Automaticity and Entrance Block Induced by Focal Depolarization of Mammalian Ventricular Tissues

GREGORY R. FERRIER AND JAMES E. ROSENTHAL

SUMMARY Isolated canine interventricular septa were studied with standard microelectrode techniques. Focal automaticity was induced by applying depolarizing current through an extracellular pipet in contact with the right bundle branch (RBB) of the ventricular specialized conducting system. Automaticity appeared with depolarization to transmembrane potentials of —50 mV or less. The spontaneous activity was neither depressed nor accelerated when overdrive suppression was attempted. Activity originating within the focus propagated into fully polarized surrounding tissue. However, entrance block, phasically related to the spontaneous cycle length, was an intrinsic property of these foci. Early premature beats initiated outside the focus failed to enter the focus, but the resulting electrotonus delayed the next automatic beat. Late premature beats captured and thereby accelerated the focus. Thus, the automatic foci could be entrained by extrafocal activity. Consequently, continuous pacing at various rates precipitated complex rhythms with fixed coupling. Similar foci with exit conduction, entrance block, and electrotonic modulation also were demonstrated in focally depolarized papillary muscles in feline septal preparations. The unique properties of focally depolarized areas in which spontaneous activity is generated at low membrane potentials provide a mechanism capable of generating a wide array of arrhythmias. Circ Res 47: 238—248, 1980

AUTOMATICITY occurring at membrane potentials less negative than —50 mV may represent an important mechanism underlying cardiac arrhythmias (Cranefield, 1975). This mechanism is of special interest because it occurs not only in specialized conduction tissues but also in ventricular muscle (Katzung, 1974). In both tissues, automaticity at low membrane potentials is generated by variations in an outward current identified as I\textsubscript{x>i} (Hauswirth et al., 1969; Katzung and Morgenstern, 1977). This is distinctly different from "normal" pacemaker activity which occurs at high membrane potentials in Purkinje fibers and is generated by a separate current, I\textsubscript{K\textsubscript{2}}. In addition, Imasishi (1971) has presented evidence that the slow inward current is responsible for the upstrokes of the regenerative spikes associated with automaticity at low membrane potentials. For descriptive purposes, we have adopted the term depolarization-induced automaticity (DIA; Katzung and Morgenstern, 1977) to refer to automaticity generated by phase 4 depolarization in either Purkinje or muscle tissues depolarized to membrane potentials more positive than approximately —50 mV. To differentiate between types of automaticity, the term phase 4 depolarization will be used to refer to pacemaker activity dependent on I\textsubscript{K\textsubscript{2}} and occurring in Purkinje tissue at high membrane potentials (greater than approximately —70 mV).

The purpose of the present study was to examine certain characteristics of DIA that might be important in the generation of arrhythmias. One important characteristic to be investigated was the response of DIA to attempts at overdrive suppression. In addition, we wished to determine whether DIA could be induced in foci of depolarized tissue contained within relatively large preparations. We proposed to do this by passing electric current through an extracellular electrode pressed lightly against a small area of Purkinje or muscle tissue. The depolarizing influence of current applied in this way would be expected to decline gradually with distance from its point of application. In the hypothetical example, illustrated in Figure 1, current applied near the middle of the preparation brings the segment bounded by b-b' to potentials of —50 mV or less. DIA should originate only within b-b' because the "threshold" for induction of DIA is approximately —50 mV (Imasishi, 1971), or about 10—20 mV negative to the threshold for the slow inward current (Trautwein, 1973; Reuter and Scholz, 1977). Immediately outside b-b' there are segments, a-b and a'-b', at membrane potentials between —50 and —70 mV. The threshold for the slow inward current lies very positive to these potentials and would not be attained readily. These segments also are depolarized sufficiently to inactivate partially the rapid inward sodium current (Trautwein, 1973; Weidmann, 1955). Thus, the automatic focus should be bounded by tissue in which neither major inward current is readily available,
and in which conduction may be compromised, even to the point of failure.

