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Original Article

Nutrient Drink Test to Assess Gastric Accommodation in Cyclic Vomiting Syndrome: Single-blinded Parallel Grouped Prospective Study

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Background/Aims
Cyclic vomiting syndrome (CVS) is characterized by episodes of nausea and vomiting, separated by symptom-free intervals. The pathogenesis of CVS is poorly understood. Limited data exist on evaluating impaired gastric accommodation as a mechanistic means for symptoms. We aim to determine if CVS patients demonstrate impaired gastric accommodation applying a nutrient drink test (NDT) protocol.

Methods
Through this single-blinded pilot clinical trial, patients with CVS per Rome IV critera and healthy controls were assessed for presence of impaired gastric accommodation by administering an established NDT protocol. Statistical analysis was performed, with data presented as medians and interquartile range.

Results
Eleven CVS patients and 15 healthy controls participated in the study between January 2018 and October 2018. Median age was 42.0 years and 37.0 years; majority of subjects were female, 72.7% and 73.3%, respectively. Demographics were similar between CVS and healthy controls. Almost all healthy controls (93.3%) ingested the complete 500 mL protocol, whereas a smaller proportion (72.7%) were able to complete all 4 doses in the CVS group ($P = 0.188$). Post-prandial visual analogue scale scores of nausea and abdominal pain were found to be significantly higher in CVS patients compared to healthy controls.

Conclusions
To our knowledge, this is the first NDT protocol in CVS evaluating the role of impaired gastric accommodation and hypersensitivity as a possible pathophysiologic mechanism. Findings from this study suggest the presence of gastric hypersensitivity in a subset of CVS patients. These results provide the foundational data necessary for future larger testing of NDT and diagnostic accuracy in CVS.
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Key Words
Nausea; Randomized controlled trial; Vomiting

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Introduction

Cyclic vomiting syndrome (CVS) is characterized by recurrent episodes of severe nausea and vomiting separated by symptom-free periods. CVS has received increased recognition among adults with unexplained vomiting and is thought to contribute to 3-14% of patients with unexplained vomiting.[1] At present, practitioners rely on clinical symptoms to make a diagnosis. Diagnostic criteria set by Rome IV include: (1) stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week); (2) at least 1 discrete episode in the prior year and 2 episodes in the past 6 months; and (3) absence of vomiting between episodes, but other milder symptoms can be present.[2]

Despite these diagnostic criteria, CVS is often underdiagnosed or misdiagnosed, leading to delays in definitive management. Length of time between symptom onset and diagnosis is consistently long, averaging 1.9 years in children,[3] and 8 to 21 years in adults.[1] CVS symptoms can mimic similar chronic vomiting disorders such as gastroparesis, irritable bowel syndrome, or psychogenic conversion disorder, contributing to this diagnostic delay. One study reported that 5% of CVS patients initially were diagnosed with gastroparesis, whereas another reported that 39% underwent unnecessary surgical procedures in an attempt to mitigate symptoms.[1] Unfortunately, misdiagnosis of CVS can lead to labels such as malingering or pain seeking behavior, frequent emergency room visits, loss of productivity, and reduced quality of life.[4]

The lack of an objective diagnostic tool for CVS diagnosis stems from an incomplete understanding of disease pathophysiology underlying the disorder. Although visceral hypersensitivity has been proposed in other functional gastrointestinal (GI) diseases including up to 40% of functional dyspepsia patients, gastric hypersensitivity has not been extensively evaluated in CVS.[5,6] One hypothesis put forth to explain CVS pathophysiology consists of abnormal gastric emptying as a consequence of abnormal gastric fundic accommodation,[7,8] based on studies reporting rapid gastric emptying, or a dumping-like emptying pattern in CVS patients.

