Effects of unilateral stellate ganglion stimulation and ablation on electrophysiologic changes induced by acute myocardial ischemia in dogs

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ABSTRACT We recorded direct-current extracellular electrograms simultaneously from 60 left ventricular epicardial sites in 38 α-chloralose-anesthetized dogs during repeated, 5 min coronary arterial occlusions. In each dog recordings made during control occlusions were compared with those made in occlusions after, or during, the following interventions on the sympathetic nervous system: left stellate ganglion stimulation, left stellectomy, right stellectomy, and clamping the abdominal aorta with intact sympathetic nerves to induce a rise of blood pressure equal to that present during left stellate stimulation. Heart rate was kept constant. Measurements included determination of TQ segment potentials and times of local activation. After 2 min of ischemia, the degree of TQ segment depression was increased by left stellate ganglion stimulation and was decreased by both left stellectomy and clamping the aorta. Also, the area showing negative TQ potentials, indicating decreased resting membrane potentials, was enlarged by both left stellate stimulation and right stellectomy and reduced by left stellectomy. No differences were found in the results of experiments in which the left anterior descending coronary artery was occluded and those in which the circumflex branch was occluded. Left stellate stimulation significantly improved conduction within the ischemic zone. No evidence was found to suggest that the arrhythmogenic effects of left stellate stimulation and of right stellectomy, confirmed in the present study, resulted from an increased likelihood for reentry in the subepicardium of the ischemic zone.


IT IS generally accepted that the sympathetic nerves play an important role in the genesis of ventricular arrhythmias caused by acute myocardial ischemia. Furthermore, studies employing unilateral denervation have shown that, by removing tonic activity or by preventing the occurrence of cardiocardiac reflexes, right and left sympathectomy are not equivalent and actually produce different results. More specifically, left stellectomy has been found to exert an arrhythmogenic effect, while right stellectomy has been found to have an arrhythmogenic effect. However, the mechanisms underlying these findings have remained elusive.

In this study we attempted to gain insight into these effects by recording direct-current extracellular electrograms simultaneously from 60 epicardial sites on both ischemic and nonischemic myocardium during short-lasting and repeated coronary occlusions coupled with specific interventions on the stellate ganglia. We measured the direct-current potential at each electrode during the TQ segment of beats propagated from the atrium, and the time of local activation. The TQ segment potential was chosen because depolarization of resting membrane causes depression of the TQ segment in direct-current recordings. The amount of TQ segment depression and the delay in activation time both served as an index for the severity of ischemia-induced changes in electrical activity.

Methods

Thirty-eight dogs ranging in weight from 18 to 30 kg were anesthetized with a short-acting barbiturate (hypnodil 2 mg iv) followed by intravenous injection of α-chloralose (50 to 100 mg/kg). Administration of α-chloralose during the experiment was repeated as necessary. No measurements were made for at least 20 min after drug administration.

A carotid artery was cannulated to monitor arterial pressure,
and a femoral vein was cannulated to administer anesthetics. The vagus nerves were isolated in the neck and cut. The chest was opened via a midsternal incision. The left or right stellate ganglion was isolated from the surrounding connective tissue and prepared for subsequent ablation or stimulation. Stimulation was carried out by a constant current stimulator, which delivered rectangular current pulses of 2 msec duration at a frequency of 10 to 20 Hz, with an intensity of 1.5 to 2 mA. Stimulation was always performed after decentralization, when the only connections of the stellate ganglion were the cardiac nerves and the ansae subclaviae, to avoid reflex activation of the contralateral stellate ganglion. Ablation was performed after topical application of 1% lidocaine to avoid the effects of injury currents through the cardiac nerves.

After a pericardial cradle was constructed, stimulating bipolar electrodes were sutured on the right atrium. After a brief period of left stellate ganglion stimulation, the success of which was judged by noting an increase in average blood pressure of 20 to 40 mm Hg and which sometimes also resulted in a slight increase in heart rate, the atrium was paced at such a rate as to ensure a constant heart rate throughout the experiment. Basic cycle length varied in the different experiments from 290 to 490 msec but usually was in the range of 300 to 350 msec. The left anterior descending coronary artery (LAD) or circumflex branch was prepared free, and a ligature was placed around the artery. This ligature served as a guide to clamp the artery with a 3 mm broad clamp.

