JACC Vol. 8, No. 3
September 1986:648–56

Contribution of Depolarized Foci With Variable Conduction Impairment to Arrhythmogenesis in 1 Day Old Infarcted Canine Cardiac Tissue: An in Vitro Study

JAMES E. ROSENTHAL, MD, FACC

Chicago, Illinois

To assess the roles of entrance and exit block after canine myocardial infarction, single stage coronary artery ligations of canine circumflex coronary arteries were performed. After 1 day, atria and ventricles were paced using single stimuli and trains. After isolation, simultaneous microelectrode impalements were made in infarcted and uninfarcted tissue. Spontaneous foci, when identifiable, were always located in infarcted tissue. They could frequently be triggered by one or more driven beats, and their activity could often be terminated ("annihilated") by a properly timed beat. Foci with varying combinations of extrance and exit conduction impairment were observed.

Variations in conduction characteristics altered the manifest arrhythmic pattern. With partial entrance block and intact exit conduction, foci could be electrotonically modulated and entrained into regular patterns. Activity that emerged from a focus with sufficient conduction delay could modulate the focus, and entrain it to discharge at a slower rate ("autoentrainment"). The results suggest that modulated parasystole may contribute to arrhythmogenesis after canine myocardial infarction and that variations in entrance and exit characteristics of depolarized foci may result in variable and complex arrhythmic patterns.

(J Am Coll Cardiol 1986;8:648–56)

The arrhythmias occurring after myocardial infarction are often complex, and their pattern may be highly variable, not only from one patient to another, but also over time within a single patient. It is well established that arrhythmias may arise through two general mechanisms, reentry and abnormal impulse formation. Each of these has been studied extensively, and each probably plays an important role in the generation of arrhythmias in ischemic tissues (1–4). The experiments described in the present study were designed to investigate arrhythmias generated by the latter of these two mechanisms, abnormal impulse formation.

Depolarized Purkinje fibers and myocardium can give rise to spontaneous activity, so-called depolarization-induced automaticity (5,6). In recent studies, Ferrier and I (7,8) showed that when a small area of isolated, healthy cardiac tissue was depolarized, generally by the focal application of current, the focus of depolarization-induced automaticity had varying entrance and exit conduction impairments. The nature of the impairments was related in large part to the degree of focal depolarization. Alterations in entrance and exit block could lead to wide variability in the expression of the focal automaticity. Although mild depolarization allowed exit conduction, greater depolarization produced exit block, thereby "silencing" the ectopic pacemaker. With lesser degrees of exit block, activity could emerge with Wenchebach periodicity.

Electrotonic modulation and entrainment. When exit pathways were intact, but entrance block existed, the depolarized area behaved as a parasystolic focus. A classic parasystolic focus has such a high degree of entrance block that its spontaneous activity is unaffected by activity occurring in tissue surrounding it. Thus, interectopic cycle lengths are constant and the coupling intervals to sinus beats are variable (9). However, in our experiments, foci had a lesser degree of entrance block, which allowed external action potentials to generate subthreshold electrotonic depolarizations, but not regenerative activity, within the foci. These electrotonic depolarizations could modulate the timing of the spontaneous activity. Such electrotonic modu-

From the Department of Medicine, Section of Cardiology, Reingold ECG Center, Northwestern University Medical School, Chicago, Illinois. This study was supported in part by a grant-in-aid from the American Heart Association, Dallas, Texas, with funds contributed in part by the Chicago Heart Association, Chicago, Illinois and by Grant RR05370 from the U.S. Public Health Service, National Institutes of Health, Bethesda, Maryland.

Manuscript received November 12, 1985; revised manuscript received March 26, 1986, accepted April 4, 1986.

Address for reprints: James E. Rosenthal, MD, Reingold Electrocardiography Center, Northwestern University Medical School, 310 East Superior Street, Chicago, Illinois 60611.

0735-1097/86/$3.50

lation is a well described phenomenon in which an electrotonus at a spontaneous focus, generated by a blocked extrafocal beat, delays or accelerates the focal activity in a predictable and reproducible manner, depending on the phase relation between focal and extrafocal activity (10–12). The modulation made it possible to "entrain" the focus to discharge at rates that were faster or slower than its unmodulated rate, and could result in regular arrhythmic patterns that included bigeminy and trigeminy. During such entrained patterns, the coupling interval between focal and extrafocal activity was frequently fixed, resulting in arrhythmias resembling those associated with a reentrant rather than an automatic mechanism. An ectopic pacemaker entrained so that its activity regularly emerges at a time when the ventricle is refractory may appear to be totally silent. The pattern of entrainment at any given moment depends on the relation between the rate of the dominant pacemaker and that of the ectopic pacemaker, as well as on the degree of electrotonic interaction between the two pacemakers. Electrotonic modulation and entrainment have been studied in vitro (7,10–12) and have also been described in studies of clinical electrocardiographic records (13,14). (This use of the term *entrainment* (11,12) differs slightly from that of Waldo et al. (15,16), who used it to describe a clinical situation in which reentrant atrial and ventricular arrhythmias were accelerated to the rate of a faster pacemaker, often an artificial one.)

Other complex behaviors observed in our preparations included reflected reentry, intermodulation of two pacemaker sites and abrupt termination of pacemaker activity by properly timed driven beats. The latter phenomenon has been called "annihilation" (17). It has been described in isolated Purkinje fibers and sinoatrial strips (17,18) as well as in diseased human ventricle (19). Castellanos et al. (14) found evidence for annihilation in clinical electrocardiograms.