A nutrient drink test is non-invasive technique to estimate gastric volumes and qualitatively assess satiation following ingestion of nutrient-containing solutions. Therefore, a nutrient protocol has served as a surrogate for gastric accommodation.[9] Furthermore, a nutrient drink test has been suggested to measure visceral hypersensitivity of the proximal stomach by evaluating dyspeptic symptoms with intake.[10] To date, there are no studies evaluating the relationship between gastric accommodation, gastric hypersensitivity and CVS symptoms. The primary aim of this study therefore is to determine if CVS patients demonstrate impaired accommodation or gastric hypersensitivity using the nutrient drink test.

Materials and Methods

Adult patients fulfilling the Rome IV criteria for CVS were recruited to participate in this single blind prospective study during a one-year period in 2018. The presence of structural GI disorders, prior foregut surgery, or alternate functional GI disorders potentially explaining symptoms were regarded as exclusions. Asymptomatic individuals as patient report were recruited during the same calendar year by advertisement to function as controls. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Investigational Review Board of Cleveland Clinic (IRB No. 17-1138). The study was enlisted into Clinical Trials (ClinicalTrials.gov Identifier: NCT03470181).

Patients

Patients with CVS reported in this investigation were prospectively identified from an accessible population of patients actively being managed at Cleveland Clinic's Division of Gastroenterology outpatient clinics. The target population consisted of adults (≥ 18 years) who met a clinical diagnosis of CVS fulfilling the Rome IV criteria, with no active CVS symptoms at the time of study visit. Patients were excluded if review of electronic medical records or clinical history demonstrated gastric pathology on esophagogastroduodenoscopy that could explain symptoms; history of major foregut and abdominal surgeries (excluding laparoscopic cholecystectomy or appendectomy); active pregnancy or lactation; active inflammatory bowel disease; severe renal disease (defined as dialysis dependent end stage renal disease); active malignancy (diagnosed in the preceding 5 years); current marijuana use defined by positive drug screen or documentation of abuse; and allergy or intolerance to liquid Ensure used for nutrient drink test. Healthy controls consisted of asymptomatic adult volunteers (≥ 18 years) without a clinical diagnosis of CVS or similar chronic vomiting or functional disorder, including functional dyspepsia, gastroparesis, and irritable bowel syndrome. Controls consisted of hospital-based volunteers who responded to advertisement flyers placed around the clinic outpatient waiting rooms and building lobby.

Nutrient Drink Protocol

CVS patients and controls were initially identified by an unblinded research coordinator. In the event that recruited CVS patients experienced a CVS flare (ie, nausea or vomiting) prior to their scheduled visit, this coordinator rescheduled their visit to an asymptomatic interval after contacting the patient 1 week later. In the event that symptoms persisted, the coordinator would contact the patient weekly until it was established that at least 1 week had passed after the CVS flare had subsided. The study visit was then scheduled with a blinded research team member who was unaware of the patient's underlying diagnosis (CVS or control). Both CVS patients and healthy controls were required to refrain from medications that may impact gastric motility (eg, prokinetics, antispasmodics, anxiolytics or sleep aides, and opiates) the day preceding the study and the day of the study. Primary CVS prophylactic medications were not discontinued.

Patients were instructed to fast overnight or for 6 hours prior to testing. Following informed consent, patients drank 125 mL of 220 calorie liquid Ensure (Abbott Nutrition, Columbus, OH, USA) 4 times, at 5 minute intervals, in accordance with established nutrient drink test protocols utilized in other disorders with impaired gastric accommodation, including functional dyspepsia.[9] As patients ingested each aliquot of 125 mL, they were instructed to rate their sensation of fullness using a 6 point graphic Likert scale, where 0 = no symptoms, 1 = first sensation of fullness, 2 = mild, 3 = moderate, 4 = severe, and 5 = maximum or unbearable fullness. Consumption of liquid Ensure was stopped when patients rated their sense of fullness at a score of 5. The total quantity of ingested liquid Ensure (maximum 500 mL) when a Likert score of 5 was reached determined that patient's "maximum tolerated volume." Patients rated their post-prandial symptoms of bloating, fullness, nausea, and abdominal pain using a 100-mm visual analogue scale 30 minutes following the completion of liquid Ensure ingestion. The sum of the post-prandial symptom score on visual analogue scale (maximum 400) was recorded as the patient's "total aggregate symptom score."[11]

