Interruption of sympathetic and vagal-mediated afferent responses by transmural myocardial infarction

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ABSTRACT We have demonstrated previously that sympathetic and vagal afferents travel in an apical-to-basal course in the heart, and can be stimulated selectively with epicardial applications of bradykinin and nicotine, respectively. In this study we tested the hypothesis that transmural myocardial infarction interrupts sympathetic and vagal afferent fibers traveling through the infarction and produces regions of afferent denervation in areas apical to the infarction. In open-chest, chloralose-anesthetized dogs, transmural myocardial infarction was created by embolizing a diagonal branch of the left anterior descending coronary artery with a vinyl latex solution that was injected directly into the artery and hardened rapidly. The transmural nature of the infarction was verified by the nitro blue tetrazolium staining technique for dehydrogenase enzymes. Epicardial applications of bradykinin (5 μg) and nicotine (50 μg) were used to stimulate chemically sensitive sympathetic and vagal afferent nerve endings, respectively. Twenty-nine dogs were studied before and 90 min after creation of transmural myocardial infarction. In 20 dogs, epicardial bradykinin applied before production of transmural myocardial infarction produced a maximal pressor response of 13 ± 3 mm Hg 40 sec after application (p < .01 vs preapplication values), while topical nicotine produced a maximal depressor response of 14 ± 2 mm Hg (p < .01 vs preapplication values) 20 sec after application at all sites tested. Ninety minutes after production of transmural myocardial infarction, epicardial sites basal to the infarction continued to respond normally to both drugs, while sites within the area of infarction and apical to the area (noninfarcted myocardium) no longer showed a pressor response to topical bradykinin or a depressor response to topical nicotine. Nerve interruptions in 12 dogs demonstrated that the sympathetic afferent responses elicited by bradykinin were eliminated with bilateral stellatomy, while vagal afferent responses elicited by nicotine were interrupted by transection of the cervical vagi. In 10 dogs, more extensive epicardial mapping of responses to the two drugs revealed that sites were not always afferently denervated in a homogeneous manner. Several sites medial and apical to the transmural myocardial infarction continued to show pressor responses to bradykinin, but were unresponsive to topical nicotine. We conclude that transmural myocardial infarction produces areas of both sympathetic and vagal afferent denervation in infarcted and in noninfarcted myocardium apical to the region of infarction. This afferent denervation is not homogeneous in all areas.


AFFERENT NERVE FIBERS have endings in the left ventricular wall. Some afferent fibers travel with sympathetic nerves and may be chemically sensitive, mechanosensitive, or both.1 These sympathetic afferent fibers mediate a pressor and a pseudoaffective response in animals that can be elicited by epicardial2-4 or intracoronary2-4, 5 administration of bradykinin and by other chemical agents. Sympathetic afferents also apparently mediate the sensation of cardiac pain in man.6,7 Other afferent fibers travel with the vagus nerves and can be activated by stretch, by epicardial2, 8, 9 or intracoronary2, 9 administration of nicotine, and by other chemical agents. These nerves are known to mediate depressor responses produced by ischemia or stretch of the left ventricular myocardium.1, 10, 11

We have demonstrated previously that epicardial application of phenol on the anterior and posterior free
wall of the left ventricle distant from the atrioventricular groove interrupts sympathetic, but not vagal afferent, nerves innervating the myocardium, suggesting that sympathetic afferent nerves travel in the subepicardium, but that vagal afferent nerves travel deeper, possibly in the subendocardium. We also have shown that acute and chronic transmural myocardial infarction interrupts sympathetic and vagal efferent transmission to viable, noninfarcted myocardium apical to the infarction, probably by damaging nerves traversing the infarction in a basal-to-apical direction. Little is known, however, of the effects of transmural myocardial infarction on transmission of afferent sympathetic and vagal fibers, the nerve endings of which can be activated by epicardial application of bradykinin and nicotine, respectively. The purpose of this study was to determine if localized transmural myocardial infarction disrupts afferently mediated sympathetic and vagal neural responses elicited apically to the infarction by interrupting afferent fibers traveling in an apical-to-basal direction through the area of infarction.

