CONTRIBUTION OF VARIABLE ENTRANCE AND EXIT BLOCK IN PROTECTED FOCI TO ARRYTHMOGENESIS IN ISOLATED VENTRICULAR TISSUES

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SUMMARY Automatic foci with membrane potentials in the range characterized by depolarization-induced automaticity exhibit entrance block. The present study demonstrates a role of variable entrance and exit block in arrhythmogenesis. We studied canine interventricular septa with the right bundle branch exposed, isolated false tendons and isolated feline papillary muscle using standard microelectrode techniques. Foci of automaticity were produced either by focal application of electric current or by exposure of the preparations to Tyrode's solution containing 1.5-2.0 mM KCl. Foci induced by mild depolarization exhibited entrance block with exit conduction and were subject to electrotonic modulation. With greater depolarization, varying degrees of exit block developed. Various rhythms, including Wenckebach periodicity, resulted. Delayed emergence of electrotonically accelerated activity led to closely coupled extrasystoles resembling reentrant activity. Exit conduction in some preparations was facilitated by enhanced normal pacemaker activity (membrane potentials -70 mV or greater) in tissue peripheral to the focus. Also, when there were two sites of automaticity separated by an area of depressed conduction, intermodulation between the two automatic regions generated complex arrhythmias. Shifts in maximum diastolic potential also changed conduction and led to changes in arrhythmic patterns. In some experiments, focal automaticity was terminated by single stimuli. We conclude that complex and variable behavior of automatic foci may result in activity with characteristics previously attributed to other arrhythmic mechanisms.

IN EXPERIMENTS in which canine ventricles are subjected to ischemia by means of coronary artery ligation, areas within the ventricles can frequently be identified in which cells are markedly depolarized. Such cells often have a maximum diastolic potential of between -40 and -60 mV, which is negative to the threshold for the fast inward sodium current but within the range from which the slow inward current can be activated. Foci of repetitive automatic activity have been identified within such ischemic areas. The automaticity at these low levels of membrane potential may be caused by a mechanism that has been called depolarization-induced automaticity, which may occur in either myocardium or Purkinje tissue.

We have shown that automatic foci with membrane potentials in the range characterized by depolarization-induced automaticity are surrounded by tissue in which conduction is depressed. Depressed conduction plus different excitabilities of the tissues within and surrounding the foci permitted entrance block with exit conduction. The depolarized areas behaved as parasystolic foci and could be modulated by activity occurring in the nondepolarized portion of the preparation. In that situation, the activity within the parasystolic focus may be delayed or accelerated in a highly predictable manner by the electrotonic influence of the activity in the surrounding, nondepolarized tissues. A consequence of this modulation is the emergence of sequences of arrhythmic activity that include patterns such as bigeminy and trigeminy, often with fixed coupling. When this occurs, the focus is said to be entrained. Thus, modulation and entrainment of an automatic focus may give rise to complex patterns of arrhythmias, many of which are difficult to distinguish from arrhythmias that arise as a result of reentrant mechanisms. Although entrance block with exit conduction was an intrinsic property of depolarized automatic foci, this situation must be much simpler than that in heart disease. For example, the instability of an ischemic area might lead to temporal variations in membrane potential, which could change the degree of automaticity or the degree of entrance or exit block. Complex and unstable arrhythmic patterns might result. Some conditions might provide a setting in which the relationship between entrance and exit delays would permit

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reflection or microentry, similar to that described by Antzalevitch et al.11 We examined some of these variables in the behavior of depolarized foci.

Methods
Mongrel dogs of either sex and one cat were anesthetized with sodium pentobarbital (dogs, 30–35 mg/kg i.v.; cat, 65 mg/kg, intraperitoneally). Hearts were rapidly excised and dissected. The interventricular septum was dissected with the right anterior papillary muscle, right bundle branch, and the initial free running strands of false tendon intact. Together, the right bundle branch and the free running strands measured 2.5–3.5 cm. In some experiments, free-running false tendons (3–6 mm) were excised with a piece of myocardi um (approximately 1 cm³) attached at one end.

