Electrotonic Modulation of Pacemaker Activity
Further Biological and Mathematical Observations on the Behavior of Modulated Parasystole

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SUMMARY An in vitro biologic model of parasystole and a mathematical model of parasystole based on the phase-response relationships derived from the biologic model were used in tandem to further develop our understanding of the patterns of ectopic activity that might arise as a consequence of the interaction of two pacemakers across a zone of block. Superfusion of the central segment of a dog Purkinje fiber with an ion-free isotonic sucrose solution provided a narrow region of block. The modulation of pacemaker activity by electrotonic potentials transmitted across the area of block was shown to be importantly influenced by the position of the "ectopic" pacemaker relative to the site of block. Effects of repetitive electrotonic influences on a single pacemaker cycle, the degree of entrance block and capture of the pacemaker during a phase of supernormal excitability were also studied in both the biologic and mathematical models. Our results indicate that marked shifts in the incidence and pattern of manifest ectopic activity can occur as a result of slight changes in heart rate, ectopic pacemaker rate, level of block and the position of the parasystolic pacemaker relative to the block border.

ELECTROTTONIC POTENTIALS transmitted across an area of depressed conductivity may modulate the activity of a spontaneously beating pacemaker beyond the region of block.1,2 Electrotonic depolarizations that occur early during phase 4 of the spontaneous pacemaker cycle delay the next discharge; those that occur later in the cycle accelerate, or "capture," the pacemaker.3 Thus, the activity of an ectopic focus, "protected" but not insulated by an area of depressed excitability, may be modulated by activity in the surrounding tissue according to a biphasic electrotonic influence or phase-response relationship.

In a computer model programmed to imitate the modulation of an ectopic pacemaker, Moe and coworkers4 defined the patterns of entrainment and ectopic activity that may be expected to result from such interaction. Jalife and Moe5 confirmed some of these predictions in a sucrose gap preparation of Purkinje tissue.

Simplifying assumptions had been incorporated into the mathematical model, with the recognition that they would at least quantitatively warp the recorded patterns if not the basic rules of behavior: (1) When two or more discharges of the ventricle occurred between pacemaker discharges, each was treated independently and sequentially, as though the starting time of the pacemaker cycle had been reset. (2) The biphasic curve defining delay and acceleration was assumed to be symmetric; e.g., 20% maximal delay, 20% maximal acceleration of the pacemaker cycle. (3) "Exit" conduction from the ectopic focus was, in most programs, assumed to be instantaneous. No provision was made for supernormal excitability. In only a few runs was a relatively refractory period considered.

In the present study, additional experiments were conducted in the sucrose gap preparation to assess the importance of these simplifications and to incorporate the biologic results into appropriately modified computer programs. Experiments were designed to test the effects of repetitive electrotonic influences on a single "ectopic" pacemaker cycle, the position of the ectopic pacemaker relative to the site of block, the degree of block between the two active segments and capture of the pacemaker during a phase of supernormal excitability.

Methods

Biologic Model

Unbranched free-running false tendons obtained from dog hearts were placed in a three-compartment tissue chamber. During a 1-hour equilibration period, all three compartments were perfused with a modified Tyrode's solution saturated with a mixture of 95% O2 and 5% CO2. The composition of the solution (mM) was: NaCl, 137; KCl, 3; NaH2PO4, 0.9; NaHCO3, 12; CaCl2, 1.8; MgSO4, 0.5; and dextrose, 5.5. Temperature was maintained at 36.5°C.

Spontaneous pacemaker activity was enhanced in the fiber segment in compartment 1 (referred to as the ectopic pacemaker [EPI]) by superfusion with a 3-mM KCl Tyrode's solution. In some cases, epinephrine (0.1 μg/ml) was added to accelerate the pacemaker. Conduction block was produced in the central fiber segment by superfusion with a solution containing 300 mM sucrose, 5 mM dextrose and 0.15 mM CaCl2 saturated with 100% O2. Compartment 3 was perfused with a 6 mM KCl Tyrode's solution to reduce pacemaker activity in that part of the fiber. In the experiments in which current pulses were passed through the fiber, compartment 3 was perfused with a 20 mM KCl Tyrode's solution.

