Mechanism of Pacing-Induced Ventricular Fibrillation in the Infarcted Human Heart

Anthony W.C. Chow, MD, MRCP; Oliver R. Segal, MRCP; D. Wyn Davies, MD, FRCP; Nicholas S. Peters, MD, FRCP

Background—The mechanisms by which ventricular fibrillation (VF) is initiated in the infarcted human heart have not been defined.

Methods and Results—Left ventricular noncontact mapping of 8 episodes of pacing-induced VF in 6 patients (age 64.8±7.9 years, with previous myocardial infarction and left ventricular ejection fraction of 36±4%) undergoing ventricular tachycardia (VT) ablation revealed a consistent mechanism of VF induction. Whether during VT or sinus rhythm, the first of a train of paced extrastimuli to capture the LV produced an arc or arcs of functional block at regions bordering scar. With subsequent extrastimuli, the arcs elongated to circumscribe an enlarging area of increasingly late activation, with reentry through part of this functional (unidirectional) block leading to wavefront fragmentation and VF. These regions had longer fibrillation intervals (263±63 ms) than remote LV regions (209±23.4 ms; \(P<0.0001\)), implying longer refractory periods, and in 6 of the 8 VF episodes, these regions correlated with VT exit sites. In each of the 2 patients with 2 episodes of VF, both episodes formed arcs of functional block in the same location, despite pacing from different sites.

Conclusions—Pacing-induced VF in the infarcted human heart is initiated by the development of functional lines of block dictated by the properties of a particular region of myocardium characterized by longer refractory periods, at or near VT circuit exit sites. Identification of these characteristic properties may help stratify risk of arrhythmic death and explain the potential for VT ablation to modify risk of VF in the infarcted heart. (Circulation. 2004;110:1725-1730.)

Key Words: ventricles ■ fibrillation ■ mapping ■ infarction

Sustained ventricular tachycardia (VT) in the infarcted heart can destabilize spontaneously and in so doing may terminate, accelerate, change morphology, or degenerate to ventricular fibrillation (VF).\(^1\)–\(^3\) Thus, the inherent instabilities in the arrhythmia substrate dictate the spectrum of clinical behavior of human VT, which ranges from asymptomatic self-limiting episodes to abrupt sudden death due to degeneration to VF. But what dictates whether an individual VT will terminate or degenerate, how this might be identified, and the mechanism by which VF evolves remains unknown. Understanding of these determinants may provide the prospect of risk assessment and a strategy for prevention.

Computer models\(^4\) and animal data\(^5\)–\(^8\) on VF initiation have shown that there is no critical coupling interval that provokes VF. Initiation of fibrillatory activity in humans also appears to occur distant from the site of pacing.\(^9\) These observations suggest that the fibrillatory tendency is dictated by properties of the ventricular myocardium in a particular region of the diseased ventricle, but the lack of spatial resolution with conventional intracardiac electrode catheters has precluded further investigation to provide mechanistic insight into these observations. In the present study, we have used opportunistic high-resolution global noncontact mapping of episodes of pacing-induced VF to address the hypothesis that in the infarcted human heart, there are regions of myocardium that are critical for the development of VF, and that they relate closely to regions critical to circuits that cause reentrant VT.

Methods

Patients

Six patients (age 64.8±7.9 years, 3 females) undergoing ablation of spontaneous and inducible VT who had 8 episodes of pacing-induced VF were studied. All had poor left ventricular (LV) function (ejection fraction 36±4%), previous myocardial infarction (4 anterior, 2 posterobasal), but no prior cardiac surgery (Table). Local ethics committee approval was obtained, and patients had given written informed consent.

Mapping Procedure

A standard quadripolar catheter was positioned at the right ventricular apex, and 2 7F mapping/ablation catheters were deployed with a retrograde and transeptal approach. ECG and contact catheter data were recorded on a conventional electrophysiology system. VT induction was attempted by programmed stimulation with the Wellens protocol.\(^10\) Entrainment mapping was performed during VT,
and ventricular overdrive pacing was used to terminate rapid, poorly tolerated tachycardias.

