Mapping of Reset of Anatomic and Functional Reentry in Anisotropic Rabbit Ventricular Myocardium

Lucas Boersma, MD; Josep Brugada, MD; Charles Kirchhof, MD; Maurits Allessie, MD

Background Premature stimulation is used to characterize the reentrant circuit during ventricular tachycardia (VT) in patients. The goal of this study was to compare the effects of premature stimulation on functional and anatomic reentrant VT.

Methods and Results In 18 Langendorff-perfused rabbit hearts, thin layers of anisotropic left ventricular subepicardium were created by a cryoprobe. In 8 hearts, rapid pacing induced reentry around a line of functional conduction block; in 10 hearts, reentry occurred around a fixed epicardial obstacle created by a cryoprobe. The cycle lengths (CL) of functional and anatomic VT were 110±10 and 167±17 milliseconds, respectively. During anatomic VT, the excitable gap measured 43% of the CL and premature stimuli could always reset VT (44±12 milliseconds). During early premature beats, conduction of the orthodromic wave was slightly depressed, but anatomic VT was never terminated. Reset curves at different sites in the ventricle revealed three different response types, both determined by and characterizing the spatial and temporal relation between pacing and recording sites. Premature stimulation during functional VT revealed a local excitable gap at the pacing site measuring 27% of the cycle length of VT. However, in only 3 of 8 hearts, premature stimuli could reset functional VT by 8%. In 5 VTs, advancement of the paced activation was fully compensated by prolongation of the return cycle, and VT was not reset. Due to slow conduction both toward and inside the circuit, the paced orthodromic wave lost its prematurity already within a distance of 6 to 10 mm from the pacing site.

Conclusions Both during anatomic and functional reentry, an excitable gap is present in the reentrant circuit. Three different response curves reveal the localization of the pacing and recording sites in the circuit. Anatomic VT can always be reset by premature stimuli, whereas in 5 of 8 hearts, functional VT could not be reset. In the other 3 hearts, VT could only be reset for less than 7% to 11% of the VT interval. Therefore, it seems very unlikely that clinical VT based on functional reentry can be reset.

Key Words • tachycardia • reentry • myocardium

The presence of a less than compensatory pause after a premature beat indicates reset of a cardiac rhythm and has been described for both normal and abnormal automaticity, as well as for reentry. The response to premature stimulation has gained special importance in the treatment of ventricular tachycardia (VT) after myocardial infarction, which most likely is due to reentry. In a number of studies, premature stimulation has provided evidence that during clinical VT a partially or fully excitable gap exists in the circuit. The response of VT to premature stimulation also is used to evaluate the effects of antiarrhythmic drugs on the reentrant circuit.

Although the reset response may reveal some of the conduction properties within and around the reentrant circuit, it has not yet been determined whether clinical ventricular tachycardia is based on reentry around a functional or an anatomic barrier. Many studies have shown that the reentrant circuit after myocardial infarction comprises an area of slow conduction and that such a segment of slow conduction influences the reset response.

All these electrophysiological studies have greatly contributed to our understanding of reset of reentrant tachycardias. However, mapping of the activation patterns of the reentrant circuit during reset has only been performed in a limited number of studies, and direct evidence of the events taking place during reset is still lacking. The goal of the present investigation was to study the response to premature stimulation by high-resolution mapping in two experimental models of sustained VT in Langendorff-perfused rabbit hearts. In one model, reentry occurred around a fixed anatomic obstacle, whereas in the other model, no gross anatomic obstacle was present, and reentry occurred around a line of functional conduction block. The specific goals of our study were (1) to determine the width and nature of the excitable gap, (2) to examine whether the different types of reentry could be characterized by a typical reset response, and (3) to study the role of an area of slow conduction in the reentrant circuit in the reset response.

