



Utility of Diagnostic Studies for Upper Gastrointestinal Symptoms in Children with Orthostatic Intolerance

Lana N. Zhang, MD¹, Jeffrey P. Moak, MD¹, John Desbiens, BS², Sridhar Hanumanthaiah, MBBS¹, Robin R. Fabian, RN¹, Lindsay Clarke, PA-C², Rashmi D. Sahay, MD³, and Anil Darbari, MD, MBA²

Objective To assess the utility of gastrointestinal (GI) diagnostic studies in the evaluation of patients with orthostatic intolerance.

Study design Medical records of 103 consecutive children/young adults with orthostatic intolerance and gastrointestinal symptoms were reviewed. All patients had undergone antroduodenal manometry in conjunction with the tilt table test, autonomic testing, and upper gastrointestinal endoscopy (EGD). A gastric emptying study (GES) was performed in 81 patients.

Results The median age of the cohort was 17 years (IQR, 15-19) with a female predominance (females:males, 3:1). As expected, the tilt table test was abnormal in all patients. Antroduodenal manometry was abnormal in 83 of 103 patients (81%), showing neurogenic intestinal dysmotility in 50%, rumination in 20%, and visceral hyperalgesia in 10%. The GES results were abnormal in 23 of 81 patients (28.4%), mostly (21 of 23) with delayed GES. None of the tilt table test or autonomic results were predictive of abnormal antroduodenal manometry or GES. Analysis of EGD biopsy samples revealed nonspecific esophagitis and/or gastritis in 16 of 103 patients (15%).

Conclusions Antroduodenal manometry with the tilt table test were the most insightful investigations in adolescents and young adults with orthostatic intolerance and gastrointestinal symptoms. GES and EGD provided limited information. Gastrointestinal symptoms were related more to functional rather than mucosal or organic etiologies, suggesting a limited role of endoscopy alone in evaluating patients with orthostatic intolerance presenting with gastrointestinal symptoms. (*J Pediatr* 2019;205:138-44).

Orthostatic intolerance, including postural orthostatic tachycardia syndrome (POTS), affects many teenagers and young adults, resulting in symptoms from multiple organ systems. The most common presenting symptoms originate from the cardiovascular system; however, up to 80% of children with orthostatic intolerance also exhibit chronic gastrointestinal symptoms, which may predominate the patient's disability.¹⁻³ These symptoms, which include nausea, bloating, and abdominal pain, can lead to significant functional impairment, with absences from school or work.^{1,4-6} Nausea is seen in up to 86% of patients, similar to the incidence of the hallmark cardiovascular symptom of lightheadedness (87%). In some studies, abdominal pain has been reported more often than the cardiovascular symptoms of presyncope and syncope.^{2,7,8}

The underlying reasons for the often medication-refractory and clinically disabling gastrointestinal symptoms are unclear.^{2,9,10} Patients are often referred to a gastroenterologist; however, typical gastrointestinal evaluations, including endoscopic and radiologic studies, frequently fail to reveal significant abnormalities.¹¹ In clinical practice, this often results in patient dissatisfaction, health care provider frustration, high costs of care, and potentially hazardous diagnostic studies.

In this study, we reviewed the medical records of a cohort of subjects with orthostatic intolerance and chronic gastrointestinal symptoms followed at our center to determine the incidence of abnormalities in different gastrointestinal studies, and to determine their association with the presenting symptoms and cardiovascular tilt table and autonomic test results.

Methods

The Children's National Institutional Review Board approved this retrospective chart review. The study population consisted of consecutive patients with orthostatic intolerance and gastrointestinal symptoms who had undergone antroduodenal manometry in conjunction with autonomic and tilt table testing between July 2011 and January 2017. We reviewed surgical pathology results from biopsy specimens of the second part of the duodenum, duodenal bulb, antrum/stomach, and distal and mid esophagus that were obtained during upper

EGD Esophagogastroduodenoscopy
GES Gastric emptying study
POTS Postural orthostatic tachycardia syndrome

From the ¹Division of Cardiology; ²Division of Gastroenterology, Children's National Health System, Washington, DC; and ³Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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gastrointestinal endoscopy (esophagogastroduodenoscopy [EGD]) for antroduodenal manometry catheter placement. We also reviewed scintigraphic gastric emptying study (GES) findings.

