Effect of Extrasystoles on Idioventricular Rhythm

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ABSTRACT

Ventricular extrasystoles exert a variable effect on idioventricular rhythm. The postextrasystolic, or the "returning," cycle may be unchanged, or it may be shorter or longer than the dominant cycle. The factors responsible for these different responses have never been investigated. Therefore, the effect of electrically induced extrasystoles was studied by microelectrode techniques in an in vitro model of idioventricular rhythm consisting of spontaneously firing Purkinje fiber bundles with their attached ventricular segments. Late extrasystoles lengthened the Purkinje returning cycle, primarily by transiently increasing the duration of spontaneous phase-4 depolarization. In contrast, early extrasystoles produced shortening of the returning cycle, primarily because of the marked abbreviation of the duration of the extrasystolic action potential. Other factors affecting the ultimate duration of the Purkinje returning cycle were delineated. The effect of extrasystoles on the electrical activity of the ventricular segments was studied by surface electrograms. This effect was complex and was modified by the direction of propagation of the extrasystole with respect to the pacemaker site and by the degree of conduction delay. Ventricular electrical activity usually reflected the electrical events occurring in the pacemaker cells, but frequent exceptions occurred: the ventricular returning cycle could be prolonged while the corresponding Purkinje returning cycle was shortened and vice versa. "Interpolation" of an extrasystole did not necessarily indicate failure of the extrasystole to discharge the pacemaker site. The effects of extrasystoles on idioventricular rhythm which have been described in the earlier literature are easily understood from the findings of this study.

KEY WORDS electrocardiogram premature ventricular contraction cardiac electrogram His-Purkinje system complete heart block transmembrane potentials spontaneous phase-4 depolarization postextrasystolic cycle pacemaker cells returning cycle

Relatively little information exists in the literature concerning the effect of ventricular extrasystoles on idioventricular rhythm in complete heart block, and much of the information that is available was accumulated in the era before electrocardiography (1–10). Scattered references can be found in the early electrocardiographic literature (8, 11–15), but to our knowledge only one clinical study of complete heart block and ventricular extrasystoles has been published since 1920 (16). The information from these studies consists of body surface records of electrical activity (electrocardiograms), electrograms of local ventricular activity, and even less satisfactory records of mechanical movements of the heart (myocardiograms). On the basis of such indirect data, various assumptions have been made about the behavior of the actual
pacemaker cells of the His-Purkinje system, which are responsible for the idioventricular rhythm, and about their response to ventricular extrasystoles.

It is assumed, for example, that extrasystoles have a "depressant" effect on the pacemaker cells and that the lengthening of the ventricular postextrasystolic interval, or "returning cycle," as registered by the indirect methods actually reflects a similar lengthening of the returning cycle of the pacemaker cells in the His-Purkinje system. The actual confirmation of this phenomenon, by direct records of the cellular events in the His-Purkinje system by microelectrode techniques (17), and its correlation with the ventricular events, observed by indirect recording methods, have never been carried out. Evidence exists, furthermore, that ventricular extrasystoles often produce shortening of the returning cycle, and this has led to an assumption that extrasystoles may have a "stimulatory" effect on pacemaker cells. But again no direct demonstration of this effect exists. The role of factors such as the relative location of the idioventricular pacemaker site and the point of origin of the extrasystoles with respect to each other has never been investigated. The influence of conduction delays within the His-Purkinje system and from it to the ventricle has been considered (6, 11, 16), but it has not been properly evaluated because of the lack of direct recording techniques.

The purpose of the present study was, therefore, (1) to induce ventricular extrasystoles in an isolated, spontaneously beating preparation consisting of a Purkinje fiber strand and its terminal ventricular muscle segments, (2) to define the changes in Purkinje membrane potentials which are responsible for the changes in cycle length induced by extrasystoles, (3) to delineate the changes in cycle length detected in the ventricular segments and to analyze the influence of conduction delays and direction of propagation of the extrasystoles on the ultimate ventricular returning cycle, and (4) to provide a firm electrophysiological basis for some of the electrocardiographic observations obtained from the heart in situ.

**Methods**

Experiments were performed on free-running strands of Purkinje fibers (false tendons) obtained from the hearts of adult sheep or mongrel dogs. The animals were anesthetized with sodium pentobarbital, 30 mg/kg, iv, and a right lateral thoracotomy was performed. The heart was removed rapidly and dissected in cool, oxygenated modified Tyrode's solution containing, in millimoles/liter, NaCl 137, NaHCO₃ 12, dextrose 5.5, NaHPO₄ 1.8, MgCl₂ 2.7, and KCl 3.0. The pH of the oxygenated solution was 7.3.

