Full Length Research Paper

Correlation Between Parasympathetic Power and Left Ventricular Ejection Fraction in Diabetes

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Cardiac diseases are more prevalent in diabetics. Prevention is possible if they are diagnosed at the preclinical stage. Such diagnostic practices can control mortality and morbidity rate. The study is conducted with 24 normal subjects, 35 diabetic subjects with and without myocardial ischemia/infarction. All the cases are recorded at Fortis-S.L.Raheja hospital Mahim (W). ECG samples of 3-5 minute duration in sitting and supine position are collected. Randomness in age, class, sex and other parameters in ensured on the basis of the data collected as per the registration of the subjects. A mathematical model is developed that supports the observation that the dominance of parasympathetic power reduces the LVEF. HRV index-parasympathetic power and echocardiographic index-LVEF is found to have a positive medium degree of correlation in normal subjects and negative medium degree of correlation in diabetic subjects with and without myocardial ischemia/infarction R2 test result is not significant showing that the parasympathetic power does not predict echocardiogram index LVEF.

Keywords: II lead ECG, heart rate variability (HRV), parasympathetic power, auto regressive analysis, end diastolic volume, end systolic volume and left ventricular ejection fraction.

INTRODUCTION

Third world countries are the largest contributors for global deaths due to cardiac diseases [1]. The effects of an unhealthy diet and physical inactivity may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, overweight and obesity. Unhealthy diet and physical inactivity are the major contributors to abnormal lifestyle diseases like diabetes [2]. Under prevailing diabetes, a gradual deterioration in cardiac performance is commonly observed. This deterioration culminates 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 of cardiac functional deterioration 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 AND IT'S 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. Diabetes causes multiple disorders starting from the glucose metabolism and several body functions are compromised. Almost all body organs are deprived of the nutrients due to protein and fat metabolism. Protein and fat metabolism cause atherosclerosis and dislipidemia. [3] Vasculature is affected due to long term hypoglycemia [3], [4]. Reduced signal conduction is observed under microvascular and microvasculature. The domination of parasympathetic hormone is observed in diabetic subjects. In diabetic subjects, the heart cannot fulfill the sudden demand of blood required to carry out different daily activities due to domination of parasympathetic hormone. As a result of dislipidemia and atherosclerosis, the different organs of diabetic subject are

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deprived of blood and nutrients [4]. As a result, diabetic subject experiences morbidity. Occlusion in blood vessels is more prevalent. If the coronary artery is occluded, the cardiac disease is resulted. The prevailing diabetic condition with a prevalence of atherosclerosis causes hypertension. Due to prevalence of diabetes, along with many other complications, the risk factor of cardiac morbidity and mortality increases.

The HRV indices like heart rate, heart rate variability, sympatho vagal balance, orthostatic stress index and the power spectral density in HF band (0.04-0.15 Hz) are found to be distinctively different in case of diabetic subjects. The HRV analysis information is available from Auto Regressive (AR) analysis of RR intervals obtained from the ECG signal acquired for the duration of 3-5 minutes in the supine and sitting position.

