Ventricular Ectopic Rhythms following Vagal Stimulation in Dogs with Acute Myocardial Infarction

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SUMMARY
Vagal stimulation inducing significant bradycardia did not precipitate ventricular fibrillation in any of 34 dogs subjected to ligation of the left anterior descending coronary artery. Vagal stimulation, however, did result in two distinct types of ventricular arrhythmias occurring at different times following coronary occlusion. Within 3 hours, couplets and salvos were provoked which were overdriven by pacing at slow rates. From 4.5 to 9 hours ventricular tachycardia resulted which was slower in rate than the intrinsic sinus rhythm and could be overdriven only by pacing at rates faster than the ectopic mechanism. The response to acetylcholine administration was similar to that of vagal stimulation. By pacing in the presence of complete heart block or by the use of beta-adrenergic blockade, bradycardia was shown to be the basis for the ventricular arrhythmias. Reentry is believed to be the mechanism for the ectopics provoked by bradycardia early after coronary occlusion, while enhanced Purkinje fiber automaticity may account for the late arrhythmias.

Additional Indexing Words:
Ventricular tachycardia  Coronary occlusion  Ventricular premature beats
Beta-adrenergic blockade  Bradycardia  

Bradycardia is known to facilitate ventricular ectopic activity. This has been noted in man after carotid sinus massage, during digitalis intoxication, after the long cycle of sinus arrhythmia, and after pauses in atrial fibrillation, as well as during slowing of heart rate in acute myocardial infarction. In animal studies bradycardia has been demonstrated to facilitate ectopic beat formation, to increase temporal dispersion of refractory period duration, and to reduce significantly the threshold for ventricular fibrillation.

Bradycardia is common in the early stages of acute myocardial infarction. It is believed to be due to vagal reflexes originating in the region of the coronary sinus and posterior portions of the interatrial septum as well as the immediate area around the left coronary artery. Since the risk of sudden death is highest at the very inception of acute myocardial infarction when bradycardia is also most common, it has been suggested that bradycardia may predispose to ventricular fibrillation.

This question was examined in dogs with myocardial infarction by determining the effects of vagal stimulation on ventricular rhythm. Harris has described three sequential phases following coronary artery ligation in the dog. Within 10–30 sec after occlusion of the LAD frequent ventricular premature beats and ventricular tachycardia emerge. This is followed by a quiescent period lasting 6–12 hours during which ectopic activity diminishes or disappears entirely. Thereafter, ventricular ectopic activity recurs most commonly in the form of multiform ventricular tachycardia, and persists for about 48–72 hours. The present investigations involved repeated vagal nerve stimulation during each of these phases. Particular attention was directed to the quiescent period because it permitted examination of the effects of vagal stimulation on cardiac rhythm independent of any dysrhythmia already present.

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Material and Methods

Thirty-eight 15–20 kg mongrel dogs were utilized in this study. Animals were anesthetized with intravenous pentobarbital 30 mg/kg and were given additional increments of 60 mg as needed. Respiration was maintained through a cuffed endotracheal tube by either a Harvard ventilatory pump or a Bird respirator. Cardiac rhythm and blood pressure were monitored and recorded with a Brush two-channel recorder, utilizing lead II of the electrocardiogram and a femoral artery catheter connected to a Statham pressure transducer.

A modification of the two-stage technic of Harris was employed for coronary artery occlusion. After exposure of the heart through a fourth intercostal space thoracotomy, a 20-gauge needle was positioned alongside the proximal portion of the LAD coronary artery. A silk ligature was placed around the vessel 20 mm from its origin, and was tightened and tied. The needle was then removed, resulting in a constricted vascular lumen approximating the diameter of the 20-gauge needle. At 15 and again 25 min following the initial occlusion, hemostats were suspended from the free ends of the ligature, thereby further decreasing the vessel lumen. At 30 min the LAD was completely ligated. This resulted in bluish discoloration of the anterosetal myocardium and ST-segment elevation in the monitor lead.

Vagal Stimulation before and after Coronary Occlusion

The cervical vagus was stimulated in 36 dogs; the right in 21, and the left in 15. In 26 animals stimuli were applied to the intact nerve using the bared end of a Teflon-coated stainless steel wire embedded into a silastic cuff of 1 cm in length secured around the nerve. In the remaining 10 dogs, the vagus nerve was transected and two 25-gauge platinum needle electrodes were inserted into the body of the distal portion of the nerve. Rectangular stimuli were delivered by a Grass SD9 pulse generator. The minimum amount of current necessary to induce complete asystole was utilized. This was achieved with stimuli of 5–40 μA, 0.5–5.0 msec in duration and 10–60 Hz. In the first 25 animals stimulation was maintained for 10 sec. Since escape rhythms were not seen in these animals during this 10-second period, vagal stimulation in the remaining 11 animals was maintained until an escape rhythm appeared. This generally required vagal stimulation for a period of 20–30 sec.