The third purpose of this study was to examine conduction in and out of the focus. We hypothesize that DIA would be protected by one-way entrance block. The membrane potential of the tissue beyond the area bounded by a-a' (Fig. 1) is displaced toward the threshold of the fast inward sodium channel. These areas should be hyperexcitable (Trautwein and Kassebaum, 1961). Thus, although spontaneous action potentials arising in the focus would be small, the high excitability of tissue outside a-a' would facilitate electrotonic excitation and therefore might promote conduction out of the focus (Wennemark and Bandura, 1974; Wennemark et al., 1975). In contrast, conduction into the focus might fail if the central zone, b-b', exhibits low excitability (Peon et al., 1978). Indeed, inexcitability and conduction block occur regularly when the membrane potential of cardiac tissues is reduced to -60 mV or less in response to a variety of conditions including stretch and hypoxia (Singer et al., 1967; Carmeliet and Vereecke, 1969; Wit and Cranefield, 1977; Brennan et al., 1978).

Finally, if entrance block could be achieved, we wished to determine whether entrainment or modulation of the automaticity could be demonstrated, as in the sucrose-gap preparations described by Jalife and Moe (1976).

Methods

Experiments were performed using the right aspect of interventricular septa of adult mongrel dogs or cats of either sex. Animals were anesthetized with sodium pentobarbital (dog: 30–35 mg/kg, iv; cat: 65 mg/kg, ip). Hearts were excised and dissected to leave the interventricular septum with papillary muscles and right bundle branch (RBB) with its initial free-running branches intact. The combined length of the RBB and free-running strands was approximately 2.5–3.5 cm. In some experiments, the free-running branches (moderator band, false tendons) were used for study as completely isolated preparations. In those experiments, the length of the preparations was limited to 3–4 mm so that all parts of the preparation would be within one space constant of the site of current application. The excised and trimmed tissues were transferred to a tissue bath through which a modified Tyrode’s solution continuously flowed. The Tyrode’s solution was gassed with a mixture of 95% O2–5% CO2, was maintained at 37°C, and had the following millimolar composition: NaCl, 137.0; KCl, 4.0; NaH2PO4, 0.9; NaHCO3, 12.0; CaCl2, 2.5; MgSO4, 0.5; and dextrose, 5.5. In some experiments with muscle, the concentration of KCl was decreased to 2.0 mM to promote depolarization induced automaticity (Imanishi and Surawicz, 1976; Katzung and Morgenstern, 1977).

Preparations were fixed to the wax bottom of the tissue bath with stainless steel pins. Stimulation was accomplished through silver electrodes insulated except at the tip. Stimuli were rectangular pulses, 3 msec in duration, and adjusted to 1.5 times threshold voltage. Pulses, delivered through an isolation transformer, were obtained from a pulse generator (Tektronix 160 series) that was triggered by a digital interval generator. Stimulation was either continuous or consisted of trains of 10 followed by 3-second pauses during which test stimuli could be interpolated.

Current pulses used to depolarize the tissue were obtained from a digital stimulator (Frederick Haer, Pulsar 6i) operating in the constant voltage mode. The optically isolated output was delivered through a current-limiting resistor and was monitored by voltage measurement across a second smaller series resistance. The current electrode consisted of a coiled chlorided silver wire inserted in a soft glass Pasteur pipet (Van-Lab disposable capillary pipet), the tip of which was bent at a convenient angle. The size of the tip orifice was adjusted to any desired diameter by fire polishing (usually approximately 0.5 mm). The pipet, held by a micromanipulator, was filled with Tyrode’s solution and placed very lightly against the tissue to be depolarized. The return electrode was a chlorided silver coil submersed in the tissue bath and was common with chassis ground. Current passage was triggered by the digital interval generator used in stimulation, and was applied either as a 3-second constant current pulse during pauses in stimulation or as continuous current.

Differential recordings from two sites were made using glass microelectrodes filled with 2.7 M KCl (resistance: 15–30 MΩ). One recording was usually

---

**Figure 1** Relationship between membrane potential and distance along a hypothetical cylindrical bundle of cardiac fibers to which depolarizing current is applied at the center. The cross-hatched areas indicate those portions of the tissue in which the membrane potential lies between -50 and -70 mV. The action potentials represent DIA occurring in the segment of tissue depolarized to approximately -50 mV or less. The size and shape of the various zones are approximations subject to variation with conditions and the geometry of a more complex tissue.
from within 1 mm of the current electrode. The impaling electrode initially was positioned immediately outside the cell to be impaled. Then, while passing short current pulses, the indifferent electrode of that pair was positioned to null the effect of current passage. The remote pair, usually a centimeter or more from the current source, was balanced easily by visual approximation of the two electrodes.