Mathematical models to demonstrate the functioning of the left ventricle

The pulsatile model describing cardiovascular dynamics is as shown in the figure 15.1a is a lumped parameter RC network system. [5] The functioning of the model is similar to the left ventricle. The ideal diodes D1 and D2 (analogous to mitral valve and aortic valve) ensure that the blood flow (analogous to current) travels in the direction shown in the diagram. The quantities Vv(t), Vh(t) and Va(t) are the pressure due to volume (ml) of blood in the veins is analogous to voltages, ventricle and arteries respectively. The condition for current I1 (t) to flow is Vv(t) > Vh(t) and I2 (t) to flow is Va(t) > Vh(t). The difference in volumes is analogous to the difference in voltages. The difference in voltage levels, initiates the current flow. Ca(t) is arterial compliance and Cv(t) is venous compliance. The quantity compliance is analogous to the capacitor. The compliance is fulfilled only when the volume is filled to full capacity (analogous to capacitor charge in electrical circuits). Once the compliance (capacitance) reaches the maximum, discharge starts. The elastance goes on increasing as the compliance reaches its minimum (negative pressure initiates ventricular filling is similar to zero charge in capacitor initiate the current flow in it). The behavior of compliance in relation to elastance is shown in figure 15.1b. R1 and R2 are the inflow and the outflow resistance of the left ventricle. Ra is the total peripheral resistance. The negative pressure creates the filling of the left ventricle by pulmonary vein at the left ventricular diastole. The negative pressure is created till the ventricle gets filled. When the ventricular compliance is fulfilled, the ventricle starts ejecting the blood in the arteries where there is less pressure. Unless the compliance is not met the current I1 (t) and I2 (t) does not flow. The ventricular compliance will be fulfilled when only the ventricular filling is complete. The elastance of the left ventricles increases till the compliance reaches a steady negative value that ensures the ventricular filling.
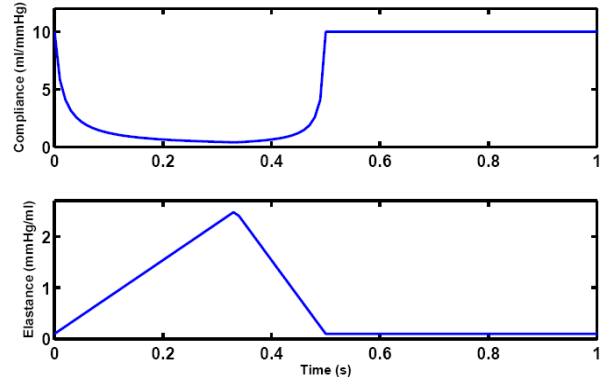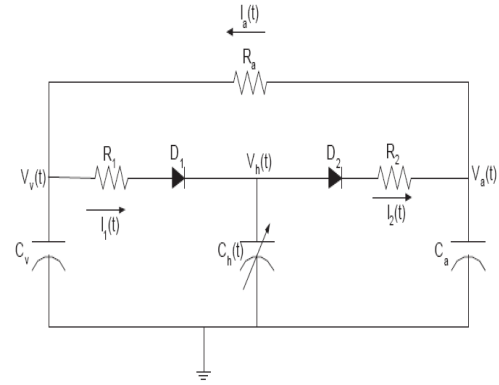
Fig 15.1a: The electrical circuit representing the left ventricle and **Fig 15.2 b:**Relation between compliance and elastance function for T=1 sec

The behavior is modeled with the following equations.
Where, Qh is the quantity of blood in the left ventricle.
Aluminum (6061 T6): UTS: 310Mpa, T: 0.7

$$\frac{dVa}{dt} = \frac{I2 - Ia}{Ca} \text{------------------------------} (5)$$

$$\frac{dVv}{dt} = \frac{Ia - I1}{Cv} \text{----------------------------} (6)$$

$$E_h(t) = \frac{3(Es - Ed)}{T} + Ed \text{ for } 0 < t < \frac{t}{3} \text{----} (7)$$

$$E_h(t) = \frac{6(Es - Ed)\left(\frac{t}{3} - t\right)}{T} + Es \text{ for } \frac{T}{3} < t < \frac{T}{2} \text{--} (8)$$

$$E_h(t) = Ed \text{ for } \frac{T}{2} < t < T \text{----------} (9)$$

$$E_h(t) = \frac{1}{Ch(t)} \text{----------} (10)$$

Where, the Es and Ed are end systolic and end diastolic elastance and Eh(t) is the time varying left ventricular elasticity. The systolic elastance is at the minimum and diastolic elastance is at the maximum value.

The elastance values formulated as discrete piecewise linearization. The unit for compliance is ml/mm Hg i.e. volume per (negative) pressure. The left ventricular elastance is reciprocal of left ventricular compliance. The different states and the corresponding slope of elastance and diode state are stated in table 15.1

Region	Slope of PWL function	Diode D1 state	Diode D2 state
I (contraction)	Positive	ON	OFF
II (isovolumic contraction)	Positive	OFF	OFF
III (ejection)	Positive	OFF	ON
IV (ejection)	Positive	OFF	ON
V (isovolumic relaxation)	Negative	OFF	OFF
VI (relaxation)	Negative	ON	OFF
VII (filling)	Zero	ON	OFF

Table 15.1 shows the ventricular state, elasticity and diode state

From the above analysis of the math model, left ventricular piecewise linear elastance of normal subject is for systole and diastole is in the range of 0.1 to 2.5 mm Hg/ml.

