Arq Neuropsiquiatr 1997;55(2):227-230

CARDIOVASCULAR AUTONOMIC TESTS IN DIABETIC PATIENTS WITH GASTROPARESIS

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ABSTRACT - The aim of this report was to study the cardiovascular autonomic tests in the evaluation of diabetic patients with gastroparesis. Forty diabetic subjects were divided into two groups: one group with gastroparesis (GP, n=20) and another group paired by age and duration of diabetes without any complaint of autonomic neuropathy (DC, n=20) . They were evaluated clinically and submitted to a battery of five cardiovascular autonomic tests. The presence and severity of autonomic neuropathy were defined according to the number of normal cardiovascular tests. Each test had a score: zero (normal), one (borderline) and two (abnormal). The GP group showed a higher abnormal total score in the cardiovascular autonomic test than the group without any complaint (6.6 ± 3.0 vs. 2.7 ± 1.4, $p < 0.01$). These data suggest that diabetic with gastroparesis presents more abnormal cardiovascular autonomic tests than diabetic without autonomic neuropathy and these tests should be included in the evaluation of diabetic patients with gastroparesis.

KEY WORDS: gastroparesis, autonomic neuropathy, cardiovascular autonomic test , diabetic neuropathy.

Testes autonômicos cardiovasculares em diabéticos com gastroparesia

RESUMO - O objetivo deste estudo foi investigar a importância dos testes autonômicos na avaliação de pacientes diabéticos com gastroparesia. Foram estudados 40 diabéticos, divididos em dois grupos: um grupo de pacientes com gastroparesia (GP, n = 20) e outro constituído de diabéticos sem qualquer queixa de neuropatia autonômica (DC, n = 20), pareados por idade e duração do diabetes. Eles foram avaliados clinicamente e submetidos a bateria de cinco testes autonômicos. A presença e a seriedade da neuropatia foi definida de acordo com os testes cardiovasculares anormais. Cada teste teve escore: zero(normal), um (limítrofe) e dois (anormal). O grupo GP teve maior escore total de testes cardiovasculares autonômicos do que o grupo DC ($6,6 \pm 3,0$ versus $2,7 \pm 1,7$, $p < 0,01$). Estes dados sugerem que diabéticos com gastroparesia apresentam maior número de testes cardiovasculares anormais do que o grupo controle e estes testes devem ser incluidos na avaliação diagnóstica do paciente diabético com gastroparesia.

PALAVRAS-CHAVE: gastroparesia, neuropatia autonômica, teste cardiovascular autonômico, neuropatia diabética.

Gastroparesis is a complication of diabetic autonomic neuropathy more frequent in long-standing insulin dependence that has been under poor control for many years, and is usually associated with other chronic microvascular complications, such as peripheral neuropathy, nephropathy and retinopathy. It has also been described in patients with early diabetes or patients in whom diabetes has been under good control[7] as well as in diabetic without autonomic neuropathy[16]. Clinically it manifests as nausea, vomiting, pos-prandial abdominal fullness, early satiety and abdominal pain. The diagnosis is made by delayed gastric emptying as demonstrated by sequencial imaging or tube studies with barium or tecnetium. Impaired vagal innervation due to autonomic neuropathy may

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lead to gastric motor dysfunction. A positive correlation between abnormal cardiovascular autonomic tests and this dysfunction have been reported by some authors based on small numbers of tests of small sample size[3,11,14]. Other authors have found no correlation[2,4,9,18]. Patients with cardiovascular autonomic tests abnormal have a poor prognosis and increased mortality by renal failure and sudden death[6].

In this paper, we analyzed these tests results in a group of diabetic patients with gastroparesis compared to diabetic patients without any complaints of autonomic neuropathy.

SUBJECTS AND METHODS

We have studied 40 patients retrospectively: one group of diabetic subjects with gastroparesis (GP, n = 20), paired by age and duration of diabetes with a group of diabetic patients without any complaint related autonomous nervous system function (DC, n = 20), that were referred to the New England Deaconess Hospital for autonomic evaluation. Thirty eight of them were taking insulin, one of GP group was on glibenclamide and one of DC group was without any medication for diabetes control.

The diagnosis of gastroparesis was made in five patients by gastric emptying time of barium contrast, and in ten others was assessed by sequential scintiscanning with isotopic tecnetium^{99} sulfur coloid. Five of these patients were diagnosed out of New England Deaconess Hospital by gastric emptying time of barium in four and tecnetium in one.

A questionaire was administered that elicited information about symptoms of autonomic neuropathy. In the group of diabetic patients with gastroparesis, nine of them had only gastrointestinal symptoms. Seven patients had also symptomatic postural hypotension and one neurogenic bladdler. The group of diabetic patients control had no complaints compatible with gastoparesis. Thirteen patients of GP group were taking metoclopramide, six were on fluorhydrocortisone and five on medications for hypertension (enalapril in one, captopril in two, clonidine in one and nifedipine in one). In the DC group, two patients were on nifedipine and two in enalapril. In the GP group seven patients had creatinine levels higher than 1,5mg% and two others had proteinuria while in the DC group no one had increase of creatinine levels or proteinuria.

All cardiovascular autonomic tests were performed in the Autonomic Evaluation Laboratory. The patient heart rate and blood pressure measurements were obtained using the Critikon Dinamap Vital signs, monitor 1846 SX, connected to a micro-computer, which analyzed the data. The battery of cardiovascular autonomic tests used included : 1) heart rate response to deep breathing at a frequency of six breaths/min (maximum - maximum heart rate oberved in the eletrocardiogram)[6,17]; 2) heart rate response to the Valsalva maneuver for a duration of 15 seconds with the determination of the ratio between the longest to the shortest heart rate interval observed in the eletrocardiogram[12]; 3) heart rate response to standing up (ratio between 30:15 beat after standing up)[5]; 4) blood pressure decrease response to standing up for one minute[1,6]; 5) blood pressure increase response to isometric exercise with a handgrip dinamometer for three minutes[10]. Each test received a score zero, if normal; one, if borderline; and two, if abnormal . The normal references values of Ewing et al. were applied[6].