The fiber segment in compartment 3, simulating the ventricle responding to impulses of sinus nodal origin, is called SN. The fiber segment in compartments 1

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(EP) and SN were studied by applying bipolar stimuli of 1–3 msec duration and twice threshold intensity to the SN segment while EP was allowed to beat spontaneously. In a second series of experiments, subthreshold depolarizing current pulses 100–200 msec in duration and 0.1 to $2 \times 10^{-6}$A in amplitude were passed through the fiber. In both cases, the stimulator or the constant current pulse generator was triggered by the upstroke of the EP action potential after varying delays to permit systematic scanning of the pacemaker cycle in chamber 1.

Transmembrane potentials were recorded differentially from one of the outer compartments to prevent short-circuiting of the two active segments through a common ground.

**Mathematical Model**

The computer model developed by Moe et al.\(^4\) was used in the analysis of most of the experimental findings in this study. In the present application, each of the experimentally determined phase-response curves (the biphasic curves of delay and acceleration that characterize the interaction between evoked and pacemaker responses across the sucrose gap) was incorporated into the computer program, after which the interaction was studied over a wide range of simulated frequencies. The intrinsic period of SN was set up at 800 msec, with a refractory period of 300 msec. The simulated intrinsic cycle length of EP was varied from 820 to 3000 msec in 20 msec steps. Complete runs of the interactions were made at each EP cycle length (EPCL). Each run continued until EP had fired 20 times. When the EP fired outside the refractory period of SN, propagation to the ventricle was set to take place immediately. Each manifest ectopic response was followed by a fully compensatory pause. The computer was further programmed to analyze the data and plot the entrainment ratios (operative EPCL/SNCL ratios) as well as the percentage of manifest ectopic complexes (PVCs) as a function of the intrinsic EPCL/SNCL ratios. The operative entrainment ratio is the ratio of the average EPCL to the SNCL when the program reaches equilibrium.

**Results**

**Effect of Multiple Intervening Electrotonic Events**

In the mathematical model of parasystole, the effect of the first of two or more SN beats falling within a single EP cycle was calculated from the programmed phase-response curve; the intervening response was assumed to reset the starting point of the EP cycle. The same phase-response relationship was then used to calculate the electrotonic influence of the second SN beat within the reset cycle. In the present study, this assumption was tested in the biologic model. Complete scans of the EP cycle with one and two intervening SN beats were performed, and the single and compound phase-response curves were derived. Figure 1 illustrates both the procedure and the results. The spontaneous, unmodulated cycle length of the pacemaker is indicated by the solid-line action potentials (interval

![](https://example.com/image1.png)

**FIGURE 1.** The effects of single and double electrotonic influences on a pacemaker cycle. Traces of transmembrane recordings obtained from the ectopic pacemaker segment of a sucrose gap preparation. Interval A represents the spontaneous pacemaker cycle length and interval B the delay imposed by the electrotonic influence of a sinus node (SN) response elicited at an interval D. Action potential 3 results from an SN response elicited at interval E and action potential 2 shows the delayed discharge of the pacemaker when both SN response (at D and E) are evoked sequentially.

A). A single SN response elicited at interval D produced an electrotonic potential in EP, and prolonged the cycle by the interval B (action potential 1). A single response evoked later in the cycle (interval E) caused a greater electrotonic potential in EP, and accelerated its discharge (action potential 3). When both of the SN responses were evoked sequentially within the same EP cycle, the result was a delay of the EP discharge by a value B + C (action potential 2). The effect of the second SN beat alone ($\Delta$BCL) can be analyzed using the equation

$$\% \Delta\text{BCL} = \frac{C}{A} \times 100 = \frac{B + C}{A} - \frac{B}{A} \times 100.$$  \hspace{1cm} (1)

