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Autonomic function in gastroparesis and chronic unexplained nausea and vomiting: Relationship with etiology, gastric emptying, and symptom severity

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Abstract

Background: Autonomic dysfunction can be present in patients with idiopathic and diabetic gastroparesis. The role of autonomic dysfunction relating to gastric emptying and upper gastrointestinal symptoms in patients with gastroparesis and chronic unexplained nausea and vomiting (CUNV) remains unclear. The aim of our study is to evaluate autonomic function in patients with gastroparesis and CUNV with respect to etiology, gastric emptying and symptom severity.

Methods: We studied 242 patients with chronic gastroparetic symptoms recruited at eight centers. All patients had a gastric emptying scintigraphy within 6 months of the study. Symptom severity was assessed using the gastroparesis cardinal symptom index. Autonomic function testing

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AUTHORS' CONTRIBUTIONS

Linda Nguyen involved in study conceptualization, patient recruitment, data interpretation, and wrote the manuscript; Laura Wilson statistical analysis, data interpretation, and wrote the manuscript; Laura Miriel involved in study conceptualization, statistical analysis, and revised manuscript; Pankaj J. Pasricha, William L. Hasler, Richard W. McCallum, Irene Sarosiek, Kenneth L. Koch, William J. Snape, and Henry P. Parkman involved in study conceptualization, patient recruitment, and revised manuscript; Braden Kuo, Gianrico Farrugia, Madhusudan Grover, John Clarke, and Frank Hamilton involved in study conceptualization and revised the manuscript; James Tonascia involved in study conceptualization, statistical analysis, data interpretation, and revised the manuscript; Thomas L. Abell involved in study conceptualization, patient recruitment, data interpretation, wrote the manuscript.

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CONFLICTS OF INTEREST

No conflicts of interest exist.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

was performed at baseline enrollment using the ANX 3.0 autonomic monitoring system which measures heart rate variability and respiratory activity measurements.

Key Results: Low sympathetic response to challenge (Valsalva or standing) was the most common abnormality seen impacting 89% diabetic and 74% idiopathic patients. Diabetics compared to idiopathics, exhibited greater global hypofunction with sympathetic (OR = 4.7, 95% CI 2.2–10.3; $P < .001$) and parasympathetic (OR = 7.2, 95% CI 3.4–15.0; $P < .001$) dysfunction. Patients with delayed gastric emptying were more likely to have paradoxic parasympathetic excessive during sympathetic challenge [(Valsalva or standing) 40% vs. 26%, $P = .05$]. Patients with more severe symptoms exhibited greater parasympathetic dysfunction compared to those with mild-moderate symptoms: resting sympathovagal balance [LFa/RFa 1.8 (1.0–3.1) vs. 1.2 (0.6–2.3), $P = .006$)] and standing parasympathetic activity [0.4 (0.1–0.8) vs. 0.6 (0.2–1.7); $P = .03$].

Conclusions: Autonomic dysfunction was common in patients with gastroparesis and CUNV. Parasympathetic dysfunction was associated with delayed gastric emptying and more severe upper gastrointestinal symptoms. Conversely, sympathetic hypofunction was associated with milder symptoms.

Inferences: Gastroparesis and CUNV may be a manifestation of GI autonomic dysfunction or imbalance, such that sympathetic dysfunction occurs early on in the manifestation of chronic upper GI symptoms, while parasympathetic dysfunction results in more severe symptoms and delayed gastric emptying.

Keywords

autonomic function; dysautonomia; gastric emptying; gastroparesis; heart rate variability

