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ORIGINAL ARTICLE

Autonomic and enteric function profiling can predict disordered gastric emptying in diabetic gastropathy

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Abstract

Gastric emptying tests (GET) are the gold standard for diagnosing gastroparesis, but many patients do not have delayed emptying. We aimed to examine the combination of autonomic nervous system testing (ANS) and the enteric measure (ENS) of electrogastrography (EGG) to predict disordered GET. Seventy-six patients (47 F, 29 M mean age 40 years) with diabetes mellitus underwent evaluation for end-organ failure including gastroparesis. ANS testing assessed autonomic function by finger capillary pulse to positional changes (PAR), vasoconstriction to cold (VC), and EKG R-R interval change (RRI) with deep breathing; the ENS measures of cutaneous EGG assessed gastric myoelectrical activity. Solid (S) GET subgroups were based on 50% emptying (TS50). Via linear regression analysis: VC, PAR, and EGG had a significant inverse correlation with GET TS50 and decreased in response to a delay in gastric emptying ($p < 0.05$). Via ordinal logistic regression RRI and EGG-predicted gastric emptying ($p < 0.01$). Patients with a higher RRI and EGG value were 0.93 and 0.14 times more likely to be diagnosed with rapid gastric emptying. The areas under the curve for receiver operator characteristics (AUROC) for all measures were 0.72 in comparison to 0.59 with EGG. Based on the results, four components (RRI, VC, PAR, and EGG) quantitatively describe gastric emptying in patients with signs of diabetic gastropathy better than EGG alone.

Keywords Gastroparesis · Dysrhythmia · Autonomic function test · Electrogastrography

Abbreviations

T50S	Time for 50% of a solid meal to emptying
GET	Gastric emptying test
EGG	Electrogastrogram
RRI	EKG R to R Interval
PAR	Postural adjustment ratio
VC	Vasoconstriction

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1 Introduction

Gastroparesis (Gp) is widely recognized as a complication of severe autonomic neuropathy in long-standing and poorly controlled diabetes mellitus [1]. According to one study, up to a third of gastroparesis cases are linked to diabetes mellitus [2]. An estimated 50% of patients with long-standing diabetes mellitus present with some form of gastric motor dysfunction [3]. In addition, delayed absorption of nutrients by the small intestine, due to impaired gastric emptying, may result in mismatched timing between blood glucose and insulin peaks, thus rendering blood glucose regulation difficult. It is worth mentioning that a percentage of gastroparesis patients, up to 21%, was associated with rapid gastric emptying studies in a small study by Bharucha et al. [4]. Studies show that patients with diabetes mellitus and symptoms of gastroparesis (nausea, vomiting, bloating, abdominal distension, anorexia, and early satiety) had a high incidence of vagal abnormalities for the whole patient group, but failed to demonstrate a strong correlation between vagal cholinergic abnormalities and delayed gastric emptying for individual patients [5]. A recent paper by Araujo et al. demonstrated that diabetic patients with gastroparesis were more likely to have abnormal cardiovascular autonomic tests than diabetics without autonomic neuropathies, such as gastroparesis [6]. Using noninvasive tests of adrenergic and cholinergic function, we investigated the hypothesis that diabetic gastroparesis is associated with both parasympathetic and sympathetic dysfunction of the autonomic nervous system. We aimed to show an association between autonomic and enteric variables with diabetic gastropathy, whether that was delayed or rapid gastric emptying.

2 Design

2.1 Patients

We studied 67 consecutive patients with the criteria of diabetes mellitus and symptoms of gastroparesis who were referred for the autonomic nervous system (ANS) and enteric nervous system (ENS) assessments. Inclusion criteria included patients who were dependent on insulin for diabetes mellitus control. In addition, all patients had symptoms of gastroparesis for at least 6 months.

Exclusion criteria included that a patient had no history of prior esophageal or gastric surgery or evidence of structural GI disease confirmed by esophageal gastro endoscopy (EGD). We also excluded patients with a history of alcohol or drug addictions, or with a recent cerebrovascular accident, or paralysis, or unable to complete our assessments. Pregnant females were also excluded.

