Analysis of beat-to-beat ventricular repolarization duration variability from Electrocardiogram signal

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Submitted in partial fulfilment of the requirements of the degree of

Doctor of Philosophy

December 2015

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The University of Melbourne

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Produced on archival quality paper

In the Name of Allah (God Almighty), the Most Gracious, the Most Merciful

Abstract

Electrocardiogram (ECG) signal analysis is a ubiquitous tool for investigating the heart's function. ECG indicates the cardiac action potential propagation characteristics within the heart chambers (from the atria to the ventricles) and any irregularity in ECG, which can be graphically detected, represents abnormality in the polarization process (i.e. depolarization and repolarization) of the cardiac muscle cell. The lower chambers of the heart termed as ventricles perform the main pumping function by directing blood to the lungs and the peripheral system including the brain and all other body parts. Abnormality in ventricular function is critical, which can cause fatal cardiac diseases, where the heart loses its normal function to maintain proper circulation. Depolarization and repolarization process of the cardiac action potential activates the contraction and relaxation operations of the heart, whose durations can be detected from the temporal distance between different ECG waves (i.e. QRS duration, RR interval, QT interval). Abnormalities in these temporal durations calculated by the different time series variability measures indicate problems in normal cardiac muscle polarization process.

Ventricular repolarization (VR) duration contains both the depolarization and repolarization durations, though the duration of depolarization is quite small in comparison to that of repolarization. Prolongation of VR duration from a normal baseline indicates the sign of ventricular dysfunction, which might initiate fatal ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation). VR duration variability represented by QT interval time series variability (QTV) in ECG contains crucial information about the dynamics of VR process, which characterises the function of the ventricles. QTV is affected inherently by heart rate, respiration, autonomic nervous system, age, gender and different genetical disorder of cardiac ion channels. Therefore, variation of VR duration may be affected by several factors, which cannot be analysed properly by using gross time series variability measures (i.e. mean, standard deviation). This thesis investigates different QTV analysis techniques from QT interval time series extracted from ECG, which investigate how different physiological and pathological conditions affect the normal VR process and how this alteration can be used as a subclinical predictive analysis technique of different cardiac diseases.

In this thesis, model based QTV analysis techniques were investigated and respiratory information based modelling approach is proposed for analysing dynamic QTV in healthy ageing and stressed condition. ECG derived respiration (EDR) was found a valid surrogate of respiration in modelling QTV, which provide only ECG based modelling technique for QTV by removing the need for collecting respiration signal separately. EDR based

modelling was found very effective in describing QTV changes with denervation of ANS branches (parasympathetic and sympathetic) in a prevalent complexity in diabetic patients (Cardiac autonomic neuropathy (CAN)). These findings can describe the effect of ANS modulation on QTV, which is important for validating QTV as a non-invasive measure of sympathetic nervous system modulation on the ventricles.

A novel approach describing systolic and diastolic time interval interaction derived from the VR duration (i.e. QT interval) and cardiac cycle duration (i.e. RR interval) in ECG was found very effective in subclinical CAN detection and CAN progression. This finding proves the feasibility of ECG based VR duration based measures in analysing left ventricular function of blood circulation.

A novel beat-to-beat QT-RR interaction analysis technique was developed, which was found very useful in analysing age related alteration in the normal VR process. The proposed measure can also be used for determining the QTV component that is not affected directly by the RR intervals (i.e. QTV component independent of heart rate variability), which is more sensitive to the sympathetic modulation of the ventricles. Moreover, this technique showed promising results in the analysis of dynamical QTV changes before arrhythmogenesis, which can be used for predictive analysis of ventricular arrhythmias.

Finally, the proposed technique for QTV analysis in this thesis will help to design low-cost and effective ECG based ambulatory care system that can be used for subclinical cardiovascular disease detection.

Declaration

This is to certify that

1. This thesis comprises only my original work towards my PhD candidature.

2. Due acknowledgement has been made in the text to all other materials used.

3. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies, and appendices.

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Mohammad Hasan Imam

Acknowledgements

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Author's Publications

The author's publications during the PhD candidature are listed in two sections. The first section lists the publications directly related to this thesis and the second section lists the other publications done during the PhD candidature. The publication list is sorted based on the type of the publication in the order of book chapter, peer reviewed journal, international peer reviewed conference papers organised in chronological order with the most recently accepted, or published article is first.

Publications directly related to this thesis

1. **Imam, M. H.,** Karmakar, C. K., Jelinek, H. F., Palaniswami, M., & Khandoker, A. H. (2015). Analysing Systolic-Diastolic Interval interaction Characteristics in Diabetic Cardiac Autonomic Neuropathy Progression. *Translational Engineering in Health and Medicine, IEEE Journal of,* doi: 10.1109/JTEHM.2015.2462339.

In this paper, an ECG based approach to analyse the temporal characteristics of the heart's mechanical function (i.e. Systolic and diastolic time interval) is described which could be derived from the dynamic ventricular repolarization (VR) and Heart rate variability (HRV) characteristics (i.e. beat-to-beat QT, TQ and RR intervals). The proposed measure is used to investigate Diabetic Cardiac autonomic neuropathy (CAN) progression, where the heart's mechanical function is normally affected due to Cardiac Autonomic Nervous system denervation with the progression of the disease. The findings of this study showed that the beat-to-beat systolic-diastolic interval interaction (SDI) measure can successfully determine the CAN progression characteristics and might be useful for detecting asymptomatic Left ventricular diastolic dysfunction (LVDD), which is very common in diabetic subjects. These findings also indicate that temporal ventricular repolarization characteristics in ECG can be used to investigate the mechanical dysfunction of the ventricles, which is a major risk factor of severe cardiac diseases like heart failure that might lead to sudden cardiac death (SCD). Chapter 5 of this thesis is written based on these study findings.

2. **Imam, M.H.,** Karmakar, C., Jelinek, H., Palaniswami, M., & Khandoker, A. (2015). Detecting Subclinical Diabetic Cardiac Autonomic Neuropathy

by Analysing Ventricular Repolarization Dynamics. *IEEE J Biomed Health Inform*. doi: 10.1109/JBHI.2015.2426206.

This paper represents a case study validating the respiratory information based QT-RR-Respiration interaction modelling technique to investigate changes in VR variability measured by the QT interval variability (QTV) in Diabetic Cardiac Autonomic Neuropathy (CAN) subjects. This study used a surrogate analytical technique to validate the causal effect of respiration on QT interval and the use of ECG derived respiration (EDR) instead of original respiration. The study results indicate that QT-RR-EDR model based technique can describe the gradual changes in QTV with the CAN associated autonomic nervous system alteration in the normal VR process. Moreover, the respiratory information based modelling technique can determine the Subclinical level of CAN, which is crucial for effective treatment of diabetic CAN. Chapter 4 of this thesis is written based on this study results.

3. **Imam, M. H.,** Karmakar, C. K., Khandoker, A. H., & Palaniswami, M. (2014). Effect of ECG-derived respiration (EDR) on modeling ventricular repolarization dynamics in different physiological and psychological conditions. *Medical & Biological Engineering & Computing, 52*(10), 851-860. doi: 10.1007/s11517-014-1188-0.

In this paper, a model-based approach using system identification technique is investigated for quantifying QTV with ageing and in a stressed condition within a healthy subject population. The traditional QTV modelling technique was found to be improved significantly by the addition of respiration, which proves the direct modulatory effect of respiration on QT interval and VR process. The case studies presented in the paper corroborate the physiological effect of respiration on QTV showing that addition of respiration in the existing QT-RR modelling technique significantly improves the model prediction capability irrespective of age and physiological stressed conditions. This study also verifies the use of EDR in place of original respiration in modelling and EDR is found equally powerful to describe the respiratory effect on QTV, which reduce the necessity of complex respiration signal recording setup. Furthermore, this modelling approach can describe the age and stress related changes of QTV in Healthy individuals through the analysis of model fitting values. Chapter 3 is written based on this analysis.

4. **M. H. Imam**, C. K. Karmakar, M. Palanaiswami, and A. H. Khandoker, "A novel technique to investigate the effect of ageing on ventricular

repolarization characteristics in healthy and LQTS subjects," in Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE, 2015, pp. 2796-2799. doi: 10.1109/EMBC.2015.7318972.

In this paper, a novel cardiac beat distribution analysis based technique is proposed for beat-to-beat QT-RR interaction analysis. This model free approach can quantify the QTV component independent of RR variability within a particular length of ECG recording. The findings of this paper indicate that the proposed methodology can reliably describe the ageing effect on QTV whereas another widely used measure QTVI cannot. Chapter 6 is written based on this paper.

5. **Imam, M. H.,** Karmakar, C. K., Khandoker, A. H. & Palaniswami, M. A novel technique for analysing beat-to-beat dynamical changes of QT-RR distribution for arrhythmia prediction. Accepted for publication in Computing in Cardiology Conference (CinC), 6-9 Sept., 2015, Nice, France.

This paper describes a novel technique for analysing dynamic or beat–to-beat QT-RR interaction pattern changes before Ventricular tachycardia (VT) onset. The findings of this paper showed that the developed technique can provide useful information about arrhythmogenesis and can describe the pattern of changes in QT-RR interaction in healthy subjects that might induce instability in VR, which might lead to initiate VT. This paper is linked with Chapter 6.

6. **Imam, M. H.,** Karmakar, C., Khandoker, A., Jelinek, H. F. & Palaniswami, M. Analysing cardiac autonomic neuropathy in diabetes using electrocardiogram derived systolic-diastolic interval interactions. Computing in Cardiology Conference (CinC), 2014, 7-10 Sept. 2014. pp.85-88.

This proof-of-concept paper presents the initial findings of a technique for analysing the temporal characteristics of Systolic and diastolic time interval measured from ECG signal. The proposed technique can describe the cardiac autonomic neuropathy related alteration in diastolic function and detect the CAN related changes in QTV. Chapter 5 of this thesis is linked to this paper.

7. **Imam, M. H.,** Karmakar, C. K., Khandoker, A. H. & Palaniswami, M. Effect of using ECG derived respiration (EDR) signal in linear parametric QT-RR modeling. Engineering in Medicine and Biology Society (EMBC),

35th Annual International Conference of the IEEE, 3-7 July 2013. 1968-197.doi: 10.1109/EMBC.2013.6609914.

This paper presents the proof-of-concept study, which verifies the effect of respiratory modulation on QT interval through a model based technique for QT variability analysis. This is the first study that validates the use of EDR in place of respiration in the model based QTV analysis. Chapter 3 is linked to this paper's findings.

8. **Imam, M. H.,** Karmakar, C. K., Khandoker, A. H. & Palaniswami, M. Effect of premature activation in analyzing QT dynamics instability using QT-RR model for ventricular fibrillation and healthy subjects. Engineering in Medicine and Biology Society (EMBC), 35th Annual International Conference of the IEEE, 3-7 July 2013. 2559-2562.,doi:10.1109/EMBC.2013.6610062.

This paper describes a limitation of model based stability analysis technique of ventricular repolarization instability. Increases in premature ventricular contraction (PVC) beats before the onset of ventricular tachycardia (VT) were reported to induce instability in the normal VR process in subjects with myocardial infarction. The normal presence of small amounts of premature ventricular contraction (PVC) beats in healthy individuals also indicate same instability pattern determined by the model pole-zero analysis. This paper recommends more in depth analysis of the QT-RR interaction for predicting VT onset. This paper is linked with Chapter 6.

9. **Imam, M. H.,** Karmakar, C., Khandoker, A., Jelinek, H. & Palaniswami, M. Detection of cardiac autonomic neuropathy using linear parametric modeling of QT dynamics. Computing in Cardiology Conference (CinC), 22-25 Sept. 2013. pp.1019-1022.

This paper presents the initial results of the first study of QT-RR-EDR model based technique for analysing QTV changes in Diabetic Cardiac Autonomic Neuropathy (CAN). Chapter 4 of this thesis is linked to this paper.

Other publications

1. Khandoker, A. H., **Imam, M. H.**, Couderc, J., Palaniswami, M., & Jelinek, H. F. (2012). QT Variability Index Changes With Severity of Cardiovascular Autonomic

Neuropathy. *Information Technology in Biomedicine, IEEE Transactions on, 16*(5), 900-906. doi: 10.1109/TITB.2012.2205010.

2. Jelinek, H. F., **Imam, M. H.**, Al-Aubaidy, H., & Khandoker, A. H. (2013). Association of cardiovascular risk using non-linear heart rate variability measures with the framingham risk score in a rural population. *Front Physiol, 4*, 186. doi: 10.3389/fphys.2013.00186.

3. Jelinek, H. F., August, K. G., **Imam, M. H.**, Khalaf, K., Koenig, A., Riener, R., Palaniswami, M. & Khandoker, A. H. Influence of stroke location on heart rate variability in robot-assistive neurorehabilitation. Biomedical Engineering (MECBME), 2014 Middle East Conference on, 17-20 Feb. 2014, pp. 253-256, doi: 10.1109/MECBME.2014.6783252.

4. Karmakar, C., **Imam, M. H.**, Khandoker, A. & Palaniswami, M. Influence of psychological stress on QT interval. Computing in Cardiology Conference (CinC), 2014, 7-10 Sept. 2014 2014. pp.1009-1012.

5. Jelinek, H. F., August, K. G., **Imam, M. H.**, Khandoker, A. H., Koenig, A. & Riener, R. Cortical response to psycho-physiological changes in auto-adaptive robot assisted gait training. *Annual International Conference of the Ieee Engineering in Medicine and Biology Society (Embc)*, 2011, pp. 7409-7412., doi: 10.1109/IEMBS.2011.6091725.

6. Jelinek, H. F., August, K. G., **Imam, M. H.**, Khandoker, A. H., Koenig, A. & Riener, R. Heart Rate Asymmetry and Emotional Response to Robot-assist Task Challenges in Post-stroke Patients. *Computing in Cardiology*, 2011, pp. 521-524.

7. Khandoker, A. H., Weiss, D. N., Skinner, J. E., Anchin, J. M., **Imam, M. H.**, Jelinek, H. F. & Palaniswami, M. PD2i Heart Rate Complexity Measure can Detect Cardiac Autonomic Neuropathy: an Alternative Test to Ewing Battery. *Computing in Cardiology*,2011, pp. 525-528.

8. Jelinek, H. F., Khandoker, A. H., Quintana, D. S., **Imam, M. H.** & Kemp, A. H. Complex Correlation Measure as a Sensitive Indicator of Risk for Sudden Cardiac Death in Patients with Depression. *Computing in Cardiology*, 2011, 809-812.

9. Jelinek, H.F.; Khandoker, A.H.; **Imam, M.H**.. Pulse wave analysis using tone-entropy algorithm in people with and without foot complaints in a rural diabetes screening clinic. Proceedings of the IASTED International Conference 2011, Biomedical Engineering (Biomed 2011). doi: 10.2316/P.2011.723-050.

Chapter 1

Introduction

1.1   Research Problem statement

Electrocardiogram (ECG) signal is a graphical representation of the electrical activity of the heart, which describes the propagation characteristics of the electrical cardiac action potential through the heart chambers (i.e.from the atria to the ventricles). Sinoatrial node (SA node) , located at the top of the right atrium generates the electrical impulse that flows to the ventricles through cardiac electric conduction pathways consisting of intermodal pathways, AV(Atrioventricular) node and AV bundle system and the purkinje system pathways consisting of left and right bundle branches in the ventricle. This cardiac impulse activates the synchronized contraction and relaxation function of both the atrias and the ventricles generating contracting forces of the ventricular muscle, which circulate blood from the atrium to the ventricle chambers. The two ventricular chambers then supply blood to the pulmonary circulation system by right ventricle and peripheral circulation system by left ventricle, which maintain the proper blood flow throughout the whole circulatory system of the body. Ventricular repolarization (VR)duration, which is measured as QT interval(i.e. Q wave to T wave end interval) from the body surface ECG signal indicates the total duration of depolarization and the repolarization of cardiac action potentials of the ventricular myocardium. The QT interval is called ventricular repolarization duration due to higher duration of the repolarization process than that of depolarization. Depolarization and repolarization of the ventricular action potential activate the contraction and relaxation operation of the ventricles respectively. Temporal variability of VR duration termed as QT interval variability (QTV) is an important parameter for investigating the normal heart function. Alteration in normal VR process indicates abnormalities in action potential propagation through the ventricles, which changes QTV and affects the synchronized mechanical function of the ventricles and lead to fatal ventricular arrhythmogenesis[1-3]. Therefore, analysis of QTV is crucial for risk stratification of cardiac arrhythmias and predictive analysis of different cardiac pathologies, especially Sudden Cardiac Death [4, 5].
SCD is the major health risk burden in the industrialized countries and SCD is the ultimate result of the majority of the cardiac and noncardiac deaths[6].The two types of lethal ventricular arrhythmias, Ventricular fibrillation (VF) and sustained Ventricular Tachycardia (VT) are the underlying reason of Sudden cardiac death (SCD), which is a fatal condition where a person can die within minutes if emergency external defibrillation is not applied timely[7, 8]. The increase in QTV from normal baseline value increases the instability in

VR process, which can initiate the onset of VT and VF [9]. Therefore, QTV can also identify the unstable VR characteristics, which necessitates efficient techniques for QTV measurement and analysis. QTV is normally investigated noninvasively through analysing QT interval characteristics in ECG. Due to the direct controlling effect of Heart Rate (measured by the inverse of RR interval from ECG) on QT intervals, analysis of the QT interval is normally done by applying some correction for heart rate called the rate correction of the QT interval. The main purpose of the heart rate correction is to determine QT interval free from the effect of heart rate though no heart rate correction formula can completely remove the effect of heart rate from QT interval. Several population based and individual correction formulas were proposed for the rate correction of the QT interval [10-12]. The main challenges in the determination of rate corrected QT interval (i.e. QTc interval) is the presence of high intersubject variability of the QT-RR relation and the modulatory effect of autonomic nervous system branches on QT-RR interval relation, which resulted in proposition of various heart rate correction formula for different population or different physiological characteristics[13-16]. Therefore, the use of a particular QTc value to analyse ventricular repolarization dynamics is not a reliable measure of VR although prolongation of the QTc interval was reported as the first sign of abnormal VR process in healthy old subjects and subjects having Long QT syndrome [17, 18]. Increased QTc interval was also reported as a marker of the onset of drug induced polymorphic ventricular arrhythmia called *Torsades de pointes*(TdP)[19]. However, variability of VR duration measured by variability of QT interval (i.e. QTV) was found to more consistent marker for the risk stratification of drug induced TdP and SCD than QTc prolongation in both animal and human studies[20-23]. Changes in temporal variability of VR duration (i.e. QTV) were reported as an established predictor of the onset of ventricular arrhythmias (i.e. VT and VF)[22, 24-27].Therefore, investigation of QTV changes ,which can be a potential marker to detect the instability of VR process is important in different pathophysiological conditions to assess the risk of inset of VT or VF and SCD[4, 9, 23-25, 28, 29].

Recent research studies showed that a major portion of SCD occurs in asymptomatic subjects without any previous history of cardiac diseases and the remaining portion of symptomatic subjects mainly have severe heart failure (i.e. Left ventricular ejection fraction<40%), acute myocardial infarction (AMI), hypertrophic and dilated cardiomyopathy and coronary arterial diseases(CAD)[7, 8, 30]. Genetical disorders in cardiac ion channel function (i.e. Long QT syndrome QT (LQTS), Short QT syndrome, Brugada syndrome), mild heart failure (i.e. diastolic heart failure with preserved left ventricular ejection fraction>40%), sympathetic nervous system over activation due to ageing and psychological stress are the major risk factors of SCD in asymptomatic subjects. Non-invasive ECG based variability measures

from both heart rate and VR are getting popularity for risk prediction and detection of subclinical cardiac disease in this asymptomatic subject group[8].

Heart rate turbulence (HRT) using RR interval time series and Microvolt T wave alternans (MTWA) from characteristic changes in beat-to-beat T wave amplitude are two ECG based measures for SCD risk stratification [6, 8]. HRT cannot provide much information about ventricular repolarization abnormality (i.e. QTV) as it is measured from the RR interval time series variation after the occurrence of a premature ventricular contraction beat (i.e. PVC) [31]. The MTWA analysis technique requires controlled increase in heart rate of the subjects and have several limitations to use in patients having atrial arrhythmias [32]. The presence of premature ventricular contraction (PVC) beats which is responsible for initiating VT also affect the TWA measurement procedure[33]. T_{peak}-T_{end} interval [34-37]and T wave morphology based parameters, which represents the spatial dispersion of T wave were also used for describing the spatial dispersion of the VR process in ECG for predicting the risk of having VT/VF in subjects with different genetical cardiac channel abnormalities (i.e. LQTS type 1, type 2, Brugada syndrome) [38-40]. Both of these techniques need 12 lead ECG recording for reliable results and cannot provide the exact beat-to-beat information about QTV changes before the onset of VT or VF. Dynamic or Beat-to-beat analysis of QTV is crucial for the prognostic analysis of arrhythmogenesis as it can identify the dynamic changes in the VR process before the onset of VT, which might lead to fatal VF and SCD if not suppressed. Therefore, recent studies focus on the use of short-term (i.e. 5 min to 10 min long ECG) single lead ECG recordings for beat-to-beat temporal QTV analysis, which were found very effective in the design of cost-effective healthcare solutions for the prediction of ventricular arrhythmogenesis and SCD [4, 5].

Temporal QTV, a measure of VR dynamics is directly affected by Heart rate variability(HRV) along with many other factors like respiration, ageing, stress, modulatory effect of sympathetic nervous system, different cardiac drug effects, cardiac ion channel dysfunction etc., although the effect of HRV is the dominant effect affecting QTV in healthy subjects [1, 41, 42]. Therefore, proper analysis techniques of QTV must consider the effect of these factors. Total QTV consists of two parts: one directly affected by the history of previous RR interval or HRV termed as QTV component dependent on RR and another component not directly affected by HRV but by other factors like respiration and sympathetic nervous system modulation[41, 43]. Modelling the interaction between beat-to-beat QT and RR intervals to quantify QTV and determining different QTV components is a popular technique, which is used to study the ANS effect on QTV[41, 42]. VR dynamicity analysis or determining dynamic relation between QT-RR interaction through regression modelling was also reported in several studies for risk prediction of ventricular arrhythmias

[44-47]. Although the current modelling methods can describe the QT-RR interactions, the model performance is not good enough to describe the effect of other inherent factors that affect QTV. Therefore, development of improved beat-to-beat QT-RR interaction analysis technique is necessary for understanding how the several factors affect QTV and the dynamical changes in VR before arrhythmogenesis. More factors affecting QTV and that are easily detectable from ECG (i.e. respiration and T wave amplitude) should be considered to improve the model performance (i.e. to increases the model prediction capability of describing QTV) and validation studies involving different cardiac pathologies are needed to evaluate the performance of the modelling technique to investigate the changes in QTV. The part of QTV not directly affected by HRV is termed as QTV component independent of RR and was found useful for providing prognostic information in different cardiac pathology [28, 48].Model based techniques are normally used for the detection of this component of QTV, which is affected by the complexity of the proper model selection and the complex spectral analysis procedure that is severely affected by ECG noise and the presence of PVC beats. Therefore, simpler methodology, which can handle the presence of PVC beats, should be explored to analyse this component of QTV. QT-RR interaction modelling technique is also used for the prediction of VT onset due to increases in the amount of PVC beats in ECG [9, 49]. However, the presence of PVC beats in normal healthy humans indicates the need for development of alternative techniques for predictive analysis s of VT.

Another widely used measure of QTV is called QT variability index proposed by Berger et al [26] which is used in several clinical studies for investigating the effect of different physiological factors on QTV (e.g. ageing, stress, physical manoeuvres, different cardiac pathologies)[27, 50-53] and also in risk stratification of VT/VF and SCD[4]. However, QTVI cannot measure exact beat-to-beat QT variability changes and cannot detect the exact timing information of an arrhythmic event, as it will measure the dynamical variability of VR within a particular length of the ECG recording (i.e. 5 min). Moreover, This measure gave inconsistent results in several studies involving the analysis of ageing on QTV as reported in [54] and in the risk prediction of VT/VF and SCD [24, 55-57]. QTVI cannot provide reliable predictive information about VT/VF onset in the presence of PVC beats[58] whose presence in the ECG can provide useful information about VT onset[9, 49]. Therefore, the field of the development of reliable beat-to-beat QTV measures are still open and requires more improvement especially in the analysis of cardiac pathology detection and the investigation of alteration of sympathetic nervous system effect on QTV due to several factors like ageing and stress induction.

Left ventricular dysfunction due to Heart failure, which is a major risk factor of SCD, is normally detected by Echocardiographic techniques. However, this cardiac imaging

technique is a bit expensive than the easily available ECG system and is not available in every clinical setting. Current challenges of the design of cost-effective efficient healthcare system requires the necessity of an ECG based system to analyse the left ventricular dysfunction for subclinical cardiac abnormality detection, which can make decisions about the patient group who are in need of further treatment like Echocardiography [59].This will prioritize the subject group, according to the severity of the disease level and make the patient care system more effective. As heart failure indicates the dysfunction of the ventricles and QTV is a measure of ventricular functionality, recent research focuses on driving techniques of analysing systolic and diastolic functions of the ventricles from temporal VR measures(i.e. QT interval, TQ interval)[60-63]. Therefore, QTV based measures should be investigated more to derive useful techniques for analysing heart's mechanical function. Finally, temporal variability measures of VR (i.e. QTV measures) need more improvement to investigate the underlying dynamics of VR, which is the most important phase of a cardiac cycle.

1.2   Aims of the research

As described in the previous section dynamic or beat-to-beat QTV measured from short-term ECG can be a useful biomarker for analysing the electrical and mechanical characteristics of the ventricles, which will provide complementary information to other ECG based markers for analysing VR dynamics and for the risk stratification of Sudden Cardiac Death (SCD). Multivariate analysis technique (i.e. Model based techniques) describing the interaction of QT interval with other factors that affect VR dynamics (i.e. Heart rate, respiration, autonomic nervous system) should be more informative of QTV than the single variable based analysis techniques (i.e. Statistical measurement tools of QT interval time series only). Therefore, improvement of the modelling techniques of VR and HR interaction is important for a better understanding of VR dynamics. More case studies are required for understanding properly the effect of ANS branch modulation, especially sympathetic nervous system (SNS) branch on QTV and to validate different QTV measures about their ability to describe the effects of SNS branch on QTV. These studies are crucial to determine the effect of altered ANS modulatory effects on QTV in different physiological and pathological conditions, which will strengthen the evidences for selecting QTV as a reliable non-invasive marker of Cardiac ANS modulation along with HRV. Reliable methods are also necessary for beat-to-beat dynamic interaction of QT and RR intervals, which could provide prognostic information about VR instability that can initiate to VT onset and lead to VF, which is the underlying cause of the SCD.

Therefore, the main objective of this research is to develop efficient techniques for beat-to-beat temporal QTV measurement from the short-term human ECG recording and examine how these QTV measures change with some major risk factors of SCD (i.e. Ageing, stress, ANS dysfunction due to diabetic cardiac autonomic neuropathy, Long QT syndrome etc.). The QTV changes (i.e. the increases in temporal dispersion of QT and the pattern of changes of QT-RR interactions with the SCD risk factors) can then be used effectively as ECG based measures for risk stratification and in predictive analysis of ventricular arrhythmias. Specific aims of this research study are:

1. Investigation of the modelling techniques of describing beat-to-beat QT-RR interval interactions to describe QTV and improvement of the existing modelling approach by incorporating the direct modulatory effect of respiration. This research will
   - ➢ Verify the causal modulatory effect of respiration on VR through modelling technique and validate the use of ECG derived respiration (EDR) instead of original respiration recording, which can make the modelling method based only on ECG by removing the necessity of extra respiration recording.
   - ➢ Analyse the effect of healthy ageing and psychological stress of QTV through modelling techniques

2. Validation of the respiratory information based modelling technique to investigate the effect on the ANS on QTV in healthy and pathological conditions where the normal VR process is altered due to ANS dysfunction (i.e. Diabetic Cardiac Autonomic Neuropathy, where both parasympathetic and sympathetic branches of the ANS are affected).

3. Derivation of novel measures from the ECG signal to analyse the mechanical functionality of the ventricles through investigating the temporal synchronization of the systolic and diastolic function and evaluate the performance of these measures in the Cardiac Autonomic Neuropathy progression.

4. Development of a novel model free approach to determine the QTV component independent of HRV, which can provide prognostic information about changes of QTV due to pathology and alteration of the effects of ANS on VR.

5. Investigation of novel techniques from a beat-to-beat QT-RR interaction distribution analysis approach for ventricular arrhythmia (VT/VF) prediction from a fixed length of ECG recording.

The common objective of the above mentioned aims is to study the physiological relevance of the proposed QTV measures in different healthy and pathological subject groups to understand the effect of Autonomic nervous system on QTV. Moreover, analysis of the sensitivity of the proposed measures with ECG data length variation was

done for the novel measures to verify the effectiveness of the suggested techniques for different short-term ECG segment analysis.

1.3 Thesis outline

This thesis consists of seven chapters presenting four main contributing chapters, which describe the methodological developments of the proposed QTV measures as discussed the research aim section. The validation of the proposed measures in different case studies was also discussed in the relevant chapters, which include healthy human and human subjects with different cardiac pathologies. Figure 1-1 shows the Thesis structure. A brief summary of the content of the different chapters is given below:

Chapter 2

This chapter discusses briefly about the physiological interpretation of the ventricular repolarization process and its variability as observed in body surface ECG. A brief review of different short-term ECG based QT interval variability (QTV) measures techniques is presented. Comprehensive literature review of a particular QTV analysis technique and its relevance with the physiological and pathological factors is given at the beginning of every contributing chapter (i.e. Chapter 3 to Chapter6).

Chapter 3

This chapter presents a respiratory information based QT-RR interaction modelling technique addressing the research aim 1, which improves the existing QT-RR modelling technique without respiration significantly, which proves the respiratory effect on QTV. A novel ECG derived respiration (EDR) based modelling technique is proposed and the use of EDR in place of respiration is validated by comparing the performance of the EDR based model with the original respiration based model in analysing QTV changes with healthy ageing and stressed condition.

Chapter 4

The chapter presents the case study for the validation of the proposed EDR based modelling technique in diabetic cardiac autonomic neuropathy (CAN) subjects to investigate the effect of ANS dysfunction on QTV, which fulfilled research aim 2. Surrogate analysis results were presented in this chapter proving that a causal coupled effect of respiration on QTV is found in both healthy and pathological subjects and this model based technique can effectively describe the QTV changes with the alteration of ANS with CAN.

Chapter 5

An ECG based technique is proposed for the analysis of Systolic-diastolic interval interaction in diabetic CAN subjects with the target of achieving research aim 3. Both type 1 and type 2 diabetic subjects are at great risks of having left ventricular diastolic dysfunction,

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which affects the temporal synchronization of systolic and diastolic time intervals and might lead to severe heart failure (both systolic and diastolic heart failure) at the later stage and sudden cardiac death. The method presented in this chapter was validated in diabetic CAN progression analysis showing that measures of temporal QTV from ECG can describe the mechanical dysfunction of the ventricles due to CAN and can complement the echocardiographic techniques for analysing left ventricular function.
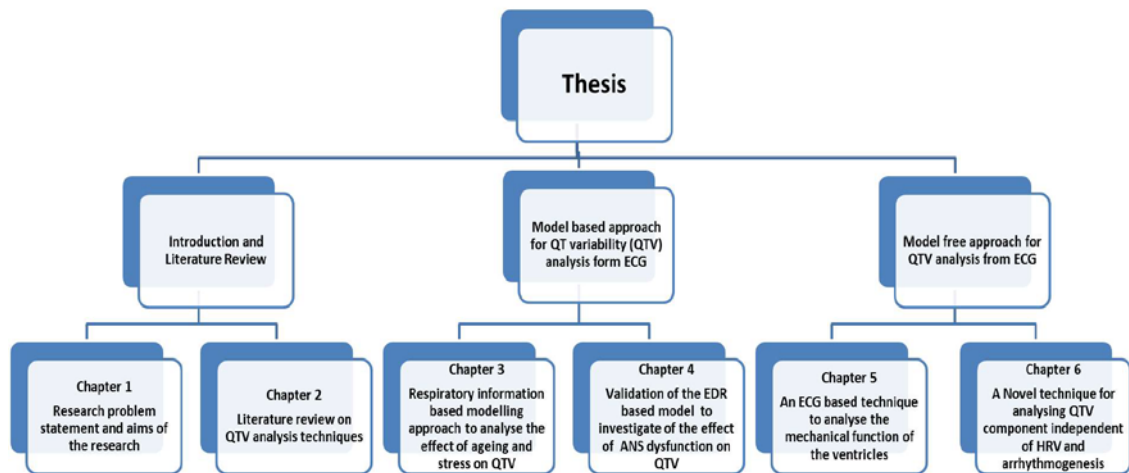
Figure 1-1: The thesis structure showing the brief contents of the chapters of the thesis, including the main contributing chapters (Chapter 3 to chapter6) except the last concluding chapter. Chapter 7 concludes the thesis with a general discussion of the findings and future directions of research in this field.

Chapter 6

A novel beat-to-beat QT-RR interval interaction analysis approach is proposed for completing the research aim 4. The developed model free technique can evaluate the QTV component independent of RR variability (i.e. HRV) which can describe the effect of ANS modulation on QTV and provide diagnostic information about pathology, which affect QTV. This point distribution analysis based method also showed promising results about prognosis of arrhythmogenesis, which addressed the research aim 5.

Chapter 7

General discussion about the findings of the different case studies for QTV analysis was presented in this chapter. This also includes a summary of the proposed QTV analysis techniques presented in the different chapters and indications of some future research.

Chapter 2

Literature review on ventricular repolarization duration variability measurement

In this chapter, a brief introduction is given about the heart's structure, the electrocardiogram (ECG) signal, the ventricular repolarization process, and the existing techniques of ventricular repolarization duration variability measurement from short-term ECG segments. This chapter mainly focuses on the brief discussion about the factors affecting the VR duration variability and how the temporal variability measurement techniques can describe the effect of these factors on QTV, which is the focus of this thesis.

2.1 Introduction

The heart is the one the most important parts cardiovascular system responsible for pumping blood to the lungs and to the remaining part of the circulatory system including the brain. The synchronized contraction and relaxation operation of the heart's lower chambers (i.e. Left and right ventricles) make the blood flow throughout the whole body. Any abnormalities in the ventricular function affect the smooth operation of the blood flow and problems in the left ventricular function causes severe problems as the body parts cannot get enough oxygen rich blood according to its need. These abnormalities can be detected from the electrical and mechanical characteristics of the heart. The two widely used measures of the heart's function derived from ECG are heart rate variability (HRV) and ventricular repolarization duration variability (VRV). Increase in VRV leads to unstable VR process, which can initiate fatal ventricular arrhythmia (VA) and leads to sudden cardiac death (SCD) [1, 2, 26, 64]. Therefore, analysis of VR duration variability from ECG is crucial.

Temporal variability (i.e. variation in beat-to-beat VR durations) of VR process is reported as a sensitive risk predictor of lethal VA (i.e. ventricular tachycardia (VT) and ventricular fibrillation (VF)) in a number of studies [4, 5, 22, 26, 65]. VRV analysis is also getting popularity in drug safety studies due to its better sensitivity than the analysis of only drug induced QT interval prolongation[20] and in the analysis of risk prediction of Torsades de pointes (TdP) in both congenital and acquired Long QT syndrome[66, 67]. Several techniques are reported to be used to measure the VRV from short-term ECG recordings in predicting the risk of arrhythmogenesis with some advantages and some inconsistencies in different subject population [5, 24, 55]. Therefore, more research studies should be focused to develop reliable and easy to use techniques to analyse VRV from ECG signal, which is

now a universal diagnostic tool. This chapter discusses briefly the heart's function, interpretation of different ECG waves, and presents a short review of the non-invasive techniques for VRV measurement from ECG.

2.2   Heart

The heart can be considered as an electromechanical pumping device, which performs the pumping function of the blood throughout the whole body and the pumping and relaxation is activated by the cardiac action potential. The heart consists of four chambers, where the upper chambers of the heart are called atria and the lower chambers are termed as ventricles. Heart actually consists of two pumps termed as right and left heart [68]. The right heart (consists of the right atrium and right ventricle) sends deoxygenated blood to the lungs through the pulmonary artery for the mixing of blood with oxygen and the left heart (consists of the left atrium and left ventricle) pumps oxygen rich blood through the aorta to the peripheral organs(Panel (A), Figure 2-1).

The pumping function is coordinated by the depolarization and repolarization of the action potential of the cardiac muscle of the atria and at the ventricles. A normal heartbeat is generated by the body's natural pacemaker, the sinoatrial node (SA node) in the right atrium, which spreads electrical activity through the heart's intrinsic electrical conduction system across the right and left atria. It creates the depolarization of the cardiac muscle at the atriums and the muscles create contraction that drives blood into and fills the chambers of the ventricles, which are responsible for pumping blood throughout the body. The muscle contraction is generated by the electrical activation, which is spread by a wave of bioelectricity (i.e. cardiac action potential) that propagates in a coordinated manner throughout the heart. This process is termed as depolarization. The action potential is transmitted from the SA node to the atria and then to the Atrioventricular (AV) node through the electrical conduction pathway (Panel (B), Figure 2-1). From the AV node the electrical signal further propagates to the ventricles through the respective bundle branches and subdivisions/fascicles. The AV node activation acts as the starting point of ventricular depolarization or ventricular contraction. The stimulated cardiac muscle produces efficient contraction of all four chambers of the heart, thus allowing selective blood perfusion through both the lungs and systemic circulation. The propagation of electric cardiac action potential is represented by an ECG signal recorded by the body surface electrodes, which shows the characteristics of atrial and ventricular depolarization and repolarization.
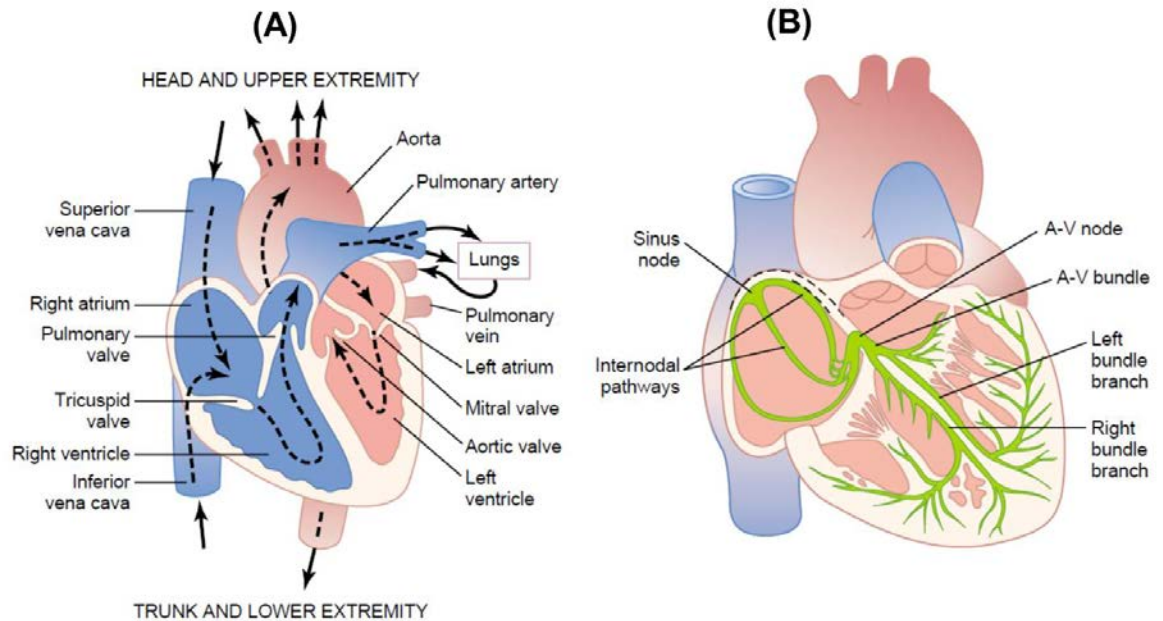
Figure 2-1: Structure of the Human heart. Panel (A) shows different heart chambers and the blood flow direction through the circulatory system through the main arteries and veins (blue colour indicates the deoxygenated blood in the right heart and red colour shows oxygen rich blood in the left heart). Panel (B) shows the cardiac electrical conduction pathways in the heart indicating the propagation path of cardiac action potential generated at the SA node to the ventricles through the AV nodal pathways and ventricular right and left bundle branch pathways. The propagation of cardiac action potential generates the contraction force of the ventricles to pump blood to the Lungs and other body parts. Adapted from [68].

