Autonomic control of ventricular tachycardia: sympathetic neural influence on spontaneous tachycardia 24 hours after coronary occlusion

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ABSTRACT This study was performed to determine whether sympathetic nerves influence the rate of ventricular tachycardia occurring spontaneously in dogs 24 hr after occlusion of the anterior descending coronary artery. Seventeen chloralose-anesthetized dogs underwent activation mapping during spontaneous ventricular tachycardia with QRS morphologies similar to those recorded in the conscious state. Bilateral stellate ganglionectiony (n = 8) decreased mean arterial pressure from 71 ± 4 (mean ± SE) to 52 ± 5 mm Hg (p < .001) and heart rate from 121 ± 9 to 79 ± 15 beats/min (p < .025) by decreasing the number of complexes of ventricular tachycardia from 120 ± 9 to 49 ± 15 per minute (p < .001). Subsequent unilateral sympathetic nerve stimulation (n = 4) was shown to accelerate ventricular tachycardia foci originating from the ipsilateral aspect of the infarct. Regional sympathetic denervation (n = 7) was performed by application of phenol to the epicardium surrounding an electrode at the site of origin of at least one morphology of ventricular tachycardia. Mean arterial pressure did not change, but total heart rate decreased from 122 ± 9 to 106 ± 9 beats/min (p < .01) and the number of complexes of ventricular tachycardia with a morphology arising from the phenol-treated area fell from 68 ± 12 to 28 ± 9 (p < .001). Evidence for regional denervation was documented by prolongation of duration of electrograms and local repolarization times limited to the phenol-treated area. We conclude that sympathetic nerves directly control rate of spontaneous ventricular tachycardia 24 hr after myocardial infarction in the dog.

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SYMPATHETIC neural influences importantly influence electrophysiologic changes in the ventricle during acute myocardial ischemia1,2 and may modulate the occurrence of ventricular fibrillation.3,4 Ventricular tachycardias occurring during the course of myocardial ischemia might also be modulated by sympathetic nerves. One such ventricular tachycardia occurs spontaneously 8 hr to 4 days after occlusion of the anterior descending coronary artery in the dog.5 Recent studies suggest that this ventricular tachycardia originates in surviving subendocardial Purkinje fibers6-11 due to triggered activity,12 abnormal automaticity,6-8,13 or both.14 While studies in vitro suggest that these arrhythmogenic mechanisms are responsive to catecholamines,15-18 sympathetic nerves may still not modulate this ventricular tachycardia if the neural transmitter does not reach the cells responsible for the tachycardia. This might occur if denervation produced by ischemia of cardiac nerves19,20 occurred at the site of origin of the tachycardia. The purpose of the present study was to determine if sympathetic neural influences control the rate of ventricular tachycardia 24 hr after occlusion of the anterior descending coronary artery. Sympathetic neural influences were removed in two ways. Bilateral stellate ganglionectiony was performed, the effects of which could then be reversed by sympathetic nerve stimulation. To exclude hemodynamic effects of stellate ganglionectiony that may modify rate of ventricular tachycardia by changing the stretch of cardiac tissue,21 irreversible but local sympathectomy limited to a focus of tachycardia was also produced by epicardial application of phenol.22

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**Methods**

**General.** Mongrel dogs of both sexes (n = 21) were anesthetized with droperidol (60 mg) and fentanyl (1.2 mg) and pentobarbital sodium (15 mg/kg) and mechanically ventilated. The heart of each was exposed through a left thoracotomy. The proximal left anterior descending coronary artery was bluntly dissected within 1 cm from the tip of the atrial appendage and proximal to the last major diagonal branch. A 21-gauge needle was placed along the artery and a 2-0 silk ligature was tied around the vessel and the needle. The needle was then withdrawn. This procedure resulted in a coronary stenosis that was maintained for 20 min. The vessel was then permanently occluded by another ligature. The ligature was always distal to the first septal perforator, as determined by subsequent necropsy. The chest was closed and the animal was allowed to recover.