The false tendons, with a segment of ventricular myocardium attached at each end, were dissected free from the endocardial surface of the ventricles and were pinned onto the wax bottom of a Lucite bath, which had a capacity of 20 ml (Fig. 1A). The tissue was continuously perfused with Tyrode's solution equilibrated with a gas mixture of 95% O₂-5% CO₂; this solution flowed through the bath chamber at a rate of 10 ml/min. The temperature of the chamber was maintained between 36° and 37°C. Action potentials were recorded through machine-pulled glass microelectrodes which were filled with 3M KCl and had tip resistances between 15 and 40 Mohms. The microelectrodes were mounted rigidly in micromanipulators and positioned in the tissue.
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under microscopic control. The bath was connected to ground by a large electrode filled with 3M KCl, using an Ag-AgCl junction. The microelectrodes were connected through Ag-AgCl junctions to the inputs of amplifiers with an input impedance of 100 Mohms and input capacity neutralization (Bioelectric Instruments, Inc., model NF-1). The output signals were then led through direct-coupled amplifiers (Tektronix, model 565) for constant monitoring, and recorded on photographic paper by a Grass oscilloscope camera. They were also displayed on a memory oscilloscope (Tektronix, model 565) for constant oscillo-

bipolar surface electrograms were recorded from a Grass oscilloscope camera. They were also displayed on a memory oscilloscope (Tektronix, model RM 564) for recording on Polaroid film. The preparations were stimulated through fine bipolar surface electrodes placed on the surface of the proximal ventricular segments, and bipolar surface electrograms were recorded from the distal ventricular segments through similar electrodes. This electrode arrangement produced antegrade propagation of the extrasystole in the usual direction seen in the in situ conduction system (Fig. 5). Recording and stimulating electrodes were sometimes positioned on the same (distal) muscle segment. This arrangement permitted retrograde propagation of the extrasystole, with respect to the in situ conduction system (Fig. 5).

For stimulation, rectangular pulses were delivered by Tektronix model 161 pulse generators and were led through radiofrequency oscillators isolated from ground (Bioelectric Instruments, Inc., model 1S2A). The pulses were 2–10 msec in duration and of strength sufficient to elicit excitation during the latter part of phase 3 and the early part of phase 4. Development of spontaneous phase-4 depolarization and of automaticity of the Purkinje fibers was facilitated by one or more of the following methods: low-frequency stimulation (20–40 impulses/min), stretch of the Purkinje fibers, low K+ concentration (2 mM/liter) in the Tyrode’s solution, perfusion of the tissue with isoproterenol (3 × 10^-5M), or incubation at room temperature in oxygenated Tyrode’s solution for 12 hours. Automaticity was present in all preparations at rates which varied between 10 and 60 beats/min from experiment to experiment. A single focus usually served at any one time as the pacemaker for the entire bundle of Purkinje fibers and both ventricular segments. During the course of any one experiment, the rhythm tended to become more stable with time, although the cycle length of some preparations continued to shift every so often by as much as 50–200 msec. Once automaticity at a relatively stable rate appeared, rectangular pulses were introduced every six to ten cycles in a random fashion so that they fell at various intervals in the dominant cycle. Only data recorded during stable rates were accepted, since the effect of extrasystoles on pacemaker rate can only be evaluated under this condition.

The following terms and abbreviations are used. The duration of the action potential was measured from the onset of the upstroke to the end of repolarization. Dominant cycles (DC), also known as spontaneous cycles, were measured from the onset of the upstroke of one action potential to that of the next during spontaneous rhythm. The "forced" or "curtailed" cycle (FC) was measured from the last spontaneous action potential to the prematurely induced action potential. The first postextrasystolic or returning cycle (RC) was measured from the onset of the premature action potential to the onset of the first postextrasystolic action potential. Subsequent returning cycles were numbered 2, 3, etc. The conjoined cycle (CC) consisted of the forced cycle and the returning cycle (FC + RC). The most negative point of transmembrane potential was designated the maximum diastolic potential.

Results

EFFECT OF EXTRASYSTOLES ON SPONTANEOUS RHYTHM OF PURKINJE FIBERS

In general, two distinct kinds of responses to premature beats were observed, depending on the timing of the extrasystoles in the dominant cycle. These two types will be treated separately. Late extrasystoles caused no change in or lengthened the returning cycle (RC ≤ DC) in over 95% of the cases. Early extrasystoles caused a shortening of the returning cycle (RC < DC) in a similar percent (90%) of the cases.

Late Extrasystoles.—Generally, extrasystoles induced after the end of repolarization, i.e., during phase 4 of the dominant cycle, propagated throughout the entire bundle of Purkinje fibers and into the opposite ventricular segment. The premature action potential had good amplitude and rate of rise, and its duration was only slightly decreased. The first returning cycle was sometimes equal to the dominant cycle, but more frequently it was prolonged by as much as 200–300 msec (Figs. 2A and B, 3A). The degree of lengthening of the first returning cycle was not necessarily related to the time of the extrasystole during phase 4. The second and third returning cycles were somewhat less prolonged or not prolonged at all, and the dominant cycle length...
FIGURE 2

