Protection Against Autonomic Denervation Following Acute Myocardial Infarction by Preconditioning Ischemia

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To examine the effects of ischemic preconditioning on efferent autonomic responses following acute transmural myocardial ischemia/infarction (MI), the time course and extent of efferent sympathetic and vagal denervation were compared between control dogs that received a one-stage sustained coronary occlusion and preconditioned dogs that received four 5-minute coronary occlusions separated by 5 minutes of reperfusion before sustained occlusion. Effective refractory periods (ERP) basal and apical to MI were determined in the baseline state and during neural stimulation before and after preconditioning occlusions and 20, 60, 120, and 180 minutes after sustained occlusion by ligature ligation of diagonal branches of the left anterior descending coronary artery. In 10 control dogs with transmural MI, ERP shortening induced by bilateral ansae subclaviae stimulation (4-msec pulses, 2–4 Hz and 2–4 mA) was unchanged at basal sites but was attenuated at apical sites. Four of 40 apical test sites exhibited efferent sympathetic denervation (<2 msec shortening) 20 minutes after sustained occlusion. Thirteen of 40 apical sites became denervated during a 3-hour period. In 10 preconditioned dogs, ERP shortening at apical sites was unchanged after preconditioning occlusions and during the first 60 minutes of sustained ischemia but was attenuated at 120 minutes. Three of 40 apical test sites became denervated during a 3-hour period. The cumulative percentage of denervated apical test sites was significantly less in the preconditioned group compared with the control group (p=0.006) despite a comparable degree of subepicardial involvement in the MI (8.2±1.0% vs. 8.4±1.4%, the ratio to the left ventricular circumference, mean±SEM). In 11 control dogs tested for efferent vagal response after MI, ERP prolongation induced by bilateral vagal stimulation (4-msec pulses, 20 Hz with current strength 0.05 mA greater than that required to produce asystole) was unchanged at basal sites, but was attenuated at apical sites, and five of 44 test sites exhibited denervation (>1 msec prolongation) 20 minutes after sustained coronary occlusion. Fourteen of 40 apical sites became denervated during a 3-hour period. In 10 preconditioned dogs, vagally induced ERP prolongation was unchanged both at basal and apical sites, and none of 36 apical test sites exhibited denervation after preconditioning and during a 3-hour period of sustained coronary occlusion (p<0.001 vs. control group) despite a comparable degree of subendocardial involvement in the MI (11.8±0.8% vs. 11.9±1.3%). In preconditioned hearts, the blood flow reduction to the ischemic myocardium measured by radioactive microspheres during sustained coronary occlusion was comparable with that during the first preconditioning occlusion, indicating that an increase in collateral blood flow during MI cannot explain the protective effects of preconditioning. We conclude that preconditioning with brief episodes of ischemia preserves efferent sympathetic and vagal responses during the early period after coronary artery occlusion in the dog by mechanisms still to be determined. (Circulation Research 1989;64:437–448)
autonomic nerves traveling through the ischemic/infarcted myocardium. Heterogeneous loss of autonomic innervation can occur within several minutes after coronary occlusion and is reversible after short-term occlusions.1,4

Murry et al3 have shown that four 5-minute episodes of coronary occlusion and reperfusion dramatically limit infarct size of myocardium that is later subjected to 40 minutes of sustained ischemia. Although the mechanism of this protective effect of preconditioning is unknown, it is not due to an increase in collateral blood flow5 and may be related to reduced depletion of high-energy phosphates and/or to reduced catabolite accumulation.6 One suggested mechanism7 is that repeated episodes of ischemia cause a regional depletion of catecholamines so that the final ischemia takes place in "sympathectomized" myocardium that can withstand the effects of ischemia better than ischemic myocardium that has a normal catecholamine content.8 Therefore, the purpose of this study was to examine the effects of ischemia on efferent sympathetically and vagally induced changes in refractoriness of myocardium basal and apical to the site of ischemia/infarction during a 3-hour coronary occlusion in dogs with and without ischemic preconditioning.