Sample Size and Data Analysis

Sample size was calculated based on Lim et al,[9] who demonstrated among 19 healthy controls and 40 functional dyspepsia patients total aggregate symptom scores measured during NDT were higher in dyspeptic patients compared to controls (mean ± SD, 368.1 ± 245.3 vs 215.9 ± 171.2; $P = 0.018$). We anticipated that the pooled standard deviation for the total aggregate symptom score would be approximately 225. Based on this assumption, 80% power to detect a difference of at least 238 between the CVS patients and healthy controls at a significance level of 0.05 using a 2-sided *t* test would require 15 patients per group (CVS and control).

Data are presented as mean ± standard deviation, median (interquartile range [IQR], 25th-75th percentiles), or frequency (percent) as appropriate. Univariable analysis compared patients with CVS to controls; *t* tests or the non-parametric Wilcoxon rank sum tests compared continuous factors and Pearson's chi-square were used to compare categorical variables. The *t* test was used to compare total aggregate symptom score, which was defined as the sum of the symptom scores (maximum 400). Receiver operating characteristics analysis was used to assess the utility of the total aggregate score to distinguish CVS from healthy controls; the area under the receiver operating characteristics curve (AUC) was reported along with the corresponding 95% confidence interval. An optimal cut point for determining abnormal gastric accommodation was determined using Youden's index.[11] In addition, scores at each time were also compared and a mixed linear model will be used to assess if the time trend differed between the 2 groups. All analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC, USA) and a $P < 0.05$ was required for statistical significance.

Results

In total, 11 CVS patients (8 female, mean age 42.0 [32.0 ± 53.0]) and 15 healthy controls [11 female, mean age 37.0 (32.0 ± 53.0)] patients participated in the study between January 2018 and December 2018. As reported in Table 1, both groups were comparable in gender, race, and body mass index. There was no difference in proportions with anxiety and depression between the 2 groups.

Upon performance of the nutrient drink test, 93.0% of healthy volunteers ingested the complete 500 mL of the nutrient drink, while only 72.7% of CVS patients were able to consume the same amount ($P = 0.188$). Within the CVS cohort, 1 patient was unable to complete the first 125 mL and an additional 2 patients were unable to complete the third and fourth dose of the 125 mL, all 3 due to unbearable fullness (Table 2).

Patients with CVS reported higher nausea and abdominal pain scores compared to the control group following completion of the nutrient drink ($P < 0.001$ and $P = 0.002$, respectively; Fig. 1). Eight (72.7%) of the CVS patients reported nausea, and 6 (54.5%) reported abdominal pain; in contrast, none of the controls reported these symptoms ($P < 0.001$ and $P = 0.002$, respectively). The proportion of CVS patients and controls that reported post-prandial

Table 1. Basic Demographics Between Patients With Cyclic Vomiting Syndrome and Healthy Controls

Demographics	CVS (n = 11)	Controls (n = 15)	*P*-value
Age (yr)	42.0 (34.5, 65.0)	37.0 (32.0, 53.0)	0.323
Gender			> 0.999
Male	3 (27.3)	4 (26.7)	
Female	8 (72.7)	11 (73.3)	
Race			0.410
African American	2 (18.2)	4 (26.7)	
Asian	0 (0.0)	1 (6.7)	
Hispanic	2 (18.2)	0 (0.0)	
Caucasian	7 (63.6)	10 (66.7)	
BMI (kg/m^2)	28.7 (27.1, 30.7)	25.8 (22.2, 29.4)	0.161
Anxiety history	2 (18.2)	0 (0.0)	0.169
Depression history	4 (36.4)	3 (20.0)	0.410
Migraine headache	7 (63.6)	4 (26.7)	0.110

CVS, cyclic vomiting syndrome; BMI, body mass index.
Data are presented as median (interquartile range) or n (%).

