

## The Dynamics of Cardiac Fibrillation

James N. Weiss, MD; Zhilin Qu, PhD; Peng-Sheng Chen, MD; Shien-Fong Lin, PhD;  
Hrayr S. Karagueuzian, PhD; Hideki Hayashi, MD, PhD; Alan Garfinkel, PhD; Alain Karma, PhD

**Abstract**—Reentry occurs when the electrical wave propagating through the atria or ventricles breaks locally and forms a rotor (also called a scroll wave or functional reentry). If the waves propagating outward from a rotor develop additional wavebreaks (which may form new rotors), fibrillation results. Tissue heterogeneity, exacerbated by electrical and structural remodeling from cardiac disease, has traditionally been considered the major factor promoting wavebreak and its degeneration to fibrillation. Recently, however, dynamic factors have also been recognized to play a key role. Dynamic factors refer to cellular properties of the cardiac action potential and  $Ca_i$  cycling, which dynamically generate wave instability and wavebreak, even in tissue that is initially completely homogeneous. Although the latter situation can only be created in computer simulations, its relevance to real (heterogeneous) cardiac tissue has been unequivocally demonstrated. Dynamic factors are related to membrane voltage ( $V_m$ ) and  $Ca_i$ .  $V_m$  factors include electrical restitution of action potential duration and conduction velocity, short-term cardiac memory, and electrotonic currents.  $Ca_i$  factors are related to dynamic  $Ca_i$  cycling properties. They act synergistically, as well as with tissue heterogeneity, to promote wavebreak and fibrillation. As global properties, rather than local electrophysiological characteristics, dynamic factors represent an attractive target for novel therapies to prevent ventricular fibrillation. (*Circulation*. 2005;112:1232-1240.)

**Key Words:** fibrillation ■ calcium ■ action potentials ■ antiarrhythmia agents ■ death, sudden

Ventricular fibrillation (VF) is the most common cause of sudden death, and atrial fibrillation, the most prevalent clinical arrhythmia, accounts for nearly one third of strokes in the elderly. Fibrillation results when an electrical wavebreak induces reentry and triggers a cascade of new wavebreaks. In the diseased heart, the increased predisposition to wavebreak → reentry → fibrillation has traditionally been ascribed to increased tissue heterogeneity caused by structural and electrical remodeling associated with disease processes. However, recent evidence indicates that dynamic factors operate synergistically with tissue heterogeneity, as well as among themselves, to promote wavebreak. Unlike tissue heterogeneity (which refers to local structure and fixed electrophysiological dispersion), dynamic factors create functional electrophysiological dispersion that destabilizes wave propagation. Dynamic factors are related to cellular membrane voltage ( $V_m$ ) and  $Ca_i$ . The former include action potential duration (APD) and conduction velocity (CV) restitution, short-term cardiac memory, and electrotonic currents. The latter are related to  $Ca_i$  cycling between the sarcoplasmic reticulum (SR) and cytoplasm. Although dynamic factors can vary in different regions of the heart and exacerbate tissue heterogeneity, dynamic instability also has global aspects. Suppressing dynamic instability may be a promising therapeutic target if it can be accomplished without exacerbating tissue heterogeneity. In this review, we provide

a brief overview of how dynamic factors synergistically interact with preexisting tissue heterogeneity to promote fibrillation.

### Electrical Waves and Wavebreak

Cardiac excitation can be viewed as an electrical wave, with a wavefront corresponding to the AP upstroke (phase 0) and a waveback corresponding to rapid repolarization (phase 3). The wavelength, ie, the distance between the wavefront and waveback, is defined as the product of APD and CV (Figure 1A). Normally, when a wave propagates through tissue, wavefront and waveback never touch. If they do, their point of intersection defines a wavebreak, sometimes called a phase singularity. When wave propagation fails simultaneously along the full length of the wavefront, the electrical wave extinguishes everywhere and no harm is done. However, if the wavebreak is spatially localized, reentry may result. Reentry begins at a localized wavebreak because the curvature of the wavefront at that point is very high. The high curvature produces a source-sink mismatch (ie, too little depolarizing current with respect to the number of locally coupled unexcited cells), which slows conduction of the propagating wave near this point,<sup>1</sup> causing the wave to rotate around the wavebreak point. If this wavebreak rotates around an anatomically defined circuit (such as a scar), it is called anatomic reentry. However, the wavebreak point can also

