Effect of Electrotonic Potentials on Pacemaker Activity of Canine Purkinje Fibers in Relation to Parasystole

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SUMMARY Isolated false tendons excised from dog hearts were mounted in a three-chamber tissue bath. Isotonic sucrose solution was perfused in the central chamber to provide a region of depressed conductivity between the fiber segments in chambers 1 and 3, which were perfused with Tyrode’s solution. The electrotonic influence of spontaneous or driven responses evoked in chamber 3 during the first half of the spontaneous cycle of a chamber 1 pacemaker delayed the next spontaneous discharge. This effect changed to acceleration when the chamber 3 segment fired during the second half of the spontaneous cycle. We found that subthreshold depolarizing current pulses 50–300 μA msec applied across the sucrose gap caused similar degrees of delay or acceleration. Furthermore, hyperpolarizing currents caused the reverse pattern. The results indicate that the discharge pattern of a parasystolic focus may be altered by the electrotonic influence of activity in the surrounding tissue. The significance of these findings is considered in relation to the mechanism of production of parasystolic rhythms.

PARASYSTOLE is considered to be the mechanism responsible for premature beats when the ectopic events are independent of the normal sinus rhythm and when the apparent interectopic intervals are simple multiples of a common denominator.

An independent ectopic pacemaker can produce a manifest or concealed extrasystole, provided it is protected from the activity of a dominant pacemaker by “entrance” block. A localized segment of depolarized tissue may induce block, one-way or total, but it need not provide complete insulation between two active sites. Electrotonic influences can be recorded beyond a block area and an electrotonically induced alteration of the membrane potential in a pacemaker site may be expected to alter the frequency of the pacemaker. Trautwein and Kassebaum showed that the frequency of an isolated pacemaker could be accelerated by low amplitude current pulses of long duration, and Weidmann demonstrated that subthreshold depolarizing pulses applied early in the pacemaker cycle of isolated sheep Purkinje fibers would delay the next spontaneous discharge.

In the present study we have used the sucrose gap technique to provide a region of depressed conductivity between two active regions in isolated false tendons excised from dog hearts. We have studied the effects of (1) spontaneous or driven responses evoked on one side of the gap, and (2) current pulses delivered across the gap, on the pacemaker activity of the tissue beyond the gap. The results have a bearing on the analysis of parasystolic arrhythmias and may explain those instances of ventricular ectopic beats in which no simple interectopic interval can be calculated.

Methods

Mongrel dogs of either sex were anesthetized with sodium pentobarbital 30 mg/kg, iv. The chest was opened through a midsternal incision and the heart was quickly removed. Free-running false tendons were excised from both ventricles and placed in a modified Tyrode’s solution saturated with a mixture of O₂ (95%) and CO₂ (5%) at room temperature.

Unbranched preparations 0.4–0.7 mm in diameter and 4–10 mm in length were transferred to a plexiglass tissue bath divided into three compartments by two rubber membranes in which small holes were punched (Fig. 1). The fibers were partially sucked into a polyethylene tube which was used to thread the strands through the holes. Equilibration was then allowed for 1 hour while all three compartments were perfused with Tyrode’s solution saturated with 95% oxygen and 5% CO₂ at a rate of 5 ml/min. Temperature was maintained at 36.5–37.5°C. The composition of the solution (mm) was: NaCl, 137; KCl, 4; NaH₄PO₄, 0.9; NaHCO₃, 12; CaCl₂, 2.5; MgSO₄, 0.5; and dextrose, 5.5.

The segment of fiber in chamber 1 was short (0.8–1.2 mm) so that the site of pacemaker activity would be close to the membrane and therefore within the effective range of electrotonic influences from the opposite compartment. Spontaneous pacemaker activity was induced in the short segment by perfusion with a low potassium (2 mm) Tyrode’s solution containing epinephrine, 0.1 μg/ml. Chamber 2, 2 mm in length was perfused with a solution containing purified sucrose, (300 mm) and dextrose (5 mm) dissolved in deionized water saturated with 100% O₂. CaCl₂ was added to the sucrose solution in a concentration of 0.1 mm to prevent cellular uncoupling. Chamber 3 was perfused with Tyrode’s solution containing KCl (4 mm), except in the experiments in which current pulses were passed through the fibers.

