Vagal Stimulation and Prevention of Sudden Death in Conscious Dogs With a Healed Myocardial Infarction

Emilio Vanoli, Gaetano M. De Ferrari, Marco Stramba-Badiale, Stephen S. Hull Jr., Robert D. Foreman, and Peter J. Schwartz

The interest for the antifibrillatory effect of vagal stimulation has been largely limited by the fact that this concept seemed restricted to acute experiments in anesthetized animals. To explore the potentially protective role of vagal stimulation in conscious animals we developed a chronically implantable device to be placed around the cervical right vagus. An anterior myocardial infarction was produced in 161 dogs; 1 month later an exercise stress test was performed on the 105 survivors. Toward the end of the test the circumflex coronary artery was occluded for 2 minutes. Fifty-nine (56%) dogs developed ventricular fibrillation and, before this test was repeated, were assigned either to a control group (n=24) or to be instrumented with the vagal device (n=35). Five dogs were excluded because of electrode malfunction. Compared with the heart rate level attained after 30 seconds of occlusion during exercise in the control test, vagal stimulation led to a decrease of approximately 75 beats/min (from 255±33 to 170±36 beats/min, p<0.001). In the control group 22 (92%) of 24 dogs developed ventricular fibrillation during the second exercise and ischemia test. By contrast, during vagal stimulation ventricular fibrillation occurred in only 3 (10%) of the 30 dogs tested and recurred in 26 (87%) during an additional exercise and ischemia test in the control condition (p<0.001 versus the vagal stimulation test; internal control analysis). Combined analysis of the tests performed in the control condition showed that ventricular fibrillation was reproducible in 48 (89%) of the 54 dogs tested. The protective effect of vagal stimulation was also significant in the group comparison analysis and even after exclusion of those four dogs in which ventricular fibrillation was not reproducible (92% versus 11.5%, control versus vagal stimulation, p<0.001). When heart rate was kept constant by atrial pacing, the vagally mediated protection was still significant (p=0.015) as five (55%) of nine dogs survived the test. This study shows that vagal stimulation, performed shortly after the onset of an acute ischemic episode in conscious animals with a healed myocardial infarction, can effectively prevent ventricular fibrillation. This striking result seems to depend on multiple mechanisms having a synergistic action. The decrease in heart rate is an important but not always essential protective mechanism. The electrophysiological effects secondary to the vagally mediated antagonism of the sympathetic activity on the heart are likely to play a major role. (Circulation Research 1991;68:1471–1481)

A substantial amount of evidence indicates that, in the setting of acute myocardial ischemia, sympathetic hyperactivity often triggers life-threatening arrhythmias.1-6 A clinical counterpart of this notion is represented by the efficacy, in reducing the incidence of sudden cardiac death among patients with ischemic heart disease, of pharmacological and surgical antiadrenergic interventions.7-9 More recent evidence indicates that high vagal tone and reflexes may be protective in patients with ischemic heart disease10,11; however, the influence of vagal activity on ischemia-dependent tachyarrhythmias is not clearly defined. Studies showing adverse or no effect of vagal hyperactivity12-15 are matched by studies indicating that vagal activity, augmented either pharmacologically16-18 or by direct electrical stimulation, is antiarrhythmic.19-23 Also, markers of cardiac electrical stability are favorably influenced by...
vagal tone in the presence of elevated sympathetic activity.18,22,24 The interesting potential implications of these findings have probably been limited by the use of anesthesia in most of the experimental preparations, by the lack of an effective cardioselective muscarinic agonist, and also by the fact that electrical vagal stimulation in the conscious animal was generally viewed as not feasible.

We have evaluated the antifibrillatory potential of vagal activation, induced by stimulation through an electrode chronically implanted around the cervical vagus,25,26 during acute myocardial ischemia in conscious dogs in which a myocardial infarction had been induced 1 month earlier.27 In this extensively described28,29 experimental model for sudden death most of the animals susceptible to ventricular fibrillation can be correctly identified by the presence of a reduction either in baroreflex sensitivity30 or in heart rate variability,31 both markers of impaired vagal activity directed to the sinus node. Conversely, daily exercise, which leads to changes mimicking increased vagal activity, improves baroreflex sensitivity when reduced and confers protection from fibrillation.32

Materials and Methods

In this study 161 mongrel dogs weighing 15–25 kg were used.