2.3 Electrocardiogram (ECG) signal analysis

Electrocardiogram (ECG) signal, invented in 1903 by the Dutch physician William Einthoven is the most widely used and easily accessible bio signal in both human and animals. ECG is used as the most effective non-invasive diagnostic technique in cardiovascular physiology to analyse the Heart's function and the information extracted from the different ECG wave intervals can indicate abnormalities of the cardiac system in different pathological conditions.

Figure 2-2 shows different ECG waves with the corresponding depolarization and repolarization patterns of the atria and ventricles. P wave indicates the depolarization of the cardiac muscle at the atria and the initiation of atrial contraction. QRS complex indicates the depolarization of the ventricular muscle and initiation of ventricular contraction. T wave indicates the repolarization of the ventricular myocardium and the corresponding relaxation of the ventricular muscle structure. QT interval consists of the total duration of depolarization and the repolarization of ventricular myocardium and commonly termed as Ventricular repolarization (VR) due to higher duration in comparison to depolarization (

Figure 2-2). Variability of QT interval in terms as ventricular repolarization variability and measured from the QT interval on the surface ECG.
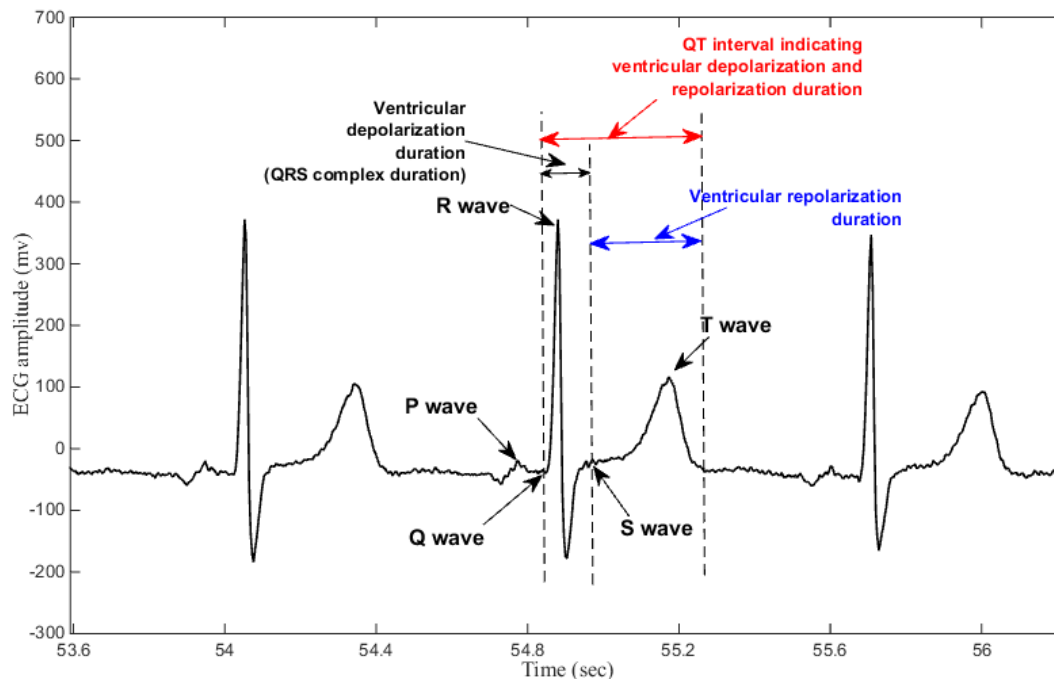
Figure 2-2: Different ECG wave components indicating the depolarization and repolarization duration of the atrium and the ventricle.

2.3.1   Generation of T wave and significance of Tpeak-Tend interval

The T wave is generated due to the transmural dispersion of the repolarization characteristics of the left ventricular myocardium. Ventricular cardiac muscle consists of three layers of cells with different electrophysiological characteristics, namely, Epicardium, Endocardium and sub endocardial M cells. The voltage gradient generated from the differences in repolarization characteristics   of the cardiac action potential in these three layers is the underlying reason of the inscription the T wave in ECG[69]. Figure 2-3 shows how normal and prolonged QT interval due to drug induction (i.e. sotalol induction) is generated from the transmural dispersion of cardiac action potential repolarization characteristics in the three layers of the ventricular myocytes. The repolarization characteristic of the M cell is found to be more sensitive with the drugs, which causes the increase in action potential duration and rapid changes in heart rate[70]. The different repolarization characteristic of M cells in comparison to Endo and epicardial ventricular myocytes causes abnormalities in QT interval like prolongation of QT that might lead to a polymorphic ventricular tachycardia known as Torsades de pointes (TdP) which is found as the increases in Tpeak-Tend interval in ECG[69, 70]. Therefore, characteristic changes in T wave downslope will characterize both the spatial and temporal variability of the VR process [35-37, 71]
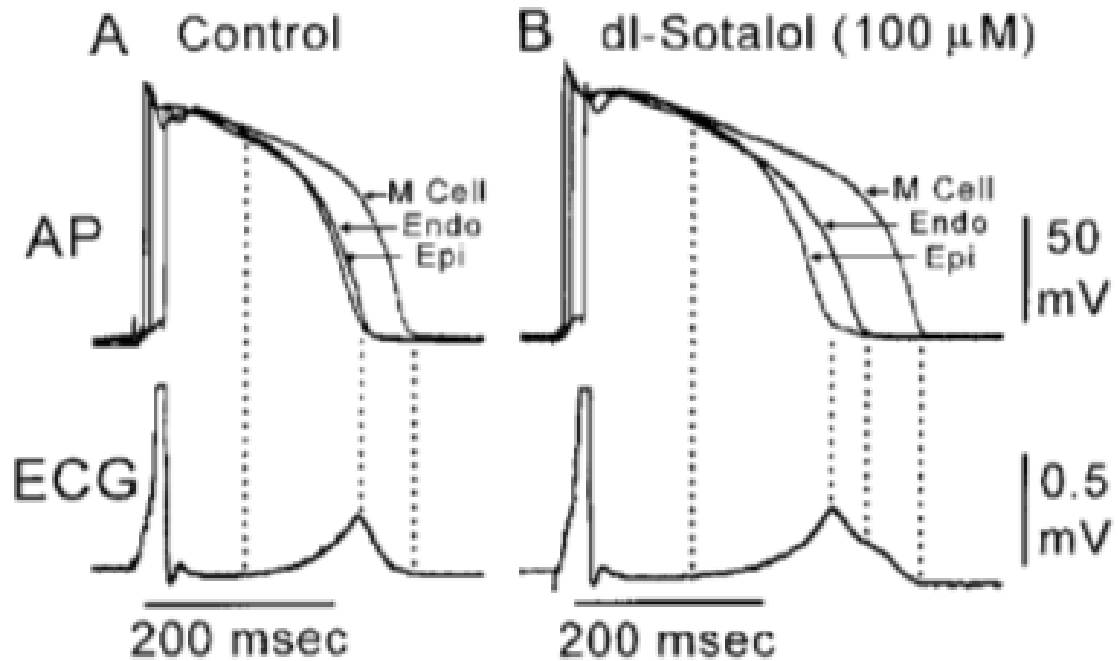
Figure 2-3: Generation of T wave in the transmural ECG in a control and drug induced arterially perfused left ventricular wedge due to transmural dispersion of repolarization at the left ventricle . This Figure is edited from the original in [69].

2.3.2   ECG recording system

Different types of lead systems are used for recording ECG signal from the body surface. The most commonly used system is the 12-lead ECG system or subset of that system which requires less number of leads (i.e. single lead, bipolar lead). The ECG data used in this thesis were recorded in the Lead II configuration for most of the case studies due to the presence of high amplitude T wave in this lead. In some cases, the other lead configuration recording was unavailable. The databases collected from Physionet (i.e. Fantasia, drivedb, MIT-BIH malignant ventricular ectopy database (VFDB), MIT-BIH Normal Sinus Rhythm Database, AHA database) also have single lead recordings[72]. ECG data used in the case studies presented in Chapter 6 were collected from THEW databases, which have Holter recordings where the ECG were acquired using three pseudo-orthogonal lead configuration (X, Y and Z) [73]. For QTV analysis, ECG Lead with the undistorted highest T wave amplitude must be chosen for reliable results in this type of Holter system. Figure 2-4 shows the ECG electrode position for recording the single lead ECG Recording (i.e. Lead I, Lead II or Lead III).
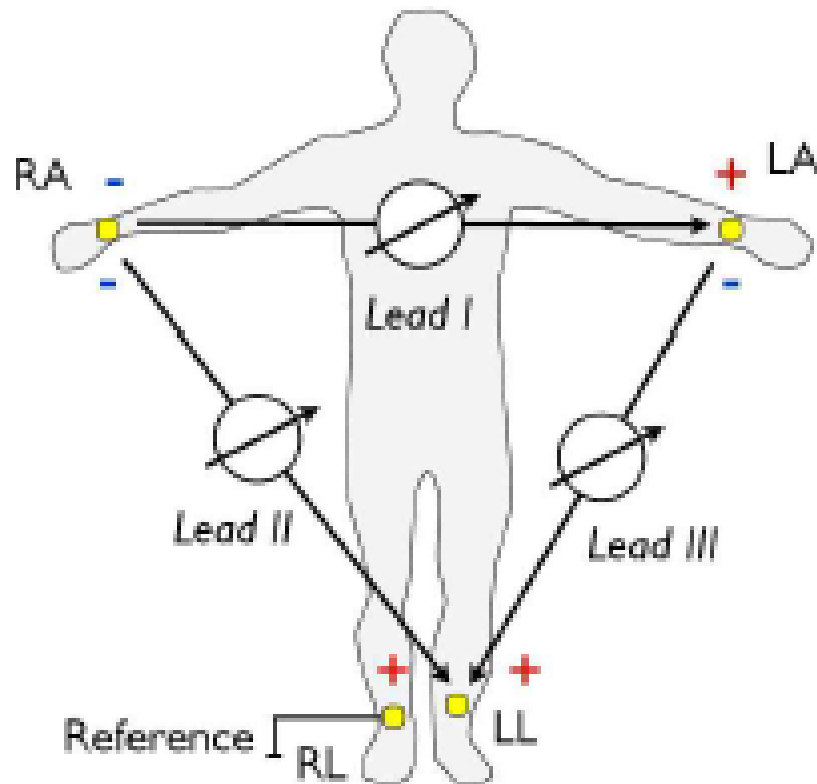
Figure 2-4: Electrode position of the limb leads or commonly termed as single lead recording. Adapted from [74].

2.3.3   Heart rate and Ventricular Repolarization parameters from ECG

RR interval in the surface ECG indicates the duration of a cardiac cycle containing the systolic (i.e. QT interval) and diastolic time intervals (i.e. TQ interval). Beat-to-beat variation of RR intervals is used as heart rate measure from ECG. QT interval consists of the duration of depolarization and repolarization of the ventricles (Figure 2-2) and used as a measure of VR. The two most important diagnostic parameters derived from the ECG signal are Heart rate variability (HRV), and VRV. HRV is calculated from beat-to-beat variation of RR interval time series using different linear and nonlinear techniques [75-77]. Temporal variability of VR (i.e. QTV) is calculated from the variability of Q wave to T wave (QTend) end or T wave peak (QTpeak) interval time series derived from the ECG. Both intervals are used in recent research studies[41] although QTend would be more predictive about QT interval abnormalities. The difference between the two measures Tpeak-Tend interval was reported to provide prognostic information in several cardiac abnormalities[34, 35] and psychological stressed conditions[52]. Figure 2-5 shows the two measurements used for studying HRV and QTV.

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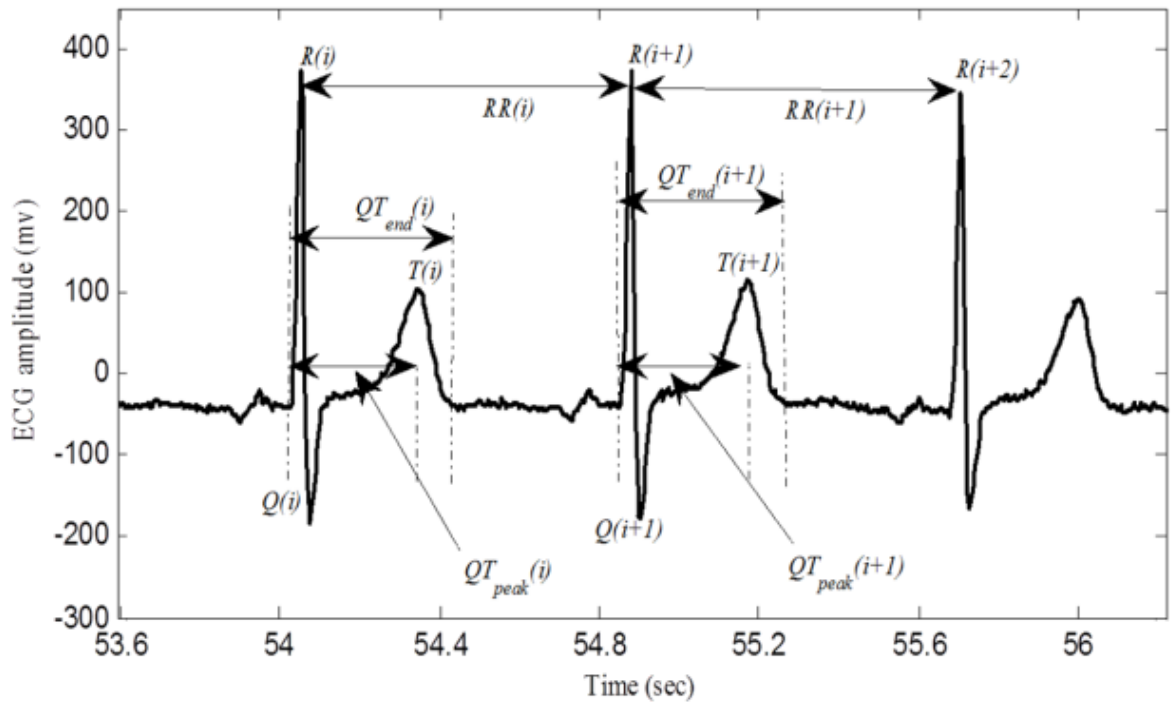
Figure 2-5: RR interval (i.e. variability of RR indicates measurement of HRV) and VR (i.e. QTpeak or QTend) measurements from surface ECG.

2.3.4 Measurement techniques of QT interval from ECG for analysing QTV

Correct measurement of the QT interval from the ECG signal is the first step for analysing VR duration variability (QTV). Reliable detection of T wave end detection is still an area of active research as erroneous detection of QT interval increases the QTV that does not represent complexity of actual VR dynamics[78].

The QT detection technique may be dynamic (i.e. beat-to-beat within the whole length of the recording) or it may be calculated as a median or mean from a number of detected QT interval within a fixed length of ECG. The widely used for beat-to-beat QT interval detection from short term ECGs are slope intercept method [79], derivative based method proposed by Porta et al. [80], the template is stretching method proposed by Berger et al. [26] and template time stretching method [81]. In this thesis, both slope intercept method and template stretching method algorithms were used for QTend interval detection.

2.4 Heart and autonomic nervous system

The heart is connected with two branches of autonomic nervous system (i.e. parasympathetic or vagal nerves and sympathetic nerves). The pacemaker of the heart (Sinoatrial node or SA node) and the AV node have a direct vagal connection and the ventricles have sympathetic nerve connections. Therefore, sympathetic activation has larger effect on ventricular

repolarization and non-invasive way of analysing sympathetic effects on heart's ventricles for the QTV analysis techniques provide crucial information about arrhythmogenesis. Heart rate variability(HRV) is dominantly controlled by parasympathetic nervous system activation as evident form the spectral analysis of heart rate or RR interval time series [75]. Time domain HRV parameter, RMSSD, and high frequency power component of heart rate time series (HF power) is now the established measures for quantifying the effect of parasympathetic nervous system (PNS) on cardiac function. Activation of PNS increases both RR and QT interval along with decrease in QTV and increase in HRV in Healthy individuals without any cardiac pathology. The low frequency power component of heart rate times is a measurement of sympathetic nervous system (SNS) on heart rate, although the reliability of this measure is still questionable. QTV is an indirect measure of the sympathetic nervous system control on the ventricles and this measure is found to be more sensitive than the HRV low frequency component in describing the effect of sympathetic nervous system control on cardiovascular function [41]. SNS activation decreases both QT and RR interval along with the increase in QTV and decrease in HRV within healthy subjects.
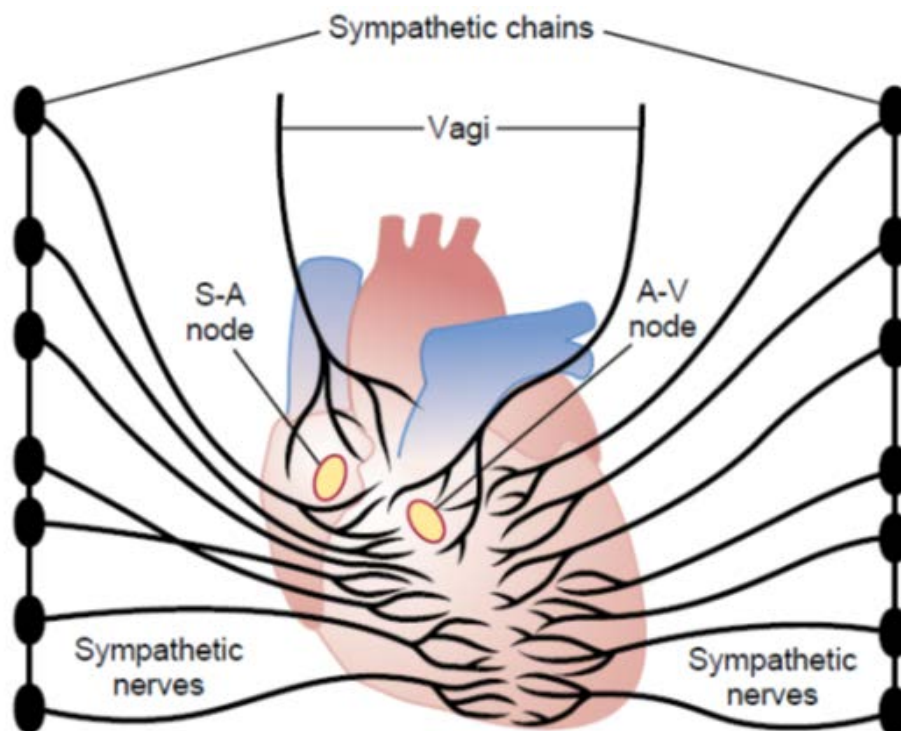
Figure 2-6: Cardiac sympathetic and parasympathetic nerve connections. Sympathetic nerves have direct connection with the ventricle indication the effect of direct sympathetic modulatory effect on the ventricles. Adapted from [68]

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2.5 Relation of VR duration to the mechanical functions of the ventricles

The ventricular muscle begins to contract slightly for supplying blood to the pulmonary and peripheral conduction system slightly after the onset of the cardiac action potential and continues to contract for a few milliseconds after the termination of the action potential cycle. Therefore, the contraction of the cardiac muscle is mainly the function of the duration of the electrical action potential (i.e. cardiac cycle). The heart's cardiac cycle is determined by the RR interval in ECG (i.e. temporal difference between two consecutive R waves). This cardiac cycle is divided into two mechanical phases of the ventricles: systole (i.e. contraction of the ventricular muscles to pump blood) and diastole (i.e. relaxation of the ventricular muscle and filling with blood after contraction phase). RR interval in ECG contains QT interval and TQ interval, which can provide temporal information about the mechanical functionality of the ventricles (i.e. contraction and relaxation functions). Contraction and relaxation functions of the ventricles are activated by the depolarization and repolarization of ventricular myocardium and are highly synchronized. Any alteration in this synchronized operation indicates abnormalities in ventricular function and this information can be derived from ECG. Recent research focus on ECG based techniques for determining the functionality of the left ventricles in a common heart function abnormality called Left Ventricular Diastolic Dysfunction (LVDD) [61-63]. VR duration or QT interval is used as electrical systolic interval in numerous studies due to its intrinsic temporal relation with left ventricular pressure variation as shown in Figure 2-7. TQ interval or the remaining part of the cardiac cycle (i.e. RR interval) is also considered as electrical diastolic time interval and their temporal synchronization is used to investigate normal functionality of the left ventricles[64, 82-84]. Therefore, temporal variability of the systolic and diastolic time intervals can be measured for the VR measurements in surface ECG and can be easily investigated from ECG for designing cost effective subclinical cardiac disease detection system. Electrical systolic and diastolic time intervals specify approximate duration of the contraction and the relaxation phases of the ventricle. The predominant type of heart failure, diastolic heart failure, which arises form left ventricular diastolic dysfunction can be analysed from the diastolic time interval in ECG. Decrease in diastolic interval indicates the left ventricular dysfunction, where the normal relaxation period of the ventricular chambers is affected and alters the proper blood filling, which causes lower ejection fraction and cardiac output. Left ventricular ejection fraction and cardiac output that are normally measured by normal Echocardiography or Tissue Doppler Echocardiography. Therefore, electrical measures of systolic and diastolic intervals can complement the echocardiographic recordings and can be used as a surrogate of diastolic function.
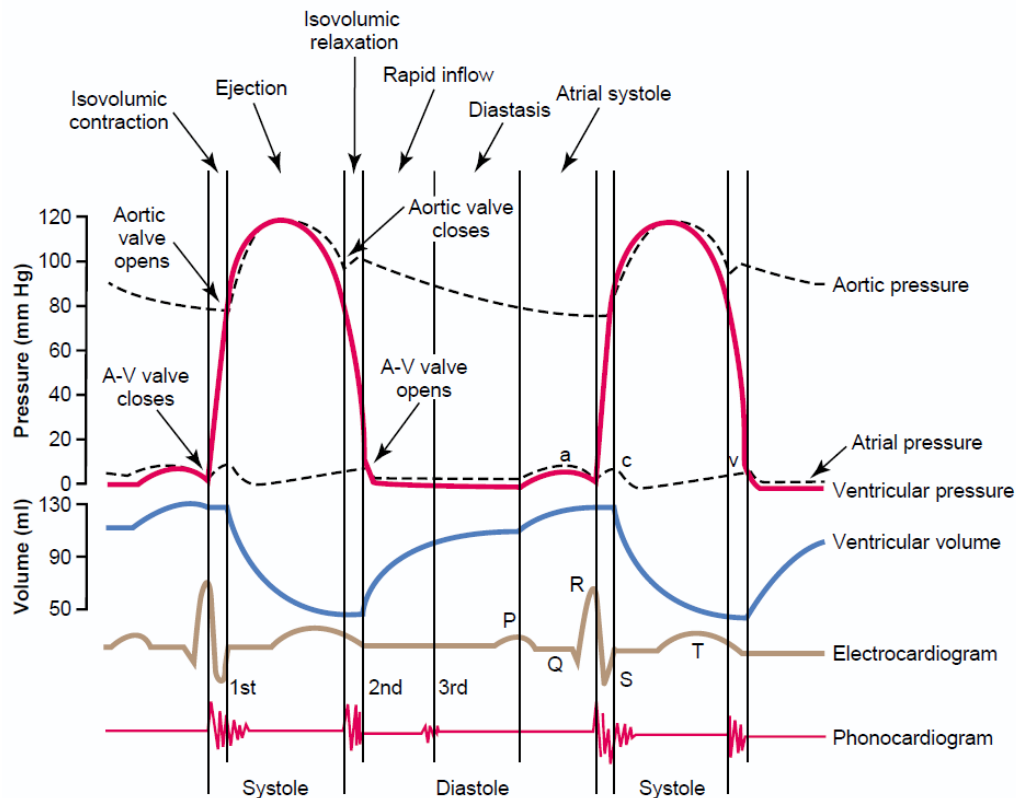
Figure 2-7: Wigger's Diagram showing the method of detecting systolic and diastolic time interval from ECG using the temporal relation between Left ventricular pressure and ECG. QT and TQ intervals are used as the surrogate electrical systolic and diastolic time intervals in analysing left ventricular dysfunction.

2.6 Factors affecting VR duration variability

VR duration variability is normally analysed from ECG by extracting the QT intervals. QT intervals are directly affected by RR intervals along with several other major factors like Respiration, Autonomic Nervous system modulation, different drug effects, stress, ageing, gender, congenital cardiac ion channelopathy (i.e. Long QT syndrome, Short QT syndrome) etc.[1]. Therefore, the variability of QT is also affected by these factors and QTV analysis techniques should consider the effect of these factors. Mathematical modelling is one useful way of considering the factors. This Thesis investigates how some of these factors (i.e. ageing, stress, Cardiac autonomic neuropathy, and Long QT syndrome) affect QTV and how to characterise these effects for predictive analysis.

Hear rate directly affects QT and in healthy subjects, the major portion of QTV is driven by heart rate variability (HRV) [43]. Ageing and stress increases QTV [51, 52, 54, 85]. Respiration also affects QTV due to the modulatory effect on QTV [86, 87] but the changes in QTV with respiration rate is not extensively explored. ANS affects the ventricular repolarization due to its direct effect on the ventricles and through the effect of heart rate. Sympathetic activation increase normally QTV and reduce QT interval in healthy individual

[13, 88]. Cardiac ion channelopathy and congenital ion channel disorder affect the QTV and QT-RR interaction along with QT prolongation [1, 20, 47, 66].
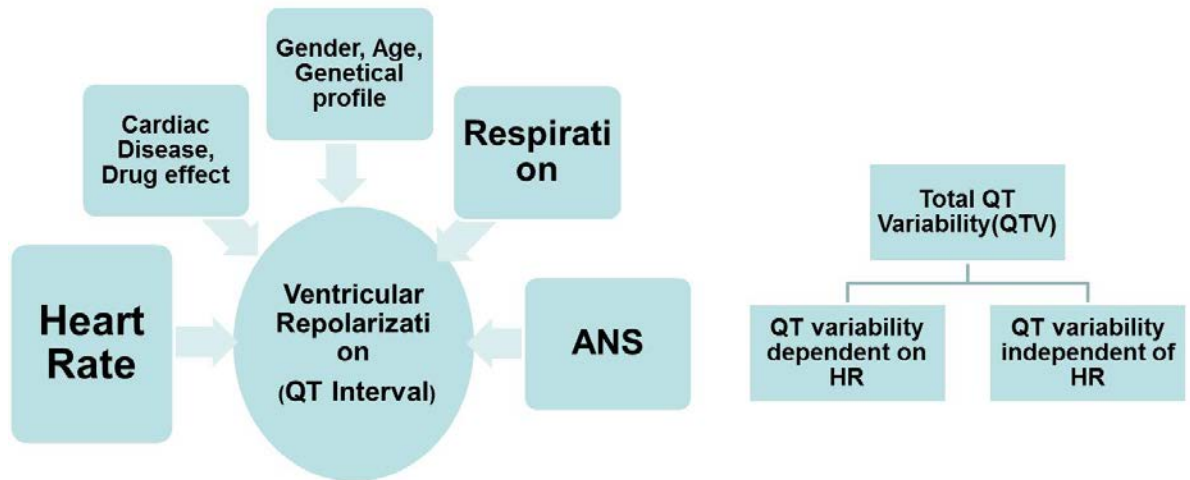
Figure 2-8: Main Factors affecting QT and QTV. Total QTV can be divided into two parts, indicated as QTV component directly affected by heart rate and QTV component independent of the effect of heart rate and affected by other factors, mainly by respiration and the autonomic nervous system.

2.7 Short-term QTV measurement techniques

QT interval prolongation is as an early indicator of ventricular abnormalities, although this measure is not widely used due to inconsistent findings in cardiac pathology [89]. QTV, derived from the temporal variability of the beat-to-beat QT interval time series shows results that are more consistent in its applicability in different cardiac pathology. Figure 2-9 shows a summary of the widely used QTV analysis techniques deriving from short-term ECG by two main techniques: model based and from time series analysis using statistical measures. These techniques are briefly discussed below:

2.7.1 Model based approach of deriving QTV

Porta et al. first proposed a linear parametric modelling structure to analyse QTV from short-term QT and RR time series [41, 80]. They used system identification techniques to model the repolarization dynamics and measure how QTV in terms of both RTpeak and RTend changes with RR variability and other inherent factors that affect QTV. Almeida et al. used the same technique using QTend interval instead of RTend and can quantify QTV successfully in healthy subjects [43]. This technique also can derive the QTV component independent of RR and dependent of RR through multivariate spectral analysis technique [43]. This method is based on the assumption that the RR and QT interval time series derived from ECG signal recording is stationary. The predicted QT interval time series is represented by the following equation:

$$QT(i) = A_{QT-QT}(z) * QT(i) + B_{QT-RR}(z) * RR(i) + n(i) \tag{2.1}$$

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Where $A_{QT-QT}(z) = \sum_{k=1}^{p} a_{QT-QT}(k) * z^{-k}$ (2.2)

$\qquad B_{QT-RR}(z) = \sum_{k=0}^{p} b_{QT-RR}(k) * z^{-k}$ (2.3)

Here $a_{QT-QT}(k)$ and $b_{QT-RR}(k)$ are p and $p+1$ constant coefficients and they were calculated using the system identification techniques. z^{-k} is the k lag delay operator in z domain. p is the identified model order, which represents the model complexity for simulation. The autoregressive noise term is identified by the following equation:

$\qquad n(i) = D_n(z) * n(i) + w_n(i)$ (2.4)

And $D_n(z) = \sum_{k=1}^{p} d_n(k) * z^{-k}$

w_n is the zero mean white noise process. The amount of QTV is quantified by model prediction capability measured by model fitting value. Decreases in model fitting value indicate the increases in QT variability and VR process complexity.

Halamek et al. developed a transfer function based model (TRF) with low model order that can describe the static and dynamic behaviour (i.e. changes is QT after rapid variation in heart rate) of QT-RR relation[90] . The model output equation of QT interval at instant i is given by:

QT(i) = b$_1$RR(i) + …….+b$_n$RR(i-n+1) - a$_1$QT(i-1) - …..- a$_m$QT(i-m) + e(i) (2.5)

where QT(i), RR(i) are the ith sample of QT and RR interval time series and e(i) is a random output. The order of such a model was defined by K= (n+m) and n,m indicates the memory effect of QT and RR intervals. The adjustable parameters of the model are collectively noted as P$_K$. The optimal transfer function was based on the minimization of three parameters. First, the mean level and standard deviation of a residual factor given by r, which is equal to

$$r = \sqrt{\frac{\sum_{i=1}^{N}(QT(i) - QTm(i))^2}{N - K}}$$ (2.6)

Here N is total number of beats analysed, QTm is the computed QT for beat i from the TRF model.

Second, the mean and standard deviation of QT variability not dependent on RR variability denoted by Rerr given by the relation: Rerr = STD (QT-QTm)/STD (QT)

And third, a reduction in the variability of the parameters of the model defined by the square root of an average over the relative variance of the model parameters Pi of the TRF model. The mathematical equation of this

$$Pvar = \sqrt{\sum_{i=1}^{K} \frac{1}{K}\left(\frac{std(Pi)}{mean(Pi)}\right)^2}$$ (2.7)

They validated the model in healthy control groups in resting condition, tilt condition with controlled breathing and cycling for inducing heart rate change to evaluate the hysteresis

effect. Based on ECG recordings including large heart-rate variations, the step or frequency response of the TRF is characterized by: (i) gain for slow RR variability, (ii) gain for fast RR variability, and (iii) QT delay within which QT attains 90% of its steady state value. These parameters can predict the steady state QT-RR relation and condition of QT changes with abrupt changes in heart rate with limited QT-RR hysteresis. This method has been proven to perform better in ECGs with very unstable heart-rate state.
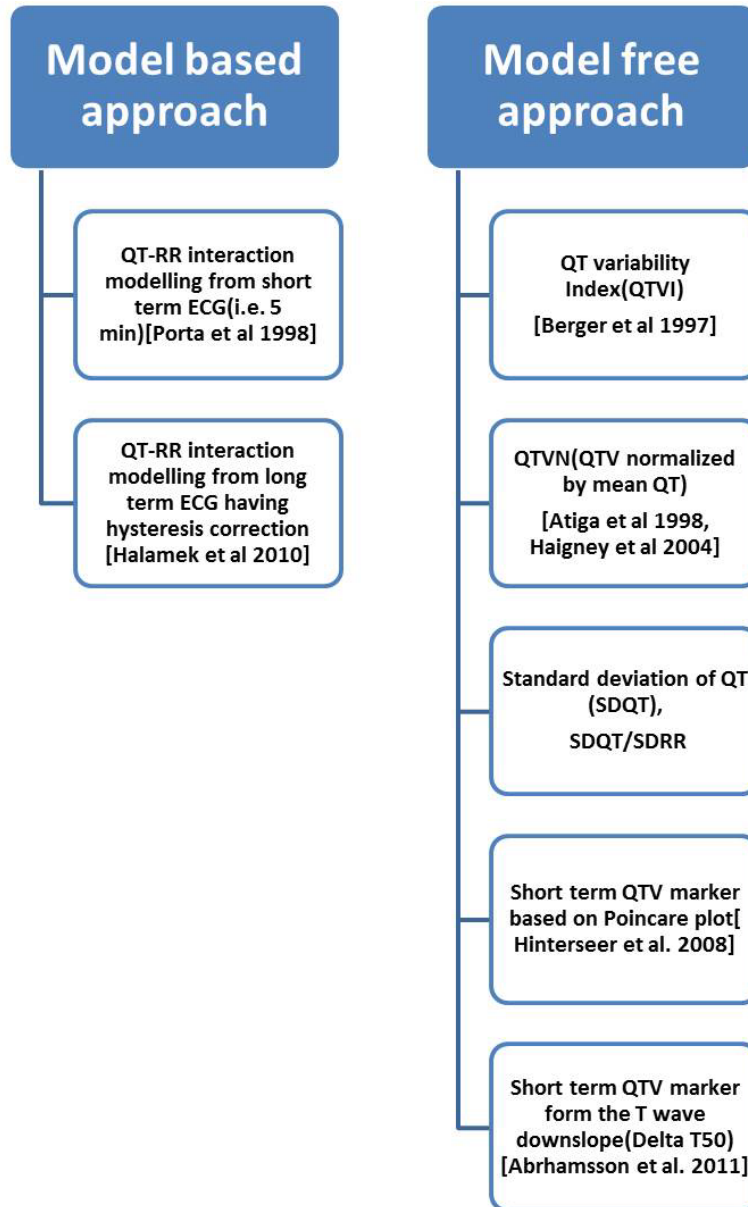
Figure 2-9: Several widely used short-term QTV measures to measure temporal variability of VR. The derivation of these measures can be divided by two main ways: using QT-RR interaction models and from QT interval and RR interval time series.

Most of the short-term QTV analysis techniques used ECG in stable conditions, which fulfil the condition of stationarity of the QT and RR interval time series. Therefore, the method proposed by Porta et al. is used in several studies successfully to investigate QTV and the effect of ANS on QTV [41, 54, 91, 92] .

2.7.2 Model free approach for QTV analysis

The most widely used QT variability marker is the QT variability index (QTVI) proposed by Berger et al [26]. The QT variability index (QTVI) was calculated as the logarithm of the ratio of normalized QT variance to the heart rate variance. The mean heart rate (HRm) and variance (HRv) and mean QT interval (QTm) and variance (QTv) were computed from the respective time series. The normalized QT variability index (QTVI) is defined as [26], which contains some normalization by heart rate.

$$QTVI = \log_{10}\left[\frac{\dfrac{QT_v}{QT_m^{\ 2}}}{\dfrac{HR_v}{HR_m^{\ 2}}}\right] \tag{2.8}$$

QTVI represents the log-ratio between the QT interval and heart rate variability, normalized by the squared mean of the respective time series. Normalizing the QT interval and heart rate variances by their respective squared mean values makes the argument of the log function a unit less quantity. Placing the QT variability in the numerator and heart rate variability in the denominator provides a measure for the degree of repolarization variability that is, in effect, out of proportion to the degree of spontaneous heart rate fluctuations.

QTVN is used in several studies for risk stratification of ventricular tachycardia or ventricular fibrillation. This parameter is used to observe the effect of QTV unadjusted for heart rate, but to reduce intersubject variability in comparison, which is measured as:

$$QTVN = \frac{QT_v}{QT_m^2} \tag{2.9}$$

Gross variability measures of QT interval time series (i.e. Standard deviation of QT time series) is used in several studies to investigate the total QT variability [28, 54]. To reduce the effect of heart rate and to make the measure comparable at different heart rate ratio of SDQT and SDRR (i.e. SDQT/SDRR) is also used in several studies to measure QTV[28].

