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IS DIABETES AN AUTONOMIC DISORDER?

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ABSTRACT

Dysfunction of the cardiac Autonomic Nervous System (ANS) in the diabetic heart is involved in cardiovascular morbidity and mortality, and in the development of degenerative complications of diabetes. ***Objectives of the study:*** Compare autonomic profile of diabetic patients and asymptomatic healthy subjects and detect the cardiac autonomic neuropathy (CAN) in patients with diabetes. ***Patients and methods:*** 66 subjects with type 2 diabetes were selected for the study. The following tests were carried out: deep breathing (DB), the isometric contraction or hand grip (HG) 3 minutes and mental stress test. The results were compared to those of a control group which age and sex were matched using the Student t test ($p < 0,005$ as significant). ***Results:*** The groups were subdivided as follows: a group of 66 diabetic patients (including 68% women) average age was 53.9 years ± 9,6 and a group of 60 control subjects, average age was 53,1 ± 8,9 years. Basic heart rate in diabetics was 77,9 ± 12,0 beats/ min vs 65,9 ± 8,7 beats / min in control subjects ($p < 0.01$). Vagal activity at DB was 24.5% ± 17,8 vs 40.1 ± 15,0 in controls ($p < 0.01$). Basic heart rate was negatively correlated to the vagal activity at DB test ($r = - 0,256$, $p = 0,04$). α central sympathetic activity was 20.1% ± 11,1 vs 16, 1% ± 10,9 ($p < 0,05$) and α sympathetic peripheral activity was 18,5% ± 8,9 vs. 14,8 ± 10,5 among controls ($p < 0.05$). ***Conclusion:*** **A**utonomic profile of diabetic patients was in favour of vagal disability, alpha central and peripheral sympathetic hyperactivity. This profile is probably involved in the pathogenesis of type 2 diabetes in worsening insulin resistance and therefore also in the micro and macrovascular complications of type 2 diabetes.

KEYWORDS: Vagal Activity, Sympathetic Activity, Mellitus Diabetes, Deep Breathing, Autonomic Nervous System.

INTRODUCTION

The heart is under permanent control of autonomic nervous system. Sympathetic system tends to speed it up and the parasympathetic nervous system slow it down.

Autonomic nerve damage is a common complication of diabetes and affects approximately 50% of diabetic patients.[1] This complication is most often subclinical, latent, insidious and needs to be diagnosed by autonomic nervous system explorations.[2,3]

Cardiac autonomic neuropathy occurs early in about 6% of patients with newly diagnosed type 2 diabetes.[4] It contributes to the aggravation of degenerative complications and is now considered as probable marker of other microangiopathic complications.[4]

Its impact on public health is significant in view of the known cardiovascular morbidity and mortality: cardiac rhythm disorders, silent myocardial ischemia and cardiac arrest[5], hence the importance of its screening at first time diagnosis Type 2 diabetes as it was recommended by the Health Authority in June 2007.[6]

PATIENTS AND METHODS

Inclusion criteria: Group 1 (n = 66) corresponds to diabetic patients, mean age was 53.9 ± 9.6 years. 68% are women, followed at diabetes consultation and mean glycated hemoglobin (A1C) of 8.3 ± 1.7%.

- Group 2 (n = 60): control group of asymptomatic healthy subjects, perfectly matched by age and sex with group 1. The average age was 53.1 ± 8.9 years. 61 % female and having glucose test less than 1.10 g / l.

Exclusion criteria

We excluded from the study patients with

- Heart rhythm disorders.
- A recent history of heart failure within 6 months.
- A history of a heart attack within 2 years.
- A neurological and / or neuropsychological abnormalities
- Respiratory diseases
- Pregnant women

Study Progress

All explorations of the autonomic nervous system (ANS) tests were performed in the Cardiology A Departement at IBN SINA UNIVERSITY HOSPITAL IN RABAT.

ANS tests were performed in fasting patients after stopping treatment that interferes with the autonomic nervous system for 48 hours. Verbal consent was obtained from all patients.

The patient was placed in supine position in a quiet atmosphere on a tilted table for 30 minutes.

