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Does maladaptive cardiovagal modulation extend to gastric modulation in women with chronic pelvic pain?

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Abstract

Background: Women with chronic pelvic pain (CPP) have poor cardiovagal modulation. It is unclear whether this finding reflects a broader abnormality across many systems such as gastro-vagal modulation.

Aim: Determine if maladaptive cardiovagal activity in females with CPP is accompanied by maladaptive gastric myoelectric activity.

Methods: 36 health controls (HC) and 75 CPP underwent supine (10 minutes), then upright (tilted 70° head up; 30 minutes), and back to supine (10 minutes) positions. High-frequency heart rate variability (HF-HRV; 0.15–0.4 Hz) was measured as an index of cardiovagal activity. Cutaneous electrogastrography (EGG) assessed gastric myoelectric activity pre- and during-upright tilt. EGG measures from 16 HC and 31 CPP patients were available for analysis and included relative percentage of gastric activity within the normal (2–4 cpm) and tachygastria (4–10 cpm) ranges, plus ratio of normal/tachygastria.

Results: HF-HRV was lower in CPP individuals at all time points (each $p < .05$). CPP individuals showed lesser decrease in HF-HRV from supine to upright, and poorer HF-HRV recovery from upright back to supine ($F(1,106) = 4.62$, $p = .034$). HC showed increase in tachygastria activity ($t(15) = -2.09$, $p = .054$) while the CPP group showed no change in tachygastria activity from pre-upright to upright ($t(30) = -0.62$, $p = .537$).

Conclusions: Individuals with CPP going from supine to upright demonstrate an impairment in both tachygastria and the parallel decrement in HRV. These results support the hypothesis of a generalized blunting in the physiological modulation in CPP individuals affecting both cardiovascular and gastric systems.

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Keywords

heart rate variability; chronic pelvic pain; electrogastrography -EGG; vagal modulation; gastric myoelectrical activity

Background

The concept that pelvic pain disorders extend beyond the pelvis has received increasing attention[1]. An autonomic perspective reveals a similar theme. Both bladder pain syndrome (BPS) and myofascial pelvic pain (MPP), two types of chronic pelvic pain, demonstrate generalized autonomic abnormalities beyond the bladder or pelvis [2, 3]. In further support of autonomic changes beyond the pelvis, chronic nausea may accompany BPS [4]. To further investigate the extent of "beyond the pelvis" autonomic abnormalities, we sought to determine if these disorders also demonstrated maladaptive gastric myoelectric activity. We hypothesized that abnormal autonomic control may not only affect the heart but also affect the upper gastrointestinal which would be reflected in abnormal gastric myoelectric activity.

The brainstem vagal neurocircuits modulate the motility and electrical activity of the upper gastrointestinal tract. Afferent fibers transmit sensory information to the nucleus tractus solitarius (NTS). This center receives information from the stomach and the aortic baroreflex afferent arc. The NTS neurons send projections to the nearby nuclei, like the dorsal motor nucleus of the vagus (DMV) the nucleus ambiguus (NA) [56]. Bidirectional modulation interconnects vagal and gastric activity [7].

Chronic pain conditions are often associated with decreased cardio-vagal modulation [89], recently demonstrated in women with interstitial cystitis/ bladder pain syndrome (IC/BPS) through heart rate variability (HRV). This study tested the hypothesis that gastric electric activity measured by cutaneous electrogastrography (EGG) would also demonstrate decreased gastro-vagal modulation. There is limited literature associating EGG with vagal modulation. Yacin et al found a correlation between the power ratio of high frequency (hf) and low frequency (lf) HRV and the EGG power [10] and also the changes in power in EGG to the changes in the hfHRV pre-and post-water ingestion [11]. Most of these studies use a water load or meal as a stimulus or stress [1112].

The aim of this study was to determine if poorer autonomic function, marked by maladaptive patterns in cardio-vagal modulation, is accompanied by maladaptive gastric myoelectric activity in those with chronic pelvic pain (CPP). In this study, passive tilt test was used as a challenge for gastro-vagal modulatory activity, rather than a water load or meal, since these can markedly and directly influence vagal function [13].

Methods:

This study was approved by University Hospitals Case Medical Center Institutional Review Board as part of the larger project "Elucidation of Psychophysiologic and Autonomic Characteristics (ICEPAC)" study.[14] The current sample is comprised of a subsample of individuals from previously published data [8] for which both EGG and HRV data were

available. The study population were women aged 18–80 with and without chronic pelvic pain (CPP). Within the pelvic pain group, we included subjects with 2 disorders: IC/BPS (defined according to slightly modified ESSIC criteria [1514] and myofascial pelvic pain (MPP defined as at least 3 months of chronic pelvic pain unrelated to bladder state and a minimum of 2 of 5 pelvic floor tender points scoring greater than 4 out of 10 on a numeric rating scale when elicited by applying 2 Kg pressure using an index finger). The control groups were females without pelvic pain as defined previously [814].

