

# Diabetic gastroparesis is associated with an abnormality in sympathetic innervation

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**Objective:** To investigate the hypothesis that diabetic gastroparesis might be associated with sympathetic, as well as parasympathetic, autonomic nervous system abnormalities.

**Patients:** We evaluated 12 consecutive patients with diabetes mellitus who presented with symptoms of gastroparesis.

**Methods:** The autonomic function tests included two measurements of sympathetic adrenergic function [reflex vasoconstriction to cold stress and the postural adjustment ratio (PAR)], and measurement of sympathetic cholinergic function (resting skin temperature) and vagal cholinergic function [EKG R-R interval (RRI)]. Gastric emptying was also measured and analysed by a power exponential model to estimate the solid gastric emptying slope. Patients were separated into delayed and nondelayed solid gastric emptying subgroups, the latter including two patients with rapid gastric emptying.

**Results:** All autonomic function measures were significantly lower in the diabetes mellitus group than in normal controls ( $P < 0.001$ ); diabetic patients as a group had slower solid gastric emptying slopes than nondiabetic controls ( $P \leq 0.01$ ). There was no significant correlation between measures of vagal cholinergic function by RRI, the sympathetic cholinergic function by PAR, or sympathetic cholinergic function by skin temperature and solid gastric emptying, but a statistically significant correlation was found between the sympathetic adrenergic measure of vasoconstriction to cold stress and the slope of solid gastric emptying ( $r = 0.79$ ,  $P > 0.01$ ). Diagnostic values for the autonomic function tests when compared to solid gastric emptying revealed sensitivities of 50% for the RRI, 88% for vasoconstriction, 63% for PAR and 71% for skin temperature.

**Conclusion:** We recommend that autonomic function measurements in patients with diabetes mellitus and upper gut symptoms should include tests of sympathetic function as well as traditional tests of vagal cholinergic function.

European Journal of Gastroenterology & Hepatology 1994, 6:241–247

**Keywords:** Gastrointestinal motility, autonomic function testing, adrenergic function, cholinergic function

## Introduction

Gastroparesis is widely recognized as an expression of severe autonomic neuropathy in long-standing and poorly controlled diabetes mellitus

[1–3]. The involvement of the gastrointestinal tract in the autonomic neuropathy of diabetes mellitus, which results in reduced smooth muscle contractility, is believed to be responsible for the relatively high incidence of gastroparesis in dia-

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Sponsorship: This study was supported in part by CRC Grant No. MO1 RR00211-23 and by grants from Syncor and Janssen Pharmaceutica.

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Date of receipt: 4 January 1993; revised: 6 August 1993; accepted: 30 September 1993.

betes mellitus [4,5]. However, a study by Buyschaert *et al.* [6] of patients with diabetes mellitus and symptoms of gastroparesis (nausea–vomiting, bloating–distension, anorexia–early satiety) showed 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. A more recent study by Werth *et al.* [7] showed that the mean gastric clearance of radioopaque markers was slower in patients with cardiovascular autonomic neuropathy than those without it. In that study, three out of the 11 patients with cardiovascular autonomic neuropathy had abnormal gastric emptying, although none of the patients had symptoms which could be attributed to delayed gastric emptying. Using noninvasive tests of adrenergic and cholinergic function, we investigated the hypothesis that diabetic gastroparesis may be associated not only with parasympathetic dysfunction but also with abnormalities of sympathetic autonomic function.

## Patients, materials and methods

### Patients

We studied 12 consecutive patients (four men and eight women; mean age 43.8 years) with diabetes mellitus and symptoms of gastroparesis who were referred for further evaluation of their illness to the University of Tennessee Gastrointestinal Motility Laboratory. All patients were dependent on insulin for control of diabetes mellitus, and many had evidence of multisystem complications (cardiovascular, renal, ophthalmologic, or neurologic) in addition to their gastrointestinal symptoms. All patients had symptoms of gastroparesis for at least 6 months, had no evidence of structural gastrointestinal disease

on either upper gastrointestinal endoscopy or upper gastrointestinal barium evaluation, and had no other known cause for gastrointestinal symptoms. Exclusion criteria included: prior gastric surgery, chemical dependency, pregnancy, previous cerebrovascular accident, or inability to complete the necessary tests. Although several patients had renal insufficiency, only one patient (number 4) had renal failure requiring dialysis. These patients are further profiled in Table 1.

