Reentrant and Focal Mechanisms Underlying Ventricular Tachycardia in the Human Heart

Steven M. Pogwizd, MD; Robert H. Hoyt, MD; Jeffrey E. Saffitz, MD, PhD; Peter B. Corr, PhD; James L. Cox, MD; and Michael E. Cain, MD

Background. To determine the mechanisms of ventricular tachycardia (VT) in humans, three-dimensional intraoperative mapping of up to 156 intramural sites was performed in 13 patients with healed myocardial infarction and refractory VT.

Methods and Results. Mapping was of sufficient density to define the mechanism of 10 VTs in eight patients. In five of 10 cases, sustained VT was initiated in the subendocardium or epicardium by intramural reentry with marked conduction delay as well as functional and anatomic block most prominent in the subendocardium and midmyocardium. The initiating beats of reentrant VT induced by programmed electrical stimulation arose in the endocardium or midmyocardium by progressive slowing of conduction leading to unidirectional block. Multiple simultaneous reentrant circuits can be present. In contrast, five of the 10 sustained VTs were initiated by a focal mechanism as defined by the absence of electrical activity between the termination of one beat and the initiation of the next despite the presence of multiple intervening intramural electrode recording sites. Comparisons of the mapping data with results of histopathological analysis of tissue demonstrated that the location of infarction as well as that of adjacent fibrotic muscle determined sites of both fixed and functional conduction block during macroreentrant VT and that slowing of conduction occurred in a direction transverse rather than longitudinal to fiber orientation.

Conclusions. Both intramural reentry and a focal mechanism underlie sustained VT in patients with healed myocardial infarction. (Circulation 1992;86:1872–1887)

Key Words • ventricular mapping • arrhythmia surgery • ventricular tachycardia

Results of studies in experimental animals and in humans suggest that reentry is the predominant mechanism of sustained ventricular tachycardia (VT) in patients with coronary artery disease and healed myocardial infarction.1 Although intraoperative mapping of the human heart during VT has provided important insights into this arrhythmia,2,3 delineation of the anatomic and electrophysiological substrates underlying sustained monomorphic VT has not been achieved because mapping procedures have been limited to the epicardium or endocardium. Harris and colleagues,4 for example, mapped hearts with epicardial and/or endocardial electrode arrays from up to 240 sites and observed direct evidence of reentry in less than 20% of cases.

Three-dimensional, computer-assisted mapping obviates these limitations of endocardial or epicardial mapping. Analysis of global ventricular activation has demonstrated that intramural reentry is critical to the development of sustained VT in a canine model of chronic infarction.5 Moreover, results of analysis of transmural ventricular activation have also demonstrated that nonreentrant mechanisms as well as intramural reentry underlie the development of sustained ventricular arrhythmias during early myocardial ischemia and reperfusion in the feline heart in vivo.6,7 Accordingly, in the present study, we have used this computer-assisted system to map VT in patients with coronary disease and remote myocardial infarction in order to 1) define the role of the intramural activation pattern in the development of sustained VT in patients with coronary disease, 2) elucidate the mechanism(s) responsible for sustained VT, and 3) characterize the structural features of tissue within regions critical to the development and maintenance of VT.

Methods

Patients Studied

Thirteen patients with ischemic heart disease and medically refractory sustained monomorphic VT underwent intraoperative mapping and arrhythmia surgery at Barnes Hospital after informed consent was obtained. Each patient had a healed myocardial infarction (4 months to 13 years), and 12 patients had a left ventricular aneurysm (Table 1). An electrophysiological study was performed preoperatively in all patients. Antiarrhythmic drugs were
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Site of myocardial infarction</th>
<th>Ejection fraction (%)</th>
<th>VT morphology/axis</th>
<th>Cycle length (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>A</td>
<td>40</td>
<td>RB/R</td>
<td>240</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>I*</td>
<td>40</td>
<td>LB/NL</td>
<td>380</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>F</td>
<td>A</td>
<td>20</td>
<td>RB/R</td>
<td>230</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>M</td>
<td>A</td>
<td>26</td>
<td>LB/LS</td>
<td>255</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>M</td>
<td>A</td>
<td>28</td>
<td>RB/RS</td>
<td>230</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>A</td>
<td>39</td>
<td>RB/RI</td>
<td>530</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>I</td>
<td>32</td>
<td>LB/LS</td>
<td>310</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>A</td>
<td>33</td>
<td>RB/RS</td>
<td>320</td>
</tr>
<tr>
<td>9</td>
<td>58</td>
<td>M</td>
<td>A</td>
<td>25</td>
<td>LB/R</td>
<td>260</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>M</td>
<td>A and I</td>
<td>46</td>
<td>LB/L</td>
<td>250</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>M</td>
<td>A</td>
<td>45</td>
<td>RB/L</td>
<td>280</td>
</tr>
<tr>
<td>12</td>
<td>66</td>
<td>M</td>
<td>I</td>
<td>35</td>
<td>RB/L</td>
<td>310</td>
</tr>
<tr>
<td>13</td>
<td>46</td>
<td>M</td>
<td>A</td>
<td>16</td>
<td>RB/RS</td>
<td>280</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia; A, anterior; I, inferior; R, right; B, bundle; L, left; S, superior; NL, normal. Patients 1–8 are the subject of this report.

