

The many faces of repolarization instability: which one is prognostic?

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Abstract

Instabilities of the STT segment's magnitude, and particularly the 0.5 beat/cycle oscillations (T-wave alternans, or TWA), have been linked to the heightened risk of ventricular tachyarrhythmias (VTA) and sudden cardiac death (SCD). During the last decade theoretical, experimental and clinical research efforts have focused primarily on TWA, examining its mechanisms and predictive value using time-invariant cutoff values. However, recent evidence suggests that such a single-snapshot test of a single-frequency (TWA) oscillation using a constant cutoff value might be suboptimal for risk stratification because of several reasons.

First, it is well known that the risk of VTA/SCD evolves over time with changes in electrophysiologic substrate, environmental and physiologic triggers, and the impact of other physiologic (eg, circadian) rhythmicity. Hence, the outcome of TWA testing might depend on the time of day, as Holter-based TWA studies have demonstrated. Furthermore, currently used single-snapshot testing with a binary cutoff value may not coincide with the periods of heightened risk for VTA/SCD and may not yield prognostic information, as a recent TWA substudy of the sudden cardiac death in heart failure trial has showed. Second, the analysis focused on TWA alone ignores the existence of multiple (alternating and nonalternating) forms of repolarization instability that have been shown to arise or increase before the onset of VTA/SCD.

Summarizing, recent studies have identified multiple forms of repolarization instabilities modulated by distinct mechanisms, which might have different prognostic values. Therefore, the assessment of TWA needs to be dynamic and personalized to take into account the time evolution of risk and individual history.

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Introduction

Beat-to-beat alterations of the electrocardiographic repolarization segment have long been recognized as a marker of increased risk for ventricular tachyarrhythmias and sudden cardiac death (SCD).¹ During the last decade, remarkable progress has been made in this knowledge area. A number of theoretical, experimental, and clinical studies have provided a wealth of evidence linking the 0.5 cycle/beat oscillations in the amplitude of the STT segment, referred to as the T-wave alternans (TWA), to the heightened risk of ventricular tachyarrhythmia (VTA).^{2,3} Moreover, the repolarization instability has been shown to have a direct pathophysiologic

connection with the initiation of arrhythmias.⁴ As a result of these multidisciplinary research efforts, T-wave alternans testing has become a clinical tool for arrhythmia risk stratification.⁵ Recently, an increase in T-wave alternans has been reported preceding the imminent onset of VTA in several animal models⁶ and clinical studies conducted in patients with structural heart disease, suggesting that the utility of TWA might be further extended to serve as a short-term predictor of these life-threatening events.^{7,8}

However, recent evidence suggests that currently used single-snapshot testing of a single-frequency (0.5 cycle/beat) oscillation using a one-size-fits-all cutoff value might be suboptimal for risk stratification because of several reasons. First, the underlying assumption that both T-wave alternans and the risk of arrhythmias do not change over time is oversimplified.^{9,10} T-wave alternans has been shown to exhibit circadian changes, peaking in the morning and

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declining at night.¹¹ Thus, the outcome of TWA testing is likely to be different if the testing is done at different times of day. Furthermore, the risk of arrhythmias and sudden death also evolves over longer time scales as well, following the changes in the underlying electrophysiologic substrate. In particular, a recent sudden cardiac death in heart failure trial has failed to show that T-wave alternans predicts arrhythmic events or mortality in patients with heart failure ($n = 490$, ischemic heart disease in 49% of subjects, left ventricular ejection fraction of 25%) but showed that its prognostic significance gradually evolves over 15- to 30-month time scale with the progression of changes in the underlying heart disease.^{9,10} This provides further support for the notion that currently used single-snapshot testing may not coincide with the periods of heightened risk for VTA/SCD and may not yield prognostic information. In addition, the analysis focused on TWA alone ignores the existence of multiple forms of repolarization instability that have been shown to arise or increase before the onset of VTA/SCD both in patients with cardiomyopathy⁷ and those with long-QT syndrome.¹² Analysis of such instabilities may provide complementary information that may help to improve the risk assessment with respect to arrhythmias and sudden death.

