Analysis of Beat-to-Beat QT Interval Variability in 12-lead ECG Signals

by

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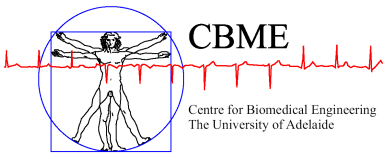

THE UNIVERSITY of ADELAIDE

Dedication

To fulfill every ambition needs self-effort as well as adroit directions of elders especially those very close to our heart and feelings.

My humble effort I dedicate to my sweet and loving

Parents,

Whose love, affection, encouragement and prayers of day and night enable me to have such success and honour.

Contents

Abstract

The human heart is a significant research topic in biomedical engineering due to the high incidence of heart disease in the developing world. Electrocardiography (ECG) is considered the primary diagnostic tool for the assessment of cardiac diseases and various heart arrhythmias. Note that ECG is the electrical representation of heart activity and can be recorded noninvasively by placing electrodes on the limbs and chest of the body. It is stated that certain heart diseases affect depolarization and repolarization. While the entire depolarization and repolarization of the heart is important, there is significant interest in the study and investigation of the ventricular depolarization and repolarization that is reflected by QT interval duration. The main reason for studying ventricular depolarization and repolarization is that some cardiac diseases, which are associated with ventricles of the heart, have an immediate effect on the body and can cause sudden cardiac death. Further, the knowledge of ventricular activation sequence and its abnormalities has contributed to our understanding of cardiac arrhythmias, but the underlying mechanisms and role of repolarization abnormalities is still not completely known. Therefore, this thesis presents several studies to explain more about the instability of repolarization duration in various cardiac patients by analysing different QT parameters.

The main results of the thesis are: (i) Beat-to-beat QT interval variability (QTV) varies between the 12 standard ECG leads and caution should be paid when comparing beat-to-beat QTV results obtained from different leads across studies. (ii) The inter-lead correlation of beat-to-beat QTV is lead dependent. (iii) A negative correlation exists between beat-to-beat QTV and T-wave amplitude. (iv) No significant effect of mean heart rate, age and gender on beat-to-beat QTV in 12-lead resting ECG in healthy subjects. (v) An improved ECG-preprocessing technique is introduced and recommended for accurate measurement of beat-to-beat QTV. It substitutes the R-peak detection algorithm and implements an efficient baseline removal algorithm in the existing template matching approach. (vi) Effects of T-wave amplitude and ECG lead on beat-to-beat QTV in patients with Myocardial Infarction (MI) compared to healthy subjects are studied and suggest that increased beat-to-beat QTV in patients with MI is partly due to the lower T-wave amplitudes and some other unknown reason. (vii) The study also confirms that patients with MI have lower heart rate variability (HRV) compared to

healthy subjects. (viii) Moreover, beat-to-beat QTV remains higher in patients with MI even after controlling the T-wave amplitudes. (ix) Two new beat-to-beat VCG (vectorcardiography) descriptors that have independent diagnostic attributes for assessing patient populations are introduced. (x) Overall spatial and temporal VCG descriptors may provide markers of electrical instability in the heart of patients with MI but need further research for the quantification and analysis of beat-to-beat VCG descriptors. (xi) Effect of pacing and pharmacologically induced autonomic nervous system modulation on VCG parameters and on beat-to-beat QTV is limited in heart failure patients.

In addition to this, the thesis offers an introductory background and overview chapter revolving around repolarization lability. The results should be taken into account in further studies, so that the beat-to-beat variations of QT interval in ECG parameters and VCG descriptors can be utilized more effectively in clinical applications.

Statement of Originality

This work contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Muhammad Asraful Hasan and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Signed

Date

Acknowledgments

I would never have been able to finish successfully this doctoral thesis without the help, encouragement and support of kind people around me, to only some of whom it is possible to give particular mention here.

Above all, first and foremost, I offer my sincerest gratitude to my supervisors **Assoc Prof Mathias Baumert** and **Prof Derek Abbott** for their excellent guidance, care, patience, support and providing me with an excellent research atmosphere. I attribute the level of my PhD degree in the field of Biomedical Engineering and Signal Processing to their continuous support, motivation and effort and without them this thesis would not have been completed or written. I wish to especially thank **Assoc Prof Mathias Baumert** for his support since the days I began working on my PhD research. He helped me come up with the thesis topic and guided me throughout my PhD candidature. His continuous flow of ideas, insightful comments, and moral support has helped me to build my confidence in research—this then gave me the freedom to move forward. Moreover, I can never forget the help of **Prof Derek Abbott**, who helped me get on the road to LaTeX for writing this thesis and most importantly his inspiration in my whole PhD journey.

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I would like to thank my parents, parents-in-law, brothers and sister. They were always supporting me and encouraging me with their best wishes.

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Thesis Conventions

The following conventions have been adopted in this Thesis:

1. **Spelling.** Australian English spelling conventions have been used, as defined in the Macquarie English Dictionary, A. Delbridge (Ed.), Macquarie Library, North Ryde, NSW, Australia, 2001.

2. **Typesetting.** This document was compiled using LaTeX2e. TeXnicCenter was used as text editor interfaced to LaTeX2e. Inkscape was used to produce schematic diagrams and other drawings.

3. **Mathematics.** MATLAB code was written using MATLAB Version R2010a; URL: http://www.mathworks.com.

4. **Referencing.** The Harvard style has been adopted for referencing.

5. **URLs.** Universal Resource Locators are provided in this Thesis for finding information on the world wide web using hypertext transfer protocol (HTTP). The information at the locations listed was current on 17 December 2009.

Publications

A brief list of selected publications are as follows:

Journal Articles

Hasan M. A., Abbott D., & Baumert M. (2013). Beat-to-beat QT interval variability and T-wave amplitude in patients with myocardial infarction, *Physiological Measurement*, **34**, pp. 1075–1083.*

Nayyar, S., Roberts-Thomson, K. C., **Hasan M. A.**, Sullivan, T., Harrington, J., Sanders, P., & Baumert M. (2013). Autonomic modulation of repolarization instability in patients with heart failure prone to ventricular tachycardia, *American Journal of Physiology–Heart and Circulatory Physiology*, **305**, pp. H1181–H1188.*

Hasan M. A., Abbott D., & Baumert M. (2012). Beat-to-beat vectorcardiographic analysis of ventricular depolarization and repolarization in myocardial infarction, *PLoS ONE*, **7**, art. no. e10602.*

Hasan M. A., Abbott D., & Baumert M. (2012). Relation between beat-to-beat QT interval variability and T-wave amplitude in healthy subjects, *Annals of Noninvasive Electrocardiology*, **17**, pp. 1249–1259.*

Hasan M. A., & Reaz M. (2012). Hardware prototyping of neural network based fetal electrocardiogram extraction, *Measurement Science Review*, **12**, pp. 52–55.

Hasan M. A., & Reaz M. (2012). Hardware approach of R-peak detection for the measurement of fetal and maternal heart rates, *Journal of Applied Research and Technology*, **10**, pp. 835–844.

Hasan M. A., Reaz M., Ibrahimy M., Hussain M., & Uddin J. (2009). Detection and processing techniques of FECG signal for fetal monitoring, *Biological Procedures Online*, **11**, pp. 263–295.

HASAN M. A., IBRAHIMY M., & REAZ M. (2009). An efficient method for fetal electrocardiogram extraction from the abdominal electrocardiogram signal, *Journal of Computer Science*, **5**, pp. 619–623.

Conference Articles

HASAN M. A., STARC V., PORTA A., ABBOTT D., & BAUMERT M. (2013). Improved ECG pre-processing for beat-to-beat QT interval variability measurement, 35th *Annual International Conference of the IEEE Engineering in Medicine and Biology Society 2013*, Osaka, Japan, pp. 4193–4195.*

HASAN M. A., ABBOTT D., & BAUMERT M. (2013). Dynamic repolarization variability in patients with myocardial infarction, *Australian Biomedical Engineering (ABEC) 2013*, Sydney, Australia, (Abstract based).*

HASAN M. A., ABBOTT D., & BAUMERT M. (2012). Beat-to-beat spatial and temporal analysis for QRS-T morphology, 34th *Annual International Conference of the IEEE Engineering in Medicine and Biology Society 2012*, San Diego, CA, USA, pp. 4193–4195.*

HASAN M. A., ABBOTT D., & BAUMERT M. (2011). Beat-to-beat QT interval variability in the 12 lead ECG, 38th *Annual Scientific Conference of Computing in Cardiology 2011*, Hangzhou, China, pp. 61–64.*

HASAN M. A., REAZ M. B. I., & IBRAHIMY M. I. (2011). Fetal electrocardiogram extraction and R-peak detection for fetal heart rate monitoring using artificial neural network and correlation, *The 2011 International Joint Conference on Neural Networks (IJCNN) 2011*, San Jose, CA, USA, pp. 15–20.

HASAN M. A., IBRAHIMY M. I., & REAZ M. B. I. (2008). NN-Based R-peak detection in QRS complex of ECG signal, 4th *Kuala Lumpur International Conference on Biomedical Engineering*, Kuala Lumpur, Malaysia, pp. 217–220.

Note: Articles with an asterisk (*) are directly relevant to this Thesis.

Awards

A list of award achievements are as follows:

- Australian Endeavour International Postgraduate Research Scholarship (**EIPRS**) for PhD research at The University of Adelaide, Australia, 2010.
- The University of Adelaide Scholarship (**UAS**) for PhD research at The University of Adelaide, Australia, 2010.
- **SMBE SA/NT ABEC Travel Grant** awarded to attend and present research paper in the Australian Biomedical Engineering Conference, 13-16 October, Sydney, Australia, 2013.
- **IEEE SA Travel Grant** awarded to attend and present research paper in the 34th Annual International Conference of the IEEE Engineering and in Medicine & Biology Society, 28 August-1 September, San Diego, USA, 2012.
- **IEEE SA Travel Grant** awarded to attend and present research paper in the Computing in Cardiology Conference, 18-21 September, Hangzhou, China, 2011.
- **Silver Medal** awarded in International Islamic University Malaysia Research, invention and Innovation (IRIIE'11) for Research performance, in International Islamic University Malaysia 2011.
- **Bronze Medal** awarded in International Islamic University Malaysia Research, invention and Innovation (IRIIE'10) for Research performance, in International Islamic University Malaysia 2010.
- **IEEE Student Scholarship** awarded to attend and present paper in the IEEE-ICIT'09 conference, 10–13 February, Monash University, Australia, 2009.
- **Silver Medal** awarded in Kulliyyah (Faculty) of Engineering Research and Innovation Exhibition (KERIE'09) for Research outstanding performance, in International Islamic University Malaysia 2009.

- **Travel Scholarship** received from Center for Postgraduate Studies (CPS), International Islamic University Malaysia to attend and present paper in 38th International Conference on Computer and Industrial Engineering, Oct–Nov, Beijing, China, 2008.
- **Dean's** award from Military Institute of Science and Technology for the outstanding performance in B.Sc. Engineering, 2006.

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Introduction

THIS chapter gives the background and motivation of this thesis. Further, the structure of the thesis is outlined by providing an overview of the forthcoming chapters.

1.1 Introduction

Physiological processes are complex phenomena and most are followed by or demonstrate themselves as signals that reflect their nature and activities. These physiological signals can be of many types such as 'biochemical' that are in the form of hormones and neurotransmitters; 'electrical' that are in the form of a potential or current; and 'physical' that are in the form of pressure or temperature. Moreover, various physiological processes in the human body generate biological signals. Biomedical signals can be electrical or non-electrical and are recorded from biological systems as a function of time with respect to amplitude which captures some aspect of a biological event. In addition, these signals in their raw form do not provide as much information in the required form and, therefore, it is required to carry out signal processing and analysis to extract the relevant information.

The ECG is perhaps one of the most commonly known, recognized, and used biomedical signal that is usually acquired from the body surface using a number of electrodes (see standard 12-lead ECG in Fig. 1.1) and allows the interpretation of the electrical heart activity. In the case of ECG signal, the cardiac signal is described as amplitude without the orientation of the heart vector direction. The analysis of the ECG is an important tool for the diagnosis of different types of the cardiac disease such as myocardial infarction, ventricular hypertrophy, ventricular tachycardia or ventricular fibrillation (Malmivuo and Plonsey 1995). In addition, some cardiac diseases that are associated with lower chambers (left and right ventricles) of the heart have an immediate effect on the body. Therefore, there is much interest to study and investigate the ventricular depolarization and repolarization for the analysis of cardiac disease.

In clinical practice, the QT interval is measured as the time between the start of the Q-wave and the end of the T-wave in the heart's ECG electrical cycle, which represents the duration of ventricular depolarization and repolarization. Since the ventricular depolarization time is relatively short, fast and constant compared to ventricular repolarization time, the QT interval duration is also simply known as the global electrical repolarization of the ventricles. From the beginning of electrocardiology, this QT interval was studied because of a suggested relationship between QT interval duration and different pathologies. Note that QT interval variability analysis from a single ECG beat demonstrates the static picture of repolarization abnormalities, but the beat-to-beat QT interval variability (QTV) establishes the dynamic changes of QT interval duration and repolarization labilities. Elevated beat-to-beat

QTV is of interest as it has been associated with increased cardiovascular morbidity and mortality (Berger *et al.* 1997, Murabayashi *et al.* 2002, Raghunandan *et al.* 2004, Hinterseer *et al.* 2008, Baumert *et al.* 2011a, Hasan *et al.* 2013a).

However, ventricular repolarization is a complex electrical phenomenon, which is not completely understood, and by characterizing the beat-to-beat variations of QT interval it may help to shed light on this complex control system. Therefore, this thesis discussess the significance of QTV analysis followed by several approaches and their findings with limitations, analyzes the ECG signals under various cardiac conditions to assess the repolarization lability for malignant ventricular arrhythmias. Further, to obtain a better insight in the dynamic behavior of the QT interval on a beat-to-beat basis, this thesis also introduces a modified technique that is robust and provides improved accuracy for the analysis of beat-to-beat QTV.

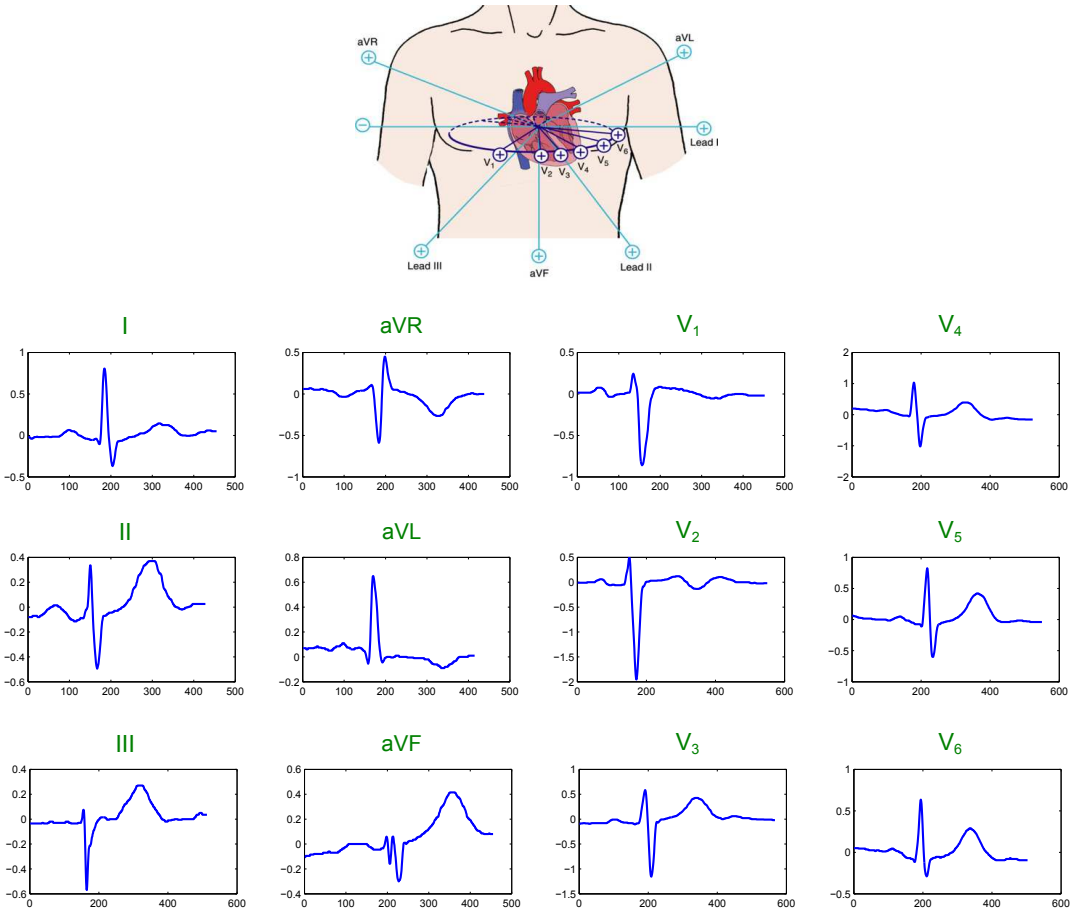

Figure 1.1. 12 lead ECG. The standard 12-lead ECG placement (top) and representation (bottom). After www.xkgfs.com/12-lead-ekg-interpretation-powerpoint.html.

1.2 Statement of original contribution

This thesis involves several original contributions in the field of biomedical signal processing and are summarized as follows.

- **Relation of beat-to-beat QTV in different leads of 12-lead ECG**: For the first time a systematic relationship of beat-to-beat QTV in 12-lead ECG is analyzed and investigated in healthy subjects. This thesis demonstrates that (i) the magnitude of beat-to-beat QTV varies between the 12 standard ECG leads and (ii) the inter-lead correlation of beat-to-beat QTV is lead dependent; (iii) there is a negative correlation between beat-to-beat QTV and T-wave amplitude; and (iv) there is no significant affect of mean heart rate, age and gender on QTV in 12-lead resting ECG of healthy subjects (Hasan *et al.* 2011, Hasan *et al.* 2012c).

- **Improved beat-to-beat QT interval variability measurement approach**: This thesis develops the ECG pre-processing modalities for beat-to-beat QTV measurement based on template matching. It substitutes the R-peak detection algorithm and implements an efficient baseline removal algorithm in existing template matching software. It recommends the updated ECG pre-processing algorithm for more accurate quantification of beat-to-beat QTV analysis (Hasan *et al.* 2013b).

- **Effects of T-wave amplitude and ECG lead on beat-to-beat QTV**: This thesis investigates the effects of T-wave amplitude and ECG lead on beat-to-beat QTV in patients with myocardial infarction (MI) compared to healthy subjects. It demonstrates that the increase in beat-to-beat QTV in patients with MI is partly due to lower T-wave amplitudes. Further, the causes of this increase in beat-to-beat QTV still remain an open question for future work. Another finding is that MI patients has lower heart rate variability compared to healthy subjects (Hasan *et al.* 2013a).

- **Beat-to-beat spatial and temporal variations of ventricular depolarization and repolarization in VCG**: This thesis proposes an approach for analysing the beat-to-beat spatial and temporal variations of ventricular depolarization and repolarization wavefronts. Further, it introduces two new VCG parameters for characterising cardiac electrical abnormalities in patients with myocardial infarction (MI). Finally, it demonstrates that there is an increase variability of depolarization as well as repolarization in patients with MI compared to normal subjects (Hasan *et al.* 2012b, Hasan *et al.* 2012a).

- **Effect of pacing and autonomic nervous system activity on beat-to-beat VCG parameters**: This thesis explores the effect of pacing and autonomic nervous system on VCG parameters. It suggests that the proposed VCG descriptors may have independent prognostic capabilities for identifying heart failure patients, but overall effect of heart rate or autonomic nervous system activity on VCG parameters appears to be absent in heart failure patients.

- **Role of autonomic nervous system activity on beat-to-beat QTV**: This thesis investigates the role of autonomic nervous system activity on beat-to-beat QTV. It demonstrates that the effect of acute autonomic nervous system modulation on QTV is limited in heart failure patients (Nayyar *et al.* 2013).

1.3 Thesis overview

This thesis is composed in total of 8 chapters and one appendix. The next 7 chapters of this thesis are outlined as described below, and a diagram of the thesis structure is also provided in Fig. 1.2.

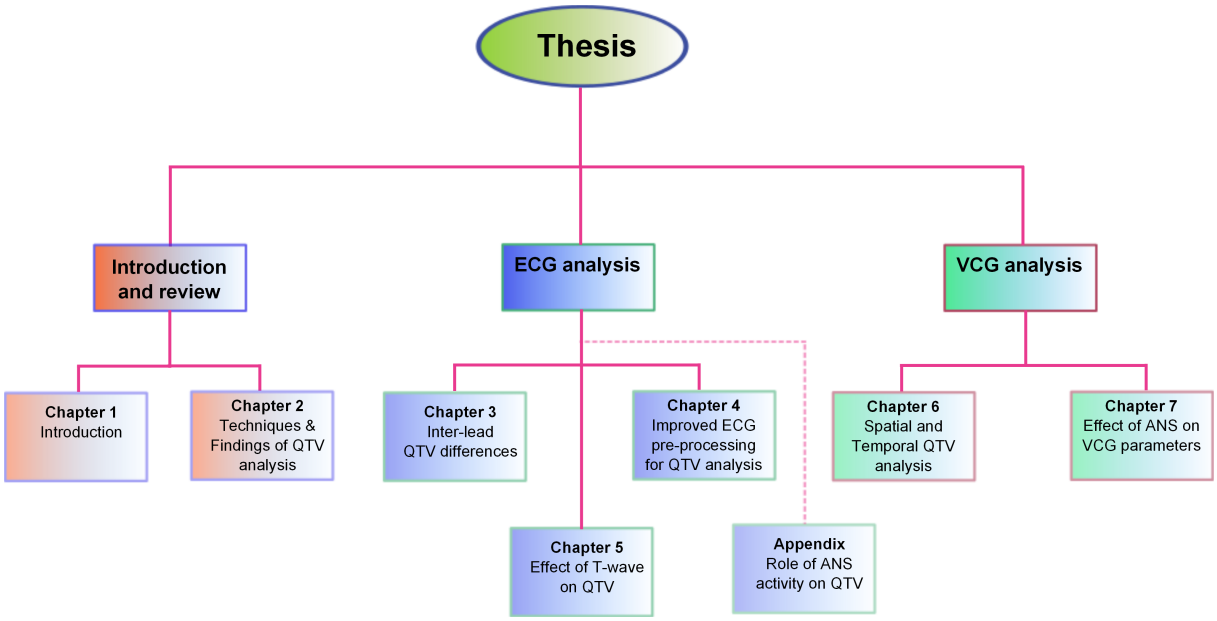

Figure 1.2. Thesis structure. The original contributions are distributed over the thesis structure.

Chapter 2 gives the basic definitions of the key words in this field of research topic as well as the significance of several other QT parameters. Further, this chapter reviews several other techniques for QTV analysis along with their findings, limitations

and rational comparisons. Moreover, the factors affecting the analysis of QTV is also discussed for further study.

Chapter 3 investigates inter-lead differences in beat-to-beat QTV of 12-lead ECG in healthy subjects and their relationship with T-wave amplitude, mean heart rate, age, and gender.

Chapter 4 aims to enhance the ECG pre-processing modalities in a widely-used computer software package for beat-to-beat QTV measurement based on template matching algorithm.

Chapter 5 investigates the effects of T-wave amplitude and ECG lead configuration on beat-to-beat QTV of 12-lead ECG in patients with myocardial infarction (MI) compared to healthy subjects.

Chapter 6 investigates the beat-to-beat VCG by quantifying different descriptors from the QRS and T-loop in patients with MI as well as healthy subjects.

Chapter 7 studies the role of heart rate and autonomic nervous system activity on beat-to-beat VCG parameters in heart failure patients.

Chapter 8 summarizes the entire thesis and recommends possible future directions.

Appendix A investigates the influence of autonomic nervous system activity on beat-to-beat QTV.

1.4 Chapter summary

This chapter has provided an overview of the thesis structure and original contributions.

In the next chapter, we will discuss the overview of the QTV analysis for different cardiac patients along with several techniques, findings and limitations.

EGC and VCG Approaches to QTV Analysis: Techniques and Findings

THE ECG is a measure of electrical activity of the heart and its analysis is considered as one of the important diagnostic tool in the field of biomedical engineering. The assessment of beat-to-beat QT interval variability (QTV) has received significant interest. This is because an increase in beat-to-beat QTV is one of the markers for repolarization instability and is thought to possess a strong association with cardiovascular mortality and morbidity. Therefore, this chapter will provide a review on beat-to-beat QTV in ECG and VCG analysis in relation to a number of techniques, findings, factors and parameters, which can be a reference point for the researchers and clinicians for further study.

2.1 Introduction

What is the QT interval?

The electrical activity of the heart produces a signal called the electrocardiogram (ECG) and contains various features such as QRS complex (ventricular depolarization), T-wave (ventricular repolarization), P-wave (atrial depolarization) as shown in Fig. 2.1.

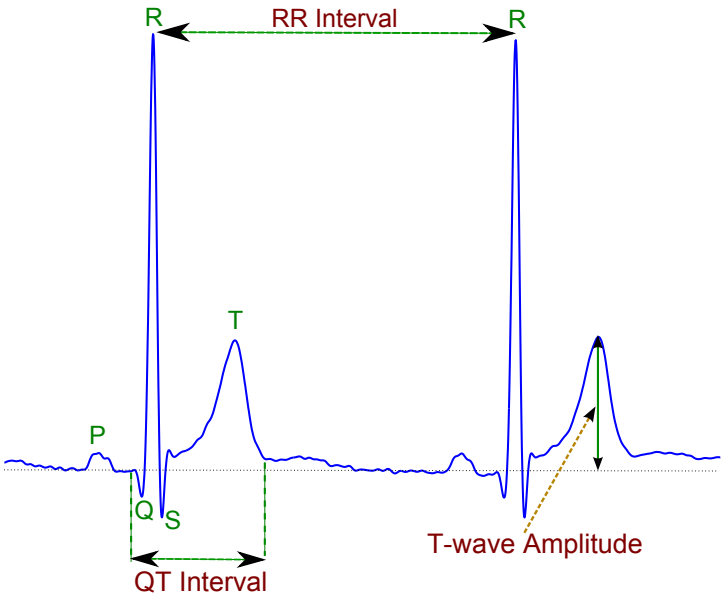

Figure 2.1. ECG signal. A typical example of the ECG morphology.

This electrical activity of the heart is normally infused through different channels, which are complex molecular structures within the myocardial cell membrane that govern the flow of ions in and out of cardiac cells (see Fig. 2.2).

The total time of ventricular depolarization and repolarization of a cardiac cycle is generally known as the QT interval. (see Fig. 2.1). Since the ventricular depolarization is relatively short and constant, the electrocardiographic QT interval represents a global measure of the ventricular repolarization duration. The QT interval is an important diagnostic measurement in clinical practice because of its instability under different cardiac conditions that are believed to be associated with pathological states. In addition, ventricular repolarization is thought to be one of the major concerns of cardiologists as it maintains a relationship with the occurrence of ventricular arrhythmias and sudden cardiac death (Kannankeril *et al.* 2010, Nayyar *et al.* 2013).

However, it is considered that the relationship between the cellular action potential duration of myocardium and the QT interval recorded at the body surface of ECG is

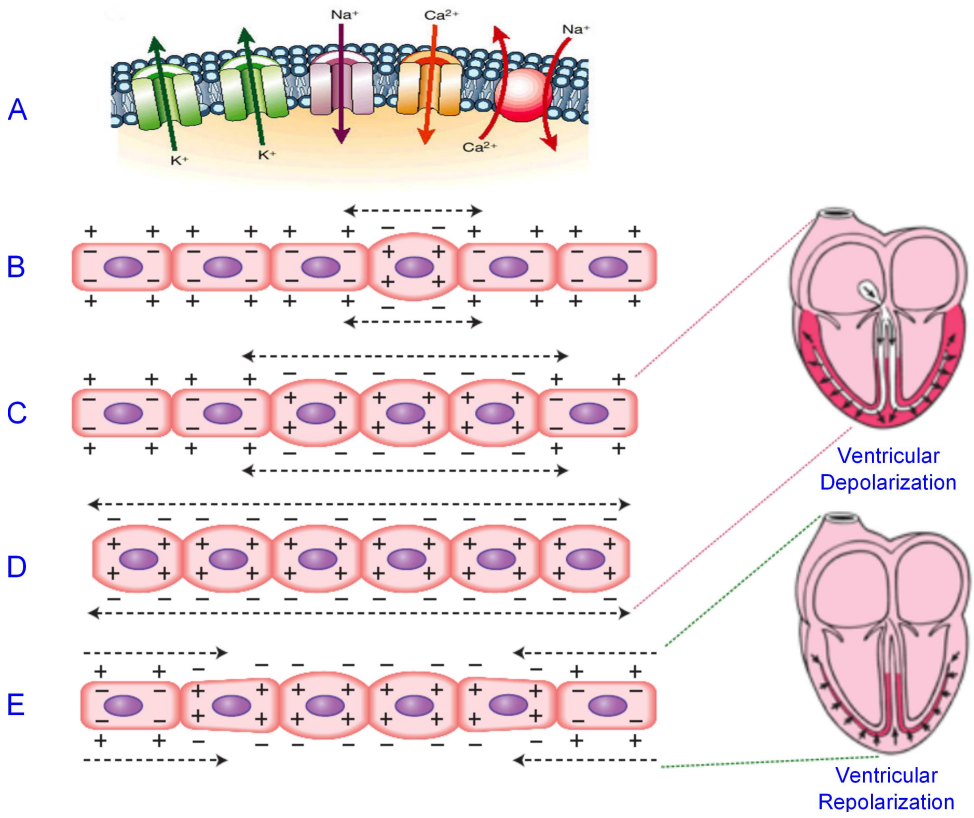

Figure 2.2. Myocardium cells depolarization and repolarization process. (A) Ion channels within the myocardium cell membrane. (B) Depolarization starts from single cells. (C) Depolarization cell to cell. (D) Depolarization complete. (E) Repolarization restores each cell's normal polarity. Adapted from Marbán (2002) and Jones (2008).

very complex. Accordingly, the QT interval is difficult to interpret from the surface of ECG with precision. Several challenges have been reported in last few decades regarding quantification of the QT interval. To detect the QT interval accurately, the first task to be considered is detection of the R-peak in QRS complexes (Hasan *et al.* 2013b). Secondly, it is generally considered that there is an inherent imprecision for identifying the T-wave offset in surface ECG (Daskalov and Christov 1999, Hunt 2005, Christov and Simova 2006, Chen *et al.* 2006). Mainly, the detection of the T-wave offset is difficult due to incomplete understanding of the recovery process and its projection on the body surface (Kautzner 2002). Further, significant variation can be found both in the onset of the QRS complex and offset of T-wave in 12-lead ECG leads, which provides different QT interval values depending upon the leads selected for measurement (Macfarlane *et al.* 1998, Kautzner 2002, Hasan *et al.* 2012c).

Furthermore, the QT interval is prolonged at slower heart rates and shortened at faster heart rates (Locati *et al.* 1998, Davey and Bateman 1999), which has also an effect of

proper identification of QT interval on surface ECG. Moreover, certain pharmacological drugs have the capability to slow down the cardiac repolarization, resulting in QT interval prolongation. As a result, this creates an electrophysiological environment that promotes the development of cardiac arrhythmias, which can lead to the cause of sudden cardiac death (Lazzara 1993). It is considered that in the presence of cardiac disease, the heterogeneity of ventricular repolarization is increased, leading to QT interval prolongation (Antzelevitch and Shimizu 2002). Nevertheless, the QT interval duration can also be affected by several non-cardiac factors, such as age, gender, inflammation, changes in autonomic tone, and electrolyte disturbances (Magnano *et al.* 2002), thereby limiting its use in the analysis of the electrophysiological properties of ventricular myocardium. A typical example of the range of QT interval (lower and upper) measurement for a healthy subject as shown in Fig. 2.3.

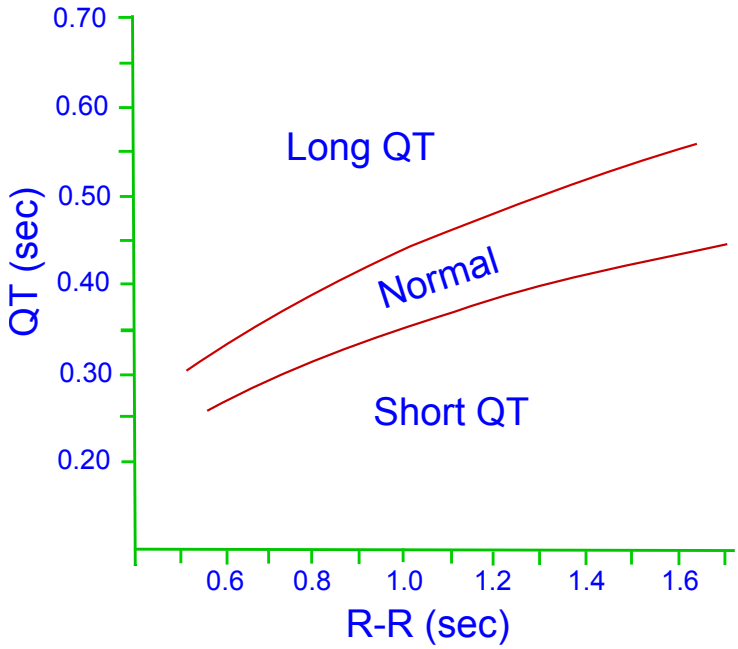

Figure 2.3. Range of QT interval. QT interval (lower and upper limit) measurement for a healthy subject.

Therefore, this chapter pays special attention to discussing the significance of QT interval and dynamic changes of repolarization duration parameters, different techniques along with factors affecting assessment of QT duration, which may serve as a reference for day-to-day practice for researchers, clinicians, physiologists, official regulatory agencies, and for the benefit of cardiovascular patients.

2.2 Significance of QT measurement

The quantification of the QT interval on surface ECG has gained clinical importance, primarily because of the ability to detect risk for malignant ventricular arrhythmia. The details of the significance of QT interval measurement are discussed in the following sections.

2.2.1 QT interval variability vs. heart rate variability

The analysis of QTV and HRV plays a important role for identifying the cardiovascular arrhythmia. However, a significant number of studies have been performed by using HRV and QTV parameters on cardiac or without cardiac diseases patients in last few decades (Atiga *et al.* 1998, Yeragani *et al.* 2002a, Bär *et al.* 2008, Baumert *et al.* 2008a, Baumert *et al.* 2008b, Sachdev *et al.* 2010, Baumert *et al.* 2011a, Falkenberg *et al.* 2013, Hasan *et al.* 2013a).

Heart Rate Variability (HRV) a physiological phenomenon used for observing the interplay between sympathetic and parasympathetic nervous systems. It is usually analyzed from the instantaneous heart rate time series by using beat-to-beat RR intervals. It is believed that heart rate can be increased due to slow acting sympathetic activity or decreased due to fast acting parasympathetic (vagal) activity. It should be mentioned that, HRV is a non-invasive measure for assessing the balance of the autonomic nervous system (ANS) (Friedman and Thayer 1998, Stein and Kleiger 1999, Sztajzel 2004), which has received greater attention, and consequently HRV analysis has become significant in ECG signal analysis. On the other hand, the QT interval for surface ECG represents the ventricular repolarization duration and the autonomic nervous system can affect QTV parameters (Merri *et al.* 1993, Shusterman *et al.* 1999, Yeragani *et al.* 2005, Baumert *et al.* 2011c). Therefore, it is considered that QTV analysis may possibly complement HRV analysis (Pan *et al.* 1998, Cuomo *et al.* 2004). In 2002, Magnano *et al.* (2002) also show the affect of autonomic alternation on QT interval and the changes in QT are independent of heart rate in normal subjects. Further, the increased QTV index (QTVI), logarithm of the ratio of normalized QT variance to heart rate variance, was found to be independent to HRV by other studies in different cardiac patients (Berger *et al.* 1997, Murabayashi *et al.* 2002).

In conjunction with the previous studies, Almeida *et al.* (2006) proposed a dynamic linear approach, which was originally introduced by Porta *et al.* (1998a), to investigate the interactions between QTV and HRV on simulated and real (healthy subjects) ECG. Through this study, they found that a relevant QTV fraction is not correlated with HRV. In addition, they concluded that an important part of QTV is not linearly driven by HRV and may hold complementary clinical information. However, a study by Hnatkova *et al.* (2013) suggests that the relationship between beat-to-beat QTV and HRV depends on postural positions, where the HRV decreased during supine to sitting and sitting to standing postural positions. On the other hand, QTV increased with these postural positions. Therefore, they suggested that with beat-to-beat QTV we should not assume universal coupling to HRV, rather it has a more complex relation than initially anticipated (Hnatkova *et al.* 2013).

2.3 QT interval measurement algorithm

Accurate QT interval measurement is challenging particularly if the patient possesses a cardiac condition such as atrial fibrillation, ventricular tachycardia or ventricular fibrillation. In recent years, QT interval measurement methods require electronically stored ECG data, where computer-processed digital-signal analysis can be employed. In most ECG leads, the onset of the QRS complex is easily identified, but the detection of the T-wave offset may be less reliable especially in the presence of low amplitude T-waves, bifid T-waves, U-waves, partial superposition of the T and U-waves and noise sources. Several QT interval measurement techniques and approaches have been proposed to analyse the ECG signal. We have mainly categorized (see Table 2.1) the QT interval measurement algorithm based on static QT measurement (i.e. not a beat-to-beat basis of the whole recording of ECGs) and dynamic QT measurement (i.e. as a beat-to-beat basis of the whole recording of ECGs). Nowadays, it is practical to use the computer processed ECG data and methods for the quantification of QT interval in a beat-to-beat manner rather than by paper based manual QT measurement.

However, there is still the debate of finding a gold standard method for the measurement of the QT interval, which is clinically accepted. The main problem of manual QT measurement lies in cost, time and accuracy that can be compensated to some degree by modern computer-processed QT measurement software as an example (Berger *et al.* 1997, Starc and Schlegel 2006). Whilst modern computer-processed QT measurement

software allows rapid measurement of a very large number of QT intervals, the best algorithms may be inaccurate in finding the QT interval offset (Hnatkova *et al.* 2006).

Table 2.1: QT interval measurement techniques

Static/ Dynamic	**Article**	**Population**	***Advantage/ Disadvantage**	**Remarks**
Static	(Lepeschkin and Surawicz 1952)	not known	Manual	A paper based QT measurement was applied. Several difficulties of QT measurement were discussed.
	(Puddu *et al.* 1982)	$n = 170$	Semi-automated	QT was measured from three non-consecutive QRS-T complexes. A computer-assisted program was used for QT measurement.
	(Campbell *et al.* 1985)	$n = 101$	Manual	Not all lead QT was measurable in this study. QT was measured on digitised ECG data, which was stored and processed in computer.
	(Cowan *et al.* 1988)	$n = 63$	Manual	QT was measured on 3 consecutive QRS complexes. QT was measured in all leads using a digitizer (Calcomp 9000, resolution 1 ms at paper speed 50 mm/s).

Continued on Next Page...

Table 2.1 – Continued

Static/ Dynamic	Article	Population	*Advantage/ Disadvantage	Remarks
	(Pye *et al.* 1994)	$n = 109$	Manual	QT was measured on 3 consecutive QRS complexes each 12 lead ECG. Measurement was manually calculated by using callipers on paper.
	(Moreno *et al.* 1994)	$n = 370$	Manual	QT was measured on three QRS complexes for each 12 lead ECG using a commercially available computer program interfaced with a Calcomp 9000 digitizer.
	(Kautzner *et al.* 1994)	$n = 28$	Manual	QT was measured using a digitizing board with a 0.1-mm resolution for each 12-lead ECG.
	(Kautzner *et al.* 1996)	$n = 30$	Manual	QT was measured on two consecutive cycles of heart rhythm in each 12-lead ECG using a digitized board with resolution of 0.1 mm.
	(Davey 1999b)	$n = 56$	Manual	QT was measured using a magnifying graticule.

Continued on Next Page...

Table 2.1 – Continued

Static/ Dynamic	Article	Population	*Advantage/ Disadvantage	Remarks
	(Christov and Simova 2006)	$n = 522$	Automatic	The main limitation of this QT measurement technique is based on only lead II of ECG data and currently not known whether the performance will be higher in other leads measurement.
Dynamic	(Berger *et al.* 1997)	$n = 143$	Semi-automated	T-wave template method based on stretched or compressed technique. Operator involvement approach.
	(Mitchell *et al.* 1998)	$n = 6$	Manual	Animal model of QT measurement. QT was measured manually by selecting onset of QRS and offset of T-wave.
	(Savelieva *et al.* 1998)	$n = 124$	Semi-automated and Manual	Agreement and reproducibility of automatic and manual measurement of QT interval was measured.

Continued on Next Page...