Monitoring of blood pressure (BP) was performed using a Dynamap (Critikon, sxp 18 46) and that of heart rate (HR) using a LCD display screen (LCD 503E, Hellige EK 512 E). Basal BP and HR were measured at rest, every 5 minutes for 30 minutes.

We then process various tests, interspersed with rest periods as described by Ewing.[7,8]

Each autonomic test gave rise to a measure of the stimulation relative to the base state. For sympathetic stimulation illustrated by the measurement of the variation of BP, only the values of systolic blood pressure were analyzed.

Selected tests for vagal and sympathetic response in our studied groups were as follows.[3]

Deep breathing: Six deep breaths are performed (5 seconds for each inspiration and expiration) the examiner raises his hand to tell the patient the level of inspiration and he lowers it for expiration. ECG is recorded continuously during the test at a speed of 25 millimeters per second. Heart rate is measured by determining the RR interval; we exclude from the analysis any aberrant response like extra systoles. The results are expressed in percentages: 100 x [(RRmax-RRmin) / RRmin]. Normal value varies between 25 and 50% according to the subject age, generally higher in younger patients.

Mental stress: The patient is asked to make a quick mental calculation out loud. BP fluctuations and heart rate above 10% indicate α central sympathetic hyperactivity.

Isometric contraction or hand grip (HG - 3 min): Hand pressure is practice by the patient using a dynamometer (isometric contraction). 50% pressure reached of the maximum pressure and maintained for 3 min. It corresponds to α sympathetic as measured by changes in BP.

An increase of 10% in BP is considered normal, above 10% we talk about α peripheral sympathetic hyperactivity.

Statistical analysis: Quantitative variables are expressed as mean plus or minus standard deviation and categorical variables are expressed as numbers and percentages. The quantitative comparison of variations between the two groups is performed using Student's T-test. A value of $p < 0.05$ is considered significant. Statistical analysis is done using SPSS 15.0 software.

RESULTS

The baseline average heart rate

Baseline HR is significantly higher in diabetic patients than in the control healthy group (77.9 ± 12.0 beats / min vs 65.9 beats / min ± 8.7 $p < 0.01$). (Table 1; Figure 1).

Table. 1: Comparison of baseline HR (beats / min) in diabetic subjects (group 1) and asymptomatic controls non-diabetic subjects (group 2).

Groups	Population	Basic HR (C/min)	SD	*p*
1 2	66 60	77,9 65,9	12,0 8,5	*< 0,01*

Vagal activity measure

Response of vagal activity assessed by testing the DB is significantly lower in diabetics than in non-diabetic control subjects (24.5 ± 17.8% vs 40.1% ± 15.0, $p < 0.01$). (Table 2; Figure 2).

Table. 2: Comparison of vagal response (expressed in %) Deep Breathing (DB-X) in diabetic subjects (group 1) and asymptomatic controls non-diabetic subjects (group 2) *p* <0.01.

Tests	Groups	Population	Mean ± SD	*p*
X-DB (%)	1 2	66 60	24,4**± 17,8 40,1 ± 15,0	*<0,001*

The increase in resting HR in the diabetic group, is negatively correlated with vagal response obtained by deep breathing test ($r = - 0.256$, $p = 0.04$). (Figure 1).

Measurement of α sympathetic activity (ASA)

Both central and peripheral α sympathetic activity assessed by the mental stress test is significantly higher in the diabetic group compared to the group of control subjects (20.1% ± 11.1 vs 16 ± 1% 10.9, $p < 0.05$).

ASA measured by the response to isometric contraction test (3 min-HG) is significantly higher in the diabetic group compared to subjects without diabetes (18, 5% ± 8.9 vs 14.8% ± 10.5, p <0.05). (Table 3).

Table. 3: Comparison of Both α sympathetic central (α SC) and peripheral (α SP) in diabetic patients (group 1) and controls subjects without diabetes (group 2) *P<0.05*.

