Mechanisms Underlying the Development of Ventricular Fibrillation During Early Myocardial Ischemia

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The mechanisms underlying the development of ventricular fibrillation (VF) during early myocardial ischemia were assessed by use of a computerized three-dimensional mapping system capable of recording simultaneously from 232 intramural recording sites throughout the entire feline heart in vivo. Occlusion of the proximal left anterior descending coronary artery led to ventricular tachycardia (VT), which degenerated to VF in 1–5 minutes in four of 15 animals. Normal sinus beats immediately preceding the initiation of VT leading to VF demonstrated delayed activation (total activation time 133±14 msec), which was not significantly different from the activation time for normal sinus beats immediately preceding nonsustained VT (149±7 msec). Most of the conduction delay occurred in the subendocardial and midmyocardial regions in both groups. Initiation of VT leading to VF occurred by intramural reentry in three of the four cases. In one case, a mechanism responsible for the initiation of VT could not be assigned. The coupling interval of the initiating beats of VT ultimately leading to VF (210±15 msec) did not differ from that of nonsustained VT. Maintenance of the VT that led to VF was due primarily to intramural reentry (84% of cases) involving multiple activation sites in and around the border region of the ischemic zone. Nonreentrant mechanisms, arising in the subendocardium and subepicardium, also contributed to the maintenance of VT before development of VT. The transition from VT to VF was due exclusively to intramural reentry with initiation of the reentrant beats in the subendocardium and, occasionally, the subepicardium. Acceleration of the tachycardia by intramural reentry, along with very rapid and inhomogeneous recovery of excitability (as low as 50–60 msec), led to increased functional block and conduction delay. As a result, the total activation time for a given beat exceeded the coupling interval for that beat and led to the multiple reentrant circuits and multiple simultaneous activations characteristic of VF. Thus, the initiation and maintenance of VT leading to VF during early ischemia is due to intramural reentry, although nonreentrant mechanisms also contribute. However, the development of VF is due to continued intramural reentry and rapid recovery of excitability. (Circulation Research 1990;66:672–695)

The precise electrophysiological mechanisms underlying the development of ventricular fibrillation (VF) during myocardial ischemia remain to be elucidated. Myocardial ischemia is characterized by a variety of electrophysiological alterations such as slow conduction and variable degrees of conduction block that provide the conditions necessary for reentry to occur.1–8 Studies by Janse and coworkers9 using 60 epicardial or intramu-
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during early myocardial ischemia is due primarily to intramural reentry, although nonreentrant mechanisms also contribute. We have also shown that the transition from VT to VF after reperfusion of ischemic myocardium is due to acceleration of the tachycardia by nonreentrant mechanisms. The present study was performed to delineate the mechanisms responsible for the development of VF during early myocardial ischemia without reperfusion.

Materials and Methods

Animal Preparation

Adult cats (n=15) were anesthetized with ketamine hydrochloride (12.5 mg/kg) and α-chloralose (75 mg/kg). Respiration was maintained by means of auffed endotracheal tube and a Harvard respirator (Harvard Apparatus, South Natick, Massachusetts). Catheters were inserted in the femoral artery and vein. The systemic arterial pressure and a lead II surface ECG were recorded on a Gould Brush Model 260 recorder (Gould, Cleveland, Ohio). Body temperature was maintained at 37°C by a thermostatic esophageal probe controlling an infrared lamp. A left thoracotomy was performed by excision of ribs 2 through 5, and the heart was supported in a pericardial cradle. The left anterior descending (LAD) coronary artery was isolated at its bifurcation from the left main artery, proximal to all branch points. A 3-0 cotton suture was placed under the vessel, and polyethylene tubing was threaded around the suture. Thirty-seven plunge-needle electrodes (described previously) containing two to eight bipolar electrode pairs per needle (232 intramyocardial sites total) were placed throughout the heart. All electrodes had an interbipole spacing of 500 μm. The left ventricular plunge-needle electrodes contained eight bipolar pairs, each separated by 500 μm. The septal electrodes consisted of four bipolar pairs, each separated by 2.5 mm. The right ventricular electrodes contained two bipolar pairs, each separated by 500 μm. The most proximal of the electrode pairs was located 500 μm from the epicardial surface. Electrodes were placed in the left ventricle (200 sites), septum (16 sites), and right ventricle (16 sites) with a distance between plunge electrodes of 4–9 mm. Right ventricular plunge electrodes were secured by small (7-0) sutures applied to the epicardial surface around the proximal shaft of the electrode. Left ventricular and septal electrodes were not sutured and remained fixed during the course of the experiment.

After 30 minutes of stabilization, the polyethylene tubing was advanced to the artery and clamped for 10 minutes, producing coronary occlusion. During the experiment, warm (37°C) saline was applied to the heart intermittently for prevention of surface cooling and for moistening of the epicardium. A thermistor on the epicardial surface ensured that the epicardial surface temperature remained at 37°C. Bipolar electrogram data from each of the 232 sites were individually amplified, filtered from 40 to 500 Hz, converted from analog to digital at a 2-kHz sampling rate, and stored on tape by use of a Sangamo Sabre IV high-density recorder (Fairchild Weston Systems, Sarasota, Florida). The recording was carried out continuously from just before anterior ischemia until 1 minute after the onset of VF. After termination of the experiment, detailed electrode localization was performed as previously described. Each plunge electrode was removed and replaced by a labeled pin. After removal of the heart and fixation in formalin for at least 24 hours, the pins were replaced with color-coded plastic brush bristles. The heart was cut transversely into 5–to 7-mm-thick slices. Because of the contraction of the heart during fixation, the cavity sizes were decreased and the wall thickness in some areas (especially the right ventricle) exceeded that observed during life. Each electrode was precisely localized as to its exact insertion site and the direction at which it entered the myocardium. The outline of each section was then traced, showing the exact location of each recording site (Figure 1). A few plunge-needle electrodes that lay along the plane of sectioning were represented on sections both apical and basal to the plane of sectioning. The tracings were enlarged for later three-dimensional construction of isochronic maps as described below. The gray areas in Figure 1 depict the ischemic region as defined below.

