Title

Development of a Risk Prediction Model for In-Hospital Cardiac Arrests Using Continuous Electrocardiographic Telemetry Monitoring Data

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A thesis submitted in partial satisfaction of the

requirements for the degree Master of Science

in Clinical Research

by

Duc Hong Do

2018

ABSTRACT OF THE THESIS

Development of a Risk Prediction Model for In-Hospital Cardiac Arrests

Using Continuous Electrocardiographic Telemetry Monitoring Data

by

Duc Hong Do

Master of Science in Clinical Research

University of California, Los Angeles, 2018

Professor Zhilin Qu, Chair

Background: Many electrocardiographic (ECG) changes occur before in-hospital cardiac arrest (ICHA) due to pulseless electrical activity (PEA)/asystole. It is not known if these are unique to this period.

Objective: Evaluate whether ECG changes provide predictive information for IHCA from PEA/asystole.

Methods: We collected continuous ECG data from case and control patients. We selected three consecutive 3-hour blocks (block 3, 2, 1 in that order) preceding IHCA in cases and randomly in controls; only case block 1 immediately preceded IHCA. In each block, we measured dominant positive and negative trends in ECG parameters and determined the presence of arrhythmias. We also compared features between consecutive blocks. We created one random forest and two logistic regression models, and tested them on differentiating case vs. control patients (case block 1 vs. control block 1), and temporal relationship to ICHA (case block 1 vs. case block 2).

Results: We evaluated 77 cases (age 62.5±17.3, 57% male) and 1783 control patients (age 63.5±14.8, 67% male). We found many significant differences in ECG trends between case and control block 1, particularly in QRS duration, QTc, RR, and ST. New episodes of atrial fibrillation and bradyarrhythmias were more common before ICHA. The optimal model developed using only ECG changes was the random forest, achieving an AUC of 0.810, 57.9% sensitivity, 95.7% specificity at differentiating case vs. control, and AUC 0.942, 88.3% sensitivity, 90.1% specificity at differentiating case block 1 vs. block 2.

Conclusions: ECG parameters during the 3-hour window immediately preceding ICHA differ significantly from other time periods, and provides very good predictive information for IHCA.

The thesis of Duc Hong Do is approved.

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2018

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INTRODUCTION

In-hospital cardiac arrests (IHCA) remain a major health care problem, affecting over 250,000 patients in the United States annually, with fewer than 30% of these patients surviving to discharge. Over the past decade, there has been considerable interest in early intervention, giving rise to hospital rapid response teams and attempts at developing early warning systems. Despite widespread interest in and implementation of these systems, well-designed studies have failed to show a significant benefit(1-4).

The use of threshold cutoffs(5), derived from population-based studies, to generate risk scores for IHCA does not account for individual patient level variations. In addition, for patients on medical-surgical floors, vital signs and labs, which form the backbone of many such systems, are only obtained every 4-24 hours. This approach has little ability to detect rapid patient deterioration(6). On the other hand, electrocardiographic (ECG)/telemetry data is continuously acquired in many patients in intensive care units (ICU), stepdown units, and some medical-surgical floors. ECG parameters reflect many physiologic changes due to stressors; many intra-patient ECG changes including PR and QRS prolongation, ST changes, and bradyarrhythmias are seen in the 24 hours and particularly the one hour period before IHCA(7-9). However, it remains unknown whether these findings are sufficiently specific to the pre-IHCA period to be useful features for cardiac arrest prediction.

In this study, we evaluate whether the measurement of trends in ECG parameters, particularly in comparison to a patient's baseline physiologic variations, and detection of new arrhythmias provides predictive information for IHCA from pulseless electrical activity (PEA) or asystole.

MATERIAL AND METHODS

We conducted a retrospective case-control study at the University of California, Los Angeles (UCLA) Ronald Reagan Medical Center, a 520-bed tertiary care hospital. Telemetry data was obtained by General Electric (GE) monitoring systems (GE Healthcare, Waukesha, WI), and pooled on a remote data server via Bedmaster (Excel Medical Electronics, Jupiter, FL). Signals were sampled at 240 Hz with 12-bit representation. Continuous electrocardiographic data was obtained using a standard 5 electrode configuration providing 4 ECG leads (I, II, III and precordial lead usually in the V2 position). A total of 200 beds, including all 130 adult intensive care unit (ICU) beds, and 70 randomly selected medical–surgical unit beds were monitored with the Bedmaster system at any one time. This study received approval from the institutional review board at UCLA.

We evaluated all 'code blues' between April 2010 and March 2013, and included IHCA cases due to PEA or asystole in patients age ≥18 years, with telemetry data available for at least 6 consecutive hours prior to and including the onset of IHCA. We excluded cases where cardiac arrest (defined as lack of central pulse, apnea, and unresponsiveness) was not the primary reason for the code blue, patients with a do-not-resuscitate order, primarily ventricular-paced rhythm, out-of-hospital cardiac arrest leading to current admission, IHCA in a procedural unit or operating room, and IHCA within the first 24 hours of a trauma admission. Only the first IHCA in any patient during a hospitalization was included. The time of cardiac arrest was determined by review of ECG data and marked at onset of asystole or initiation of chest compressions as visualized by chest compression artifact in cases of PEA. For each case, we extracted telemetry data for up to 24 hours prior to IHCA.

Control patients were selected at random from the same units where code blue patients (not specifically patients who met all inclusion/exclusion criteria) were located at the time of IHCA and temporally spread across the study period. Criteria for selecting control patients included survival to discharge, no unplanned ICU transfers or code blues during the admission. Case patients who had another admission

which met those criteria were excluded as controls. For each control patient, we extracted the first 24 hours of telemetry data available, since this was likely to be the period of greatest instability.

Telemetry Data Processing

Telemetry data was processed using a research ECG analysis program written by coauthor DM to obtain: 1) a minute-by-minute time series of ECG parameters (PR interval, QRS duration, averaged QRS amplitude, ST segment height in lead II and V2, QTc, and RR) derived from a 5-minute signal-averaged beat obtained in a rolling window fashion, and 2) a time series of all consecutive RR intervals (Figure 1).

The averaged beat-derived time series was processed with a series of filters to reduce noise and remove non-physiologic data from supraventricular arrhythmias or pacing. The RR time series, following removal of data points affected by excessive signal artifact, was processed to identify periods of atrial fibrillation (AF), second degree heart block (2° HB), and pauses greater than 3 seconds, using modifications of methods described by Lian et al(10) and Tsipouras et al(11) (see Supplemental Data for further details).

Selection of Data Blocks

Three consecutive 3-hour blocks (blocks 3, 2, 1 in that order) were selected for further analysis: in case patients these blocks immediately preceded IHCA while in control patients, these were selected at random within the extracted data. Hence, block 1 in cases is the only IHCA block (Figure 2).

Data for each ECG parameter in each block was evaluated for adequacy of information (minimum 120 data points available, out of a possible 180). If the minimum number of points was not available, the block for that ECG parameter was excluded from analysis. We found that PR interval blocks were the most commonly excluded parameter due to AF or excessive baseline artifact.

Trend Determination

For the averaged beat data, in each block of data, we determined the dominant positive and negative trend for each ECG parameter (Figure 3, Supplemental Methods). All time series processing was performed using Matlab 2017b (Mathworks, Natick, MA).

Statistical Analysis

The following features, all continuous variables, were calculated from the averaged beat data for each ECG parameter in each block:

1. Change in dominant positive and negative trends in block n (Δy_n^+, Δy_n^-). This was calculated by subtracting the maximal and minimal value for the trend.
2. Slope of the dominant positive and negative trends ($\Delta y_n^+/\Delta x_n^+$, $\Delta y_n^-/\Delta x_n^-$). This was calculated by dividing the change over the duration.
3. Difference in dominant positive and negative trend change and slope between a patient's block n and immediately preceding block (n-1). Four values were calculated: difference in dominant 1) positive change ($\Delta y_{n-(n-1)^+}$), 2) negative change ($\Delta y_{n-(n-1)^-}$), 3) positive slope ($\Delta y_n^+/\Delta x_n^+ - \Delta y_{(n-1)^+}/\Delta x_{(n-1)^+}$), and 4) negative slope ($\Delta y_n^-/\Delta x_n - \Delta y_{(n-1)}^-/\Delta x_{(n-1)^-}$).

Continuous variables were assessed for normality using the Shapiro-Wilks test. Comparisons between groups were performed using Wilcoxon rank-sum test given non-normality of many variables. For the presence of AF, 2° HB, and pauses, we calculated an indicator variable for the presence of those arrhythmias in block n, and a second for the presence of those arrhythmias in block n but not block (n-1).

Next, we divided the case and control block 1 into a stratified 75% model development and 25% validation set. Using the development set, we performed univariate logistic regression analyses, and retained any variable with $p<0.05$ for use in multivariable model development. Missing values were imputed using multiple imputations. We created 3 models: logistic regression with backward stepwise regression, forward stepwise regression, and random forest with 10000 trees. We evaluated each model

on the validation set by using the area under the curve (AUC) and sensitivity for classifying a block as IHCA while maintaining a low false positive rate (FPR).

We performed further testing of model robustness by first setting a classification threshold where FPR on the validation set was approximately 5% and evaluated the sensitivity and specificity on case block 1 vs. case block 2 (temporal differentiation of ICHA detection), validation case block 1 vs. control block 2, case block 2 vs. validation control block 1, case block 2 vs. control block 2.

Univariate analyses were performed using JMP 13 (SAS Institute, Cary, NC). Multivariable analyses were performed using R v3.4.4(12,13). A two-sided $p<0.05$ was considered statistically significant. For univariate analyses, adjustment for multiple comparison testing was evaluated by calculating q-values to estimate the false discovery rate with $q<0.05$ considered significant(14).

RESULTS

We identified 77 case (mean age 62.5±17.3, 57% male) and 1783 control patients (mean age 63.5±14.8, 67% male). The primary causes of IHCA in the case patients were respiratory in 44 (57%), multiorgan failure in 13 (17%), and metabolic acidosis in 12 (16%). Sixty-eight (88%) of IHCA occurred in the ICU setting, 53 (69%) had ROSC, and 19 (25%) survived to discharge (Table 1).

Univariate analysis

All block 1 dominant trend changes and slopes were right skewed in their distribution. Intra-patient comparisons between block 1 and block 2 for each variable were normally distributed; in controls these distributions were centered near zero. On univariate analysis, we found 39/62 variables, both block 1 measures and block1-block2 comparisons, that were significantly associated with IHCA, particularly those related to QRSd, QTc, RR, ST lead II, and ST lead V2 (Table 2, Supplemental Table 1). For these ECG parameters, increased change in both positive and negative directions were associated with IHCA.