Effect of increased concentration of Acetylcholine on the left ventricular model

This signifies that in prolonged diabetic condition, with poor glycemic control, the diastolic depolarization rate is significantly reduced. The reduced depolarization rate is associated with reduced relaxation time. This reduces the blood volume filled from the pulmonary vein, reducing the Vv and I1 referring to equation (1).

It can be deduced from equations (1) and (2) that at given time, either I1 or I2 exists. Equation (4) either represents the flow rate of either deoxygenated blood coming from pulmonary artery or oxygenated blood pumped into the aorta. The reduced flow rate reduces the cardiac throughput and LVEF.
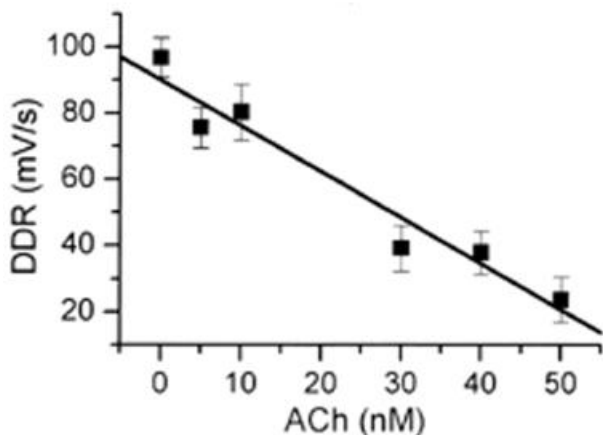

Figure 15.4 Acetylcholine concentration (nanoMol/L) and diastolic depolarization rate (MV/sec)

Effect of different concentrations of acetylcholine on diastolic depolarization rate is plotted in figure 15.4 [6]. The graph shows more or less linear relationship between the acetylcholine concentrations to diastolic depolarization rate. Acetylcholine secretion is also associated with release of Ca2+- Na2+ that enhances the contractility thereby reducing the relaxation period required for ventricular filling[7]. Also acetylcholine facilitates vasodilatation that affects the ventricular filling from the pulmonary artery. All the above stated facts combine to reduce the LVEF.

Fig 2: Area model of the Deep drawing die

QRS detector using Pan-Tompkins's algorithm

HRV analysis requires the RR interval details to be extracted from ECG signal samples. So it's essential to detect QRS peak from every RR interval.

When the ECG signal is acquired, it is superimposed by different type noise signals like:-

1. Supply frequency interference
2. Muscle artifact
3. Baseline wander
4. 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[3].

The low-pass filter is described by the formula:

$y(n)=2y(n-1) - y(n-2)+x(n)-2(n-6)+x(n-12)$

The high pass filter is described by the formula:

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

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 the derivative filter. This is followed by a square filter that converts the negative spectral amplitudes to positive and also enhances the high frequency component.

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

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[3]. The sampling rate of the signal is 500 samples /second and the window size 75. The algorithm is shown in figure-1.

$y(n) = \dfrac{1}{N} [x(n - (N\text{-}1))+ x(n\text{-}(N\text{-}2)) + x(n\text{-}(N\text{-}3)) \dots x(n)]$