Antroduodenal Manometry

The 24-hour ambulatory antroduodenal manometry study, autonomic function test, and tilt table test have been described previously.³ Antroduodenal manometry studies were performed with a 6-channel solid-state (Konigsberg) manometry catheter, with 3 antral channels spaced 2 cm apart and 3 duodenal channels spaced 15 cm apart, placed endoscopically into the antrum and proximal small bowel. The antroduodenal manometry results were analyzed (1) in the fasting state/overnight, (2) postmeal, (3) during the tilt table test (described below), and (4) following oral administration of erythromycin 100 mg and 250 mg, amitriptyline 25 mg, and metoclopramide 10 mg during the study period. The patients' families were instructed to hold all medications that could possibly alter autonomic function for 48 hours before the study.

The mean amplitude, frequency, and duration of phasic activity periods were analyzed as described previously.³ Previously published norms were used for these measures.^{12,13} Mean antral contractions were considered normal between 20 and 96 mmHg, with values below that range indicating hypoactivity and values above that range indicating hyperactivity. Mean duodenal contractions were considered normal between 20 and 40 mmHg. The presence of phase III migrating motor complexes (MMC-III) was considered to indicate normal baseline antroduodenal motility in the fasting state.

Myopathy was diagnosed if the amplitude of antral contractions was <40 mmHg and that of duodenal contractions was <10 mmHg. Neurogenic intestinal dysmotility was diagnosed if there was (1) lack of fasting MMC-III; (2) presence of simultaneous, nonpropagative, or retrograde phases; (3) prolonged (>30 minutes) high-amplitude clusters in duodenal channels; (4) increase in basal tone >30 mmHg for >3 minutes during phase II MMC (MMC-II) in a fasting state; (5) lack of conversion from fasting MMC-III to fed MMC-II after meals; or (6) bursts of nonpropagating phasic contractions within 30 minutes after meals. Regurgitation/rumination was diagnosed if vomiting was precipitated during the tilt table test, or there were simultaneous regurgitation R-waves in all channels. Visceral hyperalgesia was diagnosed if pain was reported at the time of MMC-III activity.

Autonomic Function and Tilt Table Testing

The autonomic function testing included corrected QT (QTc) measurement on a standard pediatric 15-lead electrocardiogram, performance of the Valsalva maneuver (+40 mmHg for 15 seconds), and cold pressor testing (60 seconds of hand immersion in ice-cold water). At 10 minutes after completion of baseline autonomic testing, the tilt table test was performed at 70°C for up to 30 minutes using a hydraulically controlled motorized table or concluded earlier if the subject developed moderate or intolerable symptoms or became presyncopal. On

the cold pressor test, a blood pressure (BP) increase of <15 mmHg was defined as an abnormal result. The Valsalva maneuver was defined as abnormal at a Valsalva ratio <1.5, cardioaccelerator index <25, or vasoconstrictor index <20 mmHg.³

As described previously, the following clinical criteria were considered indicative of orthostatic intolerance: (1) ≥ 30 bpm increase in heart rate (HR) within 10 minutes of assuming the upright position; (2) development of cardiovascular, neurologic, and gastrointestinal symptoms consistent with orthostatic intolerance; (3) the symptoms that occurred when upright reproduced the patient's clinical indication for the study; (4) the symptoms resolved or markedly improved when the patient was placed supine at the end of the tilt test; and (5) abrupt normalization of HR when placed back supine.³ The tilt table test results were reported to be consistent with POTS only when the HR increased by ≥ 40 bpm within 10 minutes of assuming the upright position.¹⁴ Thus, the hemodynamic response to the tilt table test was divided into 3 categories: orthostatic intolerance (30- to 40-bpm increase in HR within 10 minutes of assuming the upright position with development of orthostatic intolerance symptoms and absence of hypotension), POTS (>40 bpm increase in HR within 10 minutes of assuming an upright position with development of orthostatic intolerance symptoms and absence of hypotension), and neurally mediated cardiac syncope (≥ 30 bpm increase in HR with the development of hypotension and symptoms of presyncope or syncope).³

Statistical Analyses

All analyses were done using SAS 9.4 (SAS Institute, Cary, North Carolina). Two-sided testing was performed, with $P \leq .05$ considered to indicate statistical significance. Summary statistics were presented as median and IQR for continuous variables and as count and percentage for categorical variables. Differences in continuous variables between abnormal and normal antroduodenal manometry were examined using the Mann-Whitney test and χ^2 or Fisher exact test for categorical variables. Paired data for changes in HR (increase) and systolic BP (decrease) from baseline to the tilt table test were examined using the Wilcoxon signed-rank test. For analysis, increases in HR were categorized as normal (<30 bpm), abnormal (≥ 30 to <50 bpm), or highly abnormal (≥ 50 bpm). Decreases in systolic BP were categorized as normal (<20 mmHg), abnormal (≥ 20 to 40 mmHg), or highly abnormal (>40 mmHg). Abnormal and normal antroduodenal manometry and GES results were then associated with the results of the cold pressor test and Valsalva maneuver as binary variables and with changes in HR and systolic BP as ternary variables using the χ^2 or Fisher test.