To prevent short-circuiting between the two active segments through a common ground, transmembrane potentials were recorded differentially from the segment in chamber 1 with two glass microelectrodes filled with 2.7 M KCl (DC resistances, 10–20 MΩ) and connected to a high impedance amplification system (Frederick Haer). Resting and action potentials in the segment located in cham-

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Diagram of experimental setup, cro = oscilloscope; ccu = constant current source; su = stimulator. Chamber 1, pacemaker chamber with differential recording electrodes; 2, sucrose gap; 3, interactive chamber with recording and stimulating electrodes. Array of diodes prevents shunt between chambers 1 and 3 during passage of pulses from ccu.

Figure 2 Development of conduction block during sucrose perfusion in chamber 2. Upper and lower traces are transmembrane potentials from chamber 3 and 1, respectively. A, control; B, 17 minutes of sucrose perfusion; C, 30 minutes of sucrose perfusion. Spikes are retouched.

Results

CONDUCTION BLOCK

Bidirectional block, complete or incomplete, was achieved within 30 minutes of sucrose perfusion. The preparation illustrated in Figure 2 was allowed to beat spontaneously. As in all experiments, the slope of phase 4 depolarization was steeper in the cells located in chamber 1, because of perfusion with low KCl and epinephrine, but slow diastolic depolarization was also present at a rate of 2-3 mV/sec in chamber 3. The top record in all panels of the figure shows transmembrane potentials recorded in chamber 3, perfused with "normal" Tyrode's solution; the bottom traces were recorded from chamber 1. The same impalements were maintained throughout the experiment. Panel A shows the control records obtained before sucrose perfusion was started. The basic cycle length (BCL) in chamber 1 was 1,235 msec and conduction time between the impaled cells was 3.8 msec. Panel B was recorded 17 minutes after sucrose perfusion had begun. At this stage a 2:1 block pattern developed; action potentials that failed to propagate across the gap produced only subthreshold depolarizations in chamber 3; the conduction time for the propagated response was 50 msec. When block was essentially complete (panel C), the amplitude of the electrotonic responses increased progressively after the last propagated response, eventually bringing the membrane potential to threshold. This time-dependent change in amplitude reflects the progressive increase in membrane resistance and space constant accompanying phase 4 depolarization in chamber 3.

INTERACTION OF SPONTANEOUS RESPONSES

During the stage of advanced block, several discharges in chamber 1 occurred during the slow diastolic depolarization of the slower pacemaker in chamber 3. These events are illustrated in Figure 3, recorded after 25 minutes of sucrose perfusion in the central chamber. The dominant pacemaker (lower trace in each panel) discharged at a BCL of 700 msec, and a basically 4:1 block pattern had been established. As in the experiment illustrated in Figure 2, the amplitude of the electrotonic depolarizations induced in chamber 3 increased as slow diastolic depolarization advanced in the slower pacemaker. This is apparent in panel C of the figure, where the first
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FIGURE 3. Electrotonic interactions accompanying spontaneous discharges in chambers 1 (lower traces) and 3 (upper traces). Upstrokes are retouched.

electrotonic depolarization, occurring late in the cycle, is nearly double the last, which falls early in diastole.

The second spontaneous action potential in panel A of Figure 3 induced an "abortive" action potential in chamber 3 but this abortive response induced no significant alteration of the discharge pattern in chamber 1; the second pacemaker cycle length was about 5% briefer than the first and third responses.

