

**GINGER REDUCES HYPERGLYCEMIA-EVOKED GASTRIC DYSRHYTHMIAS IN
HEALTHY HUMANS: POSSIBLE ROLE OF ENDOGENOUS PROSTAGLANDINS**

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ABSTRACT

Acute hyperglycemia evokes gastric slow wave dysrhythmias via endogenous prostaglandin generation. Ginger exhibits slow wave antiarrhythmic effects in other models, but its actions on hyperglycemia-evoked gastric dysrhythmias are unexplored. We hypothesized that ginger prevents disruption of slow wave rhythm by acute hyperglycemia via inhibition of prostaglandin production but not its actions. 22 healthy humans underwent fasting electrogastrography (EGG) during hyperglycemic clamping to 250-290 mg/dl after double-blind placebo or ginger root (1 gm). Responses were compared to the prostaglandin E₁ analog misoprostol (400 µg). Dominant frequencies (DF) and the % recording times in the bradygastric (0.5-2 cycles per min), normal (2-4 cpm), and tachygastric (4-9 cpm) frequency ranges were analyzed. After placebo, hyperglycemia reduced normal 2-4 cpm activity from 94.4±2.6 to 66.0±10.4%, increased the DF from 2.96±0.04 to 4.09±0.45 cpm, and increased tachygastria from 2.0±1.4 to 29.3±10.7% (P<0.05). Hyperglycemia effects on normal activity (77.3±8.3%), DF (3.46±0.37 cpm), and tachygastria (15.6±8.6%) were significantly reduced by ginger (P<0.05). Misoprostol evoked decreases in normal activity from 95.4±2.0 to 81.7±3.0% and increases in tachygastria from 3.1±1.6 to 11.2±2.4 % (P<0.05). However, ginger did not correct these abnormalities versus placebo (P=NS). In conclusion, acute hyperglycemia evokes gastric slow wave dysrhythmias which are prevented by ginger root. Conversely, the compound has no effect on dysrhythmias elicited by a prostaglandin E₁ analog indicating that ginger likely acts to blunt production of prostaglandins rather than inhibiting their action. These findings suggest novel mechanisms for the traditional Chinese herbal remedy ginger.

Ginger (*Zingiber officinale*), a traditional Chinese herbal remedy, has been used to treat a number of medical conditions including headache, colds, and arthritis (Grant and Lutz, 2000). Anti-emetic actions of ginger have been reported in patients with nausea of pregnancy and in subjects with motion sickness (Vutyavanich et al., 2001; Grontved et al., 1988). Its effectiveness in preventing postoperative nausea and vomiting is uncertain with some studies observing benefits and others showing no effect (Phillips et al., 1993; Arfeen et al., 1995). The active ingredient responsible for the beneficial effects of ginger is uncertain and the mechanisms responsible for reducing nausea and vomiting are unknown, although previous investigations have demonstrated inhibitory effects on prostaglandin and leukotriene synthesis (Srivastava, 1984; Kiuchi et al., 1992).

Acute hyperglycemia delays gastric emptying and induces gastric slow wave dysrhythmias in healthy volunteers (MacGregor et al., 1976; Hasler et al., 1995). Furthermore, dysrhythmias such as tachygastria are common in patients with diabetes mellitus and are increased during periods of poor glycemic control (Jebbink et al, 1994b). In healthy volunteers, the cyclooxygenase inhibitor indomethacin prevents development of tachygastria during hyperglycemic clamping suggesting mediation of dysrhythmia formation by endogenous prostaglandin production (Hasler et al., 1995). The ability of ginger to prevent the slow wave rhythm disruptive effects of acute hyperglycemia is untested and the role of prostaglandin pathways in any antidysrhythmic effects of ginger is unknown.

Thus, we designed studies with the following specific aims. Firstly, we performed double-blind, placebo-controlled studies to test if ginger root inhibits generation of gastric slow wave dysrhythmias during acute hyperglycemia in healthy human volunteers. Secondly, we compared these results to the ability of ginger root to prevent dysrhythmic activity evoked by

administration of the prostaglandin E₁ analog misoprostol to assess if ginger acts to block the actions of prostaglandins. Through these investigations, we hoped to gain insight into the mechanisms of the traditional Chinese herbal remedy ginger.

METHODS

Study Population

Twenty-two healthy volunteers (age 19-49 years, 15 males, 7 females) with no history of gastrointestinal symptoms, no prior gastrointestinal surgery, and on no medications were recruited through campus wide advertisement to study the effects of ginger root on gastric dysrhythmias occurring as a consequence of acute hyperglycemia and administration of a prostaglandin E₁ analog. Subjects with underlying medical conditions or pregnancy were excluded. All subjects provided written informed consent prior to participation in these investigations. Studies were approved by the University of Michigan Institutional Review Board.

Study Protocol

Each volunteer underwent electrogastrographic (EGG) studies under 4 separate test conditions in random order on different days separated by at least 72 hours: (1) hyperglycemic clamping after ginger, (2) hyperglycemic clamping after placebo, (3) misoprostol after ginger, and (4) misoprostol after placebo. Prior to each study day, subjects fasted for 8 hours and abstained from caffeine, alcohol, and tobacco for at least 12 hours. On the morning of study, volunteers swallowed either two ginger root powder capsules (500 mg each, Ginger Root[®], Nature's Way Products Inc., Springville, UT) or two identical appearing placebo capsules with 20 ml water in double-blind fashion, in random order 30 minutes prior to initiation of EGG recording. Each volunteer was positioned at a 30° incline in a quiet, warm room without visual or auditory distractions and a 30 minute baseline EGG was recorded. For hyperglycemic

clamping studies, 20% dextrose was then infused intravenously to achieve a plasma glucose concentration between 250 and 290 mg/dl. Once this level was reached, a 30 minute EGG recording during stable hyperglycemia was obtained. For prostaglandin E₁ studies, volunteers swallowed 400 µg of misoprostol (Cytotec, Searle, Skokie, IL) and 60 minute EGG recordings were obtained.

Electrogastrography Methodology

EGG was performed according to a modification of previously described methods (Stern et al., 1987). After gentle skin abrasion to enhance electrical conduction, 6 Ag-AgCl electrodes (Accutac Diaphoretic ECG Electrodes, NDM, Dayton, OH) were affixed to the abdomen. The first electrode was placed in the midclavicular line below the left costal margin. The third electrode was placed midway between the xiphoid and umbilicus in the midline. The second electrode was placed equidistant between the first and the third electrodes. Three reference electrodes were affixed in the right upper quadrant below the right costal margin. Electrodes were connected via direct nystagmus couplers (model 9859, SensorMedic, Anaheim, CA) to a chart recorder for continuous display of gastric myoelectric activity. Time constants were set at 10 seconds and high frequency cutoffs at 0.3 Hz to minimize interference from non-gastric signals. Respiration and body movements were monitored by a belt pneumograph connected to an indirect blood pressure coupler (model 9863B, SensorMedic Corp.) on the chart recorder. The chart recorder was interfaced with a personal computer (4DX2-66V; Gateway 2000, North Sioux City, ND) via an analog-to digital converter (DAS-16; Metrabyte Corp., Taunton, MA). Signals were digitized at 1 Hz and filtered above 15 cpm and below 0.5 cpm to remove high- and low-frequency noise.