*Infarction without aneurysm.

discontinued for at least five half-lives with the exception of amiodarone, which was discontinued for at least 2 weeks (two patients). Programmed ventricular stimulation and endocardial catheter mapping were performed as described previously. Sustained monomorphic VT (>30 seconds in duration or associated with hemodynamic compromise) of at least one morphological type was induced in 12 patients who completed the protocol. The electrophysiological study was not completed in one patient because of transient neurological symptoms that occurred during the study.

All patients underwent map-guided endocardial resection and cryoablation. Aneurysmectomy was performed in 12 patients. The surgical resections and subsequent programmed electrical stimulation were performed under normothermic bypass (and before cardioplegic arrest was instituted in the seven patients undergoing coronary revascularization). Programmed stimulation immediately after operation failed to induce sustained monomorphic VT in all patients.

There were no operative deaths. One patient, a 41-year-old woman with a remote anterior myocardial infarction, suffered an acute myocardial infarction and died on the third postoperative day. At autopsy, her entire heart was obtained for analysis in addition to the specimen obtained intraoperatively.

Electrophysiological studies were repeated in 11 of the 12 survivors within 1 month of surgery. Sustained VT was not induced in any patient with a protocol of up to three extrastimuli during two paced cycle lengths from two right ventricular sites. There was no recurrence of sustained VT postoperatively in any patient.

Intraoperative Mapping

Transmural ventricular mapping was performed with color-coded plunge needle electrodes containing four bipolar pairs (500-μm interbipole distance) each separated by 4 mm. Plunge needle electrodes have been used routinely in patients undergoing intraoperative mapping and surgery for VT at Barnes Hospital since 1983. The incidence of bleeding is <4%, and there has been no adverse effect on patient outcome. Depending on the size and location of the infarct and the results of the preoperative electrophysiological study, up to 39 needle electrodes (156 total recording sites) were inserted throughout the left and right ventricles with interelectrode distances ranging from 1.0 to 3.0 cm. Sites of electrode insertion were identified with the use of a 53-site grid. The needle density was greatest in the region surrounding the infarct zone. In six patients with previous infarction of the interventricular septum, the right atrium was opened, and needle electrodes were inserted into the ventricular septum to delineate transseptal activation. Sites of electrode insertion were identified with the use of a 16-site septal grid. Insertion of the needle electrodes was typically completed in 10 minutes. Analysis of transmural and transseptal activation was accomplished in 12 patients without the need to open the left or right ventricle. Epicardial activation data, measured with a 96-electrode sock, was obtained in five patients before plunge needle insertion but provided no additional information pertinent to mechanisms. Only data obtained from plunge needle electrodes are presented in this study.

After electrode placement, electrograms from each of the 156 transmural sites, along with surface ECG leads I, aVF and V_{1,R}, were recorded during sinus rhythm and during induced sustained VT. In two cases, electrograms were also recorded during programmed stimulation and during the initiating beats of the induced VT. To facilitate accurate localization of all electrode recording sites, a high-resolution video camera system (Panasonic) installed directly over the operating table continuously recorded the placement of all electrodes...
Data Processing and Analysis of Electrograms

Electrograms recorded from the plunge needle electrodes were processed and analyzed with the use of a computer-assisted mapping system that has been described in detail previously. Each bipolar electrogram was sampled at 2 kHz, filtered from 40 to 500 Hz, amplified, and converted with 12-bit precision. Digital data were stored continuously in 12 parallel bits on a Sangamo-Weston Sabre IV high-density recorder and analyzed off-line by use of a MicroVAX II computer (Digital Equipment Corporation) equipped with high-resolution color graphics. Activation maps were constructed as described previously. Computer-generated activation times were based on a peak criterion but could be reassigned after editing by the operator. Individual electrograms with peak amplitudes >0.25 mV were interpreted to represent discrete activations. Double activations at a single electrode site similar to those noted by Chen et al were also assigned. Conduction block between two electrodes was considered to be present when intervening electrodes demonstrated no activation or when there were large temporal gaps (>60 msec) between two electrodes, whereas adjacent electrodes in a less direct spatial path demonstrated sequential activation.5-7

At the time of intraoperative mapping, data analysis and determination of the site of earliest activation were performed with specially designed interactive software and were typically completed in 10–15 minutes. Earliest sites of activation during VT were marked with methylene blue before the needle electrodes were removed. The position and orientation of resected tissues were recorded on videotape for later detailed analysis and localization of the position of each electrode (Figure 1).

Three-dimensional Map Construction

Activation maps were displayed on diagrams of four short-axis slices of the heart from 1.5 to 3 cm thick that were derived from scaled drawings of pathological specimens from patients with prior myocardial infarction. The wall thicknesses and shapes depicted were representative of those of hearts from patients studied in the operating room. For the patient who died, short-axis diagrams were drawn directly from tracings of the heart obtained at autopsy. By use of the epicardial and septal grid systems and measurements taken from still photographs of the heart made from video recordings during electrode insertion, electrode positions were localized on the diagrams in short-axis slices (Figure 1). The needle electrodes were assumed to be inserted perpendicular to the epicardial surface.

