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Failure in Short-term Prediction of Ventricular Tachycardia and Ventricular Fibrillation from Continuous ECG in Intensive Care Unit Patients

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Abstract

Background—Patients in the intensive care unit (ICU) setting are prone to malignant ventricular arrhythmias. We sought to test whether electrocardiographic markers of autonomic tone, ventricular irritability, and repolarization lability could be used in short-term prediction of ventricular arrhythmias in this patient population.

Methods—We studied 38 patients with sustained (> 30 seconds) monomorphic ventricular tachycardia (MVT), polymorphic ventricular tachycardia (PVT), or ventricular fibrillation (VF) while monitored in the ICU and 30 patients without arrhythmia in the ICU who served as controls. All patients had at least 12 hours of continuously recorded multi-lead ECG prior to arrhythmic event. Mean heart rate and measures of heart rate variability (HRV), QT variability (QTV), and ventricular ectopy were quantified in 1-hour epochs for the 12 hours pre-arrhythmic event and in 5-minute epochs for the last hour pre-event (and using a random termination time point in controls).

Results—A modest downward trend in QT variability and rise in heart rate were observed hours before PVT and VF events, although no significant changes heralded MVT, and no changes in any parameter predicted imminent ventricular arrhythmia of any type. There were no significant differences in ECG parameters between arrhythmia patients and controls.

Conclusions—In ICU patients, sustained ventricular arrhythmias are not preceded by change in electrocardiographic measures of autonomic tone, repolarization variability, and ventricular ectopy. Short-term arrhythmia prediction may be difficult or impossible in this patient population based on electrocardiographic measures alone.

Keywords

ventricular tachycardia; ventricular fibrillation; arrhythmia prediction; heart rate variability; QT variability

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Introduction

Sudden cardiac death is generally attributed to lethal ventricular tachyarrhythmias and carries a large public health burden, accounting for approximately three- to four-hundred thousand deaths per year in the United States (1,2). Risk stratification strategies that allow clinicians to predict these events in the minutes to hours preceding their initiation may prevent related morbidity and mortality. The relationship between autonomic tone and ventricular arrhythmias is well established (3-5). Parameters such as heart rate variability (HRV) and QT variability (QTV) are markers of autonomic tone and electrical instability, respectively, which are used in determining which patients are most likely to experience an arrhythmic event over the next few years or in long term risk stratification (6-8). However, the value of these parameters in short term risk prediction, that is deciding if an arrhythmic event is imminent, remains uncertain. Technical difficulties in obtaining noise-free ECG data immediately preceding a lethal arrhythmia often preclude investigation. Analysis of implantable cardioverter defibrillator (ICD) data is limited by the storage capacity of the devices and the advantages of holter data is offset by the low probability of capturing such events in an ambulatory population.

In our study, we evaluated the predictive power of these parameters along with heart rate and number of premature ventricular contractions (PVCs) in a cardiac intensive care population for which we were able to obtain high fidelity data. We used a system capable of recording and storing multi-lead ECG data, sampled at 1 kHz for the 24 hours preceding a ventricular arrhythmic event. We hypothesized that there would be an increase in sympathetic activity, repolarization lability, and/or arrhythmic triggers prior to an event, leading to an increase in heart rate, a decline in HRV, an increase in QTV, and an increase in the number of PVCs. While not necessarily reflective of an ambulatory population, the ability to obtain hours of ECG data preceding major arrhythmic events made this database a rare opportunity to examine short-term arrhythmia prediction from common electrocardiographic parameters.

Methods

Patient Characteristics

Patients who were admitted to the Cardiac Intensive Care Unit (CCU) of either the Johns Hopkins Hospital or Good Samaritan Hospital in Baltimore were studied according to a protocol approved by the institutional review boards of the respective institutions. Physicians on the CCU team identified patients who experienced an event of sustained (> 30 seconds) monomorphic ventricular tachycardia (MVT), polymorphic ventricular tachycardia (PVT), ventricular fibrillation (VF). Patients with a minimum of 12 hours of ECG data prior to the event constituted the study group. In addition, a group of patients who did not experience any arrhythmic event while in the CCU were identified at random to serve as a control population. For controls, a random point in time was taken as the “event” and 12 hours of ECG leading up to this time point was used for analysis. Periods of noisy ECG recordings due to motion artifact or electrical noise were excluded from analysis. Patients with intermittent bundle branch block, atrial fibrillation, or excessive background noise (>10% of record) were excluded due to difficulty in analyzing their data. Patients with more than one major event during the 12 hour period were also excluded to avoid ambiguity in the time of endpoint.