The three channels of EGG recording were initially analyzed visually to determine which lead provided the signal most free of noise. The recording from this lead then was subjected to quantitative computer analysis. All tracings were analyzed in blinded fashion so that the investigator did not know either the volunteers or the test conditions being studied. Any signals showing clear respiratory or movement artifact were excluded from EGG analysis. Analyses were performed across the frequency range from 0.5 to 12 cpm on 256-second segments of recording with a 76% overlap such that successive lines in the running analysis plot represented data from consecutive 60 second intervals. Recording segments were subjected to fast Fourier transformation and power spectral analysis as previously described (Hasler et al., 1995).

From this analysis, the dominant frequency was measured for each recording segment. From these values, the mean dominant frequency was calculated for each test condition. Furthermore, the percentages of recording time in which the dominant frequency was in the bradygastric (>0.5 and <2.0 cycles per minute [cpm]), normal (≥ 2.0 and ≤ 4.0 cpm), tachygastric (>4 and ≤ 9 cpm), and duodenal/respiratory (>9 cpm) frequency ranges were assessed.

Hyperglycemic Clamping Technique

Hyperglycemic clamping studies were performed according to the method of DeFronzo et al. to fix plasma glucose levels between 250 and 290 mg/dl (DeFronzo et al., 1979). Intravenous catheters were introduced into the left and right antecubital veins for dextrose infusion and plasma glucose monitoring, respectively. Patency of the lines was maintained with periodic infusions of heparin flush-lock solution (100 USP units per milliliter). A 15 minute priming dose of 20% dextrose was given, and the maintenance infusion rates were adjusted as needed by monitoring plasma glucose levels at 5 minute intervals throughout the study using a

portable glucose analyzer (One Touch II; Lifescan, Inc., Milpitas, CA). Using this technique, plasma glucose levels were maintained within $\pm 10\%$ of the desired values.

Statistical Analysis

All results are expressed as means \pm SEM. Paired two-tailed Student's t testing was performed to compare EGG dominant frequencies, powers of the dominant frequencies, and the percentages of recording time in the different frequency ranges. Statistical significance was defined by P values of less than 0.05.

RESULTS

Study Population

Of the 22 volunteers recruited for participation in this investigation, one subject withdrew because of pain at the site of intravenous dextrose infusion and one withdrew after developing diarrhea and abdominal pain from oral misoprostol. Fourteen volunteers completed the hyperglycemic clamping experiments while 11 finished the misoprostol studies. Gastric dysrhythmias were not inducible by hyperglycemia in 2 subjects or by misoprostol in 1 individual. Data from these studies are not included in the analysis of the effects of these interventions on EGG activity.

Effects of Ginger Root on Hyperglycemia-Evoked Gastric Dysrhythmias

Plasma Glucose Levels

Basal fasting plasma glucose levels were not significantly different after ginger root (81 ± 5 mg/dl) or placebo (78 ± 2 mg/dl) ($P=NS$). After initiation of hyperglycemic clamping, plasma glucose concentrations reached 250 mg/dl at a mean time of 26.8 ± 2.3 minutes for the ginger root studies and 25.4 ± 1.5 min for the placebo studies ($P=NS$). Thereafter, glucose levels were maintained at similar concentrations in the ginger root (269 ± 4 mg/dl) and placebo studies (272 ± 3 mg/dl) ($P=NS$). The volumes of 20% glucose infused were similar for ginger root (328 ± 21 ml) and placebo (332 ± 19 ml, $P=NS$).

Electrogastrography Findings

Induction of acute hyperglycemia elicited profound disruptions in EGG rhythm which persisted for the duration of the fasting recordings in the placebo studies. Representative tracings from one volunteer are shown in Figure 1. The raw signal prior to infusion of 20% dextrose exhibited a uniform sinusoidal oscillation with a period of 20 seconds. The grayscale plot of the frequency spectra revealed a dominant frequency of 3 cycles per minute (cpm) throughout the basal recording. During hyperglycemia, the EGG rhythm degenerated to a low amplitude, high frequency waveform with a period of approximately 7-10 seconds. The corresponding grayscale plot exhibited a predominant 6-8 cpm rhythm during this time. Conversely after ginger root, hyperglycemia had less of a disruptive effect on the raw EGG waveform. Grayscale plots in the ginger root studies showed a persistence of 3 cpm rhythm during much of the dextrose infusion, however some tachygastric activity with a dominant frequency of 7 cpm was observed indicating that ginger only partially inhibited hyperglycemia-evoked dysrhythmias in this individual.

The effects of acute hyperglycemia on EGG activity were compared before and after ginger root vs. placebo. There were no significant differences in baseline EGG parameters after ginger root or placebo. With placebo, hyperglycemia produced significant increases in the dominant EGG frequency from 2.96 ± 0.04 to 4.09 ± 0.45 cpm (Table 1) ($P < 0.05$ compared to baseline). The percentage of recording time in normal 3 cpm rhythm decreased significantly and the percent time in tachygastric activity increased (both $P < 0.05$ compared to baseline) (Figures 2 and 3). After ginger root, the dominant EGG frequency rose slightly from 2.80 ± 0.10 to 3.46 ± 0.37 cpm however the increase was significantly less than in the placebo studies (Table 1) ($P < 0.01$ compared to placebo). Similarly, the degree of tachygastric activity was much lower after ginger root than after placebo ($P < 0.05$ compared to placebo) (Figures 3). This correlated with a trend to a

reduction in the percent recording time in normal 3 cpm rhythm (Figure 2). When comparing the decreases in recording time in 3 cpm rhythm (value during hyperglycemia subtracted from value during euglycemia), the effects of ginger root were significant compared to placebo (P<0.05). Indeed, the percent recording time in 3 cpm rhythm with hyperglycemia in the ginger root studies was not significantly different than during euglycemia (Figure 2). Hyperglycemia did not affect percentages of recording time in bradygastric or duodenal/respiratory frequency ranges in both placebo and ginger root studies (P=NS).

Effects of Ginger Root on Misoprostol-Evoked Gastric Dysrhythmias

Administration of the prostaglandin E₁ analog misoprostol elicited significant gastric dysrhythmias qualitatively similar to those observed during hyperglycemic clamping. The effects of misoprostol on EGG activity were compared before and after ginger root vs. placebo. There were no significant differences in baseline EGG parameters after ginger root or placebo. In placebo studies, increases in dominant frequency did not reach statistical significance after misoprostol (from 2.98±0.06 to 3.16±0.11 cpm; P=NS)(Table 1), however significant decreases in percent recording time in 3 cpm rhythm (P<0.01 compared to baseline) and increases in tachygastric activity (P<0.05 compared to baseline) were observed (Figures 4 and 5). In ginger root studies, dominant frequencies did not significantly increase after misoprostol (from 2.93±0.04 to 3.13±0.12 cpm; P=NS)(Table 1). In contrast to the hyperglycemia studies, ginger root did not affect the decrease in 3 cpm activity or the increase in tachygastric activity elicited by misoprostol compared to placebo (P=NS)(Figures 4 and 5). Misoprostol did not affect percentages of recording time in bradygastric or duodenal/respiratory frequency ranges in both placebo and ginger root studies (P=NS).