Subjects underwent tilt test as described previously [314]. Briefly, most of the subjects were not taking any medications that could affect the autonomic response for 5 half-lives. Subjects were supine for a 10 min equilibration period. This was followed by 10 min of supine recording and 30 min of upright tilt to 70 degrees. EGG was recorded using a Digitraper-EGG (Polygram Net™ analysis package; Medtronic, Minneapolis, MN, USA) with 4 cutaneous leads. The blood pressure and heart rate were recorded with beat-to-beat by digital plethysmography (Nexfin Monitor Model 1; BMEYE B.V., Amsterdam, the Netherlands). HRV was analyzed as previously reported [8]. High-frequency heart rate variability (HF-HRV; 0.15–0.4 Hz) was measured for 10 minutes at each time point as an index of PNS activity as previously published [8]. The subset of HRV results for which EGG data were available are presented in the current manuscript.

The EGG data were downloaded at a sampling rate of 1 Hz. and analyzed by Dr. Muth. Data were first examined visually to identify recordings containing artifacts due to recording errors, motion or respiration. These artifacts were visually identified by abnormal amplitudes, flat recordings, or sudden shifts in frequency which did not fit the surrounding record. Selected EGG data were analyzed using locally developed software which utilized Prime Factor FFT for Windows, version 3.03 (Alligator Technologies, Costa Mesa, CA, USA). Data were analyzed using running spectral analysis with a Hamming window applied to four minutes, 75% overlapping successive windows until the entire segment of interest was analyzed. The spectral output of the various windows was averaged to produce one output. The spectral resolution was 0.25 cycles per minute (cpm). A frequency range between 2.5 to 3.75 cpm was regarded as normal gastric activity (normogastria) and a range between 4.0 to 9.75 cpm as tachygastria. We then calculated the percentage spectral power from the total range of 0.75 to 15.0 cpm and computed the ratio between the percentage of the normogastria and the tachygastria band. Ratio values above 1 are more indicative of normal gastric activity and values below 1 more indicative of increased tachygastria. Normogastria, tachygastria, and the associated ratio was calculated at baseline-supine (pre-tilt) and during upright (tilt).

IBM SPSS 19 (IBM Corp., Armonk, NY), StatsSoft Statistica 6.0 (StatSoft, Inc.,Tulsa, OK) examined differences in HF-HRV, the LF/HF ratio, normogastria, tachygastria, and the normo/tachygastria ratio across time between groups using multiple 2-way (1 between factor and 1 within factor) analyses of variance (ANOVAs). The within-subject factors included physiological measures (i.e., HF-HRV, LF/HF ratio, normogastria, tachygastria, normo/tachygastria ratio) during the tilt table test (supine and upright positions). Group assignment (healthy versus unhealthy individuals) was used as the between subject factor. Preplanned contrasts evaluated differences in HRV measures between groups. All within and within-

between interactions are reported using ANOVA tests. Effect sizes (r) examined the strength of between factors (group, time, group by time) associations and physiological assessments. Participants with missing data were excluded in a case-wise fashion. All tests were examined using alpha = .05.

Results:

A sample of 111 women (36 health controls (HC); 75 CPP) underwent tit test and EGG. Forty-seven females (16 healthy controls and 31 CPP) had EGG data that could be interpreted and analyzed. Individuals ranged from 18–78 years old, with a sample mean age of 40 years old. Split by group, the HC group showed a mean age of 39 years (standard deviation (SD): 15 years) and the CPP group a mean age of 40 years (SD: 13); there was no significant difference in age between groups ($p = .550$). There also was no significant difference between groups on BMI (p = .100).

HF-HRV was lower in CPP individuals at all time points (each p < .05) (Figure 1). ANOVA results showed CPP individuals also showed a lesser decrease in HF-HRV from pre-tilt supine to upright-tilt, and poorer HF-HRV recovery from upright-tilt back to pos-tilt supine, as compared to HC (F (1,106) = 4.62, r = .204, ***p* =.034**). CPP individuals showed significantly lower LF-HRV during pre-tilt supine (F (1,98) = 7.04, r = .212, ***p* = .009**), upright-tilt (F (1,98) = 4.47, r = .209, ***p* = .037**), and trending for supine post-tilt F (1,98) = 2.94, r = .167, $p = .089$) compared to HC individuals. ANOVA and preplanned contrasts showed no significant differences in patterns of LF-HRV throughout the experiment between groups (Figure 2). Compared to the HC group, CPP individuals also showed a significantly higher LF/HF ratio post-tilt supine (F (1,106) = 4.36, r = .198, ***p* = .039**); this effect was attenuated during pre-tilt supine (F (1,106) = 3.22, r = .171, $p = .075$), and not significant during upright (F (1,106) = 0.00, r = .000, $p = .999$). ANOVA and preplanned contrasts showed no significant differences in patterns of the LF/HF ratio throughout the experiment between groups (Figure 3).

ANOVA tests showed no significant interaction between groups in tachygastria activity (F (1, 45) = 1.28, r = .166, $p = .262$). Preplanned contrasts showed HC individuals to have a linear increase in tachygastria activity (F (1,15) = −4.18, r = −.204, ***p* = .054**) from pre-tilt supine to the upright-tilt, whereas the CPP group showed no change in tachygastria activity from pre-tilt supine to upright (F (1,30) = −1.24, r = −.062, $p = .537$; Figure 4). No pre-tilt supine to upright-tilt differences were found for either group in normogastria (Figure 5) or the normogastria/tachygastria ratio (Figure 6; each p > .190).