Noncontact Mapping
Noncontact mapping has been described previously. A catheter-mounted 64-wire multielectrode array was positioned inside the LV retrogradely, a 3D geometry of the LV chamber was created, and high-resolution isopotential maps were recorded.

Definitions
Regions of scar were identified on the isopotential maps as areas of endocardium with very low amplitude or absent reconstructed electrograms during sinus rhythm, pacing, and VT. These areas were then mapped with bipolar contact catheters and confirmed as scar if electrogram amplitude was \( > 0.5 \) mV. VT exit sites were defined as the point of rapidly expanding systolic activation on the isopotential map synchronous with or just before QRS onset.

Arcs of functional block were defined as lines of block that divided activation between adjacent endocardial areas by \( > 50 \) ms, were not fixed, and varied with different rates of ventricular activation. When present, they produced dissociated activation in adjacent regions and electrograms with double potentials, and when the arcs elongated to circumscribe an enlarging area of increasingly late activation, conduction through which led to VF (see Results), the circumscribed region was defined as the zone of VF initiation. VF was defined by characteristic 12-lead ECG features of chaotic, irregular, polymorphic, and rapid ventricular activation associated with complete hemodynamic collapse that required DC cardioversion (Figure 1).

Local fibrillation intervals (consecutive maximum \(-dV/dt\) in reconstructed electrograms) were used as a surrogate measure of local refractoriness\(^{14,15}\) at points on the endocardium. Intervals were measured 2 seconds after the onset of VF for a total of 5 seconds. Results were compared with the Mann-Whitney \( U \) test (SSPS 10 software), and values of \( P < 0.05 \) were considered statistically significant.

Results
All patients had at least 1 region of infarct scar identified within the LV; 4 of these scars were located anteriorly, and 2 were posterobasal. A total of 8 episodes of pacing-induced VF were recorded by the noncontact system in 6 patients. Six episodes of VF occurred during continuous pacing at 81±8% of VT cycle length (296±37 ms). The remaining 2 episodes of VF resulted from programmed stimulation during sinus rhythm with the introduction of up to 3 extrastimuli after a drive train.

Endocardial Activation Leading to VF Induction
A common finding in all cases was that over the sequence of paced beats, progressive extension of arcs of functional block circumscribed areas of increasingly late activation (Figures 2 and 3). Propagation of activation through these protected regions leading to reentry was a result of 2 processes, both dependent on unidirectional block in part of the fully evolved arc of functional block, which led to interaction with the main wavefront of LV activation and associated refractoriness, causing fragmentation into fibrillatory activation.

Unidirectional Block With Antegrade Conduction
By this mechanism, delayed antegrade conduction within the circumscribed area defined by the arcs of block was suffi-

Patient Characteristics and Summary of VF Episodes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Gender</th>
<th>MI</th>
<th>EF, %</th>
<th>No. of VF Episodes</th>
<th>Mode of Induction</th>
<th>VTCL, ms</th>
<th>Pacing Rate, ms</th>
<th>Pacing Rate as % of VTCL</th>
<th>Location ofVF Initiation*</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>Anterior</td>
<td>35</td>
<td>2</td>
<td>Entrainment</td>
<td>275</td>
<td>200</td>
<td>73</td>
<td>Exit site</td>
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<td>260</td>
<td>72</td>
<td>Exit site</td>
</tr>
<tr>
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<td>56</td>
<td>M</td>
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<td>38</td>
<td>2</td>
<td>Entrainment</td>
<td>275</td>
<td>260</td>
<td>94</td>
<td>Exit site</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>F</td>
<td>Anterior</td>
<td>30</td>
<td>1</td>
<td>Drive train and extrastimuli</td>
<td>400-ms drive train + 220 + 200 + 190</td>
<td>Exit site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>F</td>
<td>Posterobasal</td>
<td>38</td>
<td>1</td>
<td>Drive train and extrastimuli</td>
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<td>VT noninducible</td>
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<tr>
<td>6</td>
<td>72</td>
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<td>1</td>
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<td>84</td>
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<td>4</td>
<td>37</td>
<td>8</td>
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</tbody>
</table>

MI indicates myocardial infarction; EF, ejection fraction; VTCL, VT cycle length; M, male; and F, female.