The microelectrode records, stimulus pattern, and current record were displayed on an oscilloscope (Tektronix 5103N) and photographed with a Grass camera.

Results

Response to Overdrive

Automaticity induced by depolarization was studied initially in four completely isolated canine false tendons. The preparations were stimulated with a repeating pattern of 10 stimuli followed by a 3-second pause. Current applied during the pause was initiated during the refractory period of the last driven response to avoid initiating extra driven activity. Figure 2 shows records from a representative experiment. In each panel, the top line shows the stimulus pattern and the bottom line the current. The remaining trace is a microelectrode recording from a site within 0.5 mm of the current electrode. The sequence illustrates the effects of applying progressively more current during the 3-second pause. In the absence of current (panel A), no spontaneous activity occurred during the pause. Application of weak current enhanced phase four depolarization and resulted in spontaneous beats as in panel B. Progressive depolarization initially increased the spontaneous rate but, finally, a level of depolarization was reached at which spontaneous activity abruptly stopped. This is illustrated in panel C. Automaticity reappeared only when the maximum diastolic potential was reduced further to levels approaching the threshold for DIA (panel D). The maximum diastolic potential during the first spontaneous cycle in this example was —58 mV. The maximum diastolic potential achieved immediately adjacent to the current electrode would be expected to be slightly less and probably closely approximated the published value of —50 mV (Imanishi, 1971). The rate of DIA also increased with further depolarization, as shown in panel E.

The two ranges of automaticity also can be seen in Figure 3A in which the cycle length of the spontaneous activity is plotted as a function of the strength of the current. The second interval rather than the first was selected for this graph to exclude the last driven beat from the measurement. The data, which are from a different experiment than illustrated in Figure 2, show that both types of automaticity accelerated with increasing current strength within the respective ranges. In this experiment, spontaneous beats generated by phase 4 depolarization ceased when the current was increased beyond 150 µA. DIA appeared when the current was increased to 160 µA, which corresponded to a maximum diastolic potential of —53 mV.

Phase 4 depolarization and DIA not only occurred at distinctly different ranges of membrane potential but also responded differently to changes in the basic cycle length (BCL) of the driven train. Because the preparations could not be driven regularly over a complete range of BCL when depolarized sufficiently to elicit DIA (see later sections), the experiments were conducted with current applied only during the pauses in stimulation. Current application was initiated during the refractory period of the last driven beat. Data from a represent-
Figure 3 A: Relationship between the cycle length of spontaneous activity initiated by depolarizing current applied to a false tendon and the strength of the applied current. Filled symbols represent automaticity caused by phase four depolarization. Unfilled symbols correspond to activity generated by DIA. The ranges of current over which the two types of automaticity occurred were separated by a discrete range of current in which no automaticity was initiated. CL = cycle length. B: Relationship between escape interval and the basic cycle length of spontaneous activity initiated at two levels of depolarizing current. The symbols mean the same as in A. BCL: basic cycle length; MDP: maximum diastolic potential.

DIA in Focally Depolarized Portions of the Right Bundle Branch (RBB)

RBB preparations were used for this part of the study to provide segments of conducting tissue sufficiently long that test beats could be initiated at sites well beyond the influence of the depolarizing electrode. In addition, containment of the activity to be studied within a corridor of tissue permitted more rigorous demonstration of conduction and conduction block. In the experiments of this series to be described first, the RBB was stimulated near the proximal (His bundle) end. The current-passing electrode was positioned approximately midway between the stimulating electrode and the beginning of the free running segments of the conducting tissue. One differential microelectrode recording was made from a site very close to the current electrode. The other microelectrode recording was from a site between the stimulating and current-passing electrodes, and served to monitor propagated activity initiated in the depolarized focus or by stimulation.

