Non-ST-Segment Elevation Myocardial Infarction: A Novel and Robust Approach for Early Detection of Patients at Risk

Robert L. Lux, PhD

Non-ST-elevation myocardial infarction (NSTEMI) is lower on the severity spectrum of acute coronary syndromes than is myocardial infarction (MI), resulting from complete occlusion of a major coronary artery. As the name implies, it is a syndrome that does not exhibit the dramatic ST elevation observed in the standard 12-lead ECG in chest pain patients with confirmed acute MI. The important clinical significance of NSTEMI is that delay in diagnosis can lead to increased morbidity, risk of arrhythmia, and death. The article *Clinical Utility of Ventricular Repolarization Dispersion for Real-Time Detection of Non-ST Elevation Myocardial Infarction in Emergency Departments* in this issue of the Journal by Al-Zaiti et al[1] is a timely presentation of a new approach to quickly diagnose NSTEMI and significantly reduce the time to treatment in these patients. The marker, ventricular repolarization dispersion (VRD), incorporates much more information in the ECG than that provided by measuring elevation of the ST segment and, thus, heralds the emergence of more powerful and robust methods of assessing ECG morphology and dynamics than can be provided by classical interval and amplitude measurements.

Non-ST-Elevation Myocardial Infarction

As the name states, NSTEMI is myocardial infarction in which the elevation—or for that matter, depression—of ST segments is not significantly different from normal and thus the reason that the condition is not identified in patients

presenting with chest pain. Typically, chest-pain patients without significantly abnormal ST elevation are monitored, potentially for hours, until other tests confirm the presence of acute infarction (eg, elevated troponin levels). There are several explanations that account for the absence of abnormal ST elevation in acute MI. These include numerous possibilities: that the infarcts may be relatively small; that the location of the infarcts may be in locations only weakly sensed by the lead fields of the standard 12-lead ECG; or that the infarct is slowly developing. Importantly, this does not mean that the QRS and ST-T waves of the ECG do not change dynamically during the infarct's time course. At the cellular level, acute ischemia results in changes in action potential amplitude, duration, triangularization or sloping of the plateau, and even reduction in action potential (AP) upstroke velocity in affected cells. Consequently, the ECG shows a dynamic progression of changes in ST level and slope as well as T wave amplitude and morphology, in addition to widening of the QRS as a consequence of conduction slowing—all with different time course and magnitude. In NSTEMI all of these may be present although much more subtly than in ST-segment myocardial infarction, in which the ST segments show definitive elevation. Thus, any method that is sensitive to and quantitates these changes in QRS and ST-T waveform should greatly improve the sensitivity of the test for infarction as well as drastically reduce the time required to diagnose the syndrome.