2.2 Methods

All tests were conducted in a quiet room prepared to maintain stable ambient temperatures ranging from 20 to 30 °C. After a period of stabilization and adaptation, patients' temperatures, blood pressures, and heart rates were recorded at 2-min intervals using a Dinamap monitor until two successive determinations were ± 10% of preceding values. After a stabilization period for the heart rate, blood pressure, and return of digital skin temperature to 32–35 °C, the following procedures were carried out in sequence as previously reported [7, 8].

The autonomic and enteric nervous systems were evaluated in the following ways:

1. Two measures of sympathetic adrenergic function
2. One measure of vagal cholinergic function
3. One measure of gastric myoelectrical activity

Gastric emptying test (GET) measures were used to divide the patients into the following categories: delayed, very delayed, normal, rapid, and very rapid GET using T50 values.

2.2.1 Sympathetic adrenergic function

The two measurements used to determine the sympathetic adrenergic function were the postural adjustment ratio (PAR) and reflex vasoconstriction ratio (VC). Both were obtained using infrared photo-plethysmography to measure the digital arteriolar pulse amplitudes (using a Meda-sonic Vasculab model PPG-13, Mountain View, CA, USA). Arteriolar pulse amplitudes were recorded using an eight-channel model 7 grass polygraph and were used to calculate a total pulse amplitude (TPA), standardized to operate at 20 mV/cm at a paper speed of 100 mm/min. The plethysmography sensitivity was increased in patients with very low digital capillary pulse amplitude. Probes with an infrared light-emitting diode were affixed to the distal phalanx of the patient's left middle or index finger.

In order to establish a baseline for comparing the reflex vasoconstriction in response to positional changes, the left arm was placed on the side table (45° angle) 40–50 cm above the heart. Subsequently, with pulse amplitudes at a steady state (fixed pattern over a period of 1 min), calculations of TPA were made. After this baseline, TPA was obtained (at hands-up position), the left hand was then dropped to a vertical position 30–50 cm below the heart level, and the TPA was again recorded. The ratio of the TPA at hand positions above/below the heart is defined as the postural adjustment ratio (PAR), expressed as a single number ratio.

With the left hand resting on the table, we established a baseline TPA reading. Reflex vasoconstriction in the digital arterioles of the hand was measured by recording the decrease in the TPA of the left hand in response to the immersion of the right hand in ice-cold water (4 °C) for 1 min. Changes were expressed as the percentage change from baseline TPA (% vasoconstriction).

All patients were instructed to have a choice of a light breakfast; fasting was not required. Patients were instructed to not have caffeine or smoking products and hold on taking any medications that could have an effect on the test including beta blockers or vasodilators. Other medications were allowed to take as prescribed including DM medications. Patients were instructed to wear comfortable cloth and shoes. All tests were conducted in a quiet hospital room designed with additional heating unit to maintain a warm temperature between 20 and 30 °C. Using an automatic/manual blood pressure instrument, Dinamap monitor (Model 8100; Critikon Inc., Tampa, FL, USA), a proper blood pressure cuff size was placed on the left arm to monitor blood pressure and heart rate either every 10–15 min or manually when it is required by the protocol. Blood pressure and heart rate values were recorded only for monitoring patients and as a standard of care.

2.2.2 Vagal cholinergic function

Vagal cholinergic function was measured using an electrocardiogram (EKG) to determine the R-R interval (RRI). Changes to the RRI were measured under respiratory maneuvers, including the Valsalva maneuver, to evaluate the percentage change in RRI. The %RRI was calculated by subtracting the minimum HR during Out from the maximum HR duing In divided by the minimum HR during In. The result was multiplied by 100. shown in Eq. 1:

$$\%\mathrm{RRI} = \left(\frac{\mathrm{RRI\ inpiration}{-}{-}\mathrm{RRI\ expiration}) \times 100}{\mathrm{RRI\ expiration}}\right.$$

The %RRI was measured during a 2-min period of breathing at a rate of six breaths per minute. For the Valsalva portion, the subject maintained an expiration force of 40 mm Hg for 15 s using a mouthpiece. The Valsalva ratio was then calculated by dividing the highest heart rate during Valsalva by the lowest heart rate immediately after the maneuver. Autonomic function system measures were recorded in the following positions: supine and sitting.