Effect of increasing prematurity of extrasystoles on the duration of the returning cycle in a latent pacemaker cell of canine Purkinje fiber showing an unusually long spontaneous action potential (660 msec). AP = duration of action potential, FC = forced cycle, RC = returning cycle, CC = conjoined cycle, arrows = point of maximum diastolic potential, MDP. The numbers 0, 1, 2, 3, and 4 refer to the phases of transmembrane potential. Time lines = 1 second and 100 msec. In A and B, late extrasystoles are followed by prolonged returning cycles (210 msec in A). The duration of phase 4 from the point of maximum diastolic potential to first returning beat is also prolonged, but the duration of the premature action potential is moderately shortened (by approximately 120 msec in B). Maximum diastolic potential is not altered. In C, the returning cycle is equal to the dominant cycle. Action potential duration is markedly reduced (by 160 msec), but this shortening is counterbalanced by increased duration of phase 4. In D, E, and F, early premature stimuli are followed by brief and small action potentials and the returning cycle is markedly shortened (by 210 msec in E). The action potential duration is markedly abbreviated, and the duration of phase 4 is unaltered in E and shortened in D and F. Since the conjoined cycles in D–F are longer than the dominant cycles, it is clear that the extrasystole has depolarized the pacemaker prematurely and has reset its rhythm.

usually was reestablished within two or three cycles. Four changes in transmembrane potential were often observed after extrasystoles induced during phase 4. These changes consisted of: (1) an increase in negativity of the maximum diastolic potential (Fig. 4A), (2) an increase in the time between the point of maximum diastolic potential of the extrasystole to the first returning action potential (Figs. 2, 4A), (3) a decrease in the slope of spontaneous phase-4 depolarization (Fig. 4A), and (4) a change in the appearance of the upstroke, threshold potential, foot, and rate of rise of the first, or even of the subsequent, returning beats, suggesting a shift of pacemaker activity to another site in the preparation (Fig. 4B). The most important change which led to lengthening of the returning cycle was the increased duration of spontaneous phase-4 depolarization between the point of maximum diastolic potential and the onset of the next action potential. This change was consistently observed when the returning cycle was prolonged. Other changes were not always present to the same extent in all preparations. For example, the change in...
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FIGURE 3

Effect of progressively more premature extrasystoles on stable rate in automatic sheep Purkinje fiber. Action potential duration = 350 msec. In A, the extrasystole is followed by a slightly lengthened returning cycle. The duration of the action potential is unchanged and phase-4 duration is slightly increased. In B, the returning cycle is shortened because of decreased action potential duration and despite increased phase-4 duration. In C, the returning cycle is even more shortened, because of a greater decrease in action potential duration. In D, the returning cycle is shortened by 50 msec. In E, a 50-msec delay has occurred between stimulus and action potential. If the returning cycle was measured from the stimulus artifact, it would be equal to the dominant cycle. If it is measured from the onset of the action potential, however, the returning cycle is shortened. In F and G, stimuli are of opposite polarity and the premature action potentials are extremely brief. The returning cycle is shortened by more than 200 msec in G. The duration of the conjoined cycles in E–G clearly shows that the pacemaker center has been reset by the extrasystole in spite of the brevity and small amplitude of the action potential.

contour of the first returning beat was particularly evident when the preceding spontaneous action potentials suggested by their appearance that the impaled cell was far from the dominant pacemaker focus of the preparation. In such instances, the change in the first returning action potential was quite obvious and strongly suggested a shift of pacemaker activity to a site closer to the impaled cell (Fig. 4B). On the other hand, when the action potential of the impaled cell was initially highly suggestive of a pacemaker cell, the changes in the action potential of the first returning beat were negligible. Similarly, the increased negativity of the maximum diastolic potential and the depressed slope of phase-4 depolarization were more apparent in some preparations than others. As mentioned above, the first returning cycle was sometimes not lengthened but was merely equal in duration to the dominant cycle (Fig. 2C). In these instances, spontaneous phase-4 depolarization after the point of maximum diastolic potential was prolonged and should have resulted in an increase of the total returning cycle length, but this prolongation was counterbalanced by
Changes in transmembrane potential after late extrasystoles (A and B) and early extrasystoles (C and D) in four different canine Purkinje fibers. Automaticity induced by hypoxia. A: After a late extrasystole, the maximum diastolic potential is noticeably more negative; the slope of phase-4 depolarization is initially steep but is terminally more depressed than it is in the dominant cycle. Phase 4 is lengthened from the point of maximum diastolic potential to the first returning action potential. B: After a late extrasystole, the slope of phase 4 is only slightly depressed and the appearance of the postextrasystolic beats is markedly altered, suggesting the emergence of a new pacemaker cell, closer to the impaled cell. C: The returning cycle is shortened after an early extrasystole, in spite of increased negativity of maximum diastolic potential. This shortening results from an increased slope of phase-4 depolarization and shortened duration of the premature action potential. D: In a depressed fiber, an early extrasystole is followed by a shortened returning cycle, solely because of decreased duration of the extrasystolic action potential. Maximum diastolic potential is not altered.

A sufficient decrease in the duration of the extrasystolic action potential.