In panel B, the second response "captured" the pacemaker in chamber 3, with a conduction interval across the gap of 160 msec. The electrotonic influence of the chamber 3 discharge was reflected back to chamber 1, and a delay of the subsequent discharge occurred. The second cycle in the panel exceeded the first by 20% (150 msec). The second response in panel C also captured the subordinate pacemaker, but with a "conduction" delay of 220 msec. The electrotonic effect of the chamber 3 response, falling 60 msec later in the spontaneous cycle of chamber 1, now caused an acceleration of the next discharge, which occurred at a cycle length 18% briefer than the first.

Results similar to those depicted in Figure 3 were obtained in five experiments. "Captured" responses in chamber 3 occurring early in the pacemaker cycle of chamber 1 regularly delayed the next pacemaker discharge; captured responses that were sufficiently delayed always accelerated the subsequent discharge of the dominant pacemaker.

INTERACTIONS INDUCED BY EVOKED RESPONSES

The results described in the previous section indicate that the influence of a chamber 3 response on the spontaneous pacemaker in chamber 1 may either accelerate or decelerate the subsequent discharge, depending on the timing. The timing of spontaneous activity on the two sides of the sucrose gap does not, however, permit a systematic scan of the pacemaker cycle. To achieve a complete scan, the segment of fiber in chamber 3 was electrically stimulated at various intervals throughout the complete pacemaker cycle of chamber 1. The stimulator was triggered, through a variable delay circuit, after each 12th to 15th spontaneous discharge of the pacemaker. In this series, nearly complete bidirectional block was essential; accordingly, the observations were recorded after at least an hour of sucrose perfusion of the central chamber.

The results obtained in one of four experiments in this series are illustrated in Figure 4. The upper traces are intracellular recordings from chamber 3 and the lower traces from chamber 1. The BCL of the dominant pacemaker was 1,500 msec. Block of approximately 7:1 was present between the chambers. In A, the test stimulus was delivered to chamber 3 230 msec after the last spontaneous beat in chamber 1; no significant alteration of the spontaneous cycle resulted. In B, the stimulus interval was increased to 800 msec. The electrotonic influence across the gap, apparent as a significant further depolarization during the diastolic depolarization of the pacemaker, delayed the next spontaneous beat by about 350 msec (23%). When the test stimulus was delivered 200 msec later (panel C) the subsequent pacemaker discharge was accelerated by 18%. In all experiments of this series it was apparent that early discharges in chamber 3 delayed, and late responses accelerated, the chamber 1 pacemaker. It was also obvious that a rather critically timed "break" in the curve relating the two events was present at about the midpoint of the pacemaker cycle.

A graphic representation of this biphasic influence is presented in Figure 5. In this figure, percentage change of the spontaneous cycle length is plotted on the ordinate.
Delay and acceleration of the spontaneous cycle of a chamber 1 pacemaker as a function of the test stimulus interval in chamber 3. Stimuli were applied to the chamber 3 segment every 10–15 spontaneous beats. Ordinate: test cycle length as percentage of control cycle length. Abscissa: test stimulus interval expressed as percent change of the spontaneous cycle length. The broken line represents no change in cycle length. Two runs from the same experiment are shown.

FIGURE 5

Electron by influence of multiple driven responses from chamber 3 (upper traces) on pacemaker activity in chamber 1 (lower traces). Calibrations are 1,500 msec and 50 mV. The superimposed transmembrane potentials were traced from projections of the original recordings. In A, intervals bc and cd were 600 msec; in B, 800 msec.

FIGURE 6

scale as a function of test stimulus interval, also normalized as percentage of the BCL. Two successive "runs" of the same scan are shown. During the first half of the cycle, as the interval between the last spontaneous beat and the test stimulus was increased, the next spontaneous discharge was progressively delayed to a maximum of 26%. Beyond 55% of the spontaneous cycle, the relationship changed abruptly to a curve with a very steep negative slope, terminating at a maximum acceleration of 20% at about 65% of the BCL. Beyond this point the curve changed sign again, with progressively less acceleration in pacemaker activity as the test stimulus interval was increased. Within this zone the pacemaker was, in effect, "captured" by the evoked response in chamber 3.