Arrhythmias in myocardial infarction. I questioned whether phenomena similar to these, which had been observed in isolated preparations that had been artifically depolarized by focal current application or by alteration of the ionic composition of the superfusate (8), might underlie arrhythmias observed after myocardial infarction. Such arrhythmias are frequently complex and often show considerable variation over time. I hypothesized that at least some of the complex and variable arrhythmic patterns after myocardial infarction might result from variation in the expression of protected, depolarized automatic foci. Spatial heterogeneity in electrophysiologic characteristics (including maximal diastolic potential) has been shown to be present in infarcted canine ventricle at 24 hours (20). Such spatial heterogeneity would be expected to generate gradients in maximal diastolic potential that might predispose toward the occurrence of modulated parasystole. Moreover, changes over time in the resting membrane potential of tissue within or surrounding depolarized foci would be expected to result in changing conduction defects and consequently in changing arrhythmic patterns (8). Such changes might be the result of hypoxia or of the accumulation of potassium in the extracellular space (21–23).

Methods

Experimental preparation. Mongrel dogs of either sex (n = 16) were anesthetized with intravenous sodium pentobarbital, 30 to 40 mg/kg body weight. They were intubated with an endotracheal tube and ventilated with a Harvard respirator using room air. Using sterile techniques, a left thoracotomy was performed; the heart was supported in a pericardial cradle. The left circumflex coronary artery was exposed and ligated near its origin in a single stage. The chest was closed in layers and the animal was allowed to recover. When necessary, animals were given morphine sulfate or fentanyl and droperidol (Innovar) for analgesia.

After 1 day (22 to 26 hours), the dogs were reanesthetized, and the heart was rapidly excised and dissected. One day after coronary artery ligation there is a clearly visible difference in color between normal and infarcted ventricular tissue, with a well demarcated boundary. This permitted visually directed dissection of a fairly large piece of left ventricle which contained both infarcted and uninfarcted tissue. Preparations measured 4 to 8 × 4 to 5 cm. To facilitate mounting of the preparations, and to prevent them from curling upward as inner layers of myocardium died, their thickness was reduced to approximately 5 mm by careful dissection parallel to the endocardial surface (except at the area of the papillary muscle, where the myocardial thickness was greater).

Preparations were then mounted with stainless steel pins to the wax surface of a tissue bath with the endocardial surface facing up, and were continuously superfused with modified Tyrode's solution containing (in millimoles): sodium chloride, 137; sodium bicarbonate, 12; potassium chloride, 4.0; sodium phosphate, monobasic, 1.8; magnesium chloride, 0.5; calcium chloride, 2.5; and dextrose, 5.5. The solution was bubbled with a 95% oxygen to 5% carbon dioxide gas mixture; pH after bubbling was 7.0. Temperature was maintained at 37°C. A large tissue bath with a volume of 110 ml was required to contain these preparations. However, the preparations were sufficiently large to displace a large amount of the bath's contents so that the actual volume of Tyrode's solution that it contained was much smaller. A rapid flow rate of 18 to 20 ml/min and a wax dam in front of the bath's inlet, which created turbulence to prevent streaming and pooling of solution, maintained uniformity to flow and of temperature to within ±0.25°C.

Electrical recording technique. It has been demonstrated that spontaneous rhythms in infarcted canine ventricular tissue arise primarily in subendocardial Purkinje fibers (20). Impalements, therefore, were made in the sub-

JACC Vol. 8, No. 3
September 1986:648–56

endocardial Purkinje network using glass microelectrodes that were filled with 3.0 *M* potassium chloride and had a resistance of 15 to 30 MΩ. Signals were amplified by a high impedance, capacity neutralized amplifier (WPI 750). There were displayed on a Tektronix oscilloscope and recorded on a Grass Kymograph camera. Observations were made after preparations had been allowed to recover in the tissue bath for at least 1 hour.

Stimuli, generated by digital stimulators with optically isolated outputs (Frederick Haer 4i and 6i), were 1 to 3 ms in duration and were delivered to the preparations through a pair of silver wires that were insulated except at the tips. The stimulating wires were always placed on the uninfarcted portions of the preparation, and were generally at least 1 cm away from sites of abnormal impulse formation.

Preparations were mapped by means of multiple consecutive impalements by two simultaneously recording microelectrodes, one in the infarcted and the other in the uninfarcted area. A spontaneous focus was defined as an area in which cells had action potentials (viewed at a fast sweep speed on the oscilloscope), with diastolic depolarization and a fairly gradual transition from phase 4 to phase 0. At times, it was possible only to impale cells that were near but not precisely at a site of impulse generation. Such cells had a more abrupt transition to phase 0. The upstroke of action potentials in an automatic site had to precede the upstroke in any other simultaneously impaled cell at least some of the time during each experiment. Because of changes in conduction patterns (which could allow activity to reach a remote impalement before reaching one closer to, but not precisely at, a site of impulse formation) and because of shifts in sites of impulse formation, automatic foci occasionally did not "lead" throughout an entire experiment.

Definitions. The term *entrance block* will be used to describe a situation in which a beat initiated extrafocally failed to generate an action potential in the cell impaled within the focus, whereas *exit block* will be used to describe the opposite situation. Precise identification of the site of block, or of conduction pathways between the two impalements, was not relevant to the goals of this study; therefore, extensive mapping using arrays of multiple simultaneous recordings was not attempted. Other terms, such as electrotonic modulation, entrainment and annihilation, have already been defined.

