Section: Physiology

Original Research Article

EVALUATION OF VENTRICULAR FUNCTION USING T WAVE MORPHOLOGY PARAMETERS IN NORMAL SUBJECTS AND PATIENTS OF DIASTOLIC DYSFUNCTION ATTENDING CARDIOLOGY OUTPATIENTS DEPARTMENT RDJM MEDICAL COLLEGE AND HOSPITAL, TURKI, MUZAFFARPUR, BIHAR, INDIA

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Abstract

Background: In the present project, we assessed the repolarization characteristics of ventricles in a novel but easy way. The normal physiological system was compared with a disease state likely to affect repolarization phenomenon. We evaluated the patients of diastolic dysfunction as a candidate pathological entity. **Materials and Methods:** A Observational Descriptive study was conducted in the Department of Cardiology and Dept. of Physiology, RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India from December 2022 to June 2023. Patients of Diastolic Dysfunction diagnosed by standard clinical, electrophysiological, echocardiographic and biochemical criteria attended and/or admitted in the department of cardiology of RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India during the study period. Sample size for a Observational Descriptive study will be 74 as calculated in Epi.info STATCALC, version 3.4.3 (CDC Atlanta) with 95% confidence limit and 10% absolute precision. In the present study, carefully matched control subjects were also recruited as per criteria. After initiation of the research protocol and approval of the Institutional Ethics Committee, we conducted a small pilot study for feasibility evaluation, which is followed by submission of research synopsis. **Result:** The cases of diastolic dysfunction evaluated in the present study were evaluated with respect to presence or absence of same categorical variable; There are number of T wave morphology descriptors to evaluate repolarization heterogeneity like QT interval, QT dispersion, T Wave alternance, principal component analysis ratio, T-wave morphology dispersion, total cosine R-to-T, T-wave residuum etc., which were used with variable degree of success. **Conclusion:** T wave can be modelled as a combination of multiple periodic functions with varying amplitude and frequency.

INTRODUCTION

Einthoven recorded the first Electrocardiogram (ECG), more than a century ago, but the repolarization process is still the subject of debate and is an issue that has not yet been resolved.

In general term, VR is the electrophysiological phenomenon associated with the recovery or resetting of the cardiac cells, following their depolarization or excitation or activation. The T Wave in the ECG is the electrical manifestation of the Repolarization process and reflects the influence of heart rate, ANS activity, ventricular activation sequence and electrical alterations etc.[1]

The restoration of the negative transmembrane potential to a steady state is the process of repolarization. Repolarization is arranged in such a way that, difference between various parts of the heart is minimized to maintain electrical stability. It is achieved by adjusting the Action Potential Duration (APD) so that sites activated at an early stage have longer action potentials and sites activated at a later stage have shorter action potentials. The present view is that, the ventricular repolarization

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process begins in the epicardium and the polarity of the dipole wave front is same as that of depolarization. As a result, Repolarization in the normal heart tends to be as homogenous as possible, presumably to avoid the risk of re-entry VT.[2]

As long as the ventricular myocardium is not ischemic, the recovery of excitability (i.e. end of refractoriness) directly follows repolarization. Both the APD and effective refractory period (ERP), which protects the heart from too high heart rate, shortens when heart rate increases.[3]

It is apparently indicative that; studying heterogeneity of ventricular repolarization may provide a clue to the dispersion in APD in health and in various disease conditions likely to affect the repolarization phenomenon.

During various disease state like ischemia, APD changes dynamically. Initially it is prolonged and it then shortens. Also there are regional variations of APD changes across the mural thickness. Sympathetic stimulation increases dispersion of refractoriness and in homogeneity.

Inhomogeneity due to any reason causes dispersion of repolarization.[4] In congenital long QT syndrome, there is prolongation of APD with repolarization heterogeneity.

There are many different ways to evaluate repolarization heterogeneity. Measurement of QT interval, assessment of QT dispersion, measurement of T Wave alternace, various T Wave morphology descriptors.

In the present project, we assessed the repolarization characteristics of ventricles in a novel but easy way. The normal physiological system was compared with a disease state likely to affect repolarization phenomenon. We evaluated the patients of diastolic dysfunction as a candidate pathological entity.

We proposed the T Wave to be a combination of some waves of periodic function. We used certain mathematical model to decompose that T Wave into component wave forms. The characteristic visual representations and the numerical parameters of these curves in the normal controls and patients of ventricular diastolic dysfunction are objectively evaluated.