Table 2.1 – Continued

Static/ Dynamic	Article	Population	*Advantage/ Disadvantage	Remarks
	(Malik *et al.* 2002)	$n = 50$	Semi-automated	Median beat from each lead of ECG was used to measure QT interval. The end of T-wave was computed by using downslope tangent method.
	(Charbit *et al.* 2006)	$n = 108$	Semi-automated and Manual	Averaged over 3-7 consecutive beats. Manual QT interval measurement was done by a digitizing pad.
	(Starc and Schlegel 2006)	$n = 19$	Automatic	QT was measured by beat-to-beat basis in real-time environment for multichannel system.

*Note: **Manual** refers to either paper based measurement or manually computed on a digital signal. **Semi-automated** refers the computer-processed automatic but operator dependent QT measurement. **Automatic** refers to fully automatic computer-processed without operator involvement in QT measurement.

2.4 Factors affecting QT interval and QT interval variability

Over several decades, it has become a point of interest in ECG signal analysis to investigate the factors, which might implicitly or explicitly affect the quantification of QTV. There are several challenges in the quantification of the QT interval especially concerning T-waves and different morphological patterns of the T-wave and T-U complex. In addition to that, there are some other issues, which are significant such as spontaneous variability in the QT interval, leading in spurious measure of QT prolongation and QTV. Indeed, it is accepted that the QT interval is measured between onset of the QRS

complex and offset of the T-wave. However, there are a number of factors that have the capability of affecting QT interval measurement and QTV. Mainly, the variability in QT interval measurement results from two broad factors (i) technical factors and (ii) biological factors. The technical factors include the acquisition of the ECG recording, the processing of the recording, and methodological constraints. Apart from this, recording the ECG signal from different electrocardiographic leads may result in different QT intervals, which can affect the QT interval assessment (Kautzner and Malik 1997). This is due to the electrical activity of different regions of the heart that may produce a differently weighted ECG signal. Moreover, inter-lead variability also affects the QTV measurement and analysis (Hasan *et al.* 2012c). On the other hand, the biological factors may also influence the QT interval assessment such as diurnal effects, differences in autonomic tone, electrolytes, and drugs. The summary of the technical and biological factors affecting QT and QT interval variability is shown in Table 2.2.

Table 2.2: Summary of technical and biological factors affecting QT

Technical (T)/Biological (B) Factors	**Effect of QT and QTV**	**Article**
Techniques of QT recording and Measurement (T)	• Mostly QT variability is due to the variety of applied methods and techniques. • No method is considered as the gold standard method for the quantification of QT with 100% precision.	(Berger *et al.* 1997, Porta *et al.* 1998b, Starc and Schlegel 2006, Baumert *et al.* 2012, Hasan *et al.* 2013b)
Position (T)	• Some studies reported that postural position might be a factor for unstable QT interval and QTV.	(Davey 1999a, Ariagno *et al.* 2003, Lewis *et al.* 2006)

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Table 2.2 – Continued

Technical (T)/Biological (B) Factors	**Effect of QT and QTV**	**Article**
Gender (B)	• Some studies showed QTV is not independent of gender. • Several research groups reported that QTV is higher in women than man in healthy subjects. • QTV was found to be dependent on sex in some study.	(Pearl 1996, Burke *et al.* 1997, Locati *et al.* 1998, Mayuga *et al.* 2001, Hasan *et al.* 2012c)
Age (B)	• Some studies showed age is a factor to be considered for QTV analysis. • Others demonstrated QTV is independent of age.	(Mayuga *et al.* 2001, Mangoni *et al.* 2003, Piccirillo *et al.* 2006, Arai *et al.* 2012, Hasan *et al.* 2012c)
Sleep (B)	• Several studies showed that sleep apnea is associated with the elevated QTV. • In addition, it was found that the QT interval may increase during sleep.	(Browne *et al.* 1983b, Yeragani *et al.* 2002a, Ariagno *et al.* 2003, Baumert *et al.* 2008b)

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Table 2.2 – Continued

Technical (T)/Biological (B) Factors	**Effect of QT and QTV**	**Article**
Drugs (B)	• A number of studies demonstrated that the drugs can affect the normal QT interval and is malignant to ventricular arrhythmia or sudden cardiac death.	(Fermini and Fossa 2003, Morissette *et al.* 2005, Hinterseer *et al.* 2008, Kannankeril *et al.* 2010, Nayyar *et al.* 2013)
Alcoholism and Cocaine abuse (B)	• Studies found that repolarization abnormalities may occurr and affect the QTV.	(Perera *et al.* 1997, Gamouras *et al.* 2000, Malik and Camm 2001, Haddad and Anderson 2002)
Obesity and bodyweight gain (B)	• Higher QT interval was found to correlate with obesity, which may affect QTV.	(El-Gamal *et al.* 1995, Carella *et al.* 1996, Arslan *et al.* 2010)
Hypertension (B)	• Increased QT interval was found and may affect QTV.	(Trevisani *et al.* 2003)
MI and Cardiomypathy (B)	• Increased QTV was observed due to this factor.	(Schwartz and Wolf 1978, Mirvis 1985, Hasan *et al.* 2013a)

Continued on Next Page...

Table 2.2 – Continued

Technical (T)/Biological (B) Factors	**Effect of QT and QTV**	**Article**
Electrolyte disturbances (B)	• Increased QT interval was reported.	(Barr *et al.* 1994, Isbister and Page 2013)
Diabetes mellitus (B)	• Decreased QT interval was observed during circadian time.	(Tanaka *et al.* 2013)
Mental (B)	• Elevated QT interval was found in patients with eating disorders.	(Takimoto *et al.* 2004)
Heart Rate (B)	• An inverse relation was found between heart rate and QT interval duration.	(Ahnve and Vallin 1982)
Lead (B)	• QTV varies in between inter-lead measurements using 12-lead ECG.	(Hasan *et al.* 2012c)

Besides the above factors, some other considerable factors should be considered in QT interval assessment analysis is described below:

Wide QRS

The assessment of QT interval becomes unreliable and the analysis of QTV may be biased if the QRS duration is higher than 120 ms (Al-Khatib *et al.* 2003, Lanjewar *et al.* 2004). Because, wide QRS duration may result in the prolongation of the QT interval and, thereby, it elevates the beat-to-beat QTV. Moreover, the detection of QRS complex, especially the R-peak detection and baseline wander, also affect the QTV some degree (Hasan *et al.* 2013b).

Problem of finding the end of the T-wave

Another important problem for the measurement of QT interval is defining the end of the T-waves (Lepeschkin and Surawicz 1952, Malik and Camm 2001, Postema *et al.* 2008). Because, the end of the T-wave is not always distinctly defined and sometimes it merges gradually with the iso-electric line or baseline of surface ECG. Moreover, the abnormalities of T-wave morphology such as inverted T-waves or biphasic T-waves may make the T-wave end determination difficult. Furthermore, differentiating the T-wave from the U-wave may lead to find the end of the T-wave more difficult (Malik and Camm 2001) that adds variability to the QT interval.

Affect of autonomic nervous system on QTV

The other factor that can modulate the QT interval assessment is the autonomic nervous system that mainly regulates cardiac muscle through sympathetic and parasympathetic stimulation. It has been found that the autonomic nervous system has a direct influence on the ventricular myocardium, which might affect assessment of QT interval independently (Belardinelli and Isenberg 1983, Charpentier and Rosen 1994, Shimizu *et al.* 1994, Zabel *et al.* 2000b, Mine *et al.* 2008, Nayyar *et al.* 2013). Further, autonomic conditions also affect the sinus node and influence the QT interval (Browne *et al.* 1982). Moreover, it was found that the QT shortens during exercise and in response to atropine (Robinson *et al.* 1966). However, it is not possible to determine the relative contributions of changes in the sympathetic and parasympathetic nervous systems to the observed QT shortening during exercise. Because, multiple autonomic changes are occurring simultaneously during exercise (Magnano *et al.* 2002).

2.5 Overview of beat-to-beat QT interval variability in ECG

The measurement of QT interval for a single beat only gives a static picture of the repolarization, which implies a complex interplay between heart rate and the autonomic nervous system varies in duration from site-to-site and from beat-to-beat. In contrast, beat-to-beat analysis of QT interval duration allows the beat-to-beat QT dynamics. Therefore, a brief review of the findings of several study relating to beat-to-beat QT variability is discussed below.

In 1992, Nollo *et al.* (1992) assessed the beat-to-beat ventricular repolarization duration on 21 healthy subjects in a recumbent position. They analysed approximately 1,000 consecutive heart cycles for each subject by using ECG time series parameters such as RR, QT and RT intervals. In addition, they extended the analysis by applying the spectral analysis so that the rhythmical oscillations in these time series can be detected. However, the methodologies have several limitations. First of all, they considered the chest lead (V_5) rather than the widely used leads I, II or III. Note that the lead selection has great impact on the QTV analysis and results (Hasan *et al.* 2012c) and the results can be significantly biased. Their proposed method was based on the morphology of lead V_5 and it was not clear how this methodology can be used if any other lead is selected for analysis. Nollo *et al.* (1992) create a QRS template for finding the accurate fiducial points such as QRS onset, R-wave maximum, and T-wave endpoint—however, the creation of the QRS template is unclear and, in particular, how the ectopic beat is handled during this process is not evident.

Speranza *et al.* (1993) also assessed the feasibility of beat-to-beat measurement of R-T interval in Holter ECG on healthy subjects, where the main ECG parameters were R-Tm and R-Te (T-wave maximum: Tm and T-wave end: Te), respectively. This study was the continuation of the previous study. However, a very low population number was used in this study. In addition, the signal quality (in terms of SNR) was low and used the oversampling technique, which may give rise to higher computational complexity.

Likewise, Merri *et al.* (1993) and his colleagues analysed the beat-to-beat ventricular repolarization duration from 24 hour Holter ECG on healthy subjects. In this study, ventricular repolarization was considered from R-peak of QRS complex to T-wave

maximum duration. They suggested that, in normal individuals, the ventricular repolarization duration is directly influenced by the autonomic nervous system (ANS) and very similar to the heart rate. However, a significant part of the total repolarization was not considered in this study, for example, the ventricular repolarization duration was considered only between R-peak to T-max but not the T-wave end point, where, another study concluded that the duration of T-max to T-end in repolarization is critical and has significant clinical values (Hasan *et al.* 2012a). However, the proposed methods and conclusions are still valid. Another limitation of this study was the small population sample size, however, the duration of 24 hours is well-accepted.

Similarly, Vainer *et al.* (1994) investigated the beat-to-beat behaviour of QT interval on healthy subjects and patients with supraventricular techycardia under different conditions such as at rest, during recovery after short exercise, and during atrial pacing. Mainly, in that study, the beat-to-beat QT variations in ten healthy subjects during sinus rhythm at rest and after short exercise were investigated. In addition, three patients with supraventricular tachycardia were analysed by atrial pacing. This study showed the relatively slow adaption of beat-to-beat QT interval to changes in heart rate. However, the behaviour of beat-to-beat QT interval and RR interval was based on relatively a small group of subjects, where the larger set of subjects may give in depth details and strengthen the statistical results. Further, the proposed methods and results are valid but still require further research to prove the hypothesis on paced ventricular rhythm and hearts under abnormal conditions such as in the presence of heart disease, neurocontrol or different pharmacological conditions.

Couderc *et al.* (1999) proposed a new technique using a wavelet transformation that has a T-wave end point-independent method to quantify the beat-to-beat repolarization variability in 12-lead ECG. The proposed method has predictive capabilities for identification of repolarization variability in long QT syndrome patients (LQTS) with the SCN5A sodium channel gene mutation. In their work, the time-domain repolarization variability parameters (SDRTend and SDRTpeak) and wavelet parameters describing temporal (beat-to-beat) variability of repolarization in time (TVT) and in amplitude (TVA) were analysed. This study showed that SCN5A carriers have significant increased repolarization variability in amplitude and in time compared to the non-carriers of SCN5A. Nevertheless, the quantification of QT interval was not considered

of total repolarization duration that can have an affect on the proposed results. Further, the sampling frequency for recording the signal was also relatively low and may influence the methodology and results if the sampling frequency is increased.

Burattini and Zareba (1999) suggested another computerized time-domain method to measure beat-to-beat variability of repolarization morphology without T-wave endpoint identification. This proposed method was mainly based on the computation of repolarization correlation indices for consecutive beats. The authors proposed the new metric repolarization variability index (RVI), which describes the mean value of repolarization correlation in studied ECG recordings (ischemic cardiomyopathy and healthy subjects) and found that ischemic cardiomyopathy patients had significantly higher values of RVI than healthy subjects. In addition, they found no significant correlation between RVI values and the magnitude of heart, heart rate variability, QTc interval duration or ejection fraction in ischemic cardiomyopathy patients. The main limitation of this proposed method is the random selection of ECG beats rather than considering consecutive beats, which can strengthen the results. However, the advantage of the proposed method is that it is independent of determining the T-wave end points in surface ECG.

Vrtovec *et al.* (2000) proposed slightly modified technique of Berger *et al.* (1997) where the T-wave template was constructed by an averaging technique rather than using a single beat from the measured ECG signal. The proposed technique was applied on healthy subjects and coronary artery patients without prior myocardial infarction. This study showed that the coronary patient has significantly higher values of beat-to-beat QTV compared with the healthy subjects. However, no significant differences were observed between coronary patients and healthy subjects based on HRV.

In 2003, Faber *et al.* (2003) also assessed the beat-to-beat variation of ventricular repolarization in patients with myocardial ischemia, heart failure and healthy subjects. They found no significant differences between the groups of myocardial ischemia and healthy subjects by looking at QT/RR interval ratio. In contrast, significant differences were observed between heart failure patients compared to healthy subjects and myocardial ischemia patients. However, care is needed for the identification of the T-wave end in the long duration of the signal by using the proposed algorithm.

In the following year, in 2004, Jensen *et al.* (2004) investigated the beat-to-beat QT dynamics in healthy subjects and described the normal range, circadian variation, and heart rate dependence of QT dynamics. They showed reasonable reproducibility of

beat-to-beat QT dynamics with respect intra-subject, between subject and between-observer variability. In addition, they found that all the QT parameters showed circadian variation when calculated on an hourly basis. However, further research is required to validate the proposed beat-to-beat QT dynamics for risk stratification study.

In the same year, Desai *et al.* (2004) also studied the beat-to-beat QTV in patients with congestive cardiac failure compared to healthy subjects to observe the effects of controlled breathing and postural challenge. They found significant increase of QTV in standing posture at control breathing in healthy subjects but not in congestive cardiac failure patients. However, in this study, the respiratory signal was not assessed and the patients' breathing capabilities were not compared to subjects, which needs further investigation.

In 2006, Furukawa *et al.* (2006) explored the circadian variation of beat-to-beat QTV in patients with MI and the effect of β-blocker therapy compared to healthy subjects. They observed that QTV was significantly higher in MI patients and was not any more significant when comparing the β-blocker group (MI patients who received β-blocker therapy) to the healthy subjects. This study indicates that the β-blocker may reduce the ventricular arrhythmia and mortality in patients with MI.

Another interesting study was conducted by Kusuki *et al.* (2010). They investigated the age-specific standard values and growth variability curve of QTVI (QT variability index), where the variability of ventricular repolarization was significantly reduced before the age of 12 months old, but became constant until the attainment of school age.

Similarly, Baumert *et al.* (2011c) also investigated the relation between increased cardiac sympathetic activity with increased beat-to-beat QTV in patients with essential hypertension. They showed that the magnitude of QT variability is moderately correlated to cardiac sympathetic activation in hypertensive patients. In addition, they demonstrated that the QTVI and cardiac norepinephrine (NE) spillover were increased in hypertensive patients compared to healthy subjects. However, the number of healthy subjects were very small used in this study, where higher set of healthy subjects might give more insight into the relation between QTV and sympathetic activity of the studied group.

Baumert *et al.* (2013) indicated that the beat-to-beat QTV reduced significantly in elderly subjects compared to young subjects, which was not in agreement with several other studies (Yeragani *et al.* 2000a, Krauss *et al.* 2009, Hasan *et al.* 2012c). In spite of

providing the reason of the divergent results discussed in that study, further elucidation by analyzing the affect of gender and age on the data is desirable.

The following sections will be discussed in regard to the techniques and findings of beat-to-beat repolarization variability based on a VCG approach.

2.6 VCG analysis for repolarization instability

Ventricular repolarization is a complex electrical phenomenon and abnormalities in ventricular repolarization are not completely understood. To evaluate the repolarization lability, vectorcardiogram/vectorcardiography (VCG) is an alternative approach where the electrocardiographic (ECG) signal can be considered as possessing both a magnitude and direction. Recent research has shown the VCG approach is advantageous over analysing the normal ECG signal for repolarization abnormality. One of the key reasons is that the VCG approach does not rely on exact identification of the T-wave offset, which improves the reproducibility of the VCG technique. However, beat-to-beat variability in VCG is quite new for investigating repolarization abnormality and not yet fully realized. Therefore, the rest of this chapter explores the feasibility of beat-to-beat VCG parameters for analysing repolarization lability.

2.6.1 What is VCG?

Vectorcardiography (VCG) measures cardiac electrical forces with both magnitude and vectorial direction; it may be thought of as a methodological elaboration of ECG. These electrical forces are generated by billions of cardiac cells in the heart that can be modelled as a continuous series of vectors that form a resultant. Moreover, VCG aims at an orthogonal representation that reflects the electrical activity of the heart in the three perpendicular directions X, Y, and Z as shown in Fig. 2.4.

2.7 Significance of VCG analysis

Our recent findings suggest that beat-to-beat QTV varies in inter-lead measurement in 12-lead ECG, partly due to T-wave amplitude differences and together with other unknown reasons (Hasan *et al.* 2011, Hasan *et al.* 2012c, Hasan *et al.* 2013a). Therefore,

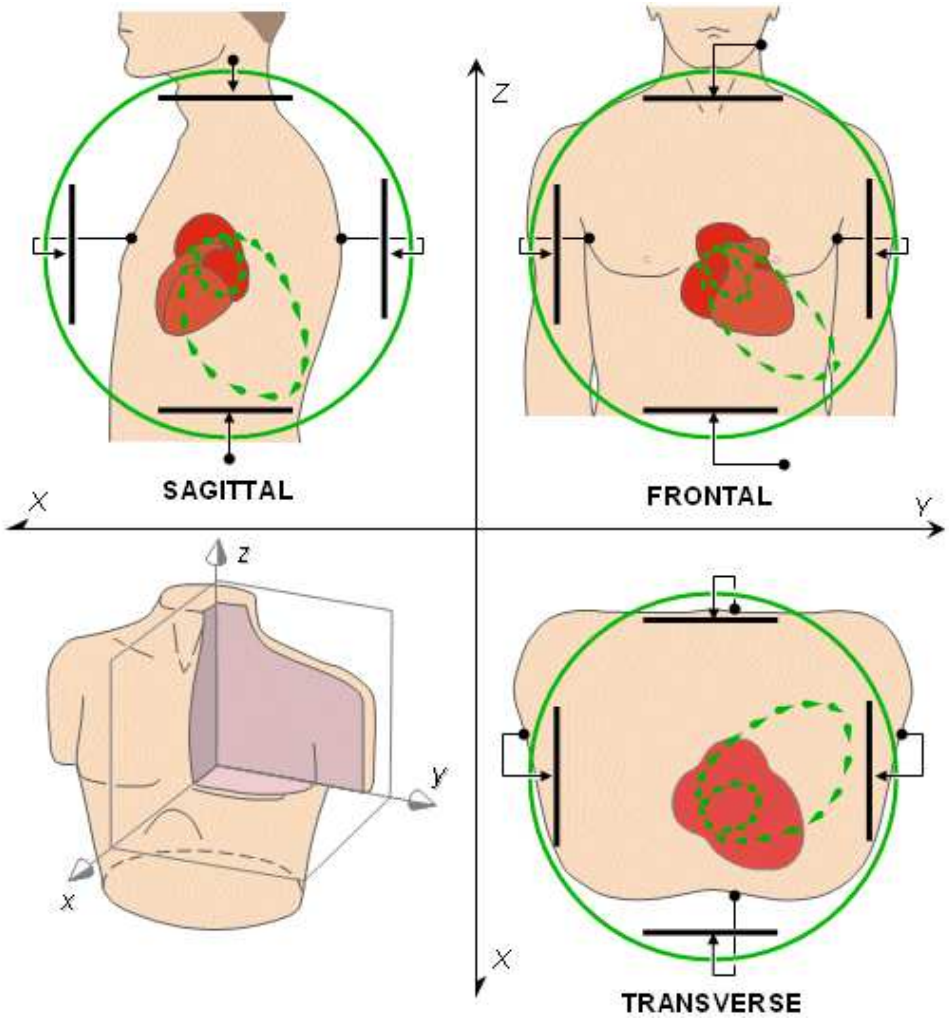

Figure 2.4. The basic principle of vectorcardiography. Top left is sagittal view, top right is frontal view and bottom right is transverse view of the heart. After Malmivuo and Plonsey (1995).

VCG may be useful for the analysis of dynamic changes of repolarization abnormalities. By contrast, the standard 12-lead ECG represents only the one-dimensional scalar value of the heart function, i.e. it represents only the cardiac signal magnitude and not the direction of the cardiac signal or spatial information of heart signal. Improved understanding for analysis and characterization of heart signals by considering both direction and magnitude of the cardiac signals as a three-dimensional phenomenon, may be then possible using techniques based on VCG.

Furthermore, the VCG display system provides an opportunity to analyse the progress of the activation front in a different way, especially its initial and terminal portions (Malmivuo and Plonsey 1995). In addition, using VCG loops, it is easier to observe the direction and magnitude of the heart vector. Additionally, the area of the loops

may have clinical importance, which is not easy to observe from a scalar ECG signal. Therefore, it has been proposed over recent decades by various researchers that VCG has significant utility compared to the standard 12-lead standard ECG (Chou 1986, Strauss *et al.* 2009). As VCG represents the spatial and temporal information of the heart action, it is thought to be a very promising tool for diagnosis of heart diseases (Rautaharju *et al.* 1973, Zabel *et al.* 2000a, Carlson *et al.* 2005, Yang *et al.* 2012) and also can be extended as a marker for biometrics (Abdelraheem *et al.* 2012).

2.7.1 Synthesis of VCG

VCG from Frank (X, Y and Z) lead

Nowadays VCG is not directly recorded from the body for clinical studies. However, previously VCG used to be recorded from the body using a special approach, based on the so-called Frank VCG lead system (Frank 1956). The Frank VCG lead system consists of seven unipolar electrodes. There are five electrodes in the transverse plane; one electrode is on the back of the neck and one on the left foot in Frank VCG lead system as shown in Fig. 2.5. By utilizing the Frank VCG lead system, a three-dimensional representation of electrical heart activity can be found directly by measuring ECG in three different directions (Fig. 2.5).

There are a number of reasons why the Frank VCG lead system is no longer used for clinical practice for obtaining a three-dimensional representation of the heart signal; mainly due to its non-standard lead configuration. In addition, due to the lack of electrode placement near to the heart, signal acquisition with the Frank VCG lead system is less accurate than standard 12-lead ECG. Hence, an important current issue is to derive VCG from standard 12-lead ECG to obtain three-dimensional X, Y and Z lead potentials for improved diagnosis of heart signals.

VCG from 12-lead ECG

Several techniques have been suggested for the derivation of VCG from standard 12-lead ECG (Guillem *et al.* 2008, Man *et al.* 2009, Shvilkin *et al.* 2009, Shvilkin *et al.* 2010). However, all the existing proposed methods are limited and not yet standardized. In the literature, one can find several approaches for estimating VCG from 12-lead standard ECG. One of the techniques is called the Inverse Dower Transform (IDT) suggested by Edenbrandt and Pahlm (1988) see Table 2.3 and equation (2.1), which is the

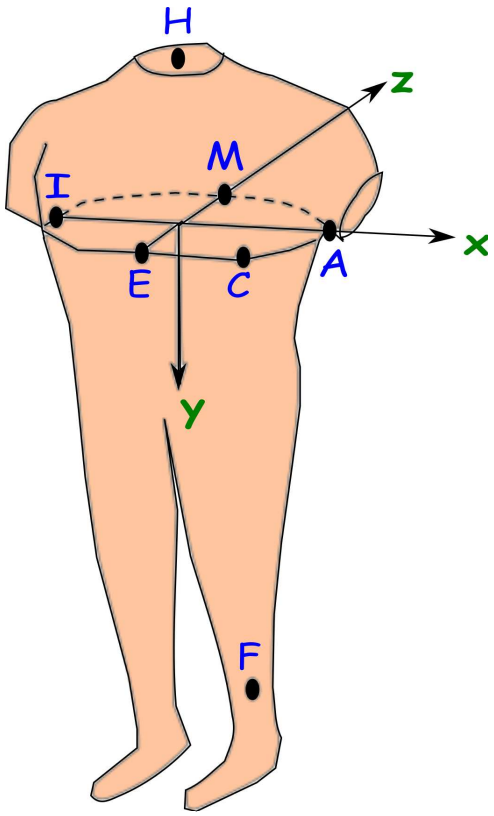

Figure 2.5. Frank VCG lead system. Right-to-left (X-axis), head-to-feet (Y-axis) and front-to-back (Z-axis). Adapted after Frank (1956).

pseudoinverse of the matrix proposed by Dower *et al.* (1980). Further, another technique is proposed by Kors *et al.* (1990) for synthesizing the VCG from standard 12-lead ECG as shown in Table 2.3 and see equation (2.2).

$$\left\{\begin{array}{l} \mathrm{X} = 0.16\,\mathrm{I} - 0.01\,\mathrm{II} - 0.17\,\mathrm{V_1} - 0.07\,\mathrm{V_2} + 0.12\,\mathrm{V_3} + 0.23\,\mathrm{V_4} + 0.24\,\mathrm{V_5} + 0.19\,\mathrm{V_6} \\ \mathrm{Y} = -0.23\,\mathrm{I} + 0.89\,\mathrm{II} + 0.06\,\mathrm{V_1} - 0.02\,\mathrm{V_2} - 0.11\,\mathrm{V_3} - 0.02\,\mathrm{V_4} + 0.04\,\mathrm{V_5} + 0.05\,\mathrm{V_6} \\ \mathrm{Z} = 0.02\,\mathrm{I} + 0.10\,\mathrm{II} - 0.23\,\mathrm{V_1} - 0.31\,\mathrm{V_2} - 0.25\,\mathrm{V_3} - 0.06\,\mathrm{V_4} + 0.06\,\mathrm{V_5} + 0.11\,\mathrm{V_6} \end{array}\right\} \tag{2.1}$$

$$\left\{\begin{array}{l} \mathrm{X} = 0.38\,\mathrm{I} - 0.07\,\mathrm{II} - 0.13\,\mathrm{V_1} + 0.05\,\mathrm{V_2} - 0.01\,\mathrm{V_3} + 0.14\,\mathrm{V_4} + 0.06\,\mathrm{V_5} + 0.54\,\mathrm{V_6} \\ \mathrm{Y} = -0.07\,\mathrm{I} + 0.93\,\mathrm{II} + 0.06\,\mathrm{V_1} - 0.02\,\mathrm{V_2} - 0.05\,\mathrm{V_3} - 0.06\,\mathrm{V_4} - 0.17\,\mathrm{V_5} + 0.13\,\mathrm{V_6} \\ \mathrm{Z} = 0.11\,\mathrm{I} - 0.23\,\mathrm{II} - 0.43\,\mathrm{V_1} - 0.06\,\mathrm{V_2} - 0.14\,\mathrm{V_3} - 0.20\,\mathrm{V_4} - 0.11\,\mathrm{V_5} + 0.31\,\mathrm{V_6} \end{array}\right\} \tag{2.2}$$

These simple estimated transformation matrices are most commonly used to synthesis the VCG from 12-lead ECG. However, a number of studies have investigated the

Table 2.3. Coefficients of the inverse Dower and Kors ECG-to-VCG synthesis matrices

	Inverse Dower Transform				Kors Matrix		
	X	**Y**	**Z**		**X**	**Y**	**Z**
I	0.16	-0.23	0.02	I	0.38	-0.07	0.11
II	-0.01	0.89	0.10	II	-0.07	0.93	-0.23
V_1	-0.17	0.06	-0.23	V_1	-0.13	0.06	-0.43
V_2	-0.07	-0.02	-0.31	V_2	0.05	-0.02	-0.06
V_3	0.12	-0.11	-0.25	V_3	-0.01	-0.05	-0.14
V_4	0.23	-0.02	-0.06	V_4	0.14	-0.06	-0.20
V_5	0.24	0.04	0.06	V_5	0.06	-0.17	-0.11
V_6	0.19	0.05	0.11	V_6	0.54	0.13	0.31

reliability of these estimated matrices, where the findings showed that this type of transformation has a number of limitations in achieving orthogonal VCG reconstruction (Guillem *et al.* 2008, Guillem *et al.* 2009, Man *et al.* 2009). The main problem of the proposed transform matrices is due to estimation during reconstruction that gives rise to potential information loss or even unwanted information. Furthermore, the derived orthogonal leads from 12-lead ECG by using these matrices may differ from those obtained from the actual VCG leads.

However, an alternative technique using singular value decomposition (SVD) was suggested by Acar and Koymen (1999) for computing the VCG from 12-lead standard ECG for a single ECG beat. Here, the SVD is applied to the eight independent leads ($I, II, V_1, V_2, V_3, V_4, V_5, V_6$) of the standard 12-lead ECG to obtain the eight decomposed signals. The first three decomposed signals are considered as ECG dipole (see Fig. 2.6) and 99% of the ECG energy can be represented in a three-dimensional minimum subspace (Acar *et al.* 1999b), which are comparable to the X, Y and Z leads of the Frank VCG. However, the method of Acar *et al.* (1999b) does not perform the analysis on a beat-by-beat basis, but is limited to single beat ECG. This is an issue because cardiac electrical activity is not regular or stationary. Therefore, to address this problem, a very recent article published by Hasan *et al.* (2012a) considered beat-to-beat VCG analysis.

Moreover, in the reconstructed VCG, the signals are resolved into three components (X, Y and Z) and from these three orthogonal directions, it is possible to construct ventricular depolarization (QRS-wave) and repolarization (T-wave) loop (see Fig. 2.6) for various parameter extractions. These parameters and indices may be essential factors

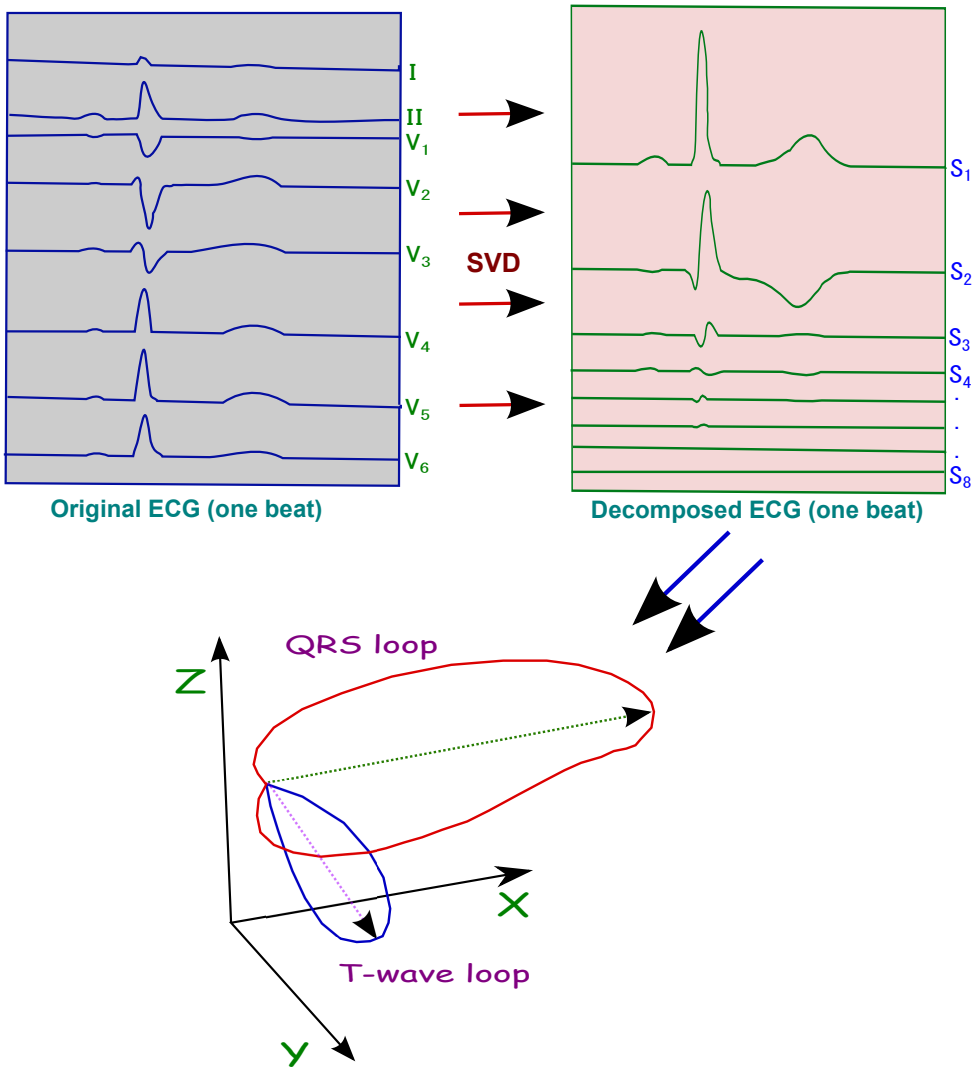

Figure 2.6. Reconstruction of VCG. Eight independent leads as input (top-left) and eight decomposed ECG signal (top-right) for a single beat ECG. The QRS and T-wave loop for a single beat ECG (bottom). The SVD (singular value decomposition) technique was applied on eight independent ECG leads $(\mathrm{I}, \mathrm{II}, \mathrm{V}_1, \mathrm{V}_2, \mathrm{V}_3, \mathrm{V}_4, \mathrm{V}_5, \mathrm{V}_6)$ and then first three decomposed signal $(\mathrm{S}_1, \mathrm{S}_2, \mathrm{S}_3)$ were used for creating the three-dimensional QRS and T-loop.

for characterizing the temporal and spatial changes in the QRS-loop and T-loop in ventricular depolarization and repolarization. The three-dimensional QRS and T vector loop is shown in Fig. 2.6, where arrows consider the main vectors of these loops.

2.8 VCG-based parameters

Several VCG-based parameters and descriptors were proposed in last few decades for identifying and characterizing various cardiac patients (Acar *et al.* 1999a, Zabel *et al.* 2000a, Zabel *et al.* 2002, Lin *et al.* 2007, Porthan *et al.* 2009, Kenttä *et al.* 2010, Hasan *et al.* 2012a). A brief description of VCG-based parameters is given below.

TCRT (Total Cosine R to T)

The TCRT measures the vector deviation between the depolarization and repolarization waves by calculating cosine values between the dominant QRS-loop vectors and the main T-wave loop vectors within the optimized decomposition space. Note that TCRT values are limited to the range of -1 to +1. Minus one corresponds to an angle of 180 degrees indicating that the QRS and T-wave loops are pointing in opposite directions. By contrast, the plus one corresponds to an angle of zero degrees, indicating that the QRS and T-wave loops are pointing at the same direction.

TMD (T-wave Morphology Dispersion)

The TMD represents the variation of morphology of T-wave between different ECG leads during complete ventricular repolarization. It is computed as the average of angles between all possible pairs of the reconstruction vector. A small TMD value implies the reconstruction vectors of different ECG leads are close to each other or T-wave morphologies in different ECG leads are similar.

PL (Percentage of Loop Area)

The PL represents the percentage of loop area. Generally, it is computed as the ratio of the T-wave loop area to the area of the surrounding rectangle. This parameter defines the irregularity of the T-wave loop. For large PL, the T-wave loop is considered to be smooth and connected, but the lower value of PL is due to the more irregular T-wave loop.

Lead Dispersion (LD)

The LD measures the temporal variation of inter-lead relationship during the ventricular repolarization. This is the measurement of the temporal homogeneity of the propagation of the repolarisation wave. If the value of the LD is significantly different between two groups of subjects, then it can be said that the T-wave loops are discriminative.

Azimuth and Elevation

Generally, the spatial orientation of the maximum T-wave vector is defined by its azimuth and elevation . Usually, the azimuth is considered as the angle in the transverse plane. The value of azimuth depicts the following way; 0° indicates left, $+90^\circ$ indicates front, -90° indicates back, and 180° indicates right. In addition, elevation of T-wave is defined from 0° (caudal direction) to 180° (cranial direction) basing the elevation of the T-wave on the angle in the cranio-caudal direction.

Complexity ratio (CR)

The index complexity ratio (CR) reflects the complexity of repolarization. The principal component analysis provides the identification of a set of eight values, which represents the relative magnitude of spatial components of repolarization. The relative contribution of these components can be used to estimate the complexity of repolarization. This index may provide correct identification of patients with abnormal repolarization

T-wave alternans (TWA)

The TWA index is defined as a periodic beat-to-beat variation in the morphology of T-waves in ECG signal, which is considered as a marker for identifying patients with increased risk for sudden cardiac death. Mainly, it represents the alternation of amplitude and vector of T-wave in an every other ECG beat. If the TWA value shows positive in patients than it is considered that patients have higher risk of sudden cardiac death. On the other hand, if it is negative then the risk of sudden cardiac death is lower.

Late potential (LP)

Late potentials (LP) are believed to be caused by early depolarizations of cells in the right ventricle. It is defined by a signal-averaged electrocardiography technique where the multiple electric signals from the heart are averaged to remove interference and to obtained small variations in the QRS complex. This index is useful in risk stratification of various clinical conditions.

In this thesis, a brief description of VCG-based parameters is discussed in the following sections based on single beat and beat-to-beat basis.

Single beat VCG parameters

Arrhythmogenesis was investigated using several VCG descriptors by Acar *et al.* (1999b). A summary of the VCG parameters employed in single beat analysis is given in Table 2.4.

Table 2.4: Analysis of single beat VCG parameters and their findings

Study	**VCG parameters**	**Groups**	**Main findings**
(Acar *et al.* 1999a)	1. TCRT 2. TMD 3. LD 4. PL	Supine resting healthy subjects ($n = 76$) HCM (hypertrophic cardiomyopathy ($n = 63$)	All the proposed VCG descriptors were able to show the prognostic capabilities between healthy subjects and patients with HCM.

Continued on Next Page...

Table 2.4 – Continued

Study	VCG parameters	Groups	Main findings
(Zabel *et al.* 2000a)	1. TCRT 2. TMD 3. Complexity ratio (CR) 4. Normalized T-wave loop area (NTLA)	Consecutive post-MI patients ($n = 280$) Men ($n = 229$) Women ($n = 51$)	TCRT value was significantly lower in the patient group with events ($p < 0.0002$) and in patients with arrhythmic events ($p < 0.004$). However, no significant TMD differences were found in studied groups. CR showed significant differences in all patient groups but was not significant in patients with and without arrhythmic events. Finally, NTLA value was significantly differences in the patient group with events ($p < 0.05$).
(Gang *et al.* 2001)	1. TCRT 2. TMD 3. Normalized T-wave loop area (NTLA)	(HC) Hypertrophic Cardiomypathy ($n = 54$) (HS) Healthy subjects ($n = 70$)	Significantly lower TCRT was found in HC compared to HS ($p < 0.01$) in supine position. However, was opposite scenario in TMD and NTLA values.
(Zabel *et al.* 2002)	1. TCRT 2. TMD 3. Complexity ratio (CR) 4. Normalized T-wave loop area (NTLA)	Male US veterans ($n = 772$) Dead ($n = 252$) Alive ($n = 520$)	Significant lower TCRT value was found in increased risk of death ($p < 0.02$). However, significant higher TMD and CR values found in increased risk of death ($p < 0.02$). Finally, no significant repolarization heterogeneity was found in patients who had events (death) during long-term follow-up.

Continued on Next Page...

Table 2.4 – Continued

Study	VCG parameters	Groups	Main findings
(Zabel and Malik 2002)	1. TCRT	Post-MI patients ($n = 280$) with 27 events (death or non-fatal sustained ventricular tachycardia/ventricular fibrillation)	TCRT value was univariately associated ($p = 0.0002$) with the events.
(Batchvarov *et al.* 2004)	1. TCRT	MI patients ($n = 334$)	Reduced TCRT value was observed in cardiac and arrhythmic death in patients post MI, which reflects increased repolarization heterogeneity.
(Critchley *et al.* 2005)	1. TCRT	Male ($n = 8$) Female ($n = 2$)	The effortful mental arithmetic and isometric handgrip exercise tasks appeared to be inhomogeneous of TCRT values compared to the effortless control condition.
(Lin *et al.* 2007)	1. TCRT 2. TMD 3. Normalized T-wave loop area (NTLA) 4. LD	End-stage renal disease (ESRD) patients, Survivors ($n = 171$) All-cause death ($n = 154$)	No significant TCRT and TMD differences were found between survivors and all-cause death patients. Further, same scenario occurred between cardiovascular mortality and non-cardiovascular mortality. However, NTLA value was significant and was not independent predictor between survivors and all-cause death patients. On the other hand, LD value demonstrated the independent predictor of repolarization heterogeneity between survivors and all-cause mortality.

