Electrocardiographic alternans, a phenomenon of beat-to-beat oscillation in electrocardiographic (ECG) waveforms, was first described by Hering in 1908. Much of the interest in the alternans phenomenon has focused on alternans during the repolarization phase of the cardiac action potential (AP), also known as repolarization alternans (RA). More specifically, RA has been associated with an increased risk for malignant ventricular arrhythmias and sudden cardiac death (SCD) across a wide range of pathophysiological conditions, including both ischemic and nonischemic congestive heart failure with impaired left ventricular (LV) ejection fraction and recent myocardial infarction.2,3 Cardiac alternans specifically, RA has been associated with an increased risk for malignant ventricular arrhythmias and sudden cardiac death (SCD) across a wide range of pathophysiological conditions, including both ischemic and nonischemic congestive heart failure with impaired left ventricular (LV) ejection fraction and recent myocardial infarction.2,3 Cardiac alternans can also be produced in structurally normal hearts under conditions of chronotropic stimulation4,5 or significant metabolic stress.6

Given that several comprehensive review papers7–10 have been published on the mechanisms of RA and the clinical risk-stratification aspects of microvolt T-wave alternans (MTWA) testing, in the present report we have attempted to present a novel framework for how an “appropriate” substrate and an “appropriate” trigger event may synergistically contribute to the mechanisms that generate cardiac alternans from the cellular to the whole-heart level, and we propose novel aspects of the use of RA to guide therapy.

Mechanisms of Alternans in Isolated Myocytes

Two major hypotheses have been developed to explain the alternans phenomenon at the cellular level. The first hypothesis suggests that alternation in sarcolemmal currents, membrane voltage, and AP morphology leads to beat-to-beat fluctuations in intracellular calcium concentration. In support of this hypothesis, it has recently been shown that modulation of sarcolemmal Ca\textsuperscript{2+}11 and K\textsuperscript{+}12,13 currents based on changes in AP morphology14 has a significant effect on the stability of Ca\textsuperscript{2+} handling processes and the transition to stable alternans15,16 (Figure 1A). In contrast, the second major hypothesis suggests that alternation of intracellular calcium concentration ([Ca\textsuperscript{2+}]) is the primary event, which then secondarily leads to alternans of membrane voltage and AP morphology.6,14,18–23 According to the second hypothesis, [Ca\textsuperscript{2+}] alternans can result from stress-induced5,18 perturbations in any number of Ca\textsuperscript{2+} transport processes, including Ca\textsuperscript{2+} entry into the cytoplasm,13 recovery of ryanodine receptors (RyRs) from inactivation, triggering of sarcoplasmic reticulum (SR) Ca\textsuperscript{2+} release,6,19 SR Ca\textsuperscript{2+} uptake,24 intra-SR Ca\textsuperscript{2+} redistribution,25,26 and linking of intracellular Ca\textsuperscript{2+} handling to surface membrane voltage14,17 (Figure 1B). The mechanisms that give rise to cardiac alternans may reside anywhere along this multistep process of intracellular calcium cycling. A preponderance of recent data has emerged in support of the second hypothesis, which suggests the primacy of perturbations in Ca\textsuperscript{2+}-handling processes as the fundamental event in the genesis of cellular alternans.

Among the many steps involved in calcium cycling, alternation of calcium entry into the cell via incomplete recovery from inactivation of the L-type calcium channel (I\textsubscript{Ca,L}) could theoretically lead to [Ca\textsuperscript{2+}] alternans.13,27 However, a number of studies have demonstrated that peak I\textsubscript{Ca,L} is unchanged during alternans,6,19,28,29 and equally importantly, I\textsubscript{Ca,L} has been shown to be unaltered in myocytes from diseased hearts,30 which makes this a less likely mechanism for the lower alternans threshold observed in the failing heart. Furthermore, alternans of [Ca\textsuperscript{2+}] can be elicited in a high-frequency–stimulated myocyte during AP clamp with similar AP morphology,20 which also suggests that the Ca\textsuperscript{2+} influx trigger of calcium-induced calcium release is not the primary event in the induction of alternans. Additionally, the use of small depolarizing pulses28 to induce alternans may account for alternans encountered at very high stimulation frequencies, when most of the L-type Ca\textsuperscript{2+} channels are unavailable, and thus provides a plausible explanation for the presence of alternans in the normal heart at unusually high stimulation frequencies.4,5

Beat-to-beat fluctuations in SR Ca\textsuperscript{2+} content have also been implicated as a potential mechanism for alternans. SR Ca\textsuperscript{2+} measurements made during alternans by use of the

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indirect approach of measurement of the caffeine-evoked Na\(^+\)/Ca\(^{2+}\) exchanger current have suggested that SR Ca\(^{2+}\) alternates.\(^{17,28,31}\) However, others have shown that although [Ca\(^{2+}\)]\(_{\text{SR}}\) exerts a major influence on SR Ca\(^{2+}\) release, beat-to-beat alternation in [Ca\(^{2+}\)]\(_{\text{SR}}\) is not required for [Ca\(^{2+}\)]\(_i\) alternans to occur.\(^{6,29}\)