Methods
We produced transmural myocardial infarction by intracoronary injection of a vinyl latex solution that hardened rapidly to eliminate the influence of collateral circulation found in the canine heart, and to ensure the production of a transmural infarction of the type that has been created with the coronary artery embolization technique. 

Animal preparation. Twenty-nine mongrel dogs of both sexes weighing 14 to 26 kg were anesthetized with α-chloralose (100 mg/kg iv); additional amounts (about 10 mg/kg/hr) were added as needed to maintain a level of light surgical anesthesia. Respiration was controlled with auffed endotracheal tube connected to a volume-cycled respirator (Harvard model 607). A left thoracotomy was performed in each dog through the fifth intercostal space, and the heart was supported by suturing the margins of the opened pericardium to the edges of the surgical wound. The cervical vagi were isolated bilaterally in the neck, and the stellate ganglia were isolated in the chest for later surgical interruption. A fluid-filled cannula placed in a femoral artery was used to monitor arterial pressure, and a jugular venous catheter was used to administer drugs. Arterial blood gases and arterial pH were monitored throughout the experiment at intervals not exceeding 30 min, and sodium bicarbonate was infused intravenously or the tidal volume or the respiratory rate was changed to maintain the values for these parameters in the normal range. Arterial pressure and the electrocardiogram were recorded throughout the experiment on a physiologic recorder.

Five to seven millimeters of the first or second diagonal branch of the left anterior descending coronary artery (LAD) was isolated, and two silk ligatures were placed loosely underneath the vessel for use in later cannulation of the artery. Because isolation of the artery itself might disrupt afferent nerve fibers traveling in the adventitia of the artery, control heart rate and blood pressure responses to topical application of bradykinin and nicotine were performed after the dissection (control recordings). This ensured that all areas tested were not afferently denervated by the isolation procedure. All sites tested in this study produced appropriate responses to bradykinin and nicotine after isolation of the coronary artery. 

After these manipulations, a banjo thermistor was secured to the epicardial surface of the left ventricular free wall, and epicardial temperature was monitored. Rectal temperature also was monitored, and a heating blanket and thermal lamp were used to keep both epicardial and core temperature within a range of 37° to 39°C. A clear plastic film that covered the wound also aided in maintaining epicardial temperature.

Protocols. In all of the experiments, bradykinin was used to stimulate sympathetic afferent nerve endings and nicotine was used to stimulate vagal afferent nerve endings. Bradykinin triacetate (Sigma) and nicotine (Sigma) were dissolved in normal saline. A 0.5 cm square of surgical gauze moistened with saline was placed on the epicardium several minutes before application of either drug. The gauze was used to prevent the spread of drug outside the area of the epicardium to be tested. Bradykinin (5 μg in 0.20 ml saline solution) or nicotine (50 μg in 0.20 ml saline solution) was dripped onto the gauze sponge. Both nicotine and bradykinin solutions were kept at temperatures between 36.5° and 38°C. At least 10 min was allowed between drug applications. No data were collected in the 15 min period after administration of anesthetic.

To test the effects of transmural myocardial infarction on the afferent innervation of the anterior left ventricle (figure 1), sites above (basal to; site 1), within (site 2), and below (apical to; site 3) the region of coronary artery distribution were tested with topical applications of bradykinin and nicotine before and 90 min after embolization of the coronary artery. Control heart rate and blood pressure responses to the drugs were recorded, and then the isolated coronary artery was cannulated with a PE-50 catheter filled with vinyl latex solution. The cannula was secured in the artery by the silk ligatures, and 0.3 to 0.5 ml of vinyl latex solution (Carolina Biological Supply) was injected

![FIGURE 1. Schematic representation of heart showing epicardial sites of drug application (circles labeled 1 through 6) and the region of transmural myocardial infarction (stippling).](image-url)
rapidly into the artery through the catheter to embolize the vasculature. The catheter was removed and the preparation was allowed to stabilize for 90 min. Responses to drugs were measured 90 min after embolization. In 10 dogs, more extensive mapping was done after multiple drug applications at additional sites (figure 1, sites 4, 5, 6) on the anterior surface of the left ventricle before and 90 min after creation of the transmural myocardial infarction.

