Proceedings of the 9th World Congress on Electrical Engineering and Computer Systems and Sciences (EECSS'23)
Brunel University, London, United Kingdom – August 03-05, 2023
Paper No. ICBES 164
DOI: 10.11159/icbes23.164

Non-invasive Assessment of Diabetes from sub- Heart Rate Variability: Coherence with HbA1c Test

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Abstract **-** Cardiac autonomic regulation reflects in heart rate variability (HRV). The dysfunction in the regulation caused by type 2 diabetes mellitus (T2DM) shows a reduction in the amplitude of HRV. Resting HRV and fasting HbA1c are recorded for six T2DM subjects. Resting HRV is recorded for fifteen control subjects. When compared to control subjects, the T2DM subjects exhibit a significantly lower low frequency (LF) power ($p < 0.05$) and non-significantly lower high frequency (HF) power. Compared to HF-HRV, which has a correlation coefficient of -0.4109, the LF- HRV exhibits a positive correlation with HbA1c values of 0.9027. The sub-LF-HRV (0.062-0.084 Hz) has a correlation coefficient of 0.89 with HbA1c in contrast to the rest sub-bands. Similarly, the sub-HF-HRV (0.35-0.4Hz) has a correlation coefficient of -0.4375 with HbA1c in contrast to the sub-bands. The reconstructed time domain signal shows the periodic contraction and expansion of LF and HF signals mimicking the cardiac function.

Keywords**:** HRV, sub-LF-HRV, sub-HF-HRV, HbA1c

1. Introduction

Diabetes in general has risen over time across the world and age groups as a global epidemic. In India and China, over half of all people with type 2 diabetes mellitus (T2DM) reside [1]. Type 2 diabetes in children, adolescents, and adults is of major concern. The distinct pathophysiological state of T2DM has two components such as inhibition in glucose metabolism by fat, muscles, and liver cells (insulin resistance) and reduced functionality of pancreatic β-cells to compensate for the resistance [2]. Therefore the concentration of glucose rises in the blood. The structural change of red blood corpuscles (RBCs) due to glucose molecule in the blood causes vascular endothelial cell dysfunction and affect blood viscosity and arterial wall tension [3], increasing the risk of cardiovascular mortality. Cardiovascular mortality has an association with cardiac autonomic neuropathy (CAN) [4]. The CAN- accompanying with and without diabetes can be assessed through heart rate variability (HRV) [5]. The HRV shows the change in heart rate over time from an electrocardiogram (ECG). The non-stationarity of the rate change is due to autonomic neural regulation of the circulatory system and the heart itself [6]. The neural control has sympathetic and parasympathetic branches governing the heart rate. Both branches are complementary to each other. An increase in sympathetic nervous system (SNS) accelerates the rate and an increase in parasympathetic nervous system (PNS) activity decelerates the rate. The HRV has time [7], geometric [8, 9], Frequency [10], and nonlinear parameters [9, 11, 12, 13, 14] which carry the information of autonomic nervous system (ANS) activity. Any one or all of the parameters can be measured from ECG for diabetes. However, the current study only focuses on the frequency domain analysis. The following Table-1 shows various frequency bands present in the HRV with their significance. The respiration has the influence in shifting the frequency zones and in literature the significance of the above division of frequency bands is not concrete. Further division of frequency bands may help in finding the relationship between ANS activity and the HRV. Certain frequencies and their amplitude of it in HRV may have a strong correlation with the magnitude of glycated hemoglobin measured by the HbA1C test. The HbA1c test measures the average value of glucose over a period of 2-3 months, whereas the BGL by prick test using Glucometer measures the instantaneous value of glucose [15].

Table 1: Frequency domain metrics of HRV and the significance of frequency bands.

Index	HRV metrics	
	Frequency (Hz)	Significance
Total power (ms^2)	0-0.4	Reflects all cyclic components of HRV
ULF Power	0-0.003	Reflects the influence of the day-night cycle (24 hours recording) [16]
VLF power	0.003-0.04	Slow recovery component, thermoregulation [17]
LF power	0.04-0.15	Transition zone between VLF and HF bands. reflects baroreceptor activity by both PNS and SNS [17, 18, 19]
HF power	0.15-0.4	Respiratory band, represents PNS activity and respiratory sinus arrhythmia (RSA) [20]
LF/HF		$\frac{PNS+SNS}{PNS}$Activity ratio, predominantly a controversial measure of sympathovagal balance [16]

The blood glucose level (BGL) causes a reduction in the total power (TP) of HRV. A significant reduction ($p<0.01$) of HF power has been observed in 154 DM subjects [21], and a further significant reduction ($p<0.005$ [22], $p<0.001$ [23]) in both LF and HF power is observed. However, the LFHF ratio increases during hyperglycemia in both control and DM subjects [24], which insinuates a relatively higher reduction in HF-power than the LF-power. In some cases, the reduction in HF-power is not significant ($p=0.17$) [25]. The sample entropy decreases significantly ($p=0.008$) [25] for T2DM groups.

