NEW TECHNIQUES FOR VENTRICULAR 
REPOLARIZATION AND HEART RATE VARIABILITY 
ANALYSES

A DISSERTATION 
SUBMITTED TO THE DEPARTMENT OF ELECTRICAL 
AND ELECTRONICS ENGINEERING 
AND THE INSTITUTE OF ENGINEERING AND SCIENCES 
OF BILKENT UNIVERSITY 
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS 
FOR THE DEGREE OF 
DOCTOR OF PHILOSOPHY

By 
Barak Arar

March 2000
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By

Burak Acar

March 8, 2000
I certify that I have read this thesis and that in my opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Doctor of Philosophy.

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ABSTRACT

NEW TECHNIQUES FOR VENTRICULAR
REPOLARIZATION AND HEART RATE VARIABILITY
ANALYSES

Burak Acar
Ph. D. in Electrical and Electronics Engineering
Supervisor: Hayrettin Köymen, Ph. D.
March 8, 2000

This thesis is composed of two parts: i) Development of a fully automatic Heart Rate Variability (HRV) analysis method, and ii) development of new methods for ventricular repolarization (T wave) analysis.

The first part of this study deals with fully automatic measurement of heart rate variability (HRV) in short term electrocardiograms. In short, HRV analysis is the spectral analysis of the heart rate signal. Presently, all existing HRV analysis programs require user intervention for ectopic beat identification which is essential for reliable HRV analysis. This makes HRV studies in large populations problematic.

A fully automatic algorithm to discriminate ventricular and supra-ventricular ectopic beats from normal beats is presented. The method incorporates several approaches and uses three ECG leads. It uses the template matching for the basic morphology check of the QRS complex and the P-wave, the timing information to avoid unnecessary computation and to adjust the thresholds and also looks for a special QRS morphology which is common in ventricular ectopic beats. The method is tested on a set of real
ECG recordings and statistically analyzed on the basis of sensitivity and specificity. Its performance using single ECG leads and different triplets of ECG leads is also studied.

We have obtained 99% specificity and SVE sensitivity and 98% VE sensitivity and thus concluded that fully automatic HRV analysis is feasible.

The second part of this thesis is on ventricular repolarization analysis (T wave analysis). It has been shown that heterogeneity in ventricular repolarization is a mark of abnormality and can be used for risk stratification. Several methods have been proposed to measure this heterogeneity, among which the QT interval measurements are the most popular ones. After a short discussion of the existing methods, we propose three new approaches for T wave analysis, which are aimed to overcome the drawbacks of the existing methods: The spatial and temporal variations in the T wave morphology and the wavefront direction difference between the ventricular depolarization and repolarization waves.

All of the descriptors are defined in an ECG decomposition space constructed by Singular Value Decomposition. The spatial variation characterizes the morphology differences between standard leads. The temporal variation measures the change in inter-lead relations throughout the T wave. The wavefront direction difference quantizes the difference between the progress of the two processes. None of them requires time domain measurements thus avoid the inaccuracies associated with conventional methods.

The new methods are compared with the conventional ones in a set of 1100 normal ECGs. The short-term intra-subject reproducibility of the new and the conventional methods is compared in a set of 760 normal (recorded from 76 normal subjects) and 630 abnormal (recorded from 63 HCM patients) ECGs. The new descriptors' ability to discriminate normal and abnormal ECGs (both in univariate and multivariate models) is also analyzed on the same data set. A two-way blind study conducted on a set of AMI (Acute Myocardial Infarction) patients have shown that the new methods are able to discriminate the high risk group. The conventional methods were shown to be useless in
this patient group in a previous study.

We have concluded that the new descriptors do not correlate with the conventional ones, are more reproducible, lead to more significant separation between normal and abnormal ECGs in both univariate and multivariate models.

Keywords: Automatic HRV Analysis, Ectopic Beat Identification, Whitehall II Study, ECG Analysis, T Wave Analysis, Repolarization Heterogeneity, Spatial and Temporal Variation, Morphology Variation, Wavefront Direction Characteristics, QT Interval, Singular Value Decomposition
ÖZET

KALP HIZI DEĞİŞKENLİĞİ ANALİZİ
VE
KARINCİKLARIN REPOLARİZASYONUNUN İNCELENMESİ
İÇİN YENİ YAKLAŞIMLAR

Burak Acar
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8 Mart 2000

Bu doktora tezi iki bölümden oluşmaktadır: i) Tam otomatik Kalp Hızı Değişkenliği analiz yönteminin geliştirilmesi, ve ii) karıncık repolarizasyonu (T dalgası) analizi için yeni yöntemlerin geliştirilmesi.

İlk bölüm kısa EKG kayıtlarında tam otomatik kalp hızı değişkenliği (KHD) analizi üzerindedir. KHD analizi kısa nabzın frekans analizi şeklinde tanımlanabilir. Kullanılmakta olan KHD analizi sistemleri, analizin güvenilirliği için çok önemli olan ektopik kalp atımlarının ayrılanması için bir kullanıcıya ihtiyaç duyarlar. Bu durum geniş hasta gruplarında KHD analizini zorlaştırır.

Bu bölümde karıncık ve kulakçıklardan kaynaklanan ektopik atımların (VE ve SVE) normal atımlardan ayırdedilmiş için tam otomatik bir algoritma sunulmaktadır. Sunulan yöntem değişik yaklaşımları birleştirirken ve üç EKG kanalını kullanmaktadır. QRS kompleksi ve P dalgası temel morfoloji analizi için şablon eşleme (template matching)
yöntemi, gerekiz işlemlerin önlenmesi ve eşik değerlerinin ayarlanması için zamanlama bilgisi (anlık nabız değeri) kullanılmaktadır. Ayrıca karıncıklardan kaynaklanan ektopik atımlarda sik görülen özel bir morfoloji de kontrol edilmektedir. Sistemimiz gerçek EKG kayıtları üzerinde denenmiş ve duyarlılık/özgüllük (sensitivity/specificity) temelinde istatistiksel olarak analiz edilmiştir. Sistemin farklı üç EKG kanalı ve tek kanal kullananlıdındaki performansı da incelenmiştir.

Sistemimizin %99 özgüllüğe, %99 SVE ve %98 VE duyarlığına ulaştığı gözlenmiş ve tam otomatik KHD analizinin uygulanabilirliği sonucuna varılmıştır.


Yeni ve konvansiyonel yöntemler öncelikle 1100 normal EKG üzerinde test edilmiştir. Bir hastadan arka arkaya yapılan ölçümlerde ölçülen parametrelerin tekrar edilebilirliği ise 760 normal (76 hastadan kaydedilmiş) ve 630 anormal (63 hastadan kaydedilmiş)

Yeni yöntemlerin konvansiyonel yöntemlere göre EKG'deki farklı bilgileri kullandığı (eski ve yeni yöntemler arasında bir örtüşmenin olmadığı), yeni yöntemlerin daha tekrar edilebilir olduğu, normal ve anormal EKG'leri daha iyi ayırabildiği sonucuna varılmıştır.

Anahtar Sözcükler: Otomatik Kalp Hızı Değişkenliği Analizi, Ektopik Atımların Tanınması, Whitehall II Projesi, EKG Analizi, T Dalgası Analizi, Repolarizasyon Heterojenliği, Uzaysal ve Zamansal Değişenlik, Morfoloji Değişkenliği, Dalga Cephesi Yönü Özellikleri, QT Aralığı, Tekil Değer Ayırtılması
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Chapter 1

INTRODUCTION

Electrocardiogram (ECG) signals are the recorded potential differences on the surface of the body due to the electrical currents on the heart itself. The invention of ECG cannot be attributed to a single person, although most of the credit goes to Willem Einthoven, a Dutch physiologist, who won the 1924 Nobel Prize for the invention of ECG.

Here is a short account of the development of ECG:

1842: Italian physicist Carlo Matteucci showed that an electric current accompanied each heart beat [1].

1878: British physiologists John Burden Sanderson and Frederick Page recorded the heart’s electrical current with a capillary electrometer and showed that it consisted of two phases (later called the QRS complex and the T wave, which correspond to ventricular depolarization and repolarization respectively) [2].

1887: British physiologist Augustus D. Waller of St Mary’s Medical School, London published the first human electrocardiogram [3].

1893: Willem Einthoven introduced the term 'electrocardiogram' at a meeting of the
Dutch Medical Association. Later he claimed that Waller had been the first to use the term [4].

1901: Einthoven modified a string galvanometer for producing electrocardiograms. His string galvanometer weighed 600 pounds (approximately 270kg) [5].

1902: Einthoven published the first electrocardiogram recorded on a string galvanometer [6].

1906: Einthoven published the first organized presentation of normal and abnormal electrocardiograms recorded with a string galvanometer. Left and right ventricular hypertrophy, left and right atrial hypertrophy, the U wave (for the first time), notching of the QRS, ventricular premature beats, ventricular bigeminy, atrial flutter and complete heart block were all described [7,8].

1920: Hubert Mann of the Cardiographic Laboratory, Mount Sinai Hospital, described the derivation of a 'monocardiogram' later to be called the 'vectorcardiogram' [9].

1942: Emanuel Goldberger added the augmented limb leads aVR, aVL and aVF to the Einthoven's three limb leads (I, II, III) and the six chest leads (V1, ..., V6) making the 12-lead electrocardiogram that is used today.

Figure 1.1 shows a typical heart beat recorded from surface ECG leads. The five deflections correspond to different phases of the heart beat: The P wave is for atrial depolarization, the QRS complex is for ventricular depolarization and the T wave is for ventricular repolarization. A great deal of information is obtained by studying these waves, namely their duration, amplitude and morphology. The dynamism of these qualities are also being studied, such as the time variation of the inter-beat durations, the T wave amplitude, variation, etc. Although ECG has been being studied for over a century, it still proves to be interesting in terms of research as its new properties are being discovered.
This thesis deals with two fields of ECG analysis: The Heart Rate Variability (HRV) analysis and the Ventricular Repolarization (T Wave) Analysis. HRV analysis deals with the beat-to-beat changes in the inter-beat durations and the T wave analysis studies the properties of the T wave. The questions addressed can be stated as follows: (i) Is fully automatic short-term HRV analysis feasible? (ii) Can the spatial/temporal variation of the T wave morphology and the wavefront direction characteristics during ventricular repolarization be indicators of ventricular repolarization heterogeneity? Do they have any clinical significance?

This thesis is organized in two parts:

The first part is devoted to HRV analysis. This part starts with some background information on HRV analysis, followed by the definition of the problem. The method and its implementation is explained in detail. The following section is about the experiments conducted. This section starts with the introduction of the data set used, the statistical analysis methods and concludes with the results. A discussion of several aspects of the method is given in the next section. A second version of the method, the associated experiments and their results, together with a discussion is given in the following section. Finally, a conclusion on this part is provided.
The second part is about ventricular repolarization (T Wave) analysis. The first section provides a thorough background on the basis of T wave analysis, the conventional and the alternative methods. The problem and our approach is explained in the following section. The method and its implementation are explained in next sections. The analysis section starts with an introduction of the data set used, a comparison of the conventional and new methods is also provided with the reproducibility of the new parameters. The performance of the new methods in discriminating normal and abnormal ECGs is also assessed via statistical methods and reported in this section. The following section provides a discussion of the results, the relation between the conventional and the new methods and the limitations of the new methods. The next section reports a 2-way blind study performed on a group of AMI (Acute Myocardial Infarction) patients. An attempt to solve some technical problems in some of the new methods is reported in a separate section. This part ends with a conclusion.

The thesis ends with some concluding remarks on the future of ECG analysis in conjunction with the analysis methods proposed in this thesis.
2.1 BACKGROUND

Autonomic Nervous System (ANS) is the feedback control mechanism of our body. It takes several inputs like blood pressure, body temperature and outputs stimuli to keep them at desired ranges. ANS is composed of two sub-systems: Sympathetic and Parasympathetic Nervous Systems. The sympathetic system is associated with stress responses whereas the parasympathetic system is associated with non-stress responses. The effects of the parasympathetic are generally to counteract the effects of the sympathetic. For example, the sympathetic system increases the heart rate and the contraction force while the parasympathetic system slows down the heart rate. The two systems operate as a pair, striking a nearly perfect balance when the body is functioning properly. A significant relation between the ANS and the cardiovascular mortality was noticed in the second half of the 1970's [10]. Increased experimental evidence for an association between lethal cardiac arrhythmia and increased sympathetic activity led researchers to
look for simple ways of assessing ANS activity.

On the other hand, clinical significance of HRV was first appreciated in 1965 [11]. They noticed alterations in the inter-beat intervals before any significant change in the heart rate itself. Wolf et al. showed the association between reduced HRV and increased risk of post-infarction mortality [12]. The spectral analysis methods, used today with the time domain parameters, were introduced in 1981 to study the heart rate fluctuations quantitatively [13]. In the late 1980's, HRV was confirmed to be a strong and independent predictor of mortality following acute myocardial infarction [14–16].

The need for a standardization of HRV analysis methods led The European Society of Cardiology and The North American Society of Pacing and Electrophysiology to form a task force. The various HRV parameters and their interpretation can be found in their report [17].

HRV is the oscillation in the inter-beat intervals as well as the oscillations between consecutive instantaneous heart rates. It should be noted that HRV does not assess the changes in the heart rate per second but rather the changes in consecutive time intervals, i.e. it is the analysis of a time series.

The HRV measurements can be grouped in two: The time domain measurements and the frequency domain measurements.

**Time Domain Measurements:**
A time series of consecutive time intervals between two consecutive normal heart beats (Normal-to-Normal -NN- interval) is formed. This is called the tachogram or the NN-series in general. The following measures are calculated in time domain:

* **Mean NN:** Average of normal-to-normal heart beat intervals.

* **Mean Heart Rate:** Average of the reciprocal of normal-to-normal heart beat intervals.
* **Max Min NN**: The difference between the maximum and the minimum NN interval.

* **DayNight NN**: The difference between the mean NN intervals during the day and the night.

* **SDNN**: The standard deviation of the NN intervals. SDNN reflects the power of all of the periodic components responsible for variability. However, its value depends on the length of the ECG record, so care must be paid while comparing two SDNN measurements.

* **SDANN**: The standard deviation of the average NN intervals calculated over short periods (5 minutes), over 24 hours. It assesses the heart rate changes in periods longer than 5 minutes.

* **SDNN Index**: The mean of the 5 minute standard deviations of NN intervals calculated over 24 hours. It assesses the heart rate changes in periods shorter than 5 minutes.

* **RMSSD**: The square root of the mean squared differences of successive NN intervals. This is an estimate of the short-term changes, like SDNN index.

* **NN50**: The number of interval differences of successive NN intervals greater than 50ms.

* **pNN50**: The percentage of NN50 over the total number of NN intervals.

* **HRV Triangular Index**: It is equal to the integral of the NN intervals' density distribution (i.e., total number of NN intervals in the tachogram) divided by the maximum of the density distribution (i.e., the number of the most common NN interval). This is also an estimate of the overall HRV, as SDNN is.

* **TINN**: The Triangular Interpolation of the NN interval histogram is the baseline width of the NN interval distribution measured by using a triangle that approximates the shape of this distribution.
* Differential Index: It is the difference between the widths of the histograms of differences between consecutive NN intervals measured at selected levels.

* Logarithmic Index: It is the coefficient of the exponential curve which best fits to the histogram of absolute differences between consecutive NN intervals.

SDNN, HRV Triangular Index, SDANN and RMSSD are recommended by the Task Force.

**Frequency Domain Measurements:**
The following measures can be calculated from the tachogram in the frequency domain:

Short-term (5 minute) analysis:

* **5 Minute Total Power**: The variance of the NN intervals in a window of 5 minutes.
* **VLF**: Power in the very low frequency range \((f < 0.04Hz)\).
* **LF**: Power in the low frequency range \((0.04Hz < f < 0.15Hz)\).
* **LFnorm**: Percentage of LF over the total power.
* **HF**: Power in the high frequency range \((0.15Hz < f < 0.4Hz)\).
* **HFnorm**: Percentage of HF over the total power.
* **LF/HF**: Ratio of LF to HF.

24 hour analysis:

* **Total Power**: The variance of all of the NN intervals in a 24 hour period.
* **ULF**: Power in the ultra low frequency range \((f < 0.003Hz)\).
* **VL F**: Power in the very low frequency range \((0.003Hz < f < 0.04Hz)\).
* **LF**: Power in the low frequency range \((0.04Hz < f < 0.15Hz)\).
* HF: Power in the high frequency range \((0.15Hz < f \leq 0.4Hz)\).

* \(\alpha\): Slope of the linear interpolation of the spectrum in a log-log scale.

The LF is associated with the parasympathetic activity while the HF is said to be associated with both sympathetic and parasympathetic activities of the ANS. There is a continuing debate on the meaning of HF components. Thus, the level of autonomic modulations can be easily assessed via HRV analysis. All of the frequency domain parameters, except the ULF and VLF related ones, are widely used. The meaning of ULF and VLF components are still to be determined.

There are two approaches for the Power Spectral Density (PSD) estimation of a given tachogram [18]:

(i) *Parametric:* An auto-regressive (AR) model is assumed for the underlying process that creates the tachogram. The Z-transform of the transfer function of the model is defined as:

\[
H(z) = \frac{1}{a_0 + a_1z^{-1} + \ldots + a_nz^{-n}}
\]  

(2.1)

where the model order is assumed to be \(n\). The model coefficients \((a_i)\) are determined by solving the Yule-Walker equations using the Levinson Recursion [19]. The problem with AR modeling is the selection of the model order, \(n\). A common approach is to use the Signal-to-Noise Ratio (SNR) and Akaike Information Criteria (AIC) curves versus model order. AIC measures the residual variance, as the model fits to the data better and better, AIC decreases [20]. Figure 2.1 shows the typical behaviour of SNR and AIC curves. The model order where both of the curves become flat is selected as the true model order. It is 8 in this example.

(ii) *Non-parametric:* The non-parametric approach uses the Discrete Fourier Transform (DFT) to estimate the PSD of the tachogram [19].
The advantage of FFT is that the algorithm is simple, there is no problem like model order determination and the processing time is low. However, the precision of PSD depends on the length of the tachogram due to the time-frequency resolution trade-off. The advantage of the parametric method is that a smoother PSD is obtained which helps to distinguish different spectral components, the post-processing of different spectral components is easy and an accurate estimation of PSD is possible even with a short tachogram. Thus the stationarity problem is overcome since we can assume that the tachogram is stationary in a short time interval. Its basic disadvantage, as stated above, is the problems in choosing the model order.

A good approach is to perform both of the analyses and then check whether they agree, which provides a sort of confidence measure.

Whatever the method applied is, the accuracy of the PSD depends on the qualities of the tachogram. The tachogram must be free of positive or negative spikes. Such spikes can mask the whole spectrum. A common source of such spikes are the ectopic beats. An ectopic beat is a heart beat that is initiated from an abnormal region of the heart, not from the sinus node as in the normal case. The course of propagation of the depolarization/repolarization waves depends on the location of this stimulus. Such an
abnormal stimulus location is termed as the *ectopic focus*. Ectopic focus can be anywhere on the heart, on the atria or the ventricles. The morphology of the ectopic beats can be very different from the normal beats' but not necessarily. The morphology difference also depends on the ectopic focus. The atrial ectopic beats look very much like normal beats except some subtle morphological differences in the P wave (which corresponds to the atrial depolarization). The ventricular ectopic beats, on the other hand, are usually very different from the normal beats because an ectopic focus on the ventricles changes the morphology of the QRS complex and the T wave which are high energy components of the ECG. Ectopic beats do not obey the normal rhythm of the heart (*sinus rhythm*). They come significantly earlier than a normal beat and a pause occurs after them. This causes a negative spike followed by a positive one in the tachogram.

The common method of eliminating such spikes is manual correction. A cardiologist checks the tachogram visually and goes over the ECG signal itself when he/she sees a spike in the tachogram [15, 21, 22]. Another approach is to check the tachogram itself and exclude the points which are above or below a preset threshold [23, 24]. However this approach implies a limit on the possible range of HRV which is determined by the thresholds used [25]. This makes the analysis results questionable.

### 2.2 PROBLEM

HRV, having become an inseparable part of risk stratification and tests for assessing the condition of the cardiovascular system, is part of a longitudinal study on British civil servants which was initiated to investigate occupational and other social influences on health and disease, namely the *Whitehall II Study* [26].

The study population was composed of 6900 men and 3414 women aged 35-55 in the London offices of 20 civil service departments [27]. Since the population was very large, HRV analysis by manual supervision/correction was not feasible. A fully automatic and
reliable HRV system was required. The only obstacle before this was the fully automatic
detection of ectopic beats. So our problem can be stated as: *Is it possible to develop
a fully automatic QRS detection and ectopic beat identification system with acceptable
reliability and fast processing?*

The new system must:

- be able to detect normal QRS complexes with high specificity,
- be able to identify ventricular and supra-ventricular (atrial) ectopic beats from the
  normal beats (the sinus rhythm beats),
- be fast, and
- require no manual supervision or post-processing.

## 2.3 METHOD

The most widely accepted method for QRS detection is the template matching method.
The detection in this method depends on the cross-correlation between a representative
QRS complex, *the QRS template*, and a QRS candidate.

The simple QRS template matching is inadequate in identifying the ectopic beats
because supra-ventricular ectopic beats (SVE) and some of ventricular ectopic beats (VE)
yield high cross-correlation coefficients with normal QRS complexes. This is because
the atrio-ventricular conduction is not affected by a SVE and the corresponding QRS
complexes have normal morphologies. This is one of the reasons why existing systems
require manual correction. The QRS complexes of VEs, on the other hand, may have
both very abnormal morphologies as well as morphologies close to normal. On the other
hand, significant changes in the heart rate can also be caused by respiration. Hence
stability of the heart rate on its own is not sufficient to identify ectopic beats.
Our method uses only three leads of the standard 12 lead ECG, namely the leads V5, V1 and II \cite{28,29}. These three leads represent the widest range of QRS morphology due to their positions on the body. II represents the limb leads, V1 represents the leads close to atria and V5 represents the leads close to ventricles. These signals will be called \( x, y \) and \( z \) in the rest of the text for the sake of simplicity. Our algorithm also makes use of the median RR intervals and the median beats. These terms correspond to the median value of the most recent nine NN intervals and the median heart rate of the most recent nine normal beats, respectively. Figure 2.2 shows the flowchart of the algorithm. The basic blocks are: i) Template Creation, ii) QRS Detection, iii) Preliminary Checks: Consists of median RR interval and QRS energy checks, and iv) Ectopic Beat Identification: Consists of QRS energy, specific QRS morphology and P wave morphology checks.