*Exit site relates to VT exit site. Remote is remote from VT exit site.

Figure 1. Contact electrogram and 12-lead ECG showing pacing-induced VF initiated by 2 premature extrastimuli (240 and 240 ms) after a 500-ms drive train during sinus rhythm. RVd indicates right ventricular apex catheter, distal pole.
ciently slow that by the time activation traversed the protected region and emerged from it, excitability had recovered in the surrounding myocardium, giving rise to a dissociated daughter wavelet, which led to reentry. This occurred in 2 VF episodes in 2 patients. An example of this is shown in Figure 2, which shows a sequence of noncontact data of pacing-induced VF from sinus rhythm. The flat isopotential maps represent the entire LV cut along 1 border and laid open. The gray area is infarct scar, and the green rectangular symbol is the site of pacing. The purple color represents resting endocardial potential that changes through a spectrum of colors on activation, with white representing maximal depolarization. The black arrows show the direction of activation, and the light blue lines represent lines of functional block. The letters A to F on the isopotential maps are the positions of the reconstructed electrograms in Figure 2C. A surface ECG (lead I) is also shown with reconstructed electrograms (Figure 2C). The numbered red lines on the electrograms in Figure 2C correspond with the numbering of the maps in Figures 2A and 2B and therefore with the points in time of these isopotential maps.

During the last stimulus of the 600-ms drive train, activation is seen propagating uniformly from the pacing site across the LV (maps 1 and 2) with no apparent lines of functional block, confirmed by the near-simultaneous normal local electrograms (lines 1 and 2, Figure 2C). With S3 (map 3), lines of functional block give rise to an area of late activation that begins in the midseptal area (asterisk, maps 3 and 4), associated with significant slowing of conduction demonstrated by the increasing stimulus to electrogram interval (lines 3 and 4, Figure 2C). An expanding arc of functional block evolves with S4 (map 4), and clear double potentials are seen on reconstructed electrograms C through E (line 4, Figure 2C).

The first nonpaced endocardial activation is seen to arise from the basal septum (map 5), which in this example is likely to have arisen from deeper myocardium, although its exact origin cannot be ascertained with noncontact mapping. Arcs of functional block bordering an area of slow conduction form a channel for antegrade and slow conduction (asterisk, map 5), which accounts for the split potentials (lines 5 and 6, Figure 2C). This wavefront emerges from this protected region (the zone of VF initiation) sufficiently late that excitability has recovered in the surrounding myocardium (map 7), and the resulting daughter wavelet emerges and propagates outside this protected region to complete a cycle of reentry. The wavefront fragments into multiple fibrillatory wavelets as it encounters fragmented lines of functional block in the same region of late activation and establishes VF (map 8).

Unidirectional Block With Retrograde Conduction

The second mechanism by which fibrillatory reentry occurs is when activation wavefronts are unable to enter a region protected by functional lines of block antegradely and have to propagate around the borders of block to enter the protected region distally in a retrograde direction. The activation wavefront propagates within this region sufficiently slowly that the unidirectional block has recovered, and it emerges from within the protected region to produce a daughter wavelet, which leads to VF. This occurred in 6 VF episodes in 4 patients.

An example of this is shown in Figure 3 (map orientation as for Figure 2). The endocardial VT exit site is represented by the red “Exit” label (maps 1 and 2), and site of entrainment is represented by the red rectangular symbol. Only the exit site and systolic portion of the circuit were mapped during this VT, with no diastolic activity identified. During native VT, systolic activation breaks out from a mid-posteroseptal region and propagates across the ventricle (maps 1 and 2). With entrainment that captures the ventricle (map 3), an area of functional block develops close to the infarct scar (blue line, maps 3 and 4), with subsequent entrainment beats (map 5), an expanding arc of functional block develops, giving rise to an area of protected and late activation and slow conduction (the zone of VF initiation; asterisk, maps 5 through 8). Activation is unable to enter the protected region antegradely, but activation of this protected region retrogradely (map 6) gives rise to a daughter wavelet (map 7), which emerges from the protected area (unidirectional block) and encounters further functional lines of block, resulting in the formation of multiple fibrillatory wavelets that establish VF (map 8).
**Group Results**