Any AF, 2° HB, or pauses in block 1 was found in 35% vs. 20% (OR 2.0, CI1.2-3.3), 38% vs. 18% (OR 2.6, CI 1.6-4.2), and 32% vs 20% (OR 1.8, CI 1.1-2.9) of cases vs. controls, respectively. Having any AF, 2° HB, or pauses in block 1 but not block 2 was found in 14% vs. 3% (OR 4.4, CI 2.2-8.8), 27% vs 3% (OR 3.8, CI 2.2-6.3), 23% vs 23% (OR 2.0, CI 1.2-3.5) of cases vs. controls, respectively (Table 2).

Significant differences in 12/62 variables for case vs. control block 2 were found(Supplemental Table 2). After adjustment for multiple comparisons, all variables for block 1 with $p<0.05$ remained significant with $q<0.05$ compared to none for block 2.

Multivariable analyses

Both logistic regression models derived by backwards and forwards stepwise regression achieved similar AUC on the development set (0.770 vs 0.778) and validation set (0.841 vs 0.849) (Table 3, Figure 4). In both models, the presence of AF and 2° HB in block n but not block n-1, QRSd Δy_n^+, QRSd $\Delta y_n^+/\Delta x_n^+$,

QTc Δy_n^-, RR $\Delta y_{n-(n-1)}^+$, and ST Lead V2 $\Delta y_{n-(n-1)}^-$ were significantly associated with the risk of IHCA (Supplemental Table 3).

The random forest model achieved an AUC of 0.730 on the development set and 0.810 on the validation set. The 5 most important variables in this model were: RR $\Delta y_{n-(n-1)}^+$, QTc Δy_n^-, QTc $\Delta y_{n-(n-1)}^-$, ST Lead V2 $\Delta y_{n-(n-1)}^+$, and QRSd Δy_n^+ (Supplemental Figure 2).

Evaluating the models based on sensitivity achieved with a low FPR, the random forest model performed best, achieving a sensitivity of 47.3%, 52.6%, and 57.9% with a FPR of 2.5%, 5%, and 10% respectively (Table 3). Using an optimal threshold determined by maintaining an approximately 5% FPR, the random forest model was the best at distinguishing block 1 from block 2 in cases (AUC 0.939, sensitivity 89.6%, specificity 90.1%). All models, as expected, performed poorly at differentiating case block 2 from either control block 1 or block 2 (Table 3).

DISCUSSION

ECG "biomarkers" as predictors of adverse events or outcomes have long fascinated clinicians. Heart rate variability and microvolt T-wave alternans are prominent examples of ECG-derived features which have been associated with a variety of adverse outcomes in a diverse group of patients ranging from those with prior myocardial infarction to cardiomyopathy and even post-menopausal women(15-17). However, the actual impact of these measures remain poorly defined; the association is clear but there are no clear therapeutic targets or feedback for clinicians, leaving these primarily as research tools (18-20).

A significant problem with most ECG "biomarkers" stems from their static nature as a snapshot in time, ignoring the inherent dynamic nature of even basic ECG parameters(21). While clinicians intuitively assess patient status by evaluating for changes from baseline, this approach has not been translated utilized in the development of ECG "biomarkers" for risk prediction, including those used for continuous ECG monitoring. While making rule-based (threshold-based) evaluations on single time-point data such as the 12-lead ECG is reasonable, studies have long shown the importance of comparison to prior ECGs to make important clinical diagnoses and management decisions(22-24). Hence, for ECG to be a useful risk prediction modality, models should reflect the dynamic nature of ECG and provide a closed feedback loop (Figure 5).

In this study, we show that: 1) it is feasible to trend changes over time in clinically relevant ECG parameters and arrhythmias using continuous ECG monitoring data, 2) trends in ECG parameters and arrhythmias differ significantly in the 3-hour window pre-IHCA as compared to controls and prior 3-hour windows in case patients, and 3) this information can be leveraged in predictive models for IHCA due to PEA or asystole. To our knowledge, this is the first study to evaluate the use of continuous ECG monitoring for the prediction of ICHA from PEA and asystole, which make up around 80% of total ICHA(25).

Utilizing trends in ECG analysis

The evaluation of trends in ECG parameters on continuous recordings, rather than absolute thresholds, allows for individualization of clinical risk prediction based on the patient's baseline electrocardiogram(9,26). For example, 0.1mV ST depression in a patient with baseline left ventricular hypertrophy confers a significantly lower risk compared to a patient with a baseline normal ST segment. While some physiologic fluctuation in ECG parameters are expected even in resting normal healthy subjects(21,27), we found that the degree of fluctuations observed prior to IHCA, particularly in the ST segment and QRS duration, exceed those normally observed.

The evaluation of trends in both the positive and negative directions allow for detection of different types of physiologic disturbances associated with different causes of cardiac arrest (Figure 6). For example, while QRS prolongation by intraventricular conduction delay can reflect progressive ischemia(28), a decrease in measured QRS duration is likely artefactual as a result of decreasing QRS amplitude(29), reported in septic shock states(30). We previously showed in a case control study with 27 bradyasystole cases and 304 controls that combinations of various ECG trend changes could be used to obtain as much as 33% sensitivity with 100% specificity(9). However, bradyasystole cases represent an ideal scenario where trends in many ECG parameters change monotonically in one direction over a long period leading up to ICHA, which is not true of the larger group of PEA cases.

Therefore, we developed further features to compare trends and arrhythmias with those during prior time periods. This is based on the rationale that some ECG parameters, particularly RR interval and ST segments, can fluctuate significantly even in healthy states with exertion/rest and other stressors. Hence, differentiation of physiologic vs. pathologic changes (eg. differentiating a slowing heart rate preceding many types of PEA compared to physiologic slowing of heart rate(31,32)), can be better deduced by comparing magnitudes and rates of change to those in earlier time periods when the patient was known to be stable (Figure 7).

Similarly, second degree HB, either AV or sinoatrial, occurs commonly during sleep, particularly in patients with sleep apnea, and hence is unlikely to be predictive unless they are of new onset(33). New episodes of AF have been associated with increased ICU length of stay and hospital mortality, but not AF in patients with a prior history(34). While we found that pauses of greater than 3 seconds were proportionately more common in the pre-ICHA period, the baseline rate in control patients is high, likely reflecting the limitations of arrhythmia detection methods that depend only on RR intervals due to their susceptibility to frequent ectopic beats, artifact, and low amplitude QRS complexes(35).

Utilization of ECG findings in the prediction of IHCA

In this study, we show that ECG changes in a 3-hour window alone have a very good ability to predict an imminent IHCA. This finding is independent of commonly used criteria such as vital signs and laboratory values(36).

While logistic regression has been the standard method of risk prediction development, it assumes that risk factors (ECG metrics in our study) are additive(37). Given the inherent correlated nature of the positive and negative trend measure for a particular ECG parameter and the potential for different types of cardiac arrest to present predominantly with one or the other (Figure 6), logistic regression models may perform poorly due to model instability. On the other hand, non-linear classifiers such as the random forest perform better with such classification problems(38), at the cost of becoming a “black box”.

In this study, while the AUC achieved by the logistic regression models were slightly superior to that of the random forest model, it must be considered that relatively few patients suffer IHCA and therefore models with low FPR for similar sensitivity achieved are preferred to prevent excessive false alarms. Using this criteria, the random forest model performed best, attaining 57.9% sensitivity with 95.7% specificity at the selected threshold. The random forest model, furthermore, showed excellent temporal discriminatory ability with an 89.6% sensitivity and 90.1% specificity at distinguishing block 1 vs. block 2.

In practice, ECG metrics can play a complementary role to predictive algorithms that combine multiple data streams including demographic, vital sign, and laboratory data using a Bayesian approach(39). Whereas the intermittently collected data for vital signs and laboratory data can predict the "at-risk" patient, ECG changes, which predominantly occur in the last hour preceding ICHA, can help pinpoint the patient at impending risk of IHCA or who is rapidly deteriorating from an unanticipated event.

Limitations

The number of ICHA cases used in the derivation of this model is small and predominantly from ICU patients, potentially introducing bias towards the findings seen in this particular sample patient population. This in large part represents the difficulties of acquiring high quality continuous ECG data due to limitations from a data acquisition and information technology standpoint. Despite the innovations in ambulatory ECG monitoring with miniaturization, accessibility, and data storage, there has been little transformation in inpatient telemetry monitoring systems, driven by a vicious cycle of lack of data availability to develop useful predictive models, feeding a lack of sufficient clinical application(40) to drive innovation in accessibility and data storage.

It should be noted, however, that cardiac arrest due to respiratory failure, the most common cause of PEA/Asystole in a general hospital population, also made up the largest group of cases in our study(41).

Due to the small number of cases, we also were unable to use an independent test set to validate our models which can lead to overestimation of the model's predictive power. However, further testing using block 2 data showed performance that was as expected. The positive predictive value is also a very important characteristic to consider in light of the pervasive problem of alarm fatigue(35), but difficult to estimate from an unbalanced-sample case-control study.

In addition, we have not investigated other potential ECG parameters such as heart rate variability, the use of different detection window durations, and concurrent changes in 2 or more ECG parameters. These will be investigated as part of future studies.

CONCLUSIONS

Trends in ECG parameters, particularly in QRS duration, QTc, ST height, and RR, differ significantly between a 3-hour window immediately preceding ICHA from PEA or asystole compared to other 3-hour windows in both case and control patients. New episodes of AF and second degree heart block are also more common immediately prior to ICHA.

Using ECG changes alone, we created a random forest model with AUC 0.810 on an independent validation set with 57.9% sensitivity achieved with 4.3% false positive rate. Using this threshold, the model was able to distinguish between the final 3-hour block preceding IHCA and the preceding 3-hour block with an AUC of 0.939, 89.6% sensitivity and 90.1% specificity. This study supports the feasibility of utilizing ECG changes over time in predictive models for IHCA.

FIGURE 1

Processing of data and model development. Block n-1 refers to the block that precedes block n temporally (eg. Block 2 which precedes block 1, or block 3 which precedes block 2).