The rate of recovery of the RyR from a refractory (adapted or inactivated) state is another step in the calcium-cycling machinery that may give rise to chronotropically induced alternans. With increased steepness of the released Ca\(^{2+}\)-SR Ca\(^{2+}\) content relationship, as may occur in diseased hearts,\(^{30}\) small changes in [Ca\(^{2+}\)]\(_{\text{SR}}\) should result in large changes in the beat-to-beat [Ca\(^{2+}\)]\(_i\), even for a constant \(I_{\text{Ca,L}}\) trigger.\(^{32,33}\) As such, a large [Ca\(^{2+}\)]\(_i\) would be produced when the [Ca\(^{2+}\)]\(_{\text{SR}}\) is relatively high and a disproportionately small [Ca\(^{2+}\)]\(_i\) when the [Ca\(^{2+}\)]\(_{\text{SR}}\) content is relatively low. A large [Ca\(^{2+}\)]\(_i\) would then cause enhanced Ca\(^{2+}\)-mediated L-type current inactivation, thus suppressing Ca\(^{2+}\) entry, as well as enhanced Ca\(^{2+}\) extrusion from the myocyte via the Na\(^+\)/Ca\(^{2+}\) exchanger,\(^{16,17}\) all of which results in a lower SR Ca\(^{2+}\) content and hence lower [Ca\(^{2+}\)]\(_i\), on the next beat. The lower [Ca\(^{2+}\)]\(_i\), then results in decreased Ca\(^{2+}\)-mediated L-type current inactivation and reduced Ca\(^{2+}\) extrusion through the Na\(^+\)/Ca\(^{2+}\) exchanger, which leads to increased SR Ca\(^{2+}\) content and a return to the higher [Ca\(^{2+}\)]\(_i\), on the following beat (Figure 2). This sequence sets the stage for concordant cellular alternans between [Ca\(^{2+}\)]\(_i\) and membrane voltage/AP duration (APD) such as may occur in diseased hearts.\(^{30}\) For definitions, please see the Table.

Although the use of small depolarizing pulses to induce alternans\(^{28}\) may differ significantly from the often-encountered chronotropic induction of alternans, the biphasic rise in [Ca\(^{2+}\)]\(_i\)\(^{16}\) has been attributed to an initial steep rise in activation of the RyRs, whereas the second, slower phase has been attributed to wavelike propagation. We\(^{16,17}\) and others\(^{34}\) have ascribed this secondary slower phase to secondary RyR openings. In computer simulations, we have shown that in

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Illustration of [Ca\(^{2+}\)]\(_i\) and action potential (AP) alternans.\(^{16,17}\) A, Representative example of concordant [Ca\(^{2+}\)]\(_i\) and AP alternans in a left ventricular canine myocyte stimulated every 0.8 seconds. The arrows indicate a subthreshold early afterdepolarization. B, Representative example of phase transitions (a) through (d) between [Ca\(^{2+}\)]\(_i\) and AP alternans obtained during the same data record as Figure 1A. In-phase (concordant) [Ca\(^{2+}\)]\(_i\), and AP alternans leads to out-of-phase (discordant) alternans (a) and (c) and back again to in-phase alternans (b) and (d). “A” and “B” denote large and small [Ca\(^{2+}\)]\(_i\), or long and short AP duration, respectively; the peak [Ca\(^{2+}\)]\(_i\) and AP duration for these beats are also shown.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Cellular calcium content and alternans threshold. Schematic of the effect of sarcoplasmic reticulum (SR) Ca\(^{2+}\) content on a proposed model for cellular alternans. Ca\(^{2+}\) cycling though calcium-induced calcium release (CICR) includes the L-type Ca\(^{2+}\) channel, the SR Ca\(^{2+}\) ATPase pump (SERCA2a), phospholamban (PLB), the ryanodine receptor (RyR) channel, and the Na\(^+\)/Ca\(^{2+}\) exchanger (NCX). The solid line shows the SR Ca\(^{2+}\) baseline ([Ca\(^{2+}\)]\(_{\text{SR,bas}}\)), and the dashed line shows the threshold SR Ca\(^{2+}\) ([Ca\(^{2+}\)]\(_{\text{SR-th}}\)) at which Ca\(^{2+}\) release occurs. In the normal heart, CICR is manifested by an operational baseline of [Ca\(^{2+}\)]\(_{\text{SR}}\) that is lower than the threshold to trigger spontaneous Ca\(^{2+}\) release; however, high stimulation frequency or \(\beta\)-adrenergic stimulation results in SR Ca\(^{2+}\) overload that raises the SR Ca\(^{2+}\) baseline level above the threshold such that spontaneous subthreshold Ca\(^{2+}\) release may occur.
isolated myocytes, elevated SR Ca\(^{2+}\) content results in both aberrant SR Ca\(^{2+}\) release and [Ca\(^{2+}\)]\(_i\), alternans and also gives rise to an inward depolarizing current that results in spontaneous early afterdepolarizations and APD prolongation, which correlates directly with the magnitude and timing of the aberrant Ca\(^{2+}\) release. We have also shown the presence of discordant cellular alternans between [Ca\(^{2+}\)]\(_i\) and APD at the myocyte level and the importance of [Ca\(^{2+}\)]\(_i\) in defining the in- or out-of-phase relationship between experimentally obtained [Ca\(^{2+}\)]\(_i\) and AP (Figure 1B).