Assuming that the 1st SN beat resets the EP cycle by a value equal to its independent delaying effect, the point in the EP cycle at which the second SN response will exert the above effect can be computed as

$$\% \text{of spontaneous cycle} = \frac{E - B}{A} \times 100.$$  \hspace{1cm} (2)

The above calculations are the reverse of those used in the computer model, and the basic assumptions made in that model can be considered valid only if the phase-response relationship calculated for a second SN response is similar to the phase-response relationship generated by a single SN response scanning the EP cycle. Reconstructions from two such experiments are shown in figure 2. In six experiments similar to those described above, the calculated phase-response relationship for a second event falling within a single EP cycle was quite similar to the phase-response relation-
ship observed when only a single event intervened. Some divergence at the point of crossover was restricted to a very limited part of the cycle in a region in which relatively large fluctuations are commonly observed even with single intervening events.

**Position of Pacemaker**

In the experiments described by Jalife and Moe, the positive and negative phases of the phase-response relationship were of nearly equal amplitude, and most of the computer programs were prepared with a similarly symmetric form. Inverse solution of some clinical records, however, yielded curves in which the delay phase was of considerably lower amplitude than the acceleration phase.

To explain this anomaly, we considered the possibility that the position of the dominant ectopic pacemaker relative to the region of block may play a determining role. The amplitude of both the delaying and accelerating phases of the electrotonic influence on the pacemaker cycle are voltage dependent. The magnitude of electrotonic depolarization in the pacemaker, greatest just beyond the blocked zone, decays with distance. If the site of the dominant pacemaker is close to the blocked area, maximal effects of the electrotonic depolarization will be exerted during both segments of the phase response relationship. If the pacemaker is more distant, one might expect that both phases would be attenuated. However, the delaying influence must be exerted on the dominant pacemaker, wherever it lies, but an accelerating influence may recruit a latent pacemaker closer to the site of block. Accordingly, the delay phase, of low amplitude, would represent the influence on the dominant distant pacemaker, while the acceleration phase, of greater amplitude, would represent excitation of a different and closer cluster of pacemaker cells. In the phase-response relationships demonstrated by Jalife and Moe, a very small EP segment was used (1 mm); the site of pacemaker activity was therefore always close to the block, and greater symmetry would be expected.

Experiments designed to test this hypothesis were performed using EP segments approximately 4 mm long in which simultaneous recordings from EP sites near to and remote from the block were obtained. The results of one such experiment are shown in figure 3. Panel A1 shows a spontaneous cycle (2330 msec) in which the dominant pacemaker fired at a site remote from the block. Delivery of a stimulus to the other side of the sucrose gap 1325 msec after the initiation of the EP cycle (A2) resulted in a relatively large electrotonic potential in the upper EP trace near the gap and a lesser deflection in the lower EP recording (more distant). The next spontaneous beat initiated by the same dominant pacemaker was delayed by only 6.4%, resulting in a BCL of 2480 msec. In panel A3, a stimulus applied to the SN segment 100 msec later (1425 msec) resulted in capture of EP and abbreviation of its cycle to 1790 msec (23%). In this instance, however, the EP discharge was initiated by a latent pacemaker closer to the site of block. Thus, when the dominant pacemaker

**Figure 3.** The significance of the position of the dominant pacemaker. A 4-mm-long ectopic pacemaker test segment was used. Transmembrane potentials were recorded 0.5 mm (top) and 3.5 mm (middle) from the area of block (sucrose gap). (Bottom) Stimulus marker indicating the time of application of a stimulus to the SN segment. Intrinsics (1), delayed (2) and accelerated (3) cycles are shown with the dominant pacemaker remote from (A) and near to (B) the region of block.
was approximately 3.5 mm from the site of block, only a small delaying action occurred, whereas a much larger accelerating influence resulted from recruitment of a latent pacemaker closer to the block.