After an activation time had been assigned or the presence of conduction block was confirmed for each electrode site, data were transferred to the appropriate location on the short-axis slices. Hand-drawn isochronic maps were constructed in 20-msec increments. Reentry was defined as the mechanism when 1) the site of termination of one beat was immediately adjacent to the initiation of the next and 2) there was continuous activity reflected by the conduction velocity of the terminal activation wave front of one beat being comparable to the conduction velocity from the site of
termination to the site of initiation of the following beat. A focal mechanism was assigned when no electrical activity between the termination of one beat and the initiation of the next beat was detectable despite multiple intervening transmural recording sites.

**Resection and Histological Analysis of Tissue**

Extended subendocardial resection was performed in all patients, and an attempt was made to resect all visible scar. Surgical margins were also determined with the aid of mapping data localizing the earliest site of activation of VT. Fibrosis that extended into a papillary muscle was cryoablated and not resected. Areas of resection included the midmyocardium to subendocardium (up to 1.5 cm thick) and portions of the overlying epicardial layer obtained during closure of the ventriculotomy. Specific landmarks on the tissue resected were denoted by methylene blue dye and/or sutures at electrode sites at which early activation was noted during VT. The entire resection procedure was recorded on videotape. An average of 42.1 ± 22.4 cm² of resected tissue was obtained from the 13 hearts. One to three large tissue blocks accounted for more than 95% of resected tissue. The tissue edge along the ventriculotomy was identified, and electrode sites at the overlying epicardium were spatially referenced to this cut edge, based on video-recorded images. Areas of tissue resection were localized in corresponding levels for each short-axis slice and compared with the activation mapping data. It was estimated that needle electrodes were localized to within 0.5 cm of their true position in the resected specimens. In cases of VT caused by macroreentry (n = 5), the entire reentrant circuit was spatially localized, and all or part of the reentrant circuit was contained in the tissue resected. Particular interest was directed to 1) initiation sites of VT, 2) the location of reentrant circuits and sites of slow conduction, 3) the sites of fixed and functional conduction block, and 4) the myocyte fiber orientation. Endocardial tissues from the site of earliest activation were available in two of the five VTs that arose focally. The tissues responsible for the other three focal VTs were cryoablated and not resected.

Tissue samples were fixed in 2% glutaraldehyde and 1% paraformaldehyde in 0.1 M sodium cacodylate buffer with 2 mM Ca²⁺, dehydrated in ethanol and xylene, embedded in paraffin, and sectioned at a thickness of 6 μm. Tissue sections were cut perpendicular to the epicardial surface and stained with hematoxylin and eosin and Masson’s trichrome for examination by light microscopy.

**Data Analysis**

The total activation time for a beat was defined as the difference between activation times for the site of latest and that of earliest activity. The coupling interval was defined as the difference between activation times for the initial sites of activation of two consecutive beats. Conduction velocity was determined when isochrons were parallel by dividing the distance between two recording sites by the difference in their activation times. Data are presented as mean ± SEM. Student’s t test for unpaired data was performed, and differences of p < 0.05 were considered significant.

**Results**

A total of 17 sustained monomorphic VTs in the 13 patients were analyzed. Four patients had VTs of two morphological types, and nine had VT of only one type. Mapping data from a mean of 128 sites (range, 92–156 sites) were sufficient to define the mechanism in 10 VTs from eight patients. In the other five patients, data from a mean of 102 sites (range, 60–156 sites) enabled surgical ablation of VT but were insufficient to definitively delineate a mechanism by the subsequent off-line detailed analysis. All data reported in the following sections are from the eight patients with 10 distinct VTs for which a mechanism was identified.

**Sinus Rhythm**

Analysis of ventricular activation during sinus rhythm demonstrated areas of fixed conduction block corresponding to regions of infarction as well as regions of delayed activation adjacent to the infarct. The total activation time ranged from 60 to 139 msec (mean, 93 ± 11 msec).

Global ventricular activation during sinus rhythm from patient 1 with a healed anterior myocardial infarct is shown in Figure 2A. Ventricular activation was initiated in the endocardium in the posterior basal region of the left ventricle (level II) and spread rapidly from endocardium to epicardium and to the apex and base. Areas of nontransmural or transmural conduction block (indicated by the blackened areas) were evident anteriorly at all four levels and corresponded to the area of myocardial infarction. The total activation time was 64 msec.

Ventricular activation during sinus rhythm from other patients demonstrated considerably more conduction delay. Earliest activation during sinus rhythm from patient 2 was recorded in the subendocardium of the lateral region of the left ventricle and spreads in both clockwise and counterclockwise directions. Transmural block was evident in the anterior septum. Latest activation was recorded in the basal aspect of the right ventricle 137 msec after initiation.

**Sustained Ventricular Tachycardia**

**Macroreentry.** Five (50%) of the 10 VTs analyzed were due to macroreentry that initiated in the subendocardium or epicardium. The mean total activation time during each beat of VT was 185 ± 22 msec, which was greater than that during sinus rhythm (p < 0.01) and was due to slow conduction and block primarily in the subendocardium and midmyocardium. All of the reentrant circuits involved intramural pathways, with delayed conduction in the midmyocardium or subendocardium constituting a critical part.

