Mathematical Model of Sino-Atrial Node Used in Assessment of Neuropathy and Cardiac Health in Diabetics

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***Abstract*-This paper proposes a novel mathematical model to demonstrate the change in neural signal conduction in diabetic condition with and without hypertension. It assesses the risk factors of neuropathy and associated cardiac diseases like myocardial ischemia/infarction.**

Background: Patients with prolonged diabetes are more likely to develop diabetic neuropathy. Neuropathy is the slow deterioration of the functioning of the nerves. Proximal neuropathy causes lack of sensation in peripheral nerves. Initially, no clinical symptoms are visible. The slow and progressive deterioration may lead to gangrene and foot amputation. To stop this irreversible process, early diagnosis at the preclinical stage is critical. The mathematical model developed in this paper demonstrates the reduced signal conduction under diabetic conditions. Reduction of signal conduction is a preclinical marker to peripheral neuropathy.

Methodology: Signal conduction changes can be verified by changes in power spectral density of the electrocardiogram ECG signal by heart rate variability (HRV) analysis. The Effects of these changes on the performance of the heart can be evaluated by the Left Ventricular Ejection Fraction (LVEF). Extraction of inter-beat R-R intervals (R wave to R interval) from 3-5 minutes long ECG signal is used to generate the information about the neural signal conduction. Total power is then obtained from conducting an HRV analysis of the R-R interval samples. This analysis is performed using Kubios HRV simulator. The performance index of the heart is acquired from the echocardiograms of the samples. Data samples of different cohorts mentioned in the Table 1 are acquired.

Details of data samples: The sample size of each cohort and the average age group is as stated in Table 1. All the cases are recorded at Fortis-S.L. Raheja hospital, Mahim (W). Randomness in age, class, sex and other parameters was ensured on the basis of the data collection as per the registration of the subjects.

TABLE 1 DETAILS OF THE DATA

Type of cohort	Normal	Diabetic	Diabetic with IHD and INHD	Diabetic and hypertensive	Hypertensive
Sample size	27	20	20	27	23
Average age group	47	58	61	62	68

Experimental Results: In this paper, a mathematical model is proposed in the paper for calculating the strength of neural signal conduction. The average neural signal conduction of diabetic cohort is found to be reduced compared to the non-diabetic cohort. The diabetic cohort with myocardial ischemia/infarction is found to have with least average neural signal conduction followed by the diabetic and hypertensive cohort. In case of hypertensive cohorts, the average neural signal conduction is found to be equal to that of the normal cohort.

The effect of the neural conduction can be observed on the total power spectral density from the frequency domain AR analysis of R-R intervals.

The average Left Ventricular Ejection Fraction (LVEF) index retrieved from the echocardiogram in all the cohorts is found to be consistent with the reduced neural signal conduction.

The above mentioned indices can be preclinical indicators of assessment of neuropathy and cardiac health.

Conclusion: preclinical diagnosis of autonomic neuropathy and cardiac health assessment is possible in diabetic subjects.

Keywords- Neuropathy; Myocardial Ischemia/Infarction; HRV Analysis; Left Ventricular Ejection Fraction

I. INTRODUCTION

Diabetes is not only a metabolic disorder but also is associated with impaired vasculature. Uniform and continuous glycemic control is difficult to maintain [1, 2]. Diabetes is always associated rallies of hypoglycemia or hyperglycemia. Hypoglycemic conditions develop into cardiovascular damage and hyperglycemic conditions damage the kidneys and almost

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all body organs [2-4]. Under diabetic conditions, the energy needs of the body are fulfilled by the proteins or fats [1, 2]. The protein or fat metabolism causes lack of nutrition to the different parts of body developing into microvasculature. As a consequence of protein or fat metabolism, the blood vessels are more likely to get blocked with lipids. This causes restriction to the blood flow. If the blood flow is restricted to the heart, the chances of cardiac diseases like myocardial ischemia/infarction are more likely [4]. Hence there are more chances of developing complications like hypertension and cardiac diseases in prevailing diabetic condition [5]. The paper proposes regular assessment of cardiac health and neuropathy for diabetic subjects using the HRV analysis techniques. The paper proposes the diagnosis of reduced signal conduction which is an indirect early marker of assessment of peripheral neuropathy using a cost effective, non invasive diagnostic tool [4]. The tool is easily deployable and the test can be conducted by paramedical staff. In the third world countries, lack of awareness, less number of doctors in rural areas and economic constraints increase the mortality and morbidity rate due to diabetes [6, 7]. To control the same, regular health assessment proves essential [4]. The mathematical model is developed to validate the pathophysiological changes in microvascular conduction due to prevailing diabetes. Paper [5] discusses the mathematical model of different physiological processes. Cardiac functioning model is discussed and different closed loop processes controlling the heart rate are discussed. Paper [8, 9] discusses about the left ventricular mathematical model and accounts to peripheral arterial pressure and heart wall elasticity affecting the performance of the heart. Several diagnostic tools are developed for different disease conditions using the deviation of the parameter value in disease conditions. Expert systems using neural network simulation are developed and tested [10-15].