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Table 2.4 – Continued

Study	VCG parameters	Groups	Main findings
(Friedman 2007)	1. TCRT	Near-consecutive cohort of patients, Healthy subjects ($n = 33$) Patients ($n = 121$)	TCRT value may distinguish a primary from secondary T-wave abnormalities.
(Koivikko *et al.* 2008)	1. TCRT	Type 1 diabetic patients ($n = 16$) Healthy subjects ($n = 8$)	TCRT values were significantly lower in the diabetic patients compared to healthy subjects ($p < 0.05$).
(Karsikas *et al.* 2008)	1. TCRT	Acute MI patients ($n = 45$) Healthy subjects ($n = 25$)	Computation of TCRT was failure in several AMI patients. However, small improvements of the basic TCRT algorithm may decrease the failures up to 82%.
(Lin *et al.* 2009)	1. TCRT 2. TMD 3. Normalized T-wave loop area (NTLA) 4. LD	Heart failure patients, with VT/VF ($n = 27$) without VT as control ($n = 54$)	TCRT, TMD and NTLA were not significant difference between these studied groups ($p > 0.05$). However, significantly, higher LD was found in patients with VT/VF compared without VT.
(Huang *et al.* 2009)	1. TCRT 2. TMD 3. PL 4. LD	Patients with systolic heart failure ($n = 650$)	No significant TCRT differences were reported between all-cause mortality and survival groups ($p = 0.07$). However, opposite scenario was found between cardiovascular and non-cardiovascular death. In addition, no significant differences of TMD, PL and LD were observed between all-cause mortality and survival groups ($p > 0.05$) as well as between cardiovascular and non-cardiovascular death ($p > 0.05$).

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Table 2.4 – Continued

Study	VCG parameters	Groups	Main findings
(Kania *et al.* 2009)	1. TCRT	Patients after MI, With VT ($n = 30$) Without VT ($n = 13$)	Significant differences of TCRT values were observed between group of patients with VT and group of patients without VT.
(Porthan *et al.* 2009)	1. TCRT 2. TMD	Total adults ($n = 5917$) Man ($n = 2674$) Women ($n = 3243$)	TCRT value was not statistically significant different in men (all-cause and cardiovascular mortality). However, was significant difference in women (all-cause and cardiovascular mortality). Similarly, women showed higher value of TMD than men did in all-cause and cardiovascular mortality.
(Scherptong *et al.* 2008)	1. Spatial QRS-T angle 2. Azimuth and Elevation	Population ($n = 660$)	Spatial QRS-T depends strongly on sex. In addition, it was found that the direction of azimuth was anterior in males than in females. Further, the elevation appeared to be significant differences between male and female.
(Rubulis *et al.* 2010)	1. Azimuth and Elevation	Patients with stable CAD ($n = 35$) Healthy subjects ($n = 10$)	Azimuth was found to be significant leftward compared with left circumflex artery patients and elevation was more downward compared with both the right coronary artery and right coronary artery patients.
(Dilaveris *et al.* 2011)	1. Spatial QRS-T angle	Healthy school-age children, male ($n = 348$) female ($n = 298$)	Significant higher spatial QRS-T angle was found in boys compared to girls ($p = 0.031$).

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Table 2.4 – Continued

Study	VCG parameters	Groups	Main findings
(Vahedi *et al.* 2011)	1. Azimuth and Elevation	Patients with structurally normal hearts ($n = 19$)	Significant increased elevation and increased Azimuth was observed with increased HR, which indicates that the T-wave vector appeared to move slightly upward and forward.

Beat-to-beat VCG parameters

Recently, a few studies have investigated beat-to-beat VCG descriptors in different cardiac populations and tested their independent predictive power for classifying patients (Tereshchenko *et al.* 2010, Hasan *et al.* 2012a, Sur *et al.* 2013). A brief description of relevant beat-to-beat VCG parameters and their relationship to the findings in a number of studies is summarized in Table 2.5.

Ikeda *et al.* (2000) investigated the combined assessment of T-wave Alternans (TWA) and Late Potentials (LP) for predicting the arrhythmic events after myocardial infarction by using orthogonal Frank leads on a beat-to-beat basis. Mainly, the TWA was analyzed using a power spectral technique during supine bicycle exercise testing. However, in this case, the testing was limited and validation by consider further data sets, such as for congestive heart failure, is required.

Another interesting study was carried out by Karsikas *et al.* (2009), where beat-to-beat variability of QRS-T angle was observed during an incremental exercise test. This study reported that the TCRT trend during exercise was negative and became more negative in healthy subjects compared to the patients with coronary artery disease (CAD). However, theoretically, TCRT ought to be towards a positive value in healthy subjects compared to the CAD patient due to the homogeneity of repolarization lability in healthy subjects, which was investigated by several studies for a single beat ECG analysis (Acar *et al.* 1999a). The greater trend of TCRT toward a negative value might be found in healthy subjects due to a consequence of the experimental setup. Nevertheless, the study of Karsikas *et al.* (2009) highlights that further research is required for beat-to-beat analysis for QRS-T angle measurements, to assess the reliability of this parameter.

Two further different studies have found that the beat-to-beat 3D ECG variability predicts ventricular arrhythmia (VA) in patients with structural disease and implanted ICD (Implantable Cardioverter Defibrillator) by using the same VCG parameters (Han and Tereshchenko 2010, Tereshchenko *et al.* 2010). They suggested that large T-peaks cloud volume (this cloud volume was computed as the volume within the convex hull) is associated with the increased risk of VA. However, this study was limited to a 30 consecutive beat analysis. The VCG analysis of a higher number of beats may increase the validity of the outcome significantly. In the same year, in 2010, Kenttä *et al.* (2010) studied the beat-to-beat rate-dependency and gender affect on spatial angle (TCRT or QRS-T angle) between QRS-T loop during exercise ECG. They suggested that the beat-to-beat individual patterns of TCRT and QRS/T angle are influenced by heart rate and gender. However, further study is required for ultimate validation before considering clinical implementation. Another study by Kenttä *et al.* (2011) suggests that spatial angles (TCRT and QRS-T angles) might be strong predictors of sudden cardiac death for risk stratification where a large database was used for analysis.

Correa *et al.* (2010) introduced six different VCG parameters to investigate the morphological changes in the QRS-loop for ischemic patients that underwent Percutaneous Transluminal Coronary Angioplasty (PTCA). They showed that the VCG parameters were significantly different before, during and after PTCA. However, they considered only the QRS loop VCG parameters for ischemic patients and the morphological changes in repolarization loop descriptors. Therefore, it might be interesting if the analysis can be extended by considering the T-wave loop as well.

Hasan *et al.* (2012a) proposed two new descriptors along with some existing depolarization and repolarization indices for beat-to-beat VCG analysis. Point-to-point distance variability (DV) is one of them, which was determined based on the coefficient of variance of point-to-point distance from each loop to the mean loop of QRS and T-wave loop. In addition, another new descriptor was mean loop length (MLL), which was calculated for the mean loop of QRS and T-loop by adding the distance from each point to the next point in the loop. Significantly higher DV of QRS and T-loop was found in MI patients compared to healthy subjects (Hasan *et al.* 2012a). However, the beat-to-beat TCRT value was not significant for identifying the MI patients in this study, which brings to attention the need for requiring further research before using these parameters for analysing repolarization heterogeneity and cardiac risk stratification study.

Recent research in 2013, Sur *et al.* (2013) suggested several VCG parameters for the analysis of ventricular depolarization and repolarization in healthy subjects based on gender. In this work, they suggested that the repolarization lability is gender dependant with mostly men having a higher repolarization lability than women. The details of the VCG parameters list are given in the Table 2.5 and their findings.

Table 2.5: Analysis of beat-to-beat VCG parameters and their findings

Study	**VCG parameters**	**Groups**	**Main findings**
(Ikeda *et al.* 2000)	1. T-wave alternans (TWA) 2. Late Potential (LP)	AMI ($n = 119$)	The TWA and LP VCG parameters were found to be a positive predictive value for an arrhythmic event after acute MI.
(Karsikas *et al.* 2009)	1. TCRT 2. Cos (QRST-angle) 3. Cos (Plane Angle)	(CAD) Coronary artery disease ($n = 10$) Healthy subjects ($n = 10$)	The trend of TCRT during exercise showed negative and it was more negative in healthy subjects compared to CAD patients.
(Tereshchenko *et al.* 2010)	1. R-peaks cloud volume 2. T-peaks cloud volume 3. T-peaks/R-peaks cloud volume	Structural heart diseases ($n = 414$)	Higher volume of T-peaks cloud seemed to be associated with higher risk of ventricular tachyarrhythmia.
(Han and Tereshchenko 2010)	1. R-peaks cloud volume 2. T-peaks cloud volume 3. T-peaks/R-peaks cloud volume	Patients with structural heart disease and ICD ($n = 81$)	Higher volume of T-peaks cloud appeared to be associated with higher risk of sustained ventricular tachyarrhythmias.

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Table 2.5 – Continued

Study	VCG parameters	Groups	Main findings
(Potter *et al.* 2010)	1. Spatial QRS-T angle 2. T-wave PCA	(HCM) Hypertrophic Cardiomyopathy ($n = 56$) Healthy subjects ($n = 56$) Athlets (n=69)	The suggested VCG parameters were found to be useful for detecting the HCM patients.
(Kenttä *et al.* 2010)	1. TCRT 2. QRS-T angle 3. TCRT/RR 4. QRS/RR	Exercise ECG recordings ($n = 1297$) Men ($n = 872$) Women ($n = 425$)	Beat-to-beat VCG descriptors from exercise ECG (TCRT-RR and QRST-RR) were found to be associated with mortality, especially with cardiac mortality and sudden cardiac death.
(Kenttä *et al.* 2011)	1. TCRT/RR 2. QRST/RR	Healthy subjects during Exercise ($n = 40$) Men ($n = 20$) Women ($n = 20$)	The suggested VCG parameters were found to be affected by HR and gender. Further, hysteresis was found in the TCRT/RR slopes for delayed rate adaptation.
(Correa *et al.* 2010)	1. Maximum Magnitude of the Depolarization Vector of QRS loop 2. Volume of QRS loop 3. Planar Area of QRS loop 4. Ratio between the Area and Perimeter of QRS loop 5. Ratio between the Major and Minor Axes of QRS loop 6. QRS Loop Energy	Ischemic patients ($n = 80$) that underwent Percutaneous Translumi-nal Coronary Angioplasty (PTCA)	The proposed VCG parameters explained more about the morphological changes of QRS loop and reflects the modifications in the levels of cardiac ischemic before, during and after PTCA

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Table 2.5 – Continued

Study	VCG parameters	Groups	Main findings
(Hasan *et al.* 2012a)	1. DV_{QRS} 2. DV_T 3. MLL_{QRS} 4. MLL_T 5. TMD 6. TMP_{pre} 7. TMD_{post} 8. PL 9. TCRT	MI patients ($n = 84$) Healthy subjects ($n = 69$)	Most of the VCG parameters showed independent prognostic capabilities for diagnostic the MI patients. However, TCRT did not seem to be capable for characterising the MI patients than healthy subjects.
(Sur *et al.* 2013)	1. Mean spatial TT angle 2. Normalized variances of T-loop area 3. Spatial T vector amplitude 4. $T_{peak} - T_{end}$ area	Healthy subjects ($n = 160$) Men ($n = 80$) Women($n = 80$)	Healthy men showed higher repolarization lability of several VCG descriptors than healthy women, where caution should be paid for gender-specific risk stratification study.

2.9 Factors affecting VCG

The affect of factors that influence the VCG parameters are perhaps lower than the standard ECG parameters. However, several factors need to be considered for the analysis of VCG parameters in clinical studies. For example, respiratory excursions slightly alter the position of the heart and, hence, also the electrical heart axis and the affected VCG. Brief descriptions of the factors that may affect the VCG descriptors are given below.

Rate Dependency

Several studies investigated the relation between heart rate (HR) and VCG parameters (Vahedi *et al.* 2011). Some of the studies were able to show the rate dependency of VCG parameters. Scherptong *et al.* (2008) investigated the VCG parameters (QRS-T angle and spatial ventricular gradient) on young healthy subjects. They found that

there was a significant influence of HR on the spatial ventricular gradient magnitude (ventricular gradient is a vector with magnitude, azimuth and elevation which derived from the QRS and T-wave vectors) where, the relation of HR and spatial ventricular gradient magnitude appeared to be inverted. The increased HR is associated with decreased spatial ventricular gradient magnitude.

Kenttä *et al.* (2010) investigated the affect of HR on spatial VCG parameters during exercise ECG for healthy subjects and concluded that the HR has significant influence on VCG parameters (TCRT and QRS-T angle). Particularly, HR affects the TCRT during exercise and recovery period. Vahedi *et al.* (2011) also found that some computed VCG parameters were rate dependent, where decrease heterogeneity of ventricular instants was observed for increasing HR.

Respiration

Respiration is one of the most important factors that may affect VCG loops/parameters. In 1998 and 2000, the articles published by Sornmo (1998) and Astrom *et al.* (2000) developed the method for reducing the affect of respiration and muscular activity on VCG loops in a beat-to-beat manner. Mainly, they reduced the respiration influence by performing spatial and temporal maximum-likelihood (ML) alignment of VCG loops and this alignment was based on scaling, rotation and time synchronization of the loops. Moreover, the affect of respiration on VCG loops has been validated further and the respiration frequency was estimated in the article proposed by Leanderson *et al.* (2003). In 2006, Bailon *et al.* (2006) also estimated the respiratory frequency from VCG during the stress testing, which has demonstrated the influence of respiration and existence in the VCG, loops. Recently, in 2009, Karsikas *et al.* (2009) suggested that the respiration significantly affects the beat-to-beat variability of all the QRS-T-angle measures. Furthermore, caution should be taken exercised when considering the reliability of VCG angle measures for one-beat analyses as opposed to a beat-to-beat basis.

Nevertheless, this proposed ML VCG loop alignment technique was limited (Sornmo 1998, Astrom *et al.* 2000). For example, the proposed technique reduces the ability to include *a priori* information in any of the transformations. Further, for low-quality signals, such as fetal ECG signal, the reliability of this method is reduced. To address this situation, in 2013, Vullings *et al.* (2013) introduced the generic Bayesian framework to derive the beat-to-beat VCG loop alignment, where the existing ML method can be derived.

Gender

The problem of gender influence on VCG parameters is not fully understood yet. However, several studies have attempted to explore the relation between gender and VCG parameters. In 1968, a study was carried on 101 healthy male and 102 healthy female subjects for analysing VCG dependency on gender (Sotobata *et al.* 1968). They found significant gender differences in several VCG parameters. Smetana *et al.* (2002) observed substantial differences in repolarization homogeneity between male and female subjects. In 2008, Scherptong *et al.* (2008) also tested spatial parameter dependency on gender and proposed that they are strongly gender dependent. Vahedi *et al.* (2012) found that there were significant differences in spatial VCG parameters with gender and that the parameters are significantly higher in men compared to women. In agreement with the previous investigation, a recent study was conducted on healthy subjects for analysing the VCG parameters by Sur *et al.* (2013). They concluded that healthy men showed higher repolarization lability for several VCG descriptors compared to healthy women, which questions the factors that may contribute to influence the VCG parameters.

Age

Several researchers have investigated the influence of VCG parameters by considering the age effect (Guller *et al.* 1977, Brohet *et al.* 1986, Edenbrandt *et al.* 1987). All of the studies have found that the VCG parameters are age dependent.

2.10 Chapter summary

In this chapter we have carried out a overview of QTV analysis based on ECG and VCG approaches. In addition, several techniques and their findings along with their limitations are also elaborated. Moreover, the significance of analysing the repolarization variability for cardiac or non-cardiac patients are discussed in detail for the ECG and VCG approaches. Further research is required to improve the methodological limitations and constraints for beat-to-beat QTV analysis in ECG for different applications.

On the other hand, the concept of VCG analysis is a known approach for testing the homogeneity of repolarization lability. However, most of the earlier VCG studies were limited to a static beat. Nevertheless, literature clearly shows that the beat-to-beat

variability of VCG parameters does not exactly follow the same pattern as single beat VCG parameters but sometimes provides new information. Therefore, further research is also required to validate the hypothesis for repolarization abnormalities by using the VCG approach in a beat-to-beat manner.

In the next chapter we will investigate the relationship of beat-to-beat QTV in different ECG leads.

Inter-lead Differences in Beat-to-Beat QT Interval Variability

ELEVATED beat-to-beat QT interval variability (QTV) has been associated with increased cardiovascular morbidity and mortality, but little is known about the inter-lead difference in QTV. The aim of this chapter is to investigate inter-lead differences in beat-to-beat QTV of 12-lead ECG in healthy subjects and their relationship with T-wave amplitude, mean heart rate, age, and gender.

3.1 Introduction

Beat-to-beat variability of the QT interval reflects lability in ventricular repolarization; elevated beat-to-beat QT interval variability (QTV) has been associated with cardiac disease and increased risk for experiencing ventricular tachycardia and ventricular fibrillation leading to sudden cardiac death (Atiga *et al.* 1998). However, the mechanisms underlying QTV are incompletely understood. Reduction in repolarisation reserve has been suggested to increase QTV (Takahara *et al.* 2008, Lengyel *et al.* 2007). Furthermore, the autonomic nervous system has been implicated in the generation of beat-to-beat QTV. More specifically, it has been debated whether elevated beat-to-beat QT interval variability is a marker of sympathetic activation. Pharmacological sympathetic activation/block and orthostatic challenges have shown to affect QT variability (Mine *et al.* 2008, Yeragani *et al.* 2000b). Spontaneous QTV appears to reflect sympathetic activity (sympathetic modulations), but only when a cardiovascular morbidity exists (Baumert *et al.* 2008a, Piccirillo *et al.* 2009, Baumert *et al.* 2011c).

The question of which leads on the body surface are most appropriate for investigating beat-to-beat QTV and its relationship to cardiac morbidity and mortality has never been addressed. In addition, in most previous studies, QTV has been investigated only in a single lead and it is currently not known how comparable the QTV values obtained from different leads are. Furthermore, how the beat-to-beat QT variability is affected by gender and age issues in 12-lead ECG requires investigation.

Therefore, this chapter explores the inter-lead relationship of beat-to-beat QTV variability in healthy subjects and extends the analysis to investigate the affect of mean heart rate, age and gender on beat-to-beat QTV.

3.2 Methods

3.2.1 Subjects

Standard resting 12-lead ECGs of 72 healthy control subjects (17 females, mean age 38 ± 14 years and 55 males, mean age 39 ± 13 years) were investigated. The data are obtained from the PTB diagnostic database http://www.physionet.org. The database contains 549 records from 290 subjects. Each record includes 15 simultaneously measured signals: the conventional 12 leads (I, II, III, aVL, aVR, aVF, V_1, V_2, V_3, V_4, V_5, V_6)

together with the 3 Frank lead ECGs (V_x, V_y, V_z). In this study, the Frank lead ECG information has been excluded. The ECGs were recorded for approximately two minutes at a sampling frequency of 1000 Hz and at 16-bit resolution over a range of $\pm$16.38 mV.

3.2.2 QT variability analysis

To analyse beat-to-beat QTV, the correct identification of the Q-wave onset and T-wave terminus are crucial, especially in the presence of noise and artefacts, which all ECG recordings typically contain to some extent. In this study, we used the algorithm proposed by Berger *et al.* (1997) and co-workers. Here, the operator defines a template of the QT interval by selecting the onset of Q-wave and offset of T-wave for one beat in a particular lead. The algorithm then finds the QT interval of all other beats in that particular lead by determining how much each T-wave must be stretched or compressed in time to best match with the template (Berger *et al.* 1997). If the operator selects a longer/shorter QT template, all of the QT intervals will be biased accordingly. In this way, a relatively robust estimation of QT interval is achieved by considering the whole T-wave instead of commonly applied threshold techniques that are based on determining the end of the T-wave and are prone to artefacts and noise sources (Berger *et al.* 1997). We identified the QT interval in lead I and used the same time interval for extracting QTV in all other leads. To quantify QTV, we calculated the standard deviation of QT intervals as well as the QT variability index, QTVI, according to the equation given by Berger *et al.* (1997) and co-workers:

$$\mathrm{QTVI} = \log \frac{\frac{\mathrm{QT_{var}}}{\mathrm{meanQT^2}}}{\frac{\mathrm{HR_{var}}}{\mathrm{meanHR^2}}} \tag{3.1}$$

where $\mathrm{QT_{var}}$ and $\mathrm{HR_{var}}$ represent the variance of beat-to-beat QT intervals and heart rate, respectively. Here, the numerator shows the variance of QT intervals ($\mathrm{QT_{var}}$) normalized to the square of the mean QT interval (meanQT). The denominator contains the variance of heart rate ($\mathrm{HR_{var}}$) normalized to the squared mean HR (meanHR). Here, the heart rate variability in the denominator and QT variability in the numerator gives the degree of repolarization lability that is out of proportion to the degree of the spontaneous heart rate fluctuations.

In addition, we measured the amplitude of the T-wave for each beat by obtaining the peak of the voltage deflection within the ST segment . For further analysis we considered the median of absolute values of the T-wave amplitudes of each lead.

As a measure of heart rate variability we computed the standard deviation of normal RR intervals (sdNN).

Statistical analysis

For the statistical analysis, we used PASW Statistics 18® (IBM SPSS, Inc., Somers, NY, USA), GraphPad Prism 5® (GraphPad Software, Inc., La Jolla, CA, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). Overall beat-to-beat QTV was calculated for each lead as standard deviation of QT intervals and QTVI and compared using one-way ANOVA. Further, beat-to-beat QTV was compared between different leads using single measure intra-class correlation coefficient (ICC) and Pearson's correlation coefficients. One-way ANOVA was applied to test for lead differences in T-wave magnitude. Pearson's linear correlation coefficient was computed to test the relation between QTV and the T-wave amplitude. Prior to correlation analysis, QTV and T-wave amplitude values were log-transformed to obtain normal distributed data. The two-way ANOVA was applied to test for gender and age differences in inter-lead QTV. The unpaired Student t-test was used to investigate age and gender differences in mean heart rate, heart rate variability and ICC values of QTV. All values were expressed as mean $\pm$ standard deviation. Test results were considered statistically significant when $p < 0.05$.

3.3 Results

Beat-to-beat QT interval variability in the 12 standard leads of a typical subject is shown in Fig. 3.1. The standard deviations of beat-to-beat QT intervals vary between 2.7 ms and 6.4 ms in this recording.

Median and inter-quartile ranges of the standard deviation of beat-to-beat QT intervals in the 12 standard leads for the whole study group are shown in Fig. 3.2A. There was a significant difference in QTV ($F = 18.93$, $p < 0.0001$) and QTVI ($F = 21.27$, $p < 0.0001$) between leads. Post-hoc test results (Tukey's multiple comparison) are summarized in Table 3.1. Prominent deviations in QTV were observed in leads III (38 ms, [inter-quartile range, 4 to 8]), aVL (32 ms, [inter-quartile range, 3 to 7]) and aVF (33 ms,

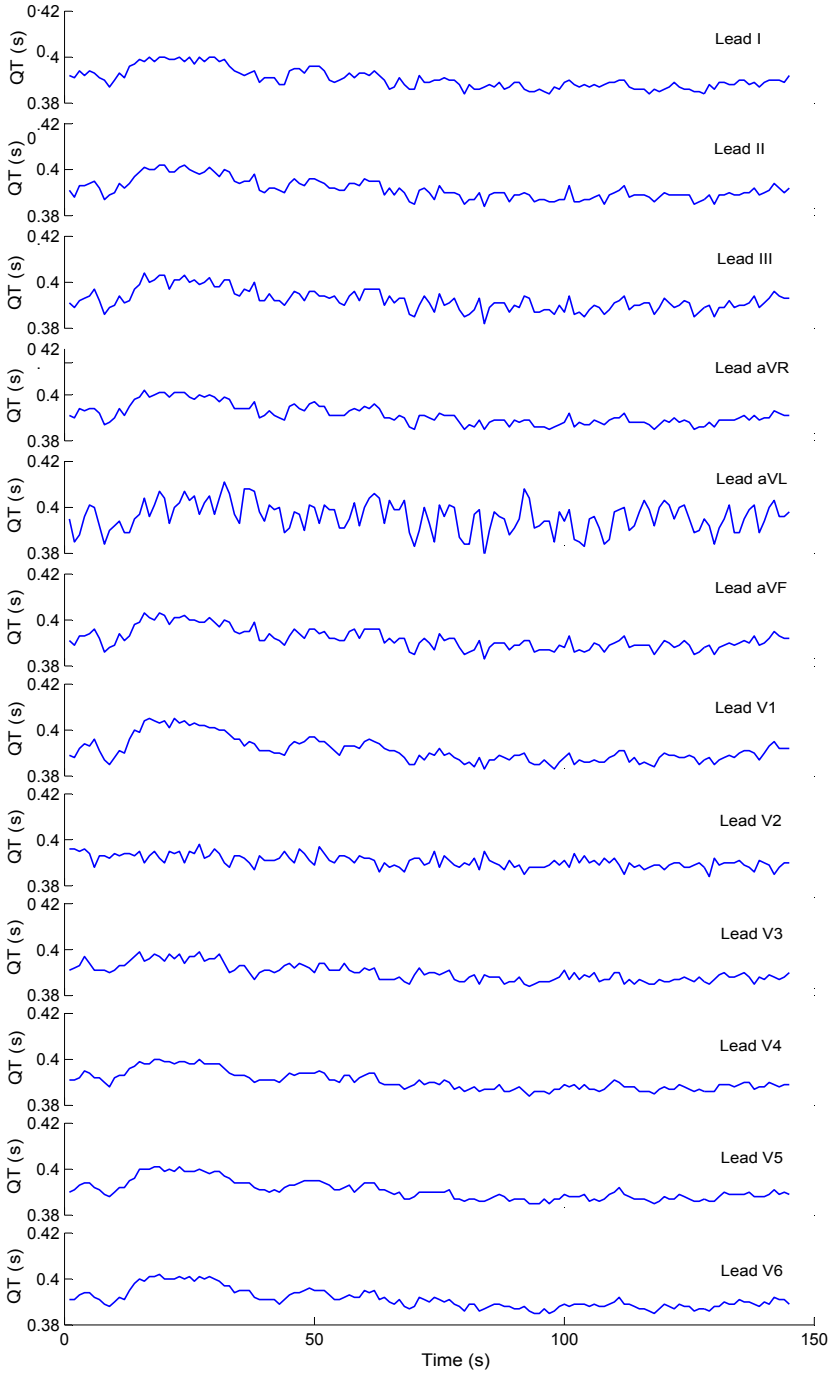

Figure 3.1. Beat-to-beat QT interval variability in 12 lead ECG. Example of beat-to-beat-QT intervals in the standard 12-lead ECG of a healthy subject recorded over 150 seconds.

Table 3.1. Post-hoc test for significant differences in the magnitude of beat-to-beat QT variability in 12-lead ECG. Multiple lead value comparison.

Lead	II	III	aVR	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
I	n.s.	***	n.s.	***	n.s.	*	n.s.	n.s.	n.s.	n.s.	n.s.
II		***	n.s.	***	n.s.	*	n.s.	n.s.	n.s.	n.s.	n.s.
III			***	n.s.	***	***	***	***	***	***	***
aVR				***	n.s.	**	n.s.	n.s.	n.s.	n.s.	n.s.
aVL					**	n.s.	***	***	***	***	***
aVF						n.s.	n.s.	*	*	*	*
V_1							**	***	***	***	***
V_2								n.s.	n.s.	n.s.	n.s.
V_3									n.s.	n.s.	n.s.
V_4										n.s.	n.s.
V_5											n.s.

*** - $p < 0.001$, ** - $p < 0.01$, * - $p < 0.05$, n.s. - not statistically significant

[inter-quartile range, 2.5 to 4.5]) compared to the majority of leads, in which QTV were below 11 ms in all subjects (I, II, aVR, V_2-V_6). The QTVI showed a similar pattern, see Fig. 3.2B.

The single measure ICC of beat-to-beat QT intervals in the 12 leads was 0.27 ± 0.18 (see Fig. 3.3), indicating a relatively low level of inter-lead consistency in beat-to-beat QT interval variability. The mean and standard deviations of Pearson's correlation coefficients of QT intervals between the 12 leads are shown in Fig. 3.4.

High correlations (i.e. $r > 0.8$) were observed between leads II and aVR (0.88 ± 0.095), leads V_5 and V_6 (0.87 ± 0.093), leads I and aVR (0.84 ± 0.16), leads V_4 and V_5 (0.84 ± 0.12) and leads II and aVF (0.84 ± 0.17). The lowest correlations were found in lead III, in particular, with lead V_1 (0.079 ± 0.33) and aVL (0.16 ± 0.43).

Relation between QTV and T-wave amplitude

The medians and inter-quartile ranges of the T-wave amplitude for each leads are shown in Fig. 3.5. One-way ANOVA demonstrated significant T-wave amplitude differences between leads ($F = 105.7$, $p < 0.0001$). The maximum T-wave amplitude was measured in lead V_3 (0.53 ± 0.22 mV) and the minimum was observed in lead III

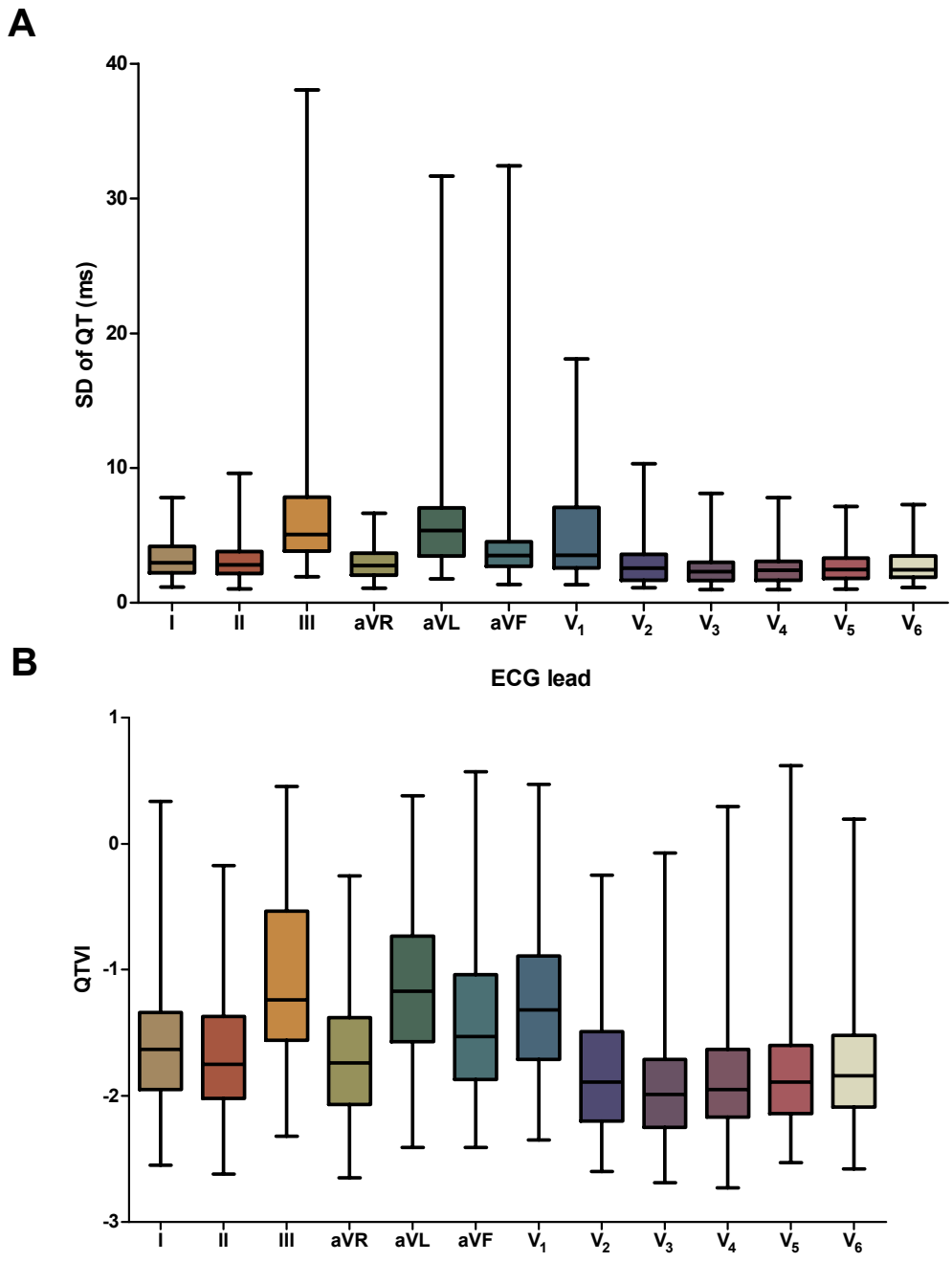

Figure 3.2. Beat-to-beat QTV and QTVI over 12-lead ECG. Median and inter-quartile ranges of standard deviations of beat-to-beat QT interval (A) and QTVI (B) in the standard 12-lead ECG of 72 healthy subjects.

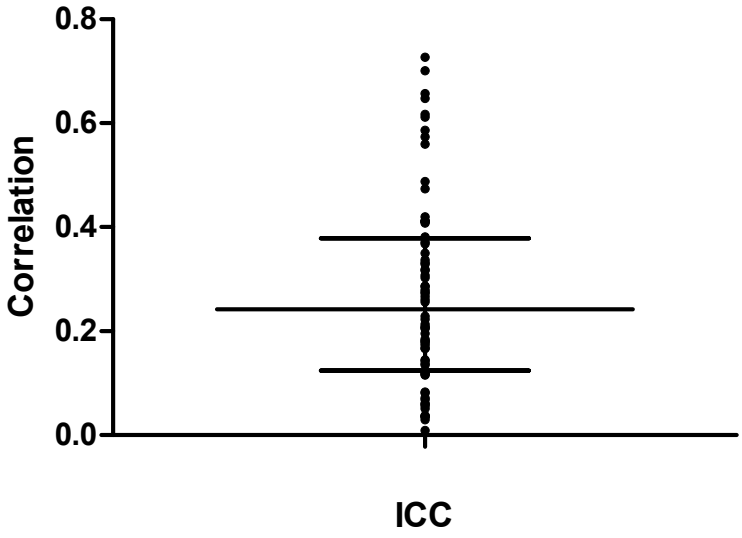

Figure 3.3. ICC (intra-class correlation coefficient) in 12-lead ECG. Single measure intra-class correlation coefficient of beat-to-beat QT interval variability in the 12 lead ECG. The ICC variable (unit less) represents in the horizontal line, where the ICC is relatively low, which indicates the inter-lead QTV is not consistent between the ECG leads.The middle horizontal line shows the median (second quartile), the lower line is for first quartile and the upper line is for third quartile of ICC, where the median value of ICC was low (24%).

(0.08 ± 0.059 mV). We observed an inverse relation between QTV and T-wave amplitude (Fig. 3.6A). To obtain normal distributed variables we log-transformed QTV and T-wave amplitude (Fig. 3.6B). Subsequently, a significant linear negative correlation was found ($r = -0.62$, $p < 0.0001$).

Relation between QTV and mean heart rate

To investigate the relationship between mean heart rate and QTV in different leads, we calculated Pearson's correlation coefficients. With the exception of lead aVF, which showed a marginal, but significant correlation between heart rate and QTV ($r^2 = 0.06$ and $p < 0.05$), no linear associations were found.

Gender comparison of QTV

To investigate the role of gender on QTV, we compared 14 age-matched males with the 14 female subjects of our data set. Mean heart rate as well as heart rate variability were

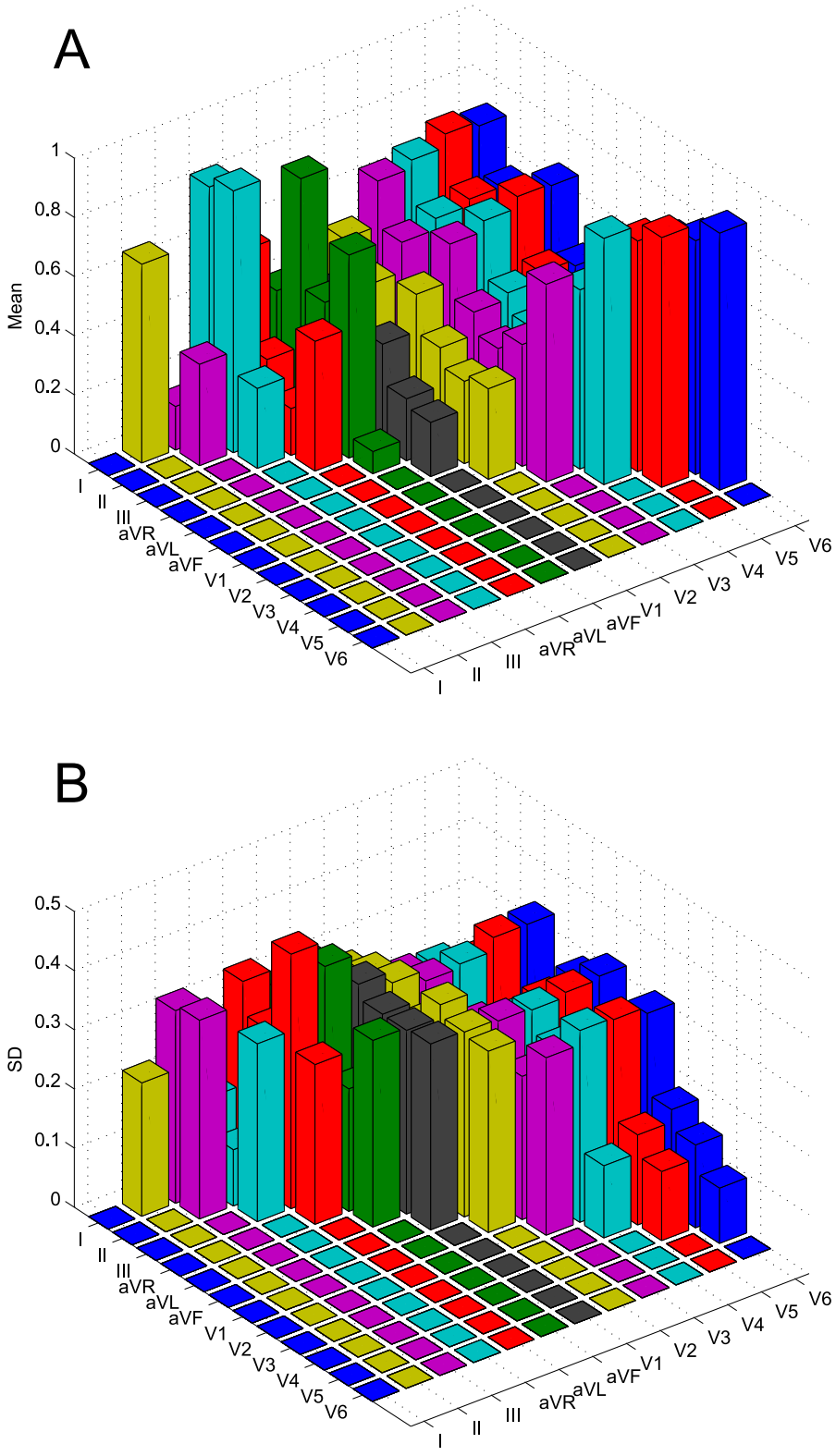

Figure 3.4. Mean and standard deviation of correlation in 12-lead ECG. Mean (A) and standard deviation (B) of correlation coefficients calculated over beat-to-beat QT interval in the standard 12 lead ECG of all subjects.

