Role of the Vagus Nerves in the Cardiovascular Changes Induced by Coronary Occlusion

By Peter B. Corb, B.S., and Richard A. Gillis, Ph.D.

Summary
The importance of vagus nerves to the heart rate, contractile force, blood pressure, and incidence of fatal arrhythmias produced by occlusion of the anterior descending branch of the left coronary artery was studied in chloralose-anesthetized cats. Occlusion performed in 20 animals with intact vagus nerves produced significant decreases in heart rate (23 ± 5.3 beats/min), contractile force (23 ± 6.6%), and blood pressure (20 ± 2.7 mm Hg). Time to onset of arrhythmias was 2.6 ± 0.4 minutes and death due to ventricular fibrillation occurred in four of 20 animals. Occlusion performed in 20 animals with bilateral vagotomy and 20 animals with intact vagus nerves but pretreated with atropine did not decrease heart rate and resulted in significantly more deaths. Time to onset of the arrhythmia was significantly less in both cases. Occlusion produced the usual decrease in contractile force and blood pressure. In addition, a delayed (i.e., after sinus rhythm was restored) decrease in blood pressure and contractile force occurred in animals with vagus nerves sectioned. Pacing hearts of animals with intact and functional vagus nerves to rates comparable to those seen in vagotomized and atropinized cats resulted in a mortality rate identical to that seen in controls. On the other hand, time to onset of the arrhythmia was significantly less than controls and equivalent to the onset times of the vagotomized and atropinized groups. These results suggest that 1) efferent vagus nerves mediate sinus bradycardia that occurs after coronary occlusion, 2) presence of efferent vagus tone per se reduces the incidence of death, 3) rate effect of efferent vagal tone increases the time to onset of arrhythmias, and 4) presence of afferent vagal tone counteracts the late decline in arterial pressure and contractile force.

Additional Indexing Words:
Cats Ventricular fibrillation Blood pressure Contractile force Heart rate
Afferent vagal tone Pacing Atropine

Experimental studies of infarction in animals show that coronary occlusion increases activity in sensory and motor nerves of parasympathetic and sympathetic cardiac nerves. However, the relationship of these neural changes to the development of arrhythmias after coronary occlusion is not clear. In a previous study an attempt was made to obtain information on this point by monitoring the spontaneous electrical activity in parasympathetic and sympathetic cardiac nerves during occlusion of the left coronary artery of the cat. It was found that coronary occlusion increased the spontaneous firing in cardiac-bound autonomic fibers and that the enhanced neural activity was correlated in time with electrocardiographic changes consisting of ventricular arrhythmias. Removal of both parasympathetic and sympathetic nervous systems conferred protection against arrhythmias. Although the role of each division was not studied separately, it was concluded that simultaneous activation of both was providing the arrhythmogenic stimulus. In confirmation of this are the results of Scarborough and Sohn showing that either parasympathetic blockade or sympathetic blockade alone failed to alter the incidence of postinfarction arrhythmias, whereas combined blockade of both systems protected animals from arrhythmias.

However, recent evidence suggests that activation of the parasympathetic nervous system may actually decrease the probability of serious arrhythmias after coronary occlusion. For example, it has
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been reported that vagal stimulation will increase ventricular fibrillation threshold in both normal hearts and hearts after coronary occlusion. In addition, administration of atropine was found to increase the incidence of arrhythmias after coronary occlusion. In view of these findings, the purpose of our present study was to determine whether sectioning the vagus nerves would exert a beneficial or harmful influence on ventricular arrhythmias induced by coronary occlusion.

Methods

Cats, unselected as to sex and ranging in weight from 1.5 to 3.9 kg, were used for these experiments. They were anesthetized with intravenously administered alpha-chloralose, 70 mg per kilogram. Mechanical ventilation with room air was instituted through a cuffed endotracheal tube. Tidal volume of the respirator was set at 20 cc/kg while the frequency was set at 19 cycles per min. Catheters were inserted into the right femoral artery and vein of all animals for the purposes of measuring blood pressure and administering drugs, respectively. The animals’ body temperatures were maintained between 37.0 and 38.0°C by an infrared lamp.

