Crescendo in Depolarization and Repolarization Heterogeneity Heralds Development of Ventricular Tachycardia in Hospitalized Patients With Decompensated Heart Failure

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Background—A critical need exists for reliable warning markers of in-hospital life-threatening arrhythmias. We used a new quantitative method to track interlead heterogeneity of depolarization and repolarization to detect premonitory changes before ventricular tachycardia (VT) in hospitalized patients with acute decompensated heart failure.

Methods and Results—Ambulatory ECGs (leads V1, V5, and aVF) recorded before initiation of drug therapy from patients enrolled in the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) trial were analyzed. R-wave heterogeneity (RWH) and T-wave heterogeneity (TWH) were assessed by second central moment analysis, for quantifying heterogeneity of depolarization and repolarization to detect premonitory increases before ventricular tachycardia (VT). The randomized, multicenter PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) trial enrolled 255 patients with NYHA class III or IV congestive heart failure who were hospitalized for symptomatic, decompensated heart failure.4 We analyzed 24-hour ambulatory ECG (AECG) recordings made in all patients immediately before randomization to treatment.

Conclusions—This investigation is the first clinical demonstration of the potential utility of tracking depolarization and repolarization heterogeneity to detect crescendos in electrical instability that could forewarn of impending nonsustained VT.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00270400. (Circ Arrhythm Electrophysiol. 2012;5:84-90.)

Key Words: depolarization ■ tachycardia ■ repolarization ■ T-wave alternans

More than 1 million patients are hospitalized for decompensated heart failure yearly among the population of >5 million Americans with heart failure.1 These individuals experience a high degree of ventricular ectopy and spontaneous ventricular arrhythmias. Sudden cardiac death constitutes a high proportion of deaths in this population (58% in New York Heart Association [NYHA] class III and 33% in NYHA class IV).2,3 However, no standard electrocardiographic markers, including ventricular ectopy or arrhythmias, have proven to be reliable indicators of in-hospital life-threatening cardiac arrhythmias.

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The objective of the present investigation was to evaluate the potential clinical utility of a new method, second central moment analysis, for quantifying heterogeneity of depolarization (R-wave heterogeneity [RWH]) and repolarization (T-wave heterogeneity [TWH]) waveforms. The specific question addressed was whether changes in RWH and TWH could provide premonitory indications of increased cardiac electrical instability before the onset of ventricular tachycardia (VT). The randomized, multicenter PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) trial enrolled 255 patients with NYHA class III or IV congestive heart failure who were hospitalized for symptomatic, decompensated heart failure.4 We analyzed 24-hour ambulatory ECG (AECG) recordings made in all patients immediately before randomization to treatment.

The rationale for combined analysis of RWH, TWH, and T-wave alternans (TWA) is the close mechanistic linkage among these electrophysiological entities.5,6 In the experimental laboratory, it was demonstrated that a progressive increase in TWH during acute myocardial ischemia precedes the development of both concordant and discordant TWA and complex forms culminating in ventricular fibrillation.7 TWA...
is an electrophysiological phenomenon associated clinically with impending ventricular arrhythmias and an important marker of arrhythmia risk supported by extensive clinical evidence of its utility in stratifying risk for sudden cardiac death. Furthermore, this phenomenon may be a trigger for arrhythmias by establishing steep repolarization gradients leading to reentry and wavebreak.

Methods

The PRECEDENT trial enrolled 255 patients aged ≥18 years with a NYHA class III or IV congestive heart failure and symptomatic, decompensated congestive heart failure for which inpatient, single-agent, intravenous therapy with either nesiritide or dobutamine (with or without diuretics) was deemed appropriate. Patients were receiving either no antiarrhythmic medications or a stable dose of these drugs for at least 48 hours before starting study treatment. Oxygen, intravenous and oral diuretics, and all noninvasive cardiac medications were permitted.