A very brief occlusion was performed to localize the ischemic area, visible as a cyanotic zone, and a multipolar electrode was then sutured on the epicardial surface so as to have as many terminals as possible overlying the ischemic area. The electrode consisted of 60 polyethylene tubes filled with saline and containing cotton wicks. The electrodes were arranged in five rows of 12, and interelectrode distance was 4 mm. In some experiments an electrode was used in which six rows of 10 terminals were arranged at intervals of 3 mm. The electrode tips were glued to a rubber sheet perforated by small holes (diameter 0.5 mm), with the wicks protruding slightly through the holes in the sheet. The sheet could easily be sutured onto the epicardial surface. Simultaneous recordings from 60 direct-current electrodes were made with respect to another cotton wick, attached to the tissue rostral to the split sternum, with a computer system (for a detailed description see refs 9 and 10). Briefly, after an initial 20-fold amplification in a high-impedance, low-pass (cut-off frequency 40 Hz), 60-channel amplifier, the signals were led into a high-speed multiplexing analog-to-digital converter (maximal sampling frequency 130 kilocycles/sec; Micro-consultants VHF MOD 15). Samples were taken every 4 msec and written into a circular buffer. Signals of a 2 sec or a 1 sec period were transferred to a high-speed digital tape recorder (Kennedy 7300). Analysis of the data was performed with the same PDP-11-34 computer, by means of an interactive program in which the stored signals were displayed on a Megatek graphic display. The simultaneous recording of 60 direct-current electrograms allowed the construction of activation maps by measuring local activation times and of determining isopotential maps at any desired moment of the cardiac cycle, which in these experiments was the TQ segment of beats propagated from the atrium.

Electrograms were also printed continuously on an Elema Inkwriter to document the occurrence of arrhythmias.

**Experimental protocol.** In five experiments, repeated coronary arterial occlusions of 5 min duration were performed, separated by 15 to 20 min reperfusion intervals, to determine whether the electrophysiologic changes were reproducible. In one additional experiment, ventricular fibrillation was induced by application of direct current at the end of the third and fifth occlusions to determine whether fibrillation and defibrillation would affect the electrophysiologic changes during subsequent occlusions.

In 32 experiments, interventions with the stellate ganglia were performed during or before occlusion of either the LAD (19 dogs) or circumflex branch (13 dogs). In each experiment, two 5 min occlusions were performed without any intervention to the sympathetic nervous system, the second of which was used as a "control occlusion" (see Results).

Fourteen experiments (seven with occlusion of the LAD, seven with occlusion of the circumflex branch) were performed to evaluate the effects of stimulation of the decentralized left stellate ganglion (third occlusion) and ablation of the ganglion (fourth occlusion). In addition, in five experiments, only the effects of left stellate ganglion ablation were measured (four LAD, one circumflex); in four experiments, only the effects of left stellate ganglion stimulation were studied (two LAD, two circumflex). To evaluate whether the effects of left ganglion stimulation might have been caused by the increase in blood pressure, the abdominal aorta was partially clamped during eight coronary occlusions (four LAD, four circumflex) to obtain a similar increase in average blood pressure in the carotid artery (40 mm Hg) as during left stellate stimulation. In four animals, when four or five occlusions had been made, systolic blood pressure fell below 90 mm Hg, and measurements made at such low pressures were discarded. Sometimes, because of ventricular fibrillation, no recordings could be made after 4 or 5 min, since reperfusion and defibrillation had to be carried out immediately. Because electrical signals during the reperfusion period quickly returned to normal and because in one experiment with repeated occlusions fibrillation and defibrillation did not affect electrophysiologic changes in subsequent occlusions, these animals were not excluded from the study and measurements made in subsequent occlusions were used.

Finally, the effects of ablation of the right stellate ganglion were measured in nine occlusions (seven LAD, two circumflex).