Surgical Preparation

Anesthesia was induced with thiopental sodium (25 mg/kg i.v.; Pentothal, Abbott Laboratories, North Chicago, Ill.) and was maintained by the inhalation of a halothane, nitrous oxide, and oxygen mixture. With aseptic procedures, a left thoracotomy was performed in the fourth intercostal space. The pericardium was opened, and the heart was suspended in a cradle. The left circumflex coronary artery was carefully dissected from the surrounding epicardial fat, and both a 20-MHz continuous-wave Doppler flow transducer and a pneumatic occluder were placed around the vessel. The Doppler transducer was proximal to the occluder, which was positioned approximately 2 cm from the origin of the coronary artery. Two pairs of insulated silver-coated copper wires were sutured to the epicardial surface of the right atrium and ventricle to pace the heart and to record the electrogram. A Tygon (Norton, Akron, Ohio) catheter was positioned in the aortic arch to record blood pressure.

A Harris two-stage occlusion was performed on the left anterior descending coronary artery just above the first diagonal branch to produce a myocardial infarction. The vessel was partially occluded for 20 minutes and then tied off completely.

All lead wires were tunneled under the skin to exit from the dorsal surface of the neck. Pentazocine lactate (30 mg i.m.; Talwin, Winthrop Pharmaceuticals, New York) was given approximately every 8 hours for the first 24 hours to control postoperative pain. We adhered to the guidelines of the American Physiological Society and of the American Heart Association for the care and treatment of experimental animals.

Experimental Protocol

One month after production of the anterior myocardial infarction a submaximal exercise stress test was performed on all dogs according to a protocol already described.33 The animals ran on a motor-driven treadmill for 12–18 minutes while the work load was increased every 3 minutes (4.8 km/hr, 0% grade during the first 3 minutes; 6.4 km/hr, 16% grade during the last 3 minutes). Whenever the animal completed 17 minutes of exercise or heart rate reached a level close to 210 beats/min, the left circumflex coronary artery was occluded for 2 minutes; after the first minute the treadmill was stopped while the occlusion was maintained for a second minute.27 Large steel plates were placed across the animals’ chests to perform electrical defibrillation (model 6217, American Optical Corp., Bedford, Mass.) within a few seconds. One or two 50-J shocks were sufficient to restore sinus rhythm in most cases. The dogs that showed ventricular fibrillation during the control exercise and ischemia test were assigned to two groups: one served as the control group and repeated the test a few days later without additional interventions; the other entered the vagal stimulation protocol, as specified below.

Vagal Stimulation Protocol

These dogs were anesthetized with thiopental sodium, and a small incision was made on the right anterior side of the neck. The right cervical vagus was carefully isolated from the carotid artery, and a bipolar cuff electrode (model SP 5539, Medtronic Inc., Minneapolis, Minn.) of the vagus nerve began 15 seconds after onset of coronary artery occlusion. Stimulation parameters (3 msec; 1.0–3.0 mA, 3–8 Hz) were set at a level that reduced heart rate to approximately 170 beats/min in a brief test performed a few minutes before coronary occlusion while the animals were running on the treadmill. The stimulation parameters chosen never induced any reaction that indicated a sensation of pain. Coughing was noted in about one third of the tests, whereas retching occurred only in a few dogs.

At the end of the study the susceptibility to ventricular fibrillation was reassessed by exposing all dogs to an additional control exercise and ischemia test. During this final test, whenever a dog did not have ventricular fibrillation it seemed fair to suspect that survival during the vagal stimulation trial had
merely reflected a spontaneous change in the animal response to ischemia; it was conservatively decided to analyze separately the entire group and the subgroup of animals that developed ventricular fibrillation in both the first and final tests.

Once the entire protocol was completed, two dogs protected by vagal stimulation underwent an additional exercise and ischemia test with vagal stimulation. In one, atropine (75 mg/kg i.v.) was administered during exercise 1 minute before coronary artery occlusion. In the second, the test was performed 2 days after surgical decentralization of the right vagus.