Figures 1 and 2 show data from an unpublished study investigating depolarization and repolarization changes induced by coronary occlusion in a canine model of acute ischemia (Lux RL, unpublished data, NIH SCOR in *Sudden Cardiac Death*, P50 HL52338, 1994–2005). Figure 1 shows 272 consecutive superimposed beats from an electrogram recorded near the anterior base of the left ventricle (LV) during atrial pacing (320-ms cycle length) and in the first minutes after temporarily occluding the left anterior descending coronary artery (LAD). Note the near identical P, QRS, ST-T complexes in this electrogram. Figure 2 shows the exact same beats but at a site 3 cm away and close to the left ventricular apex. Note the dramatic changes, not only in the ST elevation, but the ST-T and even QRS morphologies that confirm conduction (activation sequence)
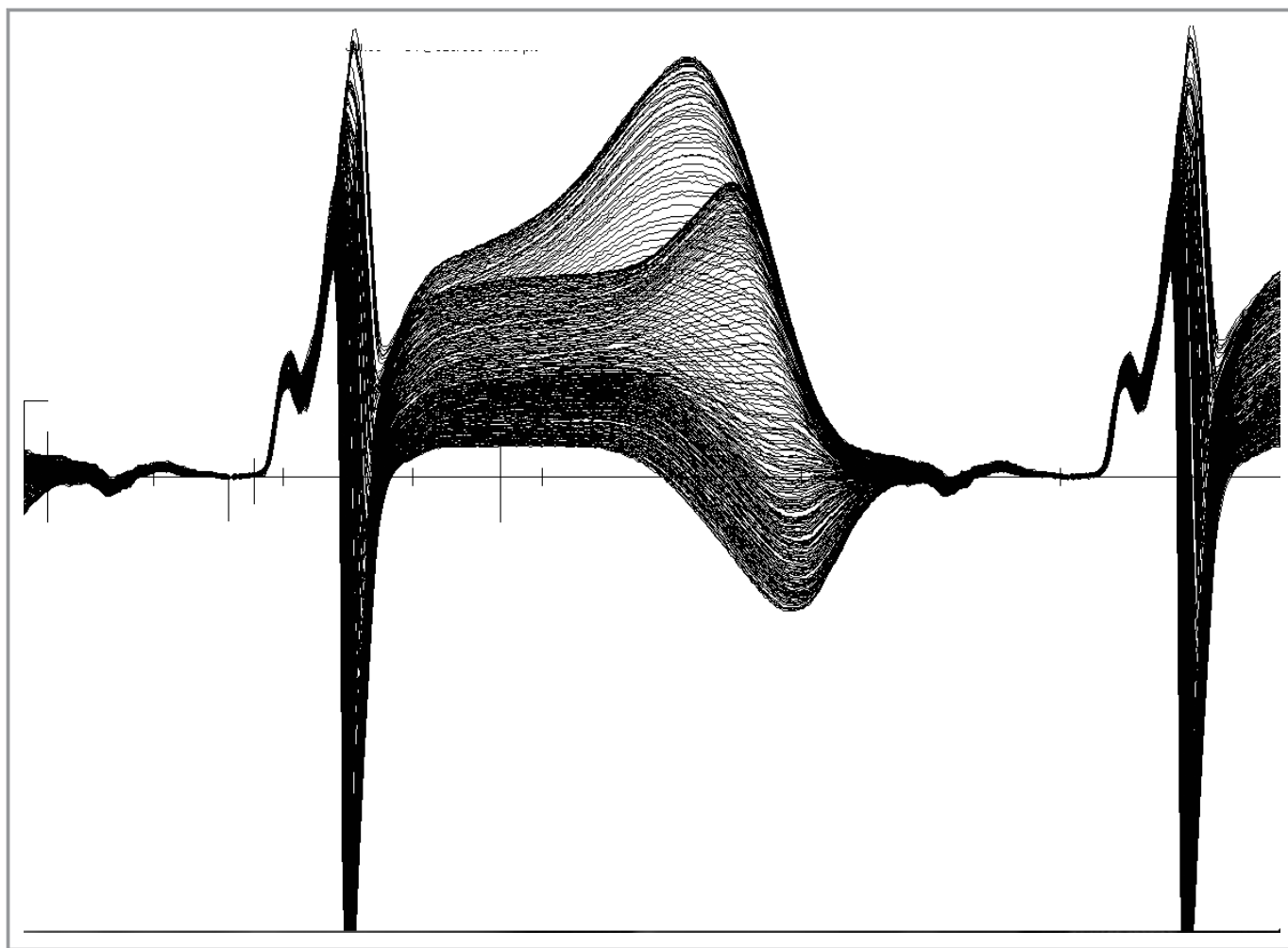
Figure 1. Two hundred and seventy-two consecutive, superimposed beats from a unipolar electrogram recorded from the basal LV epicardium during atrial pacing (cycle length=320 ms) immediately following occlusion of a major branch of the LAD in a canine model of ischemia. LV indicates left ventricle; LAD, left anterior descending coronary artery.

as well as repolarization changes. The point of these figures is that the changes during ischemia, regardless of how subtle, are regional and include the entire QRS, ST-T intervals. This underscores the importance of sampling more than a few leads and taking into account the entire QRST complex.

