Reflex Responses to Myocardial Ischemia and Reperfusion
Role of Prostaglandins
Marc D. Thames, MD, and Anthony J. Minisi, MD

Powerful vasodepressor and cardioinhibitory reflexes are activated in humans during inferior wall myocardial ischemia or infarction and during restoration of flow to the ischemic region. Experiments in dogs have demonstrated that these responses are due to stimulation of afferent vagal fibers that are located mainly in the inferior wall of the heart. Prostaglandins are released during myocardial ischemia and possibly during reperfusion. Prostaglandins stimulate chemosensitive but not mechanosensitive endings in the ventricles. Our studies determined whether blockade of prostaglandin synthesis with indomethacin or sodium meclofenamate decreased the reflex inhibitory responses to coronary occlusion and reperfusion. Experiments were done in α-chloralose-anesthetized dogs after sinoaortic baroreceptor denervation. Occlusion of the circumflex coronary artery for 5 minutes resulted in decreases in arterial pressure and in renal sympathetic nerve activity. During the first 5 minutes after release of the occlusion, renal nerve activity remained inhibited. After treatment with indomethacin (n = 6, 5 mg/kg i.v.) or sodium meclofenamate (n = 3, 4 mg/kg i.v.), coronary occlusion resulted in significantly less inhibition of renal nerve activity. Renal nerve activity returned to control during the first minute of reperfusion. In six additional experiments the responses to coronary occlusion and reperfusion were not altered by treatment with vehicle. Our data suggest that prostaglandins serve as the major stimulus to ventricular sensory endings during myocardial ischemia and reperfusion. Our data further suggest that reflex inhibitory responses during ischemia and reperfusion are due mainly to stimulation of chemosensitive endings. (Circulation 1989;80:1878–1885)

Bradycardia and hypotension occur commonly during ischemia or infarction involving the inferoposterior wall of the left ventricle in humans.1,2 These responses are thought to be reflexly mediated by stimulation of sensory endings in the ischemic myocardium. Similar reflex responses have been observed during inferoposterior ischemia in animal studies. Experiments in dogs and cats have demonstrated that stimulation of vagal sensory endings by myocardial ischemia results in bradycardia, hypotension, and inhibition of sympathetic outflow to heart, kidney, and skeletal muscle.3–5

There are two types of vagal sensory endings in the left ventricle. One type6 is subserved by nonmyelinated afferent fibers and is stimulated by a variety of naturally occurring substances (e.g., bradykinin and prostaglandins) and synthetic irritant substances (e.g., phenylbiguanide, veratridine, nicotine, cyanide, and capsaicin). These chemosensitive endings have little or no response to changes in ventricular mechanics. The other type of ending is subserved by either nonmyelinated (most) or myelinated (few) afferent fibers and is stimulated by the mechanical activity of the ventricle. These mechanosensitive endings have little or no change in activity when exposed to the agents that activate chemosensitive endings.6 Both types of endings could be activated during myocardial ischemia or infarction because under these circumstances there are changes in ventricular mechanics as well as release of bradykinin and prostaglandins. To date, only ventricular mechanosensitive vagal endings have been shown to respond to myocardial ischemia.7,8 There are no data on responses of chemosensitive endings to ischemia.

Baker and colleagues6 have demonstrated marked stimulation of ventricular vagal chemosensitive end-
ings by prostaglandins. It has also been shown that intracoronary administration of prostaglandins activates vagal afferent pathways and results in bradycardia, hypotension, and sympathoinhibition. Is it possible that prostaglandins released during myocardial ischemia contribute to the reflex responses so provoked, or are there other chemical or mechanical stimuli that account for the reflex responses to ischemia? Our data indicate that prostaglandins released during myocardial ischemia and reperfusion are largely responsible for the activation of ventricular vagal afferents and the resulting reflex sympathoinhibitory responses.

Methods

Experiments were done in 30 dogs weighing 20–32 kg. Anesthesia was induced with sodium thio- pental (25 mg/kg i.v.) followed by a-chloralose (80 mg/kg i.v.). Maintenance doses of a-chloralose (10 mg/kg) were administered hourly. The dogs were intubated and mechanically ventilated with room air supplemented with oxygen. Arterial blood gases were measured, and PCO₂ and pH were corrected when necessary by adjustment of the tidal volume or administration of sodium bicarbonate, respectively. Arterial Po₂ exceeded 100 mm Hg in all experiments. Body temperature was maintained between 37° and 39° C by external warming. Muscular movement was eliminated with pancuronium bromide (1 mg i.v.) during periods in which nerve activity was recorded. Arterial pressure was measured with a catheter in the femoral artery that was connected to a pressure transducer (Statham P23dB, Gould, Cleveland, Ohio).