Data Collection

ECG tracings were downloaded from the specialized intensive care unit MARS telemetry system (GE Medical Systems, Milwaukee, WI) which is capable of retaining up to 28 hours

of multi-lead ECG tracings, filtered between 0.3 and 100 Hz and sampled at 1 kHz, and transferred to a computer for analysis. Each tracing was considered by event type- MVT, PVT, VF, or control, as determined by an experienced observer. Automated computerized analysis was done which allowed for determination of heart rate, and number of PVC's. HRV, or the beat-to-beat variation in heart rate was measured in both the time and frequency domains. For the time domain measure, the variance of instantaneous heart rate over time was calculated (9). The fast Fourier transform was applied to the time series to create a power spectral display. The power in the low frequency (.04 - .15 Hz) and high frequency (.15 - .4 Hz) bands was quantified, and both the ratio of the two bands and high frequency power alone were analyzed. Automated QT variability was obtained as previously described (10,11) using the ECG lead with best signal-to-noise ratio for each patient. The QT variability index (QTVI) corrected QT variance for heart rate variability. All variables were evaluated by one-hour epochs for the 12 hour period prior to the event, and in 5-minute epochs for the one hour period immediately preceding the event. Automated analysis was overread by the investigators to assure integrity of analysis, e.g. exclusion of noisy segments identified in the raw ECG and tachogram. Specific demographic information including presenting diagnosis, administration of beta blockers or other antiarrhythmic drugs during the monitored period, and other related conditions were obtained by chart review.

Statistical analysis

Pearsons chi square test was used to determine demographic differences between groups. To determine if there was a predictable trend in heart rate, number of PVCs, HRV, and QTV prior to an event, graphical displays of each parameter over time were constructed and assessed grossly by visual inspection. Repeated measures ANOVA and nonparametric analysis was also performed to test for the presence of temporal relationship in each electrocardiographic parameter prior to arrhythmic event. Finally, the mean value over time was compared to the final value of each parameter, to evaluate for a sudden change that may forecast an event. Analyses were performed both for the entire patient population and segregated by event type. Student's t-test was used for comparisons between patient groups. As there were multiple comparisons, the Bonferroni correction was used. Statistical significance was inferred at the $p < .05$ divided by 7 (number of comparisons), or $p < 0.007$ for all comparisons.

Results

Clinical characteristics

Data from 68 patients were analyzed, of which there were 30 controls, 17 patients with VF, 5 patients with PVT, and 16 patients with MVT. VF and PVT were considered to be mechanistically similar and therefore analyzed as a single group (see Discussion). Patients' demographic and clinical characteristics are summarized in Table 1. The mean age of the event population was 66 years, 55% of the patients were male, and 30% were African American. The most prevalent comorbidities were heart failure (53%), hypertension (42%), and coronary artery disease. Cardiac diagnoses, beta blocker usage, and antiarrhythmic drug therapy were non-uniform among the groups as noted in Table 1.

Patient Examples

Plots showing the time course over 12 hours for each of the parameters studied are shown in Figure 1 for a patient who had VF, a patient with MVT, and a control patient. For the patients with VF and MVT, the plots represent the 12 hours leading up to the arrhythmic event, whereas for the control, the plots show a random 12-hour epoch. For most parameters, the variations from hour to hour, and within any given hour, are as large as any change that occurs prior to the arrhythmia in the VF and MVT patients. The VF patient in

this example had a rise in PVC count prior to arrhythmic event, but this was not seen in most VF patients. Also, the control patient in this example had higher HRV and lower QTV than the two arrhythmia patients, a trend seen in some but not all controls. Furthermore, the control patient exhibited fluctuations in the parameters studied that are as large as those seen in the arrhythmia patients.

Group Trends

Combined data from all patients within each arrhythmia type are shown in Figures 2 and 3. Figure 2 displays trends in hourly averages over 12 hours, and Figure 3 shows 5-minute averages over the hour immediately preceding the arrhythmic event for VF/PVT and MVT patients, and preceding a random time point in the controls. There were no visually obvious trends in heart rate, HRV, number of PVC's, or QT variability in either the hourly data or 5-minute epochs in the hour prior to an event. Repeated measures ANOVA and linear regression analyses also demonstrated lack of predictive temporally-dependent change in the parameters tested in anticipation of an impending arrhythmic event in both hourly data and 5-minute epochs over the last hour, with the exception of QTV and mean HR in the hourly data prior to PVT and VF events (Table 2). QTV exhibited a downward trend ($p=0.007$), particularly 9-12 hours prior to PVT/VF, and mean HR trended slightly higher ($p=0.005$) over the 12 hours preceding PVT/VF, although this is difficult to appreciate visually in Figure 2. There were no sudden and reproducible changes immediately prior to an event in any of the parameters evaluated. The control patients also did not exhibit any specific trends. Finally, there was no significant difference found in mean values of any of the seven parameters in comparisons between patient groups.