Figure 4 shows representative recordings from
one of these experiments. In each panel, the top line is the stimulus record and shows the last two regular stimuli before the pause and application of current. The bottom line is the current record. The top transmembrane recording is from the site near the current electrode, and the remaining trace is from the more proximal recording site. In the sequence shown in panel A, no stimuli were delivered during passage of depolarizing current. Depolarization was sufficient to initiate DIA and resulted in three spontaneous beats which successfully propagated out of the focus, as demonstrated by the recording from the proximal site. In all of these experiments, the order of occurrence of the upstrokes of the activity within and outside the focus was examined at a faster sweep speed than illustrated to confirm that activity within the focus preceded that at the other recording site. In Figure 4A, the conduction time for the first spontaneous beat was 30 msec. Panel B is identical to panel A except that a test stimulus was delivered to the proximal RBB during the second spontaneous interval. The premature action potential appears first in the proximal recording and successfully captures the automatic site. The long delay (approximately 100 msec) between the appearance of the interpolated beat at the proximal site and in the focus is apparent even with the compressed time base used in the recordings of Figure 4. Delays of this magnitude or greater were common and imply that capture occurs by means of compromised conduction or possibly via electrotonic capture across an area not supporting active propagation. In panel C, the test stimulus was delivered earlier in the second spontaneous cycle. The premature action potential was recorded at the proximal site but failed to reach the recording site within the focus. However, the blocked beat did cause a prominent but subthreshold electrotonic depolarization of the automatic tissue in the focus. The electrotonus, as predicted by earlier studies (Jalife and Moe, 1976), caused a delay in the next spontaneous discharge, as can be seen by comparing the second interval in 4C to the same interval in 4A. Essentially identical examples of second-degree entrance block were observed in six RBB preparations. Thus, foci of DIA can exhibit exit conduction and entrance block as intrinsic properties.

In the experiment illustrated in Figure 4, early blocked premature beats delayed and late premature beats captured and thereby accelerated the next discharge of the focus. The magnitude of both delay and acceleration was shown in the sucrose

![Figure 4](http://circres.ahajournals.org/)

**Figure 4** Records of automaticity in the RBB induced by focal depolarization for 3-second periods following trains of driven activity. In each panel, the top trace indicates the pattern of stimulation. The bottom trace is the record of current application. The top microelectrode recording was made from a site close to the current-passing electrode, and the remaining trace was recorded from a site between the stimulating and current-passing electrodes. Panel A shows only spontaneous activity during current passage. Panels B and C demonstrate the effects of progressively earlier interpolation of a test beat during the second spontaneous cycle.

![Figure 5](http://circres.ahajournals.org/)

**Figure 5** Curves illustrating electrotonic modulation of focal automaticity by action potentials initiated at a remote site at various times during the spontaneous cycle. The data are from the same experiment as illustrated in Figure 3. Panel A shows the relationship between the modulated ectopic cycle length (ECL) and the interval at which the test beat is interpolated (ICL). Panel B shows the same relationship, but the intervals on both axes are plotted as a percent of the spontaneous unmodulated cycle length of the focus.
gap model of Jalife and Moe (1976) to be determined by the precise timing of the interpolated beat relative to the cycle of spontaneous activity. Figure 5 shows that the same relationship applies to the present experiments. The top graph shows the relation between the interval at which the test beat was interpolated and the resulting extrasystolic cycle length. The spontaneous cycle length in the absence of an interpolated beat was 700 msec. The earliest interpolated beats arrived during the refractory period of the first discharge, and little or no alteration in the subsequent cycle length was observed. However, as the interpolated beat was initiated at progressively later times, the next spontaneous discharge was delayed progressively more. When the test stimulus was delivered 300 msec after the last spontaneous beat, the interpolated action potential captured the focus. This is reflected in Figure 5 by the abrupt transition from delay to acceleration of the discharge of the focus. As the cycle length of the interpolated beat was lengthened further, there was less and less acceleration and, finally, as the interpolated interval approached the spontaneous interval, the spontaneous interval returned to control.

The graph in Figure 5B shows the same data as in Figure 5A. However, the spontaneous cycle length is expressed as a percent of its control value and the position of the interpolated beat within that interval is also expressed as a percent of the control spontaneous interval. This plot demonstrates that the maximum delay and acceleration was approximately ±50% and that delay was caused by premature beats occurring during the first 40% of the cycle length of the automatic activity. Sufficient data to plot curves of modulation like those in figure 5, were collected in five experiments. Although the degree of modulation and the exact point of transition from delay to acceleration showed some variation, the relationships closely resembled those illustrated.