Seventeen dogs survived to be studied 24 hr later; the others either developed ventricular fibrillation on occlusion of the coronary artery or were found dead the next day. Each was sedated with 2.3 mg/kg morphine and three surface electrocardiographic recordings were obtained at a paper speed of 25 mm/sec for 1 to 3 min (see below). Each dog was then anesthetized with \(\alpha\)-chloralose (100 mg/kg). Thereafter, chloralose was administered by constant infusion at 8 mg/kg/hr to maintain anesthesia. Chloralose was prepared in a 1% solution dissolved in 40% polyethylene glycol (average molecular weight, 200). The trachea was intubated and the animal was ventilated with a volume-cycled respirator with air enriched with oxygen (2 liters/min). Tidal volume was regulated by measurement of arterial PC\(_{\text{O}_2}\) and 20 mesg/hr iv sodium bicarbonate was given to maintain pH in the normal range.

The sternum was split and the pericardium was incised and sutured to the sternal incision to support the heart. A plastic sheet was placed over the sternal incision and a temperature probe was sutured to the pulmonary artery. Temperature was maintained constant at 37.5°C by adjustment of the distance of the operating table lamp to the heart. All animals underwent bilateral vagotomy by ligation and section of the mid cervical vagi. The femoral vein was cannulated to infuse 0.9% NaCl at 200 ml/hr and to administer drugs. The femoral artery was cannulated to record arterial pressure. Mean arterial pressure was measured by electrical filtering.

**Electrophysiologic measurements.** Surface electrocardiograms were recorded in the conscious and anesthetized state by use of standard surface leads I, aVF, and either V\(_2\)R or V\(_6\). The surface morphologic appearance of each QRS complex in V\(_2\)R was categorized as either a right or left bundle branch block pattern according to whether the overall QRS deflection was positive or negative, respectively. In addition, the electrical axis in the frontal plane was determined to be in one of four quadrants (left and inferior, left and superior, right and inferior, or right and superior) by the major QRS deflection measured in leads I and aVF (figure 1).

After the chest was opened the sinus node was clamped and temporary overdrive atrial pacing was performed by attaching a bipolar electrode to the atrial appendage. Atrial pacing was performed with a programmable stimulator with constant-current outputs at two times diastolic threshold with pulses of 2 msec duration. Atrial pacing was performed at rates just greater than the rate of ventricular tachycardia (range of atrial pacing rates required was 150 to 200 beats/min) to measure His bundle, Purkinje activity, and QT intervals (see below). Bipolar His bundle recording wires (Teflon-coated stainless steel) were placed in the region of the His bundle via a needle passed through the right ventricular free wall and cavity. Ventricular origin of wide QRS morphologies was documented by absence of His bundle deflections (which were present during overdrive atrial pacing; figure 1). Junctional origin of normal surface QRS morphologies was confirmed by normal HV intervals of that complex. Heart rate was determined by counting individual surface QRS complexes for 2 to 3 min in succession. The number of complexes of ventricular tachycardia of each morphology was also tallied and averaged per minute over the 2 to 3 min sampling period.

Activation mapping was performed during spontaneous ventricular tachycardia observed during recordings made in dogs in the conscious state. Electrograms were filtered from 40 to 500 Hz, amplified, and registered on a storage oscilloscope and on an oscillographic recorder at paper speeds of 200 mm/sec. Bipolar electrograms were recorded from reference Teflon-coated stainless steel wire electrodes in the posterior left ventricular base and the outflow tract of the right ventricle and from a roving epicardial bipolar electrode (2 mm interelectrode distance) placed on the ventricular epicardium at up to 54 predetermined positions. The interval from the onset of the surface QRS to the intrinsincoid deflection on the roving electrogram was measured for each site. In this manner, the earliest epicardial electrical activity during a ventricular tachycardia of a particular morphology was determined. After this, a 16-pole electrode needle with 1 mm interelectrode spacing was placed perpendicularly to the epicardium in that site and endocardial and epicardial electrograms were recorded during spontaneous ventricular tachycardia. These positions on the needle were chosen as follows. At each needle site adjacent pairs of electrodes were recorded sequentially during atrial overdrive pacing. The endocardial bipolar electrograms were defined as those indicating the earliest electrical activation of all of that needle’s pairs and