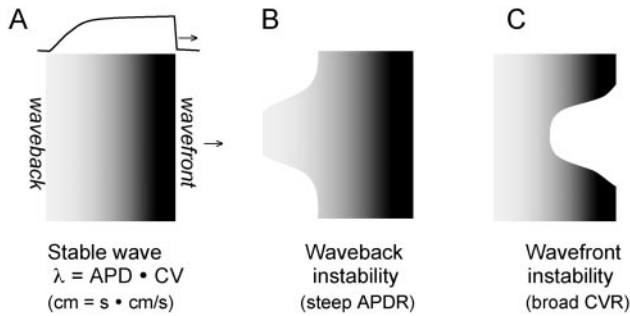
From the Cardiovascular Research Laboratory and the Departments of Medicine (Cardiology; J.N.W., Z.Q., A.G.), and Physiological Science (A.G.), David Geffen School of Medicine at UCLA, and Cedars-Sinai Medical Center (P.-S.C., S.-F.L., H.S.K., H.H.), Los Angeles, Calif, and the Department of Physics (A.K.), Northeastern University, Boston, Mass.

Correspondence to James N. Weiss, MD, Division of Cardiology, 3641 MRL Bldg, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1760. E-mail jweiss@mednet.ucla.edu

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.104.529545



**Figure 1.** The cardiac impulse as an electrical wave, with a wavefront (black) corresponding to the upstroke of the AP, and a waveback (gray to white), corresponding to repolarization. Wavelength ( $\lambda$ ) is the product of APD and CV. A, Uniform wave. B, Wave with waveback instability due to APD local prolongation. C, Wave with wavefront instability due to local CV slowing.

rotate without an anatomic circuit as functional reentry, called a *rotor*, equivalent to a spiral wave in 2D or a scroll wave in 3D tissue.<sup>2</sup> The demonstration of functional (eg, “leading circle”) reentry in the absence of an anatomic obstacle by Allesie and coworkers<sup>3</sup> and subsequent documentation of scroll wave reentry in ventricular tissue by Davidenko et al<sup>4</sup> provided key experimental evidence.

Rotors typically have a short cycle length, producing a very rapid tachycardia. If the process of wavebreak continues, fibrillation results. It is generally accepted that fibrillation requires an initial wavebreak to create the first rotor, although it is possible that focal activity underlies some types of fibrillation, especially in the atrium and thoracic veins.<sup>5,6</sup> However, controversy exists as to whether subsequent wavebreaks are required to maintain fibrillation. In the multiple-wavelet hypothesis,<sup>7</sup> ongoing wavebreak is proposed to be the engine of fibrillation. The mother rotor hypothesis,<sup>8</sup> on the other hand, postulates that a relatively stable, fast “mother rotor” caused by the initial wavebreak drives fibrillation, with subsequent wavebreaks occurring as epiphenomena due to fibrillatory conduction block in outlying regions that are unable to conduct 1:1. For both hypotheses, however, the initial wavebreak is critically important, and understanding its mechanism holds the key to developing effective pharmacological and/or gene therapy for fibrillation.

### Tissue Heterogeneity and Wavebreak

Tissue heterogeneity can cause wavebreak by several mechanisms. When a wave travels into a region with a long refractory period (eg, longer APD), wavebreak will occur if the tissue has not yet recovered excitability from the previous wave. Wavebreak can also occur if there is a source-sink mismatch between the wavefront and the excitable tissue in front of it, so that the density of the depolarizing diffusive current is too low to bring the excitable tissue to threshold. This may occur at anatomic source-sink mismatches, such as papillary or pectinate muscle insertions,<sup>9,10</sup> or when excitability is depressed regionally due to ischemia or drugs.

Tissue heterogeneity in the heart plays a key role in the susceptibility to fibrillation.<sup>7</sup> Disease processes that increase tissue heterogeneity are thought to increase the likelihood that physiological triggers, such as spontaneous premature extra-

systoles, will succeed in inducing a localized wavebreak in a region with a high degree of electrophysiological dispersion, eg, at the border zone between normal and infarcted tissue.

Once a localized wavebreak initiates reentry, a rotor may then either be unstable and break up into fibrillation or become anchored by an anatomic structure to produce monomorphic tachycardia. Tissue heterogeneity in the heart can be either anatomic, due to infarction, fibrosis, or structural remodeling, or electrophysiological, due to electrical remodeling, drugs, genetic defects, or heterogeneous autonomic innervation.