All procedures involving experimental animals were carried out in conformance with the animal welfare regulations of Northwestern University and the guiding principles of the American Physiological Society.

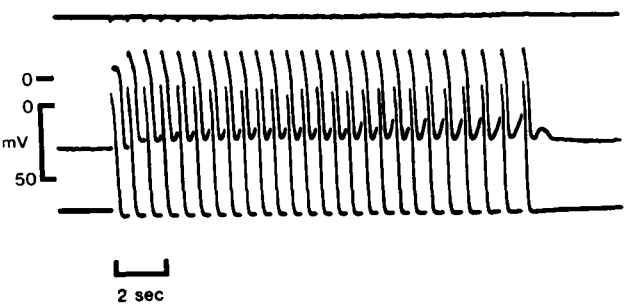
Results

Ventricular specimens from 16 infarcted dog ventricles were studied in the tissue bath. Spontaneous activity was present in all 16. In 11 experiments, sites of impulse formation could be identified by means of mapping with microelectrodes. These sites were always located within the infarcted portion of the ventricle. Their distance from the border demarcating infarcted from noninfarcted tissue ranged from 5 to 34 mm (measured by an ocular micrometer in the dissecting microscope). Data for this report were obtained from those 11 experiments. In the other five experiments, a site of impulse formation could not be located. Foci were markedly to moderately depolarized, with maximal diastolic potentials ranging from −42 to −76 mV. (In only two preparations, however, was maximal diastolic potential negative to −70 mV; no entrance or exit conduction block to the foci was present in either of these experiments.) Maximal diastolic potentials within the noninfarcted area ranged from −67 to −84 mV.

Spontaneous activity. Runs of spontaneous activity were often intermittent and, in five of the experiments, could be triggered by one or more driven beats (Fig. 1). These beats appeared to arise from oscillatory afterpotentials (delayed afterdepolarizations). In other experiments, the generative mechanism of the arrhythmia could not be identified. For example, when an arrhythmia was continuous it was not possible to determine whether it was triggerable and arose from oscillatory afterpotentials (24) or whether it was an example of depolarization-induced automaticity (5,6). In two experiments, oscillatory afterpotentials were present, but triggering could not be demonstrated and the mechanism of spontaneous activity could not be defined. Therefore, in this report, the general terms "spontaneous activity" or "spontaneous focus" will be used to encompass all mechanisms of abnormal impulse initiation.

Conduction characteristics of pathways leading to the spontaneous foci were variable. Rarely, the coexistence of complete exit and entrance block totally isolated the focus

Figure 1. Spontaneous activity "triggered" by a short train of driven action potentials. The **top trace** is a record of stimulation. The **upper intracellular recording** was recorded from an ectopic focus in the infarcted part of the preparation, and the **lower recording** was recorded from distant, uninfarcted tissue. The stimulating electrode was located near the lower trace electrode, on uninfarcted tissue. The driven train initiated a burst of automatic activity that terminated spontaneously and was followed by a subthreshold oscillatory afterpotential. Entrance and exit pathways to the focus were intact.



from the remainder of the preparation. Focal activity did not emerge to the remainder of the heart. Activity initiated extrafocally did not penetrate or electrotonically modulate the focus. Conversely, when both entrance and exit conduction were successful, as in the example illustrated in Figure 1, the dominant rhythm of the preparation as a whole was that of the fastest pacemaker at the time. Thus, in Figure 1, the seven driven beats captured the spontaneous pacemaker. When stimulation was terminated, spontaneous activity successfully captured the rest of the preparation.

Modulation and entrainment of ectopic foci. Figure 2 illustrates one of five experiments in which entrance block with intact exit conduction allowed electrotonic modulation to occur. In this experiment, stimuli were delivered to the uninfarcted portion of the preparation at varying times during the diastolic interval of the ectopic pacemaker. The driven activity was prevented by entrance block from bringing the impaled cell in the infarcted area to threshold, and thus produced only electrotonic depolarization within the focus. Exit conduction from the automatic site, however, was intact, and focal activity was successfully propagated to the remote part of the ventricle. The first driven action potential occurred early in the diastolic interval of the ectopic focus, and delayed the next discharge of the focus. The third driven beat occurred later in diastole and resulted in even greater delay of the next discharge of the focus. The second driven action potential accelerated (or captured) the focus.

The relation of the cycle length of the interpolated beat to the resulting ectopic cycle length in all experiments in which modulation of foci occurred was typical of the phase-response relation described previously for ectopic pacemakers (10,11). Figure 3 illustrates the phase-response relation for the experiment illustrated in Figure 2. Test beats delivered progressively later in the initial part of the pacemaker's cycle caused increasing delay of the next spontaneous beat. After a crossover point, test beats accelerated (or captured) the focus.

To test whether ectopic pacemakers observed in infarcted canine ventricular tissue could be entrained, continuous stimulation was applied to the noninfarcted part of the ventricle. Figure 4 illustrates a sequence from one of four ex-

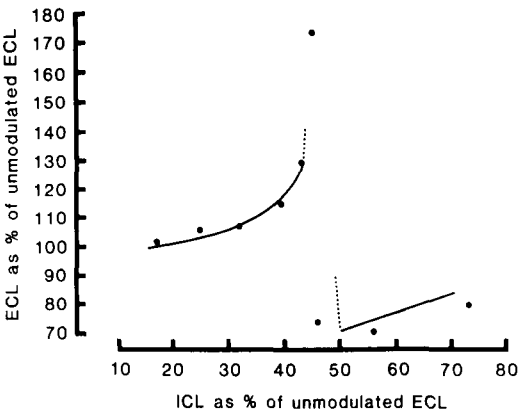


Figure 3. Phase-response curve illustrating the modulating effect of ectopic pacemaker cycle length (ECL) by test beats initiated on a remote part of the preparation and interpolated at various points during the pacemaker's cycle (interpolated cycle length, ICL). The **abscissa** represents the point at which test beats were delivered, expressed as a percent of the unmodulated cycle length. The **ordinate** represents the resulting ectopic cycle length as a percent of the unmodulated cycle length. The data are from the same experiment illustrated in Figure 2 (see text).