![FIGURE 1.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.49.4.934?w=260&h=260)
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which frequently contained Purkinje spikes (figure 1). These were usually located 7 to 8 mm in from the outermost epicardial electrode. Epicardial electrograms were taken from the outermost bipolar pair of electrodes and were the latest activated on that needle during atrial pacing rhythm. Additional multipolar electrodes were placed 1 cm from the original electrode position in four quadrants surrounding it. This procedure was repeated until the earliest electrical activity during ventricular tachycardia of a single QRS morphology was found surrounded by electrodes recording later activity (figure 1). This position was the presumed site of origin of ventricular tachycardia of that QRS morphology.

To confirm this position as the origin of a ventricular tachycardia of a particular morphology, pacing from the ventricular multipolar electrode needle was performed to produce the same surface morphology\(^1\) (figure 1). A single electrode adjacent to the bipolar electrode recording earliest activity on each multipolar needle was used for pacing. This single electrode formed the cathode while the anode was a 7 mm\(^2\) stainless steel electrode located in the subcutaneous tissue of the abdomen. Pacing was performed at two times diastolic threshold.

Local bipolar electrograms (1 mm interelectrode spacing) also were recorded for the purposes of measuring local electrophysiologic properties in the following manner. Overdrive atrial pacing was instituted at a rate just faster than that of the spontaneous ventricular tachycardia (range of basic cycle lengths required was 300 to 400 msec). Electrograms were filtered at 1.2 to 500 Hz. Recordings were made at high gain to measure T waves on each bipolar electrogram at paper speeds of 500 mm/sec. Activation times to epicardium and endocardium were recorded from the His bundle deflection or onset of the surface QRS to the intrinsocid deflection of each electrogram. Duration of individual electrograms was measured from the first to the last rapid deviation from the isoelectric line.\(^1\) Local repolarization times on each individual bipolar electrogram were recorded from the onset of the local electrogram QRS to the peak or ending of the T wave (figure 2). Data from each electrogram recording between interventions was accepted only if pacing rates between interventions were constant, electrogram activation sequences remained constant, and electrogram morphologies remained unchanged.\(^2\) All dogs in this study met these criteria.

Protocols. After activation mapping and recording of electrograms during atrial overdrive pacing, rates of spontaneous ventricular tachycardia were recorded over 2 to 3 min. Sympathectomy was then performed by one of two methods applied randomly to two groups of dogs. Stellate ganglionectomy was performed in eight dogs by isolation and incision of all proximal rami communicans from both right and left stellate ganglia; the anterior and posterior ansae were intact. In a subgroup of four of the original eight plus two additional animals, stimulation of the individual stellate ganglia was performed by placing bipolar stainless steel electrodes on the anterior ansa subclavi of each ganglion. Stimulation parameters were 4 msec pulses with suprathreshold currents at 1 to 8 Hz.

Regional sympathectomy was performed in seven dogs by application of 88% phenol to the epicardium surrounding an electrode recording the site of origin during a ventricular tachycardia of a particular morphology. The radius of the circle of phenol was 2 to 3 cm, as described previously.\(^2\) Recording of electrograms and spontaneous rates of ventricular tachycardia was performed after epicardial temperature returned to the control level after replacement of the plastic sheet covering the sternal incision and 20 min after sympathectomy.

The dogs were killed with rapid ventricular pacing to produce ventricular fibrillation. The multipolar electrode sites were related to gross white and hemorrhagic areas of infarction.

