Pulsus alternans is a condition wherein the heartbeat cyclically varies between weak and strong despite a constant heart rate. It was first described many years ago in experimental conditions, but it can be observed clinically, in particular, in patients with heart failure, where the presence of alternans portends a bad outcome (reviewed in1). Typically, alternans occurs at high heart rates, but the threshold frequency can be lowered by various conditions such as ionic disturbances or ischemia.

The alternation of the strength of the pulse, or mechanical alternans, is accompanied by alternation of the electrical activity, the so-called “electrical alternans.” This is particularly evident on the repolarization phase: action potential recordings in vitro show alternation of the duration of the action potential (AP), either concordant with the mechanical alternans (long AP with a strong beat) or discordant (short AP with strong beat) (reviewed in1). Electrical alternans can be observed at the ECG level as alternation of the ST-segment and T-wave amplitude and form; T-wave alternans is commonly referred to as TWA.

**Clinical Relevance of T-Wave Alternans and Link to Cellular Studies**

TWA directly reflects the presence of an arrhythmogenic substrate, ie, instability of repolarization resulting in temporal dispersion but also spatial dispersion. The cellular processes and (disturbed) coupling then create a substrate for micro-reentry. TWA has indeed been associated with an increased incidence of arrhythmias in a variety of conditions (reviewed in1–2). Recently there has been an increased interest in the phenomenon as a prognostic parameter, particularly within the heart failure population and in patients at increased risk of sudden arrhythmic death.3,4 Spectral analysis of the surface ECG allows detection of TWA at the microvolt level (reviewed in3). TWA is a rate-dependent parameter, to be studied at higher heart rates, which at first limited its use to invasive testing with rapid atrial pacing.5 However, later studies showed that the increase of heart rate with exercise is sufficient to make the presence of microvolt TWA a significant predictor for arrhythmias, precluding the need for invasive testing.6 With the development of more sophisticated antiarrhythmic device therapy, the role of TWA to guide therapy could become more prominent.4

The link between electrical and mechanical alternans has been studied in terms of cause and effect. It appears that the electrical phenomenon is the consequence rather than the cause of the contractile alternans, based on several observations that suppression of the contractile alternans also suppressed the electrical alternans (reviewed in3). This could be due to a direct mechanoelectrical feedback7 or through the effect of the underlying alternans of the [Ca2+]i, transient on Ca2+-sensitive membrane currents.8 Such currents can contribute to further depolarization (Na+/Ca2+ exchanger in Ca2+ extrusion or forward mode, inward current at potentials below 0 mV through Ca2+-activated nonselective cation channels, or below −35 mV through Ca2+-activated Cl− channels) or promote repolarization (Ca2+-dependent inactivation of the L-type Ca2+ current, increased activation of a Ca2+-dependent Ica, outward current during the plateau phase through Ca2+-activated Cl− channels, or nonselective cation channels). The observation that the large contractions or [Ca2+]i transients can be accompanied by the shorter as well as the longer action potential indicates that the balance between these mechanisms is not necessarily the same in all conditions or species. This issue is actually not very well studied, but there is ample evidence that alternans of [Ca2+]i, transients is the cause of the electrical alternans1,2; this clearly underscores the relevance of studying the mechanisms underlying [Ca2+]i transient alternans.

**Alternans of [Ca2+]i, at the Cellular Level: The Role of the Sarcoplasmic Reticulum**

Only single myocyte studies combining [Ca2+]i, with membrane current recordings allow the dissection of the various Ca2+ fluxes underlying the whole-cell [Ca2+]i, transient. In this issue of Circulation Research, Díaz et al10 demonstrate the power of this approach to identify the mechanisms of [Ca2+]i, alternans. Using depolarizing pulses of low amplitude (from −40 to −20 mV, for 100 ms and repeated every 2 or 3 seconds), they could consistently induce alternans of the global [Ca2+]i, transient in isolated rat ventricular myocytes. Since these were clamp pulses of fixed duration applied in unloaded single myocytes, this observation again confirms that alternans of [Ca2+]i, can occur as a primary event, in the absence of alternans of the action potential8 or mechanical loading. The Ca2+ current or trigger for Ca2+ release was not significantly different with each step, but the Ca2+ available in the sarcoplasmic reticulum, SR, varied: just before a large [Ca2+]i, transient, the Ca2+ content was large, and vice versa. The differences were small, on the order of 5 µmol/L.
Confocal imaging of \([\text{Ca}^{2+}]\), showed that the large \([\text{Ca}^{2+}]\) transients actually resulted from wave-like propagation, and the \(\text{Na}^{+}-\text{Ca}^{2+}\) exchange current extruding \(\text{Ca}^{2+}\) was large and prolonged. Although not further investigated, this alternans of the \(\text{Na}^{+}-\text{Ca}^{2+}\) exchange current is an obvious candidate for the link to electrical alternans. Further analysis of the relation between the release and the accompanying \(\text{Na}^{+}-\text{Ca}^{2+}\) exchange current on the one hand, and the amount of SR \(\text{Ca}^{2+}\) on the other hand, shows that at a given level of SR \(\text{Ca}^{2+}\), this relation becomes suddenly very steep. It is the steepness of this relation that underlies the alternans behavior and the depletion/repletion cycle of the SR. This steepness occurs beyond a threshold filling level of the SR that can build up only under certain conditions. In a previous publication, Díaz et al had used tetracaine to reduce the open probability of the ryanodine receptor, RyR, and could also observe alternans, albeit not necessarily homogeneous throughout the cell. This led to the reflection that alternans could be a “disease” of the RyR. In the current experiments, the RyR was not directly affected, but because of the low depolarizing steps, the opening of \(\text{Ca}^{2+}\) channels was reduced and thus the activation of the underlying RyRs.