Figure 2. Modulation of an ectopic focus. The **top trace** is a record of stimulation. The **upper trace** represents an impalement in the apparent site of impulse formation, and the **lower trace** represents an impalement in the remote, uninfarcted part of the preparation. Because of entrance block to the focus, driven activity initiated near the remote impalement produced only electrotonic depolarizations within the focus. The first and third driven beats delayed the next discharge of the focus, and the second driven beat, which occurred late in the spontaneous cycle, accelerated the focus.

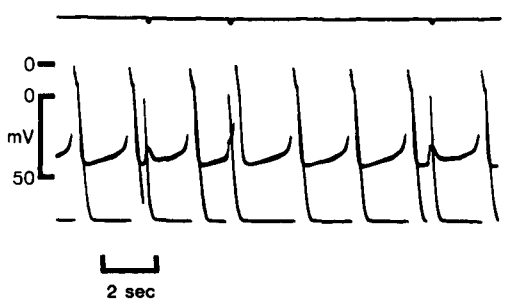
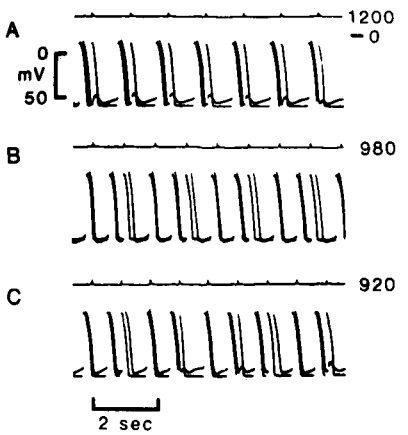
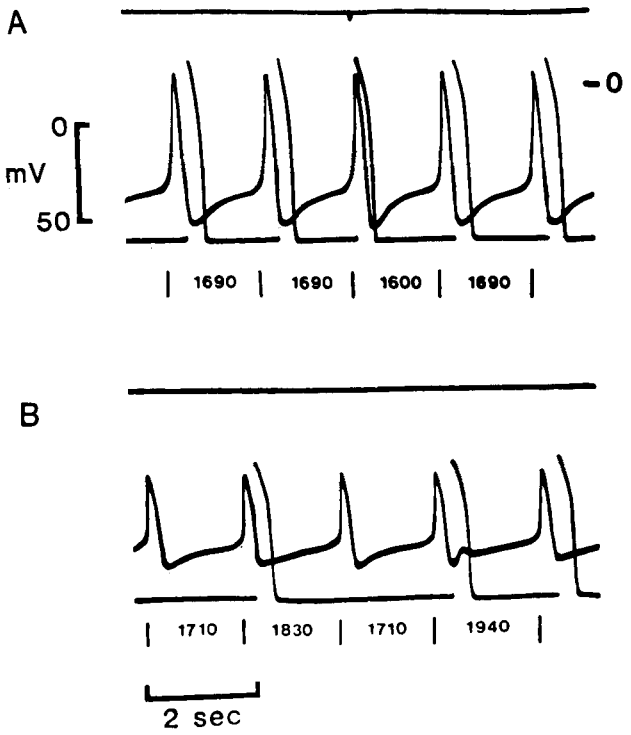


Figure 4. Entrainment of an ectopic pacemaker. The **top trace** in each panel is a record of stimulation. The **upper (thick) traces** of action potentials (voltage calibration on **left**) were recorded from an electrode in the infarcted area, probably near, but not directly at, the site of impulse formation. The **other (thin) trace** (0 indicated on the right) was recorded from the uninfarcted portion of the preparation. Altering the cycle length at which the preparation was driven resulted in various patterns of entrainment. Examples are shown at 1200, 980 and 920 ms.



periments in which entrainment could be demonstrated. In each panel, the top trace represents a record of stimulation. The action potentials with the upsloping phase 4 (voltage calibration indicated on the left) were recorded from an electrode in the infarcted region, probably near but not directly at the site of impulse formation. The other trace represents an impalement in the uninfarcted part of the preparation. In this sequence, the unmodulated cycle length was approximately 725 ms. The first cycles in both panels B and C, in which the stimulus did not capture the remote site because it was refractory, represent examples of unmodulated cycles. When the remote site was stimulated as a basic cycle length of 1,200 ms (panel A), the focus was entrained into a bigeminal pattern. Progressively decreasing the basic cycle length of the driven activity resulted in a trigeminal pattern (basic cycle length = 980 ms, panel B). At a cycle length of 920 ms (panel C), a complex pattern of entrainment resulted.