Discussion

Our study shows interesting findings associating changes in vagal modulation, as indexed by HRV, with changes in gastric electrical activity in both healthy and CPP individuals. In line with our prior work [8], individuals with CPP showed maladaptive patterns of HF-HRV compared to healthy controls. Specifically, HF-HRV was lower under all conditions in CPP individuals compared to HC individuals. Importantly, CPP individuals showed lesser reactivity from supine to upright and poorer recovery from upright back to supine, implying

poorer adaptability to each setting. This maladaptive vagal modulation was accompanied by maladaptive gastric electrical activity as demonstrated by a lack of a tachygastria response from pre-tilt to during tilt. In contrast, the HC group demonstrated a more pronounced withdrawal of HF-HRV during upright tilt, associated with a greater tachygastria response during upright tilt. Additionally, while patterns of LF-HRV and LF/HF ratio were similar throughout the experiment between groups, CPP individuals showed lower LF-HRV during both pre-tilt supine and upright-tilt, and a greater LF/HF ratio at post-tilt supine compared to HC individuals.

This study demonstrates 2 key points: 1) Abnormal cardio-vagal modulation may be associated with abnormal gastric electrical modulation; 2) reduced vagal modulation may be associated with reduced tachygastria during orthostatic tilt. Overall, our study showed that healthy controls showed adaptive regulation of both the cardiovascular and gastric systems, compared to individuals with CPP who showed maladaptive autonomic vagal cardiac and autonomic gastric electrical stimulation.

The regulation of gastric motility is complex. Most coordination occurs at the gastrointestinal tract, with input from the hormonal system, but the parasympathetic and sympathetic innervations contribute to electrical gastric modulation [16]. Electrical stimulation of the stomach in subjects with gastroparesis increases the power of the HF-HRV (vagal modulation) while it decreases the total power of LF-HRV [17].

The upright portion of the tilt is a stress to the autonomic nervous system. Vagal withdrawal with increased sympathetic outflow compensates for the shift of blood flow to the legs and abdomen [18]. Both HC and CPP groups showed a non-significant decrease in the normogastria when going from supine to upright tilt. However, the decreased cardio-vagal modulation, and increase in tachygastria that were brisk in healthy control subjects, appeared blunted in the CPP group (Figure 3), suggesting that dysregulation of the autonomic nervous system affects more than cardiovagal control and extends to vagal control of gastro-electrical activity. Since a tachygastria is typically thought to reflect withdrawal of gastro-vagal input, its absence in the upright portion of the tilt table study in subjects with CPP would suggest that vagal activity is inadequately dampened, in parallel with the same finding in cardiac vagal activity. Indeed, HRV analysis showed decreased vagal modulation in the CPP group at baseline and during tilt.

Interestingly, our results also showed LF-HRV to be lower at pre-tilt supine and while upright, and the LF/HF ratio was greater during post-tilt supine in the CPP group compared to the HC group. LF-HRV is a more complex measure reflecting decreasing baroreflex, vagal and sympathetic responses [1920]. Our findings in relation to LF-HRV are therefore compatible with a blunted sympathetic or baroreflex response as well. Nevertheless, as HF is the likely primary contributor to the LF/HF ratio [20], lower LF/HF ratio at baseline in the CPP group is consistent with our prior work [8], and in-line with gastric data presented above.

Our study has some limitations. Due to artifact in the EGG recording, we could not directly correlate simultaneous HRV and EGG recordings. On the other hand, the frequency of the gastric electrical activity and the heart are very different. Electrical activity to the stomach is

far more slowly modulated than that to the heart. Therefore, changes in the 2 systems may be far from coordinated. Second, the number of subjects in each group was small due to artifact in the EEG recording. Third, due to the small numbers, we did categorize the different CPP or the BPS/IC into Hunner lesion or non-Hunner lesion BPS/IC, which may be distinct disorders[21]. Despite these shortcomings, we believe this manuscript is novel in describing the association between abnormal vagal modulation of the heart in patients with CPP and the associated abnormal electrical modulation of the stomach. We believe future work should replicate our findings in other chronic pain diagnosis in order to determine how vagal modulation influences (ab)normal gastric activity.

In summary, we find that cardio-vagal, gastro-vagal, and probably vasomotor sympathetic responses to upright tilt are similarly sluggish and generally maladaptive in subjects with CPP compared to their healthy counterparts. These abnormalities may play a key role in the maintenance of the chronic pelvic syndrome through lack of regulation or modulation of visceral afferent traffic. Alternatively, autonomic abnormalities may constitute a response to the chronic pelvic pain syndrome. Future work may help dissect potential cause and effect.

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The study was performed at University Hospitals of Cleveland.