Experimental Preparation

A midline cervical incision was used to expose the vagi and carotid arteries bilaterally. In all dogs, the carotid sinuses were denervated bilaterally by sectioning all vessels and nerves that course between the internal and external carotid arteries and by stripping these vessels of all visible nerves. Completeness of denervation was confirmed by the failure of bilateral carotid occlusion to alter heart rate, arterial pressure, and renal sympathetic nerve activity.

In all dogs, the aortic baroreceptors also were denervated. The aortic depressor nerve was located between the sympathetic and vagal trunks just caudal to the nodose ganglion. The nerve was identified by recording its typical pattern of neural discharge and then sectioned. This method has been shown previously to markedly attenuate or abolish aortic baroreflexes. In previous studies, we have shown that the reflex inhibitory responses to myocardial ischemia are most easily demonstrated after elimination of the arterial baroreflexes. This is due to the fact that inhibitory responses mediated by activation of vagal afferents during myocardial ischemia are offset by hypotension, which reduces the input from the arterial baroreceptors and leads to sympathoexcitation. The net responses are the result of the interaction between these two changing inputs that are directionally opposite. By elimination of the arterial baroreceptors, only the responses to activation of vagal afferents remain.

A thoracotomy was performed in the fifth left intercostal space. The pericardium was opened, and its free edges were sutured to the chest wall to form a cradle for the heart. The left circumflex coronary artery was exposed 1–2 cm from its origin through small longitudinal incisions in the overlying connective tissue; care was taken to avoid damaging the nerves coursing along these vessels. A snare was placed loosely around the circumflex coronary artery for subsequent coronary occlusion.

The left flank was opened between the iliac crest and the costovertebral angle; then the left renal artery was exposed to permit access to the renal nerves.

Recording of Nerve Activity

A small branch of the renal sympathetic nerves was cut distally and dissected free from the renal artery and surrounding connective tissues. The nerve sheath was removed, and the nerve was covered with mineral oil and placed on bipolar platinum iridium electrodes for recording of sympathetic efferent nerve activity. Multifiber activity was recorded from the intact nerve branch or, in some instances, from thin filaments obtained from this nerve. The signal was amplified by a band pass amplifier (model P511, Grass Instruments, Quincy, Massachusetts) with high frequency cutoff set at 1,000–3,000 Hz and the low frequency cutoff at 30 Hz. The output of the amplifier was viewed with an oscilloscope (Tektronix, Beaverton, Oregon) and was fed into a loudspeaker and into a nerve traffic analyzer (model 706C, University of Iowa, Iowa City), which counted spike potentials exceeding a selected voltage (just above the noise). The rising phase of each spike that crossed the threshold generated a voltage pulse that was independent of spike amplitude. These voltage pulses were integrated to determine the number of spikes counted over a period of time, as described previously. This counting technique is different from integration of the raw voltage signal commonly referred to as integration. The counter is digital in design and counts linearly at instantaneous frequencies up to 10 kHz. The absolute value of the recorded traffic is dependent on the number of active fibers on recording electrodes and on the level of the window discriminator and, thus, may have limited meaning. This was particularly true in our study, because our nerve recordings were obtained from bundles of fibers of varying size obtained from the renal nerves. Thus, all responses of renal nerve traffic are normalized for the basal values.

Protocol

After completion of the surgical preparation, 30–45 minutes were allowed for stabilization of arterial
pressure and efferent renal sympathetic nerve activity. Measurements of these variables were obtained over a 60-second period immediately before coronary occlusion. The left circumflex coronary artery was occluded for 5 minutes during which continuous measurements of arterial blood pressure and renal nerve activity were obtained. After 5 minutes of coronary occlusion, the snare was released, and arterial pressure and nerve activity were monitored over the subsequent 5–10 minutes. The animals then were given an additional 30 minutes to recover from the initial coronary occlusion and reperfusion. Then each dog was randomly assigned to one of two treatment groups. One group was treated either with indomethacin (n=6, 5 mg/kg i.v.) or sodium meclofenamate (n=3, 4 mg/kg i.v.). The other group was given a volume of saline comparable with that used for the administration of the indomethacin (n=6). Although we did not test the efficacy of prostaglandin-synthesis inhibition induced by indomethacin and sodium meclofenamate, these doses have been shown previously in dogs to result in near total blockade of prostaglandin synthesis in response to administration of exogenous arachidonic acid.11 Indomethacin and sodium meclofenamate were solubilized in a phosphate buffer and diluted in saline as described previously.11 The protocol was repeated 10–15 minutes after prostaglandin-synthesis inhibition or sham treatment.