Figure 5. Autoentrainment of an automatic focus. The **top trace** in each panel is a stimulation record. The **upper trace** of action potentials (voltage calibration on **left**) was obtained from a spontaneous focus in the infarcted area, and the **lower trace** (0 on right) was obtained from uninfarcted tissue. **A**, When delayed exit conduction was prevented by introducing a driven beat simultaneously with the upstroke of the automatic beat, the spontaneous cycle length became shorter. **B**, Action potentials recorded later in the experiment, when cells in the focus had become more depolarized. (Apparent loss of maximal diastolic potential in the remote site impalement is probably due to the fact that this trace represents a different impalement from the corresponding trace in **A**.) Intermittent exit block was now present. Successful exit conduction resulted in delay of the next spontaneous beat and, in the case of the second successfully conducted beat, in a baseline deflection of the focal recording. Upstrokes have been retouched, and spontaneous cycle lengths (in milliseconds) are shown.



Autoentrainment of a spontaneous focus. Activity exiting from a focus with sufficient delay may modulate that focus (Fig. 5). In Figure 5A, the basic cycle length of the spontaneous beats was 1,690 ms. There was considerable delay in the emergence of activity from the ectopic focus. To test whether the emerging beats might be resulting in electrotonic delay of the next scheduled spontaneous beat, thereby slowing the apparent rate of the focus, test beats were delivered as soon as a spontaneous beat was sensed. This eliminated the delayed emergence of activity, and shortened the ectopic pacemaker's cycle length of 1,600 ms. Such shortening of cycle length consistently occurred when delayed emergence of exiting activity was prevented. In this experiment, resting potential and exit conduction characteristics of the focus were unstable. Figure 5B was recorded from the same experiment at a time when the maximal diastolic potential of the focus had decreased, and exit block had developed. Spontaneous activity was now conducted only intermittently to the impaled cell in the uninfarcted area, still with conduction delay. Occasionally (see fourth cycle), a large electrotonic baseline deflection was present in the depolarized spontaneous site, and corresponded in time with the conducted action potential's arrival at the remote site. As in Figure 5A, cycles in which activity emerged successfully from the spontaneous site were prolonged, suggesting that an electrotonic influence of the emerging activity affected the spontaneous cycle length. Although a large electrotonus was apparent only after the fourth beat in panel B, close examination of both panels reveals a flattening of the initial part of phase 4 depolarization after just those beats in which exit conduction was delayed. This flattening probably represents a small electrotonic baseline deflection induced by the emerging activity.

The examples illustrated in Figure 5 suggest that a spontaneous pacemaker may be "autoentrained"; that is, activity initiated by an ectopic focus may itself alter the apparent cycle lengths of that focus.

Temporal variation in conduction characteristics. Frequently, conduction characteristics varied spontaneously within brief periods of time. A recording from an experiment in which this occurred is illustrated in Figure 6. In the initial part of the recording, spontaneous beats propagated, although slowly, from the spontaneous ectopic focus to the remainder of the uninfarcted part of the preparation. A few seconds later, complete exit block appeared. Activity initiated in the uninfarcted portion was able to capture (or accelerate) the focus even at a time when exit block was present (note the last two driven beats). Throughout this experiment, transient exit block appeared and disappeared. As in the experiment illustrated in Figure 5, cycle length

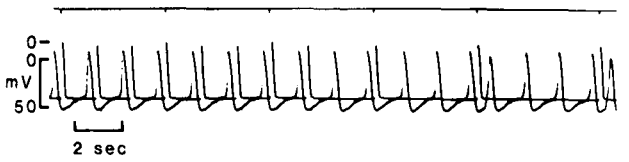


Figure 6. Temporal variation in conduction characteristics. The **top trace** is a record of stimulation. The **lower trace** of action potentials was recorded in or near an ectopic focus in the infarct, whereas the **upper trace** was recorded from a remote site in uninfarcted tissue. In the initial part of the trace, activity propagated from the spontaneous site to the area of the remote impalement. A few seconds later, complete exit block appeared, although driven activity initiated at the remote area was still able to capture or accelerate the focus. With the appearance of exit block, the cycle length of automatic activity decreased slightly, suggesting the presence of autoentrainment.

decreased in duration (from 1,514 to 1,405 ms) when exit conduction failed, suggesting the presence of autoentrainment. In this experiment there was no change in the resting membrane potential of the cell impaled in or near the focus, nor was there a change in the rate of the spontaneous activity to explain the sudden change in conduction. In other experiments, however (Fig. 5), the development of conduction block was accompanied by a loss of resting membrane potential and of action potential amplitude of cells near the spontaneous site.

Annihilation of pacemaker activity. In 4 of the 11 experiments, properly timed beats, either driven or arising from an alternate spontaneous focus, reproducibly annihilated ectopic activity or prolonged the ectopic cycle length more than expected. In the experiment depicted in the phase-response curve of Figure 3, a stimulus delivered at 45% of the spontaneous cycle resulted in disproportionate delay of the next spontaneous beat. Characteristically, such disproportionate delay results from a stimulus delivered at or near the crossover point of the phase-response curve.