In the course of this experiment, the pacemaker spontaneously shifted to a site much closer to the blocked region. In panel B1, the spontaneous cycle of the dominant pacemaker at a site close to the gap was 2930 msec. A stimulus applied to SN 1680 msec after a discharge of EP (B2) resulted in a large electrotonic potential in the dominant pacemaker recording (top) and a smaller electrotonic deflection at the more distant site. The next spontaneous beat was initiated by the dominant pacemaker after a 32% delay, prolonging the BCL to 3870 msec. In panel B3, an SN response elicited later in the cycle (2150 msec) abbreviated the cycle to 2430 msec. Firing of EP in this case was also initiated by the dominant pacemaker. Thus, with the dominant pacemaker in close proximity to the block, large delays and accelerations, both resulting from a direct influence on the dominant pacemaker, were observed.

Complete scans of the EP cycles in the experiment depicted in figure 3 are illustrated in figure 4. When the dominant pacemaker was close to the block, the EP firing was delayed by a maximum of 32% and accelerated by 22%. When the pacemaker was more remote, EP firing was delayed by a maximum of only 7.5%, although accelerated to a much greater degree (27%). The degree of acceleration is similar in both cases because this action is exerted on the pacemaker species closest to the block, regardless of the position of the dominant pacemaker.

In another set of three experiments, we established conditions that permitted us to position the pacemaker at will. A four-compartment chamber was used to allow for independent superfusion of two test segments, one of which was a 1.5-mm compartment adjacent to the sucrose gap. Addition of 0.1 μg/ml epinephrine to either chamber resulted in corresponding pacemaker shifts. Results using this method of pacemaker positioning were very similar to those described above, i.e., large changes in the delay phase with little or no change in the acceleration phase accompanying the pacemaker shift.

To determine the effects of pacemaker shift on the patterns of arrhythmia, the two electrotonic influence curves depicted in figure 4 were incorporated into the mathematical model and computer runs covering a wide range of heart rates were recorded. The results indicated that a shift of the pacemaker away from the zone of block would be attended by a decrease in the overall incidence of PVCs at fast frequencies and an increase at slower heart rates.

Degree of Block as a Determinant of Conduction Time

Modulation of the degree of block in the in vitro model may be accomplished by variation of a shunt resistance placed across the sucrose gap connecting SN and EP. Transmembrane recordings from one of four experiments in which electrotonic interactions between SN and EP were studied over a wide range of shunt resistance values are shown in figure 5. Slight progressive depolarization of EP accompanied the decrease in shunt resistance as a result of an increase of the steady-state electrotonic depolarizing influence exerted by the SN segment (exposed to 6 mM of potassium to suppress automaticity). As shunt resistance was decreased, the electrotonic influence of an SN beat (indicated by the stimulus marker) on the EP cycle became greater and capture of the pacemaker occurred progressively earlier.

Composite results of complete scans of the EP cycles in this experiment are summarized in figure 6. In the absence of a shunt, a 14% maximal delay and a maximal acceleration of 21% with crossover at 57% of the EP cycle were recorded. Facilitation of electrotonic interaction between SN and EP by placement of a 150-kΩ shunt resistance across the gap increased the maximal delay to 29% and the maximal acceleration to 33% with a small shift of the crossover point to the left. Further decreases in shunt resistance increased the de-
degree of acceleration, but reduced the maximal delay as the crossover shifted progressively earlier in the cycle.

Incorporation of these curves into the computer model permitted analysis of the changes in the behavior of the model resulting from progressive changes in the degree of block (fig. 7). At a low level of block (fig. 7A, 50-kΩ shunt resistance), the 1:1 entrainment zone extended from an intrinsic ratio of 1.0 up to a ratio of 2.75, where it broke abruptly to 2:1. No manifest ectopic activity was present throughout the range of intrinsic ratios studied under these conditions; EP always fired within the refractory period of SN. At higher levels of block, the zones of entrainment of 1:1 and 2:1 were curtailed and zones of more complex entrainment ratios emerged. Scattered zones of manifest arrhythmic activity appear as complex functions of the degree of block. At the highest level of block (fig. 7D, no shunt), the incidence of complex entrainment increased substantially, and manifest ectopic activity occurred over a wider range of intrinsic ratios.

