Mechanisms of Discordant Alternans and Induction of Reentry in Simulated Cardiac Tissue

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Background—T-wave alternans, which is associated with the genesis of cardiac fibrillation, has recently been related to discordant action potential duration (APD) alternans. However, the cellular electrophysiological mechanisms responsible for discordant alternans are poorly understood.

Methods and Results—We simulated a 2D sheet of cardiac tissue using phase 1 of the Luo-Rudy cardiac action potential model. A steep (slope >1) APD restitution curve promoted concordant APD alternans and T-wave alternans without QRS alternans. When pacing was from a single site, discordant APD alternans occurred only when the pacing rate was fast enough to engage conduction velocity (CV) restitution, producing both QRS and T-wave alternans. Tissue heterogeneity was not required for this effect. Discordant alternans markedly increases dispersion of refractoriness and increases the ability of a premature stimulus to cause localized wavebreak and induce reentry. In the absence of steep APD restitution and of CV restitution, sustained discordant alternans did not occur, but reentry could be induced if there was marked electrophysiological heterogeneity. Both discordant APD alternans and preexisting APD heterogeneity facilitate reentry by causing the wavebreak to propagate slowly.

Conclusion—Discordant alternans arises dynamically from APD and CV restitution properties and markedly increases dispersion of refractoriness. Preexisting and dynamically induced (via restitution) dispersion of refractoriness independently increase vulnerability to reentrant arrhythmias. Reduction of dynamically induced dispersion by appropriate alteration of electrical restitution has promise as an antiarrhythmic strategy.

Key Words: alternans • arrhythmias • reentry • action potentials

T-wave alternans is closely associated with the vulnerability to ventricular arrhythmias and sudden cardiac death.1-5 The transition from concordant to discordant action potential duration (APD) alternans is also a harbinger of vulnerability to ventricular fibrillation.6-10 Recent optical mapping studies by Pastore et al11 linked these 2 findings by demonstrating that with increasing pacing rate, APD first alternates concordantly throughout the tissue (causing T-wave alternans) and then becomes spatially discordant, with areas of long-short APD alternation adjacent to areas with short-long APD alternation (causing both QRS and T-wave alternans). This spatially out-of-phase APD alternation reflects a state of markedly increased dispersion of refractoriness, which predisposes the heart to wavebreak and initiation of reentry. Despite the importance of APD alternans as the basis for T-wave alternans, however, “the mechanisms responsible for initiating discordant alternans are unknown.”9

It has been shown that for APD alternans to occur, an APD restitution slope >1 is required.11-14 We hypothesize that in addition to steep APD restitution, the engagement of conduction velocity (CV) restitution is required for the transition from concordant alternans to discordant alternans to occur. In this study, we simulated 2D cardiac tissue to investigate the cellular electrophysiological basis for discordant alternans, particularly the roles of electrical restitution and tissue heterogeneity. We also examined the mechanism by which rapid pacing and premature stimuli induce reentry and ventricular fibrillation in the setting of discordant alternans and tissue heterogeneity.

Methods
We simulated a monodomain 2D sheet (with “no-flux” boundary conditions) of cardiac tissue using the equation

\[
\frac{\partial V}{\partial t} = - I_{\text{ion}} + \frac{1}{\rho_S S_v} \frac{\partial^2 V}{\partial x^2} + \frac{1}{\rho_S S_v} \frac{\partial^2 V}{\partial y^2},
\]

where \(C_m = 1 \mu F/cm^2\) is transmembrane capacitance, \(V\) is transmembrane voltage, \(\rho_s = 0.5 \text{k} \Omega \text{cm}\) are gap junction resistivity, and \(S_v = 2000 \text{ cm}^{-2}\) is the surface-to-volume ratio. \(I_{\text{ion}}\) is the current density, which was generated by phase 1 of the Luo-Rudy (LR1) action potential model.16 The LR1 model was modified to achieve desired APD and...
CV restitution properties, as stated in Figure 1; unless otherwise stated, parameter values are the same as the original LR1 model (we set \([K_i]=5.4\ \text{mmol/L}\)). We integrated Equation 1 using our advanced method\(^{16}\) with time step varying adaptively from 0.01 to 0.2 ms and fixed 0.015-cm space step.