Poincare plot based variability analysis technique is proposed and validated in some studies which show reliable performance in risk prediction in drug induced and congenital LQTS human subjects[20, 66, 93, 94]. The equation is given be low:

$$STV_{QT} = \frac{\sum|QT_{n+1} - QT_n|}{N\sqrt{2}} \tag{2.10}$$

This technique calculates the beat-to-beat variability where N indicates the number of QT intervals. This measure is normally measured from a very small number of cardiac beats (i.e. normally 30 consecutive beats) and might not be useful for analysing dynamical changes before arrhythmogenesis.

Another measure was proposed by Abrahamsson et al. to calculate QTV from the T wave downslope variability termed as Delta T50, which calculate the temporal variability of the

steepest part of T wave instead of calculating the T wave end. This method was developed to reduce the complexity involved in T wave end measurement technique and validated in LTS subjects [67, 71].

2.8 Conclusion

This chapter briefly introduces the ventricular repolarization process and how it is measured from short-term body surface ECG signal. Temporal variability of the QT interval is getting popular due to its better performance than the measures of the spatial variation of T wave in analysing cardiac pathology and in the risk stratification of sudden cardiac death. Beat-to-beat analysis techniques should be preferred for QTV analysis as this technique can detect dynamical changes in QTV before the onset of VT/VF and assist to start the protective measures in time. QT-RR model based technique can describe the QTV as well as investigate the effect of Autonomic nervous system on QTV. Therefore, model based approaches are preferred to analyse QTV where both QT and RR intervals are considered and model performance can be increased by including other factors that affect QTV. The next chapter investigates this modelling approach to analyse QTV and proposed some development of the existing modelling technique by incorporating respiration signal.

Chapter 3

Respiratory information based modelling technique of ventricular repolarization duration variability from surface ECG

In this chapter, the performance of two types of linear parametric modelling techniques (i.e. models with and without respiratory information) describing heart rate (HR), respiration, and ventricular repolarization (VR) variability interaction in healthy physiology was analysed. The use of model fitting value as a measure of changes in VR duration variability (i.e. QT interval variability) and VR process complexity in the dynamical interaction of the system variables (i.e. QT, RR, and Respiration) is validated. Bivariate QT-RR and Trivariate QT-RR-Respiration model structures were used for analysing age and stress related changes in VR variability in healthy subjects. Significant improvement of model fitting values with the addition of respiratory information further strengthened the effect of respiration on ventricular repolarization (VR). Both QT_{peak} and QT_{end} dynamics modelling results were compared to analyse the effect of T_{peak}-T_{end} in the beat-to –beat interaction of QT and RR interval. We also validated the performance of using ECG derived respiration (EDR) signal in VR dynamics modelling as a surrogate of original respiration signal. This will reduce the complexity associated with the necessity of simultaneous recording of respiration with ECG using a cumbersome recording device setup. The results of this chapter corroborated the hypothesis of adding respiration signal for better prediction of QT variability in healthy ageing and in stressed conditions. The findings of this study also prove the feasibility of using EDR where respiration signal recording is not available or not possible due to patients' health condition.

3.1   Introduction

Dynamical variability (i.e. Beat-to-beat variability) of ventricular repolarization is an important predictor of outcome in cardiovascular diseases. Modelling heart rate variability (i.e. RR interval variability) and ventricular repolarization duration variability (i.e. QT interval variability) is a non-invasive estimation of the dynamic properties of the cardiovascular system. According to the previous chapter's discussion, it is clear that beat-

to-beat analysis approach of the QT interval is the appropriate choice for examining dynamic QT variability. Moreover, the effectiveness of multivariate analysis of VR variability is preferable to single variable analysis technique as QT is affected by several major factors like heart rate, respiration, and autonomic nervous system effect along with other factors[1]. Therefore, combined analysis of QT and RR interval along with other variables that affect QT interval dynamics provide better prognostic information than single variable analysis of ventricular repolarization (VR) variability. Consequently, modelling the relation between QT and other variables derived from ECG using system identification techniques is an efficient way to investigate the dynamical variability of QT [95].

Mathematical modelling is an integral part of the system identification process [96]. The main purpose of developing models from the input and output data is to understand the underlying dynamical interactions of different system variables. The system's performance is affected if the system variables (i.e. input and output factors and other disturbances) act differently from the normal trend. Therefore, modelling of an unknown system from input and output observations provides an idea of system dynamics. Porta et al. [41, 42] first proposed a linear dynamic autoregressive model for short length ECG data describing the dynamics of RR and QT interval (both QT_{peak} and QT_{end} intervals) interactions. They used RT interval (R wave to T wave peak or T wave end intervals) instead of QT interval in describing the ventricular repolarization duration due to problems in proper "T wave end" detection [41, 42]. Almeida et al. [43] have used the same model structure reported by Porta et al. [42] except for using QT_{end} interval instead of RT interval to describe the effect of heart rate and autonomic nervous system on ventricular repolarization dynamics. These studies validated the use of linear parametric autoregressive modelling to describe the ventricular repolarization dynamics for short length ECG segments (i.e. 2 to 5 min ECG) where the RR and QT intervals derived from ECG are assumed stationary within the data length.

Ventricular repolarization variability (QTV) is directly affected by the heart rate variability (HRV) [1, 42, 95]. Both heart rate and ventricular repolarization are controlled predominantly by the autonomic nervous system (ANS) [43]. The effects of heart rate variation on ventricular repolarization can be analysed through modelling QT-RR dynamics, which provides an understanding of cardiovascular dynamics complexity [41, 42]. Besides HRV, QTV is also directly affected by respiration as reported in several studies [41, 86, 87]. The respiratory modulation of heart rate, termed as respiratory sinus arrhythmia (RSA), regulates the autonomic input of the sinus node, which causes the increase and decrease in heart rate during inhalation and exhalation respectively [97]. Since HRV directly affects QTV, so respiration also has an important effect on ventricular repolarization. Hanson et al.

[86, 87] has reported the presence of cyclic modulation of ventricular repolarization due to respiration in both healthy and heart failure subjects. From multiple left and right ventricular endocardial recordings in healthy human heart, they observed that the ventricular action potential duration varied cyclically with respiration[87]. Therefore, respiratory information in terms of original respiration or derived from ECG should be used in modelling QT and RR interactions for better comprehension of cardiac repolarization dynamics and the analysis of VR variability.

Traditionally, respiratory signal is collected using impedance pneumography, spyrometery, or inductive plethysmography techniques. In pneumography, strain gauges or piezoelectric transducer devices are strapped to the chest or abdomen for recording the velocity and force of chest movement during respiration. Strapped pressure transducer devices are used for measuring nasal air flow pressure to collect respiration signal in spyrometry. These recording procedures were not very much suited in several cases like in ambulatory monitoring, in overnight sleep studies for detecting sleep apnea and in stress testing due to the necessity of using bulky and expensive recording devices [98, 99]. Moreover, they sometimes affect the natural breathing process and involve conscious operation of the subjects, which is inappropriate for conditions such as sleep studies and ambulatory settings. These limitations of respiration signal acquisition confines the use of respiratory information in cardiac dynamics analysis. Since the cost and complexity associated with respiratory signal acquisition restrict the recording for long duration and ambulatory settings, a lot of research has been conducted to devise a surrogate for respiratory movement from other available physiological signals. Among others, ECG signal has been highly used to extract respiratory movement since modern Holter ECG recorders provide simple and easy recording in ambulatory settings. Moody et al. [100] have reported that extraction of respiratory information from ECG using different signal processing techniques is realizable as respiration modulates the ECG signal amplitude by regulating the distances of ECG electrodes from the heart which causes rotation of mean electric heart vector due to inhalation and exhalation process. The ECG derived respiration (EDR) has been successfully used as a surrogate for respiration in various studies with different physiological and pathological conditions such as detecting sleep disordered breathing [98, 101, 102] and daily dynamic activity monitoring from ambulatory single lead ECG [99]. EDR has also been found to show statistically similar performance as of original respiration in respiratory frequency determination in stress test [98].

In this chapter, we present an improved modelling technique of the QT-RR interaction as a measure of dynamical variability of VR duration by incorporating respiratory information derived from ECG in the model structure (i.e. QT-RR-EDR model) and explain the

physiological relevance of the model fitting value as a measure of QT interval variability (QTV). We replace EDR with original respiration in the existing QT-RR-Respiration model structure and validated the use of EDR instead of original respiration, which can be calculated from ECG and remove the necessity of original respiration signal recording system. To the best of our knowledge, EDR has never been used as a surrogate of respiration in modelling ventricular repolarization dynamics. We hypothesize that the respiration should be added for better understanding of VR process dynamics and variability and EDR can be used as a surrogate of respiration in this modelling analysis. To validate the hypothesis, the performance of the existing modelling techniques of QT-RR variability interaction and proposed modelling approach with EDR based QT-RR interaction models for VR variability analysis is compared to establish the importance of considering the respiratory effect on VR variability in Healthy human subjects. We also compare the model fit values with gross VR variability (i.e. Standard deviation of different QT intervals) measures to establish the importance the beat-to-beat or dynamical QTV measures for proper understanding of the alteration of the VR process with ageing and stress.

3.2   Case study details

Two case studies are presented in this chapter, which analysed the effect of respiration and the validity of using EDR in place of respiration in the study of modelling dynamical QT variability from QT, RR and respiration signals. For these studies, ARXAR (autoregressive model with exogenous input and autoregressive noise) type models were analysed. One bivariate model (QT-RR) and two multi-variate models (QT-RR-RESP and QT-RR-EDR) have been used to investigate the changes in model prediction capability of VR variability (measured by model fitting value) in a physiological (healthy ageing) and a psychological (Stress, No Stress) condition. We used both QT_{peak} and QT_{end} intervals to design the linear models to understand the effect of T_{peak}-T_{end} interval variability on the overall dynamical variability of VR.

3.2.1   Case study subjects

To investigate the changes in VR dynamics and variability with the variation of age, a total of 20 healthy young (21-34 years) and 20 healthy old subjects' (68-85 years) ECG and respiration signals were collected from Fantasia database available at Physionet [72]. In both Young and old groups, equal number of male and female (i.e. 10 male and 10 female) subjects without any history of cardiovascular diseases were recruited for data collection. From the 120 mins of simultaneous recording of Lead II ECG and respiration, we extracted 5 min long segments for modelling. 5 min ECG and respiration data section from the first 20 min segments of each subject were used for QT, RR, Respiration and EDR time series

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extraction. The selection criteria of the 5 min segments were such that the R and T waves were clearly visible within the segment and detectable and the respiration signal was free from any visible movement artefacts. Subjects were in the supine resting state in sinus rhythm and watching the movie Fantasia (Disney, 1940) to remain awake during the whole duration of the recording. The original respiration signal was recoded as respiratory movement recorded using the thoracic belt. Both ECG and respiration signals were sampled at 250 Hz.

For the second study, the ECG and respiration signals were taken from Stress Recognition in Automobile Drivers (drivedb) database available at Physionet [72]. The purpose of using this dataset was to check the validity of using EDR in place of original respiration signal for understanding the dynamical QT variability changes in altered psychological conditions. From this database, a total of 16 healthy subjects' ECG and Respiration data were taken out of 17 subjects' recordings. One recording (drive01) was dropped from our study due to problem in proper detection of T wave parameters. In this database, an experimental protocol was designed and verified for the detection of stress due to driving in heavy traffic condition from physiological signals of the healthy subjects. According to the designed procedure, subjects were driving car following a set route and their physiologic reactions were monitored by analysing several recorded physiological signals like Electrocardiogram (ECG), Electromyogram (EMG), skin conductivity and respiration [103]. The driving protocol was designed to take the driver in different road conditions with variable traffic such that different levels of stress were likely to occur. The total drive period consisted of rest, highway and city driving, which were assumed to induce low or no stress, medium and high level of stress in the driver's mind. The detail of this study protocol (i.e., driving protocol, driving period, stress measurement and validation of stress level assessment techniques etc.) were described in details by Healy et al. [103]. In this study, we have used 5 minutes ECG and respiration signal during resting (i.e. No Stress) and city driving(i.e. Highly Stressed) conditions. Recordings of resting condition were treated as data for stable physiological condition and grouped as "No stress," whereas recordings of city driving condition were considered as stressed condition data and grouped as "Stressed." ECG sampled at 496 Hz, was recorded with a modified lead II configuration for reducing the effect of motion artefact and for better detection of R waves. The respiration signal was recorded with an elastic Hall Effect sensor by measuring the chest cavity expansion of the subject at 31 Hz sampling frequency. The procedure of signal collection and analysis was described in details in [103].

3.2.2   ECG and respiratory signal parameter extraction

5 min long ECG signal was first filtered with a median filter to remove the baseline wandering. The RR and QT interval series were formed by detecting the R wave peak, Q wave onset, T wave peak and T wave end of the ECG signal. Different wave components and intervals of derived from the ECG signal used for this study are shown in Figure 3-1.

The RR interval was found from the difference between two consecutive R wave peaks, which are detected by an algorithm for detecting QRS complex proposed by Pan et al. [104]. The QT intervals were calculated as QT_{peak} (i.e. interval from the Q wave onset to the peak of T wave) and QT_{end} (i.e. interval from Q wave onset to the end of T wave). The Q wave onset (i.e. Q point) is determined by detecting the time instant where the gradient of the QRS complex becomes negative to the left of the R wave peak. The peak of the T wave was detected by searching for the highest point within a heartbeat (R peak to R peak) after the R wave. The T wave end or offset is found by searching for the point where the gradient of the T wave first changes its sign after the occurrence the T wave peak. This method of detecting the end of the T wave is similar to the maximum slope intercept method, which defines the end of the T wave as the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave [79, 105].
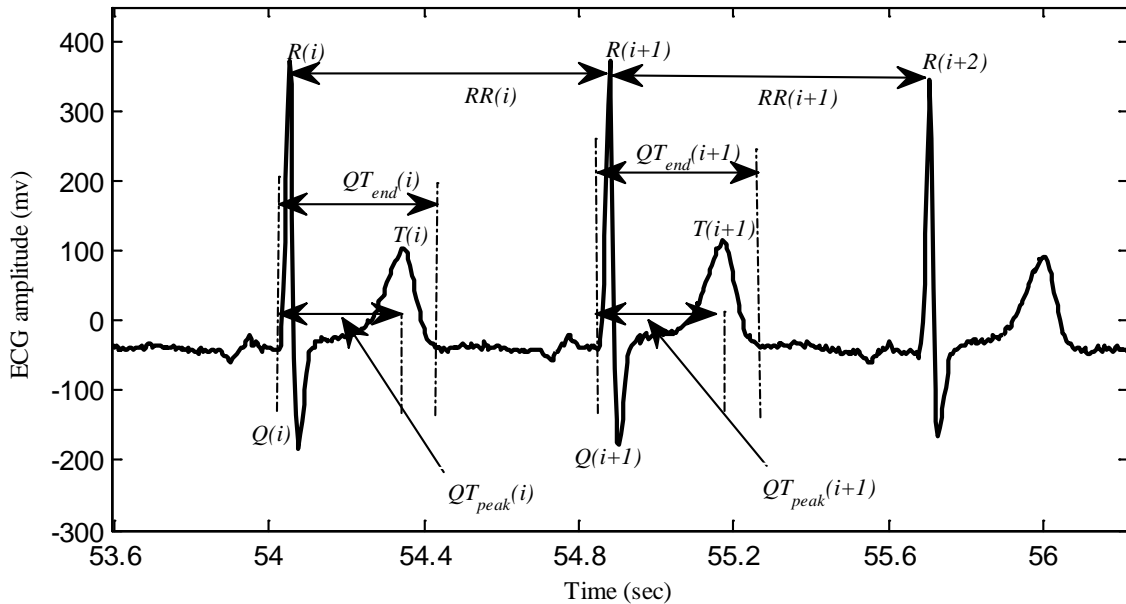
Figure 3-1: Different ECG wave components (Q, R, and T waves) and measurement of RR and QT intervals (QT_{peak} and QT_{end}) for three cardiac beats used in this study.

We used both QT_{peak} and QT_{end} intervals to build and validate the model performance. To remove the effect of nonstationarity, which affect the performance of linear modelling technique, both RR and QT time series distribution were checked after extraction form ECG.

Ectopic beats, which induce nonstationarity in RR interval time series were removed using the criteria used by Huikuri et al. [106] before used in modelling though the number of ectopic beats is negligible in the recordings. Variations in RR interval time series were also checked by the criteria proposed by Clifford et al. [107] to remove rapid fluctuations which affect the linear property of the RR series required for the model formation. QT intervals outside the range of the 3-SD band were rejected for the formation QT interval time series as a model output signal. This was done for maintaining the stationarity in the input and output time series data for this linear model analysis s discussed in a previous study [43]. The respiration signal time series (RESP) for the model was formed by sampling the continuous respiratory signal recording at each R peak of the ECG. For the derivation of EDR, we used the R wave amplitude method for single lead ECG where first a median filter filters the ECG signal for baseline wandering. Then from the baseline corrected ECG , QRS wave were detected using Pan Tompkin's algorithm [104] and the amplitude of the R wave peaks from the detected QRS wave were recorded to generate the EDR wave time series [100, 108] . The sampled respiration (RESP) and EDR calculation technique is graphically illustrated in Figure 3-2.
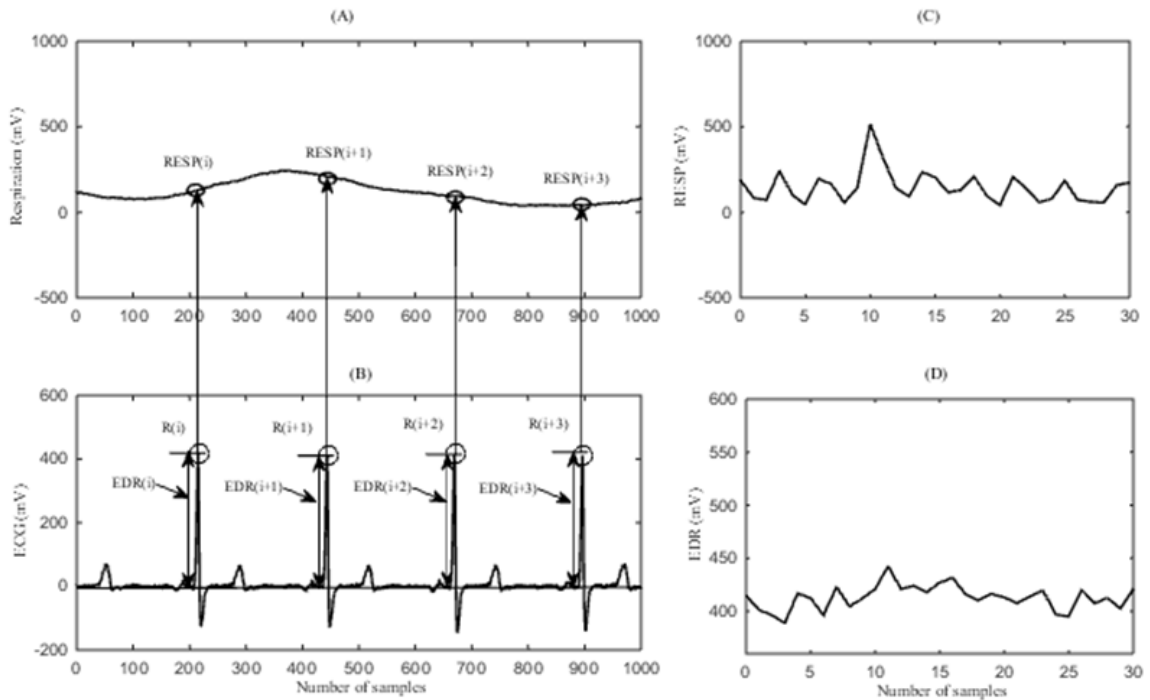
Figure 3-2: Derivation of RESP (sampled respiration signal) and EDR (ECG derived respiration) signal time series from the respiration and baseline corrected ECG signal. (A) shows that RESP(i) signal, which is formed from the sampled values of respiration signal collected by thoracic belt at every R(i) that is the magnitude of R wave at every R wave peak location and i=1,2….n where n is the number of ECG R wave peaks. (B) EDR(i) waveform is calculated from the variation of R wave peak amplitudes, R(i) in the baseline filtered ECG waveform. (C) and (D) shows a sample segment of both the RESP and EDR time series used as model input parameters.

3.3   Method

Due to subjective variation of $QT - RR$ relation [109], each subject in this study was modelled individually using the fixed model structure (i.e. $ARX_{RR}AR$ or $ARX_{RR}X_{RS}AR$) by varying the model order to measure the model performance in predicting QT interval. The following sections describe in details the model structure and the equations used for model parameter estimation and validation.

3.3.1   Linear parametric model formation

First 250 consecutive beats of the derived RR, QT (both QT_{peak} and QT_{end}), RESP and EDR time series from five minute ECG segment were used for the formation of the autoregressive models with single and double exogenous inputs with an autoregressive noise term. QT, RR, sampled respiration (RESP) and EDR time series data were linearly detrended by subtracting the mean and dividing by the standard deviation before using as model input and output parameters. We first analysed $ARX_{RR}AR$ model, a bivariate single input (i.e. RR is the single exogenous input) single output (SISO) model with an autoregressive noise without any respiration signal to study QT dynamics. Then two more trivariate multi input single output (MISO) type models ($ARX_{RR}X_{RESP}AR$ and $ARX_{RR}X_{EDR}AR$) were derived using the methodology developed by Porta et al. [41] to check model's QT variability prediction capability changes with the addition of respiration and also to check the difference in performance between original respiration and EDR. RR and RESP or EDR were used as two exogenous inputs in these multivariate model structures. Figure 3-3 shows the basic ARXXAR type model structure used in the analysis.

The beat-to-beat intervals are represented as $QT = \{QT(i), i = 1,2, \dots \dots N\}$, $RR = \{RR(i), i = 1,2, \dots \dots N\}$, $RESP = \{RESP(i), i = 1,2, \dots \dots N\}$, and $EDR = \{EDR(i), i = 1,2, \dots \dots N\}$ where N is total number of beats used for building the model, in this study $N = 250$. The ith QT_{peak} or QT_{end} interval followed the ith RR interval, thus directly linking the present QT interval with the preceding RR interval. The ith respiratory sample RESP(i) was taken as the sampled value of the respiration signal at every R-wave peak.
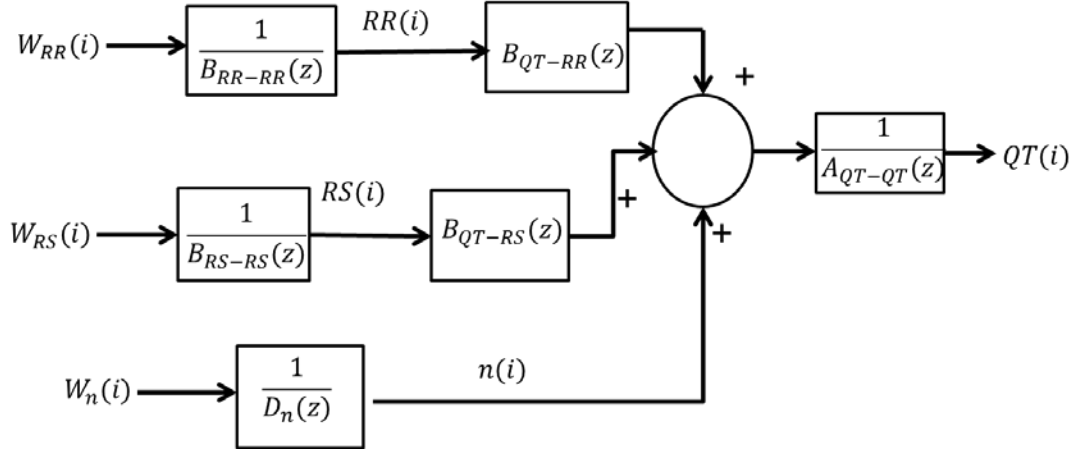
Figure 3-3: Linear autoregressive parametric model structure with multiple exogenous inputs. RS(i) may be RESP(i) or EDR(i) according to the type of the model.

The equation of the predicted QT interval for the bivariate $QT - RR$ model is:

$$QT(i) = A_{QT-QT}(z) * QT(i) + B_{QT-RR}(z) * RR(i) + n(i) \qquad (3.1)$$

and the predicted QT of the trivariate $QT - RR - RS$ model including RESP and EDR are defined as:

$$QT(i) = A_{QT-QT}(z) * QT(i) + B_{QT-RR}(z) * RR(i) + B_{QT-Resp}(z) * RESP(i) + n(i) \quad (3.2)$$

$$QT(i) = A_{QT-QT}(z) * QT(i) + B_{QT-RR}(z) * RR(i) + B_{QT-EDR}(z) * EDR(i) + n(i) \quad (3.3)$$

where RESP(i) is the sampled respiratory signal and EDR(i) is the ECG derived respiratory information derived from ECG RR time series. The model performance was validated using both QT_{peak} and QT_{end} in place of QT(i). The model equations (i.e. equation (3.1), (3.2) and (3.3)) indicate that ith QT interval depends on previous QT intervals, current and previous RR intervals, current and past RESP samples and other unknown inherent factors independent of RR and RESP, which was modelled by the noise term n(i). A and B represent the model transfer function polynomials which actually indicate the memory effect of QT, RR, and RESP that shows how a QT interval is affected by current and previous QT intervals, RR intervals, respiration and other unknown factors (i.e. The direct modulatory effect of autonomic nervous system and any other factor that affect QT other than RR or RESP). The model polynomial coefficients are defined using the following equations:

$$A_{QT-QT}(z) = \sum_{k=1}^{p} a_{QT-QT}(k) * z^{-k} \qquad (3.4)$$

$$B_{QT-RR}(z) = \sum_{k=0}^{p} b_{QT-RR}(k) * z^{-k} \qquad (3.5)$$

$$B_{QT-RESP}(z) = \sum_{k=0}^{p} b_{QT-RESP}(k) * z^{-k} \qquad (3.6)$$

$$B_{QT-EDR}(z) = \sum_{k=0}^{p} b_{QT-EDR}(k) * z^{-k} \qquad (3.7)$$

Here $a_{QT-QT}(k)$, $b_{QT-RR}(k)$ and $b_{QT-RESP\ or\ EDR}(k)$ are p, $p+1$ and $p+1$ constant coefficients and they were calculated using the system identification techniques. z^{-k} is the k lag delay operator in z domain. p is the identified model order, which represents the model complexity for simulation. The larger the value of p, the more complex is the model to identify the interaction of the system parameters.

The autoregressive noise term is identified by the following equation:

$$n(i) = D_n(z) * n(i) + w_n(i) \tag{3.8}$$

$$where \quad D_n(z) = \sum_{k=1}^{p} d_n(k) * z^{-k}$$

and w_n is the zero mean white noise.

The one step ahead prediction error (err_{QT}) of the model is calculated from the difference between the $QT(i)$ and best one step ahead predicted $QT(i)$ denoted as $\widehat{QT}(i)$ as defined by

$$err_{QT} = QT(i) - \widehat{QT}(i) \tag{3.9}$$

The value of prediction error for the trivariate model incorporating respiration will be as below:

$$err_{QT} = QT(i) - \widehat{QT}(i)$$
$$= \left[1 - \widehat{D_n}(z)\right] * \left[1 - \widehat{A_{QT-QT}}(z)\right] * QT(i) - \left[1 - \widehat{D_n}(z)\right] * \widehat{B_{QT-RR}}(z) * RR(i) -$$
$$\left[1 - \widehat{D_n}(z)\right] * \widehat{B_{QT-RS}}(z) * RS(i) \tag{3.10}$$

Where $RS(i)$ will be RESP(i) or EDR(i) according to the model input type and $\widehat{D_n}(z)$, $\widehat{A_{QT-QT}}(z)$, $\widehat{B_{QT-RR}}(z)$ and $\widehat{B_{QT-RS}}(z)$ are the model transfer function polynomials estimated from the input output data via system identification procedure.

The model goodness of fit value is calculated from the mean squared prediction error (MSPE) which measures the ability of the model structure in fitting the data using the following equations:

$$MSPE = \frac{1}{N}\sum_{i-1}^{N} err_{QT}{}^2(i) \tag{3.11}$$

The value of MSPE varies between 0(i.e. perfect fit) and 1(i.e. model cannot fit the data at all).The goodness of fit is defined as

Goodness of fit =1-MSPE $\tag{3.12}$

and the higher the goodness of fit value the higher the model prediction capability.

3.3.2 Model parameter identification and validation

The coefficients of the model transfer function polynomials were calculated using Prediction Error Estimation method (PEM) for linear models [96]. This method uses a numerical optimization technique to minimize the weighted norm of prediction error, which is defined as the cost function. Model prediction capability is determined by the mean squared

prediction error (MSPE), which is calculated from the difference between measured output and the one-step ahead predicted output of the model. Same model order of p in input and output polynomials was considered for calculating the coefficients of the model transfer function for the simplicity of model analysis. The model order represents the complexity of the model structure and is determined using system identification technique by calculating the minimum prediction error through iteration of a predetermined range. The best model was chosen with the lowest value of AIC form the iterated models. The range of model order variation was fixed for all subjects and within that range best model was selected in terms of AIC criteria [110]. Model order varied from 9 to 19 to find the best model with the lowest value of AIC. Residual analysis was performed on the derived model to check if the model passed the whiteness test and independence test to clarify that model residuals were uncorrelated with each other and not correlated with past input values[96]. In our study, 99% confidence interval was used for the residual analysis with lag 25 and the model passes the test if the residuals were found uncorrelated (i.e. residual autocorrelation function is within the confidence interval of the estimated response) and residuals were found to be uncorrelated with past inputs (i.e. cross correlation between residuals and previous inputs was inside the confidence interval with less than 3 points outside the confidence interval). All these analyses were done using System Identification Toolbox in MATLAB R2012b.

3.3.3 Statistical analysis

Wilcoxon rank sum test were performed to check the difference between model fitting values of the two groups in two databases. Non-parametric version of one way ANOVA (i.e. Kruskalwallis test) was used to check the statistical difference between three types of model fit values in each database. Then Bonferroni post hoc tests were performed to compare pairwise differences in the three model types, which contains an adjustment for multiple comparison as proposed by Bonferroni. A value of p <0.05 was considered significant. All the statistical calculations were carried out in MATLAB R2012b after checking the normality of the data distribution of every subject group by Lilliefors test.

3.4 Results

VR duration (i.e. Mean QT_{peak} and QT_{end} intervals), gross QTV measures (i.e. Standard deviation of different QT intervals), and T_{peak}-T_{end} interval variations for the two subject groups are shown in Table 3-1. Both QT_{peak} and QT_{end} interval were found to increase significantly with healthy ageing in the Fantasia database. The gross variability measures of VR ($SDQT_{peak}$ and $SDQT_{end}$) were not significantly different between the young and old group although $SDQT_{end}$ increases with ageing. Both T_{peak}-T_{end} interval and its variability were found to increase with ageing in the Fantasia group subjects. No gross variability

measures can detect the age related changes of VR dynamics in Fantasia group subjects. In drivedb database, we analysed the QTV measures for a particular subject group in two mental conditions (i.e. normal relaxed and stressed conditions). The average QT interval changes were not found significantly different between the two psychological conditions (Table 3-1). QT_{peak} remains almost unchanged and QT_{end} slightly decreases in stressed condition from unstressed condition. Both QT variability measures increase with stress induction and the increases in $SDQT_{end}$ was found significantly different from unstressed state. Changes in the duration and variability of T_{peak}-T_{end} interval ware significantly different between two psychological states. Mean T_{peak}-T_{end} interval was found to decrease and the variability of T_{peak}-T_{end} interval was found to increase significantly with stress induced. These results showed that QT_{end} interval variability, which contains T_{peak}-T_{end} interval, provides important variability information of the VR process due to autonomic nervous system modulation changes with stress induction.

Table 3-1: Different gross VR duration and variability measures (i.e. Different QT interval measures) of the study subjects

QTV features	Fantasia database			Drivedb database		
	Young	Old	*p* value	No stress	Stressed	*p* value
Mean QT_{peak}(ms)	332.44 ±18.58	365.24 ± 21.9*	2.02e-5	286.80 ± 28.59	286.11 ± 24.65	0.445
$SDQT_{peak}$(ms)	3.62 ± 1.04	3.14 ± 1.01	0.122	4.17 ± 3.27	5.36 ± 3.58	0.143
Mean QT_{end}(ms)	404.55± 17.24	445.45 ± 28.92*	1.55e-5	340.11 ± 28.70	334.55 ± 30.78	0.348
$SDQT_{end}$ (ms)	5.01 ± 1.75	7.17 ± 4.29	0.061	4.55 ± 2.84	8.96 ± 5.43^	0.021
Mean T_{peak}-T_{end}(ms)	72.10 ± 4.15	80.24 ± 16.83	0.112	53.29 ± 2.54	48.44 ± 9.62^	0.004
SDT_{peak}-T_{end} (ms)	4.66 ± 1.87	6.93 ± 4.39	0.054	4.01 ± 2.43	8.26 ± 5.68^	0.011

All values are shown as Mean ± SD
*indicates old group QTV feature is significantly different from the Young Group,
^ indicates Stressed group QTV features are significantly different from No stressed group

The goodness of fit values of the SISO (QT-RR) and MISO (QT-RR-RESP or QT-RR-EDR) autoregressive models were calculated for two populations (i.e. Young and Old groups) from Fantasia database of different ages and with no cardiovascular abnormalities. The same analysis was done for a young subject group with two different psychological conditions available in drivedb database. The results of the variations of model fit for QT_{peak} dynamics models in two databases are shown in Figure 3-4. In both databases and in both groups, it was found that the model predictability increases significantly when respiration information

(RESP or EDR) was added as an extra exogenous input with RR in comparison to that found from the model developed using only QT and RR signals. Similar results were found in QT_{end} dynamics models and shown in Figure 3-5.

The trivariate models ($ARX_{RR}X_{RESP}AR$ and $ARX_{RR}X_{EDR}AR$), which had RESP or EDR signals as respiration signal input along with QT and RR, showed statistically similar goodness of fit values for both QT_{peak} and QT_{end} dynamics models and both are significantly improved with respect to bivariate ($ARX_{RR}AR$) model. These results proved that respiration has an important effect, which should be considered for identifying the cardiovascular system parameter interactions as the models having respiration information show significantly better performance in predicting QT than the model without any respiratory information.
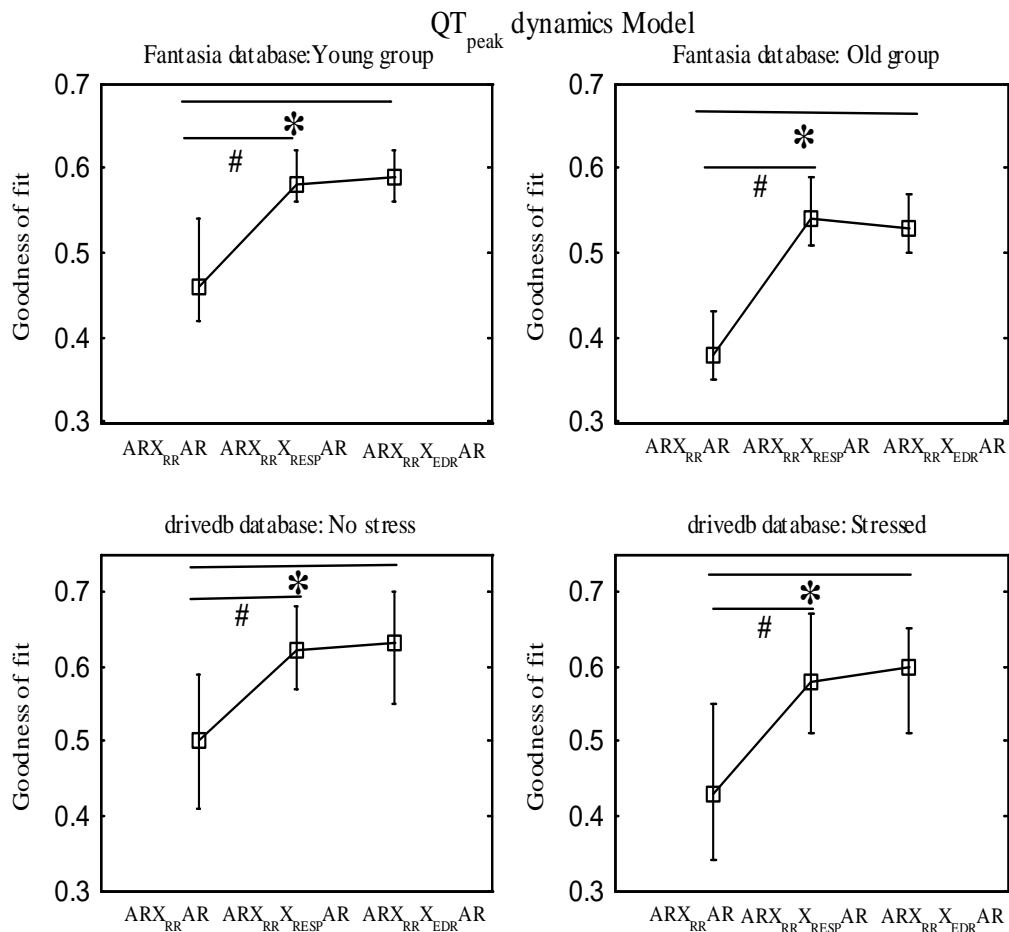
Figure 3-4: Goodness of fit variation of the analysed QT_{peak} dynamics models in Fantasia and drivedb Database at Physionet. # indicates the significant differences of model fit between $ARX_{RR}AR$ and $ARX_{RR}X_{RESP}AR$ model and * indicates the significant model fit differences between $ARX_{RR}AR$ and $ARX_{RR}X_{EDR}AR$ models.
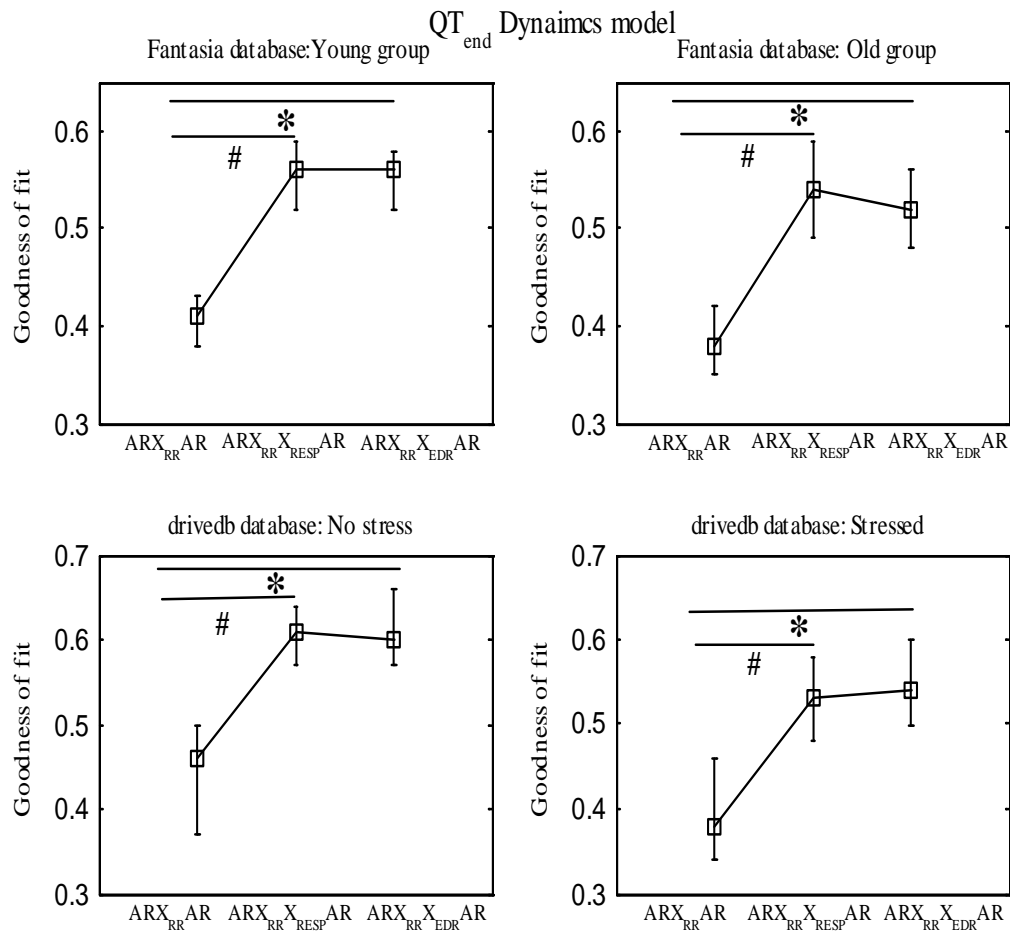
Figure 3-5: Goodness of fit variation of the analysed QT$_{end}$ dynamics models in Fantasia and drivedb Database at Physionet. # and * indicate the significant differences of model fit between ARX$_{RR}$AR and ARX$_{RR}$X$_{RESP}$AR model and between ARX$_{RR}$AR and ARX$_{RR}$X$_{EDR}$AR models respectively.

