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Prediction of Sudden Cardiac Arrest for  
Patients with Congestive Heart Failure

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**Abstract**

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Sudden cardiac death (SCD) is responsible for 200,000-450,000 adult deaths each year in the United States. Since sudden cardiac arrest (SCA) can happen unexpectedly, implantable-cardioverter defibrillators (ICDs) are inserted into patients who are at high risk of SCA so that they can provide immediate defibrillation when SCAs occur. Even though ICDs can be life-saving, there are still many problems that need to be solved. Firstly, how does one determine whether a person should receive an ICD? An ICD installed but never used is a waste of resources. On the other hand, if the patients need ICDs but do not get them, very likely they will

lose their lives through SCDs. Secondly, ICDs do not prevent life-threatening cardiac arrhythmias (LTCAs), but simply terminate such arrhythmias after they have occurred. As a result, the patients suffering from these arrhythmia can be in danger if, for example, they are driving. It would be ideal if ICDs can issue warnings for impending LTCAs. Last but not least, shocks are very painful and decrease the quality of life of patients. If one can predict the onset of these arrhythmias, it may be possible to treat the patients with pacing or modulation of autonomic nervous system thus can decrease the number of shocks received by patients. To solve these problems, we hypothesized that the patients' R-R interval statistics can be used for risk stratification for SCAs and prediction of SCAs. In addition, algorithms from machine learning were used to predict the occurrences of SCA with R-R interval statistics and demographic information of patients as features. Our study sample consists of patients who enrolled in Sudden Cardiac Death – Heart Failure Trial (SCD-HeFT). Our work shows that R-R interval statistics, particularly the short-term and long-term fractal scaling exponents from detrended fluctuation analysis (DFA), are indeed correlated to the occurrences of SCAs. Such findings certainly will aid the patient selection for receiving ICDs and will help create a new generation of ICDs which can issue warnings for the occurrences of SCAs.

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## LIST OF ABBREVIATIONS

AED	Automated external defibrillator
ATP	Anti-tachycardia pacing
AUC	Area under curve
BPS	Biomarker patterns software
CART	Classification and regression tree
CHF	Congestive heart failure
DCM	Dilated cardiomyopathy
DFA	Detrended fluctuation analysis
ECG	Electrocardiogram
EMIAT	European Myocardial Infarct Amiodarone Trial
EPS	Electrophysiological study
FN	False negative
FP	False positive
HFP	High-frequency power
HRT	Heart rate turbulence
HRV	Heart rate variability
HRVTI	Heart rate variability triangular index
ICD	Implantable Cardioverter Defibrillator
k-NN	k-Nearest Neighbor
KFD	Kernel Fisher discriminant
LFP	Low-frequency power
LTCA	Life-threatening cardiac arrhythmia
LVEF	Left ventricular ejection fraction
LS-SVM	Least square support vector machine
MC	Microcalcification
MHI	Mental Health Inventory
MLP	Multilayer Perceptron Neural Network
MPIP	Multicentre Post-Infarction Program

MUSIC	Muerte Subita en Insuficiencia Cardiaca
MWW	Mann-Whitney-Wilcoxon
NHP	Nottingham Health Profile
NN	Normal-to-normal
NPV	Negative predictive value
NYHA	New York Heart Association
PC	Principal component
PCA	Principal component analysis
PH	Proportional hazards
pNN50	Fraction of consecutive normal-to-normal intervals that differ by more than 50 ms
PPMCC	Pearson product-moment correlation
PPV	Positive predictive value
PVC	Premature ventricular contraction
QRS	The combination of Q wave, R wave and S wave seen on an electrocardiogram
QT	The start of the Q wave to the end of the T wave
QTc	Corrected QT
ROC	Receiver operating characteristic
R-R	R wave to R wave
RVM	Relevance Vector Machine
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SCD-HeFT	Sudden Cardiac Death – Heart Failure Trial
SDNN	Standard deviation of normal-to-normal intervals
SVD	Singular value decomposition
SVM	Support vector machine
TN	True negative
TO	Turbulence onset

TP	True positive
TS	Turbulence slope
TWA	T-wave alternan
VF	Ventricular fibrillation
VFL	Ventricular flutter
VT	Ventricular tachycardia

## LIST OF SYMBOLS

$\alpha$	Fractal scaling exponent from detrended fluctuation analysis
$\alpha_1$	Short-term fractal scaling exponent from detrended fluctuation analysis
$\alpha_2$	Long-term fractal scaling exponent from detrended fluctuation analysis
$h_i$	Data value
$t_i$	Observation time
$\bar{h}$	Mean
$\sigma^2$	Variance
$\omega$	Angular frequency
$f$	Frequency
$\tau$	Time-offset
$P_N(\omega)$	Lomb-Scargle normalized periodogram (spectral power as a function of angular frequency)
$\delta$	Cost of a false negative
$\gamma$	Cost of a false positive
$\sigma$	Singular value

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# **DEDICATION**

To my family

## Chapter 1. INTRODUCTION

Sudden cardiac death (SCD) is an unexpected death caused by the loss of the function of the heart. SCD is one of the leading causes of death in industrialized countries. Estimates of SCD go from less than 200,000 to more than 450,000 cases in the United States annually. That is equivalent to a rate of incidence of 1.2 per 1,000 people. Event rates in Europe are considered similar.[1]

A majority of SCDs is caused by first the generation of ventricular tachycardia (VT; abnormal acceleration of ventricular rate) which developed into ventricular fibrillation (VF), during which the ventricles contract in a disorganized manner and fail to eject blood effectively, then often results in asystole or pulseless electrical activity.[2] This sequence of events happens within minutes.

Prior to the occurrences of sudden cardiac arrest (SCA), some patients would experience no symptoms. Since SCA happens in such a sudden and unexpected way, the survival rate is very low. Once a person has an onset of SCA, he needs to be treated by bystanders immediately otherwise he will likely die. Emergency treatment is defibrillation. Normal rhythm can be restored with defibrillation which involves delivering an electric shock to the chest with automated external defibrillators (AEDs).

The major risk factors for SCA are coronary artery disease and prior myocardial infarction. Some other risk factors for SCA include low left ventricular ejection fraction (LVEF), congestive heart failure (CHF), dilated cardiomyopathy (DCM), obesity and diabetes.

Since SCA is so life-threatening and the person who experiences it can die within minutes, implantable-cardioverter defibrillators (ICDs) are used to prevent SCD in patients with heart

diseases who are at high risk of SCA. ICDs are inserted into patients' chests through surgeries. They constantly monitor the subjects' hearts and they have discrimination algorithms that would detect ventricular arrhythmias. Once they detect this life-threatening cardiac arrhythmia (LTCA), they will deliver an electric shock to heart muscle so that the heart would beat normally again.

Even though ICDs could be life-saving, its high cost of implantation inhibits it to be widely used. The cost of implantation of a single ICD ranged (2006 \$US) from \$28,500 to \$55,200 with annual follow-up costs ranging from \$4,800 to \$17,000.[3] Also, ICDs have a number of risks on the patients which include infection, unnecessary shocks, potential for proarrhythmia, device malfunction, highly publicized manufacturer advisories, and procedural complications.[4] All of these factors can adversely affect morbidity and quality of life. Therefore, careful and optimized decision should be made with whether patients should receive ICD therapy.

Another shortcoming of the current generation of ICDs is that they can only terminate the LTCAs after they have occurred, but not being able to prevent them from happening. As a result, the patients who suffer from these arrhythmias can lose consciousness briefly before they receive shocks from their ICDs. This can cause dangers to the patients and their surroundings if, for examples, the patients are driving or in situations where they can fall. Therefore, ideally, the ICDs should have the functionality of giving early warnings to patients when LTCAs are about to occur so that the patients can take precautions. In addition, shocks from ICDs are very painful. The ICD shock sensation has been described as being kicked strongly in the chest and is rated a "6" on a 0 to 10 pain scale.[5], [6] Shocks also affect the psychological states and can cause depression in patients. If ICDs can predict the occurrences of LTCAs, that creates the opportunity for preventive measures such as autonomic modulation, though that remains to be investigated.

One focus of our research is performing long-term risk stratification for SCA with the use of R-R interval statistics in the patients with mild to moderate heart failure. We did that in the hope of eliminating a portion of patients with mild to moderate heart failure from consideration for ICD therapy. Besides long-term risk stratification for SCA, our research also seeks to predict the occurrences of SCA 5 minutes ahead of their occurrences using algorithms from machine learning with R-R interval statistics and demographic information as features.

## 1.1 RISK STRATIFICATION

Risk stratification is the determination of one's risk for suffering a particular condition and need, or lack of need, for preventive intervention. Many methods have been used to perform risk stratification for SCD. They are summarized in Table 1.1. Currently, left ventricular function is the "gold" standard people look to for risk stratification for SCD.[1] And these different methods for risk stratification can be used in combination to improve accuracy. Some of these methods are invasive such as electrophysiological study (EPS) and some are not such as T-wave alternans (TWA).

Table 1.1 Techniques and Measurements for Risk Stratification for SCA according to Ikeda et al. [1]

<p><i>Left ventricular function</i></p> <ul style="list-style-type: none"> <li><i>Reduced LVEF (<math>\leq 35\%</math> or <math>\leq 40\%</math>)</i></li> <li><i>New York Heart Association (NYHA) functional class (2-4)</i></li> <li><i>B-type natriuretic peptide level (<math>&gt; 200</math> pg/ml)</i></li> </ul> <p><i>Resting electrocardiography</i></p> <ul style="list-style-type: none"> <li><i>Prolonged QRS duration <math>&gt; 130</math> ms</i></li> <li><i>Left bundle branch block</i></li> <li><i>Atrial fibrillation</i></li> <li><i>Repolarization abnormalities</i> <ul style="list-style-type: none"> <li><i>T-wave abnormalities</i></li> <li><i>Long QTc interval (<math>&gt; 440</math> ms)</i></li> <li><i>Short QTc interval (<math>&lt; 300</math> ms)</i></li> <li><i>QT dispersion (<math>&gt; 70</math> ms)</i></li> <li><i>T peak-end interval (<math>&gt; 100</math> ms)</i></li> </ul> </li> </ul> <p><i>Exercise or pharmacological stress testing</i></p> <ul style="list-style-type: none"> <li><i>Induction of serious ventricular arrhythmias</i></li> <li><i>Induction of electrocardiographic or ischemic change</i></li> </ul> <p><i>Ambulatory electrocardiography</i></p> <ul style="list-style-type: none"> <li><i>Detection of nonsustained VT</i></li> <li><i>Detection of electrocardiographic or ischemic change</i></li> </ul> <p><i>Electrophysiological techniques and measurements</i></p> <ul style="list-style-type: none"> <li><i>Repolarization abnormalities</i> <ul style="list-style-type: none"> <li><i>T-wave alternans</i></li> </ul> </li> <li><i>Depolarization (conduction) abnormalities</i> <ul style="list-style-type: none"> <li><i>Late potentials by signal-averaged electrocardiography</i></li> </ul> </li> <li><i>Autonomic nerve imbalance</i> <ul style="list-style-type: none"> <li><i>Heart rate variability</i></li> <li><i>Baroreflex receptor sensitivity</i></li> <li><i>Heart rate turbulence</i></li> </ul> </li> </ul> <p><i>Electrophysiological testing</i></p> <ul style="list-style-type: none"> <li><i>Inducibility of sustained ventricular arrhythmias</i></li> <li><i>Evaluation of antiarrhythmic drugs</i></li> </ul> <p><i>Genetic analysis</i></p>
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These are the methods we focused on for risk stratification for SCD:

- heart rate variability (HRV)
- heart rate turbulence (HRT)
- detrended fluctuation analysis (DFA)

HRV, HRT, and DFA are chosen as they can be applied to easily obtained R-R intervals extracted from patients' Holter monitors. The data collection process for electrocardiogram (ECG) is non-invasive with the Holter monitors. Also, R-R intervals are not heavily affected by noises as R peaks in the ECG are sharp. One can measure the time intervals between consecutive R peaks fairly easily.

Short-term and long-term fractal scaling exponents are the measures from DFA. They characterize how self-similar the R-R intervals are in the short term and in the long term. HRT characterizes the heart rate after premature ventricular contractions (PVCs). We also looked at different HRV measures such as standard deviation of all normal R-R intervals (SDNN).

## 1.2 PREDICTION OF SCA USING MACHINE LEARNING

As stated earlier, ICD therapy has its drawbacks. In particular, ICDs cannot prevent VF from occurring but terminate them after they have occurred. As a result, the patients can be a danger to themselves and/or surroundings if, for example, they are driving. Also, electric shocks from the ICDs are very painful and affect the patient's quality of life and psychological state. If ICDs can predict the occurrences of VT/VF 5 minutes ahead of time, they can issue warnings to the patients and medical units so that the patients can take precautions and the medical units can respond. Also, this creates the opportunity for alternate patient management. For example, anti-tachycardia pacing (ATP) therapy can also be used to treat VT and it does not cause pain. In

addition, analysis of four different major trials showed an increased risk of mortality for patients who received shocks for VT/VF than patients who received ATP therapy.[7]–[10] There also has been literature that suggests VF can be avoided through autonomic modulation.[11] If one can predict the onset of VF, the heart may be avoided going into VF through pacing and/or autonomic modulation though that remains to be investigated. If these measures are implemented successfully, safety and quality of life of patients may be improved and the number of shocks received by the patients may be reduced. We tried to predict the onset of VT/VF 5 minutes in advance using fractal scaling exponents from DFA, power of normal R-R intervals in frequency domain, mean normal R-R intervals and demographic information with algorithms from machine learning.

### 1.3 PROBLEM STATEMENT

Our research draws on signal processing methods to extract features from R-R intervals from patients with heart failure. These features were correlated with the occurrences of SCAs for long-term risk stratification. Also, a combination of such features and demographic information of patients was used to predict the occurrences of SCAs using algorithms from machine learning. Here the research questions that we addressed in each of these areas are provided.

#### 1.3.1 *Research questions: long-term risk stratification for SCA (Chapter 3)*

In Chapter 3, three key questions related to long-term risk stratification for SCA are addressed:

- 1) Is it possible to perform long-term risk stratification for SCAs for patients with mild to moderate heart failure with R-R interval statistics extracted from 24-hour Holter monitors?  
If yes, what kind of statistics?

- 2) Is it possible to design an ICD therapy screen test for patients with heart failure with their R-R interval statistics?
- 3) Are R-R interval statistics correlated with survival functions of patients with heart failure?

Our purpose here is to identify statistics of R-R intervals that are correlated with the occurrences of SCAs in the long term. With the statistics that shows correlation with SCAs, we seek to design an ICD therapy screen test to exclude patients with mild to moderate heart failure from the consideration of ICD therapy.

### 1.3.2 *Research questions: prediction of SCA (Chapter 4-5)*

In Chapters 4 and 5, we explore the questions of whether the occurrences of SCAs can be predicted using R-R interval statistics and demographic information with algorithms from machine learning:

- 1) Are there any differences between the normal rhythms and pre-cardiac-event rhythms from patients with heart failure? If there are, can the differences be detected by looking at the fractal scaling exponents, power spectrums and mean normal R-R intervals of these rhythms? Can such features of the rhythms and the demographic information of the patients be used to train algorithms from machine learning to classify these rhythms?
- 2) Is it possible to provide a 5-minute warning or a 10-second warning for the occurrences of SCAs with R-R interval statistics and demographic information of patients as predictors using algorithms from machine learning?

- 3) Can projections onto principal components (PCs) obtained from principal component analysis (PCA) on the R-R interval recordings provide improvement in performances of classification?

In the case of prediction of SCAs, our purpose is to find out if there are distinguishable differences between normal rhythms and 5-min-pre-shock rhythms or 10-second-pre-shock rhythms from the patients with mild to moderate heart failure. If there are differences, it shows promise that predicting the occurrences of SCA in real time is possible. In order to study these issues, fractal scaling exponents, power in frequency domain and mean normal R-R intervals were extracted from the normal rhythms and pre-shock rhythms and they were used in combination with demographic information of patients to train machine learning algorithms support vector machines (SVMs) and decision trees. These algorithms from machine learning were used to classify rhythms in the test set to find out classification performances. PCA was also performed on the rhythms and projections onto PCs were used as features to SVMs to find out if classification performances can be improved.

#### 1.4 SUBJECTS

All the subjects in the study presented in this dissertation were enrolled in Sudden Cardiac Death – Heart Failure Trial (SCD-HeFT). SCD-HeFT was a large National Institutes of Health funded clinical trial that was designed to study the effectiveness of ICD and amiodarone therapies in patients with mild to moderate heart failure.[12] From September 16, 1997 to July 18, 2001, 2521 patients were randomly assigned in equal proportions to receive placebo, amiodarone or a single-chamber ICD programmed to shock-only mode (model 7223, Medtronic). All patients were followed until October 31, 2003. The inclusion criteria for the study was that the patients had to

be at least 18 years old, have NYHA class II or III chronic, stable CHF due to ischemic or nonischemic causes and a LVEF of no more than 35 percent. For this study, we focused on subjects enrolled in the ICD arm of SCD-HeFT as the ICDs kept track of the patients' cardiac events.

## 1.5 DATA

There are two types of data associated with the heart rhythms of the patients enrolled in the ICD arm of SCD-HeFT. One of them is the Holter monitor data. The Holter monitor sub-study was approved by the human studies committee at the participating institutions. Holter monitor data were obtained in the two weeks prior to randomization to placebo, amiodarone, or ICD. The final status of the patients were known at the end of the trial. The heart rhythms obtained from the Holter data were used for long-term risk stratification for SCA. The other type of data is the heart rhythms recorded by the ICDs implanted in the patients. These heart rhythms are either normal rhythms which were downloaded in clinics when the patients had follow-up visits or rhythms which preceded the occurrences of shocks. This allows us to find out the different characteristics of the normal rhythms and pre-cardiac-event rhythms from the patients with mild to moderate heart failure.

## 1.6 METHODS

Here is an overview of some of the methods used in our research.

### 1.6.1 *Detrended Fluctuation Analysis (DFA)*

DFA is a predictive tool in heart disease introduced by Peng et al.[13] The DFA yields a short-term fractal scaling exponent,  $\alpha_1$ , and a long-term fractal scaling exponent,  $\alpha_2$ . These exponents tell us about the self-similarity of the R-R intervals in both the short term and the long

term and have been considered prognostic in certain disease states. [14][15] DFA has advantages over conventional spectral analysis as it is more suited for analyzing nonstationary physiological time series. Also, it can detect the intrinsic self-similarity and avoid the spurious detection of apparent self-similarity which may be an artifact of extrinsic trends. Here are the steps to compute the short-term and long-term fractal scaling exponents:[13]

1. The time series is integrated

$$y(k) = \sum_{i=1}^k [B(i) - Bave] \quad \text{Equation 1-1}$$

Where  $B(i)$  is the  $i$ -th beat-to-beat interval,  $Bave$  is the average beat-to-beat interval

2. The integrated time series is then divided into boxes of equal length,  $n$ .
3. For each box with length  $n$ , a line is fit to the data using least-squares method. The  $y$ -coordinates of the straight line segments are denoted by  $y_n(k)$ .
4. Detrend the integrated time series,  $y(k)$ , by subtracting the local trend,  $y_n(k)$ , in each box.
5. For a given box size  $n$ , the characteristic size of fluctuation for the integrated and detrended time series is calculated by the method of root mean squares:

$$F(n) = \sqrt{\frac{1}{N} \sum [y(k) - y_n(k)]^2} \quad \text{Equation 1-2}$$

6. Repeat this for each box size to examine the relationship between  $F(n)$  and the box size  $n$ .
7. Plot  $F(n)$  and  $n$  on a double log graph. The slope of the line that relates  $\log F(n)$  to  $\log n$  determines the fractal scaling exponent,  $\alpha$ . To find the short-term fractal scaling exponent,  $\alpha_1$ , one should make a least squares fit of  $\log F(n)$  vs  $\log n$  for  $4 \leq n \leq 16$ . Similarly, the long-term fractal scaling exponent,  $\alpha_2$ , is obtained from  $16 \leq n \leq 64$ .