In 12 dogs, surgical interruption of sympathetic and vagal afferents was performed to examine afferent pathways mediating pressor responses to bradykinin and depressor responses to nicotine. In half of the dogs (n = 6), the cervical vagal trunks were cut and epicardial sites (figure 1, sites 4, 5) that had demonstrated continued responses to both bradykinin and nicotine after infarction were retested. After these measurements, bilateral stelllectomy was performed to interrupt sympathetic afferent pathways and the responses to the drugs tested. In the remaining dogs (n = 6), the order of performance of bilateral stelllectomy and vagotomy was reversed.

The relationship of each site tested to the infarcted region was confirmed by the blue tetrazolium staining technique for dehydrogenase enzymes. Four to six hours after embolization, the ventricles were fibrillated and the heart was excised, with wire markers positioned to define the epicardial sites of drug applications. The left ventricle was separated from the rest of the heart and cut in a breadloaf fashion from base to apex. Tissue slices were rinsed in cold tap water and placed in a solution of distilled water (288 ml), phosphate buffer (32 ml, pH 7.4), and nitro blue tetrazolium (100 mg, Sigma) at 37°C for 7 to 12 min. With this method, we verified the location of all sites of drug application in relation to the area of infarction, as well as the transmural nature of the infarction. Data presented in this report were obtained from sites verified to be located above (basal to), within, and below (apical to) the region of latex distribution and transmural myocardial infarction.

Statistics. The responses to nicotine and bradykinin applied topically to the anterior wall of the left ventricle were compared with responses obtained 90 min after creation of transmural myocardial infarction with the use of an analysis of variance and an analysis of variance for repeated measures. Except as stated otherwise, data are reported as mean ± SEM. Statistical significance was achieved when a p value of <.05 was obtained.

Results

Twenty-nine dogs were initially entered into the protocol. Of these, 16 demonstrated both a pressor response to topical applications of bradykinin and a depressor response to topical applications of nicotine. All 16 dogs also demonstrated a decrease in heart rate in response to the topical applications of nicotine at all sites tested on the anterior left ventricle. Four of 29 dogs responded to topical bradykinin only, and four animals responded to topical nicotine only. Despite careful control of the level of anesthesia, temperature of the drug solution, epicardial and core temperature of the dogs, blood gases, and the time between drug applications, all of which influence the response to drugs, five dogs did not respond to nicotine or bradykinin. Data from these five dogs were excluded from the study. All 24 animals reported in this study had transmural myocardial infarction confirmed by nitro blue tetrazolium staining and in all, verification of test sites basal, within, or apical to the site of infarction was obtained at autopsy.

Blood pressure responses to bradykinin and nicotine. In the 20 dogs that demonstrated pressor responses to bradykinin before transmural myocardial infarction (control), application of bradykinin to sites basal, within, and apical to the area of potential infarction all produced a significant pressor response (p < .05) to the drug (figure 2). This response was maximal approximately 40 sec after application of the drug and...
While returned to baseline within 120 sec. Ninety minutes after transmural myocardial infarction, sites above (basal to) the site of infarction continued to demonstrate a significant response (p < .05) to topical bradykinin, while sites within and below (apical to) the infarction demonstrated no significant change (p > .10) in mean arterial pressure when bradykinin was applied topically (figure 2).

In 20 dogs before creation of transmural myocardial infarction, nicotine produced a significant depressor response (p < .05) that was maximal approximately 20 sec after application of the drug (figure 3). The response returned to baseline within 60 sec. Ninety minutes after transmural myocardial infarction, sites above (basal to) the infarction continued to demonstrate a significant depressor response (p < .01) to topical nicotine, while sites within and below (apical to) the infarction were unresponsive (p > .10) to the drug (figure 3).