The heart was exposed by excising ribs 2, 3, 4 and 5 on the right side. The pericardium was opened and sutured to the chest wall. Coronary occlusion was accomplished by exposing the anterior descending coronary artery and placing a ligature beneath this vessel. In detail, exposure of the vessel was made by gently reflecting the left atrial appendage while separating the left coronary artery and its two main branches from surrounding heart tissue. Care was taken to separate the pericoronary nerves from the anterior descending coronary artery so that they would not be included in the ligature surrounding the vessel. A 4.0 cotton ligature was placed under the anterior descending coronary artery 1 mm distal to its point of origin from the left coronary artery. This ligature was securely tied at the moment when occlusion was desired. Placement of the ligature at this point allowed us to occlude the anterior descending coronary vessel proximal to any branch points.

With the heart exposed, a calibrated Walton-Brodie strain-gauge arch was sutured to the right ventricular wall. The segment of heart muscle beneath the feet of the arch was stretched approximately 50% of its resting length before firmly attaching the arch to the ventricular wall. Right ventricular force was measured because changes in systemic pressures have relatively less effect on the right than on the left ventricular end diastolic fiber length. Systemic arterial pressure, heart rate and rhythm (lead II of the ECG), and myocardial contractile force were continuously monitored on a Beckman multichannel recorder.

Four types of experiments were performed to evaluate the role of the vagus nerves on cardiovascular changes evoked by coronary occlusion:

1) Occlusion was produced in 20 control animals, i.e., animals with all nerves intact.

2) Occlusion was produced in 20 animals with vagus nerves sectioned. In these cats bilateral cervical vagotomy was performed 15 minutes prior to coronary ligation.

3) Occlusion was produced in 20 animals pretreated with atropine. In these cats an intravenous dose of 1 mg/kg atropine was administered 15 minutes prior to coronary ligation.

4) Occlusion was produced in ten animals with “paced” hearts. In these cats pacing wires were sutured to the right atria and pacing was performed with a Medtronic model 5800 Pacemaker. The rate of the pacemaker was set at 230 stimuli per minute using a 1.0 milliamper current strength. Pacing was instituted 15 minutes prior to coronary ligation and was maintained throughout the duration of the experiment.

The following drugs were used: alpha-chloralose (Etablissements Kuhlmann, Paris, France); decamethonium bromide solution (Burroughs Wellcome, North Carolina); atropine sulfate (New York Quinine and Chemical Works, New York City); sodium heparin injection (Organon, New Jersey). Alpha-chloralose was dissolved by heating it in distilled water; the solution was cooled to 37°C before use. Atropine sulfate was dissolved in 0.85% sodium chloride solution. Doses of drugs were calculated and administered as the respective salt.

The data were analyzed by paired comparisons and grouped Student’s t-tests. Chi square analysis for 2 × 2 contingency with the Yates correction was utilized for the death rate data. Criterion used for significance was $P < 0.05$.

Results

To assess the influence of the vagus nerves on the cardiovascular events that occur with acute myocardial infarction, an experimental coronary occlusion model in cats was developed (see Methods). With this preparation, occlusion of the anterior descending branch of the left coronary artery resulted in consistent and therefore predictable changes in heart rate, heart rhythm, arterial blood pressure, and myocardial contractility. These changes consisted of slowing in sinus rate, depression of arterial blood pressure, decrease in cardiac contractile force, depression of the ST segment of the electrocardiogram, and occurrence of arrhythmias. Depression of all of these indices of cardiovascular function was observed within 2 min after occlusion and was followed by a disruption in cardiac rhythm. The time to onset of the arrhythmia was 2.6 ± 0.4 min after occlusion and the duration of the arrhythmia was 35.3 ± 1.8 min. The data obtained from 20 control animals are summarized in the top row of Table 1.