In aggregate, these findings support the primacy of alternation in [Ca\(^{2+}\)]\(_i\), in driving APD alternans and in determining the presence of concordance or discordance between [Ca\(^{2+}\)]\(_i\), and AP morphology within the individual myocyte. Furthermore, experimental evidence suggests that the same Ca\(^{2+}\)-cycling perturbations that give rise to cellular alternans also play a fundamental role in the pathogenesis of trigger events (eg, transient β-stimulation bursts), which in concert create the necessary conditions for the establishment of cellular alternans.

Many studies have suggested that RyRs are more likely to be triggered by cytosolic Ca\(^{2+}\) when SR lumenal Ca\(^{2+}\) is elevated\(^{35-37}\) and that increasing SR Ca\(^{2+}\) content increases spontaneous SR Ca\(^{2+}\) release\(^{18}\) and delayed afterdepolarization amplitude toward the threshold required to trigger an AP.\(^{40-42}\) Furthermore, triggered activity that arises from delayed afterdepolarizations in response to high stimulation rates\(^{43}\) or to catecholamines has been demonstrated in normal ventricular myocytes,\(^{44}\) experimental heart failure preparations,\(^{45}\) and cardiomyopathic human hearts.\(^{46}\) These studies provide a plausible justification for the hypothesis that SR Ca\(^{2+}\) “stabilization” at a submaximal value is the primary reason for the abolishment of alternans in studies in which thapsigargin and ryanodine treatment of myocytes markedly suppressed [Ca\(^{2+}\)]\(_i\), and prevented APD alternans,\(^{18}\) and ryanodine treatment alone abolished both tension and AP alternans in papillary muscles.\(^{25,26}\)

In that context, in the normal heart, calcium-induced calcium release is manifested by an operational baseline [Ca\(^{2+}\)]\(_{SR}\) that is lower than the threshold to trigger spontaneous Ca\(^{2+}\) release. However, high stimulation frequency or β-adrenergic stimulation may trigger SR Ca\(^{2+}\) overload that raises the SR Ca\(^{2+}\) baseline level close to or above the threshold at which spontaneous subthreshold Ca\(^{2+}\) release may occur. In the diseased heart, although the baseline SR Ca\(^{2+}\) level is decreased, the [Ca\(^{2+}\)]\(_{SR}\)-threshold for RyR opening is also decreased. Although β-adrenergic responsiveness is impaired in the diseased heart,\(^{47}\) even a moderate residual or transient β-adrenergic responsiveness\(^{48}\) may trigger spontaneous subthreshold Ca\(^{2+}\) release at a lower [Ca\(^{2+}\)]\(_{SR}\). The lower than normal [Ca\(^{2+}\)]\(_{SR}\)-threshold for RyR opening in diseased hearts may explain the presence of ECG alternans at lower heart rates than in normal hearts.

Further justification for the role of SR Ca\(^{2+}\) content in the genesis of alternans comes from the recent study by Xie and Weiss\(^{34}\) demonstrating that under control conditions, myocytes become susceptible to Ca\(^{2+}\) overload during rapid pacing and that interactions between spontaneous Ca\(^{2+}\) waves and AP-triggered [Ca\(^{2+}\)]\(_i\) may produce subcellular spatially discordant alternans (SDA) and even more complex subcellular [Ca\(^{2+}\)]\(_i\) patterns. Therefore, the genesis\(^{43,48}\) and propagation\(^{49}\) of Ca\(^{2+}\) waves, which are in general associated with increased SR Ca\(^{2+}\) content through increased luminal Ca\(^{2+}\) sensitization of the RyR to cytosolic Ca\(^{2+}\) and perhaps through increased ability of cytosolic Ca\(^{2+}\) to activate adjacent RyR sites, may essentially reset local [Ca\(^{2+}\)]\(_{SR}\) and give rise to subcellular alternans. According to this mechanism, a partially propagated Ca\(^{2+}\) wave triggers a gradient in SR refractoriness when the next AP occurs. In the region of the myocyte through which the Ca\(^{2+}\) wave has already passed, the affected SR is empty and partially refractory, thus minimizing Ca\(^{2+}\) release. In contrast, the region into which the Ca\(^{2+}\) wave has not entered causes the release of a normal amount of SR Ca\(^{2+}\), which results in a spatially nonuniform [Ca\(^{2+}\)]\(_i\). On the next beat, both [Ca\(^{2+}\)]\(_{SR}\) content and excitability of the refractory region will have recovered, producing a large release, therefore perpetuating the presence of subcellular SDA.

