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A POSSIBLE LINK BETWEEN R-WAVE AMPLITUDE ALTERNANS AND T-WAVE ALTERNANS IN ECGs

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THESIS
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By

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Lexington, Kentucky

2018

ABSTRACT OF THESIS

A POSSIBLE LINK BETWEEN R-WAVE AMPLITUDE ALTERNANS AND T-WAVE ALTERNANS IN ECGs

Sudden Cardiac Death (SCD) is the largest cause of natural deaths in the USA, accounting for over 300,000 deaths annually. The major reason for SCD is Ventricular Arrhythmia (VA). Therefore, there is need for exploration of approaches to predict increased risk for VA. Alternans of the T wave in the ECG (TWA) is widely investigated as a potential predictor of VA, however, clinical trials show that TWA has high negative predictive value but poor positive predictive value. A possible reason that TWA has a large number of false positives is that a pattern of alternans known as concordant alternans, may not be as arrhythmogenic as another pattern which is discordant alternans. Currently, it is not possible to discern the pattern of alternans using clinical ECGs. Prior studies from our group have showed that alternans of the maximum rate of depolarization of an action potential also can occur when Action Potential Duration (APD) alternans occurs and the relationship between these two has the potential to create spatial discord. These results suggest that exploration of the co-occurrence of depolarization and repolarization alternans has the potential to stratify the outcome of TWA tests. In order to investigate the link between depolarization alternans and changes in ECGs, we used a mathematical model created previously in our research group which simulated ECGs from the cellular level changes observed in our experimental studies. These results suggest that the changes in ECGs should appear as alternating pattern of the amplitude of the R wave. Because there are a variety of factors which may also cause the R wave amplitude to change, we used signal analysis and statistical modeling to determine the link between the observed changes in R wave amplitude and depolarization alternans. Results from ECGs recorded from patients show that amplitude of the R wave can change as predicted by our experimental results and mathematical model. Using TWA as the marker of repolarization alternans and R Wave Amplitude Alternans (RWAA) as the marker of depolarization alternans, we investigated the phase relation between depolarization and repolarization alternans in clinical grade ECG and observed that this relationship does change spontaneously, consistent with our prior results from animal studies. Results of the present study support further investigation of the use of RWAA as a complementary method to TWA to improve its positive predictive value.

KEYWORDS: Electrocardiography (ECG), Depolarization and Repolarization Alternans, R-Wave Amplitude Alternans (RWAA), Phase Relation

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CHAPTER 1.   INTRODUCTION

Cardiovascular disease is recognized as a leading cause of global mortality which results in nearly 17 million deaths annually in the world [1]. Sudden Cardiac Death (SCD), a sudden and unexpected death occurring immediately after initial onset of symptoms, accounts for about 40-50% of cardiovascular deaths [1]-[2]. SCD is the largest cause of natural deaths in the USA, accounting for over 300,000 deaths annually [1]-[3]. Therefore, there is need for exploration of the ways to predict SCD.

Many studies have shown that ventricular arrhythmia (VA) which is abnormal heart rhythm originating in the ventricles is the main reason for SCD [4]. Therefore, there has been worldwide attention in the exploration of approaches to predict the risk of VA. There are some existing markers such as Heart Rate Turbulence (HRT), Late Gadolinium Enhancement (LGE), and QRS Prolongation [5]-[6]-[7]. However, the mentioned markers mostly have shown the potentiality only in specific cases; therefore, there is still a need for a general clinical tool to predict the risk of VA.

T-Wave alternans (TWA) in electrocardiographic (ECG) recordings during a standard stress test has been considered as a potential noninvasive clinical tool for prediction of VA [8]. TWA is a subtle beat to beat fluctuation in the morphology of the T-wave and is the result of action potential duration (APD) alternans [9]. APD alternans is beat to beat alternation in the duration of action potential (i.e. short-long-short or long-short-long). Since alternation of APD is related to the electrical instability within the heart which can lead to VA, TWA has been considered a predictor of VA [10]. However, a meta-analysis of data from nearly 2,600 subjects showed that while TWA has a strong negative predictive value (97%) it suffers from a poor positive predictive value (19%) [11]-[12]-

[13]. Therefore, exploration and investigation of approaches to improve the positive predictive value of TWA is warranted.

More recent studies suggest that spatially discordant alternans has more arrhythmic potential than concordant alternans [14]. Therefore, it is possible that because TWA is not capable of distinguishing between these two types of spatial alternans this accounts for its limitations in identifying truly arrhythmogenic cases. [15]. Results of our previous animal and simulation studies have shown a possible link between depolarization and repolarization alternans in action potential [16]. The study illustrated that alternans of maximal rate of depolarization, i.e. $|dv/dt|_{max}$ alternans also appears when APD alternans (repolarization alternans) is present and the phase relation between these two alternans can change spontaneously between in phase (short-long APD follows small-large $|dv/dt|max$) and out of phase (short-long APD follows large-small $|dv/dt|_{max}$). Also, the results have shown that the phase relation between depolarization and repolarization alternans has an effect on the transition of concordant to discordant alternans [16]. However, currently there is no clinical method to discern the pattern of alternans using clinical ECGs or to detect the phase relationship between depolarization and repolarization alternans.

In order to investigate the phase relation between depolarization and repolarization alternans in ECGs, a marker for depolarization alternans in ECG is needed. We used a dipole field potential based mathematical model produced previously in our research group to simulate ECGs from the cellular level changes observed in our experimental studies during two consecutive action potentials with different $|dv/dt|_{max}$ (one larger than the other one) and different APDs. The results of our simulations showed that the changes in ECGs resulting from these cellular level changes should appear as alternating pattern of the

amplitude of the R wave (RWAA). Since a variety of factors, in addition to those predicted by the model, may cause the R wave amplitude to change, we applied statistical analysis to determine the link between the observed changes in R wave amplitude and depolarization alternans. To verify whether RWAA does occur in clinical grade ECGs, we analyzed ECGs obtained from a variety of databases available on the Physionet website [17]. The results from ECGs recorded from patients show that amplitude of the R wave can change as predicted by our experimental results and the mathematical model.

To investigate the phase relation between depolarization and repolarization alternans, ECGs from Physionet database were selected and RWAA as the indicator of depolarization alternans and TWA as the indicator of repolarization alternans were calculated. The results show that depolarization alternans and repolarization alternans can happen simultaneously and the phase relation between the two alternans can change even within a single ECG recording. The results of this study support further investigation of the phase relation between depolarization and repolarization alternans in clinical ECGs to improve the positive predictive value of TWA towards the eventual goal of development of a clinical tool, applicable in prediction of the risk of VA in an individual in the future.

CHAPTER 2. BACKGROUND

2.1   Cardiac Action Potential (AP)

Cardiac action potential is the change in the transmembrane potential (TMP) of heart cells that contract and generate force. The change in TMP is caused by the movement of specific ions through ionic channels located in the cell membrane of heart cells. Figure 1 shows a schematic of a cardiac action potential.
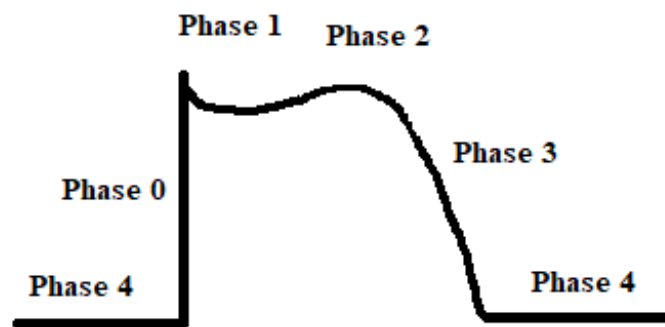
Figure 1. Cardiac Action Potential.

A cardiac AP consists of 5 phases including 0-4. In phase 4 (resting phase) which is the beginning and end phase of the cardiac AP, the TMP is constant and around -90 mV. The resting membrane potential is the result of the balance between inward (mostly Na^+ and Ca^{2+}) and outward ions (mostly K^+ and Cl^-). In phase 0, called depolarization phase, TMP rapidly increases due to the opening of Na^+ channels and a positive net flow into the cell. In Phase 1, Na^+ channels are inactivated and K^+ channels are opened and closed rapidly and let the K^+ ions briefly flow from inside to outside of the cell resulting in a slightly more positive TMP. In phase 2, which is known as the "Plateau phase", Ca^{2+} ions flow into the cell through long-type Ca^{2+} channels and causes a plateau to form. Finally, phase 3 called "rapid repolarization" phase is when the long-type Ca^{2+} channels (L type)

are closed and the K^+ channels are open. Then due to a positive net flow from the inside to the outside, the TMP decreases [18]- [19].

Based on the above information, phase 0 is the indicator of ventricle depolarization and phase 1-3 are the indicators of ventricle repolarization.

2.2 Electrocardiogram (ECG)

The electrocardiogram (ECG) is a graphical tracing of the signals resulting from the electrical activity of the heart measured from the surface of the body using electrodes placed on the skin.

