Beneficial Effects of Vagal Stimulation and Bradycardia During Experimental Acute Myocardial Ischemia

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SUMMARY

It is commonly believed that vagally-mediated bradycardia predisposes to ventricular fibrillation (VF) during acute myocardial ischemia. Recent experimental studies, however, have shown that bradycardia and vagal stimulation independently raise the threshold for electrically induced VF in the ischemic canine heart. To determine the influence of vagal stimulation on the spontaneous development of VF occurring during acute myocardial ischemia, open-chest dogs with acute coronary occlusion were observed with and without electrical vagal stimulation. When heart rate was allowed to fall, mean time to VF was 14.7 ± 2.1 min (s.e.) in the control dogs (heart rate about 180/min), 23.4 ± 1.9 (P < 0.01) in the dogs with low intensity vagal stimulation (heart rate about 100/min), and 28.6 ± 0.9 (P < 0.001) in dogs with high intensity vagal stimulation (heart rate about 60/min). Only 10% of the control animals survived after 30 min of occlusion compared with 40% (NS) of the dogs with low intensity vagal stimulation and 71% (P < 0.05) of the dogs with high intensity vagal stimulation. Thus, vagal stimulation and bradycardia were associated with a postponement or prevention of VF. In a second series of animals with heart rate maintained constant by right ventricular pacing, vagal stimulation continued to exert a protective effect against the development of VF. Time to VF was increased from 11.0 ± 2.0 min in control animals to 22.6 ± 2.5 min in dogs with vagal stimulation (P < 0.005), and percent survival was enhanced (12% in control animals versus 57% in the vagally stimulated group, P < 0.02). Similar results were observed in a third series of dogs in which electrical stimulation was applied to the peripheral ends of the cut cervical vagi. We conclude that vagal stimulation, with or without accompanying bradycardia, reduces the incidence of spontaneous VF in experimental coronary occlusion. Thus, enhanced vagal tone might act to reduce, rather than increase, the risk of arrhythmic death occurring during acute myocardial ischemia in man.

Additional Indexing Words:
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Ventricular fibrillation
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VAGALLY-MEDIATED SINUS BRADYCARDIA, when it occurs during acute myocardial infarction, has been considered an unstable rhythm that may lead to fatal ventricular arrhythmias.1, 2 However, the results of recent studies from our laboratory suggest that vagal influences may actually protect the heart against ventricular irritability instead of fostering its development.3, 4 During experimental acute myocardial ischemia: 1) both bradycardia and vagal stimulation per se increase the threshold to electrically-induced ventricular fibrilla-

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bradycardia, in a canine model of acute myocardial ischemia that has a high predilection for spontaneous ventricular fibrillation.

Methods
Preparation
Male mongrel dogs weighing 17-32 kg received sufficient sodium pentobarbitol for induction of anesthesia (mean dose = 40.3 ± 0.5 mg/kg) prior to being intubated and ventilated with a respirator. A transmural aortic catheter was inserted and the electrocardiogram was recorded using standard subcutaneous leads. Through a left thoracotomy incision, the left anterior descending and first septal coronary arteries were exposed, and electrodes were sutured to the epicardium of the right ventricle and left atrium (for pacing and recording, respectively). The cervical vagi were isolated and connected through bipolar platinum electrodes to a battery-powered phasic electric stimulator. Mean and phase aortic pressure, lead II of the electrocardiogram, and left atrial electrogram were recorded on both a direct writing recorder and magnetic tape.

Arterial oxygen saturation and pH were maintained in the physiologic range. At the beginning of each study, the ability to reduce heart rate to 50-60/min by bilateral electrical stimulation of the cervical vagi (0.3 msec, 20-60 Hz, and 1.5-6 V) was demonstrated. Animals were then entered into one of three protocols. After initiating the intervention appropriate for each protocol, acute myocardial ischemia was produced by occlusion of both the left anterior descending and first septal coronary arteries. Care was taken not to occlude or constrict the left circumflex coronary artery. Observations were continued and coronary occlusion maintained until spontaneous ventricular fibrillation occurred or until 30 min had elapsed. This time period was chosen since previous experience with the model demonstrated a high incidence of ventricular fibrillation occurring within 30 min of occlusion. Whenever necessary, the intensity of vagal stimulation was adjusted to maintain atrial rate within the designated range.

