Parasystole, reentry, and tachycardia: a canine preparation of cardiac arrhythmias occurring across inexcitable segments of tissue

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ABSTRACT A protected ectopic focus created in tissue excised from one heart was allowed to interact with the activity of the intact heart of another animal. The protected focus consisted of a Purkinje fiber in which a narrow central zone was rendered inexcitable. The model permitted us to study parasystole, modulated parasystole, reentry, and tachycardia in the same preparation. At moderate levels of electrotonic influence across the region of block, frequency scans revealed wide zones of pacemaker entrainment. The incidence and pattern of premature ventricular contractions generated were always a sensitive function of heart rate. Parasystolic patterns could be converted to apparent reentrant patterns by simple alteration of the atrial driving rate or the level of block. Suppression of pacemaker automaticity converted a modulated parasystole model to one of pure reentry. Reciprocity of the impulse across the inexcitable tissue segment generated a ventricular tachycardia that could be initiated and terminated by a single properly timed event. Our observations suggest that ectopic activity that behaves like parasystole and activity characteristic of what is commonly diagnosed as reentry, including tachycardia and idioventricular rhythms, may be a manifestation of a common mechanism whose arrhythmic expression differs as a continuous function of heart rate, level of block, or level of automaticity.

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IN PREVIOUS communications from this laboratory we have used preparations of isolated Purkinje fibers and mathematical models to describe the electrotonic interactions between cardiac tissues across an area of impaired conductivity, and we have drawn conclusions that have some relevance to the behavior of parasystolic and reentrant idioventricular activity in the clinical situation.1-6 The preparations we have studied have been useful in that certain patterns of parasystolic and extrasystolic activity observed in human electrocardiograms (ECGs) appear to fit the rules derived from them. Although the in vitro preparations developed have been useful in characterizing these mechanisms of arrhythmogenesis, they are less than ideal for studying the full spectrum of arrhythmias that may arise as a result of electrotonic interactions across inexcitable gaps of cardiac tissue. Additionally they pose some limitations in relating the ectopic behavior generated to that encountered in the clinic. Specifically, two of the major limitations are the difficulty of varying retrograde conduction across the zone of block independently of anterograde conduction and the difficulty in generating appropriate compensatory pauses following ectopic responses in studying the frequency dependence of the arrhythmias generated.

It is the purpose of this study to describe a hybrid preparation, in which a protected ectopic focus created in tissue excised from one heart is allowed to interact with the rhythm of the intact heart of another animal. The preparation is designed to overcome the limitations of those previously developed in vitro. Changes in patterns and incidence of reentrant and parasystolic activity generated by this preparation are studied as a function of heart rate, level of block, and level of automaticity.

Unlike the in vitro models previously described, our coupled preparation (1) permits a complete test of the
concepts developed based on the frequency profiles predicted by the mathematical model of parasystole, (2) permits detailed characterization of the frequency dependence of reentrant arrhythmias (both circus movement and reflection), and (3) delineates the conditions that can give rise to tachyarrhythmias.

**Methods**

The model consists of two units: (1) an open-chest dog preparation (in vivo) and (2) a Purkinje fiber–sucrose gap preparation (in vitro).

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg iv). A tracheostomy was performed and positive-pressure ventilation was applied from a Harvard respirator. Body temperature was maintained with a heating pad. The chest was opened through a midsternal thoracotomy and the heart was suspended in a pericardial cradle. Three sets of bipolar leads were affixed to the heart, two to the free wall of the right ventricle and one to the right atrium.

A second dog was similarly anesthetized and the heart was removed. Free-running false tendons (Purkinje fibers) were dissected from the ventricles and placed in Tyrode’s solution saturated with a mixture of O2 (95%) and CO2 (5%). Calf Purkinje fibers were used in some experiments. The calf hearts were obtained from a local slaughterhouse.

The excised tissue was transferred to a plexiglass chamber divided into three compartments. The fibers were threaded through holes preformed in the latex partitions. During a 1 hr equilibration period, all three compartments were perfused with an oxygenated Tyrode’s solution at a rate of about 5 ml/min. Temperature was maintained at 36.5° ± 0.5° C. The composition of the solution was (mM): NaCl, 129; KCl, 3 to 7; NaH2PO4, 0.9; NaHCO3, 20; CaCl2, 1.8; MgSO4, 0.5; and dextrose 5.5.

After equilibration, an area of block was created by superfusion of the central segment with a purified (300 mM) sucrose solution saturated with 100% O2. CaCl2 (0.1 mM) was added to prevent cellular uncoupling. One of the outer segments was superfused with 6 to 7 mM KCl Tyrode’s solution to suppress pacemaker activity. This segment, referred to as the proximal segment, was stimulated with pulses of 1 to 3 msec duration and twice threshold intensity delivered through thin silver electrodes insulated except at the tips. The distal segment, beyond the block, was superfused with 3 mM KCl Tyrode’s solution to enhance automaticity. In some cases, epinephrine (0.1 µg/ml) was added to further accelerate the pacemaker. In experiments requiring suppression of pacemaker activity at the distal site, the K concentration was elevated to 5 or 6 mM.

