

Heart Rate Variability (HRV) is a Powerful Predictor IN the Early Diagnosis of Cardiac Autonomic Neuropathy (CAN) In Patients with Type Two Diabetes Mellitus (DM II)

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Abstract: Purpose: The present study examined whether HRV is predictive of CAN in patients with DMII. **Subjects and methods:** The study group consisted of 50 patients, newly diagnosed with type 2 diabetes mellitus. The control group consisted of 50 healthy subjects. HRV was measured using a 24-hour ECG Holter monitoring system. Time domain parameters used are: SDNN, and SDANN. **Results:** There are significant differences between disease duration. Orthostatic hypotension was found in 14 patients and heart rate increased over 100 at rest was found in 28 patients. HRV parameters are lower in DM group but differences are significant only for SDNN. From the total group, more than half had HRV parameters below the normal range (56%). Of the asymptomatic patients, 14 (28%) had abnormal HRV parameters. Decreased HRV was found in newly diagnosed type two DM. **Conclusion:** HRV is decreased in newly diagnosed DM II. Heart Rate Variability (HRV) is a Powerful Predictor in the Early Diagnosis of Cardiac Autonomic Neuropathy (CAN) In Patients with Type Two Diabetes Mellitus (DM II). [Abdulhalim Salim Serafi. **Heart Rate Variability (HRV) is a Powerful Predictor IN the Early Diagnosis of Cardiac Autonomic Neuropathy (CAN) In Patients with Type Two Diabetes Mellitus (DM II).** *Life Sci J* 2013;10(2):1096-1101] (ISSN:1097-8135). <http://www.lifesciencesite.com>. 153

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1. Introduction:

Cardiovascular diseases are increasing in prevalence in KSA affecting about 10 to 20% of the adult Saudi population (1). Type II diabetes mellitus is increasing in prevalence in KSA affecting more than one fourth of the adult Saudi population (2). Diabetic cardiac autonomic neuropathy (CAN) is associated with a high risk of cardiovascular events and sudden cardiac death.

To investigate the increased risk of cardiovascular events, tests assessing the function of the autonomic nervous system, such as the response of heart rate and blood pressure to maneuvers stimulating the autonomic nervous system, including deep breathing, Valsalva maneuver and standing, allowed to detect signs of CAN in adolescents; however, the sensitivity of such tests in revealing an early impairment of autonomic nervous system proved low.

Several studies found heart rate variability (HRV) to be useful in assessing the dysfunction of the autonomic nervous system in diabetic Patients, but only few HRV parameters were evaluated in most of them (3).

There is evidence that Patients with diabetic cardiac autonomic neuropathy CAN have an increased cardiovascular mortality rate compared with diabetic patients without CAN. As Heart rate variability HRV time domain indexes are strong predictors of malignant arrhythmias and sudden cardiac death, therefore the aim of this study is to investigate the role of HRV in the early diagnosis of diabetic CAN.

Diabetes mellitus is one of the main causes of autonomic neuropathy (3). Cardiovascular autonomic

neuropathy (CAN) cause abnormalities in heart rate control (4). Diabetic autonomic neuropathy frequently coexists with other diabetic complications (5, 6). This complication, which is present in 20-40 % of diabetic patients, is a cause of increased morbidity and mortality (5, 7-9). Cardiac autonomic dysfunction has been diagnosed since the 1970s by maneuvers that elicit cardiovascular reflexes. In recent years, the use of time-domain and frequency-domain parameters of heart rate variability (HRV) has been recommended as a reliable and easy method of diagnosing autonomic neuropathy (4, 7).

There is available evidence about potential usefulness of HRV analysis for the clinical evaluation of autonomic diabetic neuropathy. HRV contains hidden information that can be extracted from tachogram sections of several hundred beats with spectral analysis. Subsequent normalization and the use of a paradigm including standardized stimuli (such as tilt) are commonly employed to assess autonomic cardiac regulation. In the resulting spectra, two major components of similar amplitude are usually observed (at low--LF--and high frequency--HF), their relative power is best appreciated using normalized units that provide an estimate of the balance between sympathetic and vagal modulators activity (10, 11).

