Heart Rate Variability (HRV) Analysis as Preclinical Diagnostic Tool in Cardiac Performance Assessment for Diabetic Subjects

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Abstract
The complications of diabetes are manifold. Episode of cardiac deaths are more in diabetic subjects than the normal cohorts. Clinical symptoms of deterioration of cardiac health are not manifested at an early stage in current diagnostic practice. Early diagnosis of the same can control morbidity and mortality rate. The paper proposes an early, safe, easily deployable, cost effective and non-invasive technique that can be used as confirmative diagnostic tool obtained from 2-lead ECG sample collected for at least 3 minutes duration. The proposed tool provides a guideline to the echo-cardiologist and saves his time and also controls inter operator diagnostic variation. Also the test can be performed by paramedical personnel saving the echo-cardiologist’s time. The proposed paper establishes correlation between HRV indices and echocardiogram finding of control group and diabetic subjects.

Keywords: Diabetes; II lead ECG; Heart rate variability; Echocardiogram; Auto regressive analysis; Sympatho vagal balance; Left Ventricular Ejection Fraction (LVEF)

Introduction
Cardiovascular disease is the world’s leading killer, accounting for 16.7 million or 29.2 per cent of total global deaths in 2003. The World Health Organization (WHO) estimates that 60 per cent of the world’s cardiac patients will be Indian by 2010 [1]. Also it has been found out that India has more number of cardiovascular deaths daiming younger population than in America [1]. The major reasons contributing to sudden deaths are lack of the ability of the diagnostic tools to diagnose cardiac health at an early stage. The diabetic subjects are more likely to be target of cardiovascular diseases due to the hypoglycemic conditions [2]. The tight glycemic control is administered to protect the kidneys. But as a result, hypoglycemic episode is more likely [3]. The hypoglycemic episode affects the cardiovascular system. Diabetic Autonomic Neuropathy (DAN) is the common risk factor with prolonged hyperglycemia. DAN is initiated and does not show any symptoms and is irreversible [4]. The paper addresses a novel and simple method to assess the cardiac health and DAN at an early stage.

The II lead ECG record acquired for 3-5 minutes can be processed to obtain HRV analysis. HRV analysis is a safe and noninvasive tool. Also it can assess the cardiac health at preclinical stage [5]. HRV analysis can also diagnose DAN at preclinical stage. Other advantages of HRV analysis are it is more cost effective than echocardiogram and takes 3-5 minutes whereas echocardiogram takes 20-30 minutes. HRV test can be performed by paramedical staff whereas echocardiogram needs an expert for interpretation. The proposed paper attempts to establish correlation between the findings of the two diagnostic modalities. The correlation between the two diagnostic modalities is essential to validate HRV analysis (that is not currently in practice) with echocardiogram.

Echocardiogram is chosen for correlation because it is an established diagnostic practice that is safe, noninvasive, less costly and gives instantaneous results. Additionally, echocardiogram gives an account of hemodynamic, structural and functional details of the prevailing cardiac performance.

Echo cardiology is difficult to interpret due to noisy images [6-9]. The intra-operator variation is 5-10%. Validation of HRV analysis can help in providing a guideline to the echo cardiologist and control the intra-operator variation. Also echo cardiologist’s time would be saved [6].

Almost two third of the population that dies due to cardiac disease is diabetic. Micro and macro vasculature is affected due to long term hypoglycemia [2,3]. The domination of parasympathetic hormone is observed in diabetic subjects. Hence the heart cannot fulfill the sudden demand of blood required to carry out different daily activities. As a result of reduced blood supply, the different organs of diabetic subject are deprived of blood and nutrients [3]. As a result, diabetic subject experiences morbidity. The diabetic subject is resistant to glucose assimilation. The protein and fat metabolism is source of energy. As a result lipids and proteins particles are found in the blood [2]. This causes atherosclerosis and causing blockages in the blood vessels and affecting the blood circulation. If the coronary artery is occluded, the cardiac disease is resulted.

The study proposes HRV analysis as an early indicator of cardiac performance deterioration. To validate the HRV indices, statistical tests are computed. Average indices of the cohort indicates the general trend, t-test ensures independency of statistical data, Pearson’s coefficient ensures the correlation between indices and regression analysis ensures whether the cardiac performance index is a function of mentioned HRV indices.

Materials and Methods

Data groups are identified; inclusion and exclusion criterion to carry out the data collection is defined. Data samples of three minute duration are acquired for control group and diabetic subjects. Signal is then denoised from low frequency DC interference and high frequency muscle artifact. The ECG sample collected is processed further to extract R-R interval samples. The R-R interval sample file is input to the HRV analysis simulator. HRV simulator lists the different HRV indices in frequency and time domain analysis.

For HRV analysis, at least 128 samples of II Lead ECG are required. HRV analysis of control group and diabetic subjects is computed. HRV indices are correlated with echocardiogram results such as left ventricular ejection fraction (LVEF) and left ventricular contractility.
Hrv Analysis Tool

The R-R interval file extracted from ECG is given as an input to the HRV simulator. The Simulator is free simulation software developed by PHYSIONET called as Kubios HRV analysis tool kit [10-14]. The result sheet generated by the simulator is shown in figure 1. The simulator lists the time domain indices, frequency domain indices and the nonlinear indices. The indices used in the proposed paper are –Heart rate variability and the heart rate. The two are compared for normal to diabetic subject.

