A Review of Heart Rate Variability and It's Association with Diseases

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Abstract*: Heart Rate variability (HRV) is a powerful noninvasive tool which can be used to detect the status of cardio-autonomic function. Its analysis gives information about the cardiac health status .HRV measures specifically nonlinear measures can be sued as predictors of mortality, hence can be used to prevent the mortality, for both cardiac and no cardiac diseased subjects. Because of its significance in this paper a review has been presented on HRV analysis methods and HRV association with various diseases.

Index Terms: Heart rate variability, Diseases, Depression, Thyroid, Nonlinear measures, Analysis

I. INTRODUCTION

Electrocardiogram (ECG) represents the electrical activity of the heart, consists of P, Q, R, S, T waves representing the polarization and depolarization activities of arteries and ventricles of heart. The ECG originates from the sinoatrial node (SA) which is a natural pacemaker present in the heart. The ECG is acquired by placing electrodes on the limbs of a subject considering the right leg as the reference. The morphology of ECG indicates the cardiac health status of the subject [1] the fine changes in the ECG cannot be significantly seen with our eyes. The biosignals exhibit nonlinear and non stationary in nature. [2]¨ Cardiovascular system is a non stationary system [3, 4] and nonlinear mechanism is believed to be involved in the Heart Rate (HR) dynamics [5]

1.2 Heart Rate Variability (HRV)

The Heart Rate (HR) refers to the variation in the beat to beat interval. The variation of the heart rate around a mean value is the Heart Rate Variability it reflects the functioning of cardio respiratory control system [6]. Heart Rate Variability (HRV) has been studied for several years with an increased interest in understanding its role and clinical utility in disease .Hon Lee (1965) was the first one to demonstrate the clinical significance of HRV for monitoring fetal distress [7]. HRV analysis based on time domain methods was carried by measuring the RR intervals of diabetic subjects [8] The association among decreased HRV and increased risk of mortality after Myocardial infarction was demonstrated [9]. HRV is a vital and independent marker of mortality after Myocardial infarction [10]. Autonomic dysfunction is the major factor for cardiac diseases [11]. The faulty function of ANS is evaluated by observing the cardio-vascular autonomic regulation. Cardio-vasdular autonomic regulation indicates the interaction between sympathetic and parasympathetic activity in autonomic system function, and can be non-invasively assessed using HRV. [6]˙

1.3 HRV Analysis Methods and Evolution

HRV analysis has become a powerful tool in cardiology, as they are based on noninvasive methods which are simple to compute also indicate information about the heart disease patients [3,12,13].HRV analysis is carried out in three different methods namely Time domain method, Frequency domain method and nonlinear methods [14]. HRV is found to depend on various factors like gender, age, respiration and health status[15]. Small Standard deviation (STD) of RR intervals found were predictive of increased mortality in post infarction patients and the source of arrhythmias is due to the abnormalities in Parasympathetic Nervous system (PNS), and Sympathetic Nervous System(SNS),Spectral analysis could be used to estimate them [16].Analysis of HRV using time domain methods is simple but it has a limitation of discriminating the sympathetic and parasympathetic contributions of HRV[4].Frequency domain analysis overcomes the limitation by providing information about parasympathetic (High Frequency HF) and sympathetic (Low frequency LF) signals [16,4].Spectral analysis is the most popular linear techniques used in the analysis of HRV signals [17,18,19,4]. Spectral power in the HF band reflects respiratory sinus arrhythmias and LF reflects related to baro-receptors control and VLF power reflects related to thermo-regulatory and vascular mechanics related power [14, 4]. Spectral analysis of HRV has been wide spread used both in physiological and clinical studies to investigate short term compensatory perturbations. Spectral analysis of HRV has been widely used to detect short time compensatory oscillations in the fields of physiological and clinical studies. Spectral analysis could be carried out using parametric methods or non-parametric methods [20,6].

1.4 HRV Analysis of Diseases

A general finding is that healthy biological systems tend to have chaotic dynamics while as diseased systems will have reduced dynamics. Most commonly Autonomic dysfunction is observed to exist in cardiac disorders or other diseases including myocardial infarction, syndrome of multiple organ dysfunction severe head and brain injuries and sepsis, [21]**.** HRV indices are found to be high for Premature Ventricular Contraction (PVC),

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Sick Sinus Syndrome (SSS) Atrial Fibrillations, (AF) and low for Congestive Heart Block (CHB) Left Branch BundleBlock, (LBBB), Ischemic/ dialated cardiomyopathy .[22] found HRV power spectrum for motion sickness.[23]proposed wavelet transforms based classification of life threatening cardiac arrhythmia.