Even though disease processes often markedly exacerbate tissue heterogeneity in the heart, the likelihood that a spontaneous premature extrasystole will induce localized wavebreak and sustained reentry is low. For example, spontaneous ventricular ectopy at a rate of 2 extrasystoles per minute, common in patients with cardiomyopathy, is equivalent to  $\approx 1$  million ventricular extrasystoles per year. However, the rate of sudden death episodes in such patients is typically measured in months to years, rather than minutes. In normal human ventricles, ventricular extrasystoles are also common,<sup>11</sup> but fortunately, normal tissue heterogeneity is insufficient for these triggers to induce localized wavebreak with enough adjacent excitable tissue for a self-sustaining rotor to form. However, a very large electrical stimulus ( $50\times$  to  $100\times$  threshold)<sup>12</sup> or very rapid pacing<sup>13</sup> can induce a rotor in the normal heart, which then almost always spontaneously degenerates to VF (the VF threshold). Atrial fibrillation can be similarly induced by electrical pacing, but it is typically nonsustained in normal human atria because the wavelength is too long in relation to normal atrial size to permit sustained reentry.<sup>14</sup>

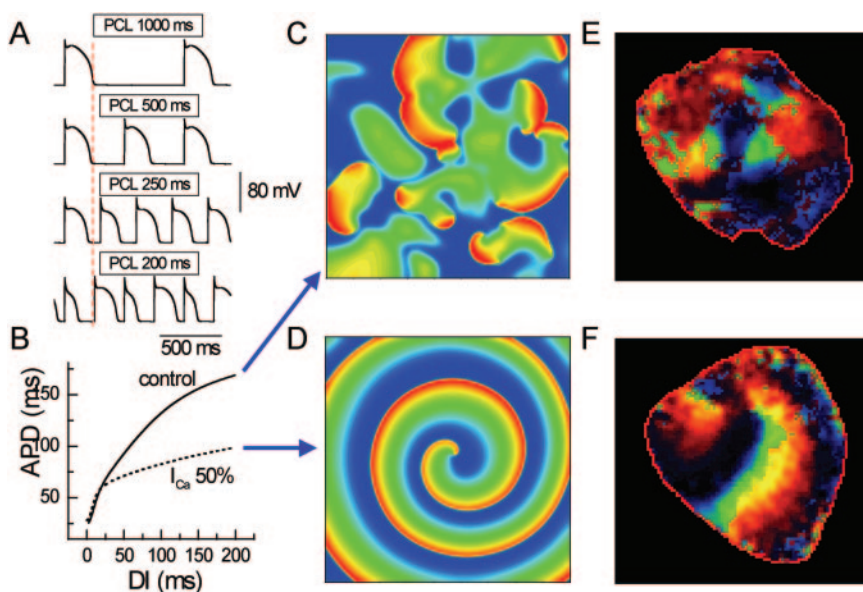
### Dynamic Factors and Wavebreak

Although the normal heart exhibits electrophysiological and structural heterogeneity, fibrillation in the normal heart also depends on dynamic factors.<sup>15</sup> Dynamic factors produce functional dispersion of electrophysiological properties, arising purely from the dynamic properties of  $V_m$  and  $Ca_i$  cycling on APD and wavelength, as demonstrated in computer simulations in which all cells in the tissue have identical properties and a normal ventricular AP. A rotor induced by rapid pacing or a large, premature stimulus spontaneously breaks up into a fibrillation-like state despite homogeneous initial conditions.<sup>16–18</sup> This happens because the normal electrical wave is inherently unstable at very rapid heart rates. Because wavelength is the product of APD and CV, factors regulating APD and CV are critical for wave stability. These can be divided into  $V_m$  and  $Ca_i$  factors. The former include APD restitution, CV restitution, short-term cardiac memory, and electrotonic currents. The latter include  $Ca_i$  cycling dynamics and spontaneous SR  $Ca_i$  release.

### $V_m$ -Related Dynamic Factors

#### APD Restitution

When heart rate increases, APD shortens physiologically to preserve a sufficient diastolic interval (DI) for ventricular filling and coronary flow (Figure 2A). This relation defines an APD restitution curve (Figure 2B). If the APD restitution



**Figure 2.** APD restitution slope and rotor stability. A, APD shortening and APD alternans as pacing cycle length (PCL) decreases (computer simulation). B, APD restitution curves, with slope  $>1$  (solid line) or  $<1$  (dashed line, obtained with 50% block of the calcium current). C and D, Spiral wave behavior several seconds after initiating a rotor in homogeneous 2D tissue. All cells are identical, with either a steep (C) or shallow (D) APD restitution slope. E and F, Optically measured surface voltage maps in an intact Langendorff rabbit heart before (E) and after (F) partially blocking the L-type calcium current with D600 (0.5 mg/mL) to flatten the APD restitution slope to  $<1$ . In E, multiple wavefronts move in a complex VF pattern. In F, VF has converted to VT, manifested as a stable double-armed rotor. See Figure 3A&B for corresponding electrograms. Reprinted from Wu et al,<sup>24</sup> with permission.