Experimental Protocols
Group I: Stimulation of intact vagi with heart rate allowed to fall
Dogs were randomly assigned (by drawing previously prepared lots) to one of three subgroups: no vagal stimulation (heart rate at control level), low intensity vagal stimulation (heart rate approximately 100 beats/min), or high intensity vagal stimulation (heart rate approximately 60 beats/min). Coronary occlusion was produced as described above.

Group II: Stimulation of intact vagi with constant heart rate
After right ventricular pacing at 180 beats/min had been instituted with slightly greater than threshold intensity (3-7 V) and duration of stimulus (2-4 msec), dogs were randomized into control or vagally stimulated subgroups and coronary occlusion produced as described above. Cardiac vagal effect was regulated by adjustment of vagal stimulation to keep the atrial rate at approximately 60 to 100 beats/min.

Group III: Stimulation of decentralized vagi with constant heart rate
The animals were studied in an identical fashion to Group II except that prior to occlusion both vagi were sectioned cranial to the position of the stimulating electrodes. This was done to exclude the possibility of alteration of results by electrical stimulation of afferent nerves contained in the vagal trunk.

Dogs were excluded from statistical consideration if autopsy did not confirm complete occlusion of both the left anterior descending and first septal coronary arteries, or if cardiogenic shock (mean aortic pressure less than 50% of preocclusion value) occurred and did not resolve spontaneously within 10 min, and at least 5 min before onset of ventricular fibrillation (three control dogs and five with vagal stimulation were excluded for the latter reason).

No significant differences existed in dog weight, dose of anesthetic agent, and pre-intervention blood pressure and heart rate between vagal and control animals in each of the three groups.

Statistical comparisons were made of length of survival by analysis of variance, serial blood pressure changes by regression analysis, and percentage survival by the Fisher exact test.

Results

Group I
In the 27 animals that qualified for study, heart rates after occlusion ranged from 140 to 215 per min in the control group, 80 to 110 per min in dogs with low intensity vagal stimulation, and 55 to 77 per min in animals with high intensity vagal stimulation. Blood pressure tended to fall after occlusion in all three subgroups and maintained a subgroup mean value relative to preocclusion levels of 69 to 96% (fig. 1, upper panel). There were no significant differences in blood pressure among the three subgroups.

Figure 1
Mean and standard error (vertical bars) of the mean arterial blood pressure for those animals alive at each observation point. Horizontal axis denotes time following coronary occlusion. Upper panel: Group I, vagal stimulation with heart rate allowed to fall. Middle panel: Group II, vagal stimulation with heart rate maintained constant. Lower panel: Group III, vagus cut, efferent vagal stimulation only, and heart rate maintained constant by ventricular pacing.
Vagal stimulation was associated with a protective effect, evident in both mean duration of survival and in percent survival to the end of the 30 min observation period. Survival time (defined as the time to ventricular fibrillation or when ventricular fibrillation did not occur, 30 min) was significantly prolonged in both subgroups with vagal stimulation relative to control (fig. 2, left panel). Mean values were 28.6 ± 0.9 min (SE) \( P < 0.001 \) with high intensity vagal stimulation, 23.4 ± 1.9 \( P < 0.01 \) with low intensity vagal stimulation, and 14.7 ± 2.1 in the control state. Although dogs with high intensity vagal stimulation tended to survive longer than those with low intensity vagal stimulation, this difference did not achieve statistical significance. In both groups with vagal stimulation, the percentage of animals alive at 30 min was increased relative to control. Moreover, the percentage survival tended to correlate directly with the intensity of vagal stimulation (71% in the group with high intensity vagal stimulation, 40% in the group with low intensity stimulation, and 10% in the control group; fig. 3, left panel). The difference in percentage survival between the group with high intensity vagal stimulation and the control group was statistically significant \( P < 0.05 \).

**Group II**

The ventricles were paced at a constant rate of 180/min in 31 animals with intact vagi. Blood pressure fell only slightly after occlusion and subgroup means ranged from 88% to 104% of preocclusion values (fig. 1, middle panel). There were no significant differences in blood pressure between control animals and animals with vagal stimulation. Even in the absence of its bradycardic action, vagal stimulation was associated with a protective effect relative to control, as evidenced by prolongation of mean survival time (22.6 ± 2.5 min for the group with vagal stimulation vs 11.0 ± 2.0 for control dogs; \( P < 0.005 \), fig. 2, middle panel) and also by increase in percent survival (57% vs 12%; \( P < 0.02 \), fig. 3, middle panel).