Aims and Objective

Objective: To evaluate ventricular repolarization using T wave morphology parameters in normal subjects and in patients of diastolic dysfunction.

MATERIALSANDMETHODS

An Observational Descriptive study was conducted in the Department of Cardiology and Dept. of Physiology, RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India from December 2022 to June 2023. Patients of Diastolic Dysfunction diagnosed by standard clinical, electrophysiological, echocardiographic and biochemical criteria attended and/or admitted in the department of cardiology of RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India during the study period. Carefully matched controls were obtained from the patients; apparently not suffering from any cardiac diseases admitted/attending RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India. T wave morphology parameters to be derived from digital Electrocardiography.

Inclusion Criteria

Patients of diagnosed of Diastolic Dysfunction diagnosed by standard clinical, electrophysiological and biochemical criteria attended and/or admitted in the department of cardiology.

Exclusion Criteria

Patients associated with cardiovascular complications other than Diastolic Dysfunction which may affect the pattern of ECG.

Patients having non-cardiovascular diseases which may affect the ECG pattern of individual like hyperkalemia.

Patients with implanted gadgets (AICD, pacemaker etc) Controls having known cardiac diseases.

Sample Size: The prevalence of Diastolic dysfunction as per literature (69) is 27.3% and total attendees per week is about 800, then the sample size for a Observational Descriptive study will be 74 as calculated in Epi.info STATCALC, version 3.4.3 (CDC Atlanta) with 95% confidence limit and 10% absolute precision. As per formula it will be Zpq/l2, where p=27.3, q=100-27.3, l=10%, Z=1.96 and the magic figure is 76. For comparison we take control @ 1:1 i.e. 76 cases and 76 controls.

Methodology: In the present study, carefully matched control subjects were also recruited as per criteria. After initiation of the research protocol and approval of the Institutional Ethics Committee, we conducted a small pilot study for feasibility evaluation, which is followed by submission of research synopsis.

Instruments: Digital electrocardiographic machine with data acquisition by an analogue to digital converter at the rate of 100Hz. with USB output drive to PC. Data archived in ASCII format Showing recording of digital ECG.

Standard PC for storage & analysis of data.

Softwares: Polylap (version 2.5) for data acquisition.

MATLAB (version 7.9.0.529) for graphics construction and data analysis.

SPSS (version 16) for statistical analysis.

Procedure: Detailed history noted following written protocol .Natural history of disease (onset, duration, family history etc) & therapeutic management also noted in details. All relevant records available with patient are collected. Patient were recruited from Dept of General Medicine on every Monday & Friday. Control were taken(age& sex matched) among the student, staff & teacher of RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India

Every subject was explained about the whole procedure & informed consent obtained. They were kept in resting state for 10-15 min. Digital ECG was performed in each subject (case & control) as per pre-

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defined Protocol, in the electro physiology lab. Of Dept. of Physiology, RDJM Medical College and Hospital, Turki, Muzaffarpur, Bihar, India.ECG data obtained are archived in PC in Excel format.

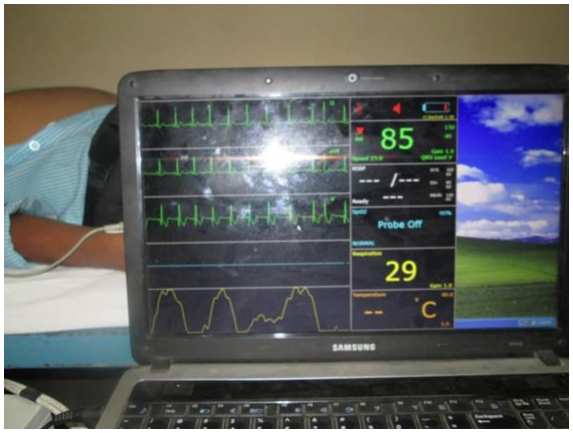

Figure 1: The Digital Electrocardiography Machine

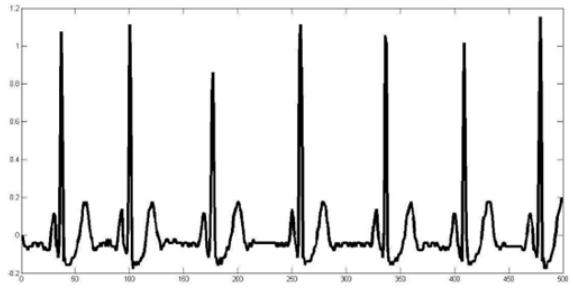

Figure 2: Time series data of digital ECG recorded (Lead I) for 5 Sec. and the ECG tracing drawn by standard graph drawing software (Data acquisition rate 100 Hz).

