Published in final edited form as:

J Electrocardiol. 2007 ; 40(6 Suppl): S70–S74.

Eight (or more) kinds of alternans

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Abstract

Cardiac electrical alternans is an alternating rhythm in the electrical properties of the heart, such as cellular action potential duration, conduction velocity, and/or intracellular calcium (Ca) concentrations. These alternations can initiate reentrant arrhythmias and can also break up ongoing reentry, creating ventricular fibrillation.

Alternans can take several forms. The alternation in time can be uniform in space (concordant alternans) or can have regions that are out of phase with other regions (discordant alternans). Alternans can be driven by voltage instabilities (involving electrical restitution) or by Ca instabilities. In addition, the relation between voltage and Ca can be positive or negative.

Anatomical factors can play a role in generating spatially discordant alternans, but there is also a critical role for instabilities that are *dynamically generated* and can only be understood as the response of a nonlinear medium to periodic excitation. This is especially true of spatially discordant alternans, the most deadly form.

We will review the role of factors such as action potential duration, conduction velocity, and Ca, which interact with each other to produce alternans. Simulations of cardiac conduction support these conclusions, as do experiments in a variety of animal and human preparations.

Keywords

Alternans; Restitution; Dynamics; Reentry; Fibrillation

Introduction

Cardiac electrical alternans takes many forms (see reference 1 for a recent review). It can appear on the surface electrocardiogram (ECG) as an alternating pattern in one or more aspects of the ECG and has also been described at the single cell and tissue levels. The relationships between various types of cellular and tissue conduction alternans and their manifestations on surface ECG are important and complex issues.

Several forms of alternans have been described in the T wave of the ECG. Fig. 1 shows an extreme form of T-wave alternans (TWA; upper tracing), in which the T wave alternates between upright and inverted. Less marked forms of TWA are also observed, even down to the level of *microvolt* TWA, which can only be observed on the signal-averaged ECG. Microvolt TWA has been linked to the inducibility of ventricular fibrillation (VF).^{2,3}

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Cellular alternans 1: action potential duration restitution

T-wave alternans is caused by the alternation of cellular action potential duration (APD), as is shown in Fig. 1. Cellular APD alternation can come from a variety of mechanisms. First, as was first observed by Nolasco and Dahlen,⁴ the APD restitution relation, in which APD is a function of the preceding diastolic interval (DI), can create alternans if it is sufficiently steep (slope, >1). This restitution-based APD alternans has been mechanistically linked to the breakdown of reentry into the multiwave chaotic state that is VF. Interventions that reduce the slope of the APD restitution curve have shown efficacy in converting multiwave VF to single-wave monomorphic tachycardia.⁵⁻⁷

However, as Zhilin Qu has observed, APD restitution is probably *not* the cause of TWA on ECG, because TWA is seen at heart rates at which the slope of the APD restitution curve is basically flat. For example, at 120 beats per minute, which is fairly rapid, the interbeat interval is 500 milliseconds. If APD is, say, 250 milliseconds, that still leaves a 250-millisecond diastolic interval. The APD restitution curve is flat at such long diastolic intervals.

Cellular alternans 2: calcium dynamics

If APD restitution is not the cause of T-wave alternation, the search for the cellular basis of ECG TWA must focus on the other principal cause of cellular APD alternans: intracellular calcium (Ca) dynamics. Intracellular Ca handling in the cardiac myocyte is a very subtle and complex process, and many detailed models have been proposed. Although detailed models are useful and important, it is equally important to capture major qualitative features of Ca dynamics. One of the most important of these qualitative features is the independence of Ca alternans from voltage (V)-driven alternans, the sort previously discussed.

If rabbit myocytes are paced rapidly, they develop both V alternans and Ca alternans (Fig. 2, left panels.) In that circumstance, it is impossible to rule out that Ca is alternating simply because it is passively responding to V alternations. Voltage is coupled to Ca by the V-gated Ca channel, so V oscillations can easily drive Ca oscillations. As a way to approach this issue, we asked whether Ca oscillations could be seen if we controlled V *not* to oscillate, by using an “action potential clamp.” By digitizing an action potential waveform and using that to drive the myocyte, we could force V to be periodic. However, when V was forced to be periodic, we still saw marked alternation in intracellular Ca (Fig. 2, right panels). We concluded that intracellular Ca has its own nonlinear dynamics, independent of V-driven oscillations.