Table 2. Comparison of Individual Rating Scores Between Patients With Cyclic Vomiting Syndrome and Healthy Controls

Nutrient drink test	CVS (n = 11)	Controls (n = 15)	*P*-value
Maximum tolerated volume			0.190
125 mL	0 (0.0)	1 (6.7)	
250 mL	1 (9.1)	0 (0.0)	
375 mL	1 (9.1)	0 (0.0)	
395 mL	1 (9.1)	0 (0.0)	
500 mL	8 (72.7)	14 (93.3)	
30-minute VAS symptoms			
Bloating	28.0 (12.5, 55.0)	10.0 (0.0, 55.0)	0.120
Fullness	70.0 (32.5, 77.5)	25.0 (2.8, 58.0)	0.130
Nausea	40.0 (2.5, 65.0)	0.0 (0.0, 0.0)	< 0.001
Abdominal pain	4.0 (0.0, 40.0)	0.0 (0.0, 0.0)	0.002
Total aggregate score	180.0 (67.5, 202.5)	59.0 (4.3, 87.5)	0.010

CVS, cyclic vomiting syndrome; VAS, visual analogue scale.

bloating and fullness between the groups were not significantly different, with 10 (90.9%) of the CVS patients reported bloating and 9 (81.8%) reported fullness; in contrast, 9 (60.0%) of the control patients reported bloating and 11 (73.3%) reported fullness (P = 0.250 and $P > 0.999$, respectively).

The total aggregate symptom score was significantly increased in CVS patients when compared to controls (180.0 vs 59.0, P = 0.010), Figure 2.

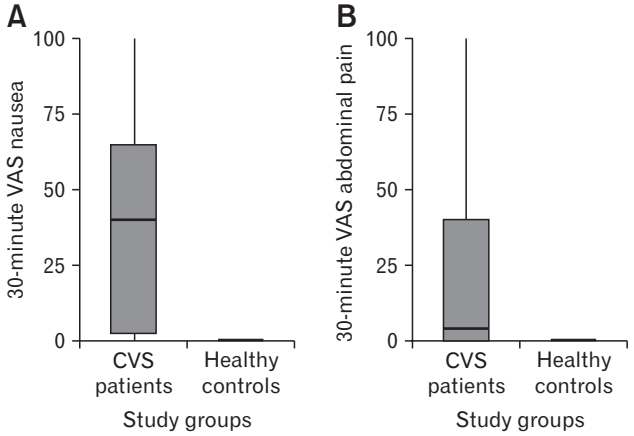

Figure 1. Box and whisker plot demonstrating higher reports of nausea (A) and abdominal pain (B) among cyclic vomiting syndrome (CVS) patients compared to controls, following the nutrient drink. VAS, visual analogue scale.

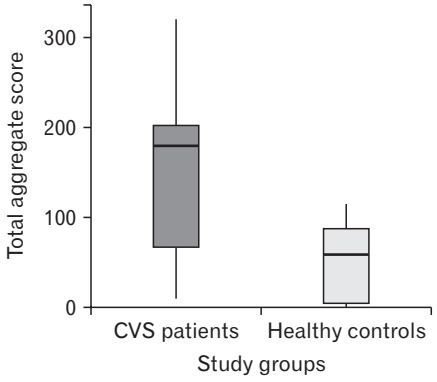

Figure 2. Box and whisker plot demonstrating significant increase in total aggregate symptom score among cyclic vomiting syndrome (CVS) patients compared to controls.

Discussion

In this study, we report the first use of a NDT to evaluate the role of gastric pathophysiology in CVS. Our findings demonstrate that CVS patients tolerate overall less nutrient drink volume compared to healthy controls, with significantly higher perceptive symptom scores, especially nausea and abdominal pain. This study suggests gastric hypersensitivity as a potential contributor to symptoms in patients with CVS.