An example of an ECG signal is shown in Figure 2. A single cardiac cycle is electrically represented by 3 main waves: P, QRS, and T waves. P-wave represent atrial depolarization, the QRS complex is the marker of ventricular depolarization, and the T-wave represents ventricular repolarization [18]-[20].
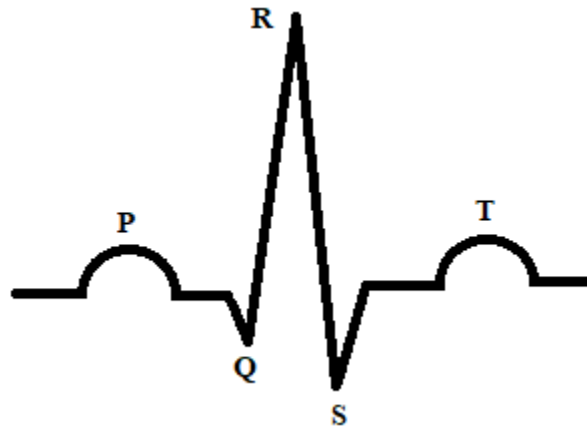
Figure 2. An example of ECG signal.

2.3 Ventricular Arrhythmia (VA)

Sudden Cardiac Death (SCD) is a sudden and unexpected death which occurs in a short period of time after the initial onset of symptoms [2]. SCD typically results from a malfunction in the electrical systems of the heart [21]. Approximately 80% of SCD events can be attributed to ventricular arrhythmias [4].

Ventricular arrhythmia represents a very fast and abnormal cardiac rhythm that originates in the lower chambers of the heart called the ventricles. Two types of ventricular arrhythmia have been described and include ventricular tachycardia (VT) and ventricular fibrillation (VF). Ventricular tachycardia is recognized as a wide complex, regular, and fast heart rhythm, whereas ventricular fibrillation is a more disorganized, often irregular and rapid heart rhythm. Both rhythms significantly compromise the mechanical function of the heart and ultimately are not compatible with life. [22]-[23].

2.4 Repolarization Alternans in Cellular Levels

Action Potential Duration (APD) alternans, which is a beat-to-beat fluctuations in the duration of the action potential, is considered as a marker of repolarization alternans [9]. A simplified sketch of APD alternans has been shown in figure 3.
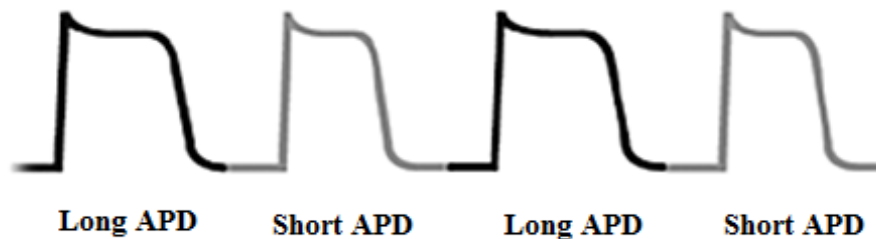
Figure 3. A simplified sketch of APD alternans.

APD alternans may cause unidirectional conduction block at the sites of the heart which show longer action potentials [9]. Unidirectional conduction block is an unsuccessful conduction of cardiac impulse in one direction and a successful one in the opposite direction. Figure 4 shows how the action potential alternans results in the conduction block.
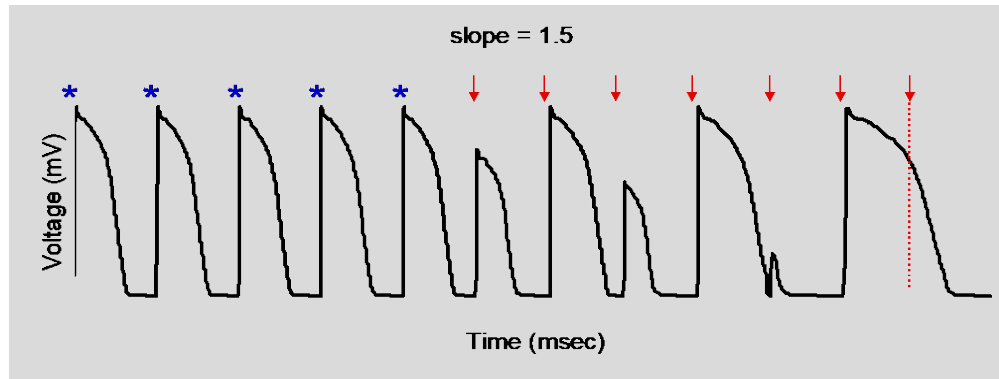
Figure 4. Conduction block.

Also, unidirectional conduction block is a necessary requirement for the onset of reentry which occurs when an action potential re-excites the heart after the end of refractory period [24]. Accordingly, it is widely accepted that reentry is a major cause of arrhythmias. Thus, it can be concluded that APD alternans (repolarization alternans) has the potentiality of initiating ventricular arrhythmia.

2.5   T-Wave Alternans

Repolarization alternans (i.e. APD alternans) at the cellular level is linked to T-wave alternans (TWA) in the ECG signals [9]. Since studies have hypothesized that APD alternans can cause VA, TWA has received attention as a noninvasive and potentially useful method for discriminating between patients who are at low and high risk of VA [9]-[11].

TWA is a beat-to-beat fluctuation in the morphology of T-wave in ECGs [25]. A simplified sketch of TWA has been shown in figure 5.

Figure 5. A simplified sketch of TWA.

TWA was first reported by Hering and Sir Thomas Lewis in the early 1900s during tachycardia and ischemia [26]. But, more recently the microvolt level TWA was considered as a potential method for the prediction of VA which is invisible to the unaided eye and is recognizable by signal processing methods [27].

However, a meta-analysis of 19 different clinical studies enrolling nearly 2,600 subjects showed that the TWA method has a high negative predictive value (NPV) (97%), while its positive predictive value (PPV) is low (19%) [11]. Thus, a negative result of TWA test means that the patient is in low risk of VA and unlikely to experience SCD in the near future, accordingly. On the other hand, if the TWA test is positive, it is not easy to conclude whether the patient is in high risk of VA and therefore SCD in the near future. Therefore although TWA is a promising index, for given prevalence it suffers from high false positives [12]-[13]. This can result in unnecessary treatment (implantable cardioverter defibrillator (ICD) is an efficient treatment method) which are costly, sometimes needs surgery for the implantation, and causes unnecessary anxiety. Therefore, there is a need for investigating approaches that complement TWA and improve PPV of arrhythmia prediction.

Since recently microvolt level TWA alternans has attracted a worldwide attention as a potential noninvasive method for the prediction of VA, many signal processing methods have been come out such as spectral analysis in the frequency domain and Modified Moving Average (MMV) in the time domain.

2.6   Concordant vs. Discordant Alternans

Most recent studies show that rather than APD alternans, spatial discord in APD alternans is more conducive to the formation of block and subsequent arrhythmia [14]. Discordant alternans is the change in APD when AP propagates spatially. In other words, discordant alternans is a situation where one region of the heart shows a short-long pattern of APD, while the other region(s) show long-short pattern. Concordant alternans means that APD pattern (e.g. long-short-long) does not change significantly when propagating spatially. Therefore, a possible reason that TWA identifies more false positives is that not all TWA reflects discordant alternans [15]. Concordant vs. discordant alternans have been depicted in figure 6.
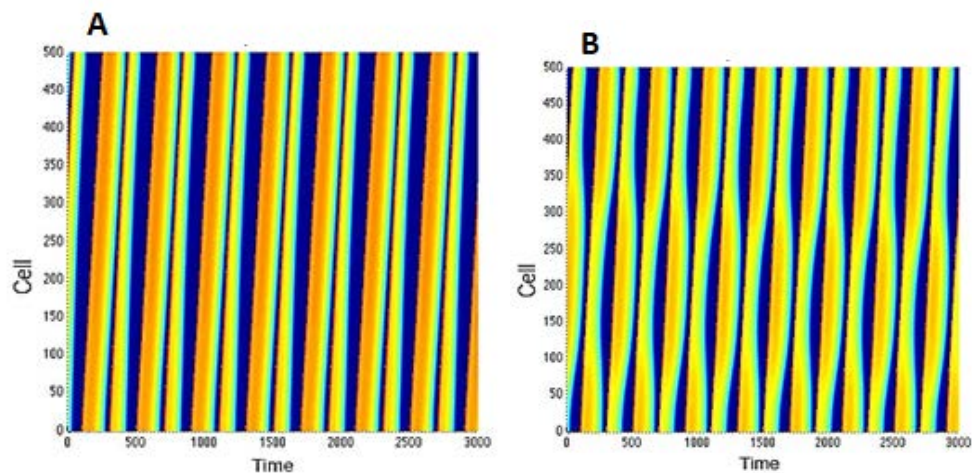
Figure 6. Concordant vs. Discordant Alternans. A) Concordant alternans B) Discordant Alternans, reproduced from Jing et al [16] with permission.