A variable resistor connected to the two outer compartments

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**FIGURE 1.** Experimental set-up. The open-chest dog preparation is represented by the heart on the left and the sucrose-gap preparation (SGP) is diagrammed on the right. Electrotonic communication between the proximal (P) and distal (D) segments was controlled by a variable shunt resistor connecting the two outer compartments. Alternatively, electrotonic modulation of activity in segment D of the SGP was effected by application of current pulses (100 to 200 msec) across the gap by means of a constant current generator (CCG). A stimulator (S1) provided right atrial drive. The extracellular signal recorded from the right ventricle triggered the delivery of a stimulus (S2) to the P segment of SGP. The response generated in this segment electrotonically depolarized the D segment. The active response in the D segment, when it occurred, triggered the delivery of a stimulus back to the right ventricle after a set delay. The D segment represents the protected ectopic focus. Entrance delay into the focus is biologically mediated. Exit delay in this preparation is simulated. CRO = oscilloscope; RA = right atrium; RV and LV = right and left ventricles; S1, S2, S3 = stimulators.
through Ag/AgCl electrodes provided an external shunt pathway through which the degree of electrotonic interaction could be finely controlled. Transmembrane potentials were recorded differentially from the distal segment with glass microelectrodes filled with 2.7M KCl (DC resistance 10 to 20 MΩ). The amplified signal was displayed on an oscilloscope along with a ventricular electrogram and a lead II ECG from the in vitro preparation. The oscillographic traces were photographed with a Grass kymographic camera.

Once the in vivo and in vitro preparations were equilibrated and independently functioning, the two were allowed to interact (figure 1). A stimulator (S1) was used to drive the heart through the bipolar atrial electrodes. In some experiments the heart rate was initially slowed by crushing the sinoatrial node and by the administration of propranolol (1 to 2 mg/kg iv). Further deceleration, when desired, was achieved by cooling the sinus node and crista terminalis regions of the right atrium.

A ventricular electrogram was recorded with one of the two bipolar leads located on the right ventricle. This signal was further amplified and used to trigger the delivery of a stimulus (S2) to the proximal segment of the in vitro preparation. The response generated in the proximal segment, although unable to propagate across the sucrose gap, caused an electrotonically mediated depolarization at the distal site. When an active response ensued in the distal segment, the transmembrane action potential recorded from that tissue triggered the delivery of a stimulus (S3) to the right ventricle after an instrumented variable delay of 20 to 210 msec.

In four of the 17 experiments, electrotonic modulation of activity in the distal segment was accomplished by application of rectangular current pulses (100 to 200 msec duration) across the sucrose gap. The constant current generator, triggered by the ventricular activation, delivered 1 to 5 μA of current through the Ag/AgCl electrodes placed in the two outer compartments. The proximal segment of the in vitro preparation in these experiments was bathed with Tyrode’s solution containing 20 mM K (to facilitate current injection).

We describe the transmission from the right ventricle in vivo to the protected focus in vitro as antegrade conduction. The “entrance” delay is imposed by the properties of the in vitro preparation. Transmission from the protected focus to the heart is described as exit or retrograde conduction; the delay in this limb of the circuit was artificially set (S3). In the parasystole and reentry preparations, exit delay was set between 20 and 80 msec. Delays of 150 to 210 msec were required to generate tachycardia. After exit conduction in the preparation is simulated, it may be considered to represent conduction over an alternate pathway or retrograde conduction over the same pathway.

Frequency scans were performed by pacing the right atrium at progressively faster rates. The driving cycle length was decreased in 10 or 20 msec steps and the activity was allowed to reach a steady state; the frequency was then maintained constant for an additional 30 sec. When no clear equilibrium state was attained, a period of approximately 90 sec was allowed between changes of the stimulation rate. Activity was continuously recorded throughout the entire scan.

On several occasions the scans were repeated in whole or in part to ascertain the reproducibility of the data. When repeat scans of progressive acceleration were separated by an interval of at least 5 min during which sinus rhythm prevailed, the results were found to be quite reproducible. Hysteresis was observed when a scan of progressive acceleration was immediately followed by one of progressive deceleration.