The completeness of conduction block in the preceding observations was questioned. It might be possible that the entire focus was not protected by entrance block, and that the records demonstrate only that propagated activity did not reach the specific cells contributing to the record. The RBB preparation allows a simple test of this hypothesis. In three experiments, the remote microelectrode was impaled at a site distal rather than proximal to the current-passing electrode. The area depolarized included the entire width of the RBB. Therefore, if entrance block prevents an interpolated beat from reaching the tissue within the focus, propagation to the distal site also should fail. The records in Figure 6 were made using this arrangement of recording electrodes. Panel A shows the effects of a 3-second current pulse in the absence of interpolated beats. DIA resulted in activity that propagated to the distal recording site. In panel B, three test stimuli were delivered during the application of current. The first interpolated beat captured the focus, as evidenced by the premature discharge in the top recording. This activity also propagated beyond the depolarized tissue and was recorded at the distal site. Conduction of the next interpolated beat failed, and the resulting electrotonus caused a delay in the automatic activity. Also, the interpolated beat failed to reach the distal electrode. The focus fired spontaneously before the third stimulus was delivered, and demonstrated again that discharge of the focus was accompanied by exit conduction and recorded activity at the distal site. Thus, the recorded activity probably represents the focus as a whole.

Continuous Depolarization: Entrainment of Spontaneous Activity

The computer model of parasystole described by Moe et al. (1977) predicts that acceleration and delay, such as that illustrated in Figure 5, will allow entrainment of a spontaneous focus by activity originating outside of the focus. If the intrinsic cycle length of the extrasystolic activity remains constant, gradual alteration of the driving frequency (representing the normally dominant pacemaker) will generate an orderly array of complex and frequently stable rhythms. To determine whether these events would occur in our preparation, it was necessary to adopt a protocol using continuous current application and indeterminate periods of continuous regular stimulation. Figure 7 shows records from one of these experiments. The preparation was the same as that from which the recordings of

![Figure 6](http://circres.ahajournals.org/figures/243fig6.jpg)
Figure 6 were made. The relative positions of the recording electrodes were also the same; the remote recording site was distal to the current-passing electrode. Thus, blocked beats did not reach the remote microelectrode. Initially, the current was applied in the absence of stimulation and was adjusted to generate DIA with a convenient cycle length (650-750 msec). Figure 7A shows that spontaneous activity with a cycle length of 650 msec propagated out of the focus and was recorded at the remote site. Then, stimulation was delivered at a BCL of 1 second. After a period of irregular activity which included both accelerated and delayed cycles, the stable pattern illustrated in Figure 7B was established. The interval between driven responses, each of which captured the focus, was long enough to allow discharge of the depolarized tissue. Thus, driven and spontaneous beats alternate and propagate to the distal microelectrode. Because of the relative lengths of the two BCL, the driven activity necessarily occurred after a moderately short interval following the spontaneous beat.

When the BCL of stimulation was shortened to 900 msec, the driven responses occurred even sooner after the spontaneous discharges of the focus. And, as shown in Figure 7C, each driven response blocked without discharging the focus and thereby delayed the next spontaneous discharge of the focus. Thus, the activity of the focus was entrained at a cycle length longer than its spontaneous cycle length (900 msec as compared to 700 msec immediately before initiation of drive).

Figure 7D shows the effect of decreasing the BCL of stimulation to 800 msec. Each driven response again occurred early with respect to the spontaneous cycles, and each response failed to enter the focus. Again, the electrotonic influence of the blocked beats caused delay of each discharge of the ectopic activity. However, the delay was not uniform for all cycles, and a relatively stable rhythm of alternating short and long spontaneous cycle lengths resulted.

When stimulation was delivered at a BCL of 700 msec, which was very close to the spontaneous cycle length of the depolarized tissue, the ectopic focus was again entrained one to one. However, now each driven response captured the automatic focus, and the activity recorded at the remote site was indistinguishable from that which would have occurred in the absence of an automatic focus (Fig. 7E). One-to-one capture or acceleration of the focus was maintained when the BCL was decreased to 600 msec (not illustrated).

Throughout these experiments, the lag between the interpolated beat and the accelerated response increased regularly when the accelerating beat was introduced progressively earlier in the spontaneous cycle. This lag contributed significantly to certain rhythms. Figure 7F shows an example recorded when the BCL of the driven activity was 500 msec. The repeating pattern includes three accelerated responses occurring with sequentially increasing lags. Because of this, each fourth driven response arrived sufficiently early in a cycle to delay rather than accelerate the next beat. The entire sequence resulted in a stable repeating 4:3 pattern of discharges with cycle lengths of 525, 550, and 900 msec.