The mechanisms underlying Ca alternans are the subject of ongoing investigation. The first mechanism proposed was based on an observation by Diaz et al⁹ that the slope of the curve relating Ca release from the sarcoplasmic reticulum (SR) to SR Ca content was highly nonlinear, with a steeply sloped region at high SR contents (Fig. 3, right panel). Shiferaw et al¹⁰ incorporated this mechanism into a mathematical model and found that it did indeed produce the right sort of Ca alternans. (Fig. 3).

More recently, evidence that suggests that intracellular Ca oscillations can also occur *without* the oscillations in diastolic SR Ca that are required by the Diaz-Shiferaw mechanism has been presented.¹¹ The work of Picht et al¹¹ has suggested that the additional mechanism might be a delay in the availability of ryanodine receptors after inactivation. The question of how many and which mechanisms exist for Ca oscillations in various conditions remains an important issue for ongoing research.

Cellular alternans 3: positive and negative V-Ca coupling

Because oscillations in V and Ca occur independently, they can occur either in phase with each other (large Ca with long APD) or out of phase (large Ca with short APD) (Fig. 4). Which of these will be seen in a particular case depends on the relative strengths of sodium-calcium exchange (NaCaX) and the L-type Ca current I_{Ca} . If NaCaX is enhanced relative to I_{Ca} then the coupling will be positive, whereas if I_{Ca} is enhanced relative to NaCaX, the coupling will be negative.¹

Alternans at the tissue level

These varieties of cellular alternans can give rise to several different phenomena at the tissue level. The simplest form of tissue-level alternans occurs when all the cells in the tissue are alternating in phase with each other. This is *spatially concordant alternans*. It is the tissue phenomenon underlying TWA on ECG. Note that the cellular oscillations in APD may be APD restitution-driven (short DIs) or Ca-driven (long DIs). As noted, the microvolt TWA seen in humans at treadmill rates is much more likely to arise from Ca-driven oscillations because of their relatively long DIs.

The more malignant types of alternans are the *spatially discordant* forms. (Fig. 5). Pastore et al,² Rosenbaum et al,³ and Walker and Rosenbaum¹³ have pioneered the study of discordant alternans in the heart. Other researchers have since classified various forms of discordant alternans (for example, see reference¹⁴) and shown that a number of distinct mechanisms can give rise to discordant alternans. Discordant alternans can be created by restitution of conduction velocity (CV),^{15,16} but also by premature beats,¹⁷ by anatomically based gradients in APD,¹⁸ by structural barriers,^{19,20} and by negative Ca-V coupling.^{12,21}

As discussed, concordant alternans manifests on the ECG as TWA. Discordant alternans, on the other hand, because it essentially involves changes in CV across the tissue, presents on ECG as alternations in tissue conduction, that is, in alternations in the QRS complex. This *QRS alternans* is evident in Fig. 1, for example, and in a number of other figures from a variety of groups studying discordant alternans.^{2,16} Discordant alternans has also been reported in the atrium.²²

Why is discordant alternans so bad? Because it is a significant cause of *wave break*, which is the phenomenon that is essential to VF. It is commonplace to say that VF is caused by a “dispersion of refractoriness.” This is a somewhat hand-waving claim that if there is a lot of variation in APD, waves will propagate through the short-APD regions (that have recovered from refractoriness) but block in the long-APD regions. This argument is not wrong, although it leaves much to be explained, such as what kinds of “dispersions” are particularly dangerous. In any event, it is obvious that the presence of discordant alternans greatly increases the dispersion of refractoriness, however that is measured.

The dispersion of refractoriness argument can be put more formally. As a number of works have argued (see Qu et al¹⁶ for references), the tendency for wave back-wave front interactions increases directly with the quantity $d(\text{APD})/dx$, the spatial gradient of APD in the tissue. Clearly, that quantity can be much larger when the longest and shortest APDs coexist in the same tissue at the same time, that is, when there is discordant alternans (Fig. 6).

Nodal lines

In discordant alternans, by definition, there are regions where the APD change in a given beat is positive (short-long), whereas there are other regions in the same beat where the change in APD is negative (long-short). Necessarily, such regions are separated by lines along which the

APD change is zero, that is, there is no alternans on that line. In an important theoretical article, Echebarria and Karma^{22,23} derived an equation for the behavior of *dynamically generated* (as opposed to *structurally generated*) nodal lines in cardiac-like excitable media. Several significant nontrivial predictions can be obtained from their equations. These include the following.