Preparations were mounted in a wax tissue bath with stainless steel pins, and superfused continuously with modified Tyrode’s solution containing (in mM) NaCl, 137.0; KCl, 4.0; NaH₂PO₄, 0.9; NaHCO₃, 12.0; CaCl₂, 2.5; MgSO₄, 0.5; and dextrose, 5.5. The solution was bubbled with a 95% O₂–5% CO₂ gas mixture. In some experiments with false tendons, the concentration of KCl was decreased to 1.5–2.0 mM to provide depolarization-induced automaticity.5,12

In septal preparations, depolarization was achieved using 3-second positive current pulses derived from a Frederick Haer Pulsar 6i digital stimulator operating in the constant voltage mode. The pulse was passed through a current limiting resistor. The output of the stimulator was monitored by voltage measurement across a smaller series resistance. Current was delivered through a soft glass Pasteur pipet (Van-Lab disposable capillary pipet) that contained a chlorided silver wire and was filled with Tyrode’s solution. The tip of the pipet was appropriately shaped by fire polishing and was applied lightly against the site to be depolarized. Such focal depolarization would be expected to result in a gradient of membrane potentials, ranging from maximally depolarized in tissues near the pipet to normal in remote tissues.7 A chlorided silver coil immersed in the tissue bath served as the return electrode. Although one might suggest that the mechanical pressure of the pipet, or hypoxia beneath its opening, might injure the tissue enough to alter the results, previous studies have suggested that this is not the case.7

Preparations were stimulated through silver electrodes insulated except at the tip. Stimuli were rectangular pulses, 3 msec in duration and approximately 1.5 times threshold voltage. Pulses were delivered through an isolation transformer and were obtained from a pulse generator (Tektronix 160 series). The pulse generator was triggered by a digital interval generator which was also used to trigger the current delivering digital stimulator. The pattern of stimulation usually consisted of trains of 10 followed by a pause during which test stimuli and current could be delivered. In other experiments, stimulation or current delivery was continuous.

In preparations depolarized via current passage, differential recordings were made from two sites. One of these sites was within 1 mm of the current electrode, while the remote site was at least 1 cm away. With the recording electrode of each pair positioned directly above the site to be impaled, the indifferent electrode of that pair was positioned so as to null the effects of current passage. In preparations in which current passage was not used, single-ended recordings were made.

Recordings were made using glass microelectrodes filled with 2.7 M KCl (resistance 15–30 MΩ). Recordings were amplified by a high-impedance, capacitance-neutralized amplifier (WPI 750) that could be used in the conventional or the differential mode. The microelectrode records, stimulus pattern and current record were displayed on a Tektronix 5103N oscilloscope and were photographed with a Grass Kymograph camera.

Results

Effect of Membrane Potential on Exit Conduction
Entrance block in depolarized foci depends on the gradient in the membrane potential between depolarized tissue and more normal tissue surrounding the focus.3 The possibility that exit conduction from a focus varies with changes in the maximum diastolic potential of the focus and the surrounding tissue was tested in experiments performed with right bundle branch (RBB) preparations. An example is shown in figure 1. The stimulating electrode was placed near the proximal (His bundle) end of the preparation. The current-passing electrode and one pair of recording electrodes were placed on the septal portion of the RBB near the beginning of the free-running false tendon. The remote pair of recording electrodes was placed near the stimulating electrode to monitor activity in the nondepolarized parts of the preparation. Current was passed only during the 3-second pauses that followed trains of 10 beats.

When current passage depolarized the focus to -54 mV, the resulting automatic activity propagated out of the focus (fig. 1A). However, a test beat delivered early during the second spontaneous interval failed to enter the focus. The blocked beat caused an electromotive that delayed the next spontaneous discharge of the focus. With slightly greater depolarization of the focus to a maximum diastolic potential of -51 mV (figs. 1B and C), automaticity persisted but complete exit block occurred. Entrance block, and modulation of the focus, persisted. A test beat delivered early in the spontaneous interval electrotonically delayed the subsequent automatic beat (fig. 1B). A test beat delivered later in the spontaneous interval accelerated the automatic activity (fig. 1C). The pattern of modulation in response to test beats was consistent with predictions of Jalife, Moe and co-workers based on experiments using a sucrose gap preparation10 and confirmed by Ferrier and Rosenthal using a preparation similar to that used here.7

We also observed second-degree exit block in the present study. The example illustrated in figure 2 was recorded from a focus continuously depolarized by means of current application to the RBB. All activity was spontaneous, and emerged from the focus to a
more distal site in the preparation with progressively increasing conduction delay, resulting in Wenckebach periodicity. The Wenckebach periods are indicated by the brackets. In this experiment, the activity emerged from the focus with enough exit delay to permit the emerging beats themselves to impose an electrotonus during the next diastolic interval of the focus. The electrotonus delayed the next discharge within the focus. Finally, when a beat failed to emerge, there was no electrotonus and the next cycle within the focus was relatively short. Thus, electrotonic modulation of a focus can occur without a second pacemaker site. This example demonstrates that when exit block is partial, an irregular pattern of ectopic beats may be manifest in the periphery, even though the focus is discharging regularly.