Construction of Isochronic Maps

Electrogram data were analyzed off-line by use of a PDP 11/34A computer system (Digital Equipment Corporation, Maynard, Massachusetts) with interactive high-resolution color graphics. Details of the mapping system have been described previously. Initially, the tape containing the electrogram data was played back, and the surface lead II tracing, also stored on digital tape, was reviewed for location of the surface electrocardiograms of interest. The electrograms were displayed eight at a time on a high-resolution color monitor. Activation times, assigned by the computer based on a peak criterion, were reviewed and manually overridden if required. Because electrograms obtained from the ischemic region were of low amplitude, an amplitude threshold of 0.25 mV was considered indication of activation of tissue by the depolarizing wave front. We have consistently found that the inclusion of electrical activity <0.25 mV fails to alter the construction of the three-dimensional isochronic maps. Conduction block between two electrodes was defined by any of three criteria: 1) Intervening electrodes exhibited no activation; 2) large temporal gaps (usually in the range of 25–130 msec over a distance of 500 μm–6 mm3) occurred between two electrodes, but adjacent electrodes in a less direct spatial path exhibited sequential activation; and 3) recording from electrode sites distal to a block demonstrated low-voltage electrotonic activity preceded
VF, when the activation sequences were very complex. Conduction velocity was determined when isochrones were parallel by division of the distance between two recording sites along the direction of the activation wave front by the difference in their activation times. The mechanism of a particular beat was defined as reentrant when 1) there was continuous depolarization from the preceding beat; 2) the site of initiation of a premature beat was adjacent to the site of termination of the preceding beat; and 3) the conduction velocity of the activation wave front from the site of termination of the preceding beat to the site of initiation of the premature beat was similar to the conduction velocity of the terminal portion of the activation wave front of the preceding beat.\textsuperscript{10,11} The mechanism was defined as nonreentrant when the site of initiation of a premature beat was remote from the site of termination of the preceding beat with no intervening depolarizations despite multiple intermediate recording sites.\textsuperscript{10,11} The ischemic zone after LAD coronary artery occlusion was not delineated by microspheres or dye. However, the ischemic zone (see Figure 1) was defined as those regions in which the transmural bipolar recordings exhibited a pronounced decrease in amplitude and an increase in duration,\textsuperscript{10} since these correlate well with the regional decrease in myocardial blood flow.\textsuperscript{18} All data are presented as mean±SEM. Statistical analyses were performed by Student’s $t$ test for paired and unpaired data as appropriate. Differences of $p<0.05$ were considered significant.

**Results**

**Incidence of Arrhythmias**

Occlusion of the LAD coronary artery led to the development of VT, which degenerated to VF within 5 minutes in four of 15 animals. The VT was polymorphic with an average cycle length of 165±5 msec. The VT continued for 11–18 beats (1.8–3.2 seconds) before the transition to VF as assessed by the rapid, irregular polymorphic pattern on the surface electrocardiogram. None of the animals demonstrated sudden onset of VF that was not preceded by VT. In three of four cases, VT leading to VF and its single preceding sinus beat immediately followed a premature ventricular complex (PVC) or a short (three-beat) run of nonsustained VT with a compensatory pause. VF never terminated spontaneously. Complete three-dimensional mapping was performed on the first 14–25 (mean=20) beats of four runs of VT leading to VF. Therefore, three-dimensional maps were constructed for 80 beats of VT, as well as eight normal sinus beats (during control and just preceding the onset of VT) for a total of 88 beats based on the analysis of over 19,000 individual activation time measurements.

**Activation Sequence During Normal Sinus Rhythm**

Normal sinus rhythm in the control interval before ischemia exhibited rapid conduction that initiated in the septum and spread rapidly through the heart with
a total activation time (TA) of 25±2 msec (n=4), similar to that reported previously in the cat heart in vivo.10 An example of the activation sequence during normal sinus rhythm is shown in Figure 2A. Activation initiates in the septum (beat NScontrol, level IV, *) and proceeds rapidly from endocardium to epicardium as well as to both the apex and the base. Ventricular activation is complete within 26 msec, equivalent to the duration of the QRS complex.

Myocardial ischemia led to fractionation, decreased amplitude, and increased duration of the bipolar electrograms. Within minutes of ischemia, normal sinus beats demonstrated conduction delay with nontransmural as well as transmural conduction block. We have previously demonstrated that sinus beats 1–5 minutes after ischemia and preceding a PVC or a run of nonsustained VT exhibit considerable conduction delay (TA=149±7 msec), which is significantly greater than that of normal sinus beats not preceding PVCs or nonsustained VT (TA=64±6 msec, p<0.001).10 The sinus beat immediately preceding the onset of VT eventually leading to VF also demonstrated a pronounced degree of conduction delay (TA=133±14 msec, n=4), but it was not significantly different from that found for sinus beats preceding nonsustained VT after early ischemia. An example of a three-dimensional activation sequence for a sinus beat preceding the onset of VT leading ultimately to VF is shown in Figure 2B. The surface electrocardiogram exhibits some loss of R wave amplitude as well as a significant degree of ST segment depression. Initiation occurs in the same septal site as during the control state (beat NSF, level IV, *). Activation again proceeds to both the apex and base, as well as from endocardium to epicardium. Activation in the posterior nonischemic zone is rapid and comparable with that of normal sinus rhythm in the control interval before ischemia. However, activation in the anterior ischemic zone is characterized by slow conduction both in a transverse (endocardial-to-epicardial) as well as in a longitudinal (side-to-side) direction. In addition, nontransmural conduction block (heavy lines) occurs both in a transverse direction (as in level II) and in a longitudinal direction (as in level IV). Slow conduction around these areas of block leads to considerable conduction delay. Activation proceeds around an area of nontransmural block in level II. Delayed epicardial activation (90-msec isochrone, level II) spreads to the adjacent midmyocardium (110-msec isochrone, level II) as well as both superiorly (110-msec isochrone, level I) and inferiorly (130-msec isochrone, level III) but fails to propagate further. Slow conduction in level IV proceeds from both a clockwise and counterclockwise direction around an area of longitudinal conduction block (60-msec isochrone), and very slow epicardial-to-endocardial activation leads to the latest activation for this beat in the subendocardium (†). This process is shown in more detail in Figure 3A. After initiation of NSF in the septum (site A), activation proceeds (A→B→C→D) in a clockwise direction around an area of unidirectional block.