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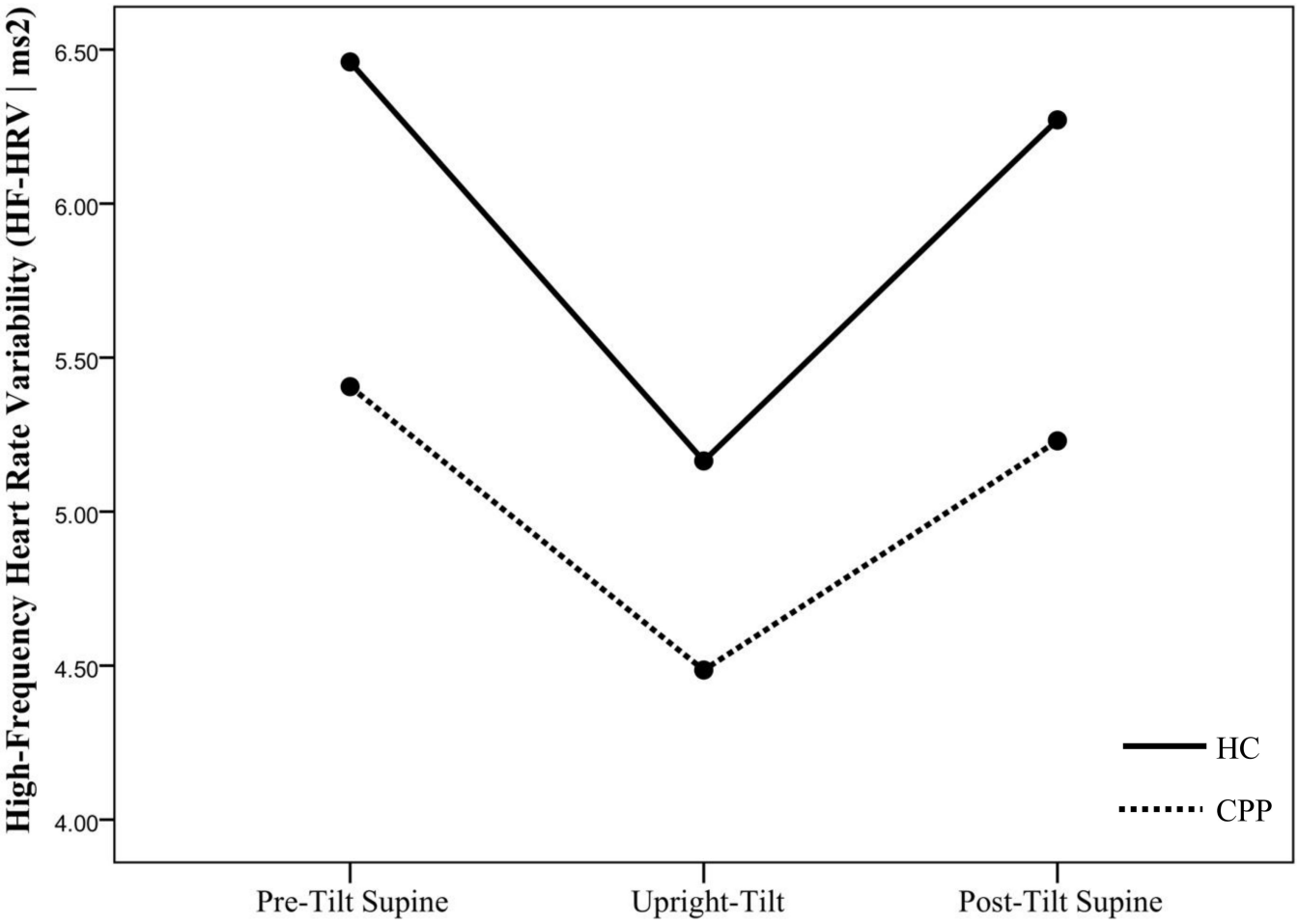

Figure 1: HF-HRV throughout the experiment stratified by group

Note: This figure depicts natural log-transformed (ln) high frequency heart rate variability (HF-HRV) throughout the experiment stratified by heathy controls (HC; solid line) and chronic pelvic pain (CPP; dotted line) groups. HF-HRV was lower in CPP individuals at all time points (each $p < .05$). CPP individuals also showed a lesser decrease in HF-HRV from pre-tilt supine to upright-tilt, and poorer HF-HRV recovery from upright-tilt back to post-tilt supine (quadratic trend), as compared to HC ($F(1,106) = 4.62$, $r = .204$, ***p* =.034**).

