EDITORIAL COMMENTARY

Implantable cardioverter-defibrillator detection of repolarization alternans: Uncovering a marker of electrical instability

David J. Christini, PhD, Bruce B. Lerman, MD

From the Department of Medicine, Division of Cardiology, Weill Medical College of Cornell University, New York, New York.

Repolarization alternans, which manifests on the surface ECG as T-wave alternans (TWA), is a beat-to-beat alternation in ventricular repolarization. In the 1980s, a close correlation was found to exist between TWA and vulnerability to ventricular fibrillation in animals.[1–3] In the 1990s, with additional technical refinements, TWA on a microvolt scale was correlated with risk for recurrent clinical ventricular arrhythmias and sudden cardiac death.[4–11]

More recently, experimental and computational studies have shown that repolarization alternans can trigger cardiac reentry,[12–15] although whether this occurs clinically is not yet known. The mechanism for reentry initiation involves spatially discordant alternans, in which areas of long–short action potential duration (APD) alternation occur adjacent to areas of short–long APD alternation. Such discordance can produce steep spatial gradients of repolarization that provide the substrate for unidirectional functional block and reentry.[13,16–20]

Given the putative link between repolarization alternans and reentry initiation, it might be clinically beneficial for implantable cardioverter-defibrillators (ICDs) to monitor for the development of alternans. The possible benefits of such an approach include (1) enabling prediction of imminent arrhythmia onset, thereby enabling the ICD to intervene earlier and/or to alert the patient of an impending shock, and (2) enabling stimulation-based termination of alternans as a means of preventing reentry.[21–24]

A number of studies have investigated endocardial detection of repolarization alternans. Nearing et al[4] quantified repolarization alternans in dogs using a bipolar measurement between an electrode placed in the apex of the left ventricle through a carotid artery and a transcutaneous needle electrode in the hip. Other investigators demonstrated that APD alternans could be detected endocardially in humans using a monophasic action potential catheter.[25] Later, it was shown that short repolarization alternans sequences (four beats) on ICD electrograms (EGMs) were present prior to the onset of ventricular tachycardia in dogs with myocardial infarctions.[26] Pursuant to these findings, an ICD lead positioned in the right ventricular apex (i.e., in a clinically realistic position) can be used to detect alternans on a beat-to-beat basis.[27] In clinical electrophysiology studies, it was shown that a high concordance exists between repolarization alternans detected from unipolar endocardial signals acquired via an electrophysiology lead and TWA detected on the surface ECG.[28]

Nevertheless, none of these studies "closed the loop" on clinical implantable device detection of alternans. In this issue of *Heart Rhythm,* Paz et al[29] have done so by using ICDs in patients to assess the correlation between alternans detection via surface ECGs and ICD EGMs.

The authors analyzed ICD EGMs from 25 patients. For each study, the ICD was reprogrammed so that its signal processing maximized T-wave amplitude. EGMs were acquired during pacing from typical ICD–lead electrode combinations and used to generate composite power spectra averaged over the duration of the T wave.

The findings of the study are compelling. Most notably, a high degree of concordance was found between the detection of alternans on the ECG and EGM signals (84%), supporting the hypothesis that the signals are markers of the same phenomenon and demonstrating that ICD signals can detect alternans effectively. In addition, both ICD and surface signals were able to predict (in 6/7 cases) appropriate ICD therapy over 6-month follow-up. As expected, EGM alternans magnitude was significantly larger (>10×) than ECG alternans magnitude, which is attributable to a larger signal-to-noise ratio for the endocardial signals.[27] In particular, EGM alternans was highest for the largest, most widely spaced electrode configuration (right-ventricular [distal] coil electrode to ICD housing [can]), which is consistent with the hypothesis that alternans is a spatially extended phenomenon involving large regions of myocardium.