Ventricular Repolarization Dispersion (VRD)

The VRD metric presented in the Al-Zaiti article is based on Principal Component Analysis, a method closely related to factor analysis and Karhunen-Loeve data representation methods. These methods provide powerful, robust statistical methods of representing data of any number of variables or signals in a signal space of orthogonal (independent) dimensions derived directly from the data itself. Given N ECGs whether N P-QRS-T complexes from one lead, or N ECGs from different leads, one can calculate a set of

independent (orthogonal) and *normalized* waveforms (principal components) that characterize the data from which they were derived. Each waveform has a magnitude (Eigenvalue) associated with it that signifies the importance of that waveform in representing the data set. Eigenvalues are ordered by magnitude and for data that are rich in variability ("nonuniform," "complex," etc), and Eigenvalue magnitudes decrease gradually with number. On the other hand, if there is significant redundancy in the data (eg, the waveforms are very similar), then only the first few Eigenvalues and associated principal components are significant.

The VRD metric is, in fact, identical to the *complexity ratio* published by Priori et al [2] and is defined as the ratio of the second to first Eigenvalue calculated from the Principal Component Analysis representation of each beat (QRS-ST-T). The acronym "VRD" is somewhat misleading given that the index, as defined, includes information in QRS as well as ST-T. In a normal ECG, there is considerable redundancy in the 12
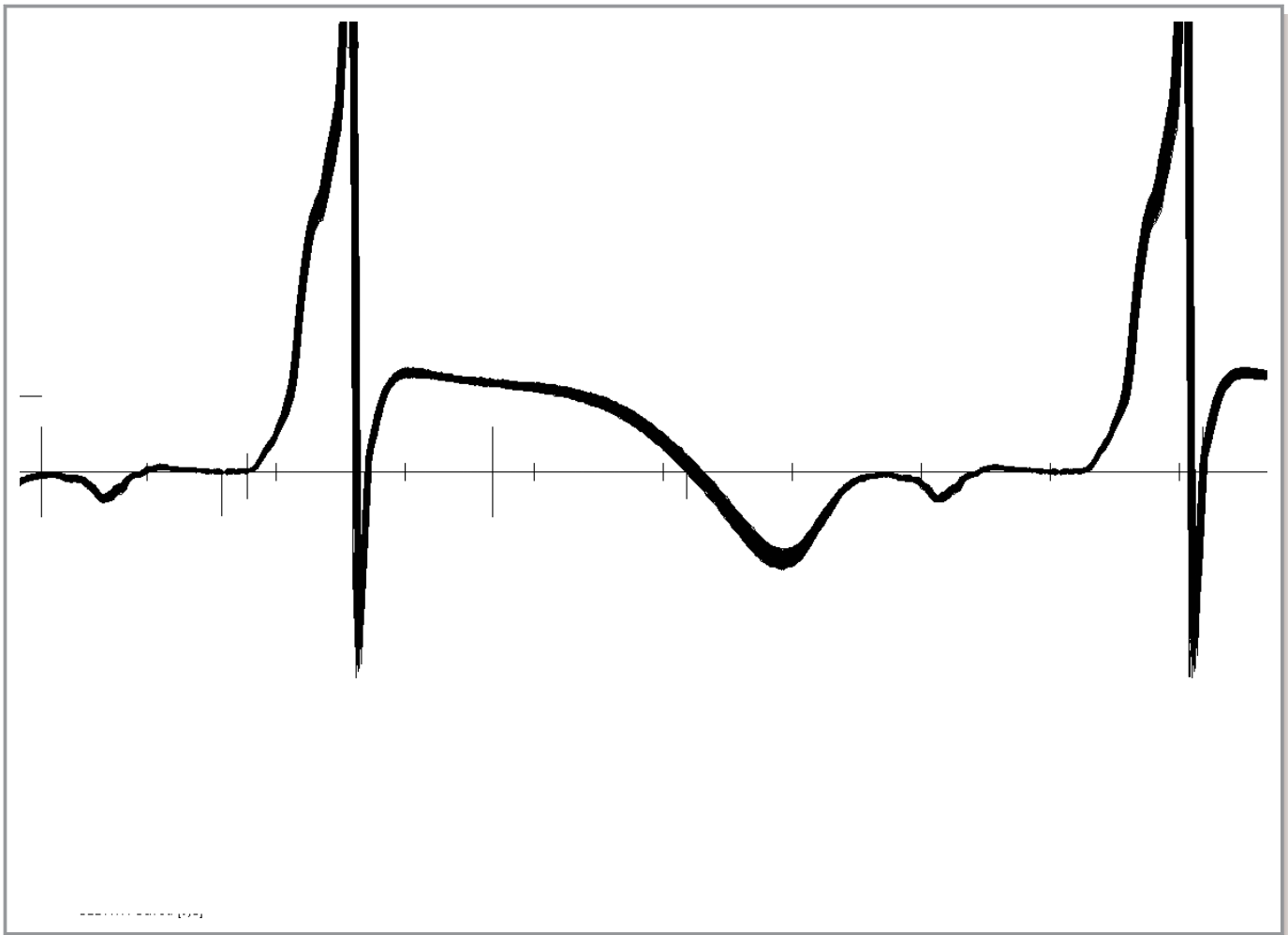
Figure 2. Superposition of the same sequence of 272 consecutive beats shown in Figure 1 but from a unipolar electrogram positioned 3 cm distant from that in Figure 1 and close to the LV apex. LV indicate left ventricle.