HRV is affected by the disorders of central and peripheral nervous system. Some disorders may independently affect HRV by modulating vagal and sympathetic fluctuations of HRV. In case of severe brain damage and depression the normal rhythm of HR is reduced.HRV may provide some information about the neurologic state of the subject. The significance of HRV analysis in psychiatric disorders arise from the fact that one can easily detect a sympathovagal imbalance, if exists in such pathologies. The nonlinear dynamics will indicate warnings about the diseases all time of the day or during certain times of a day [6]

[24] used nonlinear measures such as DFA, Hurst exponent and ApEn were used for HRV analysis of Coronary Heart Disease (CHD) subjects and found the changes in fractal properties of RR dynamics and concluded that HRV analysis using nonlinear measures gives independent information which cannot be detected with linear analysis techniques.[26]proposed nonlinear dynamic methods such as FD,1/f slope, ApEn and LE for the study of HRV in athletes and their results reflected the possible association between nonlinear indices and autonomous regulation of cardiovascular function. HRV variations can be found significantly not only in cardiac disorders but also in many types of illness or disorders Cardiac autonomic dysfunction may result cardiac arrhythmias or sudden cardiac death. [2, 25] applied nonlinear methods of analysis for clinical application in case of tiresome disease.

HRV analysis is a powerful noninvasive tool to evaluate the autonomic nervous system further autonomic dysfunction resulted reduced in HRV for some disorders like diabetes mellitus and coronary artery disease. They proposed a new technique to search pattern repeatability in the time series data [15].

1.5 HRV Analysis of ANS Dysfunction

Autonomic dysfunction is being recognized a major factor of cardiac diseases. [11] Found autonomic dysfunction as a major factor of cardiac diseases. HRV analysis can be used to measure cardiovascular autonomic regulation or asses the activities of the ANS noninvasively [4].It measures the interaction between sympathetic and parasympathetic activity in autonomic functioning. Frequency domain analysis provides for the separation of parasympathetic (HF) and sympathetic (LF) signals. Spectral power in the HF band reflects respiratory sinus arrhythmias, lf related to baroreceptors control and VLF power appears to be related to thermoregulatory and vascular mechanics [14,4]

1.6 HRV Analysis of Thyroid

The heart and peripheral vascular system gets directly or indirectly effected by thyroid due to changes in ANS. [27] [28] carried Power spectral analysis of HR for hypothyroid subjects.[29]observed autonomic dysfunction in Hypothyroid patients with higher level of vagal tone.[30] Estimated the correlation of autonomic indices as a function of the thyroid status for young females. The outcome is that no significant difference in the case of hypo and hyper thyroid cases and further negative correlation n for t3 and t4 and positive correlation for TSH was observed.. The change in the status of thyroid has effect on the metabolism of some amines in the brain. Indicating reduced parasympathetic activity with increased t3 and t4. According to Bernadette Biondi et.al (2004) Cardiovascular system is the victim of thyroid harmone, the cardiovascular system responds for more or reduced levels of thyroid hormone at the tissue level. Through genomic and non genomic functional effects T3 shows its impact on heart and vascular; its influence is reflected in the cardiac performance.

The changes in autonomic regulation of cardiovascular system and changes in cardiovascular system itself are found to be associated with thyroid dysfunction. Thyroid hormone dysfunction can result rise in blood pressure and may lead to arterial hyper tension [31]. [32] Performed nonlinear analysis of hypothyroid subjects using CD and found the value of CD to be 5.02 for hypothyroid subject as compared to 6.42 of healthy subject. Reduced CD indicated the reduced tolerance to cardiovascular stress Impact of hypothyroidism on autonomic regulation of cardiovascular system was evaluated by[33] by analyzing the influence of both Sympathetic and parasympathetic nervous system on heart. BP and Heart Rate restored to normal with thyroxine replacement[33]. [34] Evaluated the relationship of Thyroid hormones with HRV using power spectral analysis and found the sympatho vagal balance with ECG recordings of 5minute. It was found that changes in the serum levels effect the ANS regulations for hyperthyroid subjects