The pathophysiology of CVS remains incompletely understood. Proposed pathophysiologic hypotheses include mitochondrial gene mutations, autonomic dysfunction and migraine diathesis. At present, our limited understanding of the mechanistic underpinnings of CVS have left clinicians without specific tests for assessing CVS,

and therefore diagnosis relies on fulfilling clinical criteria such as those set by the Rome IV foundation.[3] In the process of establishing a diagnosis, the typical CVS patient is then subjected to a litany of tests and procedures, most often without a diagnostic or therapeutic gain.

One hypothesis put forth to explain CVS has been rapid gastric emptying, an observation in the context of CVS in 2 prior studies. Cooper et al[4] assessed the prevalence of rapid gastric emptying in patients with CVS using a standard 4-hour scintigraphy with a low fat solid meal, defining rapid gastric emptying use 2 separate predefined criteria: (1) < 50% isotope retention or (2) < 65% isotope retention at first hour and/or < 20% at second hour. Among 30 CVS adults diagnosed with CVS per Rome III criteria, the majority had either rapid or normal gastric emptying. It is unknown at what symptom period gastric emptying was measured, whether during an active or inter-episodic phase; however, the authors discuss testing should ideally occur during remission or during minimal symptoms.[6] The authors concluded rapid gastric emptying may support a diagnostic feature of CVS. Similarly, Hejazi et al[12] retrospectively measured gastric emptying profiles applying standard 4-hour scintigraphic methods with a low fat solid meal among 92 adults who met CVS Rome III criteria. Applying definitions of < 50% isotope retention at first hour and/or < 30% at second hour for rapid emptying, 59.0% of CVS had rapid gastric emptying and 27.0% had normal emptying. Whereas the majority met criteria for either rapid or normal gastric emptying, 14.0% of the patients demonstrated delayed gastric emptying (> 10% isotope retention at 4 hours). This relationship of delayed gastric emptying was significantly more associated with diabetics, chronic narcotic users and chronic marijuana smokers ($P < 0.05$).[5] These findings suggested that although CVS patients may trend towards rapid or normal gastric emptying, gastric emptying can vary within the context of CVS. Therefore, as gastric emptying relates partly to the accommodation reflex within the gastric fundus, we chose to indirectly evaluate gastric emptying applying the nutrient drink test, a surrogate for gastric accommodation, among patients meeting Rome IV criteria.

Gastric accommodation facilities the proximal stomach function as a reservoir of ingested food and liquid. Through a vagally mediated reflex, gastric tone reduces with a simultaneous increase in compliance, allowing for a post prandial rise in gastric volume without a similar increase in gastric pressure. Gastric barostat testing is considered the gold-standard to measure gastric accommodation, but this technique is limited by equipment accessibility, test invasiveness, the time-consuming nature of the study, and risk for patient discomfort.[13] The nutrient drinking test was therefore devised to measure consequences of abnormal accommodation as a surrogate to barostat testing, with sensitivity and specificity in predicting impaired accommodation reaching 92.0% and 86.0%, respectively.[6] Since the nutrient drink test is non-invasive, easy to perform and low in cost, the test has been utilized in other disorders where gastric accommodation is expected to be abnormal, ie, functional dyspepsia.[8] In contrast to impaired gastric accommodation, where patients predominantly are limited in the drinking capacity to nutrient liquid, hypersensitivity to gastric distention is the triggering of dyspeptic symptoms.[10] Visceral hypersensitivity has been proposed to stem from dysregulation between the enteric and central nervous system. In CVS patients, autonomic activation has been found to be intensified with release of corticotropin, vasopressin, norepinephrine and prostaglandin F. This release is thought to be provoked by stimuli or a stress-induced state.[14] Recognizing gastric distension with water has induced symptoms in patients with functional dyspepsia, the nutrient drink has been suggested to additionally serve as a noninvasive test of visceral hypersensitivity within the proximal stomach.[10]