**Data analysis**

_TQ segment potentials._ Zero potentials during the TQ segment were obtained from preocclusion recordings. During occlusions, measurements of TQ potentials in successive cycles were identical, and therefore TQ isopotential maps were constructed from measurements of one cycle only. In some instances, baseline shifts, or 50-cycle interference, did not allow accurate determination of TQ potentials, and these measurements had to be discarded. This never involved more than five of 60 extracellular recordings, and it occurred in seven experiments. Values for TQ potentials at each electrode during preocclusion and postocclusion recordings were printed out by the computer, and isopotential maps were made by hand. To quantify the effects of stellate ganglion ablation or stimulation on TQ potentials, the following procedure was used: only sites that recorded activity from ischemic myocardium were considered. These sites were chosen from the occlusion in which the largest number of recording sites showed negative values for the TQ potential. This was done because, for example, left stellate stimulation increased the area showing TQ depression, whereas left stellectomy decreased this zone. Thus the area showing ischemic changes such as TQ segment depression could not always be determined during the control occlusion. A ΔTQ value was obtained by subtracting the mean TQ level in the control occlusion from the mean TQ level during an intervention. In this way, a negative ΔTQ value signifies a greater TQ depression during the intervention compared with the TQ depression during the control occlusion; a positive value signifies less TQ depression. More TQ depression could mean an increase in the area showing ischemic changes or a greater degree...
of ischemic changes. The degree of ST segment elevation could not be easily quantified because the actual potential value depended greatly on the moment in the cardiac cycle when it was measured. Depending on slight changes in activation, ST potentials could, at a fixed moment of the cardiac cycle, be positive or negative, without reflecting changes in local intracellular action potential configuration.

**Activation times.** The signals were displayed in groups of five on the screen of a Megatek graphic display, and times of maximum negative dV/dt were indicated on the undifferentiated signal on the screen by the investigator using a joystick. Sites that failed to be activated during ischemia displayed monophasic potentials. Activation was manifest as an easily identifiable, sharp, large negative intrinsic deflection. Activation times were printed out by the computer, and isochronic activation maps were made by hand. In 28 experiments, two stimulation electrodes were placed in the nonischemic left ventricle, about 1 cm from the lateral edge of the recording electrode. Simultaneous pacing from these sites produced a broad waveform that propagated more or less parallel to the long axis of the multipolar recording electrode. This allowed a more reliable interpretation of the changes in conduction than during propagation of impulses originating in the atria. However, because epicardial activation patterns sometimes indicated that, even with epicardial stimulation, epicardial sites were excited via unknown intramural pathways, no accurate determination of conduction velocity was possible. We therefore measured in each occlusion the “activation delay,” which was the difference between the earliest and latest activated site (msec).

The paired Student t test was used to determine statistical significance in ΔTQ and in the differences in conduction delay.

**Results**

**Reproducibility of changes in TQ segment potential with repeated occlusions.** In three experiments, seven repeated occlusions of the left anterior descending artery were performed in the absence of any other intervention, and in two experiments five successive occlusions were made. Each occlusion lasted for 5 min, and a reperfusion period of 15 to 20 min was allowed before the next occlusion.

The extracellular potentials after a 5 min occlusion quickly returned to control values upon reperfusion, and after a 15 to 20 min reperfusion period, TQ potentials did not differ more than 1 mV from recordings made before the first occlusion.

In figure 1, direct-current electrograms from six epicardial sites are displayed during preocclusion recordings, and 5 min after occlusion in a series of five successive occlusions separated by a 20 min reperfusion period. The configuration of the complexes is not the same for the first and second occlusion, the ischemic changes tending to be more marked in the first occlusion. However, in agreement with earlier findings in isolated hearts, the extracellular potentials during the second occlusion were very similar to those in subsequent occlusions. There was some variability in ΔTQ, but no significant differences in TQ depression in the second and subsequent occlusions were found (table 1). In particular, there was no specific trend in which, for example, TQ depression became less (or greater) in later occlusions. We always used the second occlusion as the “control occlusion,” and all interventions concerning the sympathetic nervous system were performed only after two occlusions had been made.

In one additional experiment, six repeated occlusions were performed, but at the end of the third and fifth occlusion, ventricular fibrillation was induced by application of direct current. Reperfusion and defibrillation were carried out within seconds. No significant differences in TQ segment potentials and activation delays were found between second and all subsequent occlusions (after 2 min, average TQ potential in the second occlusion was $-6.5 \pm 0.3$ mV, in the third $-6.3 \pm 0.25$ mV, in the fourth $-6.4 \pm 0.3$ mV, in the fifth $-6.7 \pm 0.3$ mV, and in the sixth $-6.2 \pm 0.3$ mV). Maximal conduction delays were 115, 109, 97, 120, and 114 msec in occlusions two to six, respectively.