Sec.	mV
0.01	-0.039
0.02	-0.039
0.03	0.02
0.04	0.039
0.05	0.059
0.06	0.059
0.07	0.098
0.08	0.137
0.09	0.117
0.10	0.117
0.11	0.117
0.12	0.078
0.13	0.039
0.14	0.02
0.15	0
0.16	0
0.17	0.039
0.18	-0.039
0.19	-0.039
0.20	0
0.21	-0.02
0.22	0
4.90	-0.039
4.91	-0.039
4.92	0
4.93	0
4.94	0.039
4.95	0.039
4.96	0.078
4.97	0.098
4.98	0.098
4.99	0.117
5.00	0.117

Data Analysis-

Obtained data of ECG time series were primarily verified by reconstructing ECG tracing in Excel format [Figure 11]. After that the data was pre-processed by using noise-filter (electrical interference 50 HZ). Base line shift &drift also corrected. Whole range of data appropriately categorized, classified, tabulated and archived.

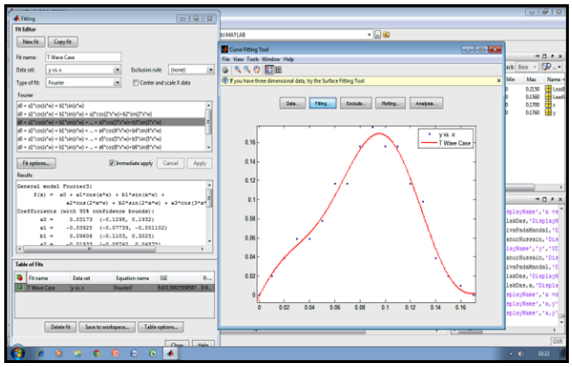

Figure 3: Sum of Sine wave transformation:

$y = \sum_{i=1}^{n} \quad aisin(bix + ci)$The **sum of sins model** is used for fitting periodic functions, and is given by the general equation

Where *a* is the amplitude, *b* is the frequency, and *c* is the phase constant for each sine wave term. *n* is the number of terms in the series. This equation is closely related to the Fourier series.

The second order sum of sine function in MATLAB is,

f(x) = a1*sin (b1*x+c1) + a2*sin (b2*x+c2)

Accordingly, we obtain six coefficients i.e. a1, b1, c1, a2, b2 and c2, which provide the morphological characteristics of each selected T wave.

In the present model, each T wave has been considered as a sum of two periodic sine waves. By means of mathematical operation, the T wave is decomposed into two sine waves and different characteristic parameters of those sine waves are obtained. a1 and a2 measure the amplitude of the greater and lesser waves respectively. Similarly b1, b2 and c1, c2 evaluate the frequency and phase constant of the two decomposed sine waves respectively. As mentioned earlier, all these parameters are measured in three different orthogonal leads (I, aVF and V2), i.e. from three different and mutually perpendicular spatial locations. This is because the shape and magnitude of these waves are different in each lead because each lead views the electrical activity of the heart from a unique position in space.

In the present model, each T wave has been considered as a sum of two periodic sine wave and cosine wave. By means of Fourier transformation, the T wave is decomposed into two sine and cosine waves and different characteristic parameters of those sine waves are obtained. a0, a1 and a2 measure

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the amplitude of the respective cosine waves along the order of the harmonic. Similarly b1 and b2 are the amplitude of the respective sine waves along the order of the harmonic. Evaluates the angular frequency. As mentioned earlier, all these parameters are measured in three different orthogonal leads (I, aVF and V2), i.e. from three different and mutually perpendicular spatial locations.

Statistical Analysis

Statistical comparison between Control and Case were conducted by Student's t Test (CI 95%). A p value of < 0.5 is considered as significant. Calculations are done in SPSS (v.16). For descriptive statistics – all scatters, clusters, plots etc. are done in MATLAB ((v.7.9.0.529).