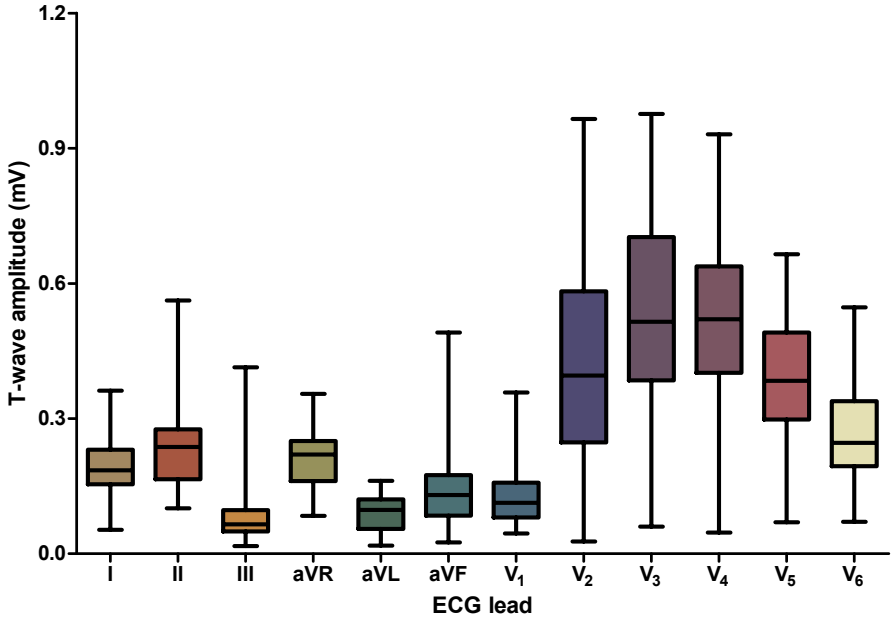

Figure 3.5. T-wave amplitude variability in the 12 lead ECG. Median and inter-quartile ranges of T-wave amplitudes of standard 12-lead ECG of 72 healty subjects.

comparable between males and females (67 ± 11 vs. 65 ± 15 bpm, $p = 0.6$; 51 ± 29 vs. 47 ± 21 ms, $p = 0.7$). Group medians and inter-quartile ranges of the standard deviation of beat-to-beat QT intervals for the 12 standard leads (in male and female subjects) are shown in Fig. 3.7. The maximum value of QTV was measured in lead aVL for females (8.56 ± 7.32 ms) and in lead III for males (8.08 ± 6.78 ms). Two-way ANOVA identified lead difference ($F = 10.01$, $p < 0.0001$), but not gender as a significant factor. The single measure ICC for male and female subjects were 0.25 ± 0.17 vs. 0.25 ± 0.16, $p > 0.05$, indicating a similarly low level of inter-lead consistency of QTV.

Age effect on QTV

To investigate the effect of age on QTV we excluded females and dichotomized the remaining data based on the medial age to groups of younger men ($17 - 37$ years) and older men ($37 - 69$ years). Mean heart rate was not significantly different between groups (68 ± 11 vs. 68 ± 6 bpm, $p = 0.8$), but heart rate variability was significantly reduced in older subjects (54 ± 27 vs. 36 ± 17 ms, $p = 0.008$). Group medians and inter-quartile ranges of the standard deviation of beat-to-beat QT intervals of young and old men are shown in Fig. 3.8. The maximum values of QTV in younger and older men were both observed in lead III (6.76 ± 5.36 ms and 9.33 ± 9.46 ms). Two-way ANOVA identified lead difference ($F = 17.98$, $p < 0.0001$), but not age as a significant

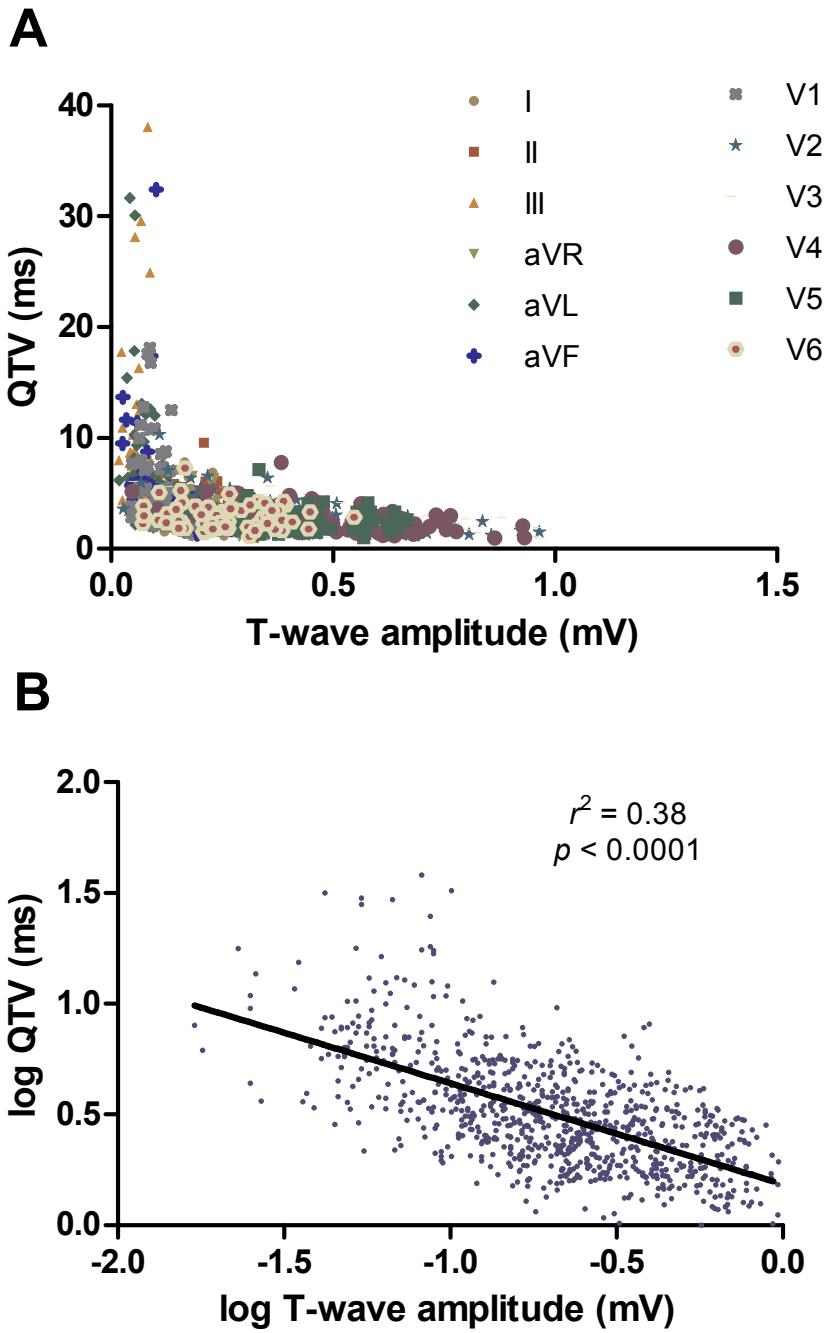

Figure 3.6. Relation between QTV and T-wave amplitude in 12-lead ECG. Correlation between QTV and T-wave amplitude of the standard 12-lead ECG of 72 healthy subject before (A) and after log-transformation (B).

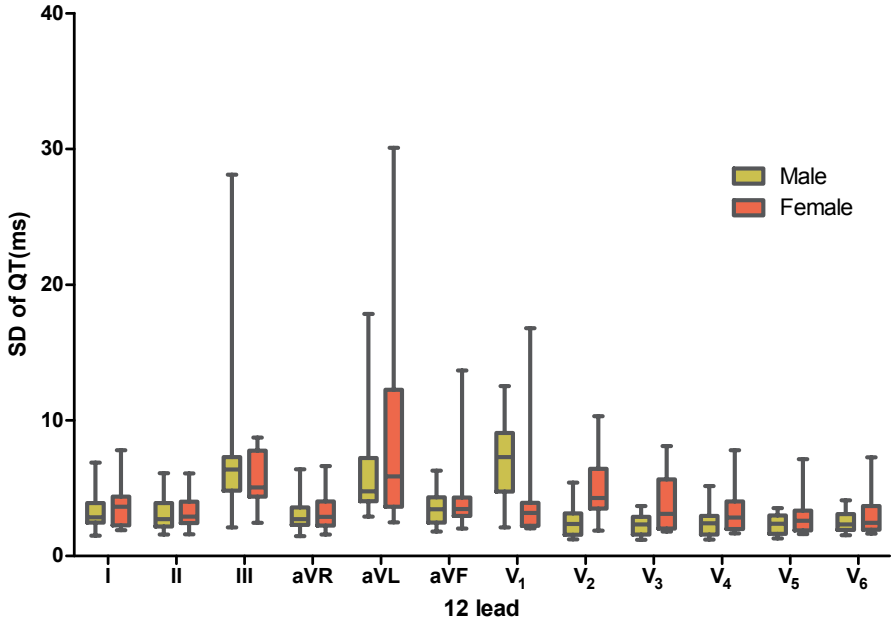

Figure 3.7. Standard deviation of beat-to-beat QT intervals in males and females. Median and inter-quartile ranges of standard deviations of beat-to-beat QT intervals in the standard 12-lead ECG of 14 males and 14 females.

factor contributing to QTV. The single measure ICC of beat-to-beat QTV for younger and older males were similarly low (0.34 ± 0.19 vs. 0.20 ± 0.16, $p < 0.05$).

3.4 Discussion

The main findings of our study are as follows: (i) the magnitude of beat-to-beat QTV varied between the 12 standard leads and (ii) the inter-lead correlation of QTV was lead dependent; (iii) there was a negative correlation between QTV and T-wave amplitude; and (iv) there was no significant affect of mean heart rate, age and gender on QTV in 12-lead resting ECG of healthy subjects.

The QT interval of body surface ECG varies among leads (Cowan *et al.* 1988) and it has been previously suggested that QTV may be lead-dependent (Avbelj *et al.* 2003). However, most previous studies quantified QTV based on a single ECG lead with varying electrode placements (Berger 2003, Baumert *et al.* 2011b, Jensen *et al.* 2004, Baumert *et al.* 2010). For practical reasons, leads with large T-waves have been typically chosen, aiming for a good signal-to-noise ratio.

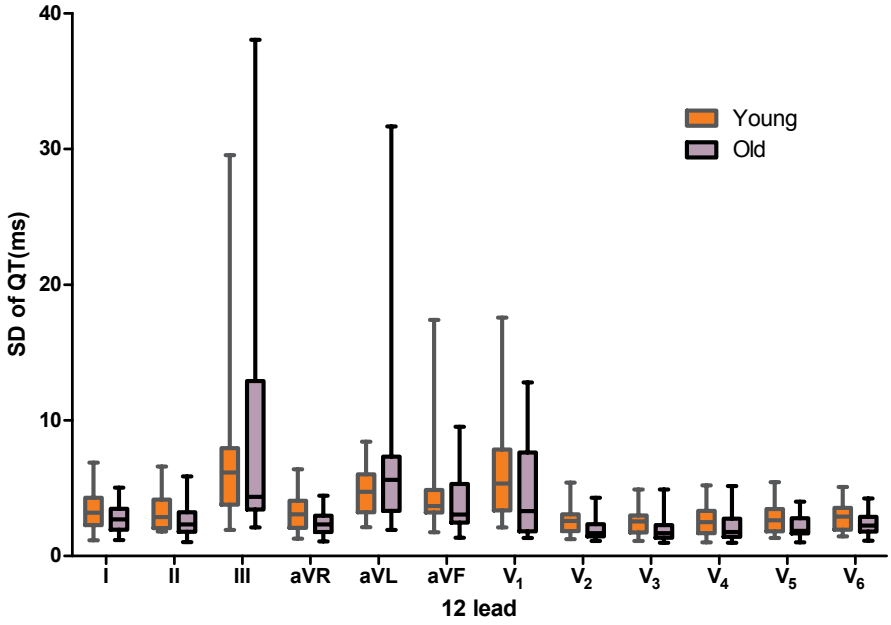

Figure 3.8. Standard deviation of beat-to-beat QT intervals in healthy younger and older males. Median and inter-quartile ranges of standard deviations of beat-to-beat QT intervals in the standard 12-lead ECG of healthy younger and older males.

Our systematic investigation of the 12-lead ECG in healthy subjects confirms that QTV and QTVI, respectively, differ notably between leads and caution should be taken when comparing QTV obtained from different leads across studies. The QTV appears to be significantly pronounced in lead III compared to all other leads, except from lead aVL, which is in the same plane and in close proximinity. No significant differences were observed between leads V_5 and V_6, leads V_4 and V_5, and V_3 and V_4, respectively, which might also be due the close proximity of electrodes. The latter finding is in contrast to those of Yeragani *et al.* (2002b), who compared QTV in leads V_1, V_3, and V_5 and found significant differences in V_5 and V_1 versus V_3. When taking into account the T-wave amplitudes across leads, our observations suggest that augmented QTV is measured in leads with a small T-waves, vice versa. There appears to be exceptions to that rule, however, as observed in leads I and II, which are charactrerised by relatively low QTV despite small T-waves. The mean heart rate does not seem to affect QTV, despite its well-known effect on the T-wave amplitude. As we investigated ECGs recorded during rest, this association might have been masked by relatively low heart rates.

Considering temporal correlations in beat-to-beat QT variations across leads, rather than magnitudes, we found very high correlations ($r > 0.8$) between several adjacent leads (II & aVR, V_5 & V_6, I & aVR) and low correlations ($r < 0.2$) between leads III and V_1 and leads III and aVL, respectively. The lack of correlation between lead III and aVL was initially unexpected, given that both leads capture similar projections of the vector angle and had similar magnitudes of QTV. However, the T-waves were small in both leads and QTV augmented, which might indicate increased sensitivity to noise (Porta *et al.* 1998b). In a previous study, Berger (2003) addressed the question of temporal correlations of QTV among a subset of leads (I, aVF, V_2) and reported correlation values between 0.6 to 0.7, which were partly confirmed by our results (Berger 2003).

In agreement with the finding of other authors (Berger *et al.* 1997, Krauss *et al.* 2009, Kusuki *et al.* 2010, Bonnemeier *et al.* 2003), our analysis suggests that there is no significant overall gender difference in the QTV of the standard 12-lead ECG of healthy subjects (ANOVA, $p > 0.05$). A closer look at the single leads, however, indicates that QTV was higher in females in most of the leads (I, II, aVR, aVL, aVF, $V_2 - V_6$) compared to males (Fig. 3.7), despite similar mean heart rates and heart rate variability. Given that gender differences in the average rate-corrected QT interval and T-wave morphology are well known—see Pham and Rosen (2002) and therein—this difference might possibly affect QTV in certain leads. In line with the overall group analysis, QTV was highest in lead III for males and lead aVL for females.

In the present study, we did not find a significant difference in the overall QTV of the 12-lead ECG in older males compared to younger males. This finding is in agreement with two previous studies that did not observe age-dependent QTV differences in adults (Bonnemeier *et al.* 2003, Yeragani *et al.* 2005), and somewhat in contrast with one study, in which QTV differences were observed in children ($6 - 14$ years) compared to adults ($22 - 55$ years) in lead II (Yeragani *et al.* 2000a). Although overall QTV across all leads was not significantly different between younger and older males in our study, QTV appeared to be higher in younger than older men in most of the leads (I, II, aVR, aVF, $V_1 - V_6$). Leads III and aVL did not follow that general pattern. The reason for the discrepancy in these two leads might be the relatively low T-wave amplitudes, which might be prone to noise. The elevation in QTV of young men may be partly explained by higher heart rate variability in young men and the rate-dependence of the QT interval. Although the relationship between RR and QT interval

is intricate, spectral analysis of RR and QT time series demonstrated similar oscillatory components in both time series (Porta *et al.* 1998a).

3.5 Limitations

The main limitation of the present study is its focus on healthy subjects. Although our findings on inter-lead correlations might not directly translate to cardiac patients that are characterised by altered substrate and repolarization heterogenities, our data suggest that the choice of lead may influence temporal analyses such as power spectrum or entropy (Porta *et al.* 1998a, Baumert *et al.* 2011a). The correlation between QTV and T-wave amplitude, on the other hand, may be generally applicable, since it is presumably caused by technical limitations of the measurement algorithm. In fact, one might speculate whether the utility of QTV for cardiac risk stratification is partly due to flatter T-waves in high risk patients (Couderc 2009). An important limitation of the gender analysis in this study is the relatively small number of subjects. We cannot exclude the possibility of an overall gender difference in QTV due to the limited statistical power of our sample. Another limitation of our study is the relatively short duration of ECG recordings. Possibly, longer recordings might reduce the inter-lead difference in QT variability to some degree. Lastly, the information on the subjects included in the PTB database used for this study is limited and, for example, does not contain BMI values.

3.6 Chapter summary

In this chapter, we have investigated the 12-lead ECGs beat-to-beat QTV and its relationship with the T-wave amplitude. In conclusion, the magnitude and temporal pattern of beat-to-beat QT interval variability varies significantly between leads. In addition to that, there is an inverse relation between QTV and T-wave amplitude in 12-lead ECG. The QTV is increased when the T-wave amplitude is lower or vice versa. In general, caution should be paid when comparing QT variability results obtained from different leads across studies.

In the next chapter we will investigate how to improve the method of quantification for beat-to-beat QT interval duration and its variability.

Chapter 4

Improved Approach for The Quantification of QTV

THE aim of this chapter was to enhance the ECG pre-processing modalities in a widely-used computer software for beat-to-beat QT interval variability (QTV) measurement based on template matching. The R-peak detection algorithm has been substituted and an efficient baseline removal algorithm has been implemented in the existing computer software. To test performance we used real ECG and simulated ECG data with fixed QT intervals featuring Gaussian noise, baseline wander and amplitude modulation and two alternative algorithms. Significantly lower beat-to-beat QTV was found in the updated approach compared the original algorithm.

4.1 Introduction

The existing measurement techniques for beat-to-beat QT interval in surface ECG are limited in their accuracy due to different reasons. Generally, the first task to be considered for accurate quantification of beat-to-beat QTV is the accurate R-peak detection followed by the detection of Q-wave onset and T-wave offset. If the R-peak detection is faulty then the whole quantification of QTV will be affected. Baseline wander or drift is one of the types of noise that causes problems for detecting the R-peaks of surface ECG. Due to the baseline wander, the T-peak can appear higher than the R-peak and detected as an R-peak instead. In addition, it may also affect the detection of the T-wave offset and thereby affect the measurement of QTV.

The real time QRS detection algorithm proposed by Pan and Tompkins (1985) is widely used and also implemented in the computer software for beat-to-beat QT measurements developed by Berger *et al.* (1997). However, a number of studies have investigated the accuracy of Pan & Tompkins' QRS detection algorithm and indicate difficulties when detecting QRS complexes in ECG complicated by cardiac disorders or arrhythmia. In particular, most of the studies reported missed and false detection of the true R-peak with less effective baseline removal in the ECG signal (Benitez *et al.* 2000, Adnane *et al.* 2009, Manikandan and Soman 2012, Debbabi *et al.* 2010, Paoletti and Marchesi 2006, Ruha *et al.* 1997, Xue *et al.* 1992).

Therefore, in this chapter, we incorporated an alternative R-peak detection technique and baseline removal approach in the existing computer software, which was developed by Berger *et al.* (1997). The performance of the updated approach has been compared with the existing method (Berger *et al.* 1997) and two other methods (conventional method (Porta *et al.* 1998b), template time shift method (Starc and Schlegel 2006)) on simulated ECG as described in a previous article (Baumert *et al.* 2012) as well as on real ECG signals.

4.2 Conventional and template time shift method

The conventional method for beat-to-beat QT interval measurement was based on derivative based algorithm which was previously described in details by Porta *et al.* (1998b). In brief, QRS complexes are detected based on a derivative-threshold algorithm. Baseline is estimated by means of cubic spline interpolation based on five cardiac beats before and after the current beat and then removed. After that the T-wave

apex is found by using a window search after the heart period (Porta *et al.* 1998b). Then, the ECG is differentiated for a constant duration that determined by the operator using a derivative finite impulse response filter (differentiating up to 25 Hz with a cutoff over 30 Hz). T-wave offset is identified where the absolute value of derivative of the T-wave down slope becomes smaller than a threshold proportional to the absolute value of derivative maximum. Finally, T-wave offset points are validated by a moving calliper while watching the ECG trace and new location of T-wave offset was labelled as manually corrected. Thus, the QT interval was calculated as the time distance between R-wave apex and T-wave offset.

On the other hand, template time shift algorithm is fully automated without the influence of operator, which was described in details by Starc and Schlegel (2006). Mainly, this technique based on separate QRS and T-wave templates and shift them in time to obtain precise QT interval estimates. Briefly, the pre-filtering is performed by a 6 pole Chebyshev low pass filter with a cut-off frequency 125 Hz. After that the algorithm detects individual beats and P, QRS and T-waves are identified. Template beats are constructed repetitively after 60 beats to meliorate the template and only those beats with shapes similar to that of the template are included. The proposed algorithm shifts the incoming wave with respect to the template until an acceptable match is found by minimising the sum of squared difference (Starc and Schlegel 2006). The matching of waves is performed in two steps. In first step, a broader time interval that contains the complete wave is used to reach the best fit, where the amplitude of the incoming wave is normalized with respect to the template area under the curve. In second step, the normalized wave is shifted in time to achieve the best fit in a smaller time window. To match the T-waves only, the interval between apex and end of the T-wave is considered for final matching, whereas for QRS complexes the interval defined by an initial slope larger than 1/5 of the QRS amplitude is considered.

4.3 Methods

4.3.1 Subjects

Simulated data

For simulated data, we considered the same simulated ECG data that was reported in an earlier article (Baumert *et al.* 2012). In brief, the original ECG (a normal noise-free

cardiac cycle of healthy subject; age: 26 years) was obtained from lead II with sampling frequency 1000 Hz and then digitized with a 12-bit A/D converter. Ten cardiac beats were computed from the original one by decreasing T-wave amplitudes by factor k from 1.0 to 0.1 (where $k = 1.0$ represents the original cardiac cycle). Finally, ten synthetic signals with 500 cardiac cycles were obtained by repeating each of the ten beats 500 times. All ECG data are characterized by no variability in heart period and ventricular repolarization duration.

Real data

The real ECG signals have been obtained from the same database as described in Chapter 3, Section 3.2. The 12-lead ECGs of 83 MI patients (22 females, mean age 64 ± 11 years and 61 males, mean age 55 ± 10 years) were considered in this study. We have analysed lead I for each of the MI patient recordings and were about 1-2 weeks after infarction. Approximately two minute ECGs were recorded with a sampling frequency of 1000 Hz for 16-bit resolution over a range of $\pm$16.384 mV.

4.3.2 ECG pre-processing for QTV analysis

The ECG pre-processing stage of the QT variability analysis software was updated in two major aspects to improve the overall performance for the quantification of beat-to-beat QT interval variability (Berger *et al.* 1997).

Firstly, a robust R-peak detection (automated R-peak finding logic) algorithm has been used to substitute the R-peak detection algorithm, which was based on the algorithm that was proposed by Pan and Tompkins (1985). Secondly, a method based on cubic spline line interpolation for removing base line wander (low-frequency drift; effect of respiration) has been incorporated in the present computer software.

R-peak detection algorithm

A slightly modified version of the R-peak detection algorithm introduced by Manikandan and Soman (2012) was implemented. The block diagram of the modified R-peak detection algorithm is shown in Fig. 4.1. It also consists of four major stages: digital filtering, Shannon energy envelope extraction, peak-finding logic and true R-peak locator as was contained in the original algorithm (Manikandan and Soman 2012).

Stage 1 (Linear Digital Filtering) consists of four processing stages that includes (i) a decision of the direction of R-wave in the ECG to determine, whether the R-wave is in an upward or downward direction, (ii) a bandpass filter, (iii) a first-order forward difference, and (iv) an amplitude normalization operation to make the QRS complex more prominent than P-wave and T-wave in the ECG. In stage 2, Shannon energy estimation and zero-phase filtering (low pass filtering) are applied to obtain a smooth Shannon energy (SE) envelope that has a significant role for detecting the true R-peak in the ECG signal. The reason for the smoothness of the SE envelope is important as the major local maxima in the SE envelope corresponds the approximate locations of R-peak in the ECG. In stage 3, the peak-detection logic is developed based on the Hilbert transform , moving average filtering (which removes the drift from signal) and positive zero crossing (ZCP) detection. Finally, in stage 4, the accurate R-peak location is determined by finding the accurate local maximum, which is detected based on the positive ZCP points in the Hilbert transform of the SE envelope. The following sections will be discuss this in detail for the each stage of the implemented R-peak detection algorithm.

Stage 1: Digital Filtering on ECG

The main purpose of this stage is to enhance the QRS complex along with noise suppression in the ECG signal. However, one crucial factor i.e. the direction of R-wave in the ECG signal was not considered in the original algorithm (Manikandan and Soman 2012), but has been incorporated in the present implementation. The previously proposed algorithm is sometimes unable to find the R-peak in ECG signal, especially when the amplitude of R-wave and Q-wave are similar or the amplitude of the R-wave is relatively smaller in the downward direction. To determine the direction of R-wave, initially, a 4^{th} order high pass Butterworth IIR filter is applied to the input ECG (0.5 Hz) to remove initial baseline wander from the ECG signal. This pre-processing step signal is not used further except from the initial determination of the direction of the R-wave. After temporarily removing the baseline wander (i.e. now the ECG signal is assumed to be near the iso-electric line), a 2 sec window is constructed. Then, a total of 15 windows are created from the whole input ECG signal. After that, the maximum and minimum amplitude of samples in each window for the whole duration of the ECG signal are computed and averaged the maximum and minimum absolute values of the amplitudes. If the average absolute minimum amplitude is higher than the average absolute maximum amplitude, then the R-wave is assumed to be in the negative

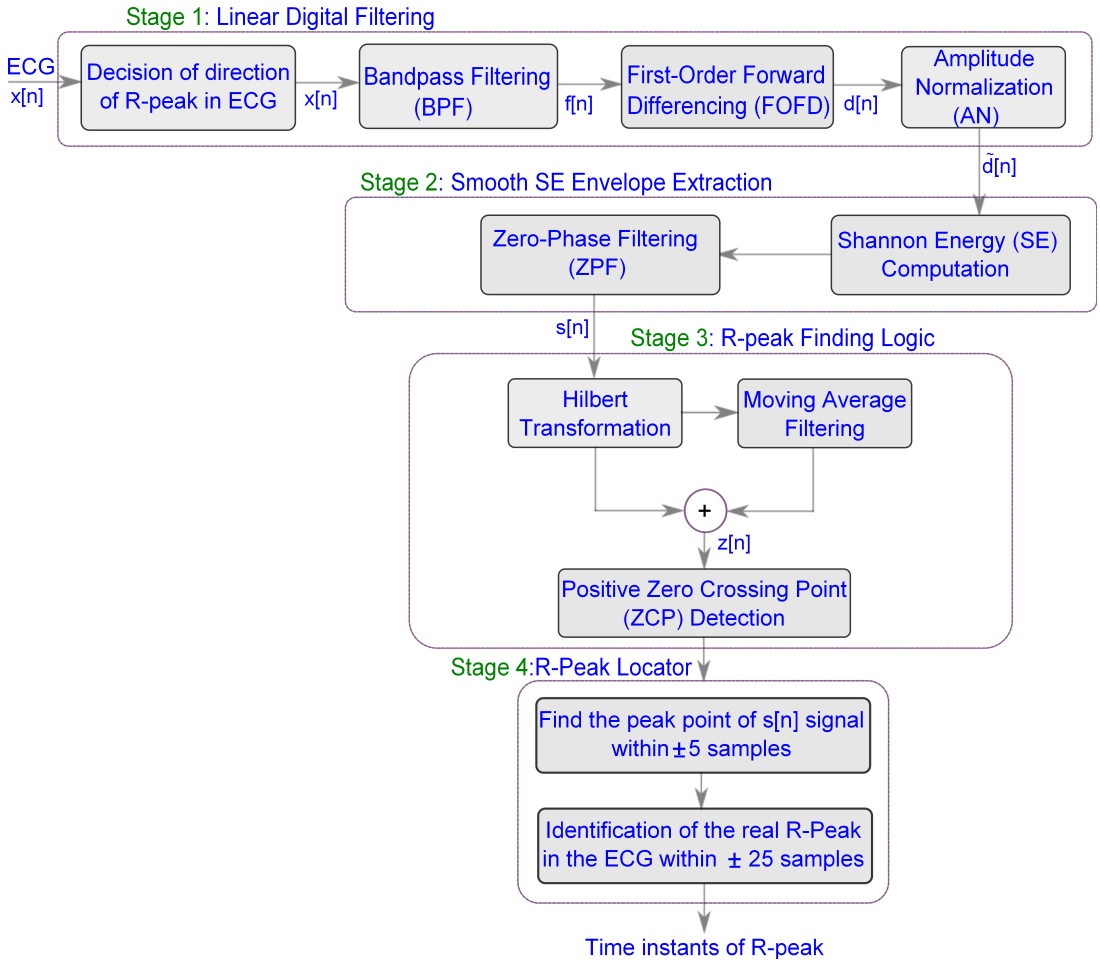

Figure 4.1. Block diagram of R-peak detection algorithm. The block diagram consists of four major stages: linear digital filtering, smooth Shannon energy envelope extraction, R-peak finding logic and true R-peak locator.

direction (i.e. downward) and is transformed to positive direction for only processing the signal in the rest of the stages otherwise R-wave is believed to be positive direction (i.e. upward) in input ECG signal $x\,[n]$.

Then, the input ECG signal, $x\,[n]$, is passed through a bandpass filter (BPF), first-order differentiation to emphasize the QRS complex and to reduce the noise sources (e.g. electrode contact noise, muscle contraction, motion artifacts) and the influence of large P and T-waves. Here, the BPF is designed based on the 4^{th} order Chebyshev type 1 bandpass filter for bandwidth of [6 18] Hz (Manikandan and Soman 2012) in forward and reverse directions of the input ECG signal $x\,[n]$ to avoid the phase distortion (i.e. zero-phase filtering). After the BPF, the filter signal, $f\,[n]$, is differentiated

(i.e. high pass filter) to provide information about the slop of the QRS complexes with the following equation:

$$d[n] = f[n+1] - f[n]. \tag{4.1}$$

This differentiation technique further reduces the interference of higher P and T-waves in the filtered ECG signal. After band-pass filtering and differentiation, the processed signal is normalized based on its amplitude by

$$\widetilde{d}[n] = \frac{d[n]}{\max_{n=1}^{N}(|d[n]|)}, \tag{4.2}$$

where, N refers the number of samples in each ECG segment.

Stage 2: Smooth Shannon Energy Envelope Extraction

In this processing stage, the normalized signal is passed through a non-linear transformation to obtain the positive peaks in spite of the polarity of QRS complexes. The reason for this transformation is to facilitate a single-sided threshold mechanism and to accentuate the QRS complexes (Pahlm and Sörnmo 1984). The absolute value, energy envelope, Shannon entropy value and Shannon energy envelope of the normalized ECG signal are computed using the following equations (4.3)–(4.6):

$$a(n) = \left|\widetilde{d}[n]\right| \tag{4.3}$$

$$e(n) = \widetilde{d}^2[n] \tag{4.4}$$

$$H(n) = -\left|\widetilde{d}[n]\right| \log\left(\left|\widetilde{d}[n]\right|\right) \tag{4.5}$$

$$s_{\text{energy}}[n] = -\widetilde{d}^2[n] \log\left(\widetilde{d}^2[n]\right). \tag{4.6}$$

Shannon entropy, $H(n)$, emphasizes the effect of low noise components as a result it provides artifacts and more unwanted spikes (Manikandan and Soman 2012). On the other hand, the Shannon energy envelope ($s_{\text{energy}}[n]$) reduces significantly the amplitude of the small R-wave than that of high-amplitude ones along with some advantages over Shannon entropy that was reported in details in the article (Manikandan

and Soman 2012). One of the major advantages of the Shannon energy envelope is that the performance of R-peak detection is maintained even in the presence of small and wider QRS complexes and non-stationary noise sources. Therefore, in the present implementation, the Shannon energy envelope, $s_{\text{energy}}[n]$, is computed on the normalized signal, $\widetilde{d}[n]$.

After computing the Shannon energy, a zero-phase filtering (i.e. low pass filter) is applied on the Shannon energy to obtain the sharp peaks around the QRS complex regions and smooth out the spurious spikes and noise bursts. This zero-phase filtering is based on a rectangular impulse response and performed both in forward and reverse direction of the Shannon energy. The smoothness of the signal depends on the filter length L and assumed to be the same as the duration of possible wider QRS complex. The length of the filter is chosen to be 152 samples for a 1000 Hz sampling frequency based on the idea of Manikandan and Soman (2012). Then, the smooth Shannon energy envelope, $s[n]$, are processed and passed to the next stage of the R-peak detection algorithm.

Stage 3: R-peak Finding Logic

In stage 3, the Hilbert transform is applied to the smooth Shannon energy envelope, $s[n]$, by following the basic equation of Hilbert transform on a real signal $x(t)$ as

$$\widehat{x}(t) = H[x(t)] = \frac{1}{\pi t} \otimes x(t) = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{x(t)}{t-\tau} dt. \tag{4.7}$$

In the time domain, the Hilbert transform is defined by convolution between $\frac{1}{\pi t}$ and $x(t)$. The Fourier transform of the $\widehat{x}(t)$ is given by

$$\widehat{X}(f) = F\left[\frac{1}{\pi t} \otimes x(t)\right] = F\left[\frac{1}{\pi t}\right] F[x(t)] = -j\text{sgn}(\text{f})\,\text{X}(\text{f}). \tag{4.8}$$

The inverse Fourier transform (IFT) of $-j\text{sgn}(\text{f})$ is $\frac{1}{\pi t}$, then, the Hilbert transform of the signal $x(t)$ can be computed as

$$\widehat{x}(t) = \text{IFT}\left[\widehat{\text{X}}(\text{f})\right] \text{ where } \begin{cases} jX(f) & f<0, \\ -jX(f) & f>0. \end{cases} \tag{4.9}$$

The Hilbert transform of the smooth Shannon energy envelope, $s[n]$, provides an odd-symmetry function (OSF) for each peak of the corresponding energy envelope (See

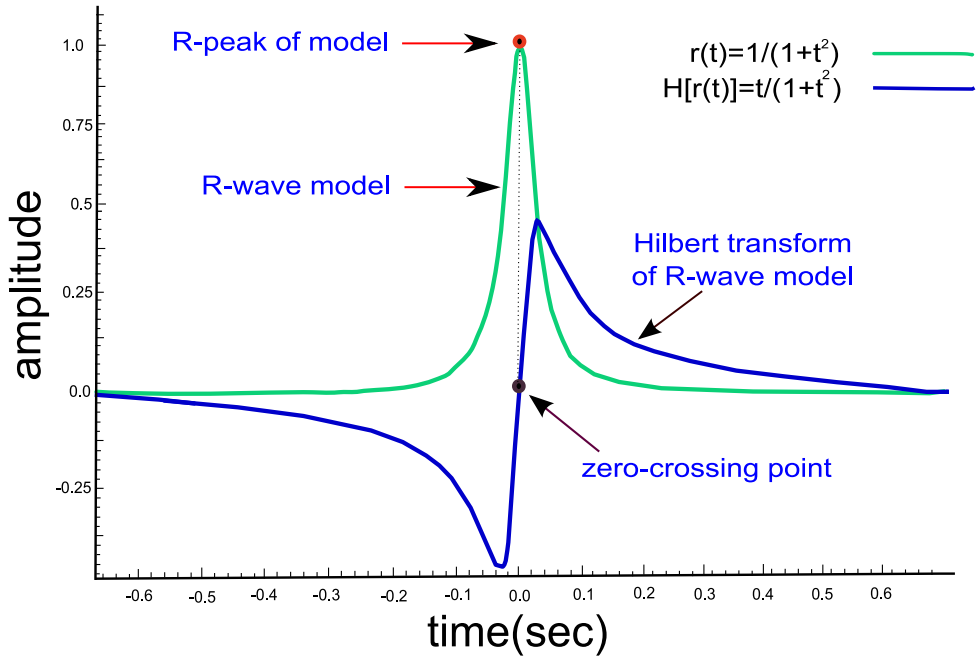

Figure 4.2. Hilbert transform of an R-peak model. The green color depicts the model of R-wave and the blue color depicts the Hilbert transform of R-wave model.

Fig. 4.2) which has been discussed in detail in the case of the original algorithm by Manikandan and Soman (2012). In addition, this corresponding energy envelopes represent the corresponding QRS complexes in the original ECG signal. Therefore, the positive zero-crossing (i.e. negative-to-positive transition) points of the odd symmetry function correspond to the locations of the nearest peaks in the smooth Shannon energy envelope. It has been observed due the low frequency drift in the signal, the zero-crossing points are shifted sometimes in the positive or negative direction with respect to iso-electric line (Manikandan and Soman 2012), and as a result, may fail to be accurate for an envelope that has a small R-wave amplitude in the original ECG. To address this problem, a low pass filter (moving average filter) has been used and subtracted from the original input. The length of the moving average filter is chosen as 2500 samples (2.5 sec) for a sampling frequency of 1000 Hz in this implementation. However, we have found that sometimes this moving average filter is not enough (Manikandan and Soman 2012) to overcome with higher baseline low-frequency drift for detecting accurate R-peak in the ECG signal. Therefore, in this research, a cubic spline line approach (details are in the following section) has been incorporated with the present implementation for removing baseline low-frequency drift from the original signal.

Stage 4: R-peak Locator

The last stage of the algorithm deals with the accurate location of the R-peak in the ECG signal. An interesting observation was found in the present implementation. In practice, the zero-crossing points correspond the location of the peaks in the smooth SE envelope but, we have observed that sometimes the peaks differ even slightly from the time instants in the smooth SE envelope that was not discussed in the original algorithm (Manikandan and Soman 2012). As a result, the quantification of the R-peak location in the original ECG sometimes found to be a false R-peak location based on the algorithm proposed by Manikandan and Soman (2012). Therefore, to solve this problem, initially the accurate time instants of the peaks in the smooth SE envelope have been found by searching for the largest amplitude within a very small range of the samples in the smooth SE envelope peaks area ($\pm$ 5 samples). After that, the correct time instants of the R-peaks in the ECG signal are found (considering the location of the corresponding peaks in the smooth SE envelope) by searching the largest amplitude within $\pm$ 25 samples of the identified location of the smooth SE energy envelope. Thus, the R-peak detection algorithm has been implemented.

Baseline wander removal

The second improvement of the pre-processing stage involves the implementation of the baseline removal algorithm from the ECG signal. It consists of four steps (see Fig. 4.3). Initially, a low pass Butterworth filter is applied to remove the high frequency from the ECG signal (40 Hz). We have observed that the construction of baseline wander (cubic spline line) is very sensitive to high frequency noise near the Q wave, because the construction of a cubic spline line becomes corrupted. After removing high frequency noise, the R-peak detection algorithm is used to obtain R-peak time instants in the ECG signal. Based on physiological considerations it is assumed that the Q points are about 50 ms before the R-peak time instants. Therefore, the iso-electric points are considered just before the Q points in this study. After that, the baseline is constructed by cubic interpolation by using the same sampling frequency as the input ECG signal. Finally, the baseline is subtracted from the ECG signal and this ECG signal is used for the quantification of beat-to-beat QT interval variability.

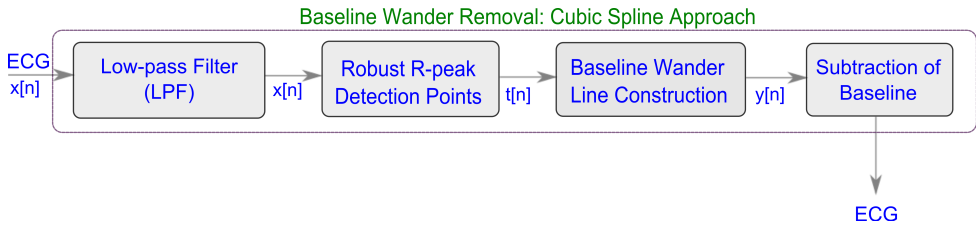

Figure 4.3. Baseline wander removal steps. Baseline wander cancellation steps; Low-pass filter, R-peak detection on ECG signal, baseline wander line construction and subtraction of the baseline.

Statistical analysis

The standard deviation of beat-to-beat QT intervals was considered as a marker for QTV in both simulated and real ECG signal. To realize the performance for quantification of QTV by different algorithms on a simulated signal, one-way ANOVA and Newman-Keuls multiple comparison test has been used in this study. To investigate the performance of the new approach with the existing approach, we have applied the Student t-test on the real ECG. The test results were considered statistical significant when $p < 0.05$.

4.4 Results

The updated approach has been tested on the same simulated ECG as described in Baumert *et al.* (2012) for the comparison of QTV measurement accuracy with the original method as well as conventional and template time shift methods. The T-wave acquisition range (TWAR) , the number of beat of A/D converter is occupied by T-wave in the ECG signal, was the same between 0.6% to 6.4% as described by Baumert *et al.* (2012). Further, the updated approach has been tested on real ECG for the comparison of QTV measurement accuracy with the original template stretch method.

A. Effect of noise on QTV measurement accuracy

The updated approach showed lower (one-way ANOVA, $p < 0.005$) noise susceptibility compared to the conventional and original template stretching method see Fig. 4.4A. The Newman-Keuls multiple comparison test showed comparable artificial QTV values ($p > 0.05$) between the updated approach and the template time shifting method. In addition, both methods produced artificial QTV less than 2 ms when the

TWAR was greater than 1.3%. Finally, the updated approach did not reject any beat even at the lowest TWAR, where the original template stretching method rejected two percent of beats (Baumert *et al.* 2012).