Early Extrasystoles.—The effects of extrasystoles induced during phase 3 of the action potential, and in some preparations also during the early part of phase 4, differed from those of late extrasystoles. In most experiments, the first returning cycle was shorter than the dominant cycle (RC < DC) (Figs. 1B–C, 2D–F, 3B–C). The shortening was usually limited to the first returning cycle; the second and third returning cycles were usually equal to or somewhat longer than the dominant cycles. The premature action potential was uniformly shorter than the spontaneous action potential, and the point of maximum diastolic potential was reached earlier after the early extrasystoles than it was after the spontaneous action potentials. The magnitude of the shortening of the premature action potential, its rate of rise, and its amplitude varied from experiment to experiment, and for a single preparation they varied in relation to the degree of prematurity of the extrasystole (Figs. 1–3). This can be clearly seen in Figure 2C–F.

The following alterations in transmembrane potential were observed. (1) The slope of phase 4 was either unchanged (Fig. 4D), depressed, or occasionally even enhanced (Fig. 4C), and the total duration of depolarization from the point of maximum diastolic potential to the first returning action potential was either decreased, unaltered, or increased (Figs. 2D–F, 3B and C). (2) The appearance of the upstroke of the first returning action potential was sometimes altered so as to suggest a shift in pacemaker location. (3) The maximum diastolic potential after the extrasystole was sometimes increased (Fig. 4C). Various combinations of these changes in transmembrane potential determined the ultimate length of the returning cycle, but the most important factor responsible for shortening of the returning cycle after early extrasystoles appeared to be the marked decrease in duration of the premature action potential.

Ordinarily, the response to early extrasystoles consisted of shortening of the first returning cycle only (over 95% of cases), but in occasional preparations the shortening of the returning cycle persisted for several beats, resulting in a net increase in rate (Fig. 8A). The returning action potentials were frequently different in appearance and suggested that pacemaker activity had shifted for several beats to a new site. Shortening of the returning cycle with early extrasystoles was more evident at slow intrinsic rates than it was at fast rates, presumably because during slow rates the action potential tends to be long. Shortening of the premature action potential was particularly evident when the spontaneous action potentials were themselves prolonged (Fig. 2) or when the point of maximum
diastolic potential was delayed, as was often the case in depressed fibers (18). In the presence of a tachycardia, the introduction of extrasystoles usually produced no shortening of the returning cycle. Presumably under the conditions of a tachycardia, the action potentials are already so shortened that additional shortening induced by an early extrasystole is not sufficient to produce shortening of the returning cycle.

The methodology used in this study warrants comment at this point. Extrasystoles were induced every six to ten beats during a stable rhythm. Evidence exists that such frequent extrasystoles may have a cumulative effect on the refractory period of cardiac cells (19) and presumably on the duration of their action potentials up to 14 cycles. This cumulative effect consists of a decrease of about 10-20 msec in the refractory period, which is still apparent six to ten beats after the extrasystoles. This cumulative effect may have influenced the results of this study only by minimizing the shortening of the action potential and, therefore, the shortening of the returning cycle after early extrasystoles.

**Effect of Site of Stimulation on Cycle Length.**—Purkinje cells situated approximately 2–3 mm away from the distal end of false tendons have action potentials of distinctly greater duration than do those situated proximally or distally (20). These long action potentials can act as a barrier or “gate” for very early premature beats which can spread as far as the gate but no farther and thus are confined on one side of the gate. Stimulation from either side of the preparation resulted in extrasystoles which were early enough to produce shortening of the returning cycle, as illustrated in Figure 1B and C.

**VENTRICULAR ELECTRICAL ACTIVITY**

Electrograms recorded over the muscle segments usually reflected the electrical events in the Purkinje network, but there were striking exceptions. Two factors were extremely important in determining the duration of the ventricular returning cycle: (1) the relative position of the stimulating and recording electrodes with respect to the pacemaker site and (2) the conduction velocity.

Figures 5 and 6 illustrate the manner in which the position of the stimulating and recording electrodes determined the direction of propagation of the extrasystole with respect to that of the spontaneous beats. A common location on the same ventricular segment was equivalent to the situation in which an extrasystole originates in peripheral tissue and spreads retrogradely through the His-Purkinje system before reaching the pacemaker site. In contrast, locating the two pairs of electrodes at opposite ends of the fiber was equivalent to the situation in which an extrasystole spreads in the same general direction (antegrade) through the His-Purkinje system and toward the myocardium, depolarizing the pacemaker site on its way.