### Diagnostic tests of systemic autonomic function

Tests of systemic autonomic function included measurement of blood pressure, skin temperature, and sympathetic adrenergic, sympathetic cholinergic, and vagal cholinergic function. These autonomic function tests have been described previously in patients with diabetes mellitus [8–10].

All tests were conducted in a hospital room prepared to maintain stable ambient temperatures ranging from 20–30°C. After a period of stabilization and adaptation to ambient temperatures of 24–26°C, the patients' blood pressures and heart rates were determined at 2-min intervals using a Dinamap monitor (Model 8100; Critikon Inc., Tampa, Florida, USA) until two successive determinations were  $\pm 10\%$  of preceding values. Skin temperatures were measured with a Mon-a-therm thermometer (Mon-a-therm Inc., St. Louis, Missouri, USA). Following the initial 10- to 15-min period of stabilization of heart rate and blood pressure, and after spontaneous warming of digital skin temperature to 32–35°C, the following procedures were carried out in sequence.

### Test of sympathetic adrenergic function

Sympathetic adrenergic function was determined by two measures: reflex vasoconstriction and postural adjustment ratio (PAR) of capillary blood flow, both made by infrared photoplethysmography preceding, during, and after immersion of the opposite hand

**Table 1.** Characteristics of diabetes mellitus (DM) patients.

Patient No.	Age (years)	Gender	Duration of DM (years)	Glycohemoglobin*	Duration of GI symptoms (years)	Other DM complications	Blood sugar levels <sup>†</sup>
1	41	F	18	6.1	3.0	O, N	156
2	56	F	16	NA	1.0	C	256
3	32	F	21	5.4	1.0	N, O, R	157
4	40	F	22	11.4	3.0	O, N	79
5	37	F	13	6.1	7.0	–	63
6	50	M	15	8.2	5.0	O	269 (214)
7	36	M	10	5.2	1.0	O, N	47
8	52	F	13	12.3	0.5	–	248
9	49	M	9	6.3	0.5	C	120 (164)
10	52	F	22	6.9	1.0	O, N	116
11	39	M	21	8.5	0.5	R, N	160 (152)
12	42	F	24	NA	3.0	R, N	205 (171)

\*Normal range for hemoglobin is <6.1. All values determined within 3 months prior to evaluation. GI, gastrointestinal; C, cardiovascular; N, neurologic; O, ophthalmologic (retinopathies); R, renal; F, female; M, male; NA, not available. <sup>†</sup>Blood sugar mg/% on day of gastric emptying test and autonomic function testing (second value given in parentheses if measured on 2 separate days).

in ice-cold water, to measure vasoconstriction to cold. Arteriolar capillary blood flow was estimated by infrared photoplethysmography through measurements of digital arteriolar pulse amplitudes (using a Meda-sonics Vasculab model PPG-13; Mountain View, California, USA). Frequencies and arteriolar pulse amplitudes were recorded using an eight-channel Model 7 Grass polygraph and were used to calculate a total arteriolar pulse amplitude (TPA), standardized to operate at 20 mV/cm at a paper speed of 100 mm/min. The polygraphic 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 and the first right toe. Next, the left arm was placed on the side table (45° angle) 40–50 cm above the heart. The right leg was placed on a resting table with the foot positioned 10–20 cm above the patient's heart. Subsequently, with pulse amplitudes at 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, expressed as a single number ratio.

Reflex vasoconstriction in the digital arterioles of the hand and foot was measured by recording the decrease in the TPA of the left hand and right foot in response to immersion of the right hand in ice-cold water (4°C) for 1 min (Fig. 1). Changes were expressed as the percentage from baseline TPA (% vasoconstriction).