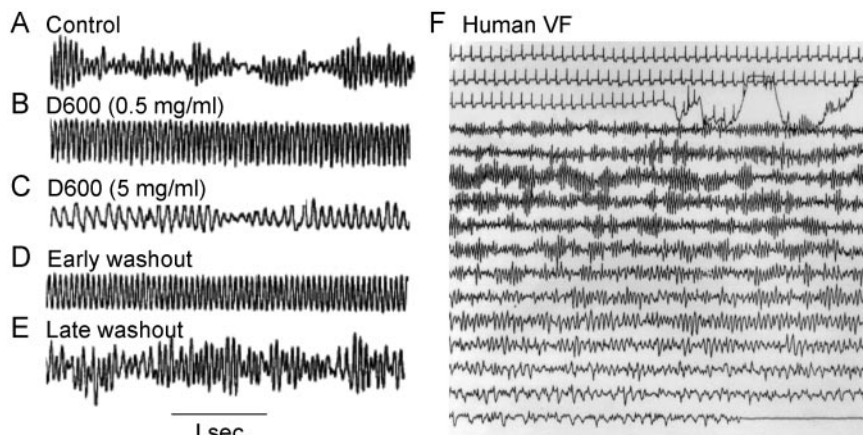
curve has a steep slope, then APD (and hence, wavelength) is sensitive to small changes in DI. During a rotor, small perturbations in DI will create large changes in APD and wavelength. If these wavelength oscillations are self-amplifying (eg, APD restitution slope  $>1$ ), then the wavelength oscillations are unstable and cause the rotor to break up. This has been clearly demonstrated in 2D and 3D cardiac tissue simulations in which every cell is assigned identical properties; yet when a rotor is induced, it breaks up spontaneously into multiple wavelets as a result of dynamically induced functional heterogeneities<sup>16–18</sup> (Figure 2C–D). These theoretical predictions have been borne out by experiments<sup>19–24</sup> demonstrating that reducing the slope of the APD restitution curve prevented VF in the normal ventricle (Figure 2E–F). Based on these findings, it has been proposed that drugs that flatten the APD restitution slope may be antifibrillatory by increasing dynamic wave stability (Figure 2D).

As the concept of dynamic stability has been examined more intensely, it has become apparent that APD restitution is not the sole source of dynamic wave instability. Several additional dimensions of instability have been identified, including CV restitution, short-term cardiac memory, elect-

rotonic currents, and especially  $Ca_i$  cycling. They interact synergistically with each other, as well as with tissue heterogeneity. Their physiological importance in promoting VF in real cardiac tissue is just beginning to be explored.

### CV Restitution

Whereas self-amplifying oscillations in wavelength caused by a steep APD restitution slope are manifested primarily in the waveback (ie, repolarization) of the wave (Figure 1B), self-amplifying oscillations in the wavefront can also cause wavebreak (Figure 1C) when coupled with a steep APD restitution curve or tissue heterogeneity. Because wavefront position is directly controlled by CV, this situation arises dynamically when CV has a strong dependence on the preceding DI (ie, “broad” CV restitution). Recently, we described a type of VF due to this mechanism<sup>24</sup> in response to the calcium channel blocker D600 (Figure 3). At concentrations selective for L-type calcium channel blockade, D600 flattened the APD restitution slope and converted VF to ventricular tachycardia (VT) (Figure 3B). However, at higher concentrations, which also blocked cardiac sodium channels and decreased excitability, D600 converted VT back to VF



**Figure 3.** Conversion of type 1 multiple-wavelet VF to type 2 mother rotor VF. Electrograms from the fibrillating rabbit ventricle. A, Under control conditions with type 1 VF (optical map shown in Figure 2E). B, After 0.5 mg/mL D600 (optical map shown in Figure 2E), showing VT. C, After high-dose D600 (sufficient to block sodium channels) converted VT to type 2 VF. D and E, Washout of D600, recapitulating the sequence in reverse. F, Holter recording of VF in a patient, showing evolving ECG changes that are consistent with a transition from rapid type 1 VF to slow type 2 VF as the effects of acute ischemia set in.



(Figure 2C), but with altered features. Whereas optical mapping showed that the original type 1 VF before D600 was typical for multiple-wavelet fibrillation, the new type 2 VF in the setting of low excitability was slower, and optical activation maps indicated a mother rotor mechanism of VF. That is, a stable mother rotor acted as a focal periodic source, and wavebreak occurred due to fibrillatory conduction block as waves from the mother rotor were unable to conduct 1:1 into the surrounding tissue. The mother rotor typically was anchored to a papillary muscle near the left ventricular apex.<sup>25</sup> Thus, in type 2 VF, broad CV restitution drives wavebreak by causing the wavefront to become unstable, and **a steep APD restitution slope is not required.**