To clarify the predictive value of T-wave alternans and other forms of repolarization instability, one needs to determine the physiologic covariates and their respective weights, modulating the relationship between the instability and arrhythmogenesis (Fig. 1).

The restitution covariate

The restitution curve, that is, the relationship between the cardiac electrical action-potential duration (APD) and a preceding diastolic interval (DI), has been introduced by Nolasco and Dahlen.¹³ In their seminal study conducted in the frog ventricular muscle strips more than 40 years ago, the researchers noticed striking similarities between the cardiac APD/DI relationship and a simple electronic amplifier with a

negative feedback. In such an electronic system, if G is a gain function, I is an input, F is a fraction of an output O , and X is an independent signal, then the output is $O = G(I)$ and $I = X - F(O)$. Similarly, the transfer functions for the cardiac tissue paced at the cycle length (CL) can be expressed as: $APD_1 = f(DI_0)$ and $DI_1 = f(APD_1) = CL_1 - APD_1$.¹³

Assuming that an APD depends only on the preceding DI (a “no-memory” assumption), the relationship between the 2 variables can be expressed by a nonlinear curve resembling a logarithmic function. If the pacing CL is kept constant, then $d(DI_1)/d(APD_1) = -1$, and a simple 1-dimensional, iterative map, referred to as the cobweb, can be used to examine this nonlinear system’s dynamics. It is not difficult to show that the slope of the curve defining the relationship between APD and DI determines the stability of this dynamical system.¹³ In particular, if the slope is between 0 and 1, the system is stable, and a small perturbation δ would produce damped oscillations (transients) that will return to the equilibrium (steady state). In contrast, if the slope is more than 1, a small perturbation would lead to an ever-growing oscillation (underdamping). And if the slope of the APD curve is exactly equal to 1, then the system is bistable, producing sustained, period-2 oscillations (ie, alternans).^{13,14}

This method provides an intuitive tool for tracking the nonlinear dynamics of the cardiac electrical activity at the expense of several important simplifications. First, it assumes that an APD depends only on a single DI, which is not realistic for cardiac myocytes. It has been shown by several investigators that an APD strongly depends on a much longer (at least 60 seconds) history of CL, which can be better approximated by 1 or 2 exponential functions.^{15,16} Second, the simplified, restitution-only approach also ignores the inverse relationship between conduction velocity and CL, which plays a crucial role in cardiac physiology and may become compromised in heart failure.^{17,18} Finally, this method disregards the impact of Ca^{2+} handling and several other important covariates (discussed later in this article), and as expected, several recent studies have showed that this

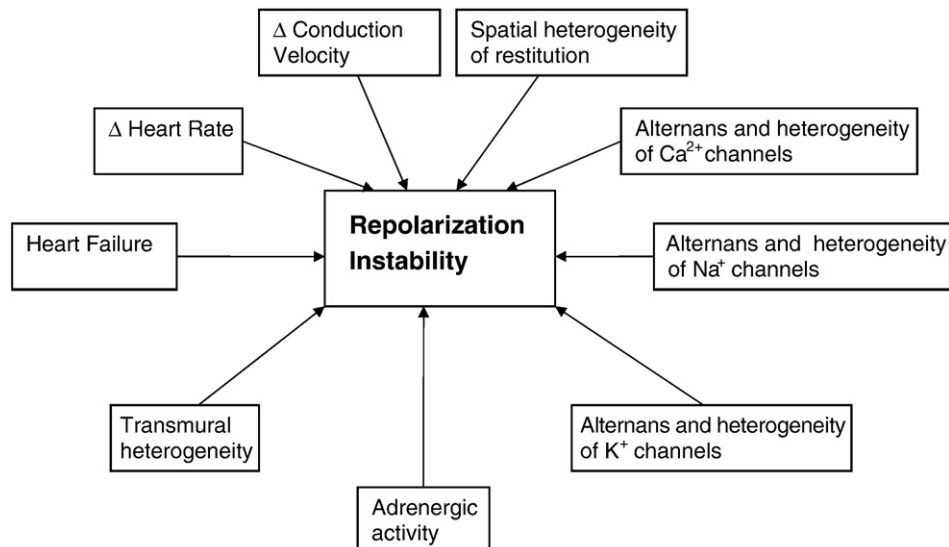


Fig. 1. Factors affecting repolarization instability.