II. MATHEMATICAL MODEL

The Sino-Atrial (SA) node triggers a pulse that results into an R peak depending upon the inputs it receives from the following. The heart rate is an output that dependes upon the different inputs [5, 6]. The most prominent are listed as:

1) Arterial blood pressure (ABP) from baroreceptors located in the peripherral organs.
2) Instantaneous lung volume (ILV) from volume receptors located in the alveoli of lungs.
3) The variation in hormonal level from parasympathetic and sympathetic control from chemoreceptors located in the central nervous system.
4) The oxygen concentration level in the blood plasma from the chemoreceptors located in the peripheral circulatory system.
5) Temperature changes from the thermo sensors located all over the body.
6) Stress hormonal level from the chemoreceptor located in the brain.
7) The relaxed status of the hear wall from the stretch receptors located in the heart wall to check whether ventricular diastole has occurred before.
8) The time at which the previous R peak is fired.

With all the above inputs, SA node fires as an autonomous system. If any of the inputs are more than the qualifying threshold level, SA node triggers an input resulting into R peak. Since the triggering /not triggering of SA node depends 8 different input conditions, the process control can be effectively modeled by neural network simulator as shown in Fig. 1. By keeping the subject relaxed by prior intimation, by maintaining the temperature at comfortable level, the variation in the body temperature conditions can be assumed to be nonconsequent. By requesting subject to maintain steady position and uniform breathing rate, changes in the R-R interval due to change in position and lung volume variations can be assumed to be nonconsequent. With the above precaution, it can be safely assumed that all the actuator of the feedback loops other than hormonal triggering of SA node can be assumed to be giving constant input.

The pacemaker (SA node) of heart is continuously controlled by sympathetic and parasympathetic hormonal secretion. In resting condition, the parasympathetic activity is more predominant whereas any physical, mental activity shows the dominance of sympathetic hormone [4].

In the data collection process of doctoral studies, R-R interval series of different types of subjects for 3-5 minutes are collected using LABVIEW interface [16]. The temporal details are required for the evaluation of heart rate at every instance. Since the subjects are well informed and made to lie down in a comfortable location, all the other weight factors except w3, the chemoreceptor hormonal conduction, are assumed to be constant. A closed loop control system with a combination of feed forward and feedback is designed with single input and single output. Parameters that determine the instantaneous firing of SA node can be modeled as shown in Fig. 1. The weights W1 to W7 show the neural conduction coupling of the hormone released by the pituitary gland. The feedback control system can be represented as shown in Fig. 2.