The presence of subcellular spatially discordant [Ca\(^{2+}\)]\(_i\) leads to increased dispersion of subcellular electrophysiological properties and, in the setting of an appropriate trigger, may lead to an arrhythmia at the cellular level. Although subcellular SDA is usually preceded by subcellular spatially concordant alternans, under certain circumstances subcellular SDA may arise spontaneously.\(^{34}\)

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**Table. Definitions of Cardiac Alternans**

<table>
<thead>
<tr>
<th>Type of Alternans</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Subcellular Spatially Concordant [Ca(^{2+})](_i), Alternans</strong></td>
<td>Oscillation of calcium concentration within the myocyte such that [Ca(^{2+})](_i) within all subcellular areas oscillates in phase (ie, all subcellular regions demonstrate high or low [Ca(^{2+})](_i)).</td>
</tr>
<tr>
<td><strong>Subcellular Spatially Discordant [Ca(^{2+})](_i), Alternans</strong></td>
<td>Oscillation of calcium concentration within the myocyte such that [Ca(^{2+})](_i) within adjacent subcellular areas oscillates out of phase (ie, some subcellular regions demonstrate high [Ca(^{2+})](_i) and adjacent subcellular regions demonstrate low [Ca(^{2+})](_i)).</td>
</tr>
<tr>
<td><strong>Cellular Concordant [Ca(^{2+})](_i), and AP Alternans</strong></td>
<td>Oscillation of intracellular calcium concentration and AP voltage such that these signals are in phase (ie, a large [Ca(^{2+})](_i) corresponds to a long APD and vice versa).</td>
</tr>
<tr>
<td><strong>Cellular Discordant [Ca(^{2+})](_i), and AP Alternans</strong></td>
<td>Oscillation of intracellular calcium concentration and AP voltage such that these signals are out of phase (ie, a large [Ca(^{2+})](_i) corresponds to a short APD and vice versa).</td>
</tr>
<tr>
<td><strong>Tissue/whole-heart Spatially Concordant APD Alternans</strong></td>
<td>Oscillation of APD such that adjacent areas of the heart are in phase (ie, adjacent regions demonstrate either long or short APDs).</td>
</tr>
<tr>
<td><strong>Tissue/whole-heart Spatially Discordant APD Alternans</strong></td>
<td>Oscillation of APD such that adjacent areas of the heart are out of phase (ie, one area of the heart demonstrates long APDs while an adjacent area demonstrates short APDs).</td>
</tr>
</tbody>
</table>

AP indicates action potential; APD, action potential duration.
Mechanisms of Alternans in the Intact Heart

In summary, these data suggest that in the diseased heart, cellular alternans requires a trigger event and the appropriate substrate to develop. A trigger event alone is sufficient to induce alternans even in the normal heart; however, it requires supraphysiological heart rates. In the diseased heart, however, the presence of an appropriate subcellular substrate makes the conditions for alternans development more favorable, and thus, a lower heart rate is sufficient for onset of alternans. \( \beta \)-stim indicates \( \beta \)-adrenergic stimulation; SR, sarcoplasmic reticulum.

**Figure 3.** Theoretical paradigm for differential mechanisms of alternans in normal and diseased hearts. In the diseased heart, cellular alternans requires a trigger event and the appropriate substrate to develop. A trigger event alone is sufficient to induce alternans even in the normal heart; however, it requires supraphysiological heart rates. In the diseased heart, however, the presence of an appropriate subcellular substrate makes the conditions for alternans development more favorable, and thus, a lower heart rate is sufficient for onset of alternans. \( \beta \)-stim indicates \( \beta \)-adrenergic stimulation; SR, sarcoplasmic reticulum.

Whole-heart level can also be spatially concordant or discordant. Early work has demonstrated significant variation across species in the ability to induce alternans and has also demonstrated that APD alternans is more easily induced at lower temperatures, which tend to prolong APD, thus suggesting a primary role for membrane voltage dynamics in alternans at the tissue level. Subsequently, Weiss et al demonstrated in computer simulations that at the cellular level, steep APD restitution (the relationship between APD and the previous diastolic interval) slope and \( [\text{Ca}^{2+}]_i \) cycling dynamics cause the APD and \( [\text{Ca}^{2+}]_i \) to alternate. They have also demonstrated that at the tissue level, additional factors, such as conduction velocity restitution and ectopic beats, promote SDA. However, despite the demonstration that sustained APD alternans occurs when the APD restitution slope is >1 at a given cycle length, experimental evidence indicates that the onset of APD alternans is primarily attributable to an instability in \( [\text{Ca}^{2+}]_i \), cycling dynamics rather than steep APD restitution. Voltage clamp experiments in isolated myocytes have demonstrated that \( [\text{Ca}^{2+}]_i \) exhibits alternans despite a constant beat-to-beat AP (voltage) waveform, which suggests that APD alternans is typically driven by \( [\text{Ca}^{2+}]_i \) dynamics and not by voltage dynamics (ie, steep APD restitution slope). In both isolated ventricular myocytes and intact tissue, the onset of APD alternans occurred at a constant cycle length at which APD restitution slope was still considerably <1, and interventions that suppressed \( [\text{Ca}^{2+}]_i \) cycling eliminated AP alternans irrespective of the APD restitution. As such, studies from both isolated myocytes and intact tissue suggest a primary role for perturbations in calcium-cycling processes in the genesis of APD alternans in the whole heart.