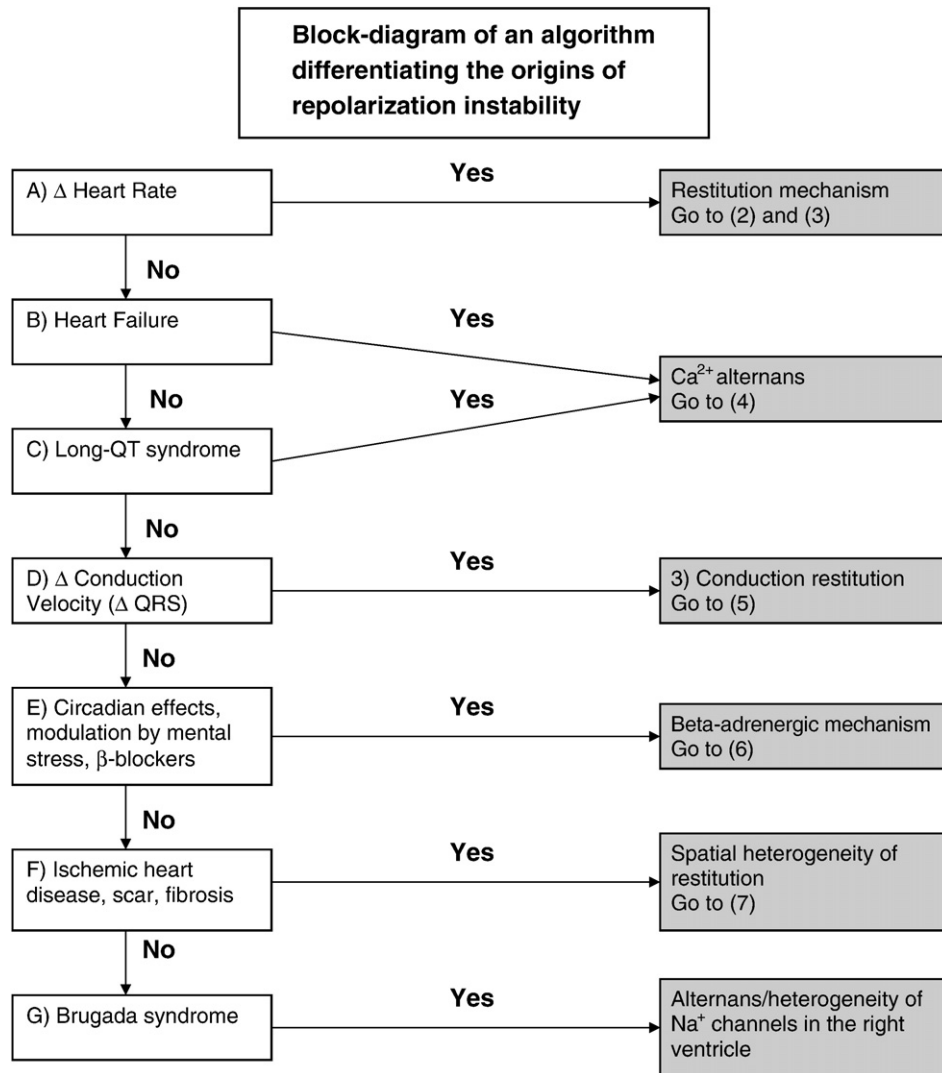


Fig. 2. Block diagram of an algorithm differentiating the origins of repolarization instability.

theoretical construct, taken alone, fails to predict T-wave alternans or arrhythmias in clinical settings.¹⁹ Nevertheless, the restitution-based approach has proved useful in several settings, where fast pacing protocols could be used to achieve a relatively short CL (Fig. 2, A), while all other covariates are kept constant.^{13,20,21}