The results presented so far suggest that an "independent" pacemaker may indeed be influenced by responses in the surrounding tissue, and that the influence may be expressed as either acceleration or deceleration of that pacemaker. In the clinical examples of parasystole, several discharges of the normal pacemaker may occur within a single cycle of the ectopic focus. We therefore studied the effect of several sequential responses evoked in chamber 3 on the pacemaker cycle of chamber 1.

Figure 6 illustrates one of two experiments in which the influence of one, two, or three successive stimuli was recorded. Perfusion conditions were arranged to establish bidirectional block between chambers 1 and 3, and to permit a relatively slow but stable spontaneous rhythm in chamber 1. Stimuli, timed as before from each 12th to 15th spontaneous action potential, were applied to the fiber in chamber 3. In panel A of Figure 6, four superimposed traces of the pacemaker are shown, corresponding to (a) no stimulus applied to chamber 3, (b) one evoked response at 850 msec, (c) two evoked responses at 850 and 1450 msec; and (d) three evoked responses at 850, 1,450, and 2,050 msec after the first discharge of the pacemaker. The spontaneous cycle of the pacemaker in the absence of electrotonic influence was 3,700 msec. The subthreshold depolarizations induced by one, two, and three sequential responses evoked in chamber 3 resulted in delays of 150, 350, and 425 msec, respectively.

Although the last of these responses fell beyond the midpoint of the spontaneous cycle (i.e., within the zone where acceleration might have been expected), the effect of the two preceding responses prevented capture by the third. Similar progressive delays were recorded when the interval between the sequential stimuli was increased from 600–650 msec.

In Figure 6B the first stimulus again was applied at 850 msec, and the intervals between stimuli were set at 800 msec. The first and second evoked responses delayed the pacemaker discharge, but the third response accelerated the subsequent response, which now occurred 300 msec in advance of the expected spontaneous response.

The effects of the sequential responses were not cumulative, in the sense that the magnitude of the alterations in pacemaker cycle length was increased, but the curve relating the change in cycle to the stimulus interval was shifted to the right. In the experiment illustrated in Figure 6, for example, the break in the curve was shifted from 48% of the spontaneous cycle for a single response to about 65% for three responses.
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When electrotonic effects across the sucrose gap are induced by spontaneous or evoked responses, neither the amplitude nor the duration of the current flow can be controlled. In the third series of experiments, current pulses of defined amplitude and duration were passed between the two active chambers at various times in the spontaneous pacemaker cycle. As in the previous experiments chamber 1 was perfused with epinephrine and low potassium, but the fiber in chamber 3 was exposed to 10 mM KCl to prevent active responses to the break of the current pulses, which were, of course, hyperpolarizing in that compartment.

In the experiment illustrated in Figure 7, representative of this series, only the differential recording from a cell in chamber 1 is presented. In panel A, depolarizing current pulses of $2.2 \times 10^{-6}$ A, and of varying duration, were applied every 10-15 beats. The five superimposed traces represent the control cycle (a), 2,875 msec, and the response to pulses 100, 150, 200, and 250 msec in duration (b, c, d, e), each beginning 850 msec after the preceding spontaneous discharge. The pulse of 100 msec caused a delay of about 60 msec in the next spontaneous discharge. The delay increased to 100, 240, and 390 msec as the pulse duration was increased. When the duration was increased to 300 msec (not shown), the next response was accelerated. Figure 8 also shows the increasing displacement of membrane potential as pulse duration increases, reflecting again the increased membrane resistance accompanying phase 4 depolarization. Each subthreshold depolarization is followed by a relative hyperpolarization that effectively reduces the slope of the continuing phase 4 depolarization and delays the approach to the pacemaker's threshold potential.