Methods

Preparation Eighteen Flemish Giant rabbits (3.7±0.3 kg) were used for this study. Animal preparation and handling were performed according to the guiding principles of the American Society of Physiology and approved by the Animal Investigation Committee of the University of Limburg. The rabbits were anesthetized with 0.5 mg/kg IM Hypnorm (10 mg fluanisone and 0.2 mg fentanyl/mL). After heparinization (1000 IU IV), the
rabbits were killed by cervical dislocation; the heart was quickly removed, and the aorta was connected to a Langendorff perfusion system. The hearts were perfused by Tyrode’s solution at 37°C with a constant pressure of 60 mm Hg, resulting in a flow of 65±5 mL/min. The composition of the Tyrode’s solution was as follows (mmol/L): NaHCO₃ 20.1, NaH₂PO₄ 1.2, NaCl 130.0, KCl 4.0, CaCl₂ 2.2, MgCl₂ 0.6, and glucose 12.0. The Tyrode’s solution was saturated with Carbogen (95% O₂ and 5% CO₂); pH was 7.35. Thin epicardial layers of anisotropic ventricular myocardium were obtained by a cryo-procedure, as described previously. In brief, a cryoprobe was inserted in the right ventricular cavity and filled with liquid nitrogen (−192°C) until the total right ventricle was frozen. The probe was then inserted in the left ventricular cavity, the heart was immersed in a tissue bath containing Tyrode’s solution at 30°C, and the coronary flow was temporarily interrupted. Subsequent filling of the cannula with liquid nitrogen for 7 minutes destroyed the endocardial four fifths of the left ventricle. After the cryoprobe procedure, the flow was restored and the heart was lifted from the tissue bath. By this technique, a thin Langendorff-perfused, two-dimensional sheet of anisotropic left ventricular subepicardium (thickness, 1.0±0.4 mm) was obtained showing normal conduction velocities and refractory periods. In 8 of 18 hearts, rapid pacing induced sustained monomorphic ventricular tachycardia based on a circulating wave in the subepicardium around a line of functional conduction block. In the other 10 hearts, a central obstacle (25×10 mm) was created parallel to the left anterior descending coronary artery (LAD) by an epicardial cryoprobe. In the resulting ring of perfused myocardium, sustained reentrant ventricular tachycardia was induced by programmed electrical stimulation. As described previously, because of tissue anisotropy, conduction velocity varied in different segments of the ring. At the base and the free wall, conduction was fast (68±4 cm/s) because the impulse propagated parallel to the epicardial fiber direction. In contrast, in the corridor between the LAD and the obstacle propagation was much slower (25±5 cm/s) because the propagation occurred transverse to the epicardial fiber direction. At the apex the fiber orientation is complex, and the relation between fiber orientation and conduction velocity could not be reliably determined. In addition, in this area, the projection of the electrode matrix seriously distorted the true distance between the isochrons.

Recording
A spoon-shaped mapping electrode, molded to the epicardial surface of the left ventricle, was used, containing 248 silver electrodes (diameter, 0.3 mm; interelectrode spacing, 2.25 mm). After amplification and filtering (bandwidth, 1 to 400 Hz), the electrograms were multiplexed (sampling rate, 1 kHz) and AD converted (8 bits). An algorithm for automatic detection of the intrinsic negative deflection in each electrogram was used to determine the local activation times and to generate color-coded activation maps. Interactive manual editing of the local activation times was performed if necessary. Details of the mapping system have been described elsewhere. In the activation maps, conduction block was defined as a delay in conduction of more than 20 milliseconds between adjacent recording sites (apparent conduction velocity <10 cm/s). In addition, the tissue distal to the site of block should be activated from a different direction.

Stimulation
A computer-controlled stimulator (Medtronic SP3084) was used for bipolar stimulation through any pair of electrodes selected from the mapping electrode. Sustained monomorphic ventricular tachycardia was induced by incremental pacing. During sustained monomorphic VT, premature stimuli were applied at 4 times diastolic threshold at 8 different sites around the ring. During functional VT, premature stimulation (4 times diastolic threshold) was performed at 2 different pacing sites located either at a pivot point of the circuit or halfway along the central line of block.

An electrogram recorded adjacent to the pacing site was used to synchronize the stimulator. The last local activation preceding the stimulus was defined as V₁. The first two activations after the stimulus were defined as V₂ and V₃. The coupling interval between activation of the reference electrogram (V₁) and the stimulus (S) was shortened in steps of 2 milliseconds. After the experiment, the exact coupling interval at the site of pacing was determined by interpolation of all actual V₁S intervals around the pacing site. The effective refractory period (ERP) was determined as the longest V₁S interval that failed to initiate a propagated response. The ERP was defined as the shortest V₁V₂ interval at the nearest electrode orthodromic to the site of pacing. The difference between the cycle length of VT and the ERP was defined as the excitable gap.

During VT, reset curves of several recording sites were obtained by premature stimulation at decreasing coupling intervals (V₁S). Two different curves were constructed. In the first curve, the interval was plotted between the last activation during VT and the first activation after the stimulus (V₁V₂). The second curve plotted the interval between the first and second (V₁V₃) activation after the stimulus. At the pacing site, the V₁V₂ interval represents the return cycle of the premature stimulus.

Statistical Analysis
Results were compared using the paired Student’s t test, ANOVA, or Bonferroni’s t test and linear regression when appropriate. Values of P<0.05 were taken as statistically significant.

Results
Characteristics of Reentry Around an Anatomic Obstacle
In 10 experiments, rapid pacing induced reentrant VT around a central anatomic obstacle. In 6 hearts, anatomic VT was based on a clockwise and in 4 hearts on a counterclockwise circulating wave. The average cycle length of anatomic VT was 167±17 milliseconds (range, 148 to 192 milliseconds) (Table 1). The cycle length of VT was mainly determined by the length of the segment of slow conduction between the LAD and the central obstacle where the impulse propagated transverse to the epicardial fiber orientation. During fast VTs, this segment of slow conduction was shorter than during slow VTs. All VTs were long-lasting and stable, with a beat-to-beat variation in cycle length <2 milliseconds. Spontaneous termination of VT was never observed.