1 | INTRODUCTION

Gastroparesis is a heterogeneous disorder defined as delayed gastric emptying in the absence of a mechanical obstruction. Symptoms of gastroparesis are variable and include nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain/discomfort, and anorexia.[1–4] However, there is poor correlation between severity of gastroparesis symptoms and the degree of delayed gastric emptying.[5–7] Gastroparesis-like syndrome or chronic unexplained nausea and vomiting (CUNV) is a disorder such that patients present with symptoms similar to those with gastroparesis but have normal gastric emptying.[8] The pathophysiology of gastroparesis and CUNV have yet to be fully elucidated. Abnormalities of gastric smooth muscle, interstitial cells of Cajal, enteric neurons, and immune cells have been implicated.[9–12] Regulation of gastric emptying also depends on a complex coordination of smooth muscle contraction and innervation by the enteric nervous system (ENS) and the central nervous system (CNS). Parasympathetic control is mediated through the vagus, while sympathetic control is mediated through the spinal cord at T5 to T10 via the celiac ganglia.[13] Sensory and motor neurons, with predominance of sensory afferent C fibers, make up 60%–80% of the vagus. Parasympathetic activity increases secretions and motility and modulates sensation, while sympathetic activity decreases secretions and motility.

The autonomic nervous system (ANS) is responsible for integrating the external environment and maintaining homeostasis via a complex system of reflex responses to

alterations in organ function. Autonomic dysfunction can lead to alterations in homeostasis and eventual target organ dysfunction. ANS abnormalities have been described in various upper gastrointestinal disorders, including diabetic gastroparesis,[14] cyclic vomiting syndrome,[15,16] and functional dyspepsia.[17] Conversely, in a cohort of patients with confirmed autonomic dysfunction, gastric emptying scintigraphy revealed both rapid and delayed gastric emptying, with rapid gastric emptying occurring more commonly.[18] In this study, demographics, symptoms, and severity of autonomic dysfunction did not predict the gastric emptying abnormality. Thus, the role of autonomic dysfunction in gastroparesis as it relates to gastric emptying and symptoms remains unclear.

The ANS and symptoms of gastroparesis can be altered by many factors, including age, gender, disease,[19] stress,[20–22] and medications. We hypothesize that autonomic dysfunction plays a role in the gastric motility and symptom severity of patients with gastroparesis and CUNV. Our aims are to evaluate autonomic function in patients with gastroparesis and CUNV with respect to (a) etiology of symptoms (diabetic vs idiopathic), (b) gastric emptying (normal vs delayed), and (c) upper GI symptom severity.

2 | METHODS

2.1 | Patient population

Two hundred and forty-two patients with gastroparesis and CUNV were recruited at eight centers of the NIDDK Gastroparesis Clinical Research Consortium into Gastroparesis Registry 2 from September 2012 through November 2016 (NCT01696747). All patients reported chronic upper GI symptoms of ≥12 weeks duration and had an upper endoscopy performed within 12 months to exclude structural causes of symptoms. The etiology of symptoms was determined to be either diabetic or idiopathic in origin. Patients with postsurgical gastroparesis were excluded from this study. Gastric emptying scintigraphy was performed on all patients within 6 months of enrollment. Patients with symptoms of gastroparesis and normal gastric emptying make up the population of patients defined as CUNV or gastroparesis-like syndrome. Patients were also excluded if other conditions were present that could explain their symptoms (obstruction, active inflammatory bowel disease, eosinophilic gastroenteritis, connective tissue disease, neurologic disease, chronic liver or renal disease, uncontrolled metabolic disorders other than diabetes) or prior gastric surgery (fundoplication, gastric resection, or pyloroplasty). Institutional Review Board approval was obtained at each Clinical Center and the Data Coordinating Center. Patients provided written informed consent.

2.2 | Autonomic function testing

Autonomic function testing was performed at baseline enrollment using the ANX 3.0 autonomic monitoring system (ANSAR Medical Technologies, Inc). ANX 3.0 is an office-based system cleared by the US Food and Drug Administration in 1995. The system measures both branches of the cardiovagal ANS using simultaneous spectral analysis of heart rate variability (HRV) and respiratory activity during a 15-minute examination. The protocol records measurements at rest and following challenges to the sympathetic and parasympathetic system: 5 minutes of rest, 1 minute of deep breathing (parasympathetic