DISCUSSION

Diabetic gastropathy produces upper gastrointestinal symptoms which may be disabling in severity. The pathogenesis of diabetic gastropathy is likely multifactorial. Motor disturbances such as delayed gastric emptying, reduced antral contractions, decreased fundic tone, abnormal intragastric distribution, and pylorospasm have been described in diabetic patients (Samsom et al., 1997; Jones et al., 1995; Samsom et al., 1995; Mearin et al., 1986). Hypersensitivity to gastric distention has been reported in symptomatic diabetics similar to that observed in patients with functional dyspepsia (Samsom et al., 1995). Finally, rhythm disturbances of the gastric slow wave have been demonstrated in patients with long-standing diabetes which are associated with impairments of antral contractility (Jebbink et al, 1994b; Mantides et al, 1997; Jebbink et al., 1994a). The importance of gastric dysrhythmias in the genesis of diabetic gastropathy is suggested by the observation that symptom improvements on medication therapy of the condition correlate with normalization of slow wave rhythm rather than acceleration of gastric emptying (Koch et al., 1989).

In diabetic patients, the degree of glycemic control can influence the magnitude of gastric motor and myoelectric dysfunction. Gastric emptying is delayed in diabetics during periods of hyperglycemia (Fraser et al, 1990). Similarly, gastric slow wave dysrhythmias such as tachygastria are more prominent during hyperglycemia compared to euglycemia (Jebbink et al, 1994b). Induction of acute hyperglycemia in healthy volunteers evokes gastric physiologic abnormalities which mimic those of diabetic gastropathy including inhibition of antral contractions, reduction of gastric fundus tone, and stimulation of pyloric motor activity (Barnett and Owyang, 1988; Hebbard et al., 1996; Fraser et al., 1991). In prior studies from our laboratory, the effects of hyperglycemic clamping on gastric slow wave rhythm were explored

(Hasler et al., 1995). Raising the plasma glucose to 230 mg/dl provoked significant increases in tachygastria and arrhythmic activity in healthy human subjects. However, volunteers pretreated for three days with indomethacin did not develop slow wave dysrhythmias during hyperglycemia indicating mediation of the slow wave rhythm disruption by endogenous production of prostaglandins. This finding provides an *in vivo* correlate of demonstrations of prostaglandin dependence of tachygastrias in isolated gastric muscle tissues excised from patients with refractory gastroparesis (Sanders et al., 1979).

The traditional Chinese herbal remedy ginger reduces symptoms in patients with nausea of pregnancy, motion sickness, and postoperative nausea and vomiting (Vutyavanich et al., 2001; Grontved et al., 1988; Phillips et al., 1993; Arfeen et al., 1995). In physiologic testing, ginger increases fasting antral contractions and the gastric motor response to eating (Micklefield et al., 1999). Furthermore, ginger reverses cisplatin-induced delays in gastric emptying in animal models (Sharma and Gupta, 1998). In a model of experimental motion sickness, gastric slow wave rhythm disturbances evoked by circularvection were prevented by treatment with ginger root (Lien et al., 2003). The effects of ginger on prostaglandin pathways as inducers of gastric dysrhythmic activity are unknown, however it exhibits inhibitory effects on prostaglandin and leukotriene synthesis in other models including platelets and RBL-1 cell lines (Srivastava, 1984; Kiuchi et al., 1992).

In the present investigation, we demonstrated that ginger blunts the induction of tachygastria in response to acute hyperglycemia in healthy humans. We further aimed to determine if inhibition of prostaglandin synthesis or its actions may play a role in the slow wave stabilizing effects of ginger. To accomplish this goal, we contrasted the effects of ginger on gastric myoelectric responses during hyperglycemia to those after oral administration of the

prostaglandin E₁ analog misoprostol. In canine models, prostaglandin E₂ exhibits potent disruptive effects on slow wave rhythm very similar to those observed with prostaglandin E₁ in humans (Kim et al., 1987; Kim et al., 1988). Unfortunately, no oral prostaglandin E₂ preparations are readily available for use in humans. Increases in tachygastric activity and reductions in normal 3 cpm cycling were qualitatively similar during hyperglycemia and after misoprostol. However, misoprostol does not disrupt slow wave activity by increasing plasma glucose as prostaglandin E analogs have no hyperglycemic actions in human volunteers (Demol and Wingender, 1989). Increases in EGG dominant frequency for the entire recording periods were less impressive because dysrhythmic activity, when present, usually occurred 20-35% of the time. The magnitude of dysrhythmic activity after misoprostol tended to be less than with acute hyperglycemia, however we believe this is secondary to the dose of misoprostol which could be administered. Unfortunately, doses higher than 400 µg tend to be poorly tolerated by healthy volunteers because of side effects including diarrhea and abdominal cramps. However unlike its effects on hyperglycemia-evoked dysrhythmias, ginger root had no effect on slow wave rhythm disruptions elicited by misoprostol. Given the relatively smaller increases in tachygastric activity with misoprostol compared to hyperglycemia, it is conceivable the lack of effect of ginger is secondary to a type II error. However in hyperglycemia studies, even small dysrhythmic responses to hyperglycemia were blunted by ginger root whereas ginger produced no trends to decreased or increased tachygastria in the misoprostol studies. Thus we believe our results likely indicate that the mechanism for the antidysrhythmic effects of ginger does not stem from inhibition of the actions of prostaglandins. As endogenous prostaglandins mediate the slow wave response to hyperglycemic clamping in healthy humans, it is possible that ginger prevents prostaglandin production during periods of elevated plasma glucose.

It is conceivable that pathways other than those relating to endogenous prostaglandins may explain the antidysrhythmic actions of ginger in this investigation. In addition to inhibiting cyclooxygenase and lipoxygenase activity, ginger exhibits effects on 5-HT₃ mediated functions (Huang et al., 1991; Shibata et al., 1999). In experimental motion sickness in healthy humans, ginger blunts the increase in plasma vasopressin levels in response to circularvection indicating possible actions on the release of this transmitter (Lien et al., 2003). Finally, loss of nitric oxide function has been proposed as a cause of impaired gastric motor function in rodent models of diabetic gastroparesis (Watkins et al., 2000). The effects of ginger on nitrergic pathways are unexplored. Another topic which deserves further assessment is which ingredient within the ginger root preparation is responsible for its slow wave antidysrhythmic actions. Certain components of ginger including gingerol, shogaol, and galanolactone are reported to possess antiserotonergic qualities (Yamahara et al., 1989; Lumb, 1993). Galanolactone specifically exhibits antagonistic effects on 5-HT₃ receptors (Huang et al., 1991). These issues pertaining to the slow wave stabilizing actions of ginger warrant further investigation.

In conclusion, the present study demonstrated that ginger root effectively prevents induction of gastric slow wave dysrhythmias by acute hyperglycemia in healthy human volunteers, myoelectric abnormalities which have been previously shown to be mediated by endogenous prostaglandin pathways. Conversely, ginger root has no effect on tachygastrias elicited by the prostaglandin E₁ analog misoprostol. These findings are consistent with the conclusion that ginger acts to blunt production of endogenous prostaglandins rather than inhibit their actions. The results of the current investigation provide novel insight into the mechanisms of action of the traditional Chinese herbal remedy ginger and raise the possibility that this agent

may have some therapeutic benefit in patients with diabetic gastropathy. Future investigations should test the efficacy of ginger in affected diabetic patients.

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TABLES

Table 1: EFFECTS OF GINGER ON EGG DOMINANT FREQUENCIES

Test Condition	<i>HYPERGLYCEMIA STUDY</i>		<i>MISOPROSTOL STUDY</i>	
	Baseline	Hyperglycemia	Baseline	Misoprostol
Placebo	2.96±0.04	4.09±0.45*	2.98±0.06	3.16±0.11
Ginger Root	2.80±0.10	3.46±0.37**	2.93±0.04	3.13±0.12

*P<0.05 vs. baseline, **P<0.01 vs. placebo

FIGURE LEGENDS

Figure 1: Sample raw waveforms (top), grayscale plots (middle), and frequency spectra (bottom) are shown for a volunteer undergoing hyperglycemic clamping after placebo and ginger root. Hyperglycemia produced a chaotic high frequency waveform after placebo which was predominantly in the 6-8 cpm range as seen on the grayscale plot and spectral analysis. Conversely after ginger root, the disruption in EGG rhythm was less profound. Although some high frequency elements were seen on the grayscale plot and frequency spectrum, most of the EGG activity during hyperglycemia was 3 cpm.