Table 3-2 demonstrated the effect of using EDR instead of respiration in modelling QTV for both databases. These results show that there is no statistically significant difference in model predictability whether it has respiration or EDR as a model input. This validates the use of EDR in modelling $QT - RR$ interaction and the effect of respiration and EDR are almost same in case of this linear parametric modelling. Another interesting finding of this type of parametric models is that it can also differentiate the effect of ageing and alteration of mental state due to stress induction on the cardiovascular system dynamics. Models describing QT$_{peak}$ variability can differentiate the young and elderly group in Fantasia database and in drivedb database, it was found that QT$_{end}$ dynamics models could significantly differentiate the changes in ventricular repolarization variability with the induction of stress. Bivariate models (QT-RR) cannot differentiate the elderly group from the young groups and cannot detect the stress related changes in VR as evident from the significantly smaller model fitting values found in comparison to respiratory information based models (Figure 3-4 and Figure 3-5).

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Table 3-2: Performance comparison using the goodness of fit values between the trivariate models developed with respiration and with EDR.

QT dynamics model	Model type	Fantasia Database			Drivedb database		
		Young	Old	p value	No stress	Stressed	p value
QT_{end}	$ARX_{RR}X_{RESP}AR$	0.56(0.52-0.59)	0.54(0.49-0.59)	0.41	0.61(0.57-0.64)	0.53$^{\#}$(0.48-0.58)	0.01
	$ARX_{RR}X_{EDR}AR$	0.56(0.52-0.58)	0.52(0.48-0.56)	0.07	0.60(0.57-0.66)	0.54$^{\#}$(0.50-0.60)	0.04
QT_{peak}	$ARX_{RR}X_{RESP}AR$	0.58(0.56-0.62)	0.54*(0.51-0.59)	0.01	0.62(0.57-0.68)	0.58(0.51-0.67)	0.19
	$ARX_{RR}X_{EDR}AR$	0.60(0.56-0.65)	0.53*(0.50-0.57)	0.003	0.63(0.55-0.69)	0.60(0.51-0.65)	0.12

All model fit values are given as median (first quartile-third quartile).
QT_{end}: Interval between Q wave onset to T wave end.
QT_{peak} : Interval between Q wave onset to T wave peak.* indicates significant difference from Young group.
$^{\#}$ indicates significant difference in model fit from No stressed condition.

3.5   Discussion

In this study, we have used dynamic linear parametric autoregressive models to analyse the interactions between HRV and QTV for predicting QTV and prove the effect of respiration on dynamical VR variability. Model fitting value is used to quantify QTV changes with ageing and stress induction form normal relaxed state is two case studies involving healthy population. Several aspects of these study results are discussed below:

3.5.1   Linear parametric modelling for short term QT-RR-Respiration analysis

Short-term heart rate variability is found to be linear in healthy subjects when the ECG is recorded at resting condition [111]. In addition, the respiration signal when collected from the thoracic belt due to pressure variation showed linear relationship with the QT interval variation [112]. The variation of EDR was also found to be linear when the thoracic pressure variation is recorded for respiratory information other than airflow volume measurement [112]. These findings validate the use of linear models in our analysis of the dynamic complexity of the ventricular repolarization (VR) process as the length of the QT, RR and respiration time series in our study were short (250 beats) and properly filtered to remove outliers which can add nonlinearity. Several studies showed that QT or RT interval signal always showed high frequency content synchronous with respiration even in the absence of RR variability where heart rate was kept fixed through atrial pacing [42, 80, 113]. Hanson et al. [86, 87] reported that ventricular repolarization process is also cyclically modulated by respiration both in healthy and pathological condition. These findings justified the use of

linear relation between ventricular repolarization and respiration in modelling and proved the exogenous effect of respiration on VR. Although the controlled respiration at a slow breathing rate may induce some nonlinearity in HRV and possibly on QTV [111], our study used spontaneous respiration recording due to unavailability of controlled respiration recording. Therefore, the possible nonlinear effect of respiration can be neglected in this modelling technique.

Although model complexity (i.e. Model order) was found not significantly different among the three types of models, QT-RR model needs relatively higher model order, but gave lower fit values to describe the QT dynamics than the models incorporating respiration information. In this study, every subject is modelled within the fixed range of model order through iteration (i.e. from 9 to 19) and the best model order was chosen of every subject from the simulated models according to AIC criteria. The average model order of a particular database is the average of all subject's best model order within that group. For Fantasia database subjects, the average model order found for the QT-RR model was 17 whereas the average model order for QT-RR-Respiration model was found 15. For drivedb database subjects, the average QT-RR model order was 17 whereas the average QT-RR-Respiration model order was found 16. These values indicate QT-RR-Respiration models could describe QT variability better with less complex model structure. Increase in goodness of fit values of the models analysed by considering respiration as an additional input established the importance of respiration for better comprehension and prognosis of VR dynamics and variability. As it is established from the system identification theory that if the addition of an extra input to the model increases the model fit significantly without much increase in complexity, then that input must have an important contribution in controlling the system dynamics [96]. In addition, the decrease in model fit values indicate the decoupling the input from output parameters which increases the complexity of system dynamics. It indicates that when respiration information was added, more information about the dynamical interaction between the system variables (i.e. QT, RR, Respiration) is added and the model can better describe the system dynamics with lower model order (i.e. with less complex models). Moreover, this significant increase in model fit due to addition of respiratory information (i.e. original respiration or EDR) in a QT-RR model indicates the presence of a coupled causal link from respiration to QT according to the Granger causality principle [91]. These findings establish the respiratory effect on VR process, whose inclusion will increase the efficiency of model based QTV analysis techniques.

3.5.2 Validity of EDR as a surrogate of respiration signal

Model prediction capability of VR variability always increases with the inclusion of respiration or EDR as an exogenous input and the increase was found statistically significant

for all groups (Young, Old, Stressed and No stress) and for models describing both QT_{peak} and QT_{end} dynamics (Figure 3-4 and Figure 3-5) in this study. EDR signal used in this study is calculated from the variation of mean cardiac electrical axis rotation due to respiration, which causes modulation of R wave amplitude. The position of the ECG electrodes varies with the variation of thoracic impedance for the filling and emptying of the lungs during the respiratory cycle. EDR represents this variation and can reproduce respiration information even with very low respiratory sinus arrhythmia (RSA) [100]. Although there is clear evidence of decreasing RSA with age, EDR [100] still can represent the respiratory information necessary for describing respiratory effect on repolarization [98]. Moreover, the method used for deriving EDR of this study (i.e. R wave amplitude method) is very simple and found to be quite robust in noisy ECG signal [114]. The study results of this chapter also showed the model fit values showed no statistically significant difference between the use of respiratory signal and EDR for subjects of both databases (i.e. Fantasia and drivedb). These results validate the hypothesis that EDR can be used as a surrogate of respiratory movement in modelling HRV and QTV interactions irrespective of age and psychological condition in healthy subjects. The validity of using EDR reduces the need for complex respiration signal recording setup and replaces the respiration signal where respiration signal recording is not present with ECG.

3.5.3 QT_{peak} vs. QT_{end} dynamics model performance in predicting QTV

The study results of Almeida et al. [43] emphasized the importance of considering QT_{end} in $QT - RR$ modelling for a complete description of ventricular depolarization dynamics. Results of different studies also established that important abnormalities in QT dynamics would be missed if only QT_{peak} instead of QT_{end} interval had been used to assess complete ventricular repolarization variability as the T wave peak to T wave end duration (i.e. T_{peak}-T_{end} interval) within the QT_{end} interval was found to be a marker of transmural dispersion of ventricular repolarization [43, 115]. Therefore, we believe that QT_{end} interval should be the first choice for analysing altered repolarization characteristics at the ventricles due to autonomic nervous system modulation and other pathological conditions for modelling repolarization dynamics. In this study, we used both QT_{peak} and QT_{end} intervals to check the effect of respiration on both types of models (i.e. models with original respiration and with EDR). The models with QT_{peak} as output showed slightly better prediction capability than the models with QT_{end} in all the groups, however the fit values for QT_{peak} and QT_{end} dynamics models were not significantly different (Table 3-2). Moreover, QT_{peak} dynamics models significantly differentiated healthy old groups' VR dynamics from that of Young

healthy group whereas QT_{end} dynamics models can detect the stress induced changes in QTV where the effect of normal ANS modulation is affected.

3.5.4 Effect of healthy ageing on QTV

Healthy ageing was found to be associated with the continual damage of integrated physiological regulatory system control [51]. Through Detrended Fluctuation Analysis (DFA), the fractal scaling of the RR interval time series was found to be lost in the elderly population in comparison to healthy young subjects [116]. Prolongation in QT interval and reduction in vagal modulation associated with sympathetic over activation on cardiovascular system with ageing was also found in a healthy elderly population, which causes the increase in VR process complexity [85, 117] that can be quantified by the decrease model fit value as found in this study. This could cause the elderly subjects susceptible to diseases and make them unable to react properly to perturbation of autonomic nervous system like stress, exercise etc.[116]. These physiological findings explained the decrease in model fit in an elderly population than the younger group (Table 3-2). Decrease in model fitting indicates increase in VR process complexity and alteration in QTV due to perturbed regulation of the ANS. Although the model predictability decreases with ageing, the model with respiration still performs significantly better than the $QT - RR$ model without respiration in classification (Figure 3-4 and Figure 3-5) and there was no statistical significant difference of model fit values between respiration and EDR based models. The gross variability measures (i.e. standard deviation) of QT_{peak}, QT_{end} and T_{peak}-T_{end} interval cannot differentiate the young and old groups (Table 3-1) although significant QT prolongation is evident in elderly groups which support previous findings [51]. Another finding of this study is that the models incorporating respiration or EDR, which describe QT_{peak} variability can differentiate the Young and Elderly groups of Fantasia database (Table 3-2). The QT_{end} dynamics models could not differentiate the two groups, but showed the similar pattern of variation in model fit values (Figure 3-5). This might be due to the absence of significant variability in T_{peak}-T_{end} interval (i.e. T wave apex to T wave end interval) dynamics in the relaxed healthy subjects, since the data was recorded in supine resting condition. T_{peak}-T_{end} interval variability was reported to increase with the alteration of psychological condition and in pathological condition [115, 118]. These results showed that the respiratory effect on both HRV and QTV changes with ageing and the earlier portion of VR (i.e. QT_{peak}interval) duration could differentiate the age related changes of the VR process in healthy subjects. The variability of the duration from Q wave to T wave peak (QT_{peak}) was found to depend mainly on heart rate variability and can describe VR variability properly in healthy subjects where QTV is predominantly affected by HRV [115, 119]. These changes can also be

described using EDR based models with the same model performance. Therefore, model-based analysis can describe the QTV changes with healthy ageing, which proves the effect of ageing on QTV although QT_{end} dynamics models cannot describe this phenomenon. This finding specifies the need for more precise measurement of QTV to describe age related alteration in VR process dynamics.

3.5.5 QTV due to psychological changes in healthy subjects

Stress induces temporal inhomogeneity through sympathetic nervous system activation in the ventricular repolarization process, which increases the complexity of $QT - RR$ interaction [120]. Mean QT_{end} interval decreases and gross variability measures of QTV increases with stress induction, although only increase in $SDQT_{end}$ is significant (Table 3-1). The decreases in QT duration and increase in QT variability were found due to sympathetic activation with stress, which is aligned with previous findings [52, 121]. The lower model fit values of "Stressed" group compared to the "No stress" group supports such increases in VR process complexity and QTV (Table 3-2). Real life stressed situations like the driving of automobile could alter the repolarization process by inducing $ST - T$ wave alteration and T_{peak}-T_{end} interval dynamics due to perturbation in ANS modulation by sympathetic activation [115, 122]. Excessive stress could initiate arrhythmias through temporal and spatial dispersion of repolarization [123]. Therefore, decrease in model fitting values in our healthy young "Stressed" group indicates the increase in sympathetic drive that causes the increase in temporal dispersion in repolarization process. Models designed with EDR showed similar performance as of respiration signal based models in interpreting these changes in repolarization dynamics. Another interesting finding of this study is that both respiration and EDR based models developed for QT_{end} variability, which represents the total polarization time of the ventricular action potential, could significantly differentiate the "Stressed" and "No stress" groups. This difference reflects the changes in ventricular repolarization due to the variability of the interval between T_{peak} (T wave peak) and T_{end} (T wave end) caused by stress induction [118]. Table 3-1 shows that T_{peak}-T_{end} dynamics significantly changes (i.e. T_{peak}-T_{end} duration decreases and T_{peak}-T_{end} variability increases significantly from the unstressed condition) with stress induction in the Healthy subject group used in our study (i.e. drivedb database). However, similar difference was not found in the model without respiration or EDR input (i.e. $QT - RR$ model). Therefore, inclusion of both respiratory information and T_{peak}-T_{end} variability by using QT_{end} interval endow the model to differentiate the stress related changes in VR between "Stressed" and "No stress" groups and both respiration and EDR showed statistically similar performance of predicting QT dynamics in altered psychological condition.

3.6   Conclusion

Changes in the proposed EDR based model fit values can describe the alteration in VR process complexity and QTV in Healthy subjects, which also establish the exogenous effect of respiration on QTV. Irrespective of age and psychological conditions of the healthy individual, the derived QT-RR-EDR linear parametric autoregressive models showed almost the same level of predictability of the models derived using original respiration. Therefore, the proposed hypothesis that EDR can be used as a surrogate of respiration signal in short term $QT - RR$ modelling was found to be correct in this study. Since EDR can be collected only from the ECG signal, this would reduce the complexity and inaccessibility involved in recording respiration using complex equipment settings. Whether respiration or EDR is used, the model prediction capability showed significant improvement in comparison to normal $QT - RR$ model. Respiration information based models can also statistically significantly differentiate the ageing effect and psychological changes due to stress on ventricular repolarization in healthy subjects. In our study, models describing QT_{peak} variability always gave better goodness of fit values than that describing QT_{end} variability, which proves less complex dynamics of VR is characterized by QT_{peak} interval and QT_{peak} interval variability might not describe complete QTV changes due to perturbed ANS modulation. Future studies should be done to explore the validity of EDR as a surrogate of respiration in controlled breathing condition and in conditions of postural changes where EDR might be affected due to changes in RSA for healthy subjects and in the subjects with different pathological conditions.

This chapter proves the effectiveness of the model based analysis of QTV quantification, established the effect of respiration on VR dynamics, and validates EDR as a surrogate of respiration in QTV modelling. The gradual decrease in both QT_{peak} and QT_{end} dynamic model fit values in healthy ageing indicate the increase in QTV due to age related sympathetic activation. In addition, EDR based QT_{end} dynamics modelling can describe the stress related increase in both QT_{end} and T_{peak}-T_{end} variability due sympathetic over activation(i.e. the significant decrease in model fitting value due to increase in QTV with sympathetic modulation) and suggested for analysing dynamical QTV in pathology. The next chapter investigates the performance of the proposed EDR based QT_{end} dynamics modelling technique in a pathological condition (i.e. Diabetic Cardiac Autonomic Neuropathy) where QT variability is affected due to alteration in ANS modulation.

Chapter 4

Ventricular repolarization variability in diabetic subjects with altered Cardiac Autonomic Nervous System control

In this chapter, we investigated the changes in dynamical ventricular repolarization variability (VRV) in a pathological condition called Diabetic Cardiac Autonomic Neuropathy (CAN), where VR is affected due to denervation of autonomic nervous system (ANS) branches in the heart. We used the respiratory information based modelling technique presented in the previous chapter and describe the physiological relevance of the changes in model fitting values with the severity of CAN stages. We also corroborate the effect of respiration on VR or QT interval variability in a pathological condition, where ANS branches are affected and validate the use of EDR as a replacement of respiration using a surrogate analysis technique in the absence of original respiration. The findings of the case study presented in this chapter indicate that respiratory information based model can provide important information about the QT-RR-Respiration interaction with altered VR process in pathology due to alteration of the normal ANS modulatory effect on heart's function.

4.1   Introduction

Mathematical modelling using system identification technique was reported as a useful tool for the analysis of the autonomic nervous system (ANS) control on cardiovascular dynamics [124]. In the previous chapter, we have discussed about the alteration of normal ventricular repolarization (VR) dynamics in Healthy subjects with ageing and stressed condition using respiratory information based modelling technique of VR variability. In this chapter, we analyse the dynamical ventricular repolarization variability (VRV) using the same model structure for analysing a prevalent cardiovascular complication in diabetes (both in type 1 and in type 2) called Cardiac Autonomic Neuropathy (CAN).

CAN is characterized by a gradual increase in damage to the autonomic nerve fibres that innervate the heart and blood vessels, resulting abnormalities in heart rate control and vascular dynamics [125-127]. Denervation of the autonomic nervous system (ANS) due to oxidative stress leading to CAN increases the complexity in ventricular repolarization (VR) dynamics, which can cause fatal arrhythmogenesis [1, 127]. The occurrence of confirmed CAN in diabetes patients is approximately 20%, and increases up to 65% with age and

diabetes duration [127]. Ewing *et al.* reported a mortality rate of 53% after five years in a cohort of diabetic patients with CAN, vs. 15% in the control group (i.e. Diabetic patients without CAN) [128]. The presence and severity of CAN are difficult to diagnose at the subclinical stage due to the absence of overt symptoms. As a result, it creates a potential negative impact on the quality of life of the patients [126, 127, 129]. A high mortality rate due to cardiovascular complications and an increase in diabetes prevalence require accurate and sensitive measures for detecting subclinical CAN. In addition, there is no established targeted treatment plan for CAN. Therefore, early or subclinical detection of CAN may lead to better treatment outcomes. The Ewing battery is the gold standard for detection and determination of severity of CAN [130]. This battery consists of five cardiovascular autonomic reflex tests, which require physical responses by the patients and the presence of overt clinical autonomic neuropathy. Thus, these tests are not suitable for subclinical CAN detection [131, 132]. Another drawback of these tests is the necessity of active participation by the patients, which is not always possible due to the patient's age, lack of mobility and different pathophysiological conditions such as the presence of arthritis, obesity, and heart or lung disease. Apart from the autonomic nervous system dysfunction, heart rhythm and the associated cardiac electrical conduction and hemodynamic characteristics are also affected by diabetic CAN.

Recently ECG based measures of heart rate variability (HRV) and ventricular repolarization variability (VRV) are gaining popularity for CAN detection and prognosis due to the easily available ECG signal recording and advanced computing algorithms to analyse the ECG for determining cardiac associated pathology [133]. Moreover, these ECG based markers need minimum patient cooperation, which removes the necessity of active participation of the subjects for CAN detection. Traditional time and frequency domain single signal analysis technique of the HRV (i.e. RR interval variability analysis) have been applied for the detection of CAN and CAN progression in several studies [127, 132, 133]. Decrease in time and frequency domain measures of HRV provide an indication of the alteration of the normal sympathetic and parasympathetic nervous system modulatory effect on heart rate, which can reliably identify patients with symptomatic or clinical CAN [127, 132]. However, the results are not very sensitive for asymptomatic CAN at a subclinical level [132]. Prolongation of heart rate corrected QT (i.e. QTc), alteration of dynamic QT-RR relation and a decrease or increase in QT dispersion (QTd) measured from the surface ECG are the reported signs of autonomic denervation and perturbed ventricular repolarization variability in diabetic CAN patients [125-127]. However, QTc prolongation is not a reliable marker of ventricular repolarization (VR) heterogeneity due to the complexity of correct determination of the heart rate corrected QT interval as a result of the inter-subject variability of the QT intervals,

QT hysteresis, and the effect of autonomic nervous system(ANS) control of the ventricles [1, 134]. Measurements of QTd require multiple lead recording of ECG, which is not always available, and this measure was found not a reliable technique for VR variability analysis [135]. Moreover, changes in short-term variability of QT interval are not reported widely in diabetic neuropathy subjects. CAN actually affect both Heart rate variability (HRV) and ventricular repolarization variability (i.e. QT interval variability) through alteration of normal ANS modulation effects on SA node and the ventricles respectively [125]. Therefore, dynamical multi signal analysis technique (i.e. system identification) of the QT interval variability (QTV) along with other factors that control QTV (i.e. HRV, respiration, age) might provide better information about CAN related alteration in VR [126, 136]. The direct modulatory effect of respiration on QT interval variability is reported in healthy human and heart failure patients [86, 87, 95]. In the case studies presented in the previous chapter, it was shown that use of respiration in modelling QTV better reflects the changes of the repolarization variability in healthy human participants due to ageing and altered psychological conditions than that of the model without respiration [95]. Moreover, ECG derived respiration (EDR) was found to be an effective alternative to represent the effect of the respiration signal in VR dynamics modelling for healthy participants [95]. However, to the best of our knowledge the effectiveness of EDR based VR variability modelling for detecting pathological conditions and disease progression has not been reported before.

In this chapter, we validated the use of QT-RR-EDR modelling technique in studying the changes in QTV for the detection of the presence and the determination of different severity levels of diabetic CAN. Changes in the model fitting value in different subject groups quantify the strength of coupling and complexity in the interaction between the model input –output parameters (i.e. QT, RR, and EDR) [95, 96]. We propose that the gradual decoupling of the QTV from HRV and respiration alters the normal VR process dynamics with increasing severity of CAN, which can be revealed through modelling of VR dynamics using QT, RR, and EDR extracted from the surface ECG and the variation of model fit value can quantify the VR process complexity, which affects QTV. Furthermore, the use of EDR in place of respiration to model dynamical VR variability in pathological conditions like diabetic CAN was validated using a surrogate analysis technique, as we do not have the original respiration signal recording unlike the previous chapter's studies for validation. The results of this study confirm that EDR is quite effective in representing the respiratory effect on VR in pathology condition where the normal VR process is altered due to ANS denervation. Moreover, the physiological significance of the changes in model fitting values in different stages of CAN is also described.

4.2   Case study details

To analyse the changes in VRV with CAN progression through EDR based modelling, we designed a study, collecting ECG data from some Diabetic subjects with and without CAN. Dynamical changes of VRV were investigated using the linear parametric modelling techniques of QT and RR signals with and without respiratory information for the detection of the presence and the progression of diabetic CAN.

4.2.1   Study Subjects

All participants in this study were enrolled in the Diabetes Complications Research Initiative (DiScRi) at Charles Sturt University [137]. The research protocol was approved by the Charles Sturt University Ethics in Human Research Committee (03/164) and complies with the declaration of Helsinki. Participants were divided into three study groups: i) without or no CAN (NCAN), ii) diabetic early CAN (ECAN), and iii) diabetic definite CAN (DCAN). Presence and the level of CAN were determined using the suggested reference ranges for the outcome of five cardiac autonomic nervous system function tests as described by Ewing et al. [130]. These tests measure changes in heart rate (HR) during postural changes from lying to standing, response of HR in deep breathing, and the Valsalva manoeuvre, and the change in blood pressure (BP) from lying to standing (fall in systolic blood pressure) and response of BP in sustained handgrip tests (increase in diastolic pressure). The criterion for no autonomic neuropathy (CAN-) was that all five tests had to be within the normal range. The criterion for no autonomic neuropathy (CAN-) was that all five tests had to be within the normal range. For early signs of CAN, one heart rate test had to be abnormal or two borderline. Definite CAN was defined as two or more heart rate tests being abnormal [130].
 In this study, ECG signals were analysed for 80 age-matched participants (40 NCAN, 25 ECAN and 15 DCAN), which include the whole population used in a previous study where different HRV measures were compared for CAN analysis [132]. Exclusion criteria of the selected subjects included the presence of cardiovascular, respiratory, renal disease or use of antihypertensive or antiarrhythmic medication and any other comorbid conditions that could influence ECG interbeat variability (i.e. RR interval variability or HRV) and QT interval characteristics. This ensured that any changes in T-wave morphology (i.e. changes in VR dynamics and variability) and the interbeat or RR interval variability were due to the presence or severity of CAN. Subjects were age matched so that VRV is not affected by ageing effect as reported in the earlier modelling study[95] presented in the previous chapter. We also carefully selected ECGs with good SNR (i.e. ECG with clearly detectable high amplitude T wave) for all groups and selected participants with ECGs having almost the

same magnitude of T wave so that QT variability due to T wave magnitude variation is minimum.

4.2.2   ECG analysis and EDR based model formation

Twenty minute long Lead II ECG traces of all participants were recorded with Powerlab and Macintosh Chart version 7 (AD Instruments) with the sampling rate set at 400 Hz in a supine resting condition after a 5-minute rest period to equilibrate the heart rate. The reliable quantification of QTV needs noise free ECG segments. A digital notch filter at 50 Hz was applied to reduce the noise due to electrical interference. Lead II was chosen for ECG recording as it normally provides the best T-wave morphology and the strongest R peaks.

A 5-minute ECG segment from the beginning of the each subject's recording was selected for analysis. The ECG signal segment was filtered with a zero phase linear high pass (cutoff frequency 0.4 Hz) and low pass filter (cutoff frequency 40 Hz) to remove the baseline wandering and broadband noise like muscle artefact. Filtered ECG segments were also manually checked for baseline wandering due to the presence of any other disturbances as they affect the EDR calculation. The RR interval was found from the difference between two consecutive R wave peaks, which were detected using the algorithm proposed by Pan et al. [104]. The Q wave onset (i.e. Q point) is determined by detecting the time instant where the gradient of the QRS complex becomes negative to the left of the R wave peak. The QT interval was calculated as the difference between the Q wave onset and T wave end (i.e. QT_{end} interval) in a cardiac cycle. The end of the T wave is detected using the maximum slope intercept method, which defines the end of the T wave as the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave [79, 105]. This method of T wave end detection was successfully used in several QT interval variability analysis studies [93, 95, 138]. The presence of non-sinus beats (i.e. ectopic beats) was checked from the detected RR time series using the approach of Huikuri et al. [106]. An ectopic beat is detected when successive differences of beat-to-beat RR interval exceeds 100 ms. Moreover, we discarded any QT interval that is outside of the 3-SD (Standard Deviation) band for modelling as used in our previous modelling study [95]. When any RR or QT interval was dropped due to the above-mentioned limits, the corresponding QT or RR interval was also discarded to have equal numbers of RR and QT intervals for model inputs. The respiratory information was extracted as ECG derived respiration (EDR) from the beat-to-beat amplitude variation of the R waves of the ECG [100, 108]. The EDR time series is generated by detecting the amplitude of each R wave peak from ECG filtered for baseline wandering [95]. Details of the EDR time series formation are described in the previous chapter.

Due to substantial inter subject variability of the QT-RR relation [134], each subject was modelled individually using the fixed model structure (i.e. bivariate ARXAR and trivariate ARXXAR) by varying the model order to measure the model performance in predicting QT interval as discussed in details in the previous chapter. First 250 consecutive beats of the derived RR, QT and EDR time series from the five minute ECG segment were used for the autoregressive models with single and double exogenous inputs with an autoregressive noise term. QT, RR, and EDR time series data were linearly detrended by subtracting the mean and dividing by the standard deviation before using the data as input to the model. Figure 4-1 shows the basic block diagram of the model used for VRV analysis in CAN. Model parameter estimation and validation technique is discussed in the previous chapter.
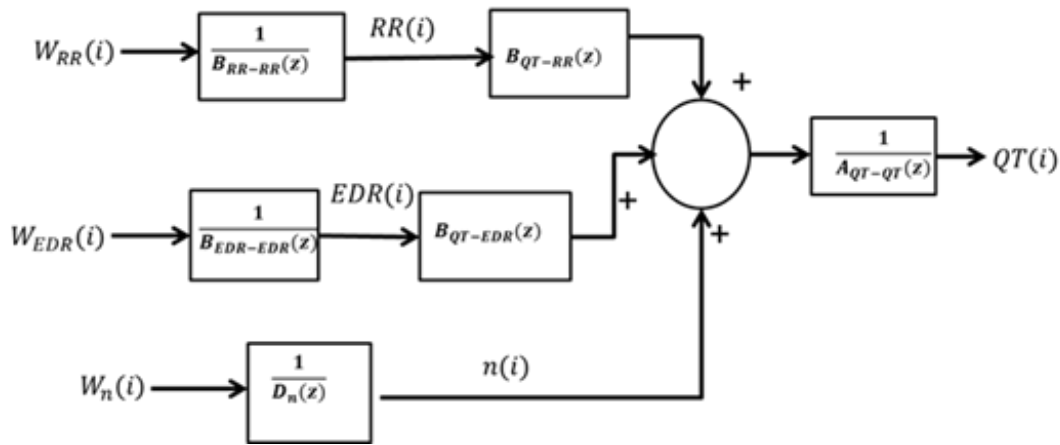
Figure 4-1: Block diagram of the trivariate ($ARX_{RR}X_{EDR}AR$) linear parametric model structure. For bivariate model ($ARX_{RR}AR$) model, the EDR branch of the block diagram is not used.

The model's goodness of fit value is calculated from the mean squared prediction error (MSPE), which measures the ability of the model structure to fit the data (Eqn. 3.12). The fit values vary from 0 to 1 where 1 indicates perfect fit and 0 indicates the model cannot describe the system dynamics for the input-output data [96]. The higher values of the goodness of fit indicate a higher model prediction capability and more coupled structure between input and output variables. A decrease in model fitting value specifies the decoupling of output (i.e. QT) from the input variables (i.e. RR and EDR) and an increase in complexity of the system dynamics [41, 95, 96].

4.2.3 Testing for classification efficiency: ROC and Effect size analysis

Non-parametric Kruskal-Wallis test was used to check the statistical difference of the model fit values and other RR and QT based parameters among the three groups after checking for normality of the data using the Kolmogorov-Smirnov test. Then the Bonferroni post hoc test was performed to compare pairwise differences between subject groups. Mann-Whitney U test was performed for pairwise comparison between two groups. A value of $p < 0.05$ was considered significant.

In order to quantify the classification efficiency of a feature, receiver-operating curve (ROC) analysis was used [139] with the area under the curve (AUC) for the classifier feature representing goodness of fit in our study. An AUC area value of 0.5 indicates that the distributions of the features are similar in the two groups with no discriminatory power. Conversely, an AUC area value of 1.0 would mean that the distribution of the features of the two groups do not overlap at all. The area under the curve was approximated numerically using the trapezoidal rule, where the larger the AUC is, the better the discriminatory performance [139].

Effect size was assessed by Cohen's d [140] values to measure the strength of the model fitting values in differentiating the study groups. A value of d =0.2 to 0.3 shows a small effect size, $d \geq 0.5$ shows medium effect size and a value of $d \geq 0.8$ shows large effect size [140, 141]. The effect size for a feature is a more reliable measure for classification and it complements the p value statistics when sample size changes [141]. All statistical calculations were carried out using the Statistical toolbox in MATLAB R2012b.

4.3   Surrogate analysis for validating the use of EDR

The use of EDR is validated in the previous study by comparing the performance of EDR and original respiration based modelling in predicting VRV. As we do not have the original respiration signal recording for the CAN subject database used in this study, we have to verify that the improvement of model prediction capability due to the addition of EDR actually comes from the effect of respiration on VR. Therefore, surrogate analysis was used in this study to validate the coupling effect of respiration (i.e. EDR) on VR dynamics. Using this technique, the model performance was calculated and compared including both original EDR and surrogate EDR signals (EDR_{rand}), which contains the power spectrum similar to that of the original EDR but uncoupled from each other. EDR_{rand} was generated by the Fourier transform based surrogate data analysis method [142, 143]. In this method, EDR_{rand} was generated by randomizing the phase (from $-\pi$ to π) of the Fourier transform of original EDR data keeping the amplitude unchanged and by applying inverse transform of the phase randomized series to generate the surrogate EDR time series. This method distorts the dynamical information of the original EDR by removing the coupling from surrogate EDR, but does not affect the spectral properties of the original EDR data. Then we used EDR_{rand} as the respiration signal input to the model and tested the model performance by measuring the model fit for every subject with surrogate EDR. In this study, the EDR time series was surrogated 60 times for each subject and each surrogate EDR was treated as EDR_{rand} for the model input. A similar model structure and model order that was used for model estimation with original EDR signal was applied to determine the model prediction capability (i.e.

model goodness of fit) with each EDR$_{rand}$ signal for every subject. Only the converged model fitting values (i.e. negative fit values were discarded) for every randomized EDR$_{rand}$ signal were recorded. Therefore, for each subject, a maximum of 60 fitting values was obtained from the EDR$_{rand}$ signal. Finally, the average of the fitting values obtained for a particular subject was taken as the fit value of the EDR$_{rand}$ based model for that subject. The hypothesis is that if EDR has a coupled effect on QT then such effect should be diminished significantly with the use of an EDR$_{rand}$ signal, which does not have actual coupling with QT, since the dynamics of EDR was destroyed in EDR$_{rand}$ signal. This effect will be reflected by the significantly lower fit values for the model with EDR$_{rand}$ as input compared to the original EDR based model. This surrogate analysis verifies whether the changes in model fitting values with the addition of EDR is due to the actual coupling effect of respiration with QT on VR dynamics or it is just a random effect due to the addition of an extra exogenous input.

4.4 Results

Beat-to-beat variation of the derived RR, QT, and EDR time series of 250 beats from the 5 min ECG segments of a single subject from each of the three groups (i.e. NCAN, ECAN, and DCAN) is shown in Figure 4-2. The duration and the variability of RR and QT interval measure by the time series variance are shown Table 4-1. Mean RR interval and RR interval variance progressively decreased in magnitude from NCAN to DCAN whereas the Mean QT interval duration increased in the ECAN and DCAN groups with respect to the NCAN group, although the increase in QT interval is not significantly different from NCAN group (Table 4-1).
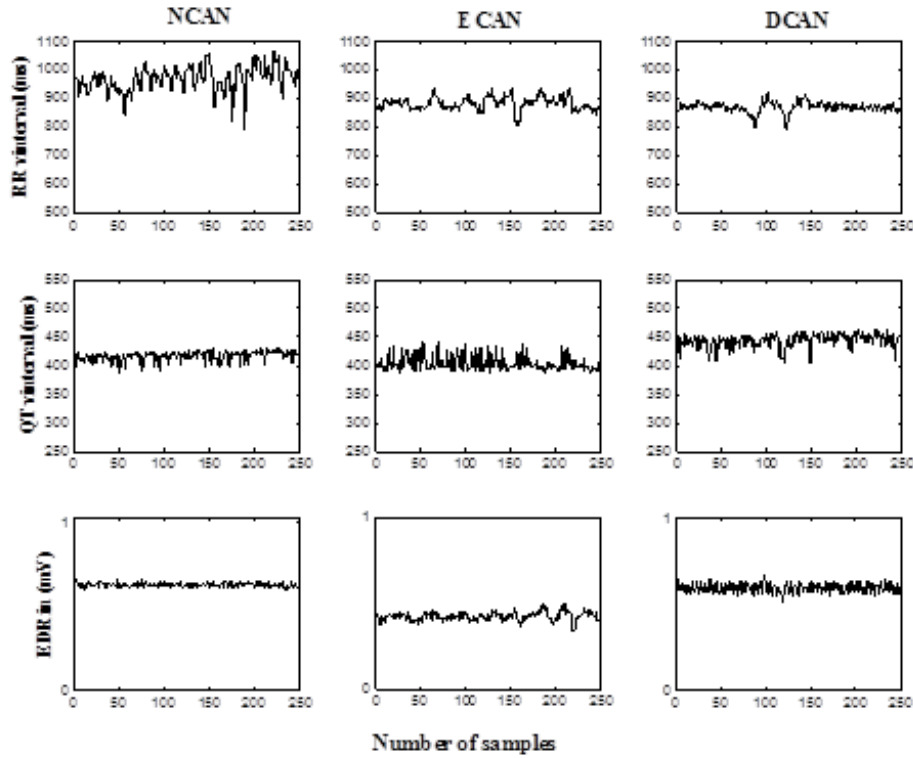
Figure 4-2: Representative figure showing the trend of changes in RR, QT and EDR time series with CAN progression for a subject in three groups.

RR variance can significantly differentiate the NCAN group from the CAN (ECAN and DCAN) groups. The variance of QT in the ECAN group is greater than for the NCAN and DCAN groups, but the QT variance is less in the DCAN group compared to the NCAN group (Table 4-1). The high variability of QT interval in the ECAN group might be the result of increased sympathetic drive due to early parasympathetic withdrawal at the subclinical stage of CAN [88, 127].

Table 4-1: Pattern of RR and QT interval variations (i.e. mean and variance) with CAN progression in three subject groups (NCAN (without can), ECAN (early can) and DCAN (definite can))

Features	NCAN	ECAN	DCAN	*p* value
Mean RR (ms)	930.45 ± 121.06	907.41 ± 149.45	903.47 ± 125.96	0.251
Variance of RR (ms^2)	1799 ± 1600	1100± 896*	520 ± 386*	0.0003
Mean QT (ms)	404.34 ± 26.62	412.05 ± 36.06	413.91 ± 40.31	0.584
Variance of QT (ms^2)	191 ± 170	233 ± 205	154 ± 150	0.356

All values are expressed in median (first-third quartile)
* indicates ECAN and DCAN groups' RR variance is significantly different from NCAN group.