**Exercise and Ischemia Test With Atrial Pacing**

In the initial part of the present study, some of the dogs were not instrumented with pacing leads; in other dogs the stimulating electrode broke during the protocol. For these reasons, the experimental protocol could be repeated with the addition of atrial pacing in 40% of the dogs protected by vagal stimulation. In these tests, during the first minute of occlusion and while the dogs were still exercising, heart rate was continuously adjusted and kept at the same level observed during the control test until the occurrence of ventricular fibrillation. After this moment, the rate of the pacing was progressively decreased to mimic the decline in heart rate observed in the animals that survived the coronary artery occlusion (207±30 beats/min at 90 seconds and 197±24 just before release of occlusion).

**Data Recording**

Arterial blood pressure, electrocardiogram, heart rate, and flow velocity in the left circumflex coronary artery (to verify the completeness of the occlusion) were recorded on an eight-channel direct writing oscillograph (R 612, Beckman Instruments, Inc., Fullerton, Calif.). These variables were also recorded on magnetic tape (Ampex FR-1300, Redwood City, Calif.) for later analysis.

**Data and Statistical Analysis**

The outcome during the exercise and ischemia test was evaluated by performing both group comparison and internal control analysis. Group comparison was performed by comparing the second exercise and ischemia test in the control group and in the vagal stimulation group; this was done to assess whether the second test was modified by the intervention (vagal stimulation). Internal control analysis was performed in the vagal stimulation group by comparing the first test in control conditions, the second test during vagal stimulation, and the final test once more in control conditions; this was done to assess not only the efficacy of the intervention but also the reproducibility of the events within the same animals. Statistical analysis was performed using analysis of variance (ANOVA), Student's t test with Bonferroni correction when appropriate for comparison of the means, $\chi^2$ with Yates correction, and Fisher exact test for comparison of frequencies. A value of $p<0.05$ was considered significant for the differences tested.

Data are reported in the text as mean±1 SD.

**Results**

The outline of the study is shown in Figure 1. Of the 161 dogs that underwent surgery and myocardial infarction, 44 (27%) died suddenly within the first week. Twelve dogs (7%) were excluded from the study for technical reasons.

Thus, the exercise and ischemia test was performed in 105 dogs: 46 of them (44%) were resistant and were used for another protocol, whereas the remaining 59 animals had ventricular fibrillation and were assigned to either the vagal protocol ($n=35$) or to the control group ($n=24$). The results will be presented separately for the effect of vagal stimulation on arrhythmias and on hemodynamics.

**Arrhythmias**

**Control tests and reproducibility.** As a primary condition to enter the study, all dogs that were used developed ventricular fibrillation in the first exercise and ischemia test.

In the control group, the test was repeated a few days later under the same conditions. During this second trial ventricular fibrillation occurred in 22 (92%) of 24 dogs.

In the vagal stimulation group, the device was malfunctioning in five of 35 dogs; therefore, the study was conducted on the remaining 30 susceptible dogs. As indicated in "Materials and Methods," in this group of dogs susceptibility to ventricular fibrillation was reassessed at the end of the study by an additional exercise and ischemia test in the control condition. During this final test ventricular fibrillation recurred in 26 (87%) of the 30 dogs tested. The combined observation in the control and vagal stim-
Vagal stimulation. The effect of vagal stimulation was evaluated first by an internal control analysis that included all dogs in which vagal stimulation was performed. As shown in Figure 2, vagal stimulation strikingly reduced the incidence of ventricular fibrillation from 100% to 10% (3 of 30). When the exercise and ischemia test was repeated without vagal stimulation, the incidence of ventricular fibrillation returned to 87%. The protection conferred by vagal stimulation was highly significant (p<0.001) versus both the first and final tests. Also, the incidence of ventricular fibrillation did not differ in the two tests in control conditions.

Subsequently, a group comparison was made between the control group (n=24) and the vagal stimulation group with the exclusion of the four animals that survived the final test (n=26). The incidence of ventricular fibrillation was significantly (p<0.001) lower in the vagal stimulation group (3 of 26, 11.5%) compared with that of the control group (22 of 24, 92%), as illustrated in Figure 3.

