Re-entrant Ventricular Arrhythmias in the Late Myocardial Infarction Period

2. Patterns of Initiation and Termination of Re-entry

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SUMMARY The electrophysiologic mechanisms for the initiation and termination of re-entrant ventricular arrhythmias (RVA) were critically analyzed in dogs 3–7 days following ligation of the anterior descending coronary artery, utilizing direct recordings of the re-entrant pathway (RP) from the epicardial surface of the infarction zone. Re-entry could occur during a regular cardiac rhythm if the heart rate is within the narrow critical range during which conduction in a potentially RP exhibits a Wenckebach-like (W) pattern with a beat-to-beat increment of conduction delay until the activation wavefront is sufficiently delayed to re-excite normal myocardium. If a regular cardiac rhythm is associated with limited conduction delay in a potentially RP, premature beats within a critical range of coupling intervals could result in sufficient conduction delay to induce re-entry. Re-entrant ventricular arrhythmias may be unmasked on abrupt termination of a critical fast rate of cardiac pacing only if pacing was terminated during those beats of a W pattern associated with marked conduction delay in a RP. RVA could be ended by one or more properly timed premature beats that would pre-excite part of the RP. An electrophysiologic mechanism for R-on-T and its relationship to onset of ventricular fibrillation was shown, based on markedly delayed RP conduction of the beat prior to the one apparently coupled to the premature beat.

MOST EXPERIMENTAL MODELS OF VENTRICULAR RE-ENTRY had relatively simple designs.1-4 Clinical studies of ventricular re-entry depend on deductive analysis of clinical records. Even in those clinical studies in which the initiation and termination of ventricular arrhythmias were induced by premature beats with critical coupling intervals,4 re-entry was no more than a speculative etiology. Myocardial infarction represents a highly likely source of re-entrant ventricular arrhythmias. Although most studies of the early phase of ventricular arrhythmias that follow acute ligation of a major coronary artery in the dog have shown some of the basic prerequisites for re-entry in the form of desynchronized slow conduction in ischemic myocardium, they all fall short of actually documenting the presence of re-entry. This was due, we believe, to the highly dynamic situation following acute ligation of a major coronary artery with constantly changing electrophysiological properties in the ischemic zone. Thus, it is difficult to conduct systematic electrophysiologic studies of the possible reentrant mechanism under such dynamic conditions. In addition, the recording techniques usually failed to demonstrate the one unequivocal evidence for re-entry, viz: the presence of continuous electrical activity originating from the infarction zone that regularly and predictably bridge the diastolic interval between the re-entrant beat and the preceding impulses, as well as between consecutive re-entrant beats.17

We have recently shown that dogs, three to seven days following ligation of the left anterior descending artery, represent a remarkably stable model for re-entrant ventricular arrhythmias and one in which systematic elec-
physiologic and pharmacologic studies could be conducted.\textsuperscript{17} We also described recordings obtained from the epicardial surface of the infarction zone utilizing a specially designed composite electrode as well as multiple bipolar electrodes that consistently depicted the electrical activity of the entire re-entrant pathway. In part 1 of this study,\textsuperscript{17} we analyzed the conduction characteristics in the infarction zone which proved to be highly complex. In part 2 we will examine in detail the electrophysiologic mechanisms for the initiation and termination of re-entrant ventricular arrhythmias, as well as some of the pertinent characteristics of re-entry.

Material and Method

The results included in this study were obtained from 40 adult mongrel dogs that were studied three to seven days following ligation of the left anterior descending artery distal to the anterior septal branch. All dogs showed evidence of a transmural infarction that involved the subepicardial layer of muscle. In these dogs, recordings were obtained from the epicardial surface of the infarction zone (IZ) and the adjacent normal zone (NZ), utilizing a specially designed composite electrode as well as multiple close bipolar electrodes. Details of the surgical procedure and the recording techniques were described elsewhere.\textsuperscript{17} In addition to the electrograms, two or more standard electrocardiographic (ECG) leads were recorded, specifically, leads II and aVR. All records were obtained on a multichannel oscilloscopic photograph recorder (E for M, DR-8) at paper speeds of 25–200 mm/sec. Electrocardiograms were recorded with the preamplifier set for frequencies of 0.1–200 cycles/sec and bipolar electrograms were recorded with filter frequencies of either 40–200 cycles/sec or 12–200 cycles/sec. Measurements were accurate to within ±3 msec at a paper speed of 200 mm/sec.