Reflection of Interpolated Beats

Under certain conditions, a test beat initiated outside

a focus may accelerate or capture the focus, but the accelerated beat occurs with a long delay. Successful propagation of the accelerated beat out of the automatic focus may depend on the degree of refactororiness of the tissue surrounding the focus at the time of its discharge. The records in figure 3 were recorded from a focus that was continuously depolarized and automatic. The arrangement of electrodes on the RBB preparation was identical to that in the previous experiments. The preparation was stimulated intermittently. The second stimulus (fig. 3A) resulted in an early premature beat that captured the focus with a marked prepotential. Although the upstroke of the accelerated beat occurred relatively late during repolarization of the surrounding tissue, the premature discharge of the focus failed to reenter the proximal right bundle. In figure 3B, the sequence is similar, but the pathway from the focus to the proximal right bundle had recovered sufficiently to result in a closely coupled extrasystole. Thus acceleration or capture with sufficient delay permits emergence of the beat as a closely coupled, reentrant extrasystole, or reflection, with an arrhythmogenic pattern characteristic of reentry.

Facilitation of Exit Conduction by Phase 4 Depolarization

The success of exit conduction from a focus depends in part on the maximum diastolic potential of the tissue (fig. 1). Phase 4 depolarization in tissue surrounding the focus also influences the success of exit conduction. An example is shown in figure 4. Depolarizing current delivered during the pauses in stimulation also slightly depolarizes the remote site (fig. 4A, bottom intracellular trace). The spontaneous activity originating within the focus exhibits 1:1 conduction to the remote site. However, when the intensity of the depolarizing current was increased (fig. 4B), complete exit block occurred. In addition to causing exit block, the stronger depolarization enhanced phase 4 depolarization at the remote site. As phase 4 depolarization progressed, the electrotonic images of the blocked beats within the focus increased in amplitude. The
increase in amplitude of the electrotonic images probably reflects the increase in membrane resistance, and therefore space constant, known to accompany phase 4 depolarization. Furthermore, the excitability of the membrane increases as its potential approaches the threshold for the fast inward sodium channel. Thus, with further depolarization (fig. 4C), the electrotonic images of alternate beats within the focus captured the peripheral site, resulting in 2:1 exit conduction. We cannot determine whether the phase 4 depolarization evident in figure 4C would have achieved threshold in the absence of activity within the focus. In either case, alternate capture and block allowed entrainment of the peripheral pacemaker with a 2:1 pattern. Further depolarization (fig. 4D) brought the remote site to a membrane potential at which the fast sodium channel is largely inactivated. Also, the amplitudes of the action potentials within the focus were smaller. Both factors may have contributed to the complete block that accompanied this level of depolarization.

**Intermodulation of Two Areas of Automaticity**

When both the central focus and adjacent tissue became automatic, modulation of the activity in one area by the other contributed to the generation of complex arrhythmias. Some degree of conduction block must exist between two areas for this to happen, as illustrated in figure 5. The lower trace in figure 5A was recorded from an electrode adjacent to the current delivering electrode on a RBB preparation. Continuous application of depolarizing current produced an automatic focus with some impairment of entrance and exit conduction. The top trace was recorded from a peripheral, less depolarized site that was also automatic. The electrotonic images of the more depolarized pacemaker are clearly visible in the recording from the peripheral site. The fourth interval in the top trace is the closest approximation available for the basic cycle length of the peripheral pacemaker. Relative to that interval, the next cycle showed abbreviation and the cycle after that showed delay as the electrotonic image of the faster pacemaker occurred progressively earlier in diastole. The fifth interval in the lower trace occurred when there was no discharge of the peripheral site and probably represents the basic cycle length of the central focus. Relative to that interval, the immediately preceding cycle was greatly abbreviated and the next two cycles were prolonged by the influence of the peripheral site. The intermodulation of the two pacemakers resulted in an irregular pattern of activity at the peripheral site. The activity recorded at the peripheral site...
FIGURE 5. Interaction of central and surrounding areas of automaticity in a right bundle branch. (A) The top trace of action potentials was recorded from a peripheral site and the bottom trace from a central focus just next to the current electrode. With continuous depolarization, both sites were automatic. The central focus displayed entrance and exit block. There was electrotonic intermodulation between the two sites, which allowed each to be both accelerated and delayed by the other. (B) One of the electrodes was moved so that the bottom trace now represents a remote recording site within a free-running false tendon beyond the influence of the depolarizing electrode. The top trace is from the same site as in A. The alternating rhythm in the peripheral site propagated to the remote tissue.