**Group III**

Thirty-three animals with vagi cut had their hearts paced at a constant rate of 180 per min. In these dogs with decentralized vagi, blood pressure fell slightly after occlusion and subgroup mean blood pressures ranged from 74 to 98% of preocclusion values (fig. 1, bottom panel). No significant difference in blood pressure between animals with and without vagal stimulation was demonstrated. As in the group with vagi intact, vagal stimulation was associated with protection against arrhythmic death. Survival time was significantly prolonged relative to control in the vagally-stimulated dogs (19.7 ± 2.2 min vs 12.3 ± 2.3; \( P < 0.05 \), fig. 2, right panel). The percent survival was also increased relative to control (38% vs 18%), but the difference did not achieve statistical significance (fig. 3, right panel).

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*Figure 2*

Effect of vagal stimulation on survival time (defined as the time from initiation of coronary occlusion to onset of ventricular fibrillation, or in the absence of ventricular fibrillation, as 30 min, the time of termination of observation). Symbols denoting the mean and standard error of the mean are located to the right of each column of points representing the individual animals in each subgroup. Low int vagal stim = low intensity vagal stimulation. \( P \) values are located in brackets above the subgroups. NS = not significant.

*Figure 3*

Effect of vagal stimulation on survival. The number of survivors (numerator) and the total number of animals studied (denominator) in each subgroup is shown at the bottom of the corresponding bar. Levels of significance are located in brackets above. NS = not significant.
Discussion

In contrast to commonly-held beliefs, the results of the present investigation demonstrate that vagal stimulation exerts a protective influence against the spontaneous development of ventricular fibrillation during acute myocardial ischemia. Thus, while only 10% of control animals survived 30 min of occlusion of the left anterior descending and first septal coronary arteries, 40% of dogs with low intensity vagal stimulation and over 70% of dogs with high intensity vagal stimulation survived (fig. 3). The protection afforded by the vagus was also demonstrated by the more prolonged survival time of the vagally-stimulated subgroups (fig. 2).

The mechanisms responsible for the protective effect seen in our studies are undoubtedly multiple. When heart rate is slowed during acute coronary occlusion, even in the absence of changes in vagal tone, ventricular electrical stability is enhanced (i.e., the threshold at which the ventricle can be fibrillated electrically is increased and the disparity of ventricular refractory periods is decreased). This effect is probably related to the more favorable balance between myocardial oxygen supply and demand produced by the reduction in heart rate, thereby leading to a reduction in the intensity of the ischemic insult. Thus, slowing the heart rates per se (from approximately 180/min in the control subgroup to approximately 100/min and 60/min in the two subgroups with vagal stimulation) probably contributed to the protective effects observed in the vagally-stimulated dogs. However, it also has been shown previously that stimulation of the vagus increases ventricular fibrillation threshold in both ischemic and nonischemic hearts even when heart rate is held constant by ventricular pacing. This finding suggested that augmented vagal tone, independent of reduction in heart rate, contributes to increased ventricular electrical stability in the presence of acute ischemia. The present investigation confirms this hypothesis: when heart rate was held constant by ventricular pacing, a highly significant increase in both survival time and percent of animals surviving coronary occlusion occurred in the dogs with vagal stimulation (figs. 2 and 3).

Thus, the beneficial effects of vagal stimulation on electrically-induced ventricular fibrillation during ischemia shown in previous studies were translated in the present study into an actual postponement or prevention of spontaneous ventricular fibrillation and death.

There are several other considerations that may be relevant to the mechanism responsible for the protective effect of the vagus. Feigl demonstrated that vagal stimulation decreased coronary artery resistance in the nonischemic canine heart. It therefore is possible that vagally-mediated changes in coronary vascular resistance could produce favorable alterations of coronary blood flow during myocardial ischemia as well. Vagal stimulation also has been shown to decrease contractility, and it is possible that during myocardial ischemia such an effect may favorably alter the balance between myocardial oxygen supply and demand and thereby diminish the incidence of ventricular fibrillation. However, this mechanism probably plays a minor role, if any, since the effects of the vagus on ventricular contractility are small and since the increase in ventricular fibrillation threshold produced by vagal stimulation occurs even in the absence of myocardial ischemia.

