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Disturbances of Gastrointestinal Transit and Autonomic Functions in Postural Orthostatic Tachycardia Syndrome

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Abstract

Background—Gastrointestinal symptoms are common in the postural orthostatic tachycardia syndrome (POTS). However, few studies have evaluated gastrointestinal transit in POTS. Our primary objectives were to evaluate gastrointestinal emptying and the relationship with autonomic dysfunctions in POTS.

Methods—We reviewed the complete medical records of all patients aged 18 years and older with POTS diagnosed by a standardized autonomic reflex screen who also had a scintigraphic assessment of gastrointestinal transit at Mayo Clinic Rochester between 1998 and 2012. Associations between specific gastric emptying and autonomic (ie, cardiovagal, adrenergic, and sudomotor) disturbances were evaluated.

Results—Among 163 patients (140 women, mean[±SEM] age 30 [± 1] years), 55 (34%) had normal, 30 (18%) had delayed and 78 (48%) had rapid gastric emptying. Fifty eight patients (36%) had clinical features of physical deconditioning, which was associated ($P=.02$) with rapid gastric emptying. Associations with delayed gastric emptying included vomiting, which was more common ($P<.003$), and anxiety or depression, which was less common ($p = 0.02$). The tilt-associated increase in heart rate and reduction in systolic BP at 1 minute was associated ($P<.05$), being greater in patients with delayed gastric emptying.

Conclusions—Two-thirds of patients with POTS and GI symptoms had abnormal, most frequently rapid gastric emptying. Except for more severe adrenergic impairment in patients with

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DISCLOSURES

AL and JI reviewed the medical records
AL, WS, DMS, and PAL reviewed autonomic function
JI reviewed the results of gastrointestinal transit
AEB, WS, and PAL designed the research study
ARZ conducted the statistical analysis
AEB, AL, and WS wrote the paper
All authors approved the final version of this manuscript

delayed gastric emptying, the pattern of autonomic dysfunction did not discriminate among gastric emptying groups. Further studies are necessary to ascertain whether extravascular volume depletion and/or deconditioning contribute to POTS in patients with gastrointestinal symptoms.

Keywords

POTS; gastric emptying; gastroparesis; dumping

Postural orthostatic tachycardia syndrome (POTS) is a disorder of reduced orthostatic tolerance. In adults aged 18 years and older, POTS is defined by a heart rate increment of 30 beats/min or more within 10 minutes of standing or head-up tilt (HUT) in the absence of orthostatic hypotension; the standing heart rate is often 120 beats/min or higher (1). The pathophysiology of POTS is multifactorial; physical deconditioning, volume depletion, hyperadrenergic states, and a limited autonomic neuropathy have been implicated (1). In addition to orthostatic symptoms, chronic headache, fatigue, fibromyalgia, sleep disturbances, and gastrointestinal symptoms are common in POTS. Indeed, in a large series of adult patients with POTS, nearly 40% had nausea, 24% had bloating, 18% reported diarrhea, and 15% each reported constipation and abdominal pain (2). While the association between autonomic neuropathy and gastrointestinal dysmotility has been extensively characterized (3–7), only two studies have evaluated gastric emptying in POTS. In these studies, gastric emptying was abnormal (ie, rapid or delayed) in more than one-third of patients (8, 9). However, these studies were small and enrolled a total of 43 patients. Therefore, we sought to evaluate the association between POTS and gastrointestinal transit in a larger cohort, particularly because subsets of patients with POTS have other features of autonomic dysfunction (ie, in addition to orthostatic tachycardia) (1). The primary objectives of this study were to (i) evaluate gastric emptying, small intestinal and colonic transit and (ii) assess the relationship between autonomic dysfunction and gastric emptying disturbances in POTS.