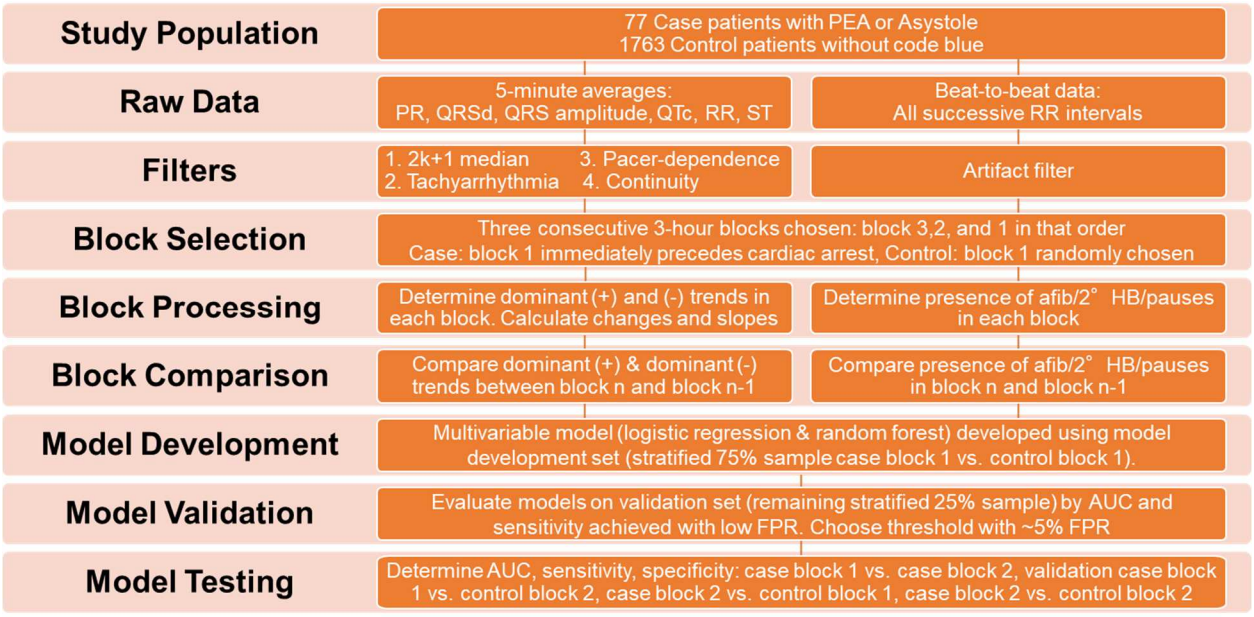

FIGURE 2

Block selection example. Three consecutive 3-hour blocks are selected in both case and control patients. For cases, the blocks immediately precede in-hospital cardiac arrest (IHCA) (Panel A). In controls, the blocks are randomly selected (Panel B). Only block 1 in cases is associated with IHCA. While only PR interval data is shown in this example, all ECG parameters for the subject are evaluated in the same blocks.

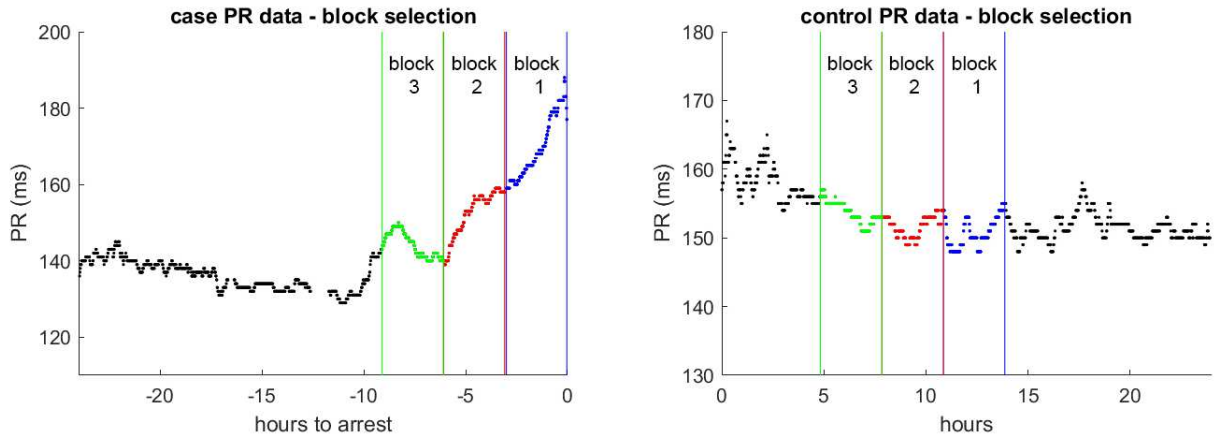

FIGURE 3

Dominant trend determination. The direction of change at each point is calculated by robust linear fitting (Panel A). Blue denotes positive trends and red denotes negative trends. Next short segments flanked by longer segments with opposite directionality are merged with the more dominant trend to remove minor fluctuations. Panel B shows the resultant dominant trends after a short negative trend segment is merged with the longer positive trend segment. The dominant trend in either direction is then determined by the trend in that direction with the longest duration.

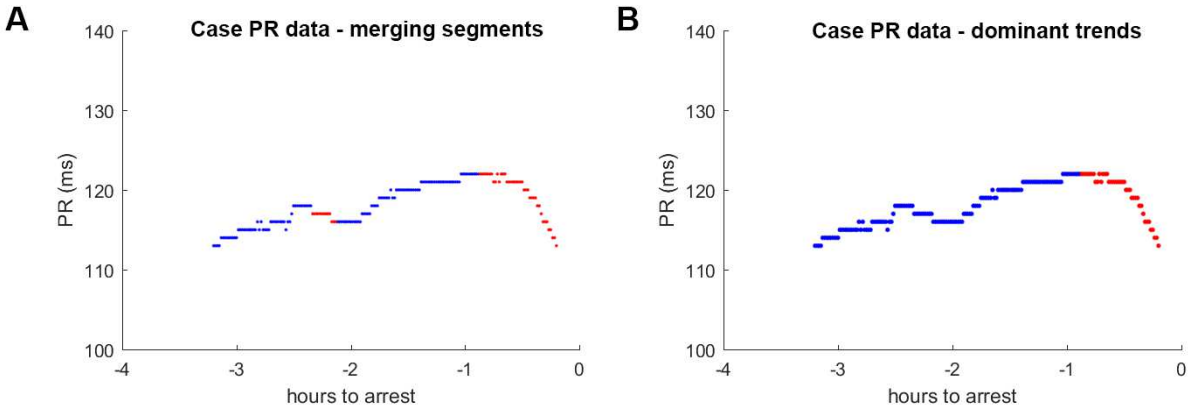

FIGURE 4

Receiver Operating Characteristics Curves for the Validation Set. Curves are shown for 3 multivariable models with their area under the curve (AUC): Panel A) Logistic regression with backward stepwise regression, B) Logistic regression with forward stepwise regression, C) Random forest with 10,000 trees. The (X) marks the threshold chosen based on a specificity of approximately 95%.

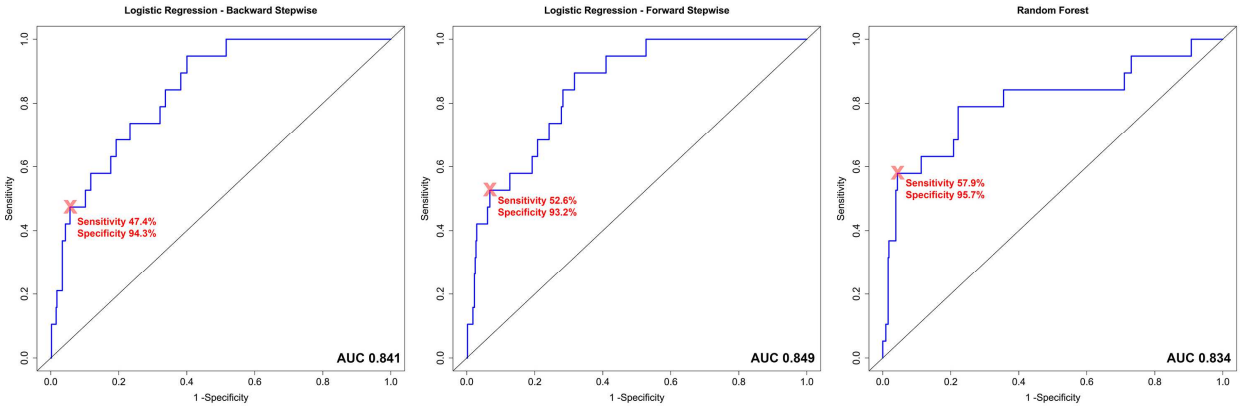

FIGURE 5

Optimal Continuous ECG Risk Prediction Model that provides a closed feedback loop, is updated continuously, and leverages the dynamic nature of ECG to provide personalized risk prediction.