A representative experiment showing the actual ECG, blood pressure, and contractile force changes...
Table 1

Influence of Coronary Artery Occlusion on Heart Rate, Blood Pressure, Contractile Force, and Cardiac Rhythm in Control, Vagotomized, Atropinized, and Paced Animals

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate before occlusion (beats/min)</th>
<th>Mean blood pressure before occlusion (mm Hg)</th>
<th>Mean contractile force before occlusion (g-tension)</th>
<th>Change in heart rate (beats/min)</th>
<th>Change in blood pressure (mm Hg)</th>
<th>Percent change in contractile force</th>
<th>Onset of arrhythmia (min)</th>
<th>Duration of arrhythmia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>196.7 ± 8.0 (20)</td>
<td>114.7 ± 5.1 (20)</td>
<td>10.3 ± 0.68 (15)</td>
<td>-23.1 ± 5.3*</td>
<td>-19.9 ± 2.7*</td>
<td>-22.7 ± 6.6*</td>
<td>2.6 ± 0.4</td>
<td>35.3 ± 1.8</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>220.3 ± 5.9† (20)</td>
<td>127.0 ± 8.5 (20)</td>
<td>11.1 ± 0.54 (14)</td>
<td>+7.4 ± 2.5†</td>
<td>-14.3 ± 3.9*</td>
<td>-36.0 ± 8.0*</td>
<td>1.3 ± 0.1†</td>
<td>34.3 ± 3.2</td>
</tr>
<tr>
<td>Atropine</td>
<td>222.5 ± 5.4† (20)</td>
<td>117.5 ± 6.7 (20)</td>
<td>10.0 ± 0.49 (18)</td>
<td>+1.95 ± 1.9†</td>
<td>-18.1 ± 3.2*</td>
<td>-19.2 ± 5.3*</td>
<td>1.3 ± 0.1†</td>
<td>33.1 ± 3.9</td>
</tr>
<tr>
<td>Paced</td>
<td>231.9 ± 1.6† (10)</td>
<td>118.3 ± 7.3 (10)</td>
<td>9.5 ± 0.2 (10)</td>
<td>0 ± 0</td>
<td>-34.9 ± 4.5*</td>
<td>-46.5 ± 6.6*</td>
<td>1.3 ± 0.2†</td>
<td>33.1 ± 3.1</td>
</tr>
</tbody>
</table>

Numbers in table are means ± SE.

Numbers in parentheses indicate number of animals in each group.

*P < 0.05 with paired comparisons (comparison was made between data obtained during postocclusion period and data obtained during preocclusion period).

†P < 0.05 with group comparisons (comparison was made between data obtained with either vagotomy, atropine or paced groups versus control groups.)

The control group demonstrated the most striking effect of occlusion. These data, depicted in the histograms of figure 2, show that the heart rate increased significantly in the control group, while it decreased in the vagotomized and atropinized groups. The paced group showed a moderate increase in heart rate, indicating that pacing maintained a constant stimulation of the heart. The mean blood pressure in the control group decreased significantly, while it remained stable in the vagotomized and atropinized groups. The contractile force also decreased in the control group, while it remained stable in the vagotomized and atropinized groups. The duration of arrhythmia was longest in the control group, while it was shortest in the vagotomized group.

The recovery of the heart rate, blood pressure, and contractile force after occlusion was slow in the control group, while it was rapid in the vagotomized and atropinized groups. The paced group showed a moderate recovery of the heart rate, blood pressure, and contractile force. The duration of arrhythmia was shortest in the pacing group, while it was longest in the control group.

The results of this study suggest that vagotomy and atropine had a protective effect on the heart, while pacing had a stabilizing effect.
bilateral vagotomv prevented the decrease in heart rate that always occurred immediately after coronary occlusion (see summarized data of table 1). Indeed, a significant increase in sinus rate was observed before the arrhythmia developed. This occurred in spite of the fact that initial heart rates of the “vagotomy” group before occlusion were significantly higher than the initial heart rates of the control group before occlusion. Furthermore, the time to onset of the arrhythmia was significantly shorter than the time to onset seen in the control group of animals (table 1). The duration of the arrhythmia, however, was identical in both groups. Likewise, the decreases in blood pressure and contractile force seen after occlusion but prior to arrhythmia in the animals with vagus nerves sectioned were similar to those decreases seen in animals with vagus nerves intact and functional.
Effects of coronary occlusion (as indicated by Occ †) on blood pressure, contractile force, and heart rate readings of an animal with its nervous system intact (control), an animal with its vagus nerves sectioned (vagotomy), and an animal pretreated with atropine (atropine). V/A at the arrow indicates the point in time when either the vagus nerves were sectioned or when the atropine was administered. Dotted lines indicate the time period that an arrhythmia was present.