Exclusion criteria were recent acute myocardial infarction (≤48 hours before study entry); unstable angina or ongoing myocardial ischemia; cardiogenic shock; baseline systolic blood pressure consistently ≤85 mm Hg or significant hemodynamic instability requiring immediate inotropic support, pressor support, or both; stroke within the past month; severe aortic stenosis; obstructive cardiomyopathy; and constrictive pericarditis. Patients were excluded if they had been treated for >4 hours with an intravenous vasoactive agent for the index episode of congestive heart failure. Patients were also excluded from the study if they could not tolerate a 24-hour baseline AECG period without intravenous vasoactive medications or the specified washout period for intravenous vasoactive medications received before the baseline AECG period, or both. Clinical characteristics of study participants are shown in the Table.

All patients were monitored by AECG recording for the 24-hour period immediately before the start of the study drug (prerandomization AECG tape). The 3-channel (leads V1, V5, and aVF) recordings were scanned with a commercially available AECG reader (Zymed model 2010; Philips Medical Systems), archived on CDs, and made available for analysis on a MARS-PC Holter Monitoring System (GE Medical Systems). For TWA, commercial software was used. For RWH and TWH, Matlab software was implemented according to our previous experimental study in which extensive validation of the algorithms was performed. AECG tapes were labeled with a unique patient code and stripped of any other identifying information.

AECGs recorded from 44 patients during the prerandomization phase of the PRECEDENT trial were analyzed, comprising 22 patients who experienced a single bout of VT (≥4 beats at heart rates of ≥100 beats/min) following 120 minutes of stable sinus rhythm and 22 age- and sex-matched patients without atrial fibrillation, VT, or other rhythm disturbances. In the latter group, RWH and TWH analyses were performed for the entire 24-hour recordings. The Beth Israel Deaconess Medical Center Committee on Clinical Investigations certified the exempt status of this reanalysis of existing data from a completed clinical trial under exemption number 4 of the Code of Federal Regulations, 45 CFR 46.101(b).

RWH and TWH are continuous, noninvasive measures of spatial depolarization and repolarization heterogeneity, respectively, and complement the temporal heterogeneity information provided by TWA. Spatial heterogeneity throughout the entire R and T waveforms was assessed as previously described using second central moment analysis, a principle drawn from Newtonian mechanics. Essentially, a quantitative estimate is derived of spay (the second moment) about the mean morphology (the first moment) of the R and T waveforms. Using this analytic technique, heterogeneity is not unduly weighted by protracted termination or inflections in the waveforms, ST-segment changes, or presence of U waves, features that limit accurate dispersion measurement by conventional analyses. RWH and TWH were analyzed in AECG data from leads V1, V5, and aVF as the maximum square root of the second central moment of the corrected waveform in the interval from the beginning of the Q wave to the end of the S wave. RWH and TWH were analyzed during 24 hours in matched controls. Comparing waveforms in leads V1, V5, and aVF, and averaged over 15-minute epochs.

TWA magnitude was analyzed for 120 minutes before VT with the Modified Moving Average (MMA) method (GE Healthcare) in leads V1, V5, and aVF. Results were computed for each 15-s interval and averaged over 15-minute epochs. MMA computes TWA as the peak difference between odd and even beats in the beat stream at any point within the JT interval. Specifically, a stream of beats is divided into odd and even bins, and the morphology of the beats in each bin is averaged over a few beats successively to create a moving average complex. TWA is computed as the maximum difference in amplitude between the odd-beat and the even-beat average complexes from the J point to the end of the T wave. This technique is based on the powerful noise reduction principle of recursive averaging; achieves an excellent signal-to-noise ratio; is relatively tolerant of nonstationary data, such as changing heart rates or motion artifact; and is independent of phase-shift perturbations. Respiratory and motion artifacts have been further reduced by cubic alignment and other filters. These characteristics make MMA analysis suitable for use during AECG monitoring because it can quantify the effects of transient events, such as surges in sympathetic nerve activity, which may occur reflexly or in response to behavioral stress and which exert a profound influence on arrhythmia vulnerability.