Figure 7G shows another rhythm that occurred
when the BCL of stimulation was 450 msec. The focus was entrained at a ratio of 2:1, and each spontaneous cycle included both a delay and an acceleration. The resulting cycle length of 900 msec was again longer than the intrinsic cycle length of the focus. Similar 2:1 ratios were maintained when the BCL of stimulation was 400, 350, and 325 msec (not illustrated).

When the BCL was decreased to 300 msec, as in Figure 7H, a more complex pattern emerged. Again, the position of the modulating beat within the spontaneous cycle shifted throughout the repeating pattern. The focus was entrained at a 12:5 ratio which was composed in sequence by three accelerations, a delay, two accelerations, and a final delay.

Finally, a stable 3:1 ratio was established when the BCL of stimulation was 250 msec, as in panel I. During each cycle, the first stimulus fell during the refractory period, the second stimulus caused a response that delayed the focus, and the third stimulus caused a response that accelerated the final discharge of the focus. Thus, the focus was entrained at regular cycle length of 750 msec by electrical stimulation at a BCL of 250 msec. Similar sequences of stable rhythms in response to different rates of stimulation and electrotonic modulation of a continuously depolarized automatic focus were observed in four of four experiments in which this was attempted and stable DIA was elicited.

When the BCL of stimulation was changed from 1000 to 900 msec, as in Figure 7B and C, the influence of the driven response on the automatic activity was changed from the acceleration to marked delay. Thus, the driven activity must have been arriving at an interval close to that corresponding to the sharp reversal point characteristic of electrotonic delay and acceleration. As previously described, when stimulation was initiated at a BCL of 1000 msec, the rhythm illustrated in Figure 7B was preceded by a period of irregular cycles exhibiting delay and acceleration. During this period, the position of the driven beats with respect to the spontaneous cycles varied greatly and provided sufficient data points to construct a phase response curve for this example. Both the interval at which the driven beat was interpolated (ICL) and the resulting cycle length of the "ectopic" focus (ECL) are plotted in Figure 8 as a percent of the spontaneous unmodulated ectopic cycle length. The relationship shows that modulation caused the spontaneous cycle length to vary approximately ±40%, and the abrupt change from delay to acceleration occurred at an ICL approximately 43% of ECL. The reversal point corresponds to an ICL of 280–300 msec and agrees well with behavior apparent in Figure 7, B and C (7B: 325 msec—acceleration; 7C: 280 msec—delay). The relationship shown in Figure 8 is very similar to that illustrated in Figure 5B, which was determined in an experiment in which 3-second periods of depolarization were utilized. Thus similar modulation was demonstrable with either technique.

**Automatic Foci Exhibiting Entrance Block in Muscle**

Although normal automaticity (phase four depolarization) is restricted to the specialized tissues of the heart, DIA can be elicited by depolarization in ventricular muscle as well as specialized conducting tissue (Katzung, 1974). Many clinically important arrhythmias occur as a result of myocardial infarction and, thus, presumably, as a consequence of damage to fibers of the ventricular conducting system or damage to muscle. Therefore, we were interested in determining whether focally depolarized muscle would also exhibit DIA with exit conduction and entrance block. We selected the interventricular septum of the cat as a preparation for this part of our study because it regularly includes several very small papillary muscles (less than 1 mm in diameter) near the base of the heart. The papillary muscles either were left attached to the septum or were excised for study. Multiple impalements in these papillary muscles revealed no evidence of Purkinje tissue. Even the most superficial impalements demonstrated action potentials typical of ventricular muscle (i.e., short duration, plateau at positive potentials, absence of phase 4 depolarization, shape of phases 1–3, etc.). When the whole septum (approximately 1.5 × 1.5 cm) was used, the orifice of the current-passing electrode was placed over the tip of one of the small papillary muscles. Driven activity was initiated by stimuli applied at a site outside the area to be depolarized. Excised papillary muscles were fixed to the bottom of the tissue bath with a pin inserted near the base of the muscle. The current electrode was slipped over the base. A force transducer (Grass FT.03C) was attached to the apex of the papillary muscle to

