Correlation between Heart Rate Variability and Left Ventricular Ejection Fraction (LVEF) for Diabetics and Diabetics with Hypertension

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ABSTRACT

Objective: Cardiac diseases have strong association in diabetic and hypertensive subjects. Episode of cardiac deaths are more in diabetic and hypertensive subjects than the normal cohorts. Current diagnostic techniques do not have a preclinical diagnostic capability. Preclinical diagnosis that can control morbidity and mortality rate can be only possible by HRV analysis. The paper proposes correlation study and pathophysiological analysis of the correlation between the Heart Rate Variability (HRV) analysis indices and echocardiogram indices. The purpose of the attempt is to validate HRV analysis results that have preclinical diagnostic ability with the echocardiogram findings.

Methods and subjects: Study is conducted with 27 normal subjects, 39 diabetic subjects with and without myocardial ischemia/infarction and 40 hypertensive subjects with and without diabetes. Data samples are collected from Fortis-S.L. Raheja hospital Mahim (W) Mumbai.

Conclusion: The value of HRV index Heart rate variability i.e. SDNN and echocardiogram index left ventricular ejection fraction (LVEF) are correlated moderately in disease cohort. R² test (goodness of fit test) index is insignificant showing that SDNN does not predict LVEF.

Keywords: II lead ECG, Heart rate variability (HRV), SDNN, Auto regressive analysis, Echocardiogram and left ventricular ejection fraction.
INTRODUCTION

About 27% of the global deaths are due to cardiac diseases. Incidence of cardiac diseases is more in diabetics and hypertensive. In lower income and middle income countries contribute to 80% of cardiac deaths.\(^1\) high carbohydrates in diet and less physical activity are the reasons of high blood pressure, glucose and lipids in the blood. Lipid deposits in the blood vessels that supply the heart or brain obstruct the blood flow causing gradual deterioration in cardiac performance culminating into a cardiac stroke. The gradual deterioration of cardiac performance is visible in only in heart rate variability (HRV) analysis at an early stage where no clinical symptoms are visible. The HRV analysis is not used in current clinical practice. The attempt to establish correlation between the echocardiogram findings and HRV analysis is focused towards validating the HRV analysis as an early diagnostic tool that can be used to control the morbidity and mortality rate due to cardiac diseases.\(^3\)

Overview of diabetes, hypertension and their complications

Almost two third of the deaths due to cardiac disease are from diabetic population. Probability of diabetic men developing into cardiac complication is two times higher than non diabetic men. In women the probability is three times higher.\(^9\) Diabetes causes multiple disorders in the several body functions. Micro and macro vasculature is affected due to long term hypoglycemia.\(^3,4\) Parasympathetic hormone is predominant in diabetics resulting into inability of the heart in fulfilling 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 resulting into morbidity.\(^4\) Resistance to glucose assimilation shifts the glucose metabolism to the protein and fat metabolism in diabetics and accelerates atherosclerosis.\(^3\) Occlusion in the coronary artery culminates into cardiac disease. The prevailing diabetic condition with prevalence of atherosclerosis causes hypertension. In case of hypertensive subjects the occlusion in blood vessels results in reduced blood supply. Heart works with extra force as a compensatory mechanism and hence in strained condition. In case of hypertension, the sympathetic activity is predominant. In case of subjects with diabetes and hypertension, the dominance of sympathetic or parasympathetic power depends upon whether the diabetic or hypertensive condition is more in prevalence. Reduced nutrient supply to heart wall develops a dead tissue is referred as myocardial ischemia permanent dead tissue causes myocardial infarction.\(^7\) Myocardial ischemia does not show any symptoms. Myocardial infarction shows symptoms like difficulty to perform regular routine, breathlessness etc. Myocardial infarction is an irreversible process. Hence early diagnosis just at the onset of myocardial ischemia is crucial.

The HRV indices like heart rate, heart rate variability and power spectral density in HF band 0.04-0.15 Hz are found to be distinctively different in case of diabetic and hypertensive subjects even when there are no clinical symptoms enabling a preclinical diagnostic diagnosis. The HRV analysis information is available from Auto Regressive (AR) analysis of RR intervals obtained from ECG signal acquired for the duration of 3-5 minutes.