Heart rate responses to bradykinin and nicotine. Figure 4 illustrates the heart rate data for topical applications of nicotine and bradykinin before and 90 min after transmural myocardial infarction. Throughout all experiments, topical bradykinin (figure 4, right) did not significantly affect heart rate (p > .10). Topical nicotine before infarction caused significant bradycardia (10 to 20 beats/min) at all sites (p < .01). This response was maximal 20 sec after application, and returned rapidly to control without subsequent tachycardia. After creation of transmural myocardial infarction, topical application of nicotine to sites above the infarction continued to elicit significant bradycardia (p < .01) 20 sec after application, while nicotine applied to sites within or below (apical to) the infarction had no significant effect on heart rate (p > .10).

Mapping of the anterior left ventricular free wall. In 10 dogs with pressor responses to bradykinin and depressor responses to nicotine at all six sites tested before transmural myocardial infarction (figure 1) and in regions above the area of infarction afterward, we mapped the responses to the drugs after infarction. Figure 5 illustrates the mean data for the 10 dogs used in this portion of the study. Sites above (site 1) and lateral to (site 5) the infarction continued to respond significantly to both drugs (p < .05), but those within (site 2) and apical (sites 3 and 6) to the infarction no longer responded to topical bradykinin or nicotine (p > .10). Sites medial to the infarction had no significant depressor response to nicotine (p > .10), but a significant response to topical bradykinin was maintained (p < .05).

Nerve interruptions. In 12 dogs that had sites responsive to both nicotine and bradykinin, nerve interruptions were performed to test the neural pathways responsible for mediating the response to each drug. As shown in tables 1A and 1B, transection of the vagi bilaterally in six dogs eliminated depressor responses to nicotine while the pressor responses of bradykinin remained intact. Subsequent stelllectomy bilaterally eradicated the remaining pressor response to bradykinin in these animals. In six other dogs, the order of nerve transections was reversed. Bilateral stelllectomy eliminated pressor responses to bradykinin, but did not significantly affect nicotine-induced depressor re-
sponses. Subsequent vagotomy prevented the remaining depressor responses to nicotine.

Discussion

The results of this study indicate that a 90 min coronary arterial occlusion produced by the injection of rapidly hardening latex into a diagonal branch of the LAD eliminates afferently mediated blood pressure and heart rate responses to bradykinin and nicotine applied apical to the infarction. Responses were lost at sites over the infarction and in areas of viable, non-infarcted myocardium located apical to the infarction, probably by interruption of afferent nerves passing through the infarction. This interruption of afferent
transmission was selective at one site examined in this study and resulted in vagal, but not sympathetic, afferent interruption. At site 4 (figure 1), the vagal afferents that were activated by nicotine apparently passed through the region of infarction while coursing toward the base of the heart and therefore were interrupted. The sympathetic afferents that were activated by bradykinin at this site probably bypassed the region of infarction in their pathway to the base of the left ventricle.

**Course of the nerves in the left ventricular wall.** Histologic studies suggest that sympathetic efferent nerves travel over the epicardium, penetrating the myocardium to innervate the endocardium.20 Parasympathetic efferent fibers appear to reach the left ventricular myocardium via the interventricular septum and travel deeper within the myocardium.20

 Removing strips of epicardium or painting phenol on the surface of the left ventricle abolishes the contractile effects that occur during stimulation of the stellate ganglia in localized epicardial regions apical to the epicardectomy or application of phenol.21-23 Painting a circle of phenol around a multipolar electrode abolishes shortening of the effective refractory period induced by stimulation of sympathetic efferent nerves at both subendocardial and subepicardial poles of the electrode without affecting the increase in effective refractory period duration produced by vagal nerve stimulation.24 Circles or arcs of phenol positioned close (within 1 to 2 cm) to or at the atrioventricular groove interrupt vagally induced lengthening of effective refractory period,25 suggesting that the vagal nerves run deep in the myocardium, perhaps in the subendocardium, but ascend as they approach (within 1 to 2 cm) the atrioventricular groove to course in the subepicardium. Consistent with this concept is the demonstration that a 2 to 3 mm deep encircling endocardial incision abolishes vagally induced lengthening of the effective refractory period at endocardial and epicardial sites located apical to the encircling endocardial incision.26 Elimination of this vagally mediated response may be due to the interruption of vagal efferent fibers coursing along the subendocardium in a basal-to-apical direction.