The literature has considerable studies on the HRV change between control and DM groups. However, The HRV changes for intra-DM subjects in terms of LF and HF power have not been elucidated. The importance of further division of frequency bands to a certain number has not been analyzed with respect to DM. Therefore, the current study focuses on the sub-band analysis of LF and HF and entropy in coherence with diabetes.

2. Materials and Methods

2.1. Subjects and Recordings

The study includes 15 healthy control subjects [Height -160±11cm, weight - 65±10 kg] and 6 diabetes mellitus subjects [153±12.35cm, weight - 38.62±16.55 kg, 4 males and 2 females] who come for a regular weekly checkup in OPD of Siddha Central Research Institute.. The diabetic subjects are under regular medication and have no symptoms of CAN.

The fasting blood glucose is measured by the HbA1c test for diabetic subjects. The control subjects have been considered to compare the HRV in terms of frequency metrics, hence excluded from the HbA1c test. The resting electrocardiogram (ECG) is recorded for 10 minutes at 182Hz in the supine position using a Lead II configuration using AD8232 with an Arduino Uno microcontroller [26]. The transmission line interference is eliminated by a 50 Hz notch filter. The 4th order Symlet as mother wavelet removes the baseline wandering in ECG and the approximate ECG is reconstructed by summing wavelet coefficients from the 3−5th level of decomposed ECG to get enhanced R-peak and QRS-region [27]. The Lomp-scargle periodogram is applied on interpolated RR-signal to find the frequency domain HRV metrics [28] to minimize the spectral leakage. The study is carried out in Siddha Central Research Institute after getting proper written informed consent from all participants.

2.2. HRV Analysis

The HRV analysis constitutes frequency domain metrics alone. This is to focus on one particular metric for a specific understanding of power under frequency bands and their physiological significance for diabetes. The primary analysis is to validate the total power change between control and diabetes as observed in the literature. In the subsequent analysis, the intra-sub-band-spectrum analysis is carried out for the DM subjects. The sub-band of LF-power is obtained by dividing the LF-range, equally into five different bands such as 0.04-0.062 Hz, 0.062-0.084 Hz, 0.084-0.106 Hz, 0.106-0.128 Hz, and 0.128-0.15 Hz. Similarly, the HF-band is also divided equally into five sub bands of 0.15-0.2 Hz, 0.2-0.25 Hz, 0.25-0.3 Hz, 0.3-0.35 Hz, and 0.35-0.4 Hz. The absolute power of each band is represented as a percentage of the total power of LF and HF. The linear correlation coefficient of HbA1c ($\boldsymbol{\rho_{HbA1c}}$) with LF, HF powers, and with their sub-band powers are analyzed.

2.3. Time domain signal reconstruction:

The temporal variation of LF and HF from the spectrogram of the sub bands can be written as follows:

$$ECGs(t)_{LF} = \sum_{j=1}^{j=n} |iFFT(LF_j)|\sin(2\pi f_{jLF} t + \phi_{LF}) \quad (1)$$

$$ECGs(t)_{HF} = \sum_{j=1}^{j=n} |iFFT(HF_j)|\sin(2\pi f_{jHF} t + \phi_{HF}) \quad (2)$$

Where, angle ϕ_{HF} and ϕ_{LF} are the angles associated with the complex value resulted from inverse Fourier transform of the amplitude in the periodogram, j = 1, 2, 3, 4……..n, n is the number of frequency components in the sub-bands. The time "t" is user defined from 0 to any time t.

3. Results

The LF and HF powers are lower for the DM-group than the control group with p=0.0477 and p=0.0905 respectively, which is in accordance with the literature as shown in Fig 1.