(table 1). Also shown in table 1 is the fact that the initial values (i.e., values before occlusion) for blood pressure and contractile force were not different between the two groups.

An experiment of an animal with vagus nerves sectioned showing the actual ECG, blood pressure, and contractile force changes that occurred with coronary occlusion appears as figure 4. Prior to occlusion, sinus rhythm was present and the rate was 240 beats per minute (panel A). One minute after occlusion, a marked decrease in contractile force was apparent (panel B), while only minor changes in heart rate and blood pressure had occurred. One and one-half minutes after occlusion, an arrhythmia developed and was characterized by the presence of numerous ectopic beats interspersed...
Table 2

Influence of Impaired Vagal Function on Recovery of Heart Rate, Blood Pressure, and Contractile Force from the Effects of Coronary Occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Before occlusion</th>
<th>After termination of the arrhythmia</th>
<th>Percent change in contractile force from control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart rate</td>
<td>Mean blood pressure</td>
<td>Change in heart rate from control</td>
</tr>
<tr>
<td></td>
<td>(beats/min)</td>
<td>(mm Hg)</td>
<td>(beats/min)</td>
</tr>
<tr>
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</tr>
<tr>
<td>Atropine</td>
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<td>-4.5 ± 4.8</td>
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<tr>
<td>Paced</td>
<td>231.9 ± 1.6†</td>
<td>118.3 ± 7.3</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

Numbers in table are means ± SE.
Numbers in parentheses indicate number of animals in each group.
*P < 0.05 with paired comparisons (comparison was made between data obtained during postocclusion period and data obtained during preocclusion period).
†P < 0.05 with group comparisons (comparison was made between data obtained with either vagotomy, atropine, or paced groups versus control groups).

between sinus beats (panel C). Within seconds, ventricular fibrillation ensued and the cat did not recover (panel D).

Some animals with vagus nerves sectioned did recover from the severe arrhythmias and the heart rate, blood pressure, and contractile force data obtained at the time of restoration to sinus rhythm are summarized in table 2. As in the control animals, contractile force continued to decrease further after normal sinus rhythm was re-established while heart rate returned to the preocclusion level. Blood pressure also continued to decrease further after the reappearance of sinus rhythm. This is in contrast to the control animals where blood pressure tended to increase toward the normal level once the arrhythmia had terminated. The degree to which pressure and force were depressed in the vagotomy group of animals after termination of the arrhythmias was significantly greater than the degree to which pressure and force were depressed in the control group of animals (table 2). The minute-to-minute changes in rate, rhythm, pressure, and force of an animal with vagus nerves sectioned are graphically displayed as part of figure 2.

In an attempt to identify whether afferent vagal or efferent vagal mechanisms were responsible for the modifications in the cardiovascular responses of animals with sectioned vagus nerves to coronary occlusion, experiments were repeated in animals with intact vagus nerves but pretreated with 1 mg/kg atropine i.v. to block the effect of the efferent vagus nerves. The data obtained are summarized in tables 1 and 2, and figure 3. Representative experiments appear as figures 2 and 5. The incidence of death matched closely that which occurred in vagotomized animals. Thus a greater number of the atropine-pretreated animals
Effects of coronary occlusion on contractile force (CF), blood pressure (BP), and on the electrocardiogram (ECG) of an animal with vagus nerves sectioned. Panel A, control recordings; panels B, C, and D, recordings obtained at 1, 1.5, and 2 minutes after the anterior descending branch of the left coronary artery was occluded, respectively.

died following coronary occlusion as compared to the animals with intact functional vagus nerves (fig. 3). Pretreatment with atropine also prevented the coronary occlusion-induced cardiac slowing and significantly shortened the time to onset of the arrhythmia (table 1). The duration of arrhythmia was identical to that seen in the previous two groups. Likewise, decreases in blood pressure and contractile force seen after occlusion but prior to arrhythmia were similar in magnitude to those decreases seen in the previous two groups of animals (table 1). Also shown in table 1 is the fact that the initial values (i.e., values before occlusion) for blood pressure and contractile force were not different between any of the three groups. However, initial heart rates of the atropine-pretreated animals were significantly higher than the initial heart rates of the control groups.