Materials and Methods

Surgical Procedures

Sixty mongrel dogs of either sex weighing 16–28 kg were anesthetized with sodium secobarbital (30 mg/kg i.v.). Additional doses were injected as needed to maintain anesthesia. The dogs were intubated and ventilated with room air using a volume-cycled respirator (model 607, Harvard Apparatus, South Natick, Massachusetts). The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. A fluid-filled cannula placed in the right femoral artery was connected to a transducer (Statham p-23Db, Gould, Cleveland, Ohio) to monitor arterial blood pressure, and a femoral venous cannula was used to infuse normal saline at 100–200 ml/hr to replace spontaneous fluid losses. In 20 dogs used for measurement of myocardial blood flow, two additional fluid-filled cannulas were placed in left femoral and brachial arteries to withdraw blood, and a cannula was inserted into the left atrial appendage to inject microspheres. Dogs were placed on a heating pad, and the thoracotomy was covered by a plastic sheet. A thermistor (model 400, Yellow Springs Instrument, Yellow Springs, Ohio) was used to monitor epicardial temperature. An operating table lamp was used to maintain epicardial temperature at 36–38°C. Arterial blood gases and pH were monitored and maintained within the physiological range.

A diagonal branch or multiple diagonal branches of the left anterior descending coronary artery were isolated, and silk sutures were passed around the branches for later occlusion. When visible anastomoses between a diagonal branch and a marginal branch of the circumflex coronary artery were seen, a mar-

![Diagram of heart indicating sites of electrode placement](image-url)

**FIGURE 1.** Diagram of heart indicating sites of electrode placement (○). Two electrodes that served as a cathode for unipolar stimulation were placed basal to sites of ischemia/infarction (stippled area) produced by occlusion of diagonal branches and a distal marginal branch. Four additional electrodes were placed apically. AO, aorta; LA, left atrial appendage; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PA, pulmonary artery; RA, right atrial appendage; RV, right ventricle.
gated response. The S1-S2 interval was then increased by 5 msec and was shortened by 1 msec decrements until S2 failed to produce a propagated ventricular response. The ERP was defined as the longest S1-S2 interval at which S2 failed to produce a propagated response. The ERP was determined twice, and values were within 1 msec of each other or the data were discarded and the determination was repeated.

**Neural Stimulation**

*Bilateral ansae subclaviae stimulation.* Shielded bipolar electrodes were placed on the right and left anterior and posterior ansae subclaviae to stimulate the efferent cardiac sympathetic nerves with separate constant current isolators driven by a programmable stimulator (Kranert Medical Engineering). Stimuli were rectangular 4-msec pulses at a frequency of 2-4 Hz and a current of 2-4 mA. Determination of the ERP was started 2 minutes after the onset of stimulation.

*Bilateral vagal stimulation.* Two Teflon-coated wire electrodes were embedded in the cardiac end of each vagal nerve. Rectangular pulses of 4-msec duration were delivered at a frequency of 20 Hz by use of separate constant current isolators. The current strength was 0.05 mA greater than that required to produce asystole for the right vagus and asystole or complete atrioventricular block for the left vagus. Effects of vagal stimulation were determined during intravenous infusion of norepinephrine at constant rates of 0.125-0.25 μg/kg/min to achieve a constant background of sympathetic effect. The ERP during norepinephrine infusion served as control for the determination of efferent vagal effects on ventricular refractoriness. The conditions of neural stimulation were kept constant in each experiment.

**Determination of Extent of Myocardial Infarction**

After the experiment, the dog was killed by fibrillation of the ventricle, and the heart was removed and cut in; five slices from base to apex with the electrodes still in place. Each slice was stained with nitro blue tetrazolium (NBT). With this technique, the presence of myocardial infarction could be confirmed macroscopically. The subepicardial and subendocardial widths of the myocardial infarction and the diameter of the left ventricle were measured in each slice. The ratio of the greatest width of subepicardial infarction to the epicardial circumference of the left ventricle was used to represent the involvement of infarction in each dog tested for sympathetic innervation, and the greatest width of subendocardial infarction relative to the epicardial circumference was used in each dog tested for vagal innervation, as reported previously.