Figure 2: The effects of placebo and ginger root on percentages of EGG recording time in normal rhythm are shown under euglycemic (open bars) and hyperglycemic (filled bars) conditions. Hyperglycemia significantly reduced the time in normal rhythm after placebo ($P < 0.05$). The reduction in time in normal rhythm was significantly less after ginger root compared to placebo. Results are expressed as means \pm SEM, $n=12$.

Figure 3: The effects of placebo and ginger root on percentages of EGG recording time in tachygastria are shown under euglycemic (open bars) and hyperglycemic (filled bars) conditions. Hyperglycemia significantly increased the time in tachygastria after placebo ($P < 0.05$). The increase in time in tachygastria was significantly less after ginger root compared to placebo ($P < 0.05$). Results are expressed as means \pm SEM, $n=12$.

Figure 4: The effects of placebo and ginger root on percentages of EGG recording time in normal rhythm are shown under baseline (open bars) conditions and after misoprostol (filled bars). Misoprostol significantly reduced the time in normal rhythm after placebo ($P < 0.01$). In

contrast to the hyperglycemia studies, ginger root had no effect on the decrease in time in normal rhythm in response to misoprostol ($P=NS$). Results are expressed as means \pm SEM, $n=10$.

Figure 5: The effects of placebo and ginger root on percentages of EGG recording time in tachygastria are shown under baseline (open bars) conditions and after misoprostol (filled bars). Misoprostol significantly increased the time in tachygastria after placebo ($P<0.05$). In contrast to the hyperglycemia studies, ginger root had no effect on the increase in time in tachygastria in response to misoprostol ($P=NS$). Results are expressed as means \pm SEM, $n=10$.

