

**Reply**

Barbara J. Drew

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## Macroscopic T-Wave Alternans

### The Tip of the Iceberg in Drug-Induced Torsade de Pointes?

We read with keen interest the excellent scientific statement on the prevention of torsade de pointes in hospital settings (1). The authors underscore the importance of averting potentially catastrophic events due to torsade de pointes resulting from excessive drug-induced QT-interval prolongation. They also indicate that while this event is generally rare, its occurrence is more prevalent among hospitalized patients who have other risk factors for arrhythmia, including underlying cardiac disease, renal or hepatic dysfunction, and electrolyte abnormalities.

Whereas the consensus statement focuses on QT-interval prolongation as a precursor of torsade de pointes, the authors draw attention in Figure 2 to a nefarious fellow traveler, specifically, macroscopic T-wave alternans (TWA). Many agents, such as amiodarone, almokalant, arsenic trioxide, and pentamidine, which induce QT-interval prolongation, may also provoke TWA and torsade de pointes (2). It is relevant that underlying cellular and ionic mechanisms are common to the triad of QT-interval prolongation, torsade de pointes, and TWA, namely, transmural dispersion of repolarization and excess intracellular calcium.

Because TWA reflects a continuum of electrical instability linked to arrhythmia risk (3,4), the presence of macroscopic TWA may, in fact, represent the tip of the iceberg of risk associated with proarrhythmic agents. In subjects during daily activity (5) as well as in hospitalized patients (6), a crescendo in TWA magnitude from nonvisible to visible levels consistently occurs before the onset of life-threatening ventricular tachyarrhythmias. Quantification of TWA magnitude in ambulatory patients may allow even earlier warning of impending arrhythmia on the basis of more subtle, microvolt levels of TWA. Prompt detection is critical because TWA is not only a marker but also a trigger of arrhythmia risk, as it enhances repolarization heterogeneity, facilitating unidirectional block and re-entry. Thus, the potential utility of quantitative TWA in hospitalized patients deserves systematic study.

In the future, real-time, continuous in-hospital monitoring of subtle, microvolt levels of TWA could complement existing electrocardiography-based indicators for early warning of impending arrhythmia to avert occurrence of drug-induced torsade de pointes.

\*Richard L. Verrier, PhD  
Tuomo Nieminen, MD, PhD

\*Harvard Medical School  
Beth Israel Deaconess Medical Center  
Harvard-Thorndike Electrophysiology Institute  
99 Brookline Avenue, RN-301  
Boston, Massachusetts 02215  
E-mail: rverrier@bidmc.harvard.edu

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#### Reply

We applaud efforts by Drs. Verrier and Nieminen to develop novel technologies to detect risk for torsade de pointes (TdP) in hospital settings. We agree that macroscopic T-wave alternans observed with continuous electrocardiographic (ECG) monitoring after administration of QT-prolonging drugs is an important sign of impending TdP. However, it is not the only ECG sign to look for, and it is not always present before the onset of TdP. Therefore, we emphasized the importance of looking for all the ECG signs of impending TdP in our summary of key points (Table 3 of our paper [1]). We stated: following initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include an increase in QTc interval from pre-drug baseline of 60 ms, marked QTc interval prolongation >500 ms, T-U wave distortion that becomes more exaggerated in the beat after a pause, visible (macroscopic) T-wave alternans, new onset ventricular ectopy, couplets and nonsustained polymorphic ventricular tachycardia initiated in the beat after a pause.

Because TdP is rare and the ECG signs are subtle and not well-understood by monitor watchers, it would be valuable to have better computer algorithms built into hospital cardiac monitors to warn for impending TdP. However, these algorithms should be tested to determine their sensitivity and specificity for detecting TdP. Prospective clinical trials would require large sample sizes to provide enough episodes of TdP for such algorithm testing. A less expensive and immediately available research strategy would be to use existing ECG databases. For example, the Telemetric and Holter ECG Warehouse (THEW) Center for Quantitative Electrocardiography and Cardiac Safety at the University of Rochester Medical Center hosts a database of TdP cases (continuous Holter ECGs with long QT syndrome and drug-induced TdPs) that scientists can access to validate ECG monitoring algorithms.

Computer algorithms in hospital cardiac monitors that warn of impending TdP might provide time to discontinue the offending drug, administer intravenous magnesium, replace potassium (if

necessary), intensify monitoring, and take measures that would shorten response time if sustained ventricular arrhythmias develop.

E-mail: [barbara.drew@nursing.ucsf.edu](mailto:barbara.drew@nursing.ucsf.edu).

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**\*Barbara J. Drew**

\*University of California, San Francisco  
2 Koret Way  
#N-631H  
San Francisco, California 94143-0610

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