Spatiotemporal Heterogeneity in the Induction of Ventricular Fibrillation by Rapid Pacing

Importance of Cardiac Restitution Properties

Ji-Min Cao,* Zhilin Qu,* Young-Hoon Kim, Tsu-Juey Wu, Alan Garfinkel, James N. Weiss, Hrayr S. Karagueuzian, Peng-Sheng Chen

Abstract—The mechanism by which rapid pacing induces ventricular fibrillation (VF) is unclear. We performed computerized epicardial mapping studies in 10 dogs, using 19-beat pacing trains. The pacing interval (PI) of the first train was 300 ms and then was progressively shortened until VF was induced. For each PI, we constructed restitution curves for the effective refractory period (ERP). When the PI was long, the activation cycle length (CL) was constant throughout the mapped region. However, as the PI shortened, there was an increase in the spatiotemporal complexity of the CL variations and an increase in the slope of the ERP restitution curve. In 5 dogs, we documented the initiation of VF by wavebreak at the site of long-short CL variations. Computer simulation studies using the Luo-Rudy I ventricular action potential model in simulated 2-dimensional tissue reproduced the experimental results when normal ERP and conduction velocity (CV) restitution properties were intact. By altering CV and ERP restitutions in this model, we found that CV restitution creates spatial CL variations, whereas ERP restitution underlies temporal, beat-to-beat variations in refractoriness during rapid pacing. Together, the interaction of CV and ERP restitutions produces spatiotemporal oscillations in cardiac activation that increase in amplitude as the PI decreases, ultimately causing wavebreak at the site of intrinsic heterogeneity. This initial wavebreak then leads to the formation of spiral waves and VF. These findings support a key role for both CV and ERP restitutions in the initiation of VF by rapid pacing. (Circ Res. 1999;84:1318-1331.)

Key Words: chaos ■ restitution curve ■ wavebreak ■ anatomical obstacles ■ bifurcation

The mechanisms responsible for ventricular fibrillation (VF) are the subject of continued interest. First, it is generally believed that spatial dispersion of electrophysiological properties such as refractoriness is the chief cause of VF.1 Second, a number of clinical2 and experimental3 studies have correlated VF with the presence of alternans, particularly in the T wave. Other investigators4–6 have proposed a causal role for alternans in the genesis of VF and have suggested that the alternans is due in turn to the property known as action potential duration (APD) restitution, which relates an APD (or equivalently, the effective refractory period [ERP]) to the preceding diastolic interval (DI).

This paper investigates the interrelations among these phenomena in the context of VF induced by rapid pacing. We show that, in this model, VF is created by wavebreak, which is in turn caused by spatiotemporal inhomogeneities created by the restitution of ERP and conduction velocity (CV).

Materials and Methods

Surgical Preparation

The research protocol was approved by the Institutional Animal Care and Use Committee of Cedars-Sinai Medical Center and followed the guidelines of the American Heart Association. Ten adult mongrel dogs were anesthetized with 25 to 35 mg/kg sodium pentobarbital, intubated, and ventilated with room air by a respirator (Harvard Apparatus). An arterial line was inserted into the right femoral artery to continuously monitor systemic blood pressure. Blood was drawn to determine the pH, PO2, PCO2, base excess, and bicarbonate concentrations. Normal metabolic status was actively maintained throughout the study. A venous line was inserted to infuse saline and to give supplemental doses of pentobarbital. Rectal temperature was monitored and maintained at 36°C to 37°C by heating the table with warm circulating water. The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. In 3 dogs, we performed atrioventricular node ablation with radiofrequency energy under fluoroscopic guidance. The purpose was to decrease the heart rate so that we could determine the restitution curve at slower heart rates, with longer DIs.

Recording Electrodes

For epicardial mapping, a recording sock electrode array was constructed by fixing stainless steel electrode wires (0.4 mm in diameter) to the inner surface of a nylon “sock.” The uninsulated ends of the electrode wires served as the recording electrodes (Figure 1A and 1B). The electrode array included 125 bipolar electrodes, with the interelectrode distance varying from 8 to 10 mm. In
addition, 3 channels of surface ECG were also recorded. In all 10 experiments, the sock was pulled over the ventricular surface for global epicardial mapping.

For high-density epicardial mapping over a small region of the epicardial surface, a recording plaque electrode array was constructed using similar stainless steel wires. This plaque electrode array included 478 bipolar electrodes (Figure 1C) plus 2 ECG leads. The wires were fully insulated except at the tips, which served as the tissue contact points. The interelectrode distance was 1.6 mm, and the interpolar distance was 0.5 mm, measured from center to center. In 5 of the 10 dogs, mapping studies were performed with both the plaque electrode array sutured to the right ventricle and septum, and the sock electrode array pulled over the entire epicardium.

