Abstract

Cardiac diseases contribute to 28.9% of the total deaths. Number of young population suffering from cardiac disease is rapidly increasing. India is the largest contributor in cardiac deaths. The diagnostic technology, equipments and quality of cardiac care in India is at par in comparison with the developed western countries. The drawback is due to the severely low ratio of cardiologist to normal population, the lack of medical help reaching the vast population and lack of awareness about the disease and factors causing the disease.

Myocardial ischemia / infarction are a major contributor of cardiac deaths. Myocardial ischemia / infarction are more prevalent in diabetic subjects than the normal population. Subjects with history of type II diabetes, (diabetes mellitus), suffer from faster deterioration of cardiac performance. The current diagnostic practice has a drawback of assessing the cardiac prognosis and risk stratification based only on the prevailing cardiac performance status. The cardiac health slowly deteriorates and there are no clinically visible symptoms at this stage. In prevailing diabetic, diabetic and hypertensive conditions, there is necrosis of nutrients due occlusion in blood vessels leading to death of the death of the muscle. If blood supply to left ventricular wall is restricted, the death of left ventricular wall muscle leads to myocardial ischemia. Myocardial ischemia reduces the contractility and Left Ventricular Ejection Fraction (LVEF). Advanced ischemic condition leads to irreversible death of left ventricular muscle causing myocardial infarction. This is a complication in prevailing diabetic condition, that severely affects the cardiac performance and can be avoided by preclinical diagnostic indicators.

The Heart Rate Variability (HRV) analysis tools are the only diagnostic tools that can assess the slow deterioration even when in absence of clinically visible symptoms. HRV tools are noninvasive, safe and provide quick results. The tests can be performed by paramedical staff saving cardiologist’s time and cost less compared to the echocardiography test. The requirement of the test is LEAD II ECG recording of the subject in supine position for 3-5 minutes (minimum 128 samples) and the same in sitting position. In the current normal practice, the cardiologist refers to an echocardiogram only after the subject complain of symptoms like fatigue breathlessness, chest pain etc. By the time the symptoms surface up, the deterioration of heart has irreversibly established which could have been diagnosed at an earlier stage by HRV analysis.

HRV analysis gives details about electrical signal generation and propagation within the heart whereas echocardiogram gives the mechanical, hemodynamic and functional performance details of the heart. Echocardiogram is costs more and takes
20-30 minutes. Generally doctors advice to perform echocardiology when there are some abnormalities observed in ECG signals. Echocardiogram gives complete information about the mechanical, hemodynamic performance but the test is normally prescribed by the cardiologists only after abnormalities in the ECG are observed or the subject’s cardiac performance is compromised.

The onset of deterioration of heart does not show any changes in ECG signals but the indication is visible in long duration statistical analysis of ECG i.e. the HRV analysis. HRV analysis includes autoregressive analysis or FFT analysis of ECG signals that give information about sensitivity of heart to respond to changing demand of blood. In diabetic condition, cardiac performance deterioration is more prevalent.

If HRV analysis is performed as routine practice in case of diabetic subjects, the cardiac assessment can be monitored regularly and preclinical diagnosis can be possible. The current diagnostic practice does not use HRV analysis. Hence there is a need to validate the HRV analysis indices with currently used diagnostic technique.

The study compares the HRV indices to the echocardiogram findings. The study is conducted on control group, diabetic subjects and diabetic and hypertensive subjects. Among the diabetic and diabetic and hypertensive subjects, subjects with myocardial ischemia and myocardial infarction are included to ensure the cardiac complications and analysis of their parameters. The study helps in providing prognosis analysis test for diabetic subjects as routine practice.

The problem stated above formulates into the problem definition of the doctoral study as-

**Study of myocardial ischemia implying echo-images and Heart Rate Variability data.**

The study has a major research contribution of quantifying deterioration due to diabetes that leads to gradual changes in the autonomous nervous system that lead to further complications in different body functions. Prevailing diabetic condition has measurable indicators in HRV analysis and changed HRV indices may indicate deterioration in cardiac as well as other systems such as central and peripheral nervous systems, kidneys, feet, skin, eyes, brain etc.

The scope of the problem is defined as-
Assessment of diabetic autonomous neuropathy and cardiac health assessment using HRV analysis in case of diabetic, diabetic and hypertensive, ischemic/infarcted and hypertensive patients.

Correlation between the two diagnostic modalities-
HRV analysis from ECG signals and echocardiograph.

To implement mathematical model to demonstrate-
1) Changes in patho-physiology in diabetic subjects affecting the neurological changes and performance of heart.
2) Changes in the left ventricular geometry affecting the performance of the heart.