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 maxim mum – 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[8].
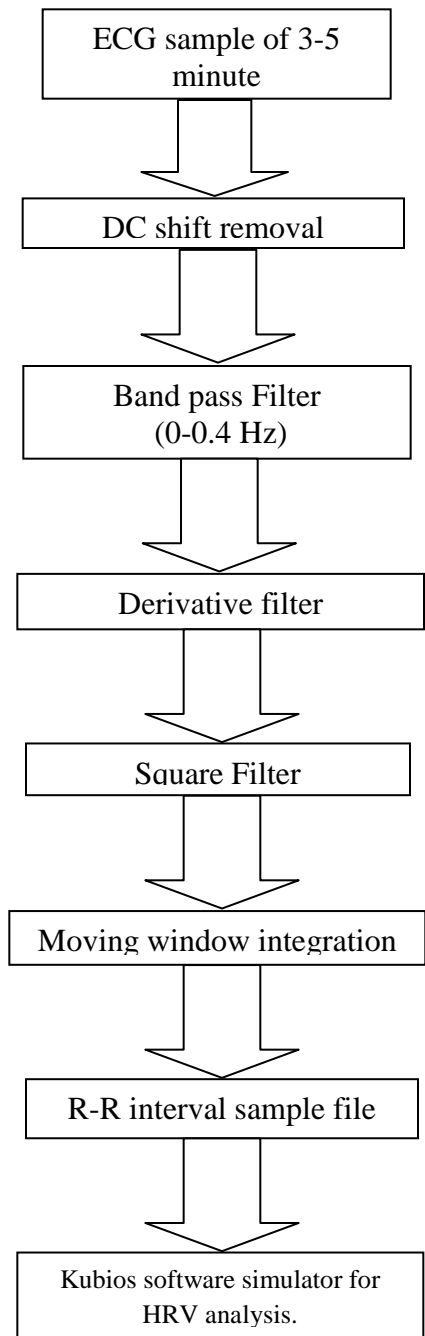
The changes in the waveform are shown step by step in figure 2 subfigures a-f denote the changes due to each signal transformation. The X axis in all the waveforms from of figure-2 (a-f) shows the time scale. The Y-axis is represented by voltages from figure-2-(a-e). The figure-2-f wave form represents the digitized state from the presence or absence of a 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[8].
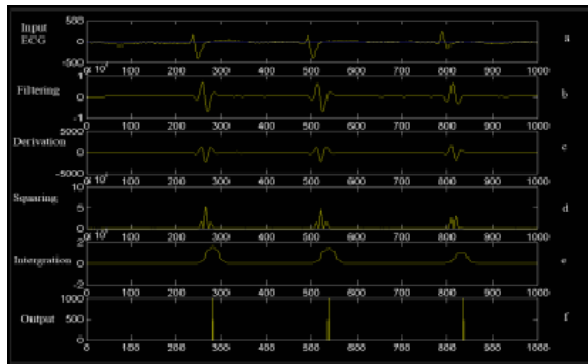

Figure-2-a-f

HRV ANALYSIS TOOL

The RR interval file extracted from ECG is given as an input to the HRV simulator. The Simulator is an open source simulation software developed by PHYSIONET called as a 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. Out of which, HF power of frequency domain analysis is analyzed in the current paper.

OVERVIEW OF HRV ANALYSIS

The HRV is an old technique stated by Hales in 1956. The RR intervals of a healthy heart show the 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 they are demanded by different activities of the 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 AR analysis represents three prominent frequency bands:-
1. VLF band -0.0-0.04Hz
2. LF band- 0.04-0.15Hz
3. HF band- 0.15 to 0.4Hz. [10]

The power variations in the two bands provide a noninvasive sympathetic measure of the autonomic dysfunction. Alterations due to mental stress, orthostatic stress, assessment post myocardial infarct, heart transplant surgery, evaluation of cardiac function after bypass can be a characteristic feature. [3] Autoregressive band is used to record the data as the technique filters out unwanted frequencies.

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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 │
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┌─────────────────────┐
│ R-R interval sample file │
└─────────────────────┘
          │
          ▼
┌─────────────────────┐
│ Kubios software simulator for │
│       HRV analysis.       │
└─────────────────────┘
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Fig 1: Pan Tompkins Algorithm

Normalized LF power

The power in these spectra represents the baroreceptor control in LF band, sympathetic hormone controlling and inhibiting the decrease in the heart rate and parasympathetic hormone controlling and inhibiting the increase in the heart rate. Increase in parasympathetic power augments this band. Every frequency spectrum represents the normalized power spectral density from the respective band in the HRV analysis report. This power is around 50 Normalized Units (NU) in case of normal subjects, decreased in diabetic patients. The Extent of decrease is related to the prevailing cardiac performance.