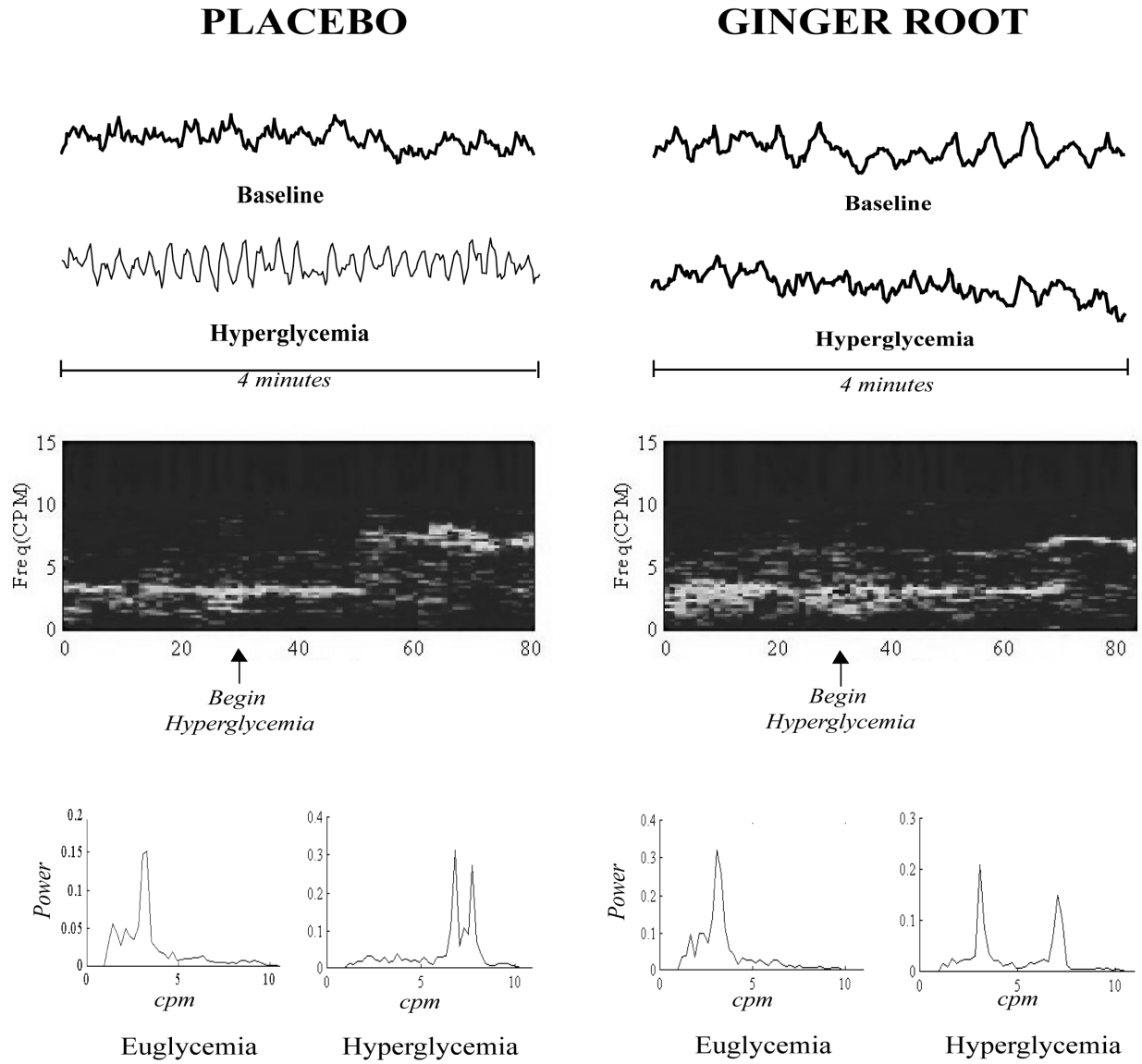


Figure 1

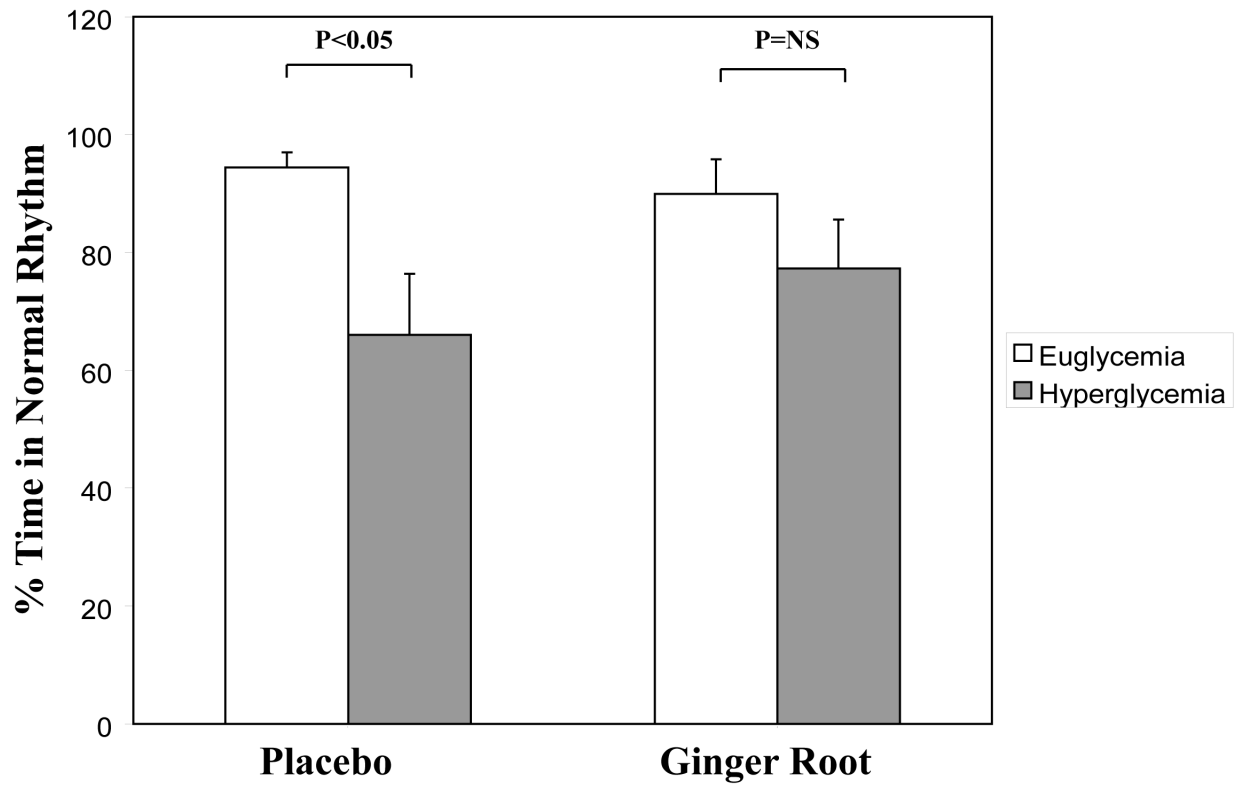


Figure 2

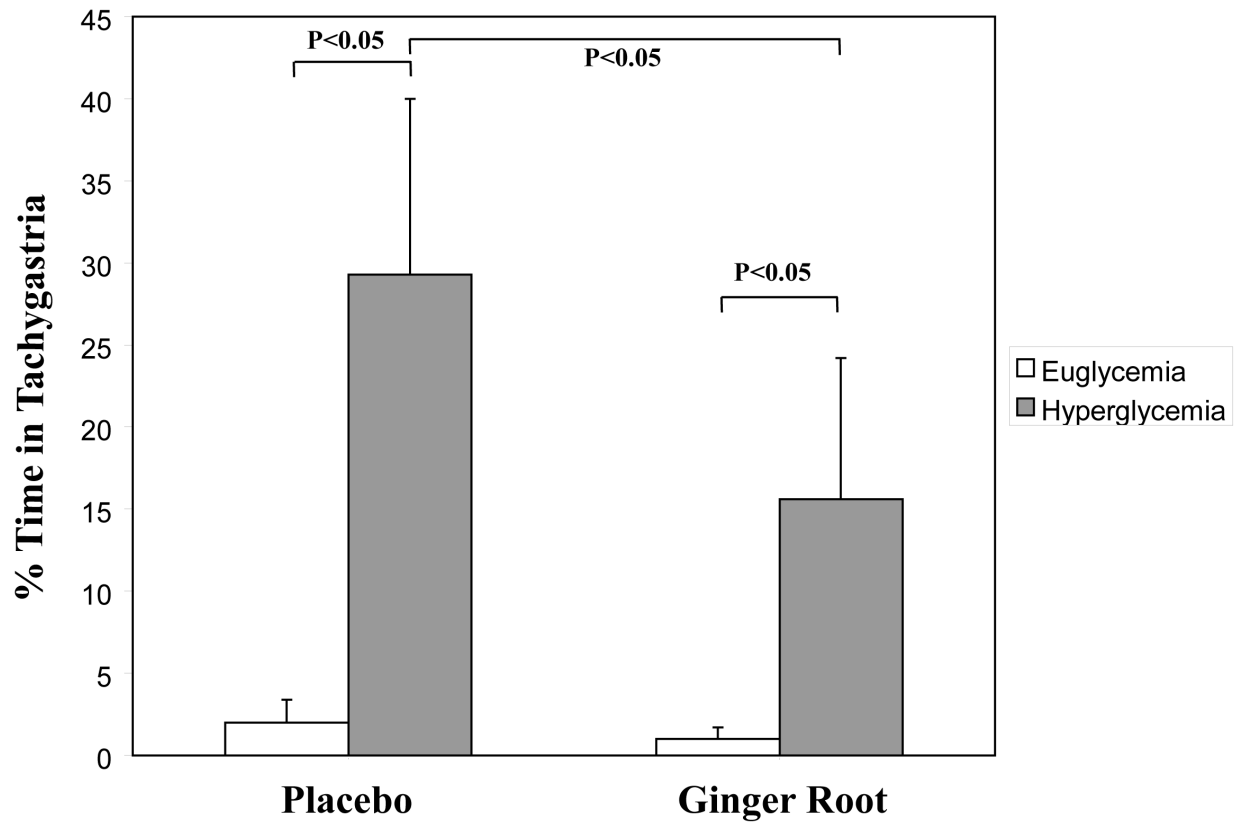


Figure 3

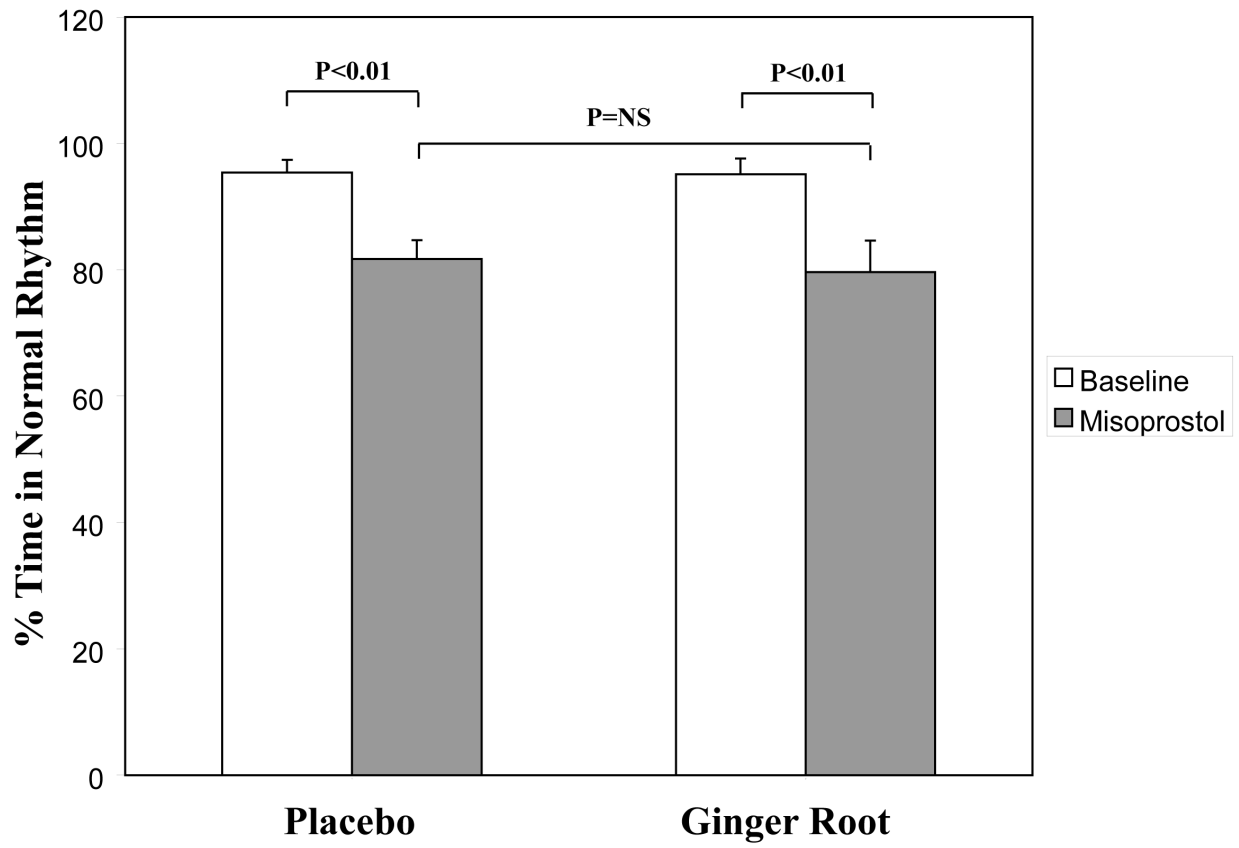


Figure 4

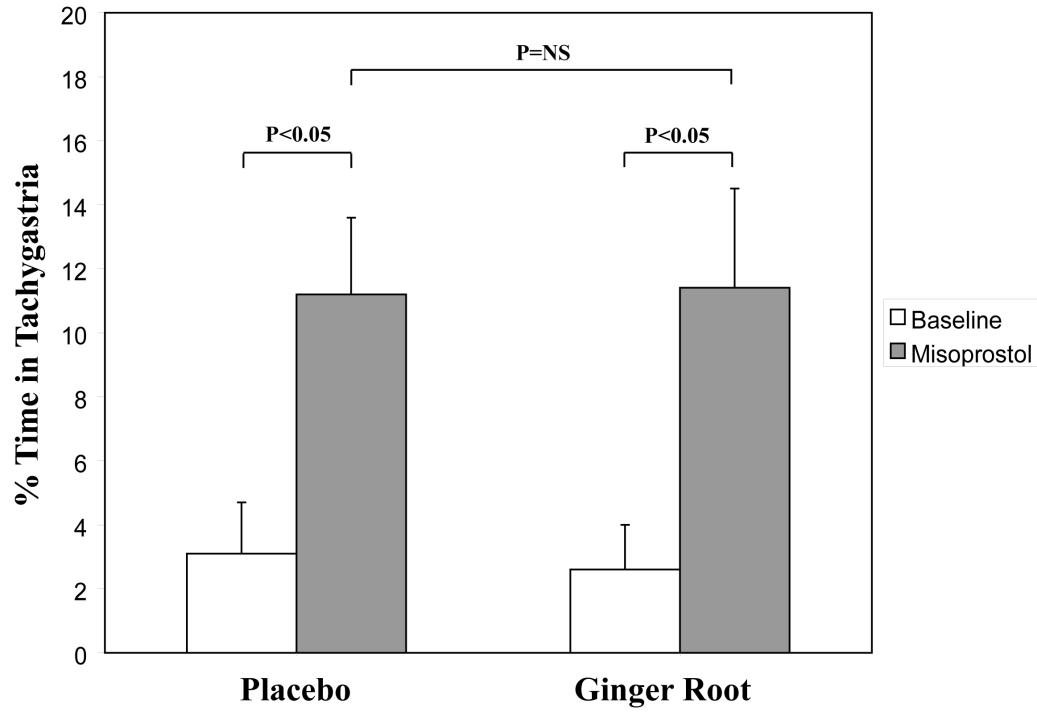


Figure 5

PLACEBO



Baseline



Hyperglycemia