challenge), 1 minute of short Valsalva maneuvers (sympathetic challenge), following by a rapid stand and 5 minutes of standing quietly (sympathetic and parasympathetic challenge). Each challenge is separated by a 1-minute period of return to baseline. HRV and respiratory activity were measured concurrently with analyses performed both independently and simultaneously to compute parasympathetic and sympathetic activity. HRV was computed from a rhythm strip, which measures beat-to-beat R-R intervals, while respiratory activity was recorded using impedance plethysmography according to standard methods.[23,24] Autonomic parameters computed by the ANX 3.0 system included the following parameters: sympathetic activity (LFa), parasympathetic activity (RFa), and sympathovagal balance (LFa/RFa). Table 1 lists normal published autonomic values.[25] Interpretation of abnormal values are defined as follows: low resting sympathetic activity (LFa <0.5), resting sympathetic excess (LFa >10.0), low resting parasympathetic activity (RFa <0.5), resting parasympathetic excess (RFa >10.0), low sympathetic response to challenge or sympathetic withdrawal (LFa <28.0 during valsalva or decrease in LFa upon standing), challenge sympathetic excess (LFa >28.0 during valsalva or upon standing), low parasympathetic response to challenge (deep breathing, RFa <28.0), and challenge parasympathetic excess (RFa increase >400% over baseline during valsalva, or any RFa increase with standing compared to baseline). Under normal conditions, the PNS activity initially increases during a sympathetic challenge such as Valsalva and standing, followed by parasympathetic withdrawal. A paradoxic or persistent rise in parasympathetic activity (RFa), during a sympathetic challenge, is a sign of dysfunction defined as challenge parasympathetic excess. The normal sympathovagal balance (LFa/RFa) is 1.0 (range: 0.4–3.0). An elevated LFa/RFa indicates either sympathetic excess of parasympathetic hypofunction, while low LFa/RFa indicates either sympathetic hypofunction or parasympathetic excess. The sympathovagal balance can be normal despite abnormal values of both sympathetic and parasympathetic function. Postural orthostatic tachycardia syndrome (POTS) is defined as a standing LFa less than the baseline LFa and either a change in HR of >30 bpm or standing mean HR >120.

2.3 | Gastric emptying

Gastric emptying of a standardized egg beaters meal was measured by scintigraphy within 6 months of enrollment. Delayed gastric emptying was defined as a 2 hour retention >60% or 4 hour retention >10%.[26] Scintigraphy was performed after an overnight fast, off opiates as well as prokinetics, anticholinergics, and other agents that affect gastrointestinal transit for ≥3 days prior to the test based on consensus guidelines[26] Patients were categorized into normal vs delayed gastric emptying while those with rapid gastric emptying (1 hour retention <30%) were excluded due to inadequate numbers (N = 14).

2.4 | Data acquisition

Demographic information, medical history, presence of absence of diabetes, physical examination, symptom severity (Patient Assessment of Upper Gastrointestinal Disorders [PAGI-SYM]),[27] Beck depression,[28] and State-Trait anxiety questionnaires were obtained at the time of enrollment. Gastroparesis and CUNV severity was determined by the Gastroparesis Cardinal Symptom Index (GCSI), which includes nine questions from the PAGI-SYM that is grouped into three symptom subscales (nausea/vomiting, postprandial fullness/early satiety, and bloating).[29] Severity of symptoms was rated on a six point scale

from 0 to 5:0 (no symptoms), 1 (very mild), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe). Severe symptoms are defined as an average GCSI score (total or subscales) ≥4. Severity of gastroparesis or CUNV symptoms was also graded as mild (controlled with diet), compensated (requiring promotility and anti-emetics) or gastric failure (requiring hospitalization, enteral, or parenteral nutritional support) as described by Abell et al.[30]