Normalized HF power

The power in this band for normal subjects is around 52 Normalized Units (NU). It is found that the parasympathetic power solely dominates this band. Parasympathetic band varies with variation related to respiration around 0.25 Hz. This error is called respiratory sinus arrhythmia. The subjects are requested to deep breath during the ECG was acquired.
The indices used in the proposed paper are – parasympathetic power derived from HRV analysis and LVEF derived from echocardiogram. A correlation coefficient of both the indices is compared for normal, diabetic subject with and without myocardial infarction/ischemia.

Figure-2 shows the HRV report of a normal subject comparing this to Figure-3 that shows the HRV report of a diabetic subject with myocardial infarction. It can be noted that heart rate is higher, heart rate variability (SDNN) is lower and sympatho vagal balance is lower than that of normal subjects. 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.
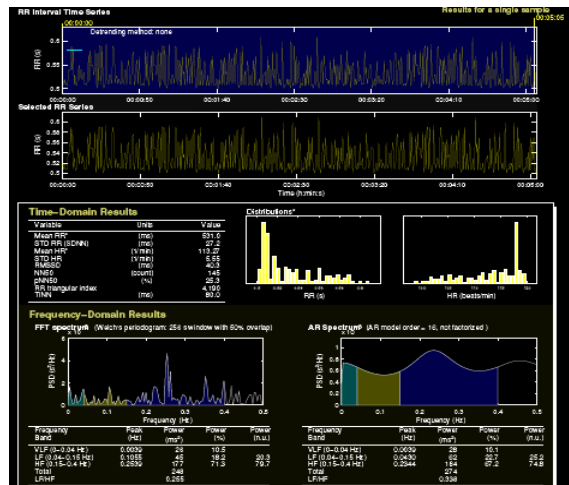

Fig 2: HRV report of a normal subject

Fig 3: HRV report of a diabetic subject with myocardial infarction

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 gray 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 inhomogeneity of most tissues. The backscattered signal is received by the same probe and converted into a grayscale 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. 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 comparatively 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. 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.[9] 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 the left ventricular directly represents 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[10]. If the heart is functioning
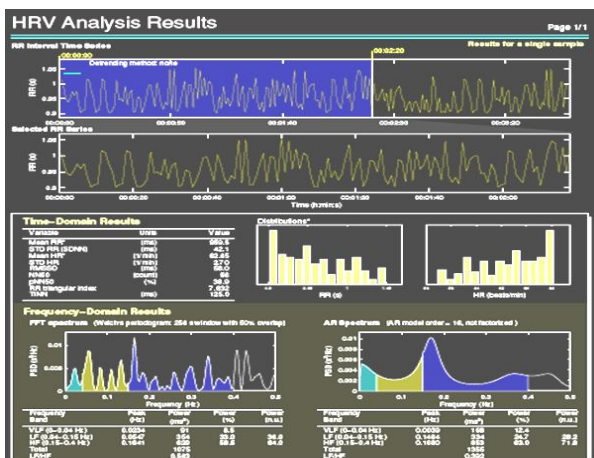
properly, the LVEF has a higher value, It has been observed the diabetic subject suffers from vasoconstriction. [4] The lack of availability of NO due to hyperglycemia causes the vasculature in a constricted state causing vasoconstriction. As a result the body organs are deprived of nutrients. The vasoconstriction and dominance of parasympathetic activity that declines the depolarization rate of the left ventricle directly affects 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. [10] As can be seen from the figure-5, 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.
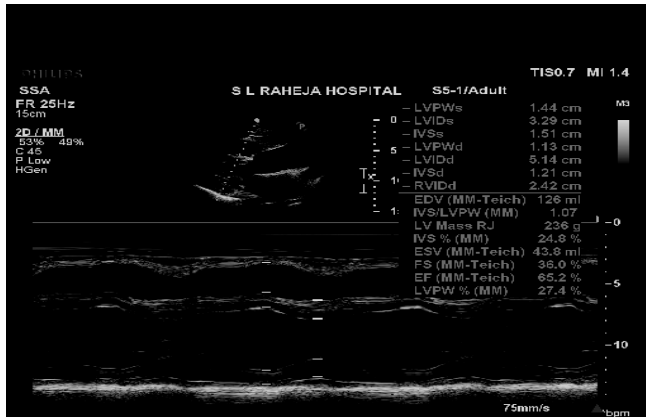