Methods

Study Participants

All patients aged 18 years or older who underwent a comprehensive autonomic reflex screen, had gastrointestinal symptoms and a scintigraphic gastric emptying study as part of the clinical assessment between January 1998 and December 2012 at Mayo Clinic in Rochester, Minnesota, and authorized review of their medical records for research were considered for inclusion in this study. POTS was diagnosed by a 30 bpm or greater increment in heart rate on head-upright tilt in adults aged 20 years or older (40bpm or greater if younger than 20yrs old) (10)) without concomitant orthostatic hypotension. Of 187 patients who met these criteria, 24 patients who had another potential explanation for abnormal gastric emptying (ie, prior gastric surgery, diabetes mellitus, paraneoplastic disease, other neurological disorders (eg, parkinsonism, myelopathy) inflammatory bowel disease, celiac disease, Hodgkin's lymphoma or were taking opioids) were excluded. The Mayo Clinic Institutional Review Board approved the study.

Review of medical records

A neurologist and a gastroenterologist independently reviewed clinical features and results of diagnostic tests from medical records. Presenting gastrointestinal symptoms were documented and the predominant symptom was categorized as follows: gastro-esophageal reflux or regurgitation, chronic nausea only, vomiting, dyspepsia, diarrhea with or without abdominal pain, constipation with or without pain, chronic abdominal discomfort, and weight loss (ie, ≥ 10 pounds). Among patients with multiple (eg, upper and lower gastrointestinal) symptoms, a single chief complaint was identified as the primary symptom for analysis. Because constipation can predispose to upper gastrointestinal symptoms (eg, nausea), constipation was designated as the chief complaint in patients with constipation and other symptoms. Physical deconditioning was determined by the clinical impression of the evaluating physician, based on the presence of reduced exercise capacity causing difficulty with normal activities of daily living (11). Chronic pain was defined as the presence of a non-malignant painful condition (eg, fibromyalgia, back pain, arthritis) for six months or longer. The etiology of GI symptoms was presumed to be post-infectious when patients reported the onset of symptoms was acute and immediately preceded by at least one symptom suggestive of an acute GI (diarrhea or vomiting) or other infection (muscle ache, fever) (12). Endoscopic and radiological reports were reviewed to ensure patients did not have mechanical obstruction or an alternative explanation for gastric emptying disturbances; none was found in the 163 patients included in this report.

Autonomic Testing

Autonomic nervous system function was assessed by standardized and validated techniques after medications that potentially affect autonomic function were stopped for 5 half-lives (13). Postganglionic sympathetic sudomotor function was evaluated by the quantitative sudomotor axon reflex test. Sweat responses are obtained from the forearm, proximal aspect of the leg, distal aspect of the leg, and foot. Results were compared with normative data taken from studies on 223 healthy individuals aged 10 to 83 years (14). Heart rate response to deep breathing and Valsalva ratio were used to assess cardiovagal function. The data were compared with normative results taken from 157 healthy individuals aged 10 to 83 years (14). Cardiovascular adrenergic function was evaluated by measuring blood pressure and heart rate responses to Valsalva maneuver and HUT (13). A semi-quantitative composite autonomic severity score (CASS) ranging from 0–10 was calculated by combining sudomotor (range, 0–3), cardiovagal (range, 0–3), and adrenergic (range, 0–4) scores adjusted for age and sex (15).

Gastrointestinal transit by scintigraphy

Gastric emptying, small bowel, and colonic transit were assessed with established validated scintigraphic techniques. The use of medications that potentially affect gastrointestinal transit was stopped for 5 half-lives before testing. A 300-kcal mixed meal containing ^{99m}Tc -sulphur colloid labelled eggs was used to assess gastric emptying in 163 and small bowel transit in 161 patients (16, 17). Delayed gastric emptying was defined by gender-specific values below the lower limit of normal range (10th percentile)) at 2 or 4 h, and rapid gastric emptying was defined by values above the upper limit of normal range (90th percentile) at 1

or 2 h. Colonic filling (i.e., the proportion of ^{99m}Tc reaching the colon) at 6 hours was used to measure orocecal transit (i.e., a surrogate for small bowel transit). In 121 patients, colonic transit was also measured by ^{111}In -labeled charcoal pellets within a capsule coated by methacrylate (18). These results were summarized as the colonic geometric center (GC), which is the weighted average of counts in the different colonic regions. Transit data were interpreted using established normal data from our laboratory.