2.5 | Statistical methods

Baseline characteristics of patients with diabetic vs idiopathic gastroparesis or CUNV are presented as means (SD) or number (%). *P*-values were derived from Fisher's exact test for categorical measures and *t* tests for continuous measures. Measures of resting, deep breathing, Valsalva, and standing autonomic activity were compared based on etiology of symptoms (diabetes vs idiopathic), gastric emptying scintigraphy (normal vs delayed), and severity of upper GI symptoms defined by mean GCSI (mild-moderate vs severe). Similar analyses were performed on the upper abdominal pain component of the PAGI-SYM and the graded gastroparesis symptom severity determination. Analyses for each parameter were performed on the entire cohort with additional subgroup analyses performed based on etiology and gastric emptying status. Due to non-normality, values are presented as median (IQR), and *P*-values were derived from linear regression models, regressing the log-transformed autonomic activity measure on the outcome. The number (%) of autonomic abnormalities was compared by etiology of gastroparesis and CUNV symptoms (diabetic vs idiopathic) and by gastric emptying scintigraphy (delayed vs normal), with *P*-values derived from Fisher's exact test. Multiple logistic regression analysis was used to measure the association between autonomic abnormality and two outcome measures: etiology of gastroparesis and CUNV symptoms (diabetic vs idiopathic) and symptom severity (GCSI ≥4 vs GCSI <4), adjusting for age, gender, Hispanic/Latino ethnicity, race (white vs non-white), depression (beck depression inventory score >19 vs ≤19, indicating moderate depression), anxiety (State-Trait Y1 and Y2 scores divided at the median value), current smoker (yes vs no), hypertension, obesity (BMI >25), and opiate use. Similar analyses were performed using the GCSI subscales to determine if symptom subtypes were associated with specific autonomic abnormalities. Nominal, 2-sided *P*-values were significant if $P < .05$; no adjustments for multiple comparisons were made. Analyses were performed using SAS software (version 9.4, SAS Institute) and Stata (Release 14, Stata Corporation). Given that we used all available patients resulting in a fixed sample size of 242 patients who were eligible for study, with 72% having delayed GE and 28% without delayed emptying, and a 2-sided Type I error of 5%, the study had 80% power to detect a relative risk of 2.4 for low resting sympathetic activity comparing the delayed gastric emptying vs the not delayed gastric emptying group, given a prevalence of 0.10 in the not delayed group.

3 | RESULTS

3.1 | Baseline characteristics

Two hundred forty-two patients with chronic upper GI symptoms suggestive of gastroparesis were enrolled in the study. Of those, 74% (N = 179) had symptoms that were idiopathic in origin and 26% (N = 63) had symptoms related to complications of diabetes. Patients were predominantly female (N = 213 [88%]) with more women in the idiopathic group [Table 2]).

The majority of patients in both groups had delayed gastric emptying ($P = .10$). Autonomic function differed between men and women, such that, women exhibited greater parasympathetic activity as demonstrated by the lower resting sympathovagal balance and greater standing parasympathetic activity (Table S1). Only four patients in the entire cohort met criteria for postural orthostatic tachycardia syndrome by ANX 3.0 criteria.

3.2 | Differences in autonomic function by etiology

At least one abnormal autonomic measure was found in the majority of patients. Sympathetic withdrawal (low sympathetic response to a sympathetic challenge) was the most common abnormality found in both groups with more diabetics affected than idiopathics (89% diabetes vs 74% idiopathic, $P = .02$). Additionally, diabetics exhibited greater global autonomic dysfunction (Table 3). Multiple logistic regression analyses found that diabetics were more likely to have resting sympathetic (OR = 4.7 [95% CI 2.2–10.3], $P < .001$) and parasympathetic (OR = 7.2 [95% CI 3.4–15.0], $P < .001$) hypofunction and sympathetic withdrawal (OR = 3.2 [95% CI 1.2–8.4], $P = .02$).

3.3 | Relationship between gastric emptying and autonomic function

One hundred seventy-five (72.3%) patients had delayed gastric emptying, while 67 (27.7%) had normal gastric emptying by scintigraphy. Overall, those with delayed gastric emptying were more likely to exhibit low resting sympathetic activity (24% vs 10%, $P = .02$) and challenge parasympathetic excess (40% vs 26%, $P = .05$) compared to those with normal gastric emptying (Table 4). However, when accounting for etiology of symptoms, challenge parasympathetic excess was the only significant abnormality observed in diabetics with delayed gastric emptying compared to diabetics with normal gastric emptying (43% vs 8%, $P = .04$, Table S2). Among the patients with diabetes (N = 63), 23 (26.5%) were found to have challenge parasympathetic excess. The mean HgA1c was similar in patients with diabetes and challenge parasympathetic excess compared to those with diabetes but without challenge parasympathetic excess (8.2 ± 1.8 vs 8.2 ± 1.7; $P = .98$). These findings suggest that the association between resting sympathetic hypofunction and delayed gastric emptying is related to diabetes rather than an independent marker of gastric emptying delay. Among those with diabetes, the challenge parasympathetic excess was not associated with the HgA1c at the time of enrollment into the study.