RWH, TWH, and TWA levels were compared with baseline at 60 to 75 minutes before the onset of the arrhythmia in patients with VT. RWH and TWH were analyzed during 24 hours in matched controls. ANOVA was used with Tukey test for multiple comparisons (P < 0.05). Discrete patient characteristics were analyzed with χ² test. Age and rate of ventricular premature contractions were analyzed by Student t test.
Results

Patient Characteristics

The clinical characteristics of the 44 patients hospitalized with symptomatic decompensated heart failure, enrolled in the PRECEDENT trial, and included in this sub-study are summarized in the Table. Of the 255 subjects enrolled in the trial, we identified the 22 who had experienced VT episodes (≥4 beats at heart rates exceeding 100 beats/min) following at least 120 minutes of stable sinus rhythm. These 22 VT episodes averaged 6.6±0.1 beats (mean±SEM; range, 4–19 beats). Patients matched on age and sex who did not experience VT at the close of similarly quiescent periods comprised the remainder of the study population (n=22). The clinical characteristics of the 2 groups did not differ significantly with respect to NYHA class, diabetes, prior MI, or VPB contractions but had differing etiologies of heart failure.

Changes in Repolarization

RWH and TWH

Patients experiencing VT exhibited marked increases in interlead RWH and TWH at 30 to 45 minutes before VT (Figure 2), thus anticipating the development of TWA by 15 minutes. Maximum RWH across leads V1, V5, and aVF rose from 164.1±33.1 μV at baseline to 299.8±54.5 μV at 30 to 45 minutes before the arrhythmia (P<0.05). Meanwhile, maximum TWH across leads V1, V5, and aVF rose from 134.5±20.6 μV at baseline to 239.2±37.0 μV at 30 to 45 minutes before the arrhythmia (P<0.05). Just before VT, maximum RWH and TWH levels remained elevated at 289.5±45.9 and 230.9±24.7 μV, respectively (P<0.05). Although the extent of change varied among patients, the crescendo pattern in ECG heterogeneity before nonsustained VT was consistent (Pearson correlation coefficient comparing RWH and TWH, 0.51; P=0.01). In 20 of 22 (91%) patients, RWH or TWH remained elevated before onset of nonsustained VT. In the remaining 2 cases, there was a relatively minor fluctuation in these parameters. The consistency of the pattern is also indicated by the relatively small SEs in the time course depicted in Figure 2.

Analysis of RWH and TWH in 15-s intervals across the entire 24-hour recordings demonstrated that these parameters were significantly higher among the cases before VT than at any time during the entire 24-hour period among the controls. Specifically, RWH before VT was higher than the 24-hour maximum of the controls (299.8±54.5 versus 185.5±29.4 μV, P<0.05). In addition, TWH before VT was higher than the 24-hour maximum of the controls (239.2±37.0 versus 157.1±27.2 μV, P<0.05).
Analysis of TWA

An example of visible TWA of 82 μV in a patient who experienced VT is provided in Figure 3. This patient exhibited increased levels of RWH and TWH that heralded the onset of TWA and VT.

Significant increases in TWA levels in all 3 leads analyzed preceded the onset of VT. Elevated levels of TWA over baseline at 60 to 75 minutes were first evident at 15 to 30 minutes before the arrhythmia, namely, 24.2±3.9, 27.9±4.6, and 25.5±3.9 μV in leads V1, V5, and aVF, respectively, and remained at high levels until VT occurred (P<0.05) (Figure 4). The peak TWA levels for V1, V5, and aVF before VT were 29.2±3.8, 27.9±4.6, and 28.3±4.2 μV, respectively, and were substantially higher than at baseline (P<0.05).

Heart Rate

Heart rate was unchanged during the 2-hour observation period in patients who experienced VT, remaining in the range of 87.0±4.8 beats/min at baseline to 86.1±4.6 beats/min at 0 to 15 minutes before the arrhythmia (Figure 5). Heart rates were similarly stable in patients without VT. Because heart rate remained relatively constant, it did not provide warning of impending arrhythmia.

