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Time and Frequency Domain Analysis of Heart Rate Variability and their Correlations in Diabetes Mellitus

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***Abstract*—**Diabetes mellitus (DM) is frequently characterized by autonomic nervous dysfunction. Analysis of heart rate variability (HRV) has become a popular noninvasive tool for assessing the activities of autonomic nervous system (ANS). In this paper, changes in ANS activity are quantified by means of frequency and time domain analysis of R-R interval variability. Electrocardiograms (ECG) of 16 patients suffering from DM and of 16 healthy volunteers were recorded. Frequency domain analysis of extracted normal to normal interval (NN interval) data indicates significant difference in very low frequency (VLF) power, low frequency (LF) power and high frequency (HF) power, between the DM patients and control group. Time domain measures, standard deviation of NN interval (SDNN), root mean square of successive NN interval differences (RMSSD), successive NN intervals differing more than 50 ms (NN50 Count), percentage value of NN50 count (pNN50), HRV triangular index and triangular interpolation of NN intervals (TINN) also show significant difference between the DM patients and control group.

***Keywords*—**Autonomic nervous system, diabetes mellitus, frequency domain and time domain analysis, heart rate variability.

I. Introduction

THE analysis of heart rate variation is becoming a powerful tool for evaluation of autonomic nervous system (ANS) activities [1]. The interval between adjacent QRS complexes is termed as the normal to normal (NN) or the R to R (RR) intervals. The variation of RR interval is referred to as the heart rate variability (HRV) [2]. Among the different available non-invasive techniques for assessing the autonomic status, HRV has emerged as a simple method to evaluate the sympathovagal balance at the sinoatrial level [3].

The sinus node is subject to both sympathetic and parasympathetic (vagal) effects. It is well accepted that conditions such as assuming an upright position, mental stress, and exercise are associated with an augmentation of sympathetic tone. In contrast, vagal tone is high during resting conditions. In normal subjects, both sympathetic and parasympathetic tone fluctuates throughout the day [4]. HRV indices such as the ratio of the low-frequency (LF) to high-frequency (HF) power or the fractional LF power have been used to describe sympathovagal balance. In the absence of any sympathetic or parasympathetic input to the sinus node, the sinus node fires at its intrinsic rate or R-R interval. When vagal effects predominate, the heart rate is less than the intrinsic heart rate; when sympathetic effects predominate, the heart rate is greater than the intrinsic heart rate [4]. It was found that the HRV decreases with age and for an individual, the HRV is maximum during sleep. It is also rate dependent i.e. the HRV is more at lower heart rates [5].

HRV analysis has been used to investigate a variety of clinical situations including diabetic neuropathy, myocardial infarction (MI), congestive heart failure (CHF) and sudden death [3]. The parasympathetic function is reduced early in the development of cardiovascular autonomic neuropathy (CAN) and HRV induced by deep breathing is almost exclusively mediated by parasympathetic fibers. Recently deep breathing HRV (DB-HRV) have been shown to be an independent prognostic marker after MI [6]. Decreased standard deviation of NN intervals (SDNN) predicts mortality in CHF [2]. Abnormal non-linear HRV may predict sudden cardiac death [7].

A. Prevalence of Diabetes

Diabetes mellitus (DM) is a major, fast growing and one of the most prevalent health issues facing the world community, especially, the developing countries [8]. It may be considered as ‘a group of diseases with one thing in common - a problem with insulin’. World health organization (WHO) has estimated that in 2006, at least 171 million people worldwide had diabetes. WHO expects that, the same would affect more than 350 million people in 2025. People with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30-40 times more likely to undergo amputation, two to four times more likely to develop myocardial infarction and twice more likely to suffer a stroke than non-diabetics. Diabetes related complications ranging

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from poor healing to cardiovascular diseases [9] - [11].

Autonomic neuropathy (AN) is one of the common chronic complications of DM associated with higher morbidity and mortality in symptomatic patients. This is possibly because it affects autonomic regulation of the sinus node, reducing HRV, which predisposes to fatal arrhythmias. AN is characterized by widespread neurological degeneration affecting the small nerve fibers of parasympathetic and sympathetic branches of autonomous nervous system [12]. Diabetic cardiac autonomic dysfunction may cause lethal arrhythmia and sudden cardiac death [13]. Type 2 DM [noninsulin dependent diabetes mellitus (NIDDM)] is an endocrino-metabolic disease that is associated with cardiovascular changes related to the autonomic nervous system [14]. Autonomous nervous system abnormalities may occur quite early in the course of diabetes, followed by a continued gradual decline. Early detection of subclinical autonomic dysfunction in diabetic individuals is important for risk stratification and subsequent management, possibly including pharmacologic and lifestyle interventions [12].