2.7   Depolarization Alternans in Cellular Level

Depolarization alternans is the beat-to-beat fluctuation in the depolarization phase of the AP in either the amplitude or the maximum rate of depolarization ($|dv/dt|_{max}$) [28]-[29]. In a prior study conducted by our research group, transmembrane potentials recorded from ventricles of swine and canines showed alternans of $|dv/dt|_{max}$ and APD [16]. The results of the study showed that alternans of $|dv/dt|_{max}$ can also occur when APD (repolarization) alternans occurs and the relationship between the APD and $|dv/dt|_{max}$ alternans can change spontaneously between being in phase (long short APD/large-small $|dv/dt|_{max}$) and out of phase (long-short APD/small-large $|dv/dt|_{max}$) [16]. Figure 7 shows the possible relationships between APD and $|dv/dt|_{max}$ alternans.

Computer simulations of the study using a canine ventricular myocyte model showed that the phase relationship between APD and $|dv/dt|_{max}$ alternans affected occurrence of discord i.e. when the relation was out of phase, it had a stabilizing effect on conduction by suppressing formation of discords. Thus, the phase relation between depolarization and repolarization alternans has the potential to complement the TWA test and possibly reduce the number of its false positives.
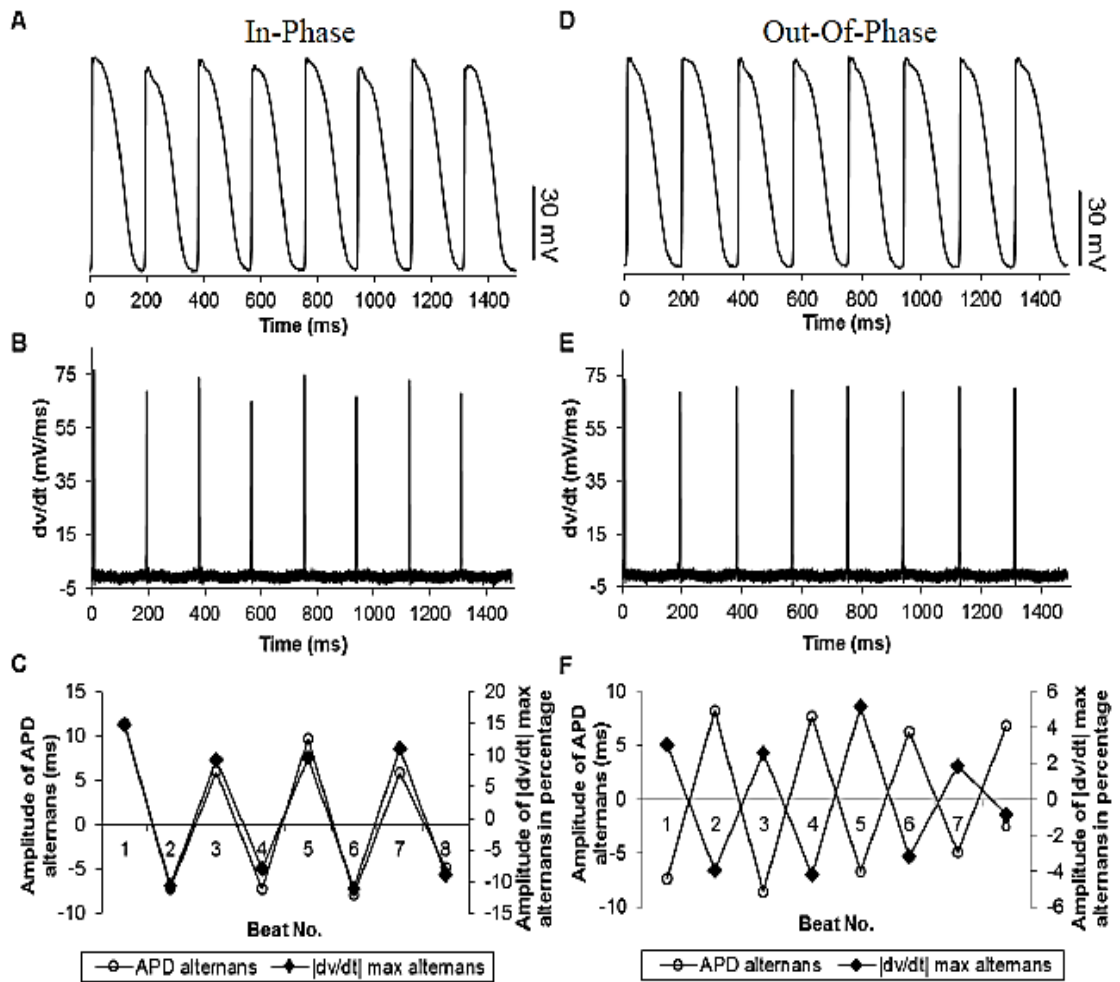
Figure 7. Swine APD and $|dv/dt|_{max}$ In-Phase and Out-of-Phase relationship. Both APD (A, D) and $|dv/dt|max$ (B, E) traces display beat-to-beat alternating patterns. (C, F) Show overlays of APD alternans (open circle) and alternans of $|dv/dt|max$ (closed diamonds), reproduced from Jing et al [16] with permission.

CHAPTER 3. METHODs

3.1   Dipole Field Potential Spatial Model

To investigate the marker of depolarization alternans in ECGs while repolarization alternans is present, a dipole field potential based on a mathematical model developed in our group was used to simulate ECGs during two consecutive APs with different $|dv/dt|_{max}$ and APDs. The model was used to simulate ECGs using cellular level rate of depolarization alternans patterns observed in our experimental studies. The model consisted of a cone-shaped heart with two ventricles and consisted of 129,826 time varying dipole elements. The thorax was considered as a homogenous volume conductor with size and conduction properties comparable to an adult human torso. The location of the electrodes from which ECG was simulated matched the standard clinical lead locations, RA, LA, LL, V1, V2, V3, V4, V5 and V6. To calculate the potential at the location for each ECG lead, the transmembrane potential and net membrane current per unit volume for each dipole element was combined to obtain the electrical field around each element. Then by integrating the electrical fields and considering the distance and direction of each ECG electrode, the body surface potential was calculated. Figure 8 shows the model from different views.

In the simulation, to save the computational load, the APs were pre-generated using piece-wise constant line segments and saved in look-up tables.
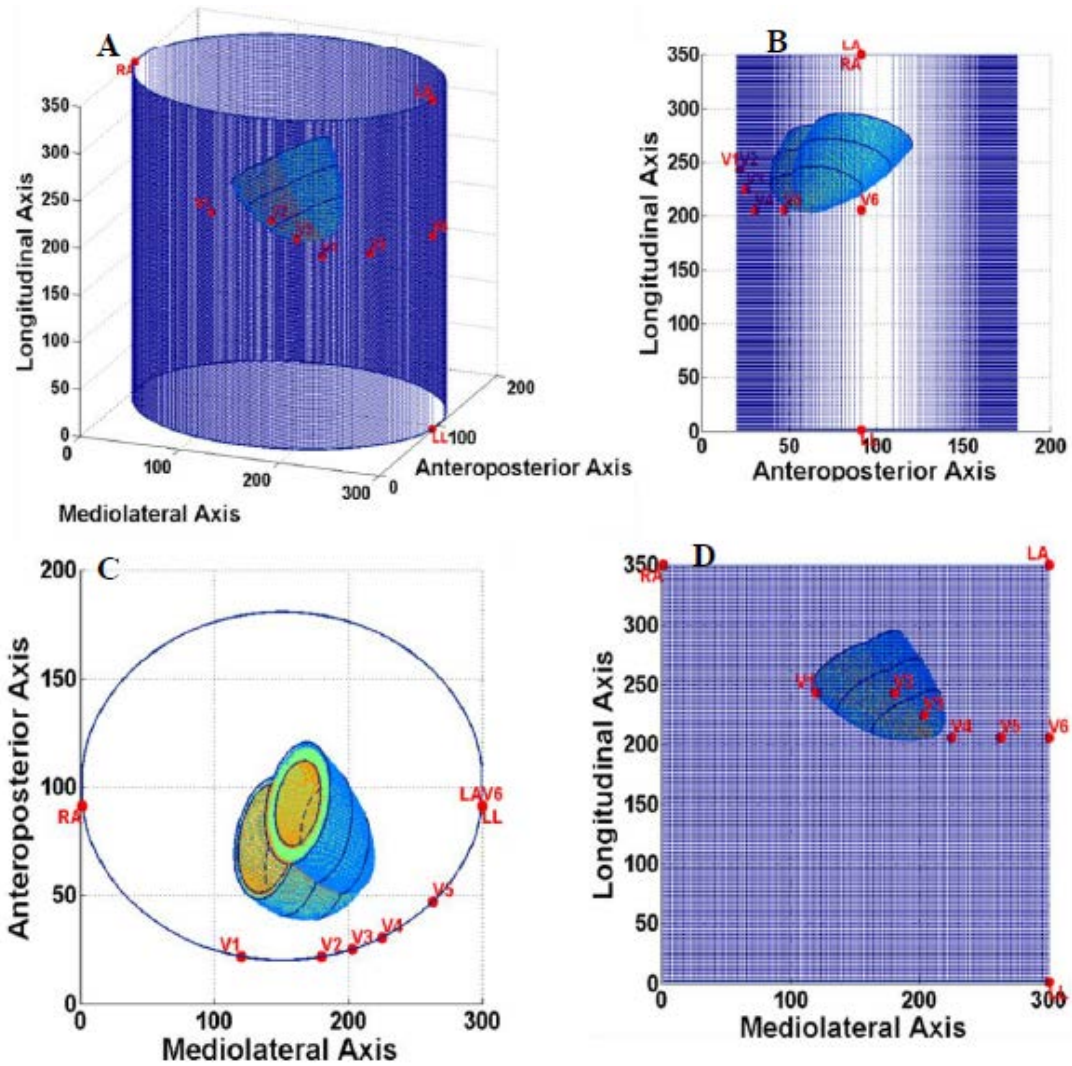
Figure 8. Dipole Field Potential Spatial Model. This figure shows a 3D view (A), front view (B) top view (C) and side view (D) of the model. The red points represent the location of the different leads typically used in an ECG. The model was generated by Dr. Siqi Wang.