Delayed activation occurs beyond the unidirectional block (E→F→G). The electrograms shown to the right of Figure 3A demonstrate that the discrete late activations for sites E and G (distal to the unidirectional block) are preceded by low-level electrotonic activity (small arrows), which reflects the electrical activity from activation that occurred proximal to the unidirectional block from adjacent sites C and I, respectively. Thus, unidirectional block can lead to pronounced activation delay between closely adjacent sites (e.g., 122-msec delay over a distance of 3 mm between sites G and I) and contribute to the development of intramural reentry (see below).

The total activation time for this sinus beat was 144 msec. Despite this marked activation delay, the QRS complex remained narrow and unchanged from that of the control preischemic state. Thus, the surface ECG remains insensitive to conduction delay occurring in small localized regions, probably because the resultant vector is insufficient to be recorded by the surface ECG.

Initiation and Maintenance of Ventricular Tachycardia Leading to Ventricular Fibrillation

VT that ultimately led to VF was initiated with a coupling interval from the preceding sinus beat of 210±15 msec (n=4), which was comparable with that of nonsustained VT (218±9 msec, p=NS).10 In three of four cases, initiation occurred by intramural reentry with delayed activation of the preceding sinus beat (in the subendocardium and midmyocardium), leading to activation of an adjacent subendocardial region. As shown in Figure 3A, late activation of the sinus beat (site G) allowed sufficient time for recovery of tissue proximal to an area of unidirectional conduction block and led to activation of an adjacent endocardial site (site H) to initiate the first beat of the tachycardia by intramural reentry (large arrow). Although there was a 61-msec time difference between the termination of normal sinus beat (NSF) and the initiation of X1, this does not represent a gap in the activation sequence but is merely due to slow conduction across these two sites. For determination that the wave front was continuous, the conduction velocity of the terminal activation of the sinus beat (110- to 150-msec isochrones) was measured and found to be 7.0 cm/sec. When the distance between the site of termination for the sinus beat (G) and the site of initiation of X1 (H) was divided by the difference in activation times between these two sites, the conduction velocity was found to be 8.1 cm/sec. Thus, the conduction velocities were similar, and the wave front was continuous. After initiation of X1 by intramural reentry to the endocardium in level III (Figure 2), activation proceeds in both a clockwise and counterclockwise direction, encountering variable degrees of nontransmural conduction block. The conduction block is functional in nature since its presence and degree was found to vary considerably from beat to beat (Figure 3B). Slow conduction around areas of nontransmural block in levels III and
IV leads to delayed midmyocardial activation, which activates an adjacent subendocardial site to initiate Xₙ, also by intramural reentry (data not shown).

Assignment of mechanism was not possible for only one ectopic beat. This beat was the initiating beat (X₁) of one of the runs of VT ultimately leading to VF 2 minutes after the onset of ischemia. In this case, the termination of the sinus beat was followed, after a very long delay, by initiation of the tachycardia at an adjacent endocardial site (Figure 4). Initiation of the last sinus beat occurs in the septum in level II (†), with rapid activation throughout the heart. Most of the heart was activated by 50 msec, except for a small region of delayed epicardial activity in level III (110-msec isochrone), which was activated by slow conduction from above (40-msec isochrone, level II) with a conduction velocity of 8 cm/sec, comparable with slow conduction observed during other beats of sinus rhythm and ventricular tachycardia during early ischemia.¹⁰ Activation beyond the area of nontransmural transverse block in level I (50-msec isochrone) was followed by initiation of X₂ at a closely adjacent (1 mm away) endocardial site (beat Xₙ, level I, *) after a considerable delay of 167 msec. Microreentry over a very slowly conducting pathway was possible and could not be ruled out. This process would require a conduction velocity of 0.53 cm/sec, a value much slower than the slowest conduction velocity noted during myocardial ischemia (9 cm/sec)¹⁰ but one consistent with conduction velocities of reflected reentry observed in vitro.¹⁹ However, because a definitive microreentrant pathway could not be delineated, a reentrant mechanism could not be assigned for the initiation of this particular VT.

The maintenance of VT leading to VF but before the transition to VF was due primarily to intramural reentry in 43 of 51 beats of VT analyzed (84%). Pronounced activation delay occurred primarily in the subendocardium and midmyocardium due to continued transmural and nontransmural conduction block. This delay (TA=139±5 msec, p=NS compared with reentrant beats responsible for maintenance of nonsustained VT) allowed sufficient time for adjacent subendocardial, and occasionally subepicardial, sites to recover their excitability and to initiate the next beat of the tachycardia by intramural reentry. An example of the maintenance of VT ultimately leading to VF secondary to intramural reentry is shown in Figure 5, which depicts the three-dimensional activation sequences for four consecutive beats during the maintenance of the same run of VT leading to VF as shown in Figure 4. Initiation of the seventh beat of the tachycardia (Xₙ) occurs at an endocardial site in level I (*) by intramural reentry from delayed activation of an adjacent midmyocardial site from Xₙ (map not shown). Due to transmural block in level I and nontransmural block in level II, activation proceeds primarily in a counterclockwise direction. Delayed activation in level I just distal to the area of transmural block (110-msec isochrone) allows sufficient time for recovery of tissue proximal to the block and activates adjacent endocardium to initiate Xₙ by intramural reentry (beat Xₙ, level I, *).