These findings help to resolve the controversy over the 2 current leading hypotheses of VF. **Type 1 VF corresponds to multiple-wavelet fibrillation, as originally proposed by Moe and colleagues,<sup>7</sup> in which continual wavebreak is the engine driving fibrillation.** Type 2 VF corresponds to the mother rotor mechanism recently emphasized by Jalife and colleagues (Zaitsev et al<sup>8</sup> and Samie et al<sup>26</sup>). Clinically, both forms of VF may be important, with type 1 VF typically occurring when VF is first induced and being replaced by type 2 VF as acute ischemia reduces tissue excitability and amplifies static tissue heterogeneities.<sup>27</sup> Figure 3F shows a Holter monitor recording from a patient during an episode of VF. Initially, the ECG shows fine, rapid undulations typical of type 1 VF. After a short time, however, the undulations slow and coarsen, consistent with type 2 VF, as the effects of ischemia on excitability set in.

However, the mother rotor mechanism has also been described in normal excitability conditions.<sup>8,26</sup> The mechanism is still unclear but may be related to electrophysiological tissue heterogeneity<sup>8,26</sup> or other effects.

### Short-Term Cardiac Memory

Electrical restitution considers APD or CV solely as a function of the immediately previous DI. Although the previous DI has a strong influence, APD and CV are influenced by the pacing history in toto. Short-term cardiac memory can be broadly defined as everything else in the pacing history besides the last DI that regulates APD and CV in the short term. Multiple factors therefore mediate short-term cardiac memory, including ionic currents with slow enough recovery kinetics to accumulate over several cardiac cycles at rapid heart rates (primarily potassium currents<sup>28</sup>) and  $Ca_i$  cycling.  $Ca_i$  cycling is important because pacing rate influences systolic and diastolic  $Ca_i$  levels,<sup>29</sup> which influence calcium-sensitive currents that modulate APD and hence, wavelength. Short-term cardiac memory should be distinguished from **long-term cardiac memory, which is related to pacing-induced changes in protein modification and/or gene expression.**

Because of short-term cardiac memory, APD and CV restitution curves assessed by pacing protocols should be viewed only as approximations of electrical restitution occurring during an arrhythmia, whose pacing history is different. APD restitution measured by different pacing methods often yields different results, and the APD restitution slope does not always predict APD alternans.<sup>19</sup> For this reason, a simple,

“magic bullet” criterion for predicting wave instability during VF, such as an APD restitution slope being  $>1$  or the presence of pacing-induced APD alternans, is not possible. Despite this limitation, however, experiments have validated that flattening the APD restitution slope (measured by pacing protocols) increases wave stability during VF and prevents type 1 VF in the normal ventricle.<sup>19–24</sup>