However, whether the same mechanisms give rise to APD alternans under all circumstances, and whether the presence of alternans is necessarily always reflective of a proarrhythmic substrate, remains an area of controversy. The presence of discordant alternans and ventricular arrhythmias in a pacing-induced model in the guinea pig, a species believed to be highly resistant to alternans, suggests that chronotropically induced alternans may generate a nonspecific proarrhythmic substrate. In contrast to pacing-induced alternans, discordant alternans induced in the setting of acute ischemia or heart failure appears to be caused primarily by subcellular \( [\text{Ca}^{2+}]_i \)-cycling perturbations and is believed to represent a truly arrhythmogenic substrate. These data further support the hypothesis that the further the diseased state of the heart, the higher the probability of inducing alternans with progressively smaller trigger events (ie, at lower heart rates that result from small, transient bursts of \( \beta \)-adrenergic stimulation).

Regardless of the method used to induce alternans, the emergence of discordant APD alternans (reflecting 2 adjacent areas of the myocardium that oscillate with opposite phase) appears to be a fundamental step in the development of an arrhythmogenic substrate. Studies in normal hearts using optical mapping techniques have shown that discordant AP alternans is associated with a state of marked cardiac electric instability, as evidenced by the fact that ventricular fibrilla-
tion is always preceded by discordant, but never by concordant, APD alternans. This unstable electrical substrate is consistently induced at a critical heart rate threshold and is largely independent of the pacing site, which suggests that it is caused by heterogeneities of cellular repolarization properties and not heterogeneous propagation delay. Interestingly, in this study, alternans most commonly involved the slope of the AP plateau and the onset of final repolarization, timing during calcium-induced calcium release that coincides with the timing of aberrant RyR release during alternans observed by our group and others.

Recently, a 2-photon confocal imaging study in the intact rat ventricle has shown that the spatial distribution of SR Ca\(^{2+}\) content and spontaneous SR Ca\(^{2+}\) release. The paradigm that RA arises from perturbations in calcium cycling within the individual myocyte and the critical role of both substrate and triggers in the pathophysiology of RA, as delineated in the preceding discussion, have important clinical implications. To date, RA has been most commonly encountered in the clinical setting through the use of MTWA testing to predict the risk of ventricular tachyarrhythmic events (VTEs) and SCD. A positive MTWA test result has been associated with a significantly heightened risk for SCD during medium- and long-term follow-up across a wide range of clinical settings, including ischemic and nonischemic cardiomyopathy and structural heart disease with preserved LV ejection fraction.

More recently, prospective studies assessing the prognostic utility of MTWA testing in cohorts in which a large percentage of patients are implanted with prophylactic implantable cardioverter-defibrillators (ICDs) have suggested that MTWA testing is not as good a predictor of “appropriate” ICD therapy as it is a predictor of VTE/SCD in patients without ICDs. This observation has been attributed to the fact that many “appropriate” ICD therapies treat arrhythmias that would have self-terminated or that ICDs may induce arrhythmias that many “appropriate” ICD therapies treat.

Clinical Relevance of RA

RA and Arrhythmia Susceptibility

The paradigm that RA arises from perturbations in calcium cycling within the individual myocyte and the critical role of both substrate and triggers in the pathophysiology of RA, as delineated in the preceding discussion, have important clinical implications. To date, RA has been most commonly encountered in the clinical setting through the use of MTWA testing to predict the risk of ventricular tachyarrhythmic events (VTEs) and SCD. A positive MTWA test result has been associated with a significantly heightened risk for SCD during medium- and long-term follow-up across a wide range of clinical settings, including ischemic and nonischemic cardiomyopathy and structural heart disease with preserved LV ejection fraction.
in patients with LV ejection fraction ≤35% predicts a very low annual risk for SCD, whereas a positive MTWA test predicts a significantly heightened risk of SCD, both in patients with LV ejection fraction ≤35% and in those with an LV ejection fraction >35%.79 If confirmed in prospective studies, these findings may have important implications for the refinement of primary prevention ICD treatment algorithms.

These clinical observations also demonstrate that an increased magnitude of RA is closely associated with the substrate that gives rise to malignant ventricular arrhythmias9,59,80 and that clinical heart failure significantly lowers the heart rate threshold to induce ventricular alternans.64,81 Other lines of evidence suggest that RA may also play an important role in the pathogenesis of atrial arrhythmias,82 a setting in which the paradigm of substrate and triggers (ie, pulmonary vein potentials) may have particular relevance. However, these observations do not necessarily prove that RA plays a causative role in the genesis of arrhythmias or that suppression of RA would be a viable therapeutic target. Although the differentiation of association from causation in the clinical setting can be challenging, several lines of clinical evidence do lend support to a causative role for RA in the genesis of cardiac arrhythmias. Analysis of ambulatory body-surface electrograms (Holter monitors) from patients with various forms of heart disease has demonstrated a sharp upsurge in both alternans and nonalternans periodicities (measured by time-domain techniques) within the minutes before spontaneous VTE.83,84 These studies demonstrate that nonalternans periodicities such as T-wave lability, a T-wave oscillation pattern that does not follow an alternans-like pattern, may also precede VTEs.85,86 However, in contrast to clinical MTWA testing that uses frequency-domain techniques, the medium- and long-term prognostic significance of heightened nonalternans periodicities has not been as well validated.