An experiment of an animal pretreated with atropine showing the actual ECG, blood pressure,
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**Figure 5**

*Effects of coronary occlusion on contractile force (CF), blood pressure (BP), and on the electrocardiogram (ECG) of an animal pretreated with atropine. Panel A, control recordings; panels B, C, and D, recordings obtained at 1, 1.5 and 2 minutes after the anterior descending branch of the left coronary artery was occluded, respectively.*

...and contractile force changes that occurred with coronary occlusion appears as figure 5. Sinus rate prior to occlusion was 214 beats per minute (panel A). One minute after occlusion, decreases in both contractile force and blood pressure were apparent, while heart rate did not change (panel B). Depression of the ST segment of the ECG was also evident. One and one-half minutes after occlusion, ventricular tachycardia of 290 beats per minute developed (panel C), and this rapidly progressed to fatal ventricular fibrillation (panel D).

In the animals that did recover, blood pressure and contractile force remained depressed after normal sinus rhythm was re-established (table 2). Interestingly, the recovery data indicates that animals pretreated with atropine resembled those animals with intact vagus nerves and differed from those animals with vagus nerves sectioned. That is,
blood pressure and contractile force in the atropine group of animals remained depressed at values similar in magnitude to those observed for the control group of animals, and were not depressed to the extent that was observed for the vagotomy group of animals. This result is further illustrated in figure 2 where the minute-to-minute changes in heart rate, heart rhythm, arterial pressure, and contractile force produced by coronary occlusion for an animal of each group appears. A factor common to, and perhaps responsible for the increased incidence of deaths was the faster heart rates that existed in both the vagotomized and atropinized animals prior to and immediately after occlusion. To assess the role of the faster heart rate in the terminal arrhythmias following coronary occlusion, ten animals with functional vagus nerves but with hearts electrically paced at the higher rates (231.9 ± 1.6 beats/min) observed in the two groups without cardiac vagal tone were studied (table 1). The death rate is presented as one of the histograms of figure 3 and indicates that the incidence of fatal ventricular fibrillation was identical to that seen in the control animals. On the other hand, the time to onset of the arrhythmias following coronary occlusion in the group with their hearts paced was similar to the onset times for the vagotomy and atropine groups, and significantly less than the onset time for the control group (table 1).

**Discussion**

The purpose of our study was to assess the role of the vagus nerves in the cardiovascular changes provoked by experimentally induced myocardial infarction. The results obtained indicate that these nerves represent a major determinant of the cardiovascular changes that occur with coronary occlusion. This was most apparent in the case of the number of animals dying from ventricular fibrillation. The presence of the vagus nerves reduced the percentage of animals dying from 60% to 20%. The vagus nerves were also found to mediate the sinus bradycardia seen immediately after occluding the coronary artery. Furthermore, the vagus nerves were found to counteract the delayed deleterious effects (i.e., effects after sinus rhythm was restored) of coronary occlusion on arterial blood pressure and contractile force. Finally, the presence of the vagus nerves delayed the appearance of the arrhythmias following coronary occlusion.

The ability of parasympathetic cardiac nerves to influence the cardiovascular changes produced by experimentally induced myocardial infarction may reflect either an alteration in the afferent neural input to the central nervous system or an alteration in the efferent neural output from the central nervous system to peripheral structures. To distinguish between these two pathways, studies were performed in animals in which the effects of efferent parasympathetic outflow were blocked by atropine. Animals thus treated were not protected from fatal ventricular fibrillation. Moreover, these animals did not exhibit bradycardia and the appearance of the arrhythmias was not delayed. However, the deleterious effects of coronary occlusion on arterial blood pressure and contractile force once sinus rhythm was restored did not become evident. These results suggest that efferent vagal tone was responsible for reducing the number of deaths, producing bradycardia, and delaying the onset of arrhythmias, while afferent vagal tone was responsible for counteracting the late decline in arterial pressure and contractile force.