**Pacing Protocol**

The hearts were paced with cathodal (unipolar) stimuli of 3 times the diastolic threshold current. Unipolar pacing was used because it is associated with a monotonic strength-interval curve. The pacing interval (PI) started at 300 ms and then was progressively shortened, in 20-ms increments to 200 ms, and then in 10-ms increments until VF was induced. A PI of 250 ms was also used for each dog. Each pacing train included 19 beats. There was an interval of at least 20 seconds between pacing trains. The pacing sites were at the left ventricular apex and the right ventricular base. For the 5 dogs in which plaque electrodes were used, pacing was performed from the left ventricular apex, the right ventricular base, and the center of the plaque. If VF was induced, a 25-J shock was delivered to the left and right ventricles for defibrillation. The heart was allowed to recover for at least 5 minutes before the resumption of data acquisition.

**Construction of the Effective Refractory Period Restitution Curve**

ERPs were measured at the pacing sites, which were either at the left ventricular apex or at the right ventricular base. Multiple baseline pacing (S1) cycle lengths were used. The protocol was as follows. After 8 (S1) stimuli at 600-ms (dogs with complete heart block) or 400-ms (other dogs) cycle lengths (CLs), a premature stimulus (S2) was given to test the ERP. The current strength for both S1 and S2 was twice the diastolic threshold with a pulse duration of 5 ms. If the S2 captured the ventricle, the S1–S2 interval was decreased by 10 ms and the test was repeated. If the S2 failed to capture the ventricle, the S1–S2 interval was increased by 10 ms, and the test was repeated at 2-ms decrements of S1–S2 interval until S2 failed to capture. The longest S1–S2 interval associated with S2 noncapture was the ERP for that S1 CL. The DI was estimated by the difference between the S1 CL and the ERP.

To determine the ERP and the DI at multiple S1 CLs, the S1 CL was progressively decreased by 50-ms increments between 600 and 300 ms, then by 20-ms increments between 300 and 200 ms, and then by 10-ms increments when the CL was <200 ms, until 1:1 capture

---

**Figure 1. Electrode location.** Panels A and B show 2-dimensional and 3-dimensional view of the 125-channel sock electrode array, respectively. Panel C shows the 478-channel plaque electrode array. The electrode array consisted of 21 columns and 23 rows of bipolar electrodes. + indicates the actual location of each bipolar electrode. The rectangle indicates the electrodes used for conduction time calculations; O, the site of the pacing electrode; LV, left ventricle; RV, right ventricle; and LAD, left anterior descending coronary artery.
by S1 was lost or VF was induced. The ERP and DI were determined for each S1, CL. The ERP restitution curve was constructed by plotting ERP against its DI.

**Data Analyses**

The method of determining the times of activation from the bipolar electrogram has been reported in detail elsewhere.\(^9\,10\) Once the activation times were selected, the patterns of activation were displayed dynamically\(^10\) or by isochronal activation maps.\(^9\)

**Construction of Isodervation Maps of Cycle Lengths**

The PI is the interval between 2 baseline-pacing outputs. The activation CL is the interval between 2 consecutive activations registered by the recording system. The activation time of each deflection was selected by the computerized mapping system according to a dV/dt criterion.\(^9\) Manual editing was then performed to eliminate the selection of noise or artifacts. The activation CL was registered at each recording channel and the corresponding PI. A negative value at a given site indicates that the activation CL is shorter than the PI, whereas a positive value corresponds PI. We calculated the CT of the wave fronts that propagated from the S1 CL averaged 299.7 ms. Activation CL is shorter than the PI, whereas a positive value at a given site indicates that the activation CL is shorter than the PI, whereas a positive value corresponds PI. A negative value at a given site indicates that the activation CL is shorter than the PI. The PI that induced VF (the "VF threshold" [VFT]) varied in Time Pacing-Induced CL Variability and CL Alternans

**Results**

**Pacing-Induced CL Variability and CL Alternans in Time**

In all dogs studied, shortening the PI resulted in a progressive increase in temporal and spatial variability of CL. Whereas the PI that induced VF (the "VF threshold" [VFT]) varied from animal to animal (mean, 174±28 ms; range, 230 to 140 ms), the magnitude of spatiotemporal inhomogeneity needed for VF induction was similar. When the heart was paced at relatively long intervals (250 ms), little variation in CL was registered by any of the recording electrodes, but when the PI was gradually shortened, CL variations began to increase. Figure 2 shows a typical example from one bipolar recording electrode in one animal. VF always occurred with PIs of 180 ms in this dog.