In our study, we found CVS patients and controls were balanced in regards to demographics and psychiatric comorbidities. Whereas the psychiatric aspect of anxiety and mood disorders has been frequently associated with CVS,[15] we found a similar rate of psychiatric comorbidity among our study controls. Presence of anxiety, depression and migraine headaches was assessed retrospectively by chart review among CVS patients and self-reported among controls, the use of a validated questionnaire was not applied. Following the application of a nutrient drink test protocol, CVS patients and healthy controls were differentiated by their total volume tolerated and post prandial symptom experiences. Specifically, CVS patients perceived significantly greater symptoms of post prandial nausea and abdominal pain compared to their healthy counterparts. As a result, the summation of post prandial symptoms (total aggregate symptom score) was found to be distinctly different between CVS patients and controls. These findings suggest the possibility of gastric hypersensitivity among CVS patients.

The presence of gastric hypersensitivity in functional dyspepsia and our study findings among a small cohort of CVS patients raises an important question—can the NDT help distinguish these conditions among patients with chronic nausea and vomiting? Our study demonstrated that with the application of a nutrient drink protocol, the optimal threshold for total aggregate symptom score among CVS patients was 144.5, with a sensitivity of 63.6%, specificity 100.0%, and AUC 80.5%. Given the overall small sample size and exploratory nature of this study, it would be premature to promote

this cutoff as a diagnostic tool in CVS, specifically to differentiate from patients with functional dyspepsia. Although our study reveals lower mean total aggregate symptom scores compared to what has been found among functional dyspeptic patients,[10] additional data may be required to compare nutrient drink findings between CVS and functional dyspepsia patients. Nonetheless, this study identifies a symptom score of 144.5 highly specific to CVS relative to healthy controls.

Our study has a few notable limitations inherent to the exploratory nature of this protocol. First, as previously acknowledged the sample size of this study was small and limited to asymptomatic CVS patients referred to a single tertiary care center. Due to the overall low prevalence of CVS and number of patients initially being diagnosed with CVS, but on further investigation were found to have met criteria for cannabinoid hyperemesis syndrome, the intended sample size of 15 CVS patients was not achieved. This decrease in power may have reduced the ability to detect greater differences between the 2 groups, specifically in maximum tolerated volumes. Despite a low CVS sample size, significant differences in post prandial symptoms nevertheless were detected between the 2 groups. Furthermore, our control group consisted of hospital-based volunteers, and therefore may not entirely represent the general population, possibly introducing external selection bias and limiting generalizability. Second, our study design did not match CVS patients to healthy controls; however, the groups were found to be comparable on analysis without significant baseline differences. Third, the nutrient drink test is possibly picking up functional dyspepsia overlapping with CVS, rather than explaining a basis for CVS. The nutrient drink test protocol does not include baseline fasting symptoms, it is unclear if the changes observed are due to the challenge meal, or overlapping functional dyspepsia. Future studies regarding this topic should obtain fasting symptoms to better determine this pathophysiology. We assessed for anxiety/depression based on patient history, we did not use a validated questionnaire, the medical records review may not represent the anxiety/depression that relates to GI symptoms in the patients with CVS.

Management of CVS may be categorized in abortive and prophylactic therapies.[16,17] Abortive agents include various antiemetics and/or medications in the triptan family in patients with underlying migraines. Interestingly, the first-line prophylactic therapy is a TCA, which has also been well studied in functional dyspepsia.[18] The exact mechanism of action is unknown for TCA in patients with CVS; however, treatment of gastric hypersensitivity is a possible explanation.

In conclusion, the application of nutrient drink test among CVS patients appears to objectively quantify differences in volume tolerance and post-prandial symptoms. The findings of this study may indicate that gastric hypersensitivity plays a role in pathogenesis of CVS.

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Conflicts of interest: None.

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