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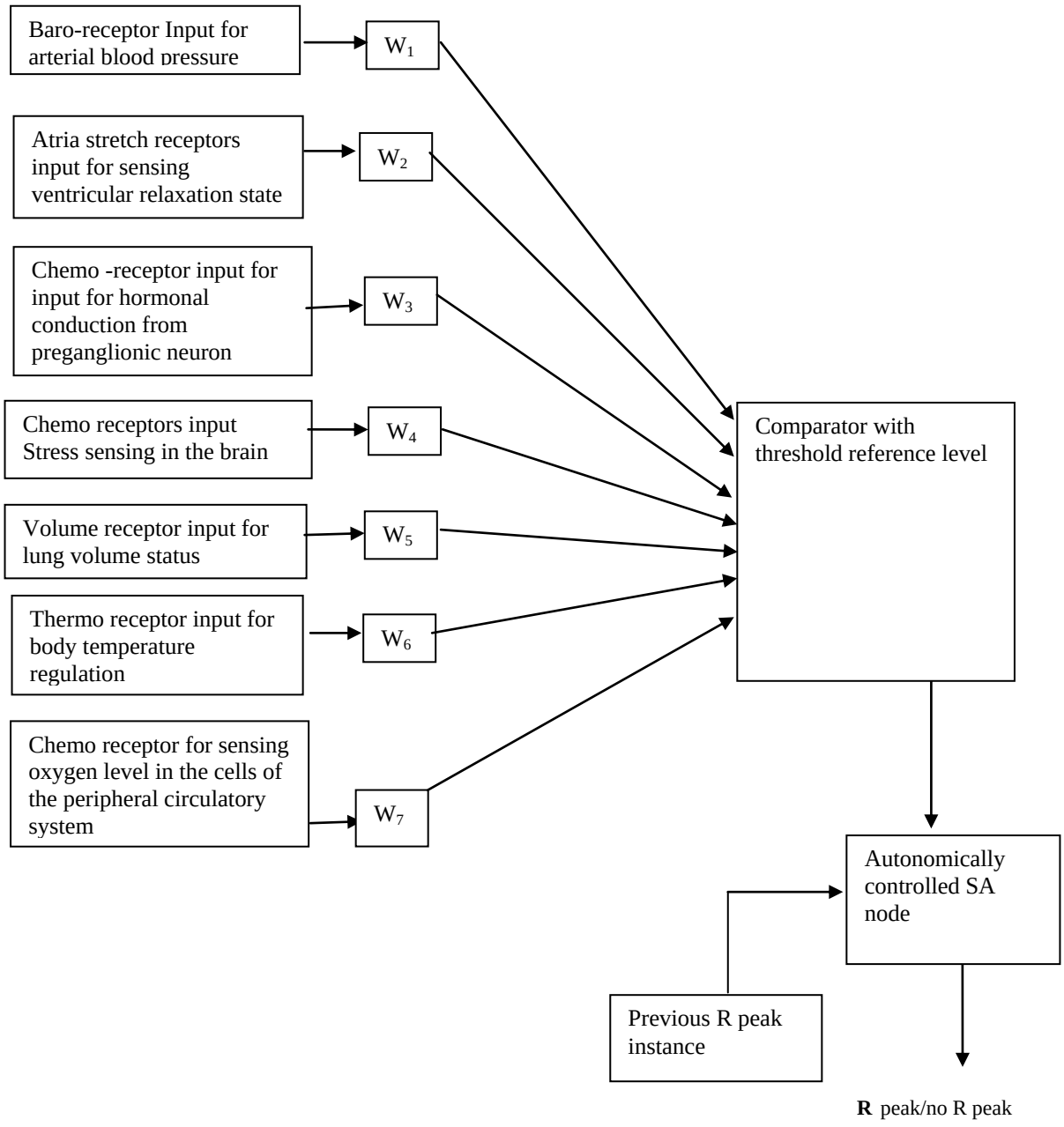

Fig. 1 Block diagram showing the SA node firing

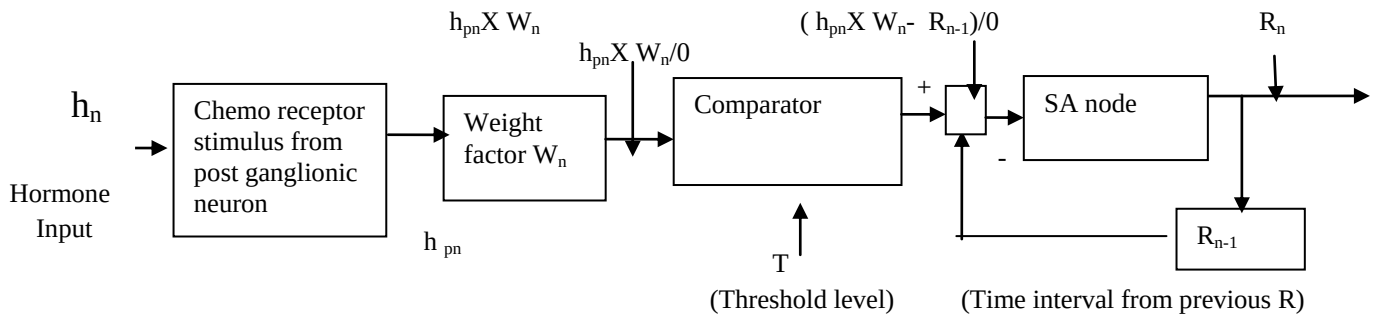

Fig. 2 Simplified block diagram showing the SA node firing with only hormonal input

where

h_n is the hormonal level at the preganglionic stage at nth instance of time.