Discussion

This study demonstrates that combined monitoring of depolarization and repolarization heterogeneity together with TWA heralds the onset of nonsustained ventricular tachyarrhythmias in hospitalized patients with decompensated heart failure. The rationale for the selection of these parameters was the extensive evidence linking these electrophysiological entities to cardiac arrhythmogenesis under diverse experimental and clinical conditions. The use of multiple leads permitted measurement of spatial as well as temporal heterogeneity, tracking the culmination in TWA and arrhythmia.
Previous Studies

Extensive experimental studies point to a close linkage among repolarization heterogeneity, TWA, and ventricular tachyarrhythmias. Using isopotential maps in canines undergoing acute myocardial ischemia, Konta and coworkers were among the first to provide evidence that TWA occurs on a background of temporospatial heterogeneity of repolarization. Importantly, they found that discordant TWA, wherein repolarization is out of phase in neighboring regions, was highly prophibrillatory. Subsequently, the importance of this observation was supported by a number of elegant optical mapping studies that indicated that the occurrence of discordant TWA is not only a marker of arrhythmia risk, but also a trigger because this phenomenon sets the stage for unidirectional block, reentry, and wavebreak. We found in canines undergoing acute myocardial ischemia that TWH increased progressively before onset of ischemia-induced ventricular fibrillation in both epicardial and precordial leads. Importantly, the increase in TWH was associated with a parallel increase in the magnitude of TWA and the development of discordant TWA followed by more complex forms of oscillations that occurred a few seconds before onset of ventricular fibrillation. These observations suggest a close linkage between heterogeneity of repolarization and severity of concordant and discordant repolarization alternans.

The utility of TWA as a prognostic indicator in heart failure patients at high risk for lethal ventricular arrhythmias is well established. Negative TWA test results are highly accurate in identifying individuals whose arrhythmic risk is low. However, when left ventricular ejection fraction is severely depressed, the strength of TWA prediction of ventricular tachyarrhythmias by Spectral Method analysis may be lost. Sakaki and colleagues determined in patients with depressed left ventricular function that TWA by time-domain MMA analysis stratifies risk for cardiovascular and sudden death, with hazard ratios of 17.1 and 22.6, respectively. Also using MMA-based TWA analysis, Stein and colleagues found that hospitalized patients with left ventricular dysfunction following myocardial infarction experienced significantly elevated levels of TWA that predicted the occurrence of sudden cardiac death and cardiovascular mortality during the 20±6-month follow-up. Moreover, these investigators illustrated the utility of QRS-aligned templates of superimposed electrocardiographic complexes to verify TWA magnitude. Kodama and colleagues demonstrated in patients with chronic decompensated heart failure that TWA can be visible during rest, tachycardia, and dobutamine loading. The latter intervention provoked visible TWA in 10 of 94 (11%) patients, suggesting an association between mechanical and electrical alternans in patients with heart failure.

TWA magnitude has also been found to parallel the increased short-term risk of VT. Shusterman and colleagues demonstrated a significant increase in TWA as well as other electrophysiological inhomogeneities before VT in the ESVEM (Electrophysiological Study versus Electrocardiographic Monitoring) trial. These findings are consistent with experimental studies in large animals, in which progressive increases in TWA magnitude were found to precede the onset of VT and ventricular fibrillation.

Chauhan and coworkers studied the interrelationship between repolarization heterogeneity and TWA in patients with cardiomyopathy, using transvenous multielectrode catheters placed along the apico basal epicardial and endocardial surface of the ventricles. They found that patients exhibiting a positive TWA test and VT experienced heightened levels of repolarization heterogeneity. The authors proposed that the association between a positive TWA test and VT resulted from steep repolarization gradients, which provided the substrate for functional conduction block and reentry. Moreover, both spatiotemporal heterogeneity and discordant alternans were evident in patients with cardiomyopathy, and greater spatial distribution of intracardiac alternans was associated with alternans detected in precordial or limb leads.

Present Investigation

The present investigation is consistent with the current literature indicating a close relationship between depolarization and repolarization heterogeneity, TWA, and nonsustained VT. The study breaks new ground in demonstrating that the electrophysiological milieu of depolarization and repolarization heterogeneity sets the stage for heightened levels of TWA before the onset of ventricular tachyarrhythmias. It is of interest that both RWH and TWH were significantly elevated in the 30- to 45-minute period before arrhythmias, preceding the appearance of TWA by ±15 minutes. This short-term indication of probable VT onset may be attributable to the fact that TWA is a more advanced and therefore delayed indicator of cardiac electrical instability than RWH or TWH.