It is possible that indomethacin or sodium meclofenamate could exert direct effects on vagal cardiopulmonary mechanoreceptors that are unrelated to blockade of prostaglandin synthesis. To exclude this possibility we determined the decreases in renal nerve activity that occurred during volume expansion with 6% dextran in normal saline (15 ml/kg) administered over 6 minutes in five dogs with sinoaortic baroreceptor denervation. Responses were determined before and after treatment with indomethacin (5 mg/kg i.v.). We measured mean pulmonary artery pressure in these experiments and used it as an index of the stimulus to the cardiopulmonary mechanoreceptors.

Data Analysis

The entire experimental protocol was completed in 20 of the 30 dogs. Ten of the dogs that were studied died from ventricular fibrillation during the first or second occlusion/reperfusion phase of the protocol. Results from these dogs were excluded from subsequent analysis because they did not complete the protocol.

Changes in efferent renal sympathetic nerve activity and arterial pressure induced by 5 minutes of coronary occlusion and reperfusion were measured. Control values for these variables were determined during the 60-second interval preceding each coronary occlusion, and the percent changes from control in nerve activity and the change in mean arterial pressure were determined for each 60-second interval of the 5-minute coronary occlusion and for each 60-second interval during the first 5 minutes after release of the occlusion (reperfusion). The average change in these variables for each minute was used for subsequent statistical analysis.

The responses of mean arterial pressure and renal nerve activity were analyzed by a repeated-measures analysis of variance. The variables in the statistical model were maneuver (i.e., ischemia or reperfusion), drug (i.e., indomethacin or vehicle), and time. Due to the small number of experiments in the sodium meclofenamate group, statistical analysis was not performed for these data. Initial analysis indicated that the variable maneuver added no significant independent information to the model. Furthermore, no significant interaction between time and drug was detected. Dunnett’s test with 10 comparisons was used to determine at which 60-second intervals the changes in nerve activity and arterial pressure were significantly different from baseline values.

For the data from experiments with volume expansion, the relation between decreases in renal nerve activity and increases in mean pulmonary artery pressure was used to provide an estimate of the sensitivity of the reflex control of renal nerve activity by vagal cardiopulmonary mechanoreceptors. Because a plot of the mean postindomethacin data appeared to be curvilinear, the data were fitted to a second-order polynomial equation (i.e., \( y = A_0 + A_1x + A_2x^2 \)). The linear coefficients of these equations (i.e., \( A_0 \)) were used as an estimate of baroreflex sensitivity. The effect of indomethacin treatment on these linear coefficients was determined with a paired t test.

Finally, in six experiments, we determined peak changes of heart rate from the arterial pressure pulse that occurred in response to coronary occlusion before and after treatment with indomethacin (n=4) or sodium meclofenamate (n=2). In three experiments, we were unable to obtain heart rate data either because the recording speed was too slow to separate the arterial pressure pulse (n=2) or because mean, rather than pulsatile, pressure was recorded throughout most of the experiment (n=1). Data are presented in the text and tables as mean±SD and in the figures as mean±SEM.

Results

Effects of Prostaglandin-Synthesis Inhibition During Coronary Occlusion

Circumflex coronary occlusion resulted in significant decreases in arterial pressure and renal sympathetic nerve activity throughout the 5 minutes of occlusion (Figure 1). On release of the occlusion, arterial pressure returned toward control (Figure 1, right panel) and was no longer significantly different from baseline values by the second minute of reperfusion (minute 7). Renal nerve activity returned toward control (Figure 1, left panel) after occluder
release, although it remained significantly inhibited until the fourth minute of reperfusion (minute 9).