4 minutes

GINGER ROOT



Baseline



Hyperglycemia

4 minutes

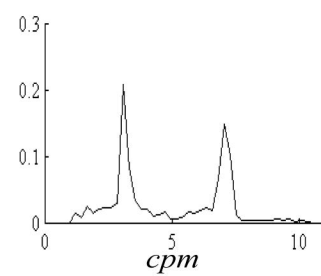
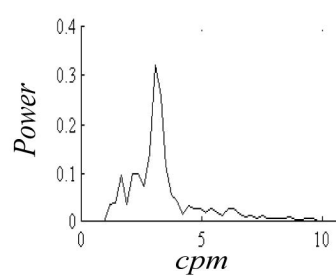
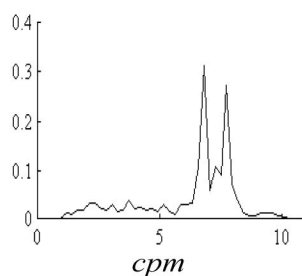
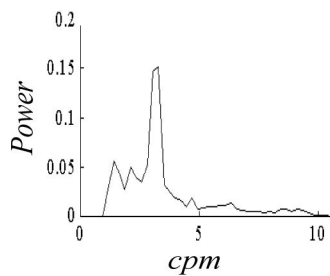
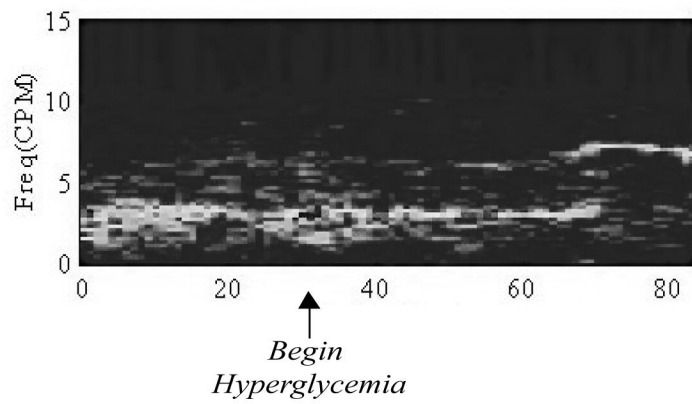
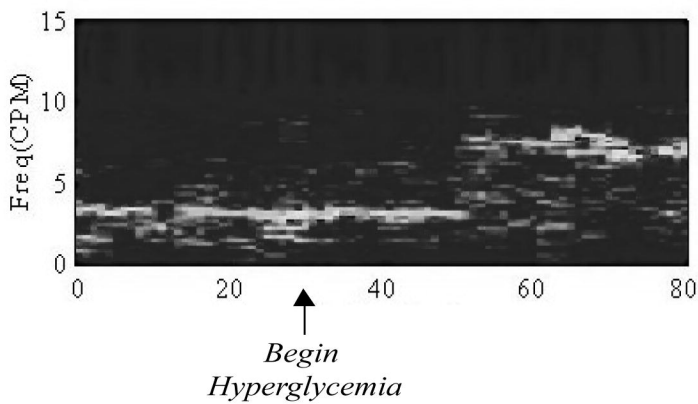