QRS detector using Pan-Tompkins’s algorithm

When the ECG signal is acquired, it is superimposed by different types 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 steps mentioned below.

1) The band pass function is realized through a design of a low pass filter and the high pass filter.\(^5\)

The low-pass filter is described by the formula:
\[y(n) = 2y(n-1) - y(n-2) + x(n-2(n-6)) + x(n-12)\]

And the high pass filter is described by the formula:
\[y(n) = y(n-1) - 1[y(n-2) + x(n-2(n-6)) + x(n-12)]\]

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.

\[y(n) = 1[2x(n) + x(n-1) + x(n-3)] + 2x(n-4)\]

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 sampling rate.\(^5\) The sampling rate of the signal is 500 samples /second and the window size 75. The algorithm is shown in figure-1.

\[y(n) = 1[ x(n - (N-1)) + x(n-(N-2)) + x(n-(N-3)) \ldots x(n)] \times N.\]

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 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.\(^5\) (See Figure 1)

The changes in the waveform are shown step by step in figure 2 subfigures a-f denote the changes due to each signal transformation. The X axis in all the waveforms from figure-2 (a-f) shows the time scale. The Y-axis is represented by voltages from figure-2(a-e). The figure-2-f wave form represents the digitized state from presence or absence of pulse. The R-R peak in figure e is observed to be matching the peak of the integrator i.e. figure-2-a to 2-f.

**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 figure-3. The simulator lists the time domain indices, frequency domain indices and the nonlinear indices. The index used in the proposed paper is - SDNN. SDNN is a sensitive indicator of cardiac health.\(^6\)

**Overview of HRV analysis**

The HRV is an old technique stated by Hales in 1956. The RR intervals of a healthy heart shows variation of greater extent compared to the impaired heart. A healthy heart is sensitive to physiological, physiological
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.

Heart Rate: heart rate at rest is known as basal heart rate. Basal heart rate of a normal healthy person is 60 beats per minute. Heart rate goes on increasing with age. Diabetic subjects are observed to have resting tachycardia causing extra load on the heart. The average value of diabetic subjects with different durations of prevailing diabetic conditions may be as high as 84 bpm.\(^{10}\)

Heart Rate Variability

The heart rate varies as the demand of blood supply from the body increases. If there is change in the parameters that control the heart rate, the heart rate varies so as to maintain homeostasis i.e. the condition of equilibrium within the different body parameters. If the body performs some physical activity heart rate should increase. Such capability of varying the heart rate is heart rate variability. Heart rate variability reduces with age. The heart rate variability reduces by 4.6 beats per minute (0.07 beats per second) per year.\(^3\) The heart rate variability is measured in SDNN which is defined as of standard deviation of NN intervals in milliseconds.\(^6\) (The R-R interval is called as N-N intervals. Actually starting point of electrical activity is P event i.e. the atrial depolarization. But it is possible to locate and measure R interval due to it’s highest derivative property. Hence N-N interval can be considered as R-R interval.) SDNN is high in case of a normal subject. The typical average value is 47 in case of a normal subject and is 15 in case of diabetic subject.\(^9\) In case of diabetic subjects the heart variability reduces at a greater extent. Longer the prevalence of diabetes, lower the heart rate variability.\(^6,9\) Heart rate variability in case of untreated hypertensive subjects is much higher. By medication, the heart rate variability is controlled in hypertensive subjects so that heart does not get strained.

SA node firing is controlled by complex interacting hormones epinephrine and nor epinephrine that are responsible for sympathetic and parasympathetic response to any stimulus to heart. The interaction between the hormones is represented in the Figure-3.