Theoretically, for data of infinite length, the following holds true:

The fractal scaling exponent of white noise is 0.5.

The fractal scaling exponent of 1/f noise is 1.

The fractal scaling exponent of Brownian noise is 1.5.

The R-R intervals from a healthy subject are described as self-similar and resemble 1/f noise.

### 1.6.2 *Heart Rate Turbulence (HRT)*

HRT was invented by Schmidt et al.[16] The method investigated fluctuations of sinus rhythm cycle length after a single PVC recorded in Holter ECGs, and characterized the fluctuations by two parameters, turbulence onset (TO) and turbulence slope (TS). This method was developed on a population of 100 patients with coronary heart disease (78 of whom had a history of myocardial infarction and 26 a history of multiple infarctions) and tested on the Multicentre Post-Infarction Program (MPIP) population and placebo population of the European Myocardial Infarct Amiodarone Trial (EMIAT). Those 100 patients with coronary heart disease presented sinus rhythm and more than ten PVCs per hour during 24-hr Holter monitoring which were used to design the method and to optimize the risk prediction power of TS and TO.

TO is the percentage difference between the R-R intervals immediately following PVC and the R-R intervals immediately preceding PVC. It is calculated using the Equation 1-3

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} * 100 \quad \text{Equation 1-3}$$

where  $RR_{-2}$  and  $RR_{-1}$  are the first two normal intervals preceding the PVC and  $RR_1$  and  $RR_2$  are the first two normal intervals following the PVC. TO is determined for each PVC, and then they are averaged to find the final value of TO. Positive values for TO indicate deceleration, negative values indicate acceleration of the sinus rhythm.

TS is the maximum positive slope of the linear regression line for each sequence of five consecutive normal intervals within the first 20 sinus-rhythm intervals after a PVC. The calculations of TS are based on the averaged tachogram and expressed in ms per R-R interval.

### 1.6.3 *Lomb-Scargle Periodogram*

Lomb-Scargle periodogram is a least-squares spectral analysis method for estimating the frequency spectrum, based on a least-squares fit of sinusoids to data samples, similar to Fourier analysis. Such least-squares spectral analysis method has better performance than Fourier analysis when the data is unevenly spaced and when the records have long gaps.[17] R-R intervals have such properties therefore Lomb-Scargle periodogram was chosen to find the frequency spectrum of R-R intervals.

Suppose there is a set of data values  $h_i, i = 1, \dots, N$  at respective observation times  $t_i$ , here are the steps for finding the Lomb-Scargle Periodogram for the time series: [18]

1. Compute the data's mean and variance by

$$\bar{h} = \frac{1}{N} \sum_1^N h_i, \quad \text{Equation 1-4}$$

$$\sigma^2 = \frac{1}{N-1} \sum_1^N (h_i - \bar{h})^2 \quad \text{Equation 1-5}$$

2. For each angular frequency  $\omega = 2\pi f > 0$  of interest, compute a time-offset  $\tau$  by

$$\tan(2\omega\tau) = \frac{\sum_j \sin(2\omega t_j)}{\sum_j \cos(2\omega t_j)} \quad \text{Equation 1-6}$$

3. The Lomb-Scargle normalized periodogram (spectral power as a function of  $\omega$ ) is

defined by

$$P_N(\omega) = \frac{1}{2\sigma^2} \left\{ \frac{[\sum_j (h_j - \bar{h}) \cos \omega(t_j - \tau)]^2}{\sum_j \cos^2 \omega(t_j - \tau)} + \frac{[\sum_j (h_j - \bar{h}) \sin \omega(t_j - \tau)]^2}{\sum_j \sin^2 \omega(t_j - \tau)} \right\} \quad \text{Equation 1-7}$$

#### 1.6.4 Receiver Operating Characteristic (ROC) Analysis

A ROC graph is a technique for visualizing the performances of classifiers and for organizing and selecting the best classifiers. ROC graphs have a long history of being used in signal detection theory to show tradeoff between hit rates and false alarm rates of classifiers. Since then, ROC graphs have been extended for use in analyzing the behavior of diagnostic systems.[19]

Table 1.2 shows a confusion matrix with each item labelled. In the ROC space, the y-coordinate is the sensitivity and the x-coordinate is 1-specificity. To get a ROC curve, one has to obtain a value of sensitivity and a value of specificity at each decision threshold of the test and the decision threshold has to be varied to obtain all the points for the ROC curve.

Table 1.2: A  $2 \times 2$  Confusion Matrix

		Condition		
		Positive	Negative	
Test outcome	Positive	True Positives (TP)	False Positives (FP)	Positive Predictive Value= $TP/(TP+FP)*100\%$
	Negative	False Negatives (FN)	True Negatives (TN)	Negative Predictive Value= $TN/(FN+TN)*100\%$
		Sensitivity = $TP/(TP+FN)*100\%$	Specificity = $TN/(FP+TN)*100\%$	

From each of the ROC curve, the area under curve (AUC) can be calculated which quantifies the discriminating power of each of the predictors or classifiers. The value of AUC goes from 0 to 1. An AUC of 0.5 is as good as classifying the sample with random guess. An AUC below 0.5 means that the test performs worse than random guess. An AUC above 0.5 means that the test has discriminating power better than random guess while an AUC of 1 means that the test achieves perfect classification.

#### 1.6.5 *Support Vector Machine (SVM)*

SVMs are supervised learning models and they are often used for binary pattern classification.[20] Given a set of training data of two different classes, SVM will try to find a hyperplane that will maximize the margin between the two classes. Then, the SVM classifies new examples by determining which side of the hyperplane the new examples fall on. Figure 1.1 shows an illustration of how the SVM works. Unlike neural nets, only the support vectors would influence the hyperplane in SVM.

The SVM has evolved a lot from when it was invented in 1979 by Vapnik.[21] In 1995, the soft margin classifier was introduced by Cortes and Vapnik.[22] The algorithms existed previously were implemented for the restricted case where the training data could be separated without errors. The soft margin classifier can be extended to non-separable training data.

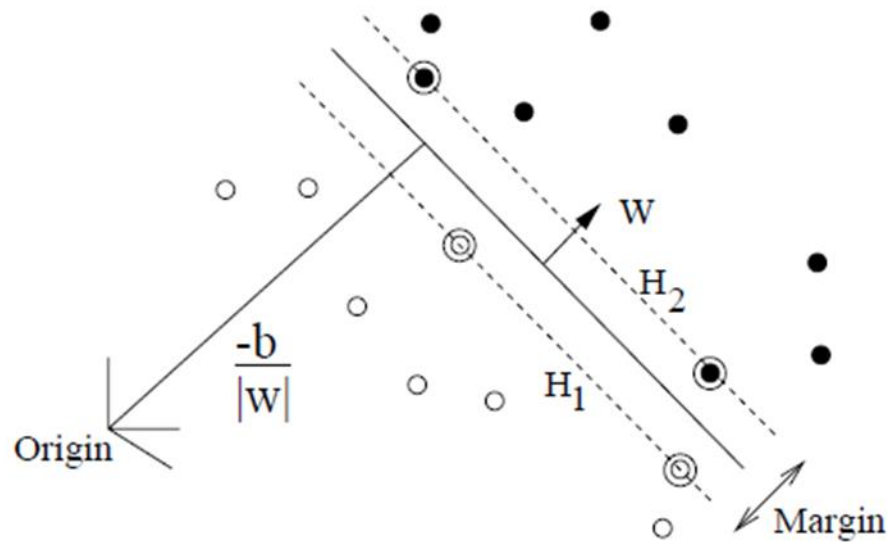


Figure 1.1: Illustration of the SVM from Burges.[20] Black circles are class one, white circles are class zero and the data points with larger circles surrounding them are the support vectors.  $W$  is the normal vector and  $b$  is bias.  $H_1$  is the hyperplane crossing the support vectors from class zero while  $H_2$  is the hyperplane crossing the support vectors from class one.

#### 1.6.6 Decision Tree

A decision tree is a nonmetric machine learning method. It classifies an object by finding its answers to a sequence of questions where the next question depends on its answer to the current question. Figure 1.2 shows an illustration of the decision tree algorithm. The questions are placed at the decision nodes as shown with the figure of decision tree in Figure 1.2B. Each question tests the value of a particular feature of the object and then provide a binary split. The starting node ( $x_2 < 1.96004$  or  $x_2 \geq 1.96004$ ) is called the root node which is the parent of all the other nodes. Each object is tested against successive questions starting from the root node until a classification is reached at the leaf node. In Figure 1.2B, all the leaf nodes are labelled as either 1 or 0 which are the results of classification. The results of classification can also be seen in Figure 1.2A as shown by the areas which are highlighted as either blue (Class 1) or red (Class 0).

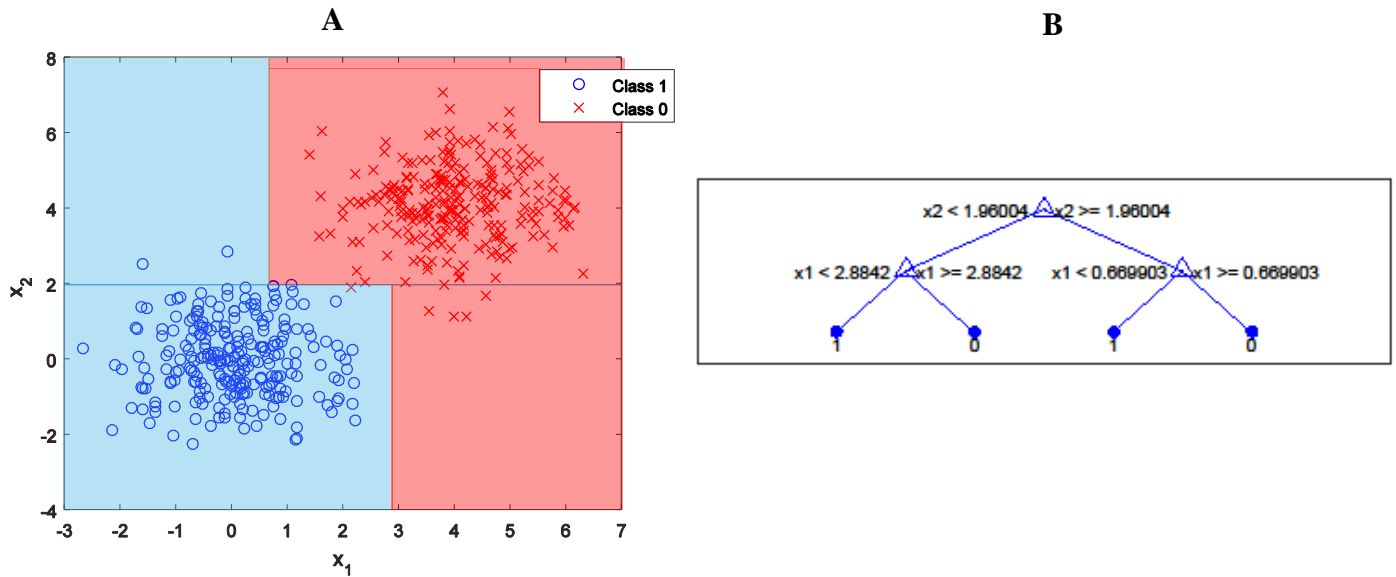


Figure 1.2: Illustration of the decision tree algorithm. A: Objects and classification results in the feature space. B: The hierarchical structure of the decision tree.

### 1.6.7 Principal Component Analysis (PCA)

PCA is a multivariate data analysis method first invented by Karl Pearson in 1901 and later developed by Harold Hotelling in the 1930s.[23]–[25] With PCA, one can perform an orthogonal transformation on a set of multivariate data to project them into a set of linearly uncorrelated variables which are called principal components (PCs) and the variances of these PCs can also be identified. In performing PCA, one should make sure that the data are centered and normalized. PCA is especially useful when one wants to analyze data that has high dimension. With PCA, one can retain the components with high variances while discard the components with low variances which would reduce redundancy. PCA is usually performed through an eigen-decomposition of the covariance matrix but it can also be performed through singular value decomposition (SVD) of the data matrix. Suppose there is a centered and normalized data matrix  $X$  which has size  $m \times n$ , then its reduced SVD is given by the following equation:

$$X = U * S * V^T \quad \text{Equation 1-8}$$

where  $U$  is of size  $m \times n$ ,  $S$  is of size  $n \times n$  and  $V$  is of size  $n \times n$ .  $S$  is a diagonal matrix with singular values along its diagonal.  $U * S$  has the PCs and  $V$  contains the projections onto the PCs.

## Chapter 2. LITERATURE REVIEW

Long-term risk stratification for SCAs and prediction of SCAs within minutes of their occurrences are two different problems with drastically different time frames. There have been a lot more works done on risk stratification for SCAs than on prediction of SCAs within minutes of their occurrences. In this chapter, we described prior studies that explained why these problems are important and how these problems may be solved.

### 2.1 LONG-TERM RISK STRATIFICATION FOR SCA

#### 2.1.1 *Motivation*

It has been shown that single-lead, shock-only ICD therapy reduced overall mortality by 23 percent in patients specified by the inclusion criteria of SCD-HeFT, while amiodarone contrarily had no favorable effect on survival.[12] Though ICD therapy can be life-saving, many of those patients who received ICDs ended up not benefiting from them. It was found that 542 patients out of 811 patients who enrolled in the ICD arm of SCD-HeFT (66.8%) received no known ICD-shock therapy during the follow-up period (median, 45.5 months). [26] Given that the cost of ICD therapy is high [3] and it has risks such as infection, unnecessary shocks, potential for proarrhythmia and device malfunction [4], risk stratification for SCA for patients with heart failure should be performed to avoid waste of resources and harms received by the patients. We performed the task of risk stratification for SCAs for patients with heart failure with HRV, HRT and DFA.

#### 2.1.2 *Methods*

This section has an overview of methods used for risk stratification for SCAs in this dissertation and how they have been used in the past.

### 2.1.2.1 Heart Rate Variability (HRV)

HRV has been shown that it was correlated with mortality in post-myocardial infarction patients. Bilchick and Berger[27] referenced the results from a number of studies on the relationship between HRV and mortality in post-myocardial infarction patients. It was found that decreased standard deviation of normal intervals (SDNN) was associated with increased mortality. Also they mentioned that studies in chronic heart failure of both ischemic and nonischemic causes had shown that low SDNN predicted mortality.

Also, van de Borne et al [28] found that the low frequency (LF) variability of sympathetic nerve activity was absent in patients with severe heart failure. That was closely consistent with the abnormal variability of R-R interval. That suggested a central autonomic regulatory impairment in patients with heart failure.

### 2.1.2.2 Heart Rate Turbulence (HRT)

Parameters from HRT, TS and TO, have been shown to be effective predictors of mortality in patients who had experienced acute myocardial infarction and in patients with CHF. Schmidt et al. [16] found that TS was the most powerful predictor of follow-up mortality in EMIAT and the second most powerful predictor in MPIP. In both MPIP and EMIAT, the combination of abnormal TO and TS was the most powerful multivariate risk predictor. Cygankiewicz et al. [29] investigated the use of HRT for prediction of all-cause mortality and sudden death in patients with CHF who enrolled in Muerte Subita en Insuficiencia Cardiaca (MUSIC). It was shown that abnormal TS and HRT category 2 were independently correlated with increased all-cause mortality, sudden death, and death due to heart failure progression after adjustment for clinical variables in multivariate analysis.

### 2.1.2.3 Detrended Fluctuation Analysis (DFA)

The two properties of objects in space or processes in time that are called fractals are self-similarity and scaling, as described in the book “Fractal Physiology”[30]. Furthermore, self-similarities could lead to power-law scalings which were revealed as straight lines when the logarithm of the measurement was plotted against the logarithm of the scale at which it was measured.

There have been evidences that aging and disease cause alterations in the fractal dynamics in physiology. Peng et al [13] wrote that cardiac beat-to-beat intervals normally fluctuated in a complex and seemingly erratic manner, which was different from traditional thinking that a healthy heartbeat was regulated according to the classical principle of homeostasis. Studies showed that under healthy conditions, beat-to-beat interval time series exhibited long-range power-law correlations. Certain disease states would cause alterations in this scale-invariant (fractal) correlation property. Furthermore, they proposed to use the method DFA to detect pathological states in patients. The method DFA yields short-term fractal scaling exponent,  $\alpha_1$ , and long-term fractal scaling exponent,  $\alpha_2$ . They showed that when the short-term and long-term fractal scaling exponents from healthy subjects and subjects with CHF were plotted on a scatter plot, there was a separation between these two groups of subjects and each group formed its own cluster.

There have been further evidences that the short-term and long-term fractal scaling exponents can be used for prognosis of patients with heart diseases. Huikuri et al[15] assessed 24-hour Holter recordings in 446 survivors of acute myocardial infarction with depressed left ventricular function (ejection fraction  $\leq 35\%$ ). Short-term and long-term fractal scaling exponents along with other traditional time and frequency domain HRV measures were extracted from these recordings. These subjects were followed for a mean $\pm$ SD period of 685 $\pm$ 360 days. It was found

that reduced short-term fractal scaling exponent,  $\alpha_1$ , was the most powerful HRV measure as a predictor of all-cause mortality. It remained an independent predictor of death after adjustment for other post-infarction clinical variables, such as age, ejection fraction, NYHA class and medication.

## 2.2 PREDICTION OF SCA

### 2.2.1 *Motivation*

There have been evidences that too many shocks from ICDs would decrease the quality of life of patients, thus, there is a need to minimize the number of shocks given by the ICDs. Irvine et al[31] aimed to compare quality-of-life outcome between patients randomized to ICD therapy and patients randomized to amiodarone treatment in the Canadian Implantable Defibrillator Study (CIDS) and to evaluate the effects on quality-of-life outcomes of receiving shocks from the device. Quality of life of patients was assessed by use of Mental Health Inventory (MHI) and the Nottingham Health Profile (NHP). Patients were followed for up to a year. It was shown that ICD therapy could improve the emotional and physical health scores of patients, whereas amiodarone therapy did not improve the quality of life of patients. On the other hand, for the patients in the ICD-treated group who received 5 or more shocks from their ICD, their quality of life did not improve.

### 2.2.2 *Development of Arrhythmia (Arrhythmogenesis)*

There have been findings that suggest that changes in autonomic activity contributed to arrhythmogenesis. Therefore, one may be able to predict the occurrences of SCA by analyzing the patients' R-R intervals. For example, Shusterman et al. [32] hypothesized that neurohormonal activity contributed to the initiation of sustained VT as seen in indices of HRV. From the Holter ECGs from 53 patients with VT, they found that heart rate rose, while low frequency power (LFP),

normalized low frequency power (LFPn) and the value of low frequency power divided by high frequency power (LFP/HFP) fell before the onset of VT. Also, Rubart and Zipes,[2] referenced two studies which suggested a causal relationship between altered autonomic innervation and SCD due to VT/VF. In the first study, chronic infusion of nerve growth factor (NGF) to the left stellate ganglion in dogs with chronic myocardial infarction and complete atrioventricular block resulted in spatially heterogeneous sympathetic cardiac hyperinnervation and a dramatic increase in the incidences of SCD from VT/VF.[33] In the second study, Liu et al [34] reported that a high-cholesterol diet would cause myocardial hypertrophy and cardiac sympathetic hyperinnervation in rabbits in the absence of coronary artery stenosis and infarction. In addition, they found a noticeable increase in the incidence of VF.