Although maintenance of the tachycardia by intramural reentry usually involved a single reentrant pathway, at times more than one reentrant pathway was present. This is also shown in Figure 5. After initiation of Xₙ in the subendocardium in level I (*), the wave front fails to propagate in a clockwise direction in levels I and II because of longitudinal conduction block. These sites of block were regions of delayed activation from the previous beat, and the block was probably due to the encounter of the activation wave front with tissue that was still refractory. Activation proceeds both in a discrete counterclockwise loop in the anterior left ventricular free wall in level II and in a counterclockwise direction in level I. Delayed activation in the counterclockwise loop in level II (170- to 220-msec isochrones) allows sufficient time for an adjacent subepicardial site to recover (Xₙ, level III, **) and initiate Xₙ by intramural reentry (solid arrow). In addition, the late activation in level I (260-msec isochrone) leads to delayed midmyocardial activation in level II (290-msec isochrone) and subsequent activation of adjacent subendocardium (beat Xₙ, level I, **) to initiate Xₙ at a second site by intramural reentry (17 msec after initiation in level III). Thus, multiple reentrant circuits can be involved in the maintenance of VT ultimately leading to VF during early ischemia.

In addition to intramural reentry, nonreentrant mechanisms also contribute to the maintenance of VT that eventually leads to the development of VF. This conclusion is based on the finding, observed in six of 51 (12%) of the beats analyzed, that the site of initiation of the ectopic beat was remote from the site of termination of the preceding beat with no intervening electrical activity noted despite the presence of multiple intermediate recording sites. This nonreentrant activity was found to arise in the subendocardium as well as in the subepicardium, as was noted for the maintenance of nonsustained VT by nonreentrant mechanisms.¹⁰ An example is shown in

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**Figure 2.** Three-dimensional isochronic maps of a control normal sinus beat (panel A) and a sinus beat and the first beat of a run of ventricular tachycardia (VT) leading to ventricular fibrillation (VF) 5 minutes after occlusion of left anterior descending coronary artery (panel B) in cat 1. The surface electrocardiogram for each beat is shown above maps within box. Areas of conduction block are indicated by thickened lines and blackened areas. Sites of earliest activation for each beat are denoted by asterisk (*); site of latest activation (for beat NSinalh is denoted by cross (†). Numbers within isochrones indicate time in milliseconds from initiation of each sinus beat. Beneath the map of each ectopic beat is its mechanism of initiation. Initiation of first beat of VT leading to VF occurs by intramural reentry, shown by dark arrow from NSinalh to X, NS, normal sinus beat; X, beat; R, reentrant.
Figure 3. Panel A: Detail of intramural reentry. In left part of panel are sections III and IV for both normal sinus beat (NS_{isch}) and first beat of VT (X_1) from Figure 2B. A through I denote individual intramural bipolar electrode sites. A through H are along reentrant pathway (arrow), and I is a site proximal to an area of unidirectional block. On right are bipolar electrograms for sites A through I during a 248-msec period of transition from NS_{isch} to X_1. Calibration scales for autocalibrated signals are shown to left of each electrogram. Vertical cursor denotes activation time of each electrogram, with its value (in milliseconds, relative to initiation of NS_{isch}) shown to upper right of cursor. Numbers on left of each tracing (221, 184, 152, etc.) indicate number of bipolar recording site. Small arrow denotes low-level electrotonic activity preceding discrete late activations at sites E and G, which reflect electrical activity from adjacent sites C and I, respectively (which are proximal to areas of unidirectional block). Panel B: Detail of functional conduction block showing bipolar electrograms for sites A and F during a 496-msec window from NS_{isch} to X_2, second beat of run of ventricular tachycardia shown in Figure 2B. While site A in nonischemic zone demonstrates consecutive activation during NS_{isch} to X_2, site F in ischemic zone demonstrates very delayed activation during NS_{isch}, conduction block during X_1, and activation during X_2 (isochronic map not shown) with considerably less delay after activation at site A. Thus, slow conduction and block could vary considerably from beat to beat.
FIGURE 4. Three-dimensional isochronic maps of the first beat ($X_1$) of another run of ventricular tachycardia leading to ventricular fibrillation 2 minutes after occlusion of left anterior descending coronary artery, and its preceding normal sinus beat (NS), in which a mechanism could not be assigned (cat 2). Surface electrocardiogram for the two beats is shown above maps within box. Areas of conduction block are indicated by thickened lines. Sites of earliest activation for each beat are denoted by asterisk (*). Numbers within isochrones indicate time in milliseconds from initiation of each sinus beat.
FIGURE 5. Three-dimensional isochronic maps of four beats (X7–X10) of a run of ventricular tachycardia (VT) leading to ventricular fibrillation (VF) 2 minutes after ischemia (cat 2) in which maintenance of VT occurs by intramural reentry (R), at times involving multiple reentrant pathways (R+R), as well as by a nonreentrant mechanism (NR). Surface electrocardiogram for the four beats is shown above maps within box. Areas of conduction block are indicated by thickened lines and blackened areas. Sites of earliest activation for each beat are denoted by asterisk (*). Numbers within isochrones indicate time in milliseconds from initiation of each sinus beat.

Figure 5. After initiation of X0 at two sites (levels I and III), activation proceeds posteriorly and in a counterclockwise direction. Again activation fails to propagate in a clockwise direction due to transmural conduction block secondary to the presence of recently activated tissue from X8 that was still refractory to activation. The latest activation of X0 occurs distal to the transmural block in level I (†). However, conduction is much more rapid. The extent of conduction delay is considerably less than in previous beats (TA=71 msec) and, as a result, is insufficient to sustain a reentrant circuit. However, the tachycardia continues because beat X10 initiates at a distant epicardial site in the apex (X10, level IV, * at arrow)
by a nonreentrant mechanism, with no intervening electrical activity despite the presence of multiple intermediate electrode sites (Figure 6). After initiation of X₁₀ in the subepicardium of level IV, activation proceeds primarily in a basal and leftward direction, with considerably less conduction block than in previous beats. The total activation time for X₁₀ was only 95 msec, which was still insufficient to maintain a reentrant circuit.