From the above data it appears that, in dogs, sympathetic efferent nerves travel from base to apex on the surface of the left ventricle, branching off to penetrate the myocardium and innervate the subendocardial portions of the left ventricular wall. Sympathetic efferent transmission can be interrupted by surgical epicardectomy, superficial sclerosis produced by phenol, or transmural myocardial infarction. Vagal efferent fibers cross the atrioventricular groove in the subepicardium, then appear to travel at deeper levels in the left ventric-

### TABLE 1A
Nerve interruption experiments: vagotomy followed by stellectomy (n = 6)

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th>Vagotomy</th>
<th>Stellectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>-13</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>1</td>
<td>-8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>-10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>-6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>-9</td>
<td>-1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>-14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>-11 ± 2</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>

All data represent maximal changes in mean arterial pressure (mm Hg) from predrug values.

### TABLE 1B
Nerve interruption experiments: stellectomy followed by vagotomy (n = 6)

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th>Stellectomy</th>
<th>Vagotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
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<td>-20</td>
<td>-2</td>
</tr>
<tr>
<td>7</td>
<td>-7</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
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<td>-5</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>-10</td>
<td>-11</td>
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</tr>
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<td>-9</td>
<td>-11</td>
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</tr>
<tr>
<td>11</td>
<td>-11</td>
<td>-11</td>
<td>0</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>-12 ± 2</td>
<td>-11 ± 2</td>
<td>-1 ± 1</td>
</tr>
</tbody>
</table>

All data represent maximal changes in mean arterial pressure (mm Hg) from predrug values.
ular wall (possibly in the subendocardium), and probably penetrate upward to innervate the epicardium. These vagal fibers are interrupted by transmural myocardial infarction, encircling endocardial incision, or the application of phenol to the atroventricular groove.

Little is known about the left ventricular course of afferent fibers that ultimately travel with the sympathetic or vagal nerves. Harken et al.6 used phenol on the surface of the heart to produce afferent denervation of the myocardium to treat intractable angina in patients. The sensation of myocardial pain is mediated by afferents traveling with the sympathetic fibers,27-29 so the assumption was made that phenol produced sympathetic afferent denervation. Mechanosensitive vagal afferents were studied by Thoren30 in cats. Using electrical stimulation of the fibers, he demonstrated that the nerves transmitting from mechanosensitive endings travel in a general apex-to-base fashion. On the anterior wall of the left ventricle, their course generally is toward the left main coronary artery. On the posterolateral wall of the left ventricle, the fibers sweep basally toward the posterior portion of the atroventricular groove. Thoren did not comment on the depth of the vagal afferents within the myocardium.

Barber et al.2 using epicardial applications of phenol, demonstrated that sympathetic afferents apical to phenol-treated myocardium no longer responded to chemical stimulation, while phenol did not interrupt vagal afferent transmission unless it was painted on the ventricular surface in the atroventricular groove. They concluded that sympathetic afferents, like their efferent counterparts, travel in the subepicardium while vagal afferents travel a deeper, perhaps subendocardial course. Both vagal and sympathetic afferent fibers cross the atroventricular groove in the epicardium.

**Methodologic consideration.** The interpretation of data from these experiments depends on the assumption that bradykinin and nicotine selectively activate sympathetic and vagal afferents, respectively. Several lines of evidence suggest that the topical application of these substances may be used for this purpose. First, bilateral stellectomy eliminated the pressor effect of bradykinin while sectioning the cervical vagi did not. Vagotomy, but not stellectomy, abolished the depressor effect of nicotine. Second, the responses to nicotine and bradykinin are affected in different ways by painting phenol on the surface of the heart,2 suggesting that the reflexes elicited by the two drugs required separate pathways.