If both sets of electrodes were situated on the same muscle segment, the ventricular returning cycle was always longer than the Purkinje returning cycle, the increment of the ventricular returning cycle being dependent on the degree of conduction delay. Under these circumstances, a prolonged Purkinje returning cycle, such as that which occurs after a late extrasystole, was accurately reflected by a somewhat longer ventricular returning cycle. Discrepancies were noted, however, between Purkinje and ventricular returning cycles when the Purkinje returning cycle was shortened. Figure 5 illustrates such a situation. The extrasystole, originating from the stimulating electrode on the right ventricular segment (Fig. 5C), is recorded initially by the surface electrode on the same segment and then by the microelectrodes as it invades the Purkinje fibers from right to left. The postextrasystolic beat is recorded first by the microelectrodes and afterwards, in its propagation from left to right, by the surface electrode on the muscle segment. As a result of this electrode arrangement, long Purkinje returning cycles would be paralleled by long ventricular returning cycles. On the other hand, shortening of Purkinje returning cycles is not well appreciated from the ventricular returning cycles. In Figure 5B, for
Influence of retrograde propagation of the extrasystole on the ventricular returning cycle. Stimulating and recording electrodes are located on the same ventricular segment as shown in C. On each record, the upper and middle traces show action potentials recorded by the left (L) and the right (R) microelectrodes. The lower trace is an electrogram showing a Purkinje spike ($P$) followed by local ventricular activity ($V$). Electrograms were retouched for clarity. 

**A:** An early extrasystole at 340 msec is followed by a Purkinje returning cycle that is 50 msec shorter than the dominant cycle. Premature ventricular and Purkinje electrograms occur simultaneously (because the stimulating electrode is close to a terminal Purkinje branch) and are labeled $V$ for simplicity. Although the Purkinje returning cycle is shortened, the duration of the ventricular returning cycle is equal to that of the dominant cycle because of antegrade conduction time ($P_{JVJ}$). 

**B:** An earlier stimulus at 250 msec is followed after a 50-msec latency period by a premature Purkinje electrogram and a premature action potential. The ventricular electrogram ($V$) is again buried in the stimulus artifact. The Purkinje returning cycle is more shortened than in A, but the ventricular returning cycle is only slightly shorter than the ventricular dominant cycle. This discrepancy is due to marked delay of the extrasystole before reaching the microelectrodes. The ladder diagram in D illustrates in schematic form the influence of conduction time on Purkinje and ventricular returning cycles. 

$S =$ stimulating electrode, $R =$ recording electrode, $V =$ electrogram of spontaneous ventricular activity, $V' =$ ventricular premature beat, $V_1 =$ returning ventricular electrogram, $P =$ Purkinje action potential and electrogram spike, $P' =$ premature Purkinje action potential and electrogram spike.

The opposite result was found when the stimulating and recording electrodes were situated on opposite ventricular segments, as in Figure 6. Here, spontaneous and premature depolarizations always proceed in the same direction, e.g., from left to right, and the extrasystole is recorded by the microelectrodes in the Purkinje network ahead of the ventricular electrogram. Conduction time of the extrasystole may be normal or increased. As a result, the ventricular returning cycle is equal to or shorter than the Purkinje returning cycle depending on conduction time. Under these circumstances, the shortening of the Purkinje returning cycle after early extrasystoles was always reflected by a similar shortening of the ventricular returning cycle, as in Figure 6C.
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Influence of antegrade propagation of the extrasystole on the ventricular returning cycle. The stimulating (S) and recording (R) electrodes are at opposite ends of the preparation as diagrammed in D. On the electrogram, a Purkinje spike (P) is followed 20 msec later by a second deflection indicative of ventricular activity (V). Purkinje action potentials and electrograms precede ventricular activity in all three extrasystoles. In A, an extrasystole 1040 msec after the action potential is followed by a Purkinje returning cycle only slightly longer than the dominant cycle. The conduction time, P'V, is 40 msec longer than during spontaneous rhythm. As a result, the ventricular returning cycle is shorter than the Purkinje returning cycle and is equal to the ventricular dominant cycle. In B, recorded during a slightly faster rhythm, the Purkinje returning cycle is equal to the dominant cycle. Because of increased P'V, the ventricular returning cycle is slightly shorter than the Purkinje returning cycle, and it is also shorter than the ventricular dominant cycle. In C, an early extrasystole induces marked shortening of the Purkinje returning cycle and of the ventricular returning cycle. E: Ladder diagram schematically representing the sequence of events of A-C. Compare with D of Figure 5. Symbols are the same as in Figure 5, and the electrograms were retouched for clarity.

On the other hand, the duration of the Purkinje returning cycle after late extrasystoles sometimes failed to be faithfully reflected by the ventricular electrogram. In Figure 6A, for example, the ventricular returning cycle is exactly equal to the dominant ventricular cycle, although the Purkinje returning cycle is actually lengthened. The discrepancy is due to prolonged conduction time of the extrasystole to the ventricular segment. In Figure 6B, more importantly, the ventricular returning cycle is actually shorter than the dominant cycle. Thus, there could be serious discrepancies between ventricular and Purkinje returning cycles after late extrasystoles when the spread of excitation is occurring in the same direction during spontaneous and premature impulse formation.