Statistical analysis. This was perfomed using Epiinfo, version 5.0, data analysis program. Student's t test was applied for analysis of data normally distributed and analysis of variance (Mann-Whitney and Kruskal-Wallis tests) for data not normally distributed. The differences were considered significant if $p \leq 0.05$.

RESULTS

The groups were similar with respect to age, duration of diabetes and degree of glycaemic control evaluated by glycosylated hemoglobin at the time of autonomic evaluation in 12 diabetics patients of group GP and 14 diabetic patients of group DC at the time of autonomic tests. The mean values and stardard deviation (SD) are on Table 1.

Results of cardiovascular autonomic tests are shown in Table 2.

The heart rate variation during deep breathing and the Valsalva ratio was smaller in the GP than in the DC group.

Blood pressure response to the isometric exercise test (hand grip) was similar in the two groups. The systolic blood pressure fall in the standing up test was higher in the GP group than the DC group ($p < 0.05$).

Table 1. Main characteristics of diabetic patients.

Group	Sex ratio (m/f)	Age (years)	Duration of DM (years)	HbA1c* (%)
Gastroparesis (GP)	6/14	34.0±13.3	15.0±7.2	11.1± 2.9
(ranging values)		16-55	0.5-29	7.1-15.1
Diabetic control (DC)	9/11	34.4±14.4	15.1±7.2	9.6±1.8
(ranging values)		21-59	3-29	7.3-12.4

Data are means ± SD; *HbA1c, glycosylated hemoglobin.

Table 2. Results of cardiovascular autonomic tests in diabetic patients.

Group	Deep breath R/R**	Valsalva ratio R/R**	Hand grip ↑ PA (mmHg)	Standing up ↓ PA (mmHg)	30:15 ratio R/R**	Total score
GP	1.13*	1.24*	7.35	-36.0†	1.03	6.6†
	± 0.21	0.32	6.14	27.4	**0.16**	3.0
DC	1.33	**1.48**	8.10	-6.35	1.13	2.7
	± 0.22	0.25	10.70	8.10	0.21	1.4

Data are means ±SD; R/R **, ratio in the eletrocardiogram; * P<0.05 (GP vs. DC group); †P<0.001 (GP vs. DC group)

The 30:15 ratio after standing up was smaller in the GP group but this difference was not significant (p >0.05).

The total score of all five tests was higher in the GP than in the DC group.

DISCUSSION

The results of this study indicated that cardiovascular autonomic tests in a group of diabetic patients with gastroparesis had a higher score of abnormalities than that of diabetic subjetes control.

Some authors have argued that heart rate response tests are more indicative of parasympathetic integrity, while blood pressure test would be abnormal with more extensive sympathetic lesion. Other authors argue that both parasympathetic and sympathetic innervation are involved in all cardiovascular autonomic tests[6]. In our study, the isometric exercise with a hand grip was unable to distinguish the two groups of diabetic patients. It would be possible that this test is not very sensitive or specific to autonomic damage.

Keshavarzian et al.[11] showed that solid emptying measured by scintiscanning technique was more prolonged in diabetic with peripheral and autonomic neuropathy than diabetic with only peripheral neuropathy or diabetic without neuropatthy. They found a significant correlation between the half time of gastric emptying solid and the severity of neuropathy. Six of eight of their diabetic with gastroparesis had autonomic neuropathy but they did not mention which or how much of these autonomic tests were abnormal. Others studies of diabetic patients with autonomic neuropathy have demonstrated that they have impaired gastric emptying compared to diabetic patients without autonomic neuropathy[2,3,18]. However, Clouse & Lustman[4] suggested that gastrointestinal symptoms are more closely associated with psychiatric illness than to neuropathy. Absence of any correlation between abnormal autonomic tests and gastric emptying is described by some studies[2,9,14]. For these authors in the diabetic autonomic neuropathy syndrome, gastric and cardiac systems are affected

independently. This discordance could be explained by differences in the diabetic population or even in the methodology employed to assess gastric emptying and autonomic neuropathy. Another possibility is that autonomic neuropathy in its earlier stage may show selective involvement as described Soler at al[16] in one diabetic patient with gastroparesis who had normal cardiac response to the Valsalva maneuver and to the change of posture. Other causes of gastroparesis should also be considered in the differential diagnosis[13].

Diabetic patients with gastroparesis have a poor diabetic control because of impredictable oral intake and poor absortion of nutrients as a result of delayed gastric emptying. High blood glucose levels may disturb gastrointestinal motility[8,18]. In a recent paper, Samsom at al.[15] studied antroduodenal motility in 12 insulin-dependent diabetic patients with autonomic neuropathy compared to 12 healthy control subjectes. The blood glucose levels was controlled and kept close to euglycemia in diabetic patients. They found antral hypomotility after dinner but no difference was shown after breakfast. So besides blood glucose level, diet composition also may have influence on gastric motility. In our patients, the groups had similar diabetic control ($p > 0.05$) but we can not discharge that some gastric abnormatilies detected would be caused by abnormal high glucose levels besides autonomic neuropathy.

In conclusion, we suggest that a battery of cardiovascular autonomic tests should be included in the evaluation of diabetics with gastroparesis. It could be useful in the differential diagnosis of other causes of gastroparesis.

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