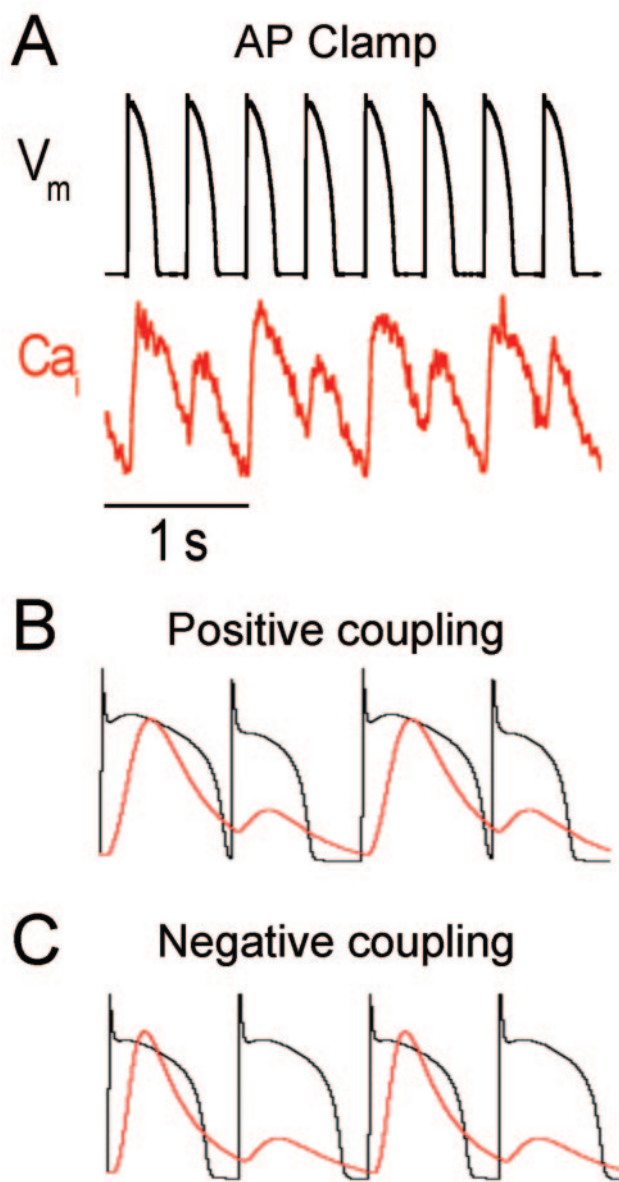
### Electrotonic Currents

In addition to membrane ion channels, electrotonic current flow, proportional to the voltage difference and gap junction conductance between adjacent cells, influences APD, CV, and wavelength. In 3D tissue, fiber rotation and other heterogeneities affecting current diffusion can generate electrotonic currents, which cause filaments of meandering scroll waves to twist, leading to wavebreak.<sup>18,30</sup> Decreasing meander by flattening the APD restitution slope or other means still prevents wavebreak by this mechanism. Electrotonic currents also play an important role in the development and evolution of repolarization alternans (see next section).

### $Ca_i$ -Related Dynamic Factors

$Ca_i$  cycling is increasingly recognized as an important regulator of dynamic wave instability. In mammalian hearts, most of the calcium that activates contraction is released from intracellular stores in the SR by the process of calcium-induced calcium release (CICR).<sup>31</sup> With CICR, a small amount of calcium flowing into the cell via L-type calcium channels triggers calcium-release channels (ryanodine receptors) in the SR membrane to open and release the larger SR calcium pool into the cytoplasm. Cytoplasmic calcium is then pumped back into the SR via an SR Ca-ATPase (ie, SERCA pump) or transported across the sarcolemmal membrane by Na-Ca exchange. Under normal physiological conditions, regulation of contractile force by  $Ca_i$  in the beating heart is tightly controlled by  $V_m$ , such that the  $Ca_i$  transient is effectively slaved to the AP. However, CICR constitutes an excitable medium in its own right and can exhibit independent dynamics. For example, when isolated rabbit ventricular myocytes are paced at rapid rates under AP clamp conditions,  $Ca_i$  transients develop alternans and more complex periodicities, despite the fact that the  $V_m$  waveform is fixed<sup>29</sup> (Figure 4A). Accumulating evidence suggests that  $Ca_i$  alternans is the predominant cause of APD alternans in intact tissue.<sup>32,33</sup> Theoretical<sup>34,35</sup> and experimental<sup>36</sup> studies suggest that a steep relation between calcium release from the SR and SR load is the underlying mechanism of  $Ca_i$  alternans in isolated cells and hence, also in tissue.

The SR is also capable of spontaneously releasing calcium when the former becomes calcium overloaded.<sup>31</sup> Rapid pacing is one modality for inducing SR calcium overload and can produce triggered activity due to delayed and early afterdepolarizations.<sup>31</sup> When repolarization reserve is reduced, as in the long-QT syndromes, early afterdepolarizations may both initiate and reinitiate reentry. In the latter case, theoretical studies<sup>37</sup> suggest that when rotors self-extinguish by colliding with a border, early afterdepolarizations arising from spontaneous SR calcium release may then perpetuate reentry. Traveling  $Ca_i$  waves due to regenerative CICR are also



**Figure 4.**  $Ca_i$  cycling and wavelength. A, Primary  $Ca_i$  alternans, during pacing of a rabbit ventricular myocyte with an AP clamp to prevent the APD from alternating.  $Ca_i$  still alternates. B, Positive coupling, in which a large  $Ca_i$  transient (red) prolongs APD (black) by increasing the inward current during the AP plateau (mainly via Na-Ca exchange). C, Negative coupling, in which a large  $Ca_i$  transient shortens APD by decreasing the inward current during the AP plateau (mainly via enhancing calcium-induced inactivation of the L-type calcium current).

observed in the setting of  $Ca_i$  overload<sup>38</sup> and can propagate intercellularly from myocyte to myocyte.<sup>39</sup> Actual subcellular  $Ca_i$  rotors due to CICR have been described in cardiac myocytes.<sup>38</sup>

Once released,  $Ca_i$  influences APD (and hence, wavelength) through calcium-sensitive ionic currents, including the L-type calcium current, the Na-Ca exchange current, and calcium-activated nonselective and chloride currents.  $Ca_i$  release has opposing effects on APD: it tends to shorten APD by potentiating calcium-induced inactivation of the L-type

calcium current but tends to prolong APD by enhancing the inward current through electrogenic Na-Ca exchange. Depending on which effect predominates, a larger  $Ca_i$  transient can cause the APD to prolong (*positive coupling*) or shorten (*negative coupling*) (Figure 4B and 4C). Conversely, these same currents influence the amount of calcium stored in the SR,<sup>31</sup> so that the coupling between  $V_m$  and  $Ca_i$  is bidirectional. This coupling raises the possibility that under pathological conditions,  $Ca_i$  release may alter the AP sufficiently to promote wavebreak, as has been observed in 2D cardiac tissue simulations.<sup>29</sup> Experimentally, we<sup>40</sup> found that the  $Ca_i$  and  $V_m$  waveforms, which tracked each other closely during pacing and VT, became desynchronized during VF. These observations all support that idea that during tachycardia and fibrillation,  $Ca_i$  dynamics may contribute independently to initiation and destabilization of reentry.