**Results**

In the traditional definition of parasystole, the pacemaker is assumed to be totally independent of events in the surrounding tissue, i.e., complete entrance block. As we have shown in previous studies, it is unlikely that a pathway that permits exit conduction can exclude any influence on the pacemaker from the normally propagated responses of the ventricle. The difference between a pacemaker protected by absolute entrance block and a pacemaker subjected to the modulating influence of ventricular responses is illustrated in figure 2. In the absence of ventricular influence, the intrinsic pacemaker cycle length was 1560 msec (panel A, top trace). In this mode, the ectopic responses recorded in the ECG followed the rigid rules of “pure” parasystole: a pacemaker firing in total independence of the ventricular events. Panels B and C illustrate the modulating influence of activity outside the pacemaker focus. In panel B the pacemaker was influenced by only the first ventricular activation, occurring 620 msec after the last pacemaker discharge (at 40% of the ectopic pacemaker cycle). Ventricular excitation (middle trace) triggered the delivery of a single stimulus to the proximal segment of the sucrose-gap preparation. The impulse generated in the proximal tissue (not shown), although it failed to propagate to the distal site, generated a subthreshold depolarization that delayed the next discharge of the pacemaker within the distal segment by 100 msec. An electrotonic influence arriving later in the pacemaker cycle accelerated the next discharge (panel C).

These interactions are described in the form of a phase-response curve in figure 2, D, obtained by introducing stimuli to the proximal segment of the sucrose-gap preparation, one after every fifth pacemaker discharge at progressively longer intervals, thus scanning the pacemaker cycle. The corresponding delay or acceleration of the pacemaker discharge is plotted as a function of the temporal position of the proximal response in the pacemaker cycle. A phase of progressively increasing delay shifted abruptly to maximal acceleration at about 57% of the cycle.

Parasystole is recognized in the ECG when premature ventricular contractions (PVCs) appear with the following characteristics: variable coupling intervals, interectopic intervals that are multiples of a simple common denominator, and fusion beats. Figure 3 illustrates these characteristics of parasystole as recorded in the same experiment as shown in figure 2. In panel A the in vitro pacemaker was free running, divorced from any influence from the in vivo preparation. The pacemaker discharges were transmitted to the ventricle after a delay of 40 msec, and a typical parasystolic rhythm was recorded in the ECG. Although the pacemaker fired at an almost constant cycle length (1530
msec), slight variations in the interectopic interval were apparent in the ECG as a result of variations of intracardiac conduction time.

The coupling interval of the premature beat to the normal beat varied between 250 and 470 msec, the longest interval appearing as a fusion beat (asterisk). Interectopic intervals were multiples of a common denominator of approximately 1530 msec, equal to the average intrinsic pacemaker cycle length.

When full in vitro-in vivo coupling was restored, beat-to-beat modulation of the pacemaker was initiated, but the characteristic behavior of unmodulated parasystole could be maintained (figure 3, B). Driving stimuli were applied to the right atrium at a cycle length of 380 msec. The coupling intervals of the PVCs ranged between 270 and 380 msec; the longest interval was again manifest as a fusion beat (asterisk). Moreover, the interectopic intervals were approximate multiples of a common denominator averaging 1265 msec. Within each pacemaker cycle there were at least two modulating events. The first of these fell in the delay phase and the second in the acceleration phase. The average pacemaker cycle (1230 msec) was significantly briefer than the free-running cycle of 1530 msec in figure 3, A; this is a result of the fact that the area of the acceleration phase (figure 2, D) exceeded the area of the delay phase (see ref. 3).

The operative ratio of cycle lengths during the strip illustrated in figure 3, B, was approximately 10:3, and manifest entrainment of the pacemaker was not apparent. The pattern was one that would be recognized as parasystole. Major departures from the parasystolic

FIGURE 2. Pacemaker modulation. Top trace, Transmembrane activity recorded from the distal segment of the in vitro unit. Middle trace, Right ventricular electrogram. Lower traces, Lead II ECG. A, No ventricular influence; the intrinsic pacemaker cycle length was 1560 msec. B, Pacemaker influenced early in its cycle; a subthreshold depolarization occurred 620 msec after the last pacemaker discharge delayed the next discharge of the pacemaker. C, An electrotonic influence arriving later in the pacemaker cycle accelerated the next discharge. D, The interactions are described in the form of a phase-response curve. The percentage change of the EPCL is plotted as a function of the temporal position of the electrotonic influence in the pacemaker cycle. Asterisks in panels C and D denote the beats that were permitted to influence the pacemaker. Calf Purkinje fiber.
FIGURE 3. Patterns of classic parasystole generated by the preparation in the absence (A) and presence (B) of modulating influence from the ventricles. Upper three traces are as in figure 2. Lowest trace is a stimulus marker. Pacemaker discharges were set to excite the ventricle after a delay of 40 msec. Numbers represent the coupling intervals of the ectopic responses to the preceding normal beats (in msec). Asterisks denote fusion beats. No atrial drive was applied in panel A (cycle length 470 msec). Classic parasystolic behavior is evident in the ECG in both cases. Calf Purkinje fiber.

In the bigeminal episode the single intervening event fell just beyond the midpoint of the phase-response curve and abbreviated the pacemaker cycle maximally. During the trigeminal episode the first intervening response fell during the delay phase (indicated by the subthreshold depolarization in the in vitro pacemaker) and the second during the acceleration phase; the cumulative effect was a net abbreviation of the pacemaker cycle by about 16%. At the 4:1 entrainment ratio (figure 4, C) the net effect was reduced to 14%.