As the authors note, a number of significant issues remain to be addressed by future studies before such an approach can be useful clinically. First and foremost is the

This work was supported by National Science Foundation Grant PHY-0513389 to Dr. Christini; National Institutes of Health Grant R01RR020115 to Dr. Christini; the Kenny Gordon Foundation; the Maurice and Corinne Greenberg Arrhythmia Research Grant; the Raymond & Beverly Sackler Foundation; and the Michael Wolk Foundation.

Address reprint requests and correspondence: Dr. David J. Christini, Weill Medical College of Cornell University, Division of Cardiology, 520 East 70th Street, Starr-463, New York, New York 10021.

E-mail address: dchristi@med.cornell.edu.

1547-5271/$ -see front matter © 2006 Heart Rhythm Society. All rights reserved. doi:10.1016/j.hrthm.2006.04.001

determination of whether alternans really is a reentry trigger (as would be required for alternans termination strategies to be useful) or even is a marker of imminent reentry onset (which at least might enable quicker ICD therapy initiation or patient alerts). Although it has been shown experimentally that alternans can trigger reentry, whether this occurs clinically is not yet known. ICD-detected alternans was shown to precede tachyarrhythmia onset in a single case study,[30] but a full-scale study is needed. Second, in the present study, the dynamic range of each ICD was reprogrammed to increase T-wave amplification and thereby aid alternans detection. It will be necessary to investigate the impact of such rescaling on other ICD detection algorithms (e.g., tachyarrhythmia detection) and/or to develop alternans detection algorithms that work using standard ICD amplifier settings. Third, if such an approach were to be used for stimulation-based termination of alternans (as a means of preventing reentry),[21–24] then beat-to-beat detection of alternans,[27,28] rather than an aggregated power spectral approach such as that used in this study, would be required.

The need for additional studies notwithstanding, Paz et al[29] have significantly advanced the state of the art of ICD alternans detection. In so doing, they have demonstrated that it is technically feasible for ICDs to detect the emergence of alternans, thereby potentially enabling an ICD response upon alternans initiation.