Studies show that in one third of the DM patients there is an early stage of autonomic neuropathy detectable by testing HRV prior to the manifestation of DM [12]. The degree of autonomic dysfunction associated with DM is related to the severity and duration of the disease. Reduction of HRV parameters seems to carry not only a negative prognostic value but also precedes the clinical expression of cardiovascular autonomic neuropathy. Parasympathetic nervous system dysfunction has been identified as a risk factor in childhood obesity

Although different tests like autonomic reflex testing associated with autonomic nervous system function [13] and myocardial scintigraphy with I-metaiodobenzylguanidine (MIBG) can be used to detect AN in people with diabetes [15], time domain and frequency domain analysis of the HRV is simpler and easier. More importantly the use of time domain and frequency domain analysis of RR interval allows early detection of autonomic dysfunction as it can detect changes before clinical signs are evident and there by allowing earlier treatment.

The aim of our study was to quantify the difference in the ANS activity of DM patients with respect to healthy subjects. We have analyzed the HR data of normal healthy persons and DM patients using time domain and frequency domain methods.

II. Subjects And Methods

Electrocardiograms (ECG) were recorded in a multi speciality hospital (Santhy hospital, Omassery, Calicut, Kerala, India) using the BIOPAC™ MP 100 data acquisition system and the associated AcqKnowledge® software. The sampling rate of the ECG was 200 Hz. Patients were selected from the departments of general medicine and orthopedics. ECG of 16 patients suffering from DM and of 16 healthy volunteers were recorded in the relaxed lying position for 60 minutes. The control group included 10 male and 6 female non-smoking volunteers without DM or any cardiac disorders. The DM group was age and sex matched with the control group. The subjects under study were in the age group of 50 - 70 years (58.5±6.42) and the duration of diabetes for the patient group was 5 -15 years. The ECG recording was performed on each investigated subject during day time, after informing them on the purpose of this study and obtaining consent. The recordings of ECG of all subjects were done by the same person of our team in order to avoid any inter–observer error. Preprocessing of the recorded data was done using Pan and Tompkinson's algorithm and heart rate computation were done using AcqKnowledge® and MATLAB® software [16]. Error due to the movement artifacts was manually edited. Time and frequency domain measures were computed for different HR data. Details of the measures used for HRV analysis are given below.

A. Time Domain and Frequency Domain Analysis

The time domain measures used for the analysis are standard deviation of all NN intervals (SDNN) in seconds, square root of the mean of the sum of the squares of differences between adjacent NN interval (RMSSD) in milliseconds (ms), number of adjacent NN intervals differing more than 50 ms. (NN50 count), percentage of difference between adjacent NN intervals differing more than 50 ms. (pNN50 %), the integral of sample density distribution of RR intervals divided by the maximum of the density distribution (RR triangular index) and baseline width of the minimum square difference triangular interpolation of the maximum of the sample density distribution of RR intervals in seconds (TINN). Standard deviation (STD) of the mean heart rate per minute is also computed.

The HRV is comprised of multiple frequencies. Frequency domain method analyses this waveform by looking at the different frequency components of the waveform. The two main frequency components that represent ANS activity are the low frequency (LF) components (0.04 to 0.15Hz) and the high frequency (HF) components (0.15 to 0.4 Hz). Frequency domain measures confirm that the LF and HF oscillatory components are relative indices of cardiac sympathetic and vagal activity respectively and HF and RMSSD indicate parasympathetic activity [13]-[16]. We have also evaluated and analyzed the very low frequency (VLF) components (0.003 to 0.04 Hz) peak, VLF power, % VLF power in the signal, LF peak, LF power, % LF power, LF power in normalized unit, HF peak, HF power, % HF power, HF power in normalized unit and the ratio LF/HF. Normalized units are obtained by the equation.

$$LF\ or\ HF\ norm\left(nu\right)=\frac{LF\ or\ HF\left(ms^2\right)\times 100}{Total\ power\left(ms^2\right)-VLF\left(ms^2\right)}$$

Frequency domain analysis was done by non- parametric

[fast Fourier transform (FFT) based] method.

III. Results

Time domain and frequency domain measures of HRV were computed for the RR intervals of healthy volunteers and DM patients. Results of analysis are presented in tables I and II. Table I summarizes the results of the frequency domain analysis by non– parametric method, based on FFT. According to table I, it can be seen that the VLF power, LF power, LF % power, LF power (nu) and HF power of the RR intervals series of DM patients were significantly lower than those from control group, ($p<0.05$). The HF power (nu) of the signals