The Median (IQR) values of goodness of fit of ARX$_{RR}$AR and ARX$_{RR}$X$_{EDR}$AR models for the participants in all three groups (NCAN, ECAN and DCAN) are shown in Table 4-2. The fit values were significantly (p<0.0001) increased for the EDR based model (ARX$_{RR}$X$_{EDR}$AR) for all three groups compared to ARX$_{RR}$AR model. In contrast to the ARX$_{RR}$AR model, ARX$_{RR}$X$_{EDR}$AR model showed clearly the gradual decreasing pattern in

median fit values from NCAN with increasing severity of CAN (Table 4-2 and Figure 4-3(left panel)) and the difference in fit values among three groups were also significant ($p < 0.001$). The Bonferroni post hoc test results showed that the fit values of $ARX_{RR}X_{EDR}AR$ model could significantly ($p<0.05$) differentiate NCAN group from both ECAN and DCAN (Figure 4-3, left panel).

Table 4-2: Improvement in goodness of fit values due to addition of respiratory information of two models ($ARX_{RR}AR$ and $ARX_{RR}X_{EDR}AR$) in three groups (NCAN, ECAN AND DCAN).

Group	$ARX_{RR}AR$	$ARX_{RR}X_{EDR}AR$	p value
NCAN (40)	0.44(0.41-0.48)	0.61(0.59-0.65)	9.15e-14
ECAN (25)	0.40(0.37-0.46)	0.59(0.54-0.63)[*]	2.89e-09
DCAN (15)	0.41(0.39-0.45)	0.56(0.53-0.60)[#]	1.10e-05

All values are expressed in median (first-third quartile).
* and # indicates that ECAN and DCAN model fit values are significantly different from the NCAN model fit in case of $ARX_{RR}X_{EDR}AR$ model.

Although, $ARX_{RR}AR$ showed decreased fit values for groups with diabetic CAN (ECAN and DCAN) compared to healthy group (NCAN), the difference in fit values with progression of CAN was not statistically significant between any groups and not pronounced particularly from ECAN to DCAN group. To check the classification efficiency between any two of the possible combinations of three groups (NCAN vs DCAN, NCAN vs ECAN and ECAN vs DCAN), we performed an ROC analysis for $ARX_{RR}X_{EDR}AR$ model. An ROC area of 0.75, 0.70 and 0.57 were found for the NCAN vs DCAN, NCAN vs ECAN and ECAN vs DCAN respectively (Figure 4-3, right panel).
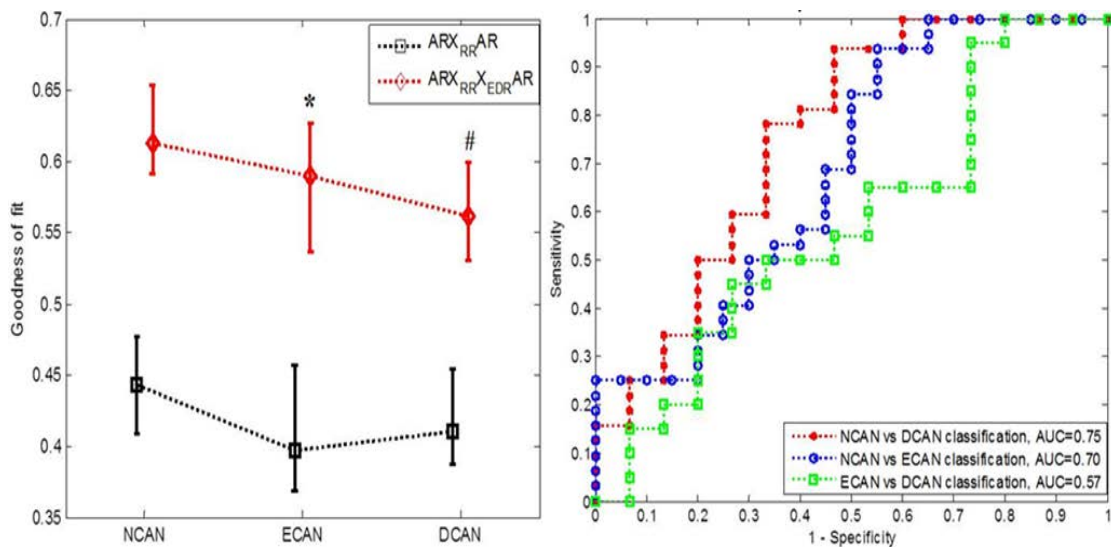
Figure 4-3: Variation in model fit in three groups for $ARX_{RR}AR$ and $ARX_{RR}X_{EDR}AR$ models (left panel); * indicates that the ECAN group is significantly different from the NCAN group (p<0.05); # DCAN is significantly different from NCAN (p<0.05). The right panel shows ROC curves and area under the curve (AUC) indicating the classification efficiency of the $ARX_{RR}X_{EDR}AR$ model fitting values when comparing between each of the two group combinations of the study.

Surrogate analysis was also performed to check whether the model fit improvement due to the addition of EDR is actually due to the effect of respiration or from some random effect that increases the model fit. Median (IQR) values of goodness of fit for the original EDR based model ($ARX_{RR}X_{EDR}AR$) and surrogate EDR (EDR_{rand}) based model ($ARX_{RR}X_{EDRrand}AR$) for all three groups of participants are shown in Table 4-3. Fit values were significantly lower ($p<0.001$) for $ARX_{RR}X_{EDRrand}AR$ model compared to $ARX_{RR}X_{EDR}AR$ model proving that the significant improvement in fit values of the $ARX_{RR}X_{EDR}AR$ model than $ARX_{RR}AR$ model (Table 4-2) is due to coupling effect of respiration (i.e. EDR) on VR dynamics rather than the addition of a random exogenous input. Moreover, EDR_{rand} based model also cannot differentiate the CAN groups from the groups without CAN whereas EDR based models can ().

Table 4-3: Comparison of model fitting values generated by the models using original EDR and surrogate EDR (EDR_{RAND})

Group	$ARX_{RR}X_{EDR}AR$	$ARX_{RR}X_{EDRrand}AR$	*p* value
NCAN(40)	0.61(0.59-0.65)	0.51 (0.50-0.55)	1.60e-10
ECAN(25)	0.59(0.54-0.63)*	0.49(0.46-0.50)	3.67e-09
DCAN(15)	0.56 (0.53-0.60)$^{\#}$	0.50(0.46-0.53)	7.01e-03

All values are expressed in median (first-third quartile).
* and # indicates that ECAN and DCAN model fit values are significantly different from the NCAN model fit in case of $ARX_{RR}X_{EDR}AR$ model.

To verify the strength of the classification efficiency of the EDR based models we also performed the effect size analysis. Table 4-4 shows the *p* values and corresponding effect sizes (i.e. Cohen's *d*) to evaluate the strength of classification of the feature (model fit values) for comparison between two groups. Larger effect size ($d > 0.75$) with significant *p* values ($p < 0.05$) were found for $ARX_{RR}X_{EDR}AR$ model in classifying NCAN from ECAN and DCAN groups, which proves the effectiveness of the use of respiration based models in a larger population of same pathological characteristics. Although the $ARX_{RR}AR$ model showed a medium effect size for classification of ECAN and DCAN groups ($d = 0.551$ and 0.561) from NCAN, the *p* values are not significant and this model cannot be reliably used for CAN prognosis.

Table 4-4: Comparing the strength of the differentiation capability using goodness of fit between every two group combinations using the *p* values and Cohen's *d* using two model types.

Groups to compare	$ARX_{RR}AR$		$ARX_{RR}X_{EDR}AR$	
	p value	Cohen's *d*	*p* value	Cohen's *d*
NCAN vs ECAN	0.05	0.56	0.01	0.76
NCAN vs DCAN	0.06	0.56	0.008	1.18
ECAN vs DCAN	0.84	0.009	0.45	0.15

4.5   Discussions

In this study, we validated the application of an EDR based autoregressive linear model based VRV analysis technique in the detection and progression of CAN in diabetes participants. In addition, we verified the effect of respiratory information on VR dynamics in pathological conditions and showed that respiratory information based models can successfully differentiated different levels of CAN while only QT-RR based models cannot. The changes in model fit values of the EDR based model can also successfully detect the presence of CAN at a subclinical level (ECAN) in addition to the clinical level (DCAN) and can describe the alteration of ANS control on VR dynamics associated with the CAN progression.

Recent studies support the effectiveness of determining CAN from short term ECG using HRV and VRV (e.g. 5 to 10 min recordings) [127, 132, 133, 136]. The analysis of the alteration of the autonomically mediated physiological coupling mechanism between respiration and heart rate as well as between respiration and blood pressure using system identification technique was previously reported in quantifying diabetic CAN and shown to be promising for disease prognosis [144]. In this study, we have investigated the changes in VR dynamics related to CAN progression using the open loop modelling of QT, RR, and EDR as a surrogate of respiration to investigate the effect of coupling of RR and respiration with QT in diabetic CAN. To the best of our knowledge, this study is the first investigation about changes in VRV and VR dynamical complexity with alteration with ANS control from modelling RR, QT and respiratory information. Several aspects of the study findings are discussed below:

4.5.1   Effect of respiration on VRV in pathology

EDR used in our modelling study to represent the respiratory information, was also found to affect VRV and VR dynamics through its effect on QT and RR intervals in healthy humans with ageing and psychological changes [95]. EDR was found to reproduce respiration information even with very low respiratory sinus arrhythmia (RSA) in aged and pathological conditions with no major respiratory abnormalities [97, 100]. The method of EDR determination (i.e. R wave amplitude method) used in this study is also quite robust against muscle artefact and broadband noise [114]. The findings of the current study showed that fit values of the EDR based model significantly increased in all groups of participants compared to models without EDR (Table 4-2 and Figure 4-3). In addition, the results of surrogate EDR (i.e. EDR$_{rand}$) based modelling showed that the significant improvement of model fitting comes from the coupling effect of respiration with QT rather than due to any random effect generated from the addition of any extra exogenous input to the model. Moreover, this

significant increase in model fit due to addition of respiratory information (i.e. EDR) in a QT-RR model indicates the presence of a coupled causal link from respiration to QT according to the Granger causality principle [91]. The decrease in model prediction capacity measured by the decrease in model fitting value with severity of CAN indicates the decrease in the strength of this causal coupling, which may play important role in CAN detection.

A recent review on the methodology for the investvgation of cardiac autonomic dysfunstion in human studies indicates that the effect of respiration on RR and QT is not fully diminished with CAN progression [145]. Most of the studies that reported the rapid decrease in high frequency power in diabetic CAN subjects used ECG with controlled or paced deep breathing [145]. Some recent studies reported the existence of ventricular action potential variation (i.e. QT interval variation) with spontaneous and controlled respiration in frequency domain in both healthy and heart failure subjects, which is evident form the spectral domain analysis of QT interval [86, 113]. Previous studies prove the existence of a non-autonomic respiratory sinus arrhythmia (RSA) component in the heart rate signal with complete pharmacologic autonomic blockade [145, 146] similar to CAN subjects where autonomic branches are affected and the autonomic modulation was lost. Spallone et al [147] reported the existence of a non-autonomic high frequency power component synchronous with respiration in diabetic CAN subjects, which might arise due the mechanical factors of breathing on the atrium. Saul et al [146] concluded that the effect might be related to the rate of change in lung volume changes, which can be detected by EDR. Lombardi et al showed that QT or RT interval signal always showed a high frequency component synchronous with respiration in spectral domain even in the absence of RR variability where heart rate was kept fixed through atrial pacing [113]. The effect of respiration is found on both QT_{peak} and QT_{end} intervals in short length (i.e. 5 to 10 min) ECGs with good SNR and high amplitude T wave [80]. These results prove that respiration affects VR variability (i.e. QTV) in the absence of HRV and we believe that it is not merely an artefact of noise that distorts the cardiac axis orientation but actually affects the VR process though the effect might not be as strong as it is by HRV. Therefore, these studies prove the effect respiratory modulation in diabetic CAN subjects in the absence or very small value of HRV and validated the results of EDR based modelling in differentiating CAN groups form non-CAN groups in diabetes found in this study. This effect can be described using respiratory signal based modelling of VR dynamics. These results also validate the use of EDR as an alternative of respiration and established the importance of considering the respiratory effect on VRV in the diagnosis of pathological condition where VR is affected like CAN.

4.5.2 Physiological interpretation of model fit value changes with ANS denervation

Since CAN is characterized by the gradual denervation of sympathetic and parasympathetic branches innervating the heart [125-127], the control mechanism of the ANS and respiration on heart rate and VR will also become affected with CAN and can be analysed by modelling VR dynamics using QT,RR and respiration signal [41, 95, 136]. The significant decrease in $ARX_{RR}X_{EDR}AR$ model fit value with the increased severity of CAN (Figure 4-3 left panel) reflects the gradual decoupling of QT from RR and respiration due to ANS denervation [41, 91, 95]. However, such trend becomes less pronounced (especially between ECAN and DCAN groups) and was not significantly different between the groups for the $ARX_{RR}AR$ model without any respiratory information. Only EDR based model can successfully detect this deterioration of VR dynamics with CAN progression in this study. The decrease in model fitting values might be the result of increased QT variability in diabetic CAN participants, which also indicates the increased risk of arrythmogenesis in CAN participants [1, 88, 127, 138]. Porta et al. reported that a gradual decoupling of QT and RR intervals occurred in healthy individuals with applied sympathetic activation by graded head up tilting is due to the greater amount of vagal withdrawal than the increase in sympathetic tone [92]. In our study, the model fitting values decrease rapidly from NCAN to the ECAN group (Figure 4-3) who are characterized as having sympathetic over activation due to early parasympathetic denervation [125-127]. Therefore, the decoupling of QT from RR and respiration is mainly due to sympathetic over activation in the early stage of CAN, which is evident from rapid decrease in model fit values. The RR variance decreased and the QT variance and variability (i.e. SD of QT) increased in the ECAN group compared to the NCAN group (Table 4-1), indicating the increases in sympathetic tone in ECAN group [88]. At the severe stage of CAN, both branches of the ANS are denervated which causes more decoupling of RR and respiration from QT as evidenced by the gradual decrease in fit values. The variance of RR decrease more than the decrease in SDQT with CAN progression indicating that HRV which measure the mainly the effect of parasympathetic nervous system, affect the decoupling more than the sympathetic branch of the ANS as also reported by Porta et al. [92]. This decoupling can only be detected by respiratory information based models, which indicate that the coupling between respiration and QT is also affected during progression of CAN. These findings indicate that the use of respiratory information in terms of EDR as an exogenous input significantly improves the modelling performance and changes in model fit values can describe the increase in VR process complexity and changes in VRV due the ANS branch denervation with CAN. Figure 4-4 graphically shows the gradual changes of HRV and VRV due to CAN progression as determined from the EDR based modelling performance analysis.
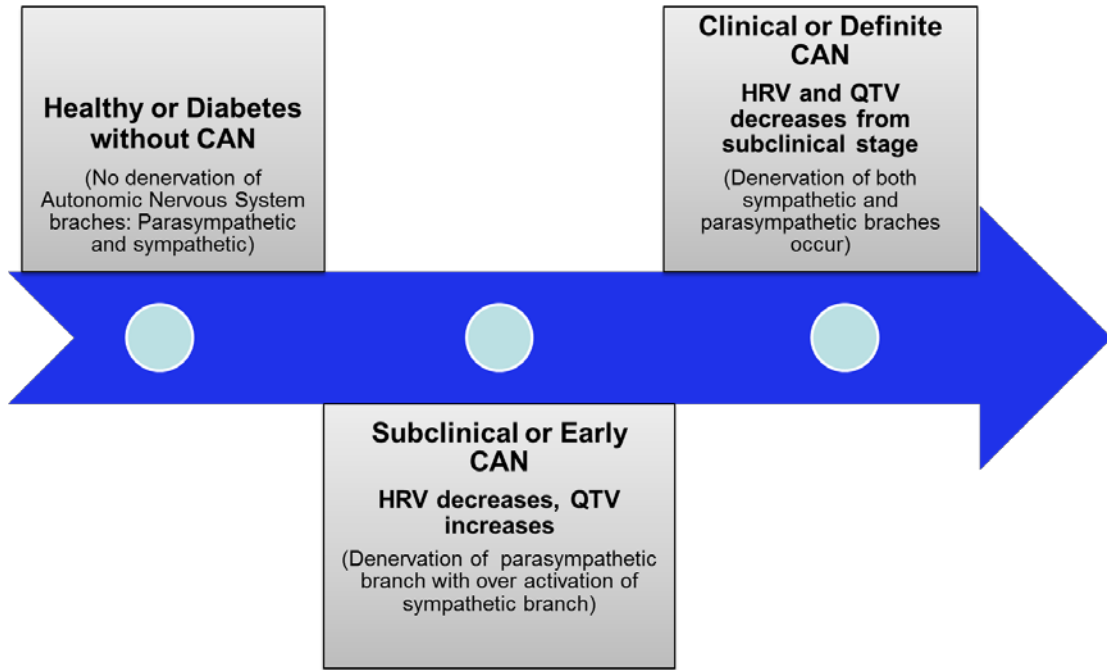
Figure 4-4: Changes in HRV and VRV (i.e. QTV) with the progression of CAN showing different stages of Autonomic Nervous System denervation.

4.5.3 Effectiveness of Model based VRV analysis for pathology detection

The study results showed the effectiveness of the model based VRV analysis technique incorporating respiratory information. Decrease in HRV, increase in resting heart rate and QT prolongation is also reported is several studies [88, 125, 127] but changes in VRV is not widely reported. Gross variability measures of QT interval of this study (i.e. Duration and variance of QT) showed the changes in CAN subjects, but cannot detect the presence of CAN from the normal group (Table 4-1). Changes in model fit values with CAN progression clearly demonstrates changes in VRV due to the alteration of ANS breaches with CAN progression and can successfully detect the presence of CAN. Another important finding of this study is that the addition of EDR as an exogenous input for dynamical analysis of VRV enhances the model capability to detect subclinical CAN (i.e. ECAN) whereas QT-RR model cannot (Table 4-2 and Figure 4-3, left panel). Analysis of effect size also strengthens our findings that the EDR based model was more effective (*d*>0.75) in classifying ECAN and DCAN groups from the NCAN group (Table 4-4) than that of the models without respiration. The large effect size indicates that this effect is expected to be present in a larger population with same pathological characteristics [141]. Autonomic reflex tests proposed by Ewing et al.[130] and traditional HRV based techniques for CAN detection are not very sensitive for identification of asymptomatic or subclinical CAN (i.e. ECAN) [132]. However, identifying subclinical CAN is crucial in providing effective timely treatment [126, 127]. Therefore, dynamical analysis of VRV by EDR based modelling

proves to be more sensitive than that of the model without respiration, which can be used as an effective marker for subclinical CAN detection. The results of ROC analysis showed that the classification efficiency of respiration based modelling in case of NCAN vs. DCAN (i.e. AUC=0.75) is better than that of NCAN vs. ECAN (i.e. AUC=0.70), although the model can differentiate ECAN from NCAN with reasonable accuracy (Figure 4-3, right panel). This finding proves that respiration based models are more sensitive in detecting the severity of CAN.

In addition, the unpublished results of our study indicated that only QT_{end} interval based models with respiratory information could detect the presence and progression of CAN whereas QT_{peak} interval based models could not. This finding establishes the importance of analysing the total duration of ventricular depolarization and repolarization (i.e. QT_{end} interval) from ECG in diagnosis of pathological condition as concluded in the previous chapter, which indicates that T_{peak}-T_{end} interval might contain important information of VRV due to ANS modulation [1]. In summary, modelling dynamical changes of VRV with CAN progression using RR, QT_{end} and EDR as surrogate respiratory information (i.e. QT-RR-EDR model) can be used effectively for diabetic CAN classification. The methodology of QT interval detection from ECG affects the amount of QT variability included in the measured QT interval series data [1, 78], which in turn can affect model performance. In our study, we used the slope intercept method for QT interval detection after applying proper filtering techniques for removing baseline wandering and broadband noise within the ECG. This method of T wave end detection is reported to be more reproducible [148] and used in several QT interval variability studies successfully where correct QT interval detection is critical [93, 95, 138]. We prefer this method for QT interval detection in pathology other than the semi-automated template based methods of QT interval detection, where a number of beats are rejected due to the absence of normal sinus rhythm ECG and results in less variability of the QT interval which might contain prognostic information of diseases [1, 78]. It may also be necessary to manually select QT intervals in certain patient cohorts for detecting pathology related T wave morphology provided proper ECG noise removal criteria were fulfilled and good quality ECGs were available with clearly visible high amplitude T waves.

4.6   Conclusion

Respiratory information (i.e. EDR) based QT-RR modelling of VRV was found to be an effective way in investigating the increases in complexity of VR dynamics in diabetic CAN participants with disease progression. EDR based models can also detect subclinical CAN (ECAN), which is crucial for better diagnosis of diabetic patients and treatment outcomes.

These results strongly suggest the use of respiratory information in analysing VRV in both healthy and pathological conditions, where an ECG signal is recorded with spontaneous breathing, participants are in stable conditions without any postural manoeuvre, and any comorbid conditions that affect normal respiratory effort are absent. VRV (i.e. QTV) not only provides information about the electrical characteristics of the ventricles, it can also provide important information about the mechanical functionality of the ventricles in blood circulation like the alteration of systolic and diastolic interval. Although the model-based analysis can detect the subclinical CAN, it cannot differentiate the level of severity between ECAN and DCAN group, which provides crucial information of disease progression. CAN progression analysis is critical for the prognosis of heart failure that alters the normal systolic and diastolic interval interactions. In the next chapter, we present another measurement technique from the VRV characteristics that can be useful for CAN progression analysis and shed more light on VRV changes in pathological conditions.

Chapter 5

Analysing systolic and diastolic time interaction variability from ECG based ventricular repolarization measures

In this chapter, we investigate the hemodynamic function of the left ventricle (i.e. systole or contraction and diastole or relaxation function of the ventricle for blood circulation) in terms of systolic and diastolic time intervals derived from the ECG. Mechanical systolic and diastolic function of the heart is normally assessed noninvasively for investigating heart failure by Cardiac Imaging techniques like Doppler echocardiography, Tissue Doppler imaging (TDI) etc. The mechanical actions of the left ventricles (i.e. systole and diastole) are controlled by the ventricular electrical characteristics (i.e. cardiac action potential propagation characteristics in the ventricle that activates the contraction and relaxation) which can be measured from the ventricular repolarization duration (QT interval) in ECG. Systolic and diastolic time intervals can be detected form ECG signal, which are termed as electrical systolic (i.e. QT interval) and diastolic time interval (i.e. TQ interval) respectively. Therefore, ECG based analysis of systolic and diastolic heart failure is gaining popularity due to the availability of cheap and easily controllable efficient ECG analysis technology and inaccessibility of comparatively costly Echocardiography procedures in every clinical setting. The case study presented in this chapter proposes some variability measures for electrical systolic and diastolic interval interaction (SDI) calculated from the ECG and analyse the performance of these measures in Diabetic Cardiac Autonomic Neuropathy (CAN) progression, where the VR process is gradually deteriorated and affect the normal mechanical function of the left ventricle leading to heart failure. The findings of this study indicate that SDI measures can identify the presence and severity level of CAN within the study groups and provide useful information about CAN related alteration in the temporal characteristics of systole and diastole. These results prove the feasibility of CAN detection using SDI measures where traditional Ewing tests cannot be performed. Moreover, the proposed SDI measure can successfully detect the CAN progression by significantly differentiating the subclinical group form clinical group, which could not be done by QT-RR-EDR modelling analysis technique reported in the previous chapter.

5.1 Introduction

Normal hemodynamic function (i.e. the rhythmic mechanical action of ventricles) of the heart depends on the synchronized temporal relation between the systole (i.e. ventricular contraction) and diastole (i.e. ventricular relaxation). Left ventricular function is more important as this heart chamber is responsible for blood flow through the peripheral circulation system of the body [68]. Both systolic and diastolic heart failure affects the mechanical function of the ventricles, which also alters the temporal characteristics of systole and diastole [64, 149]. Alteration of the synchronized interaction between systolic and diastolic time intervals indicates the presence of pathophysiology in heart's mechanical function, leading to heart failure [150-152]. The systolic time interval is reported in numerous studies to be a useful measure of Left ventricular performance in pumping blood throughout the body [64, 83, 153, 154]. The diastolic time interval was also found to be effective in analysing left ventricular dysfunction [82, 149]. Systolic and diastolic interval interaction is reported to be useful prognostic measures in different cardiovascular diseases indicating the strong relation between Diastolic time and heart rate [150, 155]. Recent studies reported the efficiency of systolic and diastolic interval ratio derived from Doppler echocardiography in analysing heart failure due to ventricular myocardial dysfunction where the heart loses its proper ability of pumping blood throughout the body parts [151, 152, 156, 157].

Cardiac Imaging techniques like Doppler echocardiography, Tissue Doppler Imaging (TDI) and Radionuclide imaging are widely used to assess the level of systolic and diastolic dysfunction and determine the extent of ventricular autonomic denervation due to cardiac pathology [62, 151, 158]. However, the increase of global healthcare cost and the absence of these cardiac imaging techniques in every clinical setting to specify the need for an alternative technique that is easily accessible and economical. Moreover, identification of the patient group who actually are in need of the cardiovascular imaging for further investigation of the available clinical data is a crucial step for both economical and effective health care service [59]. Therefore, ECG based measures for analysing left ventricular dysfunction (i.e. systolic and diastolic heart failure) are gaining popularity due to the easily available ECG signal recording systems and advanced computing algorithms to analyse the ECG for determining cardiovascular pathology [60, 61, 63, 133, 159].

The QT interval, which represents the ventricular repolarization (VR) duration can be used as a surrogate systolic interval within a cardiac cycle of the ECG signal and defined as electrical systole [60, 64, 154, 160, 161]. The duration and variability of the QT interval indicate the duration and variability of the systolic phase of a cardiac cycle, which is also affected by the RR interval (i.e. total systolic and diastolic interval duration) and the TQ

interval of the previous cardiac cycle [64, 84, 161]. The TQ interval within a cardiac cycle is considered as a surrogate measure for the diastolic interval (i.e. electrical diastole) and directly affects the QT or systolic interval of the next cardiac cycle [84, 149, 161]. Different QT interval variability measures(i.e. QTVI, QTVN) were also found related with the left ventricular dysfunction due to previous myocardial infarction and hypertrophic myocardium [22, 23, 26, 83, 162]. Therefore, ECG based VR measures can be used for investigating left ventricular systolic and diastolic function.

Predominant parasympathetic denervation in the early stages of CAN was found to be associated with altered left ventricular relaxation and filling, increased left ventricular mass, left ventricular hypertrophy and impaired myocardial blood flow regulation [126, 158, 163]. These findings indicate that CAN have a strong association with diabetes-induced systolic and diastolic dysfunction and the associated high mortality and morbidity rate [158, 164, 165]. In the previous chapter, we presented the QT-RR-EDR based modelling technique for analysing CAN related alteration in VR variability (VRV) and found that model based VRV analysis can determine the subclinical level of CAN but cannot detect the disease progression.   CAN progression determination is crucial as it describes the gradual degradation of Autonomic Nervous System control on the heart's function affecting heart rate variability (HRV) and VRV. The disease progression analysis also differentiates the early stage form the severe stage where the condition is normally cannot be reversed. In this chapter, we presented an ECG based approach for analysing systolic and diastolic interval interaction in CAN and validated its performance in CAN progression analysis.

The beat-to-beat Systolic-diastolic interval (i.e. QT-TQ interval) relationship in terms of QT/TQ interval ratio termed in this study as $QTTQ$ is described as the systolic-diastolic interval interaction (SDI) or the balance of cardiac contraction and relaxation within one cardiac cycle [84, 156, 161]. Several studies have proposed that the SDI ratio is an indicator of ventricular dysfunction in different cardiovascular disease and increases with increased abnormal cardiac function [151, 152]. Moreover, systolic and diastolic intervals can provide useful information about diastolic dysfunction [151, 163, 165], which is common in diabetic CAN patients [158]. Therefore, we hypothesize that the analysis of the beat-to-beat SDI is a potential tool for diagnosing CAN and CAN progression in diabetic patients using short-term surface ECG (i.e. 10 min ECG). To the best of our knowledge, SDI measures have not been applied before in diabetic CAN analysis. We have introduced a modified SDI parameter $TQRR$, calculated from beat-to-beat TQ/RR interval ratio indicating how the diastolic interval in every cardiac beat varies with respect to heart rate (i.e. RR interval contains the total duration of a cardiac cycle containing the systolic and diastolic intervals). Moreover, the comparison of the performance of RR interval, systolic interval duration (i.e. QT

interval), diastolic interval duration (i.e. TQ interval), the existing and the proposed SDI measures is reported in identifying the presence and the severity of CAN in diabetic patients.

5.2 Measurement of the proposed Systolic-diastolic interval interaction (SDI) measure

In this study, we proposed an improved SDI measure derived from short-term ECG signal (i.e. 10 min). The method for calculating this measure is described below:

5.2.1 Cardiac cycle length, Electrical systolic and diastolic interval detection

Firstly, cycle length (i.e. RR interval) and electrical systolic intervals (i.e. QT interval) were needed to be detected from a 10-minute preprocessed ECG segment of every subject. For this study, we collected twenty-minute long Lead II ECG traces of all participants recorded in a supine resting condition after a 5-minute rest period to equilibrate the heart rate with Macintosh Chart version 7 and a sampling rate set at 400 Hz. A digital notch filter at 50 Hz was applied to reduce the electrical interference. High frequency noise was removed with a 45 Hz low pass filter and a 3 Hz high pass filter adjusted for wandering baseline before RR and QT interval detection. Lead II was chosen as it provides the best T-wave morphology and the strongest R peaks. Ectopic beats were selected visually and deleted manually. Linear interpolation was used to replace ectopic beats immediately before and after the ectopic interval. The patients from whom an ECG recording of at least 20 minutes was not available and in those with ECGs, less than 85% normal beats were excluded from the study. ECG signals were edited using the MLS310 HRV module (version 1.0, ADInstruments, Australia) included with the LabView software package.

In this study, we derived the RR and QT intervals were detected using a semi-automated template-matching algorithm proposed by Berger *et al.* [26], which provides reliable results associated with ventricular repolarization variability in many clinical studies [4]. The template matching method requires the operator to define a template QT interval by selecting the beginning of the QRS complex and the end of the T wave for one beat of the ECG signal. The algorithm then finds the QT interval of all other beats by calculating how much each beat must be temporally stretched or compressed to best match the template interval. The QT interval (i.e. systolic interval) was calculated as the difference between the Q wave onset and T wave end (i.e. QT_{end} interval) in a cardiac cycle. Different ECG wave intervals measured for calculating SDI are shown in Figure 5-1.
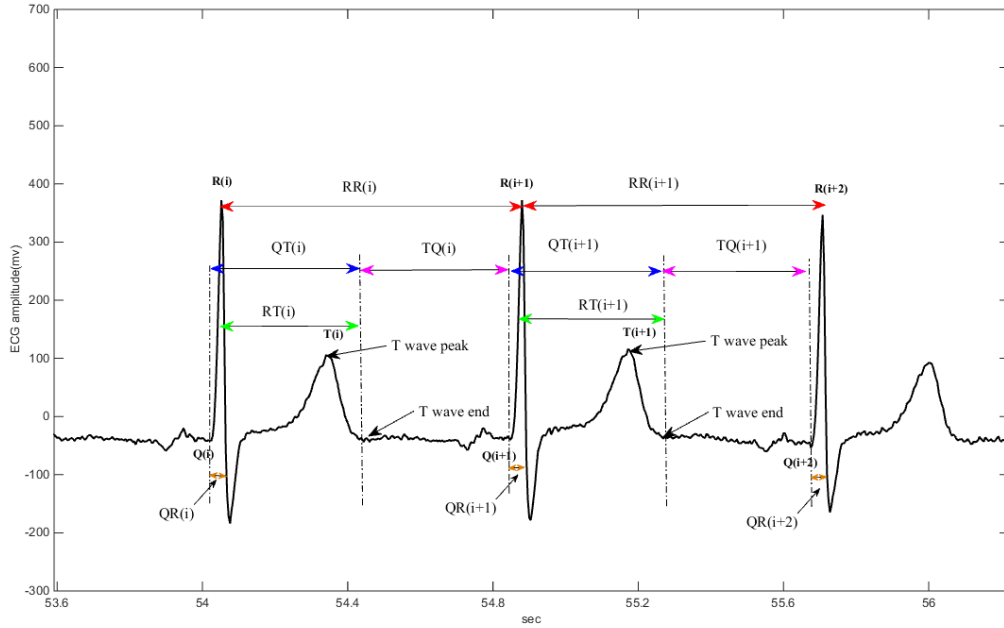
Figure 5-1: Schematic representation of different of ECG wave intervals (RR, RT, QT, QR and TQ intervals) in two cardiac cycles. The duration of QR interval is negligible in comparison to QT and TQ intervals, which is evident in the figure.

From the detected QT and RR interval time series, we also calculated the TQ interval (i.e. electrical diastolic interval) and formed three time series for variability analysis. These three beat-to-beat time series are represented as:

$$QT = \{QT(i), i = 1,2, \ldots \ldots N\},$$
$$RR = \{RR(i), i = 1,2, \ldots \ldots N\}, \text{and}$$
$$TQ = \{TQ(i), i = 1,2, \ldots \ldots N\},$$

where *N* is the total number of intervals within the 10 min ECG segment. The TQ interval is calculated by subtracting the QT interval from the RR interval within the same cardiac beat by neglecting the QR intervals (Figure 5-1). Any RR interval time series $RR(i)$ can be expressed as:

$$RR(i) = RT(i) + TQ(i) + QR(i + 1)$$
$$\Rightarrow RR(i) = QT(i) - QR(i) + TQ(i) + QR(i + 1) \qquad (5.1)$$

The RR interval can be considered as the combination of RT, TQ and QR intervals. Since the QR interval duration is negligible in comparison to the RT or QT interval, the effect of variability due to the $QR(i)$ or $QR(i + 1)$ interval is considered negligible on the overall RT or QT variability (Figure 5-1) and we can assume that $QR(i) = QR(i + 1)$. Hence, the beat-to-beat TQ interval can be calculated using the equation:

$$TQ(i) = RR(i) - QT(i) \qquad (5.2)$$

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5.2.2 Beat-to-beat systolic and diastolic interval interaction (SDI) parameter calculation

Existing beat-to-beat systolic-diastolic interval interaction (SDI) is defined as the ratio of the QT and TQ interval [84, 156, 161] and can be expressed as follows

$$QTTQ(i) = \frac{QT(i)}{TQ(i)} \tag{5.3}$$

where i=1...N and N is the total number of detected QT and TQ intervals within the 10 min ECG signal.

In this study, we proposed a modified version of the existing SDI measure for quantifying beat-to-beat systolic-diastolic interval interactions, namely $TQRR(i)$, which was calculated as $\frac{TQ(i)}{RR(i)}$. The relationship between the proposed $TQRR$ parameter and $QTTQ$ can be shown using the following equation:

$$TQRR(i) = \frac{TQ(i)}{RR(i)} = \frac{TQ(i)}{QT(i)+TQ(i)} = \frac{1}{1+\frac{QT(i)}{TQ(i)}} \approx f\left(\frac{QT(i)}{TQ(i)}\right) = f\big(QTTQ(i)\big) \tag{5.4}$$

Therefore, $TQRR$ can indicate the beat-to-beat systolic-diastolic interval interaction variations similar to $QTTQ$ as shown in (4) and it actually complements $QTTQ$ in describing synchronized mechanical function (i.e. systole and diastole) of the left ventricle. In the current study, we denote $QTTQ(i)$ and $TQRR(i)$, which characterize the beat-to-beat systolic-diastolic interval interaction within each cardiac cycle, as SDI measures.

5.3 Case study details

We validated the performance of the proposed SDI measure, $TQRR$ in diabetic CAN subjects to analyse the changes in the mechanical function of the ventricles in terms of systolic-diastolic interval interactions to assess the severity of CAN progression (no CAN, early or subclinical CAN and definite or clinical CAN). The details of the study groups and the parameters calculated are discussed below:

5.3.1 Study population

All patients in this study were enrolled in the Diabetes Complications Research Initiative (DiScRi) at Charles Sturt University [131] and this population contained the subjects used in the case study in chapter 4. The research protocol was approved by the Charles Sturt University Ethics in Human Research Committee (03/164) and complies with the declaration of Helsinki. The main difference between the two study groups is that the modelling study consists of less number of subjects due to the requirement of age-matched subjects presented in chapter 4 whereas this chapter's study group subjects are not age matched. ECG signals of 142 type 2 diabetes participants were analysed in this study. Exclusion criteria included

the presence of cardiovascular, respiratory, or renal disease or use of antihypertensive or antiarrhythmic medication and any other comorbid conditions that could influence interbeat variability or T-wave characteristics. This ensured that any changes in T-wave morphology (i.e. variability in QT and TQ intervals) and the interbeat or RR interval variability were due to the severity of CAN.

Participants were divided into three groups: i) diabetes without CAN (CAN-), ii) diabetes with early CAN (ECAN), and iii) diabetes with definite CAN (DCAN). Seventy-two participants were CAN-, 55 in the ECAN and 15 in the DCAN group. Presence and the level of CAN were determined using the suggested reference ranges for the outcome of five cardiac autonomic nervous system function tests as described by Ewing *et al.* [130]. The details of the Ewing's autonomic reflex test procedure are discussed in the previous chapter. For ECAN group subjects, one heart rate test had to be abnormal or two borderline. Definite CAN subjects were defined as having two or more heart rate tests being abnormal. The demographic information of the study groups given in Table 5-1.

Table 5-1: Subject demography of the three groups used in this study

Group	Total number	Age (years)	Gender (M, F)
CAN-	72	76 ±16	32 M, 40 F
ECAN	55	74 ±12	19 M, 36 F
DCAN	15	78 ± 15	7 M, 8 F

Values of age are given in (mean ± STD) form. M indicates male and F indicates Female subjects.

5.3.2 Calculated ECG based Measures and statistical analysis

Both the mean (mRR, mQT, mTQ) and standard deviation (SDRR, SDQT, SDTQ) of different ECG wave intervals shown in Figure 5-1 were calculated and compared between the three CAN groups to explore how these parameters change with CAN progression. The variability of the ECG wave intervals was measured as the standard deviation of the corresponding time series. The mean of all SDI measures was also studied and depicted as $mSDI_{QT-TQ}$ and $mSDI_{TQ-RR}$ respectively. Variability of the SDI parameters was determined by calculating the variances of the $QTTQ(i)$ and $TQRR(i)$ parameters, which were denoted as $vSDI_{QT-TQ}$ and $vSDI_{TQ-RR}$ respectively.