Note that when the PI shortened to 200 ms, the CL developed alternans. Further shortening of the PI to 190 ms resulted in more complex variations. The number of recording electrodes that developed significant CL variation also increased (see below). In all animals studied, the longest PIs associated with any significant CL variation ranged from 240 to 220 ms (mean 226±16 ms). Figure 2B shows the bipolar electrogamms from the same episodes as in Figure 2A. When the PI was 300 to 250 ms, significant CL and/or morphology...
variations were rarely observed. As the PI shortened, both morphology and CL variations developed. When the PI shortened to 200 and 190 ms, transient complicated patterns of CL and morphology variations were usually present in the beginning of the pacing run. The patterns then settled into stable alternans toward the end of the pacing run. (Figure 2A shows only paced beats 10 to 19.) As the PI further shortened to 180 ms, VF was initiated at the beginning of the pacing train, accompanied by large variations in CL. There was a significant positive correlation between the longest PI associated with significant CL variations ($\geq 50\%$ of the electrodes showing significant CL variations before the initiation of VF) and the PI that induced VF (VFT) in each dog ($r=0.83$, $P<0.01$). That is, the longer the PI at which $\geq 50\%$ of the sites showed variability, the longer the VFT was.

Pacing-Induced Variability in Conduction Time

Figure 3 shows a summary of the CT variations of one dog (Figure 3A) and of all dogs studied with the plaque electrode array (Figure 3B). Shortening the PI from 300 to 220 ms was associated with little change in the average CT. However, temporal (beat-to-beat) variability progressively increased. Before VF was induced, the CT associated with captured beats showed large variations. Figure 3B shows the CT deviations for each dog. When the PI was progressively shortened, there was a slight increase in CT and its beat-to-beat variability. Further shortening of the PI to $<220$ ms resulted in a large increase of CT and an even greater increase of CT beat-to-beat variability. The PI needed to induce VF varied from 200 to 140 ms. However, a critical increase of CT beat-to-beat variation (as demonstrated by a large increase of SD) is associated with the induction of VF. The critical SD associated with the induction of VF in this case was $20.2\pm 13.7$ ms ($n=5$).

Spatial Alternans

In addition to temporal variations of CL, rapid pacing also induced large spatial variations. Figure 4 shows the spatial distribution of CL in the last 4 paced beats in 1 animal. Note that with a 300-ms PI, there was little CL variability in space (top row). But as the PI shortened to 200 ms (second row), CL began to vary significantly in space. CL 16 and 18 show significant negative deviation (red) at the apex near the pacing site, while CL 17 and 19 show significant positive deviation (blue) at the same area. Note the remarkably precise alternation between red and blue areas in successive beats. At a PI of 190 ms, the amplitude of the spatial alternans increased. Further shortening of the PI to 180 ms resulted in VF.

Figure 5 shows the percentage of electrodes showing significant CL variation. There is a correlation between the percentage of sites that showed significant CL variation and the difference between the PI and the VFT ($r=0.92$, $P<0.001$).

ERP Restitution Curve

The slope of the ERP restitution curve correlated with the magnitude of the CL variations. Figure 6 shows a representative ERP restitution curve. The DI was estimated by the difference between the pacing ($S_1$) interval and the ERP determined at that PI. For each DI, there was a corresponding PI and an ERP. When the PIs were between 600 to 260 ms, the restitution curve was relatively flat, with a slope of $0.30\pm 0.25$. When the PIs were $<260$ ms, the slope became much steeper ($1.04\pm 1.38$, $P<0.001$) and was associated with the development of significant CL variations. The slope of the restitution curve within 50 ms of the VFT was $2.57\pm 1.68$. There was an inverse correlation between the slope of the ERP restitution curve and the difference between VFT and PI.
In other words, the closer the PI is to inducing fibrillation, the steeper the ERP restitution curve.

The Development of Wavebreak and VF

The consequences of spatiotemporal CL and CT variations are the creation of wavebreak and VF. When the PI was 300 ms, the activation wave front propagated smoothly, with no evidence of conduction block (Figure 7). When the PI shortened, there was greater spatial variation in wave propagation. Figure 8 shows an example in which spatial variation of conduction time led to wavebreak and VF. Figures 8A and 8B show centrifugal spread of excitation after the pacing stimulus. Figure 8D, conduction block occurred at the right lower portion of the panel. The creation of these 2 new waves coincided with the onset of VF. Figure 8H shows the activation in the center of the mapped tissue by the 13th pacing stimulus and the independent activation in the lower portion of the mapped tissue by 2 wavelets most likely generated by the previous wavebreak. The site of wavebreak in this example corresponded to the interventricular septum. The right half of the figure shows bipolar electrograms recorded during this pacing run. Note that there was little CL variation immediately next to the pacing site (channels 180 and 201). This was a consistent finding in all 5 dogs studied with the plaque electrode array.