Statistical Analysis

Univariate associations between various factors and gastric emptying, characterized as normal, delayed, or rapid was assessed by Fisher's exact test for categorical variables (e.g. weight loss > 10 lbs over 12 months) and by the Kruskal–Wallis rank test for variables. Multiple variable logistic regression models were used to assess the association between gastric emptying and the type of autonomic dysfunction (ie, cardiovagal, adrenergic, or sudomotor). Data are summarized as mean $\pm$ SEM.

Results

Demographic Features, Clinical Characteristics and Gastrointestinal Transit

Of the eligible 163 patients, 140 (86%) were females with a mean ($\pm$ SEM) age of 30 ± 1 years. Fifty five patients (34%) had normal, 30 (18%), had delayed and 78 (48%) had rapid gastric emptying (Table 1). The distribution of age, sex, and BMI were not significantly different among these groups (Table 1).

The most common *chief* GI complaints were nausea alone (34 patients, 21%) or also vomiting (16 patients, 10%), constipation (31 patients, 19%), and dyspepsia (30 patients, 18%). The chief GI symptom was not significantly associated with gastric emptying. However, a total of 56 patients reported vomiting, which was more common ($P<.003$) in patients with delayed (18 patients, 60%) than normal (19 patients, 35%) or rapid (19 patients, 24%) gastric emptying.

Among 121 patients in whom colonic transit was also evaluated, transit was normal in 80 patients (66%), delayed in 33 patients (27%), and accelerated in 8 patients (7%). Small bowel and colonic transit were not significantly associated with normal, delayed or rapid gastric emptying.

Of the 163 patients, 141 (84%) had chronic pain, which was the most common associated feature. Fifty eight patients (36%) had clinical features of physical deconditioning, which was associated ($P=.02$) with rapid gastric emptying (Table 1). Anxiety or depression was less common ($P=.02$) in patients with delayed gastric emptying. Significant weight loss and a history suggestive of infectious etiology were not associated with the presence or type of gastric emptying disturbance.

Autonomic Function Tests

The pulse increased from 70 ± 1 beats per minute in the supine position to 98 ± 1 beats per minute at 1 minute and 106 ± 1 beats per minute at 5 minutes after upright tilt. The tilt-

associated increase in heart rate was associated ($P=.04$) with gastric emptying and greater in patients with delayed gastric emptying (Table 2).

The average BP was 108/67 mmHg (mean [SEM]) in the supine position, 104/72 mmHg at 1 minute, 105/72 mmHg at 5 minutes and 104/73 at 10 minutes after upright tilt. The tilt-associated reduction in systolic BP at 1 minute but not at 5 minutes was also associated ($P=.02$) with gastric emptying, being greater in patients with delayed gastric emptying (Table 2). The BP response during late phase II of the Valsalva maneuver was absent in 8 patients (5%); absent late phase II was not associated with gastric emptying disturbance. Integrating these responses, moderate or severe adrenergic dysfunction was associated ($P=.02$) with delayed gastric emptying (Table 2).

The heart rate response to deep breathing was slightly greater ($P=.02$) in patients with delayed versus normal gastric emptying. A minority of patients had reduced heart rate responses: 6 patients (4%) during the Valsalva maneuver and thirteen patients (8%) during deep breathing. These proportions and the prevalence of moderate or severe cardiovagal dysfunction were not significantly associated with the gastric emptying disturbance.

The QSART was abnormal in 59 patients (36%), who had a CASS sudomotor score of 1 (35 patients, 21%), 2 (15 patients, 9%) or 3 (9 patients, 6%) (Figure 1); these proportions were not significantly associated with the gastric emptying disturbance.