Summaries of complete frequency scans performed in this experiment are presented in figure 5. In the absence of modulation (panel A) the ratio of the ectopic pacemaker cycle length (EPCL) to the driven cycle length (SNCL) increased as the heart rate was accelerated (top curve). The lower curve depicts the incidence of PVCs as a function of the heart rate. As expected, in the absence of pacemaker entrainment the overall incidence declined as heart rate increased. Stable patterns...
of trigeminy, quadrigeminy, and pentageminy occurred only at cycle lengths at which the EPCL/SNCL ratios were precisely 3.0, 4.0, and 5.0, respectively. Any slight deviation from these ratios resulted in destabilization of the arrhythmia.

When full interaction between the two preparations was begun, the frequency scan was repeated with the results plotted as in figure 5, B. The plateaus in the EPCL/SNCL curve represent entrainment zones, induced by electrotonic modulation of the activity of the ectopic pacemaker. As a result of entrainment, relatively wide zones of bigeminy, trigeminy, and quadrigeminy appeared. The patterns observed within these zones were those commonly attributed to reentry. On either side of each zone, more complex patterns typical of parasystole were observed.

**Degree of modulation.** In another set of three experiments, different degrees of pacemaker modulation...
were studied in the same preparation. The results presented in figures 6 and 7 were obtained from an experiment in which current pulses passed across the sucrose gap were used to modulate the activity of the ectopic pacemaker. The current pulses were triggered by the electrical signals recorded from the ventricle. Figure 6 depicts two phase-response curves obtained by scanning the pacemaker cycle with pulses of 120 msec duration and either 2.1 μA (panel A) or 4.0 μA (panel B) intensity, applied once after every tenth pacemaker discharge (intrinsic pacemaker cycle length 1690 msec). The maximum delay and acceleration obtained with current pulses of low intensity (15% and 13%, respectively) increased to 36% and 23% when the current intensity was augmented. The greater level of modulation in the latter was attended by an earlier crossover and a more abrupt transition between the delay and acceleration phases. The results are representative of what would occur if the degree of block (i.e., the impedance) had been reduced between A and B.

As in the previous examples, frequency scans were obtained by driving the right atrium at progressively faster rates (figure 7). Panel A summarizes the results of a frequency scan performed in the absence of modulation. Once again, with independent pacemaker cycling, the EPCL/SNCL ratio is a hyperbolic function of the heart rate. The incidence of PVCs declined pro-

FIGURE 5. Composite results of frequency scans performed in the experiment shown in figures 3 and 4. The points corresponding to the results illustrated in the previous figures are indicated by arrows. In each panel, the upper curve is a plot of the ratio of the operative EPCL to the SNCL as a function of heart rate; the lower curve depicts the incidence of ectopic beats (PVCs) as a function of the heart rate. A, In the absence of modulation, no stable zones were encountered. B, In the presence of modulating influence from the ventricles, wide zones of pacemaker entrainment (upper curve) and relatively wide zones of bigeminy (Bi), trigeminy (Tri), and quadrigeminy (Quad) (lower curve) occurred.

FIGURE 6. Phase-response curves obtained at two different levels of modulation. Current pulses of 120 msec duration and either 2.1 μA (panel A) or 4.0 μA (panel B) intensity were applied across the sucrose gap, once after every tenth pacemaker discharge (intrinsic EPCL 1690 msec).
gressively with increasing heart rate and no entrainment zones were encountered.

Panels B and C represent the results obtained at the two levels of modulation indicated by the phase-response curves in figure 6. When the degree of influence was moderate (panel B), there were narrow zones of entrainment and narrow zones of simple ectopic patterns. When the amplitude was increased (panel C) the zones of entrainment and stable patterns of ectopy increased in width. As in the previous examples, activity within the stable ectopic zones resembled reentry, with closely coupled ectopic responses that remained relatively fixed to the preceding impulse of supraventricular origin; activity bordering these stable zones was more typical of parasystole, with variable coupling, fusion beats, and in some cases interectopic intervals that were multiples of a simple common denominator. These results indicate that as the degree of modulation is increased, the frequency zones over which the arrhythmia resembles reentry become wider. Qualitatively similar results were obtained in two other experiments in which the level of modulation was altered by varying the shunt resistance of the in vitro preparation.

**Level of automaticity.** With complete suppression of phase 4 depolarization the preparation becomes one of "pure" reentry. The examples illustrated in figure 8 were obtained from an experiment in which the distal segment of the in vitro preparation was superfused with Tyrode’s solution containing 6 mM KCl.