Figure 8 also shows that, as the distance from the pacing site increased, there was a progressive increase of variability both in electrogram morphology and in CL. The slanted arrows on channels 348 and 369 point to the time of wavebreak. Note that there was significant CL alternans before the wavebreak. For channels 390 and 411, which registered the site of wavebreak, there was a short CL after beat 9 and a long CL after beat 10. On the basis of the ERP restitution characteristics, the ERP after paced beat 11 should be long because of a long recovery interval created by the long preceding CL. When the paced wave front of beat 12 arrived, it was unable to excite this region, resulting in conduction block and wavebreak. The area around electrode 411 was eventually excited 208 ms later. During this delay, the wave front circled around the site of block and eventually entered this area. Note that after wavebreak, the activation near the wavebreak site has a lower amplitude than the activation before the wavebreak. These fractionated low-

(r = -0.70, P = 0.037). In other words, the closer the PI is to inducing fibrillation, the steeper the ERP restitution curve.

Figure 3. CT alternans during rapid pacing. A, Typical example of rate-dependent CT alternans in dog 1 of the 5 dogs mapped with the 478-channel plaque electrode array. The CT here refers to the activation wave front propagation time from electrode 180 to 474 (see Figure 1C). All paced beats associated with 1:1 capture were plotted in this figure. Note that there was no CT alternans at 300 ms PI, whereas slight CT alternans was observed at 250 ms PI. The CT alternans accentuated with the shortening of PI. At the PI of 180 ms (VFT), the CT alternans was replaced by a more complicated pattern of CT variations, followed by the induction of VF. B, Summary of the CT variations in all 5 dogs mapped with 478-channel plaque electrode array. Only the last 10 captured beats from the 19-beat pacing run were included, because the CT variations became stable only after the initial 4 to 5 beats. The PI corresponding to the last dot in each plot is the PI that induced VF. On the ordinate are the mean and SD of the absolute beat-to-beat CT variations during pacing. Each dot indicates the mean value of the CT at the respective PI. Data are mean ± SD. Note that large SDs were associated with the induction of VF.
amplitude activations are consistent with extracellular bipolar recordings near the core of functional reentry. The rapid and irregular activity then gradually spread to the upper part of the mapped region as VF was initiated.

Among the 5 dogs mapped with the plaque electrode array, we recorded a total of 7 episodes of VF induction. Among them, wavebreak was seen within the mapped region in 4 episodes in 3 dogs. (In 2 dogs, no wavebreak was observed within the mapped area.) The site of wavebreak was 10 to 14 mm distant from the pacing site. The line of block in Figure 8 was parallel to the interventricular septum. In the other 3 episodes, the recording plaque did not overlie the septum and was limited to the right ventricular free wall. In these latter episodes, the line of wavebreak was always parallel to the myocardial fiber orientation, 10 to 14 mm from the site of pacing.

Figure 8 shows the global activation patterns at the induction of wavebreak. Panel A shows that when the heart was paced at 160 ms PI, the initial 6 captured beats had earliest activation near the pacing site (blue dot). Afterwards, the complex, nonpaced and rapid activation (Figure 9B) started to develop from the site marked by a red arrow in Figure 9A. The remainder of the epicardium continued to be captured by the pacing stimuli, resulting in fusion. The rapid VF activations took >300 ms (3 cycles) to spread to the entire epicardial surface (Figure 9B). Figure 9C shows the isodeviation map. Note that the patterns of spatial CL inhomogeneity developed as early as paced beat 2, followed by alternans. The site of wavebreak (blue arrow) was located between regions of long and short CLs. These findings are compatible with the notion that the initial wavebreak (shown better in Figure 8) induces reentry, which then induces VF in the entire ventricle.