A three-dimensional activation map of two beats of induced VT from patient 1 is shown in Figure 2B. Earliest detectable activation during VT occurred in the subendocardium of the lateral wall of the left ventricle (beat X, level II). The depolarizing wave fronts spread both clockwise and counterclockwise. Some regions of block (blackened areas) at levels I–IV were similar to those noted during sinus rhythm (Figure 2A), suggesting fixed anatomic block caused by scar. In contrast, other complex regions of nontransmural and transmural conduction block during VT at levels II–IV (thickened
lines) were not present during sinus rhythm, suggesting functional block that may be due to incomplete recovery of excitability from delayed activation during the previous beat (data not shown). Late counterclockwise activation at level III in the epicardium (120-140 msec) and midmyocardium (160-180-msec isochrons) around an area of nontransmural block resulted in markedly delayed activation of the subendocardium (200-220-msec isochrons). Activation of adjacent subendocardium (arrow) initiated the next beat of VT (X_{n+1}, level II) by intramural reentry. These features were reproducible from beat to beat. Epicardial or endocardial surface mapping alone would have failed to demonstrate a complete reentrant circuit because the pathway of activation involved both surfaces as well as intramural sites.

The reentrant pathway is illustrated in more detail in Figure 3. Note the double activation at site E. Although a large electrogram occurred at 39 msec, very discrete late activity was present at 185 msec, separated by an isoelectric baseline. Double activations were recorded because the intramural electrodes subserved tissue lying directly on a line of functional conduction block and recorded activation of tissue on both sides of the block. Double activations were noted in maps of VT from other patients and were reproducible in consecutive beats of VT. A discrete solitary late activation at site F (207 msec) indicated that the spread of activation occurred along the intramural reentrant pathway A-B-C-D-E-F and then recirculated to site A at 220 msec, the cycle length of the tachycardia.

Macreorentricular circuits were also located within the interventricular septum (Figure 4). During VT from patient 2, activation was initiated in the midseptum (Figure 4B, beat X_{n}, level I) and proceeded both clockwise and counterclockwise, encountering varying degrees of conduction block. However, because of transmural block in the midseptum at level II (thickened line) and transmural block in the posterior septum between levels I and II (evidenced by the large temporal gap of 180 msec between the initiation site in level I and the 180-msec isochron immediately apical to it in level II), the posterior septal region at level II was not activated immediately by the depolarizing wave front. Posterior activation at level I (20-100-msec isochrons) and counterclockwise activation of the myocardium at level II (40-100-msec isochrons) merged and continued as delayed activation in the posterior septum (level II, 120-180-msec isochrons). Subsequent activation of an immediately adjacent endocardial region along the basal septum (beat X_{n+1}, level I) led to initiation of the next beat of the tachycardia by intramural reentry (arrow). The 100-msec interval between the termination of X_{n} and the initiation of X_{n+1} did not represent a gap in the activation sequence but rather was due to the slow conduction velocity of the activation wave front. To verify this conclusion, the distance between the site of termination of X_{n} and the initiation site of X_{n+1} was divided by the difference in the activation times, yielding a conduction velocity during this interval of 30 cm/sec. This value corresponds to the calculated conduction velocity of the terminal activation (100-180-msec interval) of X_{n} of 28 cm/sec. Thus, the conduction velocities were similar, activation was continuous, and the mechanism was intramural reentry.

**FIGURE 2.** Three-dimensional isochronic maps of ventricular activation during normal sinus rhythm (NSR) (panel A) and during two consecutive beats (X_{n}, X_{n+1}) of sustained ventricular tachycardia (panel B) caused by intramural reentry from patient 1. Sections are oriented with the base on top and the apex on bottom. The anterior wall is at the lower edge and the right ventricle is at the left edge of each section. Right ventricular (RV) and left ventricular (LV) cavities are labeled in the most basal section on the left. Earliest sites of activation for each beat are marked by asterisks. Conduction block is denoted by blackened areas or thickened lines. Isochrons are in increments of 20 msec with times relative to the onset of the sinus beat and beat X_{n}. Intramural pathways are shown in more detail in Figure 3.
The reentrant circuit from patient 2 is shown in more detail in Figure 5. Activation proceeded over the reentrant pathway (A-B-C-D-E) and back to A. Site E demonstrated double activations. The early deflection at site E probably represented the electrical activity recorded at 31 msec from adjacent sites F and G (which bordered the right and left ventricular cavities, respectively). The discrete late activation at 180 msec, how-

**FIGURE 3.** Detailed view of the pathway of intramural reentry from Figure 2. Left panel: Activation sequence at levels II and III from beat Xn, with A–F denoting recording sites along the reentrant pathway. Arrow denotes the reentrant pathway with initiation of the next beat, Xn+1, at site A. Right panel: Bipolar electrograms from sites A–F, with A shown again at bottom. Numbers in the boxes to the upper left are the electrode channel numbers; below them are listed the height of the adjacent voltage calibration bars. To the right are shown bipolar electrogram recordings during a 236-msec interval. Vertical cursor marks activation time based on peak criterion. Numbers to the right of the cursors are the activation times in milliseconds relative to the initiation of Xn. The depolarizing wave front proceeded clockwise at level II (A-B-C) and then apically to level III (D), around an area of nontransmural block, and along an intramural pathway back to the endocardium (D-E-F). Marked endocardial conduction delay led to activation of the adjacent subendocardium (A) to initiate the subsequent beat (Xn+1) by intramural reentry. Very late activation also occurred in level II (220-msec isochron), although it was not part of the reentrant circuit.