The mechanism whereby efferent vagal tone leads to heart rate slowing is obvious from the studies of Hutter and Trautwein.10 Less obvious are the mechanisms whereby efferent vagal tone influences mortality rate and time to onset of the arrhythmias. One possibility is that vagal tone to the heart per se exerts an influential effect on arrhythmogenesis. The other possibility is that vagal tone leads to a slowing in sinus rate and as a consequence of the slower rate, alterations in the electrical stability of the heart occurs. To separate out the rate effects of vagal stimulation from vagal effects per se, hearts of animals with intact vagus nerves were electrically driven to rates comparable to those seen in vagotomized and atropinized cats. Under these conditions, animals were protected from fatal ventricular fibrillation but the appearance of arrhythmias was not delayed. These results suggest that efferent vagal tone per se was responsible for reducing the number of deaths while the rate effect of efferent vagal tone was responsible for increasing the time to onset of the arrhythmias.

Our results do not reveal how the efferent vagus exerts its protective effect. However, data of other investigators strongly suggest that efferent vagal nerves innervate the ventricle and their activation has a stabilizing influence on cardiac electrical activity. For example, numerous studies have shown that electrical stimulation of decentralized vagus nerves produces slowing of ectopic ventricular pacemakers.11–15 Greenspan, Wunsch, and Fisch18

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have reported that efferent vagal stimulation decreases the amplitude of the t wave of the ECG. Scherlag et al.17 showed that ventricular ectopic beats induced by coronary ligation could be abolished by electrical stimulation of the decentralized vagus nerves. Kent et al.6 reported that efferent vagal stimulation increased ventricular fibrillation threshold in dogs with a fixed heart rate. The same group18 also showed that destruction of the specific anatomic site supplying postganglionic cholinergic fibers to the ventricle prevented the effect of vagal stimulation on ventricular fibrillation threshold. Based on the above findings, activation of efferent fibers could exert a protective effect against fatal ventricular fibrillation by increasing ventricular fibrillation threshold. The increase in threshold may in turn be due to either a decrease in automaticity of ventricular cells or a decrease in the disparity of refractory periods of ventricular cells. The latter does not seem to be the case as Kent et al.6 have shown no change in the disparity of refractory periods of ischemic cardiac tissue when the cervical vagi were stimulated in dogs with constant heart rates. However, their refractory period measurements were made from epicardial cells and may not be a true reflection of electrical events occurring in cells lying much deeper in the myocardium. The other possibility for the increased ventricular fibrillation threshold, i.e., a decrease in automaticity, seems plausible as stimulation of the cardiac vagus has been shown to decrease the idioventricular rate of dogs with atrioventricular heart block.12,15 Consistent with this are the findings of Bailey et al.19 showing that relatively small concentrations of acetylcholine will decrease the slope of diastolic depolarization of canine Purkinje cells.

Another mechanism, albeit indirect mechanism, that may in part reduce automaticity is inhibition of norepinephrine release from cardiac sympathetic nerve terminals. The arrhythmogenic effects of catecholamines are well known and are thought to be largely due to enhancement of automaticity.20 Coronary occlusion has been shown to increase the spontaneous activity in cardiac sympathetic fibers,4 and increased levels of plasma and urinary norepinephrine are found after myocardial infarction.21–23 Vagal stimulation has been shown to decrease norepinephrine output from postganglionic sympathetic cardiac nerves,24 and in this way may prevent automaticity effects of released norepinephrine. In addition, atropine prevents vagal stimulation from inhibiting the release of transmitter from sympathetic nerves. Therefore, the deleterious effects of vagotomy and atropine should be similar and this was the case in our experiments.

As mentioned above, the rate-slowing effect of efferent vagal tone was found to be responsible for increasing the time to onset of the arrhythmias. This result may be explained by the fact that the slower heart rate decreases the metabolic myocardial requirements and the degree to which specialized automatic and conducting cells are deprived of oxygen. This would delay the ischemic injury to these cells and presumably the appearance of the arrhythmia.

Our results indicate that afferent vagal tone may have been responsible for counteracting the late decline in arterial pressure and contractile force. This might be explained by the findings of Staszewska-Barczak,25 in which sectioning both vagus nerves prevented the increase in plasma levels of epinephrine produced by occlusion of the anterior descending branch of the left coronary artery of dogs. The increase was also prevented by sectioning both thoracic splanchnic nerves. Topical application of lidocaine to the infarcted area of the heart prevented the increase in plasma levels of epinephrine. The results of Staszewska-Barczak suggest that coronary occlusion excites cardiac reflexes which in turn excites nerves controlling release of epinephrine. The afferent pathway includes the vagus nerves while the efferent pathway consists of the splanchnic nerves. Interruption of the reflex by sectioning the afferent vagal nerves in our study would mean the loss of cardiovascular support provided by circulating epinephrine released from the adrenal medulla.

