Mechanisms of Bradycardia-induced Ventricular Arrhythmias in Myocardial Ischemia and Infarction

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SUMMARY Experimental and clinical cases have been described in which bradycardia, i.e., heart rates below 60 beats/min or slowing of the heart rate, resulted in lethal ventricular arrhythmias during various stages of myocardial ischemia and infarction. The present study was designed to determine the relationship of lethal ventricular arrhythmias and slow heart rates. In 18 dogs anesthetized with sodium pentobarbital, the left anterior descending (LAD) coronary artery was ligated. Standard ECGs, His bundle electrograms and composite electrograms from intramural and epicardial areas in ischemic and normal zones were recorded during the first 3 hours of ischemia. Vagosympathetic trunk stimulation caused varying degrees of slowing and bradycardia. Of the 18 dogs, slowing of the heart rate or marked bradycardia induced ventricular ectopic beats coupled to the sinus beats in two, sustained ventricular tachycardia in two, and ventricular fibrillation in two. In another group of six dogs studied 17–25 days after LAD ligation, one dog showed sustained ventricular tachycardia in response to vagal-induced bradycardia. In all acute or chronic cases of arrhythmias after LAD ligation, continuous electrical activity was recorded on one or more of the electrograms within or overlying the ischemic or infarcted zones. This bridging electrical activation, which is indicative of slow conduction, provided strong presumptive evidence for reentry as the mechanism of lethal or potentially lethal ventricular arrhythmias triggered by bradycardia in the setting of myocardial infarction.

THE ARRHYTHMOGENIC effects of increasing the heart rate during acute myocardial infarction in experimental and clinical studies have been reported. Bradycardia has also been associated with the onset of malignant ventricular arrhythmias reported in several experimental and clinical studies. However, some reports have indicated significant beneficial effects, such as a decrease of ventricular arrhythmias or abolition of arrhythmias, due to slowing of the heart rate in acute myocardial infarction. Han et al. proposed that in the ischemic heart, both tachycardia and bradycardia could lead to reentrant arrhythmias as a result of dispersion of refractoriness, i.e., nonuniform recovery of excitability. Direct evidence for a reentrant mechanism is lacking. The purpose of the present study was to provide such evidence with the use of electrical recordings from the ischemic myocardium during the induction of bradycardia in dogs with acute and chronic myocardial infarction. Bradycardia-induced ventricular arrhythmias have been documented in the clinical setting of acute myocardial infarction, resulting in sudden death.

Methods

Eighteen adult mongrel dogs that weighed 15–25 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and studied within the first 3 hours after the onset of myocardial ischemia (group 1). Six other dogs were studied 17–25 days after the onset of myocardial ischemia and infarction (group 2).

Acute Studies — Group 1

In group 1, a left thoracotomy was performed through the fourth intercostal space. The left anterior descending coronary artery (LAD) was dissected within 1.0–1.5 cm of its origin and two ligatures were placed around the vessel. A standard lead II ECG was monitored, as were direct electrogram recordings from the heart. The His bundle electrogram was recorded from a bipolar catheter introduced through a carotid artery and positioned in the noncoronary cusp at the aortic root. An electrogram was recorded from the epicardial surface at the center of the area perfused by the LAD using a composite bipolar electrode. Electrical activity in the underlying intramural myocardium was monitored using a modification of the composite bipolar electrode technique. The intramural electrode was composed of four to six silver wires (0.012 inch in diameter) with the Teflon coating removed from the terminal 2.0–3.0 cm. Each wire was introduced into the left anterior ventricular myocardium parallel to the diagonal branches of the LAD. The bare portion was completely buried in the myocardium by using a 22-gauge needle (1½ inches long) to insert the wires. Alternate wires were connected to the same terminal to construct a bipolar electrode. Another composite electrode was positioned on the posterior left ventricle to provide a normal zone (NZ), or reference, recording.

To slow the heart rate and assess underlying ventricular automaticity, two silver wires were inserted into the left or right vagosympathetic trunk. Electrical stimuli (at a rate of 20 Hz, 0.5-msec duration, 10–20-V intensity) were applied to the nerve trunk from an S88 stimulator through an SIU5 stimulus isolation unit. To increase the heart rate, electrical driving stimuli at rates greater than the sinus rate (up to 300 beats/min) were delivered to the atrium.
through bipolar wire electrodes from another channel of the Grass stimulator and a separate stimulus isolation unit. Before the coronary artery occlusion, recordings were made during sinus rhythm, during vagal stimulation that decreased the sinus rate below 60 beats/min, and after sinus arrest that resulted in the escape of underlying ventricular pacemakers or asystole of up to 20 seconds.