After administration of indomethacin, coronary occlusion resulted in significantly less sympathoinhibition during circumflex coronary occlusion (Figure 1, left panel). On release of the occlusion, renal sympathetic nerve activity returned rapidly to baseline, unlike the reperfusion observations before indomethacin when nerve activity remained significantly depressed through the first 4 minutes after occluder release. Repeated-measures analysis of variance indicated a significant effect of indomethacin treatment on the renal nerve responses to coronary occlusion and release (p=0.015). Additionally, none of the renal nerve measurements during occlusion or reperfusion was significantly different from the baseline value after indomethacin treatment. Indomethacin had no significant effect on the response of mean arterial pressure to coronary occlusion and release (Figure 1, right panel). The basal values of renal nerve activity and mean arterial pressure for all experiments are tabulated in Table 1.

Although indomethacin is an effective antagonist of prostaglandin synthetase, it may have other effects unrelated to blockade of prostaglandin synthesis, which could account for the responses we observed. To determine whether the effect of indomethacin was due to its ability to block prostaglandin synthesis, three additional experiments were performed in which sodium meclofenamate was used to block prostaglandin synthesis. The results of these experiments are illustrated in Figure 2. Although the number of experiments is small, it is apparent that the responses are qualitatively similar to those observed with indomethacin treatment. During the initial coronary occlusion, there was a striking inhibition of renal sympathetic nerve activity. A return toward control values was noted during the first 5 minutes of reperfusion. However, in all three experiments, renal nerve activity remained below baseline levels until 10 minutes after release of the occlusion. After treatment with sodium meclofenamate, the inhibitory responses of renal nerve activity during the occlusion were mark-

**Table 1. Effect of Treatments on Basal Values of Renal Nerve Activity and Mean Arterial Pressure**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Renal nerve activity (impulses/sec)</th>
<th>Mean arterial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>92±56</td>
<td>144±27</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>113±32</td>
<td>160±20</td>
</tr>
<tr>
<td>Control</td>
<td>151±105</td>
<td>125±29</td>
</tr>
<tr>
<td>Na meclofenamate</td>
<td>164±91</td>
<td>144±32</td>
</tr>
<tr>
<td>Control</td>
<td>64±34</td>
<td>155±20</td>
</tr>
<tr>
<td>Sham treatment</td>
<td>86±59</td>
<td>143±24</td>
</tr>
</tbody>
</table>

Values shown are mean±SD. All paired values not significantly different from each other by paired t test.

**Figure 1.** Graphs showing changes of renal nerve activity (left panel) and mean arterial pressure (right panel) during circumflex coronary occlusion for 5 minutes (open symbols) and during 5 minutes of reperfusion (solid symbols), before (circles) and after (triangles) treatment with indomethacin. Values shown are mean±SEM.

**Figure 2.** Graph showing changes of renal nerve activity during circumflex coronary occlusion for 5 minutes (open symbols) and during 5 minutes of reperfusion (solid symbols), before (circles) and after (triangles) treatment with sodium meclofenamate. Responses of blood pressure are not illustrated here but were similar to those illustrated in Figure 1. Values shown are mean±SEM.
Prostaglandin Synthesis Inhibition

![Graph showing peak changes of heart rate (beats/min) from control (C) during circumflex coronary occlusion (O) in six dogs with sinoaortic denervation. Responses are illustrated before and after treatment with indomethacin (closed symbols) or sodium meclofenamate (open symbols). Mean±SEM data also are illustrated. Heart rate decreased significantly before but not after blockade of prostaglandin synthesis.](image)

edly attenuated. During reperfusion, nerve activity returned promptly toward baseline. The responses of blood pressure were similar to those observed in the indomethacin experiments.

Figure 3 illustrates the peak responses of heart rate to circumflex coronary occlusion in six dogs before and after treatment with indomethacin or sodium meclofenamate. Before treatment, coronary occlusion resulted in modest but significant bradycardia (−17±7 beats/min). After inhibition of prostaglandin synthesis, this response was abolished (0.7±7 beats/min). These responses were significantly different (p<0.002) by paired t test.

Effects of Sham Treatment

To determine the reproducibility of the renal response to successive coronary occlusions, six additional experiments were done in which vehicle was administered before the second occlusion. The results of these experiments are illustrated in Figure 4. Both coronary occlusions elicited significant decreases in renal nerve activity and mean arterial pressure that persisted through at least the fourth minute of reperfusion (minute 9). The sympathoinhibitory responses to the second circumflex coronary occlusion were not different from those that resulted from the first occlusion. Unlike treatment with indomethacin, treatment with vehicle had no significant effect on renal nerve responses to coronary occlusion and release.