Statistical analysis. The data are expressed as mean ± SE. The comparisons within groups were performed by Student’s t test.\(^2\)

Results

Mapping and gross anatomic data. In the conscious state just before study all 15 dogs from the original two groups had spontaneous ventricular tachycardia of one to five distinct QRS morphologies. One dog had five, one had four, two had three, five had two, and six had only one morphology of ventricular tachycardia. Of

FIGURE 2. Surface and intracardiac bipolar electrograms taken from one dog in this study during overdrive atrial pacing. Tracing are labeled as in figure 1, except for the addition of aortic pressure, which is labeled AP. Intracardiac electrograms were recorded at high gain with filter settings from 1.2 to 500 Hz. Duration of local repolarization is indicated by the vertical bar located on each T wave. After phenol was applied to the epicardium surrounding the electrode in IZ\(_1\), repolarization times in IZ\(_2\) were prolonged compared with their control values as well as with values in other areas after phenol was applied. Aortic pressure did not change after phenol.
The rate of ventricular tachycardia before anesthesia averaged 156 ± 6/min, but after anesthesia and during mapping the average rate was 121 ± 7/min (p < .01). To examine the stability of this tachycardia, six dogs were observed for 1 hr without intervention under the experimental conditions of constant infusion of chloralose dissolved in polyethylene glycol. Rate of tachycardia did not change (123 ± 15/min at initial control and 122 ± 10/min at late control, p > .5). In addition, the ratio of individual morphologies to the overall rate of ventricular tachycardia was also constant. To determine whether polyethylene glycol alone would influence rate of tachycardia, we also administered a constant infusion of polyethylene glycol only to two dogs. In these animals rate of ventricular tachycardia increased by 12 and 24 beats/min 1 hr after control rates of 180 and 128 beats/min, respectively, reflecting the lack of chloralose infusion. Thus, polyethylene glycol alone produced no effect on rate of ventricular tachycardia.

Effects of global cardiac sympathetic denervation. Bilateral stellate ganglionectomy (n = 8) decreased both heart rate (by 35%) and complexes of tachycardia per minute (by 60% table 1); in seven of eight dogs there was a decrease in rate while in one there was an increase. The overall heart rate decreased to a lesser extent than the rate of ventricular tachycardia after stelllectomy because of the appearance of frequent junctional complexes. In addition, the shortest cycle length of ventricular tachycardia (in msec) was pro-

### TABLE 1
Effects of global cardiac sympathetic denervation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Stellate ganglionectomy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous rhythm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>121 ± 9</td>
<td>79 ± 15</td>
<td>&lt;.025</td>
</tr>
<tr>
<td>VT complexes (per min)^a</td>
<td>120 ± 9</td>
<td>49 ± 15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shortest VT cycle length (msec)</td>
<td>464 ± 49</td>
<td>647 ± 93</td>
<td>&lt;.025</td>
</tr>
<tr>
<td><strong>Overdrive pacing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>71 ± 4</td>
<td>52 ± 5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Activation time (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To normal zone</td>
<td>28 ± 5</td>
<td>29 ± 5</td>
<td>&gt;.09</td>
</tr>
<tr>
<td>To ischemic zone</td>
<td>26 ± 4</td>
<td>29 ± 4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Electrogram duration (msec)</td>
<td>21 ± 4</td>
<td>20 ± 4</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>Normal zone</td>
<td>21 ± 3</td>
<td>24 ± 4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ischemic zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repolarization time (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal zone</td>
<td>184 ± 6</td>
<td>192 ± 8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ischemic zone</td>
<td>189 ± 9</td>
<td>206 ± 11</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

^aExcluding only junctional complexes.
longed by 40%. During continuous recording of bipolar electrograms from sites of origin of tachycardia, there was no evidence of endocardial electrical activity without an associated surface QRS; thus, there was no macro exit block (block from the endocardial origin to the rest of the heart) produced by stellate ganglionectomy. During atrial pacing mean arterial pressure fell by 27% and repolarization time was prolonged in both normal and ischemic zones (by 4% and 9%, respectively; table 1). Activation time and electrogram duration in normal zones did not change with stellate ganglionectomy, but activation time and electrogram duration in ischemic zones were prolonged by 12% and 14%, respectively (table 1).