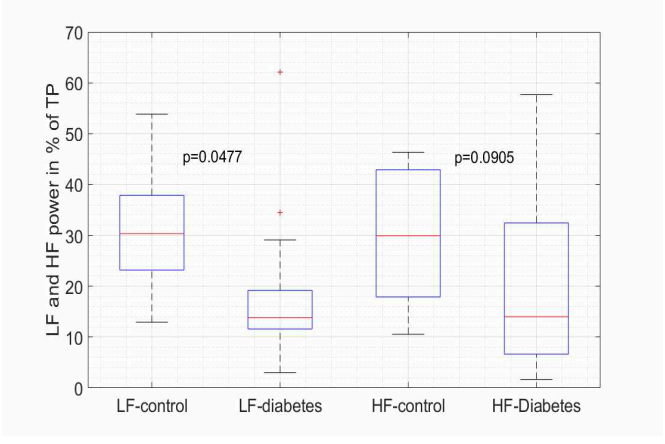

Fig 1: The box plot showing the LF and HF power in percentage of total power of HRV for control and diabetes groups.

Table 2: The correlation coefficient of frequency domain parameters of HRV and entropy in RR interval

Parameters	$\boldsymbol{\rho_{HbA1c}}$
Heart rate	-0.5018
pVLF (0.0001-0.04 Hz)	-0.4434
pLF (0.04-0.15 Hz)	0.9027
pHF (0.15-0.4 Hz)	-0.4109
pVHF (0.4-1.2 Hz)	-0.4634
pLF-pHF	0.8268
pLF/pHF	0.8047
Sample Entropy	-0.2306
Approximate Entropy	-0.0684

The LF power is higher for high HbA1c value and vice versa in most of the cases with ρ = 0.9027. However, HF-power has a negative correlation of ρ = -0.4109 with HbA1c values as evident from Table 2. Therefore the HbA1c is positively correlated with the difference and ratio of LF and HF-powers. The HbA1c has a negative correlation with heart rate and entropy. The positive correlation coefficient of LF power is dominated by the second sub-band ranging from 0.062-0.084 Hz showing a ρ of 0.8896 than other sub-bands being negatively correlated. Similarly, the negative correlation coefficient of HF power is dominated by the fifth sub-band ranging from 0.128-0.15 Hz. It shows 'ρ' of -0.4379 than other sub-bands being

positively correlated. The second sub-band of LF and fifth sub-band of HF power for a typical subject with HbA1c of 12.3 is shown in Fig 2. The correlation coefficient for the sub bands is provided in Table 3.

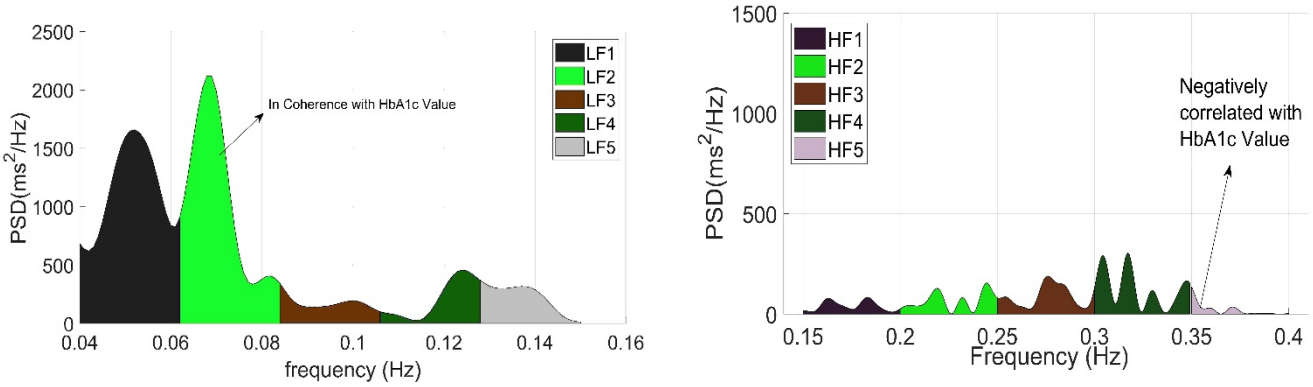

Fig 2: The sub bands of LF and HF-HRV for a typical subject having HbA1c value of 12.3