A recent analysis of the spatial distribution of the restitution curves in different regions of the human heart has showed a wide spectrum of results.²² This spatial heterogeneity suggests that the analysis needs to be extended from a single restitution curve to the entire spatial distribution of the curves in different regions of the heart. Furthermore, the restitution-based approach can also be extended from a “memoryless” APD, which depends on a single DI, to an APD, which has “memory” of a longer history of cardiac beats.²³ Yet, the recently proposed theoretical constructs incorporating such a memory still could not provide an accurate approximation of the real-life dynamical behavior of the cardiac electrophysiologic parameters.²³ This implicitly suggests the importance of other physiologic covariates that remain unaccounted for by the restitution-only based approach.

The calcium covariate

The Ca^{2+} -related mechanisms play a pivotal role in the excitation-contraction coupling, and L-type Ca^{2+} channels also determine a key ionic current that is active during the plateau phase of cardiac repolarization. In the course of the development of heart failure, calcium handling becomes compromised, including decreased peak systolic Ca^{2+} , elevated diastolic Ca^{2+} , and prolongation of the Ca^{2+} transient.¹⁸ In humans with heart failure, these changes are associated with the decreased expression of the sarco(endo)plasmic reticulum Ca^{2+} -ATPase, decreases in phospholamban, and increased expression of the Na/Ca exchanger.²⁴ The resulting prolongation of the Ca^{2+} transient and intracellular Ca^{2+} overload can lead to premature Ca^{2+} release from the sarcoplasmic reticulum and delayed afterdepolarizations.¹⁸ As a result, the Ca^{2+} alternans can often emerge at near-normal heart rates, giving rise to APD-alternans and T-wave alternans (Fig. 2, B). In particular, our group has demonstrated pronounced alternans (alternation of up to 40% of the peak amplitude of the Ca^{2+} transient) in a tumor necrosis factor α (TNF- α) genetic mouse model of

heart failure, using optical mapping of Ca^{2+} in isolated, Langendorff-perfused hearts.¹⁸ In this model, the Ca^{2+} alternans was found at relatively long pacing CLs. Furthermore, changes in the Ca^{2+} concentration affected arrhythmia inducibility in this genetic mouse model, confirming the essential role of abnormal calcium handling in the mechanism of arrhythmogenesis.¹⁸ Similarly, Wilson et al.²⁵ has recently reported that Ca^{2+} alternans was the driving force generating action-potential alternans at slow heart rates in a canine heart-failure wedge preparation.

Of note, repolarization alternans associated with Ca^{2+} alternans has been also observed in pharmacologically induced long-QT syndrome in arterially perfused canine left ventricular wedge preparations (Fig. 2, C).²⁶

The adrenergic covariate

It has long been recognized that sympathetic nervous system activity modulates the magnitude of repolarization instability. In a canine model of ischemia, Nearing et al.²⁷ have shown that modifications of the stellate ganglion activity directly affect the level of T-wave alternans. In contrast, β -adrenergic blockade has been shown to suppress the magnitude of T-wave alternans in humans with ischemic cardiomyopathy and left ventricular ejection fraction of less than 40%.²⁸ Further support for the role of autonomic activity in the emergence of T-wave alternans has been provided by the observations of circadian changes in the magnitude of T-wave alternans in Holter recordings obtained from patients with a prior myocardial infarction (Fig. 2, F).¹¹ Mental stress in humans with implantable devices has been shown to exacerbate the level of T-wave alternans, and the magnitude of the increase in T-wave alternans was strongly correlated with the level of norepinephrine and the incidence of arrhythmic events in a 2-year follow-up (Fig. 2, E).^{29–31}