**Measurement of Myocardial Blood Flow**

In 20 dogs, regional myocardial blood flow was measured before and after coronary occlusion by the microsphere technique. Approximately 2 million 15-μm carbonized plastic microspheres labeled with 53Co, 58Nb, 103Ru, or 113Sn (Biotechnology Systems, DuPont de Nemours, Boston, Massachusetts), as 1.0 mCi of nuclide suspended in 10 ml of 10% dextran with 0.01% Tween 80 added as a surfactant, were injected through the cannula in the left atrial appendage, followed by a 10-ml saline flush. Beginning 15 seconds before the injection, reference blood samples were drawn from the left brachial and femoral arteries at a rate of 2.06 ml/min until each sample volume reached 10 ml. Myocardial tissue samples of two or three slices were taken from the central ischemic/infarcted regions and the normal zone (core area) of the posterior left ventricular wall and subdivided into subendocardial, midmyocardial, and subepicardial thirds. Thus, 12-18 pieces were obtained. Each piece was weighed; the average weight of the pieces was 0.770 g. Blood and tissue sample radioactivities were measured for 1 minute per sample on a Packard Model 5530 gamma counter (Packard Instruments, Downers Grove, Illinois). Net counts-per-minute data for each isotope were provided after corrections of raw count data for interisotope interference, background, and decay. Myocardial blood flow was calculated according to the formula tissue flow = counts × reference flow / reference counts × tissue weight, where reference counts was the mean of the values obtained from the left brachial and femoral artery samples.

Blood flow of ischemic/infarcted myocardium was expressed as a percentage of the mean core area flow. The values derived from the slice in which reduction of mean transmural flow was most prominent were used to represent the degree of ischemia for each dog.

**Protocol**

Dogs were randomized to preconditioned and control groups. Each group contained two subgroups in which sympathetic or vagal innervation was tested. Dogs in the preconditioned group received four 5-minute coronary occlusions induced by tightening snare around the branches and separated by 5 minutes of reperfusion. After preconditioning, a sustained coronary occlusion was produced by ligature ligation over a 3-hour period. The number of occluded branches during sustained occlusion was the same as that during preconditioning for each experiment. The control group received only a sustained 3-hour coronary occlusion produced by ligature ligation without preconditioning. Each subgroup tested for sympathetic innervation contained one dog in which sustained coronary occlusion was produced by injection of 0.3 ml latex solution using a PE-50 catheter to obtain essentially zero subepicardial flow.

The ERP was determined at six test sites before and at 20, 60, 120, and 180 minutes after sustained coronary occlusion in the baseline state and during neural stimulation. Sympathetically induced ERP shortening and vagally induced ERP prolongation served to indicate intact efferent autonomic innerva-
Analysis of Data

No data were used from electrode sites within the myocardial infarction. As reported previously, sites were considered to be sympathetically denervated if bilateral ansae subclaviae stimulation shortened the ERP ≥ 9 msec before coronary occlusion but ≤ 2 msec on at least one occasion after coronary occlusion. Sites were considered to be vagally denervated if bilateral vagal stimulation prolonged the ERP ≥ 12 msec before coronary occlusion but ≤ 2 msec on at least one occasion after coronary occlusion. Sites with < 9 msec shortening of the ERP during bilateral ansae subclaviae stimulation or < 3 msec prolongation of the ERP during bilateral vagal stimulation before coronary occlusion were excluded because of possibly insufficient effects of neural stimulation for accurate detection of denervation. For the comparison of efferent sympathetic responses in both groups, the data from dogs with nontransmural or no definite myocardial infarction were excluded because of possibly insufficient effects of ischemia on cardiac sympathetic nerves, which are known to distribute mainly in the subendocardial layer. In contrast, the data from dogs with definite subendocardial or nontransmural myocardial infarction were included for the comparison of efferent vagal responses in both groups, since cardiac vagal fibers are distributed mainly in the subendocardial layer. For the correlation of efferent autonomic responses with myocardial blood flow reduction in the ischemic myocardium, data from all 20 dogs studied were included.

Statistical Analysis

The data in this study are expressed as mean ± SEM. The difference among mean values was determined using an analysis of variance for repeated measurements. Paired and unpaired t test was performed when two measurements were com-
pared. Cumulative percentage of denervation was compared in both groups by use of the Mantel-Cox test. Linear regression analysis was performed to correlate efferent autonomic responses with reduction of myocardial blood flow. Statistical significance was set at \( p < 0.05 \).

Results

Efferent Sympathetic Response

Of 16 control dogs tested for efferent sympathetic response, four had nontransmural or intramural myocardial infarction and two others had no definite infarction at necropsy. Data from these six dogs were excluded from a comparison of efferent sympathetic responses. Of 16 preconditioned dogs tested for sympathetic response, four had nontransmural infarction and one had no definite infarction; one other dog became hypotensive (systolic blood pressure <80 mm Hg) immediately after sustained coronary occlusion. Data from these six dogs were excluded. Therefore, data from 10 control and 10 preconditioned dogs with transmural myocardial infarction were compared. The number of occluded branches (3.4±0.3 and 3.3±0.3, respectively) and the extent of subepicardial infarction (8.4±1.4% and 8.2±1.0%, respectively) were the same in both the control and preconditioned groups. Also, spontaneous heart rate (114±7 and 115±6 beats/min, respectively) and mean arterial blood pressure (116±6 and 122±8 mm Hg, respectively) immediately before sustained coronary occlusion were the same in both groups.