Electrophysiological heterogeneity was modeled by changing \(K^+\) channel conductance as follows:

\[
G(x,y) = G_{0} + \beta\sqrt{(x-L_x)^2 + (y-L_y)^2}/(L_x^2 + L_y^2),
\]

where \(x\) and \(y\) are the tissue coordinates, \(L_x\) and \(L_y\) are the dimensions of the tissue, \(G_0=0.282\ \text{mS/cm}^2\), \(\alpha=1.2\), and \(\beta=0.8\). This produced an electrophysiological heterogeneity similar to that observed in guinea pig ventricle.\(^{18}\) Equation 2 was modified to vary the degree of heterogeneity as specified.

Pacing stimuli (\(S_1\)) and premature stimuli (\(S_2\)) were delivered to a 0.15×0.15-cm area at the lower left corner (\(x=0, y=0\)) with a strength of 30 \(\mu\text{A/cm}^2\) (<1.5 times threshold), unless otherwise specified. APD and diastolic interval (DI) were defined as the durations that \(V>V_{90}\) and \(V<V_{0}\), respectively. APD dispersion was calculated as

\[
\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\text{APDi} - \text{APD})^2},
\]

where \(N\) is the total number of grid points we used in the simulation and \((\text{APD})\) is the spatially averaged APD.

**Results**

**Electrical Restitution**

To study APD and CV restitution effects, we modified LR1 kinetics to produce 2 types of APD restitution and 3 different types of CV restitution, for a total of 6 combinations. One APD restitution type had slope >1 over a wide range of DIs (Figure 1, A through C), and the other had slope <1 everywhere (Figure 1, D through F). CV restitution types differed in the range of DIs over which CV varied: either the normal range for the LR1 model (Figure 1, A and D), a shortened range (Figure 1, B and E), or a broadened range (Figure 1, C and F). Details of the parameter changes are stated in the Figure 1 legend.

**Modulation of Dispersion by Premature Stimulus**

In intact guinea pig ventricle, Laurita et al\(^{18}\) found that dispersion of APD during a premature stimulus decreased to a minimum before progressively increasing as the coupling interval was shortened. To investigate the roles of electrical restitution and electrophysiological heterogeneity, we compared electrophysiologically homogeneous and heterogeneous tissue by use of various APD and CV restitution combinations shown in Figure 1.

**Homogeneous Tissue**

For homogeneous tissue, the dispersion of APD (\(\sigma\)) was almost zero for long \(S_1S_2\) coupling intervals, increasing monotonically as the coupling interval decreased (Figure 2A). There was no dip in \(\sigma\) before the increase, because \(\sigma\) was
already near zero. The $S_1S_2$ coupling interval at which $\sigma$ increased was determined by CV restitution. Broadening the range of DIs over which CV changed caused $\sigma$ to increase at longer $S_1S_2$ coupling intervals ($'$), and narrowing the range had the opposite effect ($E$). Figure 2C shows the spatial distribution of APD in homogeneous tissue with steep APD restitution plus normal CV restitution (corresponding to Figure 1A) during baseline pacing and during a premature stimulus at 3 different $S_1S_2$ coupling intervals.

**Heterogeneous Tissue**

For electrophysiologically heterogeneous tissue, $\sigma$ was non-zero (by construction) during baseline pacing. For steep APD restitution plus normal CV restitution (corresponding to Figure 1A), $\sigma$ decreased to a minimum and then increased as the $S_1S_2$ coupling interval was shortened (Figure 2B, ●), similar to intact guinea pig ventricle (Figures 5 and 8B in Laurita et al16 and Figure 4A in Laurita et al19). Figure 2D shows corresponding spatial maps of APD during baseline pacing and premature stimuli at 3 different $S_1S_2$ coupling intervals. Altering CV restitution affected the range of $S_1S_2$ coupling intervals over which the dip occurred (eg, $\triangle$ in Figure 2B, corresponding to steep APD restitution plus broadened CV restitution in Figure 1C), but the dip remained prominent. In contrast, flattening APD restitution (corresponding to Figure 1, D through F) markedly attenuated the dip, with $\sigma$ remaining nearly constant irrespective of CV restitution properties (Figure 2B, ○).