All the results were expressed as mean ± STD. Lilliefors test was applied to evaluate the normality of ECG wave intervals and SDI measures before statistical comparison. Non-parametric Kruskal–Wallis test and Dunn-Sidak post hoc analysis (i.e. modified Bonferroni post hoc test) were carried out for comparison among the three groups (CAN−, ECAN, and DCAN) to evaluate statistical significant differences. A value of $p < 0.05$ was considered significant. All the statistical calculations were carried out in MATLAB R2012b.

5.4 Results of different ECG based measures in SDI analysis

In this study, we investigated the systolic-diastolic time interval relations with CAN progression along with other HRV and VRV measures. The beat-to-beat variations of the derived RR, QT, TQ intervals and SDI measures (i.e. *QTTQ* and *TQRR*) derived from the ECG segments of three subjects from the three groups (i.e. CAN-, ECAN and DCAN) are shown in Figure 5-2.
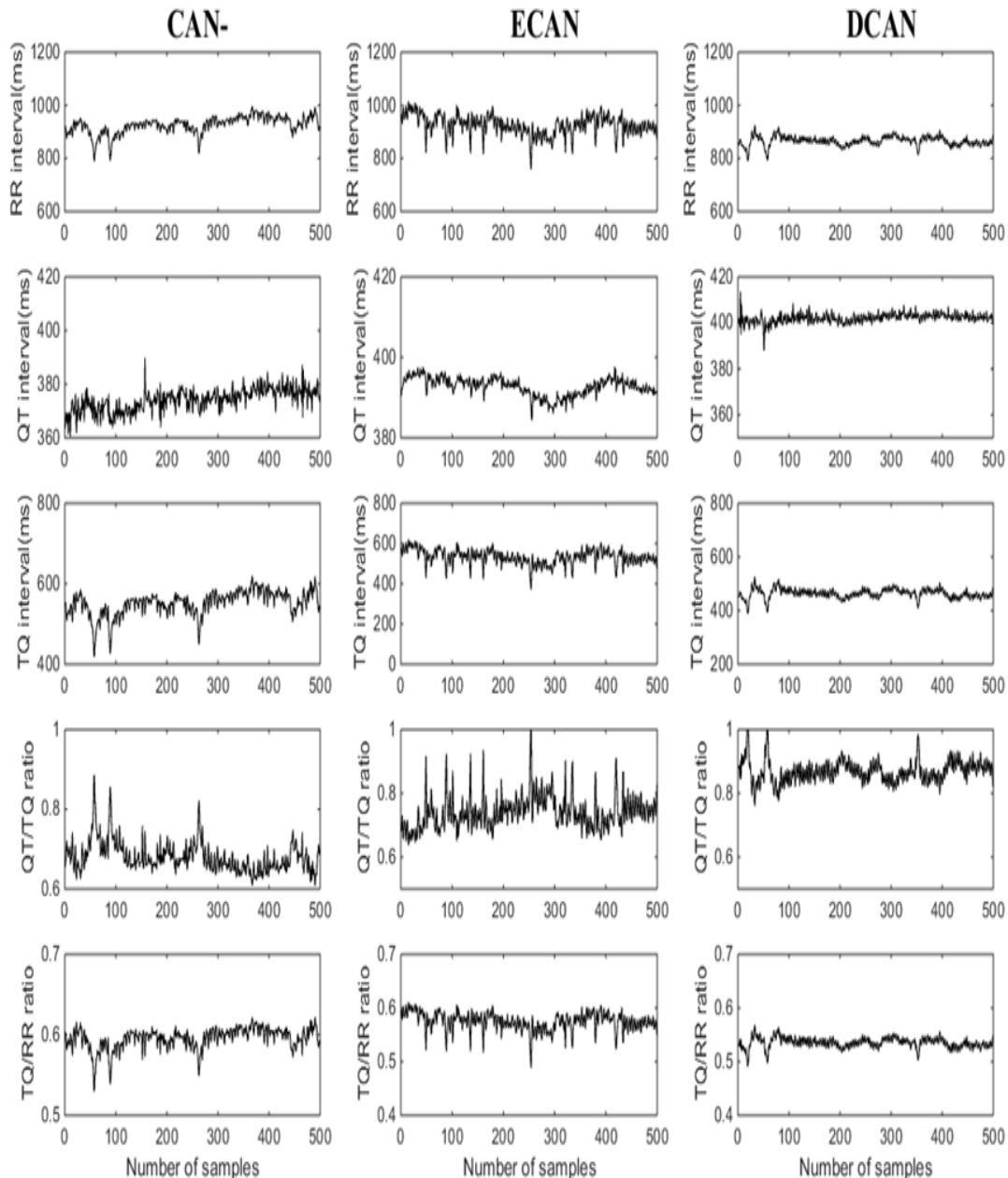
Figure 5-2: Variation of RR interval, QT interval, TQ interval, *QTTQ* and *TQRR* time series of a single subject in three groups.

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Visually, both RR and TQ interval showed a progressive decrease with CAN progression whereas the QT interval increased in the CAN positive groups with respect to the CAN-group. The variability of the RR and TQ is also noticeably decreased with the severity of CAN. The value of *QTTQ* gradually increases with the severity of CAN with a decrease in variability indicating the increase in the probability of arrhythmogenesis, whereas both the magnitude and variability of *TQRR* decreases with CAN progression (Figure 5-2).

Table 5-2 summarizes the values of these wave interval parameters for the three groups. The DCAN group had the lowest mean RR interval, mRR, (903.39 ± 129.98 ms) compared to the ECAN (914.74 ± 124.65 ms) and CAN- (931.16 ± 118.87 ms) groups, which indicates the presence of a higher heart rate in the CAN positive groups during the resting condition. However, values of mRR were not significantly different among the three groups. SDRR, one of the time domain Heart Rate Variability (HRV) measures, decreased gradually with the increase in severity of CAN but was only significantly different between CAN- and ECAN, and CAN- and DCAN groups. Mean raw QT interval (mQT) showed an increase with progression of CAN and differentiated ECAN and DCAN significantly from the CAN-group, whereas mRR and mTQ intervals could not. The gradual decrease in the mean TQ interval or diastolic interval from CAN- to DCAN gave an indication of increased stress on heart function and incomplete relaxation of the ventricles with CAN progression. The variations of RR intervals (SDRR) and TQ interval (SDTQ) time series are significantly different in both ECAN and DCAN groups from CAN-, whilst SDQT did not differentiate between any of the three groups. Moreover, the value of SDQT is quite small in comparison to SDRR and SDTQ. None of the ECG wave interval parameter changes (i.e. Mean and standard deviations of RR, QT, and TQ intervals) was significantly different among the severity of CAN.

Table 5-2: Values of the mean and standard deviation of different ECG wave interval (RR, QT and TQ) parameters in CAN-, ECAN and DCAN groups.

ECG wave interval parameters	CAN-(72)	ECAN (55)	DCAN (15)	p value
mRR (ms)	931.16 ± 118.87	914.74 ± 124.65	903.39 ± 129.98	0.545
SDRR (ms)	44.79 ± 17.01	33.25 ± 12.80#	23.38 ± 8.52*	2.55e-7
mQT (ms)	365.91 ± 25.72	387.39 ± 24.57#	392.35 ± 30.13*	1.34e-5
SDQT ms	4.14 ± 1.84	3.99 ± 2.04	3.28 ± 1.87	0.147
mTQ (ms)	565.71 ± 104.12	527.35 ± 109.44	511.03 ± 109.28	0.063
SDTQ (ms)	43.58 ± 16.64	32.32 ± 12.58#	22.91 ± 8.26*	3.33e-7

All values are shown as mean ± STD
* indicates CAN- group is statistically significantly different from DCAN group
# indicates CAN- is significantly different from ECAN group for the particular wave interval feature.

The variation of the HRV (i.e. mRR and SDRR) and VRV (i.e. mQT and SDQT) measures are shown graphically in Figure 5-3 (A-B). The values of SDI parameters are given in Table 5-3 and their variations in the three groups are displayed in Figure 5-3 (C-D). The mean SDI measure (i.e. $mSDI_{QT-TQ}$) gradually increased with the increase in severity of CAN. On the other hand, $mSDI_{TQ-RR}$ progressively decreased with the CAN progression and is lowest in the DCAN group, which demonstrated the gradual reduction in the mean diastolic interval (i.e. mTQ) in the CAN positive groups (CAN-: 565.71 ± 104.12 ms, ECAN: 527.35 ± 109.44 ms and DCAN: 511.03 ± 109.28 ms).

Table 5-3: Values of mean and variance of beat-to-beat SDI parameters in CAN-, ECAN and DCAN groups

SDI parameters	CAN-(72)	ECAN (55)	DCAN (15)	p value
$mSDI_{QT-TQ}$	0.67 ± 0.11	$0.77 \pm 0.16^{\#}$	0.80 ± 0.17*	1.01e-4
$vSDI_{QT-TQ}$	28.52 ± 20.46	24.99 ± 22.92	15.80 ± 14.72*	0.011
$mSDI_{TQ-RR}$	0.60 ± 0.04	$0.57 \pm 0.04^{\#}$	0.55 ± 0.04*	9.52e-5
$vSDI_{TQ-RR}$	3.30 ± 2.02	$2.28 \pm 1.56^{\#}$	1.32 ± 0.61*^	6.21e-6

All values are shown as mean ± STD
* indicates CAN- and DCAN groups are statistically different
# indicates CAN- and ECAN groups are statistically different
^ indicates the statistically significant difference between ECAN and DCAN group for the particular SDI measure.

Variances of the SDI parameters (vSD_{QT-TQ} and $vSDI_{TQ-RR}$) showed a decreasing pattern with severity of CAN in Figure 5-3. The variance of *QTTQ* ($vSDI_{QT-TQ}$) was found to be higher than the variance of *TQRR* measure in three groups. $vSDI_{TQ-RR}$ could successfully detect the progression of CAN by differentiating the early and definite levels of CAN in addition to identifying the presence of CAN. This is evident from the results, which showed highly statistical significant differences ($p<0.001$) between the three groups and between the ECAN and DCAN groups, whereas $vSDI_{QT-TQ}$ was only found to be different between the CAN- and DCAN group.
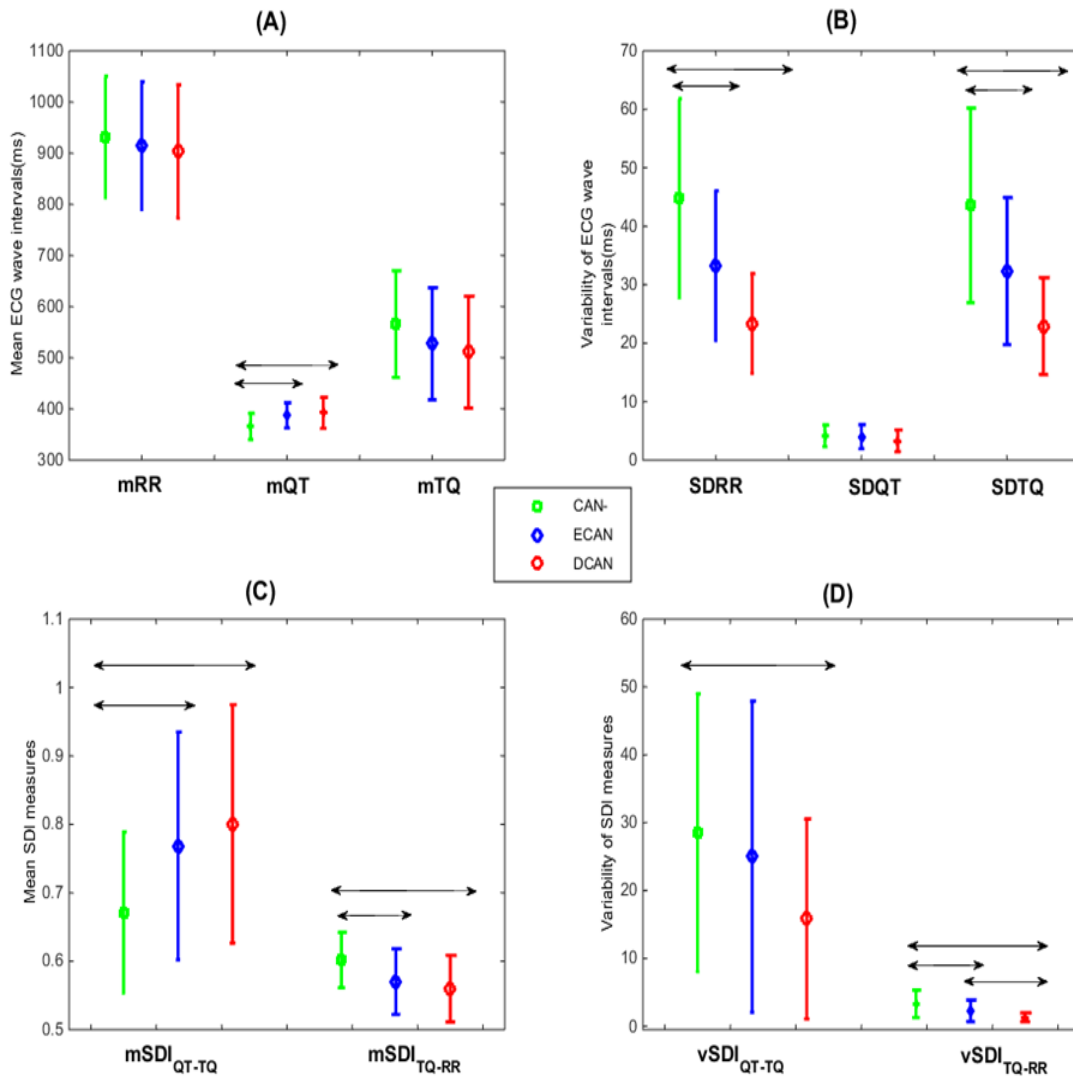
Figure 5-3: Error bar (mean ± STD) plots showing the trends in the variability of different ECG wave intervals (A, B) and SDI parameters (C, D) within the three groups. The arrow between the groups for a particular feature indicates that it can differentiate the groups with statistical significance. From panel (D), it is obvious that only the variability measures of beat–to-beat SDI parameter (vSDI$_{TQ-RR}$) can significantly differentiate all the three groups (CAN-, ECAN and DCAN) thus identifying the presence and progression of CAN.

5.4.1   Reproducibility of the SDI measure with ECG recording length variation

An efficient measure should be reproducible at different data lengths. To evaluate the sensitivity of the SDI measures in CAN analysis with ECG data length, we calculated the values of different SDI measures by varying the length of ECG from 1 min to 5 min in addition to the results reported for a 10 min recording. The variation of the values of the SDI measures is shown in Figure 5-4. The values of mSDI$_{QT-TQ}$ and mSDI$_{TQ-RR}$ showed a consistent pattern in differentiating CAN- group form CAN positive groups (i.e. ECAN and DCAN) with ECG data length from 1 min up to 5 min and also for 10 min segment [Figure

5-4 (A) and (B)]. These two measures can classify the CAN- from ECAN and DCAN groups significantly irrespective of ECG data length, which proves their reproducibility. The variability of the proposed SDI measure (i.e. $vSDI_{TQ-RR}$) showed a consistent classification pattern from 2 to 5 min ECG segment and in 10 min segment [Figure 5-4 (C) and (D)]. For ECG segment of 1 min, $vSDI_{TQ-RR}$ can differentiate DCAN and ECAN group form CAN-group, but cannot distinguish ECAN and DCAN groups (i.e. cannot describe the CAN progression). Therefore, $vSDI_{TQ-RR}$ was found robust in CAN detection and progression analysis of ECG segment length >2 min (Figure 5-4 (D)). $vSDI_{QT-TQ}$ cannot differentiate ECAN group from CAN- group for any length of ECG segment used in this study, but can only classify the DCAN from CAN- group for 2 to 5 min segment and for 10 min ECG [(C)]. Therefore, $vSDI_{TQ-RR}$ was found a reproducible measure for CAN detection and progression analysis in this study with ECG length greater than 1 min.
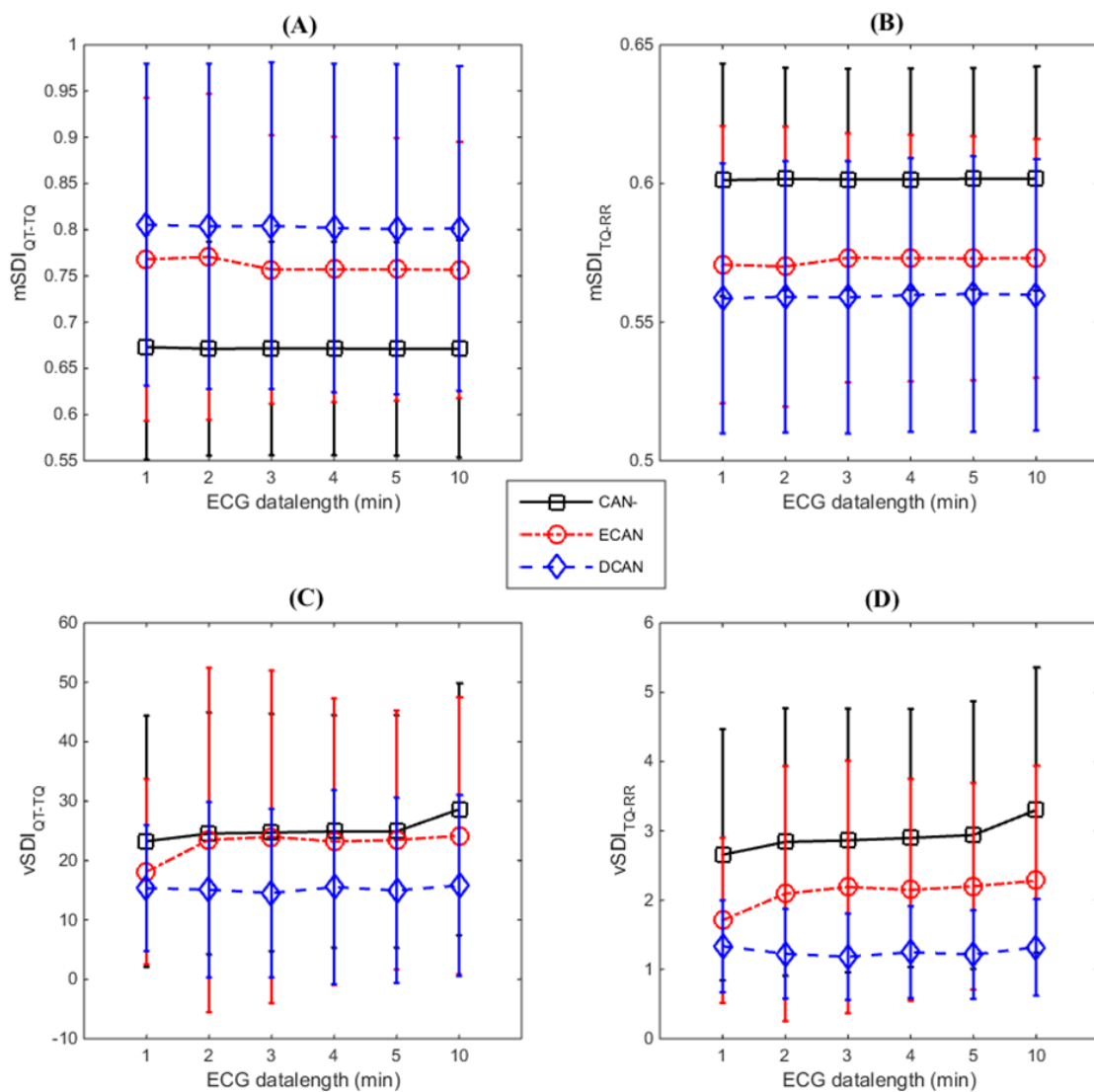
Figure 5-4: Error bar plots showing the variation of the SDI measures with ECG data length variation in CAN analysis.

5.5 Discussion

In this study, we analysed the changes in beat-to-beat variations for different ECG wave intervals (i.e. RR, QT and TQ intervals) and systolic-diastolic interval interaction parameters with the progression of CAN in diabetic subjects. The findings of this study validated our hypothesis that beat-to-beat SDI parameters derived from short term ECG recording can efficiently detect and distinguish the groups with different levels of CAN from the group having no CAN. The results of this study also suggest that the systolic-diastolic interval interaction based features performed better than the time domain HRV based methods in identifying the progression of CAN in diabetes from short-term (i.e. 10 min) ECG recordings. As 5 min long ECG recording is a widely used standard for the clinical setting, we validated shorter ECG data length for analysing reproducibility of the SDI measures and found that the proposed SDI measure (i.e. *TQRR*) can be successfully used for ECG data length > 1 min up to 5 min and for 10 min segment.

In our analysis, we considered TQ interval instead of TR interval as the surrogate diastolic interval by neglecting the QR interval within a cardiac cycle (Figure 5-1) assuming that this interval has negligible effect on QT variability (QTV). However, this modification has been reported in many studies where the RT interval instead of the QT interval was used to represent ventricular repolarization variability in a cardiac cycle [42] and applied successfully in the current study for analysing diastolic interval variability in cardiac autonomic neuropathy classification.

The findings of this study reported the Diabetic CAN related alteration in Systolic and Diastolic intervals and their interaction, which supports few previous findings [155, 158, 166]. QTVI, another widely used measure of VR variability was also found to be a useful measure in CAN progression analysis [138]. This study focuses on the temporal relation between contraction and relaxation function of the left ventricle to analyse CAN progression and found to be more sensitive than the previous results found by our group [138]. Moreover, these results prove the feasibility of using ECG based VR measures for analysing synchronized mechanical function of the left ventricle (i.e. the synchronized temporal relation between Systolic and diastolic function). Significant findings of this study are discussed in the following sub-sections.

5.5.1 Changes in electrical systolic and diastolic interval durations in CAN

The mean systolic interval (mQT) gradually increased with the severity of CAN and significantly differentiated CAN- from ECAN and DCAN groups. Prolongation in systolic interval was reported in several studies as an indicator of the presence of CAN [155, 158, 167], which supports our current study findings. One of the interesting findings of this study

is that the gradual decrease in the amplitude and variability of diastolic interval, (i.e. mTQ and SDTQ), with CAN progression, although the decrease in mTQ is not statistically significant. Decrease in the diastolic interval was reported to be related to the increases instability of ventricular repolarization process, which is a trigger for ventricular arrhythmias [9]. Therefore, the increase in systolic interval and decrease in the diastolic interval with an increase in heart rate found in the CAN positive patients (i.e. ECAN and DCAN group subjects) could indicate that they are more prone to arrhythmogenesis than the CAN- group [84, 156, 161].

In contrast to SDQT (i.e. variability of the systolic interval), SDTQ showed a similar decreasing trend with CAN progression as SDRR (Table 5-2 and Figure 5-3). It also differentiated CAN positive groups from the CAN- group. These results are aligned with some previous findings [82, 164, 168], which indicated that changes in diastolic interval variability is highly correlated with RR interval variability (i.e. SDRR) but not with systolic interval variability, which showed minimal changes with alteration of ANS modulation on heart rate in healthy subjects. Therefore, a significant decrease in SDTQ similar to the SDRR results might be associated with an impaired ANS control in CAN positive subjects. However, these parameters were unable to identify the progressive impairment of ANS control of the heart associated with CAN.

5.5.2 Changes in beat to beat systolic-diastolic interval interaction (SDI) parameter in CAN

Beat-to-beat SDI parameters are simple ECG based measurement of systolic-diastolic interval interactions, which can provide useful information about the left ventricular dysfunction in diabetic CAN patients [60]. $mSDI_{QT-TQ}$ indicates the mean interaction between systolic and diastolic intervals and was found to increase with severity of CAN. The increase in *QTTQ* observed is due to the progressive increase in the QT interval and decrease in TQ interval, which indicates that the heart is taking more time for the systolic phase and limits the proper recovery time of ventricles affecting proper filling of blood for the next ventricular contraction cycle [83, 84, 161]. This leads to increased cardiac stress and further progression of cardiac pathology such as impairment of ventricular repolarization and arrhythmia with CAN progression [61, 165]. Furthermore, a higher systolic to diastolic interval ratio was also reported as an indication of impaired ventricular function in subjects with cardiac disease and a sign of arrhythmogenesis [84, 151]. These findings suggest that DCAN patients may be more susceptible to arrhythmogenesis and heart failure than diabetes subjects without CAN and can be identified efficiently by analysing the ECG based beat-to-beat SDI. The gradual decrease in $mSDI_{TQ-RR}$ with CAN progression also supports our findings of the continuing decrease in both RR and TQ intervals. Although none of these

mean SDI parameters could differentiate between the ECAN and DCAN group, these indices can provide valuable information about changes in ventricular function that may lead to left ventricular diastolic dysfunction (LVDD).

$vSDI_{QT-TQ}$ measures the variation of systolic-diastolic interval interaction in every cardiac cycle and was found to be significantly different only between the CAN- and DCAN group. Whereas, $vSDI_{TQ-RR}$ could detect the presence and the progression of CAN, distinguishing between CAN-, ECAN and DCAN groups with very high statistical significance (Table 5-3: Values of mean and variance of beat-to-beat SDI parameters in CAN-, ECAN and DCAN groupsTable 5-3). This indicates that the changes in the variability of SDI parameters are more pronounced as interaction between TQ and RR intervals rather than QT and TQ intervals with autonomic denervation in CAN. Moreover, the complex interactions between QT and TQ intervals may not change significantly at the earlier stages of CAN but show pronounced modification in advanced stages of CAN. However, the changes in the interactions of TQ with RR intervals were evident in the early stages as well as with the advancement of CAN and also reported to be more sensitive in the detection of early diastolic dysfunction in myocardial ischemia [169]. This may then explain why $vSDI_{QT-TQ}$ could not detect ECAN from the CAN- group, but differentiated CAN- from DCAN whilst the other SDI measure (i.e. $vSDI_{TQ-RR}$) could differentiate between all three groups successfully. Variability of all SDI measures also decreased gradually similar to the decrease in SDRR with the severity of CAN, which might occur due to the gradual ANS denervation in CAN patients [158]. Thus the gradual degradation of ANS control on heart rate and the subtle pathophysiological changes occurring with CAN progression might be reflected more in the beat-to-beat TQ-RR interactions, which enable these indices to classify the progression of CAN. Therefore, $vSDI_{TQ-RR}$ was the only feature found in our study that showed a significant difference between the ECAN and DCAN group in addition to differentiating the ECAN and DCAN groups from the CAN- group, and thus proven as a sensitive marker for detecting the presence and progression of CAN in diabetic subjects. The proposed beat-to-beat SDI parameter also outperformed other HRV parameters and ECG wave interval features in identifying the progression of CAN in diabetes from short-term ECG recordings.

5.5.3 Sensitivity of TQRR in analysing CAN progression

TQRR was found to be a more sensitive parameter than *QTTQ* to track progression of CAN in diabetes, which indicates that changes in diastolic interval is more sensitive with CAN related alteration of the mechanical abnormality of ventricular relaxation. *TQRR* indicates the variation of the diastolic interval within a cardiac cycle, whereas *QTTQ* describes the balance between the systolic and diastolic interval within a cardiac cycle. Previous studies

have shown that left ventricular diastolic dysfunction (LVDD) is related to diabetic CAN and better reflected in altered HRV than in QTV [158, 164]. The change of SDQT is not significant between the CAN groups while both SDRR and SDTQ changes gradually with CAN progression. *TQRR* includes the effect of normalization with respect to heart rate and indicates the rate corrected diastolic interval variation, which has also been reported very sensitive in coronary artery disease analysis [169]. Moreover, due to the nonlinear relationship between the heart rate and diastolic interval, changes in heart rate due to CAN related alteration in ANS are more evidently reflected with the variation in diastolic rather than in the systolic time interval [82, 149]. Therefore, these findings prove the increased sensitivity of *TQRR* in CAN progression detection rather than *QTTQ*.

CAN was found to be associated with left ventricular diastolic dysfunction (LVDD) in both type 1 and type 2 diabetes patients [163, 165]. LVDD is characterized by impaired left ventricular (LV) relaxation due to LV concentric remodelling and increased LV mass even with normal ejection fraction (EF) [158]. LVDD was found to be prevalent in diabetic CAN patients [126, 165] and related to increased resting heart rate and a RR variability decrease, due to the relative predominance of sympathetic nervous system activity at the earlier stages of CAN as a result of parasympathetic denervation [126, 158]. Incomplete relaxation of the ventricles, which could be interpreted from the alteration (i.e. decrease) in diastolic interval duration [60, 84], is found in diabetic CAN subjects and associated with higher heart rate (i.e. decreased RR interval) during supine rest [126] indicating the coupled relation between heart rate and diastolic interval. Left ventricular hypertrophy, which is a result of LVDD has been shown to be a powerful predictor of cardiovascular disease (CVD) mortality similar to CAN related heart rate variability changes in diabetes [126, 129]. Therefore, analysis of the interaction between diastolic interval (i.e. TQ interval) and heart rate (i.e. RR interval) and their variability from surface ECG could provide useful information for CAN diagnosis.

5.5.4   The feasibility of using SDI parameters in clinical healthcare

The current research findings about SDI measures provide several advantages for clinical health care. The first is that the study findings indicate that SDI method can be used to detect CAN instead of Ewing battery, in places where it is not possible to perform the Ewing tests in subjects having lack of mobility due to very old age and the presence of cardiorespiratory disease, which affect the test procedure [131]. Second, the Ewing battery test results are not much sensitive if applied for identification of subclinical CAN without the presence of overt syndromes and in obese or movement-restricted patients as discussed in chapter 4. The SDI method requires the patient to be in a supine resting position only whilst recording the ECG and does not require active cooperation that are needed to perform Ewing test. Third, SDI provides additional information about cardiac systolic and diastolic

functions as well as CAN severity in addition to HRV analysis from the ECG trace. This information complements the echocardiographic techniques for analysing systolic and diastolic heart failure and therefore can be used for determining a patient group who actually should be referred for echocardiography. This ECG based technique will definitely help providing a cost effective health care service whose demand is increasing due to increase in cardiac imaging related Medicare cost and inaccessibility of echocardiographic services in every clinical setting [59].

In clinical settings, the possible sources of error associated with an ECG are the presence of noise due to power line interference, muscle artefact noise due to movement of the patient and baseline wondering noise. These must be filtered out before the analysis can be undertaken. In addition, ECG segments of only normal sinus rhythm (i.e. without any ectopic beats) should be considered for this analysis. The SDI measures are validated on Lead II ECG signal in this study. As the efficiency of the proposed measures depend on the proper detection of RR, QT and TQ intervals we believe that ECG leads having a clearly detectable high amplitude T wave (Lead I, Lead II, Precordial leads V1-V6) in a 12 lead ECG system might show similar performance.

5.6 Conclusion

Identification of cardiac autonomic neuropathy is an important part of the clinical assessment in diabetic patients. Increase in systolic interval and the decrease in the diastolic interval with CAN progression was found in this study, which can be detected in ECG by the alteration in the temporal characteristics of normal mechanical relaxation of the ventricles affecting diastolic function. Systolic and diastolic interval analyses have been shown to be associated with CAN progression, (i.e. transition from CAN- to early CAN to definite stage) whereas HRV and VRV based analysis cannot determine CAN progression. The study presented in this chapter has introduced an improved ECG based SDI feature associated with the beat-to-beat variability of TQ/RR that can successfully detect the presence and identify the progression of CAN.

SDI analysis corroborates the use of ventricular repolarization analysis in investigating the performance of mechanical function of the left ventricle. The temporal characteristics of the synchronized left ventricular function (i.e. systolic and diastolic time interval analysis) are found to be more sensitive in detecting the degradation of Autonomic Nervous System (ANS) control on the heart's function in diabetic CAN. The findings of Chapter 4 and this chapter describe the CAN related changes in VR dynamics and establish the effect of ANS modulation on the ventricles in a widespread cardiac pathology in diabetes (i.e. CAN). Moreover, these chapters describe two methodologies to investigate VR characteristics

determined from the QT interval dynamics on the ECG. The next chapter of the thesis introduces a novel approach to analyse QT-RR interval interaction technique, which can overcome several inherent problems of model-based approach of QTV analysis.

Chapter 6

A novel time domain framework for analysing ventricular repolarization variability using dynamical QT-RR interval interaction

Model based investigation of ventricular repolarization variability (VRV or QTV) was described in two previous chapters (chapters 3 and 4) in healthy and diabetic subjects. Chapter 5 presents a technique for investigating the mechanical function of the ventricles from ECG in healthy and diabetic cardiac autonomic neuropathy subjects. In this chapter, we propose a novel model free time domain framework to analyse the beat-to-beat changes in coupled QT-RR interval interactions from the surface ECG. We present two case studies in this chapter for evaluating different measures derived from the proposed technique. In the first study, the age related alteration in VR, which is affected by the sympathetic activation with ageing, is investigated using this technique. In the second study, the analysis of the pattern of coupled QT-RR interaction changes before the initiation of cardiac arrhythmias is investigated which gave predictive information about the onset of ventricular tachycardia/ventricular fibrillation. This dynamical analysis technique can determine the portion of QTV independent of HRV and successfully describe the age related alteration of the normal VR process. This method can also describe the changes in the distribution of coupled QT-RR interactions through the analysis of the pattern of dynamic or beat-to-beat QT-RR interaction, which might provide useful prognostic information about arrhythmogenesis.

6.1 Introduction

Ventricular repolarization (VR) process indicated by the QT interval on surface ECG represents the total duration of depolarization and repolarization of ventricular myocardium. VR variability measured from the variability of the QT interval (QTV) distribution in surface ECG is a crucial measure of analysing VR stability as unstable VR is the primary reason for the initiation of fatal ventricular arrhythmias [1, 5, 28, 49]. Instability in VR process can be investigated from the QTV changes in the surface ECG [9, 49]. Changes in the QTV in short-term ECG segment (i.e. 5 min or 10 min long ECG) is used in numerous studies to be a marker of the different cardiac abnormalities like in predicting sudden cardiac death(SCD) with patients with dilated cardiomyopathy [26], in subjects with myocardial infarction (MI) [22, 23] and risk stratification in population with structural heart disease [27, 55, 170].

Several QTV markers were also used for the prognosis of ventricular arrhythmias due to different drug induced and congenital Long QT syndrome (LQTS) [20, 66, 67] and with existing cardiac pathologies like chronic Heart failure (CHF) [28, 93]. QTV is also used in healthy subjects for analysing VR stability due to cardiac autonomic modulation changes with different postural manoeuvre [171], with ageing [54, 95] and with psychological changes [85, 95, 120]. Therefore, QTV is a key marker for analysing dispersion of VR in both healthy and pathological subjects.

QTV is directly affected by the variability of previous RR intervals (i.e. Heart rate variability(HRV)) along with various other factors such as autonomic nervous system(ANS) modulation on both sinus node and on the ventricles, different drug effects, respiratory modulation, ageing and different cardiac pathology [1]. The linear parametric modelling technique of QT and RR intervals reveal the presence of two components of QTV: one, which is controlled mainly by the previous RR intervals indicating the QT adaptation capability with heart rate changes (i.e. RR dependent component of QTV) and the other component, which is affected by the other factors (i.e. sympathetic modulation on the ventricles, respiration, age) except the RR interval variability that represents the intrinsic QTV component [41-43]. Therefore, measurement of the total QTV component should include the effect of heart rate correction to indicate actual VRV and the gross variability measures of QT (i.e. SDQT) cannot measure the intrinsic QTV component.

The most widely used parameter for measuring QTV is a QT variability index normalized by heart rate variability (i.e. QTVI) proposed by Berger et al [26] and used in many clinical studies to determine QTV alterations in cardiac pathology. However, the value of QTVI does not clearly indicate whether HRV or intrinsic QTV is mainly responsible for the changes in temporal dispersion of VR in a particular patient population. Increases in QTVI was found to predict Sudden cardiac death (SCD) in heart failure subjects and ventricular arrhythmias (i.e. VT/VF prediction) in several studies with male patients [22, 23, 26, 27] indicating the dominant changes in VRV affecting the value of QTVI. In several other studies the elevation of QTVI results mainly the predominant changes in HRV than QTV like in familial dysautonomia [172], in subjects with spinal cord injury [173], in obstructive sleep apnea subjects [174], patients with panic disorder and depression [175, 176] and in VT/VF prediction in female subjects [29]. Therefore, the use of QTVI actually cannot conclude strongly about the changes in QTV and it cannot provide information about the QTV component independent of HRV. Moreover, the use of QTVI to analyse VR changes with ageing gave inconsistent results in several studies. Some studies reported no significant difference in QTVI between young and old subjects [177, 178] and between children and adults[179] whereas some studies found QTVI as a predictor of age related alteration in VR

process [50, 53, 54]. Ageing is associated with the increases in sympathetic drive in both healthy and pathological conditions [180]. Recent studies reported that the QTV component independent of RR might indicate the modulatory effect of sympathetic nervous system on the ventricles [41] and could be useful for analysing prognostic changes in QTV in both healthy and diseased populations [1, 48, 90]. Therefore, analysing the QTV component independent of RR might be a reliable technique for investigating age related alteration in VR.

The determination of RR independent QT variability component is generally done through linear parametric model based multivariate spectral analysis [41, 43], which is a bit complex procedure as the correct quantification of different QTV components depends on the performance of proper model identification techniques. Moreover, this technique might be difficult to implement properly for noisy ECGs and ECGs with premature ventricular contraction (PVC) beats where better estimation of spectral characteristics of model parameters is difficult. In this chapter, we propose a simple model free approach for analysing QT variability (QTV) components from the distribution of beat-to-beat QT-RR interval interactions. We have developed a framework for analysing coupled dynamical changes in QT and RR intervals within a particular length of ECG recording which can describe how QT and RR interval variability changes in different physiological and pathological conditions. This technique can quantify QTV component independent of RR and can provide information about the intrinsic QTV component, which might indicate the effect of direct sympathetic modulation on VRV. This method also can describe the coupled changes in QT-RR interval interactions before arrhythmogenesis, which might give useful predictive information about VR instability. In this chapter, two case studies are reported in evaluating this methodology in analysing dynamical QTV changes in both healthy and pathological conditions. The first study describes a technique for analysing the intrinsic QTV component that changes with age related alteration in the normal VR process in some healthy and Long QT syndrome (LQTS) subjects. This technique is also validated as a measure describing the coupled dynamical changes in RR and QT intervals before the initiation of ventricular arrhythmias (i.e. VT/VF) in the second case study.