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h_{pn} is the chemoreceptor stimulus at post ganglionic neuron.

W_n is the weight factor associated with SA node

The output is given by the equation

$$Rn = hpn \times wn - Rn - 1 \quad (1)$$

if the least time interval has elapsed.

Else

$$Rn = 0$$

The hormonal input, h_{pn} is an outcome of complex interaction of parasympathetic and sympathetic neural signal which can be simulated by a random number sequence.

R_n and R_{n-1} can be obtained from R-R sequence of the data samples collected. Knowing the weight samples of different categories of subjects, the state of neural conduction can be evaluated. From the prevailing values of the weights, the assessment of extent of deterioration of the signal conduction can be an indicator of neural function deterioration. The weight factor can be a noninvasive preclinical indicator of extent of diabetic neuropathy. The change in the synaptic conduction is manifested in the form of reduced power spectral density obtained from HRV analysis and reduced LVEF obtained from the echocardiogram of the subject.

A. HRV Analysis

It is required to detect R-R interval from the ECG sample acquired. QRS detection algorithm is used acquire the R-R interval samples. [17]

B. QRS Detector using Pan-Tompkins's Algorithm

When the ECG signal is acquired, it is superimposed by different type's noise signals like

1) Supply frequency interference
2) Muscle artifact
3) Baseline wander
4) T-wave interference

The above mentioned algorithm extracts the RR interval from the noisy ECG signal in the below mentioned steps. The band pass function is realized through a design of a low pass filter and the high pass filter [17].

The low-pass filter is described by the formula

$$y(n) = 2y(n-1) - y(n-2) + x(n) - 2x(n-6) + x(n-1)$$

and the high pass filter is described by the formula,

$$y(n) = y(n-1) - \frac{y(n-2) + x(n) - 2x(n-6) + x(n-12)}{32}$$

The low pass filter removes the supply frequency interference (50 Hz), the baseline wander which is a low frequency and the T-wave interference. The T-wave is due to atrial repolarization that overlaps the QRS wave. The high pass filter used to remove the muscle noise interference. The derivative filter is used to detect the QRS peak. Since it has the highest slope, the detection is possible through derivative filter. This is followed by a square filter that converts the negative spectral amplitudes to positive and also enhances the high frequency component.

$$y(n) = \frac{2x(n) + x(n-1) + x(n-3) + 2x(n-4)}{8}$$

Moving window integration is used to incorporate the changes in the signal as the samples of the signal move ahead. The window size is directly related to the rate of sampling [5]. The sampling rate of the signal is 500 samples/second and the window size 75.

$$y(n) = \frac{x(n-(n-1)) + x(n-(n-2)) + x(n-3) \ldots\ldots x(n)}{N}$$

A temporal location of the QRS is marked from the rising edge of the integrated waveform. In the last step two thresholds are adjusted. The higher of the two thresholds identifies peaks of the signal. The lower threshold is used when no peak has been detected by the higher threshold in a certain time interval. In this case the algorithm has to search back in time for a lost peak. When a new peak is identified (as a local maximum – change of direction within a predefined time interval) then this

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peak is classified as a signal peak if it exceeds the high threshold (or the low threshold if we search back in time for a lost peak) or as a noise peak otherwise. In order to detect a QRS complex the integration waveform and the filtered signals are investigated and different values for the above thresholds are used. To be identified as a QRS complex, a peak must be recognized as a QRS in both integration and filtered waveform [17]. Fig. 3 shows the flow chart for the same.