3.2 R-Wave Amplitude Alternans (RWAA) Detection

Using the mathematical model described in the previous subsection, we observed that alternans of the maximum rate of depolarization (dv/dt_{max}) can manifest as alternans of the R wave amplitude on the surface ECG. In this subsection we report the analyses conducted to determine whether the alternans of R wave amplitude (RWAA) is observed

in clinical grade ECGs. The RWAA algorithm comprised of three stages: preprocessing, R-wave amplitude detection, and detection of alternans.

- Preprocessing

In the preprocessing stage, a bandpass filter (0.5 Hz to 50 Hz) was applied to the ECG signals. The filter removed high frequency noise and baseline shifts [30]. To separate the normal beats from abnormal ones, all abnormal beats were detected and labeled using the R-R interval method described by Weiss et al. [31]. R-R interval is defined as the interval between two successive R-waves on the ECG (Figure 9). Based on the R-R interval method, the current R-R interval is compared to the mean of the preceding 7 R-R intervals. If the current R-R interval was less than 90% of the mean, then the current beat along with the preceding and subsequent beats, were marked as abnormal.
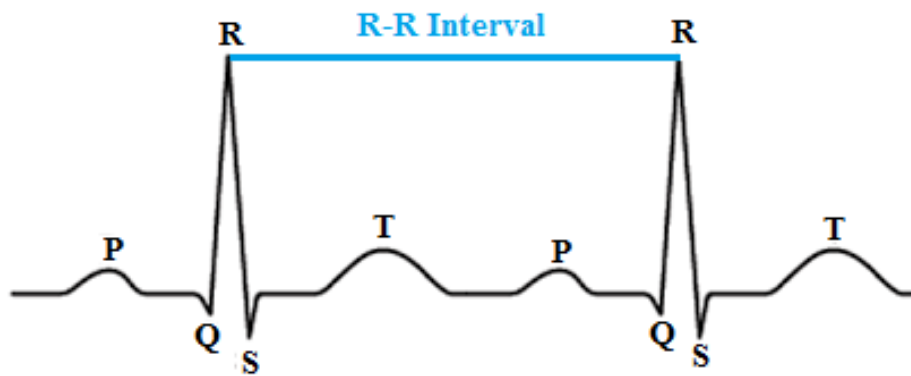
Figure 9. This figure shows the concept of R-R interval which is the distance between two consecutive R-peaks.

- R-Wave Amplitude Detection

In order to detect the R-wave amplitude, each R-wave peak was detected using an algorithm developed by Pan and Tompkins [32]. The four main steps in the Pan and Tompkins algorithm are 1) filtering of the ECG signal through a digital bandpass filter

composed of cascaded high-pass and low-pass filters to suppress noise, 2) taking the differentiation of the output signal from the previous step to derive the slope of the QRS 3) taking the square of the output signal to intensify the QRS slope and suppress the false positives as a result of T waves with higher than usual spectral energies, and 4) moving window integration to obtain information about both the slope and the width of the QRS (Figure 10).

Figure 10. Main steps in Pan and Tompkins Method.

To detect the onset of the R-wave, the local minimum before each R peak and after the end of previous T-wave (detected by the method described by Weiss et al. [31]) was detected as an estimation of the Q-wave. Then, the derivative of the ECG was computed within the Q and R wave window and a threshold (0.001 mv/msec) was applied to the derivative within this window to detect the onset of the R-wave. The R-wave amplitudes were calculated as the difference between the peak and onset of R-waves. Figure 11 shows an example of the detected R-peak and onset of R-wave using this algorithm.
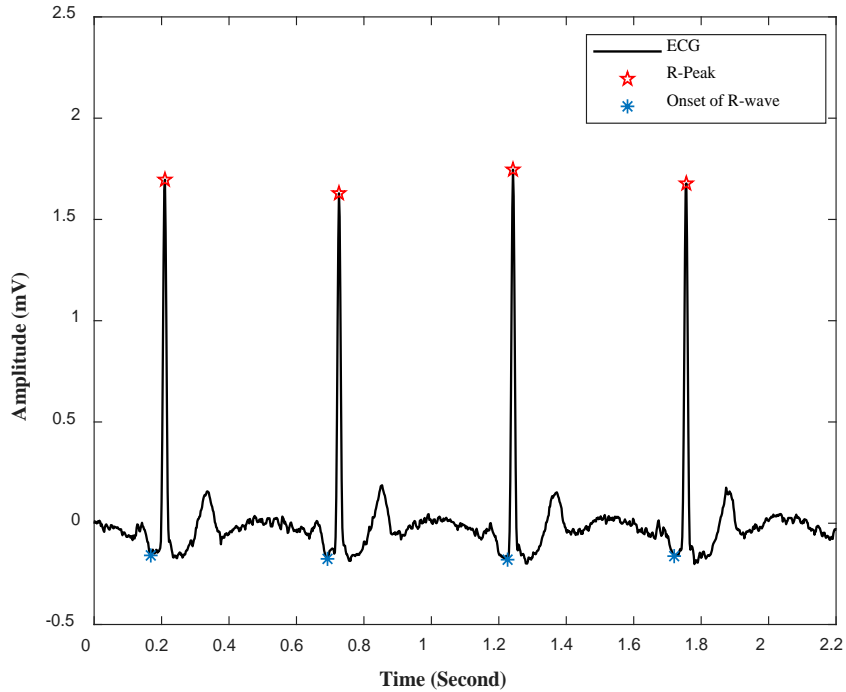
Figure 11. R-wave peaks and onset of R-wave detection. R-wave amplitude is calculated as the difference between the two points [15].

To detect the T-wave boundaries based on the proposed method by Weise et al. the following steps were taken. After the detection of R-wave peaks using the Pan and Tompkins algorithm, the R-R intervals were calculated. If the R-R interval was more than 770 msec, the preliminary start of T-wave was considered to be located 100 msec after the R-wave peak and the preliminary location of the end of T-wave was considered to be 500 msec after the R-wave peak. If the R-R interval was between 320 msec and 770 msec, the preliminary start of T-wave was considered to be located 40 msec plus 7.8 percent of R-R interval after the R-wave peak. Finally, if the R-R interval was less than 320 ms, the preliminary start of T-wave was considered to be 65 msec after the R-wave peak. In the cases with R-R intervals less than 770ms, the preliminary location of the end of T-wave was considered 65% of the R-R interval after the R-wave peak. To finalize the T-wave boundaries each sample was subtracted from the mean of the T-wave window, i.e. the linear

baseline of the window was removed. Afterwards, each sample of the window was squared and consequently the cumulative summation of each sample was calculated. The final location of T-wave boundaries was fixed on 1% and 99% of the summation.

- Detection of Alternans

The last stage in the RWAA algorithm is the detection of alternans. In order to classify a sequence of beats as containing RWAA, three criteria had to be met; first, all beats in that sequence had to be normal based on the R-R interval method. Second, the amplitude had to alternate from beat to beat (i.e. tall-short-tall or short-tall- short) at least five times, based on probability estimates for consecutive changes in random binary outcomes with equal probability for the two outcomes (see section Statistical Analysis). Third, the absolute difference between the successive amplitudes had to be greater than a threshold. Since our simulations showed that alternans of $|dv/dt|_{max}$ produced subtle changes in R wave amplitude and we wanted a specific threshold for each ECG trial to make our algorithm more robust, the threshold was set on 1% of the mean of all the normal R-wave amplitudes in that particular recording of ECG.