B. Effect of baseline wander on QTV measurement accuracy

The updated method showed a significant improvement for quantifying QTV compared to the original method ($p < 0.0001$) and provides the least artificial QTV (see Fig. 4.4B) compared to conventional method, but was comparable with the template time shift method ($p > 0.05$) based on the Newman-Keuls multiple comparison test. On average, artificial QTV was 0.67 ms in the updated approach, where with template time shift method artificial QTV was 1.48 ms. Finally, the updated approach showed a significant improvement ($p < 0.05$) in terms of beat rejection (i.e. no beat was rejected) compared with the original template stretching method (Baumert *et al.* 2012). The original template stretching method rejects 88%, 74%, 60%, 43% and 10% of beats from lowest to intermediate TWAR values (Baumert *et al.* 2012).

C. Effect of amplitude modulation on QTV measurement accuracy

Mean artificial QTV was less than 2 ms (1.68 ± 0.28 ms) with the updated approach (see Fig. 4.4C) where in the previous approach it was less than 1 ms (0.93 ± 0.26 ms). On the other hand, the template time shift method had the highest artificial QTV (2.02 ± 1.31 ms). The automated beat rejection was only 15% from each of the simulated signals, whereas it was 36% when using the original template stretching algorithm (Baumert *et al.* 2012).

Performance of original and new approach of template stretching method on real signal

A significant improvement has been observed of the new approach in real ECG data. The beat-to-beat QTV was found significantly lower (see Fig. 4.5) in the new approach compared to the original method ($p < 0.05$). For comparing the QTV obtained from original and new approach, the scatter plot is shown in Fig. 4.6, where the bias value was 2.8 ms and SD of bias was 11.1 ms.

A significant lower beat rejection ($p < 0.05$) for the new approach was found compared to the old approach as shown in Fig. 4.7A. The overall percentage of beat rejection was

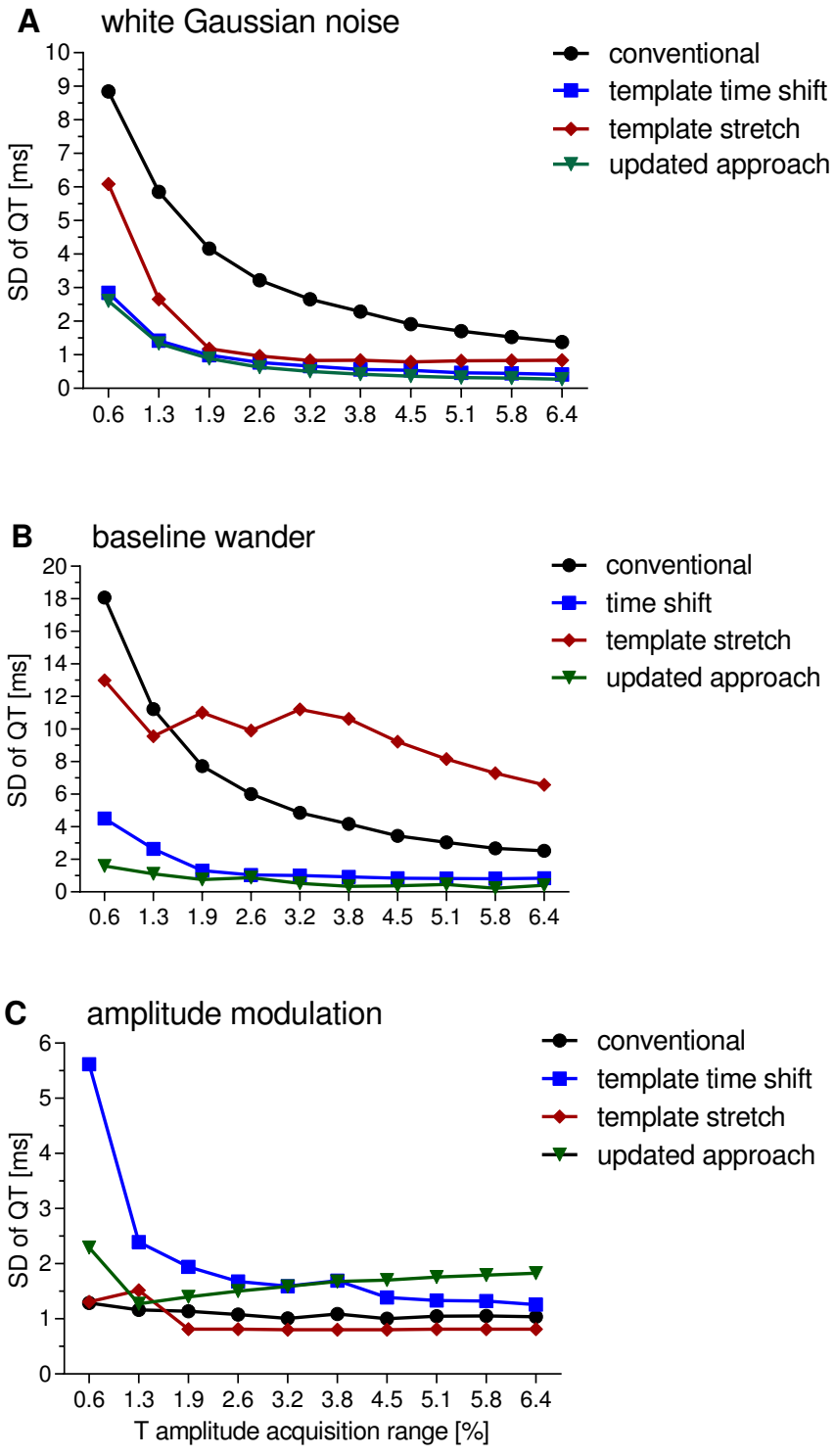

Figure 4.4. Performance of QTV measurements. The black colour line depicts the artificial QTV by conventional method, the blue colour line shows the artificial QTV by the template time shift method, the red colour shows the artificial QTV by the original template method and the green colour shows the artificial QTV by the updated approach.

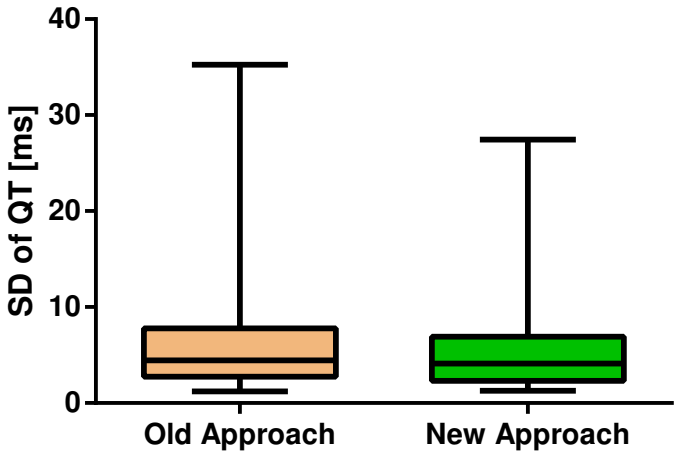

Figure 4.5. QTV measurement on MI patients; old and new approach. The orange colour depicts the QTV by the original template stretch method and the green colour depicts the QTV by updated approach on real ECG for MI patients.

found (6.67 ± 15.31 %) by using the old approach and was (3.87 ± 9.46 %) by using new approach. In addition, the Bland-Altman plot is shown in Fig. 4.7B for agreement on QTV measurement between this two approaches. According to Fig. 4.7B, it shows that the old approach has higher beat rejection than the new approach.

4.5 Discussion

Reliability of the improved approach of template stretch algorithm on simulated and real ECG

Effect of noise on QTV measurement

It has been suggested in Baumert *et al.* (2012) that the original template stretching technique is more susceptible to white Gaussian noise than the template time shift method, but less susceptible than the conventional technique. However, with the updated preprocessing the template stretch approach showed a different scenario under the same experimental setup. The updated approach demonstrated lower noise sensitivity compared to the conventional method and original template stretching method. The updated approach and template time shifting method provide similar QTV values based on the Newman-Keuls multiple comparison test. These two methods produced overall average errors less than 1 ms and error less than 0.7 ms while the TWAR was greater

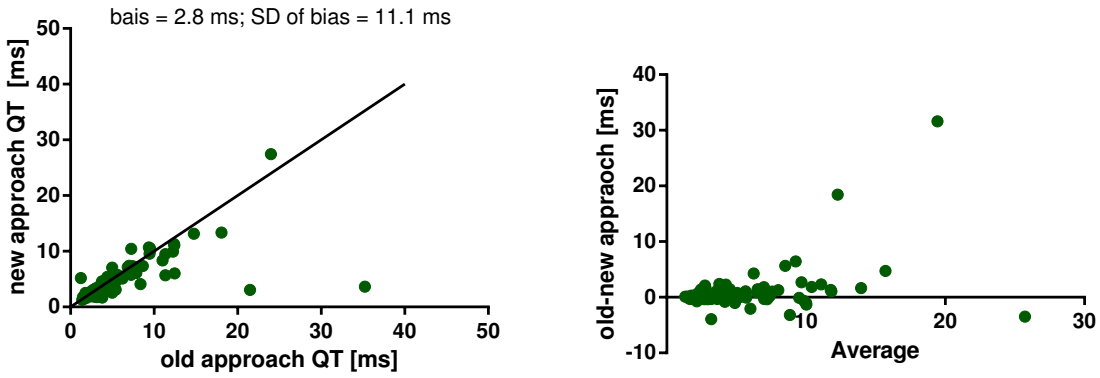

Figure 4.6. Scatter and Bland-Altman plot on MI patients; old and new approach. Scatter (left) and Bland-Altman (right) plot; agreement between old and new approach for QTV measurement.

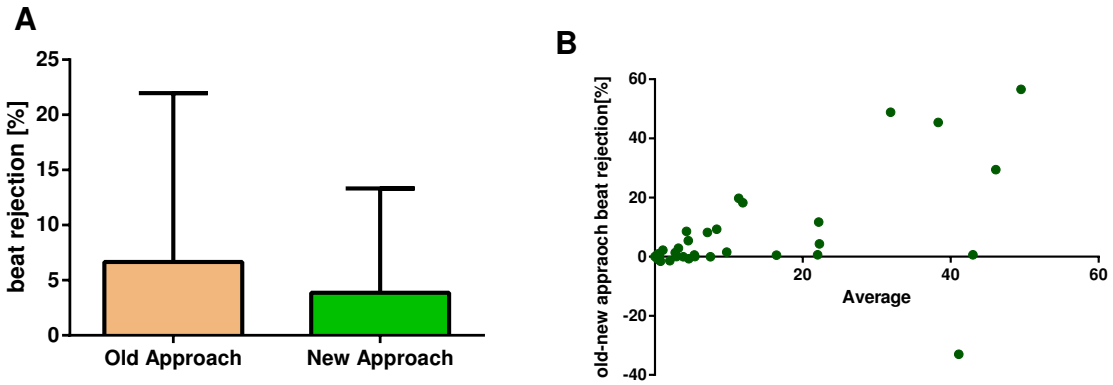

Figure 4.7. Bar and Bland-Altman plot. Beat rejection agreement between old and new approach for QTV measurement.

than 1.3%. Further, it was found that there was no beat rejected by the updated approach even in the lowest TWAR, which is in line with conventional, and template time shifting techniques.

Effect of baseline wander on QTV measurement

A previous study showed that the template stretching technique performed worst in the presence of baseline wander and the best performance was achieved by the template time shift approach (Baumert *et al.* 2012). However, the updated approach showed significant improvements compared to the original template stretch method and conventional method. The reason for higher QTV by original template stretch

method can be partially explained by this study. Firstly, perhaps the filter was not capable of removing baseline drift completely in the original method (Berger *et al.* 1997). Secondly, as a result, the automated R-peak detection employed (Pan and Tompkins 1985) in the original template stretch method was limited for finding the accurate R-peak in the ECG. In contrast, the updated approach demonstrated lower artificial QTV values (less than 2 ms), which were comparable with those of the template time shift method. Moreover, the updated template stretching approach provided a significant improvement in terms of beat rejection (i.e. no beat was discarded) compared with the original template stretch method.

Effect of amplitude modulation on QTV measurement

A recent study suggested that the template stretch method had less QTV compared to the conventional and template time shift method (Baumert *et al.* 2012). However, the underlying mechanism for obtaining lower QTV by the original template stretch method was not completely understood (Baumert *et al.* 2012). The updated approach showed a significant improvement even in the amplitude modulation conditions. In addition, the present approach may explain the reason for lower QTV in the original template stretch technique where 36% of beats were discarded from each simulated signal. Our result showed that the original template stretch method rejects more beats. This disparity in performance might be partly explained as the previous method highly depends on the threshold based R-peak detection (Pan and Tompkins 1985) where it fails to detect the lower amplitude of QRS. As a result, only higher amplitude of QRS-T waves were considered for computing the QT interval in the signal and thereby it showed lower artificial QTV compared with all other techniques. Furthermore, in the original template stretch method (Berger *et al.* 1997), it was assumed to be PVC beats (36% beats from each simulated signal) if the algorithm fails to detect the lower amplitude of QRS-T wave due to the amplitude modulation. Average artificial QTV was found less than 2 ms with updated approach where the automated beat rejection was only 15% from each of the simulated signal. In practice, real ECG signals might not be exactly the same as the simulated signals with amplitude modulation and thus the updated approach may be robust.

By considering the real ECG, our study also showed significant differences for quantifying beat-to-beat QTV in performances between old and new approaches. Our study may provide more reliable beat-to-beat QTV measurements for both theoretical and

practical application of ECG analysis. Furthermore, this study may contribute for better accuracy in beat-to-beat spectral analysis, VCG analysis and ST segment morphology analysis for different cardiac patients.

4.6 Chapter summary

In this chapter we have modified the R-peak detection algorithm with baseline wander removal for better accuracy in QTV analysis. The test results suggest that the updated ECG pre-processing approach outperforms the existing algorithm when evaluated on the simulated ECGs and real ECGs for analysing beat-to-beat QTV. In addition, the updated approach seems to perform comparable to the template time shift method. Further, the updated approach superseded the original approach in discarding less beats. This study suggests that the updated ECG preprocessing algorithm is recommended for more accurate quantification of beat-to-beat QT interval variability.

In the next chapter we will investigate the possible reason for higher beat-to-beat QTV in 12-lead ECG in MI patients using the updated beat-to-beat QT measurement technique.

Chapter 5

QT Interval Variability and T-wave Amplitude in Myocardial Infarction

THE purpose of this chapter was to investigate the effects of T-wave amplitude and ECG lead on beat-to-beat QT interval variability (QTV) in patients with myocardial infarction (MI) compared to healthy subjects. Standard resting 12-lead ECGs of 79 MI patients and 69 healthy subjects were investigated. Beat-to-beat QT intervals were measured separately for each lead using a template matching algorithm. In addition, we extracted the beat-to-beat T-wave amplitude in each lead. We computed the standard deviation of beat-to-beat QT intervals as a marker of QTV for both healthy subjects and MI patients. Significant QTV differences were observed between the 12 ECG leads as well as between the groups of healthy subjects and MI patients. Further, significant T-wave amplitude differences across leads and between groups were observed. A significant inverse relation between beat-to-beat QTV and T-wave amplitude was demonstrated. The group differences in QTV remained significant after co-varying for the T-wave amplitude. In conclusion, the increase in beat-to-beat QTV that has been repeatedly reported in patients with MI is partly due to the lower T-wave amplitudes. However, QTV remains significantly increased in MI patients after covarying T-wave amplitude.

5.1 Introduction

Myocardial infarction is one of the major causes of mortality in the world. The QT interval reflects the global depolarization and repolarization of the myocardial cells in the heart and it is thereby altered after myocardial infarction (Doroghazi and Childers 1978, Schwartz and Wolf 1978).

Further, elevated beat-to-beat QTV is thought to be indicative of cardiac repolarization lability and excessive sympathetic outflow (Baumert *et al.* 2011c, Tereshchenko *et al.* 2012, Das *et al.* 2012). A number of studies have demonstrated the prognostic power of increased QTV in patients with myocardial infarction (Furukawa *et al.* 2006, Jensen *et al.* 2005, Erikssen *et al.* 2012, Chen *et al.* 2011). However, the underlying mechanisms of elevated beat-to-beat QTV in patients with MI are currently incompletely understood. In addition to that, little is known about the factors related to the QTV measurement procedure that may cause higher beat-to-beat variability in MI patients.

Therefore, in this chapter we sought to investigate waveform dependent factors contributing to elevated beat-to-beat QTV in patients with MI compared to healthy subjects.

5.2 Methods

5.2.1 Subjects

Seventy-nine MI patients (22 female, mean age 63 ± 12 years; 57 male, mean age 57 ± 10 years) and 69 healthy subjects (17 female, 42 ± 18 years; 52 male, 40 ± 13 years) were investigated in this study. Eight patients had diabetes mellitus, 12 were obese and 27 had hypertension. Standard resting 12-lead ECGs that were recorded between 1–2 weeks after the infarction date were considered for this study. The duration of recording was on average two minutes. All data were obtained from the same database as described in Chapter 3, Section 3.2 earlier, which was collected between 1990 and 1997 at the Department of Cardiology of University Clinic Benjamin Franklin in Berlin, Germany. The sampling frequency of the ECG data was 1000 Hz with a 16-bit resolution over a range of $\pm$16.384 mV.

5.2.2 Beat-to-beat QTV analysis

To study beat-to-beat QTV, the accurate R-peak detection along with the correct identification of the QRS onset and T-wave offset are crucial, especially in the presence of noise and artefacts, which all ECG recordings typically contain to some degree. In this study, we used the template-matching approach that was originally introduced by Berger *et al.* (1997) and with an improved ECG pre-processing stage (Hasan *et al.* 2013b). The details of the updated approach have been described in Chapter 4. In brief, we have implemented a robust R-peak detection algorithm replacing the original algorithm, which was proposed by Pan and Tompkins (1985). Further, baseline removal based on cubic spline interpolation has been incorporated.

After detecting the R-peak, the operator defines a template of the QT interval by selecting the Q-wave onset and T-wave offset for one beat in a particular lead (Berger *et al.* 1997). Then, the beat-to-beat QT interval was determined for each of the 12 ECG leads by adopting the approach that has been previously described in Chapter 4. In addition, we measured the amplitude of the T-wave for each beat in all leads by following a procedure that has been published earlier (Hasan *et al.* 2012c). The median of absolute values of the T-wave amplitudes of each lead was determined and used in the subsequent analysis. The signal-to-noise ratio (SNR) was determined as the ratio of the median T-wave amplitude (signal) power to the iso-electric line (noise) power ($N_{iso-elec}$) for each individual lead in each recording. We measured the iso-electric line noise starting from the end of the T-wave over a period of 70 ms for each beat in each lead. The noise in each lead was quantified as the trimmed mean value (based on 10% rejection) of the variance in the iso-electric segment of all beats. The SNR is expressed using the logarithmic decibel scale. The equation for SNR is given below:

$$\mathrm{SNR} = 10\log_{10}\frac{T^2_{amplitude}}{N_{iso-elec}}. \tag{5.1}$$

In addition, we computed the standard deviation of normal RR intervals (sdNN) as a marker of heart rate variability (HRV) for each recording using lead II.

Statistical analysis

We used GraphPad Prism 6® (GraphPad Software, Inc., La Jolla, CA, USA), IBM SPSS Statistics 19® (IBM Inc., Armonk, NY, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). Beat-to-beat QTV was computed for each ECG

lead as standard deviation of QT intervals and compared between patients and healthy subjects using two-way ANOVA. We also performed receiver operating characteristic (ROC) curve analysis and calculated the area under the curve (AUC) for each ECG lead. In addition, two-way ANOVA was applied to test for gender differences in QTV. Further, two-way ANOVA was used to test for lead and group differences in T-wave magnitude and SNR. Post-hoc tests across the leads were performed using Sidak's multiple comparison tests. To explore the relation between QTV and T-wave amplitude, Pearson's linear correlation coefficient was computed separately for MI patients and healthy subjects. Prior to correlation analysis, QTV and T-wave amplitude values were log-transformed. Moreover, Analysis of Covariance (ANCOVA) was applied to co-vary for the effect of the T-wave amplitude on QTV. The Student's t-test was used to compare HRV between healthy subjects and MI patients. All values were expressed as mean $\pm$ standard deviation and test results were considered statistical significant if $p < 0.05$.

5.3 Results

Significant QTV differences were observed between leads ($p < 0.0001$) and between healthy subjects and MI patients ($p < 0.0001$) as shown in Fig. 5.1A. The highest QTV value in healthy subjects was observed in lead III (6.87 ± 6.71 ms) and for MI patients in lead aVF (7.42 ± 7.30 ms). In MI patients, QTV appears to be higher in six of the leads (I, II, aVR, aVF, V_5 and V_6) compared to healthy subjects (Sidak's multiple comparison tests across the leads, $p < 0.0001$), but was not significantly different in leads III, aVL, V_1, V_2, V_3 and V_4.

Similarly, ROC curve analysis demonstrated significant beat-to-beat QTV differences in ECG leads I, II, aVR, aVF, V_3, V_4, V_5 and V_6 as shown in Fig. 5.2. The highest area under the curve (AUC) was measured in lead II and the lowest in lead V_1. Table 5.1 ranks the AUC values of all 12 standard leads.

Significant T-wave amplitude differences were observed across leads ($p < 0.0001$) and between healthy subjects and MI patients ($p < 0.0001$) as shown in Fig. 5.1B. The highest T-wave amplitude in healthy subjects and patients with MI was measured in lead V_3 (0.55 ± 0.22 mV vs. 0.42 ± 0.24 mV). The T-wave amplitude in six leads was significantly lower in MI patients than the healthy subjects (Sidak's multiple comparison test across the leads, $p < 0.0001$), but was not significantly different in leads I, aVF and

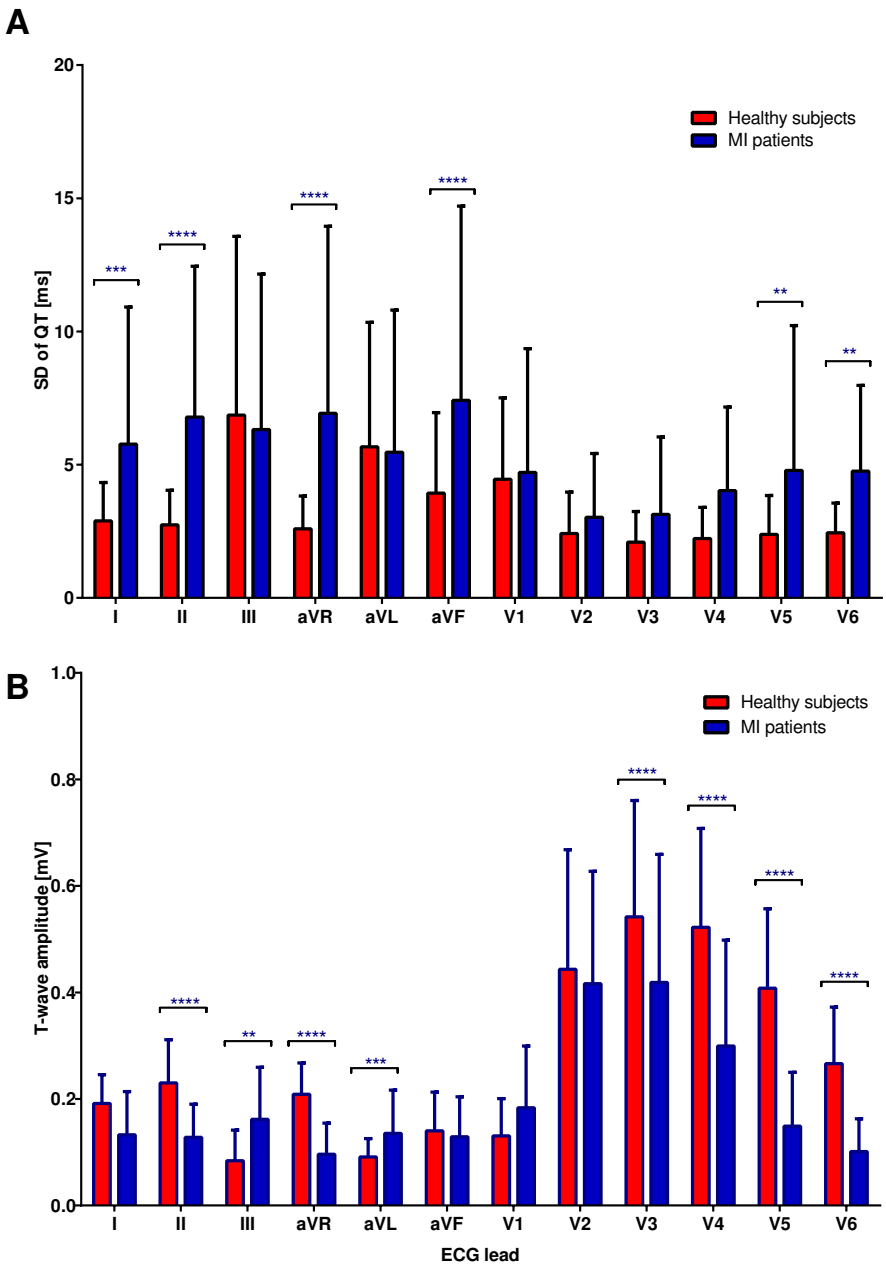

Figure 5.1. Beat-to-beat QT interval variability and T-wave amplitude in 12 lead ECG. Mean and standard deviation of beat-to-beat QT interval variability (A) and average T-wave amplitude (B) in healthy subjects and MI patients. Here, $p < 0.0001$ – ****, $p < 0.001$– ***, $p < 0.005$– **.

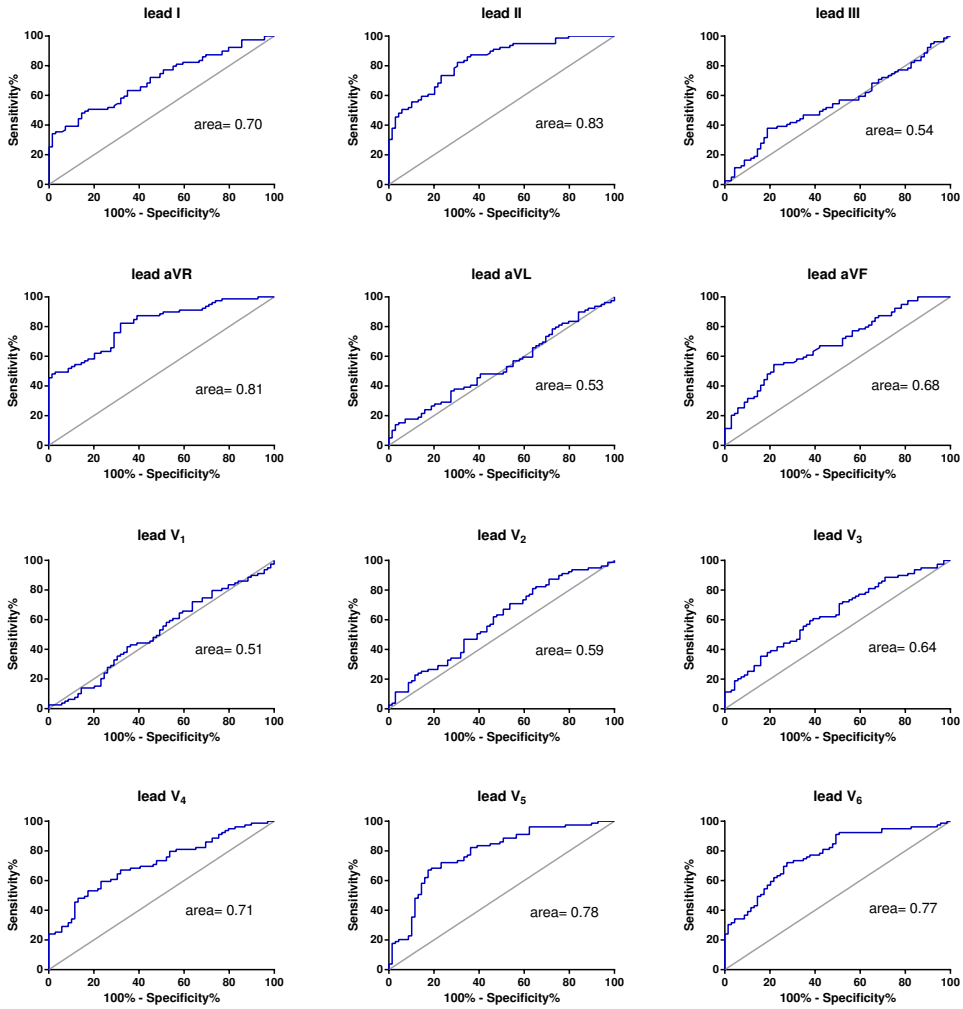

Figure 5.2. Receiver-operator-characteristics curves in 12 lead ECG. Receiver-operator-characteristics curves for beat-to-beat QTV in the 12-lead ECG, distinguishing MI patients from healthy subjects.

V_2. On the other hand, the T-wave amplitude in leads III and aVL was higher in MI patients than in healthy subjects.

Significant SNR differences were found between study groups (two-way ANOVA, $p < 0.0001$) and leads as shown in Fig. 5.3. The highest SNR in the recordings of healthy subjects was observed in lead V_3 (37.20 ± 4.90 dB) and the lowest was found in lead III (23.79 ± 5.15 dB) in healthy subjects. On the other hand, the highest SNR in MI recordings were measured in lead V_3 (30.79 ± 6.86 dB) and the lowest was measured in lead aVR (21.58 ± 5.17 dB).

Table 5.1. AUC values in 12 standard ECG leads. Ranking of the 12 standard ECG leads for distinguishing MI patients from healthy subjects using QTV, based on the area under the curve (AUC) of the ROC function.

Rank of leads	AUC	p-value
II	0.83	< 0.0001
aVR	0.81	< 0.0001
$\mathbf{V_5}$	0.78	< 0.0001
$\mathbf{V_6}$	0.77	< 0.0001
$\mathbf{V_4}$	0.71	< 0.0001
I	0.70	< 0.0001
aVF	0.68	< 0.001
$\mathbf{V_3}$	0.64	< 0.005
$\mathbf{V_2}$	0.59	> 0.05
III	0.54	> 0.05
aVL	0.53	> 0.05
$\mathbf{V_1}$	0.51	> 0.05

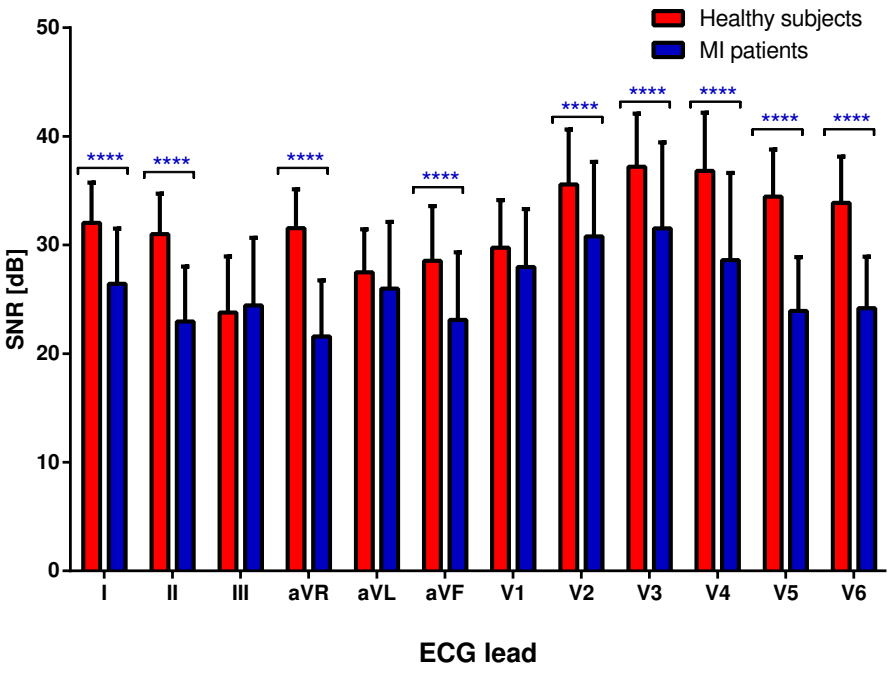

Figure 5.3. SNR in 12 lead ECG. Signal-to-noise ratio (mean and standard deviation) in 12-lead ECG of healthy subjects and MI patients. Here, $p < 0.0001$ – ****.

A significant inverse relation between log-transformed QTV and T-wave amplitude in 12-lead ECG was observed in healthy subjects ($r^2 = 0.37$, $p < 0.0001$) and MI patients ($r^2 = 0.22$, $p < 0.0001$), see Fig. 5.4A and Fig. 5.4B, respectively.

After co-varying for T-wave amplitude, significant between-group differences in QTV were still present ($p < 0.05$; ANCOVA). However, in several leads QTV was no longer significantly different between healthy subjects and MI patients as indicated in Fig. 5.5.

Gender specific comparison of QTV between healthy subjects and MI patients showed significant gender differences only in lead aVL and V_2, which were not significantly different between MI patients and healthy subjects. Elevated QTV values were observed in females, primarily in the group of healthy subjects (data not shown).

Comparing HRV between healthy subjects and MI patients, significantly lower SDNN values were found in MI patients (34 ± 39 ms vs. 48 ± 24 ms; $p < 0.05$) as shown in Fig. 5.6.

5.4 Discussion

The main finding of our study was an increase in QTV in the 12-lead ECG of patients with MI compared to healthy subjects, which was partly independent of differences in T-wave amplitude.

Increased QTV in MI patients has been repeatedly reported in earlier studies and was proposed as a marker of cardiac mortality (Murabayashi *et al.* 2002, Vrtovec *et al.* 2000, Berger *et al.* 1997). Most of these studies, however, were limited to one/two lead measurements. With this study, we were able to confirm that MI patients have higher beat-to-beat QTV than healthy subjects and this was observed in half of the 12 standard ECG leads. A reason for non-significant differences in QTV in some of the leads may be the low signal-to-noise ratio and consequently, the increase in measurement error.

Importantly, our study clearly demonstrates the inverse relation between beat-to-beat QTV and T-wave amplitude (Fig. 5.4). This is of significance as repolarization heterogeneity may result in smaller T-wave amplitudes and increased QTV may merely be a by-product of flatter T-waves and the associated increases in measurement inaccuracies of the T-wave end, as we have speculated previously (Hasan *et al.* 2012c, Baumert *et al.* 2012). Indeed, our MI patients had significantly smaller T-waves than

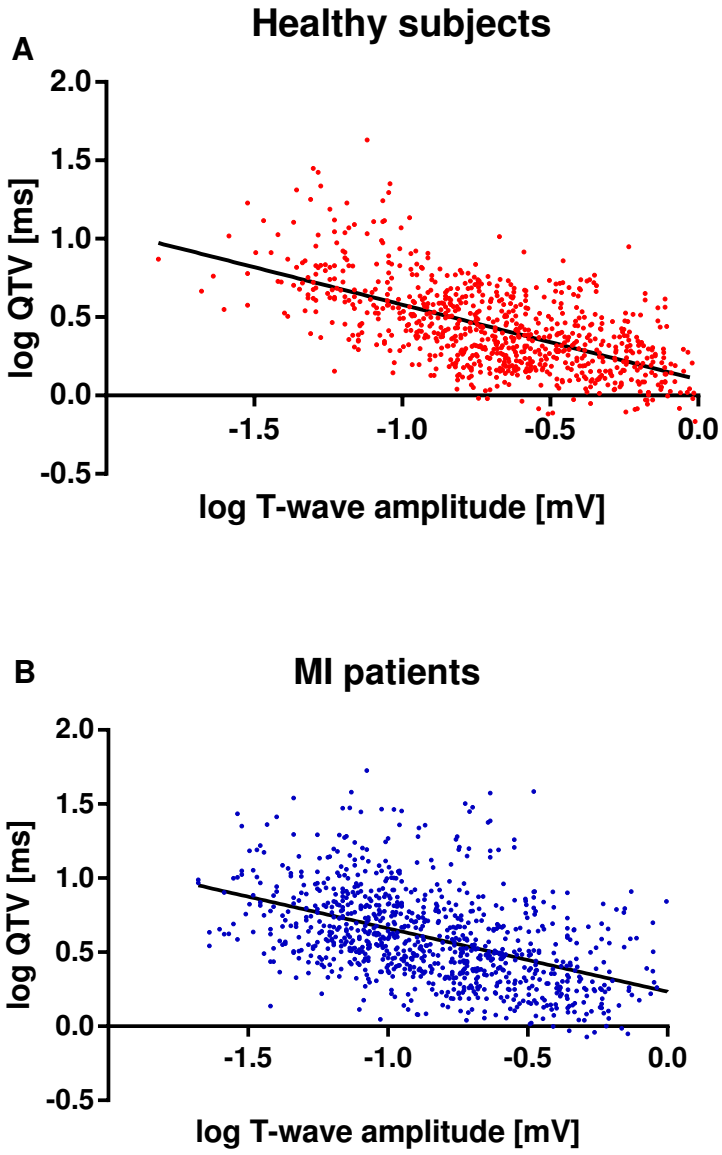

Figure 5.4. QTV and T-wave amplitude in 12 lead ECG. Relation between beat-to-beat QT interval variability (QTV) and T-wave amplitude in healthy subjects (A) and MI patients (B).

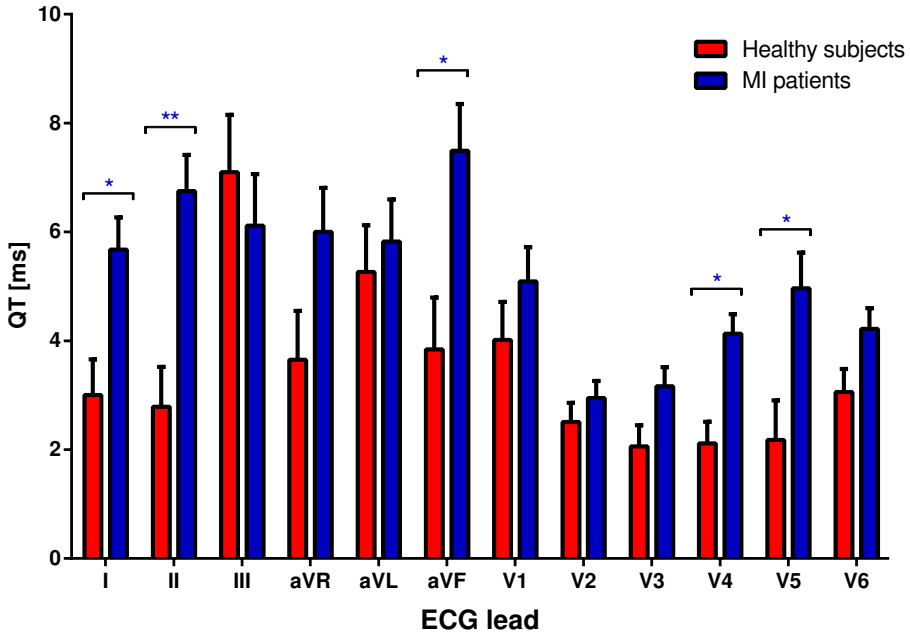

Figure 5.5. QTV in 12 lead ECG ANCOVA. QT interval variability (estimated mean and standard error of the mean) in 12-lead ECG after covarying for T-wave amplitude. Here, $p < 0.001$ – ** and $p < 0.05$ – *.

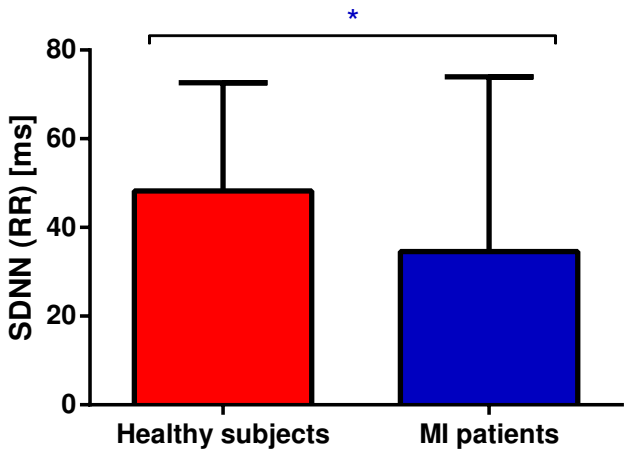

Figure 5.6. HRV in lead II for healthy subjects and MI patients. Heart rate variability (SDNN) between healthy subjects and MI patients expressed as mean and standard deviation. Here, $p < 0.05$ – *.

healthy subjects (Fig. 5.1B) and consequently, a reduced SNR (Fig. 5.3) in most of the ECG leads. We attempted to exclude the effect of T-wave amplitude differences from our analysis. By means of analysis of covariance we were able to demonstrate a T-wave amplitude independent association between MI and QTV. Although a large part of QTV increase in MI patients could be explained by flatter T-waves, QTV was still significantly increased in leads I, II, aVF, V_4 and V_5. Thus, our study suggests that higher QTV in MI patients compared to healthy subjects may not be completely explained by the T-wave amplitude. Increased complexity of T-wave morphology may have contributed to QTV, but we were not able to quantify T-wave morphology in our study.