RESULTS

The cases of diastolic dysfunction evaluated in the present study were evaluated with respect to presence or absence of same categorical variable; as for example Hypertension (HTN), Diabetes Mellitus (DM), Coronary Artery Disease (CAD) and Smoking Habits. Accordingly, in the percentage proportion of the cases are presented in respect to that group.

Ventricular Repolarization is the electrophysiological phenomenon associated with the recovery or resetting of the cardiac cells, following their depolarization or activation. The T Wave in the ECG is the electrical manifestation of the Repolarization process and represents the un-cancelled potential differences of ventricular repolarization. The process begins in the epicardium to proceed towards endocardium and the polarity of the dipole wave front is same as that of depolarization. Repolarization restores the transmembrane steady state to maintain electrical stability of the heart. It is achieved by adjusting the Action Potential Duration (APD) so that sites activated at an early stage have longer action potentials and sites activated at a later stage have shorter action potentials. It reflects the influence of heart rate, ANS activity, ventricular activation sequence and electrical alterations etc. Repolarization process is evidently heterogeneous and a subject of debate and is an issue that has not yet been resolved.

The issue of heterogeneity of ventricular repolarisation is of crucial scientific importance, which is seen in regional level, due to difference in the duration of the repolarization in different areas of the ventricle; transmural level and temporal level or beat to beat heterogeneity. Studying heterogeneity of ventricular repolarization may provide a clue to the dispersion in APD in health and in various disease conditions likely to affect the repolarization phenomenon.

There are number of T wave morphology descriptors to evaluate repolarization heterogeneity like QT interval, QT dispersion, T Wave alternance, principal component analysis ratio, T-wave morphology dispersion, total cosine R-to-T, T-wave residuum etc., which were used with variable degree of success.

In the present project, we assessed the repolarization characteristics of ventricles in a novel but easy way. We proposed the T Wave to be a combination of some waves of periodic function. We used certain mathematical model utilizing Fourier transformation and Sum of Sines decomposition to decompose that T Wave into component wave forms. The characteristic visual representations and the numerical parameters of these curves in the normal controls and patients of ventricular diastolic dysfunction are objectively evaluated.

The electrophysiological mechanisms of these changes are not well-explained. However, the change in APD is associated with change in the rate-adaptation characteristics, alteration in the refractory period, change in the (RPxCV) product or minimum re-excitable pathway length, alteration in the activation times, end of repolarization times, activation-recovery intervals, dispersion of repolarization, apico-basal repolarization gradient, change in APD/DI ratio, altered pattern of activation-deactivation cycle of Iks etc. Detail electrophysiological investigation is required to delineate the underlying mechanism.

The repolarization evaluation parameters as utilized in the present study can be appropriately standardized to assess progress and prognosis of repolarization disorders like ventricular diastolic dysfunction. However, due to number of limitation in the present study as mentioned, the goal is not fully reached.

A well-designed prospective cohort study is to be conducted to address the issue in a more efficient way and detailed objective analysis can bring about useful explanation.

The proposed method may also be utilized to validate the theoretical concepts of Intrinsic, Primary and Secondary T Waves proposed by Abildskov et al.

DISCUSSION

The present study is inspired by the landmark article of Kimmo Porthan et al (2013, 2009), where a robust epidemiological cohort studies was performed with more than 8000 samples, followed up for more than 6 years. They evidenced the role of a number of T Wave morphology parameters as gender specific prognostic parameters for cardiovascular mortality.[5]

T Wave morphology parameters or T Wave morphology descriptors are a number of measurements, based upon principle of mathematical modelling; briefly described in the review section, which forms the foundation of the present study.

However, in the present study we used certain simple and well-known mathematical tool to explore various morphological attributes of T Wave. These tools although well-known in the field of Science and Technology, but not much used in assessing wave morphologies in Clinical and Physiological Research.[6]

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For evaluation status of independent variables like DM, CAD, Smoking, HTN; we had to depend upon patients' feedback and medical records. The onset and duration of disease entities could not be objectively confirmed – thus the severity stratification could not be done. As the patients' sub-group population (DM, CAD, Smoking, and HTN) is relatively small, cross-correlation could not be performed.[7]

However, in spite of all these, there are very clear pattern of the observed difference between the Control and Case groups; which would have been statistically significant had there been adequate study sample population. Also there are statistically significant differences in certain variables like frequency components of the decomposed T Waves (e.g. b1 of Sum of Sines Decomposition and □ of Fourier Decomposition) even with these above-mentioned study limitations and deficiencies.[8]