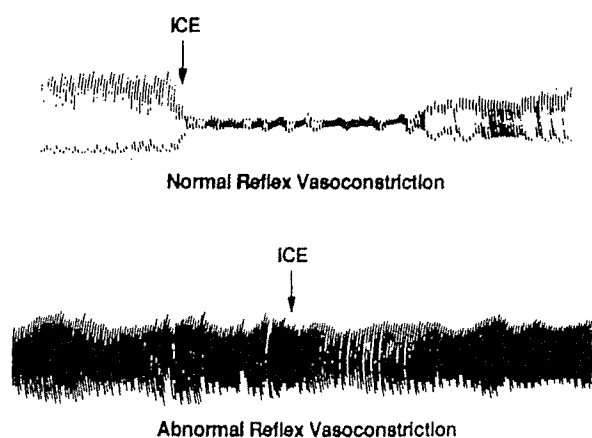


Fig. 1. The sympathetic adrenergic measure vasoconstriction to cold stress measured by capillary pulse in a normal control and a patient with diabetes mellitus and severe autonomic neuropathy. Notice the normal response to cold in the control and the lack of response in the patient with autonomic neuropathy.

#### Tests of vagal cholinergic function

Vagal cholinergic function was determined by the R–R interval (RRI) of the electrocardiogram (EKG) and by vagal functions according to changes in the RRI elicited by respiratory manoeuvres, including the Valsalva maneuver. The RRI carried out during full inspiration and expiration was expressed as:

$$\%RRI = \frac{(RRI \text{ expiration} - RRI \text{ inspiration})}{RRI \text{ expiration}} \times 100$$

The percentage change in RRI variation of the EKG during inspiration and expiration while patients breathed deeply at six breaths/min was measured after a 2-min period of regular breathing. The Valsalva ratio was calculated after the subject held an expiration force of 40 mmHg for 15 s. This ratio was derived by dividing the highest heart rate during expiratory force by the lowest heart rate immediately after the maneuver.

#### Tests of sympathetic cholinergic function

Sympathetic cholinergic function was determined by measurement of resting skin temperature in the patient's hand as well as skin temperature after exposure to cold. Skin temperature recovery time was measured following removal of the hand from ice by recording temperature at 1-min intervals for 20 min. The time required, in min, for the digital skin temperature to return to 30°C was designated skin temperature recovery time (STRT)

Measurements of these autonomic functions were compared with values from two other groups: (1) 49 normal (nondiabetic) controls, and (2) 93 patients with insulin-dependent diabetes mellitus (mean glycohemoglobin  $8.4 \pm 0.16$  SEM). Values for patients, normal controls, and the 93 diabetic control patients are summarized in Table 2. With the exception of prokinetic drugs, patient medications (including antihypertensives) were taken as usual on the day of the study. Patients stopped taking all prokinetic drugs prior to the gastric emptying test, and smoking was not allowed prior to or during the test. Fasting blood glucose values were obtained the morning of the diagnostic autonomic function tests, which was usually the same day as the gastric emptying test (Table 1).

#### Diagnostic test for gastric emptying

Gastric emptying was measured by giving a 297 calorie, solid–liquid meal labeled with solid  $^{99}\text{Tc}$ . An anterior gamma-camera was used as previously described [11] to monitor the progress of the meal in the stomach. A power exponential model was fitted to the emptying curves, resulting in kappa ( $\kappa$ ) and beta ( $\beta$ ) values, representing the slope of the solid gastric emptying curves. These results were compared with gastric emptying values obtained in 17 normal volunteers. Based on the gastric emptying

Table 2. Autonomic function test measurements for patients and controls.

