Ventricular Repolarization, T-Wave Genesis, and Risk Prediction

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The process of ventricular repolarization and its implications for arrhythmias has attracted much interest during the last decade. As a result, interest in using the body surface electrocardiogram (ECG) to extract relevant information about ventricular repolarization by noninvasive means has also increased. While there are many recent developments about the genesis and clinical applications of the T wave that deserve to be emphasized, this editorial cannot cover all of them, and thus will be biased by focussing on two issues: (1) the probable mechanism of the T-wave inscription in the surface ECG; (2) the arrhythmogenic potential of ventricular repolarization as extractable from noninvasive T-wave analysis.

DISPERSION OF VENTRICULAR REPOLARIZATION AND T-WAVE GENESIS

For a T wave to occur in the body surface ECG, there need to be electromotive forces generated within the heart during the time of ventricular repolarization. This can occur only if there are voltage gradients within the ventricle during the time course of myocardial repolarization. Two main factors can account for this. The first is that repolarization may commence or end at different times within the various portions of both ventricles. This is referred to as *spatial* variability or dispersion of ventricular repolarization. The second aspect is that, even given simultaneous onset of repolarization, the time course of ventricular repolarization (slopes of phase 3 of the action potential) may vary among different myocardial sites. This is referred to as *temporal* or *voltage* variability

or dispersion of repolarization. Both types of gradients can coexist and probably do; they may be additive, subtractive, or neutral.

Spatial Dispersion of Ventricular Repolarization

The concept of spatial dispersion of repolarization has been inaugurated during the earliest days of electrocardiography and is maintained today. In 1936, Schuetz¹ recorded injury potentials from the apex and the base of frog ventricle and demonstrated that the repolarization at the base lasted longer than that at the apex. By electrically subtracting one from the other, a differential electrogram was obtained that showed some characteristics of the T wave. In 1976, Cohen et al.² recorded intracellular action potentials from myocardial cells isolated from the ventricular base and apex of sheep heart. It was shown that apical cells had shorter action potential durations than basal cells. A shortcoming of this study was that apical cells were isolated from the ventricular epicardium, while basal cells were isolated from the endocardium. Nonetheless, when the action potentials from the two populations were electrically differentiated, a late electrical phase mimicking a T wave was again produced.

These two studies are still quoted as the mechanistic basis for the T wave in the ECG, despite the fact that such deductions present an explanation for the myocardial surface electrogram (EG) rather than the ECG. (By definition, the ECG is a body surface reading of potential differences between limb and precordial electrodes, while the EG represents the potential difference between any two

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electrodes of which one or both is in direct contact with the epicardial or endocardial surface of the heart itself.) Recent literature on the genesis of abnormal T waves, especially with regard to the long QT syndrome, still interpret the ECG by calculating the difference between two or more endocardial, epicardial, or intramural action potential recordings, whereas such measurements can, at best, explain only the endocardial or epicardial EG. For instance, the lab of Antzelevitch³ uses different responses of cardiac cells (most notably M-cells) to changes in cycle length or pharmacological agents as a means to explain T-wave changes in the ECG; however, their model allows deductions to be made only for the myocardial surface EG and not the volume conducted ECG.

Intraventricular Dispersion of Repolarization

Franz et al.⁴ and Cowan et al.⁵ using monophasic action potential recordings showed that transmural gradients exist in the human heart. Both groups independently showed that LV recordings had longer APDs than RV recordings and that endocardial recordings had longer APDs than epicardial recordings. In addition, Franz et al.⁴ showed that sites with earlier activation generally had longer APDs than sites activated later. This inverse relationship between activation and repolarization is important for two reasons. First, it helps explain the concordance of the normal T wave as it reverses the up-down configuration of the action potential into an up-up (or down-down) configuration of the R-T-wave complexes. Second, the inverse relationship between activation and APD tends to minimize the dispersion of repolarization (which is the sum of activation time and APD at a given site). This electrophysiological phenomenon, which can only be appreciated by measuring activation and repolarization in the intact heart, serves to synchronize ventricular repolarization, a feature that protects against reentrant arrhythmias.