3.4 | Significance of autonomic dysfunction and upper GI symptom severity and subtypes

Thirty-five (14.5%) patients reported severe symptoms of gastroparesis defined as an average total GCSI ≥4. Patients with more severe symptoms of gastroparesis were found to have a higher resting sympathovagal balance (LFa/RFa 1.8 [1.0–3.1] vs 1.2 [0.6–2.3], $P = .006$), which can be a reflection of either decreased resting parasympathetic or increased resting sympathetic activity (Table 5). The presence of lower standing parasympathetic activity (RFa) in patients with severe upper GI symptoms (0.4 [0.1–0.8] vs 0.6 [0.2–1.7], $P = .03$) suggests that the higher sympathovagal balance (LFa/RFa ratio) is due to lower parasympathetic activity. Conversely, patients with milder upper GI symptoms were found to have a lower sympathovagal balance in the presence of greater parasympathetic activity. Thus, the lower ratio is related to lower sympathetic activity. This is further demonstrated

when autonomic function was assessed in patients grouped by graded gastroparesis symptom severity. Patients with milder (grade 1) symptoms were more likely to have resting sympathetic hypofunction (37%) compared to those with grade 2 (15%) and grade 3 (25%) symptom severity ($P = .004$). Taken together, patients with milder upper GI symptoms tend to have lower sympathetic activity while patients with severe symptoms tend to have lower parasympathetic activity.

Multiple logistic regression analyses did confirm that a higher sympathovagal balance (LFa/RFa) was associated with severe upper GI symptoms (OR = 1.26 [95% CI 1.01–1.47], $P = .004$) compared to those with milder symptoms. However, when grouped by etiology of symptoms, the significance of the resting sympathovagal balance was only seen in patients with an idiopathic cause (OR 1.26 [1.04–1.52], $P = .02$).

Cardinal gastroparesis symptoms included in the GCSI are nausea/vomiting, bloating, and fullness/early satiety. Autonomic function abnormalities varied based on etiology and severity of nausea/vomiting and bloating but not fullness/early satiety. Diabetics reporting severe symptoms of nausea/vomiting had lower sympathetic and parasympathetic activity with standing. (Table S3) Conversely, idiopathic patients reporting severe symptoms of bloating had a higher resting sympathovagal balance (Table S4). Subgroup analyses separating those with normal or delayed gastric emptying (Table S5) found that the autonomic abnormalities were more likely found in those with delayed gastric emptying than those with normal gastric emptying. There were no differences comparing upper abdominal pain by PAGI-SYM (Table S6) or predominant symptom (nausea/vomiting predominant vs pain predominant) (Table S7).

4 | DISCUSSION

Autonomic dysfunction (predominantly vagal/parasympathetic hypofunction) has been described in gastroparesis[31,32] and functional dyspepsia.[22] This is the largest prospective study that systematically assesses both sympathetic and parasympathetic activity in patients with chronic symptoms suggestive gastroparesis (gastroparesis and CUNV). Our study found several autonomic abnormalities of the sympathetic and parasympathetic nervous system: (a) Low sympathetic response to a sympathetic challenge (sympathetic withdrawal) was the most common abnormality among all patients, (b) diabetes is associated with greater sympathetic and parasympathetic hypofunction at rest and in response to challenge maneuvers, (c) paradoxic parasympathetic excess in response to a sympathetic challenge is associated with delayed gastric emptying, and (d) sympathetic hypofunction is associated with milder upper GI symptoms while severe symptoms are associated with parasympathetic hypofunction.