As autonomic nervous system contributes to the development of arrhythmia, one may be able to prevent the occurrences of arrhythmia by modulation of autonomic nervous system. That has been shown by Vanoli et al. [11] Vanoli et al showed that vagal activation could prevent VF caused by acute myocardial ischemia. Vagus nerve stimulation reduced the occurrence of VF from 100% to 10% during the process of coronary artery occlusion. The interaction between multiple factors took part in this effect. Among all the factors the most critical were the antagonism with sympathetic activity and the reduction in heart rate, with the latter played an important but not essential role.

### 2.2.3 *Methods*

#### 2.2.3.1 Machine Learning

There has been a trend that algorithms from machine learning are being implemented to aid the process of diagnosis of different diseases and they show promising results. This section gives a small sample of results from past studies.

The following study shows that kernel-based methods such as SVM give desirable classification performances. Wei et al [35] investigated several machine learning methods for automated classification of clustered microcalcifications (MCs). The methods they considered were: SVM, kernel Fisher discriminant (KFD), relevance vector machine (RVM) and committee machines (ensemble averaging and AdaBoost). They used ROC analysis to evaluate and to compare classification performance by these machine learning methods. In their experiments, the kernel-based methods (SVM, KFD and RVM) had the best performance ( $A_z=0.85$ , SVM), performing significantly better than the well-established, clinically proven approach that was based on neural network ( $A_z=0.80$ ) at the time of the study.

The aim of the following study was to verify if methods based on a classification and regression tree (CART) would give good classification performances. Vlahou et al [36] investigated if the commercially available classification algorithm biomarker patterns software (BPS), which was based on a CART, would be effective in distinguishing ovarian cancer from benign diseases and healthy controls. Serum protein mass spectrum profiles each with one of the three conditions were analyzed. A decision tree resulted in an accuracy of 81.5% in the cross-validation analysis and 80% in a blinded set of samples in differentiating the ovarian cancer from the control groups, using five protein peaks.

Particularly, the following study used algorithms from machine learning to predict the occurrences of SCDs. Ebrahimzadeh et al [37] used linear, time-frequency and nonlinear features from HRV of ECG signals to predict occurrences of SCD. These ECG signals were obtained from the open access database prepared by MIT-BIH database with the title of Sudden Cardiac Death Holter database and Normal Sinus Rhythm database. Healthy people and people at risk of SCD were classified by k-Nearest Neighbor (k-NN) and Multilayer Perceptron Neural Network (MLP).

With the combination of features, SCD could be predicted with accuracy of 99.73%, 96.52%, 90.37% and 83.96% for the first, second, third and fourth one-minute intervals, respectively, before SCD occurrences.

#### 2.2.3.2 Principal Component Analysis (PCA)

PCA has been broadly used for analyzing ECG signals. There is a well-written summary authored by Castells et al [38]. PCA-based strategies are useful for ECG signal processing because the ECG signal exhibits redundancy. PCA can be used to find a more compact representation of the signal, to search for specific patterns or to extract a certain physiologic activity. PCA has clinical application such as characterization and diagnosis of myocardial ischemia, ventricular repolarization and atrial fibrillation.

PCA and least square support vector machine (LS-SVM) has been used in combination in the past to detect ECG arrhythmias. That was implemented by Polat and Güneş. [39] Firstly, the dimension of ECG Arrhythmias dataset is reduced using PCA. Secondly, diagnosis of ECG arrhythmias was conducted using LS-SVM classifier. Accuracy rates of 100% were achieved with 70-30% of training-test dataset and 80-20% of training-test dataset. Such method would assist the physicians to make the final diagnostic decision.

### 2.3 SUMMARY

Firstly, ICDs have been found to decrease mortality in patients with mild to moderate heart failure. Though ICDs could be life-saving, many of such patients who received ICDs ended up not benefiting from them during the follow-up period. Therefore, risk stratification for SCAs for patients with mild to moderate heart failure is necessary to avoid waste of resources and decreased quality of life for the patients. Methods such as HRV, HRT and DFA have been found to give

insights into one's cardiac health. In Chapter 3, the results of risk stratification for SCAs with such methods to better identify candidates for ICD therapy are presented. Secondly, there is a trend that machine learning is being more widely used to help with the process of diagnosis in the medical community. As for cardiac arrhythmia, currently machine learning is often used to classify cardiac arrhythmia after they have occurred, while prediction of cardiac arrhythmia using algorithms from machine learning is not common. Chapters 4 and 5 of this dissertation seek to address this deficiency in the literature by presenting the results of prediction of SCAs for patients with CHF. As stated earlier, if ICDs can predict the occurrences of SCAs accurately, they can either issue warnings or take preventive measures so that shocks may be averted. All the heart rhythms, both normal rhythms and pre-cardiac-event rhythms, which were analyzed in these chapters were obtained from the same group of patients with CHF. It makes clinical sense to have all the heart rhythms obtained from the same group of patients with heart failure as they would truly resemble the rhythms that ICDs are monitoring when the ICDs have already been inserted into the patients' chests. An ICD needs to be able to distinguish pre-cardiac-event rhythms from normal rhythms from the same patient with heart failure so that the ICD would issue warnings or take preventive measures for impending SCAs at the proper times.

## Chapter 3. SCD-HEFT: USE OF R-R INTERVAL STATISTICS FOR LONG-TERM RISK STRATIFICATION FOR ARRHYTHMIC SUDDEN CARDIAC DEATH

As described in Chapter 1, the first goal of our work was to perform risk stratification for SCAs for patients with mild to moderate heart failure by using R-R interval statistics. Among all the measures from DFA, HRT, frequency-domain and time-domain methods, fractal scaling exponents from DFA are the best predictors for SCAs. Some of the other measures such as TS from HRT and low-frequency power to high-frequency power ratio (LFP/HFP ratio) are also statistically significant predictors. When R-R interval statistics are used for the design of an ICD therapy screen test, high negative predictive values were achieved while excluding about half of the patients with CHF from consideration of ICD therapy. This work was published in *Heart Rhythm* in October of 2015. [40]

*This is an author-created, un-copyedited version of an article accepted for publication in Heart Rhythm. Heart Rhythm is not responsible for any errors or omissions in this version of the manuscript or any version derived from it. The Version of Record is available online at <http://www.heartrhythmjournal.com/article/S1547-5271%2815%2900804-8/fulltext>.*

### 3.1 ABSTRACT

#### 3.1.1 *Background*

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) a significant fraction of the CHF patients ultimately did not die suddenly from arrhythmic causes that an implantable

cardioverter-defibrillator (ICD) could have prevented. Although many patients with CHF deserve ICD therapy, CHF patients will benefit if better tools are available to identify those that are most likely to use an ICD to prevent death from ventricular tachycardia (VT) or ventricular fibrillation (VF).

### 3.1.2 *Objective*

To identify predictor variables extracted from SCD-HeFT patients' R-R intervals prior to randomization and ICD insertion that correlate to subsequent occurrences of arrhythmic sudden cardiac death (SCD) and mortality and use them to design an ICD therapy screening test.

### 3.1.3 *Methods*

Data for analysis was available in 475 subjects enrolled in the ICD arm of SCD-HeFT. A total of 10 predictor variables, including DFA, HRT and traditional HRV methods, were extracted from pre-randomization Holter data. All test variables were correlated to the occurrence of SCD using areas under curve (AUC) from ROC analysis. ICD therapy screening tests subsequently were designed by minimizing the cost of false classifications. Survival analysis which included log-rank test and proportional hazards models were also performed.

### 3.1.4 *Results*

The short-term scaling exponent,  $\alpha_1$ , and long-term scaling exponent,  $\alpha_2$ , from DFA, the ratio of low frequency power (LFP) to high frequency power (HFP), the number of PVCs per hour and turbulence slope (TS) from HRT are all statistically significant variables for predicting the occurrences of SCD ( $p < 0.001$ ) and survival (log-rank  $p < 0.01$ ). The most powerful multivariate

predictor tool using the Cox Proportional Hazard was  $\alpha_2$  with a hazard ratio of 0.0465 (95% CI: 0.00528 - 0.409,  $p < 0.01$ ).

### 3.1.5 *Conclusions*

Predictor variables extracted from patient R-R intervals correlate to the occurrences of SCD and distinguish survival among SCD-HeFT ICD patients. We believe SCD prediction models should incorporate Holter based R-R interval analysis to refine ICD patient selection for SCD prevention especially in removing patients who are unlikely to benefit from ICD therapy.

## 3.2 INTRODUCTION

Implantable Cardioverter-Defibrillator (ICD) therapy decreases mortality in select post-MI and CHF patients.[12], [41] However, many deaths occur from mechanisms unamenable to ICD therapy. New tools to better identify candidates who would benefit the most from ICD therapy remains a challenge.[42] The proof of this can be found In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) where only 182 patients received ICD shocks for VT/VF over a median follow-up period of 45.5 months out of the 811 CHF patients who received ICD therapy (22.4%).[26]

It has been shown in the past that traditional HRV measures in the time and frequency domains have prognostic power.[27] But they are neither measured in well-conducted ICD clinical trials nor harbor significant power to serve as a practical risk predictor. More recently, however, methods based on non-linear dynamics, such as DFA and HRT, which looks at the return to equilibrium of heart rate after a PVC, may yield superior predictive results.[16], [43] DFA fractal exponents of heart rate time series have been shown to correlate with one's autonomic tone while HRT parameters correlate with one's baroreflex sensitivity.[44], [45] In this paper, we investigated

the effectiveness of these methods, together with traditional Holter methods to predict which SCD-HeFT patients would benefit or not benefit from their ICD over the duration of the study.

### 3.3 METHODS

#### 3.3.1 *Subjects*

SCD-HeFT was a large National Institutes of Health funded clinical trial that was designed to study the effectiveness of ICD and amiodarone therapies in patients with mild to moderate heart failure.[12] From September 16, 1997 to July 18, 2001, 2521 patients were randomly assigned in equal proportions to receive placebo, amiodarone or a single-chamber ICD programmed to shock-only mode (model 7223, Medtronic). All patients were followed until October 31, 2003. The inclusion criteria for the study was that the patients had to be at least 18 years old, have NYHA class II or III chronic, stable CHF due to ischemic or nonischemic causes and a LVEF of no more than 35 percent.

The Holter monitor sub-study was approved by the human studies committee at the participating institutions. Holters were obtained in the two weeks prior to randomization to placebo, amiodarone, or ICD. Holter analysis included characterization of non-sustained ventricular tachycardia (NSVT). Holter staff and readers were blinded to clinical parameters, randomization status, and outcomes. Among the 2521 patients enrolled in SCD-HeFT, 2040 (81%) had  $24 \pm 6$  hours of readable data: 687 were randomly assigned to placebo, 674 to amiodarone, and 679 to ICD therapy (664 actually received an ICD).

In this analysis, we were able to study the relationship between baseline Holter data and subsequent ICD therapy in 475 ICD patients in whom high quality Holter recordings were

available. These patients were those with at least 16 hours of data and at least 90% readability.

Table 3.1 shows the characteristics of SCD-HeFT subjects included in the sample.

Table 3.1: Characteristics of the CHF patients from SCD-HeFT in the ICD arm.

Characteristic	CHF patients from SCD-HeFT (n=475)
Age at Enrollment	Average: 59.5 (19-90) Median Ag: 60
Gender	370 males 105 females
Races	372 Caucasians 83 African Americans 15 Latin Americans 1 Native American 4 Asians
NYHA	Class II: 342 Class III: 133
Heart Failure etiology	223 non-ischemic 252 ischemic
Number of patients using $\beta$ -blocker	327

### 3.3.2 *Predictor Variables derived from Holter Monitor Data*

Holter monitor data were transferred from flash cards and magnetic tapes onto the modified Marquette MARS 8000 reader system, and were then reviewed by Core Laboratory staff, and validated. Each tape scan was reviewed for accuracy, and the results tabulated.

MIT annotation files of the ECG recordings were generated using the MARS Ambulatory ECG Analysis System. R-R intervals were then extracted from the MIT annotation files using the program ann2rr from Physionet. We analyzed the variability of the R-R intervals by DFA, HRT, and traditional heart rate variability measures in the frequency-domain and time-domain methods.

#### 3.3.2.1 DFA

DFA as a predictive tool in heart disease was introduced by Peng et al.[13] The DFA yields a short-term fractal exponent,  $\alpha_1$ , and a long-term fractal exponent,  $\alpha_2$ . These exponents tell us about the self-similarity of the R-R intervals in both the short term and long term and have been considered prognostic in certain disease states.[14], [46]

In performing DFA, the record of R-R intervals of each person were broken into a sequence of segments of 8192 consecutive heartbeats shifted by 10 minutes to find  $\alpha_1$  and  $\alpha_2$  for each segment along the entire record. 8192 consecutive heartbeats were chosen to perform the calculation as recommended by Peng et al. The short-term and long-term fractal exponents for each segment were then averaged over all segments. The “fastdfa” algorithm was used for this computation.[47]

#### 3.3.2.2 HRT

HRT was introduced by Schmidt.[16] It describes the physiological response of the sinus node to PVCs. It consists of an initial acceleration followed by a deceleration of the heart rate.

Turbulence slope (TS) and turbulence onset (TO) are the two parameters associated with the HRT method.

TS is defined as the maximum slope of a regression line over any sequence of five subsequent R-R intervals within the first 20 R-R intervals after a PVC. TO is the percentage difference between the heart rate immediately following a PVC and the heart rate immediately preceding a PVC.

During the process of computing the HRT, we also determined the number of PVCs/hr for each patient and separately evaluated it as a risk stratification parameter.

#### 3.3.2.3 HRV Frequency-Domain Method – LFP/HFP ratio

In frequency domain analysis of heart rate variability, high frequency power (HFP, 0.15 – 0.4 Hz in adults) broadly reflects vagus nerve activity while low frequency power (LFP, 0.04 – 0.15 Hz in adults) reflects sympathetic activity.[28], [48], [49] Although not definitive, high LFP/HFP ratio tends to show the dominance of the sympathetic activity while low LFP/HFP ratio tends to reflect the dominance of the vagus nerve activity.

The power spectral density function for each subject was obtained through the Lomb periodogram algorithm.[17], [18] The Lomb periodogram method was chosen because R-R intervals are sampled at irregular time intervals and this algorithm performs well in the presence of artifacts and PVCs.

#### 3.3.2.4 HRV Time-Domain Methods – SDNN, mean heart rate, pNN50 and HRVTI

To determine the HRV measures in time domain we deleted all the artifacts and PVCs from the R-R intervals so that only normal-to-normal (NN) intervals were analyzed.

#### ***3.3.2.4.1 Standard Deviation of NN intervals (SDNN)***

Standard deviation of heartbeat intervals originated from the sinus nodes of the patients were calculated based on the heartbeat recordings. SDNN is a measure of the total variability of the NN intervals as it composes of the periodic fluctuations at all frequencies. Past research has shown that decreased variability in heart rate is a risk factor for mortality in post-myocardial infarction patients and patients with ischemic cardiomyopathy.[27], [50]

#### ***3.3.2.4.2 Mean Heart Rate***

Mean heart rate for each patient was expressed as the number of beats per minute (bpm). Past research has shown that elevated mean heart rate is a risk factor for mortality, cardiovascular disease and sudden death in patients with known or suspected coronary heart disease, post-myocardial infarction patients and patients with hypertension.[51]

#### ***3.3.2.4.3 pNN50***

pNN50 is the fraction of NN intervals that have a difference of more than 50ms in consecutive beats. pNN50 is a measure of how often there is a rapid change from one beat to the next one. Therefore, it is highly correlated with HFP in the frequency domain.[27]

#### ***3.3.2.4.4 Heart Rate Variability Triangular Index (HRVTI)***

With all the NN intervals from a patient plotted in a histogram, HRVTI is equal to the total number of NN intervals divided by the number of NN intervals in the modal bin in the histogram.[52] The Holter monitors in this study operated at the sampling rate of 128Hz. Therefore, the NN intervals were measured to the nearest 1/128s and the width of each bin in the histogram was equal to 1/128s.

### 3.3.3 *Outcomes*

The final status of patients and their causes of death are documented in SCD-HeFT via a blinded events committee.[53] A cardiac arrest was defined as the sudden loss of consciousness requiring transthoracic defibrillation and/or cardiopulmonary resuscitation to stabilize blood pressure and rhythm. Outcomes were SCD, VF and ventricular flutter (VFL) appropriate shock as defined by previous study. SCD-HeFT included a pre-specified protocol for ICD programming. This included a single zone of therapy at a detection rate of  $\geq 188$  beats/min. The initial detection interval was for 18 of 24 beats, and the redetect interval was for 12 of 16 beats. Shock-only mode was used with no antitachycardia pacing. Antibradycardia pacing was set to 50 beats/min with hysteresis of 34 beats/min, the minimal allowed heart rate.[54]

Based upon the final status, the subjects were separated into a positive group and a negative group. The positive group consisted of subjects who have received at least one appropriate shock for a VF episode or a VFL episode from their ICDs. Also, it included patients who have died from sudden tachy-arrhythmia as determined by the events committee.[53] The negative group consisted of all other SCD-HeFT subjects in the ICD patient sample.

### 3.3.4 *Statistical Analysis*

In order to find the prognostic power of the predictor variables, we performed a non-parametric two-sample Mann Whitney-Wilcoxon (MWW) test between the positive group and the negative group for each of the predictor variables. The null hypothesis of the MWW test is that the distributions of the two populations are the same.[55], [56] P-values less than 0.05 are considered statistically significant. Besides p-values from the MWW test, we also quantified the

prognostic power of the predictor variables by performing ROC analysis on the subjects.[57] We calculated the ROC curves and found the area under the curve (AUC) for each of the predictor variables. Also, bootstrapping was done by getting new samples for the two groups by resampling with replacement for a thousand times.[58] A new estimate of AUC was calculated at each bootstrap. Then we found the mean and the standard deviation of these AUC estimates for each predictor variable to provide a distribution of the AUC if such classification is performed with the entire population.

We combined two or three predictor variables to perform multifactorial ROC analysis in order to examine if the prognostic power can be improved.[59] With the combinations that give the highest AUC, we found the operating points by minimizing the cost of false classifications. Cost here can be defined as monetary costs and patient mortality. The cost function is the following:

$$\text{cost} = (1-p) * \gamma * x + p * \delta * (1-y) \quad \text{Equation 3-1}$$

where  $p$  is the proportion of positive cases,  $x$  and  $y$  are the  $x$ -coordinate and  $y$ -coordinate in the ROC curve which represent the values of one minus specificity and sensitivity respectively.  $\gamma$  is the cost of a false positive and  $\delta$  is the cost of a false negative. At the operating point that would minimize the cost, we listed the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and percentage of CHF patients excluded.

We plotted the Kaplan-Meier survival plots and performed log-rank test on the ICD-arm subjects on the variables from DFA, HRT, LFP/HFP and number of PVCs/hr. We also performed univariate and multivariate proportional hazards model analysis on all the variables. Time to event was the number of days to the occurrences of VF, VFL or sudden tachyarrhythmic death.

Lastly, we examined the correlations between all the measures through Pearson product-moment correlation coefficients to identify independent predictor variables.[60]

### 3.4 RESULTS

#### 3.4.1 *Prediction of Occurrences of VF, VFL or SCD*

Table 3.2 shows the respective median and interquartile range (IQR) for the positive and negative groups. As seen,  $\alpha_1$ ,  $\alpha_2$ , TS, Number of PVCs/hr and LFP/HFP are all statistically significant predictor variables with p-values less than .001. Also, TO is a statistically significant predictor variable with a p-value less than .05.