Discussion

We had hoped to find an association between changes in specific ECG parameters and onset of sustained ventricular arrhythmias based on arrhythmia type. MVT is usually mediated by excitable-gap reentry, while PVT and VF involve triggering and functional reentry (12). The results of this study, however, suggest that changes in heart rate, HRV, QTV, and ventricular ectopy are not usefully predictive of an imminent sustained ventricular arrhythmia in the acute care setting. Among our population of coronary care unit patients, there was no significant trend in any of the variables tested prior to MVT events, and only modest change in QTV and mean HR over the 12 hours prior to VF/PVT events.

Our study is limited by the small number of events studied. Obtaining 12 hours of high fidelity ECG data preceding a spontaneous major arrhythmic event is difficult in any population. These events are rare even among monitored patients. Therefore, we can not rule out the possibility that our results might be different in a larger cohort. However, given that our data showed such a high degree of variability for all the parameters tested, it appears unlikely that an electrocardiographic arrhythmia predictor with high sensitivity and specificity would emerge. Of note, there were significant differences among groups in terms of use of beta blockers, other antiarrhythmics, and presenting diagnosis, all of which influence the ECG parameters studied. We cannot rule out the possibility that with control over medications, some of the electrocardiographic parameters may emerge as predictive of some arrhythmic event types.

There is an extensive literature that considers the utility of ECG parameters in long term risk stratification - that is, predicting which cohort of patients are most at risk for a lethal arrhythmia over the next few months to years. In multiple reports, decreased HRV has been associated with increased mortality post myocardial infarction, independent of more traditional predictors, such as left ventricular ejection fraction (13-15). HRV provides a noninvasive measure of autonomic activity, which has been mechanistically linked to

triggering and sustaining malignant arrhythmias. The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) trial prospectively evaluated HRV in 1284 patients with a mean follow-up of 21 months, and found that a low HRV implied a three-fold increase in the risk of cardiac mortality (16). Increased QT variability, a measure of ventricular repolarization lability, has also been associated with arrhythmic events. A substudy of 817 patients in the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) study found that top-quartile QT variability was independently associated with appropriate ICD therapy (17). Piccirillo et al showed that QT variability was predictive of total mortality and sudden death in 396 post-infarction patients without indications for ICD (18).

However, there is insufficient information regarding the utility of these same ECG parameters in short-term arrhythmia prediction. There are multiple scenarios in which short-term prediction could be valuable. In the inpatient setting, identification of imminent arrhythmia could lead to introduction of prophylactic measures such as antiarrhythmic drugs. Similarly, in ambulatory ICD recipients, short-term arrhythmia prediction could be used to trigger patient alerts (e.g. beep tones) and perhaps to initiate preventive pacing schemes.

Several studies have examined changes in heart rate dynamics immediately preceding spontaneous ventricular arrhythmias, based on either holter (19-21) or ICD electrogram recordings (7,22,23). A consistent finding in these studies is an increase in heart rate prior to sustained arrhythmic events, although this is hardly specific for imminent arrhythmia. The mechanism underlying the heart rate increase is thought to be a shift in autonomic tone, evidenced by an accompanying fall in total HRV observed in some studies (19,22), although this was not seen in others (20,24). Furthermore, the ratio of LF to HF variability, a measure of sympatho-vagal balance, was found to rise prior to arrhythmia in some patients (7,19) and fall in others (21). Watanabe demonstrated a decline in heart rate turbulence slope prior to arrhythmia onset in ICD recipients (25), consistent with a mechanism of vagal withdrawal, while Nemec et al observed a rise in ectopic beats prior to arrhythmic events detected in ICDs, interpreted to reflect sympathetic activation (23).

The general lack of significant change in heart rate dynamics that we observed prior to arrhythmia onset differs from the findings in the prior studies noted above. An important difference between those studies and ours is that our patients were exclusively inpatients in an intensive care setting, while the other studies were primarily based on ambulatory patients. Intensive care unit patients are likely to have elevated sympathetic tone due to underlying disease, whether or not they develop malignant ventricular arrhythmia, which likely renders detection of further shift in sympatho-vagal balance problematic. Watanabe has suggested that prediction of imminent ventricular arrhythmias based on measures of autonomic function is applicable only in patients with normal baseline values (25). Our data support this conclusion.

In the patients we studied, we also did not find a significant change in repolarization variability prior to arrhythmia onset. We have previously shown that QT variability increases with acute myocardial ischemic episodes (26). Thomsen et al have demonstrated that beat-to-beat repolarization variability quantified by Poincare plots increases prior to drug-induced torsades de pointes in dogs (27,28). Shusterman et al (29) observed an increase in T-wave alternans, measured using the modified moving average technique, preceding sustained ventricular tachycardia in ambulatory Holter recordings. The lack of observed increase in QTVI from baseline in the present study likely reflects the elevated baseline repolarization lability due to the underlying disease state in this patient cohort.