2.2.3 Gastric myoelectrical activity

The electrogastrogram or EGG is a noninvasive method that measures the gastric slow waves, which determine gastric motility. The area of skin below and to the left of the tip of the xiphoid was cleaned with alcohol. Three electrodes were attached along the greater gastric curvature border with electrode jelly once the alcohol dried. Transmitted electrical impulses were then detected using the four-channel EGG recording device and recorded for a recommended 30-min period. Two channels of EGG can be recorded to improve signal quality. EGG was also done in the following positions: supine and sitting, as it is recorded simultaneously with ANS measures. The EGG was analyzed visually for an average frequency. This approach has been shown equivalent to a computer-modeled approach [9]. Normal values used for EGG were from previously published work [10, 11].

2.2.4 Gastric emptying study

Gastric emptying was measured by administering a 297-calorie solid-liquid meal labeled with solid 99Tc via an anterior gamma-camera, which was used to monitor the progress of the meal in the stomach. A power exponential model was fitted to the emptying curves, resulting in kappa (K) and beta (B) values, representing the slope of the solid gastric emptying curves. These results were compared with gastric emptying values obtained in 17 normal volunteers. Using standardized 50% gastric emptying times (T50 in minutes), patients were classified into the following subgroups: very rapid (< 100), rapid (< 130), normal (< 180), delayed (< 240), and very delayed (> 240). Based on the gastric emptying data from the normal controls, the diabetic patients were classified into delayed and non-delayed solid emptying groups using the interquartile slope values. Non-delayed patients were also classified as having normal or rapid emptying (normal slope ranged from 0.006 to 0.008; delayed slope was < 0.006; rapid slope was > 0.008). Normal values for gastric emptying were from previously published work [11–13]. The GET was done with the patients in a 45° position with standard nuclear imaging equipment.

2.3 Statistical evaluation

Patients with either "VC<12," "PAR>60," "RRI<3," "EGG>7," or "T50S>240" were excluded from statistical analysis, as these were outliers. Multiple linear regression was used to determine the relationship between autonomic functions, such as VC, PAR, RRI, and EGG and an abnormal gastric emptying time (Table 1).The gastric emptying time (GET) was further divided into the above mentioned subgroups (Table 2). Ordinal logistic regression was used to predict the likelihood of delayed gastric emptying based on patient VC, PAR, RRI, and EGG (Table 3). The area under the curve (AUC) for receiver operator characteristics (ROC) was used to assess the performance of ordinal logistic regression.

This study adheres to the Declaration of Helsinki and was approved by the University of Louisville's Institutional Review Board #13.0020. This was a waiver study for the analysis of the data. The autonomic and enteric profiling and gastric emptying were done as part of clinical care for patients being evaluated for possible pancreas or pancreas/kidney transplantation.

3 Results

The study involved seventy-six patients seen at a tertiary medical center with the criteria of diabetes mellitus (DM) and symptoms (Sx) of gastroparesis (Gp). Patients included 47 females and 29 males with an average age of 40 ± 11 years all of whom had long-term diabetes with renal insufficiency

Table 1 Multiple linear regressions of VC, PAR, RRI, and EGG on T50S

Variables	Parameter estimate (95%CI)	*p* value
Intercept	371.90 (268.68 to 475.12)	< 0.01
VC	− 0.72 (− 1.33 to − 0.12)	0.02
PAR	− 0.33 (− 1.33 to 0.66)	0.51
RRI	− 1.48 (− 2.56 to − 0.40)	0.01
EGG	− 43.49 (− 70.61 to − 16.38)	< 0.01