Table 3.2: Statistical association of predictor variables with the occurrences of VF, VFL or SCD

	Positive group Median (IQR) (n=72)	Negative group Median (IQR) (n=403)	p-values
$\alpha_1$	.4331 (.3505 – .5732)	.6140 (.4762 – .8030)	<.001
$\alpha_2$	.6865 (.6002 – .8497)	.9072 (.7313 – 1.016)	<.001
TS (ms/RRI)*	1.360 (.5421 – 2.648)	2.1746 (1.120 – 4.542)	<.001
TO (%)*	.0030 (-.0028 – .0088)	0.000 (-.0084 – .0078)	<.05
Number of PVCs/hr	17.32 (6.255 – 33.99)	5.097 (1.010 – 17.60)	<.001
LFP/HFP	.4953 (.3890 – .5885)	.6687(.4951-.9365)	<.001
SDNN (ms)	113.3 (76.63 – 154.5)	115.0 (86.98 – 151.5)	.37
Mean heart rate (bpm)	78.70 (69.82 – 85.79)	75.11 (67.68 – 84.20)	.16
pNN50 (%)	19.44 (10.36 – 35.02)	16.81 (7.718 – 29.76)	.21
HRVTI	26.80 (17.55 – 34.15)	28.50 (20.91 – 37.71)	.08

\* n=70 for the Positive group, n=388 for the Negative group

Table 3.3 shows the AUCs for each predictor variable and each combination of predictor variables in the ROC analysis. Among the univariate ROC analysis, it can be seen that  $\alpha_1$  performs the best with the mean AUC equals to .73. LFP/HFP performs second best with a mean AUC equal to .71, followed by  $\alpha_2$  with a mean AUC equal to .69. As we combined more variables together and performed multifactorial ROC analysis, the AUCs increased as seen in Table 3.3. We tried four different combinations each with three different predictor variables. An AUC of .79 was achieved for all combinations. Figure 3.1A shows the ROC curves with the five predictor variables with the highest prognostic power while Figure 3.1B shows the five multifactorial ROC curves. From Figure 3.1B one can observe that the classification performed with  $\alpha_1$  and  $\alpha_2$  has a comparable performance as the classifications performed when one more predictor variable is added.

Table 3.3: Results of AUCs from univariate and multifactorial ROC curves for prediction of occurrences of VF, VFL or SCD

	AUC Mean (SD)
$\alpha_1$	.73 (.03)
$\alpha_2$	.69 (.03)
TS	.64 (.04)
TO	.59 (.03)
Number of PVCs/hr	.67 (.03)
LFP/HFP	.71 (.03)
SDNN	.53 (.04)
Mean heart rate	.55 (.03)
pNN50	.55 (.04)
HRVTI	.57 (.04)
$\alpha_1, \alpha_2$	.78
$\alpha_1, TS$	.76
$\alpha_1, TO$	.75
$\alpha_1, \text{number of PVCs/hr}$	.75
$\alpha_1, \text{LFP/HFP}$	.76
$\alpha_1, \text{SDNN}$	.75
$\alpha_1, \text{mean heart rate}$	.74
$\alpha_1, \text{pNN50}$	.75
$\alpha_1, \text{HRVTI}$	.76
$\alpha_1, \alpha_2, TS$	.79
$\alpha_1, \alpha_2, \text{LFP/HFP}$	.79
$\alpha_1, \alpha_2, \text{number of PVCs/hr}$	.79
$\alpha_1, \alpha_2, \text{HRVTI}$	.79

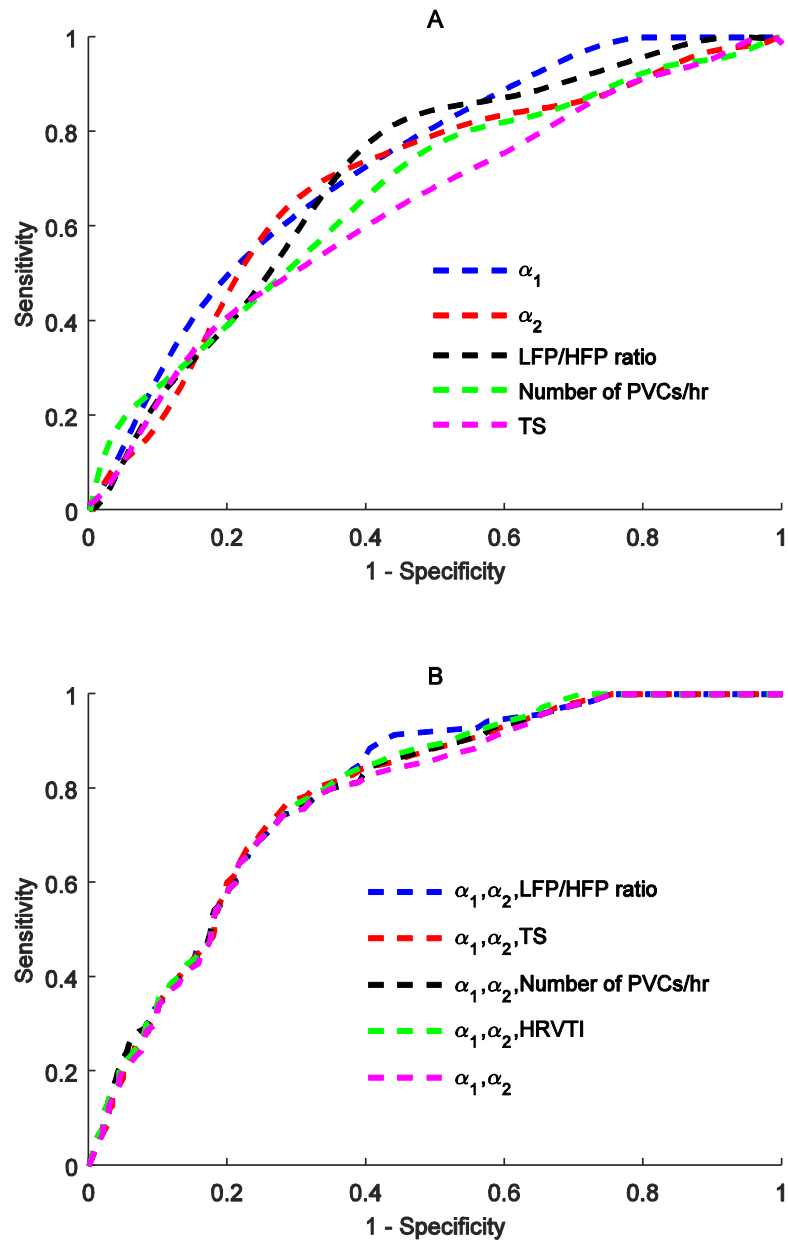


Figure 3.1: Plot of ROC curves for five predictor variables with the highest prognostic power for occurrences of VF, VFL or SCD (A). Plot of multifactorial ROC curves for occurrences of VF, VFL or SCD (B).

We assumed that the cost of a false negative ( $\delta$ ) was ten times the cost of a false positive ( $\gamma$ ). By minimizing the cost of false classifications in each of the multifactorial ROC curves with three predictor variables, we found the corresponding thresholds along with their classification performances (Table 3.4). It can be observed that for all these tests, they have moderate sensitivities and very high NPVs. The outcome of each of these tests is about half of the CHF patients can be excluded from ICD therapy consideration.

Table 3.4: Thresholds that give minimum costs and classification performance for prediction of recurrences of VF, VFl and SCD for  $\gamma = 1$ ,  $\delta = 10$ .

Thresholds with minimal costs	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	CHF patients excluded (%)
$\alpha_1 \leq .43$ or $\alpha_2 \leq .66$ or LFP/HFP $\leq .60$	91.4	55.9	27.2	97.3	48.7
$\alpha_1 \leq .40$ or $\alpha_2 \leq .71$ or TS $\leq 1.05$	84.3	60.6	27.8	95.5	53.7
$\alpha_1 \leq .45$ or $\alpha_2 \leq .69$ or number of PVCs/hr $\leq 19$	85.7	57.7	26.8	95.7	51.1
$\alpha_1 \leq .48$ or $\alpha_2 \leq .80$ or HRVTI $\leq 15.8$	87.1	56.2	26.4	96.0	49.6

### 3.4.2 Survival Analysis

Figure 3.2 shows the Kaplan-Meier survival plots for DFA variables, LFP/HFP, Number of PVCs/hr and HRT variables, each separated by quartiles. From the log-rank test p-values, it can be seen that there are statistically significant differences between the survival functions below and above the median of the predictor variables for  $\alpha_1$ ,  $\alpha_2$ , LFP/HFP, Number of PVCs/hr and TS. This fact is even more pronounced when one looks at the Kaplan-Meier survival plot by quartiles of  $\alpha_1$ . Q1 has a survival rate of 60% at the end of SCD-HeFT while the survival rate of Q4 stays almost at 100%.

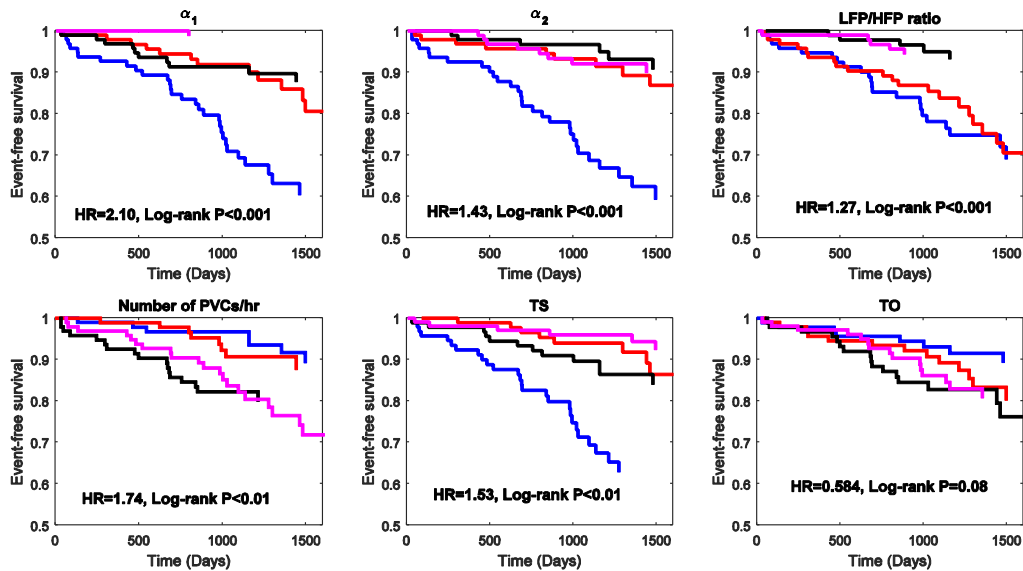


Figure 3.2: Kaplan-Meier Survival Plots for occurrences of VF, VFL or SCD by quartiles of the six predictor variables. Q1 is blue, Q2 is red, Q3 is black and Q4 is magenta. Log-rank P values were obtained from comparing the survival functions of Q1 and Q2 versus the survival functions of Q3 and Q4.

Table 3.5 shows the results from both univariate and multivariate cox proportional-hazards regression performed on the data. From the univariate analysis, by looking at the p-values, it can be seen that  $\alpha_1$ ,  $\alpha_2$ , LFP/HFP, Number of PVCs/hr and TS are all statistically significant covariates in distinguishing the survival. From the multivariate analysis, it can be seen that  $\alpha_2$  stands out as the only independent and statistically significant covariate in finding the differences in the survivals of the patients with a hazard ratio of 0.0465 (95% CI: 0.00528 – 0.409,  $p < 0.01$ ). Therefore, one can observe that the fractal scaling exponents from DFA are powerful variables in distinguishing survivals for patients.

Table 3.5: Hazard ratios from the Cox proportional hazards (PH) model for Predictions of VF, VFL or SCD.

Covariate	Univariate Analysis				Multivariate Analysis			
	Beta	HR [exp(beta)]	95% CI	p-value	beta	HR [exp(beta)]	95% CI	p-value
$\alpha_1$	-4.06	0.0173	(3.83E-3 0.0785)	<0.001	0.36706 2	1.44	(0.0823 25.3)	0.802
$\alpha_2$	-3.46	0.0316	(7.82E-3 0.127)	< 0.001	-3.06931	0.0465	(0.00528 0.409)	<0.01
TS	-0.242	0.785	(0.672 0.918)	<0.01	-0.11552	0.891	(0.763 1.04)	0.144
TO	12.4	2.45E+05	(0.732 8.2E10)	0.0559	8.64937 3	5.71E+03	(3.20E-06 1.02E13)	0.426
Number of PVCs/hr	0.032	1.03	(1.02 1.05)	< 0.001	0.01857 1	1.02	(0.997 1.04)	0.0932
LFP/HFP	-2.39	0.0919	(0.0277 0.305)	< 0.001	-1.26969	0.281	(0.0479 1.65)	0.160
SDNN	-0.0041	0.996	(0.990 1.00)	0.19	-0.00422	0.996	(0.983 1.01)	0.537
Mean heart rate	0.0201	1.02	(0.996 1.04)	0.097	0.01298 6	1.01	(0.984 1.04)	0.380
pNN50	0.0015	1.00	(0.989 1.01)	0.817	-0.00421	0.996	(0.970 1.02)	0.752
HRVTI	-0.0213	0.979	(0.955 1.00)	0.088	0.02420 6	1.02	(0.974 1.08)	0.348

### 3.4.3 Correlations between Predictor Variables

The correlation between all the predictor variables was investigated using PPMCCs and they are shown in Figure 3.3. PPMCCs are presented in absolute values. Black means perfect linear correlation (PPMCC=1). While white means no correlation (PPMCC=0). From Figure 3.3, it can be seen that LFP/HFP and  $\alpha_1$  are highly correlated. The PPMCC between LFP/HFP and  $\alpha_1$

is 0.7160. This high correlation is due to the fact that when the heart rate exhibits significant variability in the short time scale it will result in a R-R sequence with large HFP and small LFP and a small  $\alpha_1$ . Similarly, when the heart rate exhibits significant variability in the large time scale it will have small HFP and large LFP and a large  $\alpha_1$ . Therefore, even though LFP/HFP has moderate prognostic power in predicting occurrences of ventricular arrhythmia (AUC=.71, Table 3.3), it does not add significant prognostic power when combined with  $\alpha_1$ . On the other hand, even though TS has smaller prognostic power than LFP/HFP (AUC=0.64, Table 3.3), it can still add prognostic power when it is used in combination with  $\alpha_1$  as TS and  $\alpha_1$  have a low correlation (PPMCC=0.2024). From Table 3.3, it can be seen that  $\alpha_1$ , TS has the same AUC as  $\alpha_1$ , LFP/HFP (AUC=.76). Besides, DFA fractal exponents and HRT parameters have low correlation with mean heart rate (PPMCCs<.2), as shown in Figure 3.3.

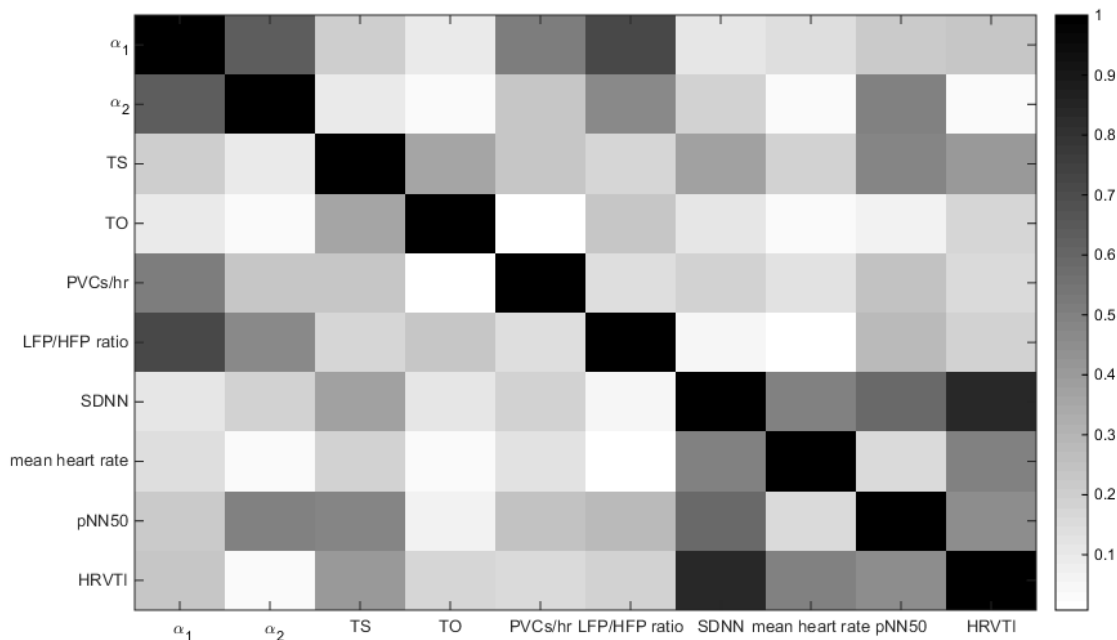


Figure 3.3: Correlation Plot for All the Predictor Variables expressed through PPMCCs.

White means no correlation. Black means perfect correlation.

### 3.5 DISCUSSION

#### 3.5.1 *Important Findings*

Heart failure has been linked to arrhythmia related sudden death. VT/VF have been the most likely cause of SCD, however reduced ejection fraction has been repeatedly associated as an independent risk factor for sudden death.[41] Evaluation of R-R intervals with non-linear dynamics in CHF patients with ICD might predict which patients are likely to experience appropriate ICD therapy or have SCD. The short-term scaling exponent,  $\alpha_1$ , (AUC = .73) and the long-term scaling exponent,  $\alpha_2$ , (AUC = .69) from DFA, LFP/HFP ratio (AUC = .71), number of PVCs/hr (AUC = .67) and TS (AUC = .64) have the highest prognostic powers in identifying candidates for ICD therapy independently among all the predictor variables investigated. When we combined  $\alpha_1$ ,  $\alpha_2$  and one other predictor variable to perform multifactorial ROC analysis, AUCs of 0.79 were achieved for the prediction of occurrences of VF, VFL or SCD. Moreover, negative predictive values from the combined DFA and spectral measures were strong enough to allow us to be confident that certain SCD-HeFT ICD patients (approximately half) did not need an ICD with 97.3% certainty.

Setting  $\delta$  10 times  $\gamma$  was an assumption, and it was used to help us find the operating point for the ICD therapy screen test and hence it should only be used as a reference.  $\delta$  being 10 times  $\gamma$  means that the screen test would rather give unnecessary ICD therapy than fail to give necessary ICD therapy. The changes in the ratio of  $\delta$  to  $\gamma$  will lead to changes in classification performances.

$\alpha_1$ ,  $\alpha_2$ , LFP/HFP ratio, number of PVCs/hr and TS can all distinguish survivals independently (log-rank p values < 0.01, univariate Cox PH model p values < 0.01). Notably from the Kaplan-Meier survival plot analysis in Figure 2, the differences in survival between Q1 in  $\alpha_1$  and Q4 in  $\alpha_1$  are very pronounced. Q1 has a survival rate of 60% at the end of SCD-HeFT while

the survival rate of Q4 stays almost at 100%. Therefore, if one's  $\alpha_1$  is in Q4, one can have confidence that one will not experience a fatal ventricular arrhythmic event for the duration of the trial. In performing the multivariate cox proportional-hazards regression,  $\alpha_2$  is the only independent and statistically significant covariate in distinguishing the survivals of the patients with a hazard ratio of 0.0465 (95% CI: 0.00528 – 0.409,  $p < 0.01$ ) as seen in Table 3.5.