EXCEPTIONAL RESPONSES

Purkinje Fiber Responses.—Although the sequence of events after extrasystoles was usually as described above, several exceptional types of responses deserve mention. Late extrasystoles occasionally led to shortening of the returning cycle instead of the usual lengthening (Figs. 3B, 7B). Two characteristic changes in transmembrane potential were delineated by which this unusual response could be elicited. In some preparations, enough shortening of the action potential could occur, for reasons that are not clear, to influence, in a decisive fashion, the duration of the returning cycle and to make it shorter than expected. This phenomenon is responsible for the slight shortening of the returning cycle observed in Figure 3B. Figure 7B–D illustrates...
Shortened returning cycle after late extrasystoles in a depressed Purkinje fiber network. A shows control cycles just before the recording shown in B. In B, the shortening of the returning cycle after a late extrasystole is caused by the earlier occurrence of the point of maximum diastolic potential (from 1000 msec to 750 msec) and by the steeper slope of phase-4 depolarization. The negativity of the maximum diastolic potential is not sufficiently increased to produce lengthening of the returning cycle. In C and D, spontaneous extrasystoles also result in an earlier point of maximum diastolic potential. Arrows = point of maximum diastolic potential.

There were also some exceptional responses to early extrasystoles. In a few preparations, shortening of the returning cycle was not noted, even after extremely early extrasystoles. The returning cycle was unaltered or even lengthened. In such preparations, two characteristics of the transmembrane potentials were responsible for the absence of shortening of the returning cycle: (1) the decrease in the duration of the action potential, which is usually observed with early extrasystoles, was not present or (2) if shortening of the action potential occurred, it was counterbalanced by

Unusual responses to early extrasystoles in canine Purkinje preparations. A: A net increase in rate has occurred because of a persistently shortened returning cycle after an early extrasystole. Returning action potentials suggest new pacemaker site. B: Depression of phase 4 after early extrasystole, particularly prominent during the second returning cycle and especially during the latter part of diastole. C: After early extrasystole, transmembrane potential forms a hump or oscillation before becoming more negative once again. The returning action potential is markedly different in appearance, suggesting a different pacemaker site. D: Two early extrasystoles induce depression of phase 4 similar to that seen in B after one extrasystole. E and F are from a different canine Purkinje preparation. E: An early extrasystole produces the expected shortening of the returning cycle. In F, maximum diastolic potential is much more negative and leads to prolongation of the returning cycle in spite of enhanced phase-4 slope.
other changes in transmembrane potential which favored lengthening of the returning cycle, such as an unusual increase in negativity of the maximum diastolic potential, as shown in Figure 8F, or a rather marked depression of spontaneous phase-4 depolarization, particularly during the latter part of diastole, as shown in Figure 8B and D. Occasionally, as shown in Figure 8C, a "hump" occurred in the transmembrane potential at the time of the expected returning action potential, suggesting that the early extrasystole had depressed conduction in the fiber to such an extent that the first returning action potential initiated by the pacemaker cell was blocked and failed to capture the entire fiber. The long pause was ultimately interrupted by an action potential with characteristics which suggested the emergence of a latent cell as the new pacemaker site.

Ventricular Responses.—Several discrepancies in the timing of Purkinje depolarization

![Figure 9](http://circres.ahajournals.org/)

Unusual responses to extrasystoles in a sheep Purkinje fiber preparation in which stimulating and recording electrodes are at opposite ends (as in Fig. 6). Electrograms were retouched for clarity. Preparation is beating spontaneously. In A, an early extrasystole depolarizes the Purkinje fiber, resulting in a markedly shortened Purkinje returning cycle; but the extrasystole is blocked between the microelectrodes with the resulting absence of a premature deflection (V' not present) on the electrogram and an unexpectedly prolonged V-V interval. In B, the Purkinje returning cycle is slightly shortened. The bipolar electrogram indicates the time of depolarization of the Purkinje fiber. The extrasystole is blocked before reaching the ventricular segment. No ventricular depolarization occurs and the ventricular cycle (V-V) is markedly prolonged (from 2,960 msec to 3,920 msec). C–F are from a different sheep Purkinje fiber experiment (similar electrode arrangement). In C, an early extrasystole at 760 msec unexpectedly results in a lengthened Purkinje returning cycle (2210 msec). The ventricular returning cycle is also lengthened (2195 msec) but less so than the Purkinje returning cycle. This discrepancy of 15 msec results from the increase in conduction delay of the early extrasystole. In D, an earlier stimulus at 730 msec is followed after a delay of 100 msec by an extrasystole and an extremely shortened returning cycle. Although the entire fiber has been depolarized, the ventricular conjoined cycle is exactly equal to the dominant cycle. In E, the returning cycle is so shortened that the ventricular conjoined cycle is even slightly shorter than the dominant cycle. In F, the extrasystole produces slightly less shortening of the returning cycle, so that the ventricular conjoined cycle is slightly longer than the dominant cycle. See text for discussion.
and ventricular electrograms were already noted above. In addition, two serious potential errors that can be made from the electrograms are illustrated in Figure 9. The stimulating and recording electrodes were located at opposite ends of the fiber. In Figure 9A and B conduction velocity from Purkinje fiber to muscle was impaired. In 9A the extrasystole was extremely early, propagated decrementally, barely managed to depolarize the pacemaker site, and decayed completely between the two microelectrodes. In 9B, the extrasystole was also blocked before reaching the ventricular segment. As a result, although the Purkinje returning cycle was actually shortened (by 410 msec in 9A), the interval between ventricular activity on the electrogram was lengthened (from 2,970 msec to 3,150 msec in 9A and from 2,960 msec to 3,920 msec in 9B), giving rise to the misleading impression that there was a "spontaneous variation" in the rate of firing of the idioventricular focus. The second serious potential error concerns "interpolation" of ventricular extrasystoles in idioventricular rhythm. This is a rare phenomenon, but when it occurs it is assumed that the extrasystole failed to depolarize the pacemaker site (an analogy to interpolation of ventricular extrasystoles during normal sinus rhythm). Figure 9C-F demonstrates that this is not necessarily the case. In all instances, depolarization of the pacemaker site has occurred, with extremely short returning cycles in D-F. Although the conjoined cycle was either slightly shorter or longer than the dominant cycle in Figure 9E and F, it was exactly equal to the dominant cycle in 9D. The surface electrogram in 9D would indicate interpolation of an extrasystole by the usual electrocardiographic criteria, but the action potential recordings indicate that the conjoined cycle was equal to the dominant cycle (CC = DC) simply because of an extremely shortened returning cycle and not because of failure to depolarize the pacemaker site.