Norepinephrine is a chemical hormone released from sympathetic nervous stimulation. Release of this hormone increases myocardial contractility. Acetylcholine is a chemical hormone released from parasympathetic activity. Release of this hormone decreases myocardial contractility. Presynaptic release of acetylcholine can inhibit sympathetic nervous stimulation thereby reducing the extent of sympathetic stimulation. The complex interactive effect is referred as accentuated antagonism. Increase in vagal drive induces bradycardia for a greater extent and is also accompanied by peripheral vasoconstriction resulting in increased SNS vascular drive. Adrenal medulla is innervated by pre synaptic release of norepinephrine to reduce the extent of release of epinephrine in the blood stream. Also the \(\beta_1\) and \(\beta_2\) adreno receptors are primed to selectively respond to Norepinephrine and epinephrine. Norepinephrine is an especially powerful vasoconstrictor hormone; epinephrine is less so and in some tissues even cause mild vasodilation. Sympathetic nervous system stimulates during stress or exercise, the sympathetic nerve endings in the individual tissues release norepinephrine, which excites the heart and contracts the veins.
and arterioles. The complex interaction between the two hormones leads to increased stress on the heart under prevailing hypertension. The hypertensive medication controls the heart from straining.

The Heart rate variability increases or reduces heart rate as per the demand of the blood from changing conditions in the body. Heart rate variability is the response dependent upon many different parameters like baro-reflex control, temperature control, psychological changes, hormonal changes etc. even at rest, the HRV is fluctuating. In fact HRV is a strong indicator of autonomous control that fires the SA node. In nondiabetic and normotensives, Heart rate variability does not bear any linear relationship with LVEF. In case of diabetic subjects, increase in parasympathetic neural signal power is higher. This indicates that autonomous neural control is modified. The premature LV filling due increased parasympathetic power is observed due to change in the cardiac fiber contractility and rate. In case of hypertensive subjects, sympathetic neural signal power is higher. This indicates the modification of neuro-humoral axis. The increase in sympathetic power is associated with improvement in cardiac output.

The figure-3 shows the HRV report of a normal subject and the figure-4 shows the HRV report of a diabetic and hypertensive subject. It can be noted that heart rate is higher, SDNN is lower and sympatho-vagal balance is lower than that of normal subject. The above observed indices provide confirmative diagnosis at an early stage before there is functional deterioration is clinically visible. The functional deterioration like reduced wall velocities and Left Ventricular Ejection Fraction (LVEF) can be clearly visible in echocardiogram.

**Interpretation of echocardiogram indices**

Since the early 1950s, ultrasound use in medicine has been the basis for several procedures that are widespread in today’s clinical practice. The principal application is in the field of medical imaging. Medical ultrasound imaging relies on the same principles as sonar or radar units. 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. 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. Since the ultrasound signals cannot pass from the bone, the probe is placed suitably to get suitable view. 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. Computational complexity needed for the image creation is comparative less. 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. Ultrasound systems are cost effective and are even available in small local low budget ambulatories. X-ray, CT and MRI, besides high costs, require extended dedicated areas. The disadvantage of Ultrasound image is it is highly noisy.

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 can be directly represent the functional indicator i.e. the LVEF. LVEF can be formulated as-

$$LVEF = \frac{EDV - ESV}{EDV}$$

EDV is the left ventricular end diastolic and ESV is the left ventricular end.
systolic volume. If the heart is functioning properly, the LVEF has a higher value. 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 and the LVEF of the heart. Figure-5 shows the echocardiogram showing the left ventricular volume change during diastole and systole.

As can be seen from the figure-4, LVIDd and LVIDs represent the left ventricular volume during diastole and systole respectively. The LVEF computed from the echocardiogram image is found to be high for normal cohort than the disease 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 subjects of control group and 20 subjects of diabetic group and 23 subjects of diabetic with hypertension 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**

The average SDNN of normal, diabetic with and without myocardial ischemia/infarction and hypertensive cohort with and without diabetes can be seen in table-1. The average SDNN for diabetic subjects is lower than hypertensive cohorts. This is due to the fact that diabetic cohort with myocardial ischemia/infarction have a very low value of SDNN.

Average SDNN and LVEF is found to be highest in normal cohort. Average SDNN and LVEF in hypertensive cohort is slightly less than normal cohort. The pathology in hypertensive cohort improves the cardiac output in the initial stage of hypertension.