waveforms, and this results in a low complexity ratio, where the first component carries a much higher information content than the second, leading to a small ratio. In the presence of acute ischemia, regional differences in action potential amplitudes and morphologies produce varying degrees of change across all 12 leads, but particularly in those leads that are most sensitive to the location of the ischemia. This leads to an increase in the complexity ratio as the second Eigenvalue will be slightly less in magnitude than the first. Thus, the magnitude and dynamics of this index over time are exquisitely sensitive to changes in amplitude and morphology changes of the QRST, no matter how subtle or in whichever leads.

Interestingly, Principal Component Analysis and related methods have been used to represent ECGs, body surface potential maps, and QRST integral (ie, *area*) as means to diagnose heart disease and assess arrhythmia vulnerability. Horan et al used factor analysis to statistically character-ize the QRS of the ECG.[3] Urie et al applied principal component analysis to QRST integral maps—related to Wilson's *ventricular gradient*[4]—to investigate its utility in identifying patients at risk of ventricular arrhythmia.[5] Lux et al[6] and Evans et al[7] used the Karhunen-Loeve expansion to statistically represent the spatial and temporal informa-tion in body surface potential maps and showed the extent of redundancy in lead systems as well as ECG wave-forms and body surface potential distributions. In each of these examples, the recorded electrocardiographic information—both waveforms and spatial potential distribu-tions—were reduced to independent variables that allowed for substantial data reduction and simplification of statis-tical analysis.

Significance of the Method

The importance of this study is that it shows a signifi-cantly higher rate of detecting NSTEMI than the classical

ST-elevation measurement in chest-pain patients with ischemia-related symptoms. This significantly reduces the time to treatment compared to the "wait and watch" approach necessitated by the time required to obtain serum enzyme results. Moreover, in addition to improved rapid detection of NSTEMI, the method shows promise in identifying NSTEMI patients at high risk for in-hospital major adverse cardiac events. The simplicity and ease with which the complexity ratio can be calculated for each beat over extended time periods provides valuable information on the time course and dynamics of ischemia that better support the diagnosis of NSTEMI than can be provided by hours of tracking the near-normal ST segments over standard 10-s ECG snapshots. The fact that the technology required to calculate the metric—both hardware and software—is already commercially available (Mortara Instruments, Inc, Milwaukee, WI) points to the potential ease of including this type of analysis in conventional ECG carts or Holter monitoring systems used in Emergency Departments.

In conclusion, the VRD metric provides a timely, powerful, and robust tool for early detection of NSTEMI in chest-pain patients and, if adopted, is likely to have a significant impact on reducing time to treatment and hence morbidity and mortality. Adoption of this diagnostic tool addresses a present need in a significant patient population.

Disclosures

The author has nothing to disclose.

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