One advantage of DFA over conventional time series methods, such as spectral analysis, is that it is more suited for non-stationary physiological signals. There are a lot of extrinsic trends in one's heart rate that arise due to one's activities or uncorrelated environmental stimuli. DFA discards these trends and focus on the intrinsic dynamics of the autonomic nervous system itself. DFA is also a better method in looking at the self-similarity in the R-R intervals when altered self-similar behaviors were found in patients with cardiovascular diseases and old age.[43] Its advantage is shown by  $\alpha_1$  from DFA having higher prognostic power than LFP/HFP ratio.

Our research showed that measures from HRT, especially TS, have decent prognostic power for predicting arrhythmic SCD among subjects in SCD-HeFT. This finding is consistent with results from past researches. For example, HRT measures have been shown to be able to do risk stratification for mortality in CHF patients enrolled in Muerte Subita en Insuficiencia Cardiaca (MUSIC).[61] Also, these measures have been shown to stratify risks for serious arrhythmic events in patients with left ventricular dysfunction.[62]

Amiodarone was associated with an overall mortality risk reduction in GESICA where survival benefit appeared to occur in those patients whose pre-treatment resting heart rate was greater than 90 bpm.[63] Fractal exponents from DFA and HRT parameters can be used as additional independent predictors for SCD as they have low correlation with the mean heart rate (PPMCCs < .2).

$\alpha_1$  from DFA has high correlation with the LFP/HFP ratio as shown by their PPMCC ( $r=0.7160$ ). This finding is consistent with the results of past research.[64] Since measures from DFA are highly correlated with the LFP/HFP ratio, nothing significant is gained by combining them. However, if DFA measures are combined with another predictor variable with moderate prognostic power but low correlation, such as TS, it is possible to achieve better classification performances.

### 3.5.2 *Study Limitations*

There are several limitations to consider. First, some of our measures are affected to various degrees by the extent of heart failure. There may be significant deviations from the norm, depending on the degree of heart failure (NYHA class II vs class III) and the underlying type of heart disease (ischemic vs nonischemic) with regard to the LFP, HFP, and LFP/HFP ratio of the spectral and fractal components of HRV. Our findings are interpreted broadly for the entire heart failure population because HRV reference values for stable heart failure subgroups are not yet described. Second, no predictive tool can be expected to provide anything but incremental benefit over the present clinical knowledge base of SCD prediction in heart failure. Clearly, the positive predictive value found in our study will not alter the ability to discern who will receive shocks from an ICD and who will not. In contrast, the negative predictive value is high (>95%). This has value as a screen test for excluding patients with CHF from ICD therapy. Third, we have endeavored to capture an economic value of this negative predictive methodology. To make any definitive arguments about the economic cost savings of these statistical tools requires detailed capture of hospital expenditures in a prospective manner tracked against mortality- and quality of

life-adjusted finances using our metrics. As such, our use of a 1 in 10 ratio is meant purely to provide a way to estimate value, not as a firm ratio upon which to make clinical decisions.

### 3.6 CONCLUSION

Survival in heart failure patients can be improved by placement of ICDs, however less than 25% of patients who receive ICDs experience SCD or appropriate shock therapy. We have shown that variables extracted from non-linear dynamic analysis of SCD-HeFT subjects' R-R interval recordings have prognostic power for predicting SCD and appropriate ICD shocks in CHF patients who have ICDs.  $\alpha_1$  and  $\alpha_2$  from DFA, LFP/HFP ratio, number of PVCs/hr and TS correlate with the occurrences of SCD and distinguish the survivals in the SCD-HeFT subjects in the ICD arm. Perhaps most importantly, the ability to determine who will not benefit from an ICD can be found in these tools. Further work should be done to examine the possibility of utilizing these variables for ICD therapy screen tests.

### 3.7 ACKNOWLEDGEMENT

Supported by grants (UO1 HL55766, UO1 HL55297, and UO1 HL55496) from the NHLBI, National Institutes of Health, and by Medtronic, Wyeth-Ayerst Laboratories, and Knoll Pharmaceuticals. Technische Universitat Munchen provided the program used for HRT calculation. The programs ann2rr and lomb from Physionet were also used in performing this research.

### 3.8 CLINICAL PERSPECTIVES

Our research confirms that the short-term and long-term fractal exponents from DFA, which describe self-similarity in patients' R-R intervals, contain valuable information about the patients' cardiovascular health. More specifically, our research shows that both of the fractal exponents can be used to do long-term prediction of the occurrences of sudden death and survivals among class II/III heart failure patients. These measures could be measured and incorporated when a decision has to be made on whether a class II/III heart failure patient should receive an ICD therapy. From SCD-HeFT, it was shown that many of the heart failure patients who received ICDs ended up not benefiting from them. Our research can help eliminate unnecessary ICD therapy and reduce waste of resources. In clinical practice, Holter data would be obtained from heart failure patients to determine the short-term and long-term fractal exponents. High values of these exponents would indicate, if supported by standard ICD screening, a high probability that the patients could be excluded from ICD therapy.

## Chapter 4. TOWARD RELIABLY PROVIDING A 5 MINUTE WARNING OF AN IMPENDING ICD SHOCK

As described in Chapter 1 of this dissertation, one of the goals of our research is to find out if it is possible to provide warnings for impending SCAs. This research topic is made possible with the normal rhythms and the pre-shock rhythms available from the ICDs implanted in the patients enrolled in SCD-HeFT. We found that the normal rhythms and the pre-cardiac-event rhythms indeed have different characteristics and it is possible to use the rhythm statistics and demographic information of patients as features to train machine learning algorithms and then use these algorithms to classify such rhythms. Also, though more subtle, pre-appropriate-shock rhythms and pre-inappropriate-shock rhythms have different characteristics and they can also be classified using machine learning algorithms. Such findings show promise that cardiac events indeed can be predicted in real time. If real-time prediction is implemented successfully, patients and medical units can be alerted when there are impending cardiac events. As a result, it will improve patient safety and create the opportunity for alternate patient management.

### 4.1 ABSTRACT

#### 4.1.1 *Objective*

The objective of this study is to demonstrate that a machine learning algorithm can be effectively predicting the onset of VF and rapid VT in ICD patients in SCD-HeFT. Such a machine learning algorithm can be implemented on ICDs providing enough time to warn the patient and health rescue systems of an impending electric shock and perhaps provide a means to avert it. At minimum, the very provision of a warning, even within a short time period, can be sufficient to improve outcomes and safety for ICD patients.

#### 4.1.2 *Background*

Cardiac risk stratification for both all-cause and sudden death mortality for the proper use of ICD therapy is well known. Appropriate ICD shocks can occur at a rate of 5-10% per year in typical candidates. Usually, ICD shocks are unheralded. Although they often result in a favorable resolution of a ventricular tachyarrhythmia, the provision of an early warning system has been long sought, so that patients can seek the additional care that is often required in patients who receive shocks, such as for heart failure and myocardial ischemia. Using the ICD ECG R-R interval database from SCD-HeFT, our goal is to predict the onset of ventricular tachyarrhythmia using machine learning tools to understand individual heart rhythm patterns and risk.

#### 4.1.3 *Methods*

The R-R intervals from 788 patients who enrolled in the ICD arm of SCD-HeFT were analyzed using DFA and the Lomb periodogram, statistical tools that correlate with non-random behavior. We used the outcome measures from such methods to form a feature vector for each of the R-R interval records. These feature vectors allow machine learning algorithms to differentiate between normal rhythm behavior and rhythms that will result in a shock. For each feature vector the demographic information of the patient was also included. All R-R intervals either preceded appropriate shocks, inappropriate shocks or were simply normal ICD rhythms periodically downloaded, which allowed differentiation of normal R-R interval behavior from that associated with impending shocks. Two-group classifications were performed with two types of machine learning algorithms: SVMs and decision trees. A sample of the recordings was randomly selected each time a classification was performed. 80% of the sample was used for training the machine learning algorithm and 20% of the sample was used for testing.

#### 4.1.4 *Results*

Machine learning algorithms were successful at predicting appropriate shock in the majority of patients 5 minutes prior to the shock. The predictive ability increased closer to the time of shock. The feature vectors combined patient demographics, mean normal R-R intervals, R-R interval fractal scaling exponents and power of R-R interval in frequency domain for normal R-R intervals and 5-minute pre-shock R-R intervals. These features were then classified using the SVM algorithm from machine learning, which yielded an accuracy of 75.2% and an AUC of 0.82 (results from test set). Using the 10-second pre-shock R-R interval data, a minor improvement in predictive accuracy occurred (77.8% and an AUC of 0.85, results from test set).

#### 4.1.5 *Conclusion*

Our study shows that it is possible to effectively predict the onset of an appropriate shock as much as 5 minutes prior to an ICD shock in SCD-HeFT patients. This early warning sign can provide an opportunity to improve patient safety and readiness, alert health care providers, and, possibly, provide a platform for ICDs to deliver preventative interventions directly.

## 4.2 INTRODUCTION

Implantable Cardioverter–Defibrillator (ICD) therapy decreases mortality in select post-myocardial infarction and CHF patients as shown in previous studies.[12], [41] On the other hand, ICD therapy does not solve some major problems associated with SCAs. ICDs do not prevent LTCAs, but ICDs terminate such arrhythmias after they occur. As a result, this can potentially cause harm to the patients themselves and/or their surroundings if, for example, they are driving, biking or in any situation where they can fall. It would be ideal if the ICDs can issue warnings for

impending SCA so that the patients can refrain from such activities or situations and healthcare providers can be alerted. Also, ICD shocks, including both appropriate and inappropriate shocks, affect a patient's quality of life and psychological state as they can cause anxiety, fear and excessive worry. In particular, ICD shocks are very painful. The ICD shock sensation has been described as being kicked strongly in the chest and is rated a "6" on a 0 to 10 pain scale.[5], [6] Therefore, if the ICDs can provide early warnings for the occurrences of SCAs, this may provide a means to avert the shock and an opportunity for developing alternate approaches to patient management.

From past research, there was evidence that a patient's autonomic tone played a role in the arrhythmogenesis of ventricular arrhythmia.[32], [65] Based upon that, we may be able to avoid the occurrences of ventricular arrhythmia by modulating the autonomic tone, though that remains to be investigated.[66] Currently, patient demographics such as NYHA functional classes or LVEF have been used as guidelines to indicate who should receive ICD therapy.[67] It would be worthwhile to investigate whether one can combine the statistics of pre-event R-R intervals with routine clinical information to predict the occurrences of SCA.

### 4.3 METHODS

Machine learning has been used in medicine in recent years.[68], [69] It was advocated for an article in Communications of the Association for Computing Machinery for prediction of patients' risks for different diseases.[70] In this chapter, we used machine learning algorithms, including SVMs and decision trees, to predict onset of VF or VT based on R-R interval data and demographics.

#### 4.3.1 *Subjects*

SCD-HeFT was a large National Institutes of Health funded clinical trial that was designed to study the effectiveness of ICD and amiodarone therapies in patients with mild to moderate heart failure.[12] Patients were randomly assigned in equal proportions to receive placebo (n=847), amiodarone (n=845) or a single-chamber ICD programmed to shock-only mode (model 7223, Medtronic) (n=829) from September 16, 1997 to July 18, 2001. All patients were followed until October 31, 2003. The inclusion criteria for the study was the following: the patients had to be at least 18 years old, have NYHA class II or III chronic, stable CHF due to ischemic or nonischemic causes and a LVEF of no more than 35 percent. The study sample for this chapter (N=788) is a proportion of the patients enrolled in the ICD arm (95.1%) in SCD-HeFT and their demographics are listed in Table 4.1.

Table 4.1: Demographics of patients in the sample

Age at Enrollment	Mean: 59.4 Median: 60 Interquartile Range: 51-69
Sex	609 Males 179 Females
Race	615 Caucasians 137 African Americans 26 Latin Americans 9 Asians 1 Native American
NYHA Functional Class	Class II: 541 Class III: 247
Cause of Heart Failure	Ischemic: 412 Non-ischemic: 376
Walking Distance	Mean: 1105 Median: 1133 Interquartile Range: 840-1350
Beta-blocker	Yes: 548 No: 240
LVEF	Mean: 23.6 Median: 24 Interquartile Range: 19-30
Handedness	Left: 77 Right: 711

#### 4.3.2 ICDs

SCD-HeFT included a pre-specified protocol for ICD programming.[12] This included a single zone of therapy at a detection rate of  $\geq 187$  beats/min. The initial detection interval was for 18 of 24 beats, and the redetect interval was for 12 of 16 beats. Shock-only mode was used hence there was no antitachycardia pacing. Antibradycardia pacing was set to 50 beats/min with

hysteresis of 34 beats /min, which is the minimal allowed heart rate. The ICD has a sampling rate of 128Hz for reading the ECG of the patient. It also can store consecutive R-R intervals up to 2048 beats.

#### 4.3.3 *R-R Interval Data*

Patients with ICDs enrolled in SCD-HeFT went to the clinics to have 25-30 minutes of their R-R intervals downloaded on-site every three months throughout the trial. Also, ICDs stored the last 2048 R-R intervals and intracardiac electrograms that immediately preceded the occurrences of shocks. Later, these ECGs were examined by a blinded events committee in SCD-HeFT to determine whether the shocks were appropriate or inappropriate. Based upon their decision, the R-R intervals that preceded the shocks were then classified into the appropriate shock group or the inappropriate shock group. Of the total of 11764 records, only those that have 1700 or more normal beats (59.9%) are included in our analysis. This minimum number is required to provide enough data for R-R interval processing.

#### 4.3.4 *R-R Interval Processing*

##### 4.3.4.1 DFA

DFA is a predictive tool for heart disease introduced by Peng et al.[13] The DFA yields the short-term and long-term fractal scaling exponents,  $\alpha_1$  and  $\alpha_2$  respectively, which are measures of the self-similarity of the R-R intervals in both the short term and the long term. DFA is suited for analyzing non-stationary physiological signals because it discards changes that are due to external environmental stimuli and focuses on the intrinsic dynamics of the heart itself. The fractal scaling exponents  $\alpha_1$  and  $\alpha_2$  have been considered prognostic in certain disease states.[15], [46] In

performing DFA, all R-R intervals were analyzed using the “fastdfa” algorithm as given by Little et. al.[47]

#### 4.3.4.2 Frequency Domain Analysis

The R-R intervals were transformed into frequency domain for analysis using the Lomb periodogram algorithm.[17], [18], [71] The Lomb periodogram method was chosen because R-R intervals are sampled at uneven time intervals and this algorithm performs well in the presence of artifacts, pacing and PVCs. The frequencies investigated range from  $5 \cdot 10^{-5}$ Hz to 0.5Hz. This frequency range was divided into logarithmically spaced bins and the power of the R-R intervals in the frequency domain in each bin was calculated using Lomb periodogram; the number of bins ranges from 2-20.

#### 4.3.4.3 Mean normal R-R Interval

While many SCAs occur without warnings, one of the symptoms of SCA is racing heart rate. Therefore, for our study, the mean normal R-R interval of each recording is calculated and used as a predictor for SCA.

#### 4.3.5 *Demographics*

Each R-R interval recording was associated with a specific patient. We included the demographic information of the patient with each of the R-R interval recordings. The demographic information of the patient includes gender, age at enrollment, race, NYHA functional class, cause of heart failure, walking distance, LVEF, handedness and whether the patient is taking the medication  $\beta$ -blocker.

### 4.3.6 *Machine Learning*

#### 4.3.6.1 Processing of Machine Learning

An overview of the process of machine learning is shown in Figure 4.1. Each column contains a single record for a patient, which consists of a vector of the information listed above (DFA, power in bins, etc.). Each row of the input matrix to the machine learning algorithms corresponds to the same information for all patients. Each column is labeled as belonging to either the normal rhythm group, the appropriate shock group or the inappropriate shock group; the labeled data are used to train classifiers. We performed two separate two-class classification tasks. The first task is to distinguish between the appropriate shock group vs. the normal rhythm group. The second task is to distinguish between the appropriate shock group vs. the inappropriate shock group. There are many more records in the normal rhythm group (6660 records) compared with the appropriate shock group (230 records) and inappropriate shock group (151 records). In order to avoid bias created by an imbalanced dataset, we randomly selected samples from the larger group to match the number of samples in the smaller group.[72] Then, we randomly selected 80% of the dataset to be the training set for the SVM and decision tree algorithms. Once a classifier is constructed using the training dataset, it is tested with the remaining 20% of the dataset (the test set) to investigate the classification performance. To achieve statistical significance, we cross-validate the classification algorithm by repeatedly re-shuffling the 80%/20% selection and repeating the train/test procedure 100 or 1000 times.

The performance of the classification is measured by accuracy rate, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and AUC. Accuracy rate is the percentage of recordings that the machine learning algorithm classifies correctly. Sensitivity is the percentage of recordings in the appropriate shock group (positive group) that the machine

learning algorithm classifies correctly. Specificity is the percentage of recordings in the normal rhythm group or the inappropriate shock group (negative group) that the machine learning algorithm classifies correctly. PPV is the percentage of recordings that truly belong to the appropriate shock group among the recordings which the machine learning algorithm classifies as appropriate shocks. NPV is the percentage of recordings that truly belong to the normal rhythm group or inappropriate shock group among the recordings which the machine learning algorithm classifies as normal rhythms or inappropriate shocks. AUC is the area under the ROC curve.[19], [73]

The goal of this chapter is to predict the imminent onset of arrhythmic sudden death. Therefore, we analyzed the R-R intervals up to 5 minutes before shocks and we also analyzed the R-R intervals up to 10 seconds before shocks. This was done to examine if there would be an early warning signature for the onset of VF/VT as far as 5 minutes before their occurrences. This also explored the added value of information between 5 minutes before shock and 10 seconds before shock from the R-R intervals.