In all experiments, before occlusions were performed recordings were made during a 2 min period of stimulation of the left stellate ganglion. No measurable effects on TQ potentials and activation patterns were observed. The only alterations in the local direct-current electrograms were those in the T wave. Usually, T waves became larger when positive or changed from negative to positive. In only one instance did the T wave become more negative, and in one heart no changes in T wave configuration were observed.

**Effects of interventions on TQ potentials**

**Left stellate ganglion stimulation.** In figure 2, TQ segment maps and selected electrograms are shown during the control occlusion and during an occlusion in which the left stellate ganglion was continuously stimulated. The degree of TQ depression is greater during left stellate ganglion stimulation, and the area showing TQ depression is also larger. In the control occlusion the 0 mV isopotential zone marks the lateral electrophysiologic border; during left stellate ganglion stimulation, TQ potentials in that region are in the order of $-8$ mV. Surprisingly, the other signs of ischemia are less marked during stellate stimulation. Sites that, during the control occlusion, show monophasic or nearly monophasic potentials, indicating absence of propagating responses, display a clear intrinsic deflection during stellate ganglion stimulation, indicating the presence of transmembrane action potentials with fairly large amplitudes.

In 16 of 18 experiments, left stellate ganglion stimulation caused a significant increase in TQ depression;
with maintained stellate stimulation, this effect was less marked after 4 to 5 min of occlusion (see table 1 and figure 4).

Left stellectomy. In the majority of cases (14 of 19), left stellectomy resulted in a reduction of the degree of depression of the TQ segment. Figure 3 shows selected direct-current electrograms 2 min after the control occlusion and 2 min after a subsequent occlusion when the left stellate ganglion had been removed. Also shown are isopotential maps during the TQ segment in both instances. The extracellular complexes show much more marked ischemic changes during the control occlusion than during the occlusion after left stellectomy. For example, the complex recorded from site E is monophasic, indicating absence of local regenerative activity. After left stellectomy, the fairly large intrinsic deflection recorded at site E demonstrates that local excitation still occurs. In the signals from sites A through D, the intrinsic deflection is faster, larger, and earlier after left stellectomy than during the control occlusion, and the degree of TQ segment depression is clearly less marked. This is more completely shown in the isopotential maps from the TQ segment; during the control occlusion, a large part of the myocardium cov-

TABLE 1
Changes in average values for TQ depression and conduction delay after occlusion with and without manipulations with the stellate ganglion

<table>
<thead>
<tr>
<th></th>
<th>Δ TQ (mV)</th>
<th>Δ Conduction delay (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 min after occl</td>
<td>5 min after occl</td>
</tr>
<tr>
<td>Repeated occlusions</td>
<td>+0.6 (±0.2) NS (n = 5)</td>
<td>+0.2 (±0.1) NS (n = 5)</td>
</tr>
<tr>
<td>Left stellate ganglion stimulation</td>
<td>−1.7 (±0.6)* (n = 18)</td>
<td>−0.6 (±0.5) NS (n = 15)</td>
</tr>
<tr>
<td>Left stellectomy</td>
<td>+1.3 (±0.4)* (n = 19)</td>
<td>+0.3 (±0.4) NS (n = 15)</td>
</tr>
<tr>
<td>Right stellectomy</td>
<td>−1.0 (±0.6) NS (n = 9)</td>
<td>−1.1 (±0.6) NS (n = 9)</td>
</tr>
<tr>
<td>Partial aortic clamp</td>
<td>+1.6 (±0.4)* (n = 8)</td>
<td>+2.7 (±0.4)* (n = 7)</td>
</tr>
</tbody>
</table>

A minus sign indicates more TQ depression and less conduction delay compared with a control occlusion; a positive sign indicates less TQ depression.

*p < .05.
erected by the electrode has a TQ potential of −8 to −16 mV, whereas this same area has a TQ potential of −4 to −8 mV after the occlusion performed after left stellectomy.

The changes produced by left stellectomy were not always so clear; in some instances changes in the opposite direction were found. When all experiments were considered together, the reduction in TQ potential after 2 min was statistically significant; after 5 min, the differences were no longer statistically significant (see table 1 and figure 4).