6.2   Development of the proposed technique

The proposed methodology uses normalized beat-to-beat changes in QT and RR interval time series for quantifying the QTV component independent of RR and detects the pattern of beat-to-beat changes in RR and QT intervals within a particular length of ECG segment. The systematic procedure for measuring different parameters from the proposed framework is described in this section.

Step 1: First, beat-to-beat RR and QT interval time series denoted as $RR(n)$ and $QT(n)$ respectively were extracted from a fixed length ECG signal (i.e. 10 min in this study) using appropriate methodology for QRS wave, R wave and T wave detection. Here *n=1,2,3…..N* which indicates the index of extracted RR or QT interval time series and *N* is the total number of extracted RR and QT intervals of the corresponding time series. Any method for QT_{end} detection (i.e. slope intercept method, threshold based method, template matching method etc.) can be used for generating *QT(n)*. We use a template matching method for the detection of RR and QT_{end} intervals as proposed by Berger et al [26]. After QT and RR time series extraction from ECG, the distribution of QT and RR intervals were checked to reduce the effect of nonstationarity. QT intervals outside the range of the 3-SD band were rejected for the formation QT percentage index time series [43]. Ectopic beats are also removed from the RR interval time before further calculation. Ectopics in RR time series is detected when successive differences of beat-to-beat RR interval exceeds 100 ms as proposed in [181]. Figure 6-1 shows an ECG segment having three ECG beasts with 2 RR intervals and 3 QT intervals (i.e. 1 ECG beat consists of P wave, Q wave, QRS complex or R wave and T wave). Beat-to-Beat changes indicates how *RR(n+1)* and *QT(n+1)* intervals change from the previous beat (i.e. *RR(n)* and *QT(n)*), which quantify the temporal dispersion of RR and QT interval within the ECG segment completely. From the RR and QT time series, percentage index (PI) time series was calculated to quantify the temporal variability of both the time series.
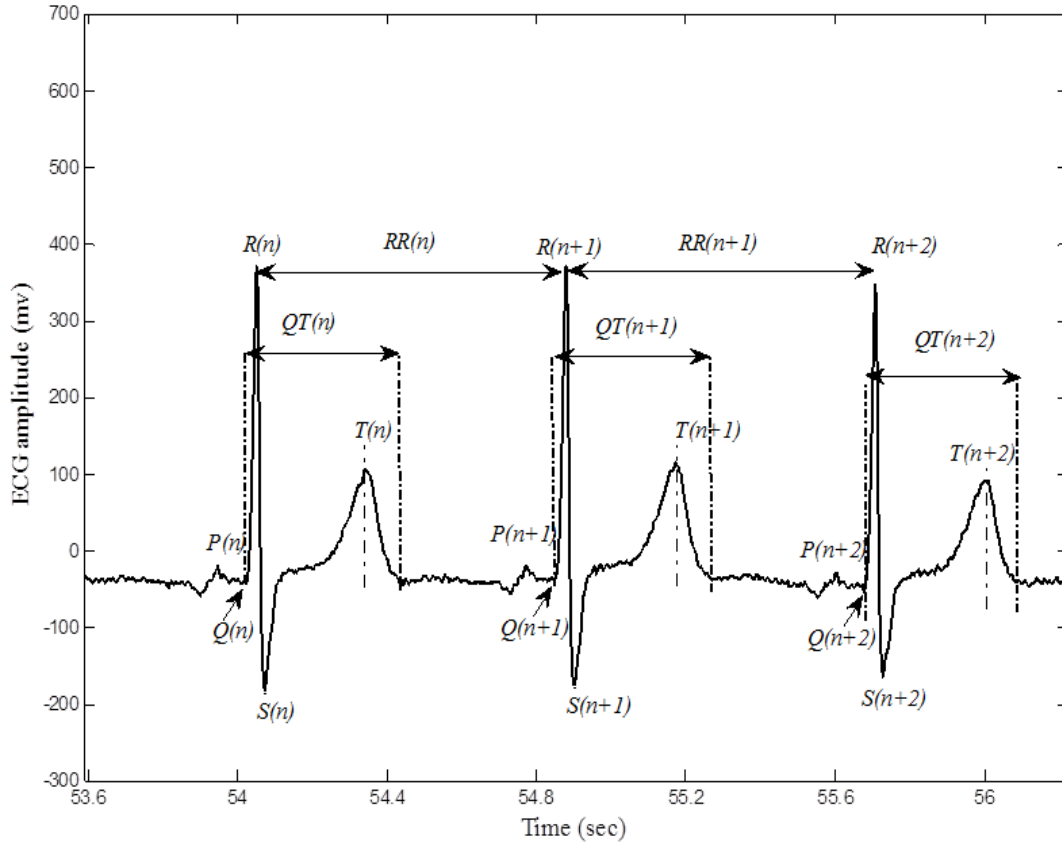
Figure 6-1 : Different ECG wave components in a short ECG segment showing 3 ECG beats and the corresponding wave intervals (i.e. RR and QT intervals). The beat-to-beat differences measure successive changes in both RR and QT intervals of each ECG beat, which describes the temporal variation of repolarization characteristics better than gross variability measures.

Step 2: The Percentage Index (*PI*) time series for both RR and QT interval time series are determined by calculating the normalized successive beat-to-beat changes using the following equations:

$$RR_{PI}(n) = \frac{RR(n+1) - RR(n)}{RR(n)} \qquad (6.1)$$

$$QT_{PI}(n) = \frac{QT(n+1) - QT(n)}{QT(n)} \qquad (6.2)$$

Here *n = 1,2,3*…to *N-1* and *N* is the total number of samples of RR and QT time series as derived in step 1. RR_{PI} and QT_{PI} series contain the magnitude of positive and negative changes of consecutive RR and QT intervals and thus calculate the total temporal variability of RR and QT interval time series derived from a particular length of ECG recording. It is reported in previous studies that when heart rate (i.e. inverse of RR interval) increases due to sympathetic nervous system activation, the RR interval is becoming shorter than the previous interval in the following beats [182]. Therefore, acceleration of heart rate is expressed as a negative difference, whereas deceleration as a positive one in RR_{PI} time series [182]. On the other hand, the increase in normal ventricular repolarization duration due to ion channel dysfunction or any abnormality in ANS control on sinoatrial node and ventricular

myocardium indicates the increase in QT interval in a beat compared to the previous one [1, 183]. Consequently, shortening of VR process is expressed as a minus difference, whereas prolongation as a plus one in QT_{PI} time series. In previous studies, the use of normalized successive RR interval differences instead of absolute difference of RR time series has been suggested in analysing Heart rate variability(HRV) changes with the change in sympathovagal balance [182]. In animal experiments, it was also verified that electrical stimuli of cardiac autonomic nerves induced the same percent changes in heart rates irrespective of absolute value of heart rate, which signifies the importance of analysing beat-to-beat successive changes in HRV and QTV due to autonomic modulation [184]. As QTV and QT-RR interaction is directly affected by HRV and by sympathetic nervous system control [1, 121, 185], normalized beat-to-beat analysis of temporal changes in QT interval could provide useful information about the variability of VR due to ANS modulation on ventricular myocardium. Therefore, we propose in this study a normalized beat-to-beat analysis method for measuring the QTV component independent of RR that comes other than HRV like from factors affecting sympathetic control on VR (e.g. ageing, respiration). To the best of our knowledge, no study has reported the normalized successive difference based method to analyse VR variability from QT-RR distribution. Moreover, the normalization of successive difference by the previous beat makes this measure population independent by reducing the high intersubject variability of QT-RR interaction [15, 134].

Step 3: RR_{PI} and QT_{PI} series derived in the previous step are used to generate a 2D (two-dimensional) scatter plot where, RR_{PI} is plotted along the horizontal axis (i.e. *x*-axis) and QT_{PI} is along the vertical axis (i.e. *y*-axis). Figure 6-2 shows the conceptual illustration of the proposed methodology. The left panel shows the RR, QT, RR_{PI} and QT_{PI} series of an example subject and the right panel shows the 2D scatter diagram. Every point in the RR_{PI}-QT_{PI} plane, which indicates the amplitude and polarity of changes in both RR and QT intervals from the previous beat is denoted as $P(x_i, y_i)$ where $x_i = i^{th}$ value of RR_{PI} time series, $y_i = i^{th}$ value of QT_{PI} time series and i=1, 2,……N-1 , where N indicates the total number of cardiac beats. The two dimensional space can be divided into four quadrants, each containing a certain number of points which measures the amount of positive or negative variation of both RR and QT intervals. The four quadrants are named as Q1 to Q4 and each quadrant contains a certain number of points of the $RR_{PI}(n)$ and $QT_{PI}(n)$ time series (Figure 6-2). For example, a point in quadrant Q1 indicates a beat where both QT and RR interval increases from the previous beat which is explained by the condition of positive change (RR_{PI}>0 and QT_{PI}>0) in the Figure 6-2. Similarly, the points in the other three quadrants (Q2, Q3, and Q4) indicate the number of beats showing the combination of both positive and negative changes in QT and RR intervals. Therefore, the density of points in

each quadrant actually quantifies the amount of normalized increment or decrement of QT and RR intervals from the previous beat of the analysed segment, which quantifies the temporal variability of the corresponding time series. There are some points located on the RR_{PI} and QT_{PI} axis as indicated by the black stars in Figure 6-2 indicating the number of beats, where either RR or QT interval changes from the previous beat with no change in QT or RR intervals. These beats indicate the presence of QT or RR interval changes without associated RR and QT interval changes respectively. As every single point in this plot indicates the pattern of changes in both QT and RR intervals in a single beat, the number of points on QT_{PI} line actually gives the number of beats with only changes in QT where RR is unchanged. Consequently, the amount of points along QT_{PI} plane actually quantifies the QTV component independent of RR interval changes (i.e. the higher the number the points on QT_{PI} axis indicate the higher the contribution of QTV component independent of RR to total QTV).
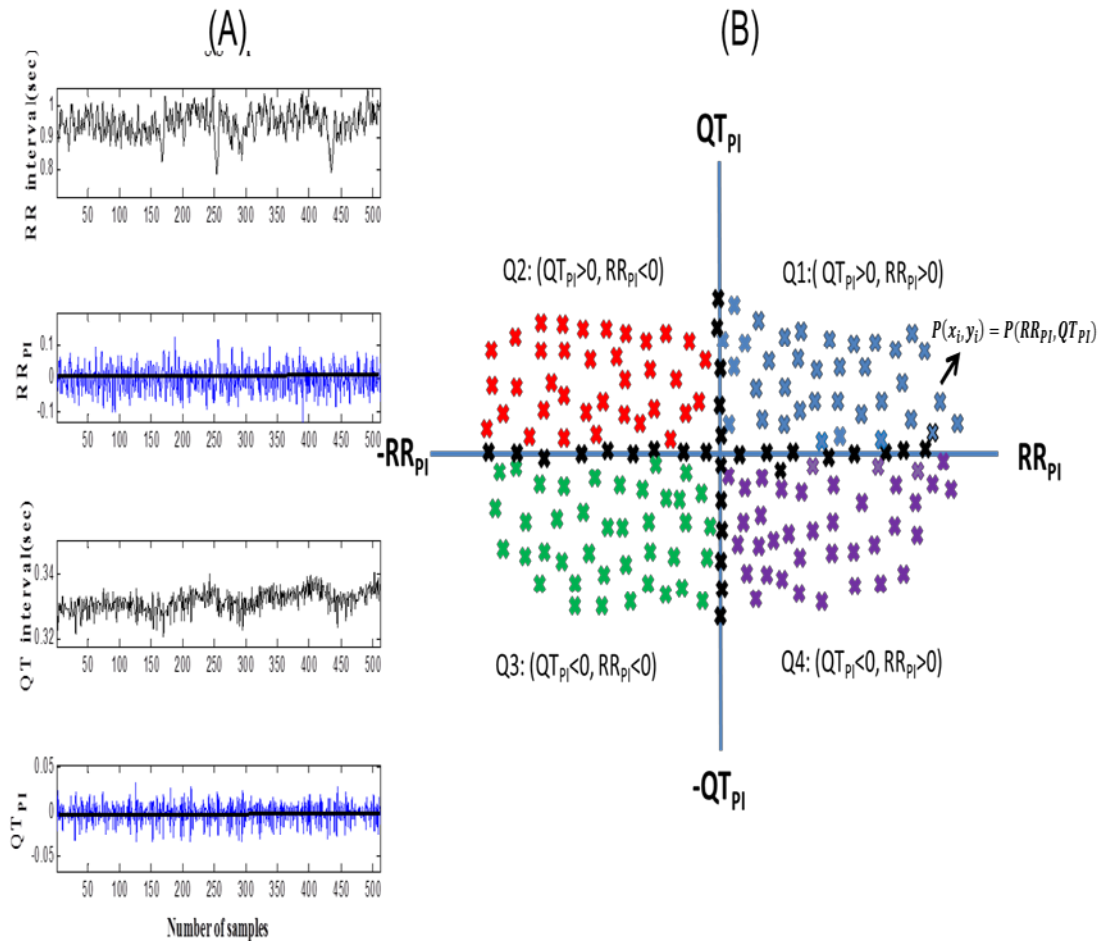
Figure 6-2: Generation of 2D scatter plot of RR_{PI} and QT_{PI} series. Left panel (A) shows the time series of RR, QT and percent index time series of RR and QT time series of an example subject. Right panel shows the RR_{PI}-QT_{PI} plane. Black coloured points on the RR_{PI} and QT_{PI} axis indicate the beats containing changes only either in QT or RR intervals from the previous cardiac beat.

Step 4: A threshold level is then defined to quantify the beats having the positive and negative changes of RR and QT without associated changes in QT and RR intervals respectively, which is used to determine the QTV component independent of RR. The threshold levels are pictorially described in Figure 6-3. Theoretically the amount of QTV independent of RR variation can be quantified using points that lie on $RR_{PI} = 0$ line of RR_{PI}-QT_{PI} plane (i.e. i.e. the red coloured circles along the *y*-axis in Figure 6-3). However, we think $RR_{PI} = 0$ is a very strict criteria to select a significant number of QT beats to define QTV components not affected by RR changes in the general population, since the widely used resolution for RR interval analysis is 1ms in almost every ECG analysis system and very small variation due to sampling or measurement noise can affect heavily. Moreover, such pattern of RR variation is rare in healthy populations as HRV defined by RR variability is normally very high and does not become zero except subjects with artificial pacing arrangements (i.e. cardiac pacemaker) and with severe pathological conditions where HRV is diminished heavily. Therefore, we defined a threshold from RR_{PI} time series to quantify QTV component, which is not directly affected by RR variability. We define a threshold level denoted as $Th_{RR_{PI}}$ for RR_{PI} time series such that for any sample of RR_{PI} series that falls within a defined limit (i.e. if $-Th_{RR_{PI}} \leq RR_{PI} \leq Th_{RR_{PI}}$) then the corresponding QT_{PI} sample is considered having $RR_{PI} = 0$. In our study, we measured the 75th percentile of RR_{PI} time series and take 1 percent of that value (i.e. 1% of 75th percentile) as the threshold using the following equation:

$$Th_{RR_{PI}} = 0.01 * (75th\ percentile(abs(RR_{PI})) \qquad (6.3)$$

The 75th percentile or the third quartile of RR_{PI} time series indicates the dominant pattern of RR_{PI} time series variation in every subject and 1% of that change is a reasonable criterion to determine the portion of cardiac beats where RR variation is quite small. The threshold region is defined from negative $Th_{RR_{PI}}$ to positive $Th_{RR_{PI}}$ value along the RR_{PI} axis (Figure 6-3). Similarly, a threshold was also defined for QT_{PI} series, which is used to discard the number of these beats in calculating the amount of beats having coupled changes in QT-RR intervals in the four quadrants. The threshold is defined as:

$$Th_{QT_{PI}} = 0.01 * (75th\ percentile(abs(QT_{PI})) \qquad (6.4)$$
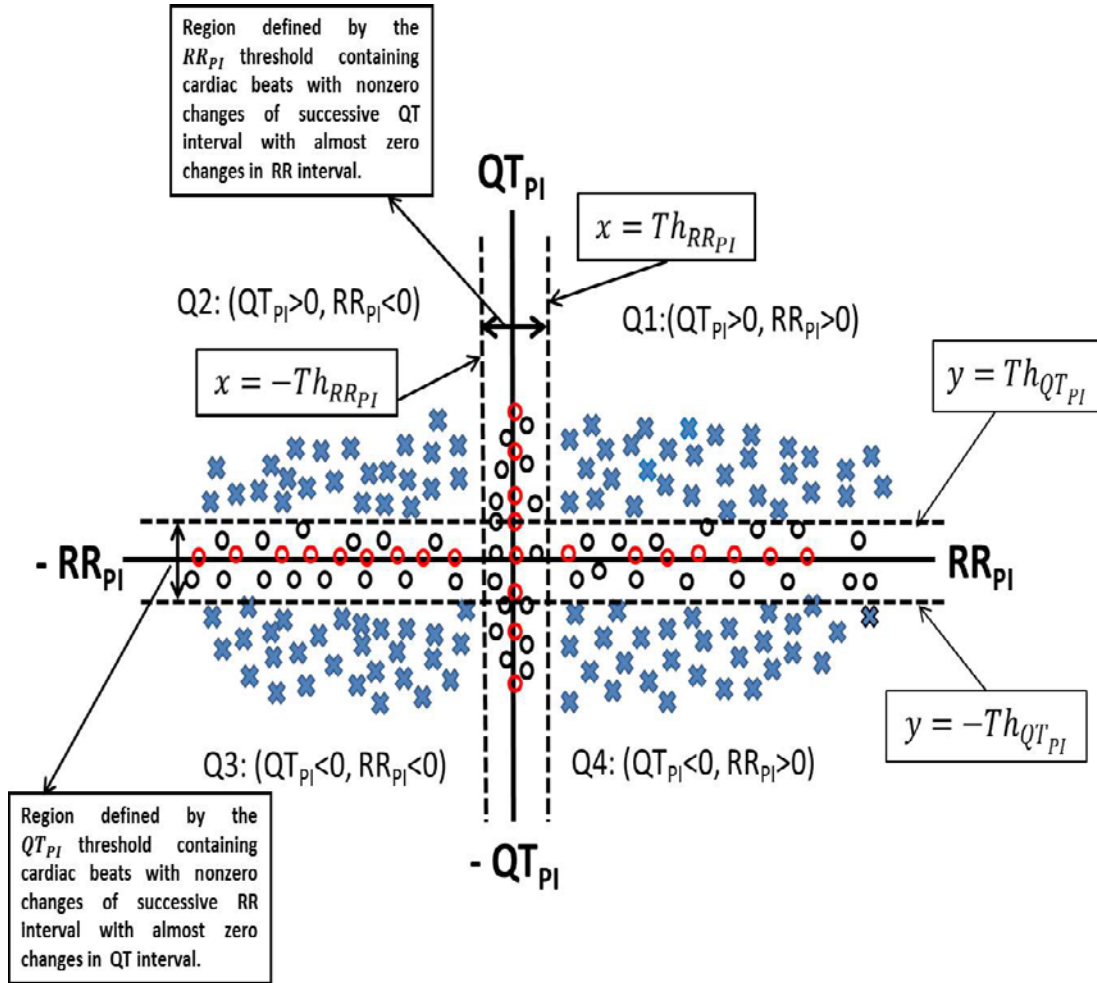
Figure 6-3: A graphical description of the two dimensional (2D) scatter plot of RR$_{PI}$ and QT$_{PI}$ series to measure cardiac beats showing the different patterns of beat-to-beat QT and RR changes. It shows the 2D x-y plane (i.e. RR$_{PI}$-QT$_{PI}$ plane) with the distribution of points plotted as stars and circles. The point density within the threshold limits (i.e. points plotted as red circles) indicates the amount of cardiac beats having either QT or RR changes with RR or QT unchanged or with a very small change from the previous beat within the threshold. The four quadrants (i.e. Q1-Q4) indicate the pattern of coupled beat-to-beat changes of QT and RR intervals. The points within the defined thresholds were discarded for analysing the coupled changes in QT-RR intervals, since they do not represent simultaneous beat-to-beat changes in both QT and RR intervals.

Step 5: In the final step, we calculated several measures quantifying the number of points in the four quadrants to determine the pattern of changes in the coupled QT-RR intervals. Four measures are calculated to count the number of cardiac beats that are outside the threshold regions in the RR$_{PI}$-QT$_{PI}$ plane as shown in Figure 6-3.

If P_{total} indicates the total number of points in the RR$_{PI}$-QT$_{PI}$ plane, it can be measured as:

$$P_{total} = |\{P(x_i, y_i)\}: (-\mathbf{RR_{PI}} \leq x_i \leq \mathbf{RR_{PI}}), (-\mathbf{QT_{PI}} \leq y_i \leq \mathbf{QT_{PI}})| \qquad (6.5)$$

where $|.|$ indicates the cardinality of the set which contains the total number of points in RR$_{PI}$-QT$_{PI}$ plane.

The number of cardiac beats having the increase in both QT and RR interval from the previous beat (i.e. positive change in QT and RR) is calculated as:

$$P_{pp} = \left|\{P(x_i, y_i)\}: (x_i > Th_{RR_{PI}} \text{ and } y_i > Th_{QT_{PI}})\right| \tag{6.6}$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q1 quadrant (Figure 6-3). Similarly, the other measures are defined as:

$$P_{pn=} \left|\{P(x_i, y_i)\}: (x_i < -Th_{RR_{PI}} \text{ and } y_i > Th_{QT_{PI}})\right| \tag{6.7}$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q2 quadrant (Figure 6-3)

$$P_{nn} = \left|\{P(x_i, y_i)\}: (x_i < -Th_{RR_{PI}} \text{ and } y_i < -Th_{QT_{PI}})\right| \tag{6.8}$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q3 quadrant (Figure 6-3) and

$$P_{np} = \left|\{P(x_i, y_i)\}: (x_i > Th_{RR_{PI}} \text{ and } y_i < -Th_{QT_{PI}})\right| \tag{6.9}$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q4 quadrant (Figure 6-3).

Finally the percentage of cardiac beats having the above mentioned patterns of coupled changes in QT-RR interval defined before (i.e. equations 6.6 to 6.9) were calculated using the following ratios:

$$QTRR_{PP}(\%) = \frac{P_{pp}}{P_{total}} \times 100$$

$$QTRR_{PN}(\%) = \frac{P_{pn}}{P_{total}} \times 100$$

$$QTRR_{NN}(\%) = \frac{P_{nn}}{P_{total}} \times 100$$

$$QTRR_{NP}(\%) = \frac{P_{np}}{P_{total}} \times 100$$

$QTRR_{PP}$, $QTRR_{PN}$, $QTRR_{NN}$, and $QTRR_{NP}$ all calculates the point density in the four quadrants showing how both QT and RR intervals (i.e. pattern of coupled QT-RR changes) are changing within a particular length of ECG recording.

6.2.1 Analysis of QTV component independent of RR variability

To analyse the QTV component independent of RR variations another three more measures are calculated to count the number of cardiac beats within the threshold in the RR_{PI}-QT_{PI} plane. For this analysis, we need to consider the number of beats within the threshold defined for RR_{PI} time series as shown in Figure 6-4.

The number of cardiac beats having the increase of QT interval from the previous QT beat (i.e. positive change in QT) within the RR_{PI} threshold is calculated as:

$$P_{pe} = \left|\{P(x_i, y_i)\}: -Th_{RR_{PI}} \leq x_i \leq Th_{RR_{PI}} \text{ and } y_i > 0\right| \tag{6.10}$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane above the x-axis within the threshold. And the number of cardiac beats having

90

the decrease of QT interval from the previous QT beat (i.e. negative change in QT) within the RR_{PI} threshold is calculated as:

$$P_{ne} = \left|\{P(x_i, y_i)\}: -Th_{RR_{PI}} \leq x_i \leq Th_{RR_{PI}} \text{ and } y_i < 0\right| \tag{6.11}$$

where $|.|$ indicates the cardinality of the set which contains the total number of points in RR_{PI}-QT_{PI} plane within the threshold below the *x*-axis.
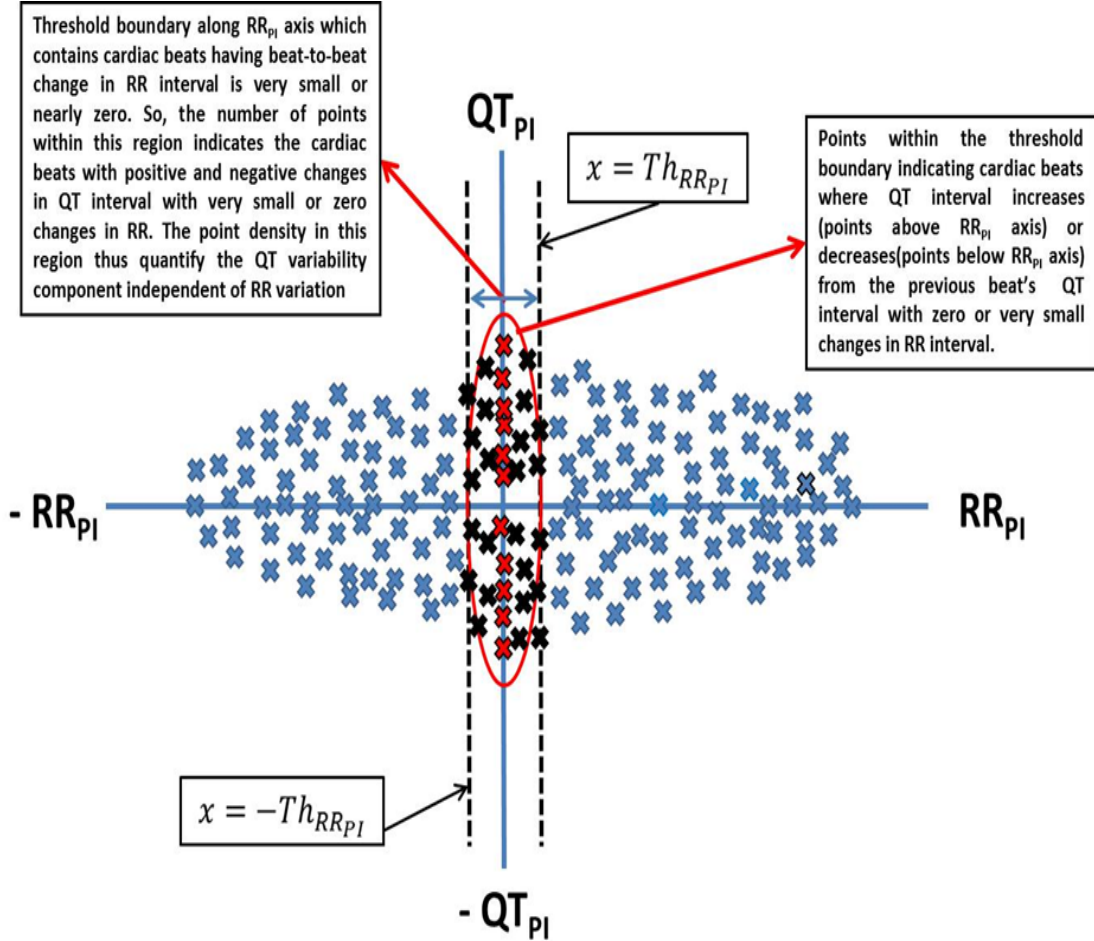
Figure 6-4: Measurement of the QTV component independent of RR using the proposed technique. The point density within the threshold limit indicates the number of cardiac beats contributing to QT variability component independent of RR. The threshold value is defined from the RR_{PI} time series termed asTh_{RRPI}

Then the percentage of cardiac beats having increment and decrement of beat-to-beat QT interval changes are calculated using the following equations:

$$QTRR_{PE}(\%) = \frac{P_{pe}}{P_{total}} \times 100$$

$$QTRR_{NE}(\%) = \frac{P_{ne}}{P_{total}} \times 100$$

Finally, the total density of beats with the combination of both positive and negative changes of consecutive QT beats within the RR threshold in the ECG segment is calculated as:

$$QTRR_{PNE} = QTRR_{PE} + QTRR_{NE} \tag{6.12}$$

Therefore, $QTRR_{PNE}$ indicates the density of beats within a particular length of ECG segment with beat-to-beat changes in QT without or very small changes in RR intervals defined by the threshold limit from the previous beat and quantify the amount of QTV component independent of RR variability. The higher the magnitude of this point density, the higher the number of ECG beats with the pattern of QT changes with almost unchanged RR within a particular length of ECG recording. Therefore, the higher value $QTRR_{PNE}$ indicates that total QT variability contains greater part of QTV affected by factors other than RR like age, respiration, and ANS modulation. The following sections of this chapter present two case studies validating the derived methodology in analysing VRV.

6.3   Case study 1: Analysing the effect of ageing on QTV using the proposed methodology

As discussed in the introduction of this chapter, contradicting results about the effect of ageing were reported in several studies using the widely used measure of QTV , QT variability index (QTVI) proposed by Berger et al [26]. Therefore, reliable measurement technique is needed for analysing ageing effect on ventricular repolarization. As QTV component independent of HRV is reported to be affected by the sympathetic nervous system modulation [92, 186, 187] and ageing increases sympathetic drive in both healthy and pathologies [180, 188], analysing this component of QTV might provide reliable results. In this study, we validated the proposed technique for determining the QTv component independent of RR in age related changes in a healthy and a group of Long QT syndrome type 1 (LQT-1) subjects. Ageing effects of VR in healthy subject population is reported in several studies, but the effect of ageing on VR in LQTS subject group is not widely explored. Young individuals with congenital LQTS-1 are reported to be prone to sudden cardiac death due to torsades de ponites(TdP) [17]. Therefore, in this study we investigate whether the young group in LQT-1 population showed any recognisable changes in QTV in comparison to the elderly group subjects. We hypothesize that the component of QTV independent of RR changes with ageing in different aged group subjects and the normal increase in sympathetic modulation with ageing might be the reason for the increases in this variability component.

6.3.1   Subjects and ECG analysis

ECG signals from a set of Healthy and LQTS type 1 subjects were collected from the Telemetric and Holter ECG warehouse (THEW, www.thew-project.org) [73]. A total of 139 Healthy subject's ECGs were used for this study form the Database named E-HOL-03-203-003. 134 subjects out of 171 patients detected with genotyped LQTS 1 were used from the

database named E-HOL-03-0480-013. The selection criteria of the ECG segment were clearly detectable high amplitude T waves and the absence of abnormal T wave morphology. In both groups, the subjects were divided into three age groups as follows: Young (20-35 years), Middle-aged (40-55 years) and Elderly (>60 years). A five-year gap is maintained within the age groups for clear discrimination of VR characteristics due to ageing. A 10 min long ECG segment form the diurnal part of the ECG recording for every subject was used for our analysis. RR intervals, QT intervals and QT variability index (i.e. QTVI) were determined from the baseline filtered 10 min ECG segment using Berger's Template matching algorithm [26]. We collected the 10 min ECG segment from the same portion of the diurnal part of each subject's Holter ECG recording and Lead Y was used for QT interval detection due to the presence of high amplitude clearly detectable T waves on this lead. Heart rate corrected QT interval (i.e. QTc) was calculated using Fridericia's equation [11]. Gross Heart rate variability (HRV) and ventricular repolarization variability (VRV) were determined from the Standard deviation of the determined RR and QT time series (i.e. SDRR and SDQT respectively). $QTRR_{PE}$, $QTRR_{NE}$ and $QTRR_{PNE}$ were measured for investigating the RR independent QTV components and their performance were compared with the other two total QTV measures, SDQT and QTVI. Figure 6-5 shows the RR, QT, RR_{PI}, QT_{PI} and the QT-RR distribution within the threshold region for an exemplary healthy subject in 3 age groups. Statistical differences in the different HRV and QTV parameters between the age groups were measured using Krukalwallis test (Non-parametric version of ANOVA test) after checking the normality of every feature distribution by Lilliefors test in MATLAB R2012b. The Bonferroni post hoc test was performed to measure multiple group comparison, which contains an adjustment for the multiple comparisons proposed by Bonferroni to handle familywise error rate.
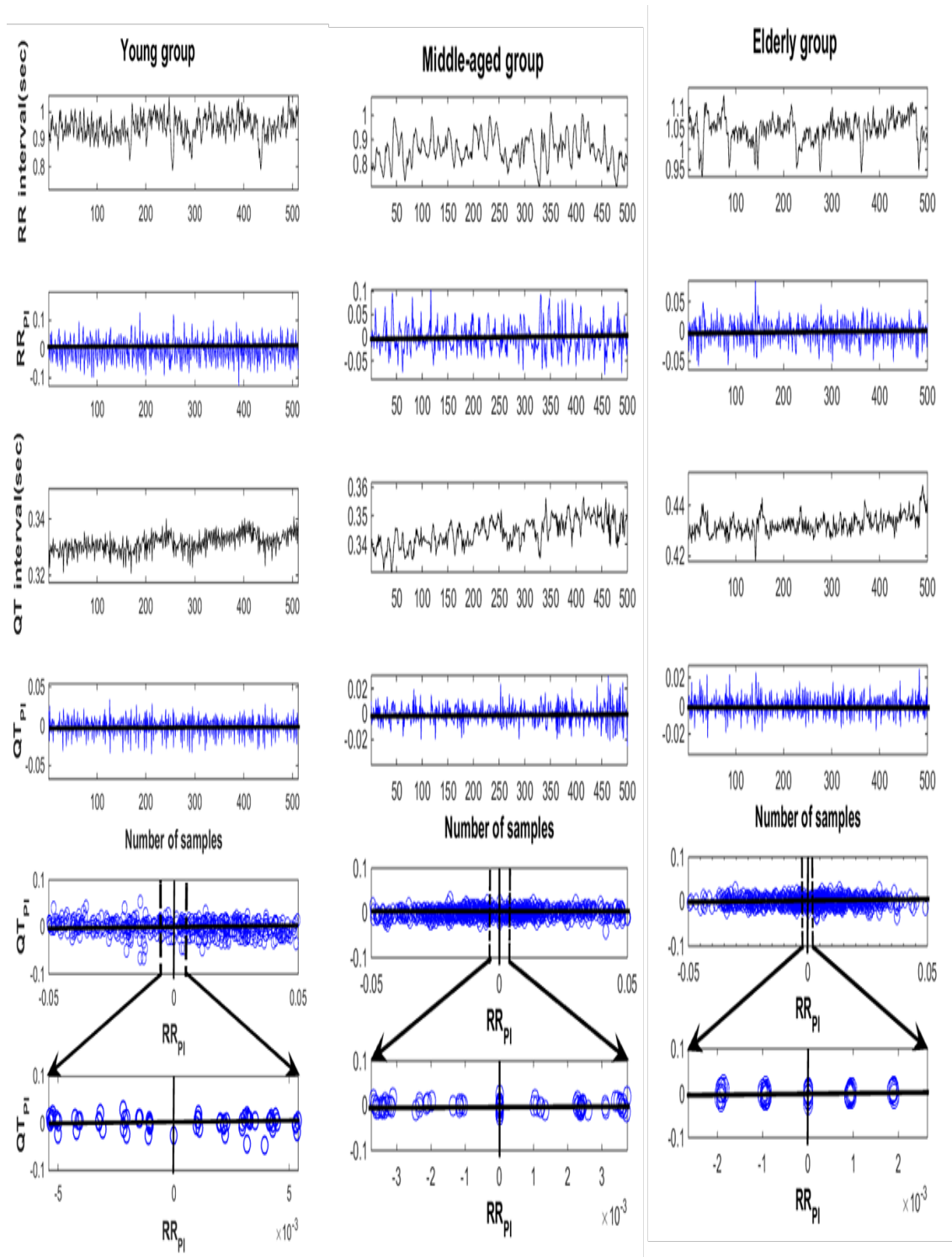
Figure 6-5: RR, QT, RR$_{PI}$, QT$_{PI}$ variations, and RR$_{PI}$-QT$_{PI}$ plots of a particular Healthy subject from the three age groups (i.e. Young, Middle-aged, and Elderly). In the Young subject group, RR$_{PI}$ vs. QT$_{PI}$ plot is more dispersed along the horizontal line (i.e. RR$_{PI}$ plane) and this dispersion decreases in the elderly group as evident in the fifth row of the figure. The threshold region is enlarged in the fifth row to examine the distribution of points. The sixth row shows that (i) point density increases significantly within the threshold area with ageing (i.e. from Young to Elderly group) and (ii) the number of points increases along the vertical line where RR$_{PI}$ =0 and within the threshold of RR$_{PI}$ where magnitude of RR$_{PI}$ is very small. The increase in the point density within this plane in the elderly groups in comparison to younger groups indicates that portion of QTV independent of RR increases with ageing.

6.3.2 Results and discussions

Results obtained using the proposed parameters including standard QT and RR variability measures are shown in Table 6-1. Mean HR (i.e. inverse of RR interval) was lower in LQT-1 group than the Healthy group as reported in previous studies [47]. The HRV measure, SDRR (i.e. standard deviation of RR intervals) decreases both in Healthy and LQT-1 subject groups, but the decrease is only significant in Healthy subjects. SDRR can significantly differentiate the old from the young group and the middle-aged subjects from the old group in Healthy group. The significant decrease in SDRR with ageing in Healthy subjects supports other previous findings [189]. The gross VRV measure, SDQT decreased with ageing in both Healthy and LQT-1 groups, but cannot differentiate any age group significantly. The magnitude of SDQT is much smaller than SDRR, which indicate that the decrease in HRV is more dominant than the decreases in VRV with ageing. The traditional QTV index (i.e. QTVI) increases with ageing in both subject groups as reported in several research studies [51, 54], but cannot classify any age group significantly in this study. The rate corrected QT interval (i.e. QTc using Fridericia's formula) increased significantly only in healthy subject group and can classify between old and young group and between middle-aged and old group. QTc was found to decrease with ageing in LQTS group, although the values remained above 450 ms in all three age groups (Table 6-1). The young LQT-1 group showed higher value of SDRR and SDQT than the other two groups. However, these gross measures cannot differentiate the young group form the elderly groups.

In contrast to standard QT and RR variability parameters, the proposed parameters ($QTRR_{PE}$, $QTRR_{NE}$ and $QTRR_{PNE}$) were found significantly different among three age groups in both Healthy and LQT-1 subjects. $QTRR_{PNE}$ increased gradually with ageing in Healthy group and can differentiate the Young and Middle-aged group and Young and Elderly group significantly. However, this index cannot differentiate significantly Middle-aged from Elderly group, though the gradual increase is found between the groups (Table 6-1). On the other hand, for LQTS group $QTRR_{PNE}$ decreased slightly from Young to Middle-aged group, but increased again from Middle-aged to Old group. Values of $QTRR_{PNE}$ were significantly ($p<0.01$) different between Middle-aged and Old group as well as Young and Old group (Table 6-1). The age related alteration of the QTV component independent of the RR is detected in the Middle-aged group in LQTS subjects, whereas this difference can be detected at the young age in the healthy subject group indicating that this QTV component changes more in healthy individuals with ageing. $QTRR_{PE}$ showed the same pattern in classification as $QTRR_{PNE}$ in both the groups, whereas the other measure $QTRR_{NE}$, can only differentiate the young and old subjects in both Healthy and LQTS subject groups.