Among 10 dogs mapped with sock electrode array, we recorded a total of 12 episodes of VF induction. In all episodes, the induction of VF was characterized by the induction of complex and rapid activation in a local site. The complex and rapid activation patterns then spread to the entire epicardial surface, leading to the induction of VF.
Computer Simulation Study

In our computer simulations of homogeneous isotropic tissue, rapid pacing near the center produced a CL alternans in time and an alternans in space that was spherically symmetrical around the pacing site. These alternating concentric rings of long and short CLs did not result in wavebreak and reentry, phenomena that were seen in the real tissue. To initiate wavebreak, and hence VF, it was necessary to introduce a heterogeneity into the tissue. We therefore lengthened the APD (by \( \sim 10\% \)) in the region indicated by box A in Figure 10, to simulate a region of increased refractoriness. As a result of this break in tissue symmetry, the spatiotemporal complexities and wavebreak induced by rapid pacing in real tissue were now reproduced. Figure 10 shows the isodeviation maps generated in the computer model. At a PI of 300 ms, there was little or no CL variation. When the PI was shortened, the activation patterns displayed spatiotemporal alternans. These patterns reproduced the experimental results shown in Figure 4. Note in particular the crescent-shaped regions of long and short CLs, similar in shape and location to those seen in the real tissue (Figure 4). As in the real tissue, further reduction of the PI to 180 ms resulted in wavebreak and VF-like activity, which continued after terminating the pacing. When the heterogeneity was removed after the onset of VF, the VF-like state persisted indefinitely. Thus, the computer simulations show that spatiotemporal oscillations in CL (alternans) result directly from the dynamic properties of the cardiac action potential model without requiring that the tissue have intrinsically heterogeneous properties. However, a small heterogeneity is required for these oscillations to cause wavebreak, since it breaks the radial symmetry of the activation wave front. Once the radial symmetry is broken, the maintenance of the VF-like state no longer depends on the continued presence of the heterogeneity.

We verified that alternans was playing a contributory role in wavebreak, by removing it (through flattening APD restitution) from the system. In the case of Figure 10, we flattened APD restitution by eliminating the Na\(^+\) channel contribution to APD restitution as we did in Reference 17. With all settings the same as in Figure 10, except for the flattening of APD restitution, wavebreak was not observed even with the PI was decreased to 100 ms (compared with the VF threshold of 180 ms in the control case [Figure 10]). In this case, wavebreak failed to occur at 100 ms PI, even when heterogeneity was increased in area A by changing \( G_{\text{Na}} \) to 0.09.

Next, we explored the relationship between CV and ERP restitution and the development of spatiotemporal CL oscillations (Figure 11 and 12). Flattening CV restitution in the action potential model eliminated spatial alternans during rapid pacing (Figure 12), indicating that spatial CL alternans is a direct consequence of CV restitution. Conversely, in the absence of CV restitution, increasing the slope of ERP restitution increased the PI required to induce temporal alternans in ERP, showing that temporal ERP alternans is sensitive to the steepness of ERP restitution, independent of CV restitution. When both CV and ERP restitutions were intact, increasing the ERP restitution slope potentiated both temporal and spatial alternans (Figure 12D). In the presence of a symmetry-breaking heterogeneity, this facilitated wavebreak and development of a VF-like state at longer PIs.
Discussion
There are 3 major findings of this study. The first shows that spatiotemporal alternans is created by cardiac restitution properties and emphasizes that both CV and ERP restitution play key roles. The second shows that the presence of an initial heterogeneity is essential in the induction of initial wavebreak by rapid pacing. Indeed, our analysis suggests that the interaction among tissue heterogeneity and cardiac restitution properties is critical for VF induction by rapid pacing. The third shows that the presence of spatiotemporal alternans facilitates the induction of initial wavebreak by heterogeneity.

Spatiotemporal Alternans and Induction of VF
We have documented that rapid pacing in the in situ canine ventricles induces an uneven spatiotemporal distribution of CL. Furthermore, we could manipulate the increase of the magnitude of spatiotemporal heterogeneity by progressively shortening the PI, until an abrupt transition to wavebreak occurred. Wavebreak was the physiological event that heralded the onset of VF and occurred as a result of a progressively increasing oscillation in the long-short coupling of CLs as the PI decreased. Because the magnitude of spatiotemporal inhomogeneity can be controlled with pacing rate, this is a useful model to study the role of spatiotemporal oscillations in cardiac activation in the transition to VF in the intact canine ventricles.

Spatiotemporal Alternans and Cardiac Restitution
To relate spatiotemporal oscillations in CL to cardiac restitution properties in real cardiac tissue is not straightforward.
Whereas ERP restitution can be accurately measured in the in situ heart, estimates of CV must rely on conduction time differences, which are subject to error if the conduction pathway changes. Nevertheless, in our experiments, any deviation of local CL from the PI must reflect a variation in either CV or conduction pathway from the pacing site to that location. It has been reported that CV in ventricular muscle depends on the rate of activation.

In one study, reentry was induced in a ring of ventricular tissue surrounding the canine mitral and aortic valves. Premature stimuli given during tachycardia resulted in advancement of tachycardia, but the extent of advancement was less than the local excitable gap, indicating that early premature impulses conducted more slowly than the unperturbed reentrant impulses. In another study, the authors showed a rate dependence of CV in guinea pig ventricles. The conduction was significantly slower during short PI than during long PI. In rabbit ventricles, significant CV restitution was demonstrated in both longitudinal and transverse directions.