After control recordings were made, the LAD was occluded completely by sliding a polyethylene collar over the ligature and clamping the snare firmly in place. In nine dogs, the occlusion was maintained for as long as 4 hours. In nine other dogs, an initial high-grade stenosis was made in the LAD by ligating the vessel against a 20-gauge needle and removing the latter. The snare was then used to completely occlude the vessel. After 30–45 minutes of complete occlusion, the snare was released to the partial occlusion; after 5 more minutes, the stenosing ligature was cut. The latter procedure minimized lethal reperfusion arrhythmias. During the occlusion period or occlusion/release period (up to 3 hours), ECGs and electrograms were monitored in sinus rhythm and with vagal slowing of the heart rate to 30–60 beats/min. A cannula placed into the aorta through the femoral artery and attached to a P23Db Statham pressure gauge allowed continuous monitoring of blood pressure throughout the experiment.

**Chronic Studies — Group 2**

In six dogs, studies were performed 17–25 days after induction of myocardial infarction by a two-stage ligation of the LAD. Six dogs were anesthetized with sodium pentobarbital, 30 mg/kg i.v., and the surgical procedure was carried out under aseptic conditions. The heart was exposed through a left thoracotomy and ECGs and electrograms were recorded as described in the acute studies except that the intramural recordings (those from the area of infarcted muscle) were not made.

Vagal-induced sinus arrest was used to assess enhanced ventricular automaticity and to cause intervals of asystole, 1–10 seconds, before recovery of sinus rhythm. The termination of these bradycardic intervals were carefully monitored to detect the occurrence of ventricular arrhythmias associated with varying degrees of bradycardia. On the other hand, atrial pacing at rates above the sinus rate up to 300 beats/min was instituted to determine the propensity for ventricular arrhythmias in response to tachycardia. The ECGs, local electrograms and blood pressure (as described above) were monitored on a multichannel oscillographic recorder (Electronics for Medicine VR-12) and recorded at paper speeds of 25–100 mm/sec either directly or through an eight-channel Hewlett-Packard tape recorder. ECGs were made at DC frequency settings to 250 Hz and local electrograms were recorded with frequency settings of 30–250 Hz.

**Results**

**Group 1**

After LAD ligation, the electrograms from the ischemic zone (IZ) consistently showed decreased amplitude, fractionation and delay. However, the fractionated activity usually does not persist beyond 30 minutes after LAD ligation. In two of nine dogs with LAD ligation and four of nine with occlusion and reperfusion, electrical activation abnormalities persisted. Figure 1 illustrates these changes in epicardial, composite recordings from the IZ two hours after LAD ligation. During sinus rhythm, evidence of myocardial ischemia and developing infarction was seen as deep Q waves and abnormal ST and T waves in the lead II ECG. The composite epicardial electrogram from the NZ was electronically clipped because its high amplitude was essentially unchanged from the control state. To compare IZ and NZ electrograms, they were displayed at similar high gain. The differences consisted of small-amplitude, delayed potentials in the IZ not seen in the NZ. Furthermore, the IZ potentials exhibited variable fractionation and delay in each of the three beats.

Figure 2 shows recordings of standard ECG leads II and a composite recording from the ischemic epicardium in another dog 3 hours after LAD ligation. Late in the diastolic interval of every third beat, a fractionated potential appears (asterisk, panel A). This potential is without apparent effect during normal rhythm except as shown in the last beat in panel B (arrow), in which the portion of the electrogram coincident with the beginning of the QRS complex is altered. The QRS complex itself is unchanged. Slight

![Figure 1. Variable degrees of fractionation of potentials from the ischemic epicardium. Lead II (L-2), a His bundle electrogram (Hbeg), composite recordings from the epicardium in the normal zone (NZeg) and the ischemic zone (IZeg) are shown. Two hours after left anterior descending coronary artery occlusion, fractionated potentials with variable delay are recorded from IZeg but not from the NZeg lead.](http://circ.ahajournals.org/content/65/7/1430.full.html)
slowing of the heart rate by vagal stimulation allows the expression of a well-defined ventricular ectopic beat (panel C). Note the association of the same fractionated potential as in panel B (arrow) with the occurrence of the late coupled extrasystole. Thus, during normal rhythm, the fractionated potentials, occurring well after ventricular repolarization, could only induce local excitations or concealed reentry not manifest on the ECG. The reentrant capability became fully manifest when the rate was sufficiently slowed so that a supraventricular beat did not preempt the weaker activation front represented by the fractionated potential.