Hyperpolarizing pulses at the same amplitude produced essentially the reverse pattern. In Figure 7B, the spontaneous cycle length was about 2,975 msec (a), current pulses passed with a delay of 1,050 msec after the last spontaneous beat caused a progressive shortening in cycle length as the pulse duration was increased from 50 to 250 msec in 50-msec increments (b, c, d, e, f). The converse situation was observed when hyperpolarizing pulses were applied during the second part of the cycle (Fig. 7C). Pulses lasting 50-250 msec, initiated 2,020 msec after the last spontaneous discharge, induced corresponding delays in pacemaker activity (response d-f).

Complete scans of the pacemaker cycle with depolarizing current pulses confirmed the results obtained with evoked responses described above. Figure 8 illustrates two examples of this set of experiments. In A, pulses 275 msec in duration and $2.6 \times 10^{-6}$ A in strength were applied every 10-15 spontaneous beats. Five recordings from a preparation with a spontaneous cycle length of 1,575 msec (a) are superimposed. The first current pulse, initiated 670 msec after the last spontaneous discharge, produced a delay of 240 msec (b). When the pulse was started at 800 msec, the next spontaneous discharge occurred with a delay of 170 msec (c). Each of these current pulses was followed by a repolarization which took the membrane potential to more negative values than the corresponding control. When the current pulse interval was increased to 880 msec, the membrane potential reached threshold before the termination of the pulse (d). The cycle was abbreviated by 425 msec. However, when the current pulse was delivered 20 msec later, capture failed to occur, even though the membrane potential crossed the expected threshold potential of the fiber (e). When the pulse was terminated, the membrane potential was not restored to the control slope, but underwent a further rapid depolarization terminating in an action potential that fired at precisely the same cycle length as the control. The discharge occurred, however, from a significantly less negative membrane potential, as indicated by the lower ampli-
A

FIGURE 8 Scanning of the spontaneous cycle of a pacemaker in chamber 1 with current pulses 275 msec in duration. Current strength was $2.6 \times 10^{-6}$ A and $5 \times 10^{-6}$ A (panels A and B, respectively). Transmembrane potentials were reconstructed from original recordings. Calibrations are 1,500 msec and 50 mV.

tude and reduced rate of rise. This phenomenon was regularly reproducible when current pulses of low amplitude were applied at intervals between 50% and 60% of the spontaneous cycle. In Figure 8B the current strength was increased to $5 \times 10^{-6}$ A. As the current pulses were delivered progressively later in the spontaneous pacemaker cycle, progressively longer delays (b, c) of the ensuing discharge occurred until, at a critical point (about 45% of the cycle), threshold was reached and the pacemaker was captured (d, e).

Composite results of this experiment are illustrated in Figure 9. The ordinate corresponds to the change in cycle length expressed as percent of control, plotted against the interval between the last spontaneous discharge and the onset of the current pulse, also expressed as percent of the spontaneous cycle. The circles represent the effects of $2.6 \times 10^{-6}$ A and black triangles $5 \times 10^{-6}$ A current pulses. Broken line represents no change in pacemaker cycle length. Points along the diagonal line represent "capture" of the pacemaker with constant latency between stimulus and response.

Fig. 8A). When the stronger pulses were used (Fig. 9) both the delaying and accelerating effects were increased. The reversal point was shifted to the left and was much more abrupt. There were no intermediate points between maximum delay and maximum acceleration. Beyond the "breaking point" the current pulses quickly depolarized the membrane to the threshold potential; in the last part of the cycle, the acceleration was a linear function of the stimulus interval.