Figure 4 is a schematic representation of the LV endocardium in all 6 patients. Infarct scar is gray, and the black pacing symbol shows pacing site location. Patients 1 and 3 have 2 pacing symbols, which represent the position of pacing for separate VF episodes. The ellipsoid areas are the zones of VF initiation, and the numbered black dots are locations of the multiple VT exit sites in each patient.

In 6 of 8 VF initiations (Figure 4, panels 1 through 4), the locations of these critical regions occurred at scar border and involved VT exit sites. The remaining 2 patients (panels 5 and 6) had an area that initiated VF remote from scar. These areas had no abnormal electrogram or conduction characteristics during sinus rhythm, pacing, or tachycardia that were predictive of initiating VF.

Two patients had 2 separate VF episodes induced during the study (Figure 4, panels 1 and 3), both during attempted VT entrainment. Despite different pacing site locations, both episodes of VF resulted from development of arcs of functional block, abnormal late activation, and reentry in the same areas.

VT was induced in 5 of the 6 patients, and 4 of these 5 zones of VF initiation coincided with VT exit sites. Of the 29 VT morphologies (4.8±2.7 per patient), 11 VT exit sites (35%) corresponded precisely with the region that

**Figure 3.** A and B, Isopotential maps showing VF initiation during entrainment of VT in patient 1.

**Figure 4.** Schematic representation of LV endocardium in all 6 patients. See text for discussion.
initiated reentry and VF (ellipses with exit sites, panels 1 through 4 in Figure 4).

**Measurement of Refractoriness as Estimated From Fibrillation Intervals**

The mean duration of VF was 16±3 seconds, before DC cardioversion restored patients to sinus rhythm. As a surrogate for local refractory periods, consecutive fibrillation intervals were measured at 10 points within the region of late activation responsible for the initiation of VF (X’s within the ellipsoid region in Figure 4; fibrillation intervals 263±63 ms) and 10 randomly selected points in a surrounding control region (209±23.4 ms, P<0.0001; X’s outside the ellipsoid regions in Figure 4). Thus, the estimated mean difference in refractoriness in myocardium responsible for VF initiation was an average of 26% (54 ms) longer than in surrounding regions of the ventricle, which may account for the formation of lines of functional block and slow activation of the partially excitable tissue.

**Discussion**

Global high-resolution activation mapping of the development of VF in the infarcted human heart in the present study has shown that premature extrastimuli result in the formation of progressively expanding arcs of functional block and areas of increasingly late activation, with reentry through part of this functional (unidirectional) block leading to wavefront fragmentation and the development of fibrillation wavelets. Areas of abnormal activation responsible for the initiation of VF are spatially related to the regions of diastolic pathways of VT circuits, particularly the exit sites, and appear constant regardless of the pacing site. Regions of VF initiation have increased refractoriness compared with surrounding myocardium, which provides a possible mechanistic explanation for the development of functional lines of block and slow conduction, determinants of both the location and behavior of circuits that cause VT and potentially the substrate that gives rise to the degeneration to VF.

**Reentry Causing VF**

Ohara et al demonstrated that premature stimulation in the infarcted canine heart results in arcs of functional block and the development of reentry. The infarct border zone in the canine model has been shown to be an area of relatively slow conduction with highly heterogeneous activation times and recovery of excitability, and this provides the substrate for the formation of arcs of functional block that can promote reentry and fibrillation. There is evidence to suggest that VF may result from the formation of spiral waves, discontinuous propagation of which may give rise to rotating daughter wavelets. Although the simultaneous mapping data in the present study clearly demonstrate distinct reentrant mechanisms for the initiation of VF, a stable rotor or spiral waves may still be implicated.