The unstable nature of the fractionated potential and the possible involvement of other areas in the reentry process are shown in figure 3, taken from the same experiment. The first few beats during the return to the spontaneous heart rate are shown. In addition to composite recordings from the IZ on the epicardium, the composite electrogram from the midmyocardium or intramural area is also shown. In the latter tracing, low-amplitude and fractionated potentials with varying durations are evident. The fractionated potential can be visualized by comparing the electrical activity seen in the interectopic intervals with the isoelectric intervals at the beginning and end of this trace. The epicardial composite exhibits higher amplitude fractionated potentials, which are also variable. Slight slowing of the heart rate, just before the last supraventricular beat, was associated with fractionated activity which extends to the end of the T wave in the epicardial recording. In this instance, there was an early activation in the midmyocardial electrogram leading to a ventricular premature complex (VPC). The bridging electrical activity encompasses potentials in the epicardial and intramural zones.

The effect of higher intensity vagal stimulation, which caused frank bradycardia (< 60 beats/min), is shown in figures 4 and 5. In figure 4, the heart rate was slowed to 40 beats/min (RR = 1500 msec). The top of the figure shows an ECG in which each supraventricular ectopic beat was coupled to one or more ventricular ectopic beats. Panels A and B are recordings

Figure 3. The unstable character of the fractionated potential could be a source of ectopic beats. During spontaneous supraventricular rhythm, unstable fractionation both in the epicardial (epi) and the midmyocardial (mid) composite recordings in the ischemic zone (IZ) was observed. L-2 = lead II; Hbeg = His bundle electrogram; VPC = ventricular premature complex.

Figure 4. The effect of bradycardia induced by further vagal slowing in the same dogs as in figure 3. The rhythm strip at the top shows bi- and trigeminal rhythms at an RR interval of 1500 msec. In panels A and B, these rhythms are shown at a faster paper speed with a His bundle electrogram (Hbeg), a composite recording from the midmyocardial region of the ischemic zone (IZmid) and the epicardium in the ischemic zone (IZepi). Arrows indicate continuous activation connecting sinus beats and ventricular ectopic beats and between successive ectopic beats. L-2 = lead II.
of the ECG and electrogram from the intramural and midmyocardial ischemic zone and ischemic epicardium. Low-amplitude fractionated activity spans the interval between the supraventricular and ectopic beat (coupling interval = 250 msec) in the midmyocardial electrogram. Fractionated activity follows the epicardial electrogram associated with the first ectopic beat. After a pause of 1500 msec, the same sequence occurs; however, the first supraventricular-ectopic coupling interval is 230 msec and the fractionated epicardial potential forms a continuous bridge to a second ventricular ectopic beat.

Figure 5 shows that further slowing of the heart rate to less than 35 beats/min (RR = 1820 msec) resulted in two coupled ventricular ectopic beats and then a brief run of ventricular tachycardia leading to ventricular fibrillation (top rhythm strip). There were closely coupled ventricular ectopic beats (200 and 180 msec, respectively) and continuous electrical activity between the supraventricular beats and the first ectopic beat. The coupling interval for the first ectopic beat in figures 4 and 5 progressively decreases. The beat initiating ventricular tachycardia and fibrillation had the shortest coupling interval of all previous coupled beats (RR/QT = 0.91). Also, the fractionated activity in the midmyocardial electrogram showed the highest amplitude of all such activity seen in that electrogram previously.

Group 2

In group 2, the arrhythmogenic effects of bradycardia were noted under conditions of chronic myocardial infarction as well as during the acute phases. The tracings in figure 6 were taken from a dog in which the LAD had been ligated 21 days before study. The composite recording revealed a low-level (about 50 μV), fractionated potential (arrow) extending into the ST interval. Over a wide range of heart rates (30–240 beats/min), obtained by vagal stimulation and atrial pacing, this potential remained unchanged in configuration and duration.

During normal sinus rhythm, a short asystolic period (1–2 seconds) was interposed by a short burst of vagal stimulation (fig. 7). A sinus beat followed cessation of vagal activity with the ensuing delayed potential and a late diastolic potential. This combination of delayed potentials was directly associated with ventricular tachycardia. Interectopic potentials and QRS morphology during the ventricular tachycardia have reproducible patterns.

Only one dog in group B showed ventricular tachycardia as a result of introducing asystolic pauses by vagal stimulation. Only in this dog did we record persistent fractionated activity extending into the ST segment during sinus rhythm and at varying heart rates.