Tests	Groups	Population	Mean ± SD	*p*
α SC (%) stress mental	1 2	66 60	20 ,1* ±11,1 16,1± 10, 9	0,037
α SP HG (3 min) (%)	1 2	66 60	18,5* ±8,9 14, 8± 10,5	0,04

DISCUSSION

Cardiovascular sympathetic and parasympathetic nervous control expressed both in basic and reflex activity facing a disruption of homeostasis response.

We compare, in this study, autonomic profile of 66 diabetic subjects with 60 asymptomatic healthy subjects by analyzing the variability of blood pressure and heart rate at rest and by cardiovascular reactivity testing.

Deep breathing is a very specific test for vagal system exploration[3,9], in fact the steady and slow deep breathing directly affects cardiac parasympathetic activity for respiratory oscillations in heart rate.[10]

Baseline HR is abnormally higher in diabetic patients, the same result was obtained previously by Spallone et al. in 1997.[11] A low variability of HR in DB test in diabetics compared to the control subjects was found indicating vagal deficiency that has already been described by other authors.[1,12]

The increase in resting HR in diabetic group can be mainly explained by the decrease of the suppressive vagal tone in the sinus node which can be aggravated by high glucose and/or insulin therapy.[13]

Central as well as peripheral sympathetic activity in diabetics was significantly higher compared to the group of asymptomatic healthy subjects. This excessive activation of cardiac sympathetic nerves induces an increase in the excitability of the sinus node, an acceleration of discharge in the atrioventricular node, an increase in conduction velocity and an increase

in myocardial contractility. This leads to an increase of the stroke volume, an increase in myocardial oxygen consumption and coronary vasodilatation which coming up against diabetes endothelial dysfunction.[10]

In this work, autonomic dysregulation found in diabetics is vagal deficiency associated with sympathetic hyperactivity. This result is also reported in earlier papers.[1,4,14] These raise the question of whether the vagal nerve damage precedes the occurrence of this sympathetic hyperactivity. In fact there is probably a balance which by reducing a system causes an activation of the other, as previously described in hypertensive patients[15] and in migrainous subjects where the reverse effect occurs: vagal hyperactivity is accompanied by alpha sympathetic system deficiency.[16]

Considering the age-related decline in the vagal response[9], it is likely that the decrease in this response in our diabetic subjects is due to an aging phenomenon, but since the two study groups were matched by sex and age, it would be an impact of diabetes on this activity.

Another question not yet resolved is the relationship degree between the autonomic nervous system and insulin resistance.

The role of the vagus nerve in glucose regulation has been proved.[12] Vagus nerve possesses efferent fibers that project on the pancreas and liver. The stimulation of this fibers causes an insulin release by pancreatic β-cells[12,17], while the stimulation of liver branch of Vagus nerve by hyperglycemia leads to reduction of hepatic glucose production, activates glycogen synthase and therefore increases glycogen production.[12,18]

Hypoglycaemia thus leads to sympathetic activation with increase in production and mobilization of glucose, Whereas hyperglycaemia produces parasympathetic activation, and therefore decrease in glucose production and increase of its storage.[12]

Vagal dysfunction could maintain chronic hyperglycemia causing hyperinsulinemia.[12] It is a hallmark of Type 2 diabetes and has been associated with parasympathetic dysfunction in humans and rats.[12,19,20]

For some authors, vagal denervation is due to the accumulation of sorbitol linked to the activation of the polyol pathway by hyperglycemia[21], but for others only hyperinsulinemia

may lead to this denervation in the presence or absence of hyperglycemia even before clinical diabetes installation.[22]

Central α sympathetic activity is high in diabetics and causes hyper-peripheral α-adrenergic activation responsible of the hypertension occurrence in diabetic patients.[23] It seems that hyperinsulinemia is the cause of the activation of ventromedial hypothalamic nucleus.[24]

Furthermore hyper sympathetic activation maintains chronic hyperglycemia by increased hepatic glucose production and a decrease in glucose utilization by skeletal muscle.[12]

Finally in obese patients, dysregulation of metabolism and immune function are associated with chronic inflammation, a critical step in the pathogenesis of insulin resistance and type 2 diabetes mellitus.[24]

A Danish study (Fredericia Study) showed that a family history of type 2 diabetes have a greater impact on cardiac autonomic function in non-diabetic subjects which is another factor for the genetic syndrome of cardiac autonomic neuropathy.[25]

From the available literature data, our results seem to favor autonomic nervous system involvement in the pathophysiology of type 2 diabetes compared to non-diabetic asymptomatic subjects. The origin of Autonomic Nervous System injury in diabetics and its implication in the pathophysiological mechanisms of diabetes requires long duration prospective studies.