The internal control portion of the study also offered the possibility of a direct and quantitative comparison of the arrhythmias observed and of their timing. In the three dogs that had ventricular fibrillation, it occurred slightly later compared with the control tests (67±20 versus 49±17 seconds, p=NS) and was not preceded by hemodynamic impairment. Of the 23 dogs that completed the test, one developed a short run of ventricular tachycardia (Figure 4). The remaining 22 dogs (84.5%) remained free of repetitive ventricular arrhythmias throughout the coronary artery occlusion, as exemplified in Figure 5. Overall, there was a clear-cut reduction of the severe
Figure 5. ECG recording in the same dog during the exercise and ischemia test. Upper tracing: Control test; lower tracing: test with vagal stimulation. Ten seconds after cessation of exercise, ventricular fibrillation that degenerated into fibrillation occurred in the control test, but when vagal stimulation was performed during coronary artery occlusion (CAO), this animal had no ventricular arrhythmias. HR, heart rate.

In the test, in which atropine was given before the coronary artery occlusion, ventricular fibrillation occurred during acute myocardial ischemia with a timing and pattern similar to that observed in the control exercise and ischemia test. Vagal stimulation after atropine did not reduce heart rate, thus indicating no consequences of the activation of vagal afferent fibers. The animal in which vagal stimulation was performed after decentralization had a reduction in heart rate similar to that observed during the stimulation of the intact vagus, and it was again protected from ventricular fibrillation.

1st CAO

2nd CAO + VAGAL STIM.

VF

VT

PVCs

0

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Vagal stimulation and atrial pacing. The following analysis does not include the four dogs that also survived the final test. In the exercise and ischemia tests in which the heart was driven by atrial pacing during vagal stimulation, five (55%) of the nine dogs survived the 2-minute coronary artery occlusion (Figures 7 and 8). Of these five surviving dogs, one developed ventricular fibrillation a few seconds after release of the occlusion while atrial pacing and vagal stimulation were still ongoing. This animal had only few ventricular beats during acute myocardial ischemia, and ventricular fibrillation occurred immediately after release of the occlusion without any warning arrhythmias. We interpreted this event as a typical instance of reperfusion arrhythmias, known to depend on mechanisms quite different from those operant during ischemia.35–37 In the four dogs that had ventricular fibrillation during ischemia with atrial pacing, this occurred somewhat later into coronary artery occlusion compared with the control tests (56±4 versus 41±15 seconds, p=NS).

Figure 7. Overall incidence of ventricular arrhythmias in nine dogs during three different coronary artery occlusions (CAO): the first in the control condition, the second associated with vagal stimulation (STIM.), and the third when heart rate was kept constant during vagal stimulation by atrial pacing. Each arrow represents one animal. VF, ventricular fibrillation; VT, ventricular tachycardia; PVCs, premature ventricular contractions; 0, no ventricular arrhythmias.
Despite the recurrence of ventricular fibrillation in four of the nine dogs tested, when the outcome of the control exercise and ischemia tests (ventricular fibrillation in 26 of 26, 100%) and of the tests with vagal stimulation and pacing (ventricular fibrillation in four of nine, 45%) were compared, the protective effect of vagal stimulation was still highly significant ($p=0.015$).

**Hemodynamics**

The hemodynamic response to the first exercise and ischemia test was similar in the control and vagal stimulation groups during exercise as well as during coronary artery occlusion (Table 1). Ventricular fibrillation was never preceded by a major hemodynamic impairment as in the overall group mean blood

**Table 1. Responses of Heart Rate and Mean Blood Pressure to Exercise and Coronary Artery Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Mid-exercise</th>
<th>Before CAO</th>
<th>30 Seconds of CAO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>MBP</td>
<td>HR</td>
<td>MBP</td>
</tr>
<tr>
<td>Control group</td>
<td>110±25</td>
<td>104±16</td>
<td>195±28*</td>
<td>99±15</td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagal stimulation group (n=26)</td>
<td>114±19</td>
<td>108±14</td>
<td>189±33*</td>
<td>103±13</td>
</tr>
</tbody>
</table>

Values are mean±SD. CAO, coronary artery occlusion; HR, heart rate (beats/min); MBP, mean blood pressure (mm Hg).

$^*p<0.001$ vs. rest.

$^†p<0.005$ vs. before CAO.
pressure just before its occurrence was 82±21 mm Hg.