An example of an anatomic VT is given in Fig 1. The upper left map shows a clockwise circulating wave around a central obstacle, with a revolution time of 169 milliseconds. In the corridor between the LAD and the obstacle, between the 20- and the 90-millisecond isochron, the impulse propagated slowly (23 cm/s) transverse to the epicardial fiber orientation. At the base and the free wall, impulse propagation was parallel to the fiber axis and proceeded at an average speed of 78 cm/s. The lower left map shows the distribution of the ERPs during this VT. In this example, the refractory periods around the ring varied between 81 and 103 milliseconds (average, 93±10 milliseconds). Thus, a large excitable gap existed in the circuit, varying between 66 and 88 milliseconds (average, 76±10 milliseconds). Compare-
son of the local ERPs in all 10 hearts did not reveal a certain area where the ERP was systematically different from the other sites (Bonferroni’s t test, P > 0.05). Because of the large excitatory gap, anatomic VT could be reset easily by single premature stimuli. In the right panel of Fig 1, the responses to various premature stimuli are shown. With increasing prematurity, the V₁V₂ interval was shortened to 162, 142, and 112 milliseconds, respectively, and VT was reset. In the lowest tracing, the V₁V₂ interval of 112 milliseconds was followed by a prolongation of V₂V₃ from 165 to 180 milliseconds because of a slight slowing of conduction of the premature wave front.

In Table 1, the cycle length, ERP, and excitatory gap are given for all 10 hearts. The ERP and the excitatory gap are given as average values of 8 pacing sites in each heart. In the table, the VTs are arranged according to their cycle length. The average ERP was 95 ± 11 milli-

![Image of a data table and a diagram](http://circ.ahajournals.org/doi/10.1161/01.CIR.89.2.854)

**TABLE 1. Characteristics of Anatomic Ventricular Tachycardia**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>CL, ms</th>
<th>ERP, ms</th>
<th>EG, ms</th>
<th>V₁V₂, ms</th>
<th>V₂V₃, ms</th>
<th>Maximal Reset, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>148</td>
<td>86±5</td>
<td>62±5</td>
<td>102±5</td>
<td>159±3</td>
<td>35±3</td>
</tr>
<tr>
<td>2</td>
<td>151</td>
<td>76±4</td>
<td>75±4</td>
<td>94±6</td>
<td>156±2</td>
<td>52±2</td>
</tr>
<tr>
<td>3</td>
<td>151</td>
<td>93±6</td>
<td>58±9</td>
<td>109±6</td>
<td>161±6</td>
<td>33±4</td>
</tr>
<tr>
<td>4</td>
<td>154</td>
<td>103±9</td>
<td>51±9</td>
<td>116±6</td>
<td>161±7</td>
<td>36±6</td>
</tr>
<tr>
<td>5</td>
<td>158</td>
<td>88±11</td>
<td>70±11</td>
<td>103±9</td>
<td>170±6</td>
<td>44±4</td>
</tr>
<tr>
<td>6</td>
<td>166</td>
<td>99±12</td>
<td>67±12</td>
<td>115±11</td>
<td>180±9</td>
<td>38±5</td>
</tr>
<tr>
<td>7</td>
<td>169</td>
<td>93±10</td>
<td>76±10</td>
<td>113±8</td>
<td>189±13</td>
<td>36±6</td>
</tr>
<tr>
<td>8</td>
<td>187</td>
<td>103±11</td>
<td>84±11</td>
<td>123±8</td>
<td>196±7</td>
<td>54±2</td>
</tr>
<tr>
<td>9</td>
<td>191</td>
<td>93±13</td>
<td>98±13</td>
<td>113±11</td>
<td>202±9</td>
<td>68±7</td>
</tr>
<tr>
<td>10</td>
<td>192</td>
<td>114±17</td>
<td>78±17</td>
<td>134±8</td>
<td>201±5</td>
<td>49±9</td>
</tr>
<tr>
<td>Average</td>
<td>167</td>
<td>95</td>
<td>72</td>
<td>112</td>
<td>178</td>
<td>44</td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
<td>11</td>
<td>14</td>
<td>11</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

CL indicates cycle length; ERP, effective refractory period; EG, excitatory gap; V₁V₂, interval between last activation before and first activation after stimulation; and V₂V₃, interval between first and second activation after stimulation.