Also,  $Ca_i$  cycling and APD restitution are interrelated. In rabbit ventricular myocytes, a normal  $Ca_i$  transient was required for a steep APD restitution slope and APD alternans, because removing the influence of the  $Ca_i$  transient on membrane ionic currents during the AP by any of several means caused the APD restitution slope to become flat and/or APD alternans to disappear.<sup>41</sup> Thus,  $Ca_i$  influences wave stability by multiple mechanisms.

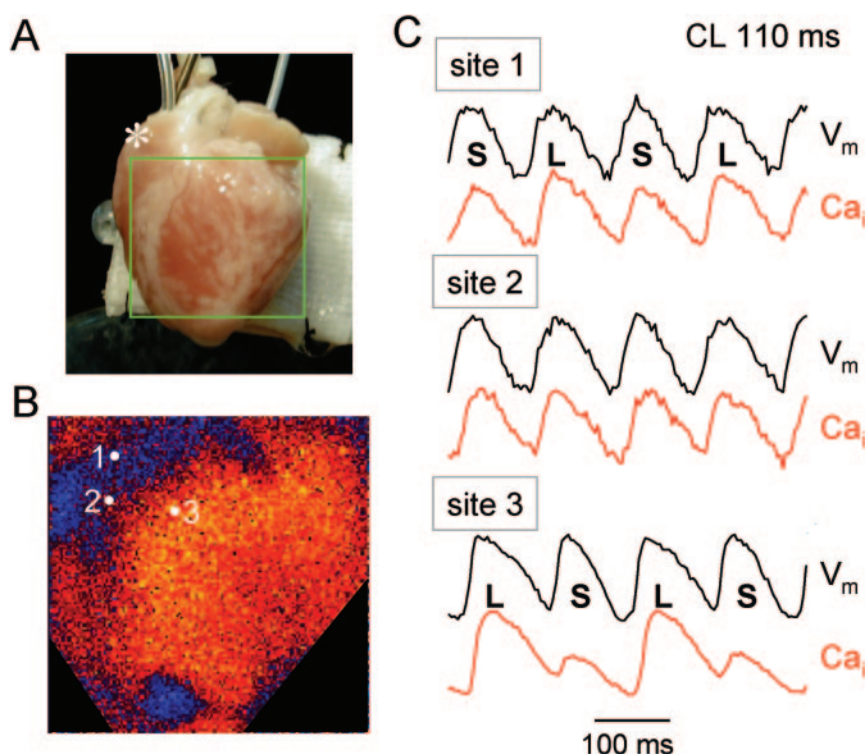
#### Dynamics of Repolarization Alternans

Repolarization alternans, detected clinically as microvolt T-wave alternans, predicts increased arrhythmia risk in patients with diseased hearts.<sup>42</sup> Repolarization alternans plays a special role in the dynamics of arrhythmogenesis because it is a direct measure of wave instability: repolarization alternans reflects beat-to-beat variations in APD and hence, wavelength, as the wave travels through cardiac tissue. There are 2 forms of repolarization alternans—concordant and discordant.

#### Concordant Repolarization Alternans

In this less-arrhythmogenic form of repolarization alternans,<sup>43</sup> successive waves alternate between long and short wavelengths. Although APD and refractoriness vary from beat to beat, the refractory period of each individual beat is relatively uniform, so that dispersion of refractoriness is not markedly increased. However, in heterogeneous tissue, this dynamic modulation of refractoriness, if localized, can lead to wavebreak and rotor formation.<sup>43,44</sup> Concordant repolarization alternans can be caused by either  $V_m$  or  $Ca_i$  dynamics. When heart rate increases and DI shortens to a point at which the APD restitution slope becomes  $>1$ , APD begins to alternate. Because APD affects the filling of SR calcium stores, this will also cause the  $Ca_i$  transient amplitude to alternate. Alternatively, if heart rate increases to a point at which  $Ca_i$  cycling causes the  $Ca_i$  transient to alternate, then APD will alternate secondarily due to calcium-sensitive membrane currents affecting APD.