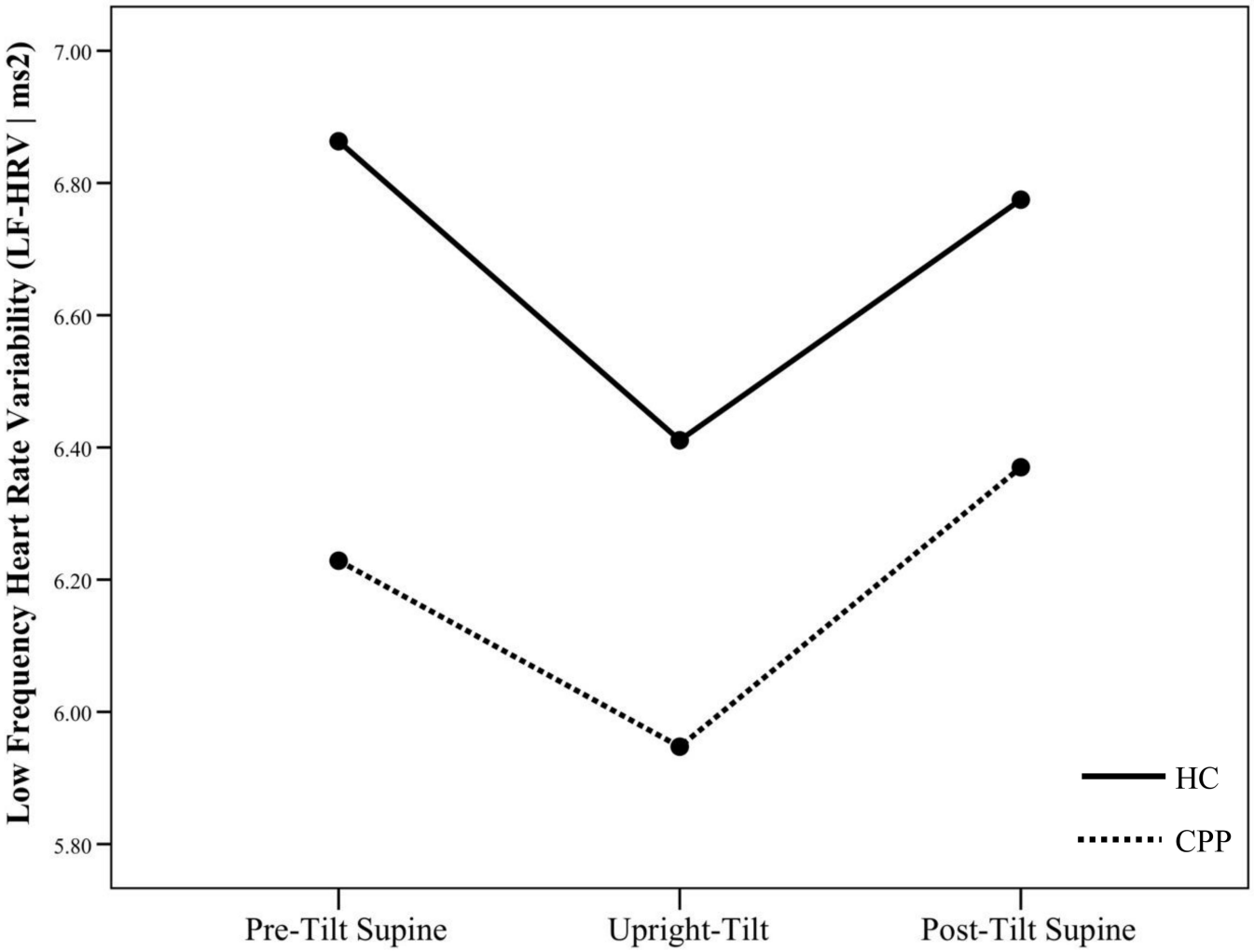

Figure 2: LF-HRV throughout the experiment stratified by group

Note: This figure depicts natural log-transformed (ln) low frequency heart rate variability (LF-HRV) throughout the experiment stratified by heathy controls (HC; solid line) and chronic pelvic pain (CPP; dotted line) groups. ANOVA and preplanned contrasts showed no significant differences in patterns of LF-HRV throughout the experiment between groups.

