Considering the Effects of Circadian Rhythm May Improve Tachycardia Discrimination Performance in Implantable Cardioverter Defibrillators

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Abstract

This analysis characterized the difference in circadian variation between ventricular and supraventricular tachyarrhythmia (VT and SVT) and examined how tachyarrhythmia discrimination algorithms in implantable cardioverter defibrillators may be improved by considering the time of day an episode occurs. Training and test sets consisting of 3886 tachyarrhythmia episodes from 653 patients were labeled as SVT or VT through visual inspection of intracardiac electrograms. A logistic regression was fit to the training episodes to estimate the probability that an episode is SVT given only the time of day it occurred. A software model of the current discrimination algorithm was enhanced with the logistic regression. The test episodes were input to both the original and enhanced models to calculate sensitivity and specificity to VT. Coefficients of the logistic regression were statistically significant. Circadian variation was different for SVT versus VT. The enhanced model showed an increase in specificity with no change in sensitivity with respect to the original model.

1. Introduction

Sudden cardiac death (SCD) is the leading cause of death in industrialized countries [1]. Certain cardiac tachyarrhythmias can lead to SCD due to loss of cardiac output. The implantable cardioverter defibrillator (ICD) has become the primary therapy to prevent SCD [2,3,4]. ICDs deliver a high energy electrical shock or a series of low energy electrical paces to convert the tachyarrhythmia to normal sinus rhythm (NSR).

Although there are increasing numbers of ICD implantations each year, the specific pathophysiological processes that cause some tachyarrhythmias remain unclear. A clue to the mechanism of onset may be found in the increased incidence of lethal tachyarrhythmias in the morning hours compared with other periods of the day [5]. The morning peak suggests that tachyarrhythmias may be triggered by the increases in adrenergic activity, systemic arterial pressure, heart rate, vascular tone, and coagulability that occur in the morning [6].

Further insight into the mechanism of onset could help the discrimination of lethal ventricular tachyarrhythmias, such as ventricular fibrillation (VF) and ventricular tachycardia (VT), from non-lethal supraventricular tachyarrhythmias (SVT), such as sinus tachycardia and atrial fibrillation. Accurate discrimination between SVT and VT/VF is a major challenge of optimal ICD function, since shocks inappropriately delivered to treat non-lethal SVTs can be painful and pro-arrhythmic.

Current ICD discrimination algorithms are based on intracardiac electrograms recorded by the ICD during the tachyarrhythmia. One example is Rhythm ID®, the discrimination algorithm in Guidant VITALITY™ and VITALITY 2™ ICDs. Rhythm ID discriminates SVT from VT/VF by considering the timing and morphology of the intracardiac electrograms [7] and has shown a sensitivity and specificity to VT/VF of 100% and 92%, respectively, in a clinical setting [11].

Some important physiological information about a patient cannot be determined from the electrograms alone. Using the time of day as an approximation to pathophysiological processes may improve Rhythm ID's ability to discriminate between SVT and VT/VF for appropriate therapy delivery.

2. Methods

A dataset of 3886 tachyarrhythmia episodes recorded from 653 ICD patients was analyzed retrospectively. All patients had received ICDs for standard indications. All episodes were labeled as SVT or VT/VF by experts through visual inspection of intracardiac electrograms. Episodes were separated into three subsets for analysis, optimization, and testing.

One subset of 2998 episodes recorded from 561 patients was separated into SVT and VT/VF classes and binned into histograms based upon the time of day each episode occurred. Each histogram had eight three-hour time bins beginning with midnight, as was done in previous work by Tofler, *et. al* [5]. In addition, the percentage of SVT episodes in each time bin was calculated by dividing the number of SVT episodes in

each time bin by the total number of episodes in that time bin. Both the SVT and VT/VF histograms were tested for uniformity using the chi-squared test.

