Serum Catecholamines and Dysautonomia in Diabetic Gastroparesis and Liver Cirrhosis

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Abstract: *Background:* Plasma catecholamine influences autonomic function and control, but there are few reports correlating them. In this study, 47 individuals (mean age, 38 years) were studied: 19 diabetes mellitus (DM) patients with gastroparesis, 16 with liver disease and 12 control subjects. *Methods:* Noninvasive autonomic function was assessed for sympathetic adrenergic functions as peripheral vasoconstriction in response to cold stress test and postural adjustment ratio (PAR) and cholinergic function as Valsalva ratio, represented by change in R-R intervals. Measurements were compared by analysis of variance and Spearman's correlation, and results were reported as mean ± standard error. *Results:* Plasma norepinephrine (1902.7 ± 263.3; $P = 0.001$) and epinephrine (224.5 ± 66.5; $P = 0.008$) levels, as well as plasma dopamine levels (861.3 ± 381.7), and total plasma catecholamine levels were highest for patients with liver disease, who also had significant negative correlation between norepinephrine level and vasoconstriction ($P = 0.01$; $r = -0.5$), PAR1 ($P = 0.01$; $r = -0.5$), sympathetic adrenergic functions ($P = 0.005$; $r = -0.6$), total autonomic index ($P = 0.01$–0.5) and total autonomic function ($P = 0.01$; $r = -0.2$) and also negative correlation between epinephrine plasma level and total autonomic function ($P = 0.04$; $r = 0.4$). DM patients were next highest in norepinephrine level (133.26 ± 7.43), but lowest for plasma catecholamine; a positive correlation between dopamine level and PAR1 ($P = 0.008$; $r = 0.6$) was also seen in this group. Plasma dopamine levels and spider score correlated negatively ($P = 0.04$; $r = -0.5$) and total plasma catecholamine positively with encephalopathy ($P = 0.04$; $r = 0.5$) in patients with liver disease. *Conclusions:* Plasma catecholamine levels correlated with adrenergic functions in control subjects and patients with DM and liver disease, with no significant correlation seen for cholinergic function.

Key Indexing Terms: Autonomic function tests; Catecholamines; Diabetic gastroparesis; Liver disease. **[Am J Med Sci 2015;350(2):81–86.]**

In the autonomic nervous system (ANS), the adrenergic and cholinergic systems work in harmony in maintaining health; however, this ANS may become disordered in a variety of disease states. Diabetes mellitus (DM) and liver cirrhosis provide particularly interesting insight into system disharmony because they show inconsistent alterations in serum catecholamine that may trigger autonomic responses.[1–4]

The main sources of plasma catecholamine are the adrenal glands, which serve as the major supplier of epinephrine and norepinephrine, and the ANS, the major supplier of dopamine. Abnormalities in autonomic function in patients with DM[4–6] or liver disease[7] and the abnormal catecholamine levels[8] seen in these 2 groups, as compared with those in normal healthy individuals, raise several questions about the cause of dysautonomia in these 2 patient groups.

Heart rate (HR) regulation is mainly controlled by the cholinergic system, while the vascular response to stress, postural and temperature changes are mainly controlled by the adrenergic system. The ANS regulation of the HR, blood pressure, vascular response to stress, postural changes and temperature changes is mediated by the direct effect of the postganglionic nerves on the targeted receptors through neurohormones.

In this study, the authors aimed to correlate total plasma catecholamine levels, including epinephrine, norepinephrine and dopamine, with the autonomic functions measured by the noninvasive autonomic function test (AFT) in 3 groups of individuals: normal healthy subjects as a control group and patients with a detailed history of either DM or liver cirrhosis. They also aimed to analyze the correlation of serum catecholamine and autonomic dysfunction with clinical status in patients with DM and liver cirrhosis.

METHODS

Patients

Forty-seven individuals (mean age, 38 years; 18 men and 29 women) were studied. Individuals were stratified into normal healthy control (12 of 47) subjects, patients with DM (19 of 47) with the clinical evidence of autonomic failure often presenting with the symptoms of gastroparesis and patients with liver cirrhosis (16 of 47). The DM and liver cirrhosis groups were accrued from consecutive patients referred to an autonomic clinic in a tertiary/transplant hospital, who agreed to having catecholamine levels drawn in addition to having autonomic testing performed. For patients with DM, many of who were being evaluated for pancreas transplant, the mean HgbA1c was 8.7, although these results were for 10 of 19 patients. The patients with liver cirrhosis, many awaiting possible liver transplant, were subclassified based on Child-Turcotte-Pugh (Child) scores as A (3 of 16) patients, B (10 of 16) patients and C (3 of 16) patients (Table 1). Of the 16 patients with liver cirrhosis, 7 had clinically significant hepatic encephalopathy and 5 had ascites. Of these 16 patients, 13 had alcoholic cirrhosis, 2 had cirrhosis secondary to viral hepatitis and 1 had primary biliary cirrhosis, and all were also assessed for a history of encephalopathy or the presence of ascites or cutaneous spiders on physical examination. Routine screening of cardiac history eliminated those patients with recent acute ischemic events. The control subjects were volunteers responding to a notice placed in the hospital and were all healthy.