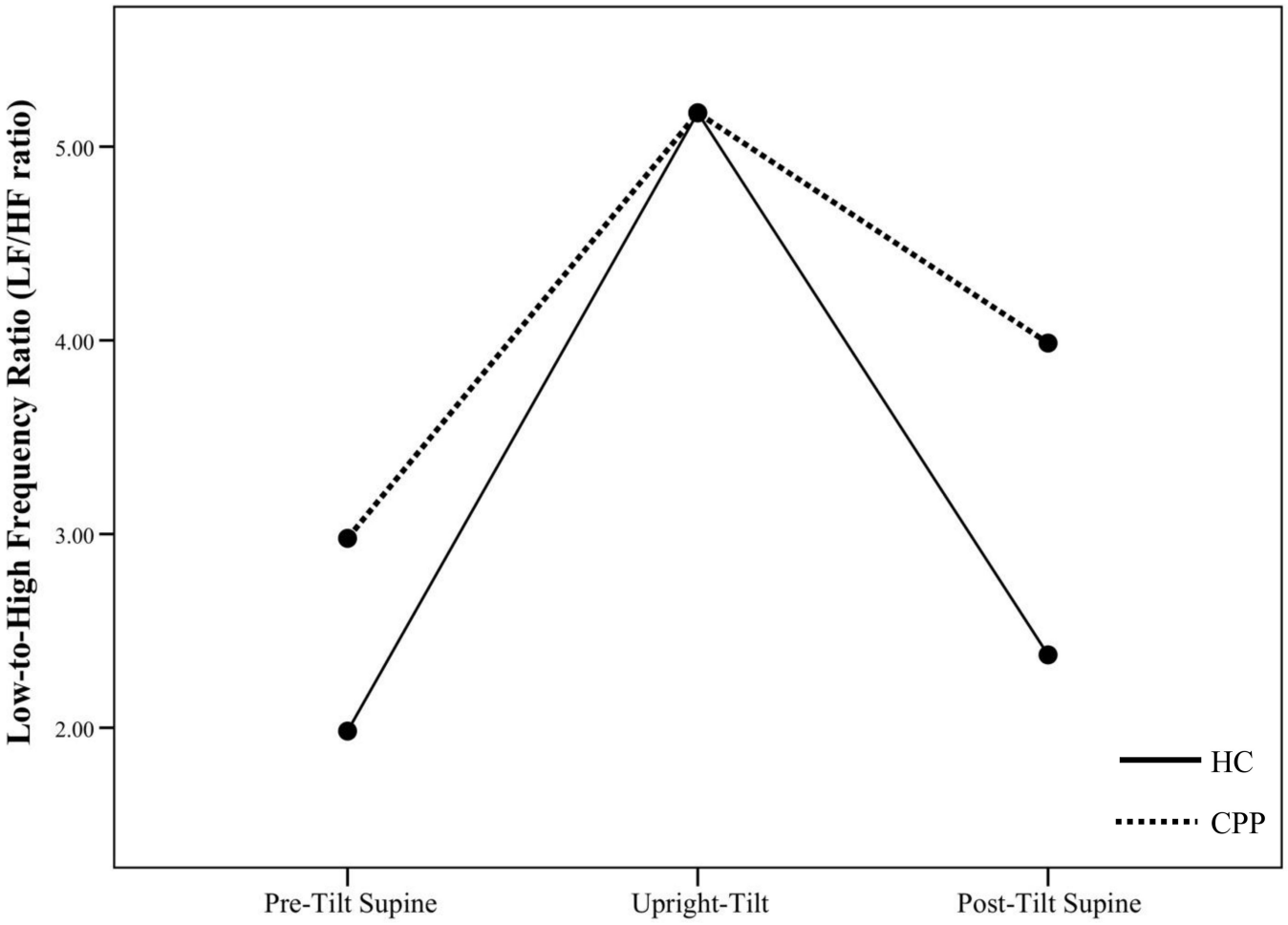

Figure 3: LF/HF Ratio throughout the experiment stratified by group

Note: This figure depicts the low-to-high frequency ratio (LF/HF ratio) throughout the experiment stratified by heathy controls (HC; solid line) and chronic pelvic pain (CPP; dotted line) groups. Compared to the HC group, CPP individuals also showed a significantly higher LF/HF ratio post-tilt supine ($F(1,106) = 4.36$, $r = .198$, $p = .039$); this effect was attenuated during pre-tilt supine ($F(1,106) = 3.22$, $r = .171$, $p = .075$), and not significant during upright ($F(1,106) = 0.00$, $r = .000$, $p = .999$). Preplanned contrasts showed no significant differences in patterns of the LF/HF ratio throughout the experiment between groups.