Our method is not for ECG diagnosis, but for automatic HRV analysis. All of the parameters were determined empirically with the aim of having a fully automatic and reliable HRV analysis.

### 2.3.1 Template Creation

A QRS template is a representative beat of the normal QRS morphology so that when a QRS candidate is met, it will be cross-correlated with this template. A composite signal of the three ECG signals is used for the initial detection of the QRS complexes before the template creation. It is defined as

\[
\text{composite signal} = \left| \frac{dx}{dt} \right| + \left| \frac{dy}{dt} \right| + \left| \frac{dz}{dt} \right| \tag{2.2}
\]

where the numeric differentiation is performed as

\[
\frac{dx}{dt} \bigg|_{t=nT} \cong \frac{\Delta x}{\Delta n}(n) = x(n + 11) - x(n - 9) \tag{2.3}
\]
where $\Delta n = 1/f_s$, $f_s = 1KHz$ (the sampling frequency). This corresponds to a bandpass filter with centre frequency at 25Hz and a zero at 50Hz, which is convenient for 50Hz noise suppression (See Figure 2.3). If precise physiological measurements were required, which is not the case when detecting QRS complexes for HRV analysis, a linear phase, symmetric FIR filter should be used. If real time processing were required, a casual FIR filter would be needed. However, in this study, the choice of coefficients was arbitrary, with the zero at 50Hz being the only constraint. This does not impose any limitation on the method itself because all of the processing including template creation, is performed using the filtered (absolute derivative) signal. This choice of composite signal provides
Figure 2.3: The frequency response of the numerical differentiation

The preliminary QRS detection is based on comparing the individual absolute derivative ECG signals with a threshold. The thresholds for each of the three signals are set to be the 70% of the maximum of the corresponding absolute derivative signal. These thresholds are saved to be used in the rest of the data for preliminary QRS detection. A 130ms window starting from 40ms before the fiducial point (the threshold crossing point) is assumed to contain the QRS complex. For each QRS candidate, the maximum correlation coefficient with each one of the other candidates is searched for by sliding it around each one of the other candidates. The algorithm selects a set of at least nine beats among which the cross-correlation coefficients are higher than 0.98. The final fiducial points are set according to the relative positions of the QRS candidates when the highest correlation coefficients are achieved. The composite QRS template is calculated by taking the median of these beats at each time instant.

Also, three individual QRS templates are calculated as the medians of the above selected beats' first order derivatives. These medians of the derivatives of the beats (not the absolute values of the derivatives, unlike the previous case) will be used in a second approach to the QRS detection, which will also be explained in Section 2.3.2 and
discussed in Section 2.6.2.

2.3.2 QRS Detection

The QRS detection is similar to the template creation. A candidate beat is detected by comparing the three absolute derivative signals with the corresponding thresholds. The final decision is given by correlating this candidate with the template. As mentioned above, two approaches were implemented for this purpose.

In the first case, the composite QRS candidate, which is computed as defined above, is cross-correlated with the composite QRS template. If the cross-correlation coefficient (cc) is higher than 0.80, the QRS candidate is accepted. Otherwise, the candidate is rejected, however the question whether it is an ectopic beat or noise still remains to be answered in the next step, during the preliminary checks. This is important because we are trying to find the inter-beat intervals between two consecutive normal beats (the NN intervals). The existence of an ectopic beat invalidates two RR intervals, just before and after the ectopic beat.

In the second case, we do not use the composite signal but the derivatives of the three ECG signals themselves and the three separate QRS templates, together with a composite correlation coefficient. This approach will be discussed in Section 2.6.2.

The algorithm assumes a minimum 200 ms. interval between consecutive QRS complexes.

2.3.3 Preliminary Checks

Some checks are applied to the detected QRS candidate, irrespective of the result of template matching. If the template was matched then these checks are aimed to find out whether the ectopic beat identification should be done or not. Otherwise, these checks
are aimed to find out whether the QRS candidate is an ectopic beat or merely noise.

In the former case, the initial decision is given based on the comparison of the most recent RR interval with the median RR interval. A difference of more than 10% activates the ectopic beat identification. Otherwise, the flag which marks whether the last detected beat was an ectopic or not, is checked. If it is, then the current QRS candidate is accepted but the RR interval is rejected, otherwise both the beat and the RR interval are accepted.

In the latter case, the total energy of the QRS candidates in three leads \((QRSe)\) is compared with the total energy of the medians of the most recent nine normal QRS complexes in the corresponding leads \((MedianQRSe)\). This is performed to avoid missing any VE that may have a very abnormal QRS complex morphology that results in a low \(cc\). If \(QRSe > 1.2 \times MedianQRSe\) then the QRS candidate is assumed to be an ectopic beat and both the beat and the RR interval are rejected. Otherwise nothing is done. Note that all QRS complexes, both normal and ectopic, have to be detected and classified correctly to obtain a discrete HR signal free from the influence of ectopic beats.

### 2.3.4 Ectopic Beat Identification

There are two blocks in Figure 2.2 responsible for the ectopic beat identification. They are necessarily the same blocks except two points.

One of them involves a 'retrospective ectopic search'. This block tries to find out whether an ectopic beat was missed by some reason (for example due to the assumed 200ms. inter-beat interval) since the last detection of a normal beat. A preliminary QRS detection is performed as explained above. If this fails then a preliminary QRS detection based on energy is performed. A QRS candidate is marked if the energy of a QRS template long data window exceed the 70% of the energy of QRS template. The rest of this block is identical to the other ectopic beat identification block and is named 'self ectopic check'.
The second difference between them is that the block which is activated if the RR interval is short, uses a dynamic threshold for the P wave check, while the other one uses a fixed threshold.

There are 3 analyses performed in this block: i) The energy check. ii) The specific morphology check. iii) The P wave check. Each one evaluates the QRS candidates separately. All of the checks in all leads are required to predict a normal beat for the final decision of a normal beat.

In the energy check, the energy of the PQRS of the candidate beat is compared with the PQRS energy of the median beat. If the former is more than 140% of the latter, in any one of the channels, then the beat is assumed to be an ectopic beat. This check is aimed to identify VEs that might have been missed by the template matching.

A specific QRS morphology is checked in the next step. This QRS morphology consists of either two steep edges and a plateau in between or three steep edges and two plateaus at different levels in between these. The absolute derivative signals are used. The algorithm sets a threshold at 30% of the maximum of the absolute derivative signal. The sections above the threshold mark the steep edges and the ones below mark the plateau. If the number and position of them match any one of the two specific morphologies then the duration of the steep edges are compared with that of the plateau. The duration of the plateau must be longer than three times the duration of steep edges in all cases. If this is also true, then the QRS candidate is assumed to be an ectopic beat.

The P wave check is performed especially to identify the supra-ventricular (SVE) ectopic beats. As you may remember, the SVEs originate somewhere from the atria, so their QRS morphologies are usually normal. The only morphological difference, although minor, occurs in the P wave, which corresponds to the depolarization of the atria. This part of the algorithm is aimed to identify such minor changes. The P waves in three leads are cross-correlated with the corresponding median P waves and a threshold is applied
for the decision making. This threshold is fixed and equal to 0.4 in case of long RR
interval (It is less probable to have an ectopic beat after a long RR interval, although it
is possible.). In the case of short RR interval, the threshold varies with the percentage
change in the RR interval according to the following formula:

\[ P_{\text{wave.correlation.threshold}} = \frac{5}{3} \times (\Delta RR - 0.1) + 0.4 \] (2.4)

This formula is determined empirically and depends on the fact that as the RR
interval gets shorter, the probability of the existence of an ectopic beat increases. The
other thresholds used were also determined empirically.

2.4 IMPLEMENTATION

The algorithm is implemented using Borland C++ 4.52 on a Pentium 133 MHz based
PC with 80Mbyte RAM. The input ECG signals were recorded with a commercially
available Kardiosis\textsuperscript{TM} standard 12-lead ECG machine. The signals were recorded from
standard 12 leads at 1000Hz with 12 bit accuracy. The program generated a text file
with the time indices corresponding to the mid-points of accepted RR intervals and the
length of the corresponding RR intervals. A second output file was also generated with
the time indices of the accepted QRS complexes. All measurements were in milliseconds.

2.5 EXPERIMENTS

2.5.1 Data Set

Each ECG recording covered a 5 minute period. The ECGs were recorded from a group
of 69 non-industrial civil servants, aged 45-68, who participated in the Whitehall II
A team, headed by Dr. Harry Hemingway from the University College London, Department of Epidemiology and Public Health, acquired the 12 lead ECGs in supine position, after 5 minutes of rest.

These recordings were selected from among 420 ECG recordings for the evaluation of the algorithm. They included ECGs with VEs, SVEs, right branch bundle block, respiratory arrhythmia, SA-block (sino-atrial block), wide and high amplitude T waves, blocked atrial extra-systole and SVT (supra-ventricular tachycardia). Since HRV studies are generally conducted on resting ECGs with high SNR, we excluded the recordings with visibly high EMG (Electromyogram: Signals due to muscle activity) interference or 50 Hz noise. Since our study is aimed at the fully automatic HRV analysis based on supine ECG recordings, this exclusion was fully acceptable. We also excluded ECG data with left bundle branch block (LBBB), pacemaker migrations or ventricular bigeminy. LBBB causes very wide QRS complexes, whereas pacemakers cause spikes on P waves, both of which cause false rejections of the beats. In the case of ventricular bigeminy (rhythm which consists of consecutive normal and ectopic beats), the heart rate cannot be monitored precisely which makes the ectopic beat identification less reliable and HRV cannot be estimated anyway.

An expert cardiologist marked the VEs and SVEs by examining 8 of the standard 12 leads simultaneously, namely the leads I, II, V1, V2, V3, V4, V5 and V6.

2.5.2 Statistical Analysis

The evaluation of the algorithm was based on the comparison of the cardiologist's ectopic beat identification and that of the algorithm. We used specificity and sensitivity measurements to evaluate the performance of the algorithm in discriminating the normal and the ectopic beats. The specificity and sensitivity were defined as follows [30]:
Specificity \[ = \frac{\text{number of correctly classified normal beats}}{\text{total number of normal beats}} \]  

VE Sensitivity \[ = \frac{\text{number of correctly identified VEs}}{\text{total number of VEs}} \]  

SVE Sensitivity \[ = \frac{\text{number of correctly identified SVEs}}{\text{total number of SVEs}} \]  

Although discriminating SVEs from VEs does not affect the overall performance of the algorithm, defining VE Sensitivity and SVE Sensitivity separately allowed to evaluate individual phases of the algorithm independently.

The overall specificity and sensitivity measures were calculated considering the whole population. We term them the Overall Statistics. We also calculated the specificity and the sensitivities for each ECG separately (whenever possible) and averaged the results. These show the performance on the basis of individual ECGs and are termed the Averaged Statistics.

Finally, the ECGs were classified into two groups, those with specificity higher than 0.95 and SVE and VE sensitivities higher than 0.90 are classified as the Correctly Diagnosed ECGs while the rest as the Poorly Diagnosed ECGs. The ratio between the number of correctly diagnosed ECG to the total number of ECG records is called the Correct Diagnosis Ratio. This is a measure of the overall performance of the algorithm.

### 2.5.3 Results

The algorithm was run on the above described data set using three of the twelve standard ECG leads, namely V5, V1 and II. These channels represent the widest range of lead locations, as stated before. Figure 2.4 shows some typical cases. In Figure 2.4.a the normal beat in the fifth position was detected correctly even though there is a prolonged RR interval preceding it, which triggered the ectopic beat identification. In a similar
case in Figure 2.4.b the normal beat at the fourth position was missed due to high 50Hz noise. The ectopic beat identification was also triggered by the prolonged RR interval preceding this beat. The two VEs in positions three and six in Figure 2.4.c were identified correctly. The decision was given based on the low correlation between the QRS template and the QRS complexes of these beats. Similarly, three VEs in positions one, three and six in Figure 2.4.d were identified. Note that the second VE's energy is very low in channels V1 and II. Using three ECG leads simultaneously which record the signals from distinct positions enabled our algorithm to detect this VE correctly. The SVE in the third position in Figure 2.4.e was also detected correctly. Note that its QRS complex has normal morphology. Its identification was based on the morphological difference in its P wave, it is inverted. The morphological abnormality of the P wave can be very subtle also, as in Figure 2.4.f. In this case the SVE in the fourth position was also detected correctly. Using dynamic correlation threshold enabled our algorithm to identify it.

Table 2.1 summarizes the results. The columns represent the actual number of beats and the rows represent the output of the program. As presented, the errors are very low. There are no non-QRS events which was detected as a normal/abnormal beat.

The overall specificity of the method, across all of the beats in the population, is 0.990, the overall SVE sensitivity is 0.990 and the overall VE sensitivity is 0.978. The corresponding averaged statistics, are 0.990, 0.923 and 0.965 respectively.

The averaged statistics are slightly poorer than the overall statistics. This suggests that the misclassifications and the missed beats are concentrated in some ECG records, rather than distributed evenly among the population. This is really the case. 136 of a total of 231 normal beats that are misclassified as ectopic beats, are in 4 of the 69 ECG records. Likewise, 3 of the 7 unidentified VEs are in 2 of the 44 ECG records with VEs.

The correct diagnosis ratio for this set of 69 electrocardiograms is 0.899.
Figure 2.4: Typical correct and incorrect identification cases of normal and ectopic beats
Table 2.1: Detection - Identification results of the algorithm using V5, V1 and II over a set of 69 5-minute ECG recordings. SVEs and VEs were not distinguished at the output of the program

<table>
<thead>
<tr>
<th>Detected</th>
<th>Actual Number Of Beats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>23419</td>
</tr>
<tr>
<td>VE or SVE</td>
<td>231</td>
</tr>
<tr>
<td>Missed</td>
<td>9</td>
</tr>
</tbody>
</table>

2.6 DISCUSSION

2.6.1 Limitations

The dependence of the performance of the P-wave morphology analysis on noise and some artifacts like pacemaker migrations, is the major drawback of this method. Such interfering signals can mask the low energy P-wave and cause false rejection of the normal beats. However, the linearly varying threshold for the P wave morphology analysis overcomes this problem to some extent and increases the ectopic beat sensitivity, esp. the SVE sensitivity. It is based on the assumption that the earlier the beat arrives, the more probable it is an ectopic beat. However, a linear relation is not necessarily the best and further research is needed in this respect. Since the resting ECGs with high signal-to-noise ratio are generally used for HRV analysis, the noisy conditions do not impose a principal limitation on the automatic HRV analysis. Moreover, short term HRV analysis is most frequently based on supine resting ECG recordings in which low noise contents can be easily achieved, and patients with a pacemaker dependent rhythm should not be considered for a HRV assessment anyway. Thus this principle drawback of the method does not have serious practical implications.

The specific QRS morphology check performed during the ectopic beat identification
is rather premature. The thresholds need to be further evaluated and verified. It is likely that the 30% threshold applied is too low, or equivalently the 300% duration threshold is too high to detect the most common morphologies of this kind. Furthermore, such morphologies are likely to be detected by simple energy checks.

The performance of this method depends on the number and the choice of the ECG leads used. We used V5, V1 and II in this study. A comparative study of the performances with different lead sets will be provided in Section 2.7. It will provide information about the required number of leads and the most appropriate lead position(s) for a reliable HRV analysis.

Using the composite signal which is a combination of absolute derivative signals may degrade the performance of QRS detection also. This is because the correlation coefficient of the QRS template and the composite beat will be rather high for a relatively wide range of misalignments around the correct alignment and it will decrease slowly with increasing misalignment. This is due to the loss of the information in the sign (+/-) of the signal. This may result in errors in the detection of exact locations of the QRS complexes. Such an error, in turn, may introduce artificial fluctuations to the inter-beat intervals, thus an artificial heart rate variation. This is not likely to cause a major problem in this case because the data is of high SNR. Another approach, which uses the three derivative signals themselves will be explained and discussed in Section 2.6.2.

2.6.2 Using A Composite Correlation Coefficient

The main idea is to use the derivative signals themselves, not their absolute values, to make use of the sign information. However, the derivative signals can only be used on their own, not incorporated in a composite signal because they may annihilate each other when summed. Such a case would result in a total loss of information.

On the other hand, using them separately has a drawback. If we have a weak signal
(low amplitude, low SNR) in one channel, then this signal may cause the rejection of a beat due to a low correlation coefficient ($cc_i$). One solution to this problem would be to use the un-normalized $cc_i$'s but in this case the sum of $cc_i$'s will not be limited but will depend on the energy of the corresponding signal. So applying a threshold would be impossible. Such a problem due to a weak signal is not present in the case of using the composite signal.

We defined a composite correlation coefficient ($ccc$) using the derivative signals themselves and separate QRS templates to overcome these problems. $ccc$ is defined as

$$ccc = \frac{< X_t, x_i > + < Y_t, y_i > + < Z_t, z_i >}{\sqrt{< X_t, X_t > X_t, x_i >} + \sqrt{< Y_t, Y_t > Y_t, y_i >} + \sqrt{< Z_t, Z_t > Z_t, z_i >}}$$

where $X_t$, $Y_t$, $Z_t$ stand for the corresponding QRS templates and $x_i$, $y_i$, $z_i$ stand for the candidate QRS complexes. $ccc$ is in the range of -1 to 1. The contribution of each correlation to $ccc$ is proportional to the energy of that signal. Thus if the correlation is high in a strong signal, then the low correlation of a weak signal will not decrease $ccc$ much. Conversely, if the correlation is low in a strong signal, then a high correlation in a weak signal (which may be due to noise) will not increase $ccc$ much.

This approach was implemented and tested on the same set of data (see Section 2.5.1). The comparison of the two approaches was made based on the overall statistics, the averaged statistics and the correct diagnosis ratio (see Section 2.5.2 for the definitions). Five correlation thresholds were used with $ccc$. Figure 2.5 summarizes the results.

We see that in general there is a slight improvement in the specificity when $ccc$ is used. However, this is not true for all threshold levels. This shows that although $ccc$ improves the QRS detection of the algorithm, it performs poorer in some ECG records when the threshold is very low or high. The SVE sensitivity is not affected at all. They are same for both methods, for all threshold levels and in both of the statistics. $cc$ on the other hand performs better than $ccc$ in terms of VE sensitivity. Correct diagnosis
Overall Specificity

Averaged Specificity

Overall VE Sensitivity

Averaged VE Sensitivity

Overall SVE Sensitivity

Averaged SVE Sensitivity

Correct Diagnosis Ratio

Figure 2.5: Statistical comparison of Composite Signal and Composite Correlation Coefficient Methods. (solid:CCC , dashed:CC)

ratio is in favour of cc with a difference up to 3%. In all cases, the differences are small. These two methods can be assessed relative to each other better with a noisy data set, which would make their advantages and disadvantages clearer.
2.6.3 The Effect of Using The Derivatives

As explained before, the derivative of the ECG signals, either in absolute value or not, are used. This provides a built-in immunity to 50Hz noise and also removes the DC, providing a better signal for analysis.

We analyzed the same data set by using the ECG signals themselves, wherever their derivatives were used, to assess the role of derivation quantitatively. Nothing else was changed in the algorithm, the correlation threshold was left to be 0.80. 61 out of 69 ECG recordings could be processed because the program could not detect any QRS in a 20 second time interval in 8 of the recordings and excluded them. Table 2.2 provides a comparison of the two methods. Only the VE sensitivity seems not to have been affected by the using ECG signal itself instead of its derivative. This is somewhat misleading because we see a significant degradation in the performance in terms of specificity and SVE sensitivity, both of which basically depend on the identification of normal QRS complexes. On the other hand VE identification depends basically on the largely abnormal QRS complexes. So, we can conclude that using the ECG signal itself makes the QRS detection significantly worse.

### Table 2.2: The effect of using the derivative signals on the performance of the algorithm

<table>
<thead>
<tr>
<th></th>
<th>Using $\text{ecg}(t)$</th>
<th>Using $\frac{d\text{ecg}(t)}{dt}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Statistics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.918</td>
<td>0.990</td>
</tr>
<tr>
<td>SVE Sensitivity</td>
<td>0.966</td>
<td>0.990</td>
</tr>
<tr>
<td>VE Sensitivity</td>
<td>0.982</td>
<td>0.978</td>
</tr>
<tr>
<td><strong>Averaged Statistics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.918</td>
<td>0.990</td>
</tr>
<tr>
<td>SVE Sensitivity</td>
<td>0.887</td>
<td>0.923</td>
</tr>
<tr>
<td>VE Sensitivity</td>
<td>0.964</td>
<td>0.965</td>
</tr>
<tr>
<td>Correct Diag. Ratio</td>
<td>0.475</td>
<td>0.899</td>
</tr>
</tbody>
</table>
2.7 SINGLE LEAD HRV ANALYSIS

In an attempt to investigate the feasibility of fully automatic HRV analysis using a single ECG lead in the proximity of the heart, we developed a single lead version of our QRS detection and ectopic beat identification algorithm. Essentially nothing is changed in the algorithm, except that all of the ectopic beat analysis is done on a single lead and the composite signal is defined to be equal to the absolute derivative of the ECG signal in hand:

\[ \text{composite\_signal} = \left| \frac{dx}{dt} \right| \] (2.9)

2.7.1 Experiments

The same data set (see Section 2.5.1) was used. The limb leads (I, II, III) were not used on their own because they are far away from the heart, so can not be used on their own for HRV analysis. The performance of the precordial leads (V1, V2, V3, V4, V5, V6) were compared with the performance of the original three dimensional (using three ECG leads simultaneously) algorithm on the basis of specificity and sensitivity measures defined in Section 2.5.2. Experiments were conducted with four different triplets, namely "II-V1-V5", "V1-V3-V5", "II-V3-V5", "II-V1-V2". Table 2.3 summarizes the results.

Then a second data set was used to compare the spectral parameters and the time domain parameters (LF power, HF power, LF/HF, SDNN), defined in Section 2.1, measured using a single lead and a triplet (II-V1-V5). This set of data consists of 5 minute supine rest ECGs recorded at St. George's Hospital Medical School Cardiology Unit with a custom built 24-lead Kardiosis ECG machine (12 standard and 12 non-standard leads). The ECG signals were sampled at 1000Hz with 12-bit accuracy. They were recorded from 110 cardiac patients, 80 male, aged 64±13 years, range 24-87. Three separate recordings
were obtained from each patient and the complete set contained 330 ECG recordings. Table 2.4 summarizes the results. The measurements are given as mean ± standard deviation. The difference column is the average of the differences between the single lead and the triplet measurements, calculated over the whole population. The mean column is the average over both the population and the single lead/triplet measurements.