**FIGURE 4.** Three-dimensional isochronic maps of ventricular activation during normal sinus rhythm (NSR) (panel A) and during two beats of sustained ventricular tachycardia, Xn and Xn+1 (panel B) from patient 2, in which initiation occurs by intramural reentry involving the interventricular septum (arrow). Isochrons are drawn with times relative to the initiation of the sinus beat and beat Xn. *Earliest sites of activation for each beat. †Site of latest activation during sinus beat.
ever, reflected spread of the depolarizing wave front from D to E and then to A by intramural reentry. The late activation at E occurred in the midmyocardium of the septum and was evident only with mapping of intramural sites. It was not detectable at adjacent left ventricular endocardial site F or adjacent right ventricular endocardial site G. These findings explain why mapping restricted to the epicardial or endocardial surfaces may often fail to detect reentry.

Figures 6 and 7 illustrate another example of intramural reentry. During sinus rhythm in patient 3 (Figure 6, left), earliest activation occurred in the subendocardium at an anterior basal region of the left ventricle (level I) and then spread rapidly in both clockwise and counterclockwise directions and from endocardium to epicardium with a total activation time of 62 msec. There was transmural conduction block in level II (blackened area). During sustained VT (Figure 6, right,
and Figure 7), initiation occurred in the subepicardium of the anterior basal region of the left ventricle (beat T7, level I in Figure 6 and labeled as site A in Figure 7) by intramural reentry from the previous beat. The depolarizing wave front (arrow) proceeded slowly in a counterclockwise direction around an area of functional conduction block in the midmyocardium (A-B-C) (Figure 7). Some areas of transmural (levels II-IV) and nontransmural (level I) conduction block were functional because they were not present during sinus rhythm. Activation continued apically (C-D-E), then clockwise at level III (E-F-G) and finally basally around an area of transmural conduction block at level II (G-H). This delayed intramural activation in the midmyocardium at site H, which was not detected on either epicardial or subendocardial surfaces, led to activation of adjacent epicardium at a site that had recovered excitability and initiated beat T8 by reentry involving intramural pathways.

**Focal Mechanism**

Five (50%) of the 10 VTs were initiated in the endocardium by a focal mechanism, based on the lack of electrical activity between the termination of one beat and the initiation of the next beat despite the presence of multiple intervening electrodes. An example is shown in Figures 8 and 9. Sustained VT in patient 2 (with a morphology different from that shown in Figures 4 and 5) was initiated at a subendocardial site in the apical lateral left ventricle (Figure 8, beat Xn, level III). Activation then proceeded both clockwise and counterclockwise and from left to right, with terminal activation occurring after 174 msec at the base of the free wall of the right ventricle. No electrical activity was detected for 111 msec at intermediate intramural recording sites at levels III and IV (as illustrated in Figure 9) as well as at levels I and II (data not shown). Initiation of the next beat, Xn+1, occurred by a focal mechanism at the same apical endocardial site at which Xn was initiated. The activation of Xn+1 was identical to that of Xn (Figure 8), with a total activation time of 174 msec. Overall, the total activation times for all beats that were initiated by a focal mechanism (138±17 msec) were not significantly
different from times for those caused by macroreentry. However, in contrast to that of reentrant VT, the initiation sites of focal VT demonstrated no significant conduction delay at any adjacent site (Figure 10), suggesting that microreentry was unlikely.

**Multiple Morphologies of Ventricular Tachycardia**

Two patients manifested VTs of multiple morphologies for which sufficient mapping data were available to define mechanisms. The VT caused by a focal mechanism shown in Figures 8 and 9 occurred in a patient who also demonstrated sustained monomorphic VT of a different type that was due to intramural macroreentry (Figures 4 and 5). Although some regions of transmural and nontransmural block at levels I and III were comparable, conduction in the basal septum differed considerably. The difference in septal conduction may be related to the direction of propa-
gation of the activation wave fronts. In two other patients with multiple VT morphologies, both a macroreentrant and a focal mechanism were identified.

**Observations During the Induction of Ventricular Tachycardia**

Maps of ventricular activation during the induction of VT from patient 3 are shown in Figures 11 and 12. The eighth beat of the basic drive, S₁, originated from a right ventricular epicardial pacing site and was first detected at the right side of the interventricular septum (level II). Activation proceeded rapidly in apical and anterior directions and encountered various degrees of transmural and nontransmural block. Activation was delayed in the anterior wall at levels I and II with a total activation time of 108 msec. The first extrastimulus, S₂, activated in a similar manner, but movement of the depolarizing wave front in a clockwise direction at level III (80–120-msec isochrons) was slower. Despite this increased conduction delay, there was no additional late activation at level II, and the total activation of 106 msec for S₂ was less than that of S₁. The second extrastimulus, S₃, activated rapidly from base to apex. However, transmural block in levels II–IV prevented rapid counterclockwise spread. Slow conduction in the midmyocardium at level III (100–160-msec isochrons) proceeded basally (level II, 200-msec isochron) and then apically to reactivate adjacent tissue that had recovered excitability and to initiate T₁ in the epicardium by intramural reentry (beat T₁, level III). Mapping limited to the endocardium and/or the epicardium would not have detected the delayed midmyocardial activation and thus would not have delineated the reentrant circuit.