At a BCL of 620 msec (panel A) conduction across the block resembled 3:2 Wenckebach periodicity. Closely coupled premature responses occurred in a trigeminal pattern. In panel B, at a BCL of 570 msec, conduction block increased to 2:1 and manifest ectopic activity ceased as a result of insufficient conduction delay of the alternately propagated beats. With further acceleration of the atrial driving rate, conduction across the block was further stressed and a bigeminal rhythm emerged (panel C). At still faster heart rates quadrigeminy (panel D) and pentageminy (panel E) were observed.

The results of a complete frequency scan are presented in figure 9. Before the initiation of atrial pacing, SNCL was 635 msec (heart rate 94 beats/min), conduction across the block was 1:1, and no arrhythmic activity was manifest. With atrial drive, the first reentry zone encountered was that of trigeminy, occurring with 3:2 conduction. The silent zone that follows coincided with a shift to 2:1 conduction and was immediately succeeded by a wide zone of bigeminy that spanned the remainder of the 2:1 conduction zone. At still faster heart rates the pattern changed abruptly to one of quadrigeminy and then pentageminy.

Qualitatively similar results were obtained in two other experiments in which automaticity was suppressed. A silent zone following trigeminy (3:2) was observed in two of the three experiments. The bigeminal zone was followed by a zone of trigeminy (3:1) in one of the other experiments and a zone of silence (due to complete block) in the other. In all cases, however, ectopic responses occurred with close and fixed coupling throughout the frequency range examined.
FIGURE 8. Reentry. Phase 4 depolarization was suppressed by increasing the concentration of K⁺ in the distal segment perfusate to 6 mM. Retrograde conduction delay was set at 80 msec. A, Trigeminy at a BCL of 620 msec. B, Silence at a BCL of 570 msec; all reentrant responses arrive during the ventricular refractory period. C, Bigeminy at a BCL of 475 msec. D, Quadrigeminy at a BCL of 450 msec. E, Pentageminy at a BCL of 425 msec. Close and fixed coupling characterized ectopic activity at all frequencies.
The results presented thus far indicate that when the electrotonic influence is large, the arrhythmia at most heart rates is characteristically reentrant whether or not a pacemaker is involved. However, a major distinguishing feature is apparent; in the reentry preparation (with no pacemaker activity within the protected focus), the transitions between simple patterns of ectopy are much sharper (compare figures 7 and 9) than those in the parasystole model. In the latter, zones of complex parasystolic behavior separate those frequency domains in which ectopic activity resembles reentry.

In two experiments we studied arrhythmic behavior in preparations incorporating a rapidly discharging pacemaker. At similar levels of electrotonic influence (as judged by the PRC amplitude) the range of heart rates over which ectopy occurred were shifted to higher values, and broader transitional zones (more typical of modulated parasystole) were observed when the intrinsic cycle length of the ectopic pacemaker was abbreviated. Moreover, when the pacemaker cycling time was sufficiently brief, a pacemaker escape occurring during a fully compensatory pause could reveal the parasystolic nature of an arrhythmia that otherwise appeared reentrant.

Tachycardia. We have long considered the possibility that the reciprocal interactions that generate reflected reentry could, under the right conditions, result in a self-sustained tachycardia. The primary prerequisite is a degree of block low enough to permit 1:1 conduction but high enough to impose significant first-degree block; that is, the "round trip" conduction time must exceed the refractory period of the ventricle (the in vivo unit) and the ectopic focus. These conditions are difficult to achieve in the in vitro reflection preparation. In the coupled preparations, however, the "exit" delay can be independently varied, simulating impulse conduction delay out of a focus through a region of impaired conductivity.

The sensitivity of the system to the exact timing of events is illustrated in figure 10. In this experiment the necessary entrance delay was achieved by a single premature stimulus applied to the ventricle. The heart was under control of the sinoatrial node (cycle length 430 msec); at the basic frequency the transmission time across the gap was 65 msec, which was too brief to result in a reentry. A premature beat at a coupling interval of 330 msec was transmitted across the gap with a 120 msec delay (panel A). After an artificially imposed delay in retrograde transmission (135 msec), a reentrant ventricular response occurred. Premature responses introduced somewhat earlier (panel B; coupling interval 255 msec) failed to induce reentry because of entrance conduction block, while those introduced later (panel C; coupling interval 360 msec) failed because of exit block.