For a more detailed comparison of each one of the single channel with the triplet, see the “Mean vs. Difference” plots in Appendix A.

### 2.7.2 Discussion

The specificities are greater than 95% for all single channel analysis. This suggests that the QRS detection is not affected by the lead position and/or different QRS morphologies. The relatively lower specificities in leads V1 and V2 are due to the low SNR, which is more common in those leads than the others. Figure 2.6 shows a case where the normal QRS complex, in the third position, was missed on V1 but detected on V5.

<table>
<thead>
<tr>
<th>Lead(s)</th>
<th>Spec.</th>
<th>SVE Sens.</th>
<th>VE Sens.</th>
<th>Spec.</th>
<th>SVE Sens.</th>
<th>VE Sens.</th>
<th>CDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>0.954</td>
<td>0.933</td>
<td>0.886</td>
<td>0.954</td>
<td>0.987</td>
<td>0.937</td>
<td>0.739</td>
</tr>
<tr>
<td>V2</td>
<td>0.976</td>
<td>0.900</td>
<td>0.948</td>
<td>0.974</td>
<td>0.799</td>
<td>0.898</td>
<td>0.783</td>
</tr>
<tr>
<td>V3</td>
<td>0.986</td>
<td>0.856</td>
<td>0.951</td>
<td>0.986</td>
<td>0.803</td>
<td>0.873</td>
<td>0.754</td>
</tr>
<tr>
<td>V4</td>
<td>0.984</td>
<td>0.889</td>
<td>0.895</td>
<td>0.983</td>
<td>0.773</td>
<td>0.833</td>
<td>0.725</td>
</tr>
<tr>
<td>V5</td>
<td>0.991</td>
<td>0.922</td>
<td>0.834</td>
<td>0.991</td>
<td>0.840</td>
<td>0.799</td>
<td>0.797</td>
</tr>
<tr>
<td>V6</td>
<td>0.988</td>
<td>0.867</td>
<td>0.858</td>
<td>0.989</td>
<td>0.829</td>
<td>0.818</td>
<td>0.754</td>
</tr>
<tr>
<td>II-V1-V5</td>
<td>0.990</td>
<td>0.989</td>
<td>0.978</td>
<td>0.990</td>
<td>0.923</td>
<td>0.965</td>
<td>0.899</td>
</tr>
<tr>
<td>V1-V3-V5</td>
<td>0.991</td>
<td>0.978</td>
<td>0.978</td>
<td>0.991</td>
<td>0.921</td>
<td>0.949</td>
<td>0.899</td>
</tr>
<tr>
<td>II-V3-V5</td>
<td>0.992</td>
<td>0.978</td>
<td>0.978</td>
<td>0.991</td>
<td>0.897</td>
<td>0.968</td>
<td>0.884</td>
</tr>
<tr>
<td>II-V1-V2</td>
<td>0.989</td>
<td>0.989</td>
<td>0.988</td>
<td>0.988</td>
<td>0.923</td>
<td>0.972</td>
<td>0.884</td>
</tr>
</tbody>
</table>

Table 2.3: Statistical comparison of QRS detection and ectopic beat identification from single channels and triplets.
Table 2.4: Statistical comparison of HRV spectral parameters calculated using single precordial leads and the triplet (II-V1-V5)

<table>
<thead>
<tr>
<th>Channels</th>
<th>LF Power $(msec^2)$</th>
<th>HF Power $(msec^2)$</th>
<th>LF/HF</th>
<th>SDNN</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>-155.3±1582.3</td>
<td>620.8±1772.3</td>
<td>-0.057±0.813</td>
<td>-1.288±28.23</td>
</tr>
<tr>
<td>V2</td>
<td>-289.6±1950.8</td>
<td>541.6±1387.6</td>
<td>-0.012±1.340</td>
<td>1.112±1.535</td>
</tr>
<tr>
<td>V3</td>
<td>-93.45±1840.2</td>
<td>651.2±1951.3</td>
<td>0.147±1.405</td>
<td>1.189±1.607</td>
</tr>
<tr>
<td>V4</td>
<td>-118.8±1505.8</td>
<td>636.9±1836.0</td>
<td>-0.015±0.919</td>
<td>1.053±1.456</td>
</tr>
<tr>
<td>V5</td>
<td>-122.2±1286.1</td>
<td>580.2±1582.7</td>
<td>0.049±1.346</td>
<td>1.111±1.617</td>
</tr>
<tr>
<td>V6</td>
<td>-61.17±1942.0</td>
<td>637.9±1793.3</td>
<td>0.008±1.515</td>
<td>1.113±1.650</td>
</tr>
</tbody>
</table>

The high SVE sensitivity in V1 shows that the P wave morphology changes during an SVE, which are observable mainly in V1, play an important role in the SVE identification. The proximity of the lead V1 to the atria is likely to be the reason of this. Figure 2.7 shows an example of such a case. The SVE in the third position was missed on V4 but detected on V1. Note that the P wave morphology in V4 is quite normal except that its amplitude is increased. However, the P wave morphology of the SVE in lead V1 is significantly different from the others, it is bi-phasic.

The detection of VEs is relatively easier because they usually have rather abnormal QRS morphologies and/or high/low QRS energy. The high QRS energies during a VE, are usually observable in leads close to the atria. An abnormal QRS morphology, if accompanied by low energy, may not be enough for the identification. This may account for the high averaged VE sensitivity of V1 and high overall VE sensitivities of V2 and V3. Figure 2.8 shows an example of such a case. The VE in the fourth position was
These results establish a trade off between the ectopic beat sensitivity and the QRS specificity, in other words, between the upper precordial leads (V1 and V2) and the lower precordial leads (V3, V4, V5, V6).

When we compare the HRV parameters calculated using a single lead and using the triplet, we see a negative bias in LF and HF powers calculated in a single channel. Nevertheless, the mean differences are small and the variation of the difference is smaller.
Figure 2.8: The VE in the fourth position was missed on V5 but detected on V1 during single channel HRV analysis in LF power calculations than in HF power calculations. The differences in LF/HF ratio are much smaller than the other spectral parameters. The differences in the time domain parameter SDNN are also small. When we consider all the HRV parameters together, it seems that V6 is the single channel that is in most agreement with the triplet. Among the other single channels, the results of the HRV analysis on V3 deviate the most from the results of the triplet analysis, except in LF power calculation. In all cases and for all parameters, most of the differences between measurements stay in $\pm 2STD$ range of the mean difference, as demonstrated in Appendix A.

As mentioned above, the model order for the parametric spectral analysis of the tachogram is determined automatically by checking the derivative of the SNR and AIC curves. Although this order was forced to be between 6 and 20, it may vary between different analysis of the same ECG recording. Such a variation may account for some of the differences between the analysis results from a single channel and the triplet.

In addition, our program excludes data in which a QRS complex could not be detected for 20 seconds or in which the average number of detected QRS complexes is below 20 beats per minute. Because of this, slightly different but greatly overlapping data sets were used for the comparison of different single lead analysis with the triplet analysis.
2.8 CONCLUSION

Statistical studies in medicine need to concern large populations to provide reliable results. The major obstacle before such large-scale HRV analysis, is the need of visual verification and manual correction in the present HRV analysis systems. We have shown the feasibility of fully automatic QRS detection and ectopic beat identification. We have concluded that

- When the timing and the morphological information in ECG is used together, the QRS detection and the ectopic beat identification task can be done without any manual correction or bias on HRV.

- While the QRS morphology is important for detection, other qualities of ECG should be used for ectopic beat identification, like P wave morphology and QRS energy.

- Some existing systems use the significant changes in the instantaneous heart rate as the only marker of ectopic beats. These systems use a threshold on the change of instantaneous heart rate to detect ectopic beats. Avoiding the use of timing information on its own for ectopic beat identification removes any bias on HRV that might have been imposed otherwise.

- Large scale automatic HRV studies are made feasible by this method.

We have also studied the effect of using the sum of the absolute derivatives of the ECG signals as a composite signal, on the performance of the algorithm. We concluded that using the derivative signals instead of the absolute derivative signals

- does not improve the QRS detection in rest ECG signals but is likely to introduce an improvement in noisy ECG signals.
- Degrade the performance of ventricular ectopic beat identification by causing false rejections of normal beats.

We also showed quantitatively that using the ECG signal itself, instead of its derivative, degrades the performance significantly.

As a result of the analysis of a single channel version of our algorithm, we assessed the effect of the position of ECG leads on QRS detection and ectopic beat identification. We concluded that

- The ECG leads close to the atria are important in the identification of ectopic beats.
- The ECG leads close to the ventricles are important in the detection of normal beats.
- Fully automatic single channel HRV analysis is feasible provided that the lead is not far away from the ventricles.
Chapter 3

VENTRICULAR REPOLARIZATION ANALYSIS

3.1 BACKGROUND

The term Ventricular Repolarization stands for the relaxation process of the ventricles. Its analysis has gained importance due to the recognition of the close relationship between the spatial heterogeneity of the relaxation process and the cardiac arrhythmia. This relation is closely related to the mechanisms that trigger the re-entrant waves (self-sustained local periodic waves) on the heart.

3.1.1 Basis of Ventricular Repolarization Analysis

The term excitable cell is used for the cells whose cell membrane can be polarized in both directions and lets the propagation of this polarization. The term depolarized stands for the state of being excited, the term repolarized stands for the resting state. These cells have several properties that determine their excitability. These properties are related to
the amplitude of the stimulus, the duration of the stimulus, the physical structure of the cells, etc. One such property is termed the *refractory period*. Refractory period stands for the time interval following an excitation, during which a second depolarization is not possible. An abnormality in the refractory periods of some cells on the heart can lead to arrhythmia easily. For example, a prolonged refractory period in a limited location on the heart would behave like a physical obstacle to the propagating depolarization wave and thus interrupt the normal sinus rhythm of the heart.

The ventricular repolarization (T wave) is the only repolarization that can be observed in ECG signals (The atrial repolarization overlaps with the high energy ventricular depolarization, the QRS complex, and can not be observed.). And as we said, each repolarization is followed by a refractory period, so is the ventricular repolarization. This relation between the ventricular repolarization and the refractory periods establishes the importance of T wave analysis, which has long been recognized [31–34].

### 3.1.2 QT Interval Analysis

In an attempt to quantify the refractory periods on ventricles, in other words of ventricular repolarization, the QT interval measurements became the popular method both due to its intuitive nature and seemingly ease of measurement. QT interval is defined to be the time interval between the starting point of the Q wave (ventricular depolarization) and the end of the T wave (ventricular repolarization), as shown in Figure 3.1. Thus it is supposed to be a measure of the time duration of the ventricular activity.

Recently, the quantification of the inter-lead differences in QT interval (QTint) durations in standard 12 lead ECG recordings became very popular [35]. This is called the QT Dispersion (QTd)(see Figure 3.2). There are different definitions of QTd: i) The range of QTint: \( QTd = max(QTint) - min(QTint) \) defined over 12 leads, and ii) the variance of QTint: \( QTd = var(QTint) \) defined over 12 leads.
Figure 3.1: QT interval starts from the beginning of Q wave and ends at the end of T wave.

Figure 3.2: QT dispersion (QTd) is defined in the variation of the QT intervals over 12 standard ECG leads.
The intuition behind the theory of QTd is that each QTint is a measure of the refractory period of the cells in the proximity of the corresponding lead. So, the inter-lead differences is a direct measure of the differences in the refractory periods of different parts of the heart. There are also studies on the cellular basis to support this hypothesis [36]. However, although increased QTd in patients with heart diseases ranging from long QT syndrome (LQTS) to hyperthropic cardiomyopathy (HCM) has been reported [37–42], significant prognostic value of QTd has been shown only in some studies [43], while other studies are inconclusive [44].

The major difficulty in QTd measurements is the localization of the T wave end point as well as the problems associated with the U waves (The low amplitude wave that is sometimes seen after the T wave) and the notched T waves. (The Q starting point is assumed to be the same for all channels. It was also shown that the variation in the Q starting point does not contribute to QTd significantly [45]). This leads to poor reproducibility of the QTd measurements and thus raises concerns about its practical value [46,47]. There are several studies showing a substantial variability of QTint measurements [44,48–54].

There are four major methods proposed for the T wave end point detection which are used for computer aided QT interval measurements [50]. All of them require the identification of specific features of the heart beat prior to the QT interval measurement. These include the identification of P, R and T wave peaks, J point, R wave onset point, isoelectric level, an upper limit for QT interval and the maximum slope point of the second half of the T wave. The peak detections are first done manually and approximately, then

---

1Prof. Malik from St.George's Hospital Medical School, London, UK, conducted a noteworthy experiment [55]. He asked 100 last year medical students to measure 15 times an artificial pattern composed of 15 points, using a digitizing board with a technical accuracy of 50μm. The participants were motivated by a cash prize of 100 pounds for the best repeated measurement. He assessed the precision of re-localizing the same point, re-measuring the same distance and re-measuring a distance dispersion. The results showed that almost every other volunteer made two localizations (among 15 measurements) of at least one point (among 15 points) that differed by more than 3mm (3mm is equivalent to 120msec. Note that the order of QT interval and QTd difference between normal and abnormal ECGs is 30msec.)
the maximum (negative or positive) is searched for around these approximate locations. The J point is first located manually and then the second derivative is used to detect the deflection that marks the J point. Two iso-electric levels are determined in the PR and the TP sections. A section of 10 consecutive samples (20 milliseconds) with the least variance is found in each section and their average is taken as the iso-electric level. The mean of these two iso-electric levels is used. The RR interval is calculated from lead I and an upper limit for QT interval is determined as

\[
Upper \_ Limit \_ for \_ QT = \frac{QT_{int}}{\sqrt{RR\_ interval}} + \frac{RR\_ interval}{5} \tag{3.1}
\]

The maximum slope point is found by searching for the maximum of the derivative of the ECG signal (calculated by the two-point difference method) between the T peak and the upper limit for the QT interval. The T wave end point detection is done in one of the following ways:

- **Threshold technique**: It is determined as the interception point of the T wave itself with a threshold level.
- **Differential threshold technique**: It is determined as the interception point of the differential of the T wave with a threshold level.
- **Slope intercept technique**: It is the intercept of the iso-electric level and the line tangent to the T wave at the maximum slope point.
- **Peak slope intercept technique**: It is the intersection point of the iso-electric level and the line passing through the T wave peak and the T wave maximum slope points.

Apart from these popular methods, there are two more approaches: i) The line fitted to the set of points around the maximum slope point in the least square sense is used
instead of the tangent line, the intersection of this point with the iso-electric level is marked as the T wave end point, ii) a parabola is fitted to the peak of the T wave and a tangent is drawn from a specific point of the parabola (i.e., 70% of the maximum of the parabola). This line is used instead of the tangent.

Several parameters can be determined from these measurements. The most promising and the popular ones are:

- **Global QT dispersion (G-QTd)** = Max(QTint in 12 leads) - Min(QTint in 12 leads)
- **Precordial QT dispersion (P-QTd)** = Max(QTint in 6 precordial leads) - Min(QTint in 6 precordial leads)
- **Area QT dispersion (A-QTd)**: All of the 12 leads are assumed to have the same T wave onset and offset points. The areas under the T waves are calculated and the points at which they reach 90% of the corresponding total area are marked for each lead. The dispersion (max-min) of these markers over 12 leads is calculated.
- **Global J to T peak dispersion (G-JTp)** = Max(J to T peak interval in 12 leads) - Min(J to T peak interval in 12 leads)
- **Corrected QT interval (QTc Interval)** = Bazett's formula corrected maximum QT interval in 12 leads (\( QTc\_interval = QTint/\sqrt{RR\_interval} \))

In one of our recent studies, we have obtained supportive evidence that there is really a heterogeneity of ventricular repolarization in high risk patient groups, which has a clinical significance but QTd seemed to be unrelated to it [56-58]. In other words, the physiological ground on which the QTd stands is firm, there is really an increased ventricular repolarization heterogeneity, however QTd is unable to assess it. In this study, time aligned median beats from 12 standard ECG leads are obtained and the QTd is measured using an evaluation version of Marquette's QT Guard System, which
uses the downslope tangent method to detect the T wave end point. Then these beats are decomposed by Singular Value Decomposition. The ratio of the sum of squares of the singular values corresponding to non-dominant decomposed channels to those of the dominant (3 channels) decomposed channels is calculated. If $\sigma_i$ is the singular value of the $i^{th}$ decomposed channel then this ratio is

$$\text{Relative T-wave residuum} = \frac{\sum_{i=1}^{3} \sigma_i^2}{\sum_{i=1}^{8} \sigma_i^2}$$

(3.2)

This ratio represents the percentage of the residual energy. In other words, these non-dominant channels represent the non-dipolar cardiac source (T wave residual power), i.e. the source of heterogeneity. An analysis of this ratio showed a significant increase in high risk patients compared to the normals, verifying the physiological hypothesis. However, no correspondence could be found between the QTd measurements and this ratio. Figure 3.3 shows the mean and the standard deviation of the two sets of measurements for different patient groups. Though the quantities are small, a significant increase in non-dipolar components is clearly seen. Figure 3.4 demonstrates the non-correspondence between the non-dipolar power ratio and the QTd. The Spearman rank correlation coefficients of the non-dipolar power ratio and QTd in normal, HCM, DCM and AMI groups were $-0.045$, $0.28$, $-0.15$ and $0.08$ respectively. Thus we concluded that the heterogeneity of ventricular repolarization is associated with cardiac abnormalities but QTd cannot represent it.

### 3.1.3 Alternative Approaches

These methodological and even theoretical problems associated with QT interval measurements and the fact that increased QT interval duration is only one aspect of the repolarization abnormalities resulted in other attempts to quantify the inhomogeneities in the repolarization patterns.
Figure 3.3: a) Mean QTd measurements for different groups b) Mean non-dipolar power ratio for different groups
Reprinted from [56].

Figure 3.4: Scatter graph of non-dipolar power ratio vs QTd in different patient groups
Reprinted from [56].
Researchers focused on morphological analysis methods of T wave, which the cardiologists have already been using qualitatively. They aimed to develop more reproducible measurements than the time-domain measurements and to provide information about the heterogeneity of ventricular repolarization in addition to the QT interval related parameters, if not an alternative to them.

These new repolarization methods can be classified into four groups [59]: i) The amplitude related parameters, ii) the frequency related parameters, iii) the parameters based on decompositions, and iv) the vector based parameters.

**The Amplitude Related Parameters:**

The most intuitive way to describe the T wave morphology quantitatively is to use its amplitude and/or to use the area under it because it is easy to establish a relation between the heuristic methods of cardiologists and such parameters.

In a recent paper, Zareba et al. defined a set of parameters derived from the amplitude and the area of the repolarization waves, i.e. TU waves [60]. They calculated the following parameters from the median beats obtained from standard 12-lead ECG recordings of 34 affected LQTS patients (with QTc interval > 0.47 sec.) and 22 unaffected family members (with QTc interval < 0.42 sec.) :

- $T_{amp}$ = Maximum T wave amplitude.
- $A_{tot}$ = Total absolute area during JP segment.
- $t_{A97}$ = Time interval to accumulate 97% of $A_{tot}$.
- $t_{A50}$ = Time interval to accumulate 50% of $A_{tot}$.
- $t_{A25-75}$ = Time interval to accumulate the mid 50% of $A_{tot}$.
- $Pt_{A50} = \frac{t_{A50}}{t_{A97}} \times 100.$
They used both the mean and the standard deviation (STD) of these parameters across 12 leads. Neither mean nor STD of $T_{amp}$ and $A_{tot}$ showed a significant difference between the two groups, whereas $t_{A50}\text{SD}$ and $t_{A25-75}\text{SD}$ provided the best discrimination of the two groups, with a sensitivity (specificity) of 76% (75%) and 68% (70%) respectively. The mean value of $Pt_{A50}$ also showed a significant difference between the normals and the LQTS patients (46±5 vs 60±10), which suggests a more asymmetric pattern in the LQTS patients.

Yang et al., on the other hand, defined two new repolarization parameters to characterize the rate of repolarization, the maximum absolute slopes of the ascending and descending limbs of T wave ($P_a$ and $P_d$) [61]. They investigated the relation between these parameters and the repolarization duration parameters, like QT interval, in 562 normal subjects. All parameters were measured on lead V5 only. The new parameters had low correlation with the duration parameters ($|r| \leq 0.30$) but high correlation with the T wave amplitude ($|r| \geq 0.91$) and they exhibited disparity between sexes.

**The Frequency Related Parameters:**

Apart from the parameters that describe T wave morphology, periodicity of the changes in the T wave morphology was also shown to have a consistent relationship with ventricular arrhythmias. Such behaviour is called T wave alternans (TWA), which is defined as a consistent beat-to-beat variation of the T wave morphology and/or polarity on an alternate beat basis during sinus rhythm. Much effort has been paid to detect such a variation. In a recent review paper, Murda’h et al. gives a background of TWA and lists the major methods of TWA detection [62]: i) Detection by visual inspection, ii) the FFT based spectral analysis, and iii) The complex demodulation method.
Burattini et al. proposed a time-domain correlation index (ACI) to detect non-stationary T wave alternans using T waves simulated by a sinusoid with changing amplitude [63]. ACI is defined for each T wave as its correlation with the median T wave and TWA is detected via the beat-to-beat variation of ACI. Hohnloser et al., on the other hand, used the spectral analysis method to show high correlation between TWA measured during exercise and atrial pacing [64]. This result suggests the use of TWA as a morphology parameter under crude conditions, like exercise testing. However, the number of technical requirements that has to be met, limits its use.

Narayan and Smith studied the temporal distribution of TWA during repolarization [65]. They calculated a separate power spectral density ($PSD_i$) for each sampling instant ($i$) throughout repolarization (RJT: data window from J point to T offset) across 64 time-aligned T waves. The summation of $PSD_i$'s was defined as the overall PSD representing the JT segment (or any sub-segment as required). They calculated the magnitude of TWA for each time instant (TWA($i$)) from the corresponding $PSD_i$ (the peak at 0.5 cycles per beat (cpb)). A parameter of temporal distribution of TWA (T) was defined as the centre of mass of the area under TWA($i$). They used the parameter T and PSD's corresponding to different segments of repolarization to show that TWA is distributed later within repolarization in patients with ventricular tachycardia. This result, together with Nearing et al.'s [66] somewhat contradictory results in favour of TWA distributed early within repolarization, clearly show the importance of the intra-beat temporal variation of the T wave morphology, as well its spatial variation.