Conducted to the rest of the preparation. This is shown in figure 5B, which was recorded after the electrode that had been in the central focus (lower trace) was moved to a free-running false tendon, beyond the influence of the depolarizing current. The electrotonic images of the activity in the central focus were present only in the top trace. The alternating rhythm in the distal site, although now slower, propagated to the remote tissues.

Termination of Focal Automaticity by a Premature Stimulus

In experiments using the sucrose gap technique, carefully timed subthreshold pulses applied across the gap can abruptly terminate pacemaker activity. This phenomenon was called pacemaker annihilation. In sucrose gap preparations, the membrane potential of the pacemaker segment is relatively uniform. We wondered whether annihilation could be demonstrated with the present technique, in which the pacemaker occurs with a gradient of membrane potential. Although potential gradients would be expected to prevent this phenomenon, several examples were observed (fig. 6). The preparation used in the experiment illustrated in figure 6A was a short, free-running false tendon attached to a small piece of myocardium. The current electrode was slipped over the free end of the false tendon and the top record of action potentials was recorded by an electrode within 1 mm of its tip. The lower trace of action potentials was recorded from the false tendon, near its myocardial insertion. The stimulating electrode was located on the myocardium. In this experiment, automaticity was enhanced by Tyrode's solution containing 1.5 mM KCl. Depolarization-induced spontaneous activity was conducted to the remote site (fig. 6A). When a test stimulus was delivered during phase 3, the premature beat resulted in a positive displacement of the membrane potential of the pacemaker and was followed by cessation of

FIGURE 6. Termination (''annihilation'') of focal automaticity by single premature beats. (A) Records are from false tendon attached to a small piece of myocardium equilibrated with Tyrode's solution containing 1.5 mM KCl. The top trace in each panel represents a stimulus record and the bottom trace a current record. The upper intracellular recording was from a site next to the current applying electrode. The lower intracellular record was from a site on the false tendon near its myocardial insertion. The top panel shows the spontaneous activity, induced by a current pulse. In the middle panel, an early beat failed to enter the focus. However, the electrotonic influence terminated the automatic activity. The bottom panel shows the same sequence, except that the premature beat occurred later and automaticity was not terminated. (B) Records from a feline papillary muscle. The intracellular recording was from a site adjacent to the current-passing electrode. The sequence is similar to that shown in A except that automaticity was terminated by the electrotonic influence of a subthreshold stimulus. A later suprathreshold stimulus captured the focus and failed to terminate the automaticity.
spontaneous activity. Figure 6A, bottom, shows a similar sequence, except that the premature beat was initiated earlier during phase 3 of the first spontaneous beat. It also caused a positive displacement, but instead of causing cessation of the spontaneous activity, it merely delayed the next spontaneous beat. Although earlier and later test beats failed to stop the activity, a properly timed test stimulus consistently terminated the automaticity.

Annihilation was also observed in papillary muscle (fig. 6B). Depolarization-induced automaticity was elicited by current applied to the tip of a feline papillary muscle. The pacemaker activity in the absence of interpolated beats is illustrated in the top panel of figure 6B. The recording electrode was located near the current passing electrode. A subthreshold stimulus delivered to the base of the papillary muscle resulted in a slight deviation in repolarization, which was followed by termination of automaticity. In figure 6B, a slightly later premature stimulus captured the focus. In that case, the automaticity was not terminated.

Effect of Shifts in Membrane Potential on Entrance Block

Canine Purkinje fibers can, under various conditions, be stable at two levels of maximum diastolic potential. At the lower resting potential — generally −40 to −50 mV — they can show repetitive automatic activity, which often stops if the membrane potential returns to the higher resting potential — generally almost −90 mV. [12, 21] In fibers exposed to Tyrode’s solution with a low concentration of KCl, we frequently observed spontaneous shifts of membrane potential, sometimes with corresponding changes in automaticity. The changes in maximum diastolic potential were accompanied by changes in the properties of the conduction pathway between the automatic focus and the normal tissue.