Figure 1

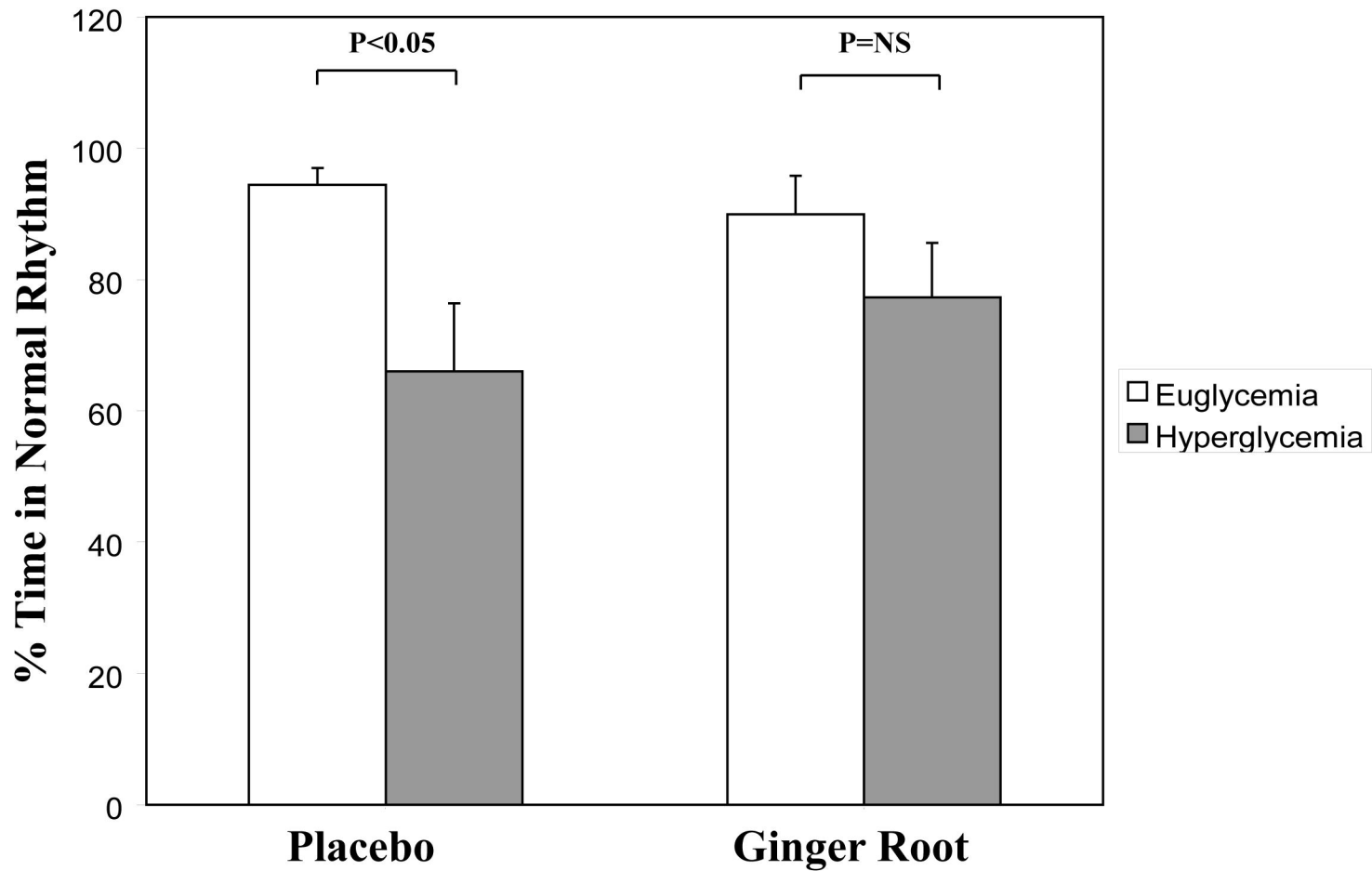


Figure 2

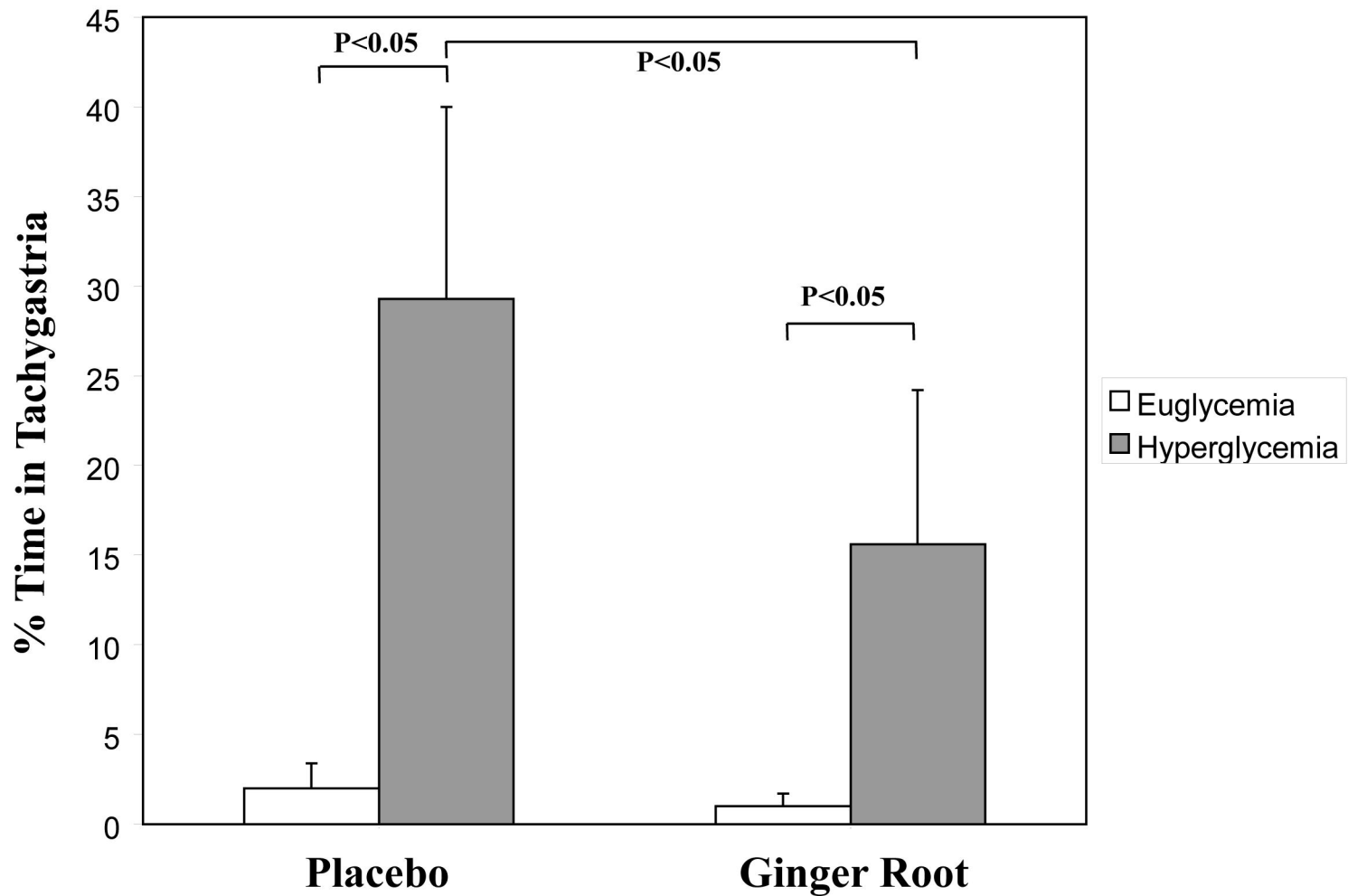