Moreover, as shown in Figure 12, late activation in the midmyocardium at level II during T₁ was crucial to the maintenance of VT. After initiation in the epicardium at level III, the activation wave front of T₁ encountered unidirectional block at levels II, III, and IV, and conduction proceeded primarily in a clockwise direction. Slow activation in the midmyocardium at level III (140–180-msec isochrons) led to activation of an adjacent subendocardial site in the apical septum at level IV to initiate T₂ by intramural reentry (lower arrow). However, late activation of the midmyocardium at level II during T₁ (240-msec isochron) led to activation of adjacent epicardial tissue at level I (beat T₂, 300-msec isochron), which had recovered excitability, to initiate T₂ at another site in the base by intramural reentry. All intervening electrode sites were activated after these two distant initiation sites. Thus, both were
discrete initiation sites from two nearly simultaneous reentrant pathways separated by only 20 msec. Mapping limited to the endocardium and/or epicardium would not have detected either intramural reentrant pathway.

The second reentrant pathway that was located in the base was the same pathway observed during the sustained portion of the VT (shown in Figure 6). After initiation of T₁ at the apical (level IV) and basal (level I) sites, conduction proceeded clockwise because of transmural conduction block at levels II, III, and IV. There was marked conduction delay in the midmyocardium of the anterior wall at level III and late midmyocardial activation at level II. However, for the initiation of T₁ as well as subsequent beats of the VT (Figure 6), only the basal pathway contributed to intramural reentry, which maintained the tachycardia.

Pathological Correlation

The heart from each patient had a solid (core) infarct region of fixed conduction block corresponding to regions demonstrating akinesia, dyskinesis, or aneurysmal expansion. The complex three-dimensional peri-infarct region immediately surrounding the core infarct in all patients exhibited interstitial fibrosis for a variable distance (up to 3 cm, typically 1 cm or less) from the infarct core. Conduction abnormalities (functional block and delayed activation) and the exit site (site of earliest activation) of the tachycardia invariably occurred in the peri-infarct region where several patterns of the arrangement of muscle fibers and collagenous tissue were identified. The histological findings from patient 1 (with VT caused by a reentrant mechanism) along with mapping data from level III (from Figures 2 and 3) are illustrated in Figure 13. The infarct was in the distribution of the left anterior descending coronary artery. The infarct core was subendocardial and nearly transmural at the medial edge of the resection (anteroseptal region) and corresponded to an area of transmural conduction block (solid black area). During VT, a transmural three-dimensional arc of functional block (solid curved black line at the lateral wall) developed at the interface of the peri-infarct zone and the rapidly conducting adjacent myocardium. Histological analysis of this area showed preservation of a midmyocardial to epicardial rim of surviving muscle with extensive interstitial fibrosis. In addition to exhibiting susceptibility to functional block, this peri-infarct region was a site of delayed activation during reentrant VT. There was a uniform apex-to-base orientation of fibers throughout this region indicated by circular (transversely oriented) myocyte profiles (Figure 13C).

The histological findings in the heart from patient 3 that was analyzed at autopsy (along with the mapping data illustrated previously in Figures 6 and 7) are shown in Figure 14. The area of infarct core at level II (Figure 14, panels C and D) was transmural and consisted primarily of dense collagenous tissue admixed with bundles of viable myocytes. The muscle-to-collagen ratio in this region was approximately 1:4. No electrical activity (>0.25 mV) was recorded except for an area of late midmyocardial activation (180 msec). The complex three-dimensional, peri-infarct region immediately (within 3 cm) surrounding the infarct core exhibited interstitial fibrosis but was otherwise normal. The epicardial initiation site (A) located in the peri-infarct zone just basal to the infarct core demonstrated minimal interstitial fibrosis. The initial relatively slow-moving
wave front (A–C; time, 0–100 msec) was oriented transverse to the long fiber axis (Figure 14, panels A and B), suggesting an important effect of fiber orientation on conduction time. Rapid apical activation (C–E) occurred in a direction longitudinal to fiber orientation in myocardium adjacent to the peri-infarct zone. Myocytes in this region exhibited hypertrophic changes but were otherwise normal with no fibrosis evident. Activation spread toward the ventricular septum at level III (E–G) and encountered a transmural plane of functional block (thickened line). The anteroseptal wall, reconstructed from the endocardial resection specimens and the rest of the heart obtained at autopsy (Figure 14), demonstrated incomplete transmural infarct with preservation of multiple intramural muscle bundles that facilitated late basal conduction (G–H–A) to initiate the next beat of VT in the epicardium by intramural reentry.

Thus, structural factors leading to delayed activation and the development of intramural reentry included 1)
transverse orientation of fibers (with respect to the direction of activation), 2) interstitial fibrosis, 3) the interface of the peri-infarct region and adjacent hypertrophied but noninfarcted muscle that was the site of functional block, and 4) the infarct region that was the site of fixed and functional block.