**Figure 8** Curve of modulation for experiment illustrated in Figure 6. Both the spontaneous ectopic cycle length (ECL) and the interval at which the driven beats are initiated (ICL) are presented as a percent of the unmodulated cycle length of the focus. BCL: Basic cycle length.
Entrance block and modulation of DIA induced in a feline papillary muscle by depolarizing current. In panels A–C, the top trace shows the pattern of stimulation. The middle trace is a microelectrode recording from a site close to the current passing electrode; and the bottom trace is a record of isometric contractions. Panels D and E show the configuration of an action potential recorded at a faster sweep speed before and during current passage. The time calibration is 100 msec for panels A–C and 2 seconds for panels D and E. The potassium concentration was 4 mM.

FIGURE 9

Discussion

In the present experiments, although spontaneous activity originating within the focus propagated to the rest of the preparation, early premature beats originating outside the focus failed to enter. Later premature beats captured the focus. In the sucrose gap model of Jalife and Moe (1976), the mechanism of "capture" was shown to be electrotonic. Whether capture represents electrotonic excitation across an inactive segment or slow propagation cannot be answered with complete assurance in the present experiments. But, regardless of the mechanism, late premature beats accelerated the discharge of the focus.

Block of early premature beats might be attributed to fractionated conduction rather than entrance block. One might envision the premature beat failing to invade only some of the cells, including that from which the recording was made. The electrotonic image would represent propagation into neighboring cells within the focus. The delay would result from resetting of the pacemaker. It is unlikely that we would consistently impale specifically those cells that were not invaded. Also, as noted in our description of Figure 6, whenever the interpolated beat failed to engage actively the site from which the recording was being made, it also failed to appear distal to the focus. Furthermore, capture of the focus always was accompanied by propagation to the distal site. It would seem improbable that a site that was not representative of the focus as a whole would demonstrate a one-to-one correlation with propagation beyond the focus. In addition, if the interpolated beat reset the pacemaker, the prolonged interval should be equal to the sum of the interpolated interval and the basic cycle length of the focus. We did record intervals that were equal to or greater than this sum, and this is not incompatible with electrotonically mediated delay. However, we frequently observed delayed discharges that occurred after intervals that were shorter than the sum of the two intervals.

Previous concepts of entrance block required that the automatic focus arise within tissue communicating with the rest of the heart through one or more pathways that permitted only one-way conduction in the appropriate direction. Although all of the prerequisites might arise consequent to a single generative event, the automaticity and block were largely independent phenomena. Whether the region of block would necessarily surround the focus or whether one-way conduction would be in the appropriate direction or exist at all, were largely...
matters of chance. In contrast, the mechanism described in the present study requires only that the automatic focus occur as a consequence of depolarization to potentials that elicit DIA. Automaticity and one-way conduction both result as consequences of the same immediate cause, and the region of one-way conduction appropriately surrounds the area of automaticity. A protected focus can be induced equally well in corridors of specialized conducting tissue or in papillary muscles with unrestricted communication with surrounding tissue. Thus, there appear to be few physical constraints imposed upon this mechanism.

For electrotonic modulation to occur in the heart in situ the focus of automatic tissue must be relatively close to the site of conduction block by which it is protected. If the actual site of automaticity were more than several space constants removed from the site of one-way block, the degree of electrotonic modulation would be weak or possibly insignificant. In the mechanism postulated in Figure 1, the regions of one-way conduction and automaticity must be contiguous. In addition, the width of the segment of tissue providing entrance block is determined by the same space constant that governs the attenuation of electrotonic potentials with distance. As would be predicted from these considerations, relatively strong modulation was demonstrable in all of our experimental examples of automaticity with entrance block (i.e., ±40 to 50% delay and acceleration in Figures 5 and 8). The degree of interaction will also be determined by the relative mass of tissue on each side of the site of conduction block and by the size of the area occupied by the automatic tissue. The present studies were conducted with the weakest current, and therefore smallest area, that provided DIA at a convenient cycle length. In the whole heart, any degree of interaction might be predicted, depending on the size, configuration, and environment of the focus.