Function test	Patients (n = 12)	Normal controls (n = 49)	Diabetes mellitus controls (n = 93)
VC (% change)	33.6 ± 7.9*	81.4 ± 1.5	73.0 ± 1.7
PAR (ratio)	13.0 ± 1.8*	27.7 ± 2.4	16.3 ± 1.0
RRI (% change)	6.9 ± 1.2*	34.6 ± 1.9	30.6 ± 0.0
Skin resting temperature (°C)	31.6 ± 0.9	34.4 ± 0.2	34.6 ± 0.1
Mean glycohemoglobin	7.6 ± 0.8	<6.1	8.4 ± 0.16

The means ± SEM of the measures of autonomic function in the patient group were lower than the normal control group (\* $P < 0.001$  by Wilcoxon rank sum tests). These are measures of sympathetic adrenergic (VC + PAR), vagal cholinergic (RRI), and sympathetic cholinergic (skin temperature) function. See text for discussion of normal and diabetes mellitus control groups. VC, vasoconstriction; PAR, postural adjustment ratio; RRI, electrocardiogram R-R interval; n, number of subjects.

data from the normal controls, the diabetic patients were classified into delayed and nondelayed solid emptying groups using the interquartile slope values. Nondelayed patients were also classified as having normal or rapid emptying (normal slope 0.006 to 0.008; delayed slope <0.006; rapid slope >0.008).

### Statistical evaluation

Results of autonomic function tests (vasoconstriction, PAR, RRI, skin temperature, and STRT) were compared with results from 49 normal controls using Wilcoxon rank sum tests as well as with results from a control group of insulin-dependent diabetic patients (n = 93). Gastric emptying data for the whole patient group and for delayed and nondelayed solid emptying subgroups were compared with values from 17 normal controls using the Kruskal-Wallis test. A correlation coefficient (r) was computed by Spearman rank test for the relationship between the slope of solid emptying and vasoconstriction, PAR, RRI, and skin temperature values.

Measurements of vasoconstriction, PAR, and RRI skin temperature were also evaluated for their association with the slope of solid emptying values. Both the Spearman rank coefficient (for continuous variables) and Fisher's exact test (for dichotomous variables) were calculated. Also, predictive values (sensitivity, specificity) were calculated for each comparison of autonomic measurements with solid gastric emptying. The cut-off point for vasoconstriction was <40% (based on visual association in the graphed data). The cut-off point for PAR (<12%) was based on results from a subgroup of 19 poorly controlled diabetes mellitus patients. Cut-off points for RRI were <6% (from the median value for patients). The cut-off point for resting skin temperature was 32.6°C (median value for the patient group). Cut-off points for the slope of solid gastric emptying data were values <0.006, based on values from 17 normal controls.

Diabetic patients were further subgrouped into delayed (n = 8) and nondelayed (n = 4), based on their solid emptying result. Delayed solid gastric emptying was defined as a slope <0.006. Nondelayed patients were also separated into normal (n = 2) or rapid (n = 2) subgroups. Also, gastric emptying re-

sults were analysed by comparing the medians of the predicted values between the whole group of 12 diabetic patients and the 17 normal individuals and between the two subgroups of diabetic patients. The equality of gastric emptying slope values was tested using a one-way nonparametric analysis of variance of the median scores between all groups, subgroups, and controls. All statistical tests were two-tailed and were evaluated at the 0.05 level of significance.

### Results

Autonomic function values, (vasoconstriction, PAR, RRI, and resting skin temperature) were all significantly lower than in normal controls ( $P < 0.001$  by Wilcoxon rank sum tests). The means and standard errors for the patient and control groups as well as for the diabetic control group are listed in Table 2. The vagal cholinergic measure of the EKG RRI was impaired in the patient group, but these values did not correlate with solid gastric emptying ( $P > 0.05$ ) by Spearman rank test (Fig. 2) nor were they predictive (sensitivity 50%). However, a statistically significant Spearman correlation coefficient was found between the sympathetic adrenergic measure of vasoconstriction and the slope of solid emptying ( $r = 0.79$ ,  $P < 0.01$ ) and Fisher's exact test for this comparison of solid emptying versus vasoconstriction was associated with  $P = 0.02$  (Fig. 3). The sensitivity and specificity of vasoconstriction to detect delayed slope of solid emptying were 88 and 100%, respectively. The association between the sympathetic adrenergic measure, PAR, with the slope of solid emptying was not statistically significant ( $P > 0.05$ ); diagnostic values had a 63% sensitivity and 25% specificity.