The site of origin of two of the five focal VTs was included in subendocardial tissue resections. In both cases, the focus was near the edge of extensively thickened and fibrotic subendocardial tissue with residual small endocardial muscle bundles and Purkinje fibers throughout. Similar findings were observed in the same hearts from other portions of resected muscle activating passively as well as in the subendocardium of hearts from some patients with VT caused by reentry (although not necessarily at sites critical to the reentrant circuit). In all five hearts with focal VT, the major portion of the subendocardial resection corresponded to areas of fixed subendocardial conduction block. Extensive areas of functional block and delayed activation were not evident during VT, in contrast to the VTs caused by reentry.
**TABLE 2. Macureenentr Ventricular Tachycardia**

<table>
<thead>
<tr>
<th>Anatomic substrates</th>
<th>Conduction abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core infarct</td>
<td>Fixed conduction block</td>
</tr>
<tr>
<td>Peri-infarct muscle</td>
<td>Slowing of conduction</td>
</tr>
<tr>
<td>Intertitial fibrosis</td>
<td></td>
</tr>
<tr>
<td>Transverse fiber orientation</td>
<td></td>
</tr>
<tr>
<td>Interface of peri-infarct and noninfarct muscle</td>
<td>Plane of functional block, exit site of tachycardia</td>
</tr>
<tr>
<td>Noninfarcted muscle</td>
<td>Early activation in reentrant circuit</td>
</tr>
<tr>
<td>Intramural pathways</td>
<td>Late activation in reentrant circuit, low-amplitude fractioned electrograms</td>
</tr>
</tbody>
</table>

**Discussion**

**Intramural Reentry**

The results of this study demonstrate that sustained monomorphic VT in patients with coronary disease often is due to intramural reentry. These results explain, in part, the infrequent delineation of reentrant pathways with endocardial, epicardial, or even combined endocardial and epicardial mapping because the marked conduction delay occurring in the midmyocardium is usually not reflected in recordings from either the subendocardial or the epicardial surface. Perhaps the presystolic activity occasionally noted with unipolar endocardial mapping and corresponding to zones of preserved intramyocardial muscle fibers reflects the conduction disturbances in the midmyocardium that are critical to the development of intramural reentry in humans. Our findings in humans are consistent with results of previous mapping studies in experimental infarct preparations in which intramural pathways and fixed and functional block were critical to the development of the reentrant circuit.

Conduction block was defined when there were marked differences in activation between adjacent sites, whereas sequential activation occurred over an adjacent but less direct spatial path. Recently, Dillon and colleagues postulated that such "apparent conduction block" may reflect very slow conduction over a localized area and may therefore not be true conduction block. However, a recent study in which a high-resolution grid electrode with an interelectrode distance of 350 μm was used revealed that in some cases, very slow conduction does exist and that in most of these cases, true conduction block was present. Discrete activations on either side of the line of block were present without intervening electrical activity. Similar findings were noted by Rastivo and colleagues. Although the spatial resolution and electrode density in our study in human hearts do not distinguish between true and apparent conduction block, we consistently noted paired electrograms reflecting discrete activations from both sides of the line of conduction block rather than multicomponent electrograms consistent with very slow conduction.

The nature of the functional block observed remains unknown. However, analysis of the initiating beats of induced VT suggests that extrastimuli lead to greater slowing of conduction and functional conduction block probably because of incomplete recovery of excitability. The development of functional block may also be secondary to alterations in cellular coupling caused by remodeling within border regions of the infarct.

Although some areas of slow conduction or block were critical to the initiation of VT, maintenance of sustained VT often involved a somewhat different intramural reentrant pathway with slow conduction in adjacent regions. In fact, the transition from one reentrant pathway to another could, at times, involve multiple reentrant circuits.

**Focal Mechanisms**

In contrast to intramural reentry, sustained VT was initiated and maintained by a focal mechanism in 50% of cases. The mechanism was designated as focal because microreentry could not be excluded with the electrode resolution available. We have demonstrated recently that microreentry can occur in an isolated, superfused preparation of epicardium overlaying an infarct in the canine heart, with reentry occurring in an area as small as 0.05 cm, one-tenth the area previously reported to maintain a reentrant circuit in this type of preparation. However, even in these very small microreentrant pathways, recordings have demonstrated a relative degree of conduction delay on the order of 100 msec, which is evident over a span of 1–2 cm. The resolution of the maps generated in this study was sufficient to enable detection of reentrant circuits within a radius as small as 10 mm (Figure 4) as well as markedly delayed activation at sites adjacent to reentrant pathways (Figure 10, bottom). For sites demonstrating focal activity, there were no significant conduction delays at any adjacent sites 1–2 cm away (Figure 10, top).

Despite the absence of slow conduction adjacent to the initiation sites of focal VT, the cycle length of the VTs with a focal mechanism was greater than that of the VTs caused by reentry. Furthermore, if microreentrant circuits were present and not detectable with the mapping resolution used, it would require, based on the cycle lengths of the VT, a conduction velocity an order of magnitude slower than the slowest measured in the human heart in the present study. Thus, it is unlikely that the focal mechanisms that we observed were due to a microreentrant circuit.

The VTs caused by reentry and those with focal mechanisms demonstrated different patterns of activation, but the degree of conduction delay was comparable. However, the sites of marked delay in focal VTs were distant from the site of initiation, a finding noted in our previous studies of nonreentrant mechanisms in the ischemic and reperfused feline heart during acute ischemia. In the human heart, both mechanisms could initiate in the subendocardium, whereas only intramural reentry was found to occur in the epicardium and midmyocardium. Some patients demonstrated VTs of multiple morphologies that were due to either reentrant or focal mechanisms. Thus, healed myocardial infarction in the human heart provides the substrate for VT occurring through either electrophysiological mechanism.

**Role of Infarct Structure**

Spatial correlation of histological and mapping data demonstrated anatomic substrates for macroreentrant VT, the key structural elements of which are shown in Table 2. The infarct core created a three-dimensional...
zone of fixed conduction block. The dimensions of the reentrant circuits were determined by isolated layers of peri-infarct subendocardial or subepicardial muscle. In some cases (Figure 7), the macroreentrant loop encircled a large transmural infarct core, yielding a path length as long as 14 cm, whereas in others (Figure 5), only a limited subendocardial infarct core determined the area of fixed block, and the VT path length was considerably shorter.