Baseline ERP values of test sites are shown in Table 1. Figure 3 shows the cumulative percentage of sympathetically denervated apical test sites. In control dogs, four of 40 apical test sites exhibited sympathetic denervation 20 minutes after sustained coronary occlusion and 13 of 40 apical sites became denervated over a 3-hour period; none of 20 basal sites became denervated (not shown). In preconditioned dogs, none of 40 apical sites became denervated after preconditioning or during the first hour after sustained coronary occlusion, although three of 40 apical sites became denervated at 2 hours. No basal sites became denervated (not shown). Cumulative percentage of denervated apical test sites in preconditioned dogs was significantly less than in control dogs (\( p = 0.006 \)). Figure 4 shows the shortening of ERP induced by bilateral ansae subclaviae stimulation at all basal and apical test sites. In control dogs, shortening of ERP at apical test sites became attenuated 20 minutes after sustained coronary occlusion and declined further thereafter. In preconditioned dogs, shortening of ERP at apical test sites was preserved after preconditioning and during the 1st hour after sustained coronary occlusion and became attenuated 120 minutes after sustained occlusion. At basal sites, shortening of ERP was not attenuated over a 3-hour period in either group.

Shortening of ERP induced by norepinephrine infusion did not differ between basal and apical test sites after the completion of preconditioning; that is, preconditioning did not cause a supersensitive
response of the apical myocardium to norepinephrine (Figure 5).

**Efferent Vagal Response**

Of 13 control dogs tested for efferent vagal response, two dogs had intramural or patchy myocardial infarction; data from these dogs were excluded. Data from two of 12 preconditioned dogs were also excluded because of patchy infarction. Therefore, data from 11 control and 10 preconditioned dogs with myocardial infarction were compared. The number of occluded branches (4.1±0.3 and 4.4±0.2, respectively) and extent of subendocardial infarction (11.9±1.3% and 11.8±0.8%, respectively) were the same in both the control and preconditioned groups. Spontaneous heart rate immediately before sustained coronary occlusion was 143±6 beats/min for control dogs and 164±7 beats/min for preconditioned dogs (p<0.05). Mean arterial blood pressure was the same in both groups (114±5 and 117±6 mm Hg, respectively). In control dogs, the current strength for vagal stimulation was 0.67±0.10 mA for the right vagus and 0.83±0.13 mA for the left vagus. In the preconditioned group, the current strength was 0.44±0.05 mA for the right vagus and 0.43±0.07 mA for the left vagus. Ventricular fibrillation was induced in one control dog during the determination of ERP 180 minutes after sustained coronary occlusion and in one preconditioned dog 120 and 180 minutes after sustained occlusion. Thus, the ERP data were not obtained at these determination points. In one control dog, one basal site was involved in myocardial infarction; therefore, data from this site were excluded.

Baseline ERP value of test sites are shown in Table 2. Figure 6 shows the cumulative percentage of vagally denervated apical test sites. In control dogs, five of 44 apical sites exhibited vagal denervation 20 minutes after sustained coronary occlusion. Fourteen of 40 apical sites became denervated over a 3-hour period. None of 21 basal test sites became denervated (not shown). In the preconditioned dogs, none of 36 apical test sites exhibited vagal denervation after preconditioning and during a 3-hour period after sustained coronary occlusion (p<0.001 vs. control) as did none of 18 basal sites (not shown).

Figure 7 shows the prolongation of ERP induced by bilateral vagal stimulation at all apical and basal test sites. In control dogs, prolongation of ERP was atten-
TABLE 2. Baseline Effective Refractory Periods During Norepinephrine Infusion in Dogs With Myocardial Infarction Tested for Vagal Innervation

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>After permanent coronary occlusion (minutes)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IP</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Control (N=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal sites</td>
<td>153±3</td>
<td>NA</td>
<td>157±4</td>
<td>156±3</td>
</tr>
<tr>
<td>Apical sites</td>
<td>157±3</td>
<td>NA</td>
<td>158±3</td>
<td>159±4</td>
</tr>
<tr>
<td>Preconditioned (N=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal sites</td>
<td>154±2</td>
<td>158±3</td>
<td>155±3</td>
<td>156±3</td>
</tr>
<tr>
<td>Apical sites</td>
<td>153±1</td>
<td>156±2</td>
<td>154±2</td>
<td>154±2</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM in milliseconds. IP, ischemic preconditioning.