If the coupling between  $Ca_i$  and  $V_m$  is positive, then the repolarization alternans is electromechanically concordant. In this case, the  $V_m$  and  $Ca_i$  dynamics sensitize each other to alternans; ie, APD alternans will occur even though the slope of the APD restitution slope is still  $<1$ , because the  $Ca_i$



**Figure 5.** Spatially discordant repolarization alternans. A, Langendorff rabbit heart, with optical mapping area in green box. B, Map showing the difference in optical  $Ca_i$  transient amplitude between 2 successive beats during pacing at a cycle length (CL) of 110 ms. Red indicates a positive difference (large-small alternation), and blue, a negative difference (small-large alternans). C, Optical  $Ca_i$  (red) and  $V_m$  (black) traces from sites 1 through 3 in B. Sites 1 and 3 show out-of-phase  $Ca_i$  and APD alternans; site 2 on the nodal line (red-blue interface in B) shows no alternans.

instability is also synergistically promoting alternans.<sup>45</sup> If the  $Ca_i$ - $V_m$  coupling is negative, then repolarization alternans will be electromechanically discordant. In this case,  $V_m$  and  $Ca_i$  dynamics oppose each other; thus, APD may fail to alternate even though the APD restitution slope is  $>1$ . When both  $V_m$  and  $Ca_i$  systems exhibit dynamic instability and coupling is negative, more complex forms of repolarization alternans, such as quasiperiodicity, may also arise.<sup>45</sup> This interaction between  $V_m$  and  $Ca_i$  instabilities is another reason why a simple criterion such as an APD restitution slope  $>1$  may fail to accurately predict the onset of APD alternans or wave stability.

### Discordant Repolarization Alternans

In spatially discordant repolarization alternans, APD alternates out of phase in different regions of tissue (Figure 5). Separating the regions with long-short and short-long APD alternans is a nodal line, along which no alternans is present. This form of repolarization alternans is highly arrhythmogenic<sup>43,44</sup> because during propagation of the same wave, the spatial APD variation produces long and short wavelengths in different regions of the same tissue. This increases dispersion of refractoriness, so that a premature beat arising in the region of short wavelength may block as it propagates into the region of long refractoriness.<sup>13,43,44</sup> Theoretical studies have demonstrated that the spontaneous formation of spatially discordant alternans is influenced by electrotonic currents.<sup>46</sup> For example, decreasing the strength of gap junction coupling increases the steepness of the spatial gradient of repolarization properties between out-of-phase regions of alternans and therefore promotes a more heterogeneous substrate for the induction of reentry.<sup>47</sup>

A number of mechanisms have been identified that cause spatially discordant repolarization alternans, all requiring dynamic factors. When a spatial repolarization gradient, such as the normal base-to-apex APD gradient in the ventricles, is present, then concordant repolarization alternans, arising from either a steep APD restitution slope or unstable  $Ca_i$  cycling, can be converted to discordant APD alternans.<sup>43,48</sup> For example, if the heart is paced from the short APD region, then as wave No. 1 propagates into the region of lengthening APD, its lengthening waveback will encroach on the DI of wave No. 2, causing its wavelength to shorten. However, this prolongs the DI encountered by wave No. 3, causing its wavelength to increase, and so forth. Thus, the waveback of a wave will oscillate as it propagates through the tissue, producing spatially discordant alternans.

However, simulations<sup>44,48</sup> show that preexisting tissue heterogeneity is not necessary for spatially discordant alternans. Another mechanism arises purely from dynamic factors and occurs when CV restitution is engaged during spatially concordant APD alternans. During spatially concordant repolarization alternans, if wave No. 1 has a long wavelength, then wave No. 2 will encounter a short DI and therefore, have a short wavelength. If the short DI also engages CV restitution, wave No. 2 will slow and its DI will lengthen. As this happens, the wavelength of wave No. 2 will increase, thereby shortening the DI encountered by wave No. 3. Thus, as the wave is subjected to a varying DI, due to the wave in front of it slowing down and speeding up, its wavelength will change as it propagates through the tissue. In the normal heart, CV slows only at very short DI values ( $<10$  ms). However, sodium channel-blocking drugs and acute ischemia both broaden the range of DI over which CV varies. These effects





sudden cardiac death in large clinical trials.<sup>49,52</sup> With improved understanding of the role of dynamic factors in causing wave instability, it may someday be possible to develop effective drug or gene-based therapies that can reduce our present reliance on devices as the only effective strategy to abort sudden cardiac death due to VF. A similar therapeutic strategy holds promise for atrial fibrillation.

### Acknowledgments

Supported by NIH SCOR in Sudden Cardiac Death grant P50 HL53219 and the Laubisch, Kawata, and Price endowments. We also thank H. Karagueuzian, D. Sato, Y. Shiferaw, S. T. Lamp, and T. K. Duong.

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