In our study using an office-based tool that measures both branches of the ANS, our study found abnormalities in sympathetic and parasympathetic function, which are similar to two smaller studies that utilized more complex traditional autonomic testing to assess ANS function in patients with gastroparesis. These studies also utilized heart rate variability (R-R interval) as a measure of vagal cholinergic (parasympathetic) activity. However, sympathetic activity was assessed by testing both the preganglionic adrenergic fibers (percent reflex

vasoconstriction to cold) and the postganglionic cholinergic fibers (basal and cold exposed skin temperature). In a study of 12 patients with diabetes and symptoms suggestive of gastroparesis, Abell et al[32] found abnormalities in both sympathetic and parasympathetic function in patients with diabetic gastroparesis compared to healthy controls and diabetics without gastroparesis. This study found that impairment in reflex vasoconstriction (sympathetic hypofunction) was associated impairment in gastric emptying ($r = .79$, $P < .01$). Similar to this study by Abell et al,[32] our study found that patients with delayed gastric emptying were more likely to exhibit low resting sympathetic activity than those with normal gastric emptying. However, using multiple regression analyses that accounted for etiology of gastroparesis, the presence of delayed gastric emptying was only associated with challenge parasympathetic excess in diabetic but not idiopathic gastroparesis. This is similar to the study by Mohammad et al,[31] comparing diabetic (N = 20) vs idiopathic (N = 21) gastroparesis. They too found that diabetics had greater parasympathetic hypofunction with reduced heart rate variability (%R-R interval change with respiration: 8% vs 33%, $P < .001$) and sympathetic hypofunction with impaired vasoconstriction to cold (%vasoconstriction to cold: 45% vs 84%, $P = .005$) compared to those with idiopathic gastroparesis. Again, using a linear regression model accounting for age and duration of symptoms, only parasympathetic dysfunction was associated with diabetic gastroparesis (aOR = 1.02, $P = .001$). These findings suggest that the association between resting sympathetic hypofunction and delayed gastric emptying is likely related to diabetes rather than an independent marker of gastric emptying delay.

Conversely, in a study of patients with confirmed autonomic dysfunction using traditional autonomic testing, 72% (44/62) of patients were found to have gastric emptying abnormalities on scintigraphy.[18] Of these, the majority of patients (61%) had rapid gastric emptying while the other 39% had delayed gastric emptying. This study measured cardiovagal (parasympathetic), adrenergic (sympathetic), and sudomotor (sweat) function. Results of the autonomic testing were used to calculate the composite autonomic scoring scale (CASS), which categorizes patients into mild, moderate, and severe autonomic dysfunction. The majority of patients in this study had mild-moderate autonomic dysfunction. Unfortunately, the authors did not differentiate whether it was sympathetic or parasympathetic dysfunction that was associated with the gastric emptying abnormalities. Our study did not include patients with rapid gastric emptying due to inadequate numbers (N = 14) to perform statistically meaningful analyses.

Using multiple logistic regression analyses that accounted for various factors that impact autonomic function, including etiology of gastroparesis, our study found that a higher resting sympathovagal balance (LFa/RFa) was associated with more severe upper GI symptoms in patients with idiopathic but not diabetic causes of gastroparesis symptoms. This suggests that patients with severe upper GI symptoms have either greater resting sympathetic activity or lower parasympathetic function. Together with the associated findings of lower standing parasympathetic activity in patients with severe upper GI symptoms, the data suggest that the higher LFa/RFa ratio is due to decreased parasympathetic activity. This finding is again demonstrated comparing autonomic function using the graded assessment of gastroparesis symptom severity described by Abell et al[30] Taken together, patients with more severe symptoms of gastroparesis are more likely to have

parasympathetic hypofunction while those with milder symptoms are more likely to have sympathetic hypofunction.

This is in contrast to studies of diabetic autonomic neuropathy which described sympathetic hypofunction as a later complication of diabetes.[33] Vinik and colleagues described a model where there was a progression of diabetic autonomic neuropathy that started with parasympathetic hypofunction, followed by sympathetic excess, sympathetic hypofunction, impaired quality of life, overt diabetic autonomic neuropathy, and finally, cardiovascular autonomic neuropathy with arrhythmias.[34,35] Our study also demonstrated that diabetics with more severe symptoms of nausea/vomiting were found to have lower challenge sympathetic and parasympathetic activity, which suggests that severe nausea and vomiting in diabetics is associated with a more generalized cardiovascular autonomic neuropathy. These disparate autonomic findings may reflect the differing pathophysiology of diabetic vs idiopathic gastroparesis or differences in the cardiac and gastrointestinal branches of the vagus.