Of the 163 patients, the overall CASS score was 0 in 75 patients (46%), between 1 and 3 in 78 patients (48%) and greater than 3 in 10 patients (6%) (Figure 1). The prevalence of any autonomic dysfunction (ie, 55% of patients with normal, 63% with delayed and 50% with rapid gastric emptying) was not associated with gastric emptying status. Moderate or severe overall autonomic dysfunction, as indicated by a total CASS score > 3 , was observed in a greater proportion of patients with slow (27%) than normal (11%) or rapid (10%) gastric emptying, but differences were not significant ($P=.09$). Because the multiple variable logistic model incorporating vagal, adrenergic, and sudomotor dysfunction variables as moderate or severe did not converge, this model incorporated these variables coded as none or any dysfunction (Table 3). In this model, vagal, adrenergic, and sudomotor impairment did not discriminate among normal, rapid, and delayed GE groups.

Other Tests

Supine and standing catecholamines were measured in 43 patients (26%). Among those, 15 patients (35%) had a standing norepinephrine of 600 pg/ml or greater. This proportion was not different among gastric emptying groups. Of 66 patients (40%) in whom ganglionic acetylcholine receptor antibodies were tested, only 1 patient had increased values. In 43 patients (26%), 24-hour urinary sodium excretion was measured as a surrogate index of plasma volume. Of those, 29 (67%) excreted less than 100mEq in 24 hours.

Discussion

Upper gastrointestinal symptoms are common in patients with POTS (2). Whether these symptoms are associated with and perhaps result from gastric emptying disturbances has

thus far only been sparsely investigated. This is the largest series to assess autonomic function and gastric emptying in patients with POTS and GI symptoms. Small bowel and colonic transit were also evaluated in 161 and 121 patients respectively. There are 3 main findings.

First, two-thirds of patients with POTS and GI symptoms had abnormal (i.e., rapid [48%] or slow [18%]) gastric emptying, which is higher than the prevalence of 36% in our earlier, preliminary report of 22 patients with POTS (9). Second, deconditioning was more common in patients with rapid than normal gastric emptying. Anxiety was less common and vomiting was more common in patients with delayed gastric emptying. Third, patients with delayed gastric emptying had more pronounced adrenergic dysfunction, as evidenced by a greater orthostatic reduction in blood pressure and heart rate increment. The CASS score suggested that a larger proportion of patients with delayed gastric emptying had moderate adrenergic impairment or worse. However, these differences in autonomic parameters among gastric emptying groups were relatively subtle.

While this study did not include a control group (eg, patients with POTS without GI symptoms), the patients in this study were predominantly women with mild autonomic dysfunction, as evidenced by an overall CASS score of 0 in 46% of patients and 1–3 in 48% of patients. This distribution is very similar to the 91% prevalence of total CASS scores 3 in a previous study of 152 patients from Mayo Clinic (2). Likewise, postganglionic sudomotor denervation and/or adrenergic impairment rather than cardiovascular dysfunction were the most common findings (2, 19).

Similar to our preliminary report in POTS and another study in patients with autonomic dysfunction, rapid gastric emptying was the most common gastric emptying disturbance (6, 9). The association between POTS and rapid gastric emptying contrasts with functional dyspepsia and diabetic neuropathy, wherein delayed gastric emptying is the more frequent gastric emptying disturbance (20). The mechanism of rapid gastric emptying in POTS is unknown. A subset of patients with idiopathic rapid gastric emptying have increased gastric motility (21); however, autonomic functions were not evaluated in that study. In this study, 42% of patients with rapid gastric emptying had migraine and 57% had anxiety or depression. These features resemble the cyclic vomiting syndrome, which is also associated with migraine, anxiety or depression, and rapid gastric emptying (6, 22–24). Indeed, POTS and even vasodepressor responses have been reported in children with cyclic vomiting syndrome (25). However, presence or absence of cyclic vomiting could not be gleaned from the records in all patients. It is plausible that the gastric emptying disturbance is secondary to autonomic dysfunction. However, it is worth noting that while most patients had mild autonomic dysfunction, gastric emptying disturbances were more pronounced, as is evident by the mean gastric emptying of 63% at 4 hours in patients with delayed and 45% at 1 hour in patients with rapid gastric emptying. Moreover, rapid gastric emptying was not associated with a specific disturbance of cardiovascular autonomic functions (eg, adrenergic dysfunction). However, it is conceivable that sympathetic denervation may be limited to the GI tract and only identifiable by specialized testing but not cardiovascular autonomic tests (26). Lastly, the importance and magnitude of the tonic-inhibitory influence exerted by the sympathetic nervous system on gastric motility is unclear. Indeed, neither sympathectomy

nor guanethidine affected gastric emptying in cats and rats respectively (27, 28). Likewise, the α_2 -adrenergic antagonist yohimbine did not affect gastric emptying or postprandial gastric accommodation in humans (29, 30).