As shown in Figure 7A, the initiation of beats X₁₁ and X₁₂ by a nonreentrant mechanism, each at a different epicardial site near the midanterior septum, results in a progressive increase in conduction delay. As a result, the degree of midmyocardial conduction
delay for \( X_{19} \) (145 msec) is sufficient for an adjacent subendocardial site to recover its excitability to initiate \( X_{15} \) by intramural reentry (maps not shown). Therefore, the maintenance of VT leading to VF is primarily due to intramural reentry, but nonreentrant mechanisms in the epicardium contribute importantly to the maintenance of the tachycardia when there is insufficient delay to maintain a reentrant circuit. The gradual increase in conduction delay induced by these nonreentrant mechanisms as the tachycardia continues leads to reinitiation of a reentrant circuit and continued maintenance of the tachycardia. In two cases (4%), initiation of a beat of VT eventually leading to VF occurred by both a reentrant and a nonreentrant mechanism (not shown) similar to that noted during nonsustained VT.\(^{10}\) Thus, the interaction between reentrant and nonreentrant mechanisms is a complex one.

As the tachycardia continued, the degree of slow conduction and unidirectional block continued to vary considerably from beat to beat but was almost always restricted to the ischemic zone. As a result, the site of latest activation and the site of initiation of the next beat of the tachycardia varied considerably from beat to beat, at times involving more than one endocardial or epicardial site. An example is shown in Figure 8, which depicts the sites of initiation of the first 21 beats of the same VT illustrated in Figure 2. Initiation occurs in the subendocardium and occasionally the subepicardium. Although initiation can occur within the ischemic zone, the majority of beats of the VT arise from the normal side of the border zone. The marked variation in initiation sites in part accounts for the polymorphic nature of the tachycardia. The heterogeneity in intramural conduction delay from beat to beat and the resultant net vectors also account for the polymorphic nature of the tachycardia.

**Transition to Ventricular Fibrillation**

The transition from VT to VF was due to pronounced acceleration of the tachycardia to a cycle length of 90–100 msec through a mechanism of intramural reentry. An example is illustrated in Figure 9, which shows four beats of the same run of VT leading to VF as shown in Figures 4 through 7 during the transition to VF. The coupling intervals shown below the activation map for each beat indicate that the tachycardia is rapidly accelerating. Initiation of the first beat in the transition, \( X_{15} \), occurs at an endocardial site in the anterior right ventricle (level

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**Figure 7.** Plots of coupling interval and total activation (panel A) and recovery period (panel B) for each of the first 21 beats of the run of ventricular tachycardia leading to ventricular fibrillation (VF) shown in Figures 4 through 6 (cat 2). Beats \( X_{10} - X_{12} \) were initiated by a nonreentrant mechanism (NR). See text for further details. \( S \), preceding sinus beat.
Multiple sites of initiation during ventricular tachycardia (VT) leading to ventricular fibrillation (VF) (for the run of VT leading to VF shown in Figure 2) (cat 1). Ischemic zone (see "Materials and Methods") is denoted by shaded area. Numbers represent sites of initiation (multiple at times) for first 21 beats of tachycardia.
FigURE 9. Three-dimensional isochronic maps of four beats (X₁₅-X₁₈) during transition to ventricular fibrillation (same ventricular tachycardia as in Figures 4 through 7) (cat 2), with acceleration of the tachycardia occurring by intramural reentry (arrows). Areas of conduction block are indicated by thickened lines and blackened areas. Sites of earliest activation for each beat are denoted by asterisk (*). Numbers within isochrones indicate time in milliseconds from initiation of each sinus beat. Beneath map of each ectopic beat is its mechanism of initiation (R, reentrant; R+R, multiple reentrant); also below map are coupling interval (CI) and recovery period (RP) in milliseconds.

I, *) by intramural reentry from the previous beat (not shown). Activation proceeds primarily in an apical and leftward direction. There is nontransmural conduction block in level IV, and the slow midmyocardial activation around this area of block leads to initiation of the next beat, X₁₆, at an adjacent subendocardial site (level III, *) by intramural reentry with a coupling interval of 164 msec. Four individual recording sites demonstrated the activation sequence from the 70-msec isochrone (X₁₅, level IV) to the initiation of the next reentrant beat (X₁₆, level III). Although it was not possible to determine the
refractory period at individual recording sites during the course of the tachycardia, we and others have evaluated refractoriness indirectly by determination of the duration of time between consecutive depolarizations at the same recording site.\textsuperscript{11} This value, which we refer to as the "recovery period," is greater than or equal to the refractory period at that particular site.\textsuperscript{11} As shown in Figure 7B, the recovery period (for the sites of initiation of each beat) gradually decreased during the course of the tachycardia such that $X_{16}$ initiates at a subendocardial site with a recovery period of 107 msec.

After initiation of $X_{16}$ (Figure 9), conduction spreads in both a clockwise and counterclockwise direction but encounters transmural block in level I and nontransmural block in levels II through IV. Activation of the anterior subendocardium and midmyocardium in level III (170- to 210-msec isochrones) proceeds in a clockwise direction. However, activation of the subepicardium is delayed because of both longitudinal and transverse conduction block. Late activation of the subepicardial region by slow conduction around this block leads to initiation of the next beat, $X_{17}$, by intramural reentry now to an epicardial site ($X_{17}$, level II, *). Here the coupling interval of the tachycardia has suddenly decreased to 92 msec, due to both the continued slow conduction and block, providing the milieu for intramural reentry, as well as the rapid recovery of tissue in the area adjacent to the ischemic zone. The recovery time for the site of initiation of $X_{17}$ was only 63 msec. This rapid recovery contributes to the gradually decreasing size of the reentrant loop necessary to maintain the tachycardia. In addition, even after initiation of $X_{17}$, activation of $X_{16}$ is still proceeding superiorly and in a counterclockwise direction (280- to 290-msec isochrones in levels I and II, respectively). The late activation of these regions leads to the pronounced degree of transmural and nontransmural block (blackened areas) seen during the activation of $X_{17}$. As a result, the activation wave front for $X_{17}$ moves in a counterclockwise direction, except for very slow clockwise activation of the midmyocardium in level II. Conduction proceeds much more slowly than in the previous beats (as reflected by the increased total activation time of 146 msec and the increased density of isochrones). At this point the total activation time of $X_{16}$ exceeds the coupling interval of the next beat with simultaneous activation by two activation wave fronts ($X_{16}$ and $X_{17}$).

