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STATE-OF-THE-ART PAPER

Pathophysiological Basis and Clinical Application of T-Wave Alternans

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We review the contemporary understanding of the pathophysiology of repolarization alternans and present a perspective on the use of T-wave alternans (TWA) as a risk stratification marker of malignant ventricular arrhythmias. Several studies have demonstrated a high correlation of susceptibility to ventricular arrhythmias and sudden cardiac death with the existence of TWA. We describe a number of cellular and molecular alterations in the diseased heart that may provide a link between electrical and mechanical alternans and arrhythmia susceptibility. Repolarization alternans is likely the result of distinct and diverse cellular and molecular alterations that are associated with exaggerated regional repolarization heterogeneity, which renders the heart susceptible to malignant arrhythmias. (J Am Coll Cardiol 2002;40:207–17) © 2002 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) remains a major challenge in developed countries; it accounts for 11% of all deaths and approximately 50% of all cardiovascular deaths (1). In the U.S. alone, nearly 300,000 patients (1 to 2 per 1,000 population) experience SCD (2). The vast majority of these cases are due to ventricular tachycardia (VT) or ventricular fibrillation (VF). Over the past two decades, tremendous progress has been made in the development of therapeutic modalities, such as the implantable cardioverter-defibrillator (ICD); however, similar progress in identifying patients at high risk has lagged behind. Large multicenter studies, such as the Multicenter Automatic Defibrillator Implantation Trial and the Multicenter Unsustained Tachycardia Trial (MUSTT), suggested that electrophysiologic (EPS) testing may be useful in identifying patients who would benefit from ICD therapy (3,4). The MUSTT suggested that EPS testing alone was not sensitive enough to identify broader groups of patients at risk for SCD (4). Moreover, noninvasive markers of risk-stratification, such as left ventricular ejection fraction (LVEF), frequent ventricular premature complexes and ventricular late potentials (LP), though sensitive, suffer from low specificity and positive predictive value (5,6). Determination of heart rate variability (HRV), especially in combination with LVEF, ventricular premature complexes and LP, has significantly improved risk prediction, but its positive predictive accuracy remains low (6).

The preceding discussion underscores the need for a screening procedure that is more sensitive and specific, with a higher predictive power for identifying patients at high risk of developing VT/VF. Recently, assessment of repolarization alternans (T-wave alternans [TWA]) in the electrocardiogram (ECG) has been suggested as a predictor of susceptibility to malignant ventricular arrhythmias (7–9). The TWA is characterized by changes in contour, amplitude or polarity of the T-wave, appearing with regular rhythmicity, usually every other beat, unaccompanied by gross changes in the cycle length.

This review discusses what is known about the cellular basis of cardiac (electrical and mechanical) alternans and the clinical relevance of repolarization alternans, with special reference to its prognostic efficacy in predicting arrhythmia susceptibility.

HISTORY OF CARDIAC ALTERNANS

Cardiac alternans has been divided into two general categories: electrical and mechanical; *electrical alternans* arises from a fundamental change in the electrical conduction pattern of the myocardium, and *mechanical alternans* arises from an alternation of the mechanical activity of the heart. Electrical alternans is a pattern of variation in the shape of ECG waveform that appears on an every-other-beat basis (10–21). Electrocardiographic alternans was first described in 1908 by Hering (10). Shortly thereafter, Thomas Lewis (11) recognized that cardiac alternans could occur in normal hearts as a result of marked acceleration of heart rate and also in the impaired or intoxicated myocardium. In 1948, Kalter and Schwartz (12) reviewed clinical ECGs from 6,059 patients and found five cases of macroscopically visible TWA, a frequency of 0.08%. Probably because of the very low incidence of visible TWA, it remained nothing more than an ECG curiosity for many decades.

In humans, visible (macroscopic) alternation in ventricular repolarization has been associated with increased vulnerability to ventricular arrhythmias under diverse pathophysiologic conditions (both experimental and clinical) such as

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