VOLTAGE DEPENDENCE OF DELAYING ACTION

Whether induced by action potentials or by subthreshold current pulses, the delay of the spontaneous pacemaker discharge increases progressively as the electrotonic influence is induced later in the cycle, up to a critical reversal point (Figs. 5 and 9). The magnitude of the electrotonic voltage change also increases with time. To assess whether the delay is proportional to elapsed time or to the membrane potential, experiments were designed to compare approximately equal displacements of voltage at different times in the pacemaker cycle. One of these experiments is illustrated in Figure 10, in which four tracings of the pacemaker discharges in chamber 1 are superimposed. Tracing a (BCL = 2,290 msec) was recorded in the absence of externally applied current. In tracing b, a depolarizing current pulse of $3 \times 10^{-6}$ A initiated 500 msec after the last spontaneous action potential delayed the subsequent discharge by 115 msec. When the pulse was delivered 200 msec later, and was reduced in amplitude (to $2.4 \times 10^{-6}$ A), the membrane was depolarized to the same level as in tracing b, and the pacemaker fired at exactly the same time as before (c). When the pulse was initiated at 900 msec, and at a further reduction in amplitude (to $2 \times 10^{-6}$ A), the membrane was depolarized slightly more than in b and c, and the pacemaker was
delayed by an additional 10 msec. These results could be systematically reproduced in six runs of three experiments. Within the early phase of the pacemaker cycle, the delay induced by electrotonic depolarization was a function of the resulting membrane potential rather than the elapsed time.

**Discussion**

Subthreshold depolarizing pulses applied during the first half of the spontaneous pacemaker cycle of an isolated strand of Purkinje fibers delay the subsequent discharge of the pacemaker; pulses of similar magnitude applied late in the cycle accelerate or capture the pacemaker. The time course and magnitude of these influences are similar, whether depolarization occurs as the electrotonic effect of a spontaneous or evoked action potential on one side of a three-chambered sucrose gap preparation, or as the result of current pulses injected across the gap. Current pulses of similar magnitude but opposite direction, causing relative hyperpolarization, have roughly opposite effects; early pulses accelerate, and later pulses delay the spontaneous discharge.

Characteristic of all the manipulations studied is a critical boundary, probably dependent on membrane potential rather than elapsed time, that marks the transition from maximal delay to maximal acceleration. When the electrotonic displacement of membrane potential in the pacemaker cells is relatively large, the transition is very abrupt; often no intermediate points can be observed. Under these conditions the maximum alterations of pacemaker cycle length may reach +40%, switching abruptly to −40%. When the shift of membrane potential is of lesser magnitude, or when several sequential subthreshold pulses are delivered, the transition point shifts somewhat later in the cycle, the magnitude of delay or acceleration is reduced, and a cluster of points can be recorded near the null point, i.e., at a time when neither acceleration nor delay occurs.

**POSSIBLE IONIC MECHANISM**

The ionic mechanism of the delay, as in the experiments of Weidmann, can probably best be explained in terms of the model developed by McAllister and Noble and computed by Hauswirth. According to the model, an outwardly directed current, presumably carried by K⁺ ions and designated as iK₂, gradually declines during phase 4 depolarization as potassium conductance progressively decreases. Depolarizing pulses, resulting in a temporary reactivation of iK₂, would lead to a partial repolarization (apparent in Figs. 7A and 8B), thereby delaying the next discharge. As a result of the progressive reduction in membrane conductance, current pulses of equal magnitude will induce progressively greater depolarizations as they are applied later in the cycle. This expected event, evident in Figure 7A, and discussed by Wennemark et al., would explain the progressive increments in cycle length up to the critical phase shift near the midpoint of the cycle. Similarly, hyperpolarizing pulses should deactivate iK₂; depolarization toward threshold would be accelerated at the break of the pulse. Capture of the pacemaker by depolarizing pulses applied during the last half of the spontaneous cycle (membrane potential less than 80 mV) probably represents activation of the inward sodium current responsible for the initiation of the action potential. At the “null” point between maximum delay and maximum acceleration (Figs. 5 and 9) a response was sometimes initiated before the end of a depolarizing pulse (maximum acceleration); at other times, partial repolarization at the termination of the pulse failed to restore the membrane potential to control levels, but the resumption of phase 4 depolarization now terminated in an action potential arising from a significantly less negative voltage (Fig. 8A). The critical shift at this stage represents, in effect, a competition between reactivation of the outward potassium current and activation of the inward sodium current. The “takeoff” potential for those responses which were neither delayed nor advanced was invariably lower than in the control situation.