In the control group the hemodynamic responses to the first and second exercise and ischemia tests were similar.

In the vagal stimulation group, the stimulation was initiated 10–15 seconds after the beginning of the coronary occlusion during exercise and significantly affected heart rate. Thirty seconds into coronary artery occlusion heart rate was of course lower than in the control tests (170±36 versus 255±33 beats/min, p<0.001), while mean blood pressure did not differ when compared with that observed during the control test (84±17 versus 85±17 mm Hg, p=NS). The reduction in blood pressure during myocardial ischemia was similar to that observed in the control test.

Table 2 shows that in the tests in which vagal stimulation and atrial pacing were combined the hemodynamic response to coronary artery occlusion was not different when compared with the control tests.

### Discussion

The recent clinical evidence linking depressed vagal activity and increased mortality has made it necessary to clearly define the relation between vagal activity and propensity to ventricular fibrillation. This required a study performed with physiological conditions (i.e., in the conscious state) and in a setting relevant to the clinical problem (i.e., combining acute myocardial ischemia and physiologically elevated sympathetic activity in the presence of a healed myocardial infarction).

The present study shows that electrical vagal stimulation is feasible in conscious animals and that, when commenced shortly after the onset of an episode of acute myocardial ischemia, it provides significant protection from ventricular fibrillation.

### Previous Studies

The relation between vagal activity and life-threatening cardiac arrhythmias is far from being clearly outlined. Protection and lack of protection were both reported by different investigators, even if there is a growing consensus for a beneficial effect of vagal activation during coronary occlusion. However, previous studies were performed mostly in anesthetized animals or sometimes in animals sedated with vagomimetic agents such as morphine. In other cases susceptibility to ventricular fibrillation was assessed by using indirect indexes of vulnerability to malignant arrhythmias. Furthermore, the experimental preparations had sometimes resulted in relatively low levels of sympathetic activity, despite its recognized importance in the genesis of ischemic arrhythmias. As discussed by the authors of the latter studies, this has probably interfered with the possibility of observing a marked electrophysiological effect of vagal stimulation at the ventricular level.

### Preparation and Protocol

The present animal model has allowed us to study the effects of vagal stimulation during acute myocardial ischemia, overcoming some of the most important limitations of previous investigations.

This preparation does not involve anesthesia or sedation and is based on the direct occurrence of ventricular fibrillation instead of its indirect markers; lethal arrhythmia occurs when sympathetic activity is physiologically elevated because of exercise.

The parameters for vagal stimulation were set to a level that did not induce major side effects or impair the capability of the dogs to exercise. The time of onset of the electrical stimulation and its duration throughout the coronary artery occlusion were chosen to increase vagal activity to the heart when reflex sympathetic response to acute myocardial ischemia is known to be maximal. Sympathetic reflex activation occurs within seconds from the beginning of coronary artery occlusion and declines within a few minutes. Coincident with the time course of sympathetic activation is the initial decrease and subsequent recovery of ventricular fibrillation threshold during the first few minutes of acute myocardial ischemia.

The significance of the data obtained in this study is strengthened by the reproducibility of the events in the model used. The possibility to repeat the same test in the same animal has allowed us to evaluate the antifibrillatory effect of vagal stimulation not only by comparing the outcome with a control group, but also by an internal control analysis. This latter analysis has made it possible to identify the few dogs in which the response to acute myocardial ischemia had changed over the time of the study. For the sake of safety, the analysis in the group comparison was restricted to dogs in which susceptibility to ventricular fibrillation had not changed over time; this resulted in the elimination of those animals that could have spuriously appeared as protected in the vagal stimulation trial.

The antifibrillatory effect of vagal stimulation observed in these experiments could be due to the combination of at least four favorable factors: the electrophysiological effects of vagal hyperactivity on the ventricles, the reflex withdrawal of efferent sympathetic activity, the direct effect of vagal stimulation on the coronary circulation, and the marked decrease in heart rate.