**Right stellectomy.** The changes induced by right stellectomy were opposite to those caused by left stellectomy: the extracellular complexes recorded from the ischemic myocardium after right stellectomy usually showed ischemic changes to a far more advanced degree than during the control occlusion. The degree, and even the direction, of changes induced by right stellectomy, however, were variable (see figure 4). Both after 2 and 5 min of occlusion, an increase in the degree of TQ depression compared with the control occlusion was found in six of seven experiments in which the LAD was occluded. A decrease was found in one occlusion of the LAD and in two circumflex occlusions.

**Increase in aortic pressure.** Left sympathetic stimulation increased the average aortic pressure by about 40 mm Hg. The consequent increase in oxygen consumption might have accelerated the development of ischemic changes, whereas the increased perfusion pressure could have had opposite effects. To evaluate the effect of an increase in aortic pressure alone, we performed eight experiments in which the abdominal aorta was partially clamped in the presence of intact sympathetic nerves to achieve an average increase in pressure in the carotid artery of 40 mm Hg.

Compared with the control occlusion, the degree of ischemic changes was less marked when aortic pressure was thus increased and much less marked than during left stellate ganglion stimulation when similar increases in aortic pressure were produced (see table 1 and figure 4), suggesting that the increased perfusion pressure, in addition to a possible reflexly induced reduction in sympathetic activity, overcame the effects of increased oxygen consumption. In figure 4, the results of all experiments are summarized, as far as the effects on TQ potentials are concerned. From this figure, it cannot be determined whether, for example, an increase in TQ depression (negative ΔTQ) signifies a greater degree of TQ depression within the same area or an increase in the area showing TQ depression, and therefore shifts in the border zone will be discussed separately.

**Shifts in the electrophysiologic border zone.** The electrophysiologic border zone, defined as the area in which TQ potentials began to become negative, could
be markedly shifted by stellate ganglion ablation or stimulation (see figures 2 and 3). In some experiments, the ischemic area was larger than the electrode, and most of the electrophysiologic border was outside the area covered by the electrodes. Therefore no quantitative assessment of the degree of shift in border zone can be given for all experiments. Of the 18 experiments in which left stellate ganglion stimulation was performed, a shift in border zone could be demonstrated in 10; in all cases the area showing ischemic changes became larger. In 13 of 19 experiments in which left stellactectomy was performed, the electrophysiologic border was within the area covered by the electrode in the control occlusion. In eight experiments, the area showing negative TQ potentials became smaller after left stellactectomy, and in five experiments no clear changes were seen. In seven experiments in which a shift of the border could be assessed after right stellactectomy, the ischemic area became larger in four, while in three experiments no clear changes occurred. Partially occluding the abdominal aorta reduced the area showing TQ depression in five experiments; in three no distinct shift in the electrophysiologic border occurred.

**Changes in conduction.** The results on the differences in conduction delay are summarized in table 1. Because conduction within the ischemic zone was only minimally affected despite marked changes in TQ potentials after 2 min of occlusion, only findings after the fourth or fifth minute were analyzed. In repeated occlusions, no differences in conduction delay were found. In experiments in which either the right or the left stellate ganglion was removed, only minimal and nonsignificant changes were found. The improvement in conduction during left stellate ganglion stimulation is shown in figure 5. In this heart, the circumflex branch was occluded and the multipolar electrode was placed on the posterolateral aspect of the left ventricle. The ventricles were paced simultaneously from two electrodes, about 1 cm from the lateral edge of the recording electrode, so that in the preocclusion situation, activity propagated as a broad wavefront parallel to the long axis of the electrode. Isochrones separate areas activated within the same 10 msec interval, time zero being the moment of stimulation. No major differences between the activation patterns can be seen during the control occlusion, and in the occlusions during which the left stellate ganglion was either decentralized (third occlusion) or completely removed (fifth occlusion). In all three situations the wavefront invading the ischemic myocardium from the right meets an area of conduction block, and activity slowly bypasses...
FIGURE 4. Effects on TQ segment potentials of repeated occlusions in the absence of manipulations to the stellate ganglion (first column), of left stellate ganglion stimulation (second column), of left stellectomy (third column), of right stellectomy (fourth column), and of partially clamping the abdominal aorta (fifth column) 2 min (A) and 5 min (B) after coronary occlusion. The data are represented as differences between the values obtained during the second (control) occlusion and subsequent occlusions. The means of the differences at each site are plotted on the ordinate. A change in the positive direction signifies less TQ depression than during the control (second) occlusion; a shift in the negative direction indicates more TQ depression. CIRC = circumflex branch.