To exclude the possibility that the results of stellate ganglionectomy were due to deterioration of the preparation, sympathetic nerve stimulation was performed in a subgroup of six animals. During atrial pacing, bilateral sympathetic nerve stimulation shortened duration of bipolar electrograms toward control from 25 ± 3 to 23 ± 3 msec in ischemic zones (p < .025 compared with data in table 1). Similarly, local repolarization time in ischemic zones was shortened from 211 ± 8 to 188 ± 6 msec (p < .01). During spontaneous rhythm, sympathetic stimulation produced a junctional tachycardia at a faster rate than the prestellectomy ventricular tachycardia in the first two dogs of the initial eight. Therefore, analysis of tachycardia response to individual right or left sympathetic stimulation was not performed until the last two dogs. The first of these dogs had ventricular tachycardia of a single morphology that slowed with right but not left stellate ganglionectomy (figure 4); stimulation of the right sympathetic nerves alone reproducibly returned tachycardia with an origin on the septal free wall side of the infarct to the prestellectomy rate (figure 5). Three more animals then underwent individual right and left sympathetic nerve stimulation to determine whether ventricular tachycardia originating from the septal side of the infarct might accelerate with right sympathetic stimulation and whether ventricular tachycardia from the lateral aspect of the infarct might accelerate with left sympathetic stimulation. Table 2 lists data demonstrating that either right or left sympathetic stimulation could reproducibly accelerate the rate of tachycardia, but that the specific origin of the tachycardia that is accelerated is predicted by its relationship to the infarction. Thus, sympathetic nerve stimulation demonstrated return of electrophysiologic

FIGURE 4. Surface electrocardiographic recordings from one animal in our study. Left, In the control state, ventricular tachycardia with a right and inferior axis, right bundle branch block morphology was recorded. Right, After right stellate ganglionectomy (RSTGX), heart rate slowed. After left stellate ganglionectomy no further slowing occurred (data not shown).

FIGURE 5. Recording from the same animal as in figure 4. Surface electrocardiographic recordings and aortic pressure were recorded simultaneously at two paper speeds indicated by the 1 sec time lines. The horizontal line at the bottom is 0 aortic pressure. On the left hand portion of the tracing ventricular tachycardia after bilateral stellate ganglionectomy is shown. The right hand portion of the figure was recorded during continuous right sympathetic stimulation (RSNS). Sympathetic stimulation produced increases in rate of tachycardia and arterial pressure.
properties and rate of tachycardia toward the presten-lectomy level.

**Effects of regional sympathetic denervation.** After application of phenol (n = 7 dogs) to the epicardium surrounding an electrode near the site of origin of ventricular tachycardia of at least one morphology, overall heart rate and the number of complexes of tachycardia with that morphology decreased by 13% and 60%, respectively (figure 6, table 3). Six of seven dogs had a decrease in rate of ventricular tachycardia while in one dog rate did not change; in the latter the origin of tachycardia was mapped to the inferior and septal, free wall side of the infarction. In addition, the shortest cycle length also increased. During continuous recording of bipolar electrograms from ventricular tachycardia origins there was no evidence of endocardial electrical activity without an associated surface QRS; thus, there was no evidence of macro exit block (block from endocardial origin to the rest of the heart) produced by regional denervation. Similar to stellectomy, duration of electrograms in the ischemic zone was prolonged by 14% and local repolarization time in the phenol-treated area was prolonged by 9% (figure 2, table 3). In contrast to results with stellate ganglionectomy, mean arterial pressure, repolarization time in the normal zone, and activation time to the ischemic zone did not change after application of phenol.