Adjusted R^2 = 0.25

Table 2 Means and standard deviations for ordinal GET groups

GET	N	VC	PAR	RRI	EGG	T50S
Very rapid (T50S < 100)	15	76.23 ± 18.35	23.48 ± 14.16	26.49 ± 22.0	3.53 ± 0.62	66.45 ± 20.70
Rapid (100 ≤ T50S < 130)	14	56.30 ± 21.49	21.08 ± 14.28	11.93 ± 6.89	3.58 ± 0.48	112.29 ± 8.08
Normal (130 ≤ T50S < 180)	18	59.42 ± 23.35	22.10 ± 13.45	16.28 ± 11.92	3.14 ± 0.21	151.49 ± 13.45
Delayed (180 ≤ T50S < 240)	10	61.01 ± 29.10	23.74 ± 17.91	10.23 ± 3.88	3.36 ± 0.30	202.02 ± 14.23
Very delayed (T50S ≤ 240)	16	46.28 ± 20.66	16.53 ± 8.66	11.15 ± 7.88	3.23 ± 0.64	240.00 ± 0.00

Units of measure: Vasoconstriction (VC) to cold is a % value. Postural adjustment ratio (PAR) is a ratio. EKG R to R interval (RRI) is a % value. Electrogastrogram (EGG) frequency is in cycles/minute. Gastric emptying test (GET) is time for 50% of solids to empty (T50S) in minutes

and were being evaluated for gastrointestinal and other organ dysfunction.

Multiple linear regression showed that VC, RRI, and EGG have a significant negative relationship with gastric emptying time (GET) ($p < 0.05$) (Table 1). It means the gastric emptying time is significantly decreased by 0.72 for each unit increase in VC, assuming other variables remain constant. Similarly, with an assumption of other variables remaining constant, the gastric emptying time is significantly decreased by 1.48 for each unit increase in RRI and decreased by 43.49 for each unit increased in EGG.

We utilized simple linear regression to determine the gastric emptying time (GET) based on the patient's EGG information. The adjusted R^2 for a model with only EGG is 0.03 compared to 0.25 when using all four components, which suggests that the model with VC, PAR, RRI, and EGG provides a better estimate for gastric emptying time than the EGG information alone. In addition, multiple partial F tests demonstrated that VC, PAR, and RRI jointly contribute significantly to the model (F value = 7.69, $p < 0.01$). The descriptive statistics of VC, PAR, RRI, EGG, and T50S for gastric emptying categories are in Table 2.

Ordinal logistic regression demonstrated that RRI and EGG significantly predict the likelihood of more rapid gastric emptying ($p < 0.01$), while VC only has borderline predictability as shown in Table 3. While VC and RRI were associated with a significantly abnormal gastric emptying study (0.98 and 0.93 respectively), patients with a higher RRI value were 0.93 times more likely to be diagnosed with more rapid gastric emptying while those with a higher EGG were 0.14 times more likely to be diagnosed with more rapid gastric emptying (Table 3).

Similarly, we also developed a simple ordinal logistic regression to predict the likelihood of gastric emptying time using only the patient's EGG information. The AUC value of ROC for a simple ordinal logistic regression with EGG was 0.59, while the full ordinal logistic model with all four components is 0.716, which suggests that the model with VC, PAR, RRI, and EGG provides the better estimates for gastric emptying time than the EGG alone.

Table 3 Odds ratio of effects for the likelihood of more rapid gastric emptying

Effects	Odds ratio (95%CI)	p value
VC	0.98 (0.96–1.01)	0.06
PAR	0.98 (0.95–1.02)	0.34
RRI	0.93 (0.90–0.97)	< 0.01
EGG	0.14 (0.05–0.38)	< 0.01