Perhaps a shared trigger, such as a viral infection, is responsible for POTS and GI dysfunctions. Alternatively, gastrointestinal symptoms might predispose to POTS by virtue of extravascular volume depletion (ie, secondary to reduced fluid intake or increased fluid losses) or because both are associated with deconditioning. Indeed, rapid gastric emptying was associated with physical deconditioning, while delayed gastric emptying was associated with vomiting in this study. Moreover, among 26% of patients in whom 24 hour urinary sodium excretion was evaluated, 67% had reduced sodium excretion, which suggests hypovolemia. This figure is higher than the prevalence (29%) among all patients with POTS (2). Intravascular volume repletion can improve orthostatic symptoms and fatigue in POTS (19). Taken together, these observations suggest that future studies evaluating the association between hypovolemia and fatigue, which is a common symptom in both patients with “functional” GI disorders and POTS, and the effects of replenishing intravascular fluid volume in these patients might be of interest.

There are several limitations to this study, which was conducted at a tertiary referral center. Gastrointestinal symptoms were not assessed by a standardized questionnaire. Transit studies were predominantly prompted by gastrointestinal symptoms, potentially confounding the assessment of the relationship between gastric emptying and symptoms. Extracellular volume status and physical conditioning was not evaluated by standardized testing in all patients. Because multiple statistical comparisons were performed, it is possible that some were significant due to chance. Thus, these observations need to be confirmed by prospective assessments utilizing symptom questionnaires and objective assessments in patients with POTS.

In summary, two-thirds of patients with POTS and GI symptoms had abnormal gastric emptying. Rapid gastric emptying was the most frequently observed abnormality. Vomiting was associated with delayed gastric emptying. Rapid gastric emptying was associated with anxiety and depression and with physical deconditioning. Except for an association between delayed gastric emptying and more severe adrenergic dysfunction, the type of autonomic dysfunction was not associated with the specific gastric emptying disturbance in patients with POTS. Further studies are necessary to ascertain whether extravascular volume depletion and/or deconditioning contribute to POTS in patients with gastrointestinal symptoms.

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KEY MESSAGES

- Our aims were to evaluate the relationship between autonomic dysfunctions and gastrointestinal transit in POTS
- We reviewed the complete medical records of all 163 adult patients with POTS who underwent scintigraphic assessment of gastrointestinal transit at Mayo Clinic Rochester between 1998 and 2012.
- Two-thirds of patients with POTS and GI symptoms had abnormal, most frequently rapid, gastric emptying. Except for more severe adrenergic impairment in patients with delayed gastric emptying, the pattern of autonomic dysfunction did not discriminate among gastric emptying groups.

Figure 1. Prevalence of autonomic dysfunctions graded by severity in patients with POTS
 The overall CASS score indicated no or mild autonomic dysfunction in 94% of patients.

Table 1Demographic Features and Clinical Characteristics by Gastric Emptying Categories^a