Analysis of beat-to-beat ventricular repolarization duration variability from Electrocardiogram signal

Table 6-1: Comparison of different QT and RR variability measures in healthy and type 1 LQTS subjects

| | Healthy subject group (E-HOL-03-203-003) | | | | LQTS type 1 subject group (E-HOL-03-0480-013) | | | |
	Young (20-35 year)	Middle-aged (40-55 year)	Elderly (above 60 year)	*P* value	Young (20-35 year)	Middle-aged (40-55 year)	Elderly (above 60 year)	*P* value
Number	64	57	18		79	38	17	
Age	27.13 ± 4.37	46.67 ± 4.58	67.89 ± 6.23	<0.05	28.25 ± 4.69	47.48 ± 3.75	67.21 ± 4.23	<0.05
RR (ms)	765 ± 116	778 ± 128	807 ± 140	0.574	906 ± 195	904 ± 184	911 ± 153	0.245
SDRR(ms)	95.10± 38.30	86.95± 34.50^	60.70±30.9*	0.0039	73.71± 40.30	63.82± 31.12	49.45 ± 18.20	0.052
QTc(ms)	375 ± 22	380 ± 23^	404 ± 19*	0.0004	484 ± 78	477 ± 70	452 ± 34	0.42
SDQT(ms)	14.30± 6.69	13.40 ± 6.58	11.80 ± 5.46	0.3683	15.30± 10.01	14.45 ±9.69	12.73 ± 7.01	0.505
QTVI	-0.98 ± 0.26	-0.96 ± 0.31	-0.74 ± 0.41	0.074	-0.79 ± 0.45	-0.72 ± 0.46	-0.59 ± 0.47	0.196
$QTRR_{PE}$(%)	0.90 ± 0.62	1.28 ± 0.92#	1.77± 1.28*	0.0008	0.89 ± 0.80	0.67 ± 0.50^	1.12 ± 0.54*	0.0037
$QTRR_{NE}$(%)	0.92 ± 0.66	1.112 ± 0.79	1.17± 1.13*	0.0064	0.95 ±0.90	1.06 ± 0.57	1.15 ± 0.54*	0.022
$QTRR_{PNE}$(%)	1.82 ± 1.19	2.47 ± 1.159#	3.46 ± 2.56*	0.0014	1.84 ± 1.07	1.75 ± 0.92^	2.231 ± 0.93*	0.0084

All values are shown as Mean ± Std. # indicates the Middle-aged group is significantly different from Young, * indicates the Old group is significantly different from Young and ^ indicates the Middle-aged group is significantly different from Old group. A value of *p* <0.05 was considered significant.

The results found in this case study clearly indicate that measures of QTV component independent of RR can differentiate the Young group form the elderly groups in both healthy and LQTS subjects consistently, whereas the gross measure of QTV, SDQT and QTVI failed to describe the age related changes in QTV in the different age groups. This finding also removes the inconsistency in model abased QTV study where it was found that QT_{peak} dynamics models could describe ageing whereas QT_{end} dynamics models cannot as presented in chapter 3. Our study findings indicate that in both healthy and LQTS subject groups, ageing actually increases the density of cardiac beats having beat-to-beat QT changes with unchanged RR, which contribute to the increase in HRV independent component of QTV and might reflect the age related increase in sympathetic activation [51, 53] affecting the normal ventricular repolarization.

6.3.3 Sensitivity analysis of *QTRR_PNE* with ECG data length variation

To examine the effectiveness of the proposed measure for quantifying the QTV component independent of RR within the total QTV, we validate the performance of the measure with SDQT and QTVI by varying the ECG data length from 1 min to 10 min in Healthy subject group. Figure 6-6 shows the variation of the three measures with ECG length from 1 min to 10 min. SDQT and QTVI increases with the ECG recording length, whereas *QTRR_PNE* values stays more stable with data length variation proving reproducibility of this measure with different data length.
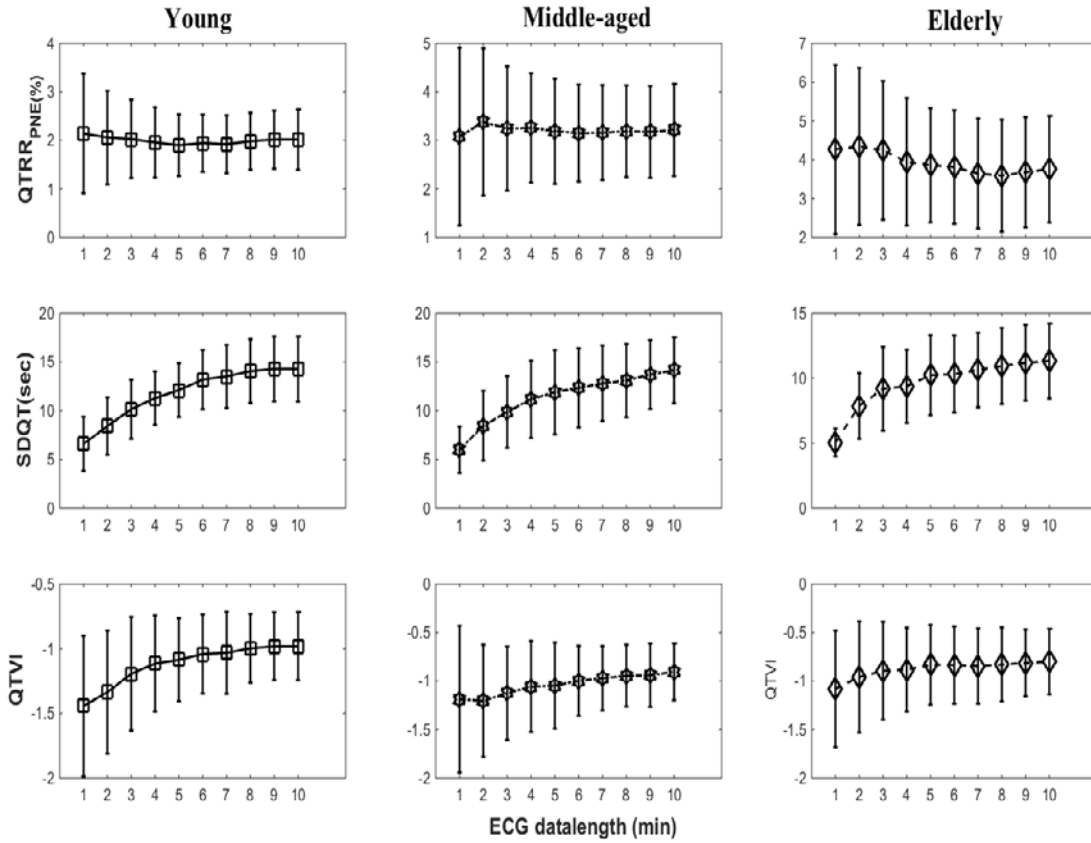
Figure 6-6: Error bar plots showing the range of variation of *QTRR*_{PNE}, SDQT, and QTVI with ECG length variation from 1 to 10 min in Healthy subject group.

Moreover, $QTRR_{PNE}$ was found to differentiate the Young group from Middle-aged and the Elderly group consistently from a shorter length (1 min) to longer length (10 min) of ECG data as shown in (First panel, Figure 6-7) except for 1 min long ECG where this parameter can only differentiate the Young group from the elderly group only. The values of SDQT and QTVI in the elderly group become more separated from that of Young and Middle-aged group in ECG recording length greater than 3 min, but these measures cannot differentiate the elderly group from the Middle aged and young group for any data length (Second and third panel, Figure 6-7). This finding indicates the robustness of our proposed measure. The next section validates the other measures in describing the dynamical changes in coupled QT-RR interaction before arrhythmogenesis.
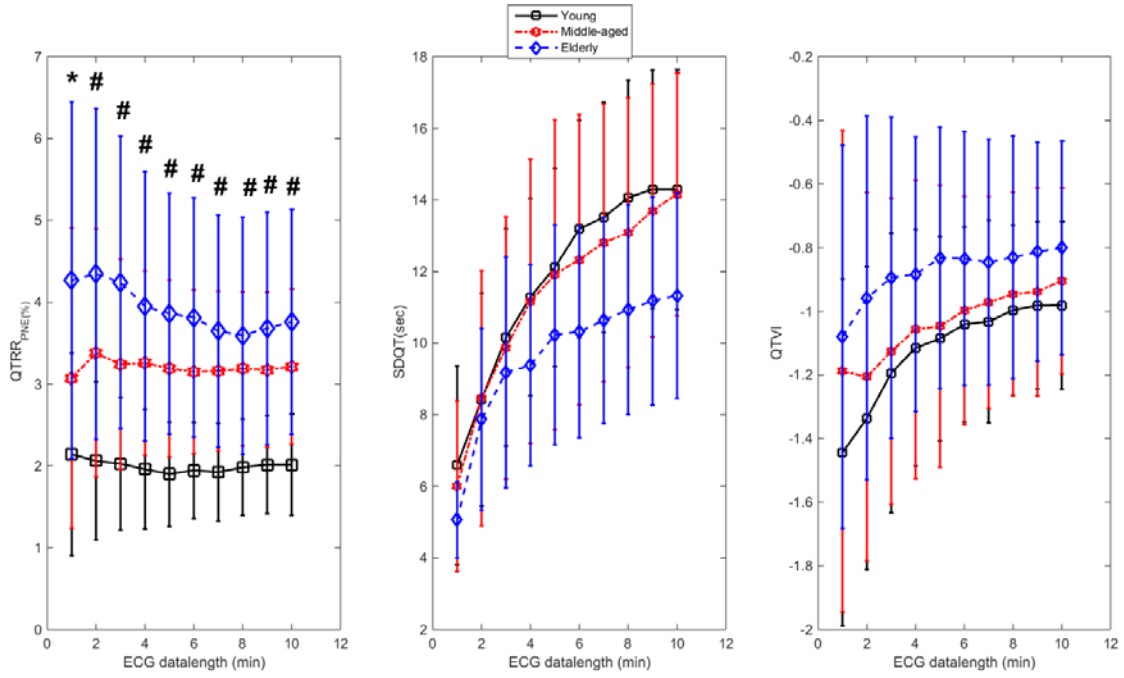
Figure 6-7: Variation of the three measures in classifying the three age groups in Healthy subjects with ECG data length variation. * indicates Young group is significantly different from the elderly group only, # indicates Young group is significantly different from Elderly and middle-aged groups with p<0.01.

6.3.4   Limitations of the study

In this study, the 10 min long ECG segments were collected from the diurnal part of the Holter recordings. QT-RR dynamic interaction is more evident in the daytime than at nighttime and the probability of arrhythmogenesis due to sympathetic activation was found greater during the day than at night [190, 191]. Therefore, diurnal recordings are preferable for the proposed technique to investigate the dynamical changes in QT-RR interaction patterns. Future investigation should be done on the nocturnal recordings to investigate the changes of the derived parameters.

We compare the performance of the derived measures by varying the length of the ECG from 1 to 10 min segments where the numbers of cardiac beats are different for every subject. The ECG duration in minutes not in terms of the number of cardiac beats is the common standard in clinical procedure to compare the performance of the different ECG based measures [26, 75] (i.e., QTVI is normally reported for 3 to10 min long recording). Therefore, the performance of the proposed measure (i.e. $QTRR_{PNE}$) for calculating the RR independent QTV component of this study was compared with SDQT and QTVI using ECG lengths in minutes. The effect of the number of beats instead of a fixed recording length of time should be investigated in future studies.

The threshold level was verified for up to 3% of the 75th percentile of RR_{PI} and QT_{PI} time series in this study, but the result was found similar for the $QTRR_{PNE}$ in differentiating the

young group from the middle aged and elderly groups. As the objective of the methodology is to detect the portion of the beats that contribute to the QTV component independent of RR, the higher threshold value might include points in RR_{PI}-QT_{PI} plane that actually does not indicate constant RR or very small changes in RR intervals and make the measure erroneous. Therefore, 1% was considered as a logical threshold for the described measure. A prospective future study will be to investigate the effect of ECG sampling frequency changes on threshold level determination.

6.4 Case Study 2: Beat-to-beat changes in dynamical QT-RR distribution as a predictive measures for arrhythmogenesis

Sudden cardiac death (SCD) is a major fatal manifestation of cardiac diseases, which is mainly caused by ventricular arrhythmias (i.e. Ventricular tachycardia (VT) and Ventricular fibrillation (VF)). The transition of sustained VT (i.e. VT existing more than 30 sec) to VF can only be fixed with electrical shock by automated external defibrillators (AED) or implantable cardioverter defibrillators (ICD). Recent clinical and healthcare studies focus on analysing non-invasive ECG based markers for risk stratification and early prediction of VT events and also for determining subject group who are at high risk of having VF and need more advanced care like ICD implantation [6, 8]. As SCD is mainly caused by ventricular dysfunction, ECG based short term VRV markers (i.e. QTV markers) are analysed in several studies for risk stratification of SCD [5, 192].

Both HRV and QTV measures were analysed for predicting arrhythmogenesis is several studies with some level of inconsistency in the findings. Heart Rate (HR) increases (i.e. RR interval decreases) before the onset of ventricular arrhythmia in most of the studies [106, 193, 194], whereas some studies report the decreases of HR or very small changes in HR before the onset of VT (i.e. RR interval increase or very small changes in RR) [195]. HRV indices also did not show consistent changes before the onset of VT [193, 196]. Prolongation of the VR duration measured by QT interval and corrected by heart rate (QTc) was reported in many studies, although it is a very disputed measure due to the challenges in the selection of a proper heart rate correction formula [197]. Moreover, the changes in QT duration in not also consistent before VT onset as QT is reported to found to increase [198] and decreases before arrhythmogenesis [199]. QTV measures showed more reliable results than QT prolongation in studies with patients with heart failure, with congenital long QT syndrome and chronic cardiovascular diseases [5]. Increase in QTVI proposed by Berger et al [26] is reported in several clinical studies as a predictor of ventricular arrhythmias and SCD [22, 27]. But a recent study reported non-significant changes in QTVI with no changes in HRV and QTV in patients of intensive care unit with VT and VF events compared to

baseline values [57] though the increase in HR and premature ventricular activation beats (PVC) was reported in that study. Another study showed the ineffectiveness of QTVI as a predictor of the onset of VT in the presence of PVC beats which is found consistently in every studies before VT onset [58]. Therefore, the reliability of QTVI is investigated in several recent studies as a predictor of VT onset [24, 55].
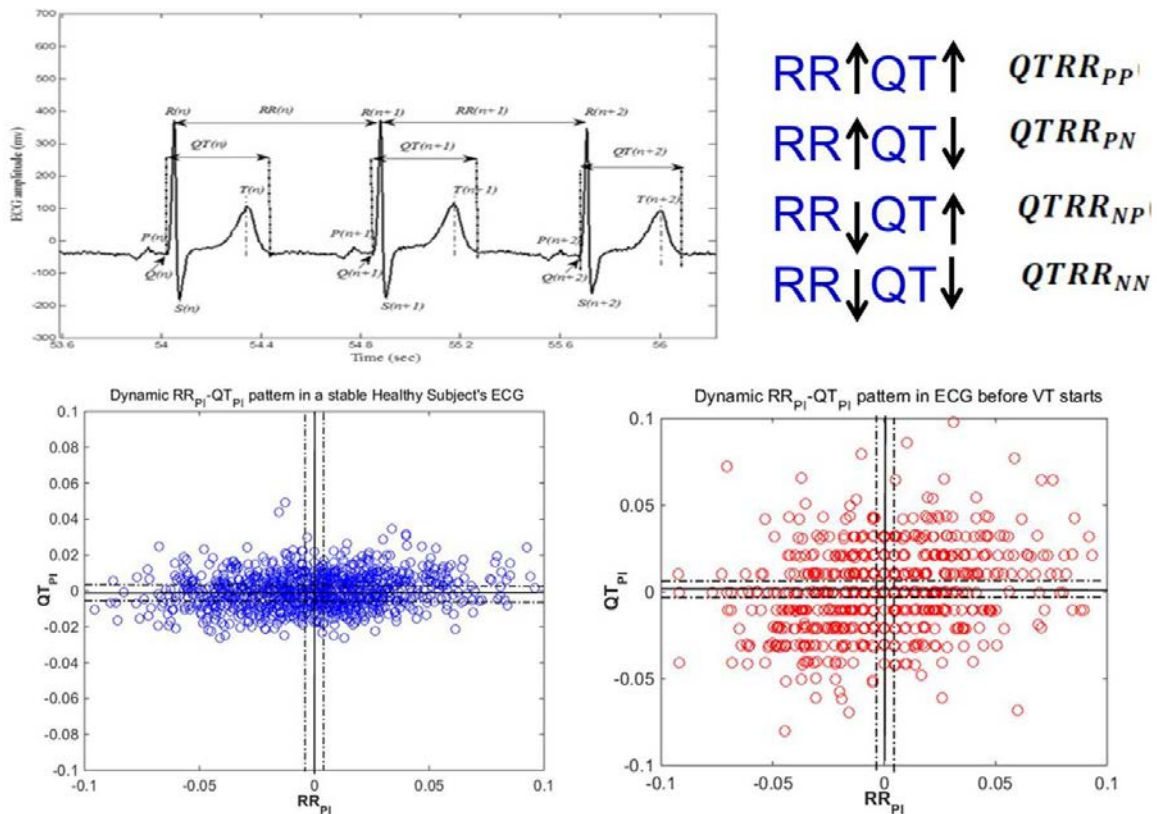
Figure 6-8: Pattern of coupled changes in dynamic QT-RR interaction in ECG. The upper panel shows an ECG segment indicating the normal beat-to-beat RR and QT interval changes, which generates the HRV and QTV. The different possible coupled pattern of changes in QT-RR interaction is shown beside the ECG. The proposed measures can quantify these patterns of changes from QT and RR interval time series. The lower panel shows the $RR_{PI}QT_{PI}$ plot for 10 min ECG of a healthy young subject (Left figure, Blue coloured) and a subject with a history of VF in a 10 min ECG segment just before the onset of VT (Right figure, Red coloured). The $RR_{PI}QT_{PI}$ plot graphically indicates the dynamic QT-RR interaction changes before VT starts in a subject with history of VT in comparison to a healthy subject.

The increase in PVC beats in ECG increase the instability in VR, which initiates VT and if not suppressed by defibrillators, it may convert to fatal VF leading to SCD where the heart completely loses its blood circulation function [9]. Therefore, detection of the instability in the VR process using QT-RR interaction modelling based stability analysis is reported to be a predictor for the onset of VT [9, 49]. The findings of the model based approach in detecting the increase in instability before VT onset showed promising results in the presence of PVC beats. The presence of PVC beats is also found in healthy subjects without any history of cardiac disease [200], which might affect the methodology proposed in the previous studies of detecting instability based on the presence of the PVC beats. Our

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previous study reported this phenomena, which showed healthy individuals' QT-RR interactions also indicate some unstable characteristics of VR in the presence of PVC like that of the subjects with a history of VT or VF through QT-RR modelling analysis [201].

As the changes in QT and RR intervals before VT onset showed inconsistent results [193, 197], we hypothesize that the analysis of both QT and RR interval changes simultaneously (i.e. coupled QT-RR interaction based analysis) for predicting the onset of VT could provide more consistent results about arrhythmogenesis. Figure 6-8 shows graphically the motivation of deriving the hypothesis, which shows analysis of dynamic QT-RR pattern changes can provide useful predictive information about arrhythmogenesis. Therefore, in this study the proposed measures of coupled QT-RR changes were used for analysing the dynamic QT-RR interactions before the VT onset to detect the pattern of changes in coupled QT-RR intervals. We analyse the proposed measures $QTRR_{PP}$, $QTRR_{PN}$, $QTRR_{NN}$, $QTRR_{NP}$ (Eqns 6.6-6.9) in the ECG segments before VT onset in a healthy group and a group of subjects with a history of VT/VF. $QTRR_{PP}$ and $QTRR_{NN}$ indicate the number of points with the pattern of normalized increase and decrease of QT and RR intervals from the previous beat (Upper panel, Figure 6-8). $QTRR_{PN}$ and $QTRR_{NP}$ indicates the number of cardiac beats having the different pattern of changes in QT-RR intervals showing the increases and decrease in QT and RR intervals from the previous beat and vice versa respectively (Figure 6-8). The normal heart rate (i.e. represented by the inverse of RR intervals) and ventricular repolarization duration (i.e. QT intervals) show an inverse relation indicating that the increase in RR interval is associated with QT interval increase and the decrease in RR intervals are followed by QT interval decrease [11, 12, 160, 161, 202]. These parameters should increase before arrhythmogenesis showing the changes in the normal QT-RR dynamic characteristics. The other two parameters $QTRR_{PN}$ and $QTRR_{NP}$ show the pattern of uncoupled changes in QT-RR distribution, which might specify important information about the unstable VR characteristics before VT onset. To the best of our knowledge, this combined approach of determining normalized beat-to-beat changes in QT-RR interaction pattern has not been used before to investigate VR characteristics before VT onset. The main objective of this case study is to investigate how these novel parameters changes before VT starts in healthy subjects and in subjects with a history VT/VF that could detect predictive changes before arrhythmogenesis.

6.4.1 Subjects and ECG processing

Two annotated public domain ECG databases were used for ECGs with sustained VT and VF episodes. 10 min long ECG segments just before the start of VT/VF of nine subjects from the MIT-BIH Malignant Ventricular Arrhythmia Database (VFDB) [72], and 10 records (8001-8010) with a history of VF from the American Heart Association Database

(AHA) were analysed [203] for this study. 20 young Healthy subject's ECG with no history of cardiovascular diseases from Fantasia database were used as controls for comparing with ECGs with VT/VF episodes [72]. Baseline filtered ECG signal segments were used to determine RR intervals using the algorithm of Pan et al [104] and QT intervals were detected as Q wave to T wave end interval using slope intercept method [79] after the use of baseline filtering as described in chapter 3 and 4. The slope intercept method was used in this study for QT interval detection in these pathological conditions, as abnormal QT intervals might contain crucial prognostic information which is lost in template based method for QT detection [78]. We collected 10 min ECG segments just before the instant when VT starts from VFDB and AHA databases and 10 min Healthy ECG segments from both Young group subjects. The timing of the onset of VT records from the annotation file available with VFDB and AHA databases. Figure 6-9 shows an example of collecting the 10 min long ECG segments for analysing the proposed measures.
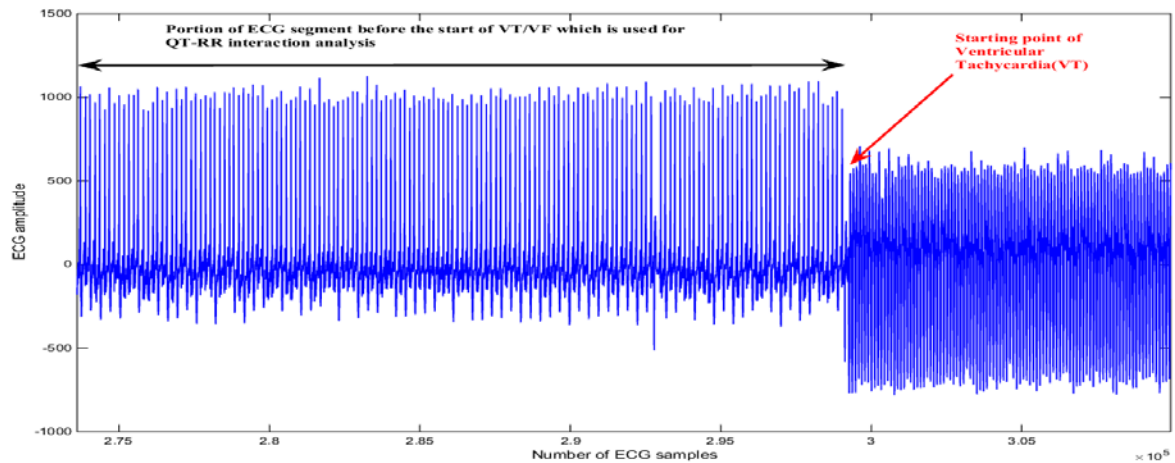
Figure 6-9: Derivation of 10 min long ECG segments from the full length of ECG recordings for the analysis of this study in subjects having VT/VF.

6.4.2   Results and Discussions

We investigated the four proposed measures, $QTRR_{PP}$, $QTRR_{PN}$, $QTRR_{NN}$, and $QTRR_{NP}$ in the 10 min long ECG segments before the onset of VT in two databases to validate the robustness of the measures in different populations. Error! Reference source not found. shows the changes of the measures in young subjects with both VFDB and AHA database subjects. $QTRR_{NN}$ increases significantly in the VF groups from the Healthy group, indicating that the amount of cardiac beats having both negative changes of QT and RR intervals increases in ECG segments of subjects having VT/VF in comparison to both young and old healthy group subjects. This finding supports the hypothesis that coupled changes in QT and RR intervals increase before VT/VF starts which is aligned with previous studies [57, 204]. $QTRR_{PN}$ was also found to significantly increase significantly in both VF group

subjects than the healthy young group, indicating that the number of beats with the coupled pattern of QT increase and RR decrease from the previous beat increases. This measure indicates the amount of beats, having different patterns of beat-to-beat QT and RR interval changes that might contribute to unstable VR.

Table 6-2: Comparison of the proposed measures for analysing arrhythmogenesis in a healthy Young subject group from Fantasia database with VFDB database and AHA database subjects having history of VT/VF.

Features	Fantasia Young (20)	VFDB(9)	p value	Fantasia Young (20)	AHA Database(12)	p value
$QTRR_{PP}$ (%)	17.42 ± 3.05	24.84 ± 3.78	<0.001	17.42 ± 3.05	18.70 ± 6.08	0.471
$QTRR_{NN}$ (%)	16.96 ± 3.58	24.70 ± 5.08	**<0.001**	16.96 ± 3.58	20.64 ± 5.98	**0.025**
$QTRR_{PN}$ (%)	15.28 ± 2.99	18.64 ± 5.51	**0.040**	15.28 ± 2.99	22.35 ± 4.80	**<0.001**
$QTRR_{NP}$ (%)	16.23 ± 3.60	18.29 ± 4.06	0.181	16.23 ± 3.60	21.30 ± 4.29	0.004

The different findings of the pattern of changes in both QT and RR changes before VT/VF starts in two databases (i.e. VFDB and AHA) indicates the subjective variation of the initiation pattern of VT which is normal due to intersubject variability of QT-RR interactions [15, 205]. The common pattern found in two groups was the change in $QTRR_{NN}$ and $QTRR_{PN}$ in both subject groups, which might indicate that electrical instability that initiates VT/VF can be determined from the change of these two patterns of dynamic changes in QT and RR intervals. Both $QTRR_{PN}$ and $QTRR_{NP}$ shows a pattern of QT and RR changes which does not follow the normal pattern of changes in these two intervals as discussed before (i.e. increase in RR is normally associated with QT and vice versa). These uncoupled changes in RR and QT intervals might be responsible for increasing the instability in VR, which can initiate VT [9]. In conclusion, the increases in $QTRR_{NN}$ and $QTRR_{PN}$ in both databases before VT onset provide important information, which can be used to describe the dynamical changes that occur before arrhythmogenesis. Rapid changes in these two measures (i.e. $QTRR_{NN}$ and $QTRR_{PN}$) in the subjects with history of VT in comparison to Healthy subject group might indicate the increases in instability in the normal VR process.

6.4.3 Limitations

The main limitation of this case study is that a small number of subjects were analysed due to unavailability of large open access database having good quality ECG recording with

VT/VF history. Therefore, the conclusions drawn from the study need more validation in a larger cohort. The determination of the QT intervals in the ECG segments having PVC must be carefully done and validated manually after automatic detection to derive reliable conclusions about the measures.

6.5 Conclusion

This chapter has discussed about a novel model free approach of normalized beat-to-beat analysis of QT-RR interaction, which accounts both HRV and QTV. Recent studies showed promising results of using the combined approach of considering both HRV and QTV in investigating the effect of autonomic nervous system on cardiovascular system in different physiological condition (i.e. ageing)[206] and cardiac pathologies(i.e. LQTS)[207]. The combined approach can better describe the overall effect of ANS on cardiac function, where the parasympathetic and sympathetic nervous system control is analysed by HRV and QTV respectively. The proposed beat-to-beat normalization approach presented in this chapter removes the necessity of considering the heart rate corrected QT interval determination as it can handle the intersubject variability of the QT-RR interaction pattern [15]. A prospective future study of this technique will be to investigate the QT-RR interaction variability in multi lead ECG system. The proposed normalization technique will assist to compare the results of QTV found form single lead and multi lead ECG system as it is reported that the amount of QTV is different in different leads in a 12 lead ECG system [178]. This beat-to-beat analysis technique also removes the hysteresis problem as it considers all the QT and RR intervals detected within the recording length. The pattern of coupled changes in QT and RR intervals within a fixed recording length of ECG derived the proposed methodology helps to quantify the relative contribution of different QTV components (i.e. RR dependent and RR independent components of total QTV) whereas the gross measures of QTV (i.e. SDQT) cannot. This technique can measure the QTV component independent of RR, which contains important prognostic information about cardiac pathology and sympathetic nervous system modulatory effect on QTV. More case studies are needed with alteration in autonomic nervous system branches by medication (i.e. parasympathetic and sympathetic blockade) or by physical manoeuvre which alters ANS modulation of QTV to validate the findings about the measure that quantify the RR independent QTV component.

Chapter 7

General discussions and conclusions

7.1   Summary of main Contributions

Analysis of the ventricular repolarization duration variability measured from the QT interval on ECG (QTV) is crucial for investigating ventricular dysfunction, which is the trigger for fatal ventricular arrhythmias (i.e. ventricular tachycardia and ventricular fibrillation) [5, 6, 24]. QTV analysis will complement the existing HRV analysis techniques in cardiovascular diagnosis, especially in the risk prediction of arrhythmogenesis as reported in recent studies [6, 8]. However, the reliability of the different QTV measures in different pathologic condition provided inconsistent results [57, 58], which indicate the necessity of the development of more reliable techniques. Moreover, the effect of autonomic nervous system branches' (i.e. parasympathetic and sympathetic branches) modulation on QTV is still an active area of research as it is not established firmly, like that of an HRV. Therefore, more dynamical or beat-to-beat analysis techniques should be investigated and developed for robust analysis of ventricular repolarization dynamics.

The objective of this thesis is to investigate the existing temporal variability measures of QTV and compare their performance with the proposed and developed measures of this research study. Another objective is to develop non-invasive ECG based simple techniques that can be used for subclinical diagnosis techniques of cardiac diseases from QTV to design effective ambulatory care clinics. The contributions of this thesis in the field of QTV analysis techniques are briefly discussed below.

7.1.1   ECG derived respiration (EDR) based modelling of QTV

Modelling QT-RR interval interactions to analyse QTV is one of the beat-to-beat dynamical analysis techniques for quantifying QTV and to investigate the effect of ANS on QTV. Several clinical studies have reported the direct modulatory effect of respiration on QTV like that of RR interval [86, 87, 113] and only one QT-RR-Respiration modelling study have reported this phenomena in healthy individuals [41]. The first contribution of this research study is to investigate the effect of respiration in age and stress related alteration in QTV by using respiration as an additional exogenous input with RR in the reported QTV modelling technique first proposed by Porta et al. [41]. The addition of respiratory information was found to improve the modelling technique significantly to predict QTV in healthy subjects

irrespective of ageing and stress induction, which establish the modulatory effect of respiration on QTV. The second contribution of this thesis is to replace the necessity of original respiration signal recording and replace it with ECG derived respiration (EDR), which can be derived from the ECG signal without the respiration signal recording. This will remove the problem of using complex respiration signal recording system set-up and make the technique applicable to all patient groups, where traditional respiration signal recording is problematic due to either the absence of the recording facility or the inability of the patients to cooperate properly with the recording system. This novel EDR based QTV modelling technique was also found very useful in describing age and stress induced changes in healthy subjects and can describe the autonomic modulation on QTV. EDR based modelling technique was also used to investigate the diabetic cardiac autonomic Neuropathy (CAN) related changes in QTV. This type of modelling approach was not being used before for diabetic CAN analysis. The results of this study validated the coupled causal effect of respiration on QTV and the effectiveness of EDR in pathological conditions. A surrogate analysis technique also validated the exogenous effect of respiration, which can be represented by EDR in a cardiac pathology like CAN and these findings establish the importance of considering respiratory information in analysing QTV for both healthy and pathology conditions.

7.1.2 Systolic-Diastolic interval interaction (SDI) analysis from ECG

Another major contribution of this thesis is a novel approach to investigate the systolic and diastolic function form surface ECG. HRV and QTV parameters in ECG (i.e. QT interval, TQ interval, RR interval) can provide useful information about the changes in the synchronized temporal coupling of systolic and diastolic functions, which is altered in left ventricular dysfunction. The proposed technique was validated in diabetic cardiac autonomic neuropathy subjects, which showed the SDI measures can detect the subclinical CAN and also describe the CAN related gradual degradation of QTV with denervation of parasympathetic and sympathetic branches. The findings of this study can complement the research in the field of investigating ECG based markers for detecting left ventricular diastolic dysfunction (LVDD), which is normally performed by Echocardiography.

7.1.3 A novel approach to investigate QTV from beat-to-beat coupled QT-RR interaction pattern

A novel model free approach was proposed to quantify the QTV component independent of RR from the dynamical distribution of QT-RR interval interactions. This method removes the necessity of the model based approach for determining the QTV component not affected by RR through spectral analysis techniques, which require precise model identification

techniques for reliable results. It is quite difficult sometimes to derive proper model structure and estimate the model coefficients correctly due to the quality of ECG.

A model free algorithm was also proposed to investigate the dynamic changes in QT and RR intervals before arrhythmogenesis. The initial findings of this technique showed promising results, which indicates that the proposed technique can be a useful predictive tool for analysing arrhythmogenesis. The proposed technique also reduces the problem of intersubject variability of QT-RR distribution [15] and does not require any specific heart rate correction method of the QT interval. This method can also be used in the presence of Ectopic beats (i.e. premature ventricular contraction beats), which provide predictive information about arrhythmogenesis.

7.2 Future Research directions

The findings of this research study have made important contributions to knowledge advancement by providing mathematical proof and validations, which will corroborate the physiological theory of the respiratory effect on QTV. This study also proposes some novel techniques that will contribute to the development of better ECG based analysis techniques of QTV in cardiac pathology detection and Sudden Cardiac Death (SCD) prediction. However, there are more areas that need to be investigated, which will improve the feasibility of the application of the developed methods in clinical studies. Some of them are listed as possible future works that should be undertaken.

- Validation of the use different techniques for calculating ECG derived respiration (EDR) in the respiratory information based modelling technique for analysing QTV as proposed in this thesis.
- Validation of EDR based modelling technique in subjects with respiratory pathology to determine the extent of the effect of respiration on QTV. Controlled breathing induces some nonlinearity in QT-RR relation. Therefore, investigating the effect of spontaneous and controlled respiration on the modelling performance could be potential future study
- Design of a non-linear modelling approach involving QT,RR and respiratory information and investigation of the feasibility of using EDR in a nonlinear model structure
- Investigation of the effect of conventional (i.e. slope intercept method) and semi-automatic template based method of QT detection techniques in modelling QTV especially in different cardiac pathology

- Investigation of the autonomic blockade of different branches of nervous system (i.e. parasympathetic and sympathetic branches) on the EDR based model performance in describing QTV.

- Comparison of the proposed systolic-diastolic interval interaction (SDI) methodology with echocardiographic data used in left ventricular diastolic dysfunction (LVDD) detection to establish the reliability of the SDI measure for analysing heart failure.

- Validation of the novel model free approach to determine QTV independent of RR in studies with drug induced autonomic blockade to strengthen the findings of the effect of sympathetic modulation of this component of QTV.

- Use of more case studies to establish the findings of the proposed methodology of determining QTV component independent of RR, which is believed to give prognostic information about ventricular dysfunction.

- Validation of the proposed technique of analysing the dynamical changes in QT-RR pattern before ventricular arrhythmogenesis using more available databases to establish the feasibility of this method in clinical use.

- To investigate the effectiveness of the proposed method in the detection of temporal variation of the QT-RR pattern changes before the onset of arrhythmia (i.e. how the QT-RR pattern changes evolve before arrhythmogenesis). This will contribute to the development of reliable real time alarm system in the intensive care unit (ICU) or in the emergency centre and assist to provide effective treatment.

7.3 Conclusion

This thesis investigates several beat-to-beat QT interval variability (QTV) analysis techniques for short-term ECG recordings in several case studies including human subjects with specific pathophysiological conditions. Some novel approaches for QTV analysis are proposed, which were found very effective in analysing QTV alteration, mainly due to ageing, stress, dysfunction in autonomic nervous system (ANS) modulation on the ventricles, genetical disorder of cardiac ion channel and arrhyhthmogenesis. The ECG derived respiratory information (EDR) based modelling technique increases the efficiency of analysing the Ventricular Repolarization (VR) process dynamics and validates the possibility of a design of only ECG based diagnostic system for QTV. Moreover, the EDR based modelling technique will be more informative in the analysis of the ANS effect on QTV than that of the modelling techniques without respiration. Model based analysis of QTV should be used to investigate the complexity of VR process dynamics in pathology, which will aid in the design of subclinical diagnostic methods as found in this thesis in the case of the

detection of subclinical diabetic Cardiac autonomic Neuropathy (CAN). Single variable analysis techniques (i.e. analysing only HRV or QTV) cannot explore the cardiovascular system level changes that generate the process dynamics. Measures of VR analysis were found useful in the design of ECG based analysis of left ventricular dysfunction, which will definitely assist the current research on ECG based techniques of Heart failure detection from either systolic or diastolic heart failure where the VR process is affected. A novel model free, simple technique is described to determine QTV component that is independent of RR variation, which can give useful information about sympathetic modulation on QTV and will enrich the understanding of the effect of ANS on QTV. Finally, the proposed technique of beat-to-beat QT-RR interaction analysis showed promising results in developing prognostic measures of ventricular tachycardia or ventricular fibrillation, which is the underlying cause of Sudden Cardiac Death (SCD). The findings of this research study will complement the current trend of QTV analysis as a predictive measure of ventricular arrhythmias, which might lead to fatal SCD.

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Title:
Analysis of beat-to-beat ventricular repolarization duration variability from electrocardiogram signal

Date:
2015

Persistent Link:
http://hdl.handle.net/11343/57549

File Description:
PhD thesis: Analysis of beat-to-beat ventricular repolarization duration variability from Electrocardiogram signal