Not every patient underwent both antroduodenal manometry and GES; therefore, a subset of the total cohort who underwent both antroduodenal manometry and GES were examined to evaluate for statistical agreement between these 2 study results using the McNemar test. Associations between antroduodenal manometry results and GES were tested against autonomic test results, and various tilt table test measures were

examined using logistic regression models and are presented as OR and 95% CI.

Results

A total of 103 consecutive patients were reviewed, including 35 individuals who had been reported previously.³ We decided to include these 35 patients in this cohort because in the previous report, antroduodenal manometry and tilt table test measures were not statistically analyzed owing to small sample size. The patients ranged in age from 8 to 29 years (median, 17 years; IQR, 15-19 years). The majority of the patients were adolescents ($n = 87$; 85%); 6 patients were aged ≤ 12 years, 10 were aged ≥ 20 years, and there was a preponderance of females (76%). The predominant symptoms at presentation were lightheadedness (87%) and nausea (86%), followed by abdominal pain (76%), presyncope (38%), syncope (22%), constipation (18%), and diarrhea (13%) (Figure 1). Overall, 30 patients (29.1%) had 1 or 2 symptoms, 28 patients (27.2%) had 3 symptoms, 21 patients (20.4%) had 4 symptoms, and 24 patients (23.3%) had more than 4 symptoms.

Fifty-six of 103 patients were evaluated initially by a cardiologist for orthostatic intolerance. The decision to pursue further evaluation was based on the patient's clinical history of cardiovascular symptoms, pattern of response of these symptoms to positional changes, and response to a 10-minute in-office standing test. If gastrointestinal symptoms were also reported, the patient was recommended for gastrointestinal evaluation for consideration of an antroduodenal manometry

study. Forty-seven patients were first seen in gastroenterology, some of whom had undergone cardiologic evaluation outside of our institution, the results of which were not readily available. If the history included cardiovascular symptoms of dizziness, presyncope, or syncope, the tilt table test was recommended along with the antroduodenal manometry test.

Among the 54 patients in whom treatment data were available, 53 patients were treated with increased fluids and salt intake before undergoing the combined tilt table test with antroduodenal manometry study. The mean interval between evaluation in the cardiology clinic and the antroduodenal manometry study was 12.6 ± 11.9 months, so some patients were started on a more aggressive treatment, such as fludrocortisone, midodrine, or other medications used to treat orthostatic intolerance.

Antroduodenal Manometry Results

During the overnight fasting period, antroduodenal manometry showed normal MMC-III findings in 83 of the 103 patients (81%). Features of neurogenic intestinal dysmotility were noted in 12 patients (12%), and significant antral hypomotility was seen in 8 (7%). Antroduodenal manometry results were abnormal in 83 patients (81%) when performed in conjunction with the tilt table test. Antroduodenal manometry showed features of neurogenic intestinal dysmotility in 51 of the 103 patients (50%), rumination/regurgitation in 23 (22%), and visceral hyperalgesia in 11 (11%); some patients had more than 1 abnormal finding. During the tilt table test, 73 patients (71%) had 1 or more gastrointestinal symptoms reproduced (mostly nausea, vomiting, and abdominal pain). During