Figure 7 illustrates an experiment in which a free-running strand of false tendon attached to muscle was exposed to Tyrode’s solution containing 0.5 mM KCl. In each panel the upper trace of action potentials was recorded from an automatic focus in the false tendon. The lower trace of action potentials was recorded from the muscle. Test beats were delivered to the surface of the muscle. Initially (fig. 7A), the focus had a resting membrane potential of −58 mV and was automatic. Second-degree exit block, generally 2:1, from the focus was present. Three stimuli were delivered to the muscle during the period illustrated in figure 7A. The first driven beat captured and thereby accelerated the discharge of the focus. The next two arrived earlier in diastole and failed to enter the focus. The resulting electrotonus in each case prolonged the spontaneous cycle length. After this sequence, several sequential beats captured the focus (not illustrated) and 1:1 drive was achieved. The trace in figure 7B was recorded from the same preparation after a period of rapid drive (basic cycle length 300 msec) that increased the maximum diastolic potential of the false tendon to −82 mV. The end of the period of rapid drive is illustrated. The preparation remained automatic. However, entrance block no longer occurred, and test beats deliv-
may have induced exit block by decreasing the amplitude of the electrotonic image of the action potentials enough that the remote tissue could no longer be brought to threshold.\(^2\) Despite the presence of exit block, the activity of a focus is still subject to electrotonic modulation. Thus, the pattern of an arrhythmia might result from the entrainment of an ectopic focus in complex sequences, including bigeminy, trigeminy or other ratios. Such an arrhythmia might disappear and reappear sporadically with slight changes in membrane potential.

Exit block contributed to the manifest arrhythmias not only by changing the number of beats successfully propagating out of the focus, but in some cases also by providing additional opportunities for electrotonic modulation. For example, prolonged conduction times during the Wenckebach cycles (fig. 2) allowed the emerging beats to modulate the activity of the focus.

When driven beats captured a focus with a long latent period, the first-degree entrance block also contributed to arrhythmogenesis. This is demonstrated in figure 3B, in which capture occurred with enough delay to allow the response in the focus to reexcite or reflect to the remote tissue as a closely coupled extrasystole. Wit, Cranefield and Hoffman\(^2\) postulated that reentry or reflection could occur within a single linear bundle of Purkinje fibers by entering and leaving a depressed area through separate longitudinally dissociated fibers. Cranefield\(^2\) also suggested that reflection might occur within a single fiber that is reexcited by a delayed systole occurring within a depressed distal segment, without the need for separate entrance and exit pathways. Antzelevitch, Jalife and Moe\(^1\) showed, in experiments using the sucrose gap to produce block, that such reflections can occur within a single fiber as a result of electrotonic delay. In this experiment, we do not know whether the reentrant beats occurred by means of electrotonically mediated reflection or by means of delayed conduction along one of two functionally separated pathways. However, the presence of an electrotonic “foot” in the focus, concurrently with an active upstroke in the remote tissue, suggests that the impulse captured the focus electrotonically rather than by slow conduction across the depressed segment.

This study demonstrates that a single generative event, namely, depolarization of a small area of the heart, can cause both parasystolic or reentrant arrhythmias. Automaticity within the depolarized area is necessary for modulated parasystole to occur. Automaticity may be present, but is not necessary for reflection. Antzelevitch et al.\(^1\) demonstrated that a slight decrease in membrane resistance can eliminate the electrotonically mediated delay phase of the phase-response curve. This allows early beats to capture the focus successfully with a prominent delay in excitation. When this delay exceeds the refractory period of the entrance pathway, reflection may occur.

Automaticity in the surrounding tissue may modify the expression of an automatic focus. Wennemark et al.\(^14\), \(^15\) and Bandura and Brody\(^17\) showed that conduction block may depend on the changes in membrane potential associated with phase 4 depolarization. Phase 4 depolarization is accompanied by an increase in membrane resistance.\(^13\) Thus, the amplitude of a local depolarization caused by a subthreshold stimulus increases as it is delivered progressively later during phase 4 depolarization, and may eventually reach threshold. As a result, highly voltage dependent interactions may occur between two automatic areas in a diseased heart. A slowly depolarizing area located within a potential exit pathway of a more rapidly depolarizing spontaneous focus may determine whether the activity of that focus is expressed as manifest premature beats. Although the more slowly depolarizing area may never itself reach threshold, by this mechanism it may have an important influence on the arrhythmogenesis.