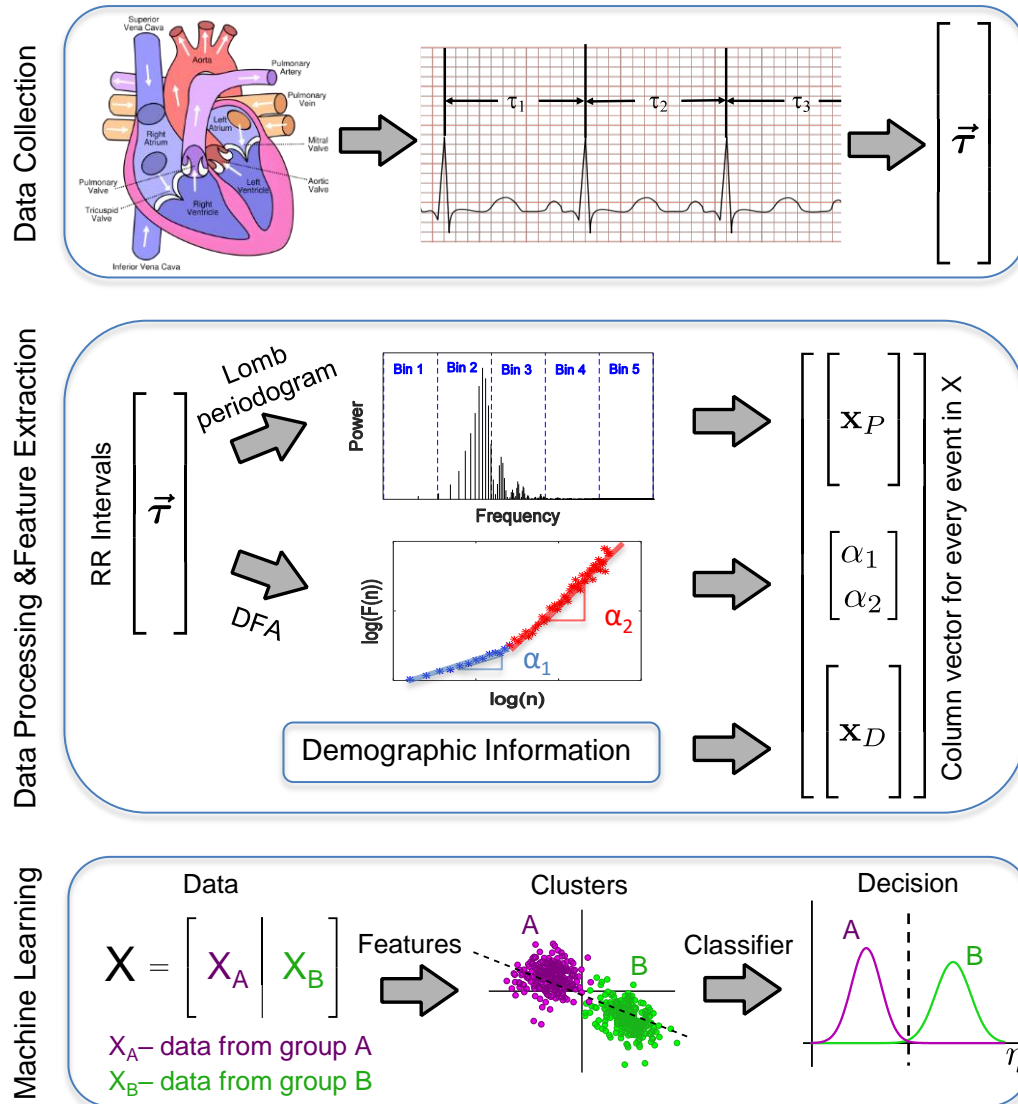


Figure 4.1: Overview of the methods used in this chapter. Firstly, ECGs were collected by the ICDs and R-R intervals were extracted from the ECGs. Secondly, each record of R-R intervals was processed using Lomb periodogram and DFA. The associated demographic information of the patient was added to the column vector. Thirdly, the column vectors were grouped by whether they preceded appropriate shocks, inappropriate shocks or normal rhythms. Then, two two-group classifications were performed with SVM or decision tree. One two-group classification was appropriate shocks vs normal rhythms. Another two-group classification was appropriate shocks vs inappropriate shocks. More detailed illustrations of SVM and decision tree can be found in Figure 4.2.

### 4.3.6.2 SVM

SVM is a supervised learning model and its goal is to find a hyperplane that gives the maximum margin between the samples from the two classes of data. Samples on the margin are called the support vectors.[20], [74], [75] An illustration of the algorithm is shown in Figure 4.2A. SVMs with linear kernels were used in this chapter, although more sophisticated kernels may be explored in future work.

### 4.3.6.3 Decision Tree

Decision tree is a supervised learning model and is formed by recursively partitioning the input space so that each region of the input space is defined by a local model.[76], [77] For example, looking at the classification illustration in Figure 4.2B, a sample would be classified as group 1 if it is in the region of  $x_2 \leq 3.11$  and  $x_1 \leq 3.74$ . Otherwise, the sample will be classified as group 0.

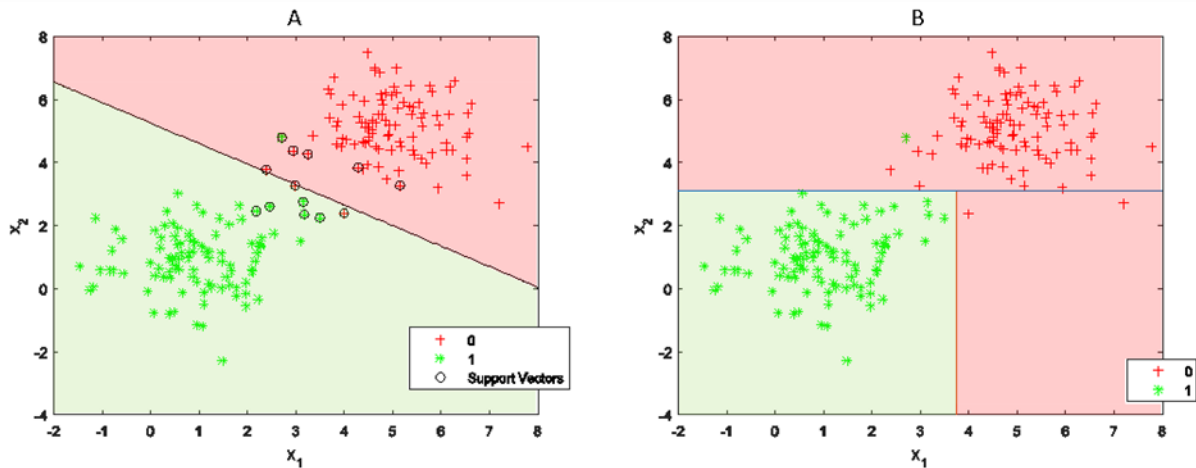


Figure 4.2: Classification illustration of SVM algorithm (A).

Classification illustration of decision tree algorithm (B).

## 4.4 RESULTS

### 4.4.1 *Appropriate Shocks vs. Normal Rhythms*

From Figure 4.3, it can be seen that SVM performs better than the decision tree with both the 5-minute-before-shock data and the 10-second-before-shock data in all the classification performance measurements. Therefore, the remainder of this chapter focuses on SVM results.

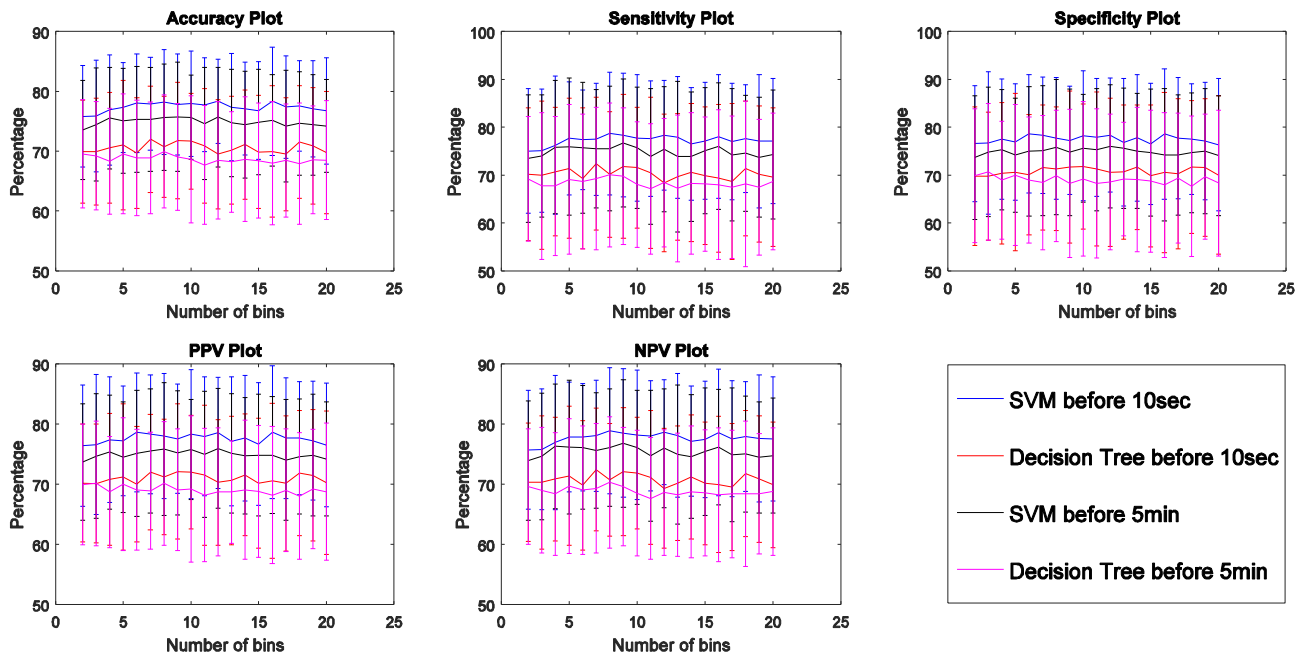


Figure 4.3: Classification Performances of Appropriate Shocks vs Normal Rhythms using  $\alpha_1$ ,  $\alpha_2$ , mean normal R-R intervals, demographics and power in bins with varying number of bins in the frequency domain. Each test was performed one hundred times. Results are from test set.

When one compares the performances of SVM 10 seconds before shock and SVM 5 minutes before shock, it can be observed that marginally better classification results are obtained with the 10-second-before-shock data. Figure 4.4 shows the mean ROC curves and the AUC histograms from classifications of appropriate shock group vs normal rhythm group performed with 10-second-before-shock data and with 5-minute-before-shock data. ROC curves were gotten by finding the classification performances at each value of the bias of the hyperplane as the bias of the hyperplane was being varied. It can be seen from Figure 4.4 that AUCs from classifications performed with 10-second-before-shock data are larger than those from classifications performed with 5-minute-before-shock data. Thus, as the R-R interval approaches the occurrence of the VF/VT events, there is more reliable information that would enable a slightly more accurate classification.

Even though better classification can be obtained when using R-R intervals closer to the events of ventricular arrhythmia, it is still remarkable how an accuracy of 70.8% can be obtained using  $\alpha_1$ ,  $\alpha_2$  and power in 5 bins with 5-minute-before-shock data (Table 4.2). This means that subtle changes could be observed in the R-R intervals 300-500 heartbeats before the occurrences of ventricular arrhythmia.

When used in isolation, better classification can be obtained with  $\alpha_1$  and  $\alpha_2$  from DFA than power in 5 frequency bins as seen in Table 4.2. The differences in classification performances between the two are more pronounced in the 5-minute-before-shock case than the 10-second-before-shock case. When we add demographic information to the input matrix, the rates of accuracy were improved by 2.6-3.2%. The mean accuracy and mean AUC of  $\alpha_1$ ,  $\alpha_2$ , power in 5 bins, mean normal R-R intervals and demographics with the 5-minute-before-shock data were 75.2% and 0.82 respectively. The mean accuracy and mean AUC of  $\alpha_1$ ,  $\alpha_2$ , power in 5 bins, mean

normal R-R intervals and demographics with the 10-second-before-shock data were 77.8% and 0.85 respectively.

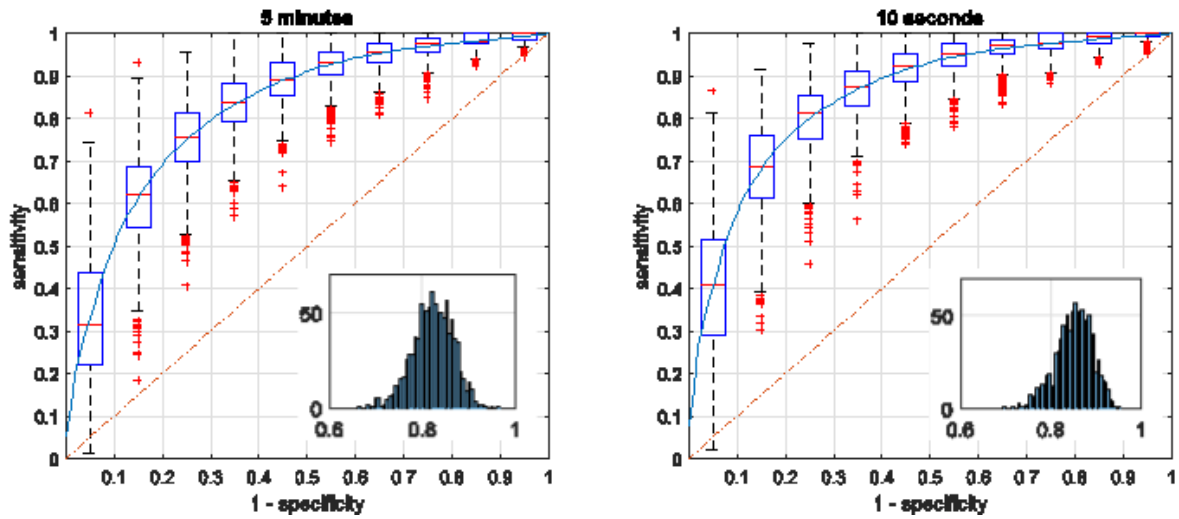


Figure 4.4: Mean ROC curves (blue line) and histograms of AUCs from one thousand tests each for the 5-minute-before-shock case (left) and 10-second-before-shock case (right) for appropriate shocks vs normal rhythms using SVM. Predictors are  $\alpha_1$ ,  $\alpha_2$ , power in 5 bins, mean normal R-R interval and demographic information. Results are from test set.

Table 4.2: Classification performance of appropriate shocks vs normal rhythms obtained with SVM with the inputs indicated. Each test was performed one thousand times. Results are from test set.

		Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
5-minute-pre-shock data	$\alpha_1, \alpha_2$	70.5 (4.58)	71.4 (6.31)	69.6 (7.00)	70.4 (5.14)	71.1 (4.93)	.755 (.049)
	Power in 5 bins	62.6 (5.13)	56.4 (20.6)	68.8 (20.2)	66.9 (8.70)	63.0 (7.31)	0.708 (.0538)
	$\alpha_1, \alpha_2$ , power in 5 bins	70.8 (4.53)	74.3 (6.62)	67.3 (7.23)	69.7 (4.85)	72.6 (5.38)	.765 (.0493)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval	74.3 (4.32)	74.9 (6.69)	73.6 (6.51)	74.2 (4.90)	74.9 (5.16)	.814 (.0442)
	$\alpha_1, \alpha_2$ , power in 5 bins, demographics	73.4 (4.57)	76.4 (6.50)	70.5 (7.13)	72.2 (5.16)	75.3 (5.44)	.789 (.0479)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval, demographics	75.2 (4.37)	76.0 (6.66)	74.4 (6.50)	74.8 (5.01)	76.1 (5.22)	.823 (.0436)
10-second-pre-shock data	$\alpha_1$ and $\alpha_2$	70.7 (4.77)	70.7 (6.85)	70.7 (7.14)	70.9 (5.32)	70.9 (5.28)	.760 (.0506)
	Power in 5 bins	65.0 (5.29)	61.3 (18.2)	68.7 (16.7)	67.9 (7.60)	65.8 (7.90)	.724 (.0526)
	$\alpha_1, \alpha_2$ , power in 5 bins	72.3 (4.18)	74.6 (6.06)	69.9 (6.75)	71.5 (4.67)	73.6 (4.8)	.795 (.0431)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval	76.9 (4.00)	77.4 (6.07)	76.5 (6.53)	77.0 (4.95)	77.4 (4.72)	.844 (.0406)
	$\alpha_1, \alpha_2$ , power in 5 bins, demographics	75.5 (4.27)	78.1 (6.49)	73.0 (6.64)	74.3 (4.79)	77.3 (5.32)	.817 (.0430)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval, demographics	77.8 (4.28)	78.1 (6.50)	77.5 (6.15)	77.7 (4.97)	78.4 (5.19)	.852 (.0407)
Results are listed as mean (SD) unless stated otherwise.							

#### 4.4.2 Appropriate Shocks vs. Inappropriate Shocks

Figure 4.5 and Table 4.3 show the performances of SVM in classifying appropriate shocks and inappropriate shocks. Comparing to the results of the previous section (appropriate shocks vs. normal rhythms), the performance of SVM to classify appropriate shocks versus inappropriate shocks is not as good. The accuracy rate achieved by  $\alpha_1$ ,  $\alpha_2$  and power in 5 bins with the 10-second-before-shock data is 66.0%. The accuracy rate achieved by  $\alpha_1$ ,  $\alpha_2$  and power in 5 bins with the 5-minute-before-shock data was 63.1%. It is notable that adding demographics information to the 10-second-before-shock data did not improve the classification performances. Also, adding mean normal R-R intervals to the feature vectors drastically improved the classification accuracies by 10-10.3%. This information is summarized in Table 4.3.

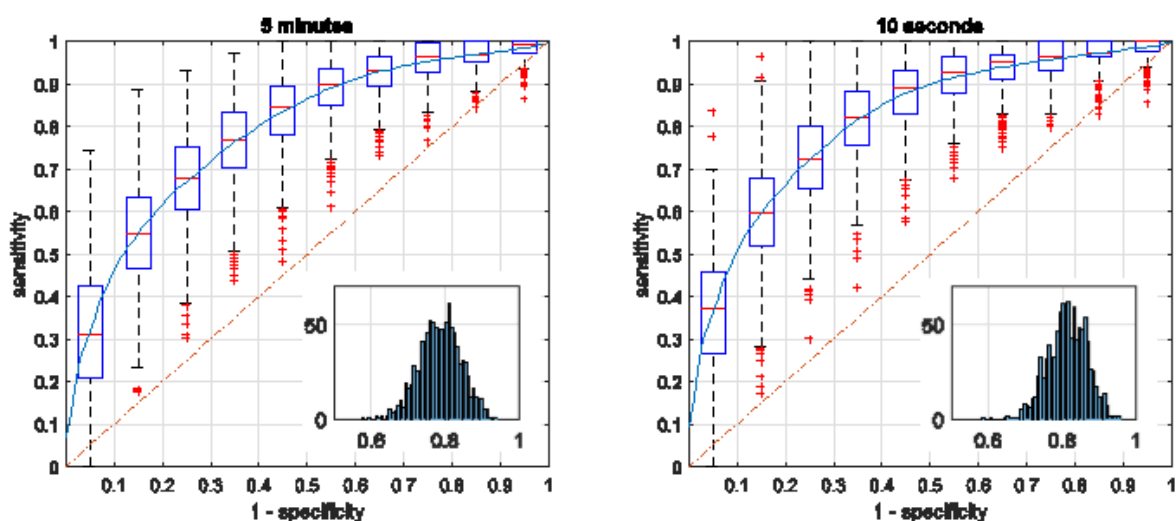


Figure 4.5: Mean ROC curves (blue line) and histograms of AUCs from one thousand tests each for the 5-minute-before-shock case (left) and 10-second-before-shock case (right) for appropriate shocks vs inappropriate shocks using SVM. Predictors are  $\alpha_1$ ,  $\alpha_2$ , power in 5 bins, mean normal R-R interval and demographic information. Results are from test set.

Table 4.3: Classification performance of appropriate shocks vs inappropriate shocks obtained with SVM with the inputs indicated. Each test was performed one thousand times. Results are from test set.

		Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
5 minutes	$\alpha_1, \alpha_2$	58.1 (5.76)	47.9 (13.2)	68.3 (11.9)	60.7 (7.99)	57.2 (5.60)	.616 (.0676)
	Power in 5 bins	54.3 (4.98)	27.9 (17.9)	80.8 (18.9)	62.0 (13.7)	52.7 (5.44)	.599 (.0722)
	$\alpha_1, \alpha_2$ , power in 5 bins	63.1 (5.82)	57.2 (10.4)	68.9 (8.42)	65.0 (6.74)	62.1 (5.93)	.662 (.0659)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval	73.1 (5.26)	76.4 (7.91)	69.8 (8.00)	71.9 (5.56)	75.1 (6.45)	.795 (.0537)
	$\alpha_1, \alpha_2$ , power in 5 bins, demographics	63.3 (5.81)	59.5 (9.26)	67.1 (8.68)	64.1 (6.79)	63.1 (5.96)	.665 (.0658)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval, demographics	71.1 (5.57)	70.4 (8.56)	71.9 (8.50)	71.4 (6.56)	71.6 (6.20)	.786 (.0557)
10 seconds	$\alpha_1, \alpha_2$	57.4 (5.82)	50.3 (14.8)	64.5 (12.9)	58.9 (7.36)	57.1 (6.23)	.599 (.0705)
	Power in 5 bins	55.4 (5.40)	49.9 (29.4)	60.8 (31.0)	59.9 (11.8)	56.5 (9.82)	.617 (.0703)
	$\alpha_1, \alpha_2$ , power in 5 bins	66.0 (5.55)	60.8 (9.70)	71.2 (8.46)	68.2 (6.51)	64.8 (5.77)	.681 (.0619)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval	76.3 (5.01)	78.4 (7.59)	74.2 (7.63)	75.5 (5.61)	77.8 (6.21)	.829 (.0504)
	$\alpha_1, \alpha_2$ , power in 5 bins, demographics	64.2 (5.72)	59.5 (9.13)	68.8 (8.34)	65.3 (6.84)	63.8 (5.80)	.674 (.0649)
	$\alpha_1, \alpha_2$ , power in 5 bins, mean normal R-R interval, demographics	73.5 (5.28)	73.6 (8.18)	73.4 (8.04)	73.3 (6.20)	74.3 (6.18)	.814 (.0532)
Results are listed as mean (SD) unless stated otherwise.							