The data samples are collected for control group, diabetic group and diabetic and hypertensive group. To ensure the different degrees of deterioration with prevailing diabetic and hypertensive disease, diabetic and hypertensive subjects with myocardial ischemia and infarction. All the samples are collected ensuring the variation of age, sex, economic class. The variation is ensured from the selection of patients as they register for examination in the hospital. ECG and echocardiogram of the selected sample is acquired. HRV analysis indices and echocardiogram findings are compared to assess correlation between the two diagnostic modalities.

The following indices from HRV analysis are acquired.

HR is the heart rate (bpm).

SDNN is standard deviation of NN intervals.

HF is normalized power in HF band.

LF is normalized power in LF band.

HF/LF ratio is the ratio of the two normalized power values.

The HRV analysis gives an important indication of status of cardiac performance. The FFT/AR analysis separates the low frequency (0.04-0.15 Hz) and high frequency (0.15-0.4 Hz) bands. The ratio of normalized power in these bands spectrum has a higher value ratio (usually around 1.0) in case of normal subjects. In case of diabetic subjects, power in HF band is higher. This reduces the ratio value. It has been observed that with ratio progressively goes on reducing as the number of years for prevalence of diabetes increases. So this in an early indication before the symptoms of reduced cardiac performance occurs.

The increase in parasympathetic (HF) power results in reduction in heart wall
motion. This change can be observed from the echocardiogram. This also reduces the left ventricular ejection fraction. Reduced value of left ventricular ejection fraction indicates the reduced cardiac performance.

It has been observed that in case of diabetic subjects, the changes are observed in HRV indices as-

1) Increase in heart rate
2) Decrease in SDNN
3) Decrease in power in HF band
4) Decrease in sympatho vagal balance
5) Decrease in orthostatic stress index [6]

It has been observed that in case of hypertensive subjects, the changes are observed in HRV indices as-

1) Decrease in SDNN
2) Increase in LF power
3) Increase in sympatho vagal balance
4) Increase in orthostatic stress index

IV  Echocardiogram results.

The functional performance of the heart can be assessed from the ability of the heart to contract and expand. This can be evaluated from noting down the left ventricular volume changes during diastole and systole. Also the posterior wall and intra ventricular wall velocities are evaluated. Also the left ventricular ejection fraction is recorded from the echocardiogram study.

From echocardiogram image,

LVID$_d$ is left ventricular internal dimension during diastole.
LVID$_s$ is left ventricular internal dimension during systole.
LVPW$_d$ is left ventricular posterior wall dimension during diastole.
LVPW$_s$ is left ventricular posterior wall dimension during systole.
IVS$_d$ is intra ventricular wall dimension during diastole.
IVS$_s$ is intra ventricular wall dimension during systole.

**Discussion of results.**
The orthostatic stress index derived from HRV analysis is the indicator that indicates about how quick the heart responds to the sudden physical change. The same is found to considerably low for diabetic subjects. This HRV finding is correlated to left ventricular ejection fraction, which is derived from echocardiogram study.

Statistical analysis concluded from the tests-
The average HRV indices are observed to be in consistent with cardiac performance index like contractility, wall velocity and LVEF. The values shown stating worst prognosis in case of Myocardial infarction/ischemia followed by diabetic, diabetic and hypertensive cohorts. There is not much variation in case of normal and hypertensive subjects.

The t-tests computed to ascertain the statistical independence of the different indices between cohorts are found to be much below the critical values.

The Pearson’s correlation test shows that there is prevalence of linear relationship between the heart rate, sympathetic power and orthostatic index and the LVEF for normal. Linear relationship is observed between heart rate, SDNN, Sympathetic and parasympathetic power and sympatho vagal ration in diabetic cohort with and without MI. Linear relationship exists between SDNN, sympathetic and parasympathetic power in hypertensive cohort with and without diabetes.

Linear regression shoes that sympathetic power contributes to 32.9% of the LVEF outcome in case of normal cohort.

The value is significant though low because heart is controlled by as many as 7 closed loop controls.

Multiple linear regression shows that heart rate, SDNN and LF power jointly contribute to 39.34% of the LVEF outcome in case of normal cohorts.

Exponential regression test shows that -
1) LF power contributes to 30.8% of the LVEF outcome in normal cohorts.
2) SDNN contributes to 33.2% of LVEF outcome in case of diabetic cohort.

The value is significant though low because heart is controlled by as many as 7 closed loop controls.

**Mathematical model implementation**
A left ventricular model is using electrical components is studied that gives complete understanding about working of left ventricle. Effects of acetylcholine, a parasympathetic hormone concentration variation and it’s effects on diastolic depolarization rate is discussed and cross verified with the results.