Steinbigler et al. extended the concept of TWA to variations at all periodicities (not only on an alternate beat basis as in conventional TWA) by defining T Wave Spectral Variance (TWSV) [67]. They computed the two dimensional PSD of 1024 time-aligned T waves using FFT. The T waves were represented in a 2D matrix, the first dimension corresponding to the time span of a single T wave and the second dimension corresponding to the sequence of consecutive T waves. Thus the resultant 2D PSD
represents the frequency content of T waves in the first dimension in Hertz (Hz) and the beat-to-beat variation in the second dimension in cycles per beat (cpb). They defined TWSV Index (TWSV-I) as

\[
TWSV - I = \frac{\text{Total Energy}_{\text{f}_1 < 60\text{Hz}} (\text{f}_1 < 0.5\text{Hz})}{\text{Total Energy}_{\text{f}_1 < 50\text{Hz}}} \quad (3.3)
\]

Assuming that all T wave components are confined to the frequency band 0-50Hz, TWSV-I represents the inter-beat T wave morphology variation as a percentage of total T wave variation. They managed to identify the patients with ventricular arrhythmias in a population of 200 post-MI patients, with 89% sensitivity and 78% specificity.

Couderc et al. demonstrated the use of Wavelet Transformation (WT) in detecting abnormal ventricular repolarization patterns in a population of 43 LQTS patients and 29 normal subjects [68]. They applied WT to the median beats of 10 second segments of each lead separately. The WT coefficients of the two groups were compared at every time and frequency (scale) point in the time-frequency plane. They selected the wavelets associated with a significant separation \([p-value < 0.0001]\) between normal and abnormal patterns and defined the sum of their coefficients as a single T wave parameter. The Receiver Operator Curve (ROC) area was 96% for the WT coefficients in lead I while it was 88% for QTc interval. (ROC curves are plots of maximum possible sensitivity for a given specificity. More detail on ROC curves will be given in Section 3.5.5.)

**The Parameters Based On Decompositions:**

The methods described in this section represent the T waves in terms of some mathematically defined functions (waveforms) which are either derived from the T wave itself or are defined independently. These functions are named as basis functions in general, although this term is not correct for all.

Padrini et al. modeled the T and U waves as a superposition of the action potentials (AP) of a set of cells [69]. They decomposed TU waves as follows:
\[ TU(t) = S_1(t) - S_2(t) + L_1(t) - L_2(t) \]  

(3.4)

The basis functions \( S_1 \) and \( S_2 \) model the T wave whereas \( L_1 \) and \( L_2 \) model the U wave. The Hill’s function \( A(t) = A_{inf} \times t^n/[T_{50}^n + t^n] \) was used to generate these basis functions. The model parameters \( (A_{inf}, T_{50}, n) \) for each function are determined by using a supervised best-fitting procedure. They showed that various TU wave morphologies can be described with this model and that the accuracy of the model is independent of the complexity of the TU wave. This model provides a separate description of the T and U waves, six parameters for each.

Priori et al. applied the Principal Component Analysis (PCA) to the ST-T segment of 12-lead Holter ECG recordings to quantify the complexity of repolarization in 40 healthy subjects (QTc: 414±18 ms.) and 36 LQTS patients (QTc: 514±59 ms.) \cite{70}. They defined the ST-T segment as starting from the QRS offset and ending at a point determined according to the Bazett’s formula (see Section 3.1.2), thus avoided the accurate time domain detection problem. Three parameters were defined using the singular values \( \sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_8 \geq 0 \) that represent the relative magnitudes of the principal orthogonal components (basis functions) of the repolarization pattern. (Note that only 8 out of 12 standard channels are used. They are the independently recorded ones and are I, II, V1, V2, V3, V4, V5 and V6). The defined complexity parameters are:

\[
CR = \frac{\sigma_2}{\sigma_1} \times 100 \\
CR1 = \frac{\sigma_2}{\sqrt{\sigma_1^2 + \cdots + \sigma_8^2}} \times 100 \\
CR2 = \frac{\sqrt{\sigma_2^2 + \cdots + \sigma_8^2}/\sqrt{\sigma_1^2 + \cdots + \sigma_8^2}} \times 100
\]

(3.5)  
(3.6)  
(3.7)

Each parameter above is a measure of the dimensionality of the repolarization. In case of identical repolarization patterns in all channels, all of them would be zero. They
used CR in their further analysis. They computed CR for four consecutive beats and used their average. CR24h, which is defined as the average of hourly CRs over 24 hours, had sensitivity and negative predictive value identical to that of QTc, 88% and 91% respectively and no significant correlation with therapy, symptoms and diagnostic score. On the other hand, a single CR measurement had a very poor diagnostic power due to the increased variability of CR over 24 hours in LQTS patients.

A similar method, the Karhunen-Loeve Transform (KLT), was applied to the ST-T segment by Laguna et al. [71]. They computed a set of basis functions (eigenvectors that represent the principal waveform patterns) using a set of beats, the training set, and used the most significant two of these functions throughout the rest of the analysis, unlike the PCA analysis described above where there was no fixed basis. They used the time series of the corresponding coefficients ($\lambda_1, \lambda_2$) for ischaemia detection. $\lambda_1$ and $\lambda_2$ are analogous to $\sigma_1$ and $\sigma_2$ in PCA analysis. 65% sensitivity and 54% specificity was achieved in the ESC ST-T database (European Society of Cardiology ST-T Database consists of 90 ECG records, two hours long each).

The Vector Based Parameters:

The problems associated with the scalar measurements and the fact that the propagating action potentials have both a direction and a magnitude lead the researchers to work on vector based parameters.

Badilini et al. used the three dimensional (3D) loop that the 3D ECG vector, $\mathbf{m}$, traverses during T wave to assess the ventricular repolarization heterogeneity in a population of 25 normals, 30 post-MI patients and 17 LQTS patients [72]. They computed the normalized eigen-values associated with the three principal components ($\lambda_{1n}, \lambda_{2n}, \lambda_{3n}$ in order of dominance) and defined the following parameters:

$$RP = \sqrt{\frac{\lambda_{2n}}{\lambda_{1n}}}$$

(3.8)
\[
\Delta Q = \frac{\text{max}(m_3) - \text{min}(m_3)}{\sum_{i=1}^{3} \lambda_i} \quad \mathbf{m} = [m_1 \ m_2 \ m_3] \tag{3.9}
\]

\[
AVQ = \frac{\text{mean}(m_3)}{\sum_{i=1}^{3} \lambda_i} \tag{3.10}
\]

\(RP\) describes the roundness of the T loop and is analogous to previously defined CR parameter [70]. It increases with increasing roundness. The other parameters, together with \(\lambda_{3n}\), describe the planarity (confinement of the loop to a 2D space which is a plane) of the loop by assessing the component of the loop in the 3rd dimension. They all increase with decreasing planarity. Their results can be summarized as follows: i) \(\lambda_{1n}, \lambda_{2n}\) and \(RP\) can discriminate between the normals and the post-MI group but not the LQTS group (increased roundness of the loop in post-MI group), ii) \(\Delta Q\) and \(AVQ\) can discriminate between the normals and the LQTS group but not the post-MI group (decreased planarity in LQTS group), and iii) \(\lambda_{1n}, \lambda_{2n}, RP\) and \(AVQ\) can discriminate between the post-MI group and the LQTS group (decreased roundness and planarity in LQTS group).

They also calculated QTd both as the difference between maximum and minimum QT intervals and as the standard deviation of QT intervals. They showed that although these parameters could separate normals from LQTS and post-MI patients, they were unable to discriminate between the LQTS patients and the post-MI patients.

Hors et al. showed an association between the orientation of the 3D mean ECG vector in the orthogonal lead system, i.e. leads X, Y and Z, (Each lead measures the electrical activity along the orthogonal dimensions of 3D space of the body) during ventricular repolarization and fatal and non-fatal cardiac events in elderly people [73]. They defined a parameter as the angle between the x-axis and the 2D projection of the 3D mean vector onto XY plane. They defined the ranges for the normal, borderline and abnormal T axis as \([15^\circ, 75^\circ]\); \([-15^\circ, 15^\circ]\) and \([75^\circ, 105^\circ]\); \([-180^\circ, -15^\circ]\) and \([105^\circ, 180^\circ]\) respectively. The new parameter had a strong association with the conventional parameters, like QTd, ST depression, T wave inversion, etc. However, the T axis parameter proved to be associated
with high risk of cardiac death in a multi-variate analysis and thus was suggested as an independent variable.

In another study, the same group investigated the predictive value of an abnormal T loop morphology (constructed from leads X, Y and Z) [74]. The T loop morphology was classified as normal, borderline or abnormal based on the following loop parameters: i) Maximal spatial amplitude, ii) width and sense of inscription of the T loop in the horizontal plane, iii) direction of the mean T axis in the horizontal and vertical planes, and iv) direction and magnitude of the J point displacement in the two planes. Both the T loop classification and the T axis parameter on its own proved to be associated with higher risks of cardiac death than any other risk indicator, including ST depression and T wave inversion. However, the T loop proved to be only slightly better in predicting cardiac deaths.

Hurst reviews the Grant method of ST segment and T wave interpretation in [75]. In this method, an EGG vector is constructed using standard 12-lead EGG signals. Hurst emphasizes the locked-in relation between the QRS complex and the T wave. An abnormal depolarization (QRS complex) predetermines an abnormal repolarization (T wave), so an abnormal T preceded by an abnormal QRS complex should be interpreted as normal. This relation is assessed by the relative orientations of the QRS and the T vectors. The method uses the absolute directions of these vectors in 3D physical space (the body).

### 3.2 PROBLEM AND APPROACH

We hypothesized that the spatial and temporal variations in T wave morphologies and the relation between the depolarization and repolarization patterns will offer new measures of repolarization abnormalities. We aimed to define a set of parameters that would
quantify ventricular repolarization abnormalities.

have sensitivity and specificity greater than the conventional measurements such as QTd in separating normal and clinically relevant abnormal electrocardiograms.

be highly reproducible.

be independent of accurate time-domain measurements such as the detection of the T wave offset (T wave end point).

Thinking that the scalar parameters, like amplitude and time duration, are more prone to contamination by external factors, we preferred a vector based approach.

We investigated the spatial variation, the temporal variation and the wavefront direction characteristics of ventricular repolarization. These concepts can be summarized as follows:

Spatial Variation stands for the inter-lead T wave morphology variation. It is a common observation that a normal ventricular repolarization is seen as a monophasic, smooth, Gaussian-like wave in all of the ECG leads. However, in abnormal cases different T wave morphologies can be seen in different leads. Since each T wave is a projection of the propagating action potentials on the heart, onto the corresponding lead, a difference in the T wave morphologies would mean a different course of propagation. We have not made any speculation on the meaning of different morphology distributions in this thesis. However, the type of morphology distribution is likely to provide detailed information on the type and location of the abnormality. The parameters $TMD, TMD_{pre}$ and $TMD_{post}$ will be introduced under this concept in the next sections. $TMD$ stands for T wave Morphology Dispersion.

Temporal Variation stands for the variation of the ECG vector during ventricular repolarization. The ECG vector is a vector in 3D space which represents the dipole
which is the source of the heart’s electrical activity. We observe the projection of this vector onto different spatial locations in standard ECG recordings. The time course of the motion of this vector during a heart beat defines the temporal variation. The following parameters will be introduced in the next sections: \( LD_1,\ LD_2,\ PL \) and \( PO \).

\( \diamond \) Wavefront direction is assessed by investigating the major direction of the ECG vector during ventricular repolarization, with respect to the direction of the ECG vector during ventricular depolarization. The parameter that will be introduced is \( TCRT \), which stands for Total.Cosine_R.to.T. \( TCRT \) is an attempt to quantify the differences between the time course of depolarization and repolarization.

## 3.3 METHOD

The term ECG decomposition means transforming the multi-lead ECG signals into some other domain, in which the analysis has several advantages, like high SNR, easy identification of dominant components, etc. Several decomposition methods have been previously used for different applications [69,76–79]. We used Singular Value Decomposition (SVD) in our analysis. SVD has been used extensively in ECG signal processing for purposes ranging from signal enhancement to fetal ECG extraction [79–85].

### 3.3.1 Mathematical Background

Singular Value Decomposition (SVD) of the standard 12-lead ECG provides orthogonal subspaces, ordered according to their energy content. Thus it provides a minimum dimensional subspace that captures the maximum ECG energy. This subspace, together with the basis that defines it, is very appropriate for subsequent ECG analysis. SVD is defined as follows [86]:

\[ A = U \Sigma V^T \]
If \( M \) is an \( m \times n \) matrix (Each row corresponds to a standard ECG lead (I, II, V1, V2, V3, V4, V5, V6) and \( n \) is the number of samples in our case) then there exist orthogonal matrices

\[
U = [u_1, \ldots, u_m] \in \mathbb{R}^{m \times m} \tag{3.11}
\]

\[
V = [v_1, \ldots, v_n] \in \mathbb{R}^{n \times n} \tag{3.12}
\]

such that

\[
\Sigma = U^T M V = \text{diag}(\sigma_1, \ldots, \sigma_m) \in \mathbb{R}^{m \times n} \tag{3.13}
\]

where \( \sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_m \geq 0 \).

The columns of \( U \) are referred to as the left singular vectors, whereas the columns of \( V \) are referred to as the right singular vectors. \( \sigma_i \) are the singular values. Furthermore, if

\[
\sigma_1 \geq \cdots \geq \sigma_r > \sigma_{r+1} = \cdots = \sigma_m = 0 \tag{3.14}
\]

then

\[
\text{rank}(M) = r \tag{3.15}
\]

\[
\text{null}(M) = \text{span}\{v_{r+1}, \ldots, v_n\} \tag{3.16}
\]

\[
\text{range}(M) = \text{span}\{u_1, \ldots, u_r\} \tag{3.17}
\]

where \( \text{range}(M) \) is the minimum dimensional space which captures the whole energy. The singular values are measures of how much energy exists along the corresponding vector \( u \). It was shown that 99\% of the total ECG energy can be captured in a 3D subspace, thus in practice \( r = 3 \) for standard 12-lead ECG signals [79].
Figure 3.5: The flowchart of the T wave analysis algorithm

3.3.2 Algorithm - ECG Processing

In the rest of this thesis, $\mathbf{M}$ will be used to designate the 8-by-$n$ ECG data matrix. Each column of $\mathbf{M}$ corresponds to a sampling instant and each row corresponds to a different ECG lead. Because of the algebraic interdependency, eight of the standard 12 ECG leads are used, namely I, II, V1, V2, V3, V4, V5, V6. The signal representations in the minimum dimensional ($r$-dimensional) subspace of $\mathbf{M}$ and the basis vectors of that subspace are used to derive the new parameters. Figure 3.5 shows the flowchart of the whole algorithm.

The SVD of $\mathbf{M}$ is performed as
Input Heart Beats - 8 Standard Leads

Decomposed Heart Beats

Figure 3.6: Input and decomposed ECG signals

\[
\Sigma = \begin{bmatrix}
\tilde{\Sigma} & 0 \\
0 & \Sigma
\end{bmatrix} = \begin{bmatrix}
\tilde{U}^T \\
\tilde{U}
\end{bmatrix} MV = U^T MV \tag{3.18}
\]

where \( \tilde{\Sigma} \in \mathbb{R}^{3 \times 3} \) and is diagonal and \( \tilde{U} \in \mathbb{R}^{8 \times 3} \). Note that the dimension of the minimum dimensional subspace (in other words, the effective rank of \( M \)) is 3. This minimum subspace is spanned by the columns of \( \tilde{U} \in \mathbb{R}^{8 \times 3} \). The decomposition of the ECG signals is performed by taking the projection of the ECG signals onto this minimal subspace as

\[
S = \begin{bmatrix}
s_1^T \\
s_2^T \\
s_3^T
\end{bmatrix} = \tilde{U}^T M, \quad S \in \mathbb{R}^{3 \times n} \tag{3.19}
\]

where \( s_i \)'s correspond to the decomposed (time-orthogonal) signals. The energy of \( s_i \) is proportional to \( \sigma_i \). Figure 3.6 shows an example of the input (M) and output (decomposed) signals. All of the eight output signals (\( S_{all} = U^T M \)) are shown.

The back-transformation of the three dominant decomposed signals back to the original ECG domain (\( \tilde{M} = \tilde{U} S \)) is equivalent to the morphological filtering of the ECG in its original domain [79–81].
Approximate QRS and T wave detection:

As will be clear in the next sections, our method does not require high precision time domain measurements or detections. All that is needed is the approximate locations of the QRS complex and the T wave. This is performed on the most significant three decomposed signals, namely $s_1$, $s_2$ and $s_3$. Let

$$s_{3D}(t) = \left[ \begin{array}{ccc} s_1(t) & s_2(t) & s_3(t) \end{array} \right]^T \in \text{span}(u_1, u_2, u_3)$$

(3.20)

$$E_{3D}(t) = ||s_{3D}(t)||_2$$

(3.22)

Figure 3.7 shows $s_{3D}$ and $E_{3D}$ for a single beat. The R wave offset is assumed to be the first point after the maximum of $E_{3D}$, where $E_{3D}$ falls below $\delta\%$ of its maximum value (an arbitrary threshold of $\delta = 70$ is used in this implementation). We denote that instant as $t'_{RE}$. Although $t'_{RE}$ is not the actual R offset point, it serves our purpose. Similarly, the $\delta\%$ point before the maximum is marked as the R wave onset, $t'_{RS}$. The representative part of the QRS complex is assumed to start $\varepsilon$ before and end $\varepsilon$ after $t'_{RE}$ (an arbitrary limit of $\varepsilon = 48ms.$ is used in this implementation). These two points are marked as $t_{RS}$ and $t_{RE}$, respectively. The T wave peak ($t_{TP}$) is assumed to be the maximum point of $E_{3D}$ after $t_{RE}$. The approximate T wave onset point $t_{TS}$ is taken to be $1/3$ of $(t_{TP} - t'_{RE})$ after $t'_{RE}$. Those points are marked on Figure 3.7. Since we are concerned with single beats in this study, there is no need to choose an end point for the search of the T wave peak. However, such a point can easily be selected based on the instantaneous heart rate, when necessary.

The detection of the T wave offset, $t_{TE}$, is more tricky. It is based on the path of the tip of $s_{2D}$. $s_3(t)$ is excluded to decrease the computation time. As it represents a small portion of the ECG energy, this exclusion does not affect the result significantly. The vector $s_{2D}(t_i)$ represents the dominant inter-lead relation at time $t_i$. There is a
3 Decomposed ECG Signals, Norm Signal and Detection Points

Figure 3.7: The approximate QRS complex and T wave detection points

continuous change of these relations throughout the ventricular repolarization (as well as depolarization). $s_{2D}$ stays stationary afterwards. This is observed as a loop when we trace the tip of $s_{2D}$. This loop is called the $T$ loop (We will call the loop corresponding to the QRS complex as the $QRS$ loop). Figure 3.8.a shows that loop in $u_1u_2$-plane for $t_i \geq t_{TS}$. The rectangle that surrounds the T loop is divided into 100 (arbitrarily chosen) equal rectangular cells. Each cell is assigned a weight equal to the number of inner data points, i.e. the time instants. This is a measure of the time spent by the tip of $s_{2D}$ in that cell, in other words it is a measure of the stationarity of $s_{2D}$. Let $D_i$ be the weight of the $i^{th}$ cell. The cells with zero weight are discarded and the other cells are ordered in respect of $D_i$. Figure 3.8.b shows ordered $D_i$ values for a single beat. Assuming that there are $Q$ cells with nonzero weights, $D_1 \leq D_2 \leq \ldots \leq D_Q$.

A threshold is set on $D_i$'s as

$$th = \text{mean}(D_i) + \mu \times \text{STD}(D_i) \quad \mu = 3 \quad (3.23)$$
The earliest time instant at which the tip of $s_{2D}$ enters one of the cells with a cell index bigger than or equal to the threshold ($th$) is set to be the approximate T offset point, $t_{TE}$. This cell is shown in Figure 3.8 and the corresponding time instant is marked in Figure 3.7.

It should be kept in mind that only approximate and global T wave offset point is required. Since the aim of our algorithm is to quantify the T wave shape between $t_{TS}$ and $t_{TE}$, rather than to measure the $(t_{TE} - t_{TS})$ interval, the approximate and the arbitrary nature of the T wave detection point is fully acceptable.

If, using the above described $th$, we get $t_{TE} \leq t_{TS}$, which should not occur, $\mu$ is increased in steps of 0.2 until $t_{TE} > t_{TS}$. Similarly, if $D_i < th \forall D_i$, $\mu$ is decreased in steps of 0.2 until $D_Q \geq th$. Such cases are rare (see Section 3.6.3).

This T wave offset detection is based on the concept that the inter-lead relations do not change in the absence of the ECG signal. Each point on the $u_1 u_2$-plane corresponds to a specific inter-lead relation defined by the vectors $u_1$ and $u_2$. Hence, each cell in this plane represents a group of similar inter-lead relations. When the repolarization pattern ends, the ECG signal remains confined to a small set of such relations.
The decomposed signal is subsequently normalized with the maximum norm of $s_{3D}$ set to 1:

$$s_{3D}(t_i) = \frac{s_{3D}(t_i)}{\max_i(E_{3D}(t_i))} \quad (3.24)$$

The QRS complex and the T wave extracted as explained above, result in the decomposed matrices $S_{QRS}$ and $S_T$. A DC vector is subtracted from both signals:

$$s_{3D}^{DC} = 0.25 \times \{s_{3D}(t_{RS}) + s_{3D}(t_{RE}) + s_{3D}(t_{TS}) + s_{3D}(t_{TE})\} \quad (3.25)$$

In the rest of this thesis, $S_T \in \mathbb{R}^{3 \times K} \quad (K = t_{TE} - t_{TS})$ and $S_{QRS} \in \mathbb{R}^{3 \times L} \quad (K = t_{RE} - t_{RS})$ will denote the decomposed, energy normalized and DC-compensated T wave and QRS complex.