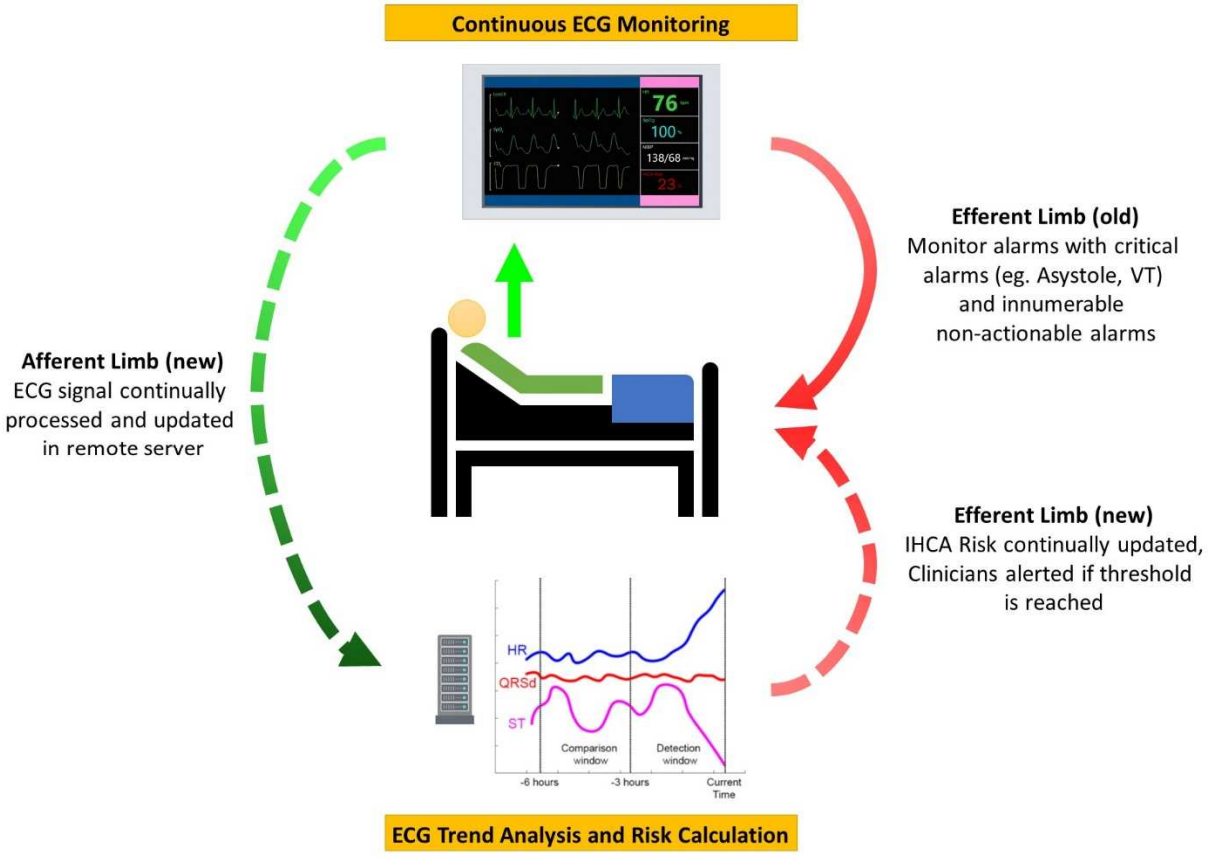

FIGURE 6

Patterns of Electrocardiographic Parameter Changes by Cause of Cardiac Arrest. The different panels show block 1 (final 3 hours before cardiac arrest) in 7 case patients, with the determined cause of the cardiac arrest. Graphs from top to bottom show trends in RR, QRS duration, ST lead II, and ST lead V2. The y-axis scaling is the same for a parameter across all cases. Positive (blue) and negative (red) trends are shown with the dominant trends for each block denoted by wider points. Similar patterns can be seen within cases from the same cause of arrest: eg. panels A, B, and C both show shortening of the RR followed by terminal prolongation of RR, with similar patterns of ST changes also seen in panels A and B. Different patterns can be noted despite similar determined cause of cardiac arrest (eg. Panel D vs. A, B, C). Unknown causes of cardiac arrest can potentially be matched to cases with known causes to determine possible cause of arrest (eg. Panels F and G).

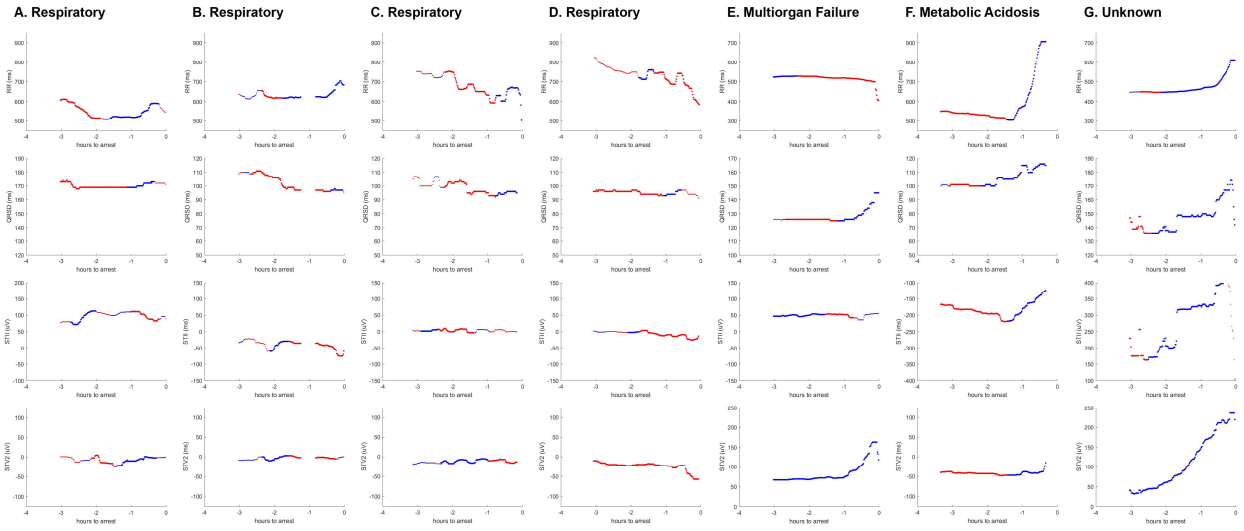

FIGURE 7

Comparison of Electrocardiographic Parameter Changes Over Time. RR and ST height in lead II data for a patient with cardiac arrest due to respiratory failure. From left to right, the graphs show 1. Each parameter over the 24 hour period preceding in-hospital cardiac arrest (IHCA) with the selected blocks labeled, 2. Block 3 (9 to 6 hours before IHCA), 3. Block 2 (6 to 3 hours before ICHA), 4. Block 1 (3 to 0 hours before ICA). A similar scaling is used for all blocks. Positive (blue) and negative (red) trends are shown with the dominant trends for each block denoted by wider points. Fluctuations in the RR and ST are noted in all blocks, which is expected. However, comparison between block 1 and the other blocks, particularly the immediately preceding block, shows a greater degree of change for both RR and ST in the negative direction in block 1.

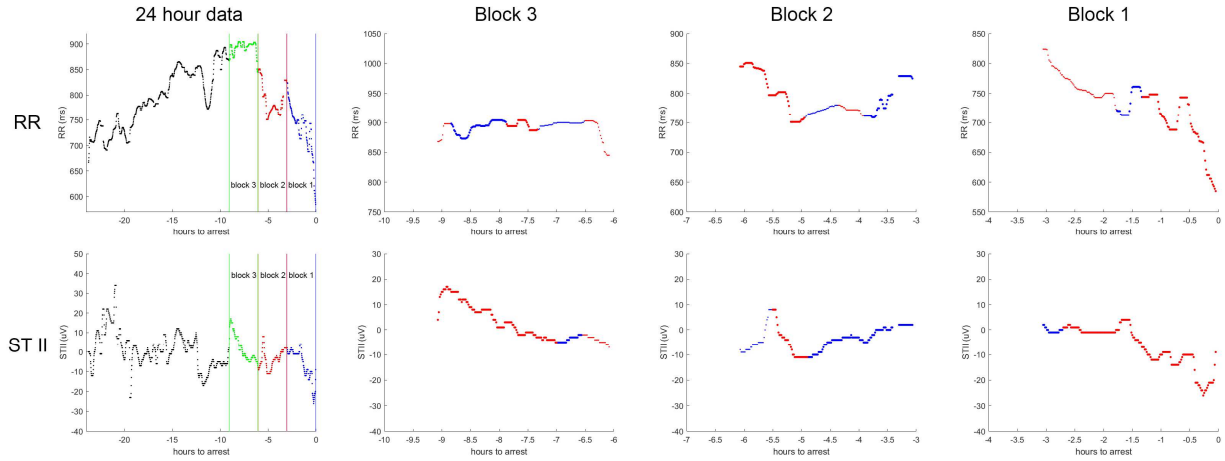

TABLE 1: DEMOGRAPHICS

	Case (n = 77)	**Control (n = 1783)**
Age	62.5±17.3	63.5±14.8
Male	44 (57%)	1201 (67%)
ICU	68 (88%)	1322 (75%)
Arrest characteristics		
ROSC	53 (69%)	
STD	19 (25%)	
Arrest Cause		
Respiratory – unintubated	23 (29%)	
Respiratory - intubated	11 (14%)	
Metabolic acidosis	12 (16%)	
Hemorrhagic shock	3 (4%)	
Cardiogenic shock	5 (6%)	
Distributive shock	1 (1%)	
Myocardial infarction	1 (1%)	
Multiorgan failure	13 (17%)	
Unknown	8 (10%)	
Abbreviations. ROSC: return of spontaneous circulation, STD: survive to discharge		

TABLE 2: ELECTROCARDIOGRAPHIC PARAMETER SUMMARY

	Case (n = 77)	Control (n = 1783)	p-value‡
Arrhythmias, n(%)			
AF, any in block 1	27 (35%)	373 (20%)	0.0067
AF, present block 1 not block 2	11 (14%)	64 (3%)	0.0002
2° HB, any in block 1	29 (38%)	332 (18%)	0.0002
2° HB, present block 1 not block 2	21 (27%)	162 (3%)	<0.0001
Pauses, any in block 1	25 (32%)	376 (20%)	0.0242
Pauses, present block 1 not block 2	18 (23%)	229 (12%)	0.0153
Trend Slope ($\Delta y_1/\Delta x_1$)†, median (IQR)			
QRS Amplitude Averaged + (μV/hr)	320 (115 – 670)	312 (138 – 627)	NS
QRS Amplitude Averaged - (μV/hr)	271 (118 – 684)	285 (137 – 608)	NS
PR Interval + (ms/hr)*	6.3 (3.7 – 13.4)	6.7 (3.6 – 12.6)	NS
PR Interval - (ms/hr)*	6.5 (3.3 – 20.2)	6.7 (3.7 – 13.4)	NS
QRS Duration + (ms/hr)	6.3 (2.4 – 13.7)	4.2 (1.8 – 8.6)	0.0134
QRS Duration - (ms/hr)	5.4 (2.7 – 13.7)	3.7 (1.6 – 8.1)	0.0002
QTc + (ms/hr)	16.7 (9.0 – 38.0)	13.9 (7.6 – 27.5)	NS
QTc - (ms/hr)	15.6 (8.5 – 48.5)	13.3 (6.9 – 25.5)	0.0238
RR + (ms/hr)	40.8 (26.3 – 77.2)	52.8 (27.2 – 98.2)	NS
RR - (ms/hr)	40.9 (12.9 – 90.7)	53.8 (25.6 – 112.9)	NS
ST Lead II + (μV/hr)	28.6 (13.1 – 68.3)	15.0 (7.8 – 29.0)	0.0023
ST Lead II - (μV/hr)	30.5 (14.0 – 61.5)	15.0 (8.0 – 30.4)	<0.0001
ST Lead V2 + (μV/hr)	17.5 (6.9 – 44.8)	10.5 (5.5 – 19.5)	0.0029
ST Lead V2 - (μV/hr)	16.8 (6.6 – 34.0)	10.5 (5.3 – 20.7)	0.0389
Trend Slope Comparison ($\Delta y_1/\Delta x_1 - \Delta y_2/\Delta x_2$) †, median (IQR)			
QRS Amplitude Averaged + (μV/hr)	69 (-183 – 323)	10 (-212 – 243)	NS
QRS Amplitude Averaged - (μV/hr)	53 (-175 – 317)	-4 (-187 – 203)	NS
PR Interval + (ms/hr)*	0.0 (-2.6 – 3.4)	0.2 (-4.8 – 5.1)	NS
PR Interval - (ms/hr)*	1.0 (-2.9 – 8.3)	0.2 (-4.8 – 5.0)	NS
QRS Duration + (ms/hr)	1.4 (-1.7 – 10.3)	0 (-3.7 – 3.9)	0.008
QRS Duration - (ms/hr)	2.4 (-1.0 – 6.1)	0.1 (-3.5 – 3.7)	<0.0001
QTc + (ms/hr)	2.2 (-7 – 22.6)	0.3 (-11.0 – 11.3)	NS
QTc - (ms/hr)	-0.3 (-10.2 – 21.2)	0.4 (-8.9 – 10.7)	NS
RR + (ms/hr)	5.3 (-23.5 – 30.9)	3.3 (-31.8 – 38.3)	NS
RR - (ms/hr)	1.4 (-13.8 – 37.9)	0.1 (-42.2 – 38.1)	NS
ST Lead II + (μV/hr)	6.3 (-8.2 – 32.9)	-0.4 (-11.5 – 11.1)	0.0164
ST Lead II - (μV/hr)	4.5 (-8.4 – 26.4)	-0.2 (-11.7 – 11.1)	0.0023
ST Lead V2 + (μV/hr)	3.1 (-8.6 – 14.2)	-0.1 (-7.9 – 7.7)	0.0355
ST Lead V2 - (μV/hr)	0.8 (-7.8 – 16.8)	0.0 (-8.2 – 7.0)	NS
Trend Change (Δy_1) †, median (IQR)			
QRS Amplitude Averaged + (μV)	89 (43 – 180)	86 (47 – 158)	NS
QRS Amplitude Averaged - (μV)	106 (58 – 190)	85 (48 – 143)	**0.0191**
PR Interval + (ms)*	8 (5 – 14.5)	7 (4 – 14)	NS
PR Interval - (ms)*	8 (4 – 17)	7 (4 – 14)	NS
QRS Duration + (ms)	9.5 (3 – 16)	4 (2 – 8)	<0.0001
QRS Duration - (ms)	7.5 (3 – 13)	5 (2.8 – 8)	0.0015
QTc + (ms)	22.6 (11.7 – 41.1)	14.6 (8.5 – 26.7)	0.0017
QTc - (ms)	30.1 (11.2 – 57.3)	14.4 (9.0 – 26.0)	<0.0001