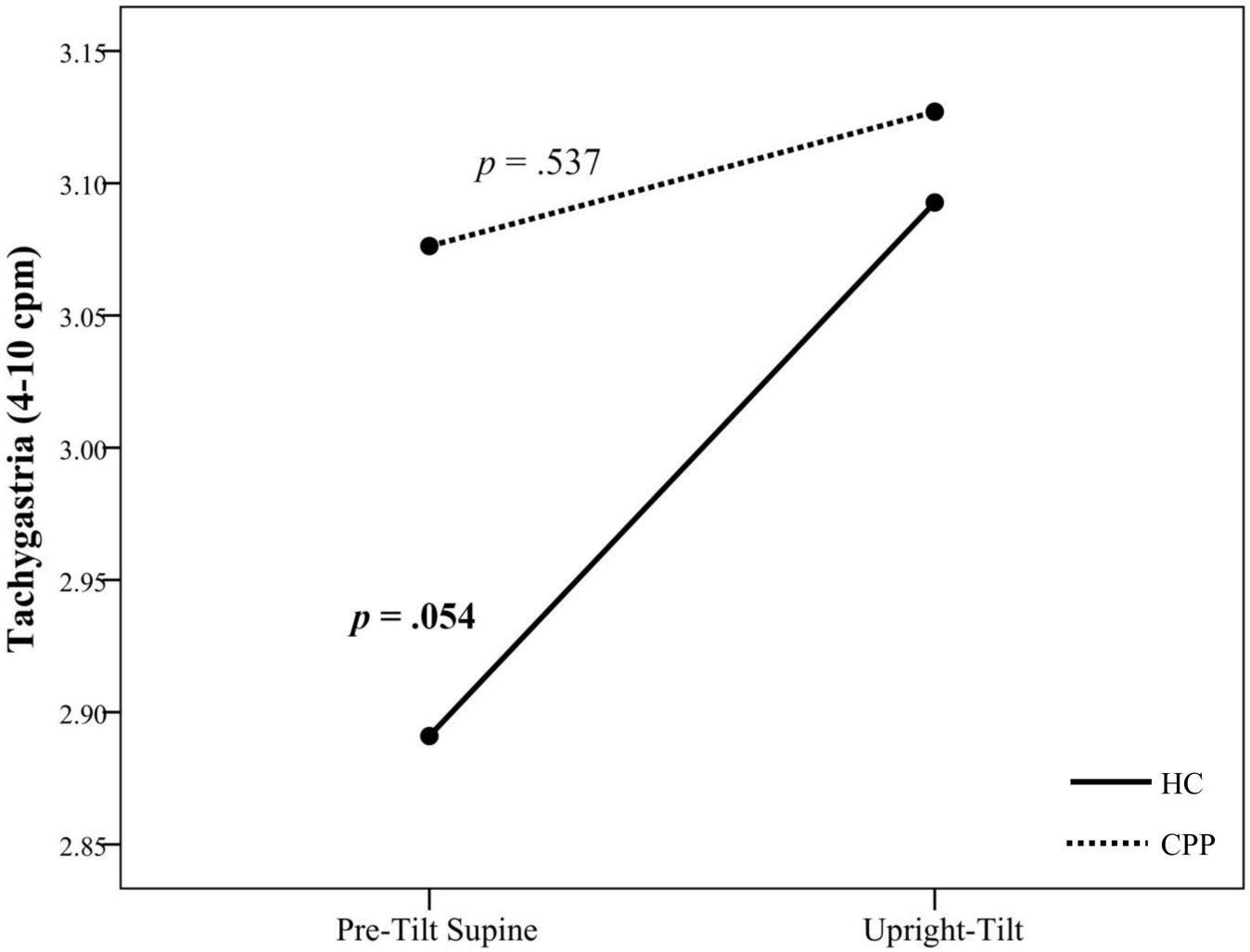

Figure 4: Tachygastria from pre-to post-tilt

Note: This figure depicts natural log-transformed (ln) tachygastria activity (4 – 10 cpm) from pre-tilt supine to upright-tilt stratified by heathy controls (HC; solid line) and chronic pelvic pain (CPP; dotted line) groups. The HC group showed a significant linear increase in tachygastria from pre-tilt to upright-tilt ($p = .034$). In contrast, the CPP group showed no significant linear trend in tachygastria from supine to upright ($p = .537$). Significant p-values bolded.