The activation during $X_{17}$ (seen in Figure 9) is shown in detail in Figure 10. After initiation of $X_{17}$ at site D, the slow counterclockwise activation in level I (D$\rightarrow$C$\rightarrow$B) leads to activation of an adjacent subendocardial site in level II that had rapidly recovered (beat $X_{18}$ at site A; recovery period 57 msec) to initiate $X_{18}$ also by intramural reentry. Again slow conduction combined with very rapid recovery of the tissue, now in an area further away from the border zone, leads to continued intramural reentry. Once again, the total activation time exceeds the coupling interval of the next beat with activation by two simultaneous wave fronts.

After initiation of $X_{18}$ in level II (Figure 9), activation proceeds, encountering varying degrees of transmural and nontransmural block. The depolarizing wave front moves slowly in a counterclockwise direction but proceeds somewhat more rapidly in a clockwise direction in level IV, such that 57 msec after the initiation of $X_{18}$ there is epicardial activation in level III (**), which proceeds in an epicardial-to-endocardial direction. It is interesting to note that this epicardial activation represents the collision of two simultaneous wave fronts: 1) the terminal activation of $X_{17}$ (D$\rightarrow$E$\rightarrow$F$\rightarrow$G$\rightarrow$H in Figure 10) proceeding around an area of nontransmural block (I,J) representing reentrant activity from the preceding beat, and 2) the early part of the activation of $X_{18}$ noted above. Therefore, the initiation of $X_{18}$ involves multiple reentrant loops and a very complex pattern of activation.

The recovery period is also decreasing substantially in both the ischemic and the nonischemic regions (Figure 7B). Figure 11 contains isochronic maps of the recovery periods for level II for the 1st, 8th, 16th, and 18th beats of this run of VT leading to VF. During initiation ($X_1$) and maintenance ($X_9$) of the VT, recovery periods are decreasing and more heterogeneous in the anterior ischemic zone, contributing to slow conduction and block. However, during the transition to VF ($X_{16}$, $X_{18}$), the recovery periods decrease even further (down to 50-60 msec in $X_{18}$), and a substantially increased heterogeneity of recovery period is now evident in the border zone as well as in the ischemic zone. As a result of this inhomogeneity of recovery, slow conduction develops for the first time in the nonischemic region (see Figure 12). This slow conduction leads to the initiation of reentrant activity further outside the border zone. Thus, the transition to VF due to intramural reentry is characterized by rapid and inhomogeneous recovery of excitability leading to slow conduction in the nonischemic region, which further contributes to the development of multiple reentrant pathways.

After initiation of $X_{18}$ in level II (Figure 9), activation also proceeds inferiorly and around an area of nontransmural block in level III (360- to 410-msec isochrones, arrow). Initiation of the next beat, $X_{19}$, occurs proximal to the unidirectional block by intramural reentry as shown in Figure 13. On the left are the middle two sections (II and III) of $X_{18}$ from Figure 9, with A to E indicating individual bipolar recording sites along the reentrant pathway. On the right are bipolar electrogram recordings from sites A to E with B shown again below E. After initiation of $X_{18}$ at site A (347 msec after initiation of $X_{15}$) and rapid activation of adjacent site B (351 msec), reactivation of site B (418 msec) to initiate $X_{19}$ occurs by conduction over the pathway (B$\rightarrow$C$\rightarrow$D$\rightarrow$E$\rightarrow$B). The development of VF involves very small intramural reentrant pathways; in this case the reentrant...
path length is 1.02 cm. Here reentry is due to unidirectional block, slow conduction around the block, delayed activation distal to the block, and reactivation proximal to the block for completion of the circuit. The small reentrant path length is due to both slow conduction and a very short recovery time. The recovery time for X18 at site B was 67 msec.

After initiation of X19, slow conduction and block led to initiation of X21 by intramural reentry (not shown) with a coupling interval of 77 msec. The initiation of X22 by intramural reentry occurred at the same time as the terminal activation of X18 as well as the propagation of X21. Thus, there were three simultaneous activation wave fronts, which are shown in detail in Figure 14. The transition to VF was due to acceleration of the tachycardia by intramural reentry, with pronounced shortening of the recovery times (Figure 7B, transition to VF). As the tachycardia continued to accelerate, the total activation time greatly exceeded the coupling interval (see Figure 7A, transition to VF), and VF developed with multiple reentrant pathways and multiple simultaneous activation wave fronts.

Ventricular Fibrillation

As VF developed, the pattern of activation became more disorganized, with the depolarizing wave front traveling in multiple directions simultaneously. Figure 15 shows the three-dimensional activation maps for the bottom two sections for the 22nd and 23rd activations (during VF) of the same run of VT leading to VF shown in Figure 2. Activation of X23 is characterized by propagation of the depolarizing wave front in multiple directions in a chaotic manner. This occurrence is simultaneous with activation by X22 and X24.

Transmural conduction during VF was very heterogeneous. As shown in Figure 16, conduction in the nonischemic region was uniform until the acceleration (by intramural reentry) and rapid recovery of excitability developed. During VF (X24, X25) intramural conduction block developed, possibly because of differing recovery properties of endocardial versus epicardial regions. This intramural conduction block contributed further to the multiple reentrant circuits during VF. In contrast, conduction in some parts of the ischemic zone was very slow, with a substantial prolongation of the recovery period and episodic conduction block. At times, epicardial conduction was preserved when subendocardial activation was blocked (Figure 16B, bottom two traces).

Discussion

The results of this study demonstrate that VT leading to VF during early myocardial ischemia is initiated and maintained primarily by intramural reentry, although nonreentrant mechanisms contribute. However, the transition from VT to VF is due to intramural reentry that leads to acceleration of the tachycardia, more rapid and inhomogeneous recovery of excitability, and further increased conduction delay. These conditions lead to the multiple reentrant circuits and multiple simultaneous activations characteristic of VF.