Figure 3

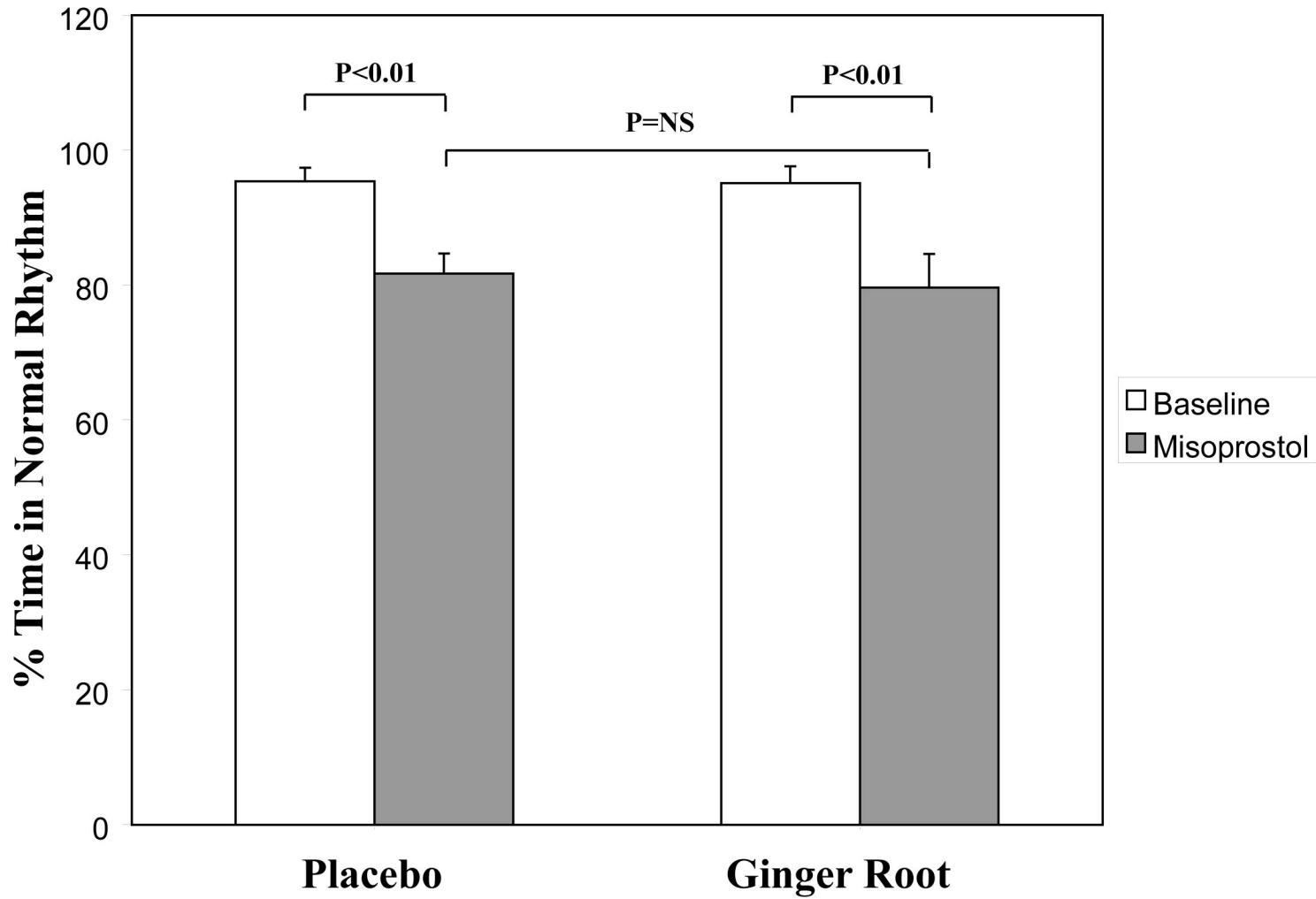


Figure 4

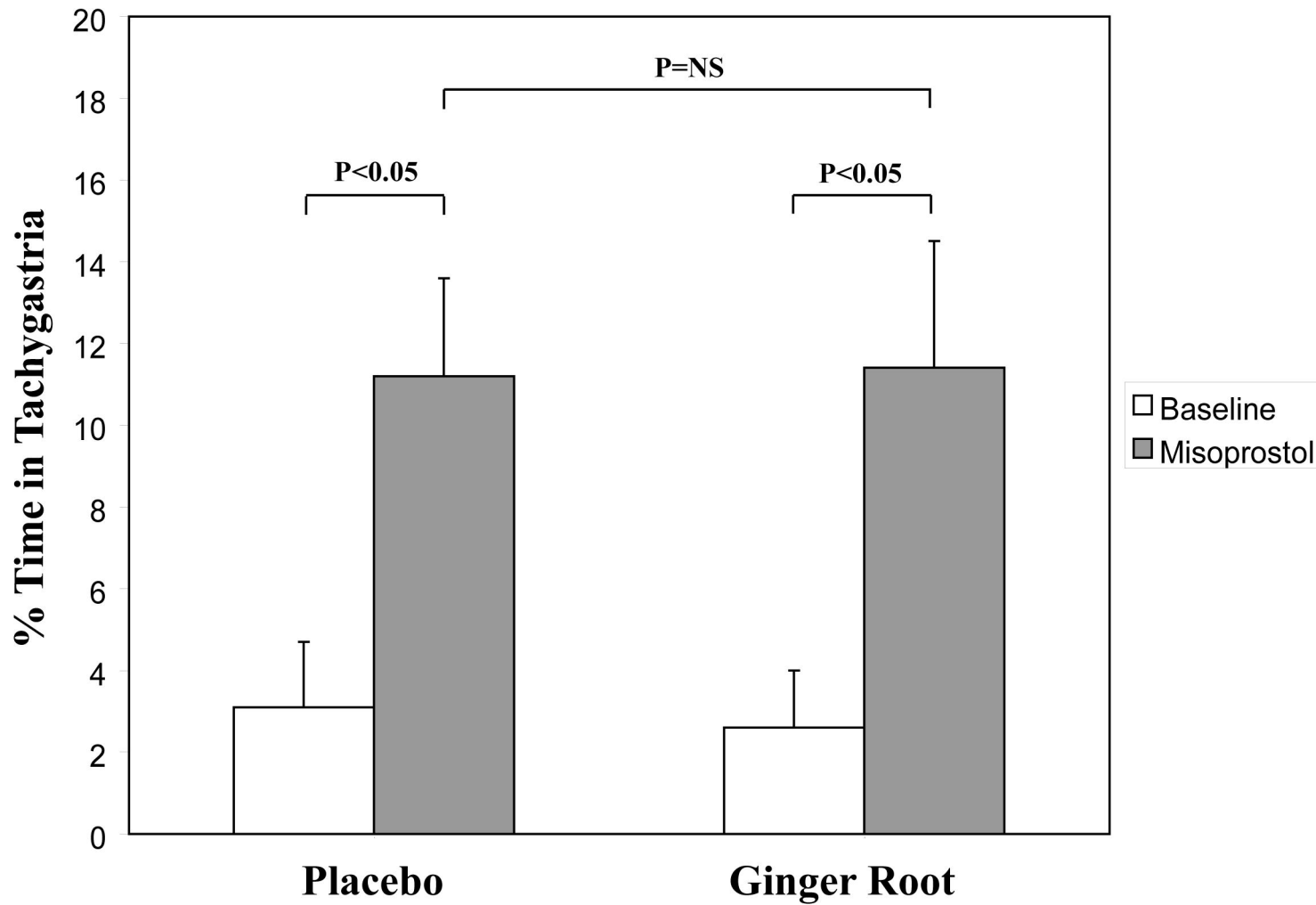


Figure 5