FIGURE 5. Effects of left stellate ganglion stimulation on conduction in ischemic myocardium. Isochrones separate areas activated within the same 10 msec interval; areas of conduction block are shaded. Activation patterns are shown 5 min after each of the following: control occlusion; the third occlusion, prior to which the left stellate ganglion was decentralized; the fourth occlusion, during which the left stellate ganglion was stimulated; and the fifth occlusion, after removal of the left stellate ganglion. Note improvement of conduction during stellate ganglion stimulation.
this area to make an unsuccessful attempt to reexcite the inexcitable zone retrogradely. In contrast, during left stellate stimulation, no conduction block occurs and conduction proceeds regularly and relatively fast at an apparent velocity of about 1 m/sec. (Since the intramural activation patterns are unknown, this figure must be interpreted with caution. Activation could spread partly from endocardium to epicardium and activate parts of the epicardium more or less simultaneously. This figure therefore almost certainly does not represent true conduction velocity.)

In 11 experiments (six occlusions of the LAD and five of the circumflex) a marked reduction of the conduction delay occurred, whereas in the five other experiments only minor changes were observed. When all experiments were considered together, this improvement of conduction was significant (see table 1). In the experiments in which the aorta was partially occluded, marked improvements in conduction occurred in five of seven experiments. However, standard deviations were too large to reach significance (see table 1).

**Arrhythmias.** The occurrence of ventricular arrhythmias during the different experiments is depicted in figure 6. An arbitrary classification was made into categories of increasing severity: (1) no arrhythmias, (2) ventricular premature beats whether single or in couplets, (3) ventricular tachycardia (three or more successive impulses), and (4) ventricular fibrillation. For each occlusion, the highest category was scored. In figure 6, for each set of experiments the maximal score during the second (control) occlusion is compared with the maximal score in subsequent occlusions. Because two occlusions were performed in some experiments during, for example left stellate stimulation, and since we could not “average” arrhythmias, we displayed the arrhythmias as they occurred per occlusion rather than in one experiment. It can be seen that in the experiments in which repeated occlusions were performed without interventions on the stellate ganglia, there is a tendency for arrhythmias to decrease in severity in later occlusions. In contrast, left stellate ganglion stimulation and right stelllectomy are either without effect or increase the severity of arrhythmias. In three instances the score was lower when left stellate stimulation was performed than in the control occlusion. In most occlusions performed after left stelllectomy the arrhythmias had the same severity as during the control occlusion of the experiment; however, both an increase and a decrease in severity was observed. Partially occluding the aorta reduced the severity of the arrhythmias in general.

**Discussion**

**TQ potentials.** These results show that the cardiac sympathetic nerves affect the electrophysiologic changes produced by coronary arterial occlusion in the same animal. Overall, stimulation of the left stellate ganglion increased the degree of TQ depression, whereas left stellate ganglion ablation and partially occluding the aorta (with possibly a baroreflex-induced reduced sympathetic activity) decreased the degree of TQ depression. These changes were statistically significant in the early phase of ischemia, i.e., 2 min

![Figure 6](https://via.placeholder.com/150)

**FIGURE 6.** Effects of manipulations with the stellate ganglia on the occurrence of arrhythmias during a 5 min coronary occlusion. VPB = ventricular premature beats (single or couplets); VT = ventricular tachycardia (three or more consecutive VPBs); VF = ventricular fibrillation; LSS = left stellate ganglion stimulation; L- and R-ect = left or right stelllectomy.
after coronary occlusion, but after 4 to 5 min statistical significance was lost. We have no explanation for this finding.