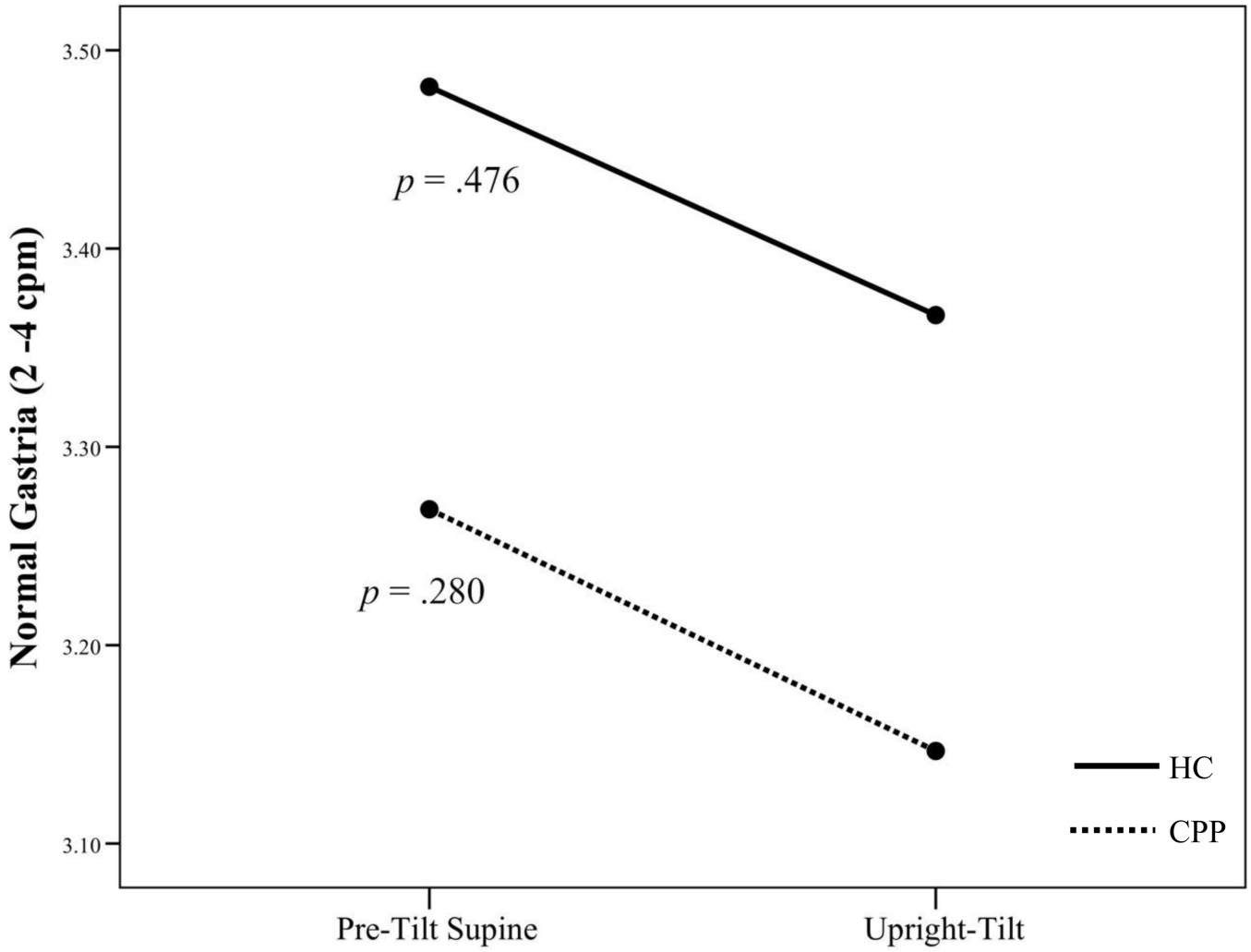

Figure 5: Normal gastria from pre-tilt supine to upright-tilt

Note: This figure depicts natural log-transformed (ln) normal gastria activity (2–4 cpm) from pre-tilt supine to upright-tilt stratified by heathy controls (HC; solid line) and chronic pelvic pain (CPP; dotted line) groups. No significant linear trends were found in either group ($p > .05$).

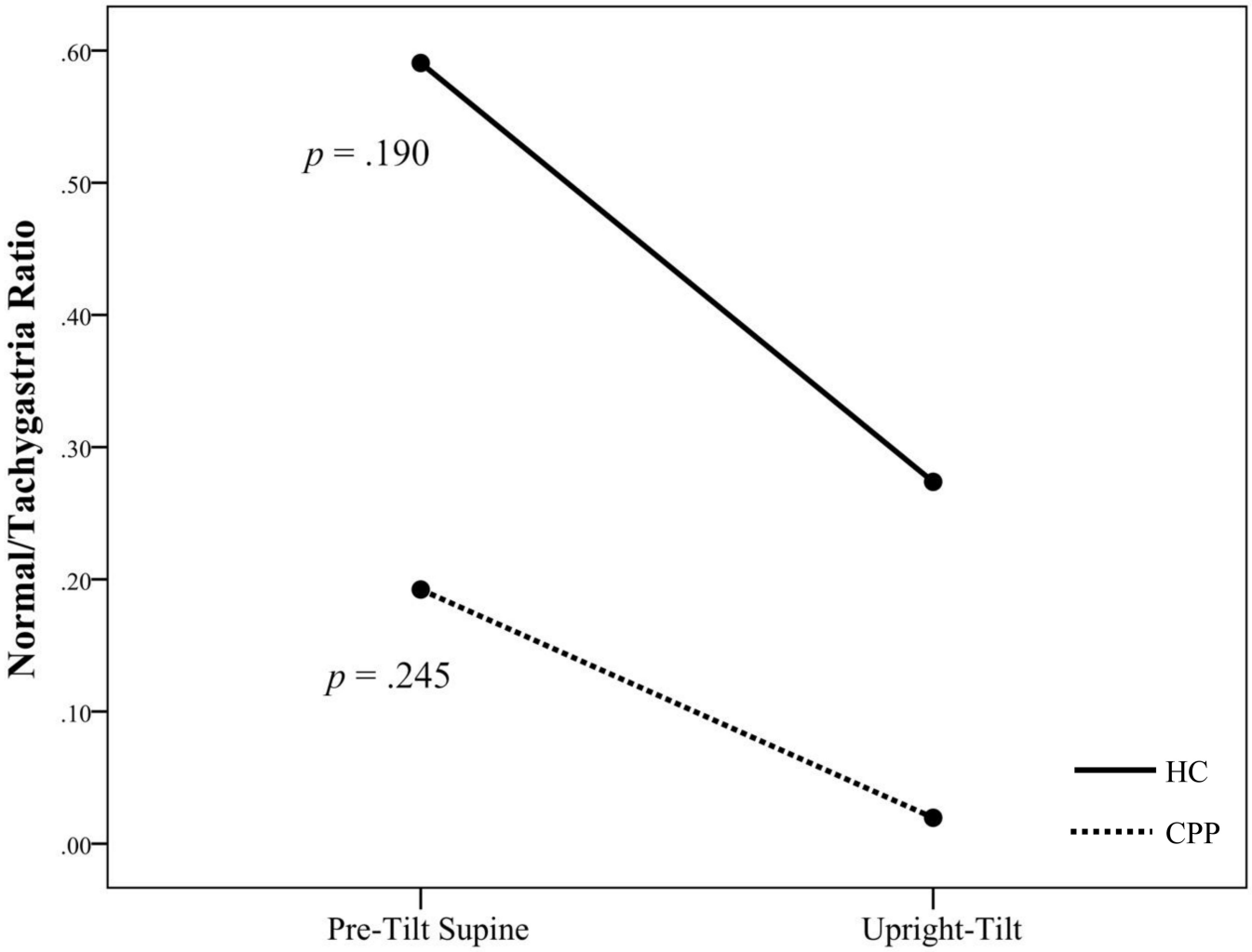

Figure 6: Normal-/tachy-gastria from pre-to post-tilt

Note: This figure depicts natural log-transformed (ln) normal/tachygastria ratio from pre-tilt supine to upright-tilt stratified by heathy controls (HC; solid line) and chronic pelvic pain (CPP; dotted line) groups. No significant linear trends were found in either group ($p > .05$).