Previous studies have provided limited insight into the mechanisms involved in the initiation of human VF. Although it is possible to fibrillate even normal hearts with premature extrastimuli, the reason for the lower threshold for inducing VF in the infarcted heart has been thought to be due to regions with nonuniform excitability and dispersion of refractoriness. Surface ECG recordings during episodes of spontaneous VF have shown that closely coupled ventricular extrasystoles or even supraventricular ectopics can provoke episodes of postinfarction VF. Josephson et al recorded endocardial and ECG data during pacing-induced and spontaneous episodes of VF. It is of interest, and in keeping with our data, that in the study by Josephson et al, the onset of fibrillation wavelets appeared to occur at a site distant from the pacing site, but the lack of spatial resolution in that study precluded further interpretation of this observation. That VF was never induced by a single extrastimulus but always required at least 2 premature stimuli is also consistent with the present study, in that the first stimulus is required to condition the ventricle to the effects of the subsequent stimulus to evolve an increasingly extensive region of block at the critical site, or to “peel back” refractoriness of the myocardium between the pacing site and the critical region. The findings in the present study that fibrillation intervals are longest in the critical region compared with surrounding regions and that the initial paced wavefronts show progressive interaction in the critical region are in keeping with this.

**Role of Functional Block in VF Initiation**

With the progressive formation of arcs of functional block, the resulting late activation emerges from the protected region and gives rise to the daughter wavelets, initiating VF. That the location of this fibrillatory initiation was consistent despite different rates of activation and pacing site (2 episodes in 2 patients) indicates that it is the abnormal behavior of a localized region of myocardium that may dictate susceptibility to VF. The characteristic features of this region are slow conduction and late activation coupled with longer refractory periods that predispose to the formation of the functional lines of block and the slow conduction that facilitates daughter wavelet formation. Of the putative mechanisms for the development of functional conduction block, high-resolution canine mapping studies have provided evidence that marked regional differences in refractoriness, such as the 26% difference demonstrated in the present study, cause functional block at their interface in an interval-dependent manner. Areas of VF initiation in most of these patients had VT exit sites located within or closely adjacent to the areas bounded by functional block, and 6 of 8 of the regions of VF initiation were located at the edge of the infarct scar, where fibrosis and disruption of normal gap junctional expression have been observed and where resulting abnormal conduction characteristics may interact with gradients of refractoriness to promote fibrillation.

**Clinical Implications: Relationship Between VT and VF**

There is an association between areas of increased refractoriness that develop functional block, late local activation, and wavefront fragmentation that initiates VF and the exit sites of VT circuits. This finding gives rise to the possibility that ablative treatment of VT circuits could modify shared substrates that initiate VF and reduce the risk of developing VF.
and sudden death. Clinical evidence of this has come indirectly from studies that show VT ablation can reduce the frequency of VF in patients with implantable defibrillators. Data from the present study provide further evidence for the influence of functional characteristics on conduction in ventricular arrhythmogenesis and demonstrate that specific localized functional characteristics predispose to VF. Further understanding of these characteristics and mechanisms may allow stratification of an individual’s risk of VF by appropriate programmed stimulation and mapping, and may possibly enable the development of strategies to treat VF susceptibility preemptively.

Study Limitations

The noncontact system can only map endocardial activation; intramural or epicardial conduction that may be important in the genesis of VF cannot be defined. In the present study, VF was artificially induced by programmed stimulation; whether the same principles occur spontaneously in the degeneration of VT to VF or in primary VF in vivo is still uncertain. In addition, VF can also be induced in normal hearts, and whether this or the VF that rarely occurs spontaneously triggered by Purkinje potentials in an otherwise apparently normal heart has any mechanistic features in common with our findings in infarcted hearts remains to be determined. Furthermore, in the present study, Purkinje potentials could not be identified during VT or VF. The numbers of observations in this opportunistic study are small and are from a selected patient population; there may be other mechanisms responsible for VF initiation not seen in the present study.

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References

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