	RR + (ms)	72 (32 – 138)	61 (32 – 103)	0.0035
	RR - (ms)	45 (19 – 123)	58 (31 – 105)	NS
	ST Lead II + (μV)	34 (15 – 70)	16 (9 – 29.8)	<0.0001
	ST Lead II - (μV)	34.5 (16.5 – 74)	16 (9 – 29)	<0.0001
	ST Lead V2 + (μV)	20 (8 – 41)	11 (6 – 20)	0.0004
	ST Lead V2 - (μV)	20 (9 – 42)	11 (6 – 20)	<0.0001
Trend Change Comparison (Δy_{1-2}) †, median (IQR)				
	QRS Amplitude Averaged + (μV)	17 (-46 – 92)	0 (-59 – 61)	NS
	QRS Amplitude Averaged - (μV)	0 (-35 – 122)	0 (-42 – 49)	0.0020
	PR Interval + (ms)*	0 (-4 – 3)	0 (-5 – 4)	NS
	PR Interval - (ms)*	1 (-2.75 – 7)	0 (-4 – 4)	NS
	QRS Duration + (ms)	2 (-1 – 12)	0 (-3 – 3)	<0.0001
	QRS Duration - (ms)	1.5 (-1 – 5.75)	0 (-3 – 3)	0.0002
	QTc + (ms)	7.0 (-5.8 – 24.9)	0.7 (-8.3 – 9.3)	0.0268
	QTc - (ms)	5.6 (-7.4 – 36.3)	-0.20 (-8.5 – 8.2)	0.0024
	RR + (ms)	26 (-13 – 86)	1 (-33 – 37)	<0.0001
	RR - (ms)	8 (-21 – 63)	2 (-31 – 35.5)	<0.0001
	ST Lead II + (μV)	9 (-7 – 50.5)	0 (-10 – 10)	0.0008
	ST Lead II - (μV)	5 (-9 – 24.5)	0 (-10 – 10)	0.0004
	ST Lead V2 + (μV)	4 (-3.25 – 19.5)	0 (-7 – 6)	0.0175
	ST Lead V2 - (μV)	7.5 (-1.5 – 26)	0 (-6 – 7)	0.0007

*Reported where measureable given this is not measureable in atrial fibrillation

†For each row, + denotes the measure for the dominant positive trend, and – denotes the measure for the dominant negative trend for that ECG parameter. All negative trend change and slope measurements are reported as the absolute value.

‡ All univariate comparisons with p-value < 0.05 were also significant at q-value < 0.05, which corrects for false discovery rate due to multiple hypothesis testing

TABLE 3: MULTIVARIATE MODEL PERFORMANCE

	Logistic Regression – Backward Stepwise	**Logistic Regression – Forward Stepwise**	**Random Forest**
Development Set (Case block 1 vs. Control block 1)			
AUC	0.770	0.779	0.730
Validation Set (Case block 1 vs. Control block 1)			
AUC	0.841	0.849	0.810
Sensitivity, FPR 2.5%	21.1%	31.5%	36.8%
Sensitivity, FPR 5.0%	42.1%	42.1%	57.9%
Sensitivity, FPR 10.0%	47.4%	52.6%	63.2%
Validation Set Performance at Selected Threshold			
Sensitivity	47.4%	52.6%	57.9%
Specificity	94.3%	93.2 %	95.7%
Test* – All Case Block 1 vs. Case Block 2			
AUC	0.764	0.761	0.942
Sensitivity	37.7%	45.5%	88.3%
Specificity	91.5%	91.5%	90.1%
Test* – Validation Set Case Block 1 vs. Control Block 2			
AUC	0.822	0.849	0.853
Sensitivity	47.4%	52.6%	57.9%
Specificity	95.2%	94.5%	95.6%
Test* – Case Block 2 vs. Validation Set Control Block 1			
AUC	0.519	0.530	0.577
Sensitivity	8.5%	8.5%	9.9%
Specificity	94.3%	93.2 %	95.7%
Test* – Case block 2 vs. Control block 2			
AUC	0.528	0.538	0.593
Sensitivity	8.5%	8.5%	9.9%
Specificity	95.2%	94.5%	95.6%
*All sensitivity and specificities are reported at the selected threshold			

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SUPPLEMENTAL METHODS

Averaged Beat-derived ECG Parameter Filter Details:

1. A median 2k+1 filter (k = 7): each time point was replaced with the median value of 15 points centered around that time point. The median filter is commonly used to reduce artifacts and outliers while preserving signal. The larger the k value, the greater the decrease in artifact but this comes at the cost of signal loss and increase in time delay. A filter size of 15 (k=7) was found to have reasonable tradeoff in our data (Supplemental Figure 1A).
2. Tachyarrhythmia filter: the post-median filter RR interval time series was processed minute by minute to look for data points that exceeded 115% of the maximum of the preceding 20 points, or was 85% less than the minimum of the preceding 15 points. Each such point was flagged; N flags resulted in N+1 segments. If the mean RR for each segment was less than 80% of the mean of the entire RR time series (ie. segment HR exceeded 20% of the mean HR), the particular segment was flagged as a tachyarrhythmia block. PR interval, P wave duration, QTc, and RR data were removed for tachyarrhythmia blocks given the lack of comparability to non-tachyarrhythmia data for the purposes of trend analysis (Supplemental Figure 1B).
3. Pacer-dependence filter: this filter identifies extended periods of extremely constant (invariable) HR, which is not physiologic. An extended constant HR was defined as lasting at least 120

consecutive HR data points. Thus, all 120 consecutive data point windows were processed to check for invariability. The median value of these 120s data points were subtracted from each of the 120 HR values. If the maximal absolute difference of these 120 differences were less than 0.12 heart beats, then the 120-data point window was extended downstream one data point at a time, undergoing the same iterative checks as described above, until the largest window of invariability was identified. Corresponding metric data was dropped as pacing would artificially change the ECG metric of interest (Supplemental Figure 1C). Multiple windows of complete pacer dependence could be identified in a single patient. The minimum of 120 data points and the 0.12 maximal allowable heart rate difference were chosen purposefully to be extremely stringent to avoid wrongfully eliminating non-paced data.

4. After the heart rate based filters, all metrics of interest, except ST, were processed through a continuity filter based on the assumption that changes to ECG metrics should be gradual and that large jumps are most likely secondary to artifacts and/or noise. A histogram was created with 10 equal sized bins. Data points belonging to the highest frequency bin were defined as “modes”. Continuity check was conducted in both a forwards and backwards fashion starting at each “mode”. Marching point by point, if a value was greater than 115% of the maximum or less than 85% of the minimum of the previous 20 continuous points, that value was defined as

discontinuous. Performing the check both forwards and backwards and from multiple starting points, the "modes", ensured that dropped values fail to meet the continuity criteria from multiple angles (Supplemental Figure 1D).

Dominant trend determination

For the averaged beat data, in each block of data, we determined if the slope at each data point was positive or negative by performing robust linear fitting of 51 data points centered at the point of interest. Consecutive points with the same slope directionality were joined to form segments. Small segments flanked by larger segments of the opposite slope sign were merged into the larger segment. The dominant positive and negative trends, defined as the trend with the longest consecutive number of data points with positive and negative slopes respectively, were then determined for each block (Figure 3, main manuscript).