3.3   Statistical Analysis

The statistical analysis done in this study was an empirical method to estimate the probabilities of 5 consecutive changes. Since R-wave amplitude alternation is binary (tall or short) subject to a selected threshold, an array of 10,000 random binary numbers with equal probability were generated to find the sequences with at least 5 consecutive changes (i.e.101010 or 010101). Then, we calculated the probability by dividing the sum of the numbers that were in the sequences of at least 5 consecutive changes by the total numbers

of the sequence. This process was repeated 10,000 times. The average of these probability was 9.4%.

3.4 TWA Detection

Since T-wave alternans can range from less than 20 microvolts to several hundred microvolts on a surface ECG, accurate measurement is challenging [33]. Therefore, many algorithms both in time and frequency domains have been developed to detect and quantify microvolt T-wave alternans (TWA) such as spectral analysis, modified moving average (MMV), complex demodulation, Capon filtering, statistical tests, etc. [34]- [35]. Since among all the algorithms the most widely used are the spectral method (SM) analysis and MMV based on superior efficiency and applicability, we limited ourselves to these two methods.

3.5 Spectral Method

Our reference for the spectral method is the algorithm laid out by Weise et al. [31]. Based on this method, a sequence of 128 beats starting from the first one is selected and then the sequence is shifted one beat to the right to have all possible sequences including 128 consecutive beats in the ECG recording. To determine whether the sequence shows TWA, the primary requirement is that the sequence be labeled as determinant. A sequence is determinant if the number of normal beats in the sequence is more than 90%. To generate the sequences, the start and end of T-waves were determined and then the T-wave interval was considered the average of all T-wave intervals in the sequence. Thus, a matrix for each sequence containing the samples of the ECG in the T-wave interval in the columns for each beat in the rows was created. To remove the effect of abnormal beats in the sequence, all even/odd abnormal beats were substituted by the generated even/odd median template from the all even/odd normal beats in the sequence. The rows of the matrix contained the beats

and the columns were the samples. In order to generate a cumulative power spectrum of the 128 beats in the sequence, a Fast Fourier Transform (FFT) of each column was calculated and the rows were summed up. The result is the cumulative power spectrum of the sequence which is used to determine whether the sequence contains TWA. A sequence with two criteria is considered to show alternans. First, the alternans voltage had to be greater than 1 microvolt which is calculated as

$$Alternans\ Voltage\ (\mu V) = \sqrt{Alternans\ Peak - \mu_{noise}}$$

where Alternans Peak is the cumulative power spectrum amplitude of the component located at 0.5 cycle/beat, and μ_{noise} is the integral of the cumulative power spectrum in the window between 0.43 and 0.46.

The second criteria requires $K_{Score} > 3$ and is calculated as follows:

$$K_{Score} = (Alternans\ Peak - \mu_{noise})/\sigma_{noise}$$

where σ_{noise} is the standard deviation of the noise window (0.43 to 0.46). That is, to determine if alternans were present, the following criteria needed to be met: $Alternans\ Voltage > 1.0\ \mu V$ and $K_{Score} > 3$ [31].

3.6   Modified Moving Average (MMV)

MMV is a signal processing algorithm in the time domain proposed by Bruce et al. for the purpose of TWA detection [33]. The first step in MMV is to separate the even and odd beats and put in one stream, *A* for even ECG beats and *B* for odd ECG beats as

$$ECG\ beat\ A_n(i) = ECG\ beat_{2n}(i)$$

$$ECG\ beat\ B_n(i) = ECG\ beat_{2n-1}(i)$$

where $i = 1 \ldots$ is the number of samples per beat, $n = 1, 2, 3, 4 \ldots N/2$, and N is the total number of beats in the ECG trial. Then the first MMV of the stream A and B are calculated as:

$$\text{Computed beat } A_1(i) = \text{ECG beat } A_1(i)$$

$$\text{Computed beat } B_1(i) = \text{ECG beat } B_1(i)$$

The next MMV is computed using the present MMV and the next ECG beat as follows:

$$\text{Computed beat } A_n(i) = \text{Computed beat } A_{n-1}(i) + \Delta_A$$

$$\text{Computed beat } B_n(i) = \text{Computed beat } B_{n-1}(i) + \Delta_B$$

where Δ_A is calculated as follows:

$$
\begin{aligned}
\Delta_A &= -32 & \text{if} && \alpha \leq -32 \\
\Delta_A &= \rho & \text{if} && -32 \leq \alpha \leq -1 \\
\Delta_A &= -1 & \text{if} && -1 < \alpha < 0 \\
\Delta_A &= 0 & \text{if} && \alpha = 0 \\
\Delta_A &= 1 & \text{if} && 0 < \alpha \leq 1 \\
\Delta_A &= \rho & \text{if} && 1 \leq \alpha \leq 32 \\
\Delta_A &= 32 & \text{if} && \alpha \geq 32
\end{aligned}
$$

And α is computed given by

$$\alpha = [\text{ECG beat } A_{n-1}(i) - \text{Computed beat } A_{n-1}(i)]/8$$

where n is the nth beat in the beats of type A.

Also Δ_B is calculated as follows:

$$
\begin{aligned}
\Delta_B &= -32 & \text{if} && \beta \leq -32 \\
\Delta_B &= \rho & \text{if} && -32 \leq \beta \leq -1 \\
\Delta_B &= -1 & \text{if} && -1 < \beta < 0 \\
\Delta_B &= 0 & \text{if} && \beta = 0 \\
\Delta_B &= 1 & \text{if} && 0 < \beta \leq 1 \\
\Delta_B &= \rho & \text{if} && 1 \leq \beta \leq 32 \\
\Delta_B &= 32 & \text{if} && \beta \geq 32
\end{aligned}
$$

And β is computed given by

$$\beta = [\text{ECG beat } B_{n-1}(i) - \text{Computed beat } B_{n-1}(i)]/8$$

where n is the *n*th beat in the beats of type B.

It is clear that if the next ECG beat is larger than the present MMV, then the next MMV will be increased and if the next ECG beat is smaller than the present MMV, then the next MMV will be decreased. In order to measure T-wave alternans, the difference between MMV of the *A* and B within the T-wave interval (error) is calculated and then the maximum absolute value of the error is determined as

$$\text{TWA}_n = \max_{i=\text{ Twavestart}}^{i=\text{ Twaveend}} | \text{ Computed beat } B_n(i) - \text{Computed beat } A_n(i)|$$

where TWA is T-wave alternans and n _ 1, 2, 3, . . . *N*/2.

3.7 Phase Relation Alternans between RWAA and TWA

As stated before, although TWA has a strong negative predictive value, its positive predictive value for VA is poor. Studies by several investigators suggest that concordant versus discordant alternans subgrouping affects arrhythmic potential. Also, results of our previous animal and simulation studies showed that the phase relation between depolarization and repolarization alternans has an effect on the occurrence of discordant alternans. Since TWA and RWAA are the indicators of repolarization and depolarization alternans on the surface ECG, respectively, an algorithm was developed for phase relation determination between RWAA and TWA and includes the following:

- Detection the sequences in the ECG trial with RWAA

- TWA calculation for the sequences with TWA and selection the sequences with both TWA and RWAA

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- Detection the phase relation between TWA and RWAA

The scheme of the algorithm is depicted in figure 12.
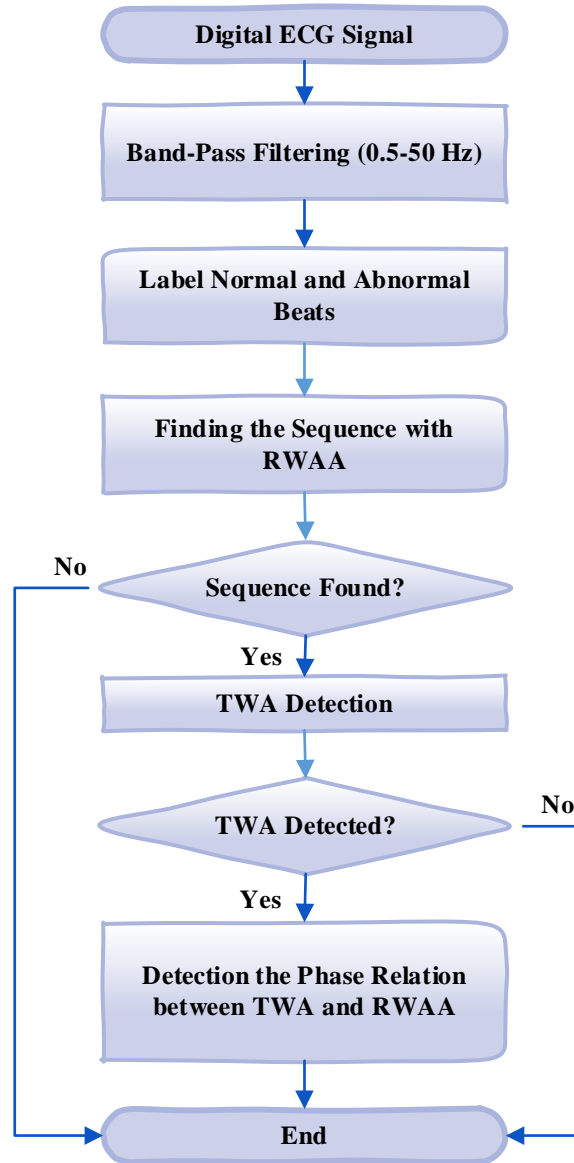
Figure 12. Flowchart of the algorithm for the detection of the phase relation between TWA and RWAA [15].