**Transition From Concordant Alternans to Discordant Alternans**

To study how concordant and discordant APD alternans develop, we rapidly paced homogeneous or heterogeneous 2D tissue with different APD and CV restitution characteristics.

**Homogeneous Tissue**

Figure 3 shows the pseudo-ECG, APD alternans, and CL alternans at different pacing cycle lengths (PCLs) in homogeneous tissue. At PCL = 300 ms, there was no alternans. At PCL = 220 ms, concordant APD alternans developed, but no CL alternans. At PCL = 180 ms, CL alternans began and APD alternans became discordant. During discordant alternans, the pseudo-ECG showed only T-wave alternans, without QRS alternans. With discordant alternans, both the T-wave and the QRS complex alternated. This result is very similar to the findings of Pastore et al9 (their Figures 4 and 6). Thus, preexisting electrophysiological heterogeneity is not required for concordant or discordant alternans or for QRS or T-wave alternans.

Figure 4, A through C summarizes the maximum differences in APD (●) and CL (○) versus PCL in homogeneous tissue with steep APD restitution and different CV restitution properties (corresponding to Figure 1, A through C, respectively). With normal CV restitution (Figure 4A), CL alternans occurred after APD alternans. With CV restitution narrowed (Figure 4B), APD alternans occurred, but CL alternans never developed. With CV restitution broadened (Figure 4C), APD alternans and CL alternans occurred simultaneously. CL alternans was invariably associated with the onset of discordant APD alternans. For flat APD restitution (corresponding to Figure 1, D through F), neither APD nor CL alternans was
observed at any PCL, although a mild dispersion of APD was present, similar to Figure 3B.

**Heterogeneous Tissue**

Figure 4, D through F compares the dispersion of APD during 2 successive beats as a function of PCL in homogeneous (Figure 4D) and electrophysiologically heterogeneous (Figure 4, E and F) tissues. The result in Figure 4E, with steep APD restitution and normal CV restitution, is similar to the results of Pastore et al9 in guinea pig ventricle (their Figure 7). When APD restitution is shallow (corresponding to Figure 1D), σ decreased slightly with decreasing PCL and never increased even at the shortest PCL with 1:1 conduction (Figure 4F), consistent with the failure of discordant APD alternans to develop. The detailed mechanism underlying discordant alternans is presented in the Appendix.

**Discordant Alternans and the Induction of Reentry**

To explore the relationship between electrical alternans and reentry, homogeneous and heterogeneous tissues were paced from the lower left corner for 15 beats at a fixed PCL (S1), followed by a premature stimulus (S2) to induce reentry.

**Homogeneous Tissue**

In homogeneous tissue, an S2 stimulus delivered at the S1 site did not induce reentry. To induce reentry, S2 had to be delivered at a different site from S1 to break symmetry. Accordingly, S2 was applied along the diagonal from the lower left to the upper right corners. Figure 5, A and B, summarizes the vulnerable window for induction of reentry versus distance of S2 along the diagonal. At long PCLs without APD alternans (Figure 5A), the S2 either propagated or failed but never induced reentry. Only when the PCL was short enough to induce discordant alternans could reentry be induced by an S2 in a proper position (Figure 5B). Thus, induction of reentry by a premature stimulus during discordant alternans did not require preexisting electrophysiological heterogeneity if S2 was delivered at a different site from S1.

**Heterogeneous Tissue**

In heterogeneous tissue, an S2 delivered at the S1 site could induce reentry, because symmetry was broken by the preexisting tissue heterogeneity. Figure 6 illustrates reentry induction by an S2, which is similar to the example shown in guinea pig heart (see their Figure 8). Conduction block occurred at a location where APDs were in their long phase during discordant alternans (Figure 6B, middle). This local conduction block resulted in figure-eight reentry (fourth panel) and subsequent breakup into a fibrillation-like state (fifth panel).