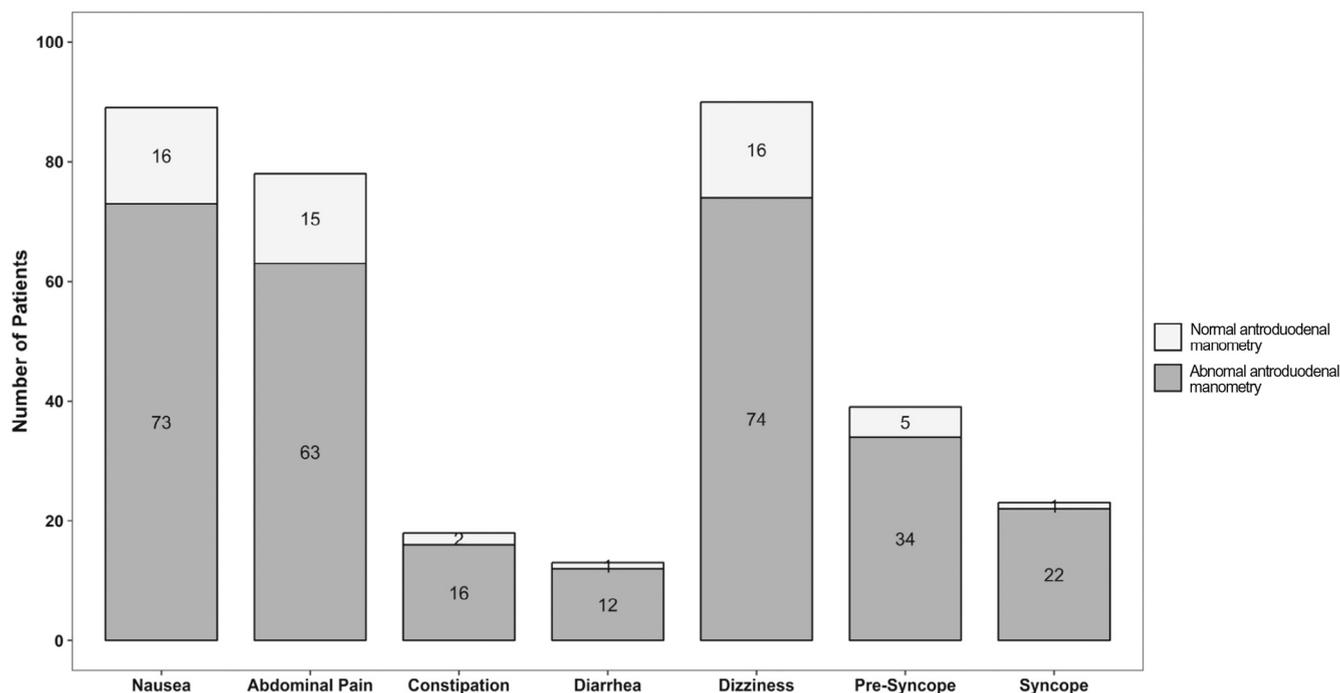


Figure 1. Distribution of gastrointestinal and cardiovascular symptoms noted in patients at presentation. Each bar represents the total number patients with each symptom and the abnormal (*dark*) and normal (*light*) results on antroduodenal manometry.

the tilt table test, abnormal findings were seen in 63 patients (61%), with features of neurogenic dysmotility in 41 (39%), antral hypomotility in 14 (13%), rumination/regurgitation in 16 (15%), and visceral hyperalgesia in 10 (9%); some patients had more than 1 abnormal finding.

The associations between antroduodenal manometry results and symptoms are presented in **Figure 1**. The association between antroduodenal manometry and syncope was significant ($P = .04$), with 96% of the patients who presented with syncope showing abnormal antroduodenal manometry results. The odds of an abnormal antroduodenal manometry result also tended to be high ($P = .06$) in the presence of multiple baseline symptoms.

Tilt Table Test Results

The tilt table test results indicated orthostatic intolerance in 16 patients, POTS in 61 patients, and neurally mediated cardiac hypotension in 26 patients. For the total cohort, the median baseline HR was 78 bpm (IQR, 67-90 bpm), increasing to a maximum of 138 bpm (IQR, 125-151 bpm; difference, 58 bpm; IQR, 47-69 bpm; $P < .001$). Baseline systolic BP was 113 mmHg (IQR, 106-119 mmHg), decreasing to 85 mmHg (IQR, 57-103 mmHg; difference, -28 mmHg; IQR, 8-58 mmHg at the end of the tilt period; $P < .001$).

GES Results

The GES was performed in 81 of the 103 patients (79%). Results were reported as normal in 58 of the 81 patients (72%), delayed in 21 (26%), and rapid in 2 (3%). Most patients showed an initial delay (<50% at 2 hours) of the standard solid meal ingested; 3 of 21 had a delay (<50%) at 3 hours, and 2 of 21 had <50% emptying at 4 hours.

Association of Antroduodenal Manometry with GES

Antroduodenal manometry results were abnormal in 83 of the 103 patients (81%) (**Figure 2**). Among the 23 patients with

abnormal GES results, antroduodenal manometry was abnormal in 18 (78%) and normal in 5 (22%). Among the 58 patients with normal GES results, antroduodenal manometry was normal in 10 (17%) and abnormal in 48 (83%). In comparison, of the 83 patients (81%) with abnormal antroduodenal manometry results, 66 (80%) underwent GES, which showed abnormal findings in 18 (27%) and normal findings in 48 (73%). The abnormality was reported as delay in 17 of the 66 patients (26%) and rapid in 1 patient (2%). Among the 17 patients with delayed GES and abnormal antroduodenal manometry, 3 (17%) had antral hypomotility. Among the 13 patients with antral hypomotility on antroduodenal manometry studies, GES was reported in 11 patients (85%) and showed a delay in 1 patient, and 1 patient had an initial delay in the first hour, followed by normal emptying. Fifteen of the 20 patients with normal antroduodenal manometry results (75%) underwent GES; GES was normal in 10 of these 15 patients (67%) and abnormal in the other 5 (33%), with a delay in 4 (80%) and rapid in 1 (20%). In the 81 patients who underwent both antroduodenal manometry and GES, no statistical agreement was found between the antroduodenal manometry and GES results.