Furthermore, analysis of intracardiac electrograms from ICD leads has also demonstrated a sharp increase in RA magnitude immediately before spontaneous ventricular arrhythmias87–89; however, a similar upsurge in RA has not been observed before induced ventricular arrhythmias or preceding inappropriate ICD shocks,87 which suggests that the presence of increased RA magnitude is not just a by-product of a ventricular arrhythmia or a consequence of an ICD shock. Simultaneous measurement of RA from body-surface and intracardiac electrograms by our group90 and others91 has shown a high degree of correlation, which suggests that these measurements are detecting the same electrical phenomenon.

The mechanisms linking RA and arrhythmogenesis have been explored by Kuo et al,92 who have shown that increased dispersion of repolarization is an important condition for the development of reentrant arrhythmias, and Chinushi et al,93,94 who have shown that increased dispersion of repolarization is associated with VTE and concordant or discordant alternans (dispersion of repolarization is greater at sites of discordant versus concordant alternans). Numerous experimental22,23,95,96 and computational97–99 studies have demonstrated that APD alternans can provide the substrate for reentry and support the notion that beyond medium- and long-term prognosis, heightened RA is also an important short-term predictor of arrhythmia susceptibility. Although the presence of discordant APD alternans leading to wave break and reentry (also known as the multiple-wavelet hypothesis) has emerged as a major model to explain the pathogenesis of VTE, other overlapping models have also been proposed, including the focal-source hypothesis, in which wave break represents a distant epiphenomenon and is not necessarily required to sustain ventricular fibrillation. Evidence to support both types of fibrillatory activity may be seen in the same heart, and both may be relevant clinically100; the extent to which these competing models may have clinical therapeutic implications remains to be defined.

In aggregate, clinical data suggest that either the heart passes through a state of heightened RA on the way to ventricular tachycardia/fibrillation or heightened RA occurs in close conjunction with developing VTE.22,23 In either scenario, these findings suggest that detection of significantly elevated levels of RA may serve as an important short-term predictor of impending arrhythmias and also raise the possibility of using upstream therapies to abort ventricular tachycardia/fibrillation before arrhythmia onset.

**Therapeutic Implications**

The ability to detect heightened levels of RA from implantable intracardiac devices opens the door to the possibility of delivering upstream therapy to suppress RA and prevent the development of a favorable substrate for arrhythmogenesis. Upstream therapy also has the important potential benefit of preventing the need for ICD shocks, which have an adverse impact on quality of life and may also have a detrimental effect on heart failure disease progression.101

The concept of upstream therapy depends on the ability to detect RA with a high degree of sensitivity. RA in vivo is known to be a spatially and temporally heterogeneous phenomenon,102 and therefore, any attempt to suppress RA is predicated on the ability to accurately detect alternans regardless of where in the heart it originates. Our group has recently identified a novel lead configuration for the optimal spatiotemporal detection of intracardiac RA.90 To examine which intracardiac lead combination is most sensitive for RA detection, in Figure 5 we plot the probability that a far-field bipolar intracardiac lead configuration is positive for RA, given that at least 1 intracardiac far-field lead is positive, for each of a right ventricular (RV), coronary sinus, LV, epicardial, and triangular RV–coronary sinus far-field intracardiac lead configuration. When an intracardiac lead is positive, the probability that a triangular RV–coronary sinus lead is positive is 85.5%, greater than any other intracardiac lead, which suggests that this lead configuration may provide an optimal approach for intracardiac RA detection. The use of an RV–coronary sinus lead configuration also has important clinical applicability, because many currently used intracardiac devices already have RV and coronary sinus leads (eg, cardiac resynchronization therapy platforms).

After detection of heightened RA, electrical therapy has been proposed as a means of suppressing RA and preemitting...
the development of a potentially arrhythmogenic substrate. The use of electrical therapy for this purpose draws on the experience with the use of pace termination of ventricular arrhythmias. Electrical therapy as a means of terminating ventricular arrhythmias may result in 1 of several outcomes: (1) termination of reentry and VTE; (2) changes in the shape and/or position of the center of the activity and induction of different reentrant waveforms or a focal pattern of repetitive activation; (3) changes in the “exit” pathway or in the direction of the activity; and (4) resetting of the activity and persistence of the same reentry.

In an analogous manner, it is conceivable that appropriately delivered pacing stimuli may suppress or terminate RA and abort reentry, thus preventing ventricular tachycardia/fibrillation. Although detection of an upsurge in magnitude of RA immediately before the onset of ventricular arrhythmias is suggestive of a causative role for RA in arrhythmogenesis, definitive proof of causation requires clear demonstration that suppression of RA prevents arrhythmias. Preclinical studies have demonstrated the feasibility of suppressing RA with dynamic pacing protocols that can be modulated on the basis of real-time measurements of APD and with the result of suppressing RA and restabilizing the myocardial substrate. However, reproduction of these findings in the whole heart has been limited by the inherent spatial and temporal variability of RA as it occurs in situ.