Under these conditions, a single premature beat, properly timed, could precipitate a tachycardia. An example is illustrated in figure 11, A. At a driven BCL of 500 msec, conduction time across the zone of block was 32 msec. No ectopic activity was manifest. A premature stimulus (arrow), applied to the right ventricle 240 msec after the second normal ventricular beat, elicited a ventricular response that activated the tissue beyond the gap (distal segment) with a delay of 165
**FIGURE 10.** Dependence of conduction and reentry on the prematurity of the impulse. A, A stimulus delivered to the ventricle (arrow) at a coupling interval of 330 msec generated a premature beat that was transmitted across the gap with a delay long enough to permit a reentry. Exit (retrograde) conduction delay was set at 135 msec. B, A premature response elicited at a coupling interval of 255 msec failed to induce reentry because of antegrade conduction block. C, At a coupling interval of 360 msec, reentry failed because of retrograde block. SNCL was 430 msec.

msec. Exit conduction, set at 185 msec, resulted in a reentry that reexcited the ventricle in time to repeat the sequence. A single premature beat thus precipitated a reciprocal tachycardia with a cycle length of approximately 350 msec. The tachycardia continued for several minutes until it was interrupted by the introduction of an interpolated ventricular stimulus (not shown). Short paroxysms of tachyarrhythmia (5 to 20 beats) were more commonly observed than sustained runs.

In the example shown in Figure 11, A, the tachycardia was precipitated by a response to an extrinsic stimulus. In a pathophysiologic state, this initiating event could, of course, arise in any one of a number of ectopic foci. Figure 11, B and C, are two examples of ventricular tachycardia, initiated by reentry occurring within the same focus. In panel B, at an SNCL of 450 msec, the first two reentrant beats occurring with coupling intervals of 375 and 380 msec failed to reexcite the "ectopic" focus. The third reentrant response (coupling interval 395 msec) initiated a slow reciprocating tachycardia. The exit conduction delay was 210 msec and the average cycle length of the reciprocating rhythm was 420 msec (range 405 to 440). The episode was terminated by a beat of sinus nodal origin that captured the ventricles prematurely (asterisk) and restored the bigeminal rhythm.

The events depicted in Figure 11, C, were derived from the same preparation as those of panel A, but at a slightly higher level of block. The transmembrane recording in this example was obtained at a site more distant from the sucrose-gap border. A trigeminal pattern with 3:2 conduction characterized activity during atrial drive at a BCL of 500 msec. Exit conduction time was set at 185 msec. When the coupling interval of the reentrant response reached a value of 272 msec (asterisk), reactivation of the tissue within the focus was effected, and a ventricular tachycardia was initiated.

**Discussion**

Ventricular extrasystoles are generated by one of two basic mechanisms: the activity of an ectopic pacemaker or reentry. In either case the ectopic responses are in large measure the result of impaired conductivity within the tissues surrounding the site of impulse generation. Impaired conduction, as at sites of ischemia, may be the result of homogeneous propagation of depressed fast or slow responses or the result of electronically mediated step delays of impulse transmission. Recent experiments conducted in "ischemic" gap preparations of Purkinje fibers suggest that reflected reentry can occur at sites of ischemia only when conditions are sufficiently severe to render a short segment of tissue inexcitable. An impulse encountering an inexcitable zone, although unable to conduct regeneratively across the area of block, will generate local circuit current flow through the inactivated cells that will cause a depolarization in excitable tissue beyond the block. If the depolarization is of sufficient amplitude, it may bring the distal membrane to threshold. Conduction may thus resume, but only after a delay as long as 350 msec. In the event of a pacemaker at the distal site, a subthreshold electrotonic influence may delay or accelerate the next discharge.

The characteristics of interactions occurring across a
narrow region of inexcitable cable in sucrose-gap and ischemic-gap preparations have been well defined, and models of parasystole and of reflected reentry in such preparations have been described.\textsuperscript{1, 2, 4, 10}

The present model was designed to overcome some limitations of these in vitro preparations. Compensatory pauses following premature responses occur naturally as a result of collisions within or above the AV node. Exit conduction out of the focus can be varied independently of entrance conduction. This capability permits the generation of multiple PVCs and tachycardia. Furthermore, because the preparation consists of two independent units, it permits the study of "classic" or unmodulated parasystole when in vivo \rightarrow in vitro coupling is deleted (complete entrance block) but exit conduction is maintained. Such uncoupling is not possible in a model consisting of only an in vitro preparation because any attempt to prevent an electrotonic influence on the pacemaker focus will also abort exit conduction from the focus. Finally, the parasystolic patterns generated by the system can be subjected to inverse analysis (i.e., the reconstruction of the phase-response curve) in a situation in which the analysis can be directly checked for accuracy.