Overview of Hrv Analysis

HRV analysis is a very sensitive tool to assess many parameters in the changing physiological and pathological conditions [11-13]. HRV analysis study is the only tool that provides early diagnosis of changed diabetic pathology [5,6].

The central nervous system controls the functioning of heart. Any intervention in neural stimulus is not possible by medication. Hence the performance of heart is a response of the autonomous system sensitive to different hormonal stimuli and their neural transmission. In healthy conditions the neuro-humoral balance is maintained whereas in diabetic and hypertensive condition, it is shifted. HRV analysis is an early, noninvasive indicator for the same. Shift in the neuro-humoral axis associated with reduced SDNN also indicates the onset of DAN [15,16].

The R-R 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 compared to that of the patient with reduced heart rate variability (HRV). Figure 2 shows the HRV and the power spectral density distribution in case of sympathetic and parasympathetic intervention of a normal subject and a diabetic subject [6].
HRV analysis has time domain analysis technique that computes the indices—heart rate and SDNN. Heart rate is expressed in beats per minute. Typically, the heart rate of a normal healthy person is 60 beats per minute. Heart rate does not vary with age. In case of diabetic subject, heart rate increases progressively as duration of diabetes increases. SDNN is heart rate variability stated as standard deviation between NN intervals. NN interval refers to p to p interval of PQRS curve. Since it is easy to locate R peak through software program, R-R interval is counted. SDNN indicates responsivity of heart to external stimuli. Heart in healthy condition responds by increasing heart rate as per the demand of the body. Heart rate decreases when body needs normal blood supply. Healthy performing hearts have higher SDNN. In case of diabetics, since basal heart rate is high, heart does not relax and SDNN is lower.

The HRV analysis from frequency domain or spectral analysis of R-R intervals using autoregressive analysis represents three prominent frequency bands VLF band -0.0 - 0.04 Hz, LF band-0.04 - 0.15 Hz and HF band -0.15 - 0.4 Hz [9]. HF band represents the parasympathetic power and LF band represents sympathetic band. Under healthy conditions, both the powers have a complex and balanced interplay. Under relaxed condition, parasympathetic power is more and when conditions are physically or mentally stressful, sympathetic power is more.

In diabetic conditions, parasympathetic power dominates even when the body is relaxed. This change in the neuro-humoral balance can be diagnosed by HRV analysis using frequency domain techniques.

The ratio of the peak power of the HF to LF band represents the sympathetic to parasympathetic balance that provides an index stating the close loop response of heart. The ratio is called sympatho-vagal balance [10]. The sympatho-vagal balance is observed to be more in case of normal subjects compared to that of diabetic subjects. This test is a popularly used in research literature though not used clinically [6].

Figure 2 shows the Autoregressive analysis in case of normal and diabetic subject. As a compensatory mechanism to reduced blood supply, the diabetic subjects also have higher value of heart rate. As the duration of diabetes increases, the heart rate increases.

Nonlinear HRV indices are not used for the study due to the fact that duration of the sample required for the analysis is large. The study is aimed at validating the HRV indices acquired from a simple and fast analysis method with less memory requirement to facilitate ambulatory diagnostic tool.

**Interpretation of Echocardiogram Indices**

The ultrasound probe produces a (pulsed) acoustic pressure field. When the ultrasound signal is incident upon an elastic medium, the signal returns back without penetrating. This delay represents lowest intensity in grey scale [9]. Depending upon the density of the target velocity of the reflected signal is modified. The field propagates through the tissue and is partially reflected and scattered due to the inherent in homogeneity of most tissues. The backscattered signal is received by the same probe and converted into a grey scale image of the organ. The probe of the ultrasound has a transmitter and a receiver in one assembly so that the organ mapping does not vary spatially. Since the ultrasound signals cannot pass from the bone, the probe is placed suitably to get suitable view [9].

Medical ultrasound is a non ionizing radiation has several advantages over other popular imaging modalities as Magnetic Resonance Imaging (MRI), X-ray and Computed Tomography (CT). At first, unlike X-ray and CT, ultrasound is a non ionizing radiation and hence practically harmless to the human body. Ultrasound systems to work at frame rates of 100 frames/sec. This makes ultrasound the standard tool for diagnosis of disease based on organs dynamics [5]. Further advantages connected with ultrasound systems are their cost effectiveness and reduced size, making their availability possible even in small local low budget ambulatories. This is instead not the case for X-ray CT and MRI whose installation, besides relevant costs, requires extended dedicated areas [3]. The disadvantage of Ultrasound image is it is highly noisy [9]. Figure 3 refers to an echocardiogram showing the M-mode echocardiogram, the left ventricle can be viewed during systole and diastole. The volume change in left ventricle is directly related to the contracting ability of the heart. Contractility can be formulated as:

\[
\text{Contractility} = \frac{(LVIDd - LVIDs)}{LVIDd}
\]

LVIDd is the left ventricular volume during diastole and LVIDs is the left ventricular volume during systole. If the heart is functioning properly, the contractility is higher. It has been observed the diabetic subject suffers from vasoconstriction. The lack of availability of NO due to hyperglycemia causes the vasculature in a constricted state.
causing vasoconstriction. As a result, the body organs are deprived of nutrients. The vasoconstriction and dominance of parasympathetic activity that declines the depolarization rate of the left ventricle directly affect the proper diastolic and systolic performance. This in turn affects the contractility of the heart. Figure 3 shows the echocardiogram showing the left ventricular volume change during diastole and systole [10].