Intramural Reentry

We have previously demonstrated, using this cardiac mapping system in the feline heart in vivo, that initiation of PVCs and nonsustained VT during isch-
Figure 12. Slow conduction in nonischemic zone during transition to ventricular fibrillation (VF) (cat 2). Second slice for cat 2 is shown at top. A, B, and C denote individual recording sites. Shown below are bipolar electrogram recordings for sites A, B, and C for beats X1, X8, and X16–X19 for the same run of ventricular tachycardia leading to VF shown in Figures 4 through 7 and 9 through 11. See legend for Figure 3 for additional details.
emias occurs by intramural reentry in 75% of cases. The basis for development of intramural reentry was the presence of slow conduction and block during normal sinus rhythm. The degree of delayed activation could vary considerably from beat to beat and was most pronounced in the subendocardium and midmyocardium; it would probably not be detected by mapping of the epicardium alone or from a limited number of intramural sites. This marked intramural delay could lead to activation of adjacent subendocardium that had recovered excitability to initiate the PVC or the run of VT by intramural reentry. Initiation of VT ultimately leading to VF also occurred primarily by intramural reentry associated with considerable conduction delay in the subendocardium and midmyocardium. Both the degree of conduction delay in the preceding sinus beat and the coupling intervals of the first ectopic beats were comparable for VT leading to VF versus nonsustained VT. Thus, neither very early-coupled (R-on-T) nor very late-coupled premature beats were uniquely responsible for a tachycardia ultimately leading to VF.

The assignment of a particular mechanism was not possible for one beat that initiated a run of VT leading to VF. Termination of the preceding sinus beat in the midmyocardium was followed, after a long delay, by initiation of the tachycardia at a closely adjacent (1 mm) subendocardial site (Figure 4). Whether this represented reflected reentry or nonreentrant activation that arose next to the site of termination either coincidently or mediated by a "current of injury," as proposed by Janse et al., could not be determined despite the high degree of reso-
**2 MINUTES ISCHEMIA**

![Heart with ischemia diagram](image)

**Figure 14.** Multiple simultaneous activation wave fronts during ventricular fibrillation (VF) (cat 2). Simultaneous isochrones from three consecutive activation wave fronts ($X_{18}$, $X_{19}$, $X_{20}$) during a 20-msec interval shown within box (large arrow) for ventricular tachycardia leading to VF shown in Figure 4. Small arrows denote direction of activation for each of the 20-msec isochrones.

[Diagram description]

...olution of the mapping procedures employed. It is interesting that a very similar pattern of activation was observed during the initiation of two runs of VT (one nonsustained, the other leading to VF) after reperfusion of ischemic myocardium in the identical animal preparation.\(^{11}\)

**Nonreentrant Mechanism**

We have previously shown that maintenance of nonsustained VT involves both intramural reentry and nonreentrant mechanisms, at times in combination in the same beat.\(^{10}\) Maintenance of VT leading to VF also involved both intramural reentry as well as nonreentrant mechanisms. Intramural reentry arose from the continued presence of conduction delay of sufficient magnitude to allow adjacent tissue to recover excitability and to be reactivated. Because of the functional nature of the conduction block and its variability from beat to beat, the location of the reentrant pathway could vary considerably from beat...
to beat (as shown in Figure 5). Although at times initiation occurred in the ischemic zone, the majority of ectopic beats due to either reentrant or nonreentrant mechanisms were initiated in the border zone adjacent to areas of substantial conduction delay within the ischemic zone. The considerable biochemical and electrophysiological heterogeneity of the border zone has been well documented and may account for its role in the genesis of reentry. The basis for nonreentrant activity arising from the border zone remains to be elucidated.

Activation could also occur by a nonreentrant mechanism arising primarily from the subepicardium and, therefore, unlikely to be secondary to an automatic mechanism arising from Purkinje tissue. Nonsustained VT was terminated because of insufficient conduction delay in the terminal beat, whether due to reentry or a nonreentrant mechanism, preventing continuation along a reentrant circuit. VT ultimately leading to VF did not differ in the extent of conduction delay of the reentrant beats compared with that during nonsustained VT. However, during VT ultimately leading to VF, when conduction delay decreased considerably to an extent insufficient to maintain a reentrant circuit, nonreentrant activation led to progressive conduction delay (over several beats) that was of sufficient magnitude to reinitiate the reentrant circuit and thereby maintain the tachycardia (Figure 4). Thus, nonreentrant activation appears to contribute to the maintenance of VT ultimately leading to VF. The presence of nonreentrant activation during VT ultimately leading to VF is similar to our previous findings during nonsustained VT. Whether this nonreentrant mechanism represents triggered activity due to delayed afterdepolarizations, mediated by increases in intracellular calcium (associated with ischemia per se, or catecholamines or amphipathic metabolites such as lysophosphoglycerides), remains to be determined. We have demonstrated previously that lysophosphatidylcholine (LPC), an amphipathic metabolite that accumulates in ischemic myocardium, can directly induce delayed afterdepolarizations and triggered activity in vitro despite the presence of hyperkalemia and acidosis. Therefore, the possibility exists that accumulation of LPC in ischemic myocardium may directly contribute to this nonreentrant activation.

**Transition to Ventricular Fibrillation**

The transition from VT to VF during ischemia was due to intramural reentry with acceleration of the tachycardia leading to increased conduction delay and block and the development of VF. Intramural reentry during the transition to VF was similar to that during the initiation and maintenance of the tachy-
cardia. Conduction proceeded slowly around areas of intramural block with delayed activation occurring most often in the subendocardium and midmyocardium. Activation of adjacent subendocardium that had recovered excitability led to initiation of the next beat by intramural reentry. On rare occasions, initiation occurred in an adjacent epicardial site.