Characteristic	Delayed (n = 30)	Normal (n = 55)	Rapid (n = 78)	P Value ^b for Association With Group Status
Demographics and Lifestyle				
Women, No (%)	28 (93%)	45 (82%)	67 (86%)	0.40
Age, y	30 ± 1	30 ± 1	30 ± 2	.95
Body mass index, kg/m ²	22.5 ± 0.6	21.3 ± 0.5	21.4 ± 0.7	.57
Gastrointestinal symptoms				
Gastroesophageal reflux or regurgitation, No	1	3	8	NA
Nausea without vomiting, No	8	15	11	NA
Vomiting, No	3	5	8	NA
Dyspepsia, No	6	8	16	NA
Diarrhea, No	3	6	7	NA
Constipation, No	4	8	19	NA
Abdominal discomfort, No	5	10	9	NA
Other clinical features				
Chronic pain, No (%)	27 (90%)	46 (84%)	68 (87%)	.70
Physical deconditioning, No (%)	5 (17%)	18 (33%)	35 (45%)	.02
Migraine, No (%)	6 (20%)	24 (44%)	33 (42%)	.06
Anxiety or depression, No (%)	6 (27%)	29 (59%)	41 (57%)	.03
Weight loss, No (%)	19 (66%)	33 (60%)	34 (45%)	.09
History of infectious etiology, No (%)	9 (30%)	18 (33%)	18 (23%)	.39
Gastrointestinal transit				
Gastric emptying at 1 hour, %	14 ± 2	21 ± 1	45 ± 2	NA
Gastric emptying at 2 hours, %	30 ± 2	51 ± 1	74 ± 2	NA
Gastric emptying at 4 hours, %	63 ± 3	91 ± 1	96 ± 0.4	NA
Small bowel transit ie, colonic filling at 6h, %	44 ± 6	48 ± 5	56 ± 4	0.1
Geometric center for colonic transit at 24h	2.1 ± 0.2	2.0 ± 0.2	2.1 ± 0.1	0.7

Abbreviations: BMI, body mass index;

^aValues mean ± SE unless specified otherwise.^bFisher exact test or Wilcoxon rank sum test.

Table 2Distribution of Autonomic Parameters by Gastric Emptying Category^a

Autonomic parameter	Delayed (n = 30)	Normal (n = 55)	Rapid (n = 78)	P Value ^b for Association With Group Status
Increase in heart rate at 1 minute during tilt, bpm	30.9 ± 2.1	29.1 ± 1.6	25.1 ± 1.2	.04
Reduction in systolic BP at 1 minute tilt, mmHg	7.8 ± 1.9	2.3 ± 1.1	2.3 ± 0.8	.02
Increase in heart rate at 5 minutes during tilt, bpm	38.0 ± 2.6	36.2 ± 1.7	33.9 ± 1.5	<.01
Reduction in systolic BP at 5 minutes during tilt, mmHg	6.0 ± 2.6	2.3 ± 1.1	2.4 ± 1.0	0.22
Absent phase II during Valsalva maneuver, No (%)	3 (10%)	2 (4%)	3 (4%)	0.4
Heart rate response to deep breathing, bpm	24.9 ± 1.4	20.2 ± 1.1	21.3 ± 0.9	.02
Heart rate ratio during Valsalva maneuver	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.96
Moderate or severe cardiovagal dysfunction, No (%)	0 (0%)	1 (2%)	3 (4%)	0.67
Moderate or severe adrenergic dysfunction, No (%)	6 (20%)	2 (4%)	4 (5%)	0.02
Moderate or severe sudomotor dysfunction, No (%)	6 (20%)	5 (9%)	13 (17%)	0.30
Moderate or severe overall autonomic dysfunction, No (%)	8 (27%)	6 (11%)	8 (10%)	0.09
Neuropathic POTS, No (%)	9 (30%)	9 (16%)	19 (24%)	.30
Hyperadrenergic POTS, No (%)	6 (20%)	11 (20%)	15 (19%)	1

Abbreviations: bpm – beats per minute

^aValues are mean ± SE unless specified otherwise.^bTest for association with group status (Kruskal-Wallis for rank transformed continuous variables or Chi-square analysis for discrete variables).

Table 3

Multiple Variable Analysis of Risk Factors for Rapid and Delayed Gastric Emptying among Patients with POTS.

Variable		Odds ratios (95% CI)	
		Rapid vs normal	Delayed vs normal
CASS sudomotor score	1	1.6 (0.7, 3.5)	2.0 (0.7, 5.1)
CASS cardiovagal score	1	0.6 (0.2, 2.0)	0.2 (0.02, 1.7)
CASS adrenergic score	1	0.8 (0.3, 1.8)	1.6 (0.6, 4.3)