In one dog isoproterenol was infused at 5 μm/min to determine whether the phenol-treated area would respond to a sympathetic agonist. Isoproterenol accelerated other foci of ventricular tachycardia that were not mapped or treated with phenol. This prevented assessment of the effect of isoproterenol on the rate of ventricular tachycardia originating from the phenol-treated site. However, as has been shown in previous experiments,22 during atrial pacing isoproterenol shortened both duration of bipolar electrograms and local repolarization time in the phenol-treated ischemic zone. In addition, bilateral sympathetic nerve stimulation did not shorten duration of bipolar electrograms or repolarization time limited to the phenol-treated area, confirming the existence of local denervation.22 Therefore, the electrophysiologic response of the denervated area to isoproterenol was normal during atrial pacing. However, because of acceleration of other foci of ventricular tachycardia, we could not assess the effect of isoproterenol on the tachycardia from the denervated site.

**TABLE 2**
Effects of right or left sympathetic nerve stimulation on rate of ventricular tachycardia (VT)

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Denervation (VT from septal side)</th>
<th>Left SNS (VT from lateral side)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>180</td>
</tr>
<tr>
<td>2</td>
<td>&lt;30</td>
<td>170</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>180</td>
</tr>
<tr>
<td>4</td>
<td>&lt;120</td>
<td>133</td>
</tr>
</tbody>
</table>

SNS = sympathetic nerve stimulation.

**FIGURE 6.** Recordings from a dog with regional denervation of the area from which tachycardia originated. Surface electrocardiographic leads were recorded with a bipolar left ventricular electrogram (LV). **Left.** In the control state, a uniform ventricular tachycardia with a rightward and superior axis, right bundle branch block morphology was recorded continuously. **Right.** After phenol was applied around the electrode indicating earliest electrical activity of this morphology of ventricular tachycardia, tachycardia was markedly slowed such that only the first, third, fourth, and seventh complexes reflect the control morphology. Other complexes reflect other foci of ventricular tachycardia or junctional escape complexes. The left ventricular electrogram decreased in size because of the change in amplification.

**TABLE 3**
Effects of regional cardiac sympathetic denervation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Phenol application</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>122±9</td>
<td>106±9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>VT complexes (per min)</td>
<td>68±12</td>
<td>28±9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shortest VT cycle length (msec)</td>
<td>429±27</td>
<td>505±32</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>During overdrive pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>78±4</td>
<td>80±4</td>
<td>&gt;.4</td>
</tr>
<tr>
<td>Activation time (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To normal zone</td>
<td>36±9</td>
<td>34±9</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>To ischemic zone</td>
<td>43±8</td>
<td>43±7</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Electrogram duration (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal zone</td>
<td>17±4</td>
<td>17±4</td>
<td>&gt;.4</td>
</tr>
<tr>
<td>Ischemic zone</td>
<td>21±3</td>
<td>24±3</td>
<td>&lt;.06</td>
</tr>
<tr>
<td>Repolarization time (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal zone</td>
<td>184±9</td>
<td>186±11</td>
<td>&gt;.4</td>
</tr>
<tr>
<td>Ischemic zone</td>
<td>212±14</td>
<td>232±17</td>
<td>&lt;.025</td>
</tr>
</tbody>
</table>

*With morphology from treated focus(i), excludes junctional and other ectopic foci.*
Discussion

This study demonstrates two new observations. First, sympathetic nerves control rate of ventricular tachycardia originating from endocardial Purkinje fibers 24 hr after coronary occlusion in the dog. Second, these effects are mediated because of the direct influence of sympathetic nerves on the focus of the tachycardia and not indirectly through hemodynamic changes.

Methodologic considerations. The origin of the ventricular tachycardia was determined by activation mapping in an effort to find the earliest electrogram activity before the onset of the surface QRS. This method, involving a single roving electrode, is valid for use under conditions of a continuously repetitive tachycardia in which information from many cardiac cycles can be added together, comparing many recordings of the roving electrode, such as in the case of patients with reentrant ventricular tachycardia when intraoperative activation mapping is used to guide antiarrhythmic surgery. The limitation of epicardial activation mapping without heart-lung bypass is that foci of tachycardia arising from the intraventricular septum are difficult to characterize accurately because the interventricular surface is not accessible except by individual plunge electrodes.