The T wave is reconstructed from $S_T$, which is equivalent to morphological filtering:

$$\tilde{M}_T = \tilde{U}S_T = \tilde{U}\tilde{U}^T M_T \quad (3.26)$$

where $m_{T,i}$ is the $i^{th}$ column of $M_T$, $m_{T,i} = m_{i+t_{TS}}$, $0 \leq i \leq K$. The reconstructed T wave, $\tilde{M}_T \in \text{span}\{u_1, u_2, u_3\}$, is once again decomposed by SVD:

$$\Sigma_T = \begin{bmatrix} \tilde{\Sigma}_T & 0 \\ 0 & \tilde{\Sigma}_T \end{bmatrix} = \begin{bmatrix} \tilde{U}_T^T \\ \tilde{U}_T \end{bmatrix} \tilde{M}_TV_T = U^T_M T_V, \quad \tilde{\Sigma}_T \in \mathbb{R}^{2 \times 2} \text{ is diagonal, } \tilde{U}_T \in \mathbb{R}^{8 \times 2} \quad (3.27)$$

The subscript $T$ indicates that we are dealing with the T wave only and the cap (') means morphologically filtered. Note that $\tilde{U}_T$ has two columns whereas $\tilde{U}$ has three columns. This is because $s_{T,3}$ has very low energy and is excluded in the calculation of
spatial and temporal variation descriptors for the sake of decreased computation time and increased noise immunity. Figure 3.9 shows the decomposed T waves.

The new descriptors will be explained in the next section with reference to the ECG processing explained in this section.

3.3.3 Algorithm - Descriptors

Spatial Variation Descriptors:

$\overline{U}_T$ is an 8-by-2 matrix. We can represent it as

$$\overline{U}_T = \begin{bmatrix} \tilde{u}_{T,1} & \tilde{u}_{T,2} \end{bmatrix} = \begin{bmatrix} z_I & z_{II} & \cdots & z_{V6} \end{bmatrix}^T, \quad \tilde{u}_{T,k} \in \mathbb{R}^{8 \times 1}, \quad z_j \in \mathbb{R}^{2 \times 1}$$

(3.28)

where $\tilde{u}_{T,1}$ and $\tilde{u}_{T,2}$ are the two most significant left singular vectors of $\widetilde{M}_T$. The vector, $z_j$, is the reconstruction vector of the $j^{th}$ input channel. Note that reconstruction (back-transformation) from the most significant two decomposed signals can be done as $\widetilde{M}_T = \overline{U}_T(\overline{U}_T^T \overline{M}_T)$.

The energies along the two orthogonal dimensions of the decomposed space (namely
along $\bar{u}_{T,1}$ and $\bar{u}_{T,2}$) are proportional to the corresponding singular values, $\sigma_{T,1}$ and $\sigma_{T,2}$. The decomposition space is rescaled to get equal energies in both directions. Thus the reconstruction vectors from the balanced domain (equal energies in both directions), $V_T$, are obtained. This is done as follows:

$$W_T^T = \bar{U}_T \bar{\Sigma}_T = \begin{bmatrix} z_I & z_{II} & z_{V6} \end{bmatrix}^T \bar{\Sigma}_T$$

$$= \begin{bmatrix} w_I & w_{II} & w_{V1} & w_{V2} & w_{V3} & w_{V4} & w_{V5} & w_{V6} \end{bmatrix}^T w_j \in \mathbb{R}^{2 \times 1}$$

Each $w_j$ represents the reconstruction coefficients of the T wave of the $j^{th}$ ECG lead.

The angle between different $w_j$’s is calculated as:

$$\theta_{ij} = \angle (w_i, w_j) \in [0^\circ, 180^\circ], \quad \forall i, j \in \{I, II, V1, V2, V3, V4, V5, V6\}, \quad i \neq j$$

The smaller $\theta_{ij}$ is, the closer the T wave morphologies in the $i^{th}$ and the $j^{th}$ ECG leads. We observed that the T wave morphology in V1 is generally different than that of the other channels, irrespective of any clinical background, mainly due to the position of the V1 electrode (see Section 3.5.4). Figure 3.10 shows examples of a normal and a HCM case.

The descriptor, T wave Morphology Dispersion (TMD), is defined as the mean of all $\theta_{ij}$ excluding $\theta_{V1,j}$’s:

$$TMD = \frac{1}{21} \sum_{i,j \in \Gamma} \theta_{ij} \quad \Gamma = \{I, II, V2, V3, V4, V5, V6\}$$

$TMD$ is a measure of the spatial T wave morphology variation. Small $TMD$ values mean that the reconstruction vectors of different ECG leads are close to each other and
this means that the T wave morphologies in different ECG leads are similar. Conversely, high $TMD$ values show high inter-lead T wave morphology variation.

Since the ascending and the descending parts of the T wave are known to correspond to different facets of the ventricular repolarization, we derived two more descriptors $TMD_{\text{pre}}$ and $TMD_{\text{post}}$, which are defined in the same way as $TMD$ with the ascending part of the T wave ($t_{TS} < t < t_{TP}$) used for $TMD_{\text{pre}}$ and the descending part ($t_{TP} < t < t_{TE}$) used for $TMD_{\text{post}}$.

**Wavefront Direction Descriptor:**

Both of the QRS and the T wave, as represented by $S_{QRS}$ and $S_T$, follow an approximate loop in the column space of $\overline{U}$. The relative orientation of these loops are determined and used as a descriptor.

The orientation of the T wave loop is determined by selecting the unit vector $e_{T,1}$ that represents the major axis of the usually elliptic T loop. $e_{T,1}$ is defined as the unit vector from the origin towards to furthest away point of the T loop. $e_{T,1}$ also defines the direction that represents the maximum T wave energy. $e_{T,2}$, on the other hand, is defined as the unit vector from the origin towards the nearest point of the T loop after its component along $e_{T,1}$ is subtracted. $e_{T,1}$ and $e_{T,2}$ define the T wave plane approximately.
Since the QRS loop is a high energy loop, no single representative vector is determined for the orientation of the QRS loop, instead the ECG vector \((s_{3D}(t_i))\) itself is used.

The descriptor Total Cosine R-to-T (TCRT) is defined as the average of the cosines of the angles between \(e_{T,t_1}\) and \(s_{3D}(t_i)\) for all \(i\) within \([t_{RS}', t_{RE}']\) (see Figure 3.7). Note that \(s_{3D}(t_i)\) correspond to the columns of \(S_{QRS}\). TCRT is a measure of the vector deviation between the depolarization and the repolarization waves. It is formally defined as

\[
TCRT = \frac{1}{t_{RE}' - t_{RS}'} \int_{t=t_{RS}'}^{t_{RE}'} \cos(\angle(e_{T,t_1}, s_{3D}(t)))
\]

Figure 3.11 shows examples of the QRS and the T loops in normal and HCM cases. TCRT measures the deviation between these loops. It, in effect, measures the difference between the propagation directions of the depolarization and the repolarization waves.

**Temporal Variation Descriptors:**

The T wave \((S_T)\) is de-normalized before computing the temporal variation descriptors. This is performed because the temporal variation descriptors depend on the area encompassed and the path followed by the ECG vector on the plane spanned by \(e_{T,t_1}\) and \(e_{T,t_2}\). Figure 3.12 shows a T loop on this plane.
The rectangular area encompassing the T loop is divided into $n \gg 1$ ($n = 4900$ in this implementation) equal size cells. Note that the time span extends from $t_{TS}$ to $t_{TE}$. The loop is closed with a straight line connecting the end-points and spatially re-sampled with equal sampling steps of the 2D space. The sampling step is selected to be 90% of the diagonal length of the cells. This re-sampling assures that there is at least one sample in every cell that the loop passes through. The number of cells in the inner loop area and the outer loop area are counted. The descriptors $\text{Percentage of the Inner Loop Area (PL)}$ and $\text{Percentage of the Outer Loop Area (PO)}$ are defined as:

$$PL = \frac{\text{# of cells in the inner loop area}}{4900}$$  
$$PO = \frac{\text{# of cells in the outer loop area}}{4900}$$

Note that $PL + PO < 1$ because there are cells occupied by the loop itself. These descriptors are defined to measure the irregularity of the T wave loop. An irregular loop with self-crossing segments, convex and concave regions indicates highly heterogeneous temporal evolution of ventricular repolarization. This 2D space can interpreted as a domain of inter-lead relations. Thus, loosely speaking, $PL$ and $PO$ is a measure of the
variation of the inter-lead relations.

Another approach to look at the same variation is to check the inter-lead relations that the ECG vector actually assumes. This is equivalent to checking the path (the loop) itself. We did this analysis in two ways:

The descriptor Lead Dispersion-1 ($LD_1$) is calculated using the decomposed, energy normalized and DC-compensated T wave ($S_T$) which is extracted from the decomposed whole beat. So the 2D subspace ($\text{span}\{u_1, u_2\}$) in which $LD_1$ is computed, is spanned by the most dominant two left singular vectors of the whole beat. It corresponds to the most dominant 2D subspace. The rectangular area encompassing the T loop is divided into 100 equal cells (arbitrary choice). $LD_1$ is defined as the number of different cells that the path involves.

The descriptor Lead Dispersion-2 ($LD_2$) represents the actual length of the T loop. It is computed on the spatially re-sampled, unnormalized T loop. It is equal to the length of the T loop, computed by counting the spatial sampling steps involved, excluding the straight line closing the loop. $LD_2$, as $PL$ and $PO$, is computed on the 2D subspace ($\text{span}\{e_1,T, e_2,T\}$) determined graphically in the 3D dominant subspace computed by the SVD of the whole beat.

The graphical determination of the 2D subspace in which $LD_2$, $PL$ and $PO$ are computed assumes a priori that the T loop is planar. This assumption, inevitably affects the computations. This will be discussed in Section 3.6 and an alternative will be discussed in Section 3.8.

3.4 IMPLEMENTATION

The system was implemented on a standard personal computer with Pentium 133MHz CPU and 80MB RAM, using Matlab Version 5.2.0 (The MathWorks Inc., 1998).
The inputs to system are eight, time-aligned median beats, each one being a representative of the ECG morphology in the corresponding standard lead. The main time consuming computations are the area calculations which involve a recursive algorithm, also implemented in Matlab. On the average, the computation of all of the parameters for a single recording takes 177 seconds. If excluding the area related parameters (PL and PO), the analysis takes 30 seconds per recording. Matlab’s commercially available library without any modification is presently used.

The computation time was decreased to 0.1 seconds per ECG recording, including the area computations, with a purpose built C library. ²

3.5 ANALYSIS

3.5.1 Data Set

The system was tested with standard 12-lead ECGs recorded by the MAC VU Electrocardiograph (Marquette Medical Systems, Milwaukee, Wisconsin, USA). 10 second recordings with 500Hz recording rate were acquired and the so-called median beat was obtained for each channel of the recording [87]. These median beats, sampled at 250HZ, were used in the analysis.

Five sets of ECG recordings were used:

1. Standard resting 12-lead ECGs recorded in 1100 normal healthy subjects, 913 male, aged 33±12 years, range 10-81 years.

2. 10 supine resting ECGs were recorded in each of 76 normal healthy subjects, 37 male, aged 38±10 years, range 13-59 years. In each individual, the serial ECGs were

²The C library was built by Katerina Hnatkova from Cardiological Sciences Department of St. George’s Hospital Medical School, London, UK.
recorded one immediately after another using the same electrode attachments and without the subject moving during the whole recording session. Data acquisition of each recording lasted 10 seconds and, including the electrocardiograph handling, each series of the 10 ECGs was obtained within 3 minutes.

3. Using the same recording strategy, 10 supine resting ECGs were recorded in each of 63 patients with hyperthropic cardiomyopathy (HCM), 44 male, aged 39±14 years, range 12-71 years.

4. Using the above described normal and HCM subjects, 9 consecutive recordings were taken under the same conditions in standing position.

5. 10 consecutive recordings are taken from 65 DCM subjects (selected among 72 DCM patients - age:48 ± 15, 29 women) under the conditions described above.

3.5.2 Correspondence Between New and Conventional Descriptors

To find out whether our method assesses ECG qualities additional to the conventional parameters, the correspondence between the new and the conventional parameters was investigated. All new and conventional parameters of 1100 ECGs acquired from normal subjects were used to calculate the Pearson Product-Moment correlation coefficient between the new and the conventional parameters and the ages of the subjects (Statistica Package, Release 5.1).

The conventional measures of ventricular repolarization were obtained with a research version of the commercial QT Guard software package (Marquette Medical System, Milwaukee, Wisconsin, USA). This software aligns all beats with respect to the Q wave onset and was programmed to use the downslope inflex tangent method to detect the T wave offset. The following parameters were considered (see Section 3.1.2):

i. Global QT Dispersion (G-QTd)
ii. Precordial QT Dispersion (P-QTd)

iii. Area QT Dispersion (A-QTd)

iv. Global J to T peak Dispersion (G-JTd)

v. Corrected QT Interval (QTc Interval)

The Principal Component Analysis (PCA) of the 12 lead T waves is also incorporated in the QT Guard package. The 12 components with associated eigenvalues ($\lambda_i$) are obtained. Each $\lambda_i$ is a measure of the $i^{th}$ principal component. There is a one-to-one correspondence between $\lambda_i$'s and $\sigma_i$'s ($\lambda_i = \sigma_i^2$). The following descriptors are calculated:

vi. PCA Ratio 1 ($PCA_1$)\[= \frac{\lambda_1}{\sqrt{\sum_{i=2}^{12} \lambda_i^2}} \times 100.
\]

vii. PCA Ratio 2 ($PCA_2$)\[= \frac{\lambda_2}{\lambda_1} \times 100.
\]

viii. PCA Ratio 3 ($PCA_3$)\[= \frac{\lambda_3}{\lambda_1} \times 100.
\]

Table 3.1 gives the Pearson Product-Moment correlation coefficients between the conventional and the new descriptors and the age of the patients. None of the new descriptors had a significant correlation with the age ($|r| < 0.11$ for all parameters). The absolute value of all the correlation coefficients between the new descriptors were less than 0.5 except for: $TMD/TMD_{post}$: 0.91, $TMD/TMD_{pre}$: 0.93, $TMD_{post}/TMD_{pre}$: 0.79, $PL/PO$: -0.94, $PL/LD_2$: -0.54, $PO/LD_2$: 0.50. The absolute values of the correlation coefficients between the conventional and the new parameters were all less than 0.5, except: $TMD/PCA_2$: 0.552, $LD_2/PCA_2$: -0.562.

These results show that the new descriptors assess different qualities of ventricular repolarization than the conventional descriptors do. The high correlation between three
types of $TMD$ descriptors in normal cases suggest that there is no specific temporal segment within the T wave for increased morphology dispersion. We also checked the Pearson Product Moment Correlation Coefficients in HCM cases between three types of $TMD$ descriptors and obtained the following results: $TMD/TMD_{post}$: 0.94, $TMD/TMD_{pre}$: 0.96, $TMD_{pre}/TMD_{post}$: 0.84. These results show that when T wave morphology dispersion exists, it is observed in the whole T wave. This somewhat explains the contradictory results that reported T wave alternans as seen in the early and late phases of the T wave [65, 66]. The negative correlation correlation between $PL$ and $PO$ is an expected result as they are the inner and the outer area of the same T loop. This high correlation also shows that there are not many self-crossing T loops in our data set. This concept will be discussed in Section 3.6.

<table>
<thead>
<tr>
<th></th>
<th>$TMD$</th>
<th>$TMD_{post}$</th>
<th>$TMD_{pre}$</th>
<th>$TCRT$</th>
<th>$PL$</th>
<th>$PO$</th>
<th>$LD_1$</th>
<th>$LD_2$</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>$TMD_{post}$</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>1.00</td>
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<td></td>
<td></td>
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<tr>
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<td>0.04</td>
<td>0.05</td>
<td>1.00</td>
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<tr>
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<td>-0.18</td>
<td>-0.08</td>
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<td>0.14</td>
<td>0.17</td>
<td>0.08</td>
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<td></td>
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<td>1.00</td>
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<td>0.50</td>
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<td>$G - QTd$</td>
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<td>0.10</td>
<td>0.01</td>
<td>-0.03</td>
<td>0.04</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-0.08</td>
</tr>
<tr>
<td>$P - QTd$</td>
<td>0.16</td>
<td>0.16</td>
<td>0.09</td>
<td>0.00</td>
<td>0.03</td>
<td>-0.02</td>
<td>0.00</td>
<td>-0.15</td>
</tr>
<tr>
<td>$A - QTd$</td>
<td>0.10</td>
<td>0.11</td>
<td>0.00</td>
<td>-0.08</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.01</td>
<td>-0.13</td>
</tr>
<tr>
<td>$G - JTpd$</td>
<td>0.23</td>
<td>0.19</td>
<td>0.09</td>
<td>-0.12</td>
<td>0.23</td>
<td>-0.22</td>
<td>0.02</td>
<td>-0.48</td>
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<td>$PCA_1$</td>
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<td>0.22</td>
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<td>0.06</td>
<td>-0.05</td>
<td>0.15</td>
<td>-0.24</td>
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<td>0.46</td>
<td>0.46</td>
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<td>0.04</td>
<td>-0.06</td>
<td>0.05</td>
<td>-0.56</td>
</tr>
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<td>$PCA_3$</td>
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<td>0.15</td>
<td>0.14</td>
<td>0.03</td>
<td>-0.11</td>
<td>0.10</td>
<td>0.11</td>
<td>-0.12</td>
</tr>
<tr>
<td>$QTc Interval$</td>
<td>0.07</td>
<td>0.07</td>
<td>0.08</td>
<td>-0.05</td>
<td>-0.17</td>
<td>0.16</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>$Age$</td>
<td>-0.06</td>
<td>-0.11</td>
<td>0.00</td>
<td>0.09</td>
<td>-0.06</td>
<td>0.01</td>
<td>0.05</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 3.1: Pearson Product-Moment correlation coefficients between the new descriptors, the old descriptors and the age of the subjects.
3.5.3 Short Term Reproducibility

The variation of the measurements between 10 consecutive ECG recordings from the same individual of the populations of 76 normal and 63 HCM subjects is used to assess the short-term reproducibility of all descriptors. The ratio of the individual range to the total range was calculated for each patient and each descriptor. For a fictional descriptor \( X \), this ratio for normal subject \( j \) (\( R_{nrm,j}^X \)) is

\[
R_{nrm,j}^X = \frac{\text{max}_{1 \leq k \leq 10}(X_{i,j}^k) - \text{min}_{1 \leq k \leq 10}(X_{i,j}^k)}{\text{max}_{1 \leq k \leq 10, \ 1 \leq i \leq n}(X_{i,j}^k) - \text{min}_{1 \leq k \leq 10, \ 1 \leq i \leq n}(X_{i,j}^k)}
\]  

(3.36)

where \( n \) is the number of subjects and \( X_{i,j}^k \) denotes the value of the descriptor \( X \) for the \( k \)th ECG recording of the \( i \)th subject.

The values \( R_{hcm,j}^X \) were obtained in a similar way for each descriptor. Figure 3.13 summarizes the results.

The significance of the differences between the reproducibilities of different descriptors was assessed by Wilcoxon non-parametric paired test using the Statistica software package. The analysis was performed on the normal and the HCM groups separately by comparing the individual reproducibilities of each descriptor for each subject in a pairwise fashion. Table 3.2 shows the p-values in normal and HCM groups.

The mean values of the reproducibilities of each descriptor show that the new ones are more reproducible than the conventional ones with the exceptions of \( PCA_1 \) and \( PCA_2 \). Their reproducibilities are close to those of the new ones. Since \( PCA_1 \) and \( PCA_2 \) are computed using a similar technique to the new ones, this is an expected result. The significance of this separation is verified by the low p-values computed by Wilcoxon Test while comparing the reproducibilities in a pairwise fashion. The high p-values (insignificance) were observed between descriptors whose reproducibilities are already close to each other's.
Figure 3.13: Short-term reproducibility of conventional and new descriptors. Each column shows the mean value + the standard deviation. Grey: Normal, Black: HCM
<table>
<thead>
<tr>
<th></th>
<th>Normal Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMD</td>
<td>TMD&lt;sub&gt;post&lt;/sub&gt;</td>
<td>TMD&lt;sub&gt;pre&lt;/sub&gt;</td>
<td>TCRT</td>
</tr>
<tr>
<td>G – QTd</td>
<td>2.62 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>1.66 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>2.07 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>4.14 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
</tr>
<tr>
<td>P – QTd</td>
<td>2.80 × 10&lt;sup&gt;-6&lt;/sup&gt;</td>
<td>7.08 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>6.54 × 10&lt;sup&gt;-7&lt;/sup&gt;</td>
<td>0.065</td>
</tr>
<tr>
<td>A – QTd</td>
<td>1.87 × 10&lt;sup&gt;-12&lt;/sup&gt;</td>
<td>2.71 × 10&lt;sup&gt;-12&lt;/sup&gt;</td>
<td>9.03 × 10&lt;sup&gt;-12&lt;/sup&gt;</td>
<td>4.80 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
</tr>
<tr>
<td>G – JTpd</td>
<td>2.71 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>3.86 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>3.00 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>2.88 × 10&lt;sup&gt;-5&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;1&lt;/sub&gt;</td>
<td>7.07 × 10&lt;sup&gt;-13&lt;/sup&gt;</td>
<td>7.07 × 10&lt;sup&gt;-13&lt;/sup&gt;</td>
<td>7.07 × 10&lt;sup&gt;-13&lt;/sup&gt;</td>
<td>7.07 × 10&lt;sup&gt;-13&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7.51 × 10&lt;sup&gt;-4&lt;/sup&gt;</td>
<td>0.103</td>
<td>0.086</td>
<td>4.86 × 10&lt;sup&gt;-6&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.16 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>1.20 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>5.64 × 10&lt;sup&gt;-12&lt;/sup&gt;</td>
<td>1.82 × 10&lt;sup&gt;-6&lt;/sup&gt;</td>
</tr>
<tr>
<td>QTc&lt;sub&gt;Interval&lt;/sub&gt;</td>
<td>7.34 × 10&lt;sup&gt;-13&lt;/sup&gt;</td>
<td>9.93 × 10&lt;sup&gt;-13&lt;/sup&gt;</td>
<td>2.34 × 10&lt;sup&gt;-12&lt;/sup&gt;</td>
<td>3.03 × 10&lt;sup&gt;-12&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Normal Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HCM Group</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>TMD</td>
<td>TMD&lt;sub&gt;post&lt;/sub&gt;</td>
<td>TMD&lt;sub&gt;pre&lt;/sub&gt;</td>
<td>TCRT</td>
</tr>
<tr>
<td>G – QTd</td>
<td>1.19 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>1.87 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>1.03 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>2.40 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
</tr>
<tr>
<td>P – QTd</td>
<td>4.12 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>7.62 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>5.28 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>1.52 × 10&lt;sup&gt;-7&lt;/sup&gt;</td>
</tr>
<tr>
<td>A – QTd</td>
<td>3.82 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>2.34 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>1.96 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>3.80 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
</tr>
<tr>
<td>G – JTpd</td>
<td>4.67 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>5.09 × 10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>6.22 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>2.50 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;1&lt;/sub&gt;</td>
<td>9.97 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>9.97 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>9.97 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
<td>9.97 × 10&lt;sup&gt;-11&lt;/sup&gt;</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.061</td>
<td>0.598</td>
<td>0.064</td>
<td>0.123</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.04 × 10&lt;sup&gt;-4&lt;/sup&gt;</td>
<td>0.058</td>
<td>1.04 × 10&lt;sup&gt;-4&lt;/sup&gt;</td>
<td>1.94 × 10&lt;sup&gt;-5&lt;/sup&gt;</td>
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<td>8.66 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
<td>2.08 × 10&lt;sup&gt;-8&lt;/sup&gt;</td>
<td>1.64 × 10&lt;sup&gt;-9&lt;/sup&gt;</td>
<td>1.50 × 10&lt;sup&gt;-10&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 3.2: P-values computed by non-parametric Wilcoxon Paired Test, showing the significance of the difference between the reproducibilities of the new and the conventional descriptors in normal and HCM groups, in supine position.
Table 3.3: Normal ranges of all descriptors calculated over 1100 normal ECG recordings

An interesting observation is that most of the new descriptors (6 of 8) have a better reproducibility in the HCM group than in the normal group. This is a good feature as it indicates better positive predictive value, i.e., the new descriptors are less likely to miss abnormal ECGs than they predict positive (abnormality) in normal ECGs.