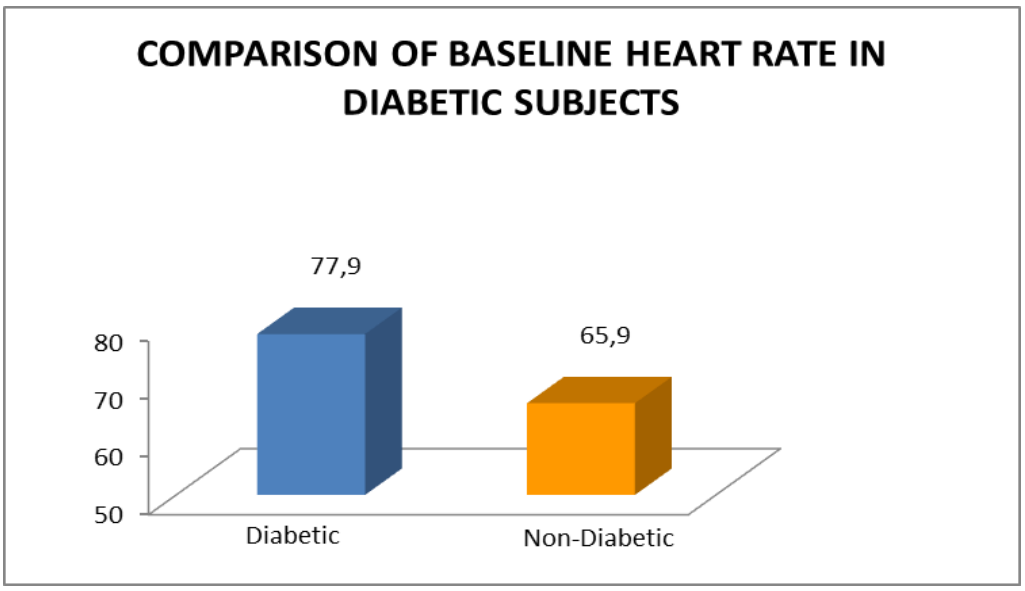

Figure. 1: Comparison of Baseline Heart Rate in diabetic and non-diabetic subjects.

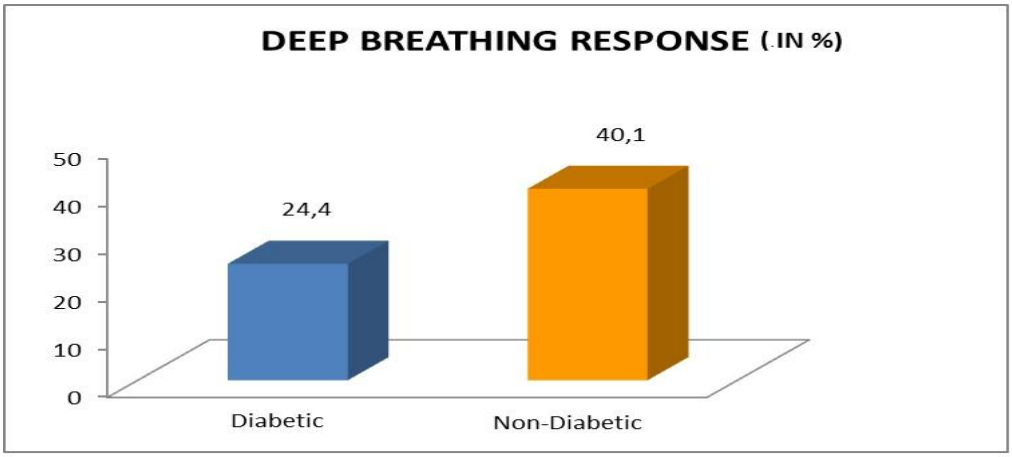

Figure. 2: Deep Breathing Response (expressed in %).