## 4.5 DISCUSSION

Based upon the results from 5 minutes before shock and 10 seconds before shock, the accuracy of the classification increases as the time to the event decreases. In the attempt of detecting early warning signs of ventricular arrhythmia in real time, the past half an hour of R-R intervals should be classified every half a minute or so using a SVM classifier that has already been trained on appropriate shocks, inappropriate shocks and normal rhythms from a large population. The SVM classifier score would indicate how likely the patient would be to have a ventricular arrhythmic event. An early warning sign that a ventricular arrhythmic event may happen would be when the score increases above a predefined threshold value.

From the results of the machine learning algorithms, it was found that adding demographics to the input matrix improved the classification of the records of appropriate shock and the records of normal rhythms. This finding has implications for the programming of the ICDs. ICDs should store demographic information of the patients so that it can be used for classification of rhythms.

The methods and algorithms presented in this chapter should be considered as a supplement to existing ICD discrimination algorithms. When the warning algorithm detects impending sudden cardiac death, it can either issue an alert or perhaps trigger an alternative treatment such as a novel pacing to prevent the person from experiencing SCD. In the event that this algorithm fails to detect early warning signs for VF, the existing ICD discrimination algorithm can still detect the VF and provide a shock.

In this chapter, SVM and decision tree classifiers were trained with an equal number of samples in both classes for the two classification tasks to have equal numbers of records in the positive (appropriate shock) and negative (either normal rhythm or inappropriate shock) groups. Classification performances were obtained from classifying test sets that had equal number of

recordings in the positive and negative groups. However, if this algorithm is installed in patients' ICDs, it will get many more normal rhythms than arrhythmia as SCAs can be considered rare events. It is almost certain that it will misclassify some of the normal rhythms as arrhythmias and falsely trigger the warning system given that the specificity is about 70%. Too many false warnings will be disrupting to the patients and medical units. This is a problem that needs to be addressed in implementing this warning algorithm. One solution is to change the warning threshold to give less warnings. But in doing so, there will be more false negatives and the patients may not get the required warnings for impending SCAs. Therefore, the warning threshold of the algorithm should be designed to balance the relative importance of sensitivity and specificity to best improve health outcomes.

The results of classification of appropriate shocks versus inappropriate shocks are not as strong as the classification of appropriate shocks versus normal rhythm. However, the classifier still has moderate discrimination power as the mean AUC is as high as 0.81 with an accuracy rate at 73.5%.

When such machine learning algorithms are implemented, the classification algorithm will benefit from patterns already learned in the existing training dataset. At the same time, the classifier could be adaptive and learn from individual patients' records of R-R intervals to optimize the performances of the machine learning algorithms.

#### 4.6 CONCLUSION

We have shown that it is possible to predict the onset of an appropriate shock as much as 5 minutes prior to an ICD shock in some SCD-HeFT patients. This early warning sign can provide an opportunity to improve patient safety and readiness, alert health care providers, and, possibly,

provide a platform for ICDs to administer direct, preventative interventions. When implemented successfully, the early warning capability will provide a major advance in current generation of ICD technology and a significant improvement in the treatment of patients with heart failure.

## Chapter 5. USE OF PCA ON R-R INTERVALS FOR PROVIDING EARLY WARNINGS OF ARRHYTHMIC EVENTS WITH MACHINE LEARNING

In Chapter 4, it has been found that one can perform a 5-minute prediction or a 10-second prediction of the occurrences of SCAs with short term and long-term fractal scaling exponents from DFA, power of R-R interval in frequency domain, mean normal R-R intervals and demographics as predictors with good accuracies (75.2-78.0%) using SVMs but improvement in prediction performances is desirable. In this chapter, we analyzed patients' R-R intervals using PCA, both independently and in combination with the already examined predictors, to investigate if prediction performances could be improved. It was found that the use of PCA could improve the prediction performances of 10-second prediction (accuracy rate of 81.4% and AUC of 0.893) but it did not improve the prediction performances of 5-minute prediction.

### 5.1 ABSTRACT

#### 5.1.1 *Background*

Current ICDs can't issue warnings of impending LTCAs to the patients, but rather terminate these events after they have occurred. As a result, patients can be at risk when they are driving or in situations where they can fall. Therefore, an early warning system for LTCAs has been long sought. It has been found in prior work that the R-R intervals that preceded LTCAs have different characteristics from normal R-R intervals in patients with heart failure.

### 5.1.2 *Objective*

The objective of this chapter is to investigate if performing PCA on the heart rhythms can be used for classifying normal rhythms and pre-cardiac-event rhythms with algorithms from machine learning. Also, it is to investigate if combining projections onto PCs from PCA with other proven predictors would improve classification accuracy.

### 5.1.3 *Methods*

We analyzed 6660 normal R-R intervals and 230 pre-cardiac-event R-R intervals from a sample of patients (N=788) enrolled in the ICD arm of Sudden Cardiac Death – Heart Failure Trial (SCD-HeFT). In order to extract dominant features of the time series, singular value decomposition was performed on training sets that contain an equal number of pre-cardiac-event R-R intervals and normal R-R intervals. PCs, singular values and projections onto PCs were found. The number of PCs included for analysis was decided using the method of hard thresholding proposed by Gavish and Donoho. Then projections onto the PCs were used as features to train the SVM algorithm from machine learning. All the classifications were 80%/20% cross-validated and the results from test sets were found. Projections onto PCs were also combined with other proven predictors such as short-term and long-term fractal scaling exponents from DFA to examine if the classification performances could be improved.

### 5.1.4 *Results*

When projections onto the first 18 PCs were used as features to SVM, an accuracy of 73.1% and AUC of 0.798 was achieved with the 10-second-pre-shock data. When these projections were combined with the other proven predictors, an accuracy rate of 81.4% and AUC of 0.893 was

achieved with the 10 second-pre-shock data. The use of PCA and SVM yields poor performance with 5-min-pre-shock data (accuracy of 57.9% and AUC of 0.579).

#### 5.1.5 *Conclusion*

The combination of PCA and SVM yields desirable results when it is used to analyze and classify 10-second-pre-shock rhythms and normal rhythms. It may be useful if there is a novel pacing method in the future that can be triggered to avoid the occurrences of arrhythmic events when the machine learning algorithm predicts that arrhythmic events are imminent.

## 5.2 INTRODUCTION

Predicting the onset of SCA is an important and challenging problem. We have previously classified patients' normal rhythms and pre-cardiac-event rhythms using features which included fractal scaling exponents from DFA, power of R-R intervals in frequency domain, mean normal R-R intervals and demographic information with the SVM algorithm from machine learning. Good accuracies and AUCs were achieved but improvements are desirable. Additional predictors should be sought to provide even slight improvement in classification performances. This chapter investigates the use of PCA to classify normal rhythms and pre-cardiac-event rhythms.

## 5.3 METHOD

### 5.3.1 *Subjects*

The subjects studied in this chapter were a subsample of the patients enrolled in SCD-HeFT. SCD-HeFT was a large National Institutes of Health funded clinical trial that was designed to study the effectiveness of ICD and amiodarone therapies in patients with mild to moderate heart failure.[12] From September 16, 1997 to July 18, 2001, patients were assigned randomly in equal

proportions to receive placebo (n=847), amiodarone (n=845) or a single-chamber ICD (model 7223, Medtronic) (n=829). These patients were followed until October 31, 2003. SCD-HeFT has the following inclusion criteria: the patients had to be at least 18 years old, have NYHA class II or III chronic, stable CHF due to ischemic or nonischemic causes and a LVEF of less than or equal to 35 percent. The study sample for this chapter (N=788) is the patients assigned to the ICD arm in SCD-HeFT and their demographics are listed in Table 5.1.

Table 5.1: Demographics of patients in the sample (N=788)

Age at Enrollment	Mean: 59.4 Median: 60 Interquartile Range: 51-69
Sex	609 Males 179 Females
Race	615 Caucasians 137 African Americans 26 Latin Americans 9 Asians 1 Native American
NYHA Functional Class	Class II: 541 Class III: 247
Cause of Heart Failure	Ischemic: 412 Non-ischemic: 376
Walking Distance	Mean: 1105 Median: 1133 Interquartile Range: 840-1350
Beta-blocker	Yes: 548 No: 240
LVEF	Mean: 23.6 Median: 24 Interquartile Range: 19-30
Handedness	Left: 77 Right: 711

### 5.3.2 ICDs

SCD-HeFT had a pre-specified protocol for ICD programming.[12],[26] There was a single zone of therapy at a detection rate of more or equal to 187 beats/min. The initial detection interval was for 18 of 24 beats, and the redetect interval was for 12 of 16 beats. Shock-only mode was used. Antibradycardia pacing was set to 50 beats/min with hysteresis of 34 beats/min, which is the

minimum allowed heart rate. ICDs have a sampling rate of 128Hz for reading the ECGs of the patients. The ICDs can also store up to 2048 consecutive R-R intervals.

### 5.3.3 *R-R Intervals*

We focused on two types of R-R intervals. One type of R-R intervals were obtained when the patients visited the clinic to have their R-R intervals downloaded on-site every three months throughout the trial. These R-R intervals were considered normal rhythms. Another type of R-R intervals is pre-cardiac-event rhythms. These were obtained by the ICDs storing the last 2048 R-R intervals preceding the occurrences of shocks. Only rhythms that preceded appropriate shocks were included for analysis. Only R-R intervals that have 1700 or more normal beats were included, so as to provide enough data for processing. Collectively, 6660 normal rhythms and 230 pre-cardiac-event rhythms satisfy these inclusion criteria.

### 5.3.4 *PCA*

PCA is a statistical method that performs an orthogonal transformation on the data to project the data into a set of linearly uncorrelated variables which are called PCs.[78], [79] PCA can identify the variances of these PCs in the data. Figure 5.1 shows an illustration of the results of PCA on a set of data points that are bivariate normally distributed. PCA can identify the direction that has the largest variance which is indicated by the long red axis and its orthogonal direction which is indicated by the short red axis. These axes are called PCs. PCA is especially useful when one wants to analyze data that has high dimension. With PCA, one can retain the components with high variances while discard the components with low variances which would reduce redundancy. PCA has been applied broadly on ECG signals.[38], [80]–[82] Besides, PCA

has been previously used on HRV data to assess cardiac autonomic neuropathy.[83] Also, a combination of PCA and least square SVM has been used for detection of ECG arrhythmia.[39]

The recordings of R-R intervals were arranged into an  $m \times n$  matrix  $R$ .  $m$  is the number of R-R intervals in each of the recordings and  $n$  is the number of recordings. Each column of the matrix had one recording of R-R intervals. Each column was mean-centered and it was also divided by its standard deviation so that each column of the matrix  $R$  has unit variance. Then the reduced singular value decomposition (SVD) of the matrix was found. This operation is shown in Equation 5-1 below and in the illustration shown in Figure 5.2:

$$R = U * S * V^T \quad \text{Equation 5-1}$$

In Equation 5-1,  $U$  and  $V$  are unitary matrices while  $S$  is a diagonal matrix with singular values along its diagonal in decreasing order.  $U * S$  has the PCs and  $V$  has the projections onto the PCs.

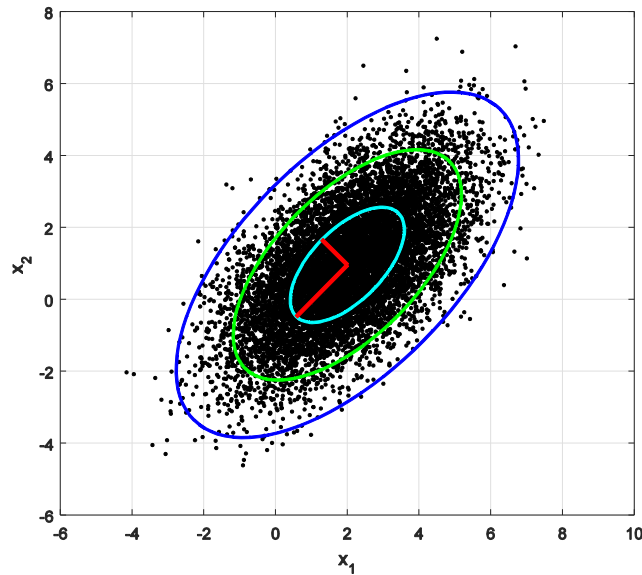


Figure 5.1: Results of finding PCs on a set of data points that have bivariate normal distribution. The red lines are the PCs. The ellipses show the first standard deviation (cyan) to the third standard deviation (blue) of the data.

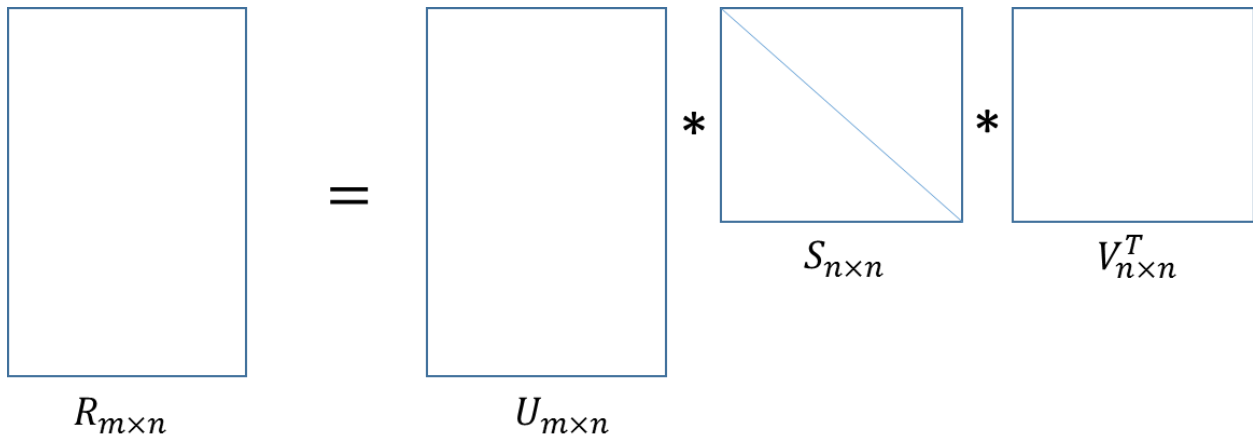


Figure 5.2: An Illustration of the singular value decomposition of the matrix  $R$  ( $m \times n$ ). Each column of the matrix  $U * S$  is a PC. The singular values are stored along the diagonal of the matrix  $S$ . The matrix  $V$  stores the projections of the R-R intervals onto the PCs.

### 5.3.5 Optimal Hard Threshold for Singular Values

Choosing the right number of singular values to keep is one of the most crucial and contentious decisions when using the SVD. Here, we examined the method of finding the optimal hard threshold proposed by Gavish and Donoho.[84] In our case, the level of noise is unknown. The optimal hard threshold is given by

$$\tau = \omega(\beta)\sigma_{med} \quad \text{Equation 5-2}$$

where  $\sigma_{med}$  is the median singular value and  $\omega(\beta)=\lambda(\beta)/\mu_\beta$ .  $\beta$  is  $n/m$ , while

$$\lambda(\beta) = \left( 2(\beta + 1) + \frac{8\beta}{(\beta+1)+(\beta^2+14\beta+1)^{1/2}} \right)^{1/2}, \quad \text{Equation 5-3}$$

and  $\mu_\beta$  is the solution to the following problem:

$$\int_{(1-\beta)^2}^{\mu_\beta} \frac{[(1+\sqrt{\beta})^2 - t)(t - (1-\sqrt{\beta})^2)]^{1/2}}{2\pi t} dt = \frac{1}{2} \quad \text{Equation 5-4}$$

We varied the number of projections onto the PCs from PCA used for the purpose of classification of normal rhythms and pre-cardiac-event rhythms and investigated the effect on classification performance by SVM.

### 5.3.6 Predictors Used Previously

The predictors used previously included short-term and long-term fractal scaling exponents from DFA, power of R-R intervals in the frequency domain, mean normal R-R intervals and demographics. Details of these predictors can be found in Chapter 4.

### 5.3.7 Machine Learning

The method of machine learning is very similar to the one described in Chapter 4. The difference is that the method of PCA is also used here. SVD is computed on the training set which has an equal number of pre-cardiac-event rhythms and normal rhythms. Then the projections of the R-R intervals onto the PCs are used as features to the SVM for the purpose of training. The

projections onto PCs of the test set are found by multiplying the matrix that has the recordings of R-R intervals from the test set by  $S^{-1}U^T$  on the left. The test set is then classified using these projections with SVM. Also, these projections are combined with other predictors for classification of pre-cardiac-event-rhythms and normal rhythms with SVM.

## 5.4 RESULTS

Figure 5.3 shows the first 12 PCs of normal rhythms and 10-second-pre-shock rhythms. These PCs resemble signals of different frequencies. From Figure 5.4, there are considerable differences between the distribution of the 1<sup>st</sup> projection of the normal rhythms and that of the pre-cardiac-event rhythms. The 1<sup>st</sup> projections from the pre-cardiac-event rhythms tend to be smaller than those from the normal rhythms. From that and the first PC in Figure 5.3, one can conclude that the heart rate tends to speed up before the occurrences of these cardiac events.

Figure 5.5 shows the classification performances as a function of the number of projections onto PCs (features) from the PCA. The classification performance peaked when the number of features equaled 15. From that point on, when more features were included, there was a slight decline in the classification performances. This finding is consistent with the result from the method of finding optimal hard threshold for singular values proposed by Gavish and Donoho.[84] According to the method proposed by Gavish and Donoho, the singular values should be truncated when  $r$  is around 18 which is shown in Figure 5.6. Figure 5.6 also shows the PC 14 and PC 50. PC 14, which should be included according to the threshold, resembles a signal of a particular frequency. On the other hand, PC 50, which should be excluded according to the threshold, has no clear structure and resembles white noise.