Studies from this laboratory recently demonstrated that Purkinje fibers present in the ventricular septum of normal dogs are encapsulated by a rich network of cholinergic nerves. When a neurotoxic agent was injected into the para-aortic area adjacent to the atrioventricular node (an area containing cholinergic ganglia that supply postganglionic fibers to the ventricles) the capacity of the vagus to increase ventricular fibrillation threshold was abolished. This elimination of the protective effect of the vagus was associated with disappearance of the cholinergic fibers previously found in abundance adjacent to the Purkinje fibers of the ventricular septum. Thus, it is possible that parasympathetic cholinergic nerves have the capacity to stabilize the electrical properties of the Purkinje system. If such is the case, it would explain an important component of the protective effects exerted by a vagal stimulation on the spontaneous development of ventricular fibrillation during acute myocardial ischemia.

The canine cervical vagal trunk contains not only vagal efferent fibers but also sympathetic efferent fibers and a variety of afferent fibers, autonomic and nonautonomic. Since a protective effect of vagal stimulation was demonstrated in experiments in which the vagal trunk was cut and stimulation confined to the peripheral end (figs. 2 and 3), increased survival during acute infarction produced by vagal stimulation cannot be ascribed to centrally mediated reflexes initiated by electrically produced afferent impulses. Moreover, when cardiac sympathetic tone is increased by stimulation of the stellate ganglia, there is a resultant decrease in electrical stability of the ventricle; this makes it unlikely that the reduced incidence of ventricular fibrillation following stimulation of the peripheral end of the vagus could be attributed to increased sympathetic activity to the myocardium.

Corr and Gillis recently have examined the in-
fluence of removal of vagal tone on the incidence of ventricular fibrillation following coronary artery occlusion in cats. In contrast to our study in which animals were anesthetized with pentobarbital (which is associated with decreased vagal tone), these investigators employed $\alpha$-chloralose anesthesia which results in substantial basal vagal tone. They demonstrated that when such basal vagal tone is eliminated by vagotomy or atropine, the occurrence of ventricular fibrillation during coronary occlusion is increased. These results are in agreement with our data, and thus the protective role of the vagus during acute ischemia does not appear to be peculiar to the canine model.

It should be noted, however, that both cat and dog studies employed acute left anterior descending occlusion in animals otherwise free of coronary or myocardial disease. It is possible that the net beneficial effect of vagal stimulation demonstrated in these investigations may be modified in posterior ischemia, in ischemia selectively affecting the atrioventricular node, or in ischemia associated with multivessel coronary disease or prior myocardial damage and fibrosis. Moreover, it also should be pointed out that in the present investigation, although blood pressure fell slightly during myocardial ischemia, severely hypotensive animals were not studied and there were no significant blood pressure differences between control and vagally stimulated dogs. Hence, our data may not be applicable to that specific situation in which vagally-mediated bradycardia results in severe hypotension. For example, it is possible that a vagolytic intervention under these circumstances may lead to a net beneficial effect if the decrease in vagal tone results in correction of the hypotension (and hence increased coronary perfusion pressure) without an excessive increase in heart rate.

It should also be re-emphasized that this study made no attempt to delineate the importance of the temporal relation of vagal activity to coronary occlusion, as vagal stimulation was maintained before, during, and after coronary occlusion. Finally, the effect of vagal stimulation alone (groups II, III) was assessed at a constant but rapid heart rate of 180/min. It is likely that the beneficial influence of vagal stimulation would have been present at lower heart rates as well since ventricular fibrillation threshold is increased by vagal stimulation at heart rates as low as 50/min.3

In conclusion, it would appear that the commonly accepted dictum that enhanced vagal activity during acute coronary occlusion exerts a potentially deleterious effect may be in error. The results of the present study, as well as the electrophysiologic and arrhythmic observations of previous studies, indicate that the incidence of spontaneously developing ventricular fibrillation occurring during acute experimental coronary occlusion is reduced by vagal stimulation, with or without accompanying bradycardia. Although these results may not be directly applicable to the clinical situation, the evidence supports the hypothesis that, in the absence of hypotension, vagal tone to the heart may tend to reduce rather than increase the susceptibility to the development of fatal arrhythmias.

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