Our findings of intramural reentry in the transition to VF are consistent with those of Janse and colleagues.9 Mapping from 60 epicardial sites in the isolated porcine and canine hearts, they found that the development of VF during early ischemia was characterized by further slowing of conduction with multiple circus movements of small diameter on the epicardial surface, many of which were incomplete. Assignment of the mechanisms for all beats was not possible due to the limited data storage capacity as well as mapping from only a portion of the epicardial surface. Intramural reentry was demonstrated on one occasion. Their finding of complete and incomplete reentrant circuits on the epicardial surface reflects the underlying reentrant pathways, which, at times,
are epicardial but more frequently are intramural and not well reflected on the epicardial surface. The importance of the endocardium in the intramural reentrant circuits that are critical to the development of VF is consistent with findings that ablation of the subendocardium prevents the development of 
VF.  

Whether there is an important contribution by Purkinje fibers within this subendocardial region or by differences between the conduction and refractory period properties of the subendocardial and subepicardial tissue remains to be clarified, but it is clear that intramural activation contributes significantly to the development of VF.

The transition from VT to VF was critically dependent on the acceleration of the tachycardia by intramural reentry due to the very rapid recovery of excitability of tissue adjacent to the ischemic zone. Early ischemia is characterized by a decrease in the refractory period in the ischemic zone. Although the refractory periods could not be assessed directly in the present study because introduction of an extrastimulus would have interrupted the normal progression of the spontaneous tachycardias, we were able to indirectly assess the refractory period by determining the recovery period, or the duration of time between consecutive depolarizations at the same recording site. The results indicated that during the transition to VF the recovery period decreases markedly, down to values as short as 57 msec. Since the recovery period represents the refractory period plus a period during which a region is excitable but has not yet encountered an activation wave front (an excitable gap), it is conceivable that the steep decrease in recovery period may merely be secondary to a decrease in the excitable gap rather than an actual decrease in the refractory period. However, this is very unlikely since the refractory periods during the initiation of VT during early ischemia in the feline heart, when measured directly by the extrastimulus technique, have not been less than 120 msec, let alone on the order of 57 msec, which is the time between consecutive activations during the transition to VF. Therefore, the refractory period, like the recovery period, likely decreases during the transition to VF. The recovery period permits a quantification of the degree of inhomogeneity of recovery of excitability not only at the site of initiation but also at each recording site.

The mechanisms underlying the marked decrease in the recovery period during the transition from VT to VF are unknown, but may be due either to acceleration of the tachycardia resulting in a direct decrease in the refractory period or secondary to electrotonic interactions between an area of depolarized tissue proximal to a region of conduction block and an area of unexcited tissue distal to the block, which may enhance repolarization and thereby shorten the refractory period. Two important alterations in the recovery of excitability appear to be critical in the development of VF: 1) The alteration in recovery of excitability is very heterogeneous and leads to further slow conduction and block, thereby contributing to the development of intramural reentry; and 2) the recovery period becomes very small, primarily in the border zone. The path length of a reentrant circuit equals the product of the conduction velocity and the refractory period at the site proximal to the region of conduction block. In the early portion of the tachycardia, relatively large reentrant circuits occur due to a large decrease in conduction velocity combined with a modest decrease in the refractory period, measured as the recovery period. However, during the transition to VF there is concomitant pronounced shortening of recovery period combined with continued slow conduction, leading to very small reentrant circuits, on the order of a 5- to 10-mm path length. The marked decrease in the recovery period during the course of the tachycardia occurs first in the border region and then in the normal regions of the heart. This heterogeneity then results in variable degrees of slow conduction and block, leading to multiple reentrant circuits and multiple simultaneous activations that are characteristic of VF. These findings support the hypothesis by Janse and colleagues that shortening of the refractory periods in the nonischemic zone will eventually lead to reentrant circuits in the normal myocardium.

Other factors critical to the development of VF may also be operative. For example, the size of the ischemic region has been correlated with the occurrence of VF. A larger ischemic region may provide a larger region of abnormal conduction and contribute to the enhanced conduction delay during the VT, which maintains a reentrant circuit from beat to beat. Metabolic alterations may contribute. We have recently demonstrated that lysophosphoglycerides increase significantly within 3 minutes of ischemia and that the severity of ventricular arrhythmias is directly related to the magnitude of the increase, with the greatest increase in LPC in animals that developed VF. Other biochemical alterations, such as inhomogeneity of extracellular accumulation of potassium or the activation of ATP-sensitive K channels may also contribute, probably through the electrophysiological mechanisms outlined above. Hemodynamic compromise during VT could substantially decrease coronary perfusion pressure, leading to global ischemia and VF. However, in the present study the transition from VT to VF occurred less than 4 seconds after initiation of VT, making a hemodynamic contribution much less likely for the present findings, although the combination of hemodynamic and biochemical alterations may be critical. Thus, the transition to VF involves a change in the characteristics of the reentrant circuit from one in which very slow conduction predominates to one in which very rapid recovery of excitability predominates.

**Ventricular Fibrillation**

Once the multiple reentrant circuits and multiple simultaneous activations develop, VF is self-
perpetuating because the chaotic complex three-
dimensional wave front propagates throughout the
heart, always findingexcitable tissue that has
recovered excitability. Regions that had demonstrated
prolonged recovery time during the initiation and
maintenance of VT continue to exhibit prolonged
recovery and contribute to the slow conduction and
block during VF (Figure 12).

The mechanism underlying the transition from VT
to VF during early ischemia differs from that during
subsequent reperfusion.11 We have demonstrated
previously that both nonsustained VT as well as VT
leading to VF during early reperfusion are due
primarily to nonreentrant mechanisms, although
intramural reentry can contribute.11 Furthermore,
the transition to VF after reperfusion is due to
acceleration by nonreentrant mechanisms arising in
the subepicardium. In contrast, acceleration of the
tachycardia by a nonreentrant mechanism was not
observed during the transition to VF during ischemia
without reperfusion. However, once acceleration of
the tachycardia occurred, albeit by different mecha-
nisms, the development of VF during ischemia and
reperfusion was similar. Both involved a progressive
decrease in recovery time and a further slowing of
conduction velocity and more extensive conduction
block, with the total activation time exceeding the
coupling interval of the tachycardia. These findings
have implications for the development of VT and VF
in the human heart in response to ischemia and may
explain the acceleration of VT before the develop-
ment of VF in humans.41

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