Our group has recently developed a method for in situ dynamic control of RA in a swine model. This method is based on the premise that adaptive subthreshold pacing impulses delivered during the absolute refractory period may be capable of controlling RA. In this model, RA is induced via an R-wave–triggered pacing protocol that delivers impulses on an every-other-beat basis and hence leads to a significant rise in RA magnitude as detected by an increase in $K_{score}$ (for a description of the use of the $K_{score}$ to quantify RA magnitude, please see Rosenbaum et al for a description of the method used to estimate $K_{score}$). The increase in $K_{score}$ is detectable from both intracardiac (RV, LV, coronary sinus) and body-surface (lead II) electrodes. After induction of significant RA, triggered pacing stimuli delivered from a remote location on alternate beats can be used to suppress RA. In this example, RA is induced by pacing from the RV12 electrode on even beats (Figure 6B) and then suppressed by pacing from RV56 on odd beats (Figure 6C). Other permutations of even- and odd-beat pacing and changes in the polarity of triggered impulses can be used to induce and suppress alternans with a high degree of fidelity (Figure 6D through 6F).

Extension of these findings raises the possibility of incorporating adaptive pacing protocols into implantable devices such that if the device detects an unstable myocardial substrate (as evidenced by heightened RA magnitude), the adaptive pacing protocol would be activated to deliver electrical therapy to restabilize the electrical substrate, so that even if a trigger event occurred (eg, a premature ventricular contraction), that trigger would no longer encounter a vulnerable electrical substrate, and the onset of arrhythmia would be prevented. The adaptive pacing protocol could be terminated when the RA magnitude falls below a predetermined threshold. Beyond adaptive pacing protocols, detection of RA by implantable devices may also be coupled to other forms of suppressive therapy. For instance, there is significant interest in coupling microelectromechanical systems (MEMS) to implantable devices to facilitate localized delivery of pharmacological agents for treatment of various aspects of chronic heart failure (ie, neurohormonal antagonists, diuretics, and antiarrhythmic agents). Se
strated to suppress RA and prevent ventricular arrhythmias, including β-blockers and certain sodium channel blockers, such as ranolazine. It is conceivable that timely and potentially localized delivery of such agents may be capable of suppressing RA and restabilizing the electric substrate. However, the hypothesis that suppression of RA in vivo can be used to preempt arrhythmia onset remains to be proven. An important proof-of-concept study recently demonstrated that the use of SR Ca2+ ATPase adenoviral gene transfer in a guinea pig model resulted in a 4-fold reduction in susceptibility to alternans-mediated ventricular arrhythmias, and has opened the door to other potential therapeutic approaches for the suppression of RA and prevention of VTs.

The potential to couple detection of elevated RA magnitude and delivery of therapy within an implantable device offers a real opportunity for developing iterative and closed-loop systems to prevent arrhythmias.

**Conclusions**

The generally accepted paradigm of requiring both substrate and triggers for the genesis of ventricular arrhythmias lends significant complexity to understanding the underlying mechanisms that give rise to life-threatening arrhythmias and SCD. ECG alternans-type oscillations represent a response of the ventricle at the first subharmonic of the driving frequency (the mean heart rate), which might be viewed as the first bifurcation in the pathway to ventricular fibrillation. This review presents a contemporary view of the mechanisms underlying [Ca2+]i, and AP alternans in the normal and diseased heart.

The prevailing hypothesis of RA is that dynamic subcellular perturbations in intracellular Ca2+ homeostatic mechanisms that occur on a beat-to-beat basis give rise to [Ca2+]i alternans, which in turn gives rise to APD alternans and ECG alternans. At the whole-heart level, the transition from concordant to discordant APD alternans is associated with a state of significantly heightened cardiac electric instability due to the fact that discordant APD alternans leads to increased spatial dispersion of refractoriness and wave-front fractionation and eventually to the onset of reentrant arrhythmias. Enhanced understanding of the pathophysiological processes that give rise to alternans at the cellular and whole-heart level may have important implications for pharmacological or electrical therapeutic approaches to the prevention of ventricular arrhythmias and SCD.

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**Disclosures**

None.