The spatial CL variation recorded during rapid pacing in this study is compatible with these known CV restitution properties, especially given that the variations become larger as the PI decreases. The nearly radially symmetrical pattern of CL alternation also argues against changes in conduction pathway, because there is no apparent reason for conduction block to occur with a symmetrical radial distribution relative to the pacing site. Finally, the computer simulations show that CV restitution properties can directly account for the experimentally observed spatial CL variations, without the need to postulate changes in conduction pathway. The computer simulations also demonstrate that without CV restitution, spatial CL variation is eliminated (Fig 11). The explanation is very intuitive: without CV restitution, CV is essentially constant throughout the tissue (ignoring the effects of wave front curvature very close to the pacing site). Therefore, the arrival time of an impulse at a given distance from the pacing site has no way to vary between successive beats (assuming the conduction pathway does not change). From these observa-

![Figure 8. The induction of wavebreak and VF mapped with the plaque electrode array shown in Figure 1C. Data were obtained from the same dog as that shown in Figure 7. The PI was 180 ms. Color panels on the left show the activation patterns of the last paced beat (12th beat in a 19-beat pacing train) before the initiation of VF. A and B, Centrifugal spread of excitation during pacing. C and D, Conduction block occurred at the right lower portion of the panel, as shown by double line segments in panel D, E and F. The original wave front split into 2 (wavebreak) around the site of conduction block. One of the 2 daughter wavelets circled around the area of block and propagated toward the lower left corner. The other wavelet excited the area inferior to the line of block (panel G). This wavebreak was coincidental with the onset of VF. When the 13th paced beat occurred (panel H), 2 additional wavelets emerged from the bottom edge of the mapping area, resulting in a situation in which 3 separate waves coexisted. Panel J shows the actual bipolar electrograms registered during this pacing run. The slanted arrows point to the site of wavebreak. See text for details. Abbreviations as in Figure 7.](image-url)
tions, we conclude that CV restitution is primarily responsible for producing the spatial variation in CL.

How does this lead to wavebreak and VF? A key point is that the spatial variation in CL, resulting from CV restitution, will also result in a spatial variation in DI, because \( CL = APD + DI \). This fact directly links CV restitution to ERP restitution. The ERP restitution curve provides the next value of ERP as a function of the previous value of DI. Suppose that, as a consequence of CV restitution, 2 nearby cells develop a slight difference in their DIs during rapid pacing. Because of ERP restitution, these differences in DI will cause the ERP of the next beat to differ at the 2 sites. That is, a functional (spatial) dispersion of refractoriness will be created for the next beat. Those two slightly different ERPs will then generate 2 different next DIs. Whether this difference will be greater or smaller than the preceding difference is determined by the slope of the ERP restitution curve in the region of those DIs. If \( >1 \), the next difference will be larger, and if \( <1 \), the next difference will be smaller. In this way, a steeply sloped ERP restitution curve is a “difference amplifier,” the gain of which is the value of the slope. Thus, any spatial differences in CL and DI resulting from CV restitution will be amplified on the next paced beat by a steeply sloped ERP restitution curve and further increase the functional dispersion of refractoriness. In this way, a steep ERP restitution amplifies over time the spatial differences in DI and ERP produced by CV restitution. That is, CV restitution excites a spatial mode of oscillations in DI, and ERP restitution a temporal mode.

In homogeneous, isotropic tissue, when the growing spatiotemporal oscillations lead to a DI, which is too short to generate an action potential, propagation fails. Because the spatial variations in CL and DI resulting from CV restitution are radially symmetrical in homogeneous tissue, propagation failure occurs everywhere along the wave front at once, leading to extinction of the target wave induced by that pacing stimulus. If a heterogeneity exists in the tissue, however, this radial symmetry is broken. Spatial oscillations in CL and DI resulting from CV restitution will now develop along the same activation wave front. As these differences in DI are translated into differences in ERP and then further amplified temporally by a steep ERP restitution slope, they lead to a break in the wave front at the point where the DI becomes too short to generate an action potential. This

![Figure 9. The induction of wavebreak and VF mapped with the sock electrode array shown in Figure 1A. A, Global patterns of activation during pacing, with pacing artifact as time 0. Dark blue dot indicates the pacing site, and the red arrow the site where rapid, non-paced activations first occurred. B, Bipolar electrogram recordings at 3 epicardial sites whose locations are shown in panel A. C, Iso-deviation maps of CL. The blue arrow at map 6 indicates the site and timing of the initial wavebreak.](https://circres.ahajournals.org/content/1327)
wavebreak heralds the onset of the VF-like state. This explanation accounts for the experimental observation that spatiotemporal oscillations in CL increased progressively as the steepness of the ERP restitution increased at shorter PI. Wavebreak presumably occurred because of the normal degree of heterogeneity, which exists in the canine ventricle.