The use of topical nicotine and bradykinin as activators of specific reflexes that could be tested after experimental interventions undoubtedly was aided by excluding data from dogs that did not respond to epicardial nicotine with a depressor response and/or to epicardial bradykinin with a pressor response. Several investigators have demonstrated that the responses to these substances can vary from animal to animal and with different doses of the drugs.4, 8, 9, 16 We attempted to minimize the variability among animals by carefully controlling level of anesthetic, body temperature, drug temperature, time between drug applications, blood gases, and the manner of drug application.2 Five of 29 dogs were excluded from the study because they did not demonstrate either a depressor response to nicotine or a pressor response to bradykinin under control (pretansmural myocardial infarction) conditions. A single dose of each drug was used throughout the experiments, so no attempt was made to demonstrate a dose-response relationship in these animals. Thus, under these restricted experimental conditions, the two drugs appeared to serve as selective activators of epicardial reflexes requiring afferent fibers and traveling different limbs of the cardiac autonomic nerves.

In addition to the ability to selectively activate sympathetic or vagal afferent fibers, epicardial application of nicotine or bradykinin on small pieces of gauze provided the advantage of more precise localization of the stimulus. This was important for the purposes of mapping, and it avoided the obvious difficulties attendant to intrapericardial9 or intravascular2 administration of drugs. The disadvantage of this method was that only the pathways of afferent nerves subserving receptors on the epicardial surface where the drug was applied could be studied.

The effectiveness of vinyl latex12, 14 in interrupting collateral blood flow to the ventricles of the canine heart has been demonstrated. One of the goals of the present study was to produce a localized transmural myocardial infarction in the region of a diagonal branch of the LAD that would involve both the endocardial and epicardial layers, where it has been postulated that the afferent nerve fibers course. Euler et al.14 showed that embolization of coronary arteries effectively and reproducibly resulted in transmural myocardial infarction within the distribution of the artery. Histochemical and histologic analyses of the infarcts studied in our own laboratory12 demonstrated similar findings. Coronary artery embolization created an infarction that was transmural, yet localized enough so as not to severely compromise left ventricular function. In contrast to these results, preliminary data from our laboratory31 suggest that coronary artery ligation, which creates a primarily subendocardial infarction.
with epicardial sparing, does not eliminate the afferent sympathetic response to bradykinin applied over or apical to the infarcted area.

Isolation of a coronary artery and placement of a nonocclusive ring produces degeneration of perivascular adrenergic nerves within 14 days as a result of the surgical procedure and subsequent fibrosis. Vagal denervation would not be expected because of the intramural or subendocardial pathways traveled by the vagus in the ventricle. We have shown repeatedly that a careful, limited dissection that exposes the diagonal branch of the LAD or nonocclusive cannulation of the vessel does not acutely interrupt afferent sympathetic responses to bradykinin or efferently induced shortening of the effective refractory period during stimulation of the stellate ganglia. Such limited dissection must not interrupt all of the perivascular adrenergic nerves. Not all of the sympathetic innervation travels with the coronary artery, since some nerves probably “branch out” to travel over the epicardium and thus are not interrupted by coronary dissection. Most recently we have shown that even an acute non-transmural coronary artery occlusion that produces a viable epicardial layer of myocardium does not interrupt the response to bradykinin in most dogs. Therefore, it would appear likely that transmural myocardial infarction, and not the surgical dissection, was responsible for the results observed in this study.

Implications of the study. The major finding of this study is that transmural myocardial infarction can interrupt afferent neural innervation and thus afferently denervate viable, noninfarcted myocardium apical to the site of infarction. These data, coupled with previously reported evidence from our laboratory, demonstrate that transmural myocardial infarction can interrupt both the afferent and efferent limbs of the autonomic nervous system, innervating the myocardium apical to the transmural myocardial infarction. These areas of denervation may modify reflexes that modulate blood pressure, myocardial and smooth muscle contractility, heart rate, and cardiac electrophysiological properties in a variety of situations. Additionally, creation of autonomic imbalance may be conducive to development of arrhythmias.

It is quite clear, however, that ischemia can also activate sympathetic and vagal reflexes. It is not known from which site or sites activation of afferent reflexes arises and the relationship between such activation and the interruption of afferent reflexes noted here is not clear.

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