Effects of Prostaglandin-Synthesis Inhibition During Volume Expansion

Figure 5 illustrates the relation between the changes in mean pulmonary artery pressure and the changes in renal nerve activity that occurred during volume expansion. The linear coefficient of these relations provides an estimate of the sensitivity of

![Graph showing relation between changes in mean pulmonary artery (PA) pressure induced by volume expansion and percent change in renal sympathetic nerve activity (RSNA) under control conditions (CTRL; open squares) and after treatment with indomethacin (INDO; closed circles). Values shown are mean±SEM.](image)
these reflex responses. There was no significant difference between the linear coefficient obtained before indomethacin (−12±6) with the value obtained after indomethacin (−20±7; p=0.35). Thus, indomethacin had no significant effect on vagal cardiopulmonary reflex responses to the mechanical stimulus of volume expansion. This stands in contrast to the effect of indomethacin on the responses of renal nerve activity to coronary occlusion (Figure 1).

**Discussion**

The major new finding of our study is that inhibition of prostaglandin synthesis markedly attenuates the reflex sympathoinhibition that results from activation of cardiac sensory endings in the left ventricle during myocardial ischemia and reperfusion. It has been shown that the cardiac sensory endings that mediate these responses are subserved by vagal afferents.3–5,10,12 This finding has important implications regarding the type of sensory receptor that mediates these responses.

There are two types of vagal sensory endings in the left ventricle: one is mainly mechanosensitive and the other is mainly chemosensitive.4 Studies by Thoren7,8 have provided direct evidence that vagal mechanosensitive sensory endings are activated by ischemia. One study by Thoren8 is of special interest. Recording directly from unmyelinated vagal afferent fibers, he found that left ventricular mechanoreceptor discharge increased during the first 15 seconds of coronary occlusion, reached a peak by 30 seconds, and then returned rapidly toward control, even when the occlusion was maintained for 20–50 minutes. On release, there was a transient increase in activity in some, but not all, such endings that lasted about 2 minutes and then returned to control. This afferent receptor behavior does not correlate well with the reflex changes in efferent nerve activity that we observed. The reflex efferent responses reported in our study appeared to be mediated by afferent endings whose discharge was increased during the first few seconds of myocardial ischemia and whose activity was maintained at this increased level for at least 4 minutes after release of occlusion. It is likely that the sustained efferent responses that we observed were mediated by afferent sensory endings, which behave differently from the transiently activated mechanoreceptors described by Thoren.8

Chemosensitive, but not mechanosensitive, endings respond to prostaglandins and bradykinin.4 These substances are released during myocardial ischemia. Prostaglandin synthesis is blocked by indomethacin and sodium meclofenamate. Our data strongly suggest that prostaglandins released from the ischemic myocardium activate vagal sensory endings and that the reflex sympathoinhibitory responses we observed are due to stimulation of chemosensitive endings. We did not repeat our coronary occlusion after vagotony, but it is well documented that the vagal nerves serve as the afferent pathway for these sympathoinhibitory responses.3–5,12

We also found that inhibition of prostaglandin synthesis prevented the reflex bradycardia that resulted from circumflex coronary occlusion. These results differ from those reported by Hintze.9 He was unable to demonstrate an effect of indomethacin on the bradycardia that resulted from left anterior descending coronary occlusion. Hintze’s study was performed in cats, and this methodological difference could account for these conflicting results. There may be important species differences for the mechanisms by which vagal afferents are activated during myocardial ischemia.

Prostaglandin-synthesis inhibition had no significant effect on the blood pressure responses noted during coronary occlusion. This apparent dichotomy can be explained by considering the mechanism responsible for the changes in the measured parameters during coronary occlusion. With our experimental model in which the influence of the sinoaortic baroreflex has been removed, changes in nerve activity and heart rate during coronary occlusion most likely represent reflex effects mediated by cardiac vagal afferents. However, changes in arterial pressure occur secondary to ischemia-induced ventricular dysfunction in addition to reflex effects. The disparate effects of prostaglandin-synthesis inhibition on the changes in heart rate, arterial pressure, and renal nerve activity during coronary occlusion suggest that the decreases in arterial pressure are predominantly related to left ventricular dysfunction induced by myocardial ischemia.