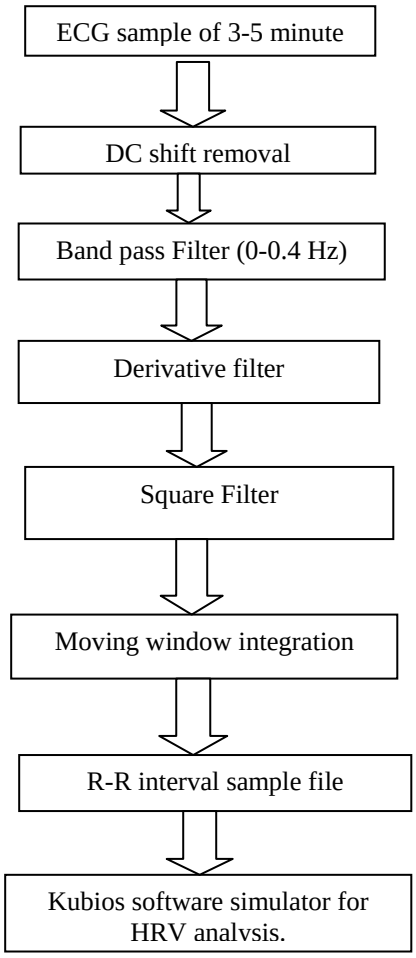

Fig. 3 Pan Tompkins Algorithm to acquire HRV analysis result from noise free sample of R-R interval. Figure adapted from [17]

The changes in the waveform are shown step by step in Fig. 4 (a-f) denote the changes due to each signal transformation. The X axis in all the waveforms from Fig. 4 (a-f) shows the time scale. The Y-axis is represented by voltages from Fig. 4 (a-f). The Fig. 4 (a-f) wave form represents the digitized state from presence or absence of pulse. The R-R peak in Fig. 4e is observed to be matching the peak of the integrator i.e. Fig. 4a to 4f.

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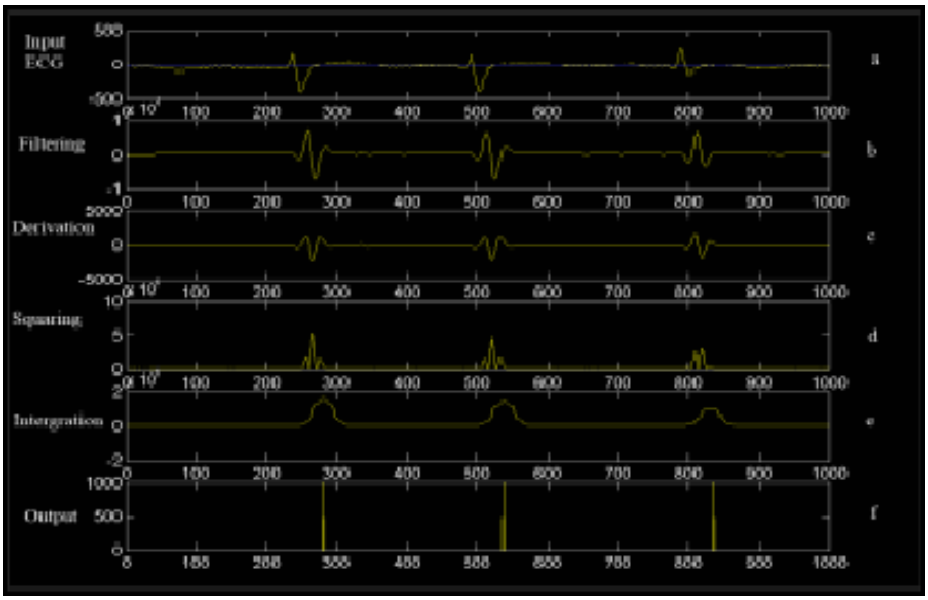

Fig. 4 a-f Output of each module described in the algorithm. Figure adapted from [17]

III. HRV ANALYSIS TOOL

The RR interval file extracted from ECG is given as an input to the HRV simulator. The simulator is open source simulation software developed by PHYSIONET called as Kubios HRV simulator. The result sheet generated by the simulator is shown in Fig. 3 [18].

IV. OVERVIEW OF HRV ANALYSIS

The HRV is an old technique stated by Hales in 1733. The RR intervals of a healthy heart shows variation of greater extent compared to the impaired heart. A healthy heart is sensitive to physiological, physical and psychological changes in the body and it modifies the heart rate accordingly. It has been observed that the impaired heart has reduced the variation in the heart rate as the demanded by different activities of body. The normal person's ECG that shows more changes in the heart rate during different activities compared to that of the subject with impaired functioning of heart. The HRV analysis produces certain diagnostic indices that are obtained from spectral analysis of RR interval acquired for 3-5 minutes. The frequency domain AR analysis results are shown in Fig. 5. The average total power in all the three bands, VLF (0-0004Hz), LF (0.04-0.15Hz) and HF (0.15-0.4Hz) is tabulated for different cohorts and is an indicator to the reduced neural conduction [4].