In addition to a fixed three-dimensional barrier provided by the infarct core, a narrow (2–20-mm) band of partly fibrotic peri-infarct muscle was also the site of conduction delay. The characteristic histological pattern in such zones of slow conduction was of parallel muscle fibers oriented transversely to the activation wave front. In recent studies correlating surface maps of VT with pathological findings in isolated, perfused human hearts, De Bakker and colleagues noted similar effects of fiber arrangement on conduction delay. This relation is also consistent with experimental data documenting the effects of anisotropic tissue structure on conduction in myocardium. Apart from broad bands of scarring, fine interstitial fibrosis was a second structural complexity characteristic of sites of slow conduction and delayed activation. Ursell and coworkers also found interstitial fibrosis to be important in the pathogenesis of nonuniform anisotropic conduction abnormalities in the canine heart. Luke and Saffitz demonstrated a decrease in myocyte interconnectivity at gap junctions in association with interstitial fibrosis in regions bordering healed canine myocardial infarcts. In addition, Spear and colleagues found a decrease in the space constant in areas surrounding a healed infarct. These results suggest that myocyte uncoupling may contribute to slow conduction in fibrotic myocardium during both VT and sinus rhythm.

De Bakker and colleagues demonstrated continuity of surviving intramural muscle bundles within the infarcted region between the sites of latest and earliest activation of successive beats during VT, thus implicating but not conclusively showing the presence of intramural reentrant pathways. Our data further establish the importance of intramural reentrant pathways in humans. In addition to observing the discrete bundles described by De Bakker, we sometimes found that a large, coherent layer of muscle overlaying the subendocardial region of the infarct core was a component of the intramural reentrant circuit (Figure 14).

In cases of VT of focal origin, pathological findings at the site of origin of the tachycardia included a thickened endocardium and subendocardial muscle bundles embedded in connective tissue similar to the tissues described by Fenoglio and colleagues. These features are nonspecific and do not appear to further elucidate the substrate underlying focal VT. However, in two cases in which pathological comparisons were possible, the site of focal VT was in peri-infarct muscle near the margin of the resected tissue.

Limitations

The detection of intramural reentrant and focal mechanisms required transmural mapping from multiple sites with a resolution that was sufficient to delineate areas of marked conduction delay, the site of initiation of the subsequent beat, and the marked delay of activation in the intervening midmyocardium. Because intramural reentry could involve the interventricular septum as well as the left ventricular free wall, transmural mapping of the septum was critical in some cases.

The major limitation to transmural mapping of the human heart is spatial resolution. Although a greater density of electrodes would have enabled delineation of the mechanisms in a greater number of VTs, the resolution obtained in the present study was sufficient to 1) delineate the mechanisms of VT in eight of the 13 patients studied, 2) delineate intramural activations critical to reentrant excitation, even in the interventricular septum, and 3) successfully localize the sites of initiation of multiple morphologies of VT to allow surgical ablation and cryoablation with resultant cure of the VTs in all 13 patients.

In addition to enhanced resolution, detailed localization of electrode position was critical to the construction of accurate maps of three-dimensional activation. In the present study, the limitations associated with detailed electrode localization were overcome with a two-step procedure. First, identification of electrode position was accomplished with reference to grids of the heart's surface and septum. Second, the site of electrode insertion was recorded by means of a video camera mounted directly above the operative field, providing detailed localization of electrode position as well as allowing determination of interelectrode distances for calculations of conduction velocity, which is helpful in the assessment of the underlying mechanism.

Implications

Multiple mechanisms underlie sustained monomorphic VT in patients with coronary artery disease and healed myocardial infarction. The localization of focal sites of excitation distant from areas of slow conduction will impact greatly on the success of catheter ablation techniques. Furthermore, the importance of delayed activation in the midmyocardium, which is a critical component of intramural reentrant circuits, may impact on the efficacy of surgical as well as catheter ablation when intramural recordings are not obtained. The results of three-dimensional mapping in the human heart provide the foundation for determining whether less extensive ablative procedures will be effective. In some cases, extension of the ablative lesion into the midmyocardium or even epicardium may be required to eliminate VT. With multiple mechanisms possible in the same individual, the ablation of one mechanism could be followed by the recurrence of VT at a different site, perhaps even by another mechanism. It remains unclear whether more detailed intramural mapping will contribute to improved results in patients undergoing surgical ablation. Finally, antiarrhythmic therapy must also be targeted at both reentrant and focal mechanisms.

Acknowledgments

The authors appreciate the medical assistance of Bruce D. Lindsay, MD, in the care of these patients and the technical assistance of Joseph Loslo, Dennis Fogarty, RN, and H. Dieter Ambos and thank Elaine Zuzack for preparation of the manuscript.

References


Reentrant and focal mechanisms underlying ventricular tachycardia in the human heart.
S M Pogwizd, R H Hoyt, J E Saffitz, P B Corr, J L Cox and M E Cain

Circulation. 1992;86:1872-1887
doi: 10.1161/01.CIR.86.6.1872
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/86/6/1872

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in Circulation 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 is online at:
http://circ.ahajournals.org//subscriptions/