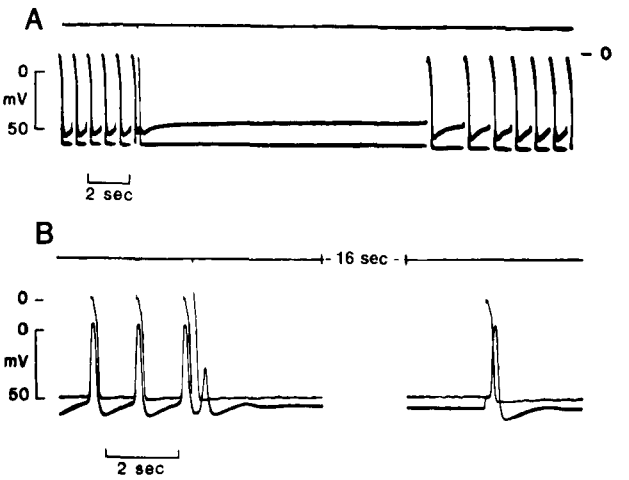
Figure 7 is the cellular record from two other experiments in which annihilation occurred. Panel A (recorded from the same experiment as in Figure 4) shows that the test beat resulted in an electrotonic deflection of the membrane potential recorded in the infarcted portion of the preparation, which was followed by a 14.7 second pause. The pause was ended by a beat that probably arose from a different pacemaker site. Panel B (recorded from a different experiment) shows that the test beat, delivered 350 ms after the last spontaneous beat, resulted in an action potential in the uninfarcted area of the preparation and in a low amplitude depolarization in the focal cell. It is impossible to say whether that depolarization was purely electrotonic or represented a depressed regenerative response. In any case, it was followed by a small, damped oscillation, and it initiated a 20.4 second pause. In this experiment, multiple test beats delivered at a similar point in the cycle resulted in pauses ranging in duration from 6.25 to 35.25 seconds. Spontaneous activity could be reinitiated by one or more driven beats or, at times, by beats that arose spontaneously elsewhere in the preparation.

Discussion

The results suggest that some of the variability in arrhythmias arising from spontaneous foci in infarcted canine ventricular tissue may arise because of variability in the characteristics of entrance and exit pathways to the foci.

Initiation and termination of spontaneous activity. The foci identified in the present experiments were markedly to moderately depolarized, and approximately half of them could be triggered by one or more driven beats or by beats arising spontaneously from an extrafocal site. This is consistent with recent reports (25,26) which have suggested that triggered automaticity may be an important mechanism of impulse formation after canine myocardial infarction. Activity at times started and stopped spontaneously. In four experiments, it could be abruptly terminated by a properly timed driven beat. Abrupt termination of pacemaker activity has been demonstrated previously in several situations, including simian mitral valve leaflet (27), Purkinje fibers and papillary muscle (8,17) and tissue treated with cardiac steroids (24). As in previously described experiments (17,18), in the present experiments termination was dependent on

Figure 7. Two examples of annihilation of pacemaker activity. **A**, Records are from the same experiment illustrated in Figure 4, and the arrangement of traces is the same. The driven test beat, initiated near the remote impalement, resulted in an electrotonic baseline deflection of the focal trace, and was followed by a 14.7 second pause, after which spontaneous activity resumed, probably initiated by a beat from a different, unidentified pacemaker site. **B**, In this experiment, the **lower trace** of action potentials was recorded near an ectopic focus in the infarct. The driven beat, initiated near the remote impalement (**lower trace**), produced only a low amplitude depolarization in the focus, which was followed by a damped oscillation and a 20.4 second pause.



JACC Vol. 8, No. 3
September 1986:648–56

the proper timing of the annihilating beat, and in some cases (Fig. 7B) cessation of the spontaneous activity was followed by one or more damped oscillations. Thus, activity generated by a depolarized focus can abruptly appear and disappear, either spontaneously or as a result of triggering and annihilation by extrafocal activity. The ability to initiate or abolish a ventricular tachyarrhythmia with properly timed beats, therefore, is not helpful in distinguishing reentrant from spontaneous arrhythmias, as had previously been suggested (28–30).

Variations in exit conduction. Manifest ectopic activity may appear and disappear, also as a result of alterations in the patency of the exit pathways of an ectopic focus. The development of exit block within pathways surrounding a spontaneous site may render the focus clinically silent, even if its activity is unchanged (Fig. 5 and 6). Such intermittent exit block may occur because of loss of maximal diastolic potential (8) (Fig. 5), which would decrease the amplitude of the focal action potential (31), thereby attenuating its electrotonic image beyond the site of block sufficently so that the remote tissue is no longer brought to threshold. Instability of maximal diastolic potential would be expected to occur after myocardial infarction because of the increased permeability of the cells to potassium (22,23). Thus, intermittent exit block of ectopic foci might be one of several possible explanations for the intermittency of ventricular arrhythimas that is often observed after myocardial infarction.

Exit block may also contribute to the manifest arrhythmic pattern by allowing activity to emerge from a focus with sufficient delay to allow it to electrotonically modulate and autoentrain itself. Jalife and Moe (12) demonstrated in a sucrose gap experiment that the electrotonic influence of beats emerging from a pacemaker with varying conduction block may result in predictable variability of that pacemaker's basic cycle length. Rosenthal and Ferrier (8) demonstrated a similar phenomenon, in which activity emerging from a focus with Wenckebach periodicity modulated that focus to result in a complex pattern. In one experiment (Fig. 5), marked exit delay and, at times, complete exit block, suggested the presence of an area of discontinuous conduction in the exit pathway of the focus. An electrotonic baseline deflection was produced in the focal recording early in diastole, approximately coincident with the arrival of activity at the extrafocal side of the area of block. This may represent a special case of reflection or reentry in which the reentrant beats did not reach threshold. Because the emerging spontaneous activity had constant exit delay, the coupling interval of the electrotonus was fixed, thereby uniformly delaying the next spontaneous beat. The focus was entrained in a 1 : 1 ratio by activity that it itself had initiated. Autoentrainment may be yet another mechanism whereby conduction delays in tissues surrounding the focus may influence an arrhythmia's rate.