As can be seen from the figure 3, LVIDd and LVIDs represent the left ventricular volume during diastole and systole respectively. The contractility computed from the echocardiogram image is found to be high for normal cohort than the diabetic cohort.

### Data Acquisition Protocol, Inclusion and Exclusion Criterion

Study is carried out on non diabetic and non hypertensive subjects that visit the hospital for checkup or admitted in the hospital. The II LEAD ECG and echocardiogram is acquired on the same day. Data of 27 control group and 20 diabetic groups are recorded.

1. All the cases were recorded from Fortis- S L Raheja Hospital.
2. Randomness in data is ensured by taking up all the cases in the stipulated period of time. The records are collected in the morning from 10.00 a.m. from 2.00 p.m.
3. All the subjects are above 25 years of age.
4. The echocardiogram and ECG acquisition equipment are same.
5. The echocardiograms from three different cardiologists are recorded.
6. The control group is non diabetic and non hypertensive subjects.
7. The diabetic subjects have at least 5 years of prevailing diabetes.
8. The clinical glycemic control record is not mandatory in diabetic cases.
9. Both male female cases are included.

The exclusion criterion states that

1. Subjects who are younger than 25 years age.
2. Subjects suffering from type-1 diabetes.
3. Subjects with less than 5yrs. of diabetes history in study group.
4. Subjects with known history of electrolyte imbalance related ECG abnormalities.
5. Subjects with known history of Digitalis induced ECG abnormalities.

6. Subjects that are only diabetic and with no other complication are considered.

**Results and Discussion**

Table 1 and table 2 show the details of the normal and diabetic cohorts respectively. It can be observed that there is lot of granularity exists in the sample space.

Table 3 shows the average heart rate and heart rate variability of the control group and the diabetic group. The average values are represented to indicate the changes in the indices depending upon the changed pathology in diabetic condition. The average heart rates of the two cohorts are tabulated also to show the deterioration of cardiac health in diabetic cohorts.

Table 4 shows the p value of one tailed test of unequal variance between normal and diabetic cohort. It can be observed that p-value is much below 0.05. The t-test results are tabulated to show the data of the indices are not dependent on each other.

An attempt is made to check the effect of the increase in heart rate and SDNN on left ventricular ejection fraction. Statistical regression analysis is computed for the two HRV indices and the echocardiogram finding of cardiac performance index i.e. left ventricular contractility.

When two different diagnostic methods are compared, the parameters are compared statistically with Pearson's correlation coefficient. Correlation coefficient signifies the degree of relation between two parameters. Correlation index of heart rate and SDNN is as shown in the table 3. The values of Pearson's correlation coefficient are tabulated for normal and diabetic cohorts. The correlation coefficient ranges between -1 to +1. Values ranging between -0.3 to +0.3 signify no correlation, Values between -0.3 to -0.7 and +0.3 to +0.7 signify medium correlation. Values between -0.7 to -1 and +0.7 to +1 signify higher value of correlation. Positive correlation signifies the correlating parameters are directly proportional and negative correlation signifies inverse proportionality between the parameters. The correlation coefficient for biological parameters is typically in the medium range [15].
HRV variations over a period of time. The same experiment could have given a clear indication about the trend of the cardiac contractility. This indicated that contractility is a function of HRV indices in case of diabetic cohorts.

From the table 5, it can be noted that the heart rate and SDNN do not show any correlation with the left ventricular contractility in control group. Correlation can be observed for the same for the diabetic cohort. This indicated that contractility is function of HRV indices in case of diabetic cohorts.

Regression analysis shows that the heart rate and SDNN jointly contribute 32.9% of the left ventricular contractility outcome in case of diabetic cohort. It can be concluded that in case of normal cohort, left ventricular contractility is not a function of HRV indices and in case of diabetic cohort, left ventricular contractility is a function of heart rate and SDNN jointly. This proves the correlation between the HRV indices and the contractility. So it can be deduced that in diabetic subjects, Deviation of heart rate and SDNN from normal values can predict deviation of left ventricular contractility.

**Further Scope and Limitations**

The same correlation can be checked for different cohorts of diabetic complication like diabetes with hypertension, diabetes with recorded evidence of cardiac disease etc. The same experiment can be tried for large number of cohorts on global basis. Three point studies could have given a clear indication about the trend of the HRV variations over a period of time.

**References**


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