Associations of Antroduodenal Manometry and GES Results with Autonomic Testing and Tilt Table Test Measures

No association was found between changes in HR and/or systolic BP and results of antroduodenal manometry ($P = .66$ and $.52$, respectively) and GES ($P = .43$ and $.78$, respectively) (**Table**). Associations of cold pressor test results with either antroduodenal manometry ($P = .22$) or GES ($P = .99$) results also were not significant. Similarly, no association was found between Valsalva maneuver results and antroduodenal manometry ($P = .77$) or GES ($P = .54$) results. Associations of QTc with antroduodenal manometry and GES also were nonsignificant.¹⁵ In evaluating tilt table test measures to predict abnormal antroduodenal manometry, a trend was seen toward

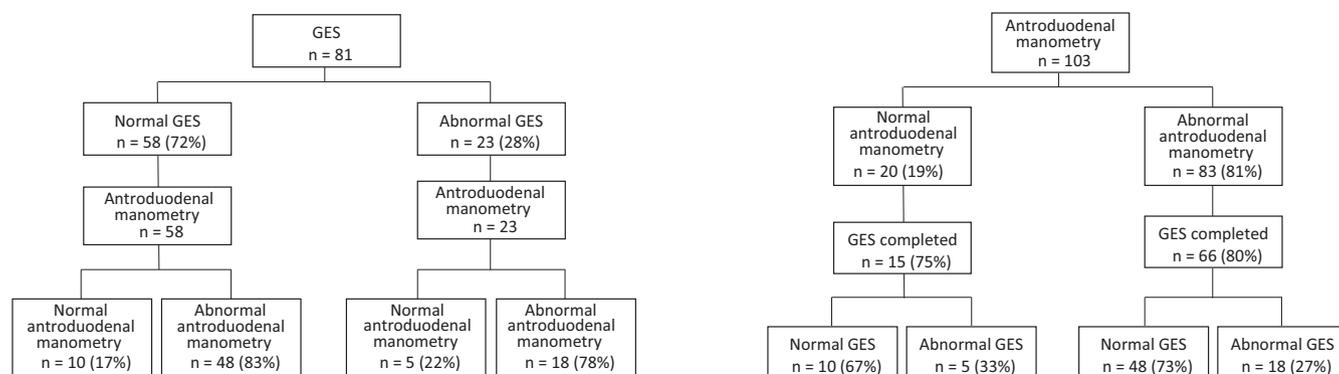


Figure 2. Antroduodenal manometry and GES results in the study population ($n = 103$). The flow diagram on the left shows antroduodenal manometry findings in 81 of the 103 patients who had also undergone GES. Antroduodenal manometry was abnormal in 83% of those with normal GES and in 78% of those with abnormal GES. The flow diagram on the right shows GES findings based on the antroduodenal manometry results (performed in all 103 patients). The GES was normal in 73% of the patients who had abnormal antroduodenal manometry and 67% of those who had normal antroduodenal manometry.

Table. Association of antroduodenal manometry and GES results with autonomic function and tilt table test parameters

Parameters	Total	Antroduodenal manometry, n (%)		P value	Total	GES, n (%)		P value
		Abnormal	Normal			Abnormal	Normal	
Δ HR during tilt table test				.66				.43
Normal	1 (1)	1 (100)	0 (0)		0 (0)	0 (0)	0 (0)	
Abnormal	28 (27.2)	24 (85.7)	4 (14.3)		23 (28.4)	8 (34.8)	15 (65.2)	
Very abnormal	74 (71.8)	58 (78.4)	16 (21.6)		58 (71.6)	15 (25.9)	43 (74.1)	
Δ BP during tilt table test				.52				.78
Normal	44 (42.7)	33 (75)	11 (25)		35 (43.2)	11 (31.4)	24 (68.6)	
Abnormal	20 (19.4)	17 (85)	3 (15)		18 (22.2)	4 (22.2)	14 (77.8)	
Very abnormal	39 (37.9)	33 (84.6)	6 (15.4)		28 (34.6)	8 (28.6)	20 (71.4)	
Cold pressor test				.22				.99
Normal	25 (69.4)	20 (80)	5 (20)		20 (71.4)	5 (25)	15 (75)	
Abnormal	11 (30.6)	6 (54.5)	5 (45.5)		8 (28.6)	2 (25)	6 (75)	
Not done=67								
Valsalva maneuver				.77				.54
Normal	23 (26.1)	19 (82.6)	4 (17.4)		16 (23.2)	6 (37.5)	10 (62.5)	
Abnormal	65 (73.9)	51 (78.5)	14 (21.5)		53 (76.8)	15 (28.3)	38 (71.7)	
Not done=5								
QTc				1.00				1.00
Normal	74 (71.8)	60 (81.1)	14 (18.9)		56 (69.1)	12 (21.4)	44 (78.6)	
Abnormal*	29 (28.2)	23 (79.3)	6 (20.7)		25 (30.9)	11 (44)	14 (56)	