Variations in entrance conduction. The characteristics of entrance conduction pathways may also have profound effects on the manifestation of spontaneous activity arising from an ectopic foci. It has been suggested that classic parasystole, modulated (and entrainable) parasystole and reflected reentry are all part of a spectrum of possible manifestations of a protected focus. Which of these expressions of the focus predominates depends on the degree of entrance block (32,33). Complete entrance block, in which the focus is totally protected from the effects of surrounding activity, would be expected to result in classic parasystole.

A low degree of entrance block, on the other hand, is characteristic of an escape pacemaker whose rate exceeds that of surrounding activity or of a pacemaker that is sufficiently rapid to render surrounding conduction pathways continually refractory. The latter mechanisms was proposed more than 30 years ago by Scherf and Schott (34) to explain the occurrence of entrance block in rapid parasystolic arrhythmias.

A spontaneous focus with an intermediate level of entrance block, in which entrance pathways allow extrafocal activity to produce electrotonic depolarizations within the focus, resulting in modulation and entrainment, may lead to a complex array of arrhythmic patterns including bigeminy and trigeminy. Spontaneous activity has been reported to arise from or near localized, depolarized areas in infarcted tissue (1–3,20,35–38). We have previously shown (7,8) that the prerequisites for modulated parasystole—automaticity, entrance block and exit conduction—may all be the consequence of a single generative event, namely focal depolarization. Therefore, the occurrence of modulated and entrained parasystole in depolarized ischemic tissue seems likely. Gilmour et al. (19) recently reported the presence of pacemaker modulation and annihilation in specimens of human ventricular tissue from patients with ischemic heart disease.

Foci with entrance conduction impairment may also result in the generation of reentrant type arrhythmias. If external activity accelerates, or captures the focus with so much delay that surrounding tissues can recover excitability, then the activity may reexcite the surrounding tissues, producing a closely coupled reentrant beat. This phenomenon has been called reflected reentry (33), and has been observed in several models, including the 1 day old canine myocardial infarction model described in the present report (39).

Limitations. The problem of precisely localizing a dominant pacemaker site has been discussed by other investigators (40). Only sites that had both action potentials, with characteristics of a pacemaker, and an upstroke that preceeded that of all other sites, were labeled as dominant pacemaker sites. Thus, any possible error in localizing the pacemaker was probably small, and should not have qualitatively affected the interpretations of the results.

The meaningfulness of any attempt to make direct cor-

relations between arrhythmic behavior in vivo and experimental results in isolated in vitro tissue preparations is highly questionable. The intact ischemic ventricle in vivo is apt to contain more foci and more potential reentrant pathways than a much smaller, isolated in vitro preparation. Moreover, the heart in the intact animal is subject to autonomic, hemodynamic and mechanical influences not present in the isolated tissue bath. Thus, arrhythmias in vivo are likely to be even more complex and variable than those observed in vitro. Alternatively, overdrive suppression of an arrhythmia by a faster sinus rhythm may lead to concealment of the arrhythmia in vivo.

Conclusions. Studies in healthy cardiac tissues have shown that small changes in entrance and exit pathways, as well as in the spontaneous activity, may profoundly alter the nature of the manifest arrhythmia. The present study provides evidence that similar mechanisms may play a role in the genesis of the profoundly variable patterns of arrhythmias seen after myocardial infarction. After myocardial infarction, the instability of resting membrane potential may affect conduction characteristics of entrance and exit pathways. Thus, for example, the sudden development of exit block may suppress an arrhythmia (or vice versa). Similar alterations in entrance pathways may also profoundly affect the manifest expression of arrhythmias. Finally, small changes in membrane potential may alter the cycle length of the spontaneous activity itself, and phenomena such as triggering and annihilation, as well as actual shifts in pacemaker sites, may further contribute to the instability and complexity of arrhythmias after myocardial infarction.

I thank Gregory R. Ferrier, PhD for review of the manuscript and for helpful suggestions, Daniel Leonard and Laura Moreth for technical assistance and Claudette P. Ledesma and Lillian Washington for help in preparing this manuscript.