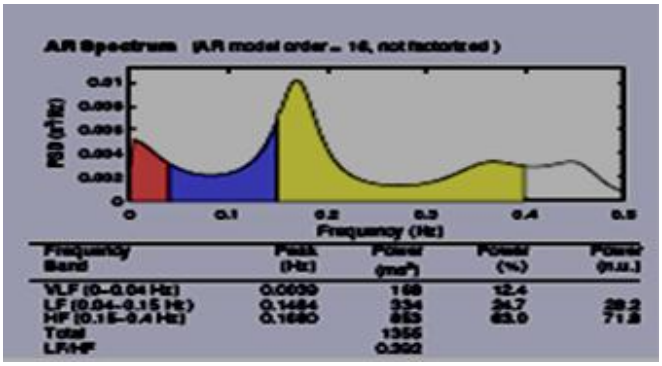

Fig. 5 Total power shown in the HRV analysis

The reduced neural conduction results into reduced average total power results in reduced LVEF. The echo-cardiogram in Fig. 6 shows the LVEF. The echocardiogram in Fig. 6 shows that parasternal 4- chamber view of heart also stating the LVEF of the subject [4].

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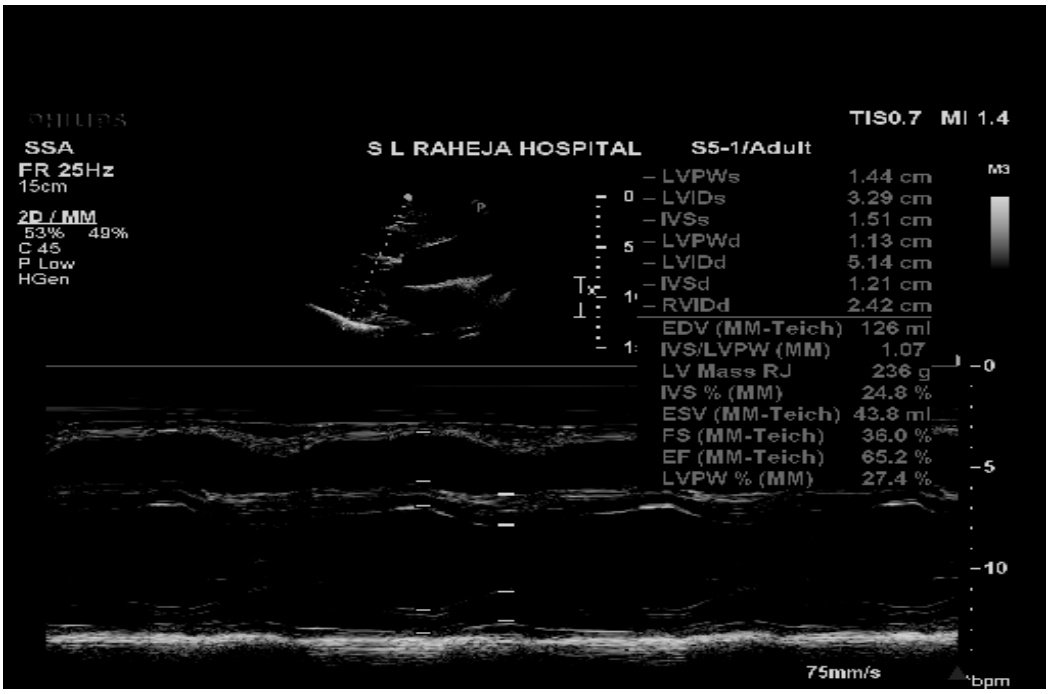

Fig. 6 sample echocardiogram showing a 4-chamber view and the cross section of the left ventricle

V. RESULTS

The average synaptic weight and their standard deviation are computed for different categories obtained from data samples are tabulated in Table 2 and the graphical representation in Fig. 7.

TABLE 2 THE AVERAGE AND STANDARD DEVIATION OF SYNAPTIC WEIGHTS FOR ALL CATEGORIES

	Normal	Diabetic	Diabetic with IHD and INHD	Diabetic and hypertensive	Hypertensive
Average synaptic weight	2.3319	1.8304	1.3933	1.9519	2.3523
Standard Deviation	0.0346	0.0659	0.0094	0.0152	0.3114