![Diagram of Reset of Anatomic VT](http://circ.ahajournals.org/doi/10.1161/01.CIR.89.2.854)

**Fig 1.** Left, Reentrant ventricular tachycardia (VT) around a central anatomic obstacle. Activation map in the upper panel shows a clockwise VT with a cycle length of 169 milliseconds. In the corridor between the left anterior descending coronary artery (LAD) and the central obstacle, conduction was slow because of propagation transverse to the epicardial fiber orientation (crowding of isochrons). In the lower panel, the refractory periods during VT are given at 8 sites around the circuit. Activation times and refractory periods are given in milliseconds. Isochrons are drawn at 10-millisecond intervals. Arrow indicates the direction of propagation of the circulating wave. Right, Reset of anatomic VT by single premature stimuli with coupling intervals of 150, 130, and 100 milliseconds, which shortened the V₁V₂ intervals to 162, 142, and 112 milliseconds, respectively. Only after the earliest premature beat (bottom tracing), the V₂V₃ interval was slightly prolonged because of slowing of conduction of the premature depolarization wave.
seconds, resulting in an excitable gap of 72±14 milliseconds. Linear regression showed that during slower VTs, the ERP tended to be longer (slope, 0.38; r=.63, P=.051) and the excitable gap was larger (slope, 0.62; r=.78, P=.006). Because of latency between the stimulus and the response, the functional refractory period adjacent to the pacing site was 112±11 milliseconds. At the shortest coupling intervals, the return cycle was slightly prolonged (178±18 milliseconds) compared with the cycle length of VT (167±17 milliseconds) because of slowing of conduction of the premature wave front. The average maximal amount of reset of anatomic VT was 44±12 milliseconds. Anatomic VT was never terminated by single premature stimuli, indicating that all segments of the ring had a high safety factor for conduction.

Mapping of Reset of Anatomic VT by Premature Stimuli

In all 10 hearts, anatomic VT could be reset from all 8 pacing sites that were tested. Fig 2 gives the activation maps during reset of a clockwise VT (cycle length, 169 milliseconds) both from a pacing site proximal and distal to the segment of slow conduction. As can be seen from the upper left map, a late premature beat (V1S=150 milliseconds) induced proximal to the segment of slow conduction reset the circuit in orthodromic direction, whereas the paced antidromic wave collided with the clockwise circulating wave. Because of the minimal degree of prematurity, only 6% of the circuit was antidromically invaded by the paced impulse. During reset of VT with shorter coupling intervals, the paced antidromic wave invaded a progressively larger part of the circuit before it collided with the circulating wave. In the upper right map (V1S=130 milliseconds) and the lower left map (V1S=100 milliseconds), the circuit was antidromically invaded for about 11% and 25%, respectively. Apart from the degree of prematurity, the amount of antidromic invasion of the circuit was also determined by the localization of the pacing site relative to the segment of slow conduction. This can be seen in the lower right map, in which the pacing site

![Fig 2](https://example.com/fig2.png)

**Fig 2.** Left, Four activation maps during reset of the anatomic ventricular tachycardia (VT) shown in Fig 1 by single premature stimuli with a coupling interval of 150, 130, and 100 milliseconds. In the first three maps, the pacing site was located proximal to the segment of slow conduction. The lower right panel shows the activation map during maximal reset (V1S=100 milliseconds) at a pacing site distal to the segment of slow conduction. During each premature stimulus, the paced antidromic wave collided with the ongoing circulating wave, whereas the paced orthodromic wave reset VT. The moment of stimulation was taken as t=0. Activation times are given in milliseconds, and isochron lines are drawn at 10-millisecond intervals. Arrows indicate the different wave fronts. Right, Three different reset curves of anatomic VT. Pacing was performed proximal to the segment of slow conduction. The three curves were obtained from recording sites A, B, and C, as indicated in the maps. The coupling interval of the premature stimulus (V1S) was plotted on the abscissa. The V1V2 (squares) and V2V3 (triangles) intervals were plotted on the ordinate. See text for discussion.
Anisotropic Conduction

Anisotropic Reentry

![Diagram showing anisotropic conduction and reentry](image)

Fig 3. Left, Activation maps during slow pacing (S1S2=500 milliseconds) and sustained ventricular tachycardia (cycle length, 120 milliseconds). During slow pacing, the ellipsoid isochrons display the anisotropic conduction properties of the epicardium, with conduction parallel to the epicardial fibers (long arrows) being faster than in the transverse direction (short arrows). Conduction velocities in the four different directions are indicated on the map (in centimeters per second). The moment of stimulation was taken as t=0. During anisotropic reentry (right map), the line of block was oriented parallel to the fiber direction. In both long limbs of the circuit, the conduction velocity was faster compared with transverse conduction at the pivoting points. Arrow indicates the direction of the circulating wave. Activation times are given in milliseconds, and isochron lines are drawn at 10-millisecond intervals. Right, Twelve electrograms (A-L) recorded along the functional anisotropic circuit. At the pivoting points, the electrograms were of low amplitude, whereas along both long limbs of the circuit, sharp deflections of high amplitude were recorded.

was located distal to the segment of slow conduction. In such a case, the antidromic wave penetrated a much smaller part of the circuit, and even a very early premature stimulus (V1V2=100 milliseconds) invaded only 9% of the circuit antidromically.