Increased levels of TWH clearly preceded the development of TWA and transition to VT. This finding is consistent with our prior experimental studies using this methodology as well as with other experimental studies. Our studies are also consistent with the clinical findings of Chauhan and coworkers that repolarization heterogeneity, TWA, and VT are closely linked. RWH and TWH establish an early background of heterogeneity of depolarization and repolarization for the subsequent development of macroscopic TWA, which may serve as a precipitating factor for VT by establishing steep repolarization gradients leading to unidirectional block and reentry. Because the strength of correlation between RWH and TWH appears to be only moderate (Pearson correlation coefficient, 0.51; P=0.01), these variables may differ in their relationship to arrhythmia onset, depending on pathophysiological changes in myocardial substrate among individual patients.

Role of Heart Rate

Heart rate remained relatively constant during the 120-minute observation period both in patients who experienced VT and in those who did not, indicating that the crescendo in RWH, TWH, and TWA occurred independently of alterations in chronotropy. This relative constancy in heart rate is consistent with the absence of major changes in autonomic balance before the arrhythmia. Had there been a significant increase in sympathetic tone, withdrawal of vagus nerve activity, or both, then heart rate would have progressively increased. Conversely, the occurrence of bradycardia would have indicated a reciprocal autonomic pattern. Because ECG heterogeneity and TWA are influenced by heart rate, the absence of a change in heart rate indicates that
the results were not confounded by alterations in chronotropic state. The progressive heart rate-independent changes in RWH, TWH, and TWA, which herald the onset of VT, suggest but do not prove the possibility that intrinsic changes in the electrophysiological milieu of the myocardial substrate underlie development of the arrhythmia.

Conclusions and Clinical Implications

The results of the present study suggest that concurrent monitoring of depolarization and repolarization heterogeneity in conjunction with TWA could potentially provide early warning of impending nonsustained VT. It remains to be determined, however, whether ECG heterogeneity is predictive of sustained VT. A prospective clinical study is needed to determine the predictive capacity of the combination of these parameters for life-threatening arrhythmias in hospitalized patients with decompensated heart failure.

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Disclosures

Drs Nearing and Verrier are inventors of the Modified Moving Average method for TWA analysis, with the patent assigned to Beth Israel Deaconess Medical Center and licensed to GE Healthcare, Inc, and Medtronic, Inc.

References


**CLINICAL PERSPECTIVE**

Hospitalized patients with decompensated heart failure exhibit heightened risk for malignant arrhythmias. To date, no standard electrocardiographic marker, including ventricular ectopy, has proven to be a reliable indicator of impending ventricular tachyarrhythmias. We investigated the potential value of our newly developed method, second central moment analysis, a measure of splay of interlead waveforms around the average waveform as its axis, which quantifies heterogeneity of depolarization and repolarization. This study examined whether the method could identify premonitory indications of increased cardiac electrical instability before the onset of ventricular tachycardia (VT) in the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) trial (www.clinicaltrials.gov; NCT00270400) of hospitalized patients with symptomatic decompensated heart failure. There are sound scientific underpinnings for this electrophysiologic measure, as heterogeneous repolarization predisposes to unidirectional block, culminating in reentrant rhythms, wavebreak, and fibrillation. Analyses were performed on routine 24-hour ambulatory electrocardiographic recordings made just before randomization to treatment. In patients with VT, depolarization and repolarization heterogeneity increased significantly by 83% and 78%, respectively, at 30 to 45 minutes before VT. Matched patients without VT did not display elevated depolarization and repolarization heterogeneity during the entire monitoring period. To our knowledge, these results constitute the first clinical demonstration that concurrent monitoring of depolarization and repolarization heterogeneity can potentially confer early warning of impending VT. Further corroboration of these findings in larger, prospective trials could provide a means for alerting hospital staff to take precautionary measures to avert cardiac arrest.
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