Discussion

Experimental7-11 and clinical6,9-11 reports have presented apparently contradictory conclusions regarding the relation of bradycardia to ventricular arrhythmias in the setting of myocardial ischemia and infarction. From experimental studies, it appears that slowing the heart rate (not necessarily to rates below 60 beats/min, i.e., bradycardia) in the first 30 minutes after coronary artery occlusion ameliorates rhythm disturbances and protects from ventricular fibrillation. Whether the same generally applies in clinical cases is uncertain, since a systematic study of heart rates and ventricular ectopy in the first few minutes of myocardial infarction is not available. In the first few hours of acute myocardial infarction in both experimental8 and clinical9-11 reports, ventricular arrhythmias and fibrillation are commonly associated with bradycardia. Han et al.14 reported an increase in the dispersion of recovery of excitability in the ventricles at very slow rates. Such dispersion was considered to favor the likelihood of fractionation and reentry of ectopic impulses.20 The present study emphasizes that a key electrophysiologic feature associating bradycardia and ventricular arrhythmias in acute myocardial infarction is the recording of continuous electrical activation in the IZ. This recorded activity can be considered strong presumptive evidence that the cardiac impulse survives in the IZ, outlasting the refractory period of the previous beat to reenter the NZ and induce single or repetitive excitations.21-23 Slowed heart rates and frank bradycardia were associated with ventricular ectopy in 30% of our cases. Within 30 minutes after coronary artery ligation, fractionation and delay of activation were noted.5,24,26 After 30 minutes, the potentials recover some of their amplitude and configuration.5 However, in some ischemic hearts, portions of the delayed potentials may remain fractionated long after 30 minutes. We saw several forms of persistently fractionated potentials. When the fractionated activity extended beyond the T wave of the preceding beats, ectopic beats were provoked (figs. 2 and 3). In this and previous studies, we also found markedly fractionated and delayed potentials that did not induce ventricular ectopic
beats, either manifest or concealed. This finding was explained by the weak and partly decremental nature of the wave front that traversed the area of slow conduction before it reached normal tissue. The "weakness" of the fractionated activity was manifest by its inability to compete with the supraventricular wave front depolarizing the ventricles normally. Only concealed extrasystoles were noted (fig. 2B).

When the heart rate was slowed by vagal stimulation (fig. 2C), the fractionated wave front activated normal tissue and resulted in a manifest ectopic beat. Langendorf et al., in their description of the rule of bigeminy, described in part the mechanism for this type of response. They ascribed this response to partial recovery of conductivity in a reentry pathway during the long cycles. In the present study, another indication of such recovery of depressed conduction was the increased amplitude of the continuous activity connecting the sinus and ectopic beat (figs. 4 and 5) as well as the increasing prematurity index of the first coupled ectopic beat. The prematurity index of the ectopic beat preceding ventricular fibrillation is the shortest in the sequence (fig. 5B).

However, the findings from the dog with chronic myocardial infarction (fig. 7) do not seem to fit the mechanistic explanation of partial recovery of markedly depressed conduction with bradycardia. The fractionated potential recorded from the epicardium overlying the IZ remained constant in configuration and duration during slow and fast heart rates. However, abrupt slowing of the heart rate for 1-2 seconds was followed by a single supraventricular beat with a late diastolic potential. Its appearance was directly and repeatedly related to the onset of ventricular tachycardia.

The initial fractionated potential and the late diastolic potential seen with the onset and maintenance of the sustained ventricular tachycardia make up the continuous electrical activity described above. The first series of delayed potentials can be regarded as representing activation of the initial portion of slow conduction in the abnormal tissue overlying the infarct. In this context, the sharp late diastolic potential represents the exit from this area, since it precedes the onset of normal ventricular muscle activation, i.e., QRS complex. During normal sinus rhythm or over a wide range of heart rates (fig. 6), the circuit is entered but propagated activity to the exit does not occur. This is probably due to slowed and decremental conduction in the exit area.

The abrupt propagation of the impulse through the exit after a short period of asystole may be the result of a high degree of functional dissociation in which the impulse blocks in the slow path with relatively shorter refractoriness and conducts in the faster pathway with relatively longer refractoriness. Whether functional longitudinal dissociation associated with a gap phenomenon is the cause or whether bradycardia-dependent block in ventricular muscle plays a role requires a model that shows this phenomenon consistently.

The present findings provide some mechanistic bases for bradycardia-induced ventricular tachyarrhythmias. The data demonstrate a close association between the occurrence of continuous electrical activation connecting the normal beat and ectopic activity. After a 1-second asystolic period induced by vagal stimulation, the first sinus beat showed the fractionated potential in the ST interval (arrow), followed by the late diastolic potential (arrowhead). Ventricular tachycardia ensues, with the same pattern of continuous activation during the interectopic intervals. L-2 = lead II; Hbeg = His bundle electrogram; IZeg = electrogram recorded over the infarct zone.
beats and between successive ectopic beats. Such abnormal activity provides strong presumptive evidence for a reentrant mechanism for these ventricular arrhythmias which can, as this study shows, be fatal.

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References
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