Although the reflex responses to transient myocardial ischemia have been investigated extensively, very little is known about the effects of reperfusion. Our data indicate that when coronary blood flow is restored after 5 minutes of myocardial ischemia, significant renal sympathoinhibition persists for at least 4 minutes. The abolition of this persistent sympathoinhibition during reperfusion by blockade of prostaglandin synthesis indicates that this response is mediated by prostaglandins. We conclude that, when coronary blood flow is restored after 5 minutes of myocardial ischemia, local concentrations of prostaglandins remain sufficiently elevated to stimulate ventricular vagal afferents and inhibit renal nerve activity. Our results may help to explain the findings of Wei and colleagues.13 They found that in patients with occluded coronary arteries and evolving myocardial infarction involving the inferior wall of the heart reperfusion of these vessels with thrombolytic therapy (streptokinase) often resulted in bradycardia and hypotension. They suggested that these responses were due to activation of sensory endings during reperfusion of the ischemic region. On the basis of our results, we speculate that locally released prostaglandins contributed to the stimulation of chemosensitive endings that
gave rise to the vasodepressor and cardioinhibitory responses they observed.

Our data do not exclude the possibility that other chemical mediators may contribute to the stimulation of chemosensitive endings. Bradykinin is released during myocardial ischemia in dogs,14 and plasma kallikrein esterase activity is increased during myocardial ischemia in humans.15 Bradykinin could alter the activity of vagal sensory endings either by a direct effect or by stimulation of prostaglandin synthesis. Local increases in K+ release also may enhance the activation of ventricular sensory endings.

Our data also do not exclude a contribution from vagal mechanoreceptors to the reflex sympathoinhibitory responses we observed. Treatment with indomethacin was without effect on the vagal cardio-pulmonary mechanoreflex control of renal nerve activity. Since these mechanoreceptors are not responsive to prostaglandins6 and since they appear to be unaffected by indomethacin, then any contribution that these endings may make to the responses to coronary occlusion would be unaltered by prostaglandin-synthesis inhibition. The residual responses of renal nerve activity to circumflex occlusion after indomethacin (Figure 1) or meclofenamate (Figure 2) may have been due to activation of ventricular mechanoreceptors or to incomplete blockade of prostaglandin synthesis with modest residual stimulation of chemosensitive ventricular endings. Our data do not allow us to differentiate between these possibilities. Based on our findings, we suggest that stimulation of vagal chemosensitive endings by prostaglandins accounts for most of the reflex responses to ischemia and reperfusion.

The effects of prostaglandin-synthesis inhibition on renal nerve responses to coronary occlusion and release could be attributed to central effects of indomethacin and sodium meclofenamate. This seems unlikely for two reasons. First, we are unaware of any evidence that supports a central effect of these agents on autonomic control. Second, responses to cardiac mechanoreceptor stimulation were not altered after inhibition of prostaglandin synthesis. If these drugs acted by a central mechanism, then alteration of responses to mechanoreceptor stimulation would be expected. Because this was not observed, we feel that the effects of prostaglandin-synthesis inhibition are related to peripheral influences on prostaglandin synthesis.

Although we studied responses only of renal nerves, inhibition of sympathetic outflow to the heart3 and skeletal muscle5 also occurs during circumflex coronary occlusion. We suggest that these responses also are due to stimulation of ventricular vagal sensory endings by prostaglandins that are released during coronary occlusion.

One concern that could be raised about the interpretation of our results is that treatment with prostaglandin-synthesis inhibitors might have reduced the extent of ischemia and that this accounted for reduced sympathoinhibitory responses after indomethacin or sodium meclofenamate, rather than reduced production of prostaglandins. We consider this unlikely because arterial blood pressure and heart rate, which are the principal determinants of myocardial oxygen demand, were not changed by such treatment. In fact, inhibition of synthesis of vasodilator prostaglandins may have increased coronary vasomotor tone and enhanced the degree of ischemia.15

Short periods of myocardial ischemia, both symptomatic and silent, occur commonly in patients with atherosclerotic coronary artery disease. It seems likely that this ischemia leads to synthesis of prostaglandins and possibly of other substances that stimulate vagal chemosensitive endings in the ventricle. This stimulation may lead to reflex cardioinhibitory, vasodepressor, and sympathoinhibitory responses. These responses may tend to reduce myocardial oxygen demand and, thereby, limit the severity of the ischemia. They also may lessen the likelihood that ventricular arrhythmias will occur.

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M D Thames and A J Minisi

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