In the present study we specifically did not perform extrastimulus pacing protocols such as those used to record refractoriness in an effort to prevent reentry tachycardias. In fact, we believe that the tachycardias studied in our preparation were not reentrant. The evidence for this assertion is based upon previous studies in the same preparation of myocardial ischemia in which both spontaneous and induced tachycardias were studied. Thus, the spontaneous tachycardias were multiformed and comparatively slow and hemodynamically tolerated, had radial activation spread away from a small region (<1 cm), and were not able to be terminated or initiated by pacing.

The phenol denervation technique used in these experiments produces electrophysiologic effects indirectly by interruption of epicardial sympathetic nerves en route to a test electrode. This electrode was placed in an area that displayed the earliest endocardial electrical activity during ventricular tachycardia compared with bipolar electrograms recorded from multipolar plunge electrodes surrounding it by only 1 cm. The phenol was applied in 3 to 5 mm thick line inscribed on a circle with a radius of 2 to 3 cm centered on the test electrode. Since phenol produced necrosis to a depth of only 0.25 mm, we would not expect direct effects on ventricular tachycardia originating in endocardial fibers 2 cm or more away. Indeed, when electrophysiologic measurements were performed in ischemic regions of reserpine-treated dogs, phenol applied as described herein produced no electrophysiologic effect. However, it is theoretically possible that tachycardias originating in the endocardium but exiting via narrow layers of viable epicardium that range from less than 1 to 2 mm in thickness could be directly slowed by epicardial phenol, which produces macro exit block, i.e., block of endocardial wave fronts in epicardium 1 to 2 cm away. In no experiment did we find evidence of macro exit block as might be evidenced by endocardial electrical activity continuing at the presympathectomy rate while tachycardia slowed. Thus, application of phenol to the epicardium as performed in the present experiments did not produce electrophysiologic effects or slowing of ventricular tachycardia by direct actions on ischemic or normal myocardium.

In this study the evidence for regional sympathetic denervation with application of phenol was based on electrophysiologic criteria. This was reasonable considering the following. The electrophysiologic effects of regional sympathetic denervation are well described in normal muscle; refractory period responses to sympathetic nerve stimulation are eliminated where noradrenaline concentrations and catecholamine histofluorescence are also absent. In addition, in the present study phenol produced electrophysiologic effects compatible with those of sympathetic denervation, which have been described previously in ischemic ventricles. In the present study phenol tended to prolong local electrogram durations and local repolarization times were definitely prolonged. These data are compatible with loss of sympathetic nerve influence, which has been shown previously to improve ischemic zone conduction by shortening overdrive cycle lengths, resulting in Wenckebach conduction delay, or by shortening electrogram duration, as in the present study. Also, as shown in this study, sympathetic denervation produced by stellate ganglionectomy prolongs local repolarization times, and we and others have shown that subsequent sympathetic nerve stimulation shortens repolarization time or refractoriness. While these electrophysiologic effects are evidence of sympathetic denervation, they do not necessarily suggest mechanisms by which sympathetic denervation affected the rate of ventricular tachycardia.

While the application of phenol is an effective technique to produce regional sympathetic denervation, its use could be limited by the fact that it cannot be applied to the intraventricular septum. Therefore, phenol ap-
Unlike the entire epicardial surface could not be expected to produce results comparable to stellate gangliectomy since morphologies of ventricular tachycardia that arise from septal origins inaccessible to phenol may not be denervated. In addition, one would like to denervate only a portion of the ischemic zone to compare denervation with innervated ischemic responses. However, denervation produced by phenol requires a 2 to 3 cm circle to ensure transmural denervation.22 Thus, it is difficult to consistently and effectively denervate a small area in order to leave a portion of the ischemic zone innervated (although this occasionally occurs; figure 2). Therefore, comparisons between innervated and denervated ischemic zones in the same heart are difficult with the phenol technique.