BP, blood pressure; HR, heart rate; QTc, corrected QT interval.

*QTc >0.44 was considered abnormal, based on criteria of Rautaharju et al.¹⁵

lower odds of an abnormal vs normal antroduodenal manometry result if the systolic BP at baseline was high (OR, 0.95; 95% CI, 0.90-1.01; $P = .08$) (data not shown).

Upper Gastrointestinal Endoscopy and Biopsy

Of the 103 patients, 87 (85%) had normal endoscopy and biopsy findings. The histological findings were reported as abnormal in 16 patients (15%), including chronic gastritis in 11, esophagitis in 4, and eosinophilic esophagitis (with >50 eosinophils per high-power field) in 1.

Discussion

In our cohort, antroduodenal manometry studies performed in conjunction with tilt table test were the most insightful investigations in explaining the underlying etiology of symptoms in children with orthostatic intolerance and gastrointestinal symptoms. We found that although the antroduodenal manometry measures were normal at baseline in most patients, abnormal findings were noted in >80% patients overall, when the antroduodenal manometry was performed in conjunction with tilt table test. In approximately 60% of the patients, the antroduodenal manometry abnormalities were noted during the tilt table test, similar to the results in our preliminary report.³ The most commonly observed antroduodenal manometry abnormalities included neurogenic intestinal dysmotility, regurgitation/rumination, and visceral hyperalgesia. The potential importance of the motility patterns noted on the antroduodenal manometry studies lies in its utility in targeting future therapies. Those patients who showed antral hypomotility would likely benefit from prokinetic therapy to improve gastric emptying. The presence of neurogenic

intestinal dysmotility, especially when noted during the tilt table test only, likely would be best approached through aggressive management of orthostatic intolerance, which in turn likely would lead to improvement in gastrointestinal symptoms. Those with visceral hyperalgesia and rumination primarily would benefit from behavioral and sensory modification therapies.

The gastrointestinal symptoms were reproduced during the tilt table test in more than two-thirds of the patients, suggesting a change in posture as a trigger for their presenting symptoms. Furthermore, >50% of the patients also had associated abnormal manometric findings. A change in posture during the tilt table test in children with POTS has been shown to lead to abnormal gastrointestinal motility as demonstrated on electrogastrogram studies.¹⁶

GES was performed in approximately 80% of the patients in our cohort and was abnormal in approximately 30% of them. Previous studies have reported abnormal GES in 30%-60% of subjects with orthostatic intolerance.^{2,10,11} Delayed GES was reported in approximately 25% of children undergoing GES for suspected gastroparesis.¹⁷ Delayed gastric emptying was a more common abnormality, in contrast to a previous study reporting rapid rather than delayed gastric emptying in two-thirds of patients with an abnormal GES.¹¹ Interestingly, in that report, it was noted that the patients with delayed gastric emptying had vomiting as a predominant symptom and more severe adrenergic dysfunction noted on autonomic testing. In another report of adults with POTS, delayed GES was noted in 50% of those who completed the study.²

Even though in our cohort, 96% of patients presenting with the cardiovascular symptom of syncope showed abnormal antroduodenal manometry findings, none of the autonomic function tests or tilt table test parameters were predictive of abnormal antroduodenal manometry and GES results,

suggesting that the autonomic nervous system may have an independent role in causing gastrointestinal symptoms in this group of patients. Changes in cardiovascular nervous activity may trigger gastrointestinal symptoms, but these appear to occur independent of changes in the cardiac nervous system. This finding suggests that the primary therapy for most patients, especially those with neurogenic intestinal dysmotility, would be to improve the orthostatic intolerance rather than to treat the nausea or modify gastrointestinal motility directly.