Apart from this, we have also investigated the relation between beat-to-beat QTV, location of infarction and T-wave amplitude in individual leads, but did not observe a clear association between QTV across leads and infarct location (data not shown). In addition to T-wave amplitude, rate-adaptation of the QT interval is a significant contributor to QTV and may account for the group differences observed between MI patients and healthy subjects. We found significantly lower HRV in MI patients compared to healthy the subjects, which is in full agreement with many previous studies (Malik *et al.* 2000, Carney *et al.* 2001, Cripps *et al.* 1991, Kleiger *et al.* 1987) Given that HRV was reduced in MI patients an increase in QTV through rate-adaptation is implausible. On the other hand, increased sympathetic nervous system activity may have contributed to the increased QTV (Sacre *et al.* 2012, Baumert *et al.* 2011c), by reducing the repolarization reserve or increasing the effects of transmural dispersion in repolarisation due to arborization of sympathetic nerves, in addition to repolarization heterogeneity directly caused by tissue damage.

Our study has several limitations. The analysis was based on a cross-sectional comparison of MI patients and healthy subjects and, therefore, our findings may not be extrapolated to post-MI risk stratification for sudden cardiac death. The average age of MI patients was significantly higher than that of healthy subjects and might have affected our results. Comorbidities (e.g. diabetes mellitus) were present in some of the patients and may have influenced our results. Similarly, we cannot exclude the possibility of medication effects on QTV. Further, the ECG recordings from the PTB database were relatively short. Our data was approximately 2 minutes and more duration (e.g. 5 minutes) of the recording might increase the consistency of the QTV measurement and thereby increase the statistical power. Moreover, there was limited patient information available in the PTB database for example not contains BMI values.

5.5 Chapter summary

In this chapter, we have investigated the waveform dependent factors contributing to elevated beat-to-beat QTV in patients with MI compared to healthy subjects. We found that the beat-to-beat QTV varies between leads and is inversely related to T-wave amplitude, both of which were reduced in MI patients. However, elevated beat-to-beat QTV cannot be solely attributed to flatter T-waves and thus may provide independent prognostic information. Finally, this study confirms that the increased beat-to-beat QTV in MI patients does not only depends on T-wave amplitude but also depends on other factors, where future research is required for further investigation.

In the following chapter we will study the QT variability using vectrocardiographic analysis to assess the predictive capabilities of descriptors for identifying the cardiac patients.

Chapter 6

Vectorcardiographic Analysis of Ventricular Activity in MI Patients

THIS chapter aims at assessing the beat-to-beat spatial and temporal variations of ventricular depolarization and repolarization in vectocardiograms (VCGs) for characterising myocardial infarction (MI) patients. Spatial and temporal variations in the QRS complex and T-wave loops were studied by investigating several descriptors (point-to-point distance variability, mean loop length, T-wave morphology dispersion, percentage of loop area, and total cosine R-to-T). Beat-to-beat assessment of VCG parameters may have diagnostic attributes that may be of assistance in identifying MI patients.

6.1 Introduction

Generally, ECG describes the cardiac signal in-terms of an amplitude, but not the orientation of the heart vector direction. In addition, our recent research suggests that beat-to-beat QTV varies in inter-lead measurement, partly due to T-wave amplitude differences (Hasan *et al.* 2012c). Vectorcardiography (VCG) is the methodological elaboration of the ECG, which measures the cardiac electrical field as a vector with both magnitude and direction. More precisely, VCG aims at an orthogonal representation that reflects the electrical activity in the three perpendicular directions X, Y, and Z. Even though the 12-lead ECG analysis is the reference setup for diagnostic purposes, the VCG is a useful alternative (Chou 1986, Belloch *et al.* 2007, Strauss *et al.* 2009, Tereshchenko *et al.* 2010) that represents the spatial and temporal information of cardiac activity (Rautaharju *et al.* 1973, Zabel *et al.* 2000a, Carlson *et al.* 2005). Several techniques have been suggested for the derivation of VCG from standard 12-lead ECG for analysis of the cardiac signal (Guillem *et al.* 2008, Man *et al.* 2009, Shvilkin *et al.* 2009). Vectorcardiographic QRS-loop and T-loop analysis was demonstrated to improve risk stratification in patients with heart disease by considering a single beat of the ECG (Acar *et al.* 1999b, Turrini *et al.* 2001, Shvilkin *et al.* 2010, Cortez and Schlegel 2010).

However, the beat-to-beat variations in VCG and its descriptors are poorly understood and little is known about how these descriptors compare in different cardiac conditions. Therefore, in this chapter, we have investigated beat-to-beat VCG by quantifying different descriptors from the QRS and T-loop in patients with myocardial infarction (MI) as well as healthy subjects. We hypothesize that beat-to-beat variability VCG parameters may provide diagnostic information for discriminating between control subjects and MI patients.

6.2 Methods

6.2.1 Subjects

Standard resting 12-lead ECGs of 84 MI patients (22 females, mean age 63 ± 12 years and 62 males, mean age 56 ± 10 years) and 69 healthy subjects (17 females, mean age 42 ± 18 years and 52 males, mean age 40 ± 13 years) were investigated in this study. Most of the MI patient recordings were carried out approximately 1–2 weeks after infarction. Concerning the location of infarction, seven were anterior, 15 were

antero-lateral, 20 were antero-septal, 20 were inferior, 12 were infero-lateral, seven were infero-postero-lateral, one was lateral and two were postero-lateral. None of the patients had bundle branch block or intra-ventricular conduction defects. The QRS widths for patients with MI were comparable to those of controls (0.084 ± 0.0130 sec vs. 0.081 ± 0.008 sec, $p > 0.05$). None of the patients had a QRS width over 0.12 sec. The data were obtained from same database as described in Chapter 3, Section 3.2. In brief, the ECGs were recorded for approximately two minutes at a sampling frequency of 1000 Hz and at 16-bit resolution over a range of ± 16.384 mV. In addition, the data were analysed anonymously, using publicly available secondary data, therefore no ethics statement is required for this work.

6.2.2 Spatial and temporal VCG analysis

The overall block diagram of ECG descriptor extraction is shown in Fig. 6.1. To analyse spatial and temporal variations in depolarization and repolarization waves, a beat-to-beat VCG approach has been investigated in this study. For finding the beat-to-beat QT intervals, we have used the template matching algorithm proposed by Berger *et al.* (1997). If any beat is missed by the proposed algorithm in one lead in a particular time instant, then a custom designed program automatically ignores the same beat of that time instant for rest of the leads. Further, this template matching algorithm uses an error function that was defined with respect to the sum of squared differences between the template T-wave and the stretched or compressed version of the T-wave for that beat. The algorithm finds the QT interval of all beats in a particular lead by determining how much each T-wave must be stretched or compressed in time to minimize the error function (Berger *et al.* 1997). The beat-to-beat QT interval was determined for each individual lead in 12-lead ECGs by adopting an approach, which has been previously described Chapter 3, Section 3.2 . Thereby, the beat-to-beat QRS complex onset (t'_{RS}) and T-wave terminus locations were found. The end point of the QRS complex (t'_{RE}) was obtained by adding 48 ms to the first point after the maximum of energy of the R wave falls below 70% of its maximum as originally proposed by Acar *et al.* (1999b). The onset of the T-wave was also computed by following the approach described by Acar *et al.* (1999b). Thus, we have found the beat-to-beat QRS and T-wave in all standard 12-lead ECGs. Ectopic beats and excessively noisy beats were automatically excluded from analysis; the latter were identified utilizing the error function of template matching.

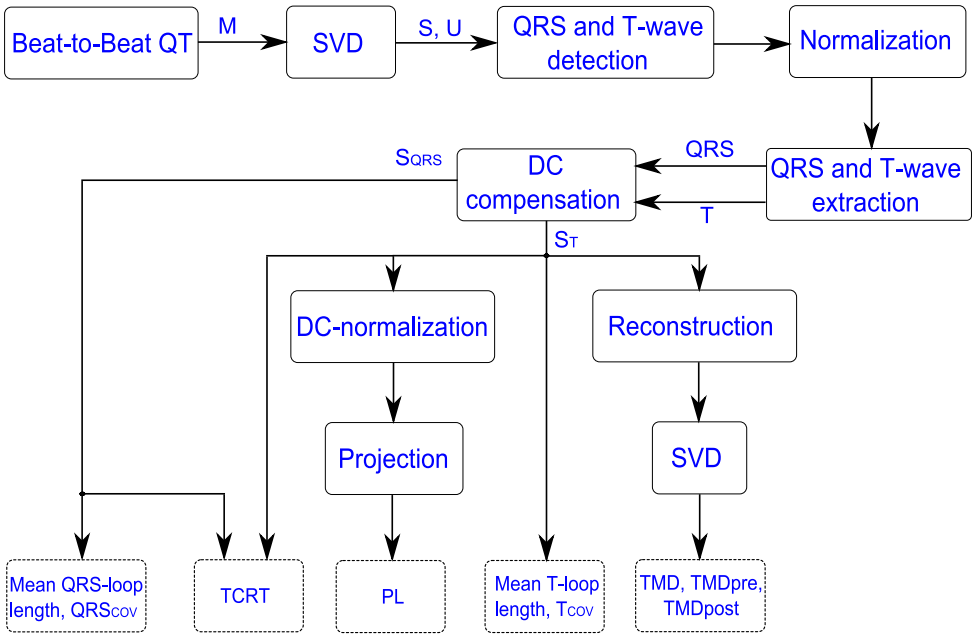

Figure 6.1. Block diagram of the overall beat-to-beat VCG approach. The solid line of rectangular or square represents the different processes or methods. The rectangles with dashed lines (at the bottom) represent the output parameters (descriptors).

Descriptors of spatial and temporal wavefront characteristics for 12-lead ECG have been proposed by Acar *et al.* (1999b). In the original and most subsequent studies only a single beat of ECG was considered. In addition, only descriptors of the T-wave morphology have been investigated. In our study, we expand this approach by developing beat-to-beat VCG analysis of ventricular depolarization and repolarization.

To derive VCG from the 12-lead ECG we employ singular value decomposition (SVD) (Acar *et al.* 1999b). It is assumed that $\mathbf{M}$ is an input matrix $(8 \times n)$, where 8 represents the number of corresponding rows of ECG leads for one QT interval (I, II, $V_1 - V_6$) and n is the number of samples. The SVD of the eight signals creates three matrices $\mathbf{U}$, $\mathbf{V}$ and $\mathbf{S}$, as follows.

$$\mathbf{U} = [u_1, \ldots\ldots, u_8] \in \Re^{8\times 8}$$

$$\mathbf{V} = [v_1, \ldots\ldots, v_8] \in \Re^{n\times n}$$

$$\mathbf{S} = [s_1, \ldots\ldots, s_8] \in \Re^{8\times n}$$

$$\Sigma = U^T M V = \mathrm{diag}\,(\sigma_1, \ldots\ldots, \sigma_8)\,, \tag{6.1}$$

where, $\sigma_1 \geq \sigma_2 \geq \ldots \geq \sigma_8 \geq 0$ and the columns of **U** are referred to as the left singular vectors, **V** are referred to as the right singular vectors and **S**, are referred to as the decomposed ECG signals for eight leads. Here, the matrix Σ (same size as **S**) pseudo-diagonal matrix, where all off diagonal elements are equal or greater than 0, but the matrix is not square.

It has been reported that 99% of the ECG energy can be represented in a three-dimensional minimum subspace (Acar and Koymen 1999). Thus, the effective rank of the matrix (**M**) is three and only first three significant decomposed signals (S_1, S_2, S_3) have been used in this study, $\mathbf{E}_{3D}$ (Acar *et al.* 1999b), where

$$E_{3D}(t_i) = \| [S_1(t_i)S_2(t_i)S_3(t_i)]^T \|_2. \tag{6.2}$$

Then, the decomposed signals were normalized with the maximum energy:

$$\bar{S}_{3D}(t_i) = \frac{S_{3D}(t_i)}{\max_i (E_{3D}(t_i))}. \tag{6.3}$$

The QRS complex and T-wave signals were extracted and stored in data matrices SQRS and ST, respectively that were proposed by Acar *et al.* (1999b). The reconstructed T-wave from ST is considered to be a form of morphological filtering.

In this study, a new parameter was computed for both QRS-complex and T-wave DV_{QRS} and DV_T, respectively, called the point-to-point distance variability (DV). This DV was determined based on the coefficient of variance of point-to-point distance from each loop to the mean loop of ventricular depolarization and repolarization. The point-to-point distance (see Fig. 6.2) was computed by finding the shortest distance from each point of the loops to the mean loop of QRS and T-loop, respectively. For finding the point-to-point shortest distance between loops, the k-nearest neighbours (kNN) algorithm was applied (Cover and Hart 1967). The kNN algorithm is a nonparametric method where the distance metric is calculated based on Euclidean distance. The distance between two vectors is computed as the length of the difference vector $|X_r - X_s|$, denoted by

$$d(X_r, X_s) = |X_r - X_s| = \sqrt{(X_{r_1} - X_{s_1})^2 + (X_{r_2} - X_{s_2})^2 + (X_{r_3} - X_{s_3})^2}. \tag{6.4}$$

In addition, another new descriptor was computed, named the mean loop length (MLL). This MLL parameter was calculated for the mean loop of the QRS and T-loop by adding

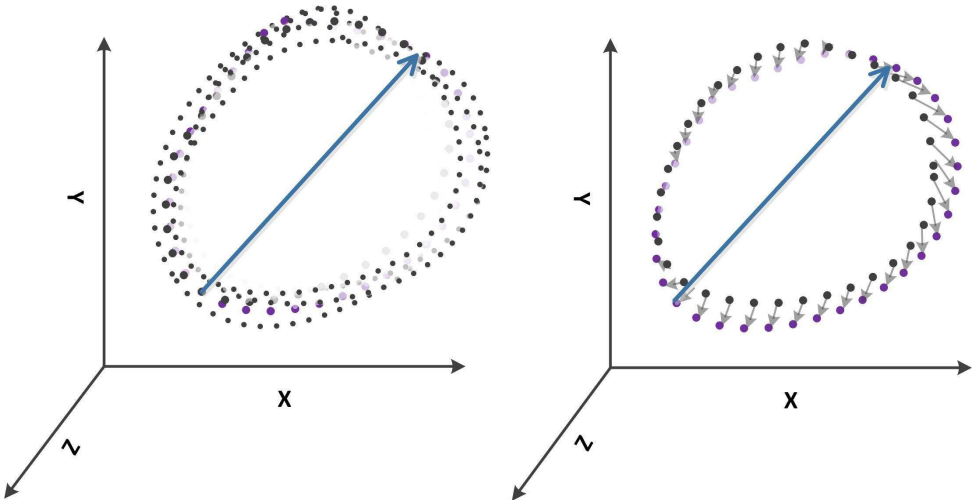

Figure 6.2. Point-to-point distance of ECG loops. The purple coloured loop depicts the mean loop. The long arrow depicts the peak of R or T-wave, respectively. Left: Schematic representation of superimposed ECG loops for several cardiac cycles. Right: The small arrows show the distance from each point of an individual loop representing one cardiac cycle to the mean loop.

the distance from each point to the next point in the loop. Moreover, for repolarization lability, three other descriptors were computed on a beat-to-beat basis, T-wave morphology dispersion TMD, TMDpre and TMDpost, as originally proposed by Acar *et al.* (1999b) for single beat ECG analysis. Further, the percentage of loop area (PL) was also determined in a beat-to-beat manner for the T-loop by following the same principle proposed by Acar *et al.* (1999b), but including the cells which were occupied by loop itself. To deal with beat-to-beat variability in QT intervals, which leads to beat-to-beat loops of different lengths, we truncated the QT intervals at the minimum length that is met by 90% of beats.

Finally, the relationship between the QRS and T-loops was also determined in a beat-to-beat manner through the 'total cosine R-to-T' (TCRT) that is the average of the cosines of the angles between the vectors of QRS (defined from t'_{RS} to t'_{RE}) and the maximum of the unit vector $e_{T,1}$ (the vector $e_{T,1}$ reflects the orientation of the T-wave loop (Acar *et al.* 1999b) as equation. 6.5 and shown in Fig. 6.3).

$$TCRT = \frac{1}{t'_{RE} - t'_{RS}} \int_{i=t'_{RS}}^{t'_{RE}} \cos\left(\angle\left(e_{T,1}, S_{QRS}(i)\right)\right). \tag{6.5}$$

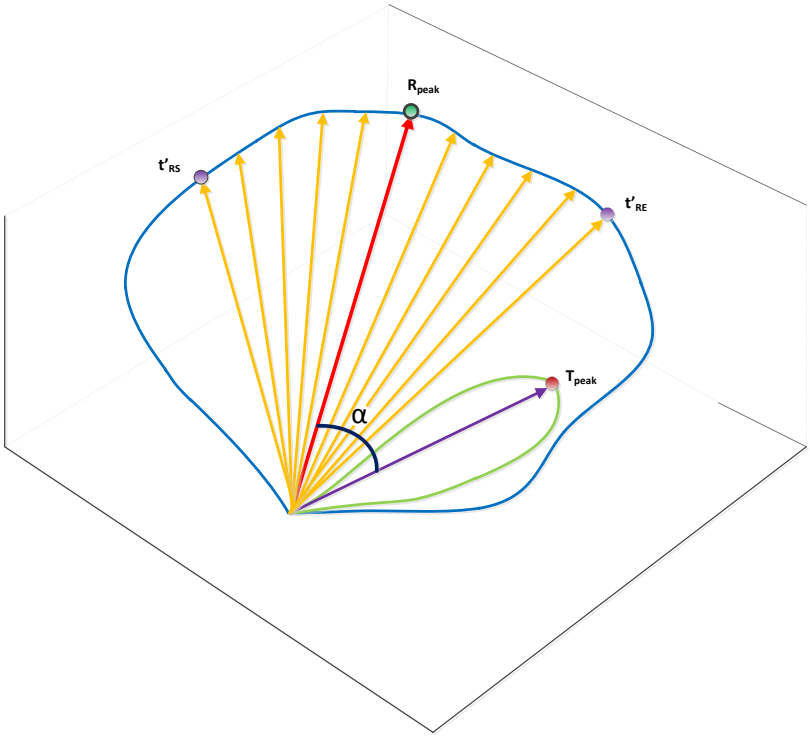

Figure 6.3. TCRT of the QRS-loop and T-loop. The 'total cosine R-to-T' (TCRT) describes the difference in global wavefront directions of depolarization and repolarization. The angle α is the angle between the main vectors of the QRS and T-loops.

Statistical analysis

We have used GraphPad Prism 5® (GraphPad Software, Inc., La Jolla, CA, USA), PASW Statistics 18® (IBM SPSS, Inc., Somers, NY, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA) for the statistical analysis. All values were expressed as mean $\pm$ standard deviation. Test results were considered statistical significant when $p < 0.05$. The beat-to-beat VCG descriptors (mean and standard deviation) were found for both the MI and the control group. Beat-to-beat variability of the VCG descriptors was calculated as standard deviation of those parameters. Further, the unpaired Student t-test was used to compare the descriptors characteristics between both studied groups.

6.3 Results

The beat-to-beat ventricular depolarization and repolarization loops are shown in Fig. 6.4, where the QRS-loops and T-loops are depicted separately as well as combined for both

Table 6.1. QRS and T-loop descriptors in the control and MI groups.

Descriptors	Control	MI	p
Mean of DV_{QRS}	0.66 ± 0.14	0.66 ± 0.17	> 0.05
SD of DV_{QRS}	0.10 ± 0.04	0.13 ± 0.04	< 0.0001
Mean of DV_T	0.63 ± 0.16	0.62 ± 0.18	> 0.05
SD of DV_T	0.13 ± 0.06	0.16 ± 0.07	< 0.05
MLL_{QRS} (mV)	18230 ± 5341	14269 ± 3507	< 0.0001
MLL_T (mV)	4332 ± 1699	3410 ± 1858	< 0.001
Mean of TMD (degree)	38 ± 16	62 ± 18	< 0.0001
SD of TMD (degree)	15 ± 6	12 ± 5	< 0.005
Mean of TMD_{pre} (degree)	40 ± 18	62 ± 20	< 0.0001
SD of TMD_{pre} (degree)	17 ± 6	16 ± 8	> 0.05
Mean of TMD_{post} (degree)	34 ± 14	60 ± 20	< 0.0001
SD of TMD_{post} (degree)	16 ± 6	13 ± 5	< 0.01
Mean PL (%)	55 ± 15	46 ± 17	< 0.001
Mean of TRCT	-0.04 ± 0.43	0.03 ± 0.45	> 0.05
SD of TCRT	0.12 ± 0.07	0.13 ± 0.12	> 0.05

typical control subjects and MI patients, respectively. Statistical results of all descriptors are summarized in Table 6.1.

Point-to-Point Distance Variability (DV) at QRS and T-loop

The mean point-to-point distance variability for QRS-loop (DV_{QRS}) was not found statistically different between control and MI patients. However, the standard deviation of point-to-point distance variability in QRS loops was found to be higher in the MI group than in the control group, as shown in Fig. 6.5A.

Similarly, the mean point-to-point distance variability of the T-loop (DV_T) was not statistically significant. However, the standard deviation of point-to-point distance variability was significantly higher in the MI group than the control group (Fig. 6.5B).

Mean Loop Length (MLL)

The mean loop length of QRS-loop (MLL_{QRS}) was found statistically higher in the control than the MI group (Fig. 6.5C). Similarly, the mean loop length of T-loop (MLL_T) was found to be higher in the control subjects than in the MI patients (Fig. 6.5D).

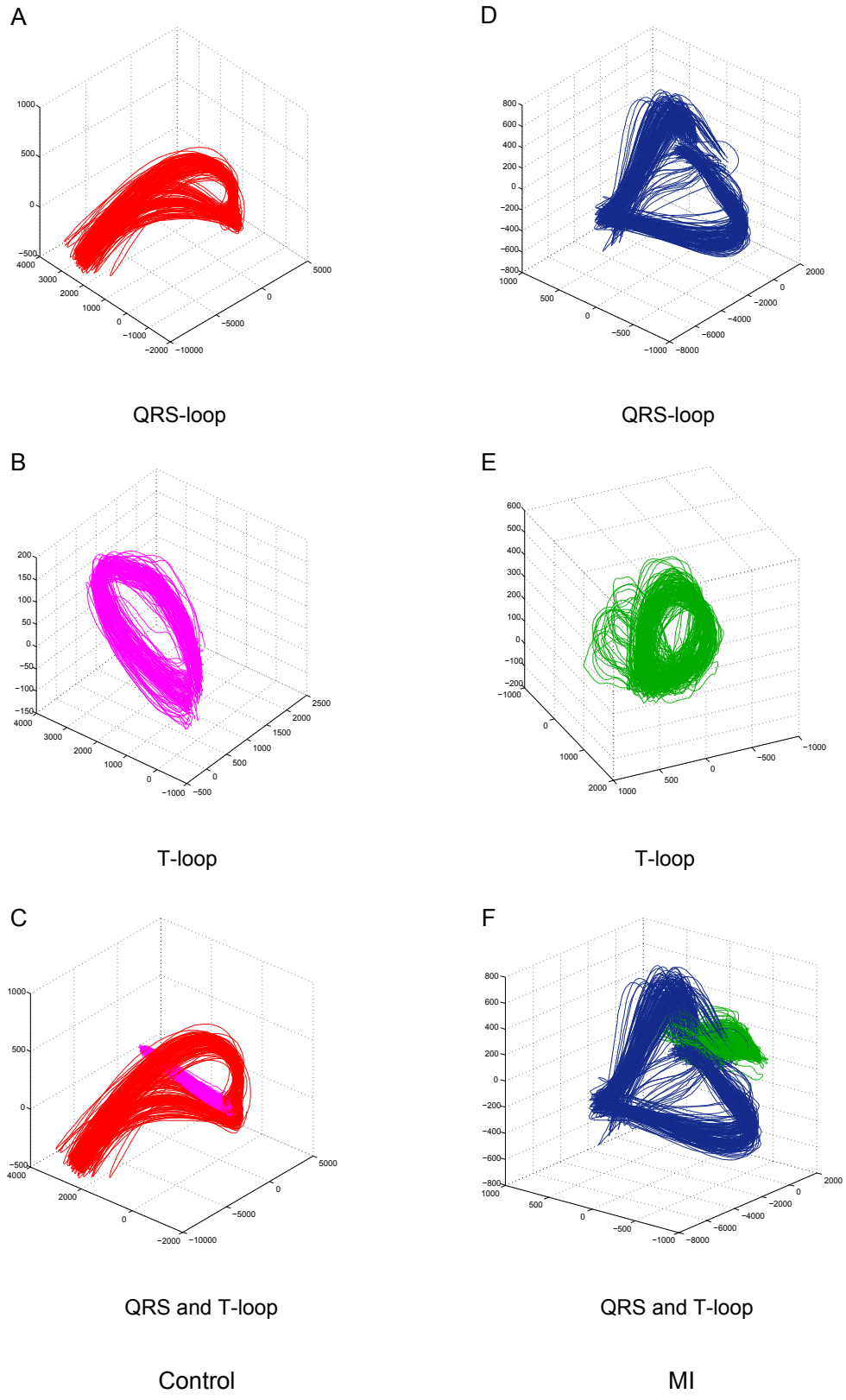

Figure 6.4. Beat-to-beat depolarization and repolarization loops in a control subject and a MI patient. The QRS (A) and T loops (B) and their combination of a normal subject are shown in red and magenta. The QRS (D) and T-loops (E) and their combination (F) of a MI patient are shown in blue and green.

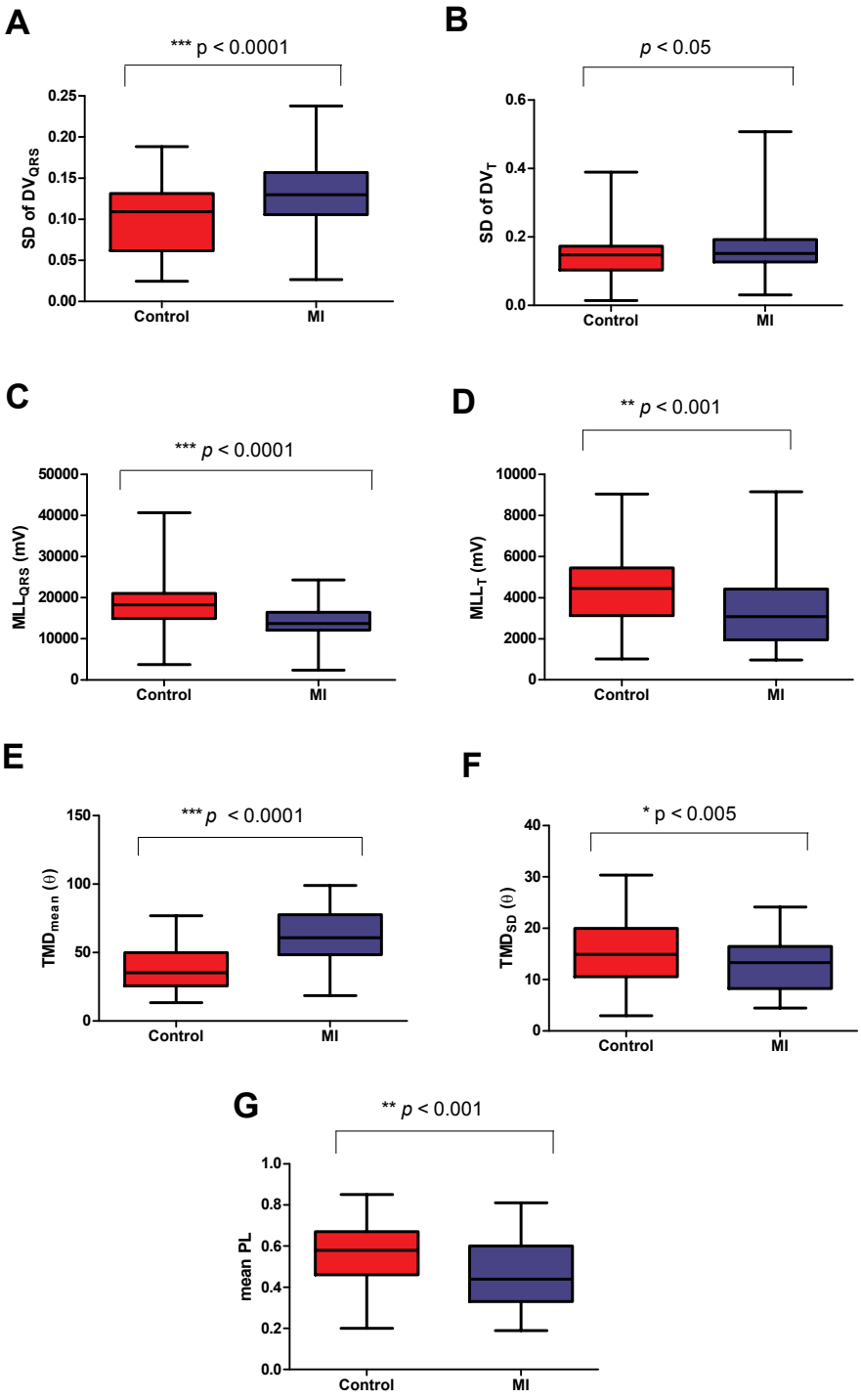

Figure 6.5. Group comparison of ventricular depolarisation and repolarization parameters. Point-to-point distance variabilityin QRS-loops (A) and T-loops (B), mean loop length of QRS-loops (C) and T-loops (D). Mean (E) and standard deviation (F) of TMD and mean PL (G) show significant differences between normal subjects and MI patients.

TMD, TMD_{pre} and TMD_{post}

The TMD parameter represents the variation of morphology of the T-wave between different ECG leads during ventricular repolarization. The mean beat-to-beat TMD was relatively lower in control subjects than MI patients, as shown in Fig. 6.5E. However, the standard deviation of beat-to-beat TMD was significantly lower in MI patients compared to controls as shown in Fig. 6.5F.

Looking at the T-wave morphology dispersion in more detail, we quantified TMD separately for the rising (TMD_{pre}) and falling (TMD_{post}) edge of the T-wave. The mean beat-to-beat TMD_{pre} was significantly higher in MI patients, but the variability of TMD_{pre} was not found to be statistically different between the control and MI group. The falling edge of mean beat-to-beat T-wave morphology dispersion was found to be lower in control subjects than in MI. Conversely, the variability of this parameter was reduced in MI patients compared to controls as shown in Table 6.1.

Loop area

The PL for mean T-wave loop was higher in the control subjects compared to MI patients as shown in Fig. 6.5G.

TCRT

The negativity of TCRT quantifies the deviation in the orientation of depolarization and repolarization loops. In our study, the mean TCRT showed no statistically significant difference between control subjects and MI patients. Similarly, the beat-to-beat variability of TCRT was comparable between MI patients and control subjects. Fig. 6.6 shows the mean and SD values of TCRT for all control subjects and MI patients.

6.4 Discussion

Our study proposes an approach for analysing the beat-to-beat spatial and temporal variations of ventricular depolarization and repolarization wavefronts and evaluates the value of those parameters for characterising cardiac electrical abnormalities in patients with MI.

The main finding of our study is an increase in variability of depolarization as well as repolarization in patients with MI compared to normal subjects. Our beat-to-beat VCG approach demonstrated increased instability in depolarization and repolarization in MI patients as demonstrated by increased point-to-point distance variability

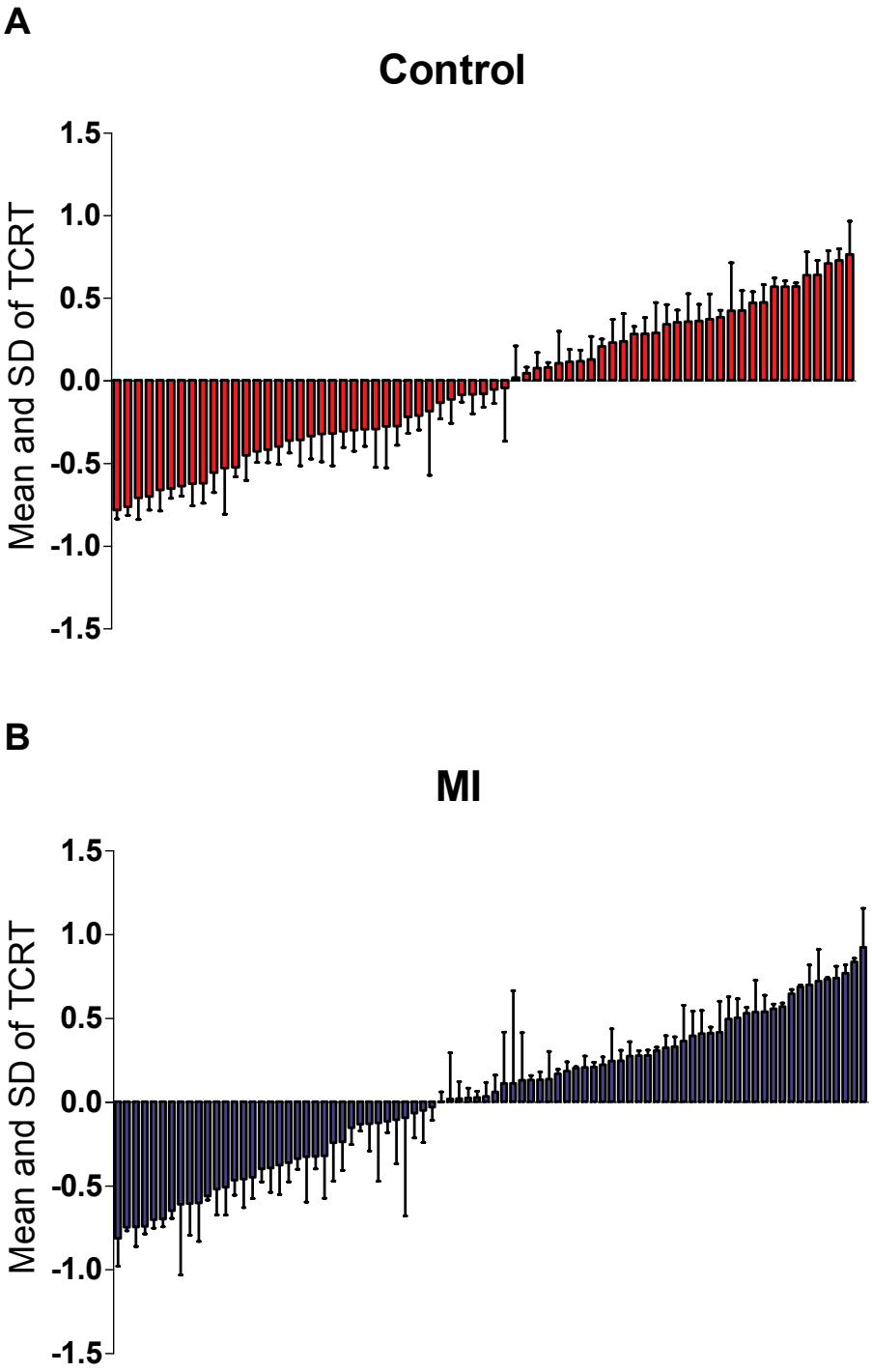

Figure 6.6. TCRT across subjects. Data are presented as mean and SD (in ascending order from left to right based on their mean value) of TCRT for individual control subjects (A) and MI patients (B).

(Fig. 6.5A and Fig. 6.5B). This is in line with previous observations of increased QRS (Sörnmo *et al.* 1998) and QT variability (Perkiömaki *et al.* 1995) observed in the 12 lead ECG in patients with coronary artery disease and following myocardial infarction. Both, QRS and T-loops were significantly shorter in MI patients compared to controls (Fig. 6.5C and Fig. 6.5D) and suggest less coordinated conduction and repolarization of the ventricular myocardium, which would result in smaller magnitudes of QRS and T vectors.

Along with our new parameters, a number of other parameters were also investigated in a beat-to-beat manner to quantify the discriminative power. Our observations confirm that MI patients have higher TMD values compared to the normal subjects (Ono *et al.* 2005), which indicates that the reconstruction vectors for control subjects were closely grouped (i.e. have similar morphology) and relatively dispersed in the MI patients. Another study showed significant predictive value of TMD for cardiovascular mortality in the general male population (Porthan *et al.* 2009). The beat to-beat variability of TMD was found decreased in patients with MI. However, our study suggests that the group difference in the average value of TMD is more significant than its beat-to-beat variability.

Further, the investigation of TMD by considering TMD_{pre} (rising edge of T-wave) and TMD_{post} (falling edge of T-wave) demonstrated that dispersion was, for both parts of the T-wave, higher in the MI than in the control subjects. However, it appears that the last part of the T-wave might be more indicative of repolarization abnormalities in MI patients and is in line with reports on the prognostic value of the $T_{peak} - T_{end}$ interval of ECG (Haarmark *et al.* 2009, Szydlo *et al.* 2010). However, the beat-to-beat variability of these parameters shows a different scenario. No significant difference between control and MI group in the variability of TMD_{pre} was observed, but a significant decrease in the variability of TMD_{post} was found in MI patients. The cause for reduced beat-to-beat variability in TMD_{post} of MI patients is not clear.

The TCRT descriptor that measures the vector deviation between the depolarization and repolarization waves has been investigated in several studies (Acar *et al.* 1999b, Smetana *et al.* 2004) and was found to be an independent predictor of cardiac mortality in some studies (Porthan *et al.* 2009, Huang *et al.* 2009), but not in others (Perkiömäki *et al.* 2006, Lin *et al.* 2007). However, the majority of previous studies were limited to single analysis of beat of QRS and T-loop. Our study did not show a significant difference in

the mean value of TCRT between MI patients and normal subjects. Beat-to-beat analysis of TCRT in our study demonstrated comparable variability in MI patients and controls and is in contrast with other studies, which suggest that TCRT might have prognostic value when analysed in a beat-to-beat manner (Kenttä *et al.* 2010, Kenttä *et al.* 2011). Importantly, the aforementioned studies investigated TCRT variability during exercise tests.

In addition, we have observed that control subjects have higher values of PL than MI patients, which indicates relatively smooth and connected average T-loops in control subjects compared to MI patients, further emphasising the presence of repolarization abnormalities.

In summary, significant changes in ventricular conduction and repolarization processes post MI could be detected in a variety of VCG parameters, capturing features of the averaged cardiac cycle and beat-to-beat lability.

6.5 Limitations

The information on the subjects included in the PTB database is limited and, for example, does not contain BMI values for both MI patients and healthy subjects. Also, the average age in the MI group was significantly higher than in the control group and might have had an impact on our results. In addition, the duration of the ECG recordings for this study was relatively short and longer duration of data could increase the statistical performance of the vectorcardiographic QRS and T-loop descriptors. Further, we did not compare the performance of our VCG approach to more established techniques, e.g. single lead QT variability assessment. The method of QRS end estimation that was employed in this study might be a considerable limitation if patients with ventricular conduction abnormalities were to be considered. However, in this study, none of the ECG signals had a QRS width over 0.12 sec.

6.6 Chapter summary

Vectorcardiographic analysis of beat-to-beat variability in ventricular depolarization and repolarization may provide markers of electrical instability in the heart of patients with myocardial infarction. In this chapter we have studied the predictive power of

the VCG descriptors that can be a marker for identifying the patients. From this study it is evident that VCG approach might be more suitable for analysing the QTV, but still it needs further study on the measurement of beat-to-beat QT interval in surface ECG.

The next chapter will investigate the effect of autonomic control system activity on beat-to-beat VCG descriptors in heart failure patients.

Chapter 7

Effect of Pacing and Autonomic Nervous System on VCG Parameters

VENTRICULAR repolarization (VR) is strongly influenced by heart rate and autonomic nervous system activity, which is important for arrhythmogenesis. However, the effect of autonomic nervous system on beat-to-beat spatiotemporal of QRS and T-loop parameters is little known. Therefore, the aim of the chapter is to assess the effect of pacing and autonomic nervous system activity on beat-to-beat VCG descriptors in heart failure patients.

7.1 Introduction

Heart failure (HF) is a physiological condition where the cardiac output is not sufficient in meeting the needs of the body and lungs. It is an increasingly common and life threatening disease linked with high morbidity and mortality rates. In addition, heart failure patients have higher risk of sudden cardiac death and most of these are the result of ventricular tachyarrhythmias (Tomaselli *et al.* 1994). Moreover, ventricular repolarization, which reflects the QT interval duration, is influenced by heart rate (HR) and is modulated by autonomic nervous system activity that plays an important role for arrhythmogenesis. The QT interval variability (QTV) indicates the repolarization lability and increased heterogeneity of QTV is believed to be ECG marker for risk predictor in cardiovascular diseases. Our previous study demonstrated that HF patients have increased variability of beat-to-beat QT interval due to the higher heart rate and limited effect of autonomic nervous system (Nayyar *et al.* 2013). However, vectorcardiography (VCG) is an alternative analysis that provides three-dimensional QRST-derived ECG parameters that precisely describes both magnitude and direction of the heart signal. Several studies showed the predictive power of VCG derived descriptors for identifying several cardiac diseases (Porthan *et al.* 2009, Tereshchenko *et al.* 2010, Hasan *et al.* 2012a) and in our previous Chapter 6.