In simulated 2-dimensional cardiac tissue, once wavebreak occurred during rapid pacing, the radial symmetry of the activation was broken. Therefore, the subsequent removal of the heterogeneity from the tissue did not cause the VF-like state to terminate. This observation highlights an important point, which is that, whereas the initiation of the VF-like state depends on the presence of tissue heterogeneity, its maintenance does not. A key but unresolved therapeutic issue is whether modifying ERP and CV restitution can prevent the ability of VF to sustain itself in the presence of heterogeneous tissue properties.

**Relationship to Previous Studies**

The argument that a steeply sloped APD restitution curve creates instabilities during rapid pacing was first made by Nolasco and Dahlen. They also showed how a steeply sloped curve results in alternans, the first time that this phenomenon was explained. Subsequently, Frame and Simmons extended this finding to the study of reentrant excitation (as opposed to external pacing). They showed that reentry in a ring of cardiac tissue could give way to an alternans due to APD restitution. They also found that CV variability gave rise to “more irregular and complex oscillations” (page 1285).

These experimental results were put in a theoretical context.
Normal CV Restitution

Flattened CV Restitution

Figure 11. CL bifurcation (A and E), APD bifurcation (B and F), APD restitution (C and G), and CV restitution (D and H) in the computer simulation. The parameters in panels A through D are the same as in Figure 10, and we refer to this case as the control. The parameters in panels E through G were chosen as follows: \( \tau_c, \tau_m, \) and \( \tau_s \) are unchanged from the Luo-Rudy I model; \( G_c = 0.432 \, \mu S/cm^2; \) \( G_m = 0.06 \, \mu S/cm^2 \) in Area A and \( G_m = 0.053 \, \mu S/cm^2 \) in the rest of the tissue. The dashed lines in panels \( C \) and \( G \) are reference lines of slope 1. The solid lines in panels \( C \) and \( G \) are the PIs at which APD alternans began. Note that APD alternans began at points where the slope of APD restitution was \( >1 \) and that in the control case with normal CV restitution (left column), APD and CL alternans onset simultaneously, at a PI of \( \approx 210 \) ms. But when CV restitution was flattened at the relevant DIs (right column), APD alternans sets in at a PI of \( \approx 245 \) ms, but there is no CL alternans at any interval \( >200 \) ms (right column). This demonstrates the role of CV restitution in creating CL alternans. Note in addition that APD alternans onset at precisely the PI at which the slope of the APD restitution curve is \( >1 \).

by Courtemanche et al.,\(^\text{15}\) who studied a mathematical model of a ring of cardiac tissue like the Frame-Simson preparation and demonstrated that if the slope of the APD restitution curve is \( >1 \), alternans will develop. They showed that if there is CV restitution, the alternans will be modulated by another, longer-period oscillation. This additional modulation frequency makes the resulting system quasiperiodic. It is interesting to note that the new modulation frequency arises because of the spatial variation in APD that is caused by CV restitution.

Previous simulation studies in 2- and 3-dimensional tissue are also generally consistent with our findings. In 2-dimensional cardiac simulated tissue, Karma\(^4\) showed that a steeply sloped restitution curve will cause alternans and that if the alternans is large enough in amplitude, it will result in wavebreak. This is analogous to a result of Frame and Simon\(^3\) with the ring; an alternans that is mild can be tolerated within the spatial extent of the ring, but an alternans that is too violent will cause wave termination by head-tail interactions. In the 1-dimensional ring, strong head-tail interaction can only result in termination of the wave, but in 2-dimensional tissue the same phenomenon causes wavebreak. Our study is compatible with the presence of this mechanism in pacing-induced VF. Recall that a PI of 190 caused a mild alternans, which did not result in wavebreak, and hence did not result in the genesis of reentry. The tissue therefore did not develop VF. But at a PI of 180, the alternans was larger and resulted directly in the genesis of wavebreak. Figures 8 and 9 show that when wavebreak was created, there was a sudden occurrence of more rapid and complicated activations in the mapped region, starting from the site of wavebreak, which spread to the entire mapped tissue. These findings support the notion that the wavebreak created by rapid pacing precedes the onset of VF.