Another methodologic consideration is that we produced acute sympathetic denervation. Effects of chronic denervation may have produced different results since it may be more effective in preventing ventricular fibrillation associated with acute ischemia.35 Chronic denervation applied before coronary occlusion may simply decrease size of infarction36 such that the same arrhythmias may not be present or significantly altered as a result of the procedure.37 In addition, supersensitivity resulting from chronic denervation may alter responsiveness to circulating catecholamines.

**Effects of sympathetic denervation on ventricular tachycardia.** Sympathetic denervation produced by either method in the present study slowed the rate of ventricular tachycardia. The effects of stellate gangliectomy were reversible in that electrical stimulation of the distal cut end of one or both of the stellate ganglia reversed electrophysiologic changes and returned the rate of tachycardia to the predenervation level. The changes in hemodynamics produced by stellate gangliectomy may alone modulate the rate of automaticity by the amount of stretch of Purkinje fibers.21 The results of phenol denervation argue against these hemodynamic mechanisms because there was no change in arterial pressure during atrial overdrive pacing. Therefore, the phenol studies support the role of a direct action of sympathetic efferent nerves acting on a tachycardia focus.

The precise mechanism(s) by which sympathetic denervation modulate(s) rate of ventricular tachycardia is unclear. There may be at least two direct effects of sympathetic nerves on foci of tachycardia. One effect could be direct action on the Purkinje fiber(s) that are abnormally automatic6, 16 or triggered.19 Another effect might be modulation of conduction out of the focus of ventricular tachycardia such that micro exit block (≤2 mm) of some of the impulses may occur, as has been reported with nifedipine in vitro.38 In the present study these two mechanisms could not be differentiated. However, the possibility that conduction in the ischemic zone is modulated by sympathetic influences is supported by the present and other studies that have shown that duration of electrograms in the ischemic zone1 or the cycle length at which conduction delay occurs33 is modified by sympathetic nerves.

In the present study we found that ventricular tachycardia originating around the entire border of the infarction responded to sympathetic denervation. This border origin of tachycardia helps to explain why the ventricular tachycardia responds to sympathetic denervation, since the center of the infarction is thought to be denervated.19 Moreover, sympathetic innervation to the anterior ventricle is redundant, coming from both right and left ganglia.27, 39, 40 This distribution of innervation with superimposed ischemia suggests a possible mechanism by which sympathetic innervation could be maintained in border areas. Ischemic damage could interfere with neural pathways from the left stellate ganglion on route to septal, free wall aspects of the infarction, since they traverse the ischemic zone,20 while the right neural pathways to septal sites would remain intact. The converse could also be true for right sympathetic denervation, with the left innervation remaining intact to lateral areas of infarction. This hypothesis is suggested by the observation that ventricular tachycardia originating from the septal free wall side of the infarct accelerates during right sympathetic nerve stimulation. The converse also appears to be true (table 2). Thus, it appears that the highly selective19, 40 cardiac control by sympathetic nerves may be even more selective after myocardial infarction such that sympathetic nerves on one side may only modulate the rate of ventricular tachycardia originating from sites of origin on the ipsilateral aspect of the infarct. Further work on this hypothesis is needed for confirmation.

**Possible clinical correlations.** We speculate that patients suffering from acute myocardial infarction may have ventricular tachycardia similar to that recorded herein 24 hr after onset of infarction. This tachycardia is not induced or terminated by pacing,41 appears multiformal,42 and is not necessarily associated with hemodynamic deterioration or subsequent development of ventricular fibrillation.43 The rhythms in the dog are faster than those reported for humans, but this may result from the prior performance of thoracotomy in the dog, which may increase sympathetic influence and accelerate the tachycardia.

Recent studies in patients52 suggest that verapamil
mays effective in eliminating these multiform accelerated idioventricular rhythms. This study suggests the possibility that other interventions that impair sympathetic neural activity or block effects of sympathetic neural transmitter may also slow these rhythms.

It is tempting to consider the possibility that local denervation might be applied to the treatment of ventricular tachycardia in general as a therapeutic measure. It must be remembered, however, that reinnervation may occur in previously denervated areas as early as 6 to 9 months after denervation.44

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