During the premature beat, the circuit was divided into a paced orthodromic segment (ORTHO), a paced antidromic segment (ANTI), and a segment in which the circulating wave was still present (ORTHO-1). At progressively premature stimuli, the ORTHO segment became smaller while the ANTI and ORTHO-1 segments occupied a larger portion of the circuit. Consequently, at different degrees of prematurity, a given site in the reentrant circuit could be located in different segments. If such a change from one to another segment occurred, the reset curve obtained at that given site suddenly changed. This is shown in the right part of Fig 2, where the reset curves are given for three different recording sites in the circuit. The top graph shows the typical reset curve for a recording site that is always located in the ORTHO segment. A progressive decrease in V1V2 interval is associated with a flat V2V3 curve, indicating reset of VT. Only at the shortest coupling intervals the return cycle (V1V2) slightly increases because of slowing of conduction of the premature wave front. The middle graph shows the typical reset curve for a recording site, which during late premature stimuli is located in the ORTHO segment but during earlier premature stimuli becomes part of the ORTHO-1 segment. During late premature stimuli, V1V2 gradually decreases, with a flat V2V3 curve. During earlier premature stimuli, however, the V2V3 curve becomes flat, and the V1V2 intervals shorten. The bottom panel shows the reset curve recorded in the area antidromic to the pacing site. During late premature stimuli, the reset curve is similar to that in the ORTHO segment. During more premature stimuli, however, the recording site first becomes part of the ORTHO-1 segment and during very early premature beats (coupling intervals <120 milliseconds) becomes located in the ANTI segment. As a result, at coupling intervals <120 milliseconds, the V1V2 interval progressively shortens again while the V2V3 interval either remains constant or prolongs a little because of slowing of conduction of the early premature paced orthodromic wave. These three typical reset responses thus reveal the relative position of the pacing and recording sites within the reentrant circuit. A reset response as in the upper panel of Fig 2 identifies a recording site close to and orthodromic from the pacing site. The middle graph indicates a more distal orthodromic recording site, whereas a reset response as in the bottom panel was exclusively found in the antidromic segment.

During pacing proximal to the area of slow conduction, the three different reset curves were all observed in fairly large parts of the circuit. However, if the pacing site was distal to the segment of slow conduction, the ANTI and ORTHO-1 segments were both very small (see right lower reset map). Consequently most reset curves were of the ORTHO type because the other response types remained concealed in the segment of slow conduction.

Characteristics of Reentry Around a Line of Functional Block

In the absence of a gross anatomic obstacle in the thin epicardial layer, slow pacing resulted in uniform anisotropic conduction. In the left panel of Fig 3, the activation map of the intact layer of epicardium during pacing at 500-millisecond intervals is given. From the site of stimulation the impulse propagated radially with elliptical isochrons. The long axis of the ellipse represents fast conduction parallel to the epicardial fiber orientation (66 and 71 cm/s), while along the short axis...
the impulse propagates perpendicular to the fiber direction (27 and 17 cm/s).\textsuperscript{25} During rapid pacing at intervals shorter than 120 milliseconds, local arcs of conduction block developed.\textsuperscript{28} In 8 of 18 hearts, stable reentrant VT around one of these arcs of functional conduction block was induced. The activation map in the middle of Fig 3 gives an example. During functional VT (cycle length, 120 milliseconds), the central line of block was oriented parallel to the fiber direction and the reentrant circuit had an oval shape. Propagation along both long limbs of the circuit was fast (40 and 73 cm/s). At the pivoting points the circulating wave made a sharp U-turn transverse to the fiber direction, and the conduction velocity became as slow as 15 cm/s. The electrograms at the right show the continuous circulation of the impulse around the line of functional block in the direction from electrodes A to L. Electrograms C-D and H-J recorded at the pivoting points of the circuit exhibited low amplitude and fragmented potentials, while the electrograms from the longitudinal limbs of the circuit were of high amplitude. In 7 of 8 hearts functional VT was based on reentry around a single line of block, while in 1 heart figure-of-eight reentry occurred.\textsuperscript{15,16} The cycle length of the 8 functional VTs ranged between 94 and 121 milliseconds with an average of 110±10 milliseconds (Table 2). All VTs were stable with a beat-to-beat variation of less than 2 milliseconds. Reset of functional VT by premature stimulation was attempted at two different pacing sites. In 6 of 8 hearts early propagated responses could only be elicited at 1 of the 2 pacing sites. In 2 hearts VT could be paced from both pacing sites. In 1 heart VT was terminated by a single premature stimulus, while in 1 other heart premature stimulation transformed sustained monomorphic VT into a polymorphic nonsustained VT. The average ERP during VT was 81±10 milliseconds; thus, in all VTs, a small excitable gap of 29±7 milliseconds could be demonstrated (Table 2). Linear regression showed that slower VTs had a somewhat longer ERP (slope, 0.86; r=.83, P=.011), whereas no correlation was found between VT cycle length and the excitable gap (r=.24, P=.57). The functional refractory period (V1V2) was 89±10 milliseconds; the average return cycle (V2V3) of 128±16 milliseconds exceeded the normal cycle length of VT (110±10 milliseconds). In 5 of 8 hearts, the shorter V2V3 interval was fully compensated by a prolongation of the V2V3 interval, and VT was not reset. In 3 hearts, the prolongation of V2V3 was less than compensatory, and VT was reset with an average of 8±2 milliseconds.