Induction of reentry by this protocol depended on both electrical restitution properties and the degree of preexisting electrophysiological heterogeneity, in addition to the S1 and S1S2 intervals. Figure 5, C through F, summarizes the phase diagrams for several restitution combinations. For steep APD restitution plus normal CV restitution (as in Figure 1A), there was a large vulnerable window for S2 to induce reentry at short PCLs, which narrowed and disappeared as the PCL increased (Figure 5C), similar to homogeneous tissue. If the degree of preexisting electrophysiological heterogeneity was reduced (by setting β=0.4 in Equation 2), there was still a large vulnerable window for reentry (Figure 5E). In addition, a new phase was observed in which S2 excited a propagating wave that was blocked a distance away from the pacing site.

If APD restitution was flattened (corresponding to Figure 1D), reentry could not be induced with the same degree of preexisting electrophysiological heterogeneity (Figure 5D). However, if the preexisting heterogeneity was increased to produce a steep local electrophysiological gradient, a small vulnerable window was observed (Figure 5F). In addition, a new phase occurred in which reentry was only transient.
Thus, with sufficiently large electrophysiological heterogeneity, reentry could be induced even when APD restitution was flat enough to prevent discordant (or even concordant) alternans.

Mechanisms of Initiation of Reentry

It is generally argued that discordant alternans facilitates induction of reentry by increasing dispersion of refractoriness. However, a detailed mechanistic explanation is lacking. To this end, Figure 7A illustrates schematically 2 successive waves in the tissue. During wave propagation, both wavefront conduction velocity (CVF) and the waveback conduction velocity (CVB) vary in time and space. Conduction fails when the wavefront velocity is below a critical velocity CVF_c. For local conduction block, eg, at location a in Figure 7A, CVB at a must be slower than CVF at a, such that the wavefront of the second wave can approach closer and closer to the waveback of the first wave until CVF becomes smaller than CVF_c. However, local wavebreak does not necessarily guarantee reentry. Wavebreak at point a may not lead to a reentry because the wavelength (and hence refractoriness) of the tissue in this region is long and the broken wave does not have sufficient surrounding excitable tissue nearby to execute a full turn. In contrast, wavebreak at point b is more likely to induce reentry, because the wavelength and refractory period are short. From this argument, it is easy to conceptualize the conditions favoring reentry: (1) a sufficiently slow propagating waveback to cause conduction failure; (2) inhomogeneities to cause conduction failure locally; and (3) alternation of wavelength, or refractory period, to facilitate reentry. With respect to slow propagation of a waveback, the relationship between CVB and CVF of a wave can be deduced as follows: the time for the waveback at position r to propagate a distance \( \Delta r \) is the time that the wavefront propagates this same distance \( \Delta r \) plus the APD difference between position r and position \( r + \Delta r \). Therefore, the waveback velocity is given by the expression

\[
CVB(r) = \frac{\Delta r}{CVF(r) + \Delta APD(r)} = \frac{CVF(r)}{1 + APD'(r) CVF(r)},
\]

where \( APD'(r) = \Delta APD(r)/\Delta r \) is the spatial derivative of APD. Equation 4 is similar to the equation derived by Courtemanche. From Equation 4, if the gradient...
APD’(r)>0, then CVB(r)<CVF(r). If APD’(r)<0 but APD’(r)·CVF(r)>−1, then CVB(r)>CVF(r). If APD’(r)<0 but APD’(r)·CVF(r)<−1, then CVB(r)<0<CVF(r). Therefore, the back of a wave can propagate either slower or faster than its front, depending on the spatial gradient of APD. Two ways to produce large spatial APD gradients are discordant alternans and tissue heterogeneity.

Figure 7, B through D, shows CVF and CVB during pacing in homogeneous tissue with steep APD restitution and normal CV restitution (corresponding to Figure 1A). At PCL=220 ms (Figure 7B), discordant alternans was present. Both CVF and CVB were almost the same except at the boundaries and were much larger than CVFc. At PCL=180 ms (Figure 7, C and D), discordant alternans was present, and CVB varied greatly over space. In 1 of the 2 alternating beats, CVB changed from large positive to large negative velocity (Figure 7C). The negative velocity was due to the large decrease of APD along the direction of propagation (see Equation 4), which is illustrated in the inset at the bottom of Figure 7C. In a later beat (Figure 7D), the waveback propagated very slowly at first (CVB<CVF and CVFb) and then became faster than the wavefront. In contrast, Figure 7E shows CVF and CVB for heterogeneous tissue, with shallow APD restitution but steep gradient of electrophysiological heterogeneity in Figure 5F. A narrow area showing slow waveback propagation (much slower than CVFb) is present at one boundary of the sharp heterogeneity, and CVB varies from positive to negative at the other boundary. The cause of the negative velocity is similar to that in Figure 7C.