Nevertheless, the role of pacing and autonomic nervous system on beat-to-beat variations in VCG descriptors is not completely understood. Therefore, in this study, we have investigated beat-to-beat VCG by quantifying several descriptors from the QRS and T-loop in patients with heart failure (HF) as well as structurally normal hearts (H_{Norm}).

7.2 Methods

7.2.1 Subjects

This study included 19 adult subjects, 11 of which possessed heart failure and 8 with a normal condition. The heart failure patients were ischemic or dilated cardiomyopathy undergoing clinically indicated ventricular tachycardia (VT) ablation and implantable cardioverter defibrillator (ICD) implantation (HF group) as per primary prevention guidelines (Epstein *et al.* 2008). The 8 healthy subjects possessed structurally normal hearts undergoing electrophysiological study (EPS) and catheter ablation for

supraventricular tachycardia (SVT) (H_{Norm} group). To exclude the active ischemia, the patients with ischemic cardiomyopathy had undergone a recent non-invasive evaluation or coronary angiography. All baseline medications were continued during the time of study. This study did not include the patients less than 18 years of age, permanent atrial fibrillation, sinus node disease (resting heart rate < 40 bpm), ventricular preexcitation, heart block, permanent atrial or ventricular pacing, idiopathic VT, uncontrolled HF, acute coronary event within the preceding 1 month and asthma. All patients provided written informed consent. The Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide approved the study.

7.2.2 ECG recording

The 12-lead ECG (sampling frequency of 1000 Hz) at resting condition was recorded before the intended procedure for 8 minutes by using a Bard electrophysiology system (LabSystem PRO v2.4a EP, Bard Inc., Lowell, MA, USA). Before starting the actual ECG recording the patients were in a resting condition for at least 30 minutes. The whole procedure was maintained with continuous hemodynamic monitoring under light conscious sedation with intravenous midazolam (1–2 mg) and fentanyl (25–50 μg).

Patients undergoing VT ablation and ICD implantation

All patients were in stable sinus rhythm condition throughout the study interventions. The femoral vein was used to place the catheters at the right ventricular apex and in the coronary sinus. For patients undergoing VT ablation, atrial pacing was performed at two cycle lengths (each for 8 minutes), 80 bpm (Pa80) and 100 bpm (Pa100) using a MicroPace EPS 320 Cardiac Stimulator, Santa Ana, CA, USA. When the intrinsic rate was fast then the maximum pacing rate was allowed up to 90 bpm and 110 bpm, respectively. On the other hand, for patients undergoing ICD implantation, the pacing lead of the implanting device was positioned temporarily in the right atrium, using a compatible pacing system. Through a peripheral vein, the pharmacological interventions were individually commenced: esmolol (a selective β_1-receptor blocker, 0.05-0.3 mg/kg/min), followed by isoprenaline infusion (1–3 μg/min) and atropine infusion (0.04 mg/kg single dose). This sequence of drug administration was followed in all subjects by following with rapid elimination pharmacokinetics of esmolol and isoprenaline compared to atropine (Brunton *et al.* 2011). During each intervention, ECG

was recorded continuously for 8 minutes (Camm *et al.* 1996). To achieve the maximal drug dose within the first 3 minutes, the infusion of esmolol and isoprenaline were rapidly up titrated and continued until the end of each recording. At least 5 minutes was allowed as a compulsory time gap for drug washout after each intervention with an end-point so that the heart rate can potentially return to the baseline level. To assess the inducibility of VT, the ventricular stimulation was subsequently performed. The procedure for VT mapping and ablation was performed by following institutional protocol after completion of all study interventions.

Patients undergoing electrophysiological study

Similarly, for patients undergoing EPS study, the catheters were positioned through femoral vein in the coronary sinus and right ventricle. The rest of the experimental protocol was similar to that of the HF group. However, pharmacological interventions were performed post EPS and catheter ablation for SVT.

7.2.3 VCG analysis

We have used the same beat-to-beat VCG technique as described in our recent article (Hasan *et al.* 2012a) and Chapter 6. In addition, we have considered same length of recording as was considered in the article published by Nayyar *et al.* (2013). To synthesis VCG from the 12-lead ECG, we applied the singular value decomposition (SVD) technique on eight independent ECG leads ($\mathrm{I}, \mathrm{II}, \mathrm{V}_1 - \mathrm{V}_6$) as described by Acar *et al.* (1999b). However, to compute the beat-to-beat QT interval duration on surface ECG we used the T-wave template algorithm proposed by Berger *et al.* (1997) with an improved ECG pre-processing stage—details are described in our recent publish article (Hasan *et al.* 2013b).

7.2.4 Statistical analysis

All VCG descriptive data were presented as mean $\pm$ standard deviation unless otherwise stated. For statistical analysis, we have used GraphPad Prism 6® (GraphPad Software, Inc., La Jolla, CA, USA), PASW Statistics 18® (IBM SPSS, Inc., Somers, NY, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). The beat-to-beat VCG descriptors (mean and standard deviation) were found for both the

HF and the H_{Norm} group. We applied two-way ANOVA to test group differences and drugs effect on beat-to-beat VCG descriptors. Post-hoc tests across the groups were performed using Sidak's multiple comparison tests. Test results were considered statistical significant when $p < 0.05$.

7.3 Results

The effect of atrial pacing and drugs on VCG descriptors for HF patients and H_{Norm} subjects are shown in Fig. 7.1 and Fig. 7.2, respectively. The summary of the statistical results are given in the following sections.

Total cosine R-to-T (TCRT)

No significant effect (two-way ANOVA) was found in mean TCRT for HF and HNorm patients during interventions (atrial pacing and esmolol, isoprenaline and atropine). However, in HF patients, the mean TCRT values were towards negative compared to H_{Norm} subjects during atrial pacing (pa80: -0.043 ± 0.48, pa100: -0.20 ± 0.455) as shown in Fig. 7.1A and during drugs interventions in HF patients (esmolol: -0.018 ± 0.29, isoprenaline: -0.198 ± 0.22 and atropine: -0.21 ± 0.36) as shown in Fig. 7.2A.

Similarly, no significant pacing effect was observed in the variability of TCRT values but found significant group differences between HF patients and H_{Norm} subjects (two-way ANOVA).

T-wave morphology dispersion (TMD)

Significant mean TMD differences were found between the studied groups ($p < 0.001$) but no effect was observed during pacing and drugs interventions (two-way ANOVA). Higher mean TMD values were observed during interventions in HF patients compared to H_{Norm} subjects during pacing (pa80: $76.02° \pm 16.28°$ vs. $43.68° \pm 15.17°$ and pa100: $73.95° \pm 14.73°$ vs. $47.19° \pm 12.16°$) and during drugs interventions (esmolol: $74.63° \pm 13.42°$ vs. $49.01° \pm 13.80°$, isoprenaline: $76.30° \pm 7.99°$ vs. $55.86° \pm 5.07°$, atropine: $72.37° \pm 10.86°$ vs. $56.71° \pm 12.40°$) as shown in Fig. 7.1C and Fig. 7.2C.

In addition, the variability of TMD values were not significant between the studied groups and no effect for pacing interventions were found (two-way ANOVA: $p > 0.05$) but observed significant group differences during drugs interventions (two-way ANOVA: $p < 0.03$).

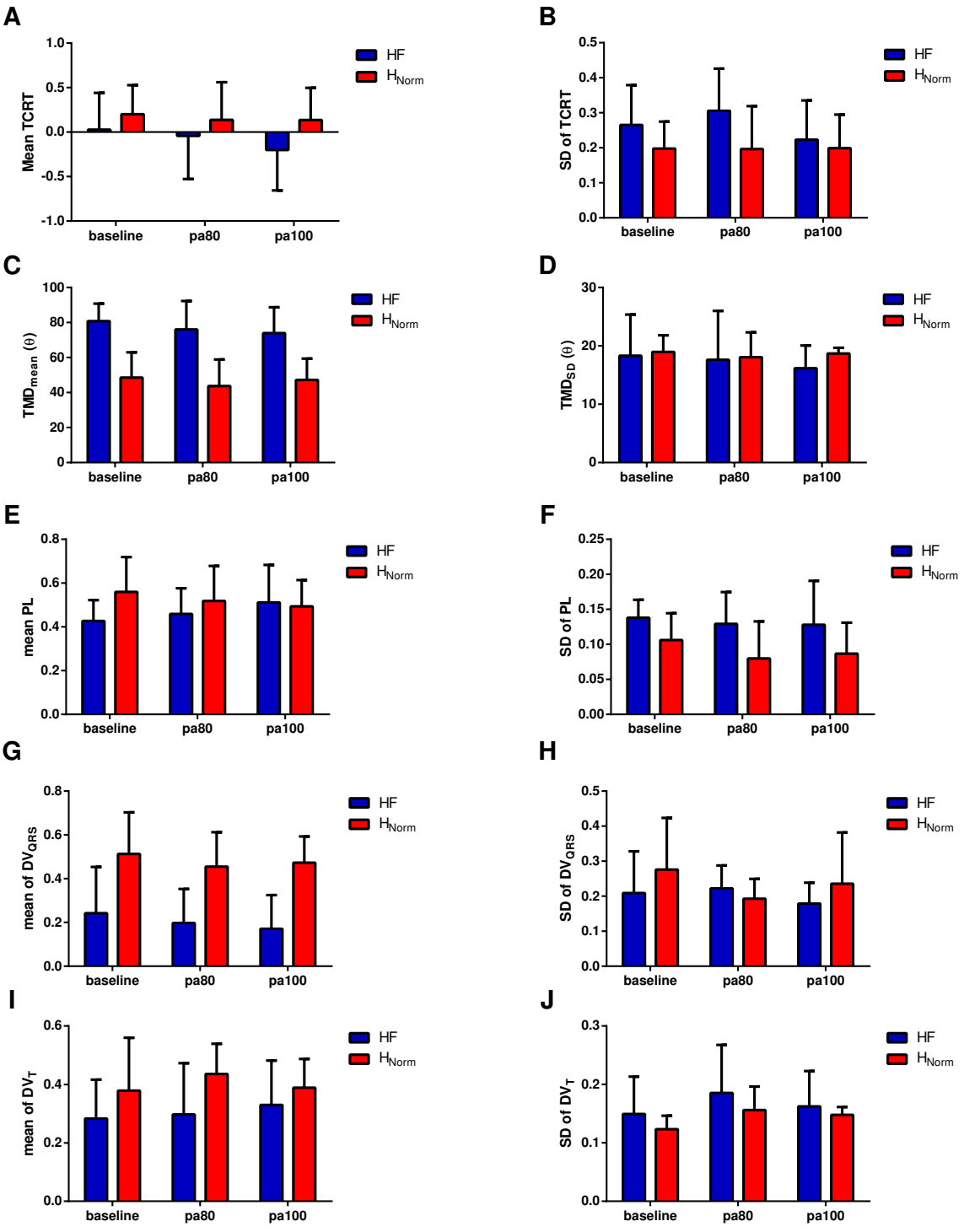

Figure 7.1. Effect of atrial pacing (pa80) and (pa100) at 80 beats/min and 100 beats/min, respectively on VCG parameters. HF patient and H_{Norm} subject's of TCRT [mean (A) and SD (B)], TMD [mean (C) and SD (D)], PL [mean (E) and SD (F)], DV_{QRS} [mean (F) and SD (G)], DV_T [mean (I) and SD (J)] are shown in blue and red, respectively.

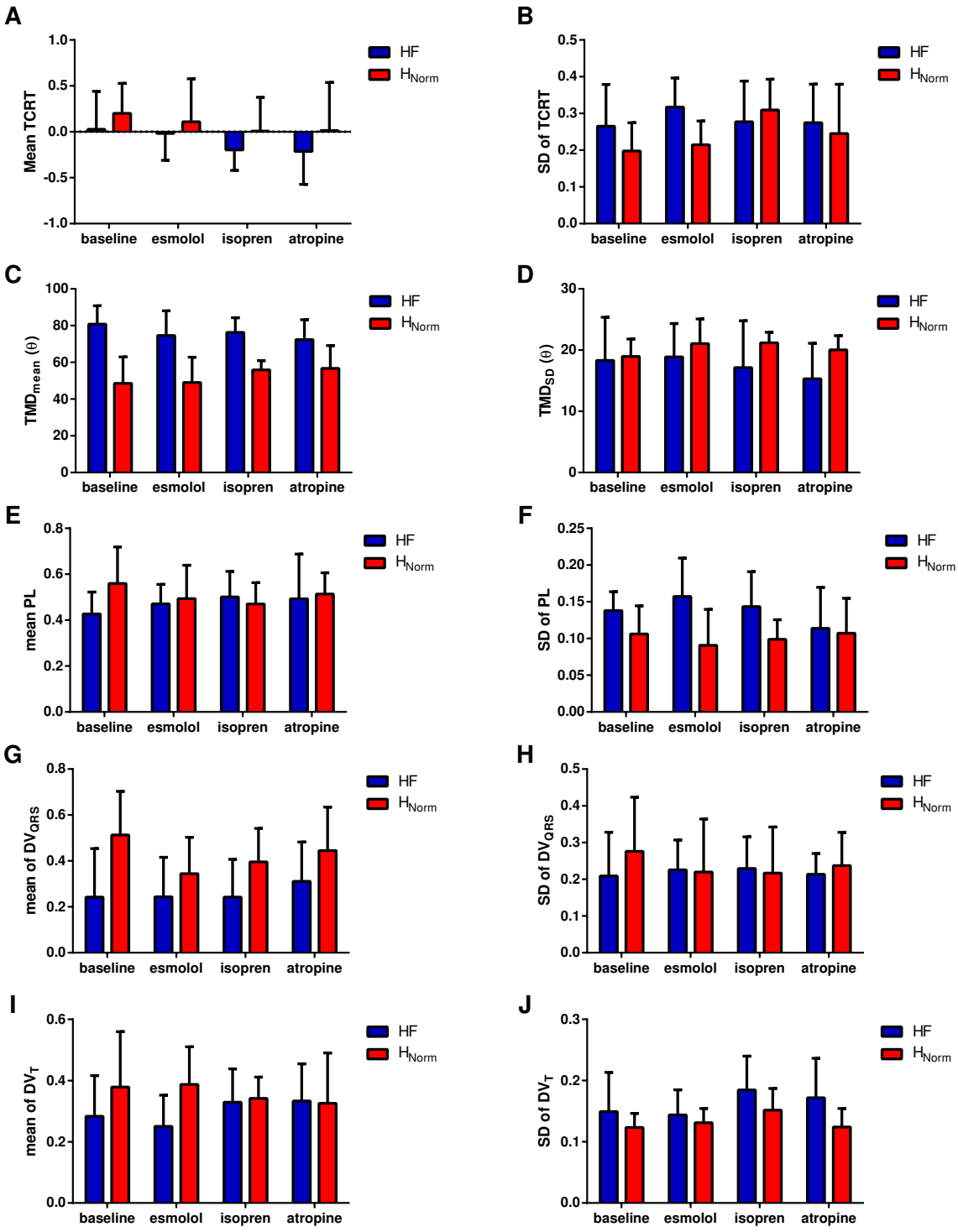

Figure 7.2. Effect of drugs (esmolol, isoprene and atropine) on VCG parameters. HF patient and H_{Norm} subject's of TCRT [mean (A) and SD (B)], TMD [mean (C) and SD (D)], PL [mean (E) and SD (F)], DV_{QRS} [mean (F) and SD (G)], DV_T [mean (I) and SD (J)] are shown in blue and red, respectively.

Percentage of Loop area (PL)

No significant mean PL differences were noticed between HF and H_{Norm} groups (two-way ANOVA: $p > 0.05$) as well as no effect due to pacing (pa80: 0.46 ± 0.12 vs. 0.52 ± 0.16, pa100: 0.51 ± 0.17 vs. 0.49 ± 0.12) and drugs interventions (esmolol: 0.47 ± 0.08 vs. 0.49 ± 0.14, isopren: 0.50 ± 0.11 vs. 0.47 ± 0.09, atropine: 0.49 ± 0.19 vs. 0.51 ± 0.09) as shown in Fig. 7.1E and Fig. 7.2E.

Similarly, no effects of atrial pacing and drugs interventions on the variability of PL were observed ($p > 0.05$) but found significant group differences between HF patients and H_{Norm} subjects (tow way- ANOVA).

Point-to-point distance variability (DV)

Significant group differences were observed between HF patients and H_{Norm} subjects in mean point-to-point distance variability for QRS-loop (mean of DV_{QRS}) during pacing and drugs interventions (pa80: 0.19 ± 0.15 vs. 0.45 ± 0.157, pa100: 0.17 ± 0.15 vs. 0.47 ± 0.12, esmolo: 0.24 ± 0.17 vs. 0.34 ± 0.16, isoprene: 0.24 ± 0.16 vs. 0.39 ± 0.15, atropine: 0.31 ± 0.17 vs. 0.44 ± 0.19) as shown in Fig. 7.1G and Fig. 7.2G. However, no significant effect was found either for atrial pacing or drugs interventions (two-way ANOVA: $p > 0.05$).

Furthermore, no significant group differences as well as effect of interventions (atrial pacing and drugs) on the standard deviation of point-to-point distance variability for QRS-loop (SD of DV_{QRS}) were found in HF patients and H_{Norm} subjects (two-way ANOVA: $p > 0.05$).

Similarly, no significant group differences were realized between HF patients and H_{Norm} subjects (two-way ANOVA: $p > 0.05$) in mean point-to-point distance variability for T-loop (mean of DV_T) during drugs interventions but found significant differences during atrial pacing interventions (pa80: 0.30 ± 0.17 vs. 0.44 ± 0.10 and pa100: 0.33 ± 0.15 vs. 0.39 ± 0.10) as shown in Fig. 7.1I and Fig. 7.2I.

Moreover, no significant effect ($p > 0.05$) for atrial pacing and drugs interventions were found in HF patients and H_{Norm} subjects on the standard deviation of point-to-point distance variability for T-loop (SD of DV_T). However, group differences between HF patients and H_{Norm} subjects were observed during drugs interventions on SD of DV_T parameters ($p < 0.01$) as shown in Fig. 7.2J.

7.4 Discussion

There are several factors that affect the ventricular repolarization, where, most important physiological factors are HR and autonomic nervous system (Ahnve and Vallin 1982, Browne *et al.* 1982, Browne *et al.* 1983a, Kawataki *et al.* 1984, Davey *et al.* 1994, Magnano *et al.* 2002, Mine *et al.* 2008). Understanding the response of ventricular repolarization is essential and plays a significant role in healthy or diseases subjects either in theoretical or practical perspective. In our study, we have assessed the role of autonomic nervous system using beat-to-beat VCG approach in HF patients and H_{Norm} subjects. The main findings of our study are as follows: (i) VCG analysis and beat-to-beat VCG descriptors are potential for identifying the HF patients. (ii) VCG descriptors are uncoupled with HR and autonomic nervous system in patients with HF.

In our study, we did not find any significant coupling between HR and TCRT values in HF patients, which is in line with the findings of the study proposed by Vahedi *et al.* (2011) in healthy subjects. However, the mean TCRT values tended to be negative in HF patients compared to H_{Norm} subjects, but these differences were not statistically significant. A similar scenario (propensity of negative mean TCRT values) was observed under drug interventions (esmolol, isoprenaline and atropine) where no affect of the autonomic nervous system was found in the studied groups. However, the negativity of mean TCRT in atrial pacing and drug interventions for HF patients reflect the higher abnormality of HF patients compared with subjects with normal hearts but need further validation. Nevertheless, our finding suggests that the mean TCRT values were not significantly different between HF patients and H_{Norm} subjects, which is in agreement with the finding by Lin *et al.* (2009). Further, no effect of pacing and drugs interventions were observed on the variability of TCRT in both groups.

We found significant higher mean TMD values in HF patients compared to H_{Norm} subjects but no significant effect of any interventions (pacing and drugs) on the studied groups. This higher TMD values correspond to the heterogeneity of T-wave morphology in HF patients and can be a marker for identification of HF patients. This finding is similar to several other studies (Lin *et al.* 2009, Huang *et al.* 2009). The beat-to-beat variability of TMD was significantly different between both groups during drug interventions only, but no significant effect of pacing and drugs on this parameter in both groups.

In addition, no significant mean PL differences were observed between HF patients and H_{Norm} subjects as well as no effect of pacing and drugs interventions on individual

groups were found in this study. However, our findings are in line with one of the previous study (Huang *et al.* 2009). Similarly, variability of PL was significantly higher in HF patients compared to H_{Norm} subjects but not significant effect of pacing and autonomic nervous system activity on this VCG parameters.

In our study, the mean point-to-point distance variability of QRS-loop (DV_{QRS}) appears to be significantly different between HF patients and H_{Norm} subjects but no effect of pacing and autonomic nervous system activity was found. In addition, DV_{QRS} was found to be lower in HF patients compared to H_{Norm} subjects. However, this finding was not comparable with our recent article (Hasan *et al.* 2012a). The probable reason for this discrepancy might be due to the shortening of QT interval (Akhras and Rickards 1981, Kawataki *et al.* 1984) or shortening of QRS complex duration (Datino *et al.* 2008, Małecka *et al.* 2010) due to pacing and drug interventions in HF patients. Further, the variation of point-to-point distance variability of QRS loop (DV_{QRS}) was not found to be significant between studied groups and affect from pacing and drugs interventions were absent. Similarly, mean point-to-point distance variability of T-loop (DV_T) was not significantly different between both groups and appears to be lower in HF patients. Moreover, the affect of pacing and drugs interventions were not present on this parameter as well. The reason for lower mean DV_T in HF patients compared to H_{Norm} subjects might be the similar as explained earlier for mean DV_{QRS}. However, the variability of DV_T was significantly difference between HF patients H_{Norm} subjects, which was in agreement with our recent study on myocardial infarction and healthy subjects (Hasan *et al.* 2012a).

7.5 Chapter summary

In this chapter, we have investigated the relationship between beat-to-beat VCG descriptors and autonomic nervous system. The proposed VCG descriptors may have independent prognostic capabilities for characterising HF from H_{Norm} subjects. However, overall effect of HR or pharmacologically induced autonomic nervous system modulation on VCG parameters appears to be limited in HF as well as in H_{Norm} patients.

The next chapter will summarize the main findings of this thesis and propose directions for future study.

Thesis Conclusion and Future Work

THIS chapter summarizes the work described in this thesis and suggests directions for future work.

8.1 Introduction

Einthoven first introduced the ECG signal into clinical practice, for diagnosis, over 100 years ago. However, still now, ECG is considered the primary tool for the diagnosis of cardiac diseases. The 12-lead ECG representation is the standard approach for clinical studies. Due to the technological progress, nowadays, VCG analysis has gained importance over ECG to some degree. The main reason for using VCG is due to its additional features such as vector loop (e.g. QRS and T loop) and spatial representation for improved assessment of heart signals for detecting abnormalities. This chapter first reviews and summarizes the main findings and results of each chapter. Moreover, it discusses the potential future directions for further development of techniques, knowledges and issues for understanding the physiological mechanisms of beat-to-beat repolarization instability.

8.2 Thesis summary and conclusions

In Chapter 1, the background of this thesis is discussed. It also discusses briefly the chapter outline and original contributions.

Chapter 2 reviews the significance of beat-to-beat QTV analysis. It also provides the overview of several other techniques for QTV analysis along with their findings and limitations. Further, it compares the findings of several studies. Furthermore, it illustrates the factors (technical or biological), which influence the analysis of beat-to-beat QTV that can be considered for further study.

Although, beat-to-beat QTV analysis has received a significant interest in the field of biomedical engineering, especially due to the linked to increased heterogeneity of ventricular repolarization lability, which is implicated in the genesis of ventricular arrhythmias in a variety of patients populations. But, unfortunately, there is no credible empirical systematic beat-to-beat QTV analysis in different ECG leads, using the 12-lead standard ECG. In addition, the relation between leads QTV based on gender and age has not been fully explored. Because, most of previous QTV studies were reported only for a single ECG lead and have not been studied across the leads. However, there may be considerable additional information contained in the subtle lead-to-lead differences observed in temporal QTV analysis. Therefore, in Chapter 3, we have investigated beat-to-beat QTV across the 12-lead standard ECG leads and their relationship to gender and age. This is the first study, to the best of our knowledge, where beat-to-beat

QTV was analysed in all 12 EGC leads, exploring the relationships between beat-to-beat QTV against T-wave amplitude, age, and gender. We observed overall significant QTV differences between 12 standard ECG leads. In addition, we have found some of the adjacent leads were higher in temporal correlations rather than their magnitudes. Further, no significant differences were observed overall in the QTV of the 12-lead ECG in older males compared to younger males as well as between male and female groups. Moreover, beat-to-beat QTV and T-wave amplitude was found to be inversely related. Finally, we have concluded in this study that caution should be taken when comparing beat-to-beat QTV results obtained from different leads across studies.

There is no gold standard approach established yet for the quantification of beat-to-beat QT interval in ECG for QTV analysis. Because, the existing measurement techniques for beat-to-beat QT interval on surface ECG still with limited accuracy due to a number of different reasons (Baumert *et al.* 2012, Hasan *et al.* 2013b). In Chapter 4, we have investigated the reliability of a widely used template matching technique and its possible modification by improving a ECG-preprocessing stage for beat-to-beat QT measurements in QTV analysis. In addition, the performance of the updated approach has been compared with the existing technique and two other methods. We have incorporated an alternative R-peak detection technique and baseline removal approach in the existing template matching technique. The results from this study suggest that the updated approach outperforms the existing algorithm and motivate the need for more accurate quantification of beat-to-beat QT interval for the analysis of repolarization lability.

Several studies have shown the predictive power of increased QTV in patients with MI. Nevertheless, the underlying mechanisms of increased beat-to-beat QTV in MI patients are still not fully known. Moreover, the factors related to the QTV measurement procedure are little is known that may cause higher beat-to-beat variability in QT interval in MI patients. Chapter 5 explored the fact for contributing higher beat-to-beat QTV in patients with MI by investigating the waveform-dependent factors. We have observed the effect of T-wave amplitude and ECG lead on beat-to-beat QTV in MI patients. We have found that the beat-to-beat QTV and T-wave amplitudes were inversely correlated. The results suggest that the elevated beat-to-beat QTV is repeatedly reported in patients with MI due to the partly lower T-wave amplitudes. However, our study concludes that the beat-to-beat QTV remains higher in MI patients even after covarying the T-wave amplitudes, which awaits further study on this issue.

In Chapter 3, we reported that beat-to-beat QTV varies in inter-lead measurement, partly due to T-wave amplitude differences. To find the correct end point of the T-wave in the ECG is a major challenge for the analysis of QTV. Because, mainly, it becomes more difficult to detect T-wave offset due to the slow transition in the signal around this point and ultimately it becomes corrupted by noise and interference. Indeed, it is a fact that the identification of T-wave peak can be as problematic as determining the T-wave terminus. The main reason is that it is believed to be a low frequency event at the T-wave. Further, the location of the time of its peak also can be easily contaminated by artifacts which sometimes cannot be possible to differentiate it from the true waveform. Therefore, in Chapter 6, we have analysed the beat-to-beat ventricular depolarization and repolarization lability by using the VCG approach, where, it does not rely on exact identification of the T-wave offset, which improves the reproducibility of the VCG technique. We have proposed two new VCG descriptors through this study which has independent diagnostic attributes for assessing patients populations. Moreover, we have observed that the overall VCG descriptors may provide markers of electrical instability in the heart of patients with MI.

Autonomic nervous system activity plays a significant role for physiological adaptation which is also crucial for some congenital and acquired conditions with increased propensity for life-threatening arrhythmias. In addition, it is believed that there is a strong association between autonomic nervous system activity and ventricular repolarization alterations. However, the role of autonomic control on VCG parameters are not fully understood. In Chapter 7, we have investigated the role of heart rate and autonomic nervous system activity on beat-to-beat VCG descriptors in heart failure patients. Our findings demonstrates that the proposed VCG descriptors may have independent predictive power for identifying heart failure patients. But, the overall effect of heart or pharmacologically induced autonomic nervous system modulation on VCG parameters seems to be absent in heart failure patients.

It is well known that the usual mechanisms which may influence the QTV are considered as heart rate, HRV, autonomic changes, and the repolarization reserve. However, the mechanisms underpinning the beat-to-beat QTV in patients with heart failure and its role in arrhythmogenesis are not completely understood. Therefore, in Appendix A, we have investigated the effect of arrhythmogenic substrate on beat-to-beat QTV in heart failure patients and examined whether it can be modulated by autonomic control

system. This study suggests that effect of autonomic nervous system on beat-to-beat QTV is limited in heart failure patients.

8.3 Potential future work

In the following sections, we propose some of the future directions that can be advanced further.

8.3.1 Optimum lead for QTV analysis in 12-lead ECG

We have investigated the beat-to-beat QTV in different leads and their relationship with T-wave amplitudes, age and sex in healthy subjects where we observed a significant variations in QTV in 12-lead ECGs. It might be interesting, if beat-to-beat QTV analysis can be carried out in an optimum lead from 12-lead ECG where this equivalent lead may be derived mathematically from 12-lead ECG and thus avoiding extra computation of QTV in each lead.

8.3.2 Novel technique for beat-to-beat QTV analysis

In this thesis, we have utilized a widely used template matching technique and its elaborations by improving an ECG-preprocessing stage for beat-to-beat QT interval measurement and QTV analysis. This updated approach is recommended for further quantification of QTV, but is still not yet standardized due to the technical challenges. Therefore, future study can be carried out by proposing and validating a novel technique which can provide better accuracy for the quantification of beat-to-beat QTV.

8.3.3 Factors affecting for higher QTV in MI patients

Through this thesis, we have learned that the T-wave amplitude is one of the potential factors that increases beat-to-beat QTV in MI patients. However, there might some other factors involved for increasing QTV in patients with MI that is currently unknown. Therefore, it would be interesting if the insight of being reason for higher beat-to-beat QTV in MI patients are investigated further by considering some other parameters.

8.3.4 Analysis of respiratory effect on VCG parameters

We have explored the feasibility of beat-to-beat VCG descriptors for assessing the prognostic capabilities, were finding problem of the T-wave offset can be avoided that can affect the analysis of repolarization variability. However, an interesting issue such as respiratory signal may influence the VCG loops and VCG descriptor characteristics that are not fully understood. Therefore, in future study, for finding the relation and affect of respiratory signal on VCG descriptors and how this effect can be minimized for improved analysis.

8.3.5 Relation between ANS and VCG parameters for fetal ECG

Autonomic nervous system modulates the ventricular repolarization and plays a significant role in several cardiac diseases. However, little is known about the relation between ANS and VCG parameters for fetal ECG. Therefore, in the future study, it could be interesting if we could assess noninvasively the ANS role on VCG parameters for fetal ECG. Because, fetal ECG signal contains potentially accurate information that could assist clinicians for making appropriate decisions during labor period. In future study, an assessment criterion can be proposed for finding the relationship of SNS activation and QRS-T loop parameters for fetal ECG. Further, new VCG metrics can be proposed and validated by analysing the fetal ECG.

8.4 Summary of author's original contributions

The summary of the key contributions are as follows:

- **Relation of beat-to-beat QTV in different leads of 12-lead ECG**: By analyzing the QTV in all 12-lead ECG, this thesis demonstrates that the magnitude of beat-to-beat QTV varies between ECG leads and caution should be paid when comparing beat-to-beat QTV results obtained from different leads across studies (Hasan *et al.* 2011, Hasan *et al.* 2012c).
- **Improved beat-to-beat QT interval variability measurement approach**: By improving ECG pre-processing modalities in template matching algorithm, this thesis recommends to use the updated approach for accurate quantification of QT interval for beat-to-beat QTV analysis (Hasan *et al.* 2013b).

- **Effects of T-wave amplitude and ECG lead on beat-to-beat QTV**: This thesis suggests that the higher beat-to-beat QTV is repeatedly reported in patients with MI due to the partly lower T-wave amplitudes and some other unknown reason and it remains significant if the T-wave is controlled (Hasan *et al.* 2013a).

- **Beat-to-beat spatial and temporal variations of ventricular depolarization and repolarization in vectocardiograms**: VCG approach for analyzing the beat-to-beat spatial and temporal variations of ventricular depolarization and repolarization provides markers of electrical instability in patients with MI (Hasan *et al.* 2012b, Hasan *et al.* 2012a).

- **Effect of pacing and autonomic nervous system activity on beat-to-beat VCG parameters**: Thesis thesis suggests that the effect of pacing and autonomic nervous system on VCG parameters appears to be limited in heart failure patients, but VCG parameters may have independent prognostic power for identifying heart failure patients.

- **Role of autonomic nervous system activity on beat-to-beat QTV**: This thesis demonstrates that the effect of autonomic nervous system modulation on QTV is limited in heart failure patients (Nayyar *et al.* 2013).

Appendix A

Modulation of QT Interval Variability in Heart Failure Patients

THIS appendix investigates the influence of autonomic nervous system activity on QT interval variability.

A.1 Introduction

It is believed that the ventricular tachyarrhythmias (VTs) relating to the structural heart disease are the most common cause of sudden cardiac death (SCD) in the Western world (Bardy *et al.* 2005). Many of these occur in patients with ventricular scarring, related predominantly to coronary artery disease or dilated cardiomyopathies. Such scarring produces non-homogenous myocyte loss, diminished myocyte coupling, ion channel dysfunction, and thus spatial heterogeneity in ventricular action potential repolarization and prolonged corrected QT interval that predispose to ventricular arrhythmias and SCD (Beuckelmann *et al.* 1992, Beuckelmann *et al.* 1993, Antzelevitch and Fish 2001, Chugh *et al.* 2009, Karwatowska-Prokopczuk *et al.* 2013). Superimposed on this spatial heterogeneity, temporal (beat-to-beat) variation in cardiac repolarization across the ventricle has been recognized and shown to be elevated in ischemia and heart failure (HF) (Berger *et al.* 1997, Hinterseer *et al.* 2010, Murabayashi *et al.* 2002). Increased QT variability (QTV) on the surface ECG, which is arguably a marker for compound spatio-temporal heterogeneity in repolarization, was found to predict appropriate device therapies in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) study, as well as total and arrhythmic deaths in HF patients without defibrillators (Haigney *et al.* 2004, Piccirillo *et al.* 2007).

Common mechanisms influencing QTV include heart rate variability (HRV), autonomic changes and repolarization reserve, each of which has been studied in normal hearts (Cheng *et al.* 2009, Yeragani *et al.* 2000b, Zaza *et al.* 1991). In contrast, the mechanisms underpinning QTV in HF as well as its role in arrhythmogenesis are poorly understood. There is evidence, suggesting that enhanced beat-to-beat fluctuations in repolarization duration in HF patients do not reflect merely incidental changes in heart rate and electrical restitution (Berger *et al.* 1997, Murabayashi *et al.* 2002, Piccirillo *et al.* 2006). As interventions that increase sympathetic stimulation shorten ventricular repolarization duration, increase spatial dispersion in repolarization and increase QTV in normal hearts (Ajijola *et al.* 2013, Yeragani *et al.* 2000b), the elevated QT interval variability seen in HF patients may result from enhanced sympathetic drive and subsequent diminution in repolarization reserve (Roden and Yang 2005, Vaseghi *et al.* 2012). On the other hand, primary reduction in repolarization reserve itself, which is commonly seen in structural heart disorders (Akar *et al.* 2005) may be the principle driver of elevated QTV in these patients (Lengyel *et al.* 2007). Given the contrasting differences

in the over-all milieu in subjects with normal and myopathic hearts, it is imperative to understand the central mechanisms underlying elevated QTV in patients with HF.

In this Appendix, we will therefore examine the effect of arrhythmogenic substrate on QTV in HF subjects and whether it can be modulated by autonomic control.

A.2 Methods

A.2.1 Subjects

The study population included total of 29 patients; ten patients with ischemic or dilated cardiomyopathy undergoing clinically indicated ventricular tachycardia (VT) ablation [HFVT(+) group], ten patients with ischemic or dilated cardiomyopathy undergoing clinically indicated implantable cardioverter defibrillator (ICD) implantation as per primary prevention guidelines (Epstein *et al.* 2008) [HFVT(-) group] and nine patients with structurally normal hearts undergoing electrophysiological study (EPS) and catheter ablation for supraventricular tachycardia (SVT) (H_{Norm} group). Details of experimental setup, patients informations and procedure of ECG recording are described elaborately in Chapter 7 and in our recent article (Nayyar *et al.* 2013).

A.2.2 Beat-to-beat QTV analysis

The recorded ECG data were stored on removable media for semi-automated off-line analysis. To measure QT intervals, usually lead I was chosen. If the signal in lead I was contaminated with noise, then an alternative lead with tall T-waves was chosen. In this study, we used the template-matching approach that was originally introduced by Berger *et al.* (1997) and with an improved ECG pre-processing stage (Hasan *et al.* 2013b). To account for slow adaptation of the QT interval to the heart rate and intervention (Zaza *et al.* 1991), only the last 3 minute epochs of each 8-minute recording were used for further analysis. The presence of atrial or ventricular ectopy and pacing was permitted unless such beats represented $> 5\%$ of all beats over the 3-minute period. Ventricular ectopic beats were detected automatically based on ECG QRS morphology, and were excluded from analysis.

QT response was calculated as the mean (meanQT) and QTV was quantified as the standard deviation (SDQT) of beat-to-beat QT intervals at baseline (3 minutes) and

during the last 3-minutes of study interventions (Jensen *et al.* 2004, Starc and Schlegel 2006). Heart period mean (meanRR) and heart rate variability (HRV) [standard deviation RR (SDRR)] were computed from the sequence of RR intervals. Note that QT variability relative to heart rate variability (QTV/HRV) was computed as the ratio of SDQT/SDRR (Jensen *et al.* 2004). Rather than separating QTV from HRV, this metric can be regarded as a composite measure of heart rate and QT variability.

Statistical analysis

Baseline demographic variables are presented as means $\pm$ standard deviation for continuous data and counts for the categorical data. Comparisons between the HFVT(+), HFVT(-) and H_{Norm} groups were carried out using one way analysis of variance with multiple Bonferroni *post hoc* comparisons, or by chi-square χ^2 test (or Fisher's exact test) as applicable.

To test for differences in electrocardiographic parameters between the three groups at baseline, one-way analysis of variance was used. To test for differences in changes in ECG measurements from baseline to pacing or pharmacological intervention between groups, linear mixed-effects models were used. Within these models, intervention (i.e. basal/ P80/P100 or basal/esmolol/isoprenaline/atropine) and group [HFVT(+), HFVT(-), H_{Norm}] were included as fixed effects and patient ID was included as a random effect to account for dependence within a patient. Initially, an interaction term between intervention and group was included in the linear mixed-effects models. Since this interaction term was not significant in every case, the final models contained only main effects, for which means and *post hoc* contrasts are reported. Results are presented as means $\pm$ standard error of means (SEM). The statistical software used was SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided $p < 0.05$ was considered statistically significant.

A.3 Results

Patient characteristics

The demographic characteristics of the patient groups are presented in Table A.1. Other than VT inducibility, the baseline features in HFVT(+) group were closely matched with the HFVT(-) group. The majority of patients in the HF groups (19/20 patients)

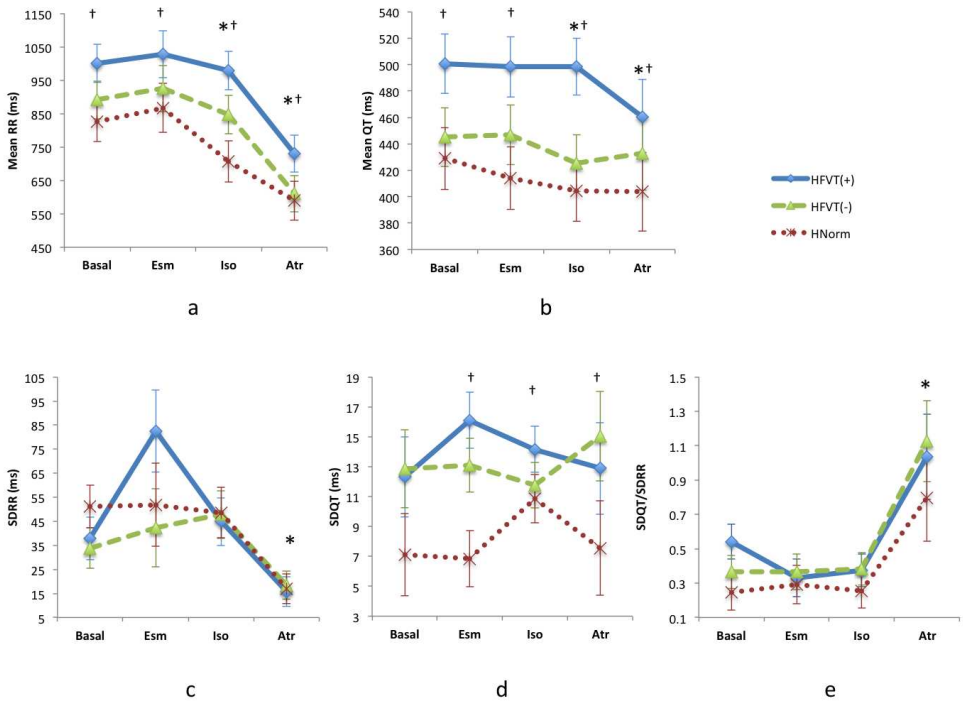

Figure A.1. Effect of atrial pacing (Pa) at 80bpm and 100bpm. (a) Mean RR: $^{*}p < 0.001$ (intervention effect); $^{\dagger}p < 0.05$ (group effect); *post hoc* test, $p < 0.05$ [HFVT(+) vs H_{Norm}]. (b) Mean QT: $^{*}p < 0.001$ (intervention effect); $^{\dagger}p < 0.05$ (group effect); *post hoc* test, $p < 0.05$ [HFVT(+) vs HFVT(-) and HFVT(+) vs H_{Norm}]. (c) SDRR: $^{*}p < 0.001$ (intervention effect). (d) SDQT: $^{\dagger}p < 0.05$ (group effect); *post hoc* test, $p < 0.05$ [HFVT(+) vs HFNorm and HFVT(-) vs H_{Norm}].

were on long-term stable dose of an oral β-blocker before investigation. The H_{Norm} group patients were younger, predominantly women, and most patients (6/9 patients) were not taking any medications.