Table-1 and Table-2 show the p-value for SDNN for diabetic cohort with and without myocardial ischemia/infarction compared to the normal cohort. Table-1 and Table-2 show the p-value for LVEF for diabetic cohort with and without myocardial ischemia/infarction.
ischemia/infarction compared to the normal cohort. The critical values of one tailed test of unequal variance between different cohorts are tabulated. It can be observed that p-value is much below the critical value. The t-test results show the data of the three cohorts for SDNN and LVEF is not interdependent on each other.

Correlation between one of the sensitive and significant HRV i.e. the SDNN and the cardiac performance indicator LVEF is a significant indicator of validation of HRV analysis. Echocardiogram though is a noninvasive and specific test; it does not have the preclinical diagnostic ability like HRV. The results stated in the proposed paper are significant as a preclinical non-invasive routine test to assess the cardiac health of diabetic and hypertensive subjects. Table-3 shows that SDNN and the LVEF are not correlated in normal cohort. A positive medium degree correlation exists in case of the disease cohort. Correlation coefficient listed in the table-3 indicates that there is some broad class of relationship between the two variables. The Pearson’s coefficient gives the degree of linearity in the relationship between the two variables. The below computed relationship shows the Pearson’s coefficient. The values of correlation range between +1 and -1. Positive values indicate positive correlation and negative values represent negative one. Any value below and upto 0.3 indicates that there is no correlation. Value above 0.3 suggests a medium degree of correlation. Any value equal and above 0.5 and upto 1 indicates strong relationship. The medium degree of correlation exhibits loose coupling between SDNN and LVEF indicating that LVEF is controlled by SDNN among the disease cohorts up to some extent and there are other controlling parameters also.

The pathophysiology of diabetic and hypertensive subjects is based upon predominance of parasympathetic and sympathetic powers. But the results show the positive correlation between both the disease cohorts. The hypertensive group includes diabetics also. The following results show that diabetic pathophysiology is predominant among the hypertensive cohort. Though parasympathetic and sympathetic power are antagonizing each other, parasympathetic power density is four times than the sympathetic power and predominates the neuro-humoral balance in supine position.13,14

FURTHER SCOPE

The same correlation can be checked for different cohorts of diabetic complication like diabetes with recorded evidence of different cardiac diseases. The same experiment can be tried for large number of cohorts on global basis.

REFERENCES

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### Table 1. t-Test: Two-Sample Assuming Unequal Variances for SDNN

<table>
<thead>
<tr>
<th>Cohort type</th>
<th>Normal</th>
<th>Diabetic with and without myocardial ischemia/infarction</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
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<td>38.04615385</td>
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<tr>
<td>Variance</td>
<td>280.6241026</td>
<td>389.9104453</td>
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<tr>
<td>Observations</td>
<td>27</td>
<td>39</td>
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<tr>
<td>Hypothesized Mean Difference</td>
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</tr>
<tr>
<td>df</td>
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<tr>
<td>t Stat</td>
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<td>t Critical one-tail</td>
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<td>P(T&lt;=t) two-tail</td>
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<tr>
<td>t Critical two-tail</td>
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### Table 2. t-Test: Two-Sample Assuming Unequal Variances for SDNN

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<th>Normal</th>
<th>Hypertensive with and without diabetes</th>
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<tbody>
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### Table 3. Correlation between the SDNN balance and LVEF

<table>
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<tr>
<th>Number of subjects</th>
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<th>Correlation coefficient for SDNN and LVEF (alpha=0.05)</th>
<th>Absolute Critical value of coefficient</th>
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<td>27</td>
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<td>0.404</td>
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<td>39</td>
<td>Diabetic with myocardial ischemia/infarction</td>
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<td>0.304</td>
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<td>40</td>
<td>Hypertensive with and without diabetes</td>
<td>0.371040557</td>
<td>0.304</td>
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ECG sample of 3-5 minute

DC shift removal

Band pass Filter (0-0.4 Hz)

Derivative filter

Square Filter

Moving window integration

R-R interval sample file

Kubios software simulator for HRV

**Figure 1.** Pan Tompkins Algorithm
Figure 2. a-f.

Figure 3. Interactions of epinephrine and norepinephrine at SA node.
Figure 4. HRV report of a normal subject
Figure 5. HRV report of a diabetic and hypertensive subject
Figure 6. Echocardiogram