To determine the effect of vagal stimulation on the normal myocardium, the vagus was stimulated three times at 5-min intervals prior to coronary artery occlusion. Following LAD ligation, vagal stimulation was repeated every 5 min. The experiment was terminated when the animal developed persistent ventricular tachycardia independent of vagal stimulation.

To clarify the mechanisms involved in cardiac rhythm alterations resulting from vagal stimulation, the following additional procedures were carried out: (1) slowing either by means of acetylcholine administration, or by cessation of ventricular pacing in animals with complete A-V block; (2) ventricular pacing during vagal stimulation; and (3) vagal stimulation during beta-adrenergic blockade.

Acetylcholine Administration and Cessation of Ventricular Pacing in Complete A-V Block before and after Coronary Artery Occlusion

Acetylcholine was given intravenously as a single bolus injection to three dogs. A dose of 5 mg was selected since it resulted in approximately 10 sec of asystole, similar in duration to that ensuing after vagal stimulation. Acetylcholine was injected once before the coronary artery was ligated and at hourly intervals after occlusion until emergency of persistent ventricular tachycardia unrelated to drug administration.

Complete A-V block was produced in two dogs by surgical interruption of the A-V nodal pathways. The ventricles were then paced with an American Optical Company demand pacemaker (model AOP) by means of two bared tipped Teflon-coated stainless steel wires attached to the right ventricular epicardium. A pacing rate of 140 beats/min was utilized to approximate the sinus rate during pentobarbital anesthesia. Abrupt cessation of pacing resulted in asystole of similar duration to that induced by vagal stimulation. Cessation of pacing was maintained for 30 sec and was performed three times at 5-min intervals prior to coronary artery occlusion. After LAD ligation, pacing was interrupted hourly until the advent of sustained ventricular tachycardia.

Ventricular Pacing during Vagal Stimulation and Acetylcholine Administration

In order to prevent cardiac slowing during vagal stimulation, pacing was employed in eight dogs. In three additional animals, the heart was paced after acetylcholine administration. During the vagal stimulation experiments, the initial pacing rate was 10 beats/min less than the prevailing sinus rate. The pacing rate was then reduced by 10 beats/min during each period of vagus stimulation until a rate of 50/min during each period of vagus stimulation until a rate of 50/min was reached. When either vagal stimulation or acetylcholine injection provoked ventricular arrhythmias, ventricular pacing was set at a level approximating the control sinus rate and the cholinergic stimulus was repeated. This provided information whether factors other than bradycardia were implicated in the cholinergic evoked ventricular arrhythmias.

Vagal Stimulation during Beta-Adrenergic Blockade

In order to exclude effects from vagal sympathetic fibers or reflex sympathetic activity, beta-adrenergic blockade was employed. This was accomplished by the pure beta-blocking drug AY 21011 (practolol) presumed to be free of direct antiarrhythmic properties. Efficacy of beta-adrenergic blockade was tested prior to the definitive experiments. The appropriate dose for each dog was determined 2 days prior to the definitive experiment by testing for antagonism to isoproterenol-induced tachycardia. Isoproterenol was administered in a dose of either 0.4 mcg/kg or 0.8 mcg/kg intravenously in order to increase the heart rate by more than 50%. Practolol 5 mg/kg was then given intravenously and isoproterenol administration was...
repeated. Dunlop and Shanks found that 5 mg/kg of practolol prevented isoproterenol-induced heart rate acceleration for a period of 2 hours.

The effect of beta-blockade on the response to vagal stimulation was studied in seven dogs. Vagal stimulation before and after coronary occlusion was performed as described above. Since the ventricular arrhythmias provoked by vagal slowing differed when stimulation was accomplished early as compared to late in the quiescent period, the effects of beta-adrenergic blockade were studied during these two phases following LAD occlusion.

**Results**

**Effects of Coronary Occlusion**

Within 30 min after total LAD coronary artery occlusion, 21 of 38 dogs (55%) developed ventricular ectopic activity. This consisted of ventricular premature beats in 21 (55%), paroxysms of ventricular tachycardia in 12 (31%), and ventricular fibrillation in seven (18%). Three of the seven dogs were successfully defibrillated and continued in the study, thus 34 animals were involved in the ensuing experiments. After the initial phase of arrhythmia, ectopic activity almost completely disappeared. A quiescent period was observed in all 34 dogs and lasted for 6-12 hours with a mean duration of 8.0 hours. In 33 of the animals ventricular tachycardia then emerged, hereafter referred to as “late VT.”