Thus, our study provides experimental evidence for a causal role for alternans, and shows how alternans caused the wavebreak; ie, long-short couplings create conduction failure, which creates a reentrant spiral wave. We also showed that the formation of the initial spiral wave precedes the sudden transition from paced rhythm to VF. These findings are consistent with the results of Pastore et al.,\(^6\) who also reported that “discordant alternans” of APD induced by rapid pacing is causally related to the initiation of VF.

Our present findings may also shed light on the mechanism for the quasiperiodic transition to chaos that we hypothesized previously with respect to VF induced by a single extrastimulus.\(^4\) In that context, we observed oscillations in CL and APD and conjectured that APD and CV restitutions could be responsible for these additional oscillatory modes. The present study shows that APD and CV restitution do indeed give rise to temporal and spatial oscillations, respectively.

Causal Relationship Between Alternans and VF

Our evidence that CL alternans, which reflects underlying spatiotemporal DI alternans and therefore also APD alternans, is a causative factor in the induction of VF by rapid pacing is significant. Previous studies in both animals and humans have established intriguing correlations between repolarization alternans and VF, suggesting that it is not benign. In the canine heart, the induction of repolarization (APD or T wave) alternans by hypothermia, tachycardia, or coronary artery ligation has been shown to significantly facilitate the induction of VF.\(^3,25\) In humans, using the T wave as a surrogate measure of the global repolarization characteristics,\(^26\) Lewis\(^27\) first reported that T wave alternation can occur during tachycardia. Subsequently, patients with long-QT syndrome,\(^28\) Prinzmetal angina,\(^29\) acute ischemia,\(^30\) and electrolyte imbalances\(^31,32\) have been found to exhibit a T wave alternation even during normal sinus rhythm. Rosenbaum et al.\(^2\) reported that the beat-to-beat T wave alternans over a broad range of physiological heart rates (95 to 150 bpm) served as a noninvasive marker of vulnerability to ventricular arrhythmias. In addition, T wave alternans was as powerful a predictor of future spontaneous clinical arrhythmic events as inducibility of
ventricular tachycardia during clinical electrophysiological studies.

Conclusions
We conclude that during VF induction by rapid pacing, CV and ERP (or APD) restitution properties underlie the functional dispersion of refractoriness that leads to wavebreak and VF. CV restitution excites a spatial mode of oscillations in CL and DI, which through ERP (or APD) restitution are translated temporally into spatial differences in refractoriness. If the ERP restitution slope is steep, its interaction with CV restitution leads to progressively larger spatial gradients in refractoriness during successive beats, culminating in wavebreak and VF. In simulated 2-dimensional cardiac tissue, some pre-existing tissue heterogeneity is required for wavebreak to occur, but it is not important for the maintenance of VF once wavebreak is initiated. During rapid pacing, differences in CL, and hence DI and APD, alternate in both space and time. Wavebreak occurs when CL alternans reaches a critical value. Alternans therefore plays a causative role in wavebreak and is a reliable precursor to VF, accounting for prior experimental and clinical correlations between alternans and susceptibility to ventricular arrhythmias. It is possible that drugs or other interventions that favorably alter CV and ERP (or APD) restitution to suppress the spatiotemporal oscillations causing wavebreak could be effective in the prevention of VF and sudden cardiac death.

Acknowledgments
This study was done during the tenure of a fellowship grant from the American Heart Association, Greater Los Angeles Affiliate (to J.-M.C. and Z.Q.); a fellowship grant from the Department of Medicine, Korea University (to Y.-H.K.); a Cedars-Sinai ECHO Foundation Award (to H.S.K.); and an AHA Wyeth-Ayerst Established Investigator Award (to P.-S.C.), and was supported in part by NIH Specialized Center of Research Grant in Sudden Death (P50-HL52319), NIH Research Grants HL50259 and HL44880, the Ralph M. Parsons Foundation (Los Angeles, Calif), the Pauline and Harold Price Endowment, Cedars-Sinai Medical Center, and the Kawata and Laubisch Endowments (UCLA). We thank Caroline Kim, Dustan Hough, Avile McCullen, Pei-Li Yan, Meiling Yuan, and Nina Wang for their technical assistance and Eliane Lebowitz for her secretarial assistance.

References


Spatiotemporal Heterogeneity in the Induction of Ventricular Fibrillation by Rapid Pacing: Importance of Cardiac Restitution Properties
Ji-Min Cao, Zhilin Qu, Young-Hoon Kim, Tsu-Juey Wu, Alan Garfinkel, James N. Weiss, Hrayr S. Karagueuzian and Peng-Sheng Chen

*Circ Res. 1999;84:1318-1331
doi: 10.1161/01.RES.84.11.1318

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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:
http://circres.ahajournals.org/content/84/11/1318

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/