### 3.5.4 Normal Ranges

The 1100 ECGs of normal subjects (see Section 3.5.1) were analyzed and the mean and the standard deviation of each descriptor is calculated. These provide the normal values of each descriptor. The same analysis was performed using the conventional descriptors also. Table 3.3 summarizes the results.

We also calculated the average $\theta_{ij}$ values used in $TMD$ calculations. As seen in Table 3.4, the $\theta_{V1,i}$'s are significantly higher than the others. This confirms our exclusion of...
Table 3.4: Normal values of $\theta_{ij}$ used in TMD calculations, calculated using 1100 ECGs of normal subjects

V1 from TMD, TMD$_{pre}$ and TMD$_{post}$ calculations.

3.5.5 Univariate Analysis - Normal vs. HCM

The new and the conventional descriptors were compared on the basis of the significance of discriminating the normal subjects and the HCM subjects in terms of specificity and sensitivity. Specificity and sensitivity are defined as:

\[
\text{Specificity} = \frac{\text{# of correctly diagnosed normal subjects}}{\text{Total number of subjects}} \quad (3.37)
\]

\[
\text{Sensitivity} = \frac{\text{# of correctly diagnosed HCM subjects}}{\text{Total number of subjects}} \quad (3.38)
\]
We applied the method to the population composed of 76 normal and 63 HCM subjects and used the mean of 10 consecutive supine ECG recordings for each subject (see Section 3.5.1).

We first performed a univariate analysis. The mean and standard deviation were computed for each descriptor for both of the sets of subjects. We then applied the Mann-Whitney Test to assess the significance of their separation. The non-parametric Mann-Whitney Test was implemented using an in-house written software according to the original description [88]. A p-value less than 0.05 was considered as statistically significant. Lower the p-value, more significant the separation of the two groups is.

Secondly, we plotted the Receiver Operator Characteristic (ROC) curves for each single descriptor. ROC curves show the dependency of specificity on sensitivity. They are plots of the highest possible sensitivity for a given specificity and vice versa. It is a monotonically decreasing curve. Both axes range from 0 to 1. The area under the ROC curves is used for comparison. The largest possible area is 1. This means that it is possible to achieve 100% specificity and 100% sensitivity at the same time. So, higher the ROC curve area, better the separation is. Figure 3.14 shows all ROC curves.

Table 3.5 summarizes the results of univariate analysis.

These results show that the three $TMD$ descriptors and the $TCRT$ are superior to all of the conventional descriptors both in terms of p-value and ROC curve area, except for $QTc.Interval$. $QTc.Interval$ had the best performance among the conventional parameters. Its performance is almost the same as $TMD_{pre}$'s but worse than $TMD$, $TMD_{post}$ and $TCRT$. There are several doubts about the value of such corrected QT interval related descriptors. There is a curious experiment that was conducted by Prof. Malik at St. George’s Hospital Medical School, London, UK. He took two groups of subjects, normal and abnormal (subjects with diagnosed cardiac disease). Then he
<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Normal n=76</th>
<th>HCM n=63</th>
<th>Mann-Whitney Test</th>
<th>Area under ROC curves</th>
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<tbody>
<tr>
<td>TMD</td>
<td>(10.72 ± 4.784)°</td>
<td>(41.10 ± 26.85)°</td>
<td>2.818 × 10⁻¹⁸</td>
<td>0.901</td>
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<tr>
<td>TMD₉₉</td>
<td>(6.141 ± 4.462)°</td>
<td>(36.68 ± 27.49)°</td>
<td>2.289 × 10⁻¹⁹</td>
<td>0.911</td>
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<tr>
<td>TMD₉₉₉₉</td>
<td>(8.682 ± 4.585)°</td>
<td>(42.14 ± 32.62)°</td>
<td>1.605 × 10⁻¹³</td>
<td>0.851</td>
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<tr>
<td>TCHR</td>
<td>(0.522 ± 0.274)°</td>
<td>(−0.351 ± 0.522)°</td>
<td>3.548 × 10⁻¹⁹</td>
<td>0.909</td>
</tr>
<tr>
<td>PL</td>
<td>(0.671 ± 0.085)</td>
<td>(0.608 ± 0.142)</td>
<td>5.935 × 10⁻³</td>
<td>0.643</td>
</tr>
<tr>
<td>PO</td>
<td>(0.273 ± 0.072)</td>
<td>(0.328 ± 0.115)</td>
<td>3.051 × 10⁻³</td>
<td>0.652</td>
</tr>
<tr>
<td>LD₁</td>
<td>(36.40 ± 1.163)</td>
<td>(34.81 ± 3.157)</td>
<td>2.522 × 10⁻⁶</td>
<td>0.718</td>
</tr>
<tr>
<td>LD₂</td>
<td>(724.5 ± 346.1)</td>
<td>(604.9 ± 458.1)</td>
<td>6.787 × 10⁻⁴</td>
<td>0.674</td>
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<tr>
<td>G–QTd</td>
<td>(19.97 ± 11.62)ms.</td>
<td>(36.55 ± 18.85)ms.</td>
<td>6.989 × 10⁻⁹</td>
<td>0.775</td>
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<tr>
<td>P–QTd</td>
<td>(10.79 ± 8.776)ms.</td>
<td>(27.87 ± 18.69)ms.</td>
<td>6.611 × 10⁻¹¹</td>
<td>0.806</td>
</tr>
<tr>
<td>A–QTD</td>
<td>(13.70 ± 8.564)ms.</td>
<td>(24.38 ± 12.23)ms.</td>
<td>2.127 × 10⁻⁸</td>
<td>0.768</td>
</tr>
<tr>
<td>G–JTDₚᵈ</td>
<td>(32.53 ± 12.18)ms.</td>
<td>(45.96 ± 20.61)ms.</td>
<td>2.463 × 10⁻⁵</td>
<td>0.708</td>
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<tr>
<td>PCA₁</td>
<td>(680.0 ± 226.3)</td>
<td>(481.4 ± 245.8)</td>
<td>6.698 × 10⁻⁸</td>
<td>0.767</td>
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<tr>
<td>PCA₂</td>
<td>(15.56 ± 6.162)</td>
<td>(23.56 ± 10.85)</td>
<td>9.886 × 10⁻⁷</td>
<td>0.744</td>
</tr>
<tr>
<td>PCA₃</td>
<td>(4.826 ± 2.373)</td>
<td>(7.765 ± 4.235)</td>
<td>6.603 × 10⁻⁹</td>
<td>0.784</td>
</tr>
<tr>
<td>QTc Interval</td>
<td>(404.4 ± 15.27)ms.</td>
<td>(435.1 ± 25.50)ms.</td>
<td>4.122 × 10⁻¹⁴</td>
<td>0.856</td>
</tr>
</tbody>
</table>

Table 3.5: Univariate comparison of all descriptors on the basis of discriminating normal and HCM subjects

Figure 3.14: Univariate ROC curves of conventional and new descriptors
measured the QT intervals of each subject and corrected them using Bazett's formula. However, instead of using the RR interval (reciprocal of heart rate) as required by the Bazett's formula, he simply used the lengths of the surnames of the patients in terms of the number of letters in their surnames. The so corrected QT intervals provided a significant separation between the two groups. It is clear that this correction has nothing to do with the physiology of the subject. Although this experiment does not disprove the use of correction formulas, it is rather interesting.

The temporal variation descriptors, on the other hand, did not perform well. This may well be due to some physiological reason or simply due to the drawbacks of our algorithm. The latter issue will be discussed in Section 3.6.

Appendix B provides a set of examples of ECG recordings from normal and HCM subjects and the measured ventricular repolarization descriptors.

3.5.6 Multivariate Analysis - Normal vs. HCM

We also performed a multivariate analysis of the conventional and the new descriptors together to assess their relative performances in discriminating the HCM and the normal subjects. Two approaches were assumed in multivariate analysis.

First, we set the dichotomy limit (separation limit for classification) of each descriptor to the mean of the average values of the normal and the HCM groups beforehand. Multiple regression models of different orders were calculated using Statistica (Statistica package, Release 5.1) in a backward stepwise fashion using those a priori classification results. We started with all of the descriptors in a single model and excluded the least significant descriptor at each step until the p-values of all of the surviving descriptors were below a significance level (p-value < 0.01). Table 3.6 summarizes the results of this analysis. The descriptors TCRT, TMD\textsubscript{pre}, P-QTd and QT\_Interval survived throughout all of the successive multivariate models. When we excluded TMD\textsubscript{pre} and
TMD\textsubscript{post} from the beginning, then the final surviving descriptors were TCRT, TMD, P-QTd and QTc\textsubscript{interval}. In both cases, TCRT outperformed all of the others in all orders of multiple regression.

The most significant descriptors identified by the above multiple regression analysis were used in multivariate ROC curve analysis. Multivariate ROC curves are similar to the univariate ones, but the decision (normal vs. HCM in this case) is given based on more than one descriptor. We assessed the simultaneous performance of the best performing two new descriptors (TCRT and TMD\textsubscript{pre}) and of the best two conventional descriptors (P-QTd and QTc\textsubscript{interval}) separately. The ROC areas obtained were: TCRT\&TMD\textsubscript{pre}(1) : 0.955, TCRT\&TMD\textsubscript{pre}(2) : 0.918, P-QTd\&QTc\textsubscript{Int}(1) : 0.916, P-QTd\&QTc\textsubscript{Int}(2) : 0.872 (The numbers in brackets indicate the number of required positive -HCM- prediction by the descriptors used, for the final positive decision. For example, in a 2 variable model, (1) means at least 1 of 2 descriptors are required to predict positive for a final positive decision). Figure 3.15 shows these curves.

We also used all four of these descriptors in a single model and computed the ROC curves for different decision criteria. Figure 3.16 shows these curves. The multivariate model involved TCRT, TMD\textsubscript{pre}, P-QTd and QTc\textsubscript{Interval}. The areas calculated for each ROC curve (one for each decision rule: 1 of 4, 2 of 4, 3 of 4 and 4 of 4) were 0.984, 0.984, 0.974, 0.932 respectively.

Secondly, we used the measured values of the descriptors in multiple regression analysis. Table 3.7 summarizes these results in the same format as in Table 3.6. Three descriptors survived at the end of multiple regression. PO survived until the last step and had a rather low p-value. So we decided to include PO in the final set of selected descriptors. Figure 3.17 shows the bi-variate ROC curves for the surviving new descriptors. (The areas under these ROC curves are: PO\&TCRT(1) : 0.925, PO\&TCRT(2) : 0.910). These four descriptors selected were also used in a four variable multi-variate ROC curve analysis. Figure 3.18 shows these four variable curves (The areas under these ROC curves are:
### Table 3.6: P-values at different levels of multivariate regression analysis of a priori classification of normal and HCM groups with respect to the mean values of the descriptors

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>P-Values in Multiple Regression Models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Order=16</td>
</tr>
<tr>
<td>( TMD )</td>
<td>0.769</td>
</tr>
<tr>
<td>( TMD_{pre} )</td>
<td>0.272</td>
</tr>
<tr>
<td>( TMD_{post} )</td>
<td>0.037</td>
</tr>
<tr>
<td>( TCRT )</td>
<td>( 1.45 \times 10^{-7} )</td>
</tr>
<tr>
<td>( PL )</td>
<td>0.880</td>
</tr>
<tr>
<td>( PO )</td>
<td>0.563</td>
</tr>
<tr>
<td>( LD_1 )</td>
<td>0.378</td>
</tr>
<tr>
<td>( LD_2 )</td>
<td>0.758</td>
</tr>
<tr>
<td>( G-QTd )</td>
<td>0.335</td>
</tr>
<tr>
<td>( P-QTd )</td>
<td>0.016</td>
</tr>
<tr>
<td>( A-QTd )</td>
<td>0.658</td>
</tr>
<tr>
<td>( G-JTd_1 )</td>
<td>0.092</td>
</tr>
<tr>
<td>( PCA_1 )</td>
<td>0.628</td>
</tr>
<tr>
<td>( PCA_2 )</td>
<td>0.397</td>
</tr>
<tr>
<td>( PCA_3 )</td>
<td>0.352</td>
</tr>
<tr>
<td>( QTc_{Interval} )</td>
<td>( 6.06 \times 10^{-5} )</td>
</tr>
</tbody>
</table>

Table 3.6: P-values at different levels of multivariate regression analysis of a priori classification of normal and HCM groups with respect to the mean values of the descriptors

![Figure 3.15: Bi-variate (selected by the multiple regression analysis of the a priori classification results of the descriptors) ROC curves. The numbers in brackets in the legend indicate the minimum number of positive (abnormal) predictions for final positive decision](image-url)
Table 3.7: P-values of conventional and new descriptors at different levels of multivariate regression analysis performed using the measured values of the descriptors

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Order=16</th>
<th>Order=10</th>
<th>Order=9</th>
<th>Order=4</th>
<th>Order=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMD</td>
<td>0.759</td>
<td>0.151</td>
<td>0.129</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TMD_{post}</td>
<td>0.732</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TMD_{pre}</td>
<td>0.568</td>
<td>0.219</td>
<td>0.194</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TCRT</td>
<td>1.37 × 10^{-7}</td>
<td>7.81 × 10^{-9}</td>
<td>7.89 × 10^{-9}</td>
<td>1.21 × 10^{-11}</td>
<td>4.95 × 10^{-13}</td>
</tr>
<tr>
<td>PL</td>
<td>0.989</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PO</td>
<td>0.736</td>
<td>0.138</td>
<td>0.093</td>
<td>0.012</td>
<td>-</td>
</tr>
<tr>
<td>LD_{1}</td>
<td>0.551</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LD_{2}</td>
<td>0.298</td>
<td>0.194</td>
<td>0.229</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G-QTd</td>
<td>0.905</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P-QTd</td>
<td>0.175</td>
<td>0.058</td>
<td>0.068</td>
<td>9.86 × 10^{-5}</td>
<td>1.39 × 10^{-4}</td>
</tr>
<tr>
<td>A-QTd</td>
<td>0.883</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G-JTd</td>
<td>0.325</td>
<td>0.418</td>
<td>0.483</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PCA_{1}</td>
<td>0.492</td>
<td>0.567</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PCA_{2}</td>
<td>0.192</td>
<td>0.139</td>
<td>0.005</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PCA_{3}</td>
<td>0.687</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>QTc_Interval</td>
<td>2.39 × 10^{-5}</td>
<td>1.47 × 10^{-5}</td>
<td>6.07 × 10^{-6}</td>
<td>1.49 × 10^{-6}</td>
<td>3.50 × 10^{-6}</td>
</tr>
</tbody>
</table>

3.5.7 Analysis of ECGs Recorded In Standing Position

Among many sources of noise during ECG recording, recording during standing position is unique because ECGs recorded in standing position have a clinical value. The circulatory system is a loop through which the blood is circulated by the pumping power of heart. More power is needed in standing position due to the gravitational force that must be overcome, which is not present in supine position. This change of load on the heart affects its behaviour through a feedback system which in turn is reflected onto the recorded ECG. However, as stated above, standing position is a source of noise as well
Figure 3.16: Four-variable (selected by the multiple regression analysis of the a priori classification results of the descriptors) ROC curves. The numbers in brackets in the legend indicate the minimum number of positive (abnormal) predictions for final positive decision.

Figure 3.17: Bi-variable (selected by the multiple regression analysis of the measured values of the descriptors) ROC curves. The numbers in brackets in the legend indicate the minimum number of positive (abnormal) predictions for final positive decision.
because the body cannot stand still, various muscles work to keep the body in balance.

Although ECG analysis in standing position is not a primary concern, it's worth assessing the performance of our method under such a condition. For this purpose, we used a set of normal and HCM subjects as reported in Section 3.5.1. We assessed the discrimination of these two groups via the mean and the standard deviation of the measured descriptors. Table 3.8 summarizes the results. The reproducibility was assessed as described in Section 3.5.3. Table 3.9 summarizes the reproducibility assessment results as the mean and standard deviation of the ratio of individual range to the total range (see Section 3.5.3 for the definition). Table 3.10 gives the p-values computed by non-parametric Wilcoxon paired test. Lower the p-value between two descriptors is, the more significant the difference in their reproducibilities. It is observed that any substantial difference in the mean reproducibility is accompanied by a low p-value.

These results show some degradation in the performance of all parameters. However, the new parameters still perform better than the conventional ones except $PL$, $PO$ and $LD_1$, which performed poorly also in the supine case. However, although $LD_2$'s
Table 3.8: Discrimination between normal and HCM subjects using the ECGs recorded in standing position

Performance is much higher in standing position than in supine. Our observation of better reproducibilities of the new descriptors in the HCM group than in the normal group, in supine case (Section 3.5.3), is repeated in standing case, too. This strengthens our point that the new descriptors have an increased sensitivity to abnormal ECGs.

### 3.5.8 Mean Values Of T Wave Descriptors In DCM Subjects

Having performed various analysis on the normal and HCM subjects, we proceeded to check the descriptors on a set of DCM subjects. The data set was defined in Section 3.5.1. The average of the 10 consecutive measurements is used of each subject. Table 3.11 summarizes the results.
Table 3.9: Short-term reproducibility of the conventional and new descriptors in standing position assessed via the ratio of individual range to the total range of measured values. 10 consecutive measurements from each subject are used.

When these results are compared with the average values in normal subjects and in HCM patients (Tables 3.3 and 3.5), a similar behaviour of the descriptors is observed. $TMD$, $TMD_{post}$ and $TMD_{pre}$ increased, $TCRT$ is negative, $PL$ decreased with an increase in $PO$, $LD_2$ decreased and finally $LD_1$ did not differ. This shows that the new descriptors are potentially capable of discriminating the DCM subjects from the normal subjects.
Table 3.10: P-values computed by non-parametric Wilcoxon Paired Test, showing the significance of the difference between the reproducibilities of the new and the conventional descriptors in normal and HCM groups, in standing position.
3.6 DISCUSSION

3.6.1 Interpretation of the Results

The new descriptors proposed in this study are defined using the decomposition space and aimed at the description of the temporal and spatial variation of ventricular repolarization. The descriptors $TMD$, $TMD_{pre}$ and $TMD_{post}$ reflect the inter-lead morphological variations of the T wave patterns, that is the spatial variations. The T loop related descriptors, which are $PL$, $PO$, $LD_1$ and $LD_2$, characterize the temporal variations. Finally, $TCRT$ uses the concept of comparing the global wavefront directions of the depolarization and repolarization processes.

Our original hypothesis was that, compared to normal ECGs, the spatial and temporal variation of the T wave morphology are increased and the depolarization and the repolarization vectors differ more in pathological recordings, such as HCM and DCM patients.

The mean of $PL$ is higher and $PO$ is lower in normal than in pathological cases. This suggests that the T loop is relatively smooth and connected (not crossing itself) in

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>DCM $\text{Mean } \pm \text{STD}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$TMD$</td>
<td>$(43.834 \pm 26.599)^\circ$</td>
</tr>
<tr>
<td>$TMD_{post}$</td>
<td>$(39.743 \pm 28.183)^\circ$</td>
</tr>
<tr>
<td>$TMD_{pre}$</td>
<td>$(45.103 \pm 32.596)^\circ$</td>
</tr>
<tr>
<td>$TCRT$</td>
<td>$(-0.348 \pm 0.622)^\circ$</td>
</tr>
<tr>
<td>$PL$</td>
<td>$0.589 \pm 0.149$</td>
</tr>
<tr>
<td>$PO$</td>
<td>$0.344 \pm 0.119$</td>
</tr>
<tr>
<td>$LD_1$</td>
<td>$35.016 \pm 3.355$</td>
</tr>
<tr>
<td>$LD_2$</td>
<td>$584.608 \pm 315.363$</td>
</tr>
</tbody>
</table>

Table 3.11: The average values of the new T wave descriptors in DCM subjects
normal subjects. On the other hand, despite the significant difference (low p-value), the lead dispersion parameters $LD_1$ and $LD_2$ have similar mean values for both the normal and pathological cases. This suggests that the loop itself is not discriminative. The loop lengths were similar in all groups. The discrimination provided by $PL$ and $PO$ seems to be due to the disconnected and narrow loop (inner area is similar to a strip), rather than due to an increased irregularity of its shape. However, there are several problems concerning the methodology regarding these parameters. These will be discussed in Section 3.6.3.

The change of sign in $TCRT$ between the normal and pathological cases provides a clear distinction between the two groups. The negativity of $TCRT$ shows an increased deviation in the major axis of the QRS and the T loops. This is in agreement with our original hypothesis. The repolarization and the depolarization waves do differ in terms of their principal direction in 3D time-orthogonal space. The mean difference between the two cases is $52^\circ$. This shows that $TCRT$ does not merely reflect T wave inversion that would result in a difference near to $180^\circ$.

The increased dispersion in the reconstruction vectors of standard channels in pathological cases is reflected in $TMD, TMD_{pre}$ and $TMD_{post}$. This shows an increase in the spatial morphology variation of the T wave which is also in agreement with our original hypothesis.

$TCRT, TMD_{pre}, P-QTd$ and $QTc_{Interval}$ were the only descriptors that survived throughout the backward stepwise multiple regression analysis performed using the a priori classification. On the other hand, $PO$ replaced $TMD_{pre}$ in the multiple regression analysis performed using the measured values of the descriptors. In both cases, $TCRT$ was by far the best performing descriptor throughout the test (see Tables 3.6 and 3.7).