Discussion

Our simulations show good agreement with the following experimental findings: (1) For a premature stimulus in heterogeneous tissue, there is an optimal coupling interval that minimizes dispersion of repolarization, after which dispersion increases.18,19 (2) During rapid pacing, there is a transition from constant APD to discordant alternans to discordant alternans. Concordant alternans is manifest electrocardiographically as T-wave alternans; discordant APD alternans is associated with QRS alternans, which causes the dynamical instability, resulting in wavelength oscillation; CV restitution converts concordant APD alternans to discordant alternans, which results in further wavebreak slowing and increased dispersion of refractoriness.

Modulation of Dispersion by a Premature Stimulus

The mechanism by which a premature stimulus modulates dispersion agrees with the conjecture by Laurita et al.18: a short S2S2 coupling interval results in a short DI for the premature beat. The premature beat thus propagates more slowly than the normal beats, so that DIs along the propagation direction increase, which, in turn, result in longer APD (see Figure 2C). In homogeneous tissue, this results in a monotonic increase in dispersion as S2S2 decreases. However, in electrophysiologically heterogeneous tissue, both APD restitution and preexisting heterogeneity are important for modulation of dispersion. If APD restitution is steep, the long APD is markedly shortened by a short DI, whereas the shorter APD is only modestly shortened by a longer DI. This results in less dispersion (Figure 2B). CV restitution changes the coupling interval and thus changes the dispersion.

Mechanism of Concordant and Discordant APD Alternans

For APD alternans (concordant or discordant) to occur, an APD restitution slope >1 is required, even in electrophysiologically heterogeneous tissue. During pacing from the same site, to proceed from concordant to discordant alternans requires that the PCL be short enough to engage CV restitution. CV restitution explains why discordant alternans is associated with QRS as well as T-wave alternans. Neither concordant nor discordant alternans requires preexisting electrophysiological heterogeneity; they can arise solely from the dynamics of electrical restitution. (See the Appendix for formal analysis of the mechanism.) Although for large heterogeneous initial conditions, transient discordant alternans can be initiated without engaging CV restitution, alternans will finally become concordant.

Facilitation of Reentry

Discordant alternans markedly increases dispersion of refractoriness and increases the ability of a premature stimulus to cause localized wavebreak and induce reentry, even in completely homogeneous tissue. Preexisting electrophysiological heterogeneity is not required if the S2 extrastimulus is delivered at a different site from the S1 pacing site. In the absence of discordant alternans, preexisting electrophysiological heterogeneity can also cause localized wavebreak.

Although reentry can be induced with or without steep APD restitution, the vulnerability is different. When APD restitution is shallow, wavebreak occurs only in regions with very large preexisting heterogeneity. Because APD and wavelength are long, reentry cannot be easily induced (Figure 5), eg, at location a in Figure 7A. The vulnerable window of reentry is much larger when APD restitution is steep enough to produce discordant alternans (Figure 5), because during discordant alternans, wavebreak always occurs in the waves with short APD and wavelength (eg, at location b in Figure 7A).

In summary, heterogeneity breaks symmetry and also can cause wavebreak by wavefront slowing; APD restitution causes the dynamical instability, resulting in wavelength oscillation; CV restitution converts discordant APD alternans into discordant alternans, which results in further wavebreak slowing and increased dispersion of refractoriness.

Clinical Implications

Combined with experimental evidence relating discordant APD alternans to T-wave alternans and increased vulnerability to ventricular arrhythmias,1–10 our findings further emphasize the importance of dispersion of refractoriness to induction of ventricular reentry. Most importantly, our analysis suggests that dispersion of refractoriness arising from purely dynamic factors, namely APD and CV restitution, is at least as
important as, if not more important than, preexisting electrophysiological heterogeneity for enhancing susceptibility to ventricular arrhythmias. This is therapeutically encouraging, because restitution properties are potentially modifiable by drugs. Drugs altering electrical restitution to reduce dynamic dispersion represent a promising antiarrhythmic strategy.