In states of sympathetic predominance, such as during orthostatic positions, LF increases and HF decreases. In diabetics, consistent alterations in spectral properties are a frequent early finding: initially a reduction of HRV (i.e. spectral power) is followed by progressive functional denervation, which is associated to severe autonomic dysfunction. The

spectral methodology provides some useful potential advantages in respect to the more traditional approach employing several simple bedside tests. In conclusion, spectral analysis of HRV appears a convenient method to assess various degrees of diabetic autonomic dysfunction: it appears easy to perform, while giving results similar to traditional methods, with greater sensibility (11, 12).

The purpose of this study is to examine the role of HRV in early diagnosis of cardiac diabetic autonomic neuropathy in type two diabetes mellitus.

2. Materials and Methods:

The study was performed on all diabetic patients referred to the elective cardiac clinic at Alnoor specialist hospital in Makkah and king Fahad general hospital in Jeddah Kingdom of Saudi Arabia over a 10-months period. All patients were considered suitable for the study provided they were not on any specific anti-arrhythmic drugs, although all patients were on a combination of nitrates, calcium channel blockers, or anticoagulant medications. All Patients with coronary heart diseases was excluded from the study. Patients who were on an antiarrhythmic agent known to affect the Heart rate variability (HRV) were also excluded, as were patients who were on angiotensin converting enzyme (ACE) inhibitor treatment.

An echocardiographic examination was performed on every patient and a twelve lead electrocardiogram (ECG) will be obtained. All patients was connected to a 24-hour Holter monitor recording. Subjects whose 12 lead ECGs had bundle branch block, atrial fibrillation, or significant ischemic changes was also excluded. 50 patients was entered in the study and another 50 control subjects. A total number of 100 patients was finally entered into the study.

All patients was connected to a 24-hour Holter monitor recording. Patients were instructed to wear

the recorder for 24 hours. Every patient was given a sheet to record any symptoms they developed and the exact time to correlate it later with the analysis of the recorder. Lifecard CF (Reynolds) was used for recording. At least two leads were recorded for each patient. All recorders was connected by professional technicians taking into account the standard criteria for their connection. Attention was taken in placing the electrodes on the patient's chest, since poor electrode contact will produce technically inadequate recordings. Analysis of the recordings was done by professional technicians using Pathfinder 700. If the card recording was not of good quality, or there was too much artefact, the data was discarded and the patient was excluded from the study.

The Lifecard CF is a compact Holter Ambulatory ECG Recorder utilizing a digital storage technique to store the ECG recording onto a Compact Flash (CF) card. The lifecard CF is small and lightweight and provides continuous recording of 2 or 3 channels of ECG. It has a built in display that enables you to monitor the ECG during connection. This enables you to verify the ECG quality before starting the recording. The lifecard CF requires only one AAA battery for 24 hours of recording. Cables cannot easily be accidentally disconnected by the patient. The patient Event button on the front of the Lifecard CF enables the patient to indicate symptomatic episodes in the recording for correlation with the patient data analysis.

Parametric and non-parametric statistical methods was employed for analysis of the results of this study. Values will be expressed as means \pm standard deviation. Differences in the frequencies of discrete variables was tested by Pearson Chi squared tests. A *P* value of less than 0.05 was taken as significant.

3. Results:

Table 1. Demographic characteristics of the study group.