A logistic regression model was fit to this subset of episodes. The model

$$\text{Prob(SVT)} = \text{logit}(\alpha + \beta*\text{time} + \gamma*\text{time}^2)$$

estimates the probability that an episode is SVT based upon a quadratic function of the time of day at which the episode occurred, where

$$\text{logit}(x) = e^x / (1 + e^x).$$

The parameters α, β, and γ were fit to the data using the statistical software package SAS. Generalized estimating equations were used to account for correlations between episodes of the same patient.

A software model of Rhythm ID was previously implemented in MATLAB. As is shown in Figure 1, if the ventricular rate of the tachyarrhythmia episode is greater than 230 bpm, the model classifies the episode as "VF"; otherwise, the episode is analyzed further. (Physicians can program this threshold in a clinical setting.) If the ventricular rate is at least 10 bpm faster than the atrial rate, the model classifies the episode as "VT"; otherwise, more analysis is required. The model compares the QRS morphology of the episode to the QRS morphology of a previously-stored segment of the patient's NSR and quantifies this comparison as a feature correlation coefficient (FCC) ranging from zero (no match) to one (perfect match). If at least three of the last 10 beats of the episode have FCC values greater than or equal to 0.94, the model classifies the episode as "SVT"; otherwise, the model analyzes the episode further. If the episode's atrial rate is faster than 200 bpm and the ventricular rate is unstable, the model classifies the episode as "SVT"; otherwise, as "VT" [7].

In this analysis, the Rhythm ID model was enhanced with the logistic regression described above. As is shown in Figure 2, if at least three of the last 10 beats of the episode have FCC values greater than a threshold F but less than 0.94, the enhanced model analyzes the episode based on the logistic regression. If the probability that the episode is SVT is greater than a threshold P, then the episode is classified as "SVT". Otherwise, the episode is further analyzed as is done with the original model.

The values of F and P were optimized using a Receiver Operating Characteristic (ROC) curve. To create the ROC curve, a second, independent subset of 441 episodes from 45 patients was input to the enhanced model. The enhanced model's sensitivity and specificity to VT/VF was calculated for different values of F and P. Sensitivity versus one minus specificity was plotted for each value of F and P. The optimum values of F and P were chosen to be those which led to the greatest increase in specificity with little to no change in sensitivity, with respect to the original model.

The optimum values of F and P were tested using a third, independent subset of 447 episodes from 47 patients. These episodes were input to both the original and enhanced models. Values of F and P in the enhanced model were held constant at their optimum values. Sensitivity and specificity to VT/VF was calculated for both models.

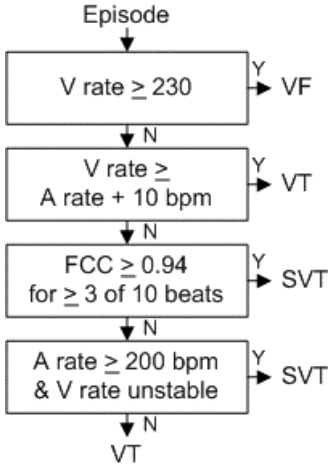

Figure 1: The original Rhythm ID model. The FCC quantifies how closely the QRS morphology of a patient's arrhythmia episode matches the QRS morphology of the patient's NSR.

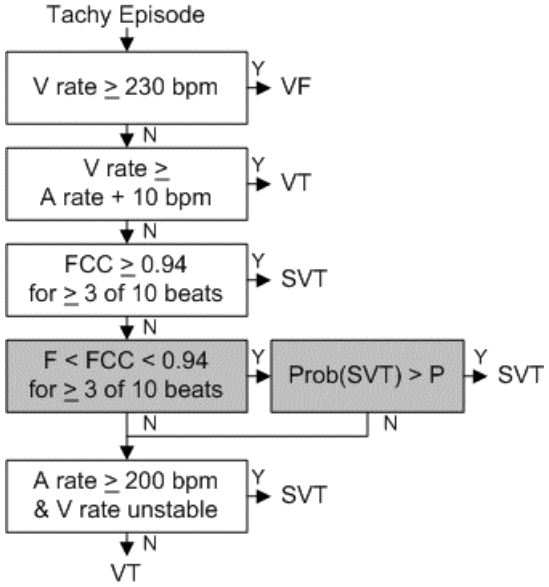

Figure 2: The enhanced Rhythm ID model. The probability that an episode is SVT based on time of day is estimated using the logistic regression model.