AUC for ROC = 0.716

4 Discussion

The autonomic nervous system (ANS) plays a significant role in the functions of the alimentary tract even though the gastrointestinal tract contains its own nervous system that maintains physiological functions. Both the sympathetic and parasympathetic nervous systems have significant effects on the function of the stomach by altering mucosal secretion, blood flow, gastric tone, and motility. Numerous pathologies have been linked with ANS dysfunction including diabetes mellitus, renal failure, heart failure, cirrhosis, and multiple system atrophy [14–17]. Impaired gastric motility was frequently found in patients with severe cardiovascular autonomic neuropathy (CANP), suggesting that the former was a consequence of the latter [6]. Despite reports that delayed gastric emptying correlates with the severity of neuropathy, there is no good evidence that this disorder is etiologically related to CANP. In one study, it was shown that gastric dysfunction might have resulted from a neuropathy affecting enteric nerves but not the cardiovascular system [18]. This study demonstrated that neuropathy findings included inflammatory changes in autonomic ganglia and unmyelinated nerves, a loss of myelinated fibers in the vagus nerve and sympathetic trunks, and focal hyaline degeneration of smooth muscle in many viscera [18]. These results suggest the presence of mechanisms other than just vagal cholinergic denervation. In addition, prior small studies have demonstrated a significant effect between gender and gastric emptying [19, 20]. These studies demonstrate that females had significantly slower gastric emptying compared with males, suggesting that sex hormones play a role in gastric motility as well.

Current concepts of the enteric nervous system suggest that there is a delicate balance between adrenergic and cholinergic tone. Thus, abnormalities of the sympathetic (particularly sympathetic adrenergic function) and parasympathetic nervous systems may explain some of the defects observed in diabetic gastroparesis. Other clinical conditions where gastroparesis exists support this hypothesis, including abnormalities of the cervical cord (injuries resulting in quadriplegia), which are associated with delayed liquid gastric emptying. Similarly, an abnormal vagal cholinergic function, via the vagus nerve, would be detected by a low RRI variation, indicating an impaired autonomic function. As the importance of the ANS in the function of the stomach has been outlined before, we hypothesized that we would detect an association of sympathetic adrenergic (VC), vagal cholinergic (RRI), and electrogastrography (EGG) with some degree of impaired gastric emptying time (from very rapid to very delayed). Through the multiple linear regression analysis, we can conclude that sympathetic adrenergic, sympathetic cholinergic tone, and electrogastrography have significant inverse relationships to gastric emptying time. This analysis was also confirmed through ordinal logistic regression, proving the significance of ANS dysfunction in the development of gastroparesis, similar to the findings by Stocker et al. [21].

While gastroparesis is classically associated with a delayed gastric emptying time, patients may also present with rapid gastric emptying times. Rapid gastric emptying has been previously reported to be more common in patients with autonomic dysfunction as well as those with diabetes [22, 23]. Roughly forty percent of our study participants presented with rapid and very rapid gastric emptying times, which is similar to forty-four percent reported in a study by Lawal et al. [22]. This consensus indicates that rapid gastric emptying may be another manifestation of diabetic enteropathy and autonomic system dysfunction.

There are a number of drawbacks to this study. First, the patients had varying degrees of organ failure(s), which may affect the results of the autonomic function testing and gastric emptying. Second, we had limited anthropomorphic data which makes comparisons of BMI and gastric emptying not obtainable in this data set. Third, the potential influence of both daily and monthly circadian rhythms was not taken into account in this study. Given these limitations, the work presented here would need further validation.

In conclusion, we have demonstrated that autonomic and enteric profiling using all four components (VC, PAR, RRI, and EGG) can quantify gastric emptying in patients with diabetic gastropathy. This non-invasive, non-radioactive, and relatively straightforward technique is easy to perform and may offer promise for identifying disordered gastric emptying in a variety of clinical conditions. In the future, this autonomic and enteric model may be a valuable tool in assessing a variety of patients' response to treatments, including those with organ failure and specific symptoms, in relation to disordered gastric emptying.

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Author contribution All authors made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. All assisted in drafting the article or revising it critically for important intellectual content. They have all given final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest Drs. Abell, Johnson, and Rashed have certain aspects of autonomic and enteric function covered under intellectual property awarded to the University of Mississippi.

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