Patterns of driven activity that suppress “normal” phase four depolarization, did not cause overdrive suppression of DIA. Insensitivity to overdrive suppression increases the potential importance of DIA as a mechanism of arrhythmia. This consideration may apply to protected foci when they are subjected to strong electrotonic modulation. Even if the foci cannot be invaded by normally conducted impulses, they can be entrained at rates well above the intrinsic rate of the focus. This might suppress focal automaticity generated by phase four depolarization but, in our experiments, it did not suppress focal activity caused by DIA. The experiments illustrated in which rapid stimulation was applied before the depolarizing current also may have a parallel in genesis of arrhythmias. Gadsby and Cranefield (1977) have shown that the membrane potential of cardiac tissue can shift abruptly from the normal high level to a second low resting potential which is within the range associated with DIA. If activity is triggered at this low resting potential, it is self-sustaining. The present study suggests that the previous dominant rhythm at the high membrane potential would not prevent the ectopic rhythm from emerging abruptly.

There is a growing body of evidence that DIA occurs spontaneously and therefore may provide an important mechanism of arrhythmia. Depolarization to approximately −45 mV occurs as a characteristic response of cardiac tissues to a wide variety of conditions. Coraboeuf et al. (1976) observed automaticity at this range of membrane potentials in canine Purkinje fibers that depolarized to this level in response to CO2-induced acidosis. Similar activity has been reported in partially depolarized Purkinje tissue (Lazzara et al., 1973) and deep muscle (Ten Eick et al., 1976) excised from experimentally induced infarcts. Identification and differentiation between DIA and phase four depolarization in situ is more difficult. Interestingly, in this respect, Harris and Moe (1942) reported oscillatory activity recorded with epicardial electrodes in situ in response to application of DC current to the canine heart. The oscillations were more rapid (80-msec cycle length) than characteristic of DIA, and may have represented a different phenomenon. However, the study suggests that demonstration of focal activity with entrance block in the open-chest preparation may be possible.

The method adopted to generate automatic foci in this study required a pipet lightly touching the tissue. It might be suggested that conduction block was caused by hypoxia beneath the electrode. However, conduction block and modulation were observed with equal facility whether the stimulating electrodes and the recording site in the focus were on the same or opposite sides of the current electrode. Thus, the phenomenon was demonstrable in tissue completely external to the area beneath the current electrode. Also, in a certain fraction of false tendon-muscle preparations, the Purkinje tissue fails to recover fully from the trauma of isolation. These preparations frequently exhibit DIA. Previously, these preparations were discarded and, in only a few experiments were photographic records made. Reexamination of those records disclosed three examples in which the false tendon exhibited DIA, and the attached muscle had fully recovered. Stimulation of the muscle initiated action potentials that failed to propagate into the false tendon. Although not recognized at the time of recording, the records clearly show examples of entrance block with delay and acceleration indistinguishable from examples from the present study.

In the present experiments, progressive alteration of the rate of stimulation elicited an array of different rhythms including examples corresponding to zones of silence described by Moe et al. (1977). Many rhythms were not typical of those
encountered clinically. However, a recent study in which the sucrose gap was used to provide entrance block demonstrated that introduction of compensatory pauses in modulated rhythms resulted in rhythms analogous to clinical arrhythmias (Jalife and Moe, 1979). The present study indicates that DIA occurring in depolarized areas of cardiac tissue in communication with more normally polarized tissue provides a potentially important mechanism of arrhythmia.

References

Brennan F, Cranefield PF, Wit AL (1978) Effects of lidocaine on slow response and depressed fast response action potentials of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 204:312-324
Carmeliet E, Vereecke J (1969) Adrenaline and the plateau phase of the cardiac action potential. Pfluegers Arch 313:300-315
Gadsby DC, Cranefield PF (1977) Two levels of resting potential in cardiac Purkinje fibers. J Gen Physiol 70:725-746
Harris AS, Moe GK (1942) Idioventricular rhythms and fibrillation induced at the anode or the cathode by direct currents of long duration. Am J Physiol 136:318-331
Reuter H, Scholz H (1977) A study of the ion selectivity and the kinetic properties of the calcium dependent slow inward current in mammalian cardiac muscle. J Physiol (Lond) 264:17-47
Trautwein W (1973) Membrane currents in cardiac muscle fibers. Physiol Rev 53:793-835
Automaticity and entrance block induced by focal depolarization of mammalian ventricular tissues.
G R Ferrier and J E Rosenthal

Circ Res. 1980;47:238-248
doi: 10.1161/01.RES.47.2.238

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/47/2/238

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/