The mechanisms by which adrenergic stimulation promotes repolarization alternans may involve additional influx of Ca^{2+} into the myocytes, overloading the calcium-handling cascades, which are chronically impaired in heart failure.^{32,33} In particular, it is likely that Ca^{2+} alternans and impaired Ca^{2+} handling are the driving forces behind the emergence of T-wave alternans with β -adrenergic stimulation in our studies of the TNF- α genetic mouse model of heart failure because Ca^{2+} alternans play a pivotal role in the mechanisms of repolarization instability and arrhythmias accompanying development of heart failure in these animals.³⁴

The conduction velocity covariate

The inverse relationship between the conduction velocity and basic CL is well documented.¹⁷ This relationship plays a particularly important role at short CL, and conduction-velocity alternans have been observed at faster heart rates, during various types of a narrow-QRS tachycardia.³⁵ Preferential conduction slowing at short pacing CLs (CL < 80 milliseconds) has been also observed in a TNF- α genetic mouse model of heart failure, suggesting that impaired adaptation of the conduction system to faster heart rates may

contribute to the emergence of alternans in the setting of heart failure (Fig. 2, D).¹⁸

Other physiologic covariates

In addition to the L-type Ca^{2+} channels, an incomplete recovery, temporal instability, or heterogeneous distribution of other ionic currents, which are active during repolarization, may also lead to the emergence of repolarization instability. Indeed, a number of intracellular processes, including modifications of repolarizing potassium currents (I_{Kr}) and changes in excitability, have been implicated in the mechanisms of repolarization instability.^{4,36,37} We note also that functional changes in the repolarizing ionic channels, including diminished repolarizing K^+ currents (I_{to} and I_{K1}), have been documented in heart failure, suggesting possible involvement of these channels (in addition to the Ca^{2+} -related mechanisms discussed earlier) in the emergence of instabilities in this setting.¹⁸

Adding to the complexity of the “repolarization-instability” conundrum, the alternans has been also reported in association with pharmacologically induced Brugada syndrome in the right ventricular canine tissue (Fig. 2, G). In contrast to the other settings described above, the alternans occurred at slow pacing rates and disappeared when the pacing accelerated. The presumable mechanism of this instability includes the alternating I_{Na} causing alternations in I_{to} and L-type Ca^{2+} currents in the right ventricular epicardium.³⁸

Discerning the impact of physiologic covariates in real-life data

Summarizing, the results of clinical, experimental, and theoretical studies have provided a wealth of evidence supporting statistical and mechanistic links between the occurrence of repolarization instability and arrhythmias. The notion that the measurement of repolarization instability may provide important diagnostic and prognostic information for the arrhythmia risk assessment has become well recognized.^{1,2,5,7–9,11,31}

Several clinical trials have confirmed the predictive value of T-wave alternans,^{1,2,11,31} whereas other trials have failed to demonstrate a strong predictive value.¹⁰ The inconsistencies most likely arise from the differences in the underlying physiologic mechanisms driving the instabilities in different settings, leading to a common end point from a multitude of subcellular, intracellular, and multicellular processes (Fig. 1). Thus, a better understanding of these physiologic covariates, along with the measurement caveats,³⁹ is needed for improving the accuracy of arrhythmia risk assessment.

In a real-life setting, electrophysiologic data are usually collected at the time when at least some of the covariates exhibit simultaneous changes. Thus, the algorithms are needed to differentiate the respective impacts and weights of each participating covariate. Fig. 2 shows one possible algorithm that allows, to a first approximation, determine the relative weights of the primary physiologic covariates. We view the flow chart in Fig. 2 as a working hypothesis guiding

our ongoing studies. More experimental and clinical data will be needed to determine the quantitative weight of each covariate and refine the probabilities of transition from one mechanism to another. We note, however, that the flow chart might fail when all covariates have similar weights, making it difficult to discern predominant, major effects. The practical implementation and testing of this algorithm will require continuous or serial tracking of individual repolarization dynamics, along with other electrophysiologic parameters, including changes in heart rate, QRS duration, circadian variability, physical activity, and psychological status.^{11,31} The improvement can also be achieved by tracking the changes against the individual's baseline and using "personalized" (ie, individually tailored) pattern recognition analysis.^{7,39,40}

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