3. Results

Figure 3 shows the number of SVTs and VT/VFs in the first subset of episodes versus the time of day they occurred. VT/VFs had a peak occurrence in the morning (09:00 to 12:00) relative to other periods of the day. In contrast, SVTs occurred in high numbers beginning in the morning and continuing through the afternoon (09:00 to 21:00). SVTs were more common than VT/VFs in the afternoon hours (12:00 to 21:00).

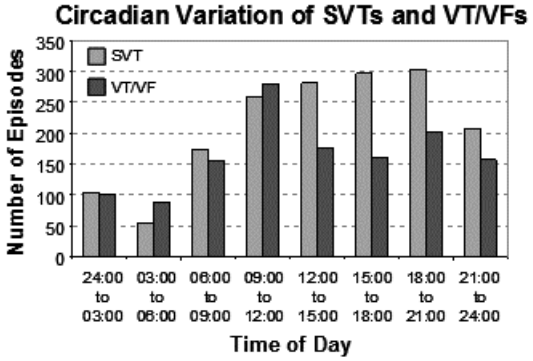

Figure 3: Number of SVT (grey) and VT/VF (black) episodes vs. time of day.

The chi-square test found both the SVT and VT/VF distributions to be statistically different from the uniform distribution ($p<0.05$). The logistic regression was:

$$\text{Prob(SVT)} = \text{logit}(-0.309+0.057*\text{time}-0.002*\text{time}^2).$$

All coefficients of the logistic regression were statistically significant ($p<0.5$). Figure 4 shows the percent of SVT episodes in each time bin (grey bars) and the probability that an episode is SVT based on time of day, estimated using the logistic regression (black line).

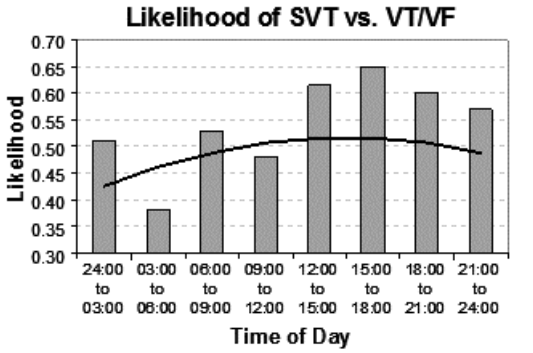

Figure 4: Percentage of SVT episodes (grey bars) and probability that an episode is SVT (black line) vs. time of day.

Figure 5 shows the ROC curve used to optimize the values of F and P in the enhanced model using the second subset of episodes. Four of the 445 episodes in this subset were too short to be analyzed by the models and were therefore removed from analysis. (In a clinical setting, episodes too short for analysis would not be considered for treatment.) Each series in the ROC curve represents a different value of P: 0.51, 0.50, 0.48, 0.45, and 0. As P decreases, the enhanced model is more likely to classify an episode as "SVT". Within each series of P, individual points represent different values of F: 0.75, 0.80, 0.85, 0.90, and 0.94.

The circled point in Figure 5 represents all points for which F=0.94. Referring to the illustration of the enhanced model in Figure 2, when F=0.94, no episodes are analyzed using the logistic regression (*i.e.* all episodes follow the "No" branch after the "F<FCC<0.94" module) and the original and enhanced models function identically. The point outlined in a square represents the point F=0.80 and P=0.50. These values are considered optimum, as they lead to the greatest increase in specificity with only a minor change in sensitivity.