There are certain basic differences between depolarization and repolarization with respect to the directionality of their trans-mural dipole propagation, although the polarity of the repolarization wave front is same as that of depolarization. Also there is a time delay, between transmembrane repolarization currents following depolarization and the propagation of repolarization is slower with longer refractory period and of heterogeneous pattern with regional difference. Hence the propagation pattern of repolarization is different from that of depolarization.[9]

As stated earlier APD is inversely proportional to the Heart Rate and directly proportional to the refractory period.[1,8,9] This is related to the phenomenon of rate adaptation, by means of which the repolarization stability and synchrony is maintained.

The cellular and molecular mechanism of repolarization heterogeneity and its adaptation in diastolic dysfunction depends on several factors. It is known that, the repolarising K+ current turns on very slowly (IK;) and is responsible for repolarizing the membrane at the end of the action potential (phase 3 of CAP).

Two currents that underlie IK—a relatively rapid component (IKR) carried by heteromeric HERG/miRP1 channels and a relatively slow component (IKS) carried by heteromeric KvLQT1/minK channels undergo slow activation with depolarization. For understanding repolarization heterogeneity it is the slow component IKS current which is important

In an electrical syncytium, such as myocardium, the direction of propagation is indifferent. The extinction of retrospective excitation during each cycle is appropriately achieved by various proposed mechanism.[10-12] The "leading circle" theory states the RP×CV product as re-excitable minimum path length.

This requirement is fulfilled by prolonged RP, resulting from long APD. Feedback harmonization of APD regulates the rate-adaptation of repolarization and the preserve of correct temporal and spatial repolarization patterns.[13]

Ventricular dysfunction produces certain electrophysiological changes both at cellular and organ level and lead to the alterations of the electro-mechanical properties of heart. Ventricular Diastolic dysfunction causes defects in myocardial relaxation by altered inactivation pattern and increasing repolarization heterogeneity, myocardial stiffness, wall thickness and altered chamber geometry.[14]

In the current investigation, the temporal characteristics of the wave form like frequency, phase constant underwent marked change. The decreased frequency content of the component wave forms in ventricular dysfunction found in the present study may be related with the change in the action potential duration (APD), change in the rate-adaptation characteristics, alteration in the refractory period, change in the (RPxCV) product or minimum re-excitable pathway length etc. Detail investigations are required to pinpoint and specify the underlying mechanism.[15]

The result also shows a phase shifting in the positive direction of the decomposed waves of T Wave in Cases of Diastolic Dysfunction. This finding is quite interesting in that, phase shift is a well know factor of alteration of T Wave morphology.[16]

There is an increase in the area subtended under the curve of T wave in Case groups to the extent of 44 %, as compared to controls. This is due to increased maximum resultant T wave vector (22 %) and increased duration of T wave by 41 % ($p = 0.001$). Increased AUCT indicates a higher energy of the T wave in diastolic dysfunction, the finding which was also seen in an earlier study by the present group on estimation of ventricular gradient in repolarization disorder like LVH.[17-19]

A well-designed prospective cohort study is to be conducted to address the issue in a more efficient way and detailed objective analysis can bring about useful explanation.

Finally, the methodology of decomposing T wave by using age-old mathematical tool utilizing user-friendly MATLAB tool and its implication in the biomedical research needs special mention. In the present context, as described earlier, there are theoretical concepts of Intrinsic, Primary and Secondary T Waves proposed by Abildskov et al,[20] which till the present time are used mostly as concepts and constructions made in the course of better understanding the source of the actual T waves, rather than as waveforms routinely constructed for physiological or clinical interpretation.

CONCLUSION

T wave can be modelled as a combination of multiple periodic functions with varying amplitude and frequency. There is decreased frequency content and increased amplitude of the decomposed waves of T Wave in Cases of Diastolic Dysfunction. There is

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phase shifting in the positive direction of the decomposed waves of T Wave in Cases of Diastolic Dysfunction. There is no alteration of the pattern of all the variables recorded from the different leads, representing different spatial position. There is increased energy of the T Wave; due to increase in T Wave area with increased duration and increased vector magnitude in Cases of Diastolic Dysfunction. The proposed method may also be utilized to validate the theoretical concepts of Intrinsic, Primary and Secondary T Waves proposed by Abildskov et al.

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