1.7 HRV Analysis of Depression

The ANS disregulation is a risk factor for cardiovascular mortality HRV analysis gives information about the ANS in various diseases.HRV methods are used to quantify ANS dysfunction linked with psychiatric disorders especially in depression, anxiety and schizophrenia Established results say that ANS dysfunction are associated with depression. Which has risk of cardiac diseases [35]

Researchers have established the link between Depression and ANS dysfunction. Studies of Epidemiology showed depression as an independent risk of cardiovascular morbidity and mortality. HRV and its measures of Cardiac disease subjects with depression and subjects with depression alone are smaller [36,37,38]. Depression is linked with increased rates of cardiovascular morbidity and mortality, may be due to increased risk of coronary artery disease and myocardial infarction. Cardiac autonomic innervation of the brain are measured by HRV. It is proposed that a reduction in parasympathetic innervation allows unopposed stimulation by sympathetic nerves which may result in arrhythmias and death. This chronic sympathetic stimulation is also noted in Heart transplant subjects with severe neuropathy and also in major depression .

Major depression disorder is reported to be associated with increased cardiovascular morbidity and mortality [39]. The subjects with major depression were diagnosed using frequency domain methods, time domain and also with nonlinear measures such as correlation dimension. Major depression disorder is reported to be associated with increased cardiovascular morbidity and mortality. The subjects with major depression were diagnosed using frequency domain methods, time domain and with nonlinear measures such as correlation dimension. HRV varies as a function of illness severity [6, 39, 40, 41].

1.8 HRV Analysis of Arrhythmias

HRV analysis proved to provide hidden information which is having clinical significance with respect to the health of the system producing the dynamics. HRV varies as a function of illness severity 60].Calculation of complexity of HRV time series data.[42]Used nonlinear HRV and Plethismogram analysis for normal and cardiovascular abnormal subjects. The measures used are DFA and RQA.

[43] Compared performance of non-linear indices in HRV analysis. They compared the robustness of non-linear indices and evaluated their applicability to HRV in presence of noise [44] showed the feature set extension for HRV analysis by using non-linear, statistical and geometric measures [45] performed non-linear analysis of HRV signal for characterization of cardiac heart failure patient to detect physiological and pathological states clearly using DFA, Higuchi Exponent, ApEn, SampEn and MSE. They proposed new regulating index Gaussian Entropy by modifying ApEn and Sample

Nonlinear parameters like correlation Dimension (CD) are used for pathological signals and they are useful indicators of pathologies.CD is one of the most widely used measure of FD.CD is estimated using the Grass Berger algorithm proposed by [46]. [47] CD and LE gave information about ANS process. [48] Proposed modified GrassBerger algorithm to find CD. Also proposed methods for the selection of parameters for calculation of CD and characterized HRV using CD of Hypertension group. CD value of Hypertension group is lower as compared to normal group. [49] applied CD for the HRV analysis of Healthy and Morbid group and found CD of Morbid group is less than the healthy group. [50] applied DFA and spectral analysis for HRV in Sleep and sleep Apnea. Spectral analysis was suitable for identification of cyclical variations and DFA can analyse scaling behavior and detect long range correlations. LF/HF increased for sleep and reduced with sleep Apnea. Changes in HRV are better quantified by scaling analysis than by spectral analysis [6].

[48] Characterised HRV using Correlation dimension(CD) of healthy and hypertension subjects and found that CD values of healthy subjects were more compared to hypertension subjects. [4]studied the nonlinear HRV measures for subjects in the age group of 5-70 and found that nonlinear measures of HRV reduced with age.[49] compared HRV of healthy subjects with morbid group using CD and found that CD values of Morbid group were less as compared to Healthy subjects. [50] Applied DFA and spectral analysis for HRV in Sleep and sleep Apnea.

HRV indexes have been used to study to cardiac diseases, renal failure , heart failure , diabetes , stroke , Alzheimer's disease , leukemia , obstructive sleep apnea , epilepsy, headache [6,51].[52] have evaluated and quantified nonlinear dynamic changes based on chaos theory for the analysis of heart failure subjects using FD, DFA and ApEn The observation of the study revealed lower ApEn and higher FD for heart failure patients.