Myocardial Blood Flow

Myocardial blood flow was measured in five dogs from each of the following four subgroups (n=20): 1) control dogs tested for sympathetic innervation, 2) preconditioned dogs tested for sympathetic innervation, 3) control dogs tested for vagal innervation, and 4) preconditioned dogs tested for vagal innervation. Myocardial blood flow in the core areas before coronary occlusion was 103.6±8.6 ml/min×100 g (n=20). To correlate effenter autonomic responses with the degree of ischemia, ERP change...
Figure 8. Correlation of shortening of effective refractory period (ERP) induced by bilateral ansae subclaviae stimulation at apical test sites with reduction of subepicardial blood flow. Extent of ERP shortening at 20 and 60 minutes after permanent coronary occlusion at each apical test site compared with mean value of two basal sites (intact innervation) is shown on ordinate as a percentage; degree of blood flow reduction in ischemic subepicardium measured 15 minutes after permanent occlusion is shown on abscissa as a percentage of core area flow. Each vertical column of data points indicating the same blood flow percentage represents data taken from the same dog. See text for details.

Figure 9 shows correlation of ERP prolongation induced by bilateral vagal stimulation in the apical...
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FIGURE 9. Correlation of prolongation of effective refractory period (ERP) induced by bilateral vagal stimulation at apical test sites with reduction of subendocardial blood flow. Extent of ERP prolongation at 20 and 60 minutes after permanent coronary occlusion at each apical test site compared with mean value of two basal sites (intact innervation) is shown on ordinate as a percentage; degree of blood flow reduction in ischemic subendocardium measured 15 minutes after permanent occlusion is shown on abscissa as a percentage of core area flow. Each vertical column of data points indicating the same blood flow percentage represents data taken from the same dog. See text for details.

The major observations from this study were that 1) preconditioning ischemia (four 5-minute periods
of coronary occlusion, each separated by 5 minutes of reperfusion) did not attenuate efferent vagal and sympathetic responses at the sites apical to the ischemic area; 2) preconditioning ischemia did not cause sympathetic supersensitivity to infused norepinephrine; 3) in preconditioned hearts, the efferent sympathetic response was preserved during the first hour of the subsequent sustained ischemia, while the efferent vagal response was preserved during at least 3 hours of the subsequent sustained ischemia; and 4) preconditioning ischemia did not increase collateral blood flow to the ischemic myocardium during a 3-hour occlusion, and, therefore, increased blood flow could not be the responsible mechanism.

Denervation of Efferent Autonomic Nerves After Acute Myocardial Infarction

In control dogs with acute myocardial infarction, efferent sympathetic and vagal responses became lost or attenuated at apical test sites within 20 minutes after sustained coronary occlusion, with additional sites losing responsiveness over time. This observation is concordant with our previous report.2 In this model4 is consistent with the lack of a cumulative effect produced by four 5-minute episodes of coronary occlusion and with the notion that early denervation is a functional phenomenon and is not due to structural or biochemical neural changes or to the depletion of substances such as tyrosine hydroxylase and choline acetyltransferase,13

Spontaneous Recovery of Function

In this study, as in our previous studies,3 some apical test sites that were designated initially as denervated by our arbitrary criteria subsequently showed responses to neural stimulation that exceeded the denervation cutoff value (Figures 3 and 6). This spontaneous return of response also suggested that early loss of autonomic responses might have been due to functional neural disturbances. The mechanism responsible for restoration of neural function did not seem to be due to alterations in blood flow. A possible related phenomenon has been observed electrophysiologically in cardiac tissues.
modifies the myocardium to resist the effects of subsequent ischemia on electrophysiological changes. For example, initial occlusion of a coronary artery produces more severe electrical disturbances than do subsequent occlusions. In less pronounced electrophysiological changes occur in superfused epicardium and endocardium during a second exposure to altered Tyrode's solution containing 8.0 mM KCl (pH 6.85, PO₂<50 mm Hg) than occur during the first superfusion. It is quite possible that the mechanism responsible for the increased survival in dogs subjected to the so-called two-stage Harris occlusion relates to the preconditioning effect of the first subtotal coronary occlusion.