Our previous study demonstrated that complex arrhythmic patterns arose when automatic foci were entrained by trains of driven beats at various basic cycle lengths.\(^7\) This is analogous to a situation in which the focus is entrained by activity initiated at a remote pacemaker, such as the sinus node. The present experiments demonstrate that a depolarized focus also can interact with a nearby pacemaker, which not only can modulate the focus, but which also can be modulated by the focus. Such intermodulation between two pacemakers can lead to complex patterns of arrhythmias (fig. 5) and may account for the irregularity that frequently is observed clinically during runs of ventricular tachyarrhythmias.

Previously, the ability of a single premature beat to terminate an ectopic rhythm was considered diagnostic of a reentrant mechanism.\(^26\) Recently, several exceptions have been demonstrated. Ferrier et al.\(^27\) showed that digitalis-induced repetitive activity could be terminated by interpolation of a single driven beat. Wit and Cranefield\(^28\) demonstrated a similar phenomenon in muscle fibers of the simian mitral valve leaflet. Jalife and Antzelevitch\(^18\), \(^19\) showed that a single subthreshold stimulus with the proper timing and intensity can terminate spontaneous activity in sinoatral nodal cells and in Purkinje fibers. They called this phenomenon annihilation. In their experiments, the subthreshold stimulus was followed by several oscillations and, finally, quiescence. When annihilation was not achieved the oscillations became progressively larger until they reached threshold. In our experiments, annihilation also occurred with a series of damped oscillations. Pacemaker annihilation may be responsible when ventricular tachyarrhythmias stop abruptly, or are suddenly subplanted by slower rhythms originating from a different site.

Pacemaker activity might also be terminated by sudden shifts in membrane potential. A sudden increase in the resting potential of a depolarized automatic fiber would be expected to eliminate depolarization-induced automaticity. Such shifts in resting potential with corresponding changes in automaticity occur either spontaneously or with the application of brief current pulses.\(^12\), \(^20\), \(^21\), \(^29\) We observed spontaneous shifts in resting membrane potential in preparations exposed to low [K\(^+\)]. In some of these preparations, automatic activity was present only at the less negative resting
potential. In addition, entrance block to a test beat delivered early in diastole and modulation of the automatic activity, was present only when the fiber was at the lower resting potential.

In our study, automatic, depolarized foci were created artificially, either by means of depolarizing current applied to the tissue or by means of perfusion with Tyrode’s solution containing an extremely low potassium concentration. In clinical situations, such as myocardial infarctions, depolarization of ischemic cardiac tissues probably occurs because of an increase in extracellular potassium concentration. Thus, the means by which depolarization was achieved in our experiments was not analogous to that which occurs clinically. The arrhythmogenic potential of depolarized cardiac tissue may differ, depending on the means by which depolarization was achieved. Nonetheless, both automaticity and block may well be intrinsic properties of depolarized foci. Recent microelectrode studies of human cardiac tissue from patients with ischemic heart disease have suggested that abnormal automaticity and impaired conduction, occurring in depolarized areas, may be important in the genesis of clinically significant arrhythmias. We investigated in vitro the consequences of the interactions of depolarized foci with their surrounding tissues. That some of the arrhythmic patterns were similar to those observed clinically suggests that such interactions may be important. However, we are not implying that our findings are directly applicable to clinical situations, but suggest mechanisms of arrhythmogenesis.

Myocardial infarction is accompanied by instability of cellular metabolism, both within the infarct zone in islands of living cells, and in the border zone. This leads to loss of resting potential and to spontaneous arrhythmias. We demonstrated in a previous study that entrainment of a protected ectopic focus by another pacemaker may give rise to a wide variety of arrhythmic patterns, often with fixed coupling and periods of complete silence. In this study, we have shown that minor changes in resting membrane potential may result in significant alterations in the behavior of spontaneous depolarized foci and in the patency of both entrance and exit pathways. This may lead to significant changes in the clinical expression of automatic activity. Events such as intermodulation between pacemakers, reflections, and annihilation of automatic activity by properly timed stimuli may all increase the complexity of the expression of spontaneous activity. Many or all of the phenomena that we have demonstrated could occur during the course of an ischemic event, and would allow a single ectopic focus to display characteristics both of modulated parasympathetic and of reentry.

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