References

1. Scherlag BJ, El-Sherif N, Hope R, Lazzara R. Characterization and localization of ventricular arrhythmias resulting from myocardial ischemia and infarction. Circ Res 1974;35:372–83.
2. Wit AL, Friedman PL. Basis for ventricular arrhythmias accompanying myocardial infarction. Arch Intern Med 1975;135:459–72.
3. Elharrar V, Zipes DP. Cardiac electrophysiologic alterations during myocardial ischemia. Am J Physiol 1977;233:H329–45.
4. El-Sherif N, Mehra R, Gough WB, Zeiler RH. Ventricular activation patterns of spontaneous and induced ventricular rhythms in canine one-day old myocardial infarction: evidence for focal and reentrant mechanisms. Circ Res 1982;51:152–66.
5. Imanishi S, Surawicz B. Automatic activity in depolarized guinea pig ventricular myocardium. Circ Res 1976;39:751–9.
6. Katzung B. Electrically induced automaticity in ventricular myocardium. Life Sci 1974;14:1133–40.
7. Ferrier GR, Rosenthal JE. Automaticity and entrance block induced by focal depolarization of mammalian ventricular tissues. Circ Res 1980;47:238–48.
8. Rosenthal JE, Ferrier GR. Contribution of variable entrance and exit block in protected foci to arrhythmogenesis in isolated ventricular tissues. Circulation 1983;67:1–8.
9. Katz LN, Pick A. Clinical Electrocardiography, Part I: The Arrhythmias. Philadelphia: Lea & Febiger, 1956:182–4.
10. Jalife J, Moe GK. Effect of electrotonic potentials on pacemaker activity of canine Purkinje fibers in relation to parasystole. Circ Res 1976;39:801–8.
11. Moe GK, Jalife J, Mueller WJ, Moe B. A mathematical model of parasystole and its application to clinical arrhythmias. Circulation 1977;56:968–79.
12. Jalife J, Moe GK. A biologic model of parasystole. Am J Cardiol 1979;43:761–72.
13. Nau GJ, Aldariz AE, Acunzo RS, et al. Modulation of parasystolic activity by nonparasystolic beats. Circulation 1982;66:462–9.
14. Castellanos A, Luceri RM, Moleiro F, et al. Annihilation, entrainment and modulation of ventricular parasystolic rhythms. Am J Cardiol 1984;54:317–22.
15. Waldo AL, Plumb VJ, Arciniegas JG, et al. Transient entrainment and interruption of the atrioventricular bypass pathyway type of paroxysmal atrial tachycardia. Circulation 1983;67:73–83.
16. Waldo AL, Henthorn RW, Plumb VJ, MacLean WAH. Demonstration of the mechanism of transient entrainment and interruption of ventricular tachycardia with rapid atrial pacing. J Am Coll Cardiol 1984;3:422–30.
17. Jalife J, Antzelevitch C. Phase resetting and annihiliation of pacemaker activity in cardiac tissue. Science 1979;206:695–7.
18. Jalife J, Antzelevitch C. Pacemaker annihilation: diagnostic and therapeutic implications. Am Heart J 1980;100:128–30.
19. Gilmour RF, Heger JJ, Prystowksy EN, Zipes DP. Cellular electrophysiologic abnormalities of diseased human ventricular myocardium. Am J Cardiol 1983;51:137–44.
20. Friedman PL, Stewart JR, Fenoglio JJ, Wit AL. Survival of subendocardial Purkinje fibers after extensive myocardial infarction in dogs. Circ Res 1973;33:597–611.
21. Morena H, Janse MJ, Fiolet JWT, Krieger WJG, Crijns H, Durrer D. Comparison of the effects of regional ischemic hypoxia, hyperkalemia and acidosis on intracellular potentials and metabolism in the isolated procine heart. Circ Res 1980;46:634–46.
22. Harris AS. Potassium and experimental coronary occlusion. Am Heart J 1966;71:797–802.
23. Hill JL, Gettes LS. Effect of acute coronary artery occlusion on local myocardial extracellular K^+ activity in swine. Circulation 1980;61:768–78.
24. Ferrier GR, Saunders JH, Mendez C. A cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin. Circ Res 1973;32:600–9.
25. El-Sherif N, Gough WB, Zeiler RH, Mehra R. Triggered ventricular rhythms in 1-day-old myocardial infarction in the dog. Circ Res 1983;52:566–79.
26. Rosenthal JE, Hsieh AM, Leonard DR. Oscillatory afterpotentials in infarcted canine tissue (abstr). Fed Proc 1983;42:1112.
27. Wit AL, Cranefield PF. Triggered activity in cardiac muscle fibers of the simian mitral valve. Circ Res 1976;38:85–98.
28. Moe GK, Cohen W, Vick RL. Experimentally induced paroxysmal A-V nodal tachycardia in the dog. Am Heart J 1963;65:87–92.
29. Burchell HB, Merideth, J. Management of tachyarrhythmias with cardiac pacemakers. Ann NY Acad Sci 1969;167:546–56.
30. Zipes DP. The contribution of artificial pacemaking and understanding of the pathogenesis of arrhythmias. Am J Cardiol 1971;28:211–22.
31. Weidman S. The effect of cardiac membrane potential on the rapid availability of the sodium carrying system. J Physiol (Lond) 1955;127:213–24.
32. Jalife J, Antzelevitch C, Moe GK. Models of parasystole and reflec-

tion. In: Rosenbaum MB, Elizari MV, eds. Frontiers of Cardiac Electrophysiology. Boston: Martinus Nijhoff, 1983:217–38.

33. Antzelevitch C, Jalife J, Moe GK. Characteristics of reflection as a mechanism of reentrant arrhythmias and its relationship to parasystole. Circulation 1980;61:182–91.

34. Scherf D, Schott A. Extrasystoles and Allied Arrhythmias. New York: Grune & Stratton, 1953:174.

35. Friedman PL, Stewart JR, Wit AL. Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res 1973;33:612–26.

36. Lazzara R, El-Sherif N, Scherlag BJ. Electrophysiological properties of canine Purkinje cells in one-day-old myocardial infarction. Circ Res 1973;33:722–34.

37. Ten Eick RE, Singer DH, Solberg LE. Coronary occlusion: effect on cellular electrial activity of the heart. Med Clin North Am 1976;60:49–67.

38. Janse MJ, VanCapelle FJL, Morsink H, et al. Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolate porcine and canine hearts. Circ Res 1980;47:151–65.

39. Rosenthal JE, Leonard DR. Contribution of conduction impairment in automatic foci to arrhythmogenesis in myocardial infarction (abstr). Circulation 1983;68(suppl III):III–77.

40. Bleeker WK, Mackaay AJC, Masson-Pevet M, Bouman LN, Becker AE. Functional and morphological organization of the rabbit sinus node. Circ Res 1980;46:11–22.