PARAMETERS	DM	CONTROL
NUMBER	50	50
GENDER MALES	32 (64%)	32
GENDER FEMALES	18 (36%)	18
AGE	55 \pm 7.7	50 \pm 6.9
DISEASE DURATION (Years)	3.2 \pm 0.3	NA
FASTING BLOOD SUGAR (mg%)	169 \pm 57	81 \pm 13
HbA1C(%)	7.2 \pm 1.6	4 \pm 2
Cholesterol	236 \pm 67	165 \pm 39
Triglycerides	183 \pm 93	110 \pm 50
Insulin Treatment	12 (24%)	NA
Oral Hypoglycemic (Sulfonylurea)	14 (28%)	NA
Oral Hypoglycemic (Biguanids)	26 (52%)	NA

Table 2. Demographic characteristics according to the presence and absence of symptoms.

PARAMETERS	SYMPTOMATIC	NON SYMPTOMATIC
NUMBER	50	50
GENDER MALES	8 (16%)	24 (48%)
GENDER FEMALES	6 (12%)	12 (24%)
AGE	55 ± 3.7	53 ± 2.3
DISEASE DURATION	3.3 ± 0.5	2.1 ± 0.3
FASTING BLOOD SUGAR	163 ± 41	141 ± 27
HbA1C(%)	7.9 ± 0.5	6.7 ± 0.3

Table 3. Heart rate variability parameters according to the presence and absence of symptoms.

PARAMETERS	SYMPTOMATIC	NON SYMPTOMATIC
SDNN	101 ± 23	93 ± 19
SDANN	83 ± 17	79 ± 13

4. Discussion:

Cardiovascular autonomic neuropathy (CAN) is associated with several abnormalities in autonomic cardiovascular function. Subclinically, the disease is defined by cardiovascular reflex testing, which may have prognostic implications. Clinically, the impairment in autonomic function is associated with resting tachycardia, exercise intolerance, orthostatic hypotension, intraoperative cardiovascular instability, silent myocardial infarction (MI), ischemia, and increased mortality (13, 14).

CAN is best evaluated using heart rate variability (HRV) on 24-hours recordings. A reduction in time-domain parameters of heart rate variability seems not only to carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy [15-18]. In diabetic patients without evidence of autonomic neuropathy, decreased heart rate variability can occur very early due to parasympathetic dysfunction. In advanced cardiac autonomic neuropathy all the components of HRV are reduced (both for sympathetic and parasympathetic activity).

In our study, we found a positive correlation between disease duration and HRV parameters, and the presence of cardiovascular symptoms. The correlation between disease duration and autonomic damage is still under debate. As we already said, at the time of diagnosis, a reduced HRV is frequently discovered in type 2 DM patients, which reflects the manifestation of the asymptomatic process during many years. HRV is decreased as early as three years from diagnosing DM II. The connection between autonomic neuropathy and disease duration of diabetes and patient's age are still unclear.

On the other hand, symptoms and signs of autonomic dysautonomy may be stable over time, in type 2 DM patients (19). This suggests the need of reliable, objective diagnostic tools, other than clinical ones, to allow early risk stratification. Exercise

tolerance is limited as a result of impaired sympathetic/parasympathetic response. For diabetic patients suspected of CAN, cardiac stress testing should be performed before beginning an exercise rehabilitation program (20). The use of heart rate to evaluate exercise tolerance may be inappropriate in these patients, as maximal heart rate is depressed in patients with CAN.

Exercise intolerance is usually due to impaired augmentation of cardiac output resulting from inadequate sympathetic modulation. Persistent sinus tachycardia can occur and there may be no variation in heart rate during activities that normally increase parasympathetic vagal tone, such as deep breathing and the Valsalva maneuver. Sympathetic tone may be increased during the day and parasympathetic tone decreased at night, which may predispose to nocturnal arrhythmogenesis (21, 22). Considerable interest has centered upon the role of abnormal myocardial electrical activity in arrhythmogenesis including, for example, QT prolongation and altered ventricular repolarization.

In the EURODIAB Type 1 Complications Study, the prevalence of QT prolongation was 16 percent overall (11 percent in men, 21 percent in women) (23). Cardiac denervation can occur in diabetic patients with advanced autonomic neuropathy. It is characterized by a fixed heart rate, in the range of 80 to 90 beats per minute, and is associated with painless myocardial infarction and sudden death.