When we compare the bivariate ROC curve areas, we see that the combinations of new descriptors are always superior to those of the best conventional ones. When we consider the four variable ROC curves, we see that the second cases (decision rule : 2
of 4) is better than the other in both of the four variable ROC curves. Considering
that the bivariate ROC curves of the new descriptors have larger areas than those of the
conventional ones, we can conclude that inclusion of the conventional descriptors in the
multivariate model, degraded the performance of the model.

These observations show that the new spatial and temporal variation descriptors and
the TCRT are very potent descriptors of ventricular repolarization abnormalities.

3.6.2 Relation to Previous Methods

All of the new descriptors are defined using the decomposition space. This provides an
inherent noise immunity. Since the new methods do not depend on accurate time domain
measurements, the inaccuracies associated with time domain measurements, which are
common in QT interval related parameters, are avoided. This independence of time
domain measurements makes the new descriptors highly reproducible, which is very
important for their potential clinical applicability. Among the conventional parameters,
only PCA based parameters have a reproducibility in the same order as the new ones'.

The weak correlation between the new and the conventional parameters shows that
the new concepts quantify different properties of the ventricular repolarization. The
concept of TCRT is different from both spatial and temporal variations and the descriptor
does not correlate strongly with any other descriptor.

3.6.3 Limitations

The relatively poorer reproducibility of the T loop area related parameters is due to
the algorithmic problems. An open loop may result from baseline wander, as well as
ST-segment elevation/depression. We used a straight line to connect the ends of the
loop, which is not necessarily the best approach. An alternative may be to connect the
ends of the loop and its centre of gravity or to transform the \( \mathbf{u}_1, \mathbf{u}_2 - plane \) creating a closed loop. It is also possible that the loop crosses itself, resulting in more than one closed area. We named such loops as the disconnected loops. In this study, we defined the inner area as the closed area neighbouring the beginning of the loop. The other closed areas are called the pockets and were ignored. It is an open question whether the existence and/or the area of these pockets is of any significance. The poor performance of the loop related descriptors in differentiating normal and abnormal ECGs may well be due to these problems.

The arbitrary choice of constants, used in dividing the plane of ECG into equal size cells, have an influence on \( LD_1, LD_2, PL \) and \( PO \) calculations as well as on approximate T wave offset detection. These constants define the precision of these descriptors. Increasing these constants would increase the precision at the cost of increased computation time. However, the precision is also restricted by the ECG sampling rate which determines (in no exact fashion) the smallest distance between two consecutive ECG vectors. Unreasonably decreased cell size (increased constants) would also degrade the performance of the T wave offset detection because then the ECG vector would not stay in a cell for a significantly long time and thus the detection of its stationarity would be difficult.

On the other hand, the T wave onset/offset definitions may have an influence on the temporal variation descriptors but do not affect the others. Setting the constant \( \mu \) to 3 in the threshold definition in the T wave offset detection is an appropriate choice. As explained in Section 3.3.2, the algorithm readjusts \( \mu \) (see Equation 3.23) in case of failed T offset detection. Such a readjustment was done in 91 of 1100 normal ECGs. The QRS onset/offset definitions on the other hand, are robust and able to handle wide QRS complexes. However, the choice of 70% threshold in determining the region of QRS used \( ([t'_{RS}, t'_{RE}] \) in TCRT calculation is critical. A too low threshold may result in a too general estimation of the QRS loop orientation, whereas a high threshold may
misinterpret the orientation of the depolarization wavefront vector.

We used the principal direction of the ECG vector during T wave, $e_{T,1}$, in TCRT calculation. Subsequently, the unit vector $e_{T,2}$ perpendicular to $e_{T,1}$ and $e_{T,3}$ perpendicular to both $e_{T,1}$ and $e_{T,2}$ were determined graphically and approximately. We ignored these lower energy components in TCRT calculation. The average ratio of the energy along the second component to that of the first was 0.14 for normals and 0.22 for HCM patients. This shows that the T loop generally resembles a narrow ellipsoid even in the HCM case and we are interested in the direction of this loop. Using $e_{T,2}$ and/or $e_{T,3}$ would not improve the concept of TCRT, mainly due to a decreased noise immunity. There is no ambiguity in the $e_{T,1}$ definition because the DC-compensation ensures that $e_{T,1}$ has the correct sign.

Since the descriptors except $TMD$, $TMD_{pre}$ and $TMD_{post}$, attempt to quantify some geometrical properties of the QRS and the T loops in relation with each other, the T plane determination was done geometrically. The left singular vectors would correspond to the principal axis ordered with respect to the corresponding singular values, i.e. their dominance. However, if we want to use the left singular vectors as they are as the major and the minor axis, the QRS complex and the T wave must be decomposed independently and the comparison of the left singular vectors must be done in a common space, say in the original eight dimensional ECG space for TCRT. The graphical definitions in our method are totally satisfying as the analysis results show.

A similar problem exists in the determination of the plane of the T loop, which is used in the computations of $PL$, $PO$ and $LD_2$. The present algorithm assumes that the T loop is planar. The basis vectors of the T loop plane are determined graphically in the optimum 3D space spanned by the most significant three left singular vectors of the SVD of the whole beat. A more proper way to determine the optimum 2D space for the T loop is to decompose the T wave on its own by SVD and to use the two most significant left singular vectors. This approach removes the planarity assumption, but
changes the definition of $PL$, $PO$, $LD_2$ also because thus we would have eliminated the effect of QRS complex on these descriptors. This approach will be discussed in more detail in Section 3.8.

3.7 A 2-WAY BLIND STUDY ON AMI GROUP

An important goal of non-invasive ECG analysis is risk stratification of patients prone to sudden cardiac death. Ventricular repolarization analysis is an important tool for non-invasive risk stratification because an abnormal sequence of ventricular repolarization may play a causal role in the genesis of malignant ventricular arrhythmias. Multi-electrode body surface potential mapping could identify abnormal repolarization processes and thus indicate arrhythmogenic substrate. However, body-surface potential mapping is not a practical method. So, much attempt has been done to do ventricular repolarization analysis using standard 12 lead ECG. QT analysis has been the most common method for this, supported by various, mostly retrospective, studies that reported high prognostic utility. However, a recent prospective study failed to confirm the earlier results [89].

We evaluated the prognostic value of the new ventricular repolarization descriptors in a prospectively enrolled cohort of post myocardial infarction patients, the same population used by Markus Zabel [89]. A two-way blind study was performed [90,91]. Dr. Zabel sent us the ECG signals without any information about the patients and we sent him the measurement results without any information on the definition of the descriptors, even the names of the descriptors were different.
3.7.1 Data Set

The population consisted of 280 post myocardial infarction patients (229 male; age $58\pm11$). The patients were enrolled 6-30 days ($9 \pm 3$ days) after the infarction. 12 lead resting ECGs were recorded with a paper speed of 50mm/sec. These printed ECG recordings were digitized by scanning and editing the image file and sampling at 1kHz by a custom written Labview program [89]. 19 of the ECG records were excluded by the cardiologist due to signal loss or very low SNR.

3.7.2 ECG Analysis

We first performed a supervised pre-processing of the ECG data by means of a custom written Matlab program. The preprocessing involved of time aligning the single beats used on all 12 standard leads, cropping the beats so that no part of a second beat is present in each data file. The alignment was done based on the energy of the QRS complex and was supervised continuously by an expert cardiologist (Dr. Johan E. Waktare from St. George’s Hospital Medical School, London, UK).

The following ventricular repolarization descriptors were computed on each ECG: $TCRT$, $TMD$, $PL$, $LD_1$ and $CR_1$ (as described in Section 3.1.3).

3.7.3 Statistical Analysis

The statistical evaluation is done by Dr. Markus Zabel (Free University of Berlin, Berlin, Germany) independently. The following conventional descriptors were considered: $QRS$ width, $G-QT_d$, $JT_d$ ($J$ to $T$ offset dispersion), $T$ peak to $T$ offset interval, $Area$ under the $T$ wave, $SDNN$ from Holter recordings (Holter recordings are day long ECG recordings) (see Section 2.1), $LVEF$ (left ventricular ejection fraction). The following clinical variables were also considered: Age, reperfusion therapy, beta blocker treatment, heart
rate, gender. All these parameters are exactly the same as the ones used in [89].

During a follow-up of 32 ± 10 months, 20 patients died (10 due to sudden cardiac death, 5 due to pump failure, 5 due to non-cardiac causes). Sustained ventricular tachycardia (VT) was seen in 5 patients. 2 patients were resuscitated from ventricular fibrillation (VF). These constitute the patients who reached primary end point (27 of 261 patients). 17 patients reached secondary endpoint (arrhythmic events). Note that the two sets intersect. A strong correlation was observed between the $TCRT$ and Left Branch Bundle Block (LBBB) cases, so the statistical analysis were performed once on the complete population (261 subjects) and once after excluding the LBBB cases (252 subjects) to remove any possible bias.

**Correlations with conventional descriptors and clinical variables**

Pearson's product linear correlation coefficients were determined to check the correspondence between different descriptors.

All of the correlation coefficients ($r$-value) among the new descriptors were below 0.25 and were of no clinical relevance. The correlation between $TCRT$ and $LD_2$ was especially low ($r-value = 0.11$, $p-value > 0.05$). None of the continuous clinical variables were related the new descriptors. This was also true for SDNN and LVEF. $TCRT$ was influenced by LBBB (Average $TCRT$ in LBBB cases = $-0.77 \pm 0.25$ . Average $TCRT$ in non-LBBB cases = $0.11 \pm 0.12$). None of the other new descriptors were influenced by LBBB.

A relatively high correlation was observed between the average area under the T wave and $CR1$ ($r-value = -0.40$, $p-value < 0.001$).

All other correlation coefficients were also irrelevant and below 0.25. This is in agreement with our previous results that show no relation between the new and the conventional descriptors (see Section 3.5.2).
Table 3.12: T wave descriptors in patients with and without primary endpoints during follow-up

Univariate analysis of new descriptors

Table 3.12 gives the mean and the standard deviation of the ventricular repolarization descriptors in two groups: The patients who have reached the primary endpoints and the event-free cases. Table 3.13 provides the same analysis results for the groups with and without arrhythmic events (secondary endpoint).

These results show that $TCRT$ and $LD_1$ can differentiate between the event positive and event negative patients in case of both primary and secondary endpoints. It is observed that negative $TCRT$ value and low $LD_1$ value predicts the event positive patients. $TMD$ could not differentiate the two groups in both cases and $PL$ provided a borderline discrimination in some cases. A paradoxical result that we observed is that $CR1$ (a complexity ratio derived from PCA analysis) exhibited lower values in the event positive groups in both cases. Although the discrimination, thus obtained, is either not significant or has a borderline significance, this result contradicts with the previously
Table 3.13: T wave descriptors in patients with and without secondary endpoints during follow-up

reported results in the literature.

**Kaplan-Meier event probabilities of the new descriptors [92]**

Kaplan-Meier curves summarize the survival of patients during the follow-up. The x-axis is the time axis that spans the follow-up period. The y-axis is the percentage of the patients that survived (that still live). Curves of two groups, separated with respect to the descriptor's value, are plotted on the same graphic. A clear, consistent and increasing separation between the curves show that the descriptor is capable of identifying the patients that would/would not survive in time. In other words, these curves give the probability of the occurrence of a given event in a given group at a given time.

This analysis was performed for TCRT and $LD_1$. The two groups, in each case, were formed with respect to the median value of the corresponding descriptor (0.158
Figure 3.19: Kaplan-Meier survival curves of two groups separated with respect to TCRT values in the AMI group. Reprinted from [91]

For TCRT and 37 for LD₁. Figures 3.19 and 3.20 show these curves (Reprinted with permission from Dr. Markus Zabel from Free University of Berlin, Berlin, Germany).

These curves show that TCRT and LD₁ can identify the patients that would survive in time with high significance, \( p - value < 0.003 \) for TCRT and \( p - value < 0.001 \) for LD₁. These results were not affected by excluding or including the LBBB patients. A significant separation was also observed in the prediction of arrhythmic events (secondary endpoint) by these two descriptors. The other three descriptors \( \{CR₁, TMD, PL\} \) did not result in different event probabilities.

**Multivariate analysis**

Multivariate analysis was performed using backward stepwise multivariable Cox regression analysis. A set of descriptors were entered as independent variables and at each step the least significant descriptor is excluded.

At first, all clinical variables, SDNN and TCRT and LD₁ were included. Table 3.14 shows the final descriptors in the case of predicting the primary endpoints. Table 3.15
3.7.4 Discussion

The above described analysis showed that even the PCA descriptor $CR_1$ did not show a significant discrimination, although it uses the dominant components of the T wave, as we do. More importantly, in this specific patient population we observed a paradoxical relationship between the abnormality of T wave and $CR_1$. $CR_1$ decreased in high risk group.
<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Cox Regression</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All (n=261)</td>
<td>Excluding LBBB (n=252)</td>
</tr>
<tr>
<td>Reperfusion Therapy</td>
<td>0.014</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.016</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>0.017</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>TCRT</td>
<td>0.025</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LD₁</td>
<td>0.064</td>
<td>0.024</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.14: The final p-values of the surviving descriptors in a backward stepwise Cox regression analysis, into which all univariately predictive clinical, Holter and T wave morphology descriptors were included initially and in which the goal was to predict the primary endpoints.

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Cox Regression</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All (n=261)</td>
<td>Excluding LBBB (n=252)</td>
</tr>
<tr>
<td>Reperfusion Therapy</td>
<td>0.012</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.010</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>0.056</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LD₁</td>
<td>0.008</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.15: The final p-values of the surviving descriptors in a backward stepwise Cox regression analysis, into which all univariately predictive clinical, Holter and T wave morphology descriptors were included initially and in which the goal was to predict the secondary endpoints.
The importance of this study lies in the fact that we have shown that at least one of the new ventricular repolarization ($T_{CRT}$ and $LD_1$) descriptors is an independent and strong risk stratifier in a population of post MI patients, in which the conventional descriptors were shown to provide no prognostic post MI information [89]. Thus, this study establishes the advantages of our technique over the conventional ones in an objective manner.

This study also verified our previous findings that the new descriptors do not correlate with the conventional ones and thus assess different qualities of the ventricular repolarization process. This is somewhat in contradiction with Kors et al.'s results in which he showed a correlation between QT dispersion and T wave loop morphology [93].

We observed that $T_{CRT}$ is closely linked to the occurrence of LBBB, however, it proved to be a strong risk predictor in both cases, including or excluding the LBBB patients.

The basic drawback of this study is that although the size of this study was large enough to demonstrate the accuracy of the new descriptors, it was not large enough to assess the use of these variables in more strictly defined sub-categories.

### 3.8 UPGRADE ON TEMPORAL ANALYSIS

The method that was explained in Section 3.3.3 for the calculation of temporal variation descriptors $PL$, $PO$ and $LD_2$ uses the decomposition of the complete beat. This approach requires the determination of the major and minor axis ($e_{T,1}$, $e_{T,2}$) of the T loop graphically. The determination of $e_{T,1}$ is rather easy. We just look for the furthest away point of the loop to determine its direction. However the determination of $e_{T,2}$ is problematic. There is an a priori assumption that the T loop is planar in the detection of $e_{T,2}$. 
In this section, we will remove this assumption, recalculate $PL$, $PO$ and $LD_2$ and provide the statistical analysis results of the upgraded descriptors.

$LD_1$ was not considered because it, by definition, uses the 2D dominant subspace of the whole beat. This upgrade is also unrelated to the other descriptors.

### 3.8.1 Method

As an upgrade, we performed a SVD on the approximately detected T wave section and used the first and the second left singular vectors in place of $e_{T,1}$ and $e_{T,2}$ respectively, in the computation of $PL$, $PO$ and $LD_2$. Thus the optimum 2D subspace for the T loop was determined, however there is also a more major difference between the two versions of these descriptors. The new versions are free from the influence of the QRS complex because we use the independent decomposition of the T wave in this upgraded version. The rest of the definitions are the same as described in Section 3.3.3.

### 3.8.2 Analysis

The statistical analysis of the upgraded versions of $PL$, $PO$ and $LD_2$ were performed on the same data sets described in Section 3.5.1 and in the same way as described in Section 3.5.

**Normal Ranges**

1100 ECGs recorded from normal subjects were analyzed with the new method and the descriptors $PL_{new}$, $PO_{new}$ and $LD_{2,new}$ were calculated. These results were used to determine the normal ranges of the upgraded descriptors and their correlations with the first versions of the same descriptors. Table 3.16 summarizes the mean values and standard deviations of the upgraded descriptors in the normal population. Thus they define the normal ranges. Table 3.16 also gives the Pearson Product-Moment Correlation
<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Normal Population (n=1100)</th>
<th>Correlation Coef. Version 1 vs. Version 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± STD</td>
<td></td>
</tr>
<tr>
<td><em>PL</em>.<em>new</em></td>
<td>0.596 ± 0.153</td>
<td>0.772</td>
</tr>
<tr>
<td><em>PO</em>.<em>new</em></td>
<td>0.337 ± 0.131</td>
<td>0.854</td>
</tr>
<tr>
<td><em>LD</em>2.<em>new</em></td>
<td>779.701 ± 361.970</td>
<td>0.868</td>
</tr>
</tbody>
</table>

Table 3.16: Normal ranges of *PL*.*new*, *PO*.*new* and *LD*2.*new* and the correspondence between the two versions

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Individual Range / Total Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Range</td>
</tr>
<tr>
<td></td>
<td>Mean ± STD</td>
</tr>
<tr>
<td><em>PL</em>.<em>new</em></td>
<td>0.097 ± 0.068</td>
</tr>
<tr>
<td><em>PO</em>.<em>new</em></td>
<td>0.103 ± 0.071</td>
</tr>
<tr>
<td><em>LD</em>2.<em>new</em></td>
<td>0.066 ± 0.059</td>
</tr>
</tbody>
</table>

Table 3.17: Short-term reproducibility of *PL*.*new*, *PO*.*new* and *LD*2.*new* in 10 consecutive recordings from normal and HCM subjects

coefficients between the two versions of *PL*, *PO* and *LD*2.

A comparison of Table 3.16 with the Table 3.3 shows that the upgraded descriptors are quite in agreement with the first versions of the same descriptors. This observation is also verified by the rather high correlation between the two versions of the same descriptors.

**Short-Term Reproducibility**

Short-term reproducibility of the upgraded descriptors was assessed via the variation of each descriptor within 10 consecutive ECG recordings from the same object. The reproducibility measure is the ratio of the individual range to the total range, exactly as described in Section 3.5.3. Table 3.17 summarizes the results.

When we compare these results with the ones shown in Figure 3.13, it is seen that
Table 3.18: Correspondence between the conventional ventricular repolarization descriptors and $PL_{new}, PO_{new}$ and $LD_{2,new}$

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>$PL_{new}$</th>
<th>$PO_{new}$</th>
<th>$LD_{2,new}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G - QTd$</td>
<td>0.042</td>
<td>-0.017</td>
<td>-0.099</td>
</tr>
<tr>
<td>$P - QTd$</td>
<td>0.021</td>
<td>0.015</td>
<td>-0.196</td>
</tr>
<tr>
<td>$A - QTd$</td>
<td>0.066</td>
<td>-0.037</td>
<td>-0.162</td>
</tr>
<tr>
<td>$G - JTpd$</td>
<td>0.237</td>
<td>-0.223</td>
<td>-0.518</td>
</tr>
<tr>
<td>$PCA_1$</td>
<td>-0.001</td>
<td>0.033</td>
<td>-0.346</td>
</tr>
<tr>
<td>$PCA_2$</td>
<td>0.009</td>
<td>-0.008</td>
<td>-0.653</td>
</tr>
<tr>
<td>$PCA_3$</td>
<td>-0.110</td>
<td>0.103</td>
<td>-0.228</td>
</tr>
<tr>
<td>$QTc_Interval$</td>
<td>-0.149</td>
<td>0.146</td>
<td>-0.015</td>
</tr>
<tr>
<td>$Age$</td>
<td>0.005</td>
<td>-0.023</td>
<td>0.086</td>
</tr>
</tbody>
</table>

The reproducibilities of $PL$ and $PO$ were improved slightly, whereas $LD_2$ was affected slightly in the reverse way.

**Correspondence With Conventional Descriptors**

The correspondence between the $PL_{new}, PO_{new}$ and $LD_{2,new}$ and the conventional descriptors and the age of the subjects was assessed via the Pearson Product-Moment correlation coefficient. Table 3.18 summarizes the results.

A comparison of Table 3.18 with Table 3.1 shows that the correspondence between the upgraded descriptors and the conventional descriptors are similar to those of the first versions of the same descriptors. As in the previous case, $LD_2$ is somewhat correlated with $G - JTpd$ and $PCA$ parameters.

**Univariate Analysis - Normal vs. HCM**

A univariate analysis was performed to assess the power of the upgraded descriptors in discriminating the normal and the HCM subjects. The analysis composed of calculating the mean and the standard deviation of each descriptor in both groups, performing a Mann-Whitney U-Test and calculating the area under the univariate ROC curves.
Table 3.19: Univariate comparison of PL new, PO new and LD2 new on the basis of discriminating normal and HCM subjects

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Normal n=76</th>
<th>HCM n=63</th>
<th>Mann-Whitney Test</th>
<th>Area under ROC curves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± STD</td>
<td>Mean ± STD</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL new</td>
<td>0.621 ± 0.107</td>
<td>0.584 ± 0.159</td>
<td>0.407 (NS)</td>
<td>0.549</td>
</tr>
<tr>
<td>PO new</td>
<td>0.326 ± 0.102</td>
<td>0.348 ± 0.120</td>
<td>0.359 (NS)</td>
<td>0.553</td>
</tr>
<tr>
<td>LD2 new</td>
<td>642.647 ± 244.716</td>
<td>531.743 ± 353.276</td>
<td>4.02 × 10⁻⁵</td>
<td>0.708</td>
</tr>
</tbody>
</table>

Figure 3.21: Univariate ROC curves of the upgraded new descriptors

The analysis was done in exactly the same as described in Section 3.5.5. Table 3.19 summarizes the results. Figure 3.21 shows the univariate ROC curves of the upgraded descriptors.