Depression of the TQ segment in local direct-current extracellular electrograms is caused by the decrease in resting potential and by the resulting local current circuit set up between the ischemic and the normally perfused cells. An increase in TQ depression can therefore be interpreted as an increase in the degree of depolarization of ischemic cells. However, geometrical factors also play a role; in many experiments in which a sufficient number of electrodes were on both sides of the electrophysiologic border during control occlusions (i.e., the 0 mV isopotential line during the TQ segment), shifts in the position of this border could be demonstrated after manipulations with the sympathetic nerves. In general, the size of the ischemic area was increased by left stellate stimulation and reduced by left stellactomy. An increase in TQ depression could thus be interpreted either as an increase in the depolarization of ischemic cells or as an increase in the area in which a decrease in resting membrane potential occurs. Furthermore, a change in the geometry of the ischemic zone could alter TQ potentials. Because no intramural recordings were made, no information about the three-dimensional characteristics of the ischemic zone can be given. Finally, since the coupling resistance between ischemic and normal cells also determines the magnitude of TQ segment changes, possible effects of sympathetic nervous activity on cell coupling must be considered. If in the early phase of ischemia coupling resistance increases and sympathetic stimulation reverses the uncoupling, TQ depression would increase, even when resting membrane potentials remained the same. However, it is unlikely that sympathetic stimulation would decrease coupling resistance. Since catecholamines stimulate glycolysis, one could expect a further decrease in intracellular pH, which is known to cause uncoupling.11

**Variability and the effects of collateral flow.** A certain degree of variability was found in this study. Thus, although in most animals distinct effects were observed on TQ depression and conduction when the left or right stellate ganglion was removed, in some animals no effect was found or changes in the opposite direction occurred. This variability may have depended on several factors such as the anatomic distribution of the coronary arteries and the extent of their functional collaterals, the metabolic effects of changes in sympathetic activity, and the effects on blood pressure.

Sympathetic activation can cause coronary vasoconstriction, which may overcome metabolically induced vasodilatation.12 Therefore, sympathetic stimulation may enlarge the area showing ischemic changes by constricting collateral vessels. In some dogs with abundant collateral connections, such effects may be large; in others, with few collaterals, shifts in the electrophysiologic border would be insignificant.13 Indeed, it has been found that stellate stimulation during coronary occlusion could result in opposite electrophysiologic responses; in dogs in which regional myocardial blood flow increased, the amplitude of bipolar electrograms increased and their duration shortened. In animals in which regional flow decreased, the electrograms were prolonged and the amplitude became smaller.14 The size of the ischemic zone per se may also be of influence. With a large ischemic area and with little or no collateral circulation, the ischemic changes may be so severe that a reduction of sympathetic tone will have little effect, nor will an increase in sympathetic activity do much to increase the already maximal electrophysiologic changes. With a small ischemic zone, the electrophysiologic alterations may be so discrete that a reduction in sympathetic tone will be without effect, whereas an increase in tone may induce a noticeable increase in the degree of ischemic changes.

An increased sympathetic activity could increase the degree of ischemic changes because of the increased oxygen consumption and the faster depletion of energy stores. The increased afterload, which also will increase oxygen consumption, does not in itself appear to be of great influence. When afterload was increased by clamping the aorta and sympathetic activity was presumably reduced via the baroreflexes, the changes in TQ potentials were opposite to those during left stellate stimulation, the effects being significant at both 2 and 5 min after coronary occlusion. Possibly, the increased perfusion pressure in the coronary arteries and the partial removal of vasoconstrictor tone overcame the extra workload imposed on the heart. The net effect of increased sympathetic activity on collateral flow, and thus on size of the ischemic area, will depend on the relative contribution of increased blood pressure on one hand and of coronary vasoconstriction on the other.

**Right stellactomy vs left stellate ganglion stimulation.** The changes induced by right stellactomy were in most experiments qualitatively similar to those produced by left stellate stimulation. Although at first glance it may seem difficult to conceive how a reduction in sympathetic activity on one side may induce the same kind of changes produced by augmented activity on the other side, this phenomenon has recently been described in a
variety of experimental conditions. There is evidence that stellatectomy interrupts afferent fibers that inhibit part of the sympatheoexcitatory pathways located in the vicinity of the intermediolateral spinal nucleus; this results in increased sympathetic activity through the contralateral stellate ganglion.

**Activation.** In 11 of 16 experiments, left stellate stimulation markedly improved conduction within the ischemic zone at 4 or 5 min of occlusion; in four experiments there were no effects, and in one a slight increase in conduction delay occurred. An improvement in conduction in ischemic myocardium has also been reported during bilateral stellate ganglion stimulation. It could be argued that the increase in blood pressure caused by sympathetic stimulation is responsible for the improvement in conduction by increasing perfusion of the ischemic zone. In that case, one would expect TQ depression to diminish. However, in the experiments in which conduction improved, TQ depression was increased. This seems paradoxical, since an increased TQ depression indicates a more advanced degree of depolarization of resting potential of ischemic cells. Action potential amplitude and upstroke velocity both decrease at lower resting membrane potential. Conduction velocity is partly determined by upstroke velocity, and in general the lower the rate of rise of action potential upstroke, the lower the conduction velocity. However, conduction velocity is also determined by the difference between resting potential and threshold potential, and action potentials elicited at a reduced membrane potential can indeed be conducted faster when threshold potential does not change. Also, the coupling resistance between cells determines conduction velocity, since conduction depends on local current circuits bringing adjacent cells to threshold. As argued before, it is unlikely that increased sympathetic activity would decrease coupling resistance. It is unknown whether catecholamines have an effect on threshold potential in ischemic cells.