### Table 2. Characteristics of Functional Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Experiment</th>
<th>CL, ms</th>
<th>ERP, ms</th>
<th>EG, ms</th>
<th>V1V2, ms</th>
<th>V2V3, ms</th>
<th>Maximal Reset, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>68±3</td>
<td>27±3</td>
<td>72±5</td>
<td>108±4</td>
<td>10±2</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>70±2</td>
<td>28±3</td>
<td>77±4</td>
<td>114±4</td>
<td>6±8</td>
</tr>
<tr>
<td>3</td>
<td>107</td>
<td>79</td>
<td>28</td>
<td>88</td>
<td>114</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>74</td>
<td>35</td>
<td>87</td>
<td>126</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>114</td>
<td>93</td>
<td>21</td>
<td>100</td>
<td>128</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>90</td>
<td>30</td>
<td>98</td>
<td>140</td>
<td>...</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>79</td>
<td>41</td>
<td>84</td>
<td>156</td>
<td>...</td>
</tr>
<tr>
<td>8</td>
<td>121</td>
<td>95</td>
<td>26</td>
<td>100</td>
<td>136</td>
<td>8</td>
</tr>
<tr>
<td>Average</td>
<td>110</td>
<td>81</td>
<td>29</td>
<td>89</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CL indicates cycle length; ERP, effective refractory period; EG, excitable gap; V1V2, interval between last activation before and first activation after stimulation; and V2V3, interval between first and second activation after stimulation.

### Mapping of Reset of Functional VT

Fig 4 shows an example of reset of a functional VT with a cycle length of 98 milliseconds. A premature stimulus with a coupling interval of V1S=70 milliseconds shortened the V1V2 interval to 77 milliseconds (top tracing). Despite an increase of V2V3 to 109 milliseconds, the sum of the V1V2 and V2V3 intervals (186 milliseconds) was less than twice the VT cycle length (196 milliseconds) and VT was reset by 10 milliseconds. The left activation map shows that during regular VT, the circulating wave propagated in a counterclockwise direction around a line of functional block. In this case, the premature stimulus was applied close to the left pivoting point. As can be seen from the right map (V2), the early stimulus initiated an antidromic wave that collided with the counterclockwise circulating wave at t=15 milliseconds. In the meantime, the paced orthodromic wave restarted a new circulating wave around the same line of functional block. However, as this paced orthodromic wave turned around the right pivoting point, the line of block slightly extended in an upward direction. Despite the slight increase in path length, the paced orthodromic wave returned earlier at the site of pacing than during VT and thus reset the circuit (lower left map).

As was the case during reset of anatomic VT, the functional reentry circuit was also divided into ORTHO, ANTI, and ORTHO-1 segments. However, because of the small excitable gap, the latter two segments were always very small, and the far majority of the recording sites were located in the ORTHO segment. The lower right panel of Fig 4 shows the reset response curve obtained orthodromic to the pacing site. The V2V3 intervals shortened at progressively premature V1S intervals. During late premature stimuli, the V2V3 intervals were completely compensatory, and VT was not reset. However, during earlier premature beats, the V2V3 curve became flat, and VT was reset.
earliest stimuli, the $V_1V_3$ interval increased slightly because of slowing of conduction and lengthening of the line of functional block, but VT was still reset by 10 milliseconds.

Failure of Reset of Functional VT

There were two different mechanisms responsible for failure of reset of VT. Figs 5 and 6 show two examples. In Fig 5, a counterclockwise VT with a cycle length of 120 milliseconds had an excitability gap of 21 milliseconds (shortest $V_1V_2$ interval, 90 milliseconds). However, even this earliest premature beat was followed by a completely compensatory pause of 141 milliseconds (top tracing). From the activation maps it can be seen that, as in Fig 4 in which VT was reset, the stimulus did initiate an antidromic wave that collided with the circulating wave at $t=15$ milliseconds. The stimulus also started a new orthodromic wave that restarted the reentrant VT. However, in this heart, the conduction velocity of the premature orthodromic wave was markedly depressed, as indicated by the crowding of isochrons between $t=20$ and $t=100$ milliseconds in map $V_2$. As a consequence, the premature impulse gradually lost its prematurity while propagating along the lower limb of the circuit. The map at the bottom gives the local intervals between $V_1$ and $V_2$ and shows that the $V_1V_2$ interval gradually prolonged from 99 milliseconds at the pacing site to 120 milliseconds at the opposite pivoting point. Thus, only part of the reentrant circuit was reset and the $V_2V_3$ interval at the site of pacing was fully compensatory.