Capture During the Supernormal Phase
Under all of the conditions described above, the phase-response relationship took the form of a biphasic curve in which a delay phase was followed by a phase of acceleration. In some preparations, however, a triphasic curve was encountered (fig. 8A). A test pulse delivered to SN at 10–16% of the spontaneous EP cycle produced an acceleration of 75–80%. Beyond 16% of the spontaneous cycle, the relationship changed abruptly to delay and the typical biphasic curve was resumed.

The electrophysiologic basis for the triphasic relationship is illustrated in figure 8B. The intrinsic pacemaker cycle length was 1870 msec. In panel B1, a stimulus pulse was delivered to SN 230 msec after the beginning of an EP cycle; a large electrotonic deflection interrupted the terminal part of phase 3 repolarization and spontaneous cycle was prolonged by 8%. A test pulse delivered slightly later in the cycle (panel B2) captured EP, abbreviating its cycle by 80%. The supernormal phase of excitability was brief; a test pulse delivered 120 msec later than in panel B2 no longer captured EP but delayed the next spontaneous firing by 10% (panel B3).

The phase-response curve of figure 8A was incorporated into the computer program. The recorded patterns were not influenced by the early phase of major acceleration because only at very high driving rates (not within the range examined in the model) would a response of SN fail so early in the EP cycle.

Discussion
In the present study, we have used the computer model and the sucrose gap technique in tandem to study further the patterns of ectopic activity that might be expected to develop when two pacemakers interact across a zone of depressed conductivity.
One of the assumptions, suggested but not extensively tested in the experiments described by Jalife and Moe, was that each of two or more sequential depolarizations occurring within a single EP cycle would act in accordance with the same phase response curve as that defined for a single intervening event. Within the limits of experimental scatter, the assumption was shown to be valid (fig. 2).

The simple mathematical treatment that yielded the curves in figure 2 can also be applied to clinical examples of parasystolic (or “nearly” parasystolic) arrhythmias, particularly in cases in which one and two intervening sinus beats alternately occur between manifest ectopic events. One such example is the case report (case 3) described by Cohen et al. Inverse analysis of two electrograms in their report, in which one SN(R) intervened between two EP(X) responses, yielded a biphasic phase-response curve (ΔBCL range = +6% to −8.5%). The electrotonic influences of the second beats in the cases in which two SN beats intervened were calculated using equations 1 and 2 and were found to superimpose on the original curve. This result is consistent with the assumptions made in the mathematical model. Moreover, this simple electrotonic modulating sequence (delay followed by acceleration of EP) accounts for what was termed the “early period
of protection" from SN impulses. Inverse analysis of several other clinical records of parasystole yielded similar results.

Pacemaker Position

In parasystole, the length of the "protected" zone may range from less than one to several space constants. In the latter case, the distance of the dominant pacemaker from the zone of block will influence the electrotonic modulation of pacemaker activity by the activity of the surrounding tissue (figs. 3 and 4). When the dominant pacemaker is more remote from the area of block, the delay phase becomes attenuated but the acceleration phase is maintained due to electrotonically mediated activation of latent or nonpacemaking tissue closer to the block boundary (fig. 4). Ectopic responses resulting from SN modulation during the late phase may appear with relatively fixed and close coupling to the preceding beats of sinus origin. Sinus beats that fall early in the ectopic pacemaker cycle will, however, exert only a slight delaying effect, one that may be easily missed during inverse analysis of ECG records; during this early phase of protection, the patterns may closely mimic the behavior of classic parasystole.9

The result is an essentially monophasic phase-response curve (fig. 4) similar to that described by Castellanos and co-workers.9 No alternative mechanism need be invoked to explain this phenomenon. Electrotonically mediated interactions give rise to both parasystolic and extrasystolic (reflection) activity. These two forms of ectopy represent two extremes of a common mechanism.10-12 Modulated parasystole and reflection may coexist and arrhythmic expression of one or the other may be determined by the SN frequency. In the case of a remote pacemaker, "pure" parasystole and reflected reentry may coexist and their respective expression may likewise be phase-dependent.