**RELATION TO PARASYSTOLE**

A number of features of this experimental model are applicable to the analysis of parasystolic and other extrasystolic rhythms. When a ventricular focus fires at various intervals all of which are simple multiples of a common denominator, entrance block must be assumed to explain the apparent independence of the ectopic pacemaker. It has often been assumed that phase 4 depolarization in the pacemaker itself provides the “protection”, i.e., impedes the penetration of the propagated responses in the surrounding tissue. This explanation does not apply to the present experiments. In the record displayed in Figure 2C, for example, it is clear that block between chambers 1 and 3 would have been total if the segment of tissue in chamber 3 had not also been exhibiting phase 4 depolarization. The “propagated” responses successfully traversed the
gap because the electrotonic manifestations of the action potentials in chamber 1 grew progressively in amplitude as the very slow diastolic depolarization in chamber 3 developed. When the amplitude was great enough to reach the Na threshold, "capture" occurred. This is not, of course, propagation in the sense of a continuously advancing wavefront; it is more nearly analogous to the interaction between a slowly developing stimulus and an adapting excitable tissue. The latency, which may be considerable, represents the rise time of the electrotonic response. Similar delays can occur without the use of a sucrose gap in, for example, the atrioventricular node,10 or during the application of electrically induced block in otherwise normal conducting tissue.1 The facilitation of capture as a result of phase 4 depolarization has recently been reported by Bandura and Brody.11

The results of these experiments suggest that a parasystolic focus need not fire at a fixed rate. In other words, apparently random extrasystoles could still be "parasystolic," even though the criteria for the diagnosis of parasystole are absent. The ectopic focus is "protected" by entrance block, but the degree of such block need not be complete. If an impulse cannot invade the pacemaker, but the pacemaker impulse can escape, then clearly there must be a viable ionic pathway across the blocked region. If the zone of block is wide enough or if the pacemaker cells are located far enough away from the region of block, the electrotonic influence of activity in surrounding tissue will be too weak to alter the pattern of discharge in the pacemaker; this would be the situation in which the diagnosis of parasystole is unequivocal. If the pacemaker cells are within the effective range of the electrotonic influence of the normal rhythmic activity, it is obvious that the intrinsic cycle length of the ectopic focus can be either prolonged or abbreviated by that activity. A single intervening response of supraventricular origin could prolong the ectopic cycle by as much as 40%, or curtail it by 40%. With that much variation in the "common denominator," the diagnosis of parasystole would not be made. With lesser variations in cycle length, the arrhythmia would be considered as "almost" parasystolic. Whether a focus is precisely rhythmic, or approximately rhythmic, or apparently arrhythmic, is then a function of the distance from the focus to the proximal margin of the zone of blocked conduction. It also follows that if the zone of block is sufficiently great, both entrance and exit block will be present: a parasystolic focus could fire rhythmically but never become manifest.

Fixed coupling of ectopic responses, usually considered as prima facie evidence of a reentrant mechanism, can occur with a parasystolic focus. Two ways in which relatively long periods of fixed coupling can occur have been described,13 the parasystolic nature of the arrhythmia becomes exposed when the basic heart rate is altered. It is clear that fixed coupling could also appear in the sucrose gap model. The critical conditions necessary are (1) truly one-way conduction, with propagation possible only from chamber 1 to chamber 3 but effective electrotonic interactions from 3 to 1; and (2) a suitable relationship between the driven frequency in chamber 3 and the spontaneous frequency in chamber 1. Manipulation of the driving frequency should then exhibit (1) phases of apparently random appearance of extrasystoles, with variations of both cycle length and coupling intervals of the "ectopic" pacemaker; (2) phases of entrainment of the pacemaker at 1:1, 2:1, or higher degrees of block; (3) phases of trigeminal, or even higher ratios of ectopic activity, with fixed or alternating coupling intervals; and (4) periods of intermittence followed by assumption of a new ectopic cycle length as the driving frequency crosses critical boundaries.

References

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