Detection of the sequences which show RWAA was done by the method described in the R-wave amplitude alternans section. Since for this study we needed a TWA detection method in the time domain which has the property of accepting or rejecting a sequence contains TWA, we used a TWA detection method in the time domain. In this method the

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initial and end of the T-waves were detected using a method similar to the one described by Weiss et al. [31]. Then, the difference between the average of all normal even T-waves (T waves for even beats) and the average of all normal odd T-waves in the sequence was computed as the error signal. Since TWA is known to contain subtle fluctuations in TWA morphology, the sequence was considered to contain TWA if the absolute area under the error signal was greater than 1% of the threshold which is defined as the average of the area under the T-waves of all normal beats in the ECG trial.

The last stage was the selection of the sequences with both RWAA and TWA to determine the phase relation between RWAA and TWA in the detected sequences. Afterwards, the average of R-wave amplitude of all normal even beats and the average of R-wave amplitude of all normal odd beats in the sequence was calculated and the sign of the difference between these two was determined. Also, the integral of the error signal was calculated and the sign of the integral was considered as the sign of TWA in the sequence. The phase relation was determine based on the sign of TWA and RWAA; if the two signs were the same (both plus or both minus), the phase relation between RWAA and TWA was determined in phase. Otherwise, the phase relation was determined out of phase [15].

CHAPTER 4. RESULTS

The clinical data used in this study came from 5 different databases on PhysioNet.org [34]. The physioNet website contains a large number of recorded human physiological signals that are freely available to the public under the ODC Public Domain Dedication and License v1.0 for the purpose of research [34]. The databases include St.-Petersburg Institute of Cardiological Technics 12-lead arrhythmia database (INCARTDB), MIT-BIT arrhythmia Database (MITDB), MIT-BIH ST Change Database (STDB), MIT-BIH ST Supraventricular Arrhythmia Database (SVDB), and T-Wave Alternans Database (TWADB).

The INCARTDB data base includes a collection of 75 half an hour ECGs sampled in the frequency of 257 Hz collected from the patients who were in the risk of coronary artery disease [36]. The MITDB data base contains 48 half an hour ECG trials sampled in the frequency of 360 Hz recorded from 47 subjects that participated in the study of cardiac arrhythmias [36]-[37]. The STDB database contains 28 ECG recordings sampled in the frequency of 360 Hz which have abnormality in the ST segment [36]. The SVDB database compromises 78 half an hour ECG trials selected to supplement the examples of supraventricular arrhythmias in the MIT-BIH Arrhythmia Database [34]. Finally TWADB database includes 100 ECGs in which 56 ECGs are recorded from the subjects at the risk of SCD, 12 ECG recordings are from healthy individuals, 6 ECGs from sinus rhythm database, and the rest 32 ECG trials are synthetic ECGs with known TWA magnitude [34].

4.1   Result of Mathematical Model

In this study we used a dipole field potential based mathematical model (developed by Dr. Siqi Wang in our research group) to simulate ECGs during two consecutive APs

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with different $|dv/dt|_{max}$ to find an appropriate index for depolarization alternans in ECG signals. Our simulation results indicated that the difference in $|dv/dt|_{max}$ between two beats could be seen in different locations of the ECG but was most pronounced in the amplitude of the R-wave. Figure 13 shows two action potential with different $|dv/dt|_{max}$ and figure 14 shows the difference in ECGs related to the beats with different $|dv/dt|_{max}$.
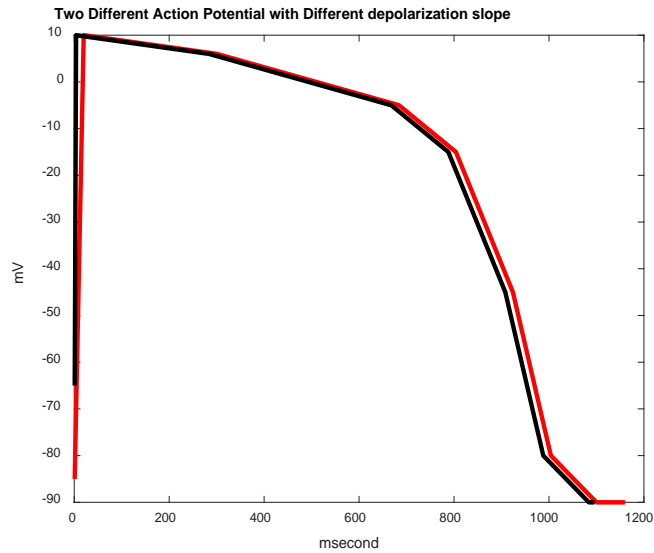
Figure 13. Two Different AP related to the beats with different $|dv/dt|_{max}$
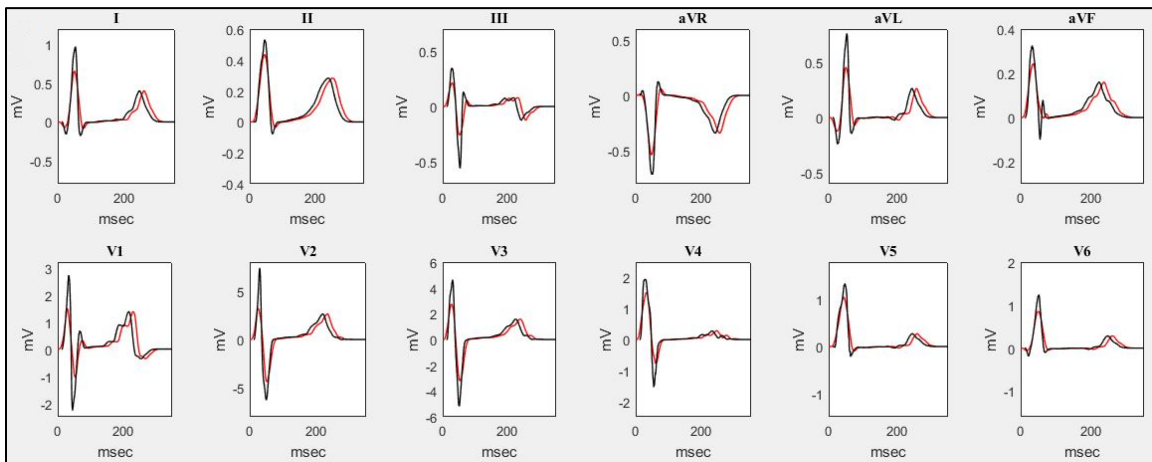
Figure 14. Changes in $|dv/dt|_{max}$ shows itself in the amplitude of the R-wave in ECG.

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4.2   Result of RWAA Detection