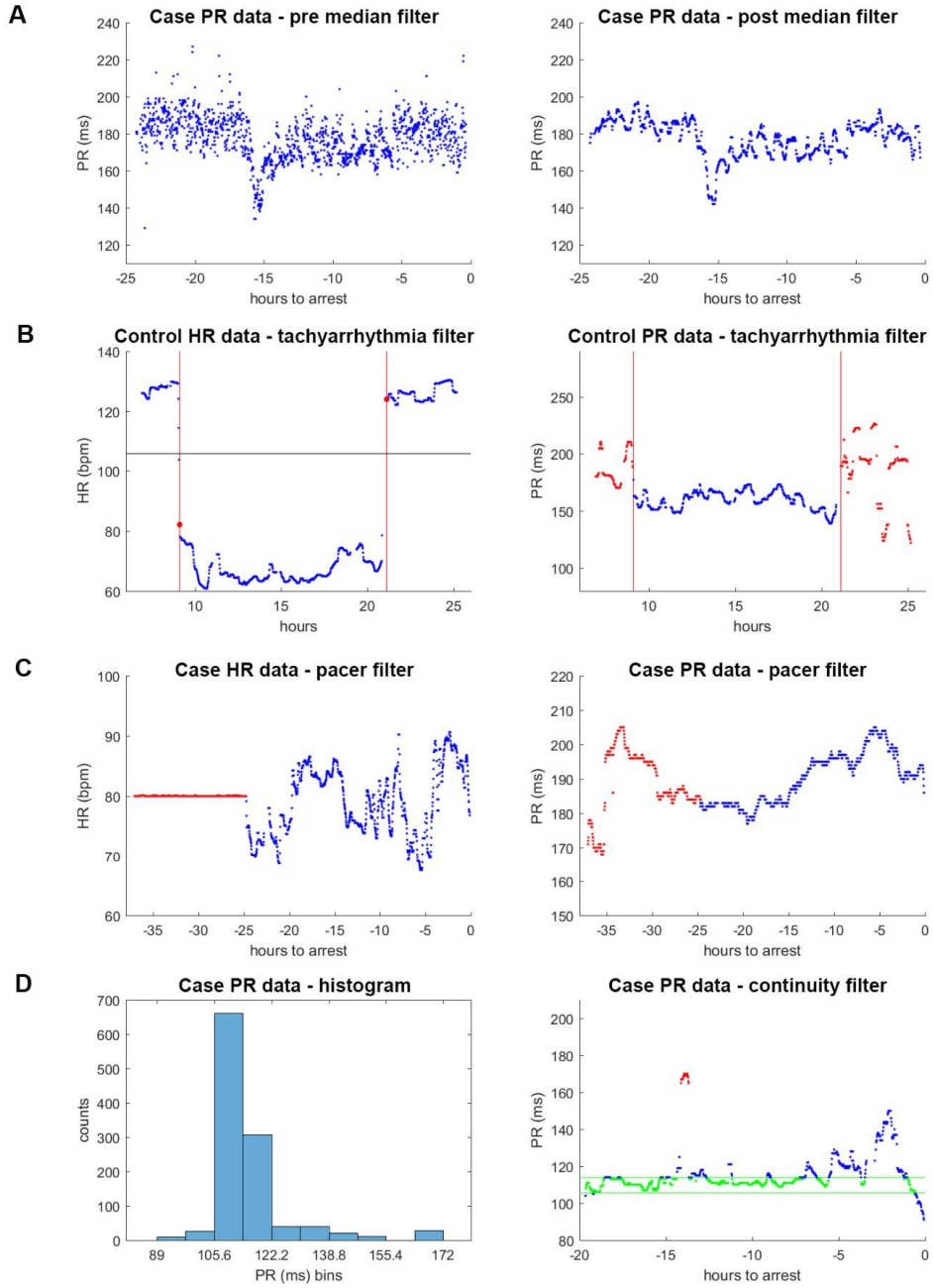
Beat-to-beat data processing:

1. Atrial fibrillation detection. We used a modified method of non-empty-cells described by Lian et al(10). A sliding window size of 128 beats was chosen with the window sliding/shifting by a single beat across time. As such, each beat was covered by 128 consecutive sliding windows containing 128 consecutive beats. For each beat the RR interval in milliseconds (ms) was noted.

The differential RR interval (dRR), also in ms, was also calculated for each beat by subtracting the RR interval at any particular beat by the RR interval of the preceding beat. The (RR, dRR) pair of each beat is then graphed on a 2-D plot with RR on the x-axis and dRR on the y-axis. The plot was then segmented into squares or "cells" that are 25 by 25 ms in size. The number of cells that contain at least 1 pair of (RR, dRR) is defined as a non-empty cell (NEC). The number of NECs is the surrogate for the degree of irregularity with higher NECs correlating with higher degree of irregularity and higher probability of atrial fibrillation. In order to determine an optimal threshold to define a point as being atrial fibrillation (both number of NECs and number of sliding windows including that point), we annotated atrial fibrillation episodes in 117 cases and 117 controls. We then performed 700 iterations of random sampling, with replacement, from these cases/controls and calculated the F1 statistic (which balances sensitivity and positive predictive value) using every combination of NEC and number of windows. We then compiled this data to determine the optimal threshold over the 700 iterations. We found that the optimal F1 statistic was obtained with a threshold of 52 NEC and 100% of windows, with an F1 value of 0.87 (Sensitivity 92.4%, Specificity 97.5%, PPV 81.6%, NPV 99.1%).

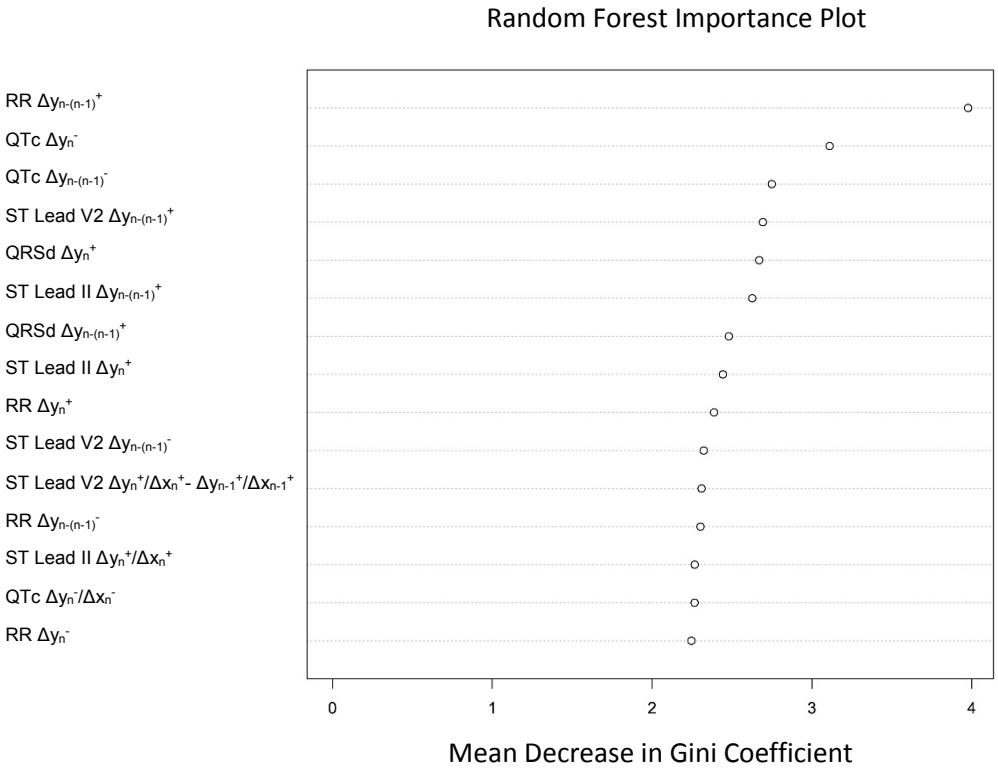
SUPPLEMENTAL FIGURE 1

Averaged-beat ECG parameter filters. The examples shown are for PR interval data from different patients. Points that are labeled blue are retained following application of the filter while points labeled red were removed from further analysis. Green markings represent calculations made for filtering. Panels A. Median filter for reducing signal noise, B. Tachyarrhythmia filter to remove segments of noncomparable data due to tachyarrhythmias, C. Pacer dependence filter removes segments of paced data from analysis, 4. Continuity filter removes significant outlier points which are likely artefactual. Data points for cases more than 24 hours from arrest are shown here only for illustration purposes of filters.



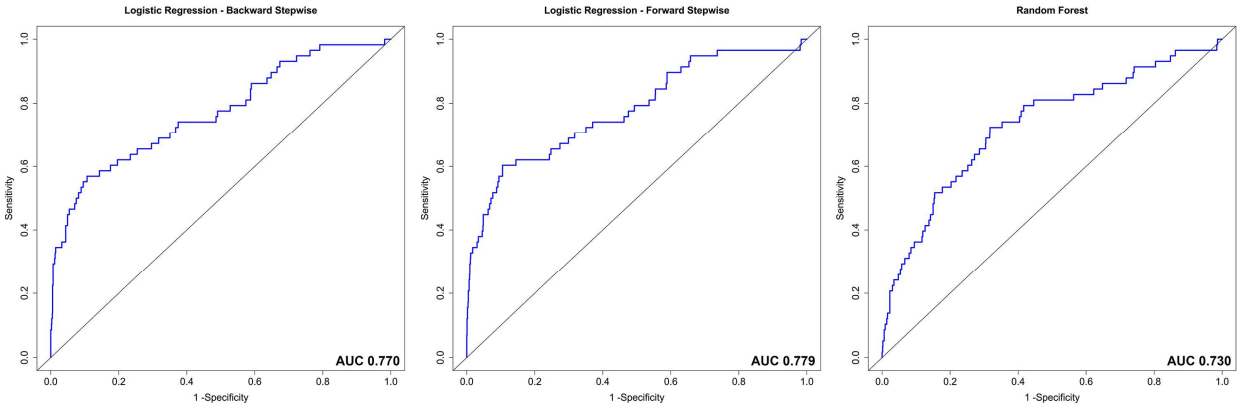
SUPPLEMENTAL FIGURE 2

Random Forest Importance Plot. This shows the 15 variables with the highest importance in the random forest, based on mean decrease in the Gini coefficient (measure of how much each variable contributes to homogeneity of the nodes and leaves in the random forest). Higher values signify higher importance of the variable.



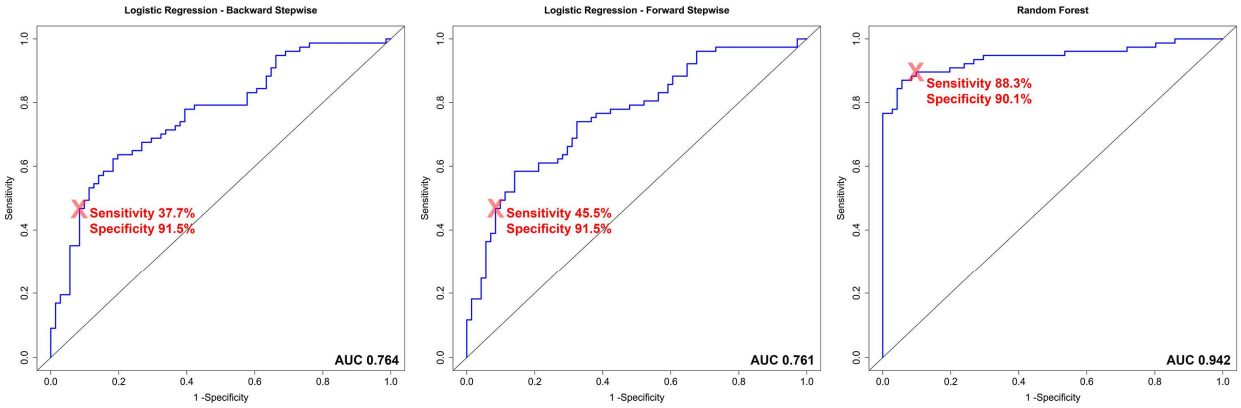
SUPPLEMENTAL FIGURE 3

Receiver Operating Characteristics Curves for the Model Development Set.