Our finding that the presence of cardiac vagal nerves protected animals against fatal ventricular fibrillation is not new but was reported in a rarely quoted study of Dokukin.26 Using cats anesthetized with urethan, compression of the anterior descending branch of the left coronary artery resulted in a decrease of ventricular fibrillation in animals with intact vagus nerves as compared to animals with bilateral vagotomy. Dokukin's and our findings however achieve special significance in view of the widespread practice of using atropine to increase heart rates of patients with acute myocardial infarction. The atropine would of course remove the effects of the cardiac vagus nerves on the heart and presumably increase the chances for fatal ventricular fibrillation.

The controversy over using atropine in myocardial infarction patients has recently been brought to
light in the studies performed by investigators at the National Institutes of Health. Their studies were performed in dogs undergoing occlusion of the anterior descending branch of the left coronary artery. They found that: 1) atropine administration significantly increased the incidence of arrhythmias (i.e., 93% incidence as compared to 48% in controls), 2) vagal stimulation increased the ventricular fibrillation threshold when heart rate was held constant, and 3) increasing heart rate by decreasing vagal stimulation decreased ventricular fibrillation threshold. Our findings concur with their findings, but whereas they conclude that both heart rate and vagal tone per se are important factors in protecting animals from serious ventricular arrhythmias, we conclude that vagal tone per se is the predominant factor in protecting animals from fatal ventricular arrhythmias.

There are four studies that we are aware of with results that are somewhat at odds with our results. Leroy, Fenn, Gilbert reported that administration of atropine reduces the mortality rate of either anesthetized or conscious dogs after occlusion of the circumflex branch of the left coronary artery. Ascanio et al. reported that bilateral vagotomy prevented ventricular fibrillation of dogs following myocardial infarction produced by injecting a necrotizing agent—hexachlorotetrafluorobutane—into the circumflex branch of the left coronary artery. The difference between these findings and ours may be related to the site of occlusion. Our study as well as the studies of others involved interfering with blood flow in the anterior descending branch of the left coronary artery while Leroy et al. and Ascanio et al. were interfering with blood flow in the circumflex branch of the left coronary artery. It may be that efferent vagal tone influences electrical stability of the heart in opposite directions depending on which coronary vessel is occluded. Another reason for the differing results obtained in our study as compared to the study of Ascanio and colleagues is the method we used for producing myocardial ischemia. We occluded the coronary artery whereas they injected hexachlorotetrafluorobutane. This agent might stimulate myocardial chemoreceptors and therefore activate cardiac reflexes that are unaffected by mechanical occlusion of a coronary artery.

In a third study, Scarborough and Sohn reported that the combination of thoracic epidural block and atropine protected cats from ventricular arrhythmias after occlusion of the anterior descending branch of the left coronary artery, whereas neither procedure by itself resulted in protection from ventricular arrhythmias. Their results suggest that atropine might have beneficial effects when given to animals with depressed cardiac sympathetic function. Finally, Madan and Gupta observed that atropine administration to dogs with ventricular arrhythmias produced by the two-stage coronary ligation technique of Harris caused total suppression of ectopic beats and restoration of sinus rhythm. Conversion with atropine was not due to overdrive suppression of the ventricular rate as the rate of the sinus was less than the ventricular rate. Interestingly, acetylcholine was also found to suppress ectopic beats and to restore the rhythm to a sinus mechanism. In our study we did not attempt either to administer atropine or to perform vagotomy once the arrhythmia had developed. Therefore, while the results of Madan and Gupta with atropine appear to contradict our results, they are not really analogous to ours. Furthermore, the fact that both atropine and acetylcholine were antiarrhythmic implies action of these agents on nonmuscarinic cholinergic sites.

In conclusion, the most significant finding of the present study was the protective effect of cholinergic nerves on cardiac rhythm. Animals with functional cardiac vagus nerves had a higher survival rate from ventricular arrhythmias induced by coronary occlusion. The higher survival rate occurred independent of heart rate, and appeared to be due to a stabilizing influence of the vagus nerves on the ventricle.

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