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Assessment of Gastric Electrical Activity and Autonomic Function Among Diabetic and Nondiabetic Patients with Symptoms of Gastroesophageal Reflux

ANITA L. JACKSON, MD, HANI RASHED, MD, SERGIO CARDOSO, MD, FRANK WONG, MD, ROBERT WERKMAN, MD, JEROME THOMPSON, MD, and THOMAS L. ABELL, MD

Gastroesophageal reflux disease (GERD) may present differently in patients with diabetes mellitus (DM) than in nondiabetics (NDM). We compared three tests in two patient groups with GERD symptoms: a DM group ($n = 10$) and a NDM group ($n = 13$). The tests were 24-hr esophageal pH, autonomic function testing (AFT), and electrogastrography (EGG). Analysis of the 23 patients revealed the DM group had normal 24-hr pH values (9 of 10 patients, mean pH 3.1 $\pm$ 1.7), while NDM displayed abnormal pH values (9 of 13 patients, mean pH 21.2 $\pm$ 5.9). AFT results were abnormal in DM (demonstrating cholinergic/adrenergic dysfunction), but normal in NDM. EGG values were abnormal in both groups (mean 3.31 $\pm$ 0.1 in each). We conclude that in GERD-symptomatic patients, those with DM frequently have normal 24-hr pH, but abnormal autonomic functioning, in contrast to NDM, who have abnormal 24-hr pH but normal autonomic function. Both groups had identically abnormal mean EGG values.

KEY WORDS: gastroesophageal reflux; diabetes mellitus; autonomic nervous system; stomach diseases.

Gastroesophageal reflux disease (GERD) is one of the most common human diseases (1), often seen in primary care, gastrointestinal, pulmonary, and ENT practices. The diagnosis of GERD is frequently based solely on patients' symptoms of heartburn and indigestion, with or without hoarseness, chronic cough, and/or globus sensation (2, 3) and is confirmed by 24-hr esophageal pH monitoring (4, 5). These symptoms of GERD are commonly seen in patients with diabetes mellitus (DM), particularly those with symptoms of gastroparesis (nausea, vomiting, abdominal pain, bloating/distension, anorexia/early satiety). Our study sought to investigate characteristics of confirmed GERD between two groups of patients (diabetics and nondiabetics), since GERD symptoms occur among both groups. We hypothesized that symptoms of GERD may be expressed through different pathophysiologic mechanisms in these two groups.

Abnormalities of gastroesophageal activity have focused primarily on lower esophageal sphincter (LES) function, gastrointestinal motility disorders, and/or acid hypersecretion. However, more recent reports indicate that the pathogenesis of GERD, including gastric esophageal motor function, may be multifactorial, including autonomic nervous system abnormalities in some patients (6). The physiology of gastroesophageal activity is also controlled in part by a

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From the Departments of Otolaryngology and Medicine (Gastroenterology), University of Tennessee, Memphis, Tennessee.
Address for reprint requests: Dr. T.L. Abell, University of Tennessee–Memphis, 951 Court Avenue, Room 555D, Memphis, Tennessee 38163.

TABLE 1

t *Tests*	*Normal*	*DM (mean ± SE)*	*NDM (mean ± SE)*	P
Age	—	47.2 ± 3.3	50 ± 4.4	0.3
pH	<6	3.1 ± 1.7	21.23 ± 5.9	0.015*
RRI	>34.6†	11.5 ± 3.9	42.0 ± 0.8	0.026*
VR	>1.21‡	1.18 ± 0.07	1.8 ± 0.2	0.004*
VCF Ind.	>35.81	12.7 ± 3.9	43.9 ± 10.9	0.025*
TPA	>3800‡	3652.5 ± 845.1	6303.1 ± 613.5	0.017*
%VC	>81.4†	66.9 ± 8.0	72.7 ± 6.3	0.289
PAR	>27.7†	27.0 ± 11.3	46.0 ± 12.7	0.137
SAF Ind.	>109.1	93.9 ± 15.7	118 ± 14.8	0.267
TAS	>143.7	105.4 ± 17.8	160.9 ± 15.4	0.028*
EGG	<3.3	3.3 ± 0.1	3.3 ± 0.1	0.3

*A significant difference existed between diabetic (DM) and nondiabetic (NDM) patients at $P < 0.05$.
†As previously reported (8).
‡As previously reported (11).

balance of the sympathetic and parasympathetic autonomic nervous systems. Previous reports have hypothesized that abnormal vagal function contributes to the pathogenesis of reflux, since gastric motor function is impaired in some patients with symptoms of upper gastrointestinal motility disorders (7).