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Submitted April 30, 2014; accepted in revised form April 28, 2015.
The authors have no financial or other conflicts of interest to disclose.
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TABLE 1. Patient characteristics

	Control	DM	Cirrhosis
Mean age, yr	30 (20–49)	39 (23–66)	43 (21–60)
Mean HgbA1c		8.7 (5.7–12.7)	
Mean albumin			3 (1.5–3.7)
Mean total bilirubin			9.3 (0.9–34.8)
Mean prothrombin time			4 (0.1–12.5)
Mean creatinine			1.7 (0.5–3.7)

Methods

After reviewing the medical history, 47 individuals were enrolled in this study. Each individual was instructed not to take any medication(s) for at least 24 hours before the autonomic test. No alcohol, cigarettes or any caffeine products were allowed before the evaluation. The subject was instructed to wear comfortable clothes and abstain from all forms of excessive activities on the day of evaluation. Each participating subject was measured with a standard blood pressure and HR monitor using a Dinamap (model 8100; Critikon, Inc, Tampa, FL), a thermometer (Mon-a-Therm, Inc, St Louis, MO) secured with a tape on the tip of the middle finger on the right hand and an infrared light–emitting diode probe connected to a MedaSonics photoplethysmograph (model PPG-13; MedaSonics, Mountain View, CA) secured with a nonallergic double stick-tape to maintain good skin contact and prevent any additional pressure on the index finger tip of the left hand. The blood flow probe was captured as a waveform recorded on polygraph (model 79D1E; Grass Medical Instruments, Warwick, RI). The change in amplitude and frequency of the formed waves at 1-minute intervals, in response to cold stress and arm posture, represented the blood vessel capacity. No patients showed clinical symptoms of dehydration when studied. The AFT was conducted in the same manner after the initial skin temperature and baseline measurements showed stability for at least 10 to 20 minutes of relaxation in a quiet room with a warm temperature between 22 and 26°C. With subject in a supine position, he/she was instructed to breathe deeply in and out for approximately 6 cycles per minute. During deep inhalation, maximum HR was recorded, and during deep expiration, the lowest HR was also recorded. Subject then was instructed to blow continuously through a mouthpiece connected to a 1-valve tube and a blood pressure monitor, for 10 to 15 seconds with a pressure of 40 mm Hg. Maximum and minimum HRs were recorded.

The individual then assumed a sitting position with left hand and arm in a 45° angle above the heart level rested on a comfortable chair armrest for approximately 5 minutes. After recording a stable peripheral blood flow, the subject was asked to drop his/her arm down freely next to the side of the chair without touching or holding anything for 1 minute. The change in blood vessel capacity was then calculated. Subject was asked to return the hand and arm back to the original position above the heart level and another measurement for blood flow was calculated. Maximum blood flow in 1 minute was recorded and used as a baseline flow at rest. The individual was then instructed to immerse the right hand in ice-cold water for 1 minute, and again, the blood flow on the opposite hand was calculated as before.

The values which were recorded from this standard noninvasive AFT evaluation were used to calculate cardiovagal arch function and adrenergic arch function. While the cardiovagal arch function was represented by the change in HR to either deep or forced respiration, the adrenergic arch function was assessed through the change in peripheral cutaneous blood flow in response to posture and cold stress testing.

Two measurements of vagal cholinergic function were performed through minute-to-minute blood pressure and HR monitoring for HR: the differences in HR in response to deep respiration and forced respiration (Valsalva maneuver) were tabulated. The sum of the percent of change in HR with deep respiration (lowest HR with expiration subtracted from maximum HR during inspiration divided by the lowest HR) is represented by R-R intervals and the ratio of maximum (phase II) to minimum (phase IV) HR ratio during Valsalva (Valsalva ratio).

Two measurements of sympathetic adrenergic function were performed through the changes in peripheral circulation each by using capillary photoplethysmography.[10] Postural adjustment ratio (PAR) was calculated by dividing the capacity of blood vessel with the arm in down position by the value with the hand and arm in a 45° above the heart level and percent vasoconstriction (%VC), in response to 1-minute hand immersion in ice-cold water with a temperature of 14°C, while rate of blood flow was monitored through the opposite hand and calculated as follows: 100 − capacity of blood vessel during cold stress/capacity of blood vessel at rest × 100. %VC is a measure of the change in capillary pulse amplitude caused by reflex vasoconstriction and is expressed as a percentage of change from baseline. Blood vessel capacity during rest was represented by total pulse amplitude "hand" and measured from the amplitude and frequency of wave recorded on the polygraph before the arm movements or the opposite hand's immersion in ice-cold water.

Total autonomic score was calculated as the sum of % VC, PAR and R-R intervals. Total autonomic index and total autonomic function (TAF), calculated in a similar manner, were also tabulated.

All 3 individual groups performed AFT during the daytime. Patients with liver disease also underwent a clinical evaluation for Child scoring, Maddrey scoring and symptoms/signs scoring, including cutaneous evidence of cirrhosis and plus additional laboratory studies (sodium, potassium, albumin, bilirubin, alkaline phosphatase, prothrombin time, gamma glutamine transpeptidase). Measurements were compared by analysis of variance and Spearman's correlation to compare catecholamine levels either between or within the 3 groups, and results were reported as mean ± standard error. This study was approved by the Institutional Review Board of the University of Tennessee-Memphis.

RESULTS

Catecholamine Levels by Group

Individuals were stratified as follows: control group (Cont), patients with DM and patients with liver cirrhosis (Liver).

Analysis of variance showed that plasma norepinephrine level was highest in the Liver group followed by DM and Cont groups (1902.7 ± 263.3, 133.26 ± 7.43 and 110.7 ± 23.3, respectively; $P = 0.001$). Plasma epinephrine levels showed a similar pattern; the Liver group was again the highest followed by DM and Cont groups (224.5 ± 66.5, 37.8 ± 3.2 and 2 ± 0.6, respectively; $P = 0.008$). Plasma dopamine levels were higher in the Cont group (155.7 ± 37.2) than in the DM group (55.6 ± 4.8) but were still highest in the Liver group (861.3 ± 381.7) ($P = 0.026$). Total plasma catecholamine levels were highest in the Liver group (2960.7 ± 502.6) than in the