\textbf{Parasystole.} In establishing the criteria for parasystole, Kaufmann and Rothberger\textsuperscript{14, 15} reasoned that unless a pacemaker is protected by entrance block, it must be discharged and reset by each impulse of sinus origin. Thus the assumption arose that a parasystolic pacemaker must be independent and unperturbed, in any way, by electrical activity in the surrounding tissues.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{tachycardia.png}
\caption{Initiation and termination of ventricular tachycardia. A, Initiation of a reciprocating tachycardia by a single critically timed extrinsic stimulus applied to the ventricle (arrow). B, Initiation of a tachycardia by a reentrant beat occurring within the same focus. The episode was terminated by a beat of sinus nodal origin that captured the ventricles prematurely (asterisk). C, Tachycardia associated with trigeminy. Again, a reentry occurring with a critical coupling interval (asterisk) precipitated a reciprocal tachycardia. Panels A and C were derived from the same preparation; electrotonic interaction in this preparation was achieved with current pulses (100 msec duration) passed across the gap. See text for further explanation. Vertical calibrations = 100 mV.}
\end{figure}
Careful scrutiny of electrocardiographic records exhibiting parasystolic behavior indicates that departure from these rigid criteria is the rule rather than the exception. Minor nonconformities have, in the past, been attributed to fluctuations of the intrinsic cycle length of the pacemaker, whereas more important deviations from classic behavior have been explained in terms of exit block, intermittence, or local reentry within the exit pathway. Although these hypotheses are certainly tenable, recent studies, including the present one, provide evidence for an alternative interpretation. Any functional pathway that permits exit conduction of an impulse out of a protected focus must also permit some degree of electrotonic influence from activity outside the focus to be exerted on activity within. In the case of a protected pacemaker, electrotonic influences arriving early in the pacemaker cycle delay the next discharge while those arriving late in the cycle accelerate it. The result is a biphasic phase-response relationship (figures 2, 6, and 10) whose amplitude and crossover are functions of the intensity of the local circuit (electrotonic) current transmitted across the area of block (figure 6).

Frequency scans performed in the present preparation revealed wide zones of entrainment of the pacemaker (figure 7, C), as in the mathematical and biologic models described earlier. The incidence and pattern of the ectopic responses generated were thus a sensitive function of driving frequency. At some frequencies, typical parasystolic patterns were observed even when beat-to-beat electrotonic modulation of the pacemaker was present. Parasystolic patterns (figure 3, B) could be changed to apparent reentrant patterns (figure 4) by simple alteration of the atrial driving rate. Clinical examples of this type of behavior have been described.

The level of block (i.e., the level of electrotonic interaction across the inexcitable gap) was shown to importantly influence the arrhythmic behavior of the preparation. A decrease in the level of block may not only alter the incidence of manifest ectopic events occurring at any given frequency but may also widen the frequency domains over which the arrhythmic expression is reentrant (figure 7).

These results provide direct experimental support for the basic concepts previously developed based on the mathematical model of parasystole. The experiments provide the first complete biologic characterization of the frequency-dependent behavior of modulated parasystolic arrhythmias incorporating physiologic compensatory pauses. Unlike the predictions of the mathematical model, we encountered no completely silent zones during the parasystolic frequency scans.

Reentry. Suppression of automaticity within the protected focus may convert a modulated parasystole preparation to one of reentry (figures 8 and 9), in which parasystolic behavior cannot be uncovered at any heart rate. The incidence and pattern of ectopic activity generated by a model of reentry remain governed by the prevailing heart rate and bear a striking resemblance to the patterns of "group beating" described by El-Sherif et al. in an in vivo infant preparation of reentry. In this situation the ectopic responses are directly dependent on and coupled to the responses of the ventricle, although fixed coupling is not mandatory, as we have shown previously. Transitions between simple patterns in the reentry mode are generally sharp, but silent zones may occur (figure 9). As a result, the incidence of PVCs may plummet from 50% to 0% as a consequence of a slight deceleration of sinus rate (figure 9; beginning of 2:1 zone).

In previous studies we have shown that when two active areas of cardiac tissue devoid of significant pacemaker activity are separated by a high-impedance barrier, electrotonically mediated impulse transmission across the barrier may be attended by step delays long enough to permit reexcitation of the proximal site by the delayed distal response. This form of reentry is not the result of a circus movement but rather represents a reflected response generated by the to-and-fro passage of an impulse across a common pathway. This mechanism may well occur in regions of impaired conductivity in the heart in situ.

Because exit conduction in our preparation is simulated, the results may represent the behavior of either a circus movement reentrant mechanism in which reexcitation occurs over an alternative pathway or reentry caused by reflection in which reexcitation occurs over the same pathway. In either case, the frequency-dependent changes in ectopic manifestation may be attributed to the frequency dependence of conduction across an inexcitable gap.

In earlier studies of reflected reentry performed in the in vitro preparations, we have reported an inverse relationship between heart rate and the incidence of reflection (PVCs). In a recently developed mathematical model of reflection (Antzelevitch and Moe: unpublished observations), we discovered that this relationship depends critically on the level of block. At low levels of block the computer model predicted a direct relationship between PVC incidence and heart rate at low frequencies shifting to an inverse relationship at high frequencies. We tested these predictions in our preparation by initiating the frequency scans at a

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low level of block (i.e., a low resistance in the external pathway shunting the sucrose gap). The results (Figures 8 and 9) provide experimental confirmation of the mathematical predictions, which indicated a direct relationship between ectopic incidence and heart rate when conduction across the depressed zone ranged between 1:1 and 2:1 (e.g., 5:4, 4:3, 3:2) but an inverse relationship at higher levels of conduction impairment (2:1 to 5:1). These results may provide a mechanistic explanation for the remarkable correlation between ectopic beat frequency and heart rate in patients with frequent PVCs as recently described by Winkle.21