**Appendix**

**Mechanism of Discordant Alternans**

Assume APD and CV restitution are valid in a spatially uniform system:

\[ \text{APD}_{n+1}(t) = f[D_{n}(t)] = F[\text{CL}_{n}(t) - \text{APD}_{n}(t)]. \]

\[ \text{CV}_{n+1}(t) = g[\text{DI}_{n}(t)]. \]

In Equation 5, \( \text{CL}_{n}(r) \) can be expressed as

\[ \text{CL}_{n}(t) = \text{PCL} + \int_{0}^{r} \frac{\text{dr}'}{\text{CV}_{n+1}(t')} - \int_{0}^{r} \frac{\text{dr}'}{\text{CV}_{n}(t')} \]

\[ = \text{PCL} + \int_{0}^{r} \frac{\text{CV}_{n}(t') - \text{CV}_{n+1}(t')}{\text{CV}_{n+1}(t') \text{CV}_{n}(t')} \text{dr}' \]

\[ = \text{PCL} + \frac{\Delta \text{CV}(t')}{\text{CV}_{n}(t') \text{CV}_{n}(t')} \int_{0}^{r} \frac{\text{dr}'}{\text{CV}_{n}(t')} \]

\[ = \text{APD}_{n}(r) + \text{DI}_{n}(r). \]

Starting from a uniform initial condition, we can derive from Equations 5 and 6 the following.

1. For long PCLs without APD alternans, the system remains uniform.
2. For PCLs at which APD alternates but CV restitution is not engaged, \( \text{CV}_{n}(t) = \text{CV}_{n}(t') \). In this case, the integral in Equation 6 is zero, ie, \( \Delta \text{CL}_{n}(r) = 0 \). Therefore, \( \text{CL}_{n}(r) = \text{PCL} \) everywhere in space, which indicates from Equation 5 that \( \text{APD}_{n}(r) \) and \( \text{DI}_{n}(r) \) must both be uniform in space, ie, uniform concordant alternans occurs.
3. For PCLs in a range in which both APD alternans occurs and CV restitution is engaged, assume that the system is in a stable alternating state such that \( \text{DI}_{n+1}(r) = \text{DI}_{n}(r) > \text{DI}_{n-1}(r) = \text{DI}_{n}(r) \) at position \( r \). According to Equation 6, \( \Delta \text{CL}_{n}(r) = -\Delta \text{CL}_{n}(r) \) and \( \text{DI}_{n}(r) = \text{CL}_{n}(r) - \text{APD}_{n}(r) \), we then have

\[ \text{DI}_{n+1}(r) = \text{PCL} - \Delta \text{CL}_{n}(r) - \text{APD}_{n}(r) = \text{PCL} - \frac{\Delta \text{CL}_{n}(r)}{2} \int_{0}^{r} \frac{\text{dr}'}{\text{CV}_{n+1}(t')} - \frac{\text{dr}'}{\text{CV}_{n}(t')} \]

Rearranging and substituting Equation 7,

\[ \text{APD}_{n+1}(r) - \text{APD}_{n}(r) > -2 \Delta \text{CL}_{n}(r) \]

\[ = 2 \frac{\text{CV}_{n+1}(t') - \text{CV}_{n}(t')}{\text{CV}_{n+1}(t') \text{CV}_{n}(t')} \int_{0}^{r} \frac{\text{dr}'}{\text{CV}_{n}(t')} \]

Uniform concordant alternans, with \( \text{APD}_{n+1}(r) - \text{APD}_{n}(r) \) constant over space, is impossible, because the integral in Equation 8 changes with \( r \). Nonuniform discordant alternans can exist when \( \text{CV}_{n+1}(r) - \text{CV}_{n}(r) \) or \( r \) is small, for which Equation 8 can be satisfied. However, when either \( \text{CV}_{n+1}(r) - \text{CV}_{n}(r) \) or \( r \) is large, then the integration in Equation 8 becomes larger and larger, and Equation 8 cannot hold for discordant alternans. Therefore, \( \text{CV}_{n+1}(r) - \text{CV}_{n}(r) \) must change its sign along \( r \) so as not to violate Equation 8, resulting in discordant alternans.

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