Recent work from our autonomic function testing lab has demonstrated that diabetic gastroparesis (6) is associated with an abnormality in sympathetic innervation (8). Recently, electrogastrography (EGG) and autonomic function tests (AFT) have been proposed as noninvasive measures for evaluating gastropathy in DM, since both gastric electrical activity of enteric nervous system (ENS) and autonomic nervous system (ANS) balance may play a role in the pathogeneses of GERD.

This study aimed to compare the standard measure of 24-hr esophageal pH, with AFT and EGG, in two different populations of patients (DM and NDM), all of whom had symptoms of gastroesophageal reflux. We hoped that comparison of these measures might provide further information on the pathophysiology of GERD and evaluated these noninvasive tests for the diagnosis of GERD.

MATERIALS AND METHODS

We studied 23 patients (9 men, 14 women; mean age 48.8 years) with symptoms of GERD. Ten of these patients had DM and 13 were NDM. All 23 patients underwent 24-hr pH monitoring, as well as ANS testing and electrogastrography (EGG). The 24-hr pH was measured by placing a pH electrode through the nose and down into the distal esophagus. Lower esophageal pH was measured over a 24-hr period, recorded, and reported as percent total reflux time below pH 4 (normal <6%).

Autonomic function tests included tests of both vagal cholinergic function (VCF) and sympathetic adrenergic function (SAF). Total autonomic score (TAS) (TAS = VC + PAR + RRI) was reported as well. VCF measures were R-to-R interval (RRI) and Valsalva ratio (VR), as previously reported (9). The RRI was determined from the ECG measures during full inspiration and expiration. The VR was calculated after the patient held an expiration force of 40 mm Hg for 15 sec. VCF index was reported as the sum of RRI + VR.

The SAF measures were postural adjustment ratio (PAR) of capillary blood flow, percent vasoconstriction (%VC), and total pulse amplitude (TPA). SAF was measured by infrared photoplethysmography preceding, during, and after immersion of the opposite hand in ice cold water. Arteriolar capillary blood flow was estimated using frequencies of arteriolar pulse amplitudes measured by a polygraph, as previously reported (9). SAF Index was reported as the sum of VCF + PAR.

The electrogastrogram (EGG), a measure of the gastric electrical activity of the enteric nervous system (normal <3.3), was measured by transcutaneous serosal recordings. This test was performed by placing electrodes on the abdominal skin and recording electrical waves of gastric electrical activity, as previously reported (8).

Results of the 24-hr pH, AFT, and EGG were compared by *t* test and reported as mean ± standard error (SE).

RESULTS

The results of the 24-h pH probe monitoring were quite different between our two patient populations with symptoms of GERD. In the DM group 9 of 10 patients had normal pH values, while in the NDM group 9 of 13 patients had abnormal pH values (DM mean 3.1 ± 1.7%, vs NDM mean 21.2 ± 5.9%; $P = 0.01$) (normal pH is <6).

Measures of autonomic function among DM patients differed significantly from those of NDM patients (Table 1). Vagal cholinergic measures—R-to-R interval (RRI), Valsalva ratio (VR), and vagal cholinergic function (VCF) (VCF = RRI + VR)—were

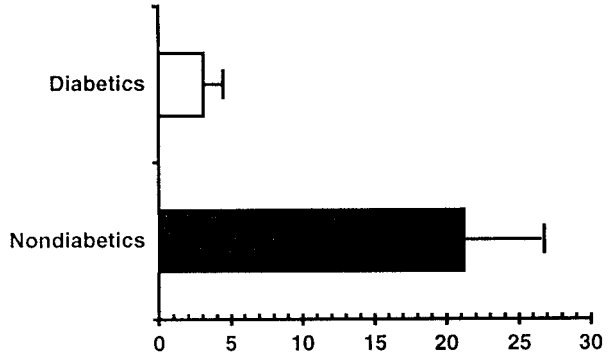

Fig 1. 24-hour pH in diabetics and nondiabetics. There was a statistically significant difference in 24-hr pH between diabetic and nondiabetic patients ($P = 0.05$).