Limitations

The major limitation to our work is the small sample size due to difficulties in obtaining 12 hours of high quality ECG data prior to an event, which allows for the possibility that our study is under-powered to detect slight but significant changes in an electrocardiographic parameter prior to arrhythmia onset. However, as discussed above, we found such a large variation in individual response for each parameter that it is unlikely that a consistent clinically useful predictive trend would emerge even in a larger patient population. Importantly, the mechanistic etiologies of arrhythmia even within each of the 3 groups may have been heterogeneous. In addition, this was a non-controlled observational study, and differing treatments among the 3 groups may have masked differences between them. The primary purpose of the study, however, was to test for predictive changes in ECG parameters within individuals prior to arrhythmia onset, rather than for differences between patient groups. There may also be short-term predictive value in other ECG parameters not studied here, including ST segment shifts, T-wave alternans, and heart rate turbulence, and in non-ECG measures such as hemodynamic and respiratory parameters. We also did not test whether some combination of ECG markers would have been predictive. Finally, since our population was an intensive care cohort, our results may not be generalizable to an ambulatory population.

Conclusion

When sustained ventricular arrhythmias occur in patients hospitalized in the intensive care unit setting, the arrhythmia is generally not heralded by a significant change in mean heart rate, HRV, QTV, or level of ventricular ectopy. It is unlikely that arrhythmia prediction can be accomplished by traditional ECG analysis alone in this patient population. Novel forms of ECG analysis and non-electrocardiographic markers for short-term arrhythmia prediction should be pursued.

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Figure 1.

Parameters tested over time for three patients. Patient with monomorphic ventricular tachycardia, ventricular fibrillation, and control. Units: QTV: ms^2 , QTVi: unitless, #PVCs: per epoch, HR: bpm, HRV: bpm^2 , LF/HF power: unitless, HF power: ms^2 .

Figure 2. Mean values and standard deviations of all parameters tested by 1 hour epochs for the 12 hours preceding an event for the cohort with MVT, PVT or VF, and for controls. Units as in Fig 1.

Figure 3. Mean values and standard deviations of all parameters tested by 5 minute epochs for the one hour preceding an event for the cohort with MVT, PVT or VF, and for controls. Units as in Fig 1.

Table 1

Demographic Characteristics.

	PVT+ VF N=22	MVT N=16	Controls N=30	P value
Mean age (yrs)	67	64	59	0.75
Male	55%	50%	57%	0.77
Race				0.27
% White	55%	87%	60%	
% AA	41%	13%	23%	
% other	4%	0%	17%	
Diagnosis				0.03
Acute MI	41%	63%	40%	
Unstable angina	0%	0%	10%	
Heart Failure	32%	13%	17%	
Arrhythmia	5%	13%	7%	
Other	27%	13%	27%	
Beta blocker	14%	25%	47%	0.03
Antiarrhythmics	23%	44%	7%	0.004
Comorbidities				
CAD	41%	31%	47%	0.55
Heart Failure	45%	69%	40%	0.19
Diabetes	36%	25%	17%	0.37
Hypertension	32%	63%	30%	0.05
Hyperlipidemia	32%	13%	17%	0.63
CRF	23%	6%	20%	0.38

AA, African American; PVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; MVT, monomorphic ventricular tachycardia, CAD coronary artery disease, CRF chronic renal failure.

Table 2

P values for repeated measures ANOVA analyses shown for each parameter by event type by 1-hour epochs and 5-minute epochs.

Per 1-hour epoch							
	QTVI	QTV	PVC's	HR	HRV	LF/HF	HF
MVT	P= 0.94	P= 0.02	P= 0.87	P=0.42	P=0.60	P=0.04	P=0.07
PVT /NF	P=0.69	P=0.007 *	P= 0.82	P=0.005 *	P= 0.20	P=0.91	P=0.38
Control	P= 0.89	P= 0.29	P=0.91	P=0.21	P=0.59	P=0.98	P=0.71

Per 5-minute epoch							
	QTVI	QTV	PVC's	HR	HRV	LF/HF	HF
MVT	P=0.81	P=0.65	P=0.01	P=0.02	P=0.03	P=0.91	P=0.14
PVT /NF	P=0.56	P=0.56	P=0.62	P=0.21	P=0.49	P=0.07	P=0.22
Control	P=0.77	P=0.16	P=0.04	P=0.74	P=0.26	P=0.55	P=0.58

* Significance (in time-dependence) is accepted at $p<0.007$ to account for multiple comparisons.