Discussion
The results of this study indicate a difference in the response of automatic Purkinje fibers to early and late extrasystoles. They also provide a sound electrophysiological basis for understanding the disturbances in heart rate which are induced by ventricular extrasystoles in the idioventricular rhythm of the heart in situ. Since idioventricular rhythm originates within the His-Purkinje system rather than in ordinary ventricular myocardium (21), the effect of extrasystoles on automaticity of Purkinje fibers as analyzed by transmembrane potentials will be discussed first.

EFFECT OF EXTRASYSTOLES ON PURKINJE FIBER RHYTHMICITY
A comparison of previous studies on the sinoatrial node (22, 23) with results of the present experiments indicates a similarity between the responses of sinoatrial nodal cells and automatic Purkinje cells to electrical stimuli of varying prematurity. In general, extrasystoles impart a new rhythm to spontaneously automatic Purkinje fibers as they do to sinoatrial nodal pacemaker cells. Extrasystoles which occur during the latter part of repolarization (phase 3) almost always induce a transient increase in the rate of firing of Purkinje fibers. This increased rate does not usually result from some stimulating effect of the extrasystole on the intrinsic rhythm but simply from the abbreviated duration of the extrasystolic action potential (Figs. 1-3), which is seen with early extrasystoles. Although this decreased action potential duration with early extrasystoles had previously been described (21, p 275), its role in influencing the duration of the returning cycle has never been emphasized. Such shortening of the returning cycle is also seen in some preparations with extrasystoles occurring shortly after phase 3; in these cases, the shortened returning cycle is also due to shortening of the extrasystolic action potential duration. On the other hand, extrasystoles elicited after repolarization is complete lead to returning cycles that are equal to or longer than the dominant cycle (Figs. 2, 3). In the case of late extrasystoles, it may be proper then to speak of a depressant effect of extrasystoles on automaticity of Purkinje fibers. This depressant effect is accounted for...
at least partly by the following changes in transmembrane potential: (1) the slope of phase-4 depolarization may be depressed and (2) the maximum diastolic potential may be increased.

Exceptions to these patterns of response of Purkinje fibers to extrasystoles may be seen. For example, early extrasystoles may be followed, not by shortened, but by unaltered or even lengthened Purkinje returning cycles. This is likely to occur if the action potential of the extrasystole is not substantially abbreviated, as happens at relatively fast rates for reasons previously explained. Conversely, shortening of the returning cycle after late extrasystoles is sometimes observed instead of the expected lengthening. This occurs particularly in depressed Purkinje fibers in which the point of maximum diastolic potential is markedly delayed (18). In these instances, an extrasystole shortens the returning cycle by accelerating the arrival of the point of maximum diastolic potential, by transiently enhancing spontaneous phase-4 depolarization, or both (Fig. 7).

In conclusion, the ultimate length of the returning cycle of the Purkinje cell (and, hence, the rhythm alteration caused by the extrasystole) is modulated by several factors operating singly or in combination: (1) the intrinsic rate of the idioventricular rhythm and the relative difference of action potential duration between spontaneous beats and extrasystoles (Figs. 1–4), (2) the timing of the extrasystole in the dominant cycle (Figs. 1–3), (3) the degree of negativity of the maximum diastolic potential and its timing after the spontaneous beats and the extrasystole (Figs. 4, 7, 8), and (4) the degree of depression or enhancement in the slope of phase 4 after an extrasystole (Figs. 2–4, 8). Two other factors which may influence the Purkinje returning cycle duration are: (1) the degree of conduction delay (Figs. 3E, 8C) and (2) the capability of latent pacemaker cells to emerge temporarily as the new pacemaker site for the preparation (Figs. 4B, 8A compared to 8C).