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**Table 2. Responses of Heart Rate and Mean Blood Pressure to Coronary Artery Occlusion During Atrial Pacing**

<table>
<thead>
<tr>
<th></th>
<th>Before CAO</th>
<th>30 Seconds of CAO</th>
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<tbody>
<tr>
<td></td>
<td>HR (bpm)</td>
<td>MBP (mm Hg)</td>
</tr>
<tr>
<td>Control</td>
<td>200±32</td>
<td>104±17</td>
</tr>
<tr>
<td>Atrial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pacing</td>
<td>203±46</td>
<td>110±18</td>
</tr>
</tbody>
</table>

Values are mean±SD. CAO, coronary artery occlusion; HR, heart rate (beats/min); MBP, mean blood pressure (mm Hg).

*p<0.01 vs. before CAO.
**Electrophysiological Effects**

Acetylcholine has direct electrophysiological effects in in vitro preparations, where it induces a dose-dependent decrease in automaticity in canine Purkinje fibers and His bundle. Action potential duration is either shortened or not modified; moreover, different effects have been reported in the epicardium but not in the endocardium. Vagal stimulation in vivo decreases the idioventricular rate both in experimental preparations and in humans. However, the primary electrophysiological effect of vagal activity seems to be the direct consequence of antagonizing the effects of sympathetic activity.

Indeed, the electrophysiological effects of vagal activity are greatly enhanced in the presence of a concomitant elevated sympathetic activity. For instance, acetylcholine markedly reduces the electrophysiological changes induced by isoproterenol at both the atrial and ventricular levels and abolishes isoproterenol-induced slow-response action potentials in potassium-depolarized canine cardiac Purkinje fibers. The pathway of this antagonism is likely to depend on the effect of inhibitory G proteins on the catecholamine-induced increase in adenylate cyclase activity. The vagally induced decrease in ventricular vulnerability and the increase in refractory period of the left ventricle are also mainly due to antagonism of the existing sympathetic activity.

Overall, these observations and the presynaptic muscarinic inhibition of norepinephrine release represent the cellular basis for the sympathetic-parasympathetic accentuated antagonism, which has also been recently demonstrated in conscious dogs and in humans. This mechanism may play an important role in the present animal model, as strongly suggested by the observation that accentuated antagonism is diminished in the ventricles of susceptible dogs. Mucosal stimulation by oxotremorine is effective in preventing malignant arrhythmias triggered by the combination of acute myocardial ischaemia and sympathetic hyperactivity in cats.

In humans, reflex vagal activity has an arrhythmogenic effect partly independent from heart rate decrease and can terminate episodes of ventricular tachycardia. Removal of vagal tone by atropine shortens the ventricular refractory period.

Thus, vagal activity modifies the electrophysiological properties of the ventricle in a way that could interfere with reentrant and nonreentrant mechanisms responsible for the initiation and perpetuation of ventricular tachyarrhythmias.

**Reflex Effects**

To study the effects of chronically implanted electrodes and to avoid the adverse consequences of chronic vagotomy, the intact nondecentralized cervical vagus nerve was stimulated. This implies that, besides the vagal efferent fibers, cervical sympathetic fibers, which in the dog run in the cervical vagal trunk, and vagal afferent fibers were also simultaneously stimulated.

The stimulation of the cervical sympathetic fibers might have, in theory, counteracted to some extent the beneficial effects of vagal activity. The heart rate increases during vagal stimulation in the presence of atropine are relatively modest in conscious and running dogs. The uniform protection provided by vagal stimulation indicates that this effect played no significant role in our results.

In theory, the consequences of the activation of vagal afferent fibers could be quite different. Their excitation, besides increasing the contralateral efferent activity, produces a reflex withdrawal of cardiac efferent sympathetic activity. This could be particularly important during acute myocardial ischaemia because at that time a cardiocardiac sympathetic reflex is initiated and contributes to the occurrence of ventricular tachyarrhythmias. Verrier and associates demonstrated that tonic vagal afferent activity exerts a protective effect on ventricular vulnerability and that this effect is likely to be mediated by reflex inhibition of the sympathetic outflow. In addition, activation of vagal afferent fibers interferes with the initiation of sympathetic reflexes in the spinothalamic and spinoreticular tract, where electrical stimulation of vagal afferent fibers can inhibit the increased discharge of cells activated during coronary artery occlusion.