Transmural Dispersion of Repolarization

While it has been recognized that there are substantial differences in ventricular repolarization duration between the epicardium and endocardium,^{4,5} Antzelevitch's lab has emphasized during the last decade that there may also be a population of intramural cells (M-cells) that contribute to the dispersion of ventricular repolarization across the ventricular wall and to the genesis of the T wave.⁶

M-cells have longer APDs than endocardial or epicardial cells, most notable at slow heart rates or during administration of certain ion channel-blocking drugs.⁷ However, the magnitude of dispersion due to M-cells may be less when assessed in vivo and during physiological rates.⁸

Temporal Dispersion of Ventricular Repolarization

Temporal or *voltage* dispersion of ventricular repolarization as a mechanism of T-wave genesis requires that action potentials differ in their repolarization time course and, as such, produce repolarization gradients within the ventricle regardless of whether repolarization began or ended at the same time. Behrens et al.⁹ recorded simultaneously 10 monophasic action potentials from multiple sites of an isolated rabbit heart immersed in a fluid-filled tank. In addition to the different onset and offset times of MAPs, there was large variability in phase 3 slopes of the simultaneously recorded signals. The greatest difference in repolarization level between the multiple MAP recordings occurred during the mid-portion of phase 3, which coincided with the peak of the T wave in the simultaneously recorded volume-conducted ECG.⁹ Onset and offset times of MAPs played a minor role compared to the repolarization gradients due to different phase 3 slopes in explaining the T wave.

The *temporal* dispersion of ventricular repolarization has also been defined as alterations in action potential duration (APD) or configuration from one beat to the next. Usually referred to as "electrical alternans," it can produce T-wave alternans if APD alternans occurs nonuniformly in space. Thus, T-wave alternans is also akin to *spatial* dispersion. To distinguish between these two forms of temporal dispersion of ventricular repolarization, the former may also be defined as "voltage dispersion" of action potentials during a single beat while the latter may be referred to as "beat-to-beat dispersion."

CARDIAC "MEMORY"

The early studies by Schuetz¹ and by Cohen et al.² assumed that repolarization is a fixed property of individual cardiac cells. It was subsequently discovered that APD is *not* a genetically ingrained feature but is molded by alterations in the ventric-

ular activation sequence. This electrophysiological plasticity of repolarization, also known as "cardiac memory," was suggested by Rosenbaum et al.¹⁰ from careful inspection of ECG records in patients with ventricular pacemakers. The authors observed that ectopic ventricular activation by continuous pacemaker stimuli not only altered the T wave *during* pacing (known as secondary T-wave changes) but also resulted in long-lasting T-wave changes *after* pacing and resumption of normal sinus rhythm. They noted that the "postpacing" T waves had a polarity similar to that of the R wave during pacing and suggested that the heart had "memorized" the previous change in activation sequence. They further implied that the T-wave vector had reconfigured itself to once again match the direction of the R-wave vector, resulting in a concordant R-T-wave direction. Costard-Jaeckle et al.¹¹ subsequently demonstrated at the myocardial tissue level that ventricular APD indeed is influenced by the sequence of ventricular depolarization. A normal activation sequence (as produced during atrial activation with normal AV conduction) resulted in APDs that were longer at sites of early activation and shorter at sites of late activation. This inverse gradient supports the postulate underlying the concordant T wave. The discovery that cardiac memory exists at the myocardial tissue level¹¹ inspired the lab of Rosen to further explore the molecular and ion channel basis of this phenomenon.¹²

The plasticity ("memory") of ventricular action potential durations (dependence on ventricular activation sequence or local timing of activation) challenges the traditional dichotomy between primary and secondary T-wave changes.¹³ Primary T-wave changes are defined as those that result from changes in the duration, wave shape, or amplitude of ventricular action potentials. Such changes, especially when nonuniform within the ventricles (i.e., regional ischemia), will lead to changes in the ST-segment, T-wave configuration, and T-wave duration. Secondary T-wave changes are defined as changes caused not by changes in ventricular action potentials but by changes in the ventricular activation sequence. Ectopic ventricular beats or left bundle branch block are prominent examples of how a change in activation sequence can dramatically alter the configuration of the T wave, without any underlying myocardial disease or electrolyte change that would directly affect the myocardial action potential.

T-WAVE CHARACTERISTICS, DISPERSION OF VENTRICULAR REPOLARIZATION, AND MORTALITY

It has long been a goal to identify a noninvasive marker for cardiac mortality based on the analysis of the surface ECG. Signal-averaged ECG analysis, heart rate variability data, T-wave alternans evaluations, and so forth have been championed but are of minor predictive value or cumbersome to perform and require special equipment. During the last decade, QT dispersion has been heralded as a predictor of ventricular arrhythmias and sudden death.¹⁴ QT dispersion (QTD) is defined as the time difference between the longest and shortest QT interval in the 12-lead body surface ECG. While initial studies were very optimistic,^{15,16} later studies using prospective, blinded, and computer-assisted analysis of QTD failed to show predictive power of QTD for cardiac death.¹⁷ The failure of QTD as a reliable prognosticator may be due to several factors. First, differences in interlead QT duration are likely to be influenced by projection variables of the repolarization vector.¹⁸ Second, manual measurement of the QT interval is error-prone, especially when T-wave abnormalities are present as is often the case in a hospital population. This may lead to greater errors in QT interval measurements ("noise") and hence to larger QTD values. Also, QTD measurements ignore the T wave proper, as by definition QTD measures only the difference between the end of T waves in different leads. Information contained within the repolarization process itself therefore will go undetected.

