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

Bruce D. Nearing, PhD; Gregory A. Wellenius, ScD; Murray A. Mittleman, MD, DrPH; Mark E. Josephson, MD; Andrew J. Burger, MD; Richard L. Verrier, PhD

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 and T-wave alternans (TWA) by modified moving average analysis. Of 44 patients studied, 22 had experienced episodes of VT (≥4 beats at heart rates >100 beats/min) following ≥120 minutes of stable sinus rhythm, and 22 were age- and sex-matched patients without VT. TWA increased from 18.6±2.1 μV (baseline, mean±SEM) to 27.9±4.6 μV in lead V5 at 15 to 30 minutes before VT (P<0.05) and remained elevated until the arrhythmia occurred. TWA results in leads V1 and aVF were similar. RWH and TWH were elevated from 164.1±33.1 and 134.5±20.6 μV (baseline) to 299.8±54.5 and 239.2±37.0 μV at 30 to 45 minutes before VT (P<0.05), respectively, preceding the crescendo in TWA by 15 minutes. Matched patients without VT did not display elevated RWH (185.5±29.4 μV) or TWH (157.1±27.2 μV) during the 24-hour period.

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.

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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.

Clinical Perspective on p 90

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 TWA during acute myocardial ischemia precedes the development of both concordant and discordant TWA and complex forms culminating in ventricular fibrillation.7 TWA
AECG tape). The 3-channel (leads V1, V5, and aVF) recordings were performed immediately before the start of the study drug (prerandomization received before the baseline AECG period, or both). Clinical characteristics specified washout period for intravenous vasoactive medications AECG period without intravenous vasoactive medications or the exclusion if they could not tolerate a 24-hour baseline for the index episode of congestive heart failure. Patients were also with impending ventricular arrhythmias8 and an important electrophysiological phenomenon associated clinically with impending ventricular arrhythmias8 and an important marker of arrhythmia risk supported by extensive clinical evidence of its utility in stratifying risk for sudden cardiac death.9–12 Furthermore, this phenomenon may be a trigger for arrhythmias by establishing steep repolarization gradients leading to reentry and wavebreak5,6,13–15.

### 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.4 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 nonintravenous 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.7 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 described7 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 waveform in the interval from the beginning of the Q wave to the end of the S wave. TWH was the maximum of the heterogeneity waveform in the interval between the J point and the end of the T wave. The analysis window began at 120 minutes before VT in patients with arrhythmia. In control patients without arrhythmia, the entire 24-hour recording was analyzed. RWH and TWH maxima were computed for each 15-s interval, 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.16 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 ratio17; is relatively tolerant of nonstationary data, such as changing heart rates or motion artifact; and is independent of phase-shift perturbations.16 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 reflexively 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 χ 2 test. Age and rate of ventricular premature contractions were analyzed by Student t test.
Patients experiencing VT exhibited marked increases in RWH and TWH at 30 to 45 minutes before VT. PRECEDENT patients without VT (light gray bars) did not exhibit significant changes in RWH or TWH during a quiescent 120-minute observation period at a similar time of day (both nonsignificant). Abbreviations as in Figure 1. *P<0.05.

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 substudy 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 events averaged 8.6±2.1 minutes of stable sinus rhythm. These 22 VT events averaged 8.6±2.1 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).

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.

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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.

Figure 3. Crescendo in depolarization and repolarization heterogeneity culminating in TWA before VT. Example of development of VT heralded by crescendo in RWH (●), TWH (□), and TWA (upper panel) in lead V5 before the arrhythmia in a PRECEDENT trial patient. TWA indicates T-wave alternans; VT, ventricular tachycardia. Other abbreviations as in Figure 2.

Figure 4. Increase in TWA before VT. At 0 to 30 minutes preceding VT, TWA was increased significantly above baseline in leads V1, V5, and aVF in the 22 PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) patients with VT (dark gray bars) following a 2-hour quiescent period. Baseline was determined at 60 to 75 minutes before VT. PRECEDENT patients without VT (light gray bars) did not exhibit significant changes in TWA in these leads during a quiescent 120-minute observation period at a similar time of day. Abbreviations as in Figure 3. *P<0.05.

Figure 5. Time course of heart rate before ventricular tachycardia (VT). Heart rates across the 120-minute observation period did not change either in patients with VT (dark gray bars) or in patients without VT (light gray bars). bpm indicates beats per minute.
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 profibrillatory. 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 compensated 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 apicobasal 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. 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 compensated 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.

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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 Deaconess Medical Center and licensed to GE Healthcare, Inc, and Medtronic, Inc.

References


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CLINICAL PERSPECTIVE

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