A limitation of our study is that HRV is an indirect measure of autonomic function compared with traditional autonomic testing. However, a pilot study indicated that both HRV and traditional ANS testing can detect abnormalities in patients with the symptoms of gastroparesis.[36] Our study assumes that cardiac autonomic dysfunction is representative of gastrointestinal autonomic dysfunction. This assumption is supported by a study of diabetics with cardiac autonomic neuropathy determined by HRV, which found that cardiac autonomic neuropathy was associated with decreased gastric acid output and pancreatic polypeptide stimulated by sham feeding.[37] Our study is also limited by the lack of simultaneous measurements of autonomic function, gastric emptying, and symptom severity. These measures were obtained prior to enrollment into the Gastroparesis Registry; however, these studies were on different days, which does not take into account day-to-day variability in autonomic testing and gastric emptying, or any interim medication changes. Additionally, our study did not stratify patients by duration of symptoms or presence of systemic autonomic symptoms to determine if our findings represent an imbalance of autonomic activity or a more generalized autonomic neuropathy.

Although the presence of autonomic dysfunction or sympathovagal imbalance is common among patients with gastroparesis symptoms, further studies are needed to confirm our hypothesis that gastroparesis symptom severity may reflect a progression of autonomic dysfunction, starting with sympathetic impairment followed by parasympathetic dysfunction. Further studies are also needed to determine if autonomic testing can help to guide therapy by choosing treatments that restore balance to the ANS. For example, in a study assessing the impact of neurostimulation on gastroparesis symptoms and autonomic parameters, Stocker et al[36] found that neurostimulation increased vagal cholinergic (parasympathetic) and decreased sympathetic adrenergic activity (sympathetic). As such, neurostimulation may not be the ideal choice in patients with parasympathetic excess or sympathetic hypofunction.

In summary, our present study found that measures of autonomic dysfunction were common among patients with symptoms of gastroparesis and CUNV. Not surprisingly, those with

diabetes were more likely to exhibit both sympathetic and parasympathetic hypofunction. Parasympathetic dysfunction was associated with the presence of delayed gastric emptying and severe symptoms of upper GI symptoms. Conversely, patients with milder symptoms had findings of sympathetic hypofunction. Based on this data, we speculate that gastroparesis and CUNV may be a manifestation of gastrointestinal autonomic dysfunction or imbalance, such that sympathetic dysfunction occurs early on in the manifestation of gastroparesis and CUNV, while parasympathetic dysfunction results in more severe symptoms and delayed gastric emptying.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Chronic upper gastrointestinal symptoms are associated with both sympathetic and parasympathetic dysfunction.
- Sympathetic hypofunction is associated with milder upper GI symptoms.
- Parasympathetic dysfunction is associated with more severe upper GI symptoms and delayed gastric emptying.

TABLE 1

Definition of normal ANX 3.0 autonomic measures[25]

Autonomic function parameters	**Normal values (bpm^s/Hz)**
Resting sympathetic activity (LFa)	0.5–10.0
Resting parasympathetic activity (RFa)	0.5–10.0
Resting LFa/RFa	0.4–3.0
Sympathetic challenge (Valsalva)	Age adjusted: on average 28.0 < LFa <120.0 for the fourth decade.
Parasympathetic challenge (Deep breathing)	Age adjusted: on average 28.0 < LFa <109.0 for the fourth decade.
Parasympathetic response to sympathetic challenge (Valsalva or stand)	RFa increase <400% over baseline during Valsalva or absence of an increase in RFa with standing
Sympathetic response to stand	LFa increase between 10% and 500% over baseline during stand