**EFFECT OF EXTRASYSTOLES ON VENTRICULAR ELECTRICAL ACTIVITY**

The disturbances in His-Purkinje rhythm which are induced by extrasystoles are usually not directly recorded in the heart in situ, but have been inferred from surface records of ventricular electrical activity such as ventricular electrograms and electrocardiograms. This study provides electrophysiological correlates for these indirect recording methods in idioventricular rhythm, but it also serves to emphasize that information obtained from these methods may lead to mistaken inferences concerning the events in the His-Purkinje system. Although the events recorded in Purkinje cells are often reflected relatively faithfully by records of ventricular activity, two factors so modify the Purkinje-ventricular relationship that determination of Purkinje cellular events from the electrogram or electrocardiogram alone is often impossible. These two facts are: (1) the point of origin and direction of propagation of extrasystoles with respect to the site of origin of the idioventricular rhythm, as illustrated in Figures 5 and 6, and (2) the degree of conduction delay between the Purkinje pacemaker site and ventricular muscle. These factors interact with each other and with the duration of the Purkinje returning cycle to result in ventricular events which may be different from the Purkinje fiber events. Thus, an unaltered ventricular returning cycle may be the result of a shortened, lengthened, or unaltered Purkinje returning cycle depending on the direction of propagation of the extrasystole, the duration of the Purkinje returning cycle, and the conduction time. Furthermore, the existence of a lengthened ventricular returning cycle on the electrogram or the electrocardiogram is no assurance that the corresponding Purkinje returning cycle is lengthened; it may be simply unaltered or even shortened, again depending on the degree of conduction delay. Likewise, shortening of a ventricular returning cycle is not an absolute indication that the corresponding Purkinje returning cycle is shortened. It may be lengthened or unaltered, if the extrasystole originated somewhere beyond the site of
intrinsic pacemaker activity and propagated to the ventricular muscle in the same general direction as the spontaneous beats (Fig. 6), again depending on the duration of the Purkinje returning cycle and the degree of conduction delay of the extrasystole from Purkinje fiber to ventricle. The timing of the extrasystole in the dominant cycle is helpful, of course, since usually (although not invariably) early and late extrasystoles have a different effect on the His-Purkinje pacemaker sites.

The dissociation of Purkinje and ventricular events and the roles of decremental conduction and direction of propagation of the extrasystole are further illustrated by the finding that an extrasystole may sometimes succeed in reaching and depolarizing the pacemaker site in the His-Purkinje system but fail altogether to propagate to ventricular muscle. No sign of the extrasystole is visible on the surface record (Fig. 9A and B) and, were it not for the Purkinje record, the sudden decrease in ventricular rate would be explained as a spontaneous variation in the rate of firing of the intrinsic pacemaker site.

RELEVANCE TO THE HEART IN SITU

Although care must be exercised in extrapolating experimental results obtained from in vitro models to the heart in situ, it becomes apparent from a review of the literature that the two general patterns of response to extrasystoles, namely, long returning cycles after late extrasystoles and short returning cycles after early extrasystoles, also exist in the heart in situ. Lengthening (1-6), shortening (2, 3, 5, 8, 9, 12, 16, 24), and lack of alteration (13, 14) of the ventricular returning cycle after ventricular extrasystoles have all been reported. Furthermore, occasional examples of shortening of the Purkinje returning cycle can be found scattered in the literature (25-27). It is evident from a review of all published examples that lengthening of the ventricular returning cycle is usually observed in the heart in situ after late extrasystoles and that almost all recorded instances of shortened returning cycles occur after early extrasystoles (2, 3, 8, 12 [Fig. 33], 16 [Figs. 1C, 2, 6], 25-27). These observations are consistent with the findings of the present study. The occasional shortening of the ventricular returning cycle after a late extrasystole on the electrocardiogram (28 [Fig. 70]) is also consistent with the present study. The same can be said for unaltered returning cycles or for lengthened ventricular returning cycles after early extrasystoles.

These exceptions serve as a useful reminder that surface records of electrical activity are not a faithful reflection of the electrical events within the His-Purkinje system. This is so in a single, linear strand of Purkinje fibers such as those used in a tissue bath in vitro. The situation is even more complex in the His-Purkinje system in the heart in situ, where multiple sites of automaticity and local conduction blocks are possible. The additional demonstration that spontaneous variation of idioventricular rate can actually be due to blocked extrasystoles (Fig. 9A and B) and that interpolation of extrasystoles (Fig. 9C-F) is not synonymous with failure of the extrasystole to depolarize the pacemaker site as theorized by others (16, 28 [p 93]) emphasize the limitations of surface records. Since the electrocardiogram fails to reveal the disturbances induced by extrasystoles in the transmembrane potential of Purkinje cells, care must be exercised in the determination of events in the His-Purkinje system from the electrocardiogram. Although it is tempting to infer from an electrocardiogram that an extrasystole has or has not discharged the pacemaker site and to speak of inhibition or excitation of pacemaker cells by extrasystoles, it must be kept in mind that many variables operate to modify the Purkinje-ventricular responses to extrasystoles.

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EXTRASYSTOLES AND IDIOVENTRICULAR RHYTHM


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