The relationship between resting skin temperature and solid gastric emptying is shown in Fig. 4. Resting skin temperature was not significantly associated with solid gastric emptying by the Spearman rank test ( $P > 0.01$ ) or by Fisher's exact test ( $P = 0.26$ ). The reason for the nonsignificant association is primarily due to the value from one outlying patient. This particular patient had rapid solid emptying (slope

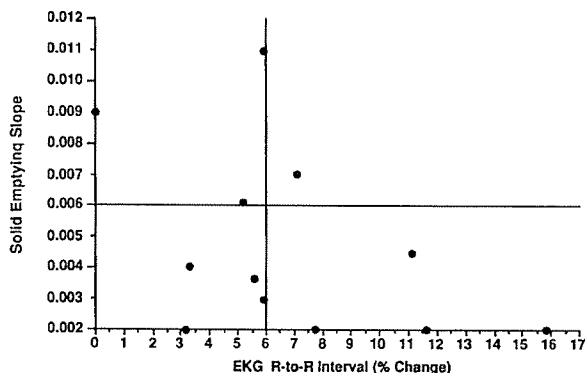


Fig. 2. Slope of solid gastric emptying compared with vagal cholinergic measure electrocardiogram (EKG) R-R interval. Note the lack of correlation between the R-to-R interval and solid emptying ( $P > 0.05$ ) by Spearman rank test.

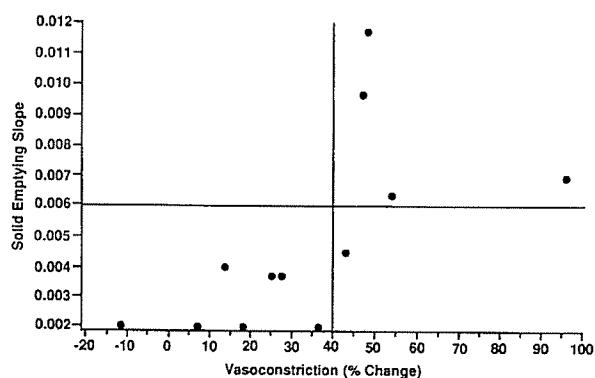


Fig. 3. Slope of solid gastric emptying compared with the sympathetic adrenergic measure, vasoconstriction. In this group of diabetic patients, most individuals with delayed solid emptying (slope  $< 0.006$ ) had less than 40% vasoconstriction ( $r = 0.79$ ,  $P < 0.01$  by the Spearman rank test;  $P = 0.02$  by Fisher's exact test).

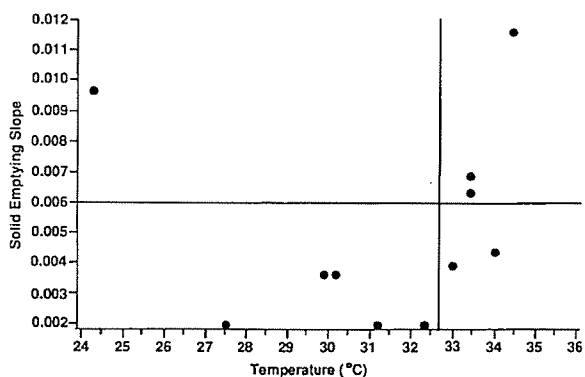


Fig. 4. Slope of solid emptying compared with the sympathetic cholinergic measure, resting skin temperature. This association was not statistically significant ( $P > 0.05$ , note the outlying patient, who actually had rapid emptying).

$> 0.008$ ), as is seen in Fig. 4. However, skin temperature diagnosed abnormal solid emptying with a sensitivity of 71% and a specificity of 80%.