In our review, we found no agreement between GES and antroduodenal manometry results. Among those patients with an abnormal antroduodenal manometry study, only one-fourth had an abnormal GES. A normal GES did not rule out the possibility of an abnormal antroduodenal manometry. In fact, GES was normal in 70% of all patients who underwent the test, similar to findings in other studies of GES in children with nausea.¹⁷ The antroduodenal manometry study was abnormal in 83% of the patients with a normal GES and in 78% of those with an abnormal GES, indicating the different physiological bases of these 2 tests. The GES primarily evaluates the transit of gastric contents into the proximal small bowel, regardless of antroduodenal motility, whereas the antroduodenal manometry is a test of the motor function of the antral and proximal small bowel muscles and does not always correlate with the transit of gastric contents.^{18,19}

Adult subjects with POTS have similar severity of autonomic symptoms across all functional domains as seen in patients with autonomic failure.²⁰ It has been suggested that individuals with POTS have an element of autonomic dysfunction that extends beyond their orthostatic intolerance.²⁰ In a group of adolescents with POTS, 42% had abnormal GES results; gastric emptying was delayed in 6 and accelerated in 7 of the 13 abnormal studies.⁵ The authors could not find a correlation between GES results and HR response to the tilt table test. Among the adult patients with POTS, 66% had an abnormal GES, with rapid gastric emptying predominating, in contrast to the delayed GES noted in our report.²⁰ Measures of autonomic function and orthostatic testing did not discriminate among normal, rapid, or delayed GES. Collectively, the 2 studies suggest the independence of autonomic dysfunction in cardiovascular and gastrointestinal functions.

We found normal endoscopic biopsy results in most patients, with a few patients showing nonspecific chronic gastritis and esophagitis and only 1 patient with evidence of eosinophilic esophagitis. Upper endoscopy has been shown to be of limited value in children with gastroparesis; however, in a recent study unrelated to orthostatic intolerance, it revealed increased evidence of gastritis in both patients with gastroparesis and age-matched controls.^{21,22} Our data suggest that even in patients with significant gastrointestinal symptoms, routine endoscopic investigation might not reveal underlying mucosal or organic conditions. In fact, the upper gastrointestinal symptoms are nonspecific and are similar to those typically reported by most patients with functional motility disorders.⁴

Our review of this cohort of patients with orthostatic intolerance and gastrointestinal symptoms favors investigation

by antroduodenal manometry performed in conjunction with the tilt table test. However, this approach is possible in only a limited number of institutions, because it requires staff with expertise in gastrointestinal motility studies and capital-intensive equipment, is labor-intensive, and includes the nociceptive burden of antroduodenal manometry for patients. Since the GES had poor diagnostic yield, and had a poor correlation with antroduodenal manometry findings, and the other routine gastrointestinal investigations such as upper endoscopy with biopsy provide no meaningful insight, other centers with expertise in performing gastrointestinal motility studies could incorporate an evaluation of gastrointestinal symptoms in patients with orthostatic intolerance through a combined antroduodenal manometry and tilt table test study. Further corroboration of this finding from other centers could aid in developing a pathway for diagnostic evaluation of the gastrointestinal symptoms in this complex systemic condition.

Limitations of our study include its retrospective nature. The diagnostic workup was based mainly on the subjects' presenting symptoms, which were not assessed using a standardized questionnaire. GES was performed in 80% of the patients, and antroduodenal manometry was performed in 100%. This might introduce a symptom-based confounding factor in comparison between these 2 diagnostic studies. We classified our patient into 2 disease groups: orthostatic intolerance and postural orthostatic tachycardia syndrome. Changes in the accepted definition of a positive tilt table test have resulted in an asymptomatic population of normal children, which in our experience underestimates the number of symptomatic patients with true orthostatic intolerance using the new criteria.¹⁴

We conclude that gastrointestinal symptoms in patients with orthostatic intolerance/POTS are mostly related to functional gastrointestinal disorders. Although orthostatic challenge may be a common trigger for the gastrointestinal symptoms, alterations in cardiovascular and gastrointestinal function appear to be independent. The diagnostic utility of antroduodenal manometry with the tilt table test is high, and routine gastrointestinal studies such as upper gastrointestinal endoscopy with biopsy and GES have a limited role in the diagnostic workup of children with orthostatic intolerance/POTS and gastrointestinal symptoms. ■

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Reprint requests: Anil Darbari, MD, MBA, Pediatrics, George Washington University School of Medicine & Health Sciences, Children's National Health System, Division of Pediatric Gastroenterology, 111 Michigan Ave, NW, Washington, DC 20010. E-mail: adarbari@cnmc.org

References

- Sullivan SD, Hanauer J, Rowe PC, Barron DF, Darbari A, Oliva-Hemker M. Gastrointestinal symptoms associated with orthostatic intolerance. *J Pediatr Gastroenterol Nutr* 2005;40:425-8.
- Wang LB, Culbertson CJ, Deb A, Morgenshtern K, Huang H, Hohler AD. Gastrointestinal dysfunction in postural tachycardia syndrome. *J Neurol Sci* 2015;359:193-6.