Fig 4: echocardiogram

DATA ACQUISITION PROTOCOL, INCLUSION AND EXCLUSION CRITERION

The study is carried out on non diabetic and non hypertensive subjects that visit the hospital for a checkup or admitted in the hospital. The II LEAD ECG and echocardiogram is acquired on the same day. Data of 25 subjects of the control group and 34 subjects of diabetic group 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 a 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 shows the average parasympathetic (HF) power for the different cohorts. The results match the pathophysiology of the diabetic subjects. It can be noted that there is an increase in diabetic subjects with myocardial ischemia/infarction as expected. The prolonged diabetic condition and poor glycemic index develops into myocardial ischemia/infarction and also consistently, the parasympathetic power in this cohort is maximum. Diabetic subjects with hypertension also have increased average parasympathetic power indicating predominant diabetic condition. Also it can be noted the table-2 shows the average LVEF is much lower in the diabetic cohort.

Table-1 shows the p-value for t-test parasympathetic power and table-2 shows the same for LVEF. The critical values of one tailed test of unequal variance between normal and diabetic cohort with and without hypertension are tabulated. It can be observed that p-value is much below the critical value. The t-test results show the data for the aforementioned parameters in the three cohorts is not interdependent on each other.

t-Test: Two-Sample Assuming Unequal Variances		
	HF Power Normal Cohort	HF Power Diabetic Cohort
Mean	65.10833333	71.31142857
Variance	32.75905797	19.20751261
Observations	24	35
Hypothesized Mean Difference	0	
df	41	
t Stat	-4.484006234	
P(T<=t) one-tail	2.89658E-05	
t Critical one-tail	1.682878003	
P(T<=t) two-tail	5.79315E-05	
t Critical two-tail	2.019540948	

t-Test: Two-Sample Assuming Unequal Variances		
	LVEF Normal Cohort	LVEF Diabetic Cohort
Mean	0.669125	0.503142857
Variance	0.00288881	0.022181008
Observations	24	35
Hypothesized Mean Difference	0	
df	46	
t Stat	6.044271553	
P(T<=t) one-tail	1.24267E-07	
t Critical one-tail	1.678660414	
P(T<=t) two-tail	2.48534E-07	
t Critical two-tail	2.012895567	

Table 1 and 2: T-test between normal and diabetic cohort for HF Power and LVEF

Table-3 shows the correlation between the parasympathetic power and LVEF between the control group and diabetic cohorts. The correlation indicates that there is some broad class of relationship between the two different variables. The Pearson's coefficient gives the degree of linearity in the relationship between the two variables[12]. 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 up to 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 up to 1 indicates strong relationship [12]. It can be concluded from the Table-3, parasympathetic power HF power has a medium positive correlation with LVEF for normal cohort whereas, and medium negative correlation is evident from diabetic cohort diabetic with and without myocardial ischemia/infarction cohort.

The medium degree of correlation exhibits loose coupling between the parasympathetic power and LVEF indicating that the LVEF is controlled by parasymapthetic power up to some extent and there are other controlling parameters also.

Positive correlation in normal subjects indicates that LVEF increases with increase in parasympathetic power. This is pathophysiologically consistent because in case of normal cohorts, the cardiac performance is an interplay of sympathetic and parasympathetic activity.

Negative correlation between diabetic cohort with and without myocardial ischemia/infarction indicates that LVEF decreases with increase in parasympathetic power. This is in consistence with the pathophysiology proposed in the mathematical model. The critical coefficients indicate the minimum value of correlation coefficient for the given number of subjects for the accuracy of 0.05% [13].

The computed coefficients are higher than the critical correlation coefficients indicated in the table-3.

Category	Correlation coefficient HF and LVEF	Absolute critical coefficient alpha=0.05
Normal	0.417568095	0.396
Diabetic with and without myocardial ishemia/infarction	-0.360560721	0.325

Above findings are highly significant for the validation oh HRV parameters.

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 a large number of cohorts on a global basis.

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