Fig 6 shows a second mechanism for failure of reset of functional VT. During a functional VT with a cycle length of 120 milliseconds, the shortest coupling interval that elicited a propagated response was 79 milliseconds. Again, the resulting shortening of the $V_1V_2$ interval (84 milliseconds), however, was fully compensated by prolongation of the return cycle ($V_2V_1=156$ milliseconds). During VT (left activation map), the impulse circulated in a clockwise direction around a line of functional block. The premature stimulus was applied at the apex, which was part of the lower limb of the circuit. At first sight, the antidromic wave appears to collide with the circulating wave while the paced orthodromic wave restarts a new VT around the same line of block ($V_2$). However, the $V_1V_3$ interval map at the bottom
shows that this was actually not the case. Although around the pacing site the local intervals were shortened to <90 milliseconds, the V1V2 intervals at the lower limb of the reentrant circuit along the line of block remained 120 milliseconds. The premature stimulus thus failed to penetrate the reentrant circuit despite the fact that the pacing site was very close to the central line of block. This can be explained by the anisotropic properties of the ventricular myocardium. In the lower limb of the reentrant pathway, conduction was fast because it was longitudinal to the epicardial fiber axis. In contrast, in order to reach the line of block, the paced premature wave had to propagate transverse to the fiber orientation. The resulting slow conduction prevented the premature wave to short-circuit the circulating wave despite the fact that the pacing site was close to the center of the circuit, and as a result VT was not reset.

Discussion

Premature Stimulation During Reentrant VT

A large number of experimental and clinical studies have shown that in the chronic phase after myocardial infarction, VT is based on reentrant excitation. Reset of VT by premature stimulation has been used to characterize the conduction properties of the reentrant pathway. In clinical studies, a reset window of 43% of the VT cycle length was found. The reset curve usually has a flat part, which is taken as evidence for an anatomic reentrant circuit with a fully excitable gap. The prolongation of the return cycle has been explained by decremental conduction either within the reentrant pathway itself or in the tissue between the pacing site and the circuit. Several investigations have studied reset of reentrant VT in 4- to 6-day-old canine myocardial infarction. In this experimental model, VT is due to reentry in the epicardial border zone of the infarct, either as a single circulating wave around a line of functional conduction block or as figure-of-eight reentry. El-Sherif et al showed that premature stimuli could reset figure-of-eight reentry and that decremental conduction of early premature impulses within the central common pathway could terminate VT. In their study, only a partially excitable gap was demonstrated. In the same experimental model, the reset response was systematically investigated by Hanna et al. They found that late premature beats were conducted without a delay in the reentrant circuit, demonstrating the presence of a fully excitable gap.

In our study, the reset characteristics of functional and anatomic reentry in a thin epicardial layer of the left ventricle were compared. During anatomic reentry,
all sites in the circuit had a refractory period that was markedly shorter than the conduction time around the obstacle, resulting in an excitatory gap measuring 43% of the VT interval. The reset curve was flat, indicating that during premature beats the excitability was fully recovered. Only during the earliest premature stimuli was the return cycle slightly increased because of partial recovery of excitability. Similar data were reported by Bernstein and Frame in a canine model of ventricular reentry around the orifice of the mitral and aortic valves. The reset characteristics of these experimental models of anatomic VT thus are similar to the reset response of clinical VT. It should be noted that in our study, anatomic VT was always reset from a pacing site within the circuit. This may explain the larger window of reset in our model compared to clinical VTs, in which pacing from a site within the circuit is not always possible.

In contrast to our model of anatomic VT, the majority of functional VTs usually could not be reset despite the presence of an excitatory gap of 28% of the VT interval. Failure of reset was due to two different mechanisms: (1) Despite the fact that the pacing site was close to the circuit, slow anisotropic conduction prevented paced impulses from short-circuiting the circulating wave. Also in clinical VTs, a long conduction time from the pacing site to the circuit has been demonstrated to prevent reset of the tachycardia. (2) In case the premature impulses did penetrate the circuit, reset of the whole circuit was prevented by slowing of conduction of the premature wave front within the circuitous pathway. Thus, although the premature impulse did interrupt the circulating wave, its prematurity was gradually lost. As a result, only part of the circuit was reset, and the curtailed cycle was followed by a fully compensatory pause.