The first step in exploring whether co-occurrence of RWAA with TWA is a better predictor of arrhythmia risk was to determine whether RWAA occurs in clinical grade ECGs. Results from ECG recordings from Physionet databases show that the R wave amplitude does change as an alternating pattern. The results shown in the figure 15 show the occurrence of RWAA sequences of 5 or more beats as a percentage of the total number of beats within each ECG recording from different databases of the Physionet that we analyzed. The ECG recordings were ordered in terms of percent occurrence of RWAA. In the chart related to TWADB database, the zero RWAA detected trials are correspondence to the synthetic ECGs that, as expected, did not show any RWAA. Also, table 1 shows the maximum and the average occurrence of RWAA in ECG trials from the analyzed databases. The results of figure 15 and table 1 show that although the average RWAA occurrence ranged from around 11% to 19%, some ECG recordings in MITDB database has shown the RWAA occurrence up to 87%.
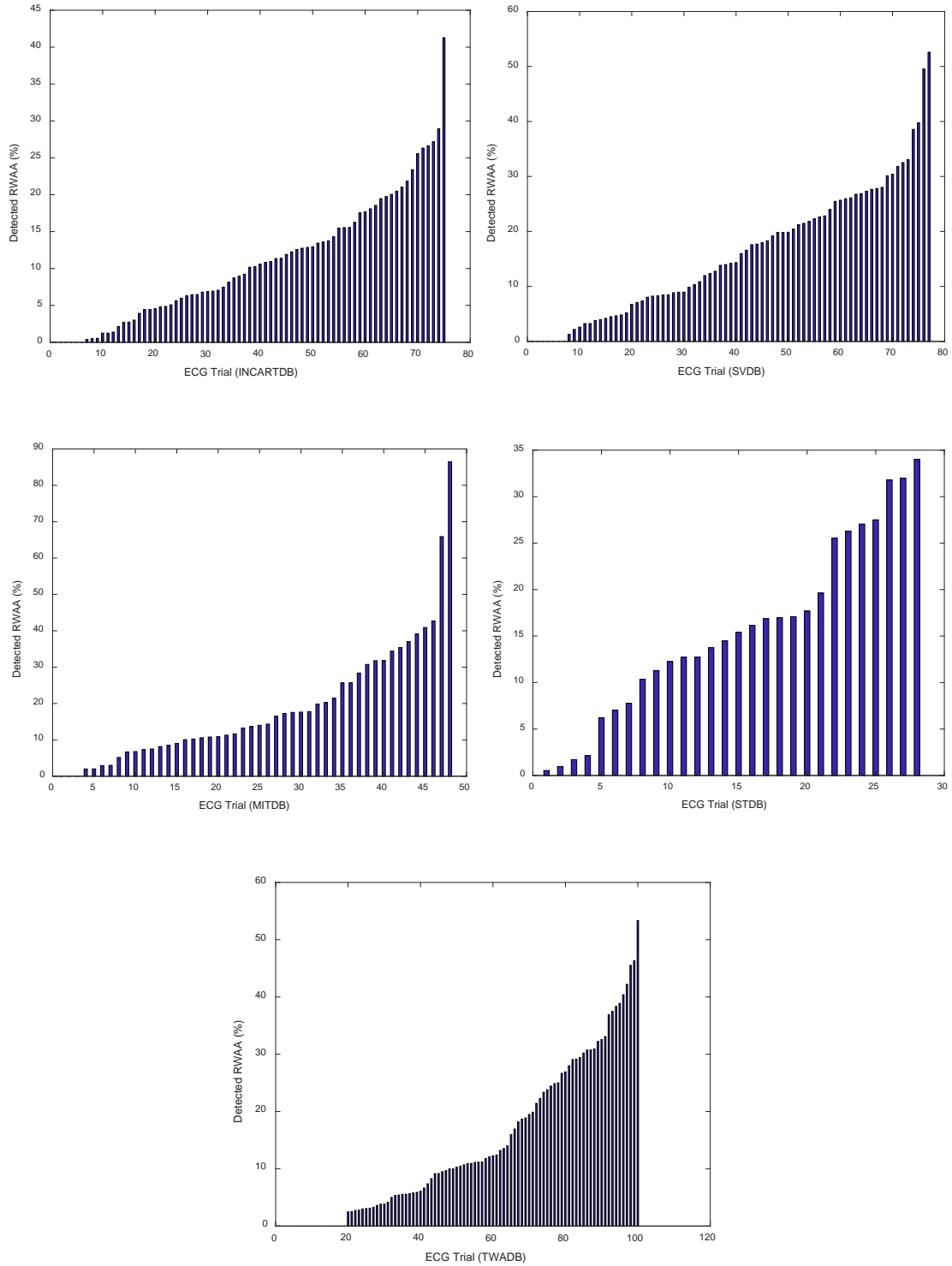
Figure 15. Charts show the ratio of R-Wave Amplitude Alternans sequences of 5 or more beats to the total R-waves for all ECG recordings from the different Databases (INCARTDB, SVDB, MITDB, STDB, TWADB) from the Physionet website.

Table 1. Average (Ave) and maximum (Max) occurrence of RWAA in ECGs from 5 Databases (Lead II) [15].

ECG Database	Total of ECG	Ave of RWAA	Max of RWAA
INCARTDB	75	10.82	41.28%
MITDB	48	18.83	86.46%
STDB	28	15.64	34.00%
SVDB	78	15.88	52.61%
TWADB	74	14.06	53.33%

4.3   Result of Phase Relation Detection

To investigate the phase relation between depolarization and repolarization alternans in ECGs, we analyzed clinical ECGs from different databases in Physionet. For each ECG trial, the sequences which showed both TWA and RWAA were detected and then the phase relation between TWA and RWAA in each sequence was determined. Tables 2 to 6 show the results of this analysis.

Also, figure 16 shows example of detected in-phase and out-of-phase sequences in an ECG trial that contains both in-phase and out-of-phase sequences. In this figure two consecutive beats from two different sequences (one in phase and the other one out of phase) have been selected. The figure shows that in the in-phase sequence, the ECG signal with taller R-wave was followed by a taller T-wave, as well. But in the out-of-phase sequence, the ECG signal with taller R-wave was followed by a shorter T-wave.

Table 2. Total number of sequences which show both TWA and RWAA and the number of in-phase and out-of-phase sequences in 16 ECG trials in TWADB [15].

File Number	TWA Ranking	Total Sequences	In Phase Sequences	Out of Phase Sequences
1	3	9	0	9
2	7	1	0	1
3	9	5	4	1
4	14	3	1	2
5	18	7	4	3
6	23	1	0	1
7	24	1	0	1
8	31	1	0	1
9	44	3	2	1
10	50	5	2	3
23	54	3	2	1
12	58	3	2	1
13	63	1	0	1
14	68	7	6	1
15	76	1	1	0
16	81	2	1	1

Table 3. Total number of sequences showing both TWA and RWAA and the number of in-phase and out-of-phase sequences in 17 ECG trials in INCARTDB.

File Number	Total Sequences	In Phase Sequences	Out of Phase Sequences
1	43	12	31
2	44	14	30
3	37	12	25
4	78	45	33
5	1	1	0
6	8	4	4
7	23	12	11
8	12	4	8
9	4	3	1
10	9	4	5
11	3	2	1
12	120	32	88
13	2	1	1
14	9	7	2
15	17	13	4
16	18	10	8
17	10	1	9

Table 4. Total number of sequences showing both TWA and RWAA and the number of in-phase and out-of-phase sequences in 5 ECG trials in MITDB.

File Number	Total Sequences	In Phase Sequences	Out of Phase Sequences
1	43	10	33
2	182	0	182
3	51	10	41
4	11	4	7
5	20	3	17

Table 5. Total number of sequences showing both TWA and RWAA and the number of in-phase and out-of-phase sequences in 10 ECG trials in SVDB.

File Number	Total Sequences	In Phase Sequences	Out of Phase Sequences
1	41	11	30
2	7	6	1
3	39	17	22
4	38	9	29
5	7	1	6
6	71	45	26
7	54	4	50
8	89	3	86
9	17	11	6
10	28	17	11

Table 6. Total number of sequences showing both TWA and RWAA and the number of in-phase and out-of-phase sequences in 5 ECG trials in STDB.

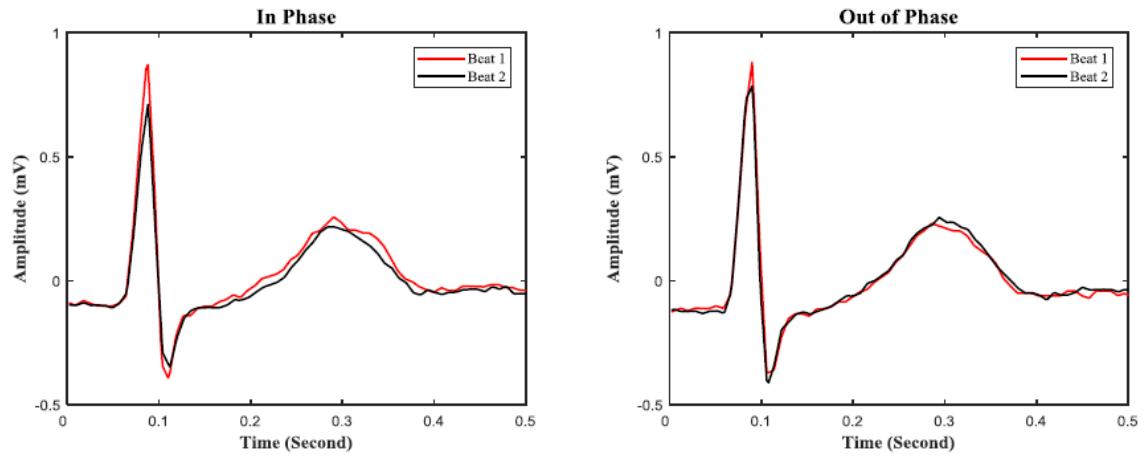| File Number	Total Sequences	In Phase Sequences	Out of Phase Sequences
1	19	5	14
2	72	35	37
3	18	9	9
4	69	29	40
5	49	23	26

Figure 16. Two consecutive beats from two different sequences (in phase and out of phase) from ECG recordings with TWA score of 54 in TWADB [15].

CHAPTER 5. DISCUSSION

TWA test has been considered as a potential predictor of ventricular arrhythmia [8]. However, TWA has a strong negative predictive value but poor positive predictive [11]. Therefore, there is need for improving the low positive predictive value of TWA.

Results of our previous animal and simulation studies have shown a possible link between depolarization and repolarization alternans in action potentials [16]. Also the study illustrated that the phase relation between depolarization and repolarization alternans has an effect on the initiation of arrhythmia and can change from in-phase to out-of-phase spontaneously.