Ischemic preconditioning limits infarct size after 40 minutes of circumflex artery occlusion but not after 3 hours of occlusion. Repeated short-term occlusions separated by reperfusion do not produce cumulative deficits in myocardial adenosine nucleotide content; cumulative disturbances of myocardial ultrastructure, tissue water, or electrolyte content; or contractile deficits. In the present model, we showed protective effects against denervation apical to an area of ischemia/infarction. The mechanism of this protective effect is unknown but can be attributed to the decreased accumulation of ischemic catabolites during the final ischemic episode and/or to the generation of some sort of protective agent that permits the myocyte to make ATP from phosphocreatine or anaerobic glycolysis, prevents it from becoming overloaded with calcium, or protects it in other ways. While multiple possibilities have been suggested and a few have been explored, the mechanism remains unknown.

**Catecholamine Depletion**

We investigated the possibility that repeated short-term occlusions regionally depleted catecholamines from sympathetic nerve terminals and served to protect the myocardium against the final ischemic event. Preservation of efferent sympathetically induced refractory period change after the four short-term preconditioning coronary occlusions and protection against the denervating effects of the long-term ischemia eliminate that possibility. Janes et al demonstrated preservation of the effects of stellate ganglion stimulation on contractility of the postischemic myocardium in dogs after 12 cycles of 5-minute occlusion of the left anterior descending coronary artery and reperfusion, which agrees with our data. The failure of β-blockade with propranolol to limit infarct size in 40-minute or 3-hour occlusions also supports our findings.

**Vagal and Sympathetic Responses**

Our data show that preconditioning ischemia preserved the efferent vagal response for a longer period of sustained ischemia than it preserved the efferent sympathctic response. This result is somewhat puzzling, considering the greater susceptibility of the subendocardial myocardium, where vagal fibers are mainly distributed, to blood flow reduction during ischemia compared with that of the subepicardial layer, where sympathetic fibers are mainly distributed. Less severe ischemia during the preconditioning occlusions might have prevented the subepicardium from being as well preconditioned as the subendocardium. Another explanation is that there may be differences in the accumulation of catabolites after acute myocardial infarction that affect neurotransmission in sympathetic versus vagal nerves, or there may be differences in the response of these two nerves. It is also possible that cavity blood helps protect the subendocardial vagal nerves.

**Myocardial Blood Flow**

Conclusions based on data shown in Figures 8 and 9 must be made cautiously because myocardial blood flow measured with radio-labeled microspheres in the dog may give false values because of interdigitation of occluded and normally perfused coronary vasculature. Perhaps this accounts for the preservation of sympathetic response at 20 minutes in one dog with myocardial blood flow reduction to 21% of the core area and the loss of vagal response at 60 minutes in one dog with myocardial blood flow reduction to only 59%. Nevertheless, a reasonable correlation with loss of afferent neural response when myocardial blood flow falls to 40% of the core area has been made before and is consistent with the data in Figure 8 for the control group. The correlation is less certain during vagal denervation (Figure 9). It does seem clear, however, that blood flow was reduced equivalently in control and preconditioned groups, with preservation of neural responses in the latter.

**Methodological Consideration**

In the dog, the size of the ischemic vascular bed (area at risk), collateral blood flow to the ischemic region, and, less importantly, myocardial oxygen demand are the major modulators of myocardial viability after ischemia. In the present study, the number of occluded branches and subepicardial and subendocardial involvement in the infarction after the 3-hour period of sustained ischemia measured by the extent of the infarcted area and reduction in myocardial blood flow were similar in control and preconditioned dogs. Heart rate and arterial blood pressure were also similar in both groups tested for sympathetic denervation, and heart rate was slightly higher in preconditioned dogs than in control dogs tested for vagal denervation. Therefore, differences in these variables in both groups cannot account for the preservation of neural responses in the preconditioned dogs.

**Implication**

The importance of the observations on protective effects of preconditioning on autonomic activity, made in an animal model without preexisting coro-
nary disease, is unknown. However, it is possible that a heterogeneous loss of efferent sympathetic response after coronary occlusion increases the electrical heterogeneity between innervated and denervated regions and enhances the genesis of ventricular tachyarrhythmias. Therefore, protection by preconditioning ischemia against the heterogeneous development of efferent sympathetic and vagal denervation during the early period of acute myocardial infarction may help suppress ventricular arrhythmias that occur early after acute coronary occlusion.

Acknowledgments

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