Tachycardia. By controlling entrance and exit conduction intervals independently, we were able to demonstrate tachycardia in this preparation. Such independence cannot be achieved in a model consisting of only an in vitro preparation, since any maneuver designed to alter conduction delay in one direction alters conduction in the opposite direction as well. Tachycardia occurred when exit conduction delays (retrograde) equaled or exceeded the delays in entrance transmission. In the sucrose-gap model not coupled to an in vivo preparation, retrograde conduction across the gap is commonly faster than in the antegrade direction; the converse situation, however, does occur.1, 2, 22, 23 Single reflected responses are readily demonstrable, and occasionally double reflections have been observed (Antzelevitch: unpublished observation), but self-sustained tachycardia has not yet been achieved.

Ventricular tachycardias can be induced by premature stimulation in patients who experience recurrent bouts of the arrhythmia.24-28 This is analogous to the procedure used in the experiment shown in Figure 11, A. The premature stimulus set the stage by prolonging the input conduction time to a range in which self-sustained reciprocation was possible. A single additional stimulus terminated the episode; in the example shown in Figure 11, B, the terminating event was a ventricular response of supraventricular origin.

The ability to initiate and terminate a ventricular tachycardia by means of programmed electrical stimulation has long been accepted as evidence of an underlying circus movement mechanism (although a triggered automatic mechanism cannot always be excluded).29 If the preparation is taken to represent a circus movement mechanism, then this capability is consistent with previous experimental in vivo demonstrations of initiation and termination of repetitive reentry, the only major difference being the delineation of the mechanism responsible for "slow conduction," which in this model involves a narrow zone of inexcitable tissue giving rise to discrete step delays in impulse transmission. If, on the other hand, we consider exit conduction (which in our preparation is simulated) as taking place over the same pathway as entrance conduction, then we may consider repetitive reflection as a possible mechanism for tachycardia. In this framework, our results would further suggest that a reflected tachycardia generated by to-and-fro reciprocation of the impulse may likewise be initiated and terminated by a properly timed event.

Clinical and therapeutic implications. Based on our observations, it follows that ectopic activity that behaves like classic parasystole and activity characteristic of what is commonly diagnosed as reentry, including tachycardia and idioventricular rhythms, may in fact be manifestations of a common mechanism whose arrhythmic expression differs as a function of heart rate, level of block, or level of automaticity. The common mechanism involves the electrotonic interaction of active tissues across a localized region of inexcitability.

The possibility of reflection as a mechanism of reentrant arrhythmias in situ was substantiated by mapping experiments conducted in acute infarct preparations.20, 30 The general concept of modulated parasystole has also been confirmed in clinical studies.31-33 These studies lend support to the mechanisms we have proposed.

Reentrant activity could be demonstrated, with or without pacemaker activity, and over a wide range of frequencies and levels of block. It is possible that a similar mechanism is responsible for many of the ectopic events that are so common in the general population. Tachycardia could be induced only when a critical balance of entrance and exit conduction intervals was reached. If a similar mechanism and similar constraints occur in human subjects, it is perhaps not surprising that ventricular tachycardia is far less common than premature ventricular beats.

The preparations we have described, although they mimic the intracellular electrophysiology observed in diseased and depressed cardiac tissues34 and generate arrhythmias that behave similarly to those encountered clinically, provide only circumstantial evidence for the mechanisms proposed. After decades of research, however, the evidence in support of circus movement microreentry and related mechanisms is no less circumstantial.

The results provide a basis for diagnostic distinction between parasystole and reentry through manipulation of the basic heart rate. In some cases, as in the experiment illustrated in Figures 3, B, 4, and 5, B, modulated parasystole, although it resembles reentry at most fre-
quencies, may be uncovered by acceleration (preferably through intran-atrial stimulation) or slowing (via vagal maneuvers) of heart rate. The parasystolic nature of the arrhythmia will become apparent at select frequencies where complex entrainment of the pacemaker prevails. Ectopic activity that at most heart rates displays fixed coupling will, within these limited frequency ranges, exhibit variable coupling, fusion beats, and at certain rates, interectopic intervals that are approximate multiples of a common denominator. In other cases, similar to that illustrated in figure 7, B, in which modulation is of a lesser degree, parasystolic activity may be discerned over wider ranges of heart rate and activity characteristic of reentry may now be limited to more discrete zones. Finally, when the mechanism is reentry, relatively fixed coupling is likely to be maintained at all heart rates and changes in pattern are likely to be more abrupt. Clinical examples of such behavior have been described.16

Although the practical significance of a distinction between mechanisms remains to be investigated, it is important to recognize that slight changes in heart rate can lead to gross alteration of arrhythmic manifestation in either case.

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