Recently, new T-wave analysis algorithms have been developed and tested for the ability to predict cardiac mortality. These new algorithms extract information on the T-wave vector and complexity of a single beat of the 12-lead standard ECG.¹⁹ Two T-wave variables stood out for their ability to predict sudden cardiac death, and in a multivariate analysis were independent of ejection fraction. These were the total cosine R-to-T (TCRT; describes the global angle between repolarization and depolarization wavefront) and T-wave loop dispersion.²⁰ While these new algorithms have not yet been validated to reflect dispersion of ventricular repolarization or refractoriness, the clinical test results of these new T-wave indices appear most promising. In 261 postinfarction patients moni-

tored over a 3-year period, 27 prospectively defined events were univariately associated with these two indices ($P = 0.0002$).²⁰

There are grounds to reconsider the body surface ECG and specifically the T wave as an important tool to understand the ventricular repolarization process, and in particular, to risk-stratify cardiac mortality using modern, computer-based algorithms based on theoretical and experimental evidence. The T wave is the result of repolarization incongruences within the ventricle and, given proper methodology, its mystery and prognostic value may finally be revealed.

REFERENCES

- Schuetz E. Elektrophysiologie des Herzens bei einphasischer Ableitung. *Ergebn Physiol Exper Pharmacol* 1936;38:493-620.
- Cohen I, Giles W, Noble D. Cellular basis for the T wave of the electrocardiogram. *Nature* 1976;262:657-661.
- Weissenburger J, Nesterenko VV, Antzelevitch C. Transmural heterogeneity of ventricular repolarization under baseline and long QT conditions in the canine heart in vivo: Torsades de pointes develops with halothane but not pentobarbital anesthesia. *J Cardiovasc Electrophysiol* 2000;11:290-304.
- Franz MR, Bargheer K, Rafflenbeul W, et al. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. *Circulation* 1987;75:379-386.
- Cowan JC, Hilton CJ, Griffiths CJ, et al. Sequence of epicardial repolarisation and configuration of the T wave. *Br Heart J* 1988;60:424-433.
- Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. *The M cell. Circ Res* 1991;68:1729-1741.
- Liu DW, Gintant GA, Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ Res* 1993;72:671-687.
- Anyukhovskiy EP, Sosunov EA, Feinmark SJ, et al. Effects of quinidine on repolarization in canine epicardium, midmyocardium, and endocardium: II. In vivo study. *Circulation* 1997;96:4019-4026.
- Behrens S, Li C, Knollmann BC, Franz MR. Dispersion of ventricular repolarization in the voltage domain. *PACE* 1998;21:100-107.
- Rosenbaum MB, Blanco HH, Elizari MV, et al. Electrotonic modulation of the T wave and cardiac memory. *Am J Cardiol* 1982;50:213-222.
- Costard-Jackle A, Goetsch B, Antz M, et al. Slow and long-lasting modulation of myocardial repolarization produced by ectopic activation in isolated rabbit hearts. Evidence for cardiac "memory." *Circulation* 1989;80:1412-1420.
- Rosen MR, Cohen IS, Danilo P, Jr., et al. The heart remembers. *Cardiovasc Res* 1998;40:469-482.
- Surawicz B. Transient T wave abnormalities after cessation of ventricular preexcitation: Memory of what? *J Cardiovasc Electrophysiol* 1996;7:51-59.
- Day CP, McComb JM, Matthews J, et al. Reduction in QT dispersion by sotalol following myocardial infarction. *Eur Heart J* 1991;12:423-427.
- Glancy JM, Garratt CJ, Woods KL, et al. QT dispersion and mortality after myocardial infarction. *Lancet* 1995;345:945-948.
- Cui G, Sen L, Sager P, et al. Effects of amiodarone, sotalol, and sotalol on QT dispersion. *Am J Cardiol* 1994;74:896-900.
- Zabel M, Klingenhoben T, Franz MR, et al. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: results of a prospective, long-term follow-up study. *Circulation* 1998;97:2543-2550.
- Malik M, Acar B, Gang Y, et al. QT dispersion does not represent electrocardiographic interlead heterogeneity of ventricular repolarization. *J Cardiovasc Electrophysiol* 2000;11:835-843.
- Acar B, Yi G, Hnatkova K, et al. Spatial, temporal and wavefront direction characteristics of 12-lead T-wave morphology. *Med Biol Eng Comput* 1999;37:574-584.
- Zabel M, Acar B, Klingenhoben T, et al. Analysis of 12-lead T-wave morphology for risk stratification after myocardial infarction. *Circulation* 2000;102:1252-1257.