1.9 Non Linear Methods and Applications

The traditional indices of HRV cannot detect the fine changes in the Heart Rate(HR) as the cardiovascular system is non stationary system [3,4] and nonlinear mechanism is believed to be involved in the HR dynamics[5]further cardiovascular system needs to be treated as a nonlinear system rather than a simple linear for better understanding of the system dynamics. Hence the variations in HRV gives information about the present disease and warnings about the hidden disease [53,4)].The cardiovascular system is too complex to be linear and treating it as nonlinear system can lead to better understanding of the system dynamics. Conventional methods of linear analysis failed to give full information about the HRV because of the nonlinear origin of HRV [54]. [55] Observed the difficulty to identify the physiological process based on the measured time series particularly in identifying nonlinear stochastic process and chaotic processes .Hence it is required to get information about positive Lyapunov Exponent (LE), non integer Correlation Dimension (CD) and nonlinearity. Consideration of both linear and nonlinear properties may improve diagnostic classification [56]proposed nonlinear techniques for arrhythmia detection using the ECG signal.[57]applied Largest Lyapunov exponent for the short term data analysis, [58] used nonlinear dynamics modeling in ECG arrhythmia detection and classification. [59] Classified arrhythmias into six classes using AR modeling. The classification of biological signals based on nonlinear features of HRV was done by [60].They used combination of linear and nonlinear features for the classification of heart rhythms. The linear features used were SDNN,RMSSD,PNN20 and HRV Triangular index and nonlinear features were spatial filling index,

The HRV analysis is based on the concept that fast fluctuations may specifically reflect changes of sympathetic activity and vagal activity and may contain indicators of current behavior or even warnings about impending diseases according to. [53] Adopted Detrended Fluctuation Analysis (DFA) method for the tiresome diagnosis. [24] used nonlinear measures such as DFA ,Hurst exponent and ApEn DFA could be used quantitatively and qualitatively to study HRV towards tiresome diagnosis. HR signals for classification of cardiac abnormalities into eight classes by extracting [4]. Spectral entropy, Poincare plot geometry and Largest Lyapunov Exponent (LLE) from HR signals for the classification using neural network and fuzzy classifiers. They concluded that HR signals can be used as reliable indicators of heart diseases .The demerit of LLE is that it cannot be used for short and noisy data Pincus introduced ApEn as a solution to apply it to relatively short and noisy data. The length of the data must of 10^{m}-30^{m} where ‘m’ is the embedding dimension [61, 62, 63].

There exists inherent bias with ApEn calculation to make the entropy independent of data length and bias is Sample Entropy(SampEn)In theory SampEn does not depend on N for N<200. where N is the length of the data. When N and r are large SampEn and ApEn are same [64].To estimate the behavior of HRV data in terms of complexity and regularity Multi Scale Entropy (MSE) is used [65] .

Nonlinear indices such as compression entropy (CE),DFA, and symbolic dynamics (SD) and standard linear analysis are applied for 24hr Holter ECG to investigate which of these indices enhance risk prediction in case of CHF subjects. The nonlinear indices with clinical information gave more risk stratification [66].[67] evaluated and quantified nonlinear dynamic changes based on chaos theory and applied Fractal dimension(FD),DFA and ApEn for the analysis of heart failure patients. Their study revealed lower ApEn and higher FD for heart failure patients. [68] Applied Power law slope, the short term fractal scaling exponent and measures based on Poincaré plots in cardiac patients. [25] Showed application of DFA as both quantitative and qualitative tool for HRV analysis.[69] applied ApEn and SampEn for the calculation of complexity of HRV time series data.

[48] characterised HRV using Correlation dimension(CD) of healthy and hypertension subjects and found that CD values of healthy subjects were more compared to hypertension subjects. [4] studied the nonlinear HRV measures for subjects in the age group of 5-70 and found that nonlinear measures of HRV reduced with age.[49] compared HRV of healthy subjects with morbid group using CD and found that CD values of Morbid group were less as compared to Healthy subjects. Spectral analysis for HRV in Sleep and sleep Apnea was performed using DFA[52].[46] have evaluated and quantified nonlinear dynamic changes based on chaos theory and applied FD, DFA and ApEn for the analysis of heart failure patients. Their study revealed lower ApEn and higher FD for heart failure patients.

1.10. Conclusions

Taking inspirations from previous studies that used techniques to quantify HRV and that demonstrated the hidden coupling between HRV and illness, Association of HRV with Non cardiac diseases can be considered for analysis. Further, the best suitable method in diagnosing effect of Thyroid, and Depression on ANS using nonlinear techniques is not reported in the literature. It may be proposed to find the best suitable nonlinear method in diagnosing Thyroid and Depression by exploring all the nonlinear techniques. Further the work may be extended to any other disease.

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