The closed loop control system implementation is implemented to demonstrate the SA node trigger. Also the synaptic weight conduction in different disease condition are simulated and are cross checked with different power values obtained in the HRV study.

The modification of neuro humoral axis in case of diabetics is implemented and verified by isolating sympathetic and parasympathetic power. A novel, computationally efficient, deployable and non linear technique is used for the same.

The contractility of left ventricle is modeled through left ventricular volume changes during diastole and systole and verified with left ventricular ejection fraction. The results are found to be consistent with the theoretical inferences.

**Conclusion from the results.**

The HRV indices can diagnose the shift in the neuro-humoral balance, the increase in parasympathetic power and decrease in total power in diabetic condition.

Shift in the neuro-humoral balance indicates inadequacy of the blood supply. The reduced blood supply indicates the compromised performance of the target organ.

Increase in parasympathetic power reduces the diastolic filling rate and indicates necrosis.

Reduced total power at SA node indicates the compromised performance of heart and insufficient pumping.

Increase in heart rate indicates the insufficient blood supply and overload on heart.

In case of hypertensive subjects, increase in sympathetic power is an early indicator of compromised heart performance.

Increase in SDNN is one of the significant markers in case of hypertensive subjects. SDNN in maintained at lower values by pharmacological intervention so that heart is not strained. Hence, SDNN cannot be considered as reliable marker.
The Left ventricular posterior wall thickness changes i.e. $\frac{\Delta R}{R}$ contribute by 25.35% to the contractility outcome in diabetic condition.

The HRV indices are useful preclinical tools that can assess diabetic autonomous neuropathy and cardiac health in case of diabetic subjects with and without hypertension and myocardial ischemia/infarction. They are effective in improving the morbidity and mortality rate in case of diabetic subjects with and without hypertension and myocardial ischemia/infarction.
Organization of the thesis

The contents of the thesis are stated briefly as-

1. Introduction
   Introduction to background and context that leads to the Problem definition.

2. Significance of the problem.

3. Problem definition statement.

Chapter 1. Introduction in detail.

1.1 Scope of the study.

1.2 Comparison of different diagnostic modalities used in diagnosis of cardiac disease.

1.3 Significance of the above mentioned doctoral studies.

1.4 Scope of the problem.

1.5 Details of the data specification.

1.6 Study Considerations inclusion and exclusion criterion

Chapter 2. Literature Survey.

Chapter 3. Theoretical background

3.1 Study of HRV and the related indices.

3.2 Detail of data acquisition methodology for HRV analysis.

3.3 QRS detector using Pan-Tompkins’s algorithm.

3.4 Simulation software
3.5 Study of Echocardiogram as a diagnostic modality.

3.6 Details of data acquisition from echocardiogram.

Chapter 4. Physiology and functioning of human heart.

4.1 Functional description and related anatomy.

4.2 Types of Cardiac Muscle.

4.3 Action Potentials in Cardiac Muscle.

4.4 Velocity of Signal Conduction in Cardiac Muscle.

4.5 Relationship of the Electrocardiogram to the Cardiac Cycle.

Chapter 5. Pathology of Diabetes and Hypertension.

5.1 Definition of Diabetes Mellitus and it’s impact on different organs.

5.2 Complication due to hypertension.

Chapter 6. Results and discussions.

6.1 HRV results.

6.2 Tables for patient data, HRV and echocardiogram indices.

6.3 The Average and Standard Deviation of HRV Indices and their Tabulations.

6.4 Correlation Results

6.5 Statistical Analysis of the Results.

6.6 Conclusion, limitations and further scope.

Chapter 7. Implementation of Mathematical model.

7.1 Mathematical model to demonstrate the functioning of left ventricle.
7.2 Effect of acetylcholine on functioning of heart.

7.3 Mathematical model to demonstrate the reduced signal conduction in neurons in diabetic condition.

7.4 Mathematical model to demonstrate the change in autonomous power in diabetic condition.

7.5 Mathematical model for quantitative assessment of cardiac performance based upon the changes in left ventricular geometry during systole and diastole.

Chapter 8. Early diagnosis of LVDD and LVH.

8.1 Left ventricular dysfunction.

8.2 Poincare plot analysis.

8.3 Modified Poincare Plot Analysis Used In Proposed Method.

8.4 Complication of Left Ventricular Hypertrophy (LVH)

Chapter 9. Conclusion, limitations of the study, further scope

9.1 Conclusion from statistical findings.

9.2 Conclusion mathematical mode.

9.3 Limitations of the study.

9.4 Further scope:

Publications and list of references.

Appendix A Sample case papers.

Appendix B statistical results simulations.

Appendix B Publication reviews.