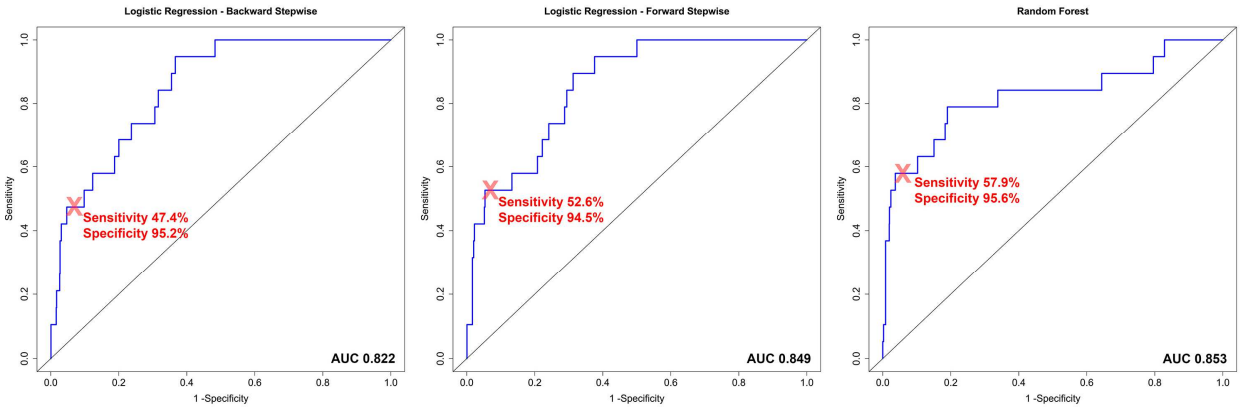
SUPPLEMENTAL FIGURE 4

Receive Operating Characteristic Curves for Model Testing on Case block 1 vs. Case block 2. Block 1 is the 3-hour block immediately preceding in-hospital cardiac arrest, while Block 2 is the 3-hour block preceding block 1. Only blocks from case patients are included in this analysis. Block 1 is considered true-positive for in-hospital cardiac arrest, while block 2 is considered false-positive for cardiac arrest. The red (X) marks the sensitivity and specificity at the threshold chosen based on the validation set. AUC = area under the curve.



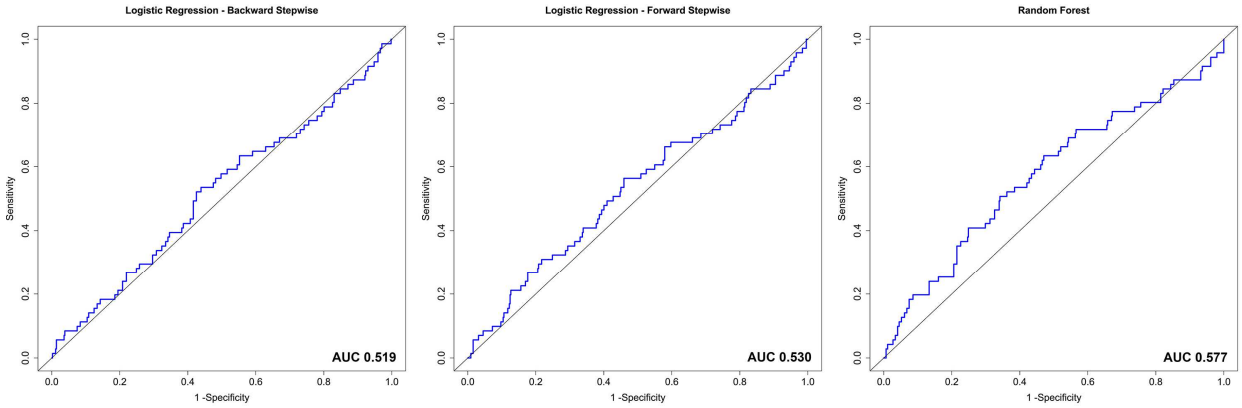
SUPPLEMENTAL FIGURE 5

Receive Operating Characteristic Curves for Model Testing on Validation Case block 1 vs. Control block 2. Block 1 is the 3-hour block immediately preceding in-hospital cardiac arrest, while Block 2 is the 3-hour block preceding block 1. Validation set case block 1 and all control block 2 are included in this analysis. The red (X) marks the sensitivity and specificity at the threshold chosen based on the validation set. AUC = area under the curve.



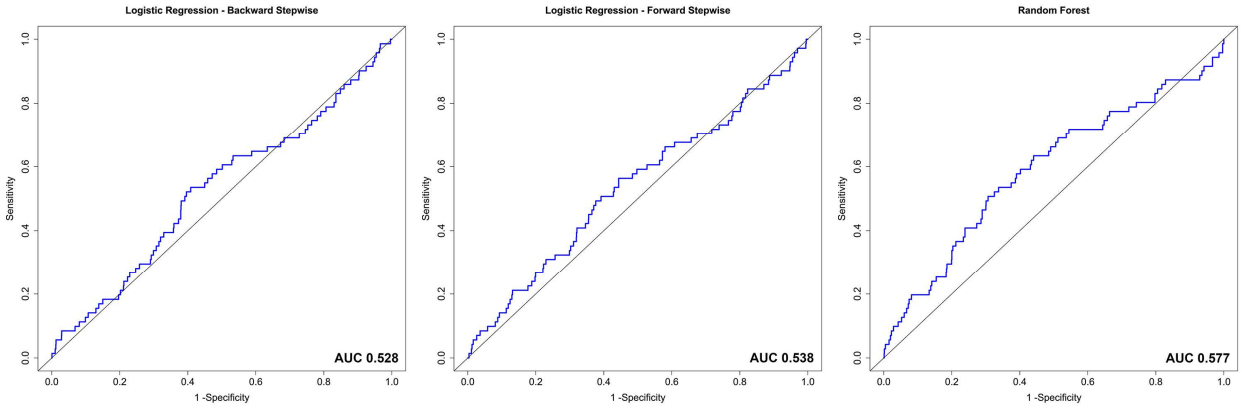
SUPPLEMENTAL FIGURE 6

Receive Operating Characteristic Curves for Model Testing on Case block 2 vs. Validation set Control block 1. Block 1 is the 3-hour block immediately preceding in-hospital cardiac arrest, while Block 2 is the 3-hour block preceding block 1. All case block 2 and validation set control block 1 are included in this analysis. AUC = area under the curve.



SUPPLEMENTAL FIGURE 7

Receive Operating Characteristic Curves for Model Testing on Case block 2 vs. Control block 2. Block 1 is the 3-hour block immediately preceding in-hospital cardiac arrest, while Block 2 is the 3-hour block preceding block 1. All case block 2 and all control block 2 are included in this analysis. AUC = area under the curve.



SUPPLEMENTAL TABLE 1

Significant Univariate analyses, Development Set (Case block 1 vs. Control block 1)

Variable	OR Estimate*	AUC
Slope†		
QRSd $\Delta y_1^+/\Delta x_1^+$	1.3 (1.04 – 1.5)	0.587
QRSd $\Delta y_1^-/\Delta x_1^-$	1.4 (1.2 – 1.6)	0.611
QTc $\Delta y_1^-/\Delta x_1^-$	1.06 (1.00 – 1.1)	0.557
ST lead II $\Delta y_1^+/\Delta x_1^+$	1.5 (1.1 – 1.9)	0.677
ST lead II $\Delta y_1^-/\Delta x_1^-$	1.5 (1.2 – 1.9)	0.667
ST lead V2 $\Delta y_1^+/\Delta x_1^+$	1.8 (1.2 – 2.7)	0.620
ST lead V2 $\Delta y_1^-/\Delta x_1^-$	1.6 (1.02 – 2.5)	0.603
Trend†		
QRS amplitude Δy_1^-	1.3 (1.04 – 1.7)	0.562
QRSd Δy_1^+	2.4 (1.8 – 3.0)	0.677
QRSd Δy_1^-	1.6 (1.3 – 2.1)	0.600
QTc Δy_1^+	1.1 (1.04 – 1.2)	0.620
QTc Δy_1^-	1.2 (1.1 – 1.3)	0.664
RR Δy_1^+	1.4 (1.1 – 1.7)	0.552
ST lead II Δy_1^+	1.7 (1.3 – 2.2)	0.684
ST lead II Δy_1^-	2.0 (1.5 – 2.6)	0.698
ST lead V2 Δy_1^+	2.3 (1.4 – 3.7)	0.634
ST lead V2 Δy_1^-	3.3 (1.8 – 6.0)	0.672
Slope Comparison		
QRSd $\Delta y_1^+/\Delta x_1^+ - \Delta y_2^+/\Delta x_2^+$	1.3 (1.1 – 1.6)	0.605
QRSd $\Delta y_1^-/\Delta x_1^- - \Delta y_2^-/\Delta x_2^-$	1.5 (1.2 – 1.8)	0.631
ST lead II $\Delta y_1^+/\Delta x_1^+ - \Delta y_2^+/\Delta x_2^+$	1.4 (1.06 – 1.9)	0.611
ST lead II $\Delta y_1^-/\Delta x_1^- - \Delta y_2^-/\Delta x_2^-$	1.6 (1.2 – 2.1)	0.609
ST lead V2 $\Delta y_1^+/\Delta x_1^+ - \Delta y_2^+/\Delta x_2^+$	1.5 (1.02 – 2.2)	0.572
Trend Comparison		
QRS amplitude $\Delta y_{1\text{-}2}^-$	1.5 (1.1 – 1.9)	0.577
QRSd $\Delta y_{1\text{-}2}^+$	2.4 (1.8 – 3.3)	0.661
QRSd $\Delta y_{1\text{-}2}^-$	1.7 (1.3 – 2.3)	0.617
QTc $\Delta y_{1\text{-}2}^+$	1.1 (1.01 – 1.2)	0.602
QTc $\Delta y_{1\text{-}2}^-$	1.1 (1.04 – 1.3)	0.597
RR $\Delta y_{1\text{-}2}^+$	1.7 (1.3 – 2.2)	0.632
ST lead II $\Delta y_{1\text{-}2}^+$	1.9 (1.3 – 2.9)	0.625
ST lead II $\Delta y_{1\text{-}2}^-$	2.2 (1.4 – 3.3)	0.629
ST lead V2 $\Delta y_{1\text{-}2}^+$	1.8 (1.1 – 3.0)	0.599
ST lead V2 $\Delta y_{1\text{-}2}^-$	3.8 (1.7 – 8.4)	0.681
Arrhythmias		
Afib, any in block 1	2.0 (1.2 – 3.3)	
Afib present block 1 not block 2	4.4 (2.2 – 8.8)	
2° HB, any in block 1	2.6 (1.6 – 4.2)	
2° HB present block 1 not block 2	3.8 (2.2 – 6.3)	
Pauses, any in block 1	1.8 (1.1 – 2.9)	
Pauses present block 1 not block 2	2.0 (1.2 – 3.5)	

* OR for QRSd and QTc are shown per 10ms change (trend change) or 10ms/hr (slope). OR for QRS amplitude, ST lead II, and ST lead V2 are shown per 0.1mV change (trend change) or 0.1mV/hr (slope). OR for RR is shown per 100ms change (trend change) or 100ms/hr (slope)
† All OR for slopes and trend changes are reported for absolute values of the parameter.