At least two meta-analyses of diabetic patients have found that cardiovascular autonomic neuropathy is associated with an increased risk of mortality (24,25). In an earlier meta-analysis, the mortality of autonomic neuropathy-free subjects over 5.5 years was approximately 5 percent, but this increased to 27 percent with the onset of abnormal cardiovascular reflex tests (24). In a subsequent meta-analysis, the magnitude of the association was stronger for studies that required more than one abnormality of

cardiovascular function to define cardiovascular autonomic neuropathy (25).

Longitudinal studies of patients with CAN have typically found mortality rates over five years ranging between 16 and 53 percent (mean about 30 percent) (26 – 30). Although the majority of deaths result from associated macrovascular and microvascular disease, cardiorespiratory arrest secondary to autonomic denervation has been implicated in some diabetic patients (30, 31). In the EURODIAB Prospective Complications Study of over 2700 subjects with type 1 diabetes, an annual mortality rate of 5 per 1,000 person-years was reported, with peripheral neuropathy (standardized hazard ratio [SHR] 1.88, 95% CI 1.06-3.35) and autonomic neuropathy (SHR 2.40, 95% CI 1.32-4.36) being the most important risk markers for mortality (32).

Despite the evidence that CAN is associated with increased cardiac morbidity and mortality, sudden cardiac death in patients with CAN may have a stronger relationship with atherosclerotic heart disease and nephropathy than with CAN itself. In the Rochester Diabetic Neuropathy Study (RDNS), a prospective, longitudinal, population-based study, 21 cases of sudden cardiac death occurred in 462 patients with diabetes (151 with type 1) who were followed for over 15 years (33). All 21 with sudden cardiac death had evidence of preceding severe atherosclerosis and myocardial damage. After adjusting for ECG abnormalities (including evolving or previous Q wave changes indicative of myocardial infarction, left bundle branch block, or pacing) and stage of nephropathy, autonomic dysfunction was not significantly associated with sudden cardiac death.

Conversely, in a prospective observational study that followed patients with type 1 diabetes who had nephropathy (n = 197) or no nephropathy (n = 191) for 10 years, the presence of cardiovascular autonomic neuropathy (as measured by decreased heart rate variability) in the patients with nephropathy was an independent risk factor for cardiovascular morbidity and mortality (34).

Studies reporting the highest mortality rates have typically enrolled symptomatic patients with abnormalities of both the sympathetic and parasympathetic divisions of the autonomic nervous system. Postural hypotension appears to predict a poorer prognosis (29). The presence of cardiovascular autonomic neuropathy (CAN) is associated with adverse cardiac outcomes and with silent ischemia, as illustrated by the following studies:

A study of 120 patients with type 1 or type 2 diabetes and no history of myocardial infarction or angina but at least two additional cardiovascular risk factors followed for an average of 4.5 years found that a major cardiac event was significantly more common

in patients with CAN than in those without CAN (24 versus 7 percent) (35).

A meta-analysis of 12 cross-sectional studies found that patients with CAN had a significantly higher frequency of silent myocardial ischemia than patients without CAN (pooled prevalence rate ratio 1.96, 95% CI 1.53-2.51) (13).

Conclusions and Recommendations:

HRV is decreased in newly diagnosed DM II. Heart Rate Variability (HRV) is a Powerful Predictor in the Early Diagnosis of Cardiac Autonomic Neuropathy (CAN) In Patients with Type Two Diabetes Mellitus (DM II).

It is important that autonomic dysfunction can be detected at the time of diagnosis, correlates with poor glycemic control; there is a long period of time in which patients are asymptomatic but the disease progress; this so called subclinical autonomic neuropathy could and should be detected using autonomic function tests, including 24-hour Holter monitoring. Waiting for symptoms to appear is not recommended, as clinical signs and symptoms not always progress, so are not reliable tools in early diagnosis risk stratification.

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