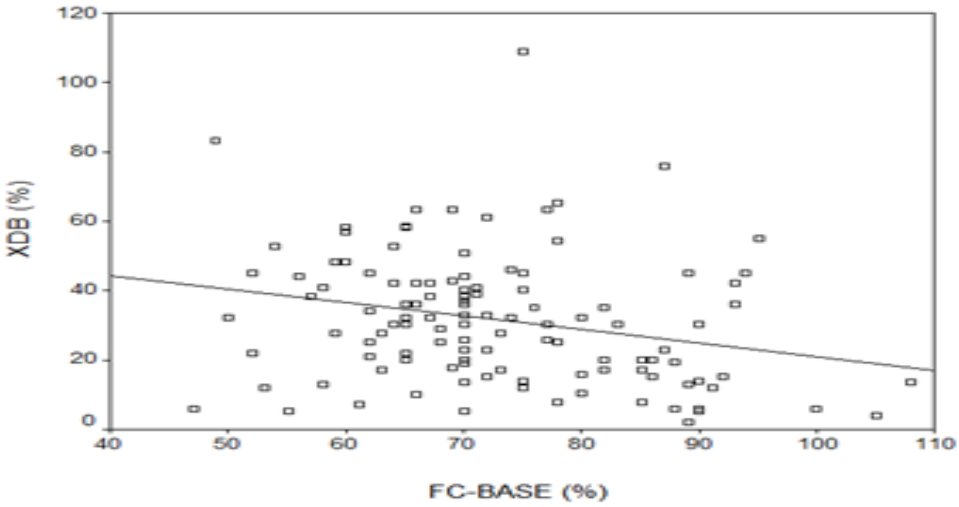

Figure. 3: Correlation between resting heart rate in the group of diabetic and vagal activity obtained by deep breathing test (r = -0.256, P = 0.04).

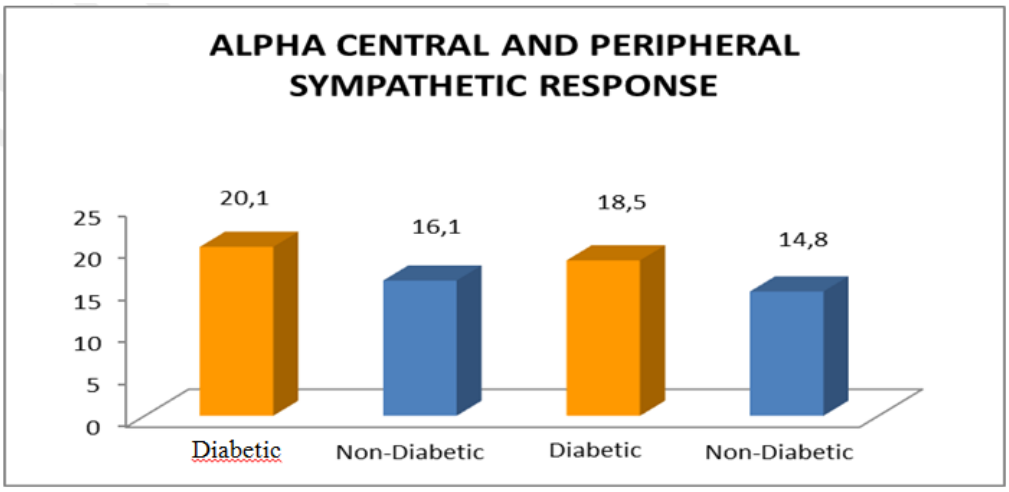

Figure. 4: α central and peripheral sympathetic response.

CONCLUSION

Autonomic profile study of cardiovascular reactivity tests showed a significantly higher sympathetic response and significantly lower vagal response in diabetic patients compared to control subjects without diabetes symptoms. This profile is probably involved in Type 2 diabetes pathogenesis, in insulin resistance worsening and therefore also in the micro and macrovascular complications of type 2 diabetes.

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