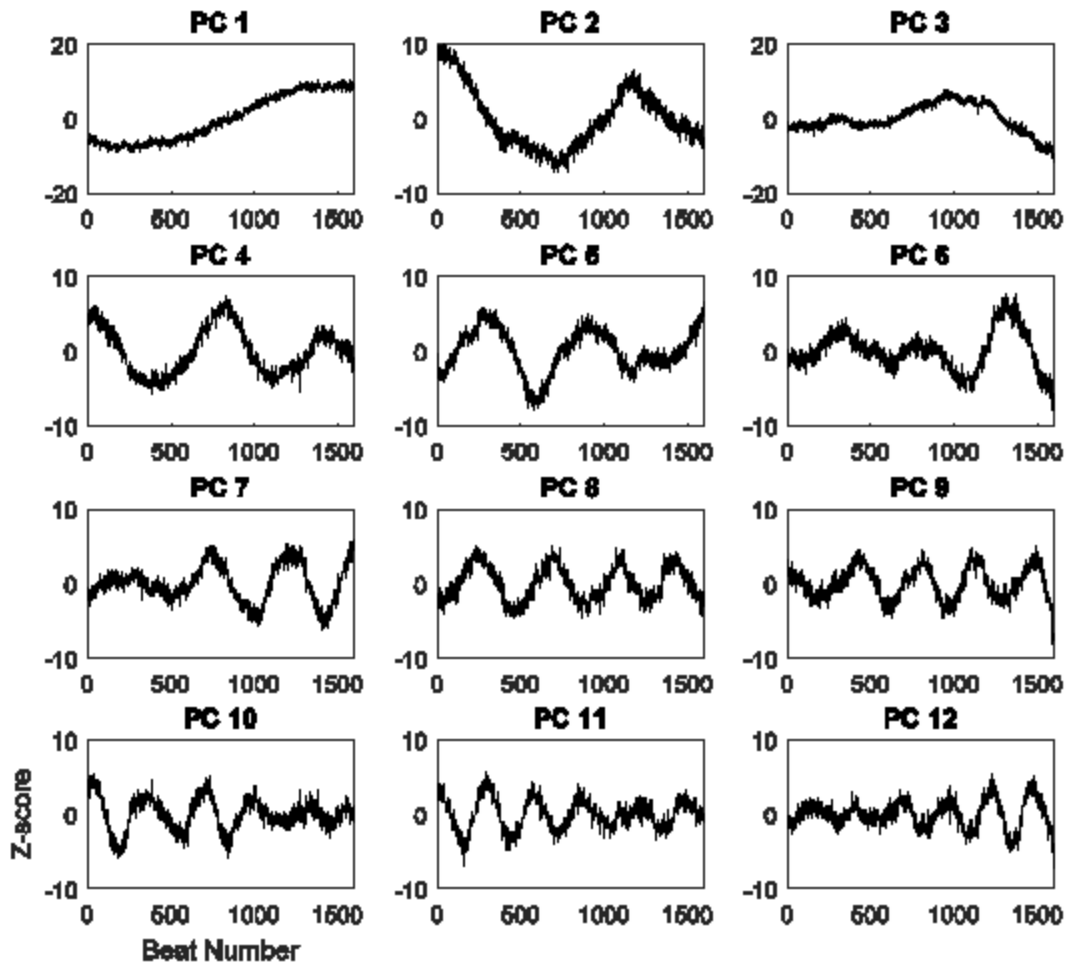


Figure 5.3: The first 12 PCs of the normal rhythms and 10-second-pre-shock rhythms.

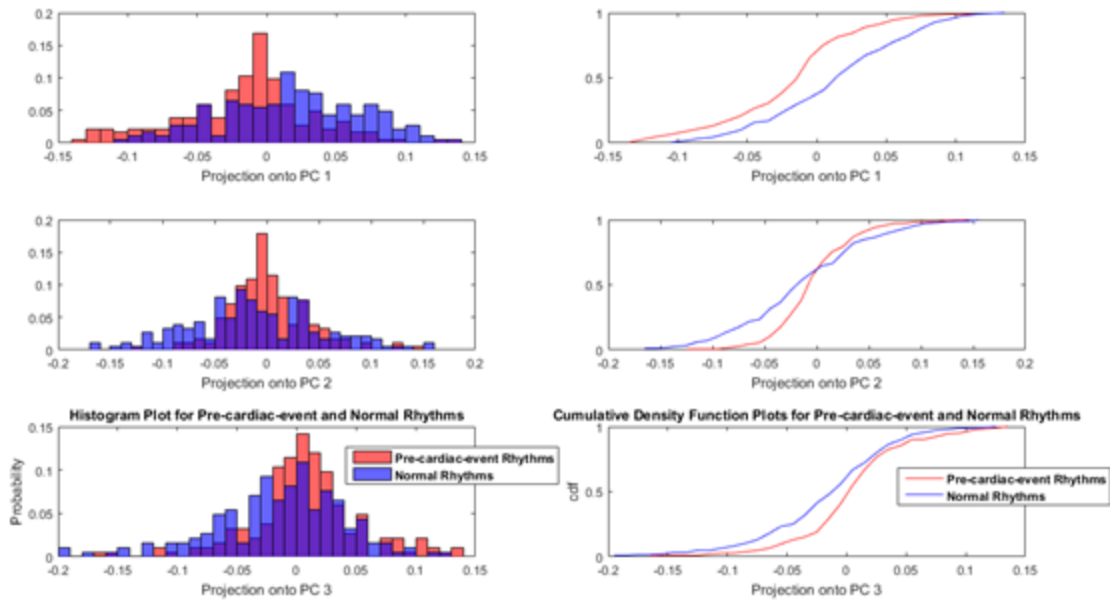


Figure 5.4: Histograms and cumulative density function plots for the projections onto the first three PCs from the training set that has normal rhythms and 10-second-pre-shock rhythms.

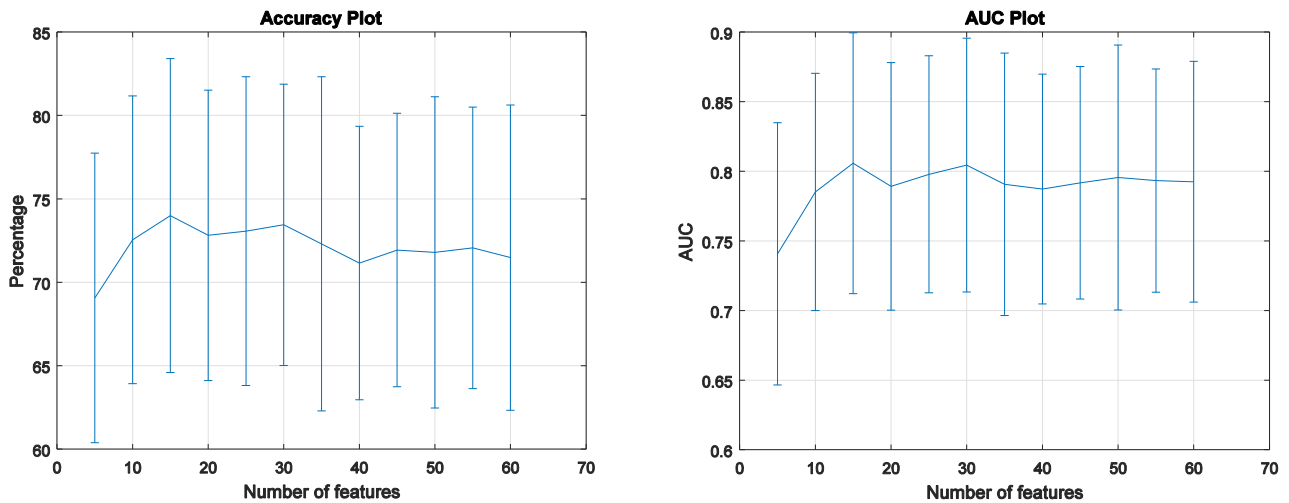


Figure 5.5: Left: Accuracy plot of classification between the normal rhythms and the 10-second-pre-shock rhythms as a function of number of features from PCA. Right: AUC plot of the same classification as a function of number of features from PCA.

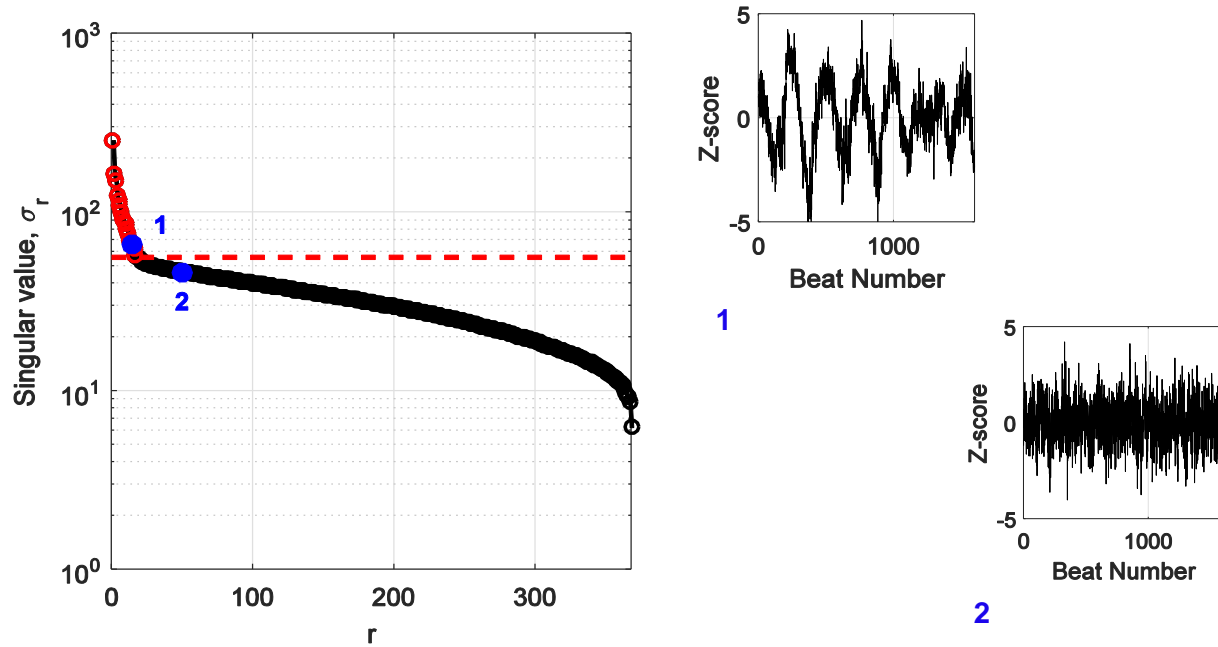


Figure 5.6: Left: Plot of singular values with the optimal hard threshold found by the method proposed by Gavish and Donoho.[84] The singular values that are above the threshold are plotted in red while the ones that are below the threshold are plotted in black. The dot labelled 1 corresponds to the 14<sup>th</sup> singular value. The dot labelled as 2 corresponds to the 50<sup>th</sup> singular value. 1: PC 14. 2: PC 50.

Table 5.2 shows the classification performances using various combinations of data and predictors. The use of PCA and SVM yields poor performances with 5-min-pre-shock data (accuracy of 57.9% and AUC of 0.579). Adding the first 18 projections onto the PCs to the already examined predictors did not improve the accuracy when one tried to do a prediction of the occurrences of cardiac events 5 minutes ahead of time. On the other hand, the use of PCA and SVM yields good results with 10-second-pre-shock data (accuracy of 73.1% and AUC of 0.798). Also, there is a considerable amount of improvement in accuracy and AUC by combining PCA with other proven predictors when one tried to predict the occurrences of ventricular tachyarrhythmia 10 seconds ahead of time. Accuracy of 81.4% and AUC of 0.893 was achieved.

Table 5.2: Classification performances for various combinations of input data and predictors. 5-minute-pre-shock data are 1000 beats long while 10-second-pre-shock data are 1600 beats long. SVMs were used and each test was performed one hundred times.

	Features	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
5-minute-pre-shock data	First 18 PCs	57.9 (5.33)	67.0 (9.00)	48.7 (8.67)	56.7 (4.62)	60.0 (7.21)	0.579 (0.066)
	power in 5 bins, $\alpha_1$ , $\alpha_2$ , mean normal R-R intervals, demographics	75.2 (4.93)	76.3 (7.41)	74.1 (6.41)	74.5 (4.98)	76.4 (6.04)	0.830 (0.044)
	First 18 PCs, power in 5 bins, $\alpha_1$ , $\alpha_2$ , mean normal R-R intervals, demographics	74.2 (4.68)	75.1 (7.34)	73.3 (6.93)	73.9 (5.32)	75.1 (5.65)	0.813 (0.047)
10-second-pre-shock data	First 18 PCs	73.1 (4.16)	79.1 (6.84)	67.2 (7.02)	70.9 (4.37)	76.6 (5.54)	0.798 (0.042)
	power in 5 bins, $\alpha_1$ , $\alpha_2$ , mean normal R-R intervals, demographics	78.0 (4.12)	78.8 (5.67)	77.2 (6.17)	77.7 (4.77)	78.7 (4.80)	0.854 (0.043)
	First 18 PCs, power in 5 bins, $\alpha_1$ , $\alpha_2$ , mean normal R-R intervals, demographics	81.4 (3.94)	83.1 (6.09)	79.7 (6.22)	80.5 (5.05)	83.0 (5.08)	0.893 (0.036)
Results are listed as mean (SD) unless stated otherwise.							

## 5.5 DISCUSSION

The use of PCA for the prediction of ventricular tachyarrhythmia is particularly useful if the prediction is made when the ventricular tachyarrhythmia will occur within the next 10 seconds. It may be implemented when one wants to pace the hearts to avoid the occurrences of ventricular tachyarrhythmia. On the other hand, the use of PCA does not improve the prediction accuracy when one tries to predict the occurrences of ventricular tachyarrhythmia 5 minutes ahead of time. Therefore, the use of PCA may not add prognostic value when one wants to alert patients and medical units 5 minutes before the occurrences of ventricular tachyarrhythmia.

The graph of classification performances vs the number of projections onto PCs included from PCA showed that the classification performances declined slightly when more than 15 projections were included for analysis. According to Gavish and Donoho, singular values that are below the threshold are associated with PCs that are noisy and should be discarded.[84] In extracting the R-R intervals of the patients, there can be noises from detecting the R peaks and also noises from the measurement of the ECGs. As shown from Figure 5.5, when one includes noises as predictors, the classification performances by SVM will deteriorate.

## 5.6 CONCLUSION

Combining the method of PCA with other methods such as DFA and power of R-R interval in frequency domain has been proven to improve the performances of prediction of ventricular arrhythmia when one is performing a 10-second prediction. It may be implemented if there is a novel pacing method in the future that can be triggered to prevent the occurrences of arrhythmic events when the machine learning algorithm predicts that arrhythmic events are imminent.

Continuous research efforts should be taken to find methods that can improve the prediction accuracy of ventricular tachyarrhythmia.

## Chapter 6. CONCLUSIONS

The intent of this work was to examine if risk stratification for SCA and prediction of SCA can be accomplished with the use of R-R interval statistics and demographic information of patients. In the pursuit of these goals, we completed three projects:

- 1) 10 different R-R interval statistics were extracted from the Holter data of SCD-HeFT patients and they were correlated with the occurrences of VF. With the R-R interval statistics that were correlated with the occurrences of VF, we designed a screening test to exclude patients with heart failure from consideration for ICD therapy. The relationships between the R-R interval statistics and survival functions were also examined.
- 2) Feature extraction was performed on normal rhythms and pre-shock rhythms from the patients enrolled in the ICD arm of SCD-HeFT. Features included the short-term and long-term fractal scaling exponents, power of R-R interval in frequency domain and mean normal R-R intervals. With the combination of these features and the demographic information of the patients, the algorithms from machine learning, decision trees and SVMs, were trained and classifications were performed on the test set. It was shown that good classification performances could be achieved with these features. This shows promise that cardiac events indeed can be predicted in real time.
- 3) PCA was performed on the ICD recorded R-R intervals from the patients. Projections onto PCs of these R-R intervals were used as features for training SVMs. Projections onto PCs were used in combination with the features examined previously to investigate if classification performances could be improved. It was shown that PCs from PCA were useful for classification when the classification was done with R-R intervals up to 10 seconds before the shocks.

The work described in this dissertation is novel in a way that there were no works analyzing the Holter monitor data and the ICD R-R interval data obtained from the patients enrolled in SCD-HeFT in the past. Our analyses enable a much better understanding of how to treat the population of patients specified by the inclusion criteria of SCD-HeFT.

While there was work done to predict the occurrences of SCAs and to provide warnings within minutes of their occurrences, there has not been a lot of work that used a dataset of rhythms (normal rhythms and pre-cardiac-event rhythms) from the same patients with CHF. It makes clinical sense to have all the heart rhythms obtained from the same group of patients with heart failure for the purpose of classification as they would truly resemble the rhythms that ICDs are monitoring when the ICDs have already been inserted into the patients' chests. Our work was made possible by the ICD ECG R-R interval database from SCD-HeFT.

Future work includes examining the relationship between the R-R interval statistics extracted from the Holter data and the other easily obtained clinical variables. Currently, patients with heart failure qualify for ICD therapy based upon several clinical variables such as NYHA functional class and LVEF.[67], [85], [86] If variables extracted from the R-R intervals of patients with heart failure can add prognostic power to what is provided by these clinical variables, this may change the existing criteria for which patients will be selected for ICD therapy.

Another future work would be to implement the prediction algorithm in real time to examine practical limitations and challenges that may arise. From our work we showed that there were distinguishable differences between normal rhythms and pre-cardiac-event rhythms. But predicting the cardiac events in real time may have some unforeseen challenges. For example, cardiac events can be considered as rare events. Therefore, it is likely that false warnings may arise if the threshold is not set properly. False warnings will be very disrupting for patients and medical

units and may bring unnecessary stress to patients. In order to minimize the number of false warnings, the specificity has to be close to 100% while currently the specificity is around 74.4%. The threshold may be adjusted to increase the specificity but then the sensitivity will decrease. As a result, the ICD may fail to issue a warning when there is an impending SCA. This is one of the issues that definitely needs to be resolved if the predictive algorithm is to be implemented effectively in real time. Also, from our analysis, it was shown that a more accurate classification of normal rhythms vs pre-shock rhythms can be obtained with 10-second-pre-shock rhythms than with 5-minute-pre-shock rhythms, which means that rhythms closer to the occurrences of these cardiac events enable better classification performances. But in actual implementation of such predictive algorithm, the ICDs ideally should provide warnings minutes before the occurrences of these cardiac events in order to provide enough time for patients to take precautions and for medical units to respond. The more time the ICDs will provide for the patients, the more likely the classification of the algorithm will be false. Accurate classification and providing ample time for precaution are difficult to be achieved at the same time. Finally, each record of normal rhythms and pre-cardiac-event rhythms lasts about half an hour due to the fact that the ICDs used in SCD-HeFT can store a maximum of 2048 R-R intervals. Due to such limited availability of data, we could only conclude that there were distinguishable differences between normal rhythms and the half an hour of rhythms that preceded the occurrences of cardiac events. We cannot know if subtle differences in the rhythms can be observed long before these cardiac events occurred. This is an issue that is worth investigating.

To conclude, SCAs among patients with heart failure are an important problem. ICD therapy has been shown to better treat patients with heart failure compared with amiodarone but the high costs of ICD therapies prohibit them to be given to the entire population with heart failure.

Also, one of the shortcomings of ICD therapy is its inability to prevent the occurrences of SCAs but simply terminates them after they have occurred. Our first goal was risk stratification for SCAs for patients with heart failure using R-R interval statistics. These statistics, especially short-term and long-term fractal scaling exponents, showed correlation with the occurrences of SCAs and they could be used to exclude patients from consideration for ICD therapy. Future work would be to examine if the use of R-R interval statistics would increase the prognostic power provided by other clinical variables such as NYHA classes and LVEF. Our second goal was to find out if early warnings of SCA could be achieved using algorithms from machine learning. For this, we used fractal scaling exponents from DFA, power of R-R intervals in frequency domain, mean normal R-R intervals, projections onto PCs from PCA and demographic information as predictors and the machine learning algorithms used were SVMs and decision trees. We found that there were distinguishable differences between normal rhythms and pre-cardiac-event rhythms from patients enrolled in SCD-HeFT. Future work will be to implement these machine learning algorithms in real time to examine any practical limitations and challenges that may arise.

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## VITA

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