Gastric emptying for the whole group of diabetic patients was comparable to that of normals for the first

hour of observation and became slower over time (Fig. 5). The whole group of patients differed significantly from the control group in the slope of solid gastric emptying; the median value for the slope was 0.004 for all diabetic patients compared with 0.007 for controls ( $P = 0.01$  by the Kruskal-Wallis test). The subgroup of diabetic patients with delayed solid emptying ( $n = 8$ ) had significantly different slope (median 0.0029,  $P < 0.05$ ) values from the control group values. The slope values in the subgroup of diabetic patients with nondelayed solid emptying ( $n = 4$ ) were not significantly different (median 0.008,  $P = 0.3$ ) when compared with controls by the Kruskal-Wallis test. When the slope values of the delayed ( $n = 8$ ) and nondelayed ( $n = 4$ ) solid gastric emptying subgroups were compared with the control group values, the median slope values of all three groups were found to be significantly different from one another. These solid gastric emptying curves are shown in Fig. 5. There was no significant correlation between fasting blood sugar or glycohemoglobin levels and the slope of gastric emptying ( $P > 0.05$ ) or any of the autonomic parameters measured.

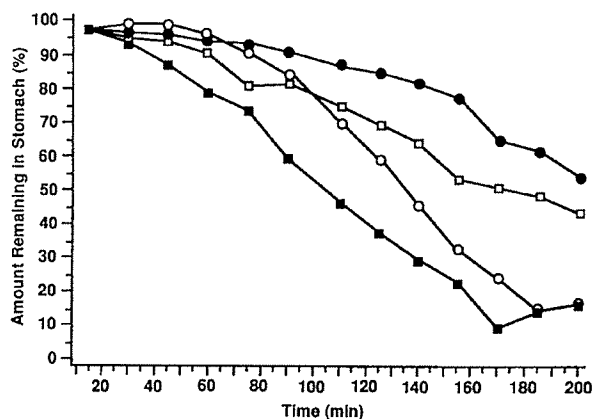


Fig. 5. Median solid gastric emptying curves for the whole group of diabetic ( $n = 12$ ), the subgroup of delayed ( $n = 8$ ) and nondelayed ( $n = 4$ ) solid emptying, and control ( $n = 17$ ) patients. The slope values of the nondelayed solid emptying subgroup were not significantly different from control values ( $P > 0.05$ ), and the slope values of the two subgroups were different from one another and from the control group values ( $P < 0.07$ ). ■, Nondelayed solid emptying subgroup; ●, delayed solid emptying subgroup; □, all diabetic patients; ○, normal controls.

## Discussion

The classic concept of diabetic gastroparesis proposed that cholinergic (parasympathetic) abnormalities are responsible for the observed gastrointestinal dysfunction, a concept often called autovagotomy [3,12,13]. Recent studies evaluating individuals with diabetic autonomic neuropathy involving

the vagus nerve and affecting the cardiac conduction system (resulting in a resting tachycardia with little respiratory-induced RRI variation) did not find any significant correlations between cholinergic abnormalities and gastroparesis, as measured by the slope of gastric emptying for individual patients [6]. These results suggest the presence of mechanisms other than just vagal cholinergic denervation. Indeed, recent morphologic work has not found abnormalities of the vagus nerve or gastric wall in individuals with diabetic gastroparesis [4].

Our measurements of both sympathetic adrenergic and sympathetic cholinergic tone raise the possibility of additional factors associated with the development of gastroparesis. Current concepts of the enteric nervous system suggest that both adrenergic and cholinergic tone may play equally important roles in the maintenance of normal gastrointestinal neurologic function [15]. Thus abnormalities of sympathetic function (particularly sympathetic adrenergic function) may help explain some of the abnormalities observed in diabetic gastroparesis [16,17]. Evidence from other clinical conditions where gastroparesis exists supports this hypothesis. For example, abnormalities of the cervical cord (injuries resulting in quadriplegia) are apt to be associated with delayed liquid gastric emptying [18], since the cervical sympathetic chain has been damaged (at a point above or near there the sympathetic nerves leave the spinal cord). Since reflex vasoconstriction to cold stress is mediated, in part, through the cervical sympathetics, our observations could reflect similar deficits in sympathetic function. One reason for the observed difference in sympathetic adrenergic measures between vasoconstriction to cold stress (which was markedly depressed compared with controls) and PAR (which was only minimally depressed compared with controls) may be explained in part by the length of the nervous fiber tracts involved. Vasoconstriction to a contralateral cold stimulus involves a longer reflex pathway than PAR, which is a venoarteriolar reflex involving local sympathetic fiber axons [19]. The importance of abnormalities of adrenergic tone as a possible factor in gastroparesis are emphasized by our recent reports of uremic diabetic patients showing improvement of both gastric emptying and sympathetic adrenergic tone 1 year after pancreas-kidney transplantation [8-10].