**Vagus Stimulation**

Vagal stimulation resulted in asystole in all animals. Prior to coronary artery occlusion, asystole lasted 12-23 sec before an idioventricular escape rhythm emerged (fig. 1a). Ventricular arrhythmias did not occur with vagal stimulation prior to coronary artery occlusion.

Following coronary artery occlusion, stimulation of the vagus during the quiescent period provoked ventricular arrhythmias in all 34 dogs. Ventricular
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fibrillation never resulted. Stimulation while the animal was in ventricular tachycardia either immediately after occlusion or following the quiescent period also failed to precipitate ventricular fibrillation.

The ventricular arrhythmias in the quiescent period resulting from vagal stimulation were of two distinct types. Within 3 hours after coronary artery occlusion, beginning at an average of 83 min, vagal stimulation caused ventricular couplets and salvos (figs. 1b, 2a). The arrhythmias of this early quiescent period were characterized by a short interectopic interval of lesser duration than the cycle length of the preceding sinus rhythm. The period of vagal-induced asystole preceding this arrhythmia was always greater than 2 sec. In 12 of 34 dogs (35%) the ectopic response was of multiform configuration and at times of bizarre morphology.

Later in the quiescent period, vagal stimulation resulted in a different response. Within 4.5–9 hours beginning at an average of 6.6 hours after coronary artery occlusion, stimulation of the vagus evoked ventricular tachycardia in all dogs (figs. 1c & 2c). The rate of this arrhythmia ranged between 80 and 130 beats/min, increasing as more time elapsed after coronary occlusion but always slower than the sinus rate. It was not preceded by a long period of asystole but appeared within about 600 msec after the onset of vagal stimulation. QRS configurations were uniform in 23 dogs (68%) and multiform in 11 (32%) (fig. 3). In eight dogs (23%) the QRS complex of the ventricular tachycardia was identical in configuration to the late VT which occurred in the absence of vagal stimulation. The average time between onset of vagal-induced VT and the appearance of late VT was 96 min (range 15–195 min).

Figure 2

Vagal stimulation and ventricular pacing. (Top) Two hours after coronary occlusion vagal stimulation induces asystole which, after 2 sec, is followed by couplets of ventricular ectopic beats. (Second band) Two hours after occlusion, when the ventricles are paced at a rate of 38/min during vagal stimulation, couplets do not appear. (Third band) Six hours after coronary occlusion, within 0.5 sec of vagal stimulation VT appears at a rate of 100/min, the concurrent sinus rate being 115/min. (Bottom) Six hours after occlusion, when the ventricles are paced before and during vagal stimulation at the sinus rate of 120/min, VT does not appear during vagal stimulation.
Cessation approximately of pacing means in VT was provoked by vagal stimulation late in quiescent period (7 hours and 8 min following coronary occlusion) results in ventricular ectopic mechanisms of two morphologies.

Acetylcholine Administration and Cessation of Ventricular Pacing in Complete A-V Block

A 5-mg bolus of acetylcholine injected intravenously in three dogs resulted in at least 10 sec of asystole. Cessation of ventricular pacing in two dogs with complete heart block resulted in asystole of approximately equal duration. Prior to coronary artery occlusion slowing of the heart rate by these means did not provoke any ventricular ectopic activity. However, the response was identical to that of vagal stimulation when these procedures were accomplished during the quiescent period. Couplets and salvos of ventricular ectopic beats occurred in the early period after occlusion while VT was precipitated in the late quiescent period.

Ventricular Pacing during Vagal Stimulation and Acetylcholine Administration

When slowing of the heart rate was prevented by ventricular pacing at a rate approximating that of the sinus node, vagal stimulation or acetylcholine administration did not provoke ventricular ectopic activity (fig. 3d). When the heart was paced at rates faster than 50/min, vagal stimulation did not induce couplets or salvos early in the quiescent period (figs. 3a, b). Later in the quiescent period, vagal-provoked VT could only be prevented if the rate of artificial pacing was faster than the rate of the arrhythmia (figs. 3c, d).

Vagal Stimulation during Beta-Adrenergic Blockade

Beta-adrenergic blockade with propranolol in seven dogs did not prevent either the couplets and salvos or the VT from appearing during vagal stimulation. In three dogs VT occurred following administration of propranolol prior to vagal stimulation and without a change in heart rate.

Discussion

Vagal stimulation within 30 min after coronary artery ligation and at frequent intervals during the ensuing 6–8 hours did not precipitate ventricular fibrillation in any of 34 dogs. This not withstanding the fact that significant bradycardia and asystole were produced. Ventricular fibrillation did not occur in any of the four animals resuscitated from this very arrhythmia which followed ligation of the left anterior descending coronary artery. Likewise, ventricular fibrillation did not develop when the vagus was stimulated while VT was already present. Thus the temporal association between vagally mediated bradycardia and ventricular fibrillation observed in the early stages of acute myocardial infarction in man finds no replication in the present animal model.