The computer model predicts that as a result of pacemaker shift, ectopic activity may convert to silence, may become manifest, or may change in pattern depending on the existing heart rate.

Degree of Block

Moe et al.4 discussed an approximation of the effect of the level of electrotonic influence on the behavior of the mathematical model. We determined experimentally the specific changes that occur in the electrotonic influence curve as a result of changes in the level of block (shunt impedance) between SN and EP (figs. 5 and 6) and studied the effect of these changes on the behavior of the model (fig. 7). The results indicate that as the block progresses to higher levels the incidence of manifest responses increases, silent zones become narrower, and the pattern of ectopic activity approaches that of "pure" parasystole. Progressive isolation of a parasystolic focus from the electrotonic influence of the surrounding myocardium would be expected to result in changes in the pattern of ectopic activity similar to those shown in figure 7. Although the overall incidence of premature activity increases as the shunt impedance increases, at certain heart rates (e.g., intrinsic ratio of 2.6), manifest ectopic activity may appear at low degrees of block, fall to silence at intermediate levels and reappear at higher levels.

Capture During the Supernormal Phase

Periods of supernormal excitability have been described in sheep and calf Purkinje fibers13 and in dog Purkinje fibers.14 Weidmann13 attributed the supernormal period to the more complete recovery of the threshold potential as opposed to the membrane potential during the later phase of repolarization. As a result, the membrane potential needs to undergo a smaller degree of additional depolarization to reach the threshold potential; this depolarization can be achieved by
smaller depolarizing current. Spear and Moore further demonstrated that changes in input resistance late in phase 3 contribute, although in a lesser degree, to supernormal excitability. We have demonstrated that periods of supernormal excitability may influence impulse transmission across an inexcitable gap.

This characteristic of the system may play an important role in the generation of couplets (double manifest premature responses) as well as salvos and tachyarrhythmic episodes. For example, when an SN beat captures EP late in its cycle with a delay long enough to allow recovery of excitability in the surrounding ventricle, a manifest and closely coupled premature response will occur. If the premature beat falls during the supernormal period of EP, the pacemaker will fire a second time. The second pacemaker discharge may now reexcite the ventricle and thus generate a second premature response. Experimental demonstration of couplets and tachyarrhythmias involving this phenomenon has recently been achieved in vitro and in vivo.  

Therapeutic Implications

Antiarrhythmic drug efficacy is often evaluated on the basis of reduction in the incidence of PVCs. Winkle emphasized that spontaneous variability in the frequency of ventricular ectopic responses can mimic antiarrhythmic drug effects.

Shifts in patterns and incidence of ectopic activity can result from slight changes in heart rate, ectopic pacemaker rate, degree of block and pacemaker position relative to the margin of block. It follows that spontaneous variability in ventricular ectopy may result from spontaneous changes in any or all of the variables. Mere changes in heart rate can also alter the manifestations of PVCs in models of reflected reentry. The assessment of antiarrhythmic drug efficacy should be done with caution; major changes in the incidence and pattern of ectopic activity may result from spontaneous or drug-induced changes in sinus rate.

Ectopic pacemaker rate, degree of block and the position of the pacemaker relative to the site of block are variables that cannot be readily and independently controlled in the clinical setting. Drug-induced changes in these variables, however, may be inferred by examination of alterations of the phase-response relationships. The intrinsic cycle length of an idioventricular pacemaker may be exposed with the aid of reflexly induced vagal slowing and a phase-response curve can be constructed when single responses of sinus origin are allowed (or induced) to fall within the ectopic cycle. Drug-induced changes in the behavior of the ectopic pacemaker may then be assessed. Alterations of the degree of block and the pacemaker position relative to the site of block may be estimated from the relative changes in the delay and acceleration phases of the phase relationship.

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