EKG RRI variation involves vagal cholinergic pathways via the vagus nerve and thus would not be affected by abnormalities of sympathetic innervation. The diabetic patients in this study had significantly depressed RRI variation, suggesting severely decreased vagal cholinergic functioning. However, there was no correlation between abnormal vagal cholinergic measurements and solid gastric emptying. In fact, those individuals with delayed solid gastric emptying also had abnormal vasoconstriction,

suggesting a sympathetic adrenergic abnormality. Thus, all the diabetic patients studied had pre-existing vagal cholinergic abnormalities, but the presence of a sympathetic abnormality seems to predict the presence of delayed solid gastric emptying.

The association of the sympathetic cholinergic measures of resting skin temperature with delayed solid emptying values confirms the clinical observation that many gastroparetic patients have cool skin, often associated with multiple diabetic complications. Since skin temperature measurements are easily performed, this observation may warrant further investigation into the clinical application of skin temperature values. Recently, diabetic men with autonomic dysfunction have been found to have abnormal bilateral thermograms after immersion of one hand in ice-cold water [20], indicating abnormal thermoregulation reflexes.

We also noted that two of the patients with nondelayed solid gastric emptying actually had rapid solid gastric emptying. Rapid gastric emptying, both solids and liquids, has previously been reported in a minority of patients with diabetes mellitus, both with and without intestinal symptoms [21-23]. Thus, rapid gastric emptying may be a manifestation of diabetes enteropathy in a minority of patients. This tentative conclusion could have clinical impact and deserves further investigation, especially if abnormal gastric emptying is defined as the presence of a delay in solid emptying only.

This study did not specifically investigate the association between hyperglycemia and gastric emptying, which has been documented recently [24]. Although we did not find any significant correlation between either glycohemoglobin measurements, fasting blood sugar levels and the results of gastric emptying/autonomic testing, our findings do not mean that a relationship between blood sugar and gastric and/or autonomic values does not exist in this group of patients. In addition, our findings of a significant association between certain autonomic values (e.g. abnormal vasoconstriction to cold) and delayed gastric emptying of solids do not eliminate elevated blood sugar values as part of the mechanism of delayed gastric emptying in these patients. However, the existence of a possible relationship between autonomic parameters, blood sugar levels and gastric emptying cannot be addressed by this study.

## Conclusion

In this group of patients with diabetes mellitus and symptoms of gastroparesis, we conclude that vagal cholinergic measurements by EKG RRI are severely impaired, but these measurements do not correlate

with, or diagnose, delayed solid gastric emptying. In addition, sympathetic adrenergic measurements of vasoconstriction to cold correlate with delayed solid gastric emptying and may have use as a diagnostic measure. Sympathetic cholinergic measurements of skin temperature do not correlate as well with delayed solid gastric emptying but may have a possible diagnostic use. Although most patients have delayed gastric emptying, a small number have rapid gastric emptying, which may represent another manifestation of diabetic enteropathy. Noninvasive tests of autonomic function, including measurements of sympathetic autonomic function, may be helpful in the evaluation of patients with diabetes and symptoms of gastroparesis.

## Acknowledgements

The authors would like to thank the staff of the Clinical Research Center (The University of Tennessee, Memphis, USA), the Department of Nuclear Medicine (Regional Medical Center, Memphis, USA), and Dave Wilson for data entry; Dan Davis, Karen Whitehead, and Vicki Bizzle for data acquisition; Frances Kabakoff for technical assistance; Jim Karas for statistical advice; Geneva Reed and Dr Barbara Kuyper for editorial assistance; Dr Robert Fealy and Dr Michael Camilleri for helpful comments; Jeff Horton for figure preparation, and Rebecca Potter for manuscript preparation.

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