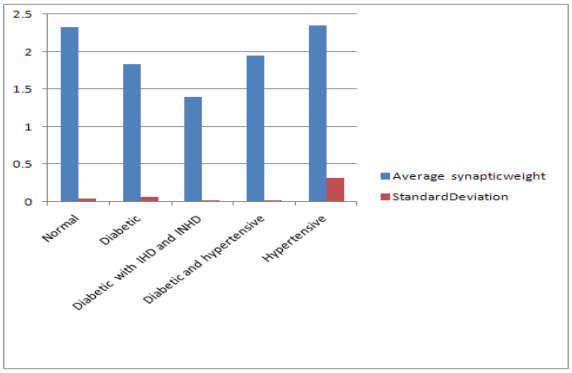

Fig. 7 Average and standard deviation of synaptic weights for all categories

The above outcome of the mathematical model can be explained with pathophysiological facts as under -The prevailing diabetic condition, the blood circulation is observed to be restricted in micro and macro level [1]. The prevailing vasoconstrictor condition reduces supply of blood to the different organs. As a result the hormone transport from the blood plasma also gets reduced. Prolonged diabetes and hyperglycemia develop the neuropathy that results in reduced conduction from neurons. Hence the preganglionic hormones secreted in pituitary gland are poorly conducted by the post ganglionic neurons of SA node [1]. This is demonstrated mathematically by the implementing the Eq. (1). The results in Table 1show that neural conduction is reduced the most in diabetics with myocardial ischemia/infarction and in diabetics. In case hypertensive

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subjects since some subjects are in early stage of left ventricular hypertrophy the neural conduction is higher than normal subjects [19]. Also it is observed to be higher in diabetic and hypertensive subjects [5].

The deteriorated neuron conduction manifests into low total power in decreasing order in case of diabetic, diabetic with myocardial ischemia infarction subjects and slightly reduced in case of diabetic with hypertensive subjects as can be verified from the Table 2 and Fig. 8 shows the graphical representation of the same.

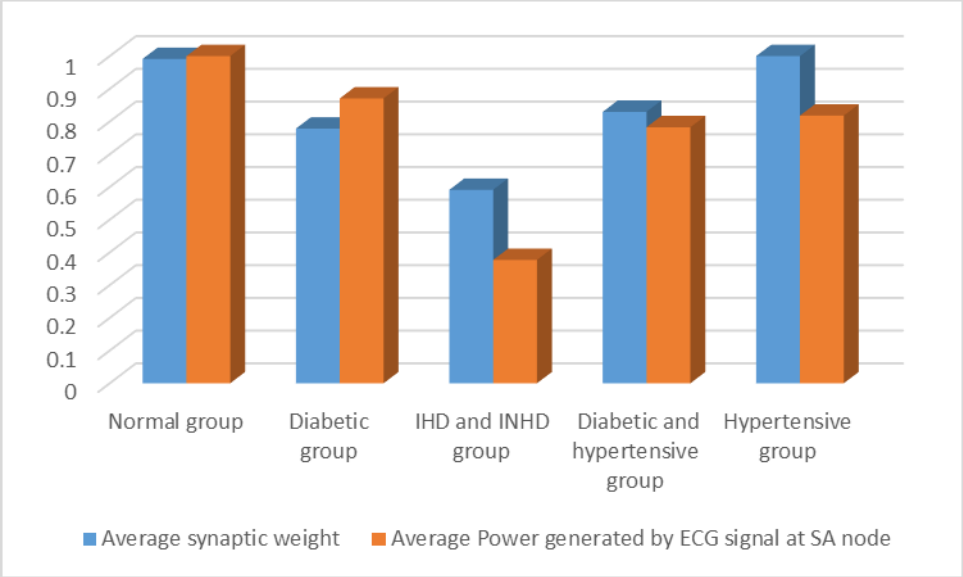

Fig. 8 Mathematical model parameters and the observed parameters

VI. CONCLUSION

The average synaptic weights of the neural signal in diabetic condition are reduced and can be verified by the manifestation in reduced average total power from the HRV analysis. The outcome of the prevailing condition is the reduced LVEF. In case of diabetic cohort with myocardial ischemia/infarction, the further deterioration is observed. In case of diabetic and hypertensive cohorts, hypertensive conditions are more prevailing and hence the results of the both indices show similar variation. It can be concluded from the results of the average indices, that the synaptic weight from the proposed mathematical model and the total power from the HRV analysis is a preclinical marker of the neuropathy and cardiac assessment.

VII. FURTHER SCOPE

The study can be carried out for the same subjects at a regular time interval of time with one group under glycemic control and another without glycemic control and change in the parameters can be analysed.

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