In the very early phase of ischemia, the upstroke of the transmembrane action potential of myocardial cells is often separated into two components, the first of which is most likely caused by the depressed fast Na⁺ inward current, the second to the slow inward current, carried mainly by Ca²⁺ ions. A similar separation of the upstroke is seen when isolated muscle preparations are exposed to elevated extracellular K⁺ concentrations. The latter authors found that β-adrenergic stimulation has an inhibitory effect on the first component but increases the second component. The negative effect on conduction velocity caused by the decrease of the first component might be overcome by the simultaneous stimulation of the Ca²⁺ inward current. However, detailed information on the relative contribution of both components of the action potential upstroke on conduction velocity is lacking. It should be emphasized that in this study, only the first 5 min of ischemia were considered. The effect of sympathetic stimulation on conduction in later phases might be quite different.

**Arrhythmias.** In agreement with the results of previous studies, left stellate ganglion stimulation and right stellatectomy increased the incidence of ventricular arrhythmias during the short-term occlusion in our study. Left stellatectomy, however, did not result in a significant reduction of arrhythmias in this study, in contrast to other reports. The reasons for this are not clear, but several factors can be considered.

First, it is known that the antiarrhythmic effect of short-term surgical denervation is much less marked than that produced by chronic denervation. Second, the limiting effects of anesthesia on autonomic responses must be taken into account. Indeed, the greatest antiarrhythmic efficacy of left stellatectomy has been observed in long-term studies with conscious dogs.

Other parameters, apart from an increased or decreased left sympathetic tone, may determine whether arrhythmias will become manifest. One of these is the size of the ischemic area, which in our experiments was not determined accurately. Because the site of the occlusion was not the same in all dogs in our experiments, the size of the ischemic zone may have varied considerably from dog to dog. If the ischemic zone is very large, arrhythmias will occur regardless of a decreased sympathetic tone; if the zone is very small and arrhythmias do not occur in control occlusion, a reduction in sympathetic tone will also be without apparent effect. Moreover, since the effect of left stellatectomy depends on the level of sympathetic tone before the stellatectomy and since this could have varied from dog to dog, the number of experiments in this study may have been too small to uncover a protective effect of left sympathectomy.

Because reentry plays an important role in the genesis of ventricular arrhythmias in acute ischemia and because an increase in left sympathetic activity increases the likelihood for these arrhythmias to occur, it seems reasonable to expect that left stellate stimulation would induce electrophysiologic changes that would facilitate reentry. Slow conduction and the occurrence of areas of (unidirectional) block are factors that increase the likelihood of reentry, yet left stellate stimu-
ulation had effects in the opposite direction. Areas of
conduction block were converted into zones of con-
duction, and conduction was more regular and faster
than in control occlusion or in occlusions made after
left stellectomy. Because we recorded electrogro-
grams only from the ischemic subepicardium, reentry in
intramural or subendocardial sites cannot, of course, be
ruled out. Previous studies indicated that although
reentry is the predominant mechanism in the later
phase of ventricular tachycardia and fibrillation, the
initial ectopic premature impulses that initiate reen-
trant mechanisms are caused by a “focal” mechanism
localized on the nonsischemic side of the ischemic bor-
der. Although the exact nature of this “focal” mech-
anism remains to be determined, one may speculate
that it could be some form of abnormal automaticity or
triggered activity, in which one of the triggers could be
the current of injury. Since it is well known that
both abnormal automaticity and delayed afterdepolariz-
ations are enhanced by catecholamines, it may be
that left sympathetic stimulation exerts its arrhythmo-
getic influence, not so much by promoting reentry but
rather by enhancing the likelihood of the “focal”
mechanism to become manifest.

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