- Dynamically generated nodal lines will always appear perpendicular to the local direction of wave conduction.
- As the pacing interval is decreased, dynamically generated nodal lines will move toward the pacing site.

(The article also discusses the dependence of nodal lines on CV restitution and the diffusion coefficient D .)

The 2 predictions, made by Echebarria and Karma²³ on purely theoretical grounds, were subsequently tested in work led by Hideki Hayashi et al,²⁴ under the direction of Shien-Fong Lin and Peng-Sheng Chen. Using mapping data in a rabbit Langendorff preparation, they showed that nodal lines do in fact occur in rapidly paced hearts and that their behavior exactly confirms the 2 theoretical predictions.

These mapping data provide striking confirmation of the general idea of discordant alternans and additionally suggests that the lines produced by rapid pacing can be dynamically generated (Fig. 7).

Summary

Discordant alternans can be due to a variety of cellular and tissue conduction instabilities. Both APD restitution and Ca dynamics can give rise to cellular alternans, and cellular APD and Ca alternations can be in phase or out of phase with each other. Cellular alternans can be translated into tissue-level alternans that is either spatially concordant (all areas in phase) or spatially discordant (areas out of phase with each other and separated by nodal lines). Nodal lines are critical phenomena in cardiac dynamics: they follow mathematical laws and are major causes of wave break and fibrillation in cardiac tissue.

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Fig. 1.

Alternans in ECG in guinea pig heart (upper tracing) and in 2 local action potential sites (as recorded by V-sensitive dyes; reproduced with permission from Pastore et al2).

Fig. 2.

Left panels, When a rabbit myocyte is paced at 180 milliseconds, membrane V and intracellular Ca both alternate; VAPDs alternate long-short, and Ca transients alternate large-small. Right panels, When an action potential clamp protocol maintains a constant waveform in V , Ca still shows marked alternations. (Reproduced with permission from Chudin et al.8)

Fig. 3.

Upper panels, 3 slightly different curves modeling Ca release from the SR as a function of SR Ca content. The slope of the rightmost segment of the curve increases from left to right. Lower panels, The change in release curves gives rise to a qualitative change in behavior. Shown are Ca releases as a function of the pacing interval T . Note that, in the relation on the left, shorter pacing intervals do not give rise to alternans, only to increases in the release level, but for the 2 curves on the right, a bifurcation to alternans occurs with increasing slope of the SR release curve. (Right-hand panel data reproduced with permission from Diaz et al.9)

Fig. 4.
 12 Positive vs negative V-Ca coupling (left) gives rise to V-Ca oscillations that are electromechanically in phase or out of phase.

Fig. 5.

Concordant and discordant alternans in a Langendorff guinea pig heart. Left, Paced at 220 milliseconds, the ECG (tracing) shows TWA, with the T wave alternately upright and inverted. The maps at bottom show that repolarization takes longer on beat 1 than on beat 2 (note more light shades and less black in beat 2, indicating faster repolarization). Thus, there is global APD alternans. Right, However, when the heart is paced at 180 milliseconds, very light and very dark areas are found in the same beat, with the areas alternating out of phase from beat to beat. This is discordant alternans, and it manifests on ECG as alternation in the QRS complex as well as the T wave (upper right tracing; reproduced with permission from Pastore et al2).

Fig. 6.

To model the observations of Laurita et al,¹⁷ a gradient of APD was created across the tissue by slowly changing the K current as a function of space. Upper maps, V is shown in gray scale. Middle, When an S2 stimulus is delivered 110 milliseconds after beat 15, it blocks, creating wave break and reentry (next panel), which finally break up into fibrillation (last panel). Lower maps, Here, APD is shown in gray scale for beats 14 and 15. Note that the wave break in the upper panels occurs precisely at the spatial boundary between the positive and negative APD changes, that is, the nodal line (see text that follows; reproduced with permission from Qu et al¹⁶).

Fig. 7.

Anterior view of the lower (apical) half of a rabbit heart Langendorff preparation, with wave fronts imaged by V-sensitive dyes. The pacing site is at the rectangular pulse in the upper center. At a pacing interval of 140 milliseconds, 5 consecutive nodal lines all lie together near the apex (dark lines). However, at the faster interval of 130 milliseconds, 5 consecutive nodal lines all lie closer to the pacing site and still perpendicular to the direction of conduction. (Reproduced with permission from Hayashi et al.²⁴)