A more general hypothesis then would be that alternans could occur in any condition where the probability of opening of the RyR is reduced, allowing a buildup of SR \(\text{Ca}^{2+}\) to the level where a steep relation between \(\text{Ca}^{2+}\) content and release, and \(\text{Ca}^{2+}\) efflux, exists and wave-like release occurs. This in turn maintains the cycle of depletion/repletion and the alternans of release.

**Perspectives for Cardiac Alternans Observed In Vivo**

Could the paradigm above underlie the alternans typically observed at high heart rates? Slow recovery from inactivation of either the RyR or the \(\text{Ca}^{2+}\) channel could lead to a very similar situation. Although there is still some debate regarding the nature of the inactivation of the RyR, a recovery process exists (reviewed in). Recovery of the release process due to the delay between reuptake into the SR and transport of \(\text{Ca}^{2+}\) back to the release sites is a possibility that has however recently been challenged, as intra-SR \(\text{Ca}^{2+}\) measurements indicated nearly immediate refilling. In addition to the RyR, refractoriness of L-type \(\text{Ca}^{2+}\) channel could have a similar effect. Reduction of the amplitude of the \(\text{Ca}^{2+}\) current, and therefore of the likelihood of activating RyR, has been described at higher frequencies of stimulation in normal myocytes and could also lead to the alternans phenomenon in a very similar way as described in the present study.

Will the alterations in heart failure contribute to reduced opening probability of the RyR and promote alternans? The increased phosphorylation described in heart failure would rather lead to increased open probability and leak of \(\text{Ca}^{2+}\) from the SR, neither of which would promote alternans in the current paradigm. Yet some other alterations will. In heart failure, recovery of the \(\text{Ca}^{2+}\) channels appears to be compromised in particular at high heart rates, and the reduced probability of opening at higher heart rates could promote alternans in a similar way as described. As suggested by Díaz et al, a reduced coupling between the \(\text{Ca}^{2+}\) channel and the RyR would create the conditions for alternans. A physical substrate for reduced coupling could be the loss of T-tubules with preserved density and function of the RyR. Such a loss of T-tubules has been observed in the dog with tachycardia-induced heart failure. Loss of T-tubules indeed leads to reduced coupling and local wave-like propagation of \([\text{Ca}^{2+}]\) transients, as we have recently described, but it remains unclear whether a loss of T-tubules is present and important in human heart failure.

Sinoatrial node cells, atrial myocytes, and Purkinje cells have no or very few T-tubules and in this paradigm would form an excellent substrate for alternans. Blatter and coworkers have studied alternans in single atrial myocytes in detail. They could induce alternans by high stimulation rates and/or metabolic substrate modulation. During the alternans, the large transients were accompanied by wave-like propagation. Unlike in the present study however, Huser et al could not detect significant differences in sarcoplasmic reticulum \(\text{Ca}^{2+}\) content during alternans. Whether this indicates the presence of a different mechanism in atrial cells or is due to a limitation of the caffeine-induced transient to detect small differences in sarcoplasmic reticulum \(\text{Ca}^{2+}\) content remains to be established.

Purkinje cells may also contribute to the electrical alternans, and their behavior may be different from the ventricular myocardium. The small voltage of the TWA in vivo could be consistent with a limited mass being responsible for it, and this could be the conduction system. The link between TWA and the typical \(\text{Ca}^{2+}\) release mechanism of Purkinje cells that can be associated with wave-like propagation and feedback on the action potential waveform remains at present speculative and needs to be investigated.

**Conclusions**

The study of Díaz et al has focused on the sarcoplasmic reticulum and the regulation of \(\text{Ca}^{2+}\) release from this compartment as a key element in cardiac alternans. Although it is likely that mechanisms additional to the one observed under the particular experimental conditions of this study contribute to alternans in clinical conditions, their findings provide a paradigm that may have wide application. Future research will have to link these observations to the electrical alternans and its role in arrhythmogenesis. Such basic studies will further help to evaluate the use of TWA as a predictor and guide for antiarrhythmic therapy in patients at risk for sudden death.

**References**


**Key Words:** cardiac alternans, Ca\(^{2+}\) transients, sarcoplasmic reticulum
Understanding Cardiac Alternans: The Answer Lies in the Ca2+ Store
Karin R. Sipido

Circ Res. 2004;94:570-572
doi: 10.1161/01.RES.0000124606.14903.6F
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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