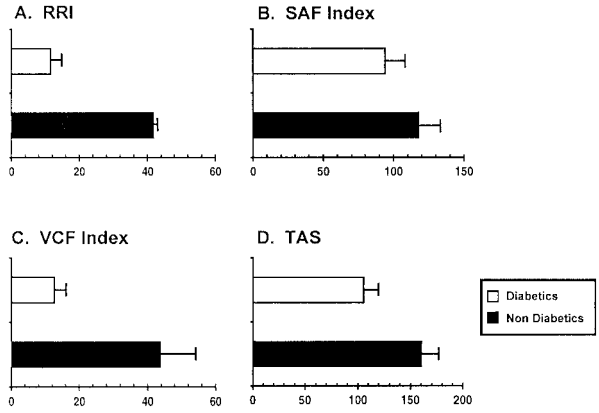

Fig 2. Autonomic function values in diabetics and nondiabetics. The diabetics had significantly abnormal autonomic function values. RRI: R-to-R interval; SAF: sympathetic adrenergic function; VCF: vagal cholinergic function, TAS: total autonomic score. All P values <0.05 between groups.

all significantly different between the two groups. Mean RRI was 11.5 ± 3.9 in DM patients vs 42 ± 0.8 in NDM patients ($P = 0.02$; normal RRI is >34.6). Mean VR was 1.18 ± 0.07 in DM patients vs 1.8 ± 0.2 in NDM patients ($P = 0.04$; normal VR is >1.21). Mean VCF index was 12.7 ± 3.9 in DM patients vs 43.9 ± 10.9 in NDM patients ($P = 0.02$; normal VCF Index is >35.81). Sympathetic adrenergic measures were significantly different only for TPA (mean TPA = 3652.5 ± 845.1 in DM vs 6303.1 ± 613.5 in NDM, $P = 0.01$; normal TPA is >3800). Total autonomic score (TAS = %VC + PAR + RRI) (see Table 1) was significantly different between the two groups (mean TAS = 105.4 ± 17.8 in DM vs 160.9 ± 15.4 in NDM, $P = 0.028$; (normal TAS is >143.7). EGG data was abnormal, and similar in each of the two groups (DM EGG = 3.31 ± 0.1, NDM EGG <3.31 ± 0.1, $P = 0.3$). Data are reported in Table 1 and Figures 1 and 2.

DISCUSSION

In this group of patients with symptoms of GERD, diagnostic tests of adrenergic and cholinergic function demonstrate differences among diabetic and nondiabetic patients. Our results indicate that among these patients, there are two different populations of patients with similar symptoms of GERD, and the difference depends on whether they are diabetic or not.

The results also show that 24-hr pH values are within normal limits for the DM group when compared to the NDM patient group and are statistically significant.

Autonomic function studies also differentiate diabetic and nondiabetic patients with symptoms of GERD. The %VC and PAR values did not show a statistically significant difference between diabetic and nondiabetic groups but were numerically lower in the DM group. Nondiabetic patients have normal %VC (mean 72.7 ± 6.3) and PAR values (mean 46 ± 12.7), whereas DM patients have a borderline normal %VC (mean 66.9 ± 8, $P = 0.28$) and PAR values (mean 27 ± 11.3, $P = 0.13$).

In this group of patients, although EGG values were abnormal in both groups, they did not delineate a difference between diabetic and nondiabetic patient groups with GERD. These patient groups with similar symptoms of GERD may vary in their diagnostic tests of 24-hr pH and autonomic function measures. GERD may be influenced by the autonomic dysfunction as a manifestation of DM. However, the symptomatic nondiabetic patients had abnormal pH values, but normal AFT results. Surface EGG is a measure of gastric electrical activity and the enteric nervous system and can detect a change in gastric frequency but not directional propagation (10).

CONCLUSIONS

In this study, we demonstrated that different populations of patients, each with the clinical symptoms of GERD, differ in their response to several noninvasive tests. These noninvasive measures may help to better identify these subsets of patients with various physiological mechanisms of GERD and provide more information about the pathophysiology of GERD in an effort to better direct specific treatments.

Further prospective research is needed to differentiate the autonomic function variables among both

diabetic patients and nondiabetic patients with or without GERD symptoms. We conclude that within the population of patients with GERD symptoms, a differention may be necessary among those with and those without diabetes mellitus, as these two groups present with the same symptoms but from different etiologies; thus, different approaches to diagnosis and treatment may be needed.

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