When we compare Table 3.19 with Table 3.5, we see that although the relative mean values of the descriptors did not change much in normal and HCM groups, PL new and PO new are not a significant separator of the two groups. This observation is supported by the decrease in the ROC curve areas of these descriptors also. On the other hand, LD2 new performed slightly better than its first version.
Table 3.20: P-values of conventional and new descriptors at different levels of multivariate regression analysis (performed on the a priori classification results) with $PL_{new}$, $PO_{new}$ and $LD_z_{new}$

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Order=16</th>
<th>Order=10</th>
<th>Order=9</th>
<th>Order=8</th>
<th>Order=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>$TMD$</td>
<td>0.621</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$TMD_{post}$</td>
<td>0.782</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$TMD_{pre}$</td>
<td>0.133</td>
<td>0.074</td>
<td>0.027</td>
<td>0.026</td>
<td>0.006</td>
</tr>
<tr>
<td>$TCRT$</td>
<td>$3.69 \times 10^{-10}$</td>
<td>$2.90 \times 10^{-11}$</td>
<td>$1.83 \times 10^{-11}$</td>
<td>$2.06 \times 10^{-11}$</td>
<td>$4.21 \times 10^{-11}$</td>
</tr>
<tr>
<td>$PL_{new}$</td>
<td>0.261</td>
<td>0.100</td>
<td>0.055</td>
<td>0.035</td>
<td>-</td>
</tr>
<tr>
<td>$PO_{new}$</td>
<td>0.636</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$LD_1$</td>
<td>0.469</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$LD_2_{new}$</td>
<td>0.383</td>
<td>0.422</td>
<td>0.432</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$G-QTd$</td>
<td>0.290</td>
<td>0.096</td>
<td>0.120</td>
<td>0.110</td>
<td>-</td>
</tr>
<tr>
<td>$P-QTd$</td>
<td>0.025</td>
<td>0.011</td>
<td>0.010</td>
<td>0.012</td>
<td>$2.68 \times 10^{-4}$</td>
</tr>
<tr>
<td>$A-QTd$</td>
<td>0.727</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$G-JTpd$</td>
<td>0.337</td>
<td>0.325</td>
<td>0.373</td>
<td>0.254</td>
<td>-</td>
</tr>
<tr>
<td>$PCA_1$</td>
<td>0.572</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$PCA_2$</td>
<td>0.164</td>
<td>0.028</td>
<td>0.015</td>
<td>0.021</td>
<td>-</td>
</tr>
<tr>
<td>$PCA_3$</td>
<td>0.501</td>
<td>0.428</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$QTc Interval$</td>
<td>$5.08 \times 10^{-5}$</td>
<td>$3.63 \times 10^{-5}$</td>
<td>$2.25 \times 10^{-5}$</td>
<td>$2.18 \times 10^{-5}$</td>
<td>$6.47 \times 10^{-6}$</td>
</tr>
</tbody>
</table>

Multivariate Analysis - Normal vs. HCM

Backward stepwise multiple regression analysis was performed on the new and conventional descriptors after replacing the $PL$, $PO$ and $LD_2$ with their new versions. The analysis was performed in exactly the same way as described in Section 3.5.6 and on the same data set. Table 3.20 gives the p-values of the surviving descriptors at several steps of backward stepwise multiple regression analysis when the a priori classification of the patients with respect to the mean values of the descriptors is used. Table 3.21 shows the results when the actual measured values were used instead of the a priori classification.

Comparing Table 3.20 with Table 3.6, no significant difference can be seen. The surviving descriptors are the same and their p-values have not changed much. When we compare Tables 3.21 and 3.7, we see that none of $PL_{new}$, $PO_{new}$ or $LD_2_{new}$ could
In any case, TCRT remained to be superior to all other descriptors.

**Discrimination of DCM Subjects**

We also assessed the discrimination power of $PL_{\text{new}}$, $PO_{\text{new}}$ and $LD_2_{\text{new}}$ on the DCM population. Table 3.22 summarizes the mean values and the standard deviations of the three descriptors in DCM population.

Comparing the values in Table 3.22 with the ones in Table 3.11, it is observed that the mean values did not differ much between the two versions.
<table>
<thead>
<tr>
<th>Descriptors</th>
<th>DCM Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± STD</td>
</tr>
<tr>
<td>$PL_{\text{new}}$</td>
<td>0.554 ± 0.174</td>
</tr>
<tr>
<td>$PO_{\text{new}}$</td>
<td>0.372 ± 0.135</td>
</tr>
<tr>
<td>$LD_{2\text{new}}$</td>
<td>494.470 ± 196.590</td>
</tr>
</tbody>
</table>

Table 3.22: Mean values and standard deviations of the upgraded $PL_{\text{new}}$, $PO_{\text{new}}$ and $LD_{2\text{new}}$ in DCM population

### 3.8.3 Discussion

The problem with the first version was that we had made an a priori assumption that the T loop was planar. This assumption was used in determining $e_{T,2}$, which is used in $PL$, $PO$ and $LD_2$ computations. The new version removes this assumption, but it also changes the meanings of these descriptors. The QRS complex was a part of the decomposition (thus was affecting these descriptors) in the first version, whereas this effect does not exist in the new version.

The following observations were made by comparing the analysis results of the two versions:

There has neither been a significant change in the mean values of the descriptors in both the normal and HCM groups nor a change in their reproducibilities except some minor improvements in those of $PL$ and $PO$. However, their discrimination capability and significance decreased considerably for $PL$ and $PO$ and increased slightly for $LD_2$. These were assessed by Mann-Whitney U Test and univariate ROC curve analysis.

The multiple regression analysis results on the a priori classifications, showed no significant change in the performance of the descriptors. The surviving descriptors were the same as they were in the first version. The $LD_{2\text{new}}$ survived longer than its first version. The same seems to be true for $PL_{\text{new}}$ also but since there is a strong coupling between $PL_{\text{new}}$ and $PO_{\text{new}}$ and since the first version of $PO$ had survived longer, we
concluded that no difference could be observed in multiple regression analysis of \( PL/PO \) and \( PL_{\text{new}}/PO_{\text{new}} \).

Concerning the multiple regression analysis on the actual measured values, we observed that unlike the first version, \( PO \) could not survive. Other than that, the results were similar to those of the first version.

Comparison of the mean values of the two versions of \( PL, PO \) and \( LD_2 \) in the DCM group showed that the mean values are close in both cases.

As a result of these observations, we can conclude that the new approach did not add to \( PL, PO \) and slightly improved \( LD_2 \). This supports our a priori assumption that the T loop is mainly planar. In light of the other analysis performed, it seems that lead dispersion parameters (\( LD_1 \) and \( LD_2 \)) are the most promising temporal variation descriptors and that \( LD_2 \) should be isolated from the effects of the QRS complex. Conversely, \( PL \) and \( PO \) seem to be descriptors of ventricular repolarization in conjunction with the whole beat. A possible improvement in them should incorporate the QRS complex into the computations and should eliminate the T loop planarity assumption, even though this assumption seems to be valid.

### 3.9 CONCLUSION

We reached at the following conclusions:

- All of the new descriptors can be assessed in a minimum dimensional space constructed by SVD of 12-lead ECG. This provides a built-in immunity to noise.
- None of the new descriptors requires accurate time domain interval measurements. This makes the new parameters more reproducible than the conventional QT interval related descriptors.
The new descriptors assess different ECG qualities than the conventional descriptors. This is evident by their poor correlation with the conventional descriptors.

The spatial variation and the wavefront direction descriptors can discriminate between normal and abnormal ECGs substantially better than the conventional descriptors. TCRT is the strongest of all considered alternatives in this study.

Lead dispersion descriptors, esp. \( LD_1 \), are the most promising temporal variation descriptors.

The performance of the new descriptors in other patient groups must be assessed.

The physiological background of the processes in the heart which are assessed via the new descriptors need to be determined.

The dynamism of the new descriptors (both in short and long term) must be analyzed.

Type of the inter-lead T wave morphology variation may be an indicator of the location and the type of abnormality.
Among several types of ECG analysis, the Heart Rate Variability (HRV) Analysis and the Ventricular Repolarization Analysis are considered in this thesis. Their common features are as follows: i) Both of them are non-invasive methods and use standard 12-lead surface ECG recordings. They have a wide application area. ii) Both are important tools of risk stratification in cardiac patients. These are important features especially when the financial issues are considered, because these methods are low cost to apply and help to decide on the appropriate treatment, which can be rather expensive.

We have reached the following conclusions in the HRV analysis part of this thesis:

◇ The QRS detection and the ectopic beat identification task, which is an important step of HRV analysis, can be done without any manual correction or supervision and without any bias on HRV by using the timing and the morphological information in ECG signal simultaneously.

◇ In addition to the QRS morphology, the P wave morphology and the QRS energy are important qualities of the ECG signal that must be considered in ectopic beat identification.
Since the proposed system uses the timing information together with the morphology information, it avoids any bias on HRV analysis that might have been imposed in the case of using the timing information only. It is known that some of the existing computerized HRV analysis systems use only the timing information in ectopic beat identification.

The proposed system makes large scale HRV analysis feasible by saving time and human power. It must be noted that the system is not proposed, with its present performance figures, as a substitute for manually supervised/corrected HRV analysis of single patients. However, our study shows that a QRS detection and ectopic beat identification system with a performance comparable with that of an expert cardiologist can be designed.

We quantitatively showed the advantage of using the first derivative of the ECG signal instead of the ECG signal itself, in QRS detection and ectopic beat identification.

We showed that using the derivative signals instead of the absolute derivative signals in rest ECG recordings, does not improve QRS detection and degrade the performance of ventricular ectopic beat identification by causing false rejections of normal beats. However, we think that using the derivative signals would increase the performance in noisy ECG recordings. This needs to be further investigated.

After studying the performance of the algorithm when single ECG lead is used, we concluded that i) the ECG leads close to the atria are important in the identification of ectopic beats and ii) the ECG leads close to the ventricles are important in the detection of normal beats.

Our contribution to ventricular repolarization analysis is to introduce new concepts and to show their applicability and significance in comparison with the conventional methods. The concepts that were introduced are the followings: i) The spatial T wave
morphology dispersion ($TMD, TMD_{pre}, TMD_{post}$), ii) the temporal T wave morphology variation ($LD_1, LD_2, PL, PO$), and iii) the wavefront direction characteristics of the QRS complex and the T wave ($TCRT$). We have reached at the following conclusions:

◊ The proposed T wave descriptors have a built-in noise immunity due to the fact that all of them are computed in a minimum dimensional space constructed by SVD of 12-lead ECG.

◊ None of the new descriptors depends on accurate time domain measurements. This makes them more reproducible than the conventional QT interval related descriptors and increases their clinical applicability.

◊ The new descriptors assess different qualities of ECG signal than the existing descriptors. This is shown by their poor correlation between the two sets of descriptors. Thus, the new descriptors add to the information extracted from ECG signals.

◊ The spatial variation and the wavefront direction descriptors can discriminate between normal and abnormal ECGs substantially better than the existing descriptors. An increase in the spatial T wave morphology variation and an increased deviation between the wavefront directions of the ventricular depolarization and repolarization waves are observed in pathological cases. TCRT is by far the strongest of all descriptors.

◊ The temporal variation descriptors do not seem to differ between normal and abnormal cases. This may be due to some methodological problems associated with the temporal variation descriptors. Lead dispersion descriptors, esp. $LD_1$ which describes the variation of interlead relations during ventricular repolarization, are the most promising temporal variation descriptors.

◊ The new descriptors are analyzed in HCM, DCM and AMI patient groups and in normal subjects. Their performance in other patient groups must also be assessed.
The physiological background of the processes in the heart which are assessed via the new descriptors need to be determined. This would establish the physiological basis of the new descriptors more firmly.

The dynamism of the new descriptors (both in short and long term) must be analyzed. An adaptive version of the proposed algorithm can be developed and used in assessing the variation of the new T wave descriptors under several conditions, like exercise ECG testing. Time domain and frequency domain analysis, similar to the ones performed in HRV analysis, can be performed on the time series of the new T wave descriptors.

Type of the inter-lead T wave morphology variation may be an indicator of the location and the type of abnormality in the heart. The present spatial variation descriptors are computed with an averaging, which may be destroying some of the available information. Different versions of the spatial variation descriptors, like assessing the morphology variation between specific pairs of ECG leads, can be defined and analyzed.

There is still an on-going debate on the proper method of assessing the ventricular repolarization heterogeneity. Despite the long-lasting debate, the QT interval related descriptors have not been accepted fully yet. This is due to several methodological problems. We expect the methods/concepts introduced here to receive wide acceptance and be standard methods together with QT interval related descriptors, if not a replacement to them. This requires further testing of the new descriptors in several patient categories. We anticipate that this requires time.
Appendix A

COMPARISON OF 1D VS 3D HRV ANALYSIS RESULTS

This appendix consists of the comparison of four HRV measurements done on single ECG leads with the same measurements done on three ECG leads (II-V1-V5). The measured quantities are LF power, HF Power, LF/HF ratio and SDNN. Their definitions are given in Section 2.1. The parametric method (AR Modeling) was used in the spectral analysis. The model order was set automatically by checking the derivative of the SNR and AIC curves, as mentioned in Section 2.1. The model order was forced to be between 6 and 20.

The Bland-Altman method is used to assess the agreement between the two sets of measurements [94]. Each graphic is a plot of the mean of two measurements versus their difference. Each data point corresponds to a single pair of measurements from the same ECG record. The plots demonstrate the relation between the measured quantity and the error made. In each graphic the outliers, with abnormally high mean values, were excluded. There were 1 or 2 outliers in each case. The mean and ±2 Standard deviation levels are also marked on each graphic with the corresponding 95% confidence intervals, which are defined as explained in [94].
Comparison of V1 vs II-V1-V5
Comparison of V2 vs II-V1-V5
Comparison of V3 vs II-V1-V5
Comparison of LF Power (V4 vs. II-V4-V5)

Comparison of HF Power (V4 vs. II-V4-V5)

Comparison of LF/HF (V4 vs. II-V4-V5)

Comparison of SDNN (V4 vs. II-V4-V5)

Comparison of V4 vs II-V1-V5
Comparison of $L_f \cdot R_{owor}$ (V5 vs. II-VS-V5)

Comparison of HF Power (V5 vs. II-VS-V5)

Comparison of LF/HF (V5 vs. II-VS-V5)

Comparison of SDNN (V5 vs. II-VS-V5)

Comparison of V5 vs II-V1-V5
Comparison of V6 vs II-V1-V5
Appendix B

DEMONSTRATION OF THE NEW VENTRICULAR REPOLARIZATION DESCRIPTORS

10 normal and 10 HCM subjects were analyzed by the first version of the algorithm for demonstration purposes. There are 5 figures for each subject: i) The input median beats from leads I, II, V1, V2, V3, V4, V5, V6 in order, ii) the 3 most significant decomposed signals and the norm signal, together with the approximate detection points: QRS onset ($t_{RS}$), QRS offset ($t_{RE}$), T onset ($t_{TS}$) and T offset ($t_{TE}$), iii) the T loop in 2D space and the encompassing rectangle, iv) The T loop in 2D space and the 2D reconstruction vectors used in $TMD$ calculation (the reconstruction vector of V1 is shown with a dashed line), v) the 3D plot of the QRS loop and the T loop. The viewing point is along the third dimension (the least significant one). The unit vectors marking the two dimensions, the major and minor axis of the loops are shown. The green section of the QRS loop corresponds to the time interval $[t'_{RS}, t'_{RE}]$ and is the section used in $TCRT$ calculation.
NORMAL SUBJECT - CASE 1

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

Decomposed ECG Signals, Norm Signal, and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and Its center of gravity With Corresponding PC's

Ventricular Repolarization Descriptors:

TMD: 7.905°
TMDpost: 9.441°
TMDpre: 12.083°
TCRT: 0.950
PL: 0.509
PO: 0.435
LD1: 36.0
LD2: 1007.0
NORMAL SUBJECT - CASE 2

Input ECG Beats (V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop In 2D Space and The Encompassing Rectangle

T Loop In 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

- TMD: 5.483°
- TMDpost: 2.343°
- TMDpre: 4.390°
- TCRT: 0.279778
- PL: 0.594
- PO: 0.344
- LD1: 36.0
- LD2: 1068.0
NORMAL SUBJECT - CASE 3

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Value</th>
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<tbody>
<tr>
<td>TMD</td>
<td>14.551°</td>
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<tr>
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<td>9.595°</td>
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<td>TMDpre</td>
<td>11.402°</td>
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<tr>
<td>TCRT</td>
<td>0.329</td>
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<tr>
<td>PL</td>
<td>0.779</td>
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<tr>
<td>PO</td>
<td>0.168</td>
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<tr>
<td>LD1</td>
<td>36.0</td>
</tr>
<tr>
<td>LD2</td>
<td>434.0</td>
</tr>
</tbody>
</table>
NORMAL SUBJECT - CASE 4

Ventricular Repolarization Descriptors:

TMD: 24.162°
TMDpost: 18.676°
TMDpre: 20.259°
TCRT: 0.175
PL: 0.742
PO: 0.208
LD1: 35.0
LD2: 382.0
NORMAL SUBJECT - CASE 5

Input ECG Beats (I, II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop In 2D Space and The Encompassing Rectangle

T Loop In 2D Space and The Reconstruction Vectors

SVD of Median beat and Its center of gravity With Corresponding PC's

Ventricular Repolarization Descriptors:

TMD: 16.741°
TMDpost: 9.154°
TMDpre: 16.700°
TCRT: 0.752
PL: 0.644
PO: 0.296
LD1: 38.0
LD2: 1125.0
NORMAL SUBJECT - CASE 6

Ventricular Repolarization Descriptors:

TMD: 7.480°
TMDpost: 6.970°
TMDpre: 5.448°
TCRT: 0.490
PL: 0.682
PO: 0.266
LD1: 37.0
LD2: 623.0
NORMAL SUBJECT - CASE 7

- Input ECG Beats (II, V1, V2, V3, V4, V5, V6)
- 3 Decomposed ECG Signals, Norm Signal and Detection Points
- SVD of Median beat and its center of gravity with Corresponding PC's

Ventricular Repolarization Descriptors:
- TMD: 9.672°
- TMDpost: 7.726°
- TMDpre: 4.406°
- TCRT: 0.646
- PL: 0.697
- PO: 0.252
- LD1: 37.0
- LD2: 610.0
NORMAL SUBJECT - CASE 8

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

- TMD: 4.033°
- TMDpost: 1.106°
- TMDpre: 3.950°
- TCRT: 0.893
- PL: 0.577
- PO: 0.363
- LD1: 35.0
- LD2: 1384.0
NORMAL SUBJECT - CASE 9

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

TMD: 9.013°
TMDpost: 6.698°
TMDpre: 5.863°
TCRT: 0.696
PL: 0.744
PO: 0.201
LD1: 38.0
LD2: 805.0
NORMAL SUBJECT - CASE 10

Input ECG Beats (U, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and Its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

- TMD: 8.246°
- TMDpost: 4.505°
- TMDpre: 6.399°
- TCRT: 0.475
- PL: 0.735
- PO: 0.212
- LD1: 35.0
- LD2: 729.0
HCM PATIENT - CASE 1

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

TMD: 57.826°
TMDpost: 36.758°
TMDpre: 78.005°
TCRT: -0.945
PL: 0.718
PO: 0.238
LD1: 35.0
LD2: 249.0
HCM PATIENT - CASE 2

Input ECG Beats (I, II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

- TMD: 37.652°
- TMDpost: 16.774°
- TMDpre: 43.444°
- TCRT: -0.858
- PL: 0.615
- PO: 0.333
- LD1: 38.0
- LD2: 806.0
HCM PATIENT - CASE 3

Input ECG Beats (I, II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PC's

Ventricular Repolarization Descriptors:

- TMD: 44.743°
- TMDpost: 50.170°
- TMDpre: 52.042°
- TCRT: -0.717
- PL: 0.686
- PO: 0.262
- LD1: 36.0
- LD2: 518.0
HCM PATIENT - CASE 4

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

- TMD: 44.743°
- TMDpost: 50.170°
- TMDpre: 52.042°
- TCRT: -0.717
- PL: 0.686
- PO: 0.262
- LD1: 36.0
- LD2: 518.0
HCM PATIENT - CASE 5

Input ECG Beats (I,L, V1, V2, V3, V4, V5, V6)

Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

Ventricular Repolarization Descriptors:

TMD: 81.238°
TMDpost: 82.491°
TMDpre: 79.978°
TCRT: -0.914
PL: 0.531
PO: 0.419
LD1: 31.0
LD2: 525.0
HCM PATIENT - CASE 6

Input ECG Beats (I, II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PCs

Ventricular Repolarization Descriptors:

- TMD: 83.94°
- TMDpost: 84.63°
- TMDpre: 84.36°
- TCRT: -0.919
- PL: 0.416
- PO: 0.526
- LD1: 33.0
- LD2: 1591.0
HCM PATIENT - CASE 7

Input ECG Beats (II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Wedlan beat and Its center of gravity With Corresponding PC's

Ventricular Repolarization Descriptors:
- TMD: 84.085°
- TMDpost: 70.896°
- TMDpre: 92.687°
- TCRT: -0.856
- PL: 0.629
- PO: 0.325
- LD1: 35.0
- LD2: 283.0
HCM PATIENT - CASE 8

Input ECG Beats (II, III, V1, V2, V3, V4, V5, V6)

Time (msec)

3 Decomposed ECG Signals, Norm Signal and Detection Points

Time (msec)

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PC's

Ventricular Repolarization Descriptors:

TMD: 23.891°
TMDpost: 33.004°
TMDpre: 8.375°
TCRT: -0.478
PL: 0.623
PO: 0.328
LD1: 32.0
LD2: 356.0
HCM PATIENT - CASE 9

Input ECG Beats (I, II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Median beat and its center of gravity With Corresponding PC's

Ventricular Repolarization Descriptors:

- TMD: 69.321°
- TMDpost: 60.462°
- TMDpre: 80.616°
- TCRT: -0.547
- PL: 0.652
- PO: 0.302
- LD1: 28.0
- LD2: 203.0
HCM PATIENT - CASE 10

Input ECG Beats (I, II, V1, V2, V3, V4, V5, V6)

3 Decomposed ECG Signals, Norm Signal and Detection Points

T Loop in 2D Space and The Encompassing Rectangle

T Loop in 2D Space and The Reconstruction Vectors

SVD of Medtrime beat and its center of gravity with corresponding PCs

Ventricular Repolarization Descriptors:
- TMD: 91.902°
- TMDpost: 88.042°
- TMDpre: 98.466°
- TCRT: -0.889
- PL: 0.170
- PO: 0.456
- LD1: 30.0
- LD2: 874.0
Bibliography


[59] B. Acar, “New approaches to T wave analysis from surface ECG,” Accepted for publication in Cardiac Electrophysiology Review (CEPR).