**References**

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53. Pillon J, Kereiakes DJ, Bartonie C, Booth T, Schloss EJ, Waller T, Chung ES, Menon S, Nallamothu BK, Chan PS. Prognostic utility of...
microvolt T-wave alternans in risk stratification of patients with ische-
72. Salerno-Uriarte JA, De Ferrari GM, Klersy C, Pedretti RF, Tritto M, 
Sallusti L, Libero L, Pettinati G, Molon G, Curnis A, Occhetta E, 
Morandi F, Ferrero P, Accardi F. Prognostic value of T-wave alternans 
in patients with heart failure due to nonischemic cardiomyopathy: results 
73. Ikeda T, Yoshino H, Sugi K, Tanno K, Shimizu H, Watanabe J, 
Kasamatsu Y, Yoshida A, Kato T. Predictive value of microvolt T-wave 
alternans for sudden cardiac death in patients with preserved cardiac 
function after acute myocardial infarction: results of a collaborative 
74. Chow W, Kereiakes DJ, Osmuler J, Woelfel A, Gursoy S, Peterson BJ, 
Pow ML, Pu W, Benditt DG. Does microvolt T-wave alternans testing 
predict ventricular tachyarrhythmias in patients with ischemic cardio-
myopathy and prolylacthin defibrillators? The MASTER (Microvolt T 
Wave Alternans Testing for Risk Stratification of Post-Myocardial 
75. Gold MR, IP JH, Costantino O, Poole JE, McNulty S, Mark DB, Lee KL, 
Bardy GH. Role of microvolt T-wave alternans in assessment of ar-
rhythmia vulnerability among patients with heart failure and systolic 
dysfunction: primary results from the T-wave alternans sudden cardiac 
76. Hohnloser SH, Ikeda T, Cohen RJ. Evidence regarding clinical use of 
77. Ellenbogen KA, Levine JH, Berger RD, Daubert JP, Winters SL, 
Greenstein E, Shalaby A, Schaechter A, Subacius H, Kadish A. Are 
implantable cardioverter defibrillator shocks a surrogate for sudden 
2006;113:776–782.
78. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and 
causes of implantable cardioverter-defibrillator therapies: is device 
79. Merchant FM, Zheng H, Ikeda T, Pedretti RFE, Salerno-Uriate JA, 
Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and 
Mechanism of discordant T-wave alternans of atrial 
80. Armoundas AA, Albert CM, Cohen RJ. Utility of implantable 
cardioverter defibrillator electrograms to estimate repolarization 
amplitude T-wave alternans precedes spontaneous ventricular tachycardia 
82. Weiss EH, Merchant FM, d’Avila A, Foley L, Reddy VY, Singh JP, 
Mela T, Ruskin JN, Armoundas AA. A novel lead configuration for 
optimal spatio-temporal detection of intracardiac repolarization 
83. Squa O, Zhou X, Gillberg J, Tseng H, Gang E, Swardlow C. Detection 
of T-wave alternans among an implantable cardioverter-defibrillator. 
of monophasic action potential durations and activation times during atrial 
pacing, ventricular pacing, and ventricular premature stimulation in 
85. Chinushi M, Restivo M, Caref EB, El-Sherif N. Electrophysiological 
basis of arrhythmogenic QT-T alternans in the long QT syndrome: 
tridimensional analysis of the kinetics of cardiac repolarization. Circ 
86. Chinushi M, Kozhevnikov D, Caref EB, Restivo M, El-Sherif N. 
Mechanism of discordant T wave alternans in the in vivo heart. J 
87. Tachibana H, Kubota I, Yamaki M, Watanabe T, Tomoike H. Discordant 
S-T alternans contributes to formation of reentry, a possible mechanism 
88. Shimizu W, Antzelevitch C. Cellular and ionic basis for T-wave 
89. Fox JJ, Riccio ML, Hua F, Bodenschatz E, Gilmour RF Jr. Spatial-
temporal transition to conduction block in canine ventricles. Circ Res. 
90. Z Q, Garfinkel A, Chen PS, Weiss JN. Mechanisms of discordant T 
wave alternans and induction of reentry in simulated cardiac tissue. 
91. Watanabe MA, Fenton FH, Evans SJ, Hastings HM, Karma A. Mech-
196–206.
92. Weiss JN, Chen PS, Wu TJ, Siegeman C, Garfinkel A. Ventricular 
fibrillation: new insights into mechanisms. Ann NY Acad Sci. 2004; 
1015:122–132.
93. Cevik C, Perez-Verdia A, Nugent K. Implantable cardioverter defibril-
ators and their role in heart failure progression. Europace. 2009;11: 
710–715.
94. Selvaraj RJ, Picton P, Nanthakumar K, Mak S, Chauhan VS. Endo-
cardial and epicardial repolarization alternans in human cardiomyopa-
y: evidence for spatio-temporal heterogeneity and correlation with 
95. MacLean WA, Plumb VJ, Waldo AL. Transient entrainment and inter-
ruption of ventricular tachycardia. Pacing Clin Electrophysiol. 1981;4: 
358–366.
96. Atogbe JN, Chen PS, Wu TJ, Siegman C, Garfinkel A. Ventricular 
fibrillation: new insights into mechanisms. Ann NY Acad Sci. 2004; 
1015:122–132.
97. Cevik C, Perez-Verdia A, Nugent K. Implantable cardioverter defibril-
ators and their role in heart failure progression. Europace. 2009;11: 
710–715.
98. Selvaraj RJ, Picton P, Nanthakumar K, Mak S, Chauhan VS. Endo-
cardial and epicardial repolarization alternans in human cardiomyopa-
y: evidence for spatio-temporal heterogeneity and correlation with 
99. MacLean WA, Plumb VJ, Waldo AL. Transient entrainment and inter-
ruption of ventricular tachycardia. Pacing Clin Electrophysiol. 1981;4: 
358–366.


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