SUPPLEMENTAL TABLE 2

Electrocardiographic parameter summary for block 2

	Case (n = 71‡)	Control (n = 1679‡)	p-value
Arrhythmias, n(%)			
AF, any in block 2	17 (24%)	365 (22%)	NS
AF, present block 2 not block 3	3 (4%)	74 (4%)	NS
2° HB, any in block 2	7 (10%)	309 (18%)	NS
2° HB, present block 2 not block 3	3 (4%)	153 (9%)	NS
Pauses, any in block 2	8 (12%)	331 (20%)	NS
Pauses, present block 2 not block 3	5 (7%)	207 (12%)	NS
Trend Slope ($\Delta y_2/\Delta x_2$)†, median (IQR)			
QRS Amplitude Averaged + (μV/hr)	250 (114 – 541)	283 (134 – 609)	NS
QRS Amplitude Averaged – (μV/hr)	199 (92 – 499)	281 (127 – 588)	NS
PR Interval + (ms/hr)*	5.7 (3.1 – 17.7)	6.3 (3.4 – 12.2)	NS
PR Interval – (ms/hr)*	5.2 (2.5 – 12.2)	6.4 (3.5 – 12.6)	NS
QRS Duration + (ms/hr)	3.1 (1.7 – 6.3)	4.0 (1.6 – 8.3)	NS
QRS Duration – (ms/hr)	3.6 (1.8 – 8.2)	3.5 (1.4 – 7.7)	NS
QTc + (ms/hr)	13.0 (7.3 – 23.9)	13.7 (7.2 – 26.7)	NS
QTc – (ms/hr)	12.4 (6.3 – 35.7)	12.5 (6.7 – 23.4)	0.023
RR + (ms/hr)	33.1 (13.3 – 63.4)	48.4 (24.8 – 92.7)	0.031
RR – (ms/hr)	28.9 (14.3 – 65.3)	54.7 (24.7 – 110.8)	NS
ST Lead II + (μV/hr)	20.8 (8.6 – 40.1)	14.8 (7.5 – 28.6)	NS
ST Lead II – (μV/hr)	19.6 (10.4 – 33.9)	14.6 (8.1 – 29.1)	NS
ST Lead V2 + (μV/hr)	12.6 (6.6 – 28.3)	10.0 (5.1 – 20.3)	0.012
ST Lead V2 – (μV/hr)	12.2 (6.3 – 23.2)	10.5 (5.4 – 20.1)	NS
Trend Slope Comparison ($\Delta y_2/\Delta x_2 - \Delta y_3/\Delta x_3$) †, median (IQR)			
QRS Amplitude Averaged + (μV/hr)	8 (-149 – 187)	8 (-228 – 241)	NS
QRS Amplitude Averaged – (μV/hr)	24 (-162 – 159)	-3 (-216 – 194)	NS
PR Interval + (ms/hr)*	-0.8 (-3.8 – 5.9)	-0.1 (-5.2 – 4.4)	NS
PR Interval – (ms/hr)*	-0.3 (-5.8 – 3.9)	0.0 (-5.0 – 4.5)	NS
QRS Duration + (ms/hr)	0.3 (-3.2 – 2.1)	0.0 (-3.6 – 3.8)	NS
QRS Duration – (ms/hr)	0.4 (-2.7 – 3.2)	-0.2 (-3.8 – 3.1)	NS
QTc + (ms/hr)	0.3 (-7.2 – 12.2)	-0.2 (-10.3 – 10.5)	NS
QTc – (ms/hr)	-2.6 (-13.0 – 21.2)	-1.0 (-10.9 – 8.0)	0.014
RR + (ms/hr)	0.2 (-16.8 – 33)	-3.0 (-40 – 33)	NS
RR – (ms/hr)	-0.5 (-16.9 – 16.9)	-0.4 (-43.7 – 41.8)	NS
ST Lead II + (μV/hr)	-1.1 (-13.1 – 21.6)	-0.1 (-10.4 – 10.9)	NS
ST Lead II – (μV/hr)	2.3 (-13.6 – 12.8)	-0.2 (-11.2 – 10.6)	NS
ST Lead V2 + (μV/hr)	0.9 (-10.8 – 14.8)	-0.5 (-8.1 – 6.7)	NS
ST Lead V2 – (μV/hr)	3.4 (-6.0 – 13.8)	-0.5 (-8.4 – 7.5)	NS
Trend Change (Δy_2) †, median (IQR)			
QRS Amplitude Averaged + (μV)	79 (41 – 159)	86 (44 – 159)	NS
QRS Amplitude Averaged – (μV)	64 (26 – 126)	83 (44 – 143)	0.041
PR Interval + (ms)*	7.5 (4 – 17)	7 (4 – 13)	NS
PR Interval – (ms)*	6 (3 – 13)	7 (4 – 14)	NS
QRS Duration + (ms)	4 (2 – 11)	4 (2 – 8)	NS
QRS Duration – (ms)	4 (2 – 9)	4 (2 – 8)	NS

QTc + (ms)	16.3 (7.7 – 35.6)	14.3 (8.2 – 26.2)	NS
QTc – (ms)	15.6 (8.3 – 40.4)	14.6 (8.5 – 25.7)	0.013
RR + (ms)	35 (16 – 70)	59 (30 – 106)	0.023
RR – (ms)	33 (21 – 63)	56 (30 – 105)	0.017
ST Lead II + (μV)	19 (9 – 41)	16 (9 – 29)	0.006
ST Lead II – (μV)	20 (12 – 45)	16 (9 – 28)	NS
ST Lead V2 + (μV)	14 (8 – 28)	11 (6 – 20)	0.002
ST Lead V2 – (μV)	12 (6 – 22)	11 (6 – 20)	NS
Trend Change Comparison ($\Delta y_{2\text{-}3}$) [†], median (IQR)			
QRS Amplitude Averaged + (μV)	0 (-38 – 66)	0 (-62 – 59)	0.042
QRS Amplitude Averaged – (μV)	11 (-59 – 48)	2 (-43 – 50)	NS
PR Interval + (ms)*	0 (-5 – 5)	0 (-4 – 4)	NS
PR Interval – (ms)*	0 (-3 – 6)	0 (-5 – 4)	NS
QRS Duration + (ms)	0 (-4 – 4)	0 (-3 – 3)	NS
QRS Duration – (ms)	-1 (-6 – 2)	0 (-3 – 3)	NS
QTc + (ms)	2.6 (-9.3 – 13.1)	-0.4 (-9.7 – 8.0)	NS
QTc – (ms)	-2.6 (-9.2 – 15.0)	0.0 (-9.6 – 9.3)	0.031
RR + (ms)	-9 (-40 – 23)	-1 (-37 – 32)	NS
RR – (ms)	-8 (-29 – 13)	1 (-39 – 34)	NS
ST Lead II + (μV)	0 (-12 – 15)	0 (-10 – 10)	NS
ST Lead II – (μV)	4 (-5 – 12)	0 (-10 – 9)	NS
ST Lead V2 + (μV)	-1 (-12 – 10)	0 (-7 – 6)	NS
ST Lead V2 – (μV)	0 (-7 – 10)	0 (-7 – 6)	NS

*Reported where measureable given this is not measureable in atrial fibrillation

[†]For each row, + denotes the measure for the dominant positive trend, and – denotes the measure for the dominant negative trend for that ECG parameter. All negative trend change and slope measurements are reported as the absolute value.

[‡]This reflects the number of patients with both block 2 and block 3 available. 6 case patients and 104 control patients who had both block 1 and 2 were missing a block 3

SUPPLEMENTAL TABLE 3

Multivariable Logistic Regression Models

	OR (95% CI) *	p-value
Logistic Backward Stepwise		
Atrial fibrillation (present block n, not block n-1)	3.7 (1.5 – 9.0)	<0.001
2° HB (present block n, not block n-1)	4.6 (2.4 – 9.0)	<0.001
QRSd $\Delta y_n^+/\Delta x_n^+$	0.62 (0.39 – 0.97)	0.032
QRSd Δy_n^+	3.1 (1.9 – 5.1)	<0.001
QTc Δy_n^-	1.1 (1.06 – 1.2)	<0.001
RR $\Delta y_{n-(n-1)}^+$	1.5 (1.2 – 2.0)	0.002
ST Lead V2 $\Delta y_{n-(n-1)}^-$	4.6 (1.8 – 11.7)	0.001
Logistic Forward Stepwise		
Atrial fibrillation (present block n, not block n-1)	3.9 (1.6 – 9.5)	0.002
2° HB (present block n, not block n-1)	4.8 (2.5 – 9.4)	<0.001
QRSd $\Delta y_n^+/\Delta x_n^+$	0.63 (0.40 – 0.99)	0.044
QRSd Δy_n^+	2.9 (1.7 – 4.8)	<0.001
QTc Δy_n^-	1.1 (1.0 – 1.2)	0.002
RR $\Delta y_{n-(n-1)}^+$	1.5 (1.1 – 2.0)	0.002
ST Lead II $\Delta y_{n-(n-1)}^+$	1.7 (1.01 – 2.8)	0.043
ST Lead V2 $\Delta y_{n-(n-1)}^-$	4.4 (1.7 – 11.6)	0.002

Block n is the 3-hour block being evaluated. Block n-1 is the preceding 3-hour block.

* OR for QRSd and QTc are shown per 10ms change (trend change) or 10ms/hr (slope). OR for ST lead II and ST lead V2 are shown per 0.1mV change (trend change) or 0.1mV/hr (slope). OR for RR is shown per 100ms change (trend change) or 100ms/hr (slope)

SUPPLEMENTAL REFERENCES

1. Lian J, Wang L, Muessig D. A simple method to detect atrial fibrillation using rr intervals. *The American Journal of Cardiology*. 2011;107:1494-1497