References

1. Adam DR, Smith JM, Akselrod S, Nyberg S, Powell AO, Cohen RJ. Fluctuations in T-wave morphology and susceptibility to ventricular fibrillation. J Electrocardiol 1984;17:209–218.
2. Ritzenberg AL, Adam DR, Cohen RJ. Period multupling-evidence for nonlinear behaviour of the canine heart. Nature 1984;307:159–161.
3. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ. Electrical alternans and cardiac electrical instability. Circulation 1988;77:110–121.
4. Nearing BD, Huang AH, Verrier RL. Dynamic tracking of cardiac vulnerability by complex demodulation of the T wave. Science 1991;252:437–440.
5. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994;330:235–241.
6. Verrier RL, Nearing BD. Electrophysiologic basis for T wave alternans as an index of vulnerability to ventricular fibrillation. J Cardiovasc Electrophysiol 1994;5:445–461.
7. Hohnloser SH, Klingenheben T, Li YG, Zabel M, Peetermans J, Cohen RJ. T wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers. J Cardiovasc Electrophysiol 1998;9:1258–1268.
8. Klingenheben T, Cohen RJ, Peetermans J, Hohnloser SH. Predictive value of T wave alternans in patients with congestive heart failure. Circulation 1998;98:I-864.
9. Armoundas AA, Rosenbaum DS, Ruskin JN, Garan H, Cohen RJ. Prognostic significance of electrical alternans versus signal averaged electrocardiography in predicting the outcome of electrophysiological testing and arrhythmia-free survival. Heart 1998;80:251–256.
10. Armoundas AA, Osaka M, Mela T, Rosenbaum DS, Ruskin JN, Garan H, Cohen RJ. T-wave alternans and dispersion of the QT interval as risk stratification markers in patients susceptible to sustained ventricular arrhythmias. Am J Cardiol 1998;82:1127–1129.
11. Gold MR, Bloomfield DM, Anderson KP, El-Sherif NE, Wilber DJ, Groh WJ, Estes NA 3rd, Kaufman ES, Greenberg ML, Rosenbaum DS. A comparison of T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol 2000; 36:2247–2253.
12. Chinushi M, Restivo M, Caref EB, El-Sherif N. Electrophysiological basis of arrhythmogenicity of QT/T alternans in the long QT syndrome: tridimensional analysis of the kinetics of cardiac repolarization. Circ Res 1998;83:614–628.
13. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999; 99:1385–1394.
14. Shimizu W, Antzelevitch C. Cellular and ionic basis for T-wave alternans under long-QT conditions. Circulation 1999;99:1499–1507.
15. Pastore JM, Rosenbaum DS. Role of structural barriers in the mechanism of alternans-induced reentry. Circ Res 2000;87:1157–1163.
16. Tachibana H, Kubota I, Yamaki M, Watanabe T, Tomoike H. Discordant S-T alternans contributes to formation of reentry: a possible mechanism of reperfusion arrhythmia. Am J Physiol 1998;275:H116–H121.
17. Qu Z, Garfinkel A, Chen PS, Weiss JN. Mechanisms of discordant alternans and induction of reentry in simulated cardiac tissue. Circulation 2000;102:1664–1670.
18. Watanabe MA, Fenton FH, Evans SJ, Hastings HM, Karma A. Mechanisms for discordant alternans. J Cardiovasc Electrophysiol 2001;12:196–206.
19. Fox JJ, McHarg JL, Gilmour RF Jr. Ionic mechanism of electrical alternans. Am J Physiol 2002;282:H516–H530.
20. Fenton FH, Cherry EM, Hastings HM, Evans SJ. Multiple mechanisms of spiral wave break. Chaos 2002;12:852–892.
21. Christini DJ, Stein KM, Markowitz SM, Mittal S, Slotwiner DJ, Scheiner MA, Iwai S, Lerman BB. Nonlinear-dynamical arrhythmia control in humans. Proc Natl Acad Sci U S A 2001;98:5827–5832.
22. Hall GM, Gauthier DJ. Experimental control of cardiac muscle alternans. Phys Rev Lett 2002;88:198102.
23. Echebarria B, Karma A. Spatiotemporal control of cardiac alternans. Chaos 2002;12:923–930.
24. Christini DJ, Riccio ML, Culianu CA, Fox JJ, Karma A, Gilmour RF Jr. Control of electrical alternans in canine cardiac Purkinje fibers. Phys Rev Lett 2006;96: 104101-1–104101-4.
25. Narayan SM, Karasik PL, Smith JM. Alternans in ventricular monophasic action potentials precedes the induction of ventricular tachycardia. Pacing Clin Electrophysiol 2000;23(Pt II):738.
26. Tsai J, Cao JM, Zhou S, Swissa M, Cates AW, Kenknight BH, Chen LS, Karagueuzian HS, Chen PS. T wave alternans as a predictor of spontaneous ventricular tachycardia in a canine model of sudden cardiac death. J Cardiovasc Electrophysiol 2002;13:51–55.
27. Maybhate A, Hao SC, Iwai S, Lee JU, Guttigoli AB, Stein KM, Lerman BB, Christini DJ. Detection of repolarization alternans with an implantable cardioverter defibrillator lead in a porcine model. IEEE Trans Biomed Eng 2005;52: 1188–1194.
28. Christini DJ, Stein KM, Hao SC, Markowitz SM, Mittal S, Slotwiner DJ, Iwai S, Das MK, Lerman BB. Endocardial detection of repolarization alternans. IEEE Trans Biomed Eng 2003;50:855–862.
29. Paz O, Zhou X, Gillberg J, Tseng H-J, Gang ES, Swerdlow CD. Detection of T-wave alternans using an implantable cardioverter-defibrillator. Heart Rhythm 2006;3:791–797.
30. Armoundas AA, Albert CM, Cohen RJ, Mela T, TOVA Investigators. Utility of implantable cardioverter defibrillator electrograms to estimate repolarization alternans preceding a tachyarrhythmic event. J Cardiovasc Electrophysiol 2004; 15:594–597.