3. Moak JP, Fabian RR, Clarke LC, Hanumanthaiah S, Desbiens J, Darbari A. Antroduodenal manometry is abnormal in children presenting with orthostatic intolerance and gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr* 2016;63:329-35.
4. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc* 2012;87:1214-25.
5. Antiel RM, Risma JM, Grothe RM, Brands CK, Fischer PR. Orthostatic intolerance and gastrointestinal motility in adolescents with nausea and abdominal pain. *J Pediatr Gastroenterol Nutr* 2008;46:285-8.
6. Chelimsky G, Chelimsky TC. Gastrointestinal manifestations of pediatric autonomic disorders. *Semin Pediatr Neurol* 2013;20:27-30.
7. Sandroni P, Opfer-Gehrking TL, McPhee BR, Low PA. Postural tachycardia syndrome: clinical features and follow-up study. *Mayo Clin Proc* 1999;74:1106-10.
8. Ojha A, Chelimsky TC, Chelimsky G. Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome. *J Pediatr* 2011;158:20-3.
9. Seligman WH, Low DA, Asahina M, Mathias CJ. Abnormal gastric myoelectrical activity in postural tachycardia syndrome. *Clin Auton Res* 2013;23:73-80.
10. Park KJ, Singer W, Sletten DM, Low PA, Bharucha AE. Gastric emptying in postural tachycardia syndrome: a preliminary report. *Clin Auton Res* 2013;23:163-7.
11. Loavenbruck A, Iturrino J, Singer W, Sletten DM, Low PA, Zinsmeister AR, et al. Disturbances of gastrointestinal transit and autonomic functions in postural orthostatic tachycardia syndrome. *Neurogastroenterol Motil* 2015;27:92-8.
12. Uc A, Hoon A, Di Lorenzo C, Hyman PE. Antroduodenal manometry in children with no upper gastrointestinal symptoms. *Scand J Gastroenterol* 1997;32:681-5.
13. Bortolotti M, Annese V, Coccia G. Twenty-four hour ambulatory antroduodenal manometry in normal subjects (co-operative study). *Neurogastroenterol Motil* 2000;12:231-8.
14. Singer W, Sletten DM, Opfer-Gehrking TL, Brands CK, Fischer PR, Low PA. Postural tachycardia in children and adolescents: what is abnormal? *J Pediatr* 2012;160:222-6.
15. Rautaharju PM, Mason JW, Akiyama T. New age- and sex-specific criteria for QT prolongation based on rate correction formulas that minimize bias at the upper normal limits. *Int J Cardiol* 2014;174:535-40.
16. Safder S, Chelimsky TC, O'Riordan MA, Chelimsky G. Gastric electrical activity becomes abnormal in the upright position in patients with postural tachycardia syndrome. *J Pediatr Gastroenterol Nutr* 2010;51:314-8.
17. Jericho H, Adams P, Zhang G, Rychlik K, Saps M. Nausea predicts delayed gastric emptying in children. *J Pediatr* 2014;164:89-92.
18. Quigley EM, Donovan JP, Lane MJ, Gallagher TF. Antroduodenal manometry. Usefulness and limitations as an outpatient study. *Dig Dis Sci* 1992;37:20-8.
19. Cassilly D, Kantor S, Knight LC, Maurer AH, Fisher RS, Semler J, et al. Gastric emptying of a non-digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal manometry, gastric emptying scintigraphy. *Neurogastroenterol Motil* 2008;20:311-9.
20. Rea NA, Campbell CL, Cortez MM. Quantitative assessment of autonomic symptom burden in postural tachycardia syndrome (POTS). *J Neurol Sci* 2017;377:35-41.
21. Wong GK, Shulman RJ, Chiou EH, Chumpitazi BP. Decreased relative diagnostic yield of esophagogastroduodenoscopy in children with gastroparesis. *J Clin Gastroenterol* 2014;48:231-5.
22. Altepeter TA, Shaffer S. Yield of endoscopy in pediatric gastroparesis. *J Pediatr Gastroenterol Nutr* 2017;65:22-5.