Three lines of evidence argue against a role for vagally mediated sympathetic inhibition in the protection afforded by vagal stimulation in our experiments. Atropine completely blocks the chronotropic effects of vagal stimulation performed during high sympathetic activity induced by submaximal exercise with a protocol similar to that used for the exercise and ischemia test in the present study. In this condition, if activation of efferent vagal fibers had importantly inhibited the sympathetic outflow, vagal stimulation would still have reduced heart rate. The protective effect of vagal stimulation was completely prevented by atropine, thus indicating that protection was dependent on efferent vagal stimulation. When in one dog stimulation was limited to vagal efferent fibers by surgical decentralization, thus eliminating central activation and potential sympathetic withdrawal, the animal was still protected from ventricular fibrillation.

We are not denying that cardiac sympathetic efferent activity is influenced by afferent vagal stimulation. However, our experiments were performed during exercise when the level of circulating catecholamines is such that a transient decrease in the firing of sympathetic nerves would hardly be able to affect cardiac electrophysiology.

**Effects on Coronary Circulation**

Sympathetic activation during coronary artery occlusion may worsen the degree of ischemia not only by increasing heart rate, but also by reducing the capability of collateral coronary vessels to dilate. The
α-adrenoceptor–mediated vasoconstrictor effect of sympathetic activity can limit local metabolic vasodilation even during exercise and can reduce reactive hyperemia after a short coronary artery occlusion.

In these experiments, vagal activation may have antagonized the vasoconstrictor effect of sympathetic activity by acting on norepinephrine release and also by a direct vasodilatory effect. Indeed, electrical vagal stimulation or reflex vagal activation produces coronary vasodilation in dogs. Acetylcholine produces coronary vasodilation both in dogs and in baboons independent of interaction with sympathetic activity. However, acetylcholine may also produce coronary constriction, particularly in the presence of endothelium damage. Such an effect would not have occurred in our preparation involving dogs with normal coronary vessels.

Thus, a vagally dependent amelioration of collateral perfusion of the acutely ischemic myocardium could have in theory contributed to the protection from ventricular fibrillation observed in our experiments.

**Role of Heart Rate**

Heart rate reduction diminishes myocardial oxygen consumption, increases diastolic perfusion time, and may improve collateral coronary flow distribution. These combined effects may reduce the degree of myocardial ischemia, as documented in anesthetized dogs and conscious dogs subjected to acute coronary artery occlusion. This may explain why in ischemic hearts a slower heart rate produces effects opposite those observed in normal hearts, in which bradycardia increases the disparity of refractory periods and decreases ventricular fibrillation threshold. Indeed, in anesthetized dogs with a coronary artery occlusion, an increase in pacing rates above 150 beats/min causes a marked increase in ventricular premature beats, tachycardia, and fibrillation.

Also, the antiarrhythmic effect of antiadrenergic interventions has been shown to depend largely on the attendant decrease in heart rate.

During the exercise and ischemia tests with vagal stimulation the reduction in heart rate was considerable, but it never produced bradycardia. Thus, huge reductions in heart rate are not necessary for the antifibrillatory effect of vagal stimulation.

Furthermore, the protective effect of vagal stimulation remains highly significant even when the contributing effect of the reduction in heart rate is prevented. The experiments performed with atrial pacing indicate that the vagally mediated protection can be, in some animals, independent of the heart rate reduction. Thus, a lower heart rate was not always an essential prerequisite for the antifibrillatory effect of vagal stimulation.

**Clinical Implications**

It may be premature to extrapolate directly from this study to clinical applicability. On the other hand, there is a growing mass of data pointing to favorable effects of vagal activation on cardiac electrical stability. The possibility of using direct or pharmacological stimulation of the cardiac muscarinic receptors in an attempt to reduce the incidence of ventricular fibrillation during acute myocardial ischemia warrants further and specific investigations.

**Conclusions**

These experiments in conscious animals conclusively demonstrate that vagal activation can prevent ventricular fibrillation caused by acute myocardial ischemia. This effect depends on the interaction between multiple factors, among which the most critical are the antagonism with sympathetic activity and the reduction in heart rate. The latter plays an important but not essential role.

**Acknowledgments**

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**Key Words**: autonomic nervous system, ventricular fibrillation, acetylcholine
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