The Nature of the Partially Excitable Gap in Anisotropic Reentry

The nature of the excitatory gap during anisotropic reentry is not well understood. Three possible mechanisms should be considered: (1) Microanatomic barriers at the pivoting points of the circuit may enlarge the central line of functionally determined block. This may also anchor the functional circuit to a fixed position in the ventricles. (2) Sudden changes in axial current load caused by branching of the myocardial fibers or a sudden change in direction of propagation may lead to decremental conduction or conduction block despite the fact that the cells are readily excitable.
puter simulations have shown that a sharp curvature of a circulating wave greatly diminishes its stimulating efficacy and conduction velocity. During the sharp U-turn at the pivoting points of an anisotropic circuit, the circulating wave suddenly encounters a high axial current load of the well-coupled fibers in the longitudinal limb of the circuit. Such a mismatch between the amount of generated excitatory current and the high electrotonic load at the pivoting point may result in an initial failure to activate the longitudinal limb of the circuit, and only after a certain delay, when a larger part of the circulating wave has rotated around the pivoting point, the impulse may succeed to complete its 180° turn. Such a delay in conduction at the pivoting points will result in prolongation of the cycle length of VT, creating an excitable gap in the circuit. (3) During anisotropic reentry, the considerable differences in activation time between the cells at opposite sides of the pivoting points may result in electrotonic prolongation of the action potential. The associated lengthening in refractory period at the pivoting points may create an excitable gap in all other parts of the circuit.

During reset of one of the functional VTs in the present study, the central line of functional block lengthened when the premature wave front tried to make a sharp U-turn at one of the pivoting points. This observation indicates that at the pivoting points, the safety factor for conduction is lower than in other parts of the circuit. The resulting conduction delay at the pivoting points will create a small excitable gap in the other parts of the circuit.

**Importance of Localization of the Pacing and Recording Sites**

Rosenthal et al found that in 55% of cases, reset of clinical VT was accompanied by fusion beats in the surface ECG, indicating that the pacing site was located proximal to the area of slow conduction. Absence of changes in QRS morphology during reset has been attributed to pacing distal to or within the area of slow conduction. In our study, the relative positions of the pacing and recording electrodes in the reentrant circuit were distinguished by three characteristic reset curves, the position of the pacing site relative to the segment of slow conduction determining the likelihood of each of these reset curves. If the pacing site was proximal to the segment of slow conduction, reset curves with either a single or a double sudden change in the reset were seen in up to 50% of the recording sites. In contrast, when the pacing site was located distal to the segment of slow conduction, more than 85% of the recording sites showed a regular ORTHO reset curve. In a study on the reset response of clinical VT, Kay et al have postulated that during pacing proximal to the area of slow conduction, the electrograms recorded distal to the area of slow conduction should show a conduction time that exceeded the VT cycle length. In our study this was never observed, indicating that in clinical VTs, the area of slow conduction shows a higher degree of decremental conduction during premature beats than the area of slow anisotropic conduction in normal myocardium. This is also indicated by the observation that in clinical VTs, at least part of the reset curve is increasing while up to 45% of VTs can be terminated by premature stimuli. In our study, the return cycle during reset of anatomic VT was almost completely flat, and VT could not be terminated by premature stimulation.

**Clinical Implications**

Our results show that functional VT in anisotropic tissue has a small partially excitable gap. However, despite the fact that the pacing site was very close to the circuit, most functional VTs could not be reset. This was due to slowing of conduction of the premature wave in the reentrant circuit or failure to penetrate the circuit. This implies that if the excitable gap of functionally determined reentrant circuits in patients is also very small, there is almost no chance that these functional VTs can be reset, especially since pacing is usually performed outside the reentrant circuit. Several studies on the reset characteristics of clinical VT have indicated that a fully excitable gap exists in the circuit. The results of our study suggest that these clinical VTs are probably not based on a functionally determined reentrant circuit. Ventricular reentrant circuits in patients are very complex and usually comprise an area of slow conduction, which is the target for ablative therapy of VT. We found that the localization of the pacing and recording sites relative to the area of slow conduction could be identified on the basis of three typical reset curves. Recognition of these reset curves may be useful to localize the area of slow conduction in reentrant circuits in patients. However, a major limitation of our study was that all the pacing sites were located within the reentrant circuit. Since in the clinical setting, pacing is usually performed outside the circuit, the value of these three typical reset curves thus remains to be determined.

**Acknowledgments**

The technical assistance by Frits Schmitz and Jan Hollen is gratefully acknowledged.

**References**


Mapping of reset of anatomic and functional reentry in anisotropic rabbit ventricular myocardium.
L Boersma, J Brugada, C Kirchhof and M Allessie

Circulation. 1994;89:852-862
doi: 10.1161/01.CIR.89.2.852
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 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/89/2/852

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/