The effects of pacing and pharmacological interventions on electrocardiographic parameters in the three groups of patients have been summarized in Table A.2, and further illustrated with respective means plots in Fig. A.1 and Fig. A.2.

Heart rate response

The basal meanRR was longer in HFVT(+) patients compared to the H_{Norm} group ($p = 0.01$). Compared to the basal state, the meanRR increased marginally with esmolol ($p = 0.09$), shortened significantly after isoprenaline ($p = 0.02$) and with atropine ($p < 0.001$) in all the three groups. The relative baseline difference between HFVT(+) and H_{Norm} patients was maintained during all pharmacological interventions ($p = 0.04$).

Table A.1. Patient characteristics.

	HFVT(+)Group	HFVT(−)Group	H_{Norm}	p
n	10	10	9	
Age, year	63 ± 12	54 ± 13	36 ± 19	0.004*
Men/women, n	9/1	10	2/8	0.002†
Cardiomyopathy, n				
Ischemic	8	8		1.00
Nonischemic	2	2		
Ejection fraction, %	30 ± 10	29 ± 8	63 ± 3	< 0.001†
New York Heart Association class				
I	2	4	9	0.01
II	7	5		
III	1	1		
Time to first infarction, year	19 ± 12	10 ± 8		0.17
Coronary bypass surgery, n	5	2		0.35
QRS duration, ms	140 ± 25	128 ± 33	95 ± 11	0.03†
Inducible VT	10	1		< 0.001
$\beta -$ Blocker, n	9	10	3	0.002
Amiodarone, n	3	0	0	0.07
Other antiarrhythmic drugs(Sotalol, Mexilitene)	2	0	0	0.18

Values are means $\pm$ SD; n, no. of patients/group. The following groups were evaluated: heart failure (HF) patients with spontaneous ventricular tachycardia (VT) [HFVT(+) group], HF patients without spontaneous VT [HFVT(-) group], and subjects with structurally normal hearts (H_{Norm} group). *HFVT(+) group vs. H_{Norm} group; †HFVT(+) and HFVT(-) groups vs. the H_{Norm} group.

Table A.2. Effect of various interventions on ECG parameters in the three study groups.

	Baseline	Pacing80		Pacing100		Esmolol		Isoprenaline		Atropine	
	Mean ± SEM	Mean ± SEM	*p value**	Mean ± SEM	*p value**	Mean ± SEM	*p value**	Mean ± SEM	*p value**	Mean ± SEM	*p value**
MeanRR, ms											
HFVT(+)group	1001 ± 58§	743 ± 14		594 ± 12		1027 ± 70§		979 ± 58§		731 ± 56§	
HFVT(−)group	891 ± 56	748 ± 14	< 0.001	600 ± 11	< 0.001	926 ± 69	0.091	847 ± 58	0.02	611 ± 55	< 0.001
H_{Norm}	823 ± 59	711 ± 14		600 ± 11		926 ± 69		847 ± 58		611 ± 55	
p value†	0.03	0.21		0.21		0.04		0.04		0.04	
SDRR(ms)											
HFVT(+)group	36 ± 8	4 ± 1		3 ± 1		83 ± 17		45 ± 10		16 ± 6	
HFVT(−)group	34 ± 8	4 ± 1	< 0.001	5 ± 1	< 0.001	42 ± 16	0.085	48 ± 10	0.03	18 ± 6	< 0.001
H_{Norm}	51 ± 9	3 ± 1		2 ± 1		52 ± 17		49 ± 11		17 ± 6	
p value†	0.26	0.25		0.25		0.63		0.63		0.63	
MeanQT, ms											
HFVT(+)group	509 ± 21‡§	441 ± 16§		425 ± 17§		498 ± 23‡§		498 ± 21‡§		460 ± 29‡§	
HFVT(−)group	445 ± 21	437 ± 16	< 0.001	423 ± 16	< 0.001	447 ± 22	0.45	425 ± 21	0.03	433 ± 28	< 0.02
H_{Norm}	429 ± 22	398 ± 17		381 ± 17		414 ± 24		404 ± 28		404 ± 30	
p value†	0.009	0.08		0.08		0.02		0.02		0.02	
SDQT(ms)											
HFVT(+)group	12 ± 3	11 ± 2§		11 ± 2§		16 ± 2§		14 ± 2§		13 ± 3§	
HFVT(−)group	13 ± 3	10 ± 1§	0.099	11 ± 2§	0.35	13 ± 2	0.47	12 ± 2	0.39	15 ± 3	0.42
H_{Norm}	7 ± 3	5 ± 1		5 ± 2		7 ± 2		11 ± 2[a]		8 ± 3	
p value†	0.21	0.008		0.008		0.02		0.02		0.02	
SDQT/SDRR(ms)											
HFVT(+)group	0.54 ± 0.10					0.33 ± 0.11		0.37 ± 0.09		1.03 ± 0.25	
HFVT(−)group	0.37 ± 0.10					0.37 ± 0.11	0.51	0.38 ± 0.09	0.50	1.13 ± 0.24	0.001
H_{Norm}	0.24 ± 0.10					0.29 ± 0.11		0.26 ± 0.10		0.80 ± 0.25	
p value†	0.094					0.30		0.30		0.30	

SDRR, SD of RR intervals; SDQT, SD of QT intervals. *Intervention effect; †group effect; ‡compared with HF without VT; § compared with normal hearts. [a] $P = 0.02$ compared with baseline (linear regression).

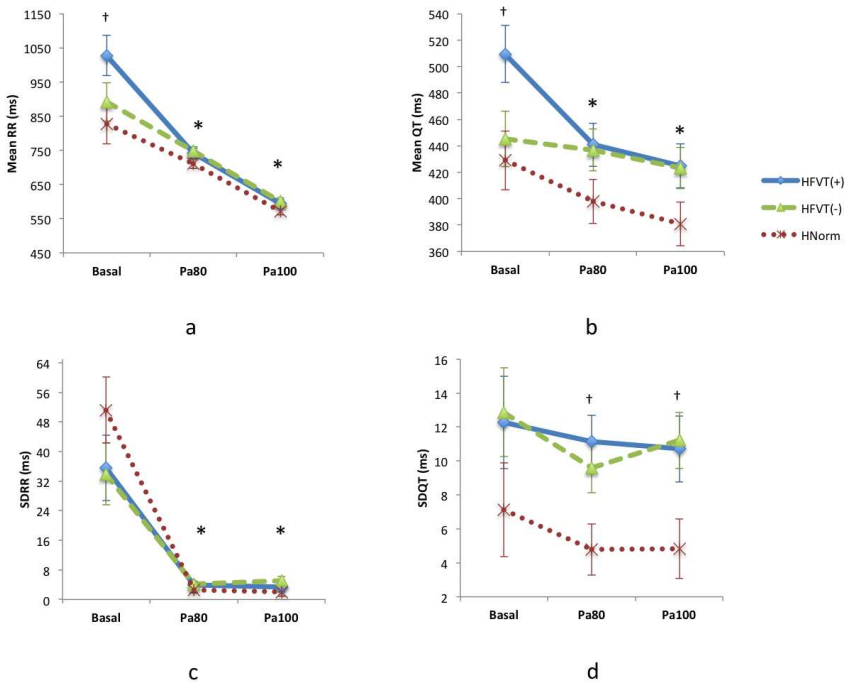

Figure A.2. Effect of drugs (Esm= esmolol, Iso= isoprenaline, Atr= atropine). (a) Mean RR: $^{*}p < 0.05$ (intervention effect Iso); $^{*}p < 0.001$ (intervention effect Atr); $^{\dagger}p < 0.05$ (group effect); *post hoc* test, $p < 0.05$ [HFVT(+) vs H_{Norm}]. (b) Mean QT: $^{*}p < 0.05$ (intervention effect); $^{\dagger}p < 0.05$ (group effect); *post hoc* test, $p < 0.05$ [HFVT(+) vs HFVT(-) and HFVT(+) vs H_{Norm}]. (c) SDRR: $^{*}p < 0.001$ (intervention effect). (d) SDQT: $^{\dagger}p < 0.05$ (group effect); *post hoc* test, $p < 0.05$ [HFVT(+) vs H_{Norm}]. (e) SDQT/SDRR ratio: $^{*}p = 0.001$ (intervention effect).

Heart rate variability

Basal SDRR was < 50 ms in both the HF groups but this was not significantly different from the H_{Norm} group ($p = 0.26$). Atrial pacing abolished HRV in all groups of patients ($p < 0.001$). There was a trend towards improvement in SDRR after β-blockade with esmolol ($p = 0.08$) mainly in the HFVT(+) group. It did not change with isoprenaline infusion ($p = 0.63$), but reduced drastically after atropine ($p = 0.001$) in all the three groups.

QT Response

The mean basal uncorrected QT interval (meanQT) was longer in HFVT(+) patients compared to HFVT(-) ($p = 0.02$) and H_{Norm} ($p = 0.004$) groups. Compared to the basal state, meanQT shortened with atrial pacing at 80 bpm ($p = 0.001$) and 100 bpm

($p < 0.001$), with isoprenaline ($p = 0.03$) and atropine infusion ($p = 0.02$) in all the three groups. The relative baseline differences among HFVT(+), HFVT(-) and H_{Norm} groups were maintained during all pharmacological interventions ($p = 0.02$).

QT variability

Group mean values in basal SDQT tended to be higher in HF patients compared to the H_{Norm} group, but these differences were not significant ($p = 0.21$). Atrial pacing augmented these differences. Both HF groups had significantly higher SDQT than the H_{Norm} group during atrial pacing [$p = 0.008$; $p = 0.006$ for HFVT(+) vs H_{Norm} and $p = 0.007$ HFVT(-) vs H_{Norm}]. Considered independently, atrial pacing did not reduce QTV in any of the patient groups ($p = 0.1$). Esmolol ($p = 0.47$) and atropine ($p = 0.42$) failed to induce any significant change in SDQT in HF subjects; it remained significantly higher than in H_{Norm} patients ($p = 0.02$). Isoprenaline increased SDQT in H_{Norm} patients ($p = 0.02$), but not in the HF groups (overall main effect of intervention $p = 0.39$).

QT Variability/Heart rate variability ratio

In the basal state, there was a trend towards higher SDQT/SDRR in HFVT(+) patients compared to HFVT(-) and H_{Norm} patients ($p = 0.09$). While esmolol ($p = 0.51$) and isoprenaline ($p = 0.50$) had a neutral effect, SDQT/SDRR increased considerably after atropine infusion ($p = 0.001$), principally due to a reduction in HRV in all the three groups.

A.4 Discussion

Major findings

This study explored mechanisms involved in the generation of electrocardiographic beat-to-beat QTV in HF patients in comparison to normal hearts. The main findings from the study are:

- Beat-to-beat repolarization instability is high in patients with HF, who are prone to recurrent VT.
- This appears to be at least in part independent of HRV, and remains high after uncoupling the effect of heart rate.

- Acute therapy with a β-blocker improves HRV, however fails to reduce QTV.

Previous studies

Short-term variability in QT intervals is considered a surrogate marker of subtle fluctuations in repolarization duration between consecutive beats (Baumert *et al.* 2008a). The control of sinus node activity via sympatho-vagal modulation resulting in HRV is well established (Lombardi *et al.* 1996a). In contrast, the physiological mechanisms that give rise to or alter QTV are not fully recognized. In healthy hearts, interventions that increase sympathetic tone such as sudden standing and infusion of isoprenaline were shown to increase QTV (Yeragani *et al.* 2000b), while pharmacological blockade of β-adrenoreceptors reduces QTV (Mine *et al.* 2008)). Similarly, hypertensive subjects with otherwise normal heart were shown to have high QTV that correlated with their cardiac norepinephrine spillover and systolic blood pressure (Baumert *et al.* 2011c). A recent study in dogs also showed that QT variability was related to left stellate-ganglion activity, but only after the dogs had developed HF (Piccirillo *et al.* 2009). As sympathetic tone is elevated in HF (Kaye *et al.* 1995), and QTV is elevated in HF (Berger *et al.* 1997), it is appealing to believe that autonomic influences have bearing on ventricular repolarization lability in these patients. However, we recently challenged the notion that QTV provides an assessment of the cardiac autonomic activity, when resting QT variability measures did not correlate with norepinephrine levels in blood sampled from the coronary sinus in subjects with depression and panic disorder (Baumert *et al.* 2008a). It is possible that in normal subjects during rest, the sympathetic tone is too low to affect QTV and it needs stimulation to stage a proportionate change above background QTV.

In this study, augmented β-blockade with esmolol failed to attenuate repolarization instability in both HFVT(+) and HFVT(-) patients. This suggests that other local competing mechanisms possibly override sympathetic influences on QTV in electrically remodeled hearts. The down-regulation and desensitization of β_1- adrenoceptors in chronic HF (Bristow 2000, Feldman *et al.* 2005) can only partly explain the lack of efficacy of acute β-adrenoceptor blockade on QT as the trend towards heart rate slowing in HF patients observed following esmolol was comparable to that in the H_{Norm} patients. Nonetheless, high baseline QTV in chronically treated HF patients, as observed in our as well as in previous studies (Tereshchenko *et al.* 2012), suggests that even long-term β-blockade therapy is probably insufficient to reduce high repolarization instability at least in some of these patients.

As observed in previous studies (Yeragani *et al.* 2000b), we were able to replicate the increase in QTV with isoprenaline infusion in H_{Norm} subjects. However, this effect was absent in HF groups, strengthening the notion that sympathetic influences may only have limited influence on beat-to-beat repolarization stability in HF (Baumert *et al.* 2008a, Desai *et al.* 2004). As protracted sympathetic stimulation in chronic HF reduces repolarization reserve (Roden and Yang 2005), the autonomic status presumably ceases to notably affect QTV. Furthermore, in H_{Norm} patients, we were not able to demonstrate a reduction in QTV from baseline values by β-blockade with esmolol. It is possible that high repolarization reserve in these patients from functionally normal ion currents raises the threshold for repolarization lability and resists modulation with pharmacological sympathetic blockade. It is also conceivable that QTV, especially during rest, is already at its nadir in normal hearts and the sympathetic tone is too low for β-blockade to have a significant effect. This is also in line with the observation that QTV did not correlate with left stellate ganglion activity in dogs with normal heart (Piccirillo *et al.* 2009). The contrasting results of a previous study (Mine *et al.* 2008) where β-blockade with propranolol reduced QTV in individuals with structurally normal hearts, are likely due to methodological differences. The effect of propanolol was evaluated during fixed rate atrial pacing, where it may have only abolished the effects of the incidental surge in sympathetic outflow that is associated with cardiac pacing (Berglund *et al.* 1995).

Relation with heart rate variability

The QT interval is intimately linked to heart rate, reflecting the adaptation of ventricular action potentials to the diastolic interval under physiological conditions (electrical restitution) (Zaza *et al.* 1991). The QT interval adaptation to heart rate changes comprises an immediate response to RR interval change paralleled by a slow, more gradual change that may take several minutes (Franz *et al.* 1988). Constant pacing abolishes the effect of physiological HRV on QTV; residual variance in QT despite a lack of HRV likely indicates genuine fluctuations in ventricular activity independent of changes in heart rate (Lombardi *et al.* 1996b). These may be due to a direct autonomic influence, respiration or underlying ventricular pathology (Porta *et al.* 2010). Increased short-term QTV uncoupled from HRV has been shown in ischemic and non-ischemic heart disease (Berger *et al.* 1997, Hinterseer *et al.* 2010, Murabayashi *et al.* 2002, Piccirillo *et al.* 2006) and was an independent predictor of future VT and SCD in these patients (Haigney *et al.* 2004, Piccirillo *et al.* 2007, Tereshchenko *et al.* 2011). Alongside

this strong evidence, a recent study detected changes in RR and QT dynamics during the few hours preceding malignant ventricular arrhythmias (Chen *et al.* 2011).

We demonstrated persistently high QTV in HFVT(+) group during short-term fixed rate atrial pacing, suggesting mechanisms other than HRV may have a dominant role in QT regulation in these patients. Although inconclusive from this study, it is likely that the arrhythmia risk associated with high QTV cannot be evaded with pacing. This observation is in accordance with the results of the Dual Chamber and VVI Implantable Defibrillator trial where chronic prophylactic atrio-ventricular pacing at 70 bpm in ICD recipients without indications for anti-bradycardia pacing had no advantage or was even detrimental compared to back-up VVI pacing (Wilkoff *et al.* 2002). However, these results cannot be extrapolated to biventricular pacing in HF patients. Reverse ventricular remodeling achieved with cardiac resynchronization may improve dynamics of ventricular repolarization and bring down QTV and thus arrhythmia risk in these patients (Ouellet *et al.* 2012, Tereshchenko *et al.* 2011).

Heart rate variability tended to improve in HF patients following acute β-blockade with esmolol, and reduced rapidly during vagal blockade by atropine. In comparison, both these drugs had neutral effect on high QTV values observed in these patients. This dichotomy in response of sinus node activity and ventricular repolarization to pharmacologic autonomic modulation reinforces the impression of mostly independent physiological mechanisms controlling impulse formation and conduction in HF patients.

Clinical significance and future directions

The characteristics of QTV in the HFVT(-) group were more comparable to those of HFVT(+) patients than H_{Norm} subjects. This indirectly demonstrates the progression of spatio-temporal heterogeneity in ventricular repolarization observed as high beat-to-beat QTV in ventricles with cardiomyopathy at high risk for ventricular tachyarrhythmia. β-blockers are the mainstay of therapy in patients with systolic dysfunction, and were shown to improve survival in these patients in large studies (Fauchier *et al.* 2007). The antiarrhythmic effect of β-blockers is mainly achieved by suppression of triggers for ventricular arrhythmias, improved HRV, and secondarily by improved coronary perfusion and cardiovascular dynamics. This study suggests that β-blockers are ineffective in reducing cardiac repolarization lability at least on the short-term. Nonetheless, this failure to achieve desirable changes in ventricular repolarization, cannot be

translated for gradual adaptive changes in QTV that may occur slowly with long-term β-blocker therapy and resultant HF improvement (Bristow 2000, Piccirillo *et al.* 2002). However, high baseline QTV in HF patients despite chronic treatment with β-blockers suggests that long-term β-blockade may only have limited effect on QTV. A key implication from this analysis is that since increased QTV is a risk predictor in HF, QTV reduction may in fact be a clinical target for improving life expectancy. However, increased QTV is not altered by acutely varying the autonomic outflow to the myopathic heart. This entails that high QTV perhaps needs its own different set of possible interventions beyond purely neurohumoral management.

Study limitations

While various QT related metrics standard deviation of QT (SDQT) (Jensen *et al.* 2004), Normalized QTV (QTVN) (Haigney *et al.* 2004), QTV index (QTVi) (Berger *et al.* 1997), Short-Term Variability Ratio (STV_{Ratio}) (Oosterhoff *et al.* 2011), $T_{peak} - T_{end}$ interval variability (Piccirillo *et al.* 2012) have been proposed to quantify repolarization variability, the association of individual measures with future adverse events has been inconsistent among studies (Haigney *et al.* 2004, Piccirillo *et al.* 2007, Tereshchenko *et al.* 2012). Nevertheless, SDQT has been shown to correlate significantly with QTVN and QTVi in HF patients (Piccirillo *et al.* 2007). Due to ethical constraints of studying high-risk patient populations with HF, pharmacologic interventions could not be performed at higher maximal doses and longer infusion periods in these patients. For similar reasons, the regular β-blocker therapy was not withheld before the planned interventions. The lack of response to esmolol due to an insufficient dosage is possible. Esmolol bolus and high-dose infusion, however, frequently produce hypotension (Haney 2012) that can smudge the effects on QT variability and were suitably avoided. Patients with normal heart were significantly younger and predominant females compared with the other study groups, which is in accordance with the general demographic profile of patients with SVT without other cardiovascular diseases (Orejarena *et al.* 1998). However, QTV has been found to be relatively insensitive to age and does not differ between healthy younger and older adults (Hasan *et al.* 2012c, Krauss *et al.* 2009). Although gender differences in QTV have been insufficiently investigated, as with the rate corrected QT interval (Nakagawa *et al.* 2005), QTV (Hasan *et al.* 2012c) and QTV/HRV (Krauss *et al.* 2009) were shown to be higher in women than in men. A higher proportion of females in the H_{Norm} group may therefore have diminished the observed

differences in QTV and QTV/HRV between H_{Norm} and HF groups. Beat-to-beat fluctuations in the QT interval are typically small, and measurement noise might have a considerable impact on QT variability measures. In this study, we mostly used lead I, which is characterized by relatively tall T waves and a good signal-to-noise ratio. Although larger number of patients could possibly have unequivocally demonstrated the interaction between groups and interventions, we could still reveal clinically relevant observations and trends in HF patients. The sample size was inadequate to demonstrate small differences between HFVT(+) and HFVT(-) patients that may exist. The duration of ECG recording for the assessment of QTV was based on recommendations for short-term HRV analysis (Camm *et al.* 1996). The suitability of this duration for the assessment of short-term QT variability has not been systematically investigated. Longer periods of recording may be required to allow lengthier time for adaptation of QT interval, which may be a case in HF patients.

A.5 Summary

The study shows that patients with HF and spontaneous VT have larger fluctuations in beat-to-beat QT intervals. This repolarization instability appears to persist despite uncoupling the effect of heart rate. The effect of acute autonomic nervous system modulation on QTV appears to be limited in HF patients.

Matlab Codes

THIS appendix presents some of the Matlab algorithms code. These algorithms are available as m-files on the attached DVD-ROM.

B.1 R-peaks detection and baseline removal

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%        Matlab code for  detection of R-peak in ECG signal                   %
%                                                                             %
%                                                                             %
%                                                                             %
%  This program is used to detect the R-peak in ECG signal                    %
%  As a input, the real ECG signal and sampling frequency is given            %
%  The program will return the R-peak position and amplitude                  %
%                                                                             %
%                                                                             %
%                                                                             %
% Variabble information                                                       %
% ecg=the ECG data                                                            %
% freq=sampling frequency                                                     %
%                                                                             %
%                                                                             %
% Muhammad A. Hasan                                                           %
% The University of Adelaide                                                  %
% December 2011                                                               %
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

clear all
close all
clc

% Load ECG signal from saved file
Data=load('ECG file.mat');

ecg=DATA;
freq=1000;

%apply the high pass filter
[B,A]=butter(4,0.5/(sampling*0.5),'high');
    Highpass=filtfilt(B,A,ecg);
    temp_ecg=Highpass;

%to findout R-wave of ECG is upwards or downwards
maxR=[];
minR=[];
```

```
windows=sampling*2;
i=1;

Nofwindow=15;
Nofsample_in_window=floor(length(ecg)/(Nofwindow));

if windows>Nofsample_in_window
    windows=Nofsample_in_window;
end

for j=1:1:Nofwindow


    maxR=[maxR max(temp_ecg(i:i+windows-1))];
    minR=[minR min(temp_ecg(i:i+windows-1))];


     i=i+Nofsample_in_window;


end

Rpositive=mean(abs(maxR));
Rnegative=mean(abs(minR));

if Rnegative>Rpositive
   temp_ecg=(-1)*ecg;
else
    temp_ecg=ecg;
end
%---

s=temp_ecg; %s contains the ECG signal

% Filter ECG by cheby
n = 4;
r = 0.1;
Wn = ([6 18]/(sampling*0.5));
ftype = 'bandpass';

[b,a] = cheby1(n,r,Wn,ftype);
```

```
f=filtfilt(b,a,s);

% First-Order Forward Differenciation
d=diff(f);

% Amplitude Normalization
dECG=d/max(abs(d));

% Shanon energy and smooth envelop extraction

aECG=abs(dECG);
eECG=dECG.^2;
seECG=-abs(dECG).*log(abs(dECG));
SNECG=-dECG.^2.*log(dECG.^2);

% Zero-phase filtering
N=ceil((55/360)*sampling);
h=ones(1,N)/N;
b=h;
a=1;
sp2=filtfilt(b,a,SNECG);

% Hilbert Transform

sp2_H=imag(hilbert(sp2));

L=ceil((900/360)*sampling);
b=ones(1,L)/L;
a=1;

sp2_HM1=filtfilt(b,a,sp2_H);

sp2_H=sp2_H-sp2_HM1;

idx=find(diff(sp2_H>0)>0);

new_idx=[];

for i=2:1:length(idx)-1


    range=idx(i)-5:idx(i)+5;
```

```
   [C,I]=max(sp2(range));
   new_idx=[new_idx range(I)];
end

peaks=new_idx;

Rloc=[];
Ramp=[];

for i=1:1:length(peaks)

    range= peaks(i)-30:peaks(i)+30;

    m=max(s(abs(range)));

     l=find(s(abs(range))==m);

    pos=range(l);
    Rloc=[Rloc pos];
end

%%=================== Baseline removal ===================

% Filter ECG
iso_t=[];

fs=1000;
[B,A]=butter(4,40/(fs/2),'low');
ecgin=filtfilt(B,A,ecg);

ecg=ecg-mean(ecg); %subtract the mean ECG from original ECG

t = [1:1:length(ecg)]/fs;

if(isempty(iso_t))
R_index= ecg(Rloc);
a=50;
    notR=find(R_index<=a);
       R_index(notR)=[];
    iso_t = t(R_index-a);
end
```

```
iso_x=ecg(R_index-a);
baseline_t = iso_t;
baseline_x = iso_x;

%interpolation
[baseline_t,baseline_x] =  interp1(baseline_t,baseline_x,fs,3);

% remove baseline
ecgtmp = ecg(R_index(1):R_index(length(R_index)));
ecgout = ecgtmp-baseline_x;

ecgout_final=[ecg(1:R_index(1)-1) ecgout ...
    ecg(R_index(length(R_index))+1:end)];
```

B.2 Matlab code for VCG analysis

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%        Matlab code for  VCG analysis                                       %
%                                                                            %
%                                                                            %
% This program takes the 8 independent ECG (QT duration) with                %
% sampling frequency, return orthogonal representation of ECG                %
% It computes several spatial and temporal parameters                        %
%                                                                            %
%                                                                            %
% variable information                                                       %
% I=lead I of ECG                                                            %
% II=lead II of ECG                                                          %
% V1=lead V1 of ECG                                                          %
% V2=lead V2 of ECG                                                          %
% V3=lead V3 of ECG                                                          %
% V4=lead V4 of ECG                                                          %
% V5=lead V5 of ECG                                                          %
% V6=lead V6 of ECG                                                          %
% freq=sampling frequency                                                    %
% S=decomposed ECG signal                                                    %
% E3D=Energy signal                                                          %
%                                                                            %
%                                                                            %
% Muhammad A. Hasan                                                          %
% The University of Adelaide                                                 %
% February 2011                                                              %
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

clear all
close all
clc

Data=load('ECG file.mat');

freq=1000;

% leads ECG
M = [I; II; V1; V2; V3; V4; V5; V6];

 [U,S,V]=svd(M);
```

```
SS=U'*M;

S1=SS(1,:);
S2=SS(2,:);
S3=SS(3,:);

S3D=[S1; S2; S3];

E3D=sqrt(sum(S3D.^2));

lemda=0.7; % 70% threshold
R_end=max(E3D)*0.7;

[y,x]=max(E3D);

%For finding the tprs and tpre point in the QRS complex
for i=x:-1:1;
 if R_end > E3D(1,i)           %tprs point
      tpRS=i;
     break;
 end
end

for i=x:1:length(E3D);
 if R_end > E3D(1,i)           %tpre point
      tpRE=i;
     break;
 end
end

shi=48;
tRS=1;
tRE=x+shi;

ii=tRE:1:length(E3D);
[Y,X]= max(E3D(ii));
tTP=X+tRE-1;
tTS=tpRE+round((tTP-tpRE)/3);

tTE=length(E3D);
```

```
%Normalization
S3D_norm = S3D/max(E3D);

St = S3D(:,tTS:1:tTE)/max(E3D);
SQRS = S3D(:,tRS:1:tRE)/max(E3D);


St=St-0.25*(S3D_norm(tRS)+S3D_norm(tRE)+S3D_norm(tTS)+S3D_norm(tTE));
SQRS=SQRS-0.25*(S3D_norm(tRS)+S3D_norm(tRE)+S3D_norm(tTS)+S3D_norm(tTE));

MperimT=U(:,1:3)*St;

[Utt,Stt,Vtt]=svd(MperimT);

SUM_T=Utt(:,1:2)'*MperimT*Vtt;

%% Reconstruction Coefficient
Wt_T=Utt(:,1:2)*SUM_T(1:2,1:2);

Wt_T=Wt_T';

for oi=1:1:7
for ai=oi:1:8
    if (oi~=ai)
    CosTheta = ...
        dot(Wt_T(:,oi),Wt_T(:,ai))/(norm(Wt_T(:,oi))*norm(Wt_T(:,ai)));
    ThetaInDegrees(oi,ai)= acos(CosTheta)*180/pi;
    else continue;
    end
end
end

ThetaInDegrees (:,3)=0;
ThetaInDegrees (3,:)=0;

TMD =sum(sum(ThetaInDegrees))/21;

MperimT=U(:,1:3)*St(:,1:tTP-tTS-1);

[Utt,Stt,Vtt]=svd(MperimT);

SUM_T=Utt(:,1:2)'*MperimT*Vtt;
```

```
%% Reconstruction Coefficient
Wt_T=Utt(:,1:2)*SUM_T(1:2,1:2);

Wt_T=Wt_T';

for oi=1:1:7
for ai=oi:1:8
 if (oi~=ai)
 CosTheta = dot(Wt_T(:,oi),Wt_T(:,ai))/(norm(Wt_T(:,oi))*norm(Wt_T(:,ai)));
 ThetaInDegrees(oi,ai)= acos(CosTheta)*180/pi;
 else continue;
 end
end
end

ThetaInDegrees (:,3)=0;
ThetaInDegrees (3,:)=0;

TMDpre =sum(sum(ThetaInDegrees))/21;

MperimT=U(:,1:3)*St(:,tTP—tTS:length(St));

[Utt,Stt,Vtt]=svd(MperimT);

SUM_T=Utt(:,1:2)'*MperimT*Vtt;

%% Reconstruction Coefficient
Wt_T=Utt(:,1:2)*SUM_T(1:2,1:2);

Wt_T=Wt_T';

for oi=1:1:7
for ai=oi:1:8
 if (oi~=ai)
 CosTheta = dot(Wt_T(:,oi),Wt_T(:,ai))/(norm(Wt_T(:,oi))*norm(Wt_T(:,ai)));
 ThetaInDegrees(oi,ai)= acos(CosTheta)*180/pi;
 else continue;
 end
end
end
```

```
ThetaInDegrees (:,3)=0;
ThetaInDegrees (3,:)=0;

TMDpost = sum(sum(ThetaInDegrees))/21;

for rti=tpRS:1:tpRE
    coli=rti-tpRS+1;
    CosTheta = dot(St(:,tTP-tTS+1),SQRS(:,rti-tRS+1))/...
        (norm(SQRS(:,rti-tRS+1))*norm(St(:,tTP-tTS+1)));
    ThetaRT(coli) = acos(CosTheta);

end

AVG_ThetaRT = sum(cos(ThetaRT))/(tpRE-tpRS);

% PCA1 ratio finding
    i=2:8;
    Sum_S1to8=sqrt(sum(SS(i,tTS:tTE).*SS(i,tTS:tTE)));
    PCA1 =(nonzeros(S1(tTS:tTE))./nonzeros(Sum_S1to8))*100;

% PCA2 ratio finding
    PCA2 =(nonzeros(S2(tTS:tTE))./nonzeros(S1(tTS:tTE)))*100;

 % PCA3 ratio finding
    PCA3 =(nonzeros(S3(tTS:tTE))./nonzeros(S1(tTS:tTE)))*100;

ti=tTS:1:tTE;
S2D_T=[S1(1,ti); S2(1,ti);];

minS1=min(S1(1,ti));
maxS1=max(S1(1,ti));
minS2=min(S2(1,ti));
maxS2=max(S2(1,ti));

Xdiv=abs(maxS1-minS1)/10;
Ydiv=abs(maxS2-minS2)/10;

in_out=zeros(10,10);
x_axis=minS1:Xdiv:maxS1;
y_axis=minS2:Ydiv:maxS2;

for point=1:length(S2D_T(2,:))
```

```
        xin=1;
        while xin<=length(x_axis)-1 %x axis

            if((S2D_T(1,point)>=x_axis(xin)) && (S2D_T(1,point)<= ...
               x_axis(xin+1)))

                get_x=xin; %get the indexes of x-axis
                break;
            end

            xin=xin+1;
        end

        yin=1;
        while yin<=length(y_axis)-1 %y axis

            if((S2D_T(2,point)>=y_axis(yin)) && (S2D_T(2,point)<= ...
               y_axis(yin+1)))

                get_y=yin; %get the indexes of y-axis
                break;
            end

            yin=yin+1;
        end

        in_out(get_x,get_y)=1;
end

    inner_box=0; %initially inner box number will zero
  for roww=1:length(in_out(:,1)) %

      box_r=find(in_out(roww,:));

          if isempty(box_r)
             continue;
          elseif length(box_r)==1
              inner_box=inner_box+1;
          else
              inner_box=inner_box+box_r(end)-box_r(1)+1;
          end
```

```
end

matrix_size=size(in_out);
total_box=matrix_size(1)*matrix_size(2);

outer_box=total_box-inner_box;

 %Percentage of Loop area
 PL = (inner_box/total_box);

 %Percentage of outer area
 PO = (outer_box/total_box);

 b=1;
  ti=tRS:1:tRE;
  S2D_QRS=[S1(1,ti); S2(1,ti); S3(1,ti)];


  QRS_S1 = S1(1,ti);
  QRS_S2 = S2(1,ti);
  QRS_S3 = S3(1,ti);
  %% To draw the QRS-loop
  subplot(3,1,1);
  plot3(S2D_QRS(1,:),S2D_QRS(2,:),S2D_QRS(3,:));
  hold on


              QRS_SS1=mean(QRS_S1);
              QRS_SS2=mean(QRS_S2);
              QRS_SS3=mean(QRS_S3);

              hold on
              plot3(QRS_SS1,QRS_SS2,QRS_SS3,'color','c');

  axis square; grid on

  %%To find the T-loop
  ti=tTS:1:tTE;
  S2D=[S1(1,ti); S2(1,ti); S3(1,ti)];


          T_S1=[T_S1 zeros(nofbeat,length(ti)-length(T_S1(b,:)))];
```

```
            T_S1(b,1:length(ti))=S1(1,ti);

            T_S2=[T_S2 zeros(nofbeat,length(ti)-length(T_S2(b,:)))];
            T_S2(b,1:length(ti))=S2(1,ti);

            T_S3=[T_S3 zeros(nofbeat,length(ti)-length(T_S3(b,:)))];
            T_S3(b,1:length(ti))=S3(1,ti);

            %---mask
            T_S1_mask=[T_S1_mask ...
                zeros(nofbeat,length(ti)-length(T_S1(b,:)))];
            T_S1_mask(b,1:length(ti))=ones(1,1:length(ti));

            T_S2_mask=[T_S2_mask ...
                zeros(nofbeat,length(ti)-length(T_S2(b,:)))];
            T_S2_mask(b,1:length(ti))=ones(1,1:length(ti));

            T_S3_mask=[T_S3_mask ...
                zeros(nofbeat,length(ti)-length(T_S3(b,:)))];
            T_S3_mask(b,1:length(ti))=ones(1,1:length(ti));


            T_S1(b,1:length(ti))=S1(1,ti);
            T_S2(b,1:length(ti))=S2(1,ti);
            T_S3(b,1:length(ti))=S3(1,ti);

            %mask
            T_S1_mask(b,1:length(ti))=ones(1,1:length(ti));
            T_S2_mask(b,1:length(ti))=ones(1,1:length(ti));
            T_S3_mask(b,1:length(ti))=ones(1,1:length(ti));

    %% To draw the T-loop 3D
    subplot(3,1,2);
    plot3(S2D(1,:),S2D(2,:),S2D(3,:));
    hold on


             hold on
               plot3(T_newSS1,T_newSS2,T_newSS3,'color','r');

    axis square; grid on
```

```
%%----------QRS and T loop combined----------------------

    subplot(3,1,3);
    plot3(S1(tRS:tRE),S2(tRS:tRE),S3(tRS:tRE));  %for QRS loop
    hold on
    subplot(3,1,3);
    plot3(S1(tTS:tTE),S2(tTS:tTE),S3(tTS:tTE),'color','g'); %for T loop ...
       green color
    hold on
        if b ==1
            title('The QRS and T-loop Morphology');
        end

    axis square; grid on
```

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Glossary

ANOVA	analysis of variance
ANCOVA	analysis of co-variance
ANS	autonomic nervous system
AUC	area under the curve
BMI	body-mass index
ECG	electrocardiogram
HF	high-frequency power
HR	heart rate
HRV	heart rate variability
ICC	intraclass correlation coefficient
kNN	k-nearest neighbours
LF	low-frequency power
MI	myocardial infarction
QT	QT interval
QTV	QT interval variability
RR	ECG R to R interval
ROC	receiver operating characteristic
SNS	sympathetic nervous system
SNR	signal to noise ratio
SVD	singular value decomposition
TCRT	total cosines R-to-T
TMD	T-wave morphology dispersion
SD	standard deviation
VCG	vector-cardiogram

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Biography

Muhammad Asraful Hasan received his BSc. in Computer Science and Engineering from University of Dhaka, Bangladesh and MSc. in Engineering degree with Honours in Computer and Information Engineering from The Islamic University of Malaysia, Malaysia, in 2006 and 2009 respectively.

After finishing his MSc. degree he was awarded an Australian Endeavour International Postgraduate Research Scholarship (EIPRS) and University of Adelaide Scholarship (UAS) for Postgraduate Research (PhD.) in the School of Electrical and Electronic Engineering under the supervision of Assoc Prof Mathias Baumert and Prof Derek Abbott, the University of Adelaide, 2010.

He worked as a research assistant in Malaysia from Dec. 2006–Jun. 2010 in the Department of Electrical and Computer Engineering, International Islamic University Malaysia. He was a researcher on a project entitled *Hardware Prototyping of Fetal Heart Rate Monitoring System using Artificial Intelligence* funded by Ministry of Science, Technology and Innovation (MOSTI), Malaysia, and Development of an Emergency Medical Care System for Cardiac Telemedicine Monitoring funded by a Research Cluster Grant, International Islamic University Malaysia. He has worked as an Instructor in the First Abdus Salam International Center for Theoretical Physic (ICTP) regional Microelectronics Workshop and Training on VHDL for Hardware Synthesis and FPGA Design in Asia-Pacific 2008, Malaysia. He has been awarded as an IEEE Student Scholarship to attend and present a research paper in the IEEE-ICIT'09 conference, 10-13 February, 2009 at Monash University, Australia. In addition, he received Silver Medal award in Kulliyyah (Faculty) of Engineering Research and Innovation Exhibition (KERIE'09) for research performance, International Islamic University Malaysia 2009. He achieved the Dean's award from Military Institute of Science and Technology for outstanding performance at the undergraduate level, 2006.

During his PhD candidature, he received the 'IEEE South Australia Travel Assistance Award' in 2011 (Computing in Cardiology Conference, China) and 2012 (IEEE-EMBS conference, USA). Further, he was awarded the SMBE SA/NT Travel grant for presenting paper in the Australian Biomedical Engineering conference, 2013. He has authored and co-authored more than 35 peer-reviewed publications, and has given at least 8 presentations at international conferences.

Muhammad Asraful Hasan is a member of the Institute of Electrical and Electronics Engineers (IEEE), IEEE Engineering in Medicine and Biology Society, e-Cardiology of of the European Society of Cardiology, Australian Society of Medical and Biological Engineering and European Alliance of Medical and Biological Engineering and Science.

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Scientific Genealogy of

Muhammad Asraful Hasan