To investigate the phase relation between two alternans in ECGs, depolarization and repolarization alternans' indicators were needed. Since TWA is the known indicator of repolarization alternans in ECG signals, exploring an indicator for depolarization alternans in ECG signals was essential. The result of our simulation study using a dipole field potential spatial model showed that the alternans of maximum slope of AP (depolarization alternans) at the cellular level shows itself in the amplitude of the R-Wave in ECG signal. Since 80-100 mV/msec is a common range for the maximum slope of human AP [38], table 7 shows the percentage of changes in the amplitude of R-wave for two APs with $|dv/dt|_{max}$ of 80 and 100 mV/msec from different leads. The percentage of amplitude change is around 0.1%. The amplitude of the R-wave is in the order of mV and we were looking for the subtle changes in the order of microvolt which justifies the percentage change on the order of 0.1 that was used as a threshold.

Table 7. Percentage of changes in the amplitude of R-wave for two AP with $|dv/dt|_{max}$ of 80 and 100 from different leads.

Lead	R-wave amplitude ($|dv/dt|_{max} = 80$)	R-wave amplitude ($|dv/dt|_{max} = 100$)	Percentage of amplitude change
Lead I	0.9684	0.9694	0.1027%
Lead II	0.5302	0.5303	0.0130%
Lead III	0.3469	0.3471	0.0488%
aVR	0.1222	0.1224	0.1966%
aVL	0.7564	0.7569	0.0675%
aVF	0.3231	0.3234	0.1221%
V1	2.7077	2.7081	0.0148%
V2	7.3185	7.3248	0.0859%
V3	4.5693	4.5640	-0.1173%
V4	1.9479	1.9501	0.1112%
V5	1.3317	1.3331	0.1062%
V6	1.2335	1.2349	0.1080%

Also to verify that we can consider these small changes in the amplitude as alternans, we synthesized a sequence of 128 ECG signals which alternate from beat-to-beat in which the changes correspond to APs with maximum slope of 80 and 100 mV/msec. The alternans of amplitude for 10 consecutive beats is shown in figure 17. Afterwards, we used the spectral method described in the previous section to obtain the power spectrum of the sequence which is shown in figure 18 and then we calculated $Alternans\ Voltage$ and K_{Score}. $Alternans\ Voltage$ greater than 1.0 µV (4.47 µV) and K_{Score} greater than 3 (infinity) confirmed that, as expected, this sequence contains R-Wave amplitude alternans. Thus, R-wave amplitude alternans has the potential to be the marker of depolarization alternans in ECGs.

Furthermore, our results show that RWAA does occur in clinical grade ECGs. Although there are several causes that could affect the amplitude of the R-wave,

observation of sequences of 5 or more consecutive changes suggests a pattern of change consistent with alternans type behavior. Conditions such as pericardial effusion can also cause alternans of the QRS; however, these conditions are usually diagnosed during work up and treated. Therefore, it is reasonable to interpret the RWAA results as suggestive of alternans of the depolarization phase of APs.

Although there is some literature that focused on R amplitude change as a potential predictor of arrhythmia [39]-[40], none of them considered the phase relation between TWA and RWAA. The results obtained from table 2-6 show sequences with both RWAA and TWA at the same time exist in some ECG trials. Also, the result verifies that both in-phase and out-of-phase sequences do occur within an ECG recording and the number of out-of-phase sequences are more than the number of in-phase sequences. Based on our hypothesis, out-of-phase sequences could be considered to have a stabilizing effect on the electrical activity of the heart. These results support further investigation of the hypothesis that when the incidence of spontaneous phase change is high, TWA may not be indicative of increased risk of ventricular arrhythmia.

Since we did not have detailed information such as race, age, gender, etc. about the analyzed databases, we could not find if there was a relation between these variables and the observed results. Following up the patients who are at risk of arrhythmia and recording their ECG, computing the TWA and RWAA indexes and the phase relation between these two and compare with clinical outcome (longitudinal study) would be the next step for these studies.
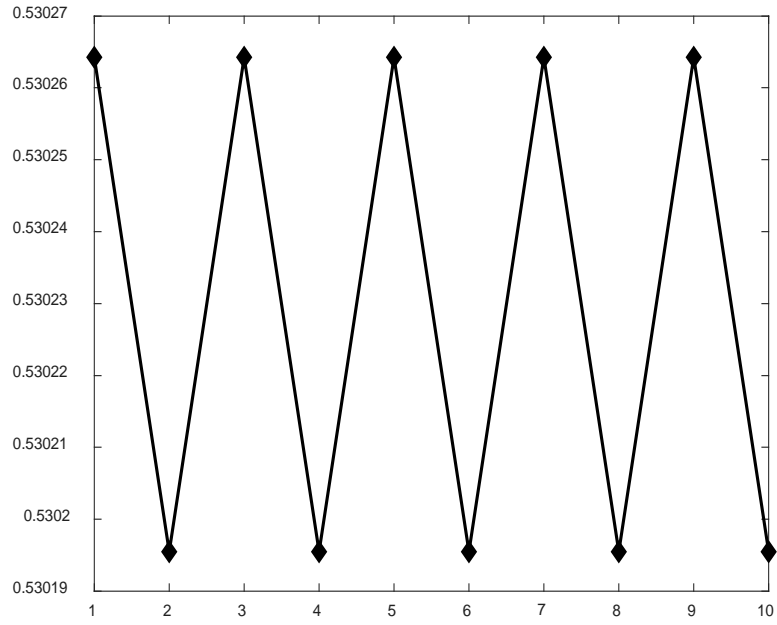
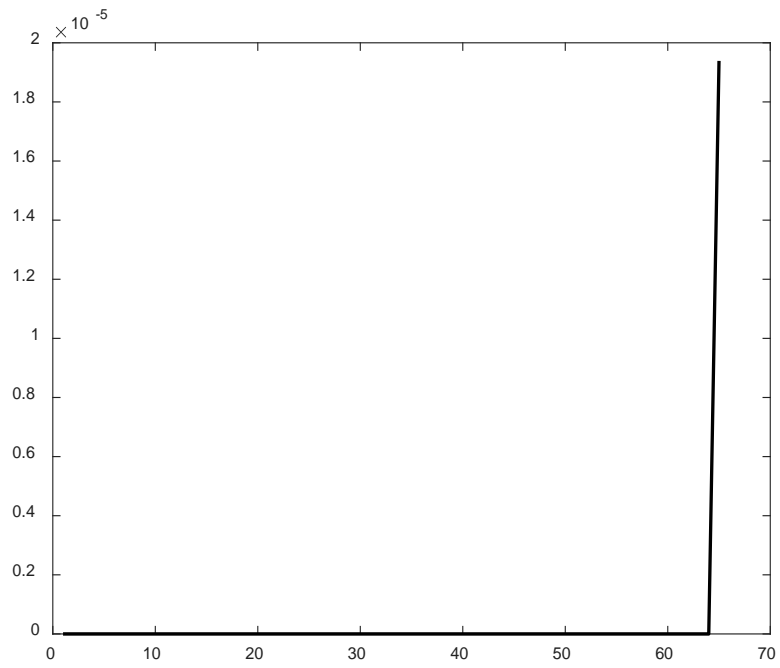Figure 17. The alternans of amplitude for 10 consecutive beats.   .

Figure 1 Power spectrum of the sequence for lead II.

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RECENT WORK EXPERIENCE

VenoStent,

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- Assist with ex vivo flow system work
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University of Kentucky, Department of Biomedical Engineering

Graduate Research Assistant (Jan 2017-June 2018)

- Performed analytical testing of clinical ECGs using MATLAB and Microsoft Excel, analyzed, interpreted and summarized test results.
- Developed a new algorithm using the analytical testing and simulation of the human heart model for prediction of Ventricular Arrhythmia (a common and killing disease).
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Sahar Alaei, Siqi Wang, Paul Anaya, Abhijit Patwardhan, "Phase relation between R-Wave Amplitude Alternans (RWAA) and T-Wave Alternans (TWA), a Potential method to predict ventricular arrhythmia", *under preparation for transaction of Computers in Biology and Medicine.*

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Sahar Alaei, Siqi Wang, Paul Anaya, Abhijit Patwardhan, "R-Wave Amplitude Alternans (RWAA) a Potential Indicator of Depolarization Alternans in ECGs", *BMES Annual meeting*, 2018.

Sahar Alaei, David Wasemiller, Siqi Wang, Paul Anaya, Abhijit Patwardhan, "Alternating Heights of the R Wave in ECG: Possible Link with Depolarization Alternans", *BMES Annual meeting*, 2017.

HONORS AND AWARD

2018: **Travel Scholarship**, EMBC Annual Conference Meeting (Honolulu, Hawaii)

2017: **Travel Scholarship**, BMES Annual Conference Meeting (Phoenix, Arizona)

2016: **Isfahan Regional Electricity fellowship**

2013: **Ranked top 0.1%,** among all Electrical engineering participants in a nationwide graduate entrance exam

2009: **Ranked top 0.2%** among nearly 300,000 participants in the undergrad National University Entrance Exam

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