TABLE I
SUMMARY OF THE RESULTS FOR THE FREQUENCY DOMAIN ANALYSIS

Indices	Control Group	Diabetes Mellitus	p Value
VLF Peak(Hz)	0.0219±0.0058	0.0201±0.0061	0.6167
VLF Power (ms^2)	371.8±354.8495	49.2±85.3148	0.0117
VLF % Power	31.88±14.6713	40.87±14.5463	0.2363
LF Peak(Hz)	0.0639±0.0226	0.05±0.0087	0.0696
LF Power (ms^2)	476.4±307.2401	55±123.1025	2.37e-04
LF % Power	46.71±12.6228	28.95±8.2953	0.0087
LF Power(nu)	68.54±10.2309	50.66±18.7156	0.0163
HF Peak(Hz)	0.2779±0.0906	0.244±0.0896	0.4692
HF Power (ms^2)	260.7±237.2959	85.7±223.3766	0.0097
HF % Power	21.42±8.1686	30.18±15.3245	0.0609
HF Power(nu)	31.46±10.2309	49.34±18.7156	0.0163
LF/HF	2.5722±1.3967	1.4812±1.4019	0.0996

from DM patients was considerably higher than those from control group, with p value 0.0163. There was no significant difference in VLF peak, VLF % power, LF peak, HF peak, HF % power and LF/HF ratio.

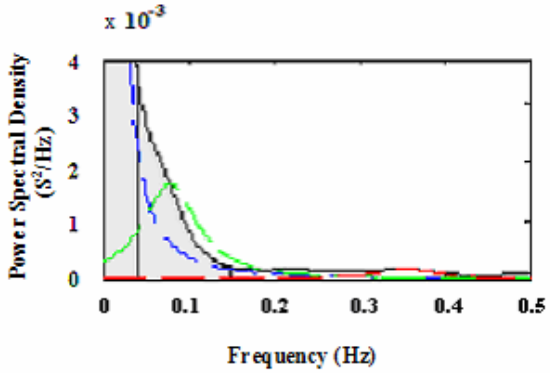

Fig. 1 Power Spectral Density of the RR interval of a 62 year old woman suffering from diabetes for the last 15 years.

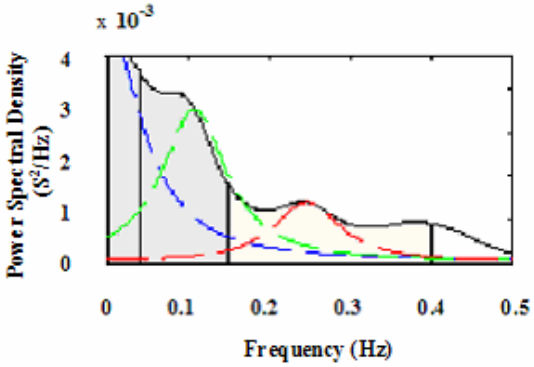

Fig. 2 Power Spectral Density of the RR interval of a 55 year old healthy volunteer.

From figures 1 and 2 it can be seen the Power Spectral Density is shifted towards the low frequency side in the case of the diabetic patient.

TABLE II
SUMMARY OF THE RESULTS FOR THE TIME DOMAIN ANALYSIS OF HR DATA

Indices	Control Group	Diabetes Mellitus	p Value
SDNN (seconds)	0.0464±0.0992	0.0153±0.0147	6.78e-05
RMSDD (ms)	41.43±22.0886	16.02±19.2761	0.0037
NN50 Count	582.8±620.1397	83.2±245.2191	0.0148
pNN50 Count	19.45±20.69	2.76±8.1668	0.0146
HRV Δlar Index	0.0984±0.0407	0.0315±0.0234	1.48e-04
TINN (ms)	316.5±109.3539	164.5±110.3391	0.0032
Mean RR(sec.)	0.9278±0.1294	0.7168±0.0606	1.16e-04
Mean HR (per min.)	66.206±10.2297	84.371±7.2996	1.26e-04
STD (1/min.)	3.538±1.2075	1.771±1.3047	5.28e-04

The results of time domain analysis are summarized in table II. It can be seen from this table that there is a decline in the time domain measures SDNN, RMSDD, NN50 count, pNN50 count, HRV Δlar Index, TINN, Mean RR interval and STD (1/Min.) for the DM patients and the mean HR of the DM patients was significantly higher than that of the control group.

IV. Discussion

HRV analysis has gained much importance in recent years, as a technique employed to explore the activity of ANS, and as an important early marker for identifying different pathological conditions. DM is a disease in which the cardiac autonomic activity is progressively compromised. Our investigation indicates that different time domain and frequency domain measures of HRV would be able to provide valuable information regarding the autonomic dysfunction due

to DM

V. CONCLUSION

Time domain and frequency domain analysis of the RR interval variability of diabetic and normal subjects shows that there is significant difference in these measures for DM patients with respect to normal subjects. Variation of the HRV parameters indicates changes in ANS activity of DM patients. This can provide valid information regarding autonomic neuropathy in people with diabetes. It may be noted that these methods can detect changes before clinical signs appear [2]. So we can expect that these measures enable early detection and treatment/subsequent management of patients and thus can avoid acute and chronic complications.

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