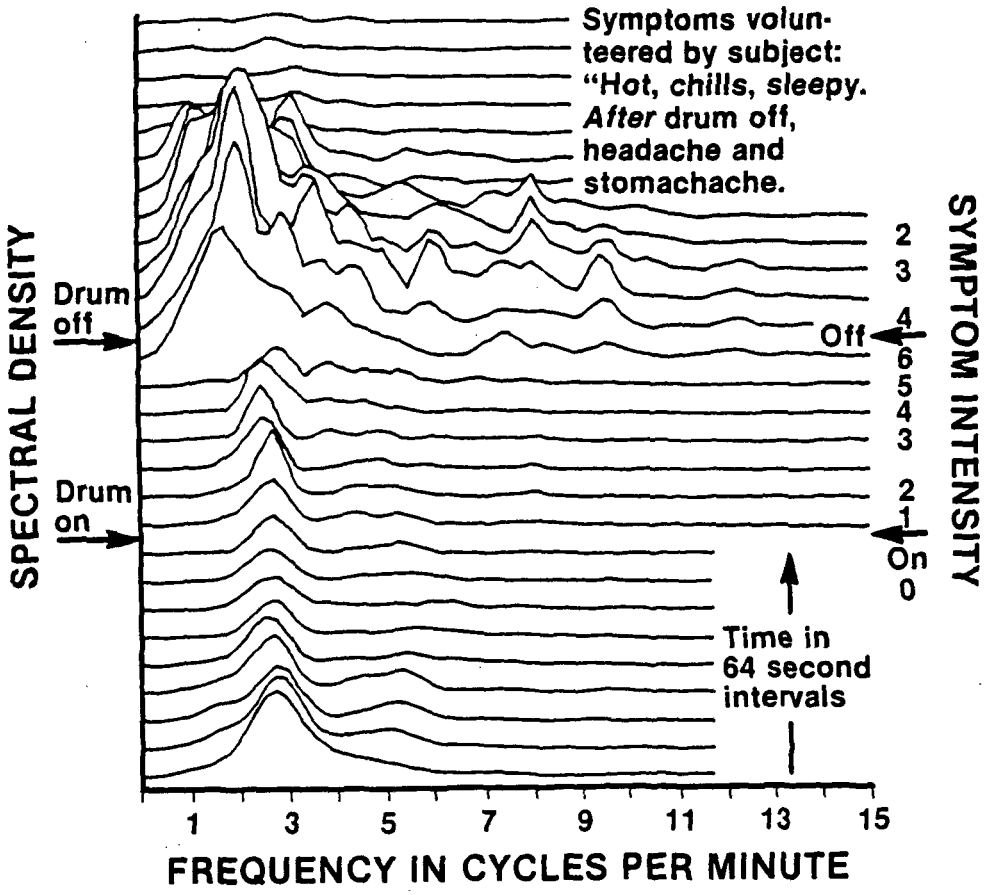
Symptoms volunteered by subject: "Hot, chills, sleepy. After drum off, headache and stomachache.
SPECTRAL DENSITY
Drum off
Drum on
SYMPTOM INTENSITY
2
3
4
Off
6
5
4
3
2
1
On
0
Time in 64 second intervals
1
3
5
7
9
11
13
15
FREQUENCY IN CYCLES PER MINUTE

Fig. 3

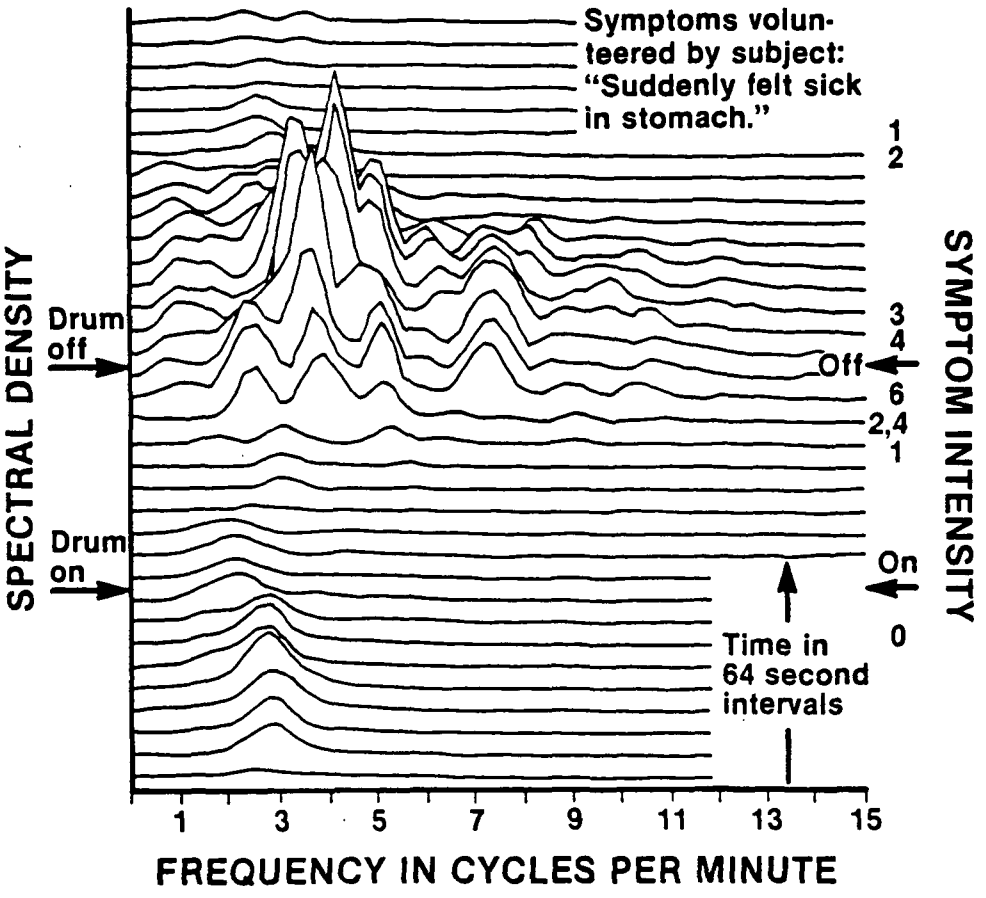
Symptoms volunteered by subject: "Suddenly felt sick in stomach."
SPECTRAL DENSITY
SYMPTOM INTENSITY
Drum off
Drum on
Off
On
1
2
3
4
6
2,4
1
0
Time in 64 second intervals
1
3
5
7
9
11
13
15
FREQUENCY IN CYCLES PER MINUTE

Fig. 4