During the quiescent period following coronary artery occlusion, vagal stimulation consistently provoked ventricular ectopic activity in all animals studied. That vagal stimulation may incite ventricular arrhythmia is not a novel observation. One of the earliest reports is that of Herring. He noted that a sudden rise in left ventricular pressure in the isolated heart did not produce extrasystoles unless the vagus was simultaneously stimulated. Rothberger and Winterberg in experiments on dogs produced ventricular ectopic beats by stimulating...
the accelerator and vagus nerves, stimulating either alone was without such effect. Production or arrhythmia was facilitated by pretreatment with barium chloride or calcium chloride. When aconitine was administered to dogs in a dose insufficient to produce extrasystoles, Scherf found that cardiac stimulation of either vagus resulted in bigeminal rhythm.17 Similar findings were noted after subepicardial injection of hypertonic saline.18 Vassale and Greenspan10 demonstrated that vagal stimulation exposed enhanced Purkinje fiber automatically resulting from ouabain administration. These various experimental studies indicate that vagus stimulation may provoke ventricular ectopic beats in the heart predisposed to arrhythmia by the operation of diverse factors such as aconitine, hypertonic saline, calcium, sympathetic stimulation, digitalis drugs, and from the present investigation, acute myocardial infarction.

Scherf20 proposed that vagus nerve stimulation exerts direct arrhythmogenic effect independent of its bradycardic action. He based this conclusion on the observation that topical application of acetylcholine to the ventricular myocardium of dogs precipitated ectopic activity. The present study, however, finds that vagus nerve-induced ventricular arrhythmia in the infarcted heart is completely rate dependent. If heart rate slowing was prevented by pacing, arrhythmias did not occur. Conversely, if bradycardia was induced by maneuvers other than vagus nerve stimulation, the same arrhythmias resulted.

Sympathetic stimulation, either reflexly, by sympathetic fibers contained in the vagosympathetic trunk,21 or by release of endogenous catecholamines did not appear to play a role in the provocation of arrhythmia since the arrhythmia continued to be evoked by vagal stimulation in the presence of complete beta-adrenergic blockade.

The differences between the two patterns of arrhythmias resulting from vagal stimulation in the quiescent period suggest that two distinct mechanisms were involved. The arrhythmias observed early consisted of brief salvos of ventricular ectopic beats consisting of an escape beat followed by one or more coupled beats. The long pause preceding their onset and the close coupling intervals between complexes suggest that the recurring beats were due to a reentrant mechanism. Han and co-workers7–8 have shown that long pauses facilitate reentry by enhancing asynchrony of repolarization of adjacent muscle elements. Reentry is also suggested by the fact that these salvos were prevented by pacing the ventricles at rates slower than that of the arrhythmia itself. Hunt et al. have shown that such a response to pacing is associated with a reentrant mechanism.22

Later in the quiescent period an entirely different ventricular arrhythmia resulted from vagal stimulation. VT emerged without a prolonged pause at a rate slower than that of the intrinsic sinus rhythm. Pacing suppressed the VT only if the driven rate exceeded that of the arrhythmia. The QRS configuration of the tachycardia was at times similar in morphology to that of the late VT which developed within less than 3 hours following elicitation of the vagal induced arrhythmia. These observations suggest that the vagal-induced VT of the late quiescent period resulted from exposure of latent foci of enhanced automaticity. The enhancement was a consequence of ischemia and/or infarction. The tendency to this type of VT increased with the time elapsed after coronary occlusion as demonstrated by a progressive acceleration in rate of the arrhythmia until it became the dominant rhythm.

The vagally induced VT appears similar to the accelerated idioventricular rhythms observed with acute myocardial infarction in man.23 It is a transient nonparasystolic arrhythmia generally not exceeding 20 sequential cycles with a rate ranging from 60–90 min. It is usually limited to the initial 24 hours after onset of infarction. Like the experimental arrhythmia, it is exposed by bradycardia, thus it is more likely to occur when the infarction is diaphragmatic in location and during the slow phase of sinus arrhythmia.24 The present study provides an experimental model for reproducing accelerated ventricular rhythms observed in patients with acute myocardial infarction.

It is possible that the arrhythmias elicited by vagal stimulation reflect changing conditions of electrical instability during acute myocardial infarction. Thus, in the earliest stages of infarction reentrant rhythms predominate and therefore, the high risk of ventricular fibrillation. Later in the course of infarction, increased automaticity of Purkinje fibers predominates and therefore the high frequency of ventricular ectopies and paroxysms of tachycardia. Vagal slowing can therefore serve as a useful tool for uncovering latent electrical instability.

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