TABLE 2

Demographics and baseline patient characteristics

	Etiology of upper GI symptoms			
Characteristic	**Diabetic (N = 63)**	**Idiopathic (N = 179)**	**Total (N = 242)**	***P***
Age (years) – mean (SD)	45 (11)	42 (13)	43 (13)	.12
Gender				
Male	13 (21%)	16 (9%)	29 (12%)	.02
Female	50 (79%)	163 (91%)	213 (88%)	
Ethnicity				
Hispanic/Latino	14 (22%)	19 (11%)	33 (14%)	.02
Not Hispanic/Latino	49 (78%)	160 (89%)	209 (86%)	
Race				
White	54 (86%)	161 (90%)	215 (89%)	.05
Black	8 (13%)	9 (5%)	17 (7%)	
Asian	0 (0%)	3 (2%)	3 (1%)	
Native Hawaiian/Pacific Islander	1 (2%)	0 (0%)	1 (<1%)	
More than one race	0 (0%)	6 (3%)	6 (2%)	
BMI – mean (SD)	31.0 (8.5)	26.7 (7.6)	27.8 (8.1)	<.001
Gastric emptying				
Normal	12 (19%)	55 (31%)	67 (28%)	.10
Delayed	51 (81%)	124 (69%)	175 (72%)	
Smoking history				
Current smoker	7 (11%)	25 (14%)	32 (13%)	.67
Ever smoker	28 (44%)	57 (32%)	85 (35%)	.09
State-trait anxiety				
Mod/severe state anxiety	35 (56%)	85 (47%)	120 (47%)	.31
Mod/severe trait anxiety	36 (57%)	86 (48%)	122 (50%)	.24

TABLE 3

Comparison of autonomic abnormalities in patients with diabetic vs idiopathic cause of gastroparesis symptoms

	Diabetic (N = 63)	**Idiopathic (N = 179)**	***P***
Low resting sympathetic activity	29 (46%)	20 (11%)	<.0001
Resting sympathetic excess	3 (5%)	21 (12%)	.14
Low resting parasympathetic activity	38 (60%)	29 (16%)	<.0001
Resting parasympathetic excess	1 (2%)	19 (11%)	.03
Low sympathetic response to challenge	54 (89%)	123 (74%)	.02
Challenge sympathetic excess	2 (4%)	16 (12%)	.16
Challenge parasympathetic excess	23 (37%)	63 (36%)	1.00

TABLE 4

Autonomic abnormalities comparing patients with delayed vs normal gastric emptying

	Normal emptying (N = 67)	**Delayed emptying (N = 175)**	***P***
Low resting sympathetic activity	7 (10%)	42 (24%)	.02
Resting sympathetic excess	6 (9%)	18 (10%)	1.00
Low resting parasympathetic activity	13 (19%)	54 (31%)	.08
Resting parasympathetic excess	4 (6%)	16 (9%)	.60
Low sympathetic response to challenge	49 (79%)	128 (78%)	.86
Challenge sympathetic excess	2 (4%)	16 (11%)	.16
Challenge parasympathetic excess	17 (26%)	69 (40%)	.05

TABLE 5

Comparison of autonomic activity in patients with severe upper gastrointestinal symptoms

	GCSI < 4 (N = 207)	GCSI ≥ 4 (N = 35)	*P*
Initial baseline (resting)			
Sympathovagal balance (LFa/RFa)	1.2 (0.6–2.3)	1.8 (1.0–3.1)	.006
Deep breathing			
Parasympathetic activity (RFa)	14.4 (3.5–43.8)	9.2 (2.6–29.5)	.49
Valsalva			
Sympathetic activity (LFa)	18.5 (4.7–40.8)	19.6 (6.2–43.1)	.91
Parasympathetic activity (RFa)	2.7 (0.8–7.5)	2.1 (0.8–5.9)	.61
Standing			
Sympathetic activity (LFa)	1.7 (0.5–5.0)	1.4 (0.5–3.0)	.32
Sympathovagal balance (LFa/RFa)	2.7 (1.2–4.8)	3.9 (1.5–6.0)	.08
Parasympathetic activity (RFa)	0.6 (0.2–1.7)	0.4 (0.1–0.8)	.03