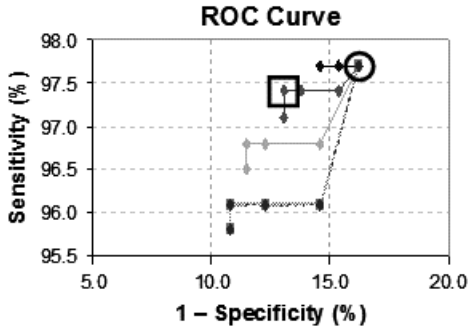

Figure 5: Sensitivity vs. one minus specificity for different values of F and P in the enhanced model. The circle and square show the performance of the original and optimized enhanced models, respectively.

Tables 1-2 show the performance of the original and optimized enhanced models, respectively, on the third subset of episodes. Two of the 447 episodes in this subset were too short to be analyzed. The enhanced model correctly classified four more SVTs from four different patients compared with the original model, resulting in a +3.1% increase in specificity with a 0.0% change in sensitivity. For no episode was the original model correct when the enhanced model was incorrect. Note that results are based on a retrospective analysis of a limited subset of episodes using a software model of Rhythm ID and may not represent actual ICD performance in a clinical setting.

Table 1: Performance of original model.

		Original Model	
		"VT/VF"	"SVT"
Truth	VT/VF	313	3
	SVT	35	94

Table 2: Performance of enhanced model.

		Enhanced Model	
		"VT/VF"	"SVT"
Truth	VT/VF	313	3
	SVT	31	98

4. Discussion and conclusions

This analysis showed that SVTs were common than VT/VFs in the afternoon between 12:00 and 21:00. Furthermore, both SVTs and VT/VFs occurred more often during the day than at night. While the number of VT/VFs peaked in the morning between 09:00 and 12:00, the number of SVTs plateaued throughout the afternoon until as late in the day as 21:00. Similar results were reported by Tofler *et al.* [5] in a large population of ICD recipients, in which the number of VTs peaked between 09:00 and 12:00. In addition, a study by Lee *et al.* [9] showed that peak SVT occurrences at 08:00-09:00, 12:00-13:00, and 17:00-18:00 were equal to each other in magnitude and SVT occurrence reached a trough at night.

The differences in peak occurrences between SVT and VT/VFs could be attributed to differences in the sympathetic / parasympathetic balance between waking and sleeping. Possibly, VT/VFs are more susceptible to abrupt changes in the pathophysiological processes regulated by the sympathetic / parasympathetic balance that will occur soon after waking. SVTs, however, may be triggered by other factors such as increased stress that may or may not be related to the sympathetic / parasympathetic balance.

This analysis also showed that considering the time of day an episode occurs could lead to more accurate discrimination between SVTs and VT/VFs. The discrimination algorithms in current ICDs use only intracardiac electrograms to perform discrimination. Many biological functions have a circadian rhythm, and thus the time of day may provide a useful measure for a patient's status that may not be already available from the intracardiac electrogram.

Limitations

The episodes used to fit the parameters of the logistic regression and to optimize and test the enhanced model were labelled by different experts.

The goodness-of-fit of the logistic regression was not assessed directly, as there are few well-defined goodness-of-fit tests for logistic regression models that make use of generalized estimating equations [10]. However, the ability of the logistic regression to estimate the probability that an episode is SVT based on time of day was tested indirectly as part of the enhanced model using an independent test set of episodes.

The increase in specificity exhibited by the enhanced model was not tested for statistical significance.

Other predictors, in addition to the time of day, may contribute to the relative occurrence of SVTs versus VT/VFs. A subset of various patient demographics has been briefly studied, including age, gender, and left ventricular ejection fraction. No linear relationships have been found between these demographics and the time of occurrence of SVT or VT/VF. More extensive analysis is required to determine if any relationships exist.

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