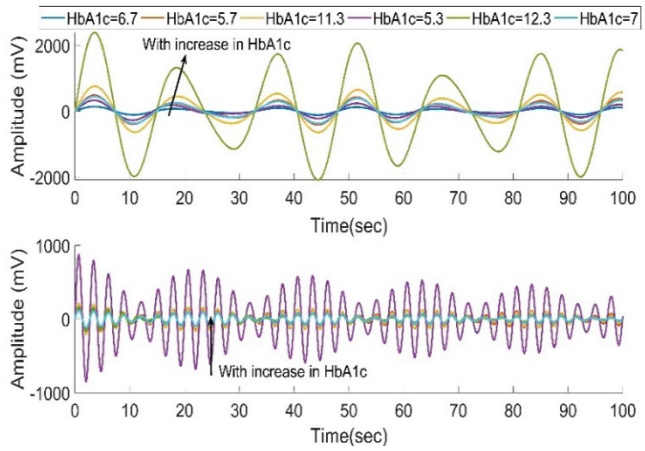

Fig 3: Reconstructed time domain signal for frequency band of 0.062-0.084Hz and 0.35-0.4 Hz for respective HbA1c values. The arrow shows the relative change in signal amplitude with HbA1c.

Table 3: The correlation of sub-bands in LF and HF – HRV with HbA1c value.

LF sub-bands(Hz)	ρ_{HbA1c}	HF sub-bands(Hz)	ρ_{HbA1c}
0.04-0.062	-0.79	0.15-0.2	0.18
0.062-0.084	0.88	0.2-0.25	0.72
0.084-0.106	-0.11	0.25-0.3	0.01
0.106-0.128	-0.57	0.3-0.35	0.04
0.128-0.15	-0.60	0.35-0.4	-0.43

The time domain signal reconstruction of both sub-LF and sub-HF zones constituting of the second and fifth bands respectively are shown in Fig 3. It provides the compression and expansion of amplitude over time for both the sub-LF and sub-HF signals. However, the peak of amplitude compression and expansion of the signals occur at different time instances due to the phase difference in them.

4. Discussion

The sub-division of frequency bands into further segments aids in detecting the connectivity between a physiological function with HRV. This aids in nullifying the breath effect on choosing the frequency bands for LF and HF, which may not be fixed for a particular individual. As physiological conditions affects the breathing pattern and hence the frequency bands in HRV.

Gastrointestinal (GI) motility is impaired during diabetes [29]. The frequency of the GI motility varies between 1.5-4.5 cycles per minute (0.025-0.075 Hz) [30], and the frequency in the sub-LF-HRV, corresponding to HbA1c is 3.72-5.04 cycles

per minute from the current analysis. Therefore the second sub-LF band contains the spectral energy analogs to the GI-motility. The heat with a parasympathetic predominance by finger-induced auto thermogenesis [32] or using a steam-generating sheet [33] as a therapeutic measure can enhance GI motility [33].

The positive correlation of sub-HF-HRV may be attributed to the increase in respiration rate of control subjects from 15.34±2.99 bpm to 17.77±2.04 bpm with T2DM [31]. The temporal picture of the sub-band frequency domain signals shows the relative contraction and expansion of magnitude imitating the function of the heart.

5. Conclusion

This study has a novel approach to frequency segmentation in HRV. The conventional method divides the spectrum distribution of RR-interval majorly into three zones, such as VLF, LF, and HF. However, the sub-divisional analysis of each band into further sub-bands fine-tunes the relationship between the amplitude and phase of frequency components with specific physiological conditions. In this study, the authors have tried to find a similar frequency band particularly for diabetes as one of the single dominant features. The sub-division of LF and HF frequency bands of HRV provides a better insight into the physiological phenomenon occurring due to diabetes. The LF and HF power in HRV is significantly less in DM subjects compared to control subjects. However, the LF power in 0.062-0.084 Hz may be one of the biomarkers for identifying diabetes which has a connection with GI motility. Equivalently a negative HF power in the range of 0.35-0.4 Hz is coupled with the LF power change. The HF power from 0.2-0.25 Hz has the highest positive correlation of 0.72 signifies a higher resting breathing rate associated with diabetes. The time domain reconstruction of the positively correlated LF band and negatively correlated HF band constitutes a periodic compression and expansion envelope whose amplitude of oscillation may be related to the HbA1c value. The study may help in replacing the prick test for the neonatal. In the future, the study can be conducted clinically with a large population with therapeutic intervention through parasympathetic mediated heat.

Acknowledgements

I thank the nurses of SCRI for helping in assisting patients to collect data and the IIT madras for funding the research.

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