Recordings were obtained during spontaneous sinus rhythm, vagal-induced cardiac slowing, and atrial, His bundle or ventricular pacing, with either gradual or abrupt increase of the heart rate. Details of the pacing procedures and procedures to slow the heart rate were described elsewhere.\textsuperscript{17} The single test stimulus method was utilized during sinus rhythm, atrial, or ventricular pacing. Extrastimuli of

![Figure 1](https://circ.ahajournals.org/doi/abs/10.1161/01.CIR.70.5.703)

**Figure 1.** Initiation of ventricular re-entrant tachycardia by rapid cardiac pacing (panel C) and following abrupt termination of cardiac pacing (panel E). Tracings from top to bottom include ECG, leads II, aVR, the His bundle electrogram, the composite infarction zone electrogram, and the normal zone electrogram. Panel A was obtained during sinus rhythm while panels B to E were recorded during His bundle pacing. The infarction zone composite electrogram (IZeg) illustrates the presence of a continuous series of multiple asynchronous spikes preceding the onset of the re-entrant arrhythmia as well as between consecutive re-entrant beats. Note that the spontaneous termination of the re-entrant tachycardia in panel E was associated with a change of the QRS configuration of the last beat as well as abrupt cessation of the multiple asynchronous spikes in the IZeg early in the diastolic interval following the last beat. Hbeg = His bundle electrogram; NZeg = normal zone electrogram; H = His bundle potential; PI = pacer impulse; F = fusion beat. In this and subsequent figures, the timelines are set at 1 sec intervals.
either atrial, His bundle or ventricular origin were applied at progressively shorter intervals until the stimulus failed to capture because of cardiac refractoriness. The range of R-R coupling intervals of the extrastimulus resulting in ventricular re-entry was carefully determined. During re-entrant ventricular tachycardias the single test stimulus was also applied at progressively shorter intervals until either the tachycardia was terminated or cardiac refractoriness was reached. If the tachycardia was not terminated by a single test stimulus, a series of two or more stimuli in close succession were tried at varying coupling intervals of the first stimulus as well as varying rates of stimulation. The onset and termination of ventricular arrhythmias were monitored in the ECG leads as well as the corresponding changes in the IZ and NZ electrograms. If ventricular fibrillation did occur, the experiment was terminated and defibrillation was not attempted.

**Results**

**Initiation of Re-entry by Shortening the Basic Cardiac Cycle Length**

We have shown in part 1 of this study that the spontaneous occurrence of re-entrant ventricular beats was due to the fact that an IZ pathway showed a Wenckebach-like conduction pattern at the basic sinus rate. In these experiments in which re-entrant ventricular beats were not present during spontaneous sinus rhythm, the arrhythmia could be initiated by one or more of three electrophysiologic procedures that consistently entailed shortening of the cardiac cycle. This is illustrated in figures 1 and 2 which were obtained from the same experiment and described below.

**Rapid Cardiac Pacing**

This could be obtained through atrial, His bundle, or ventricular pacing. At a critically fast heart rate that varied from one experiment to the other, one or more re-entrant ventricular beats would develop. These beats either shared with or totally replaced the regular paced beats in activation of the ventricles. The rate of the re-entrant arrhythmia was approximately equal to or only slightly faster than the critically fast pacing rate that induced the arrhythmia. This is illustrated in panels A, B, and C in figure 1. Panel A shows the recording during spontaneous sinus rhythm. The NZeg records a sharp multiphasic deflection with a duration approximately equal to the QRS complex in ECG leads. On the other hand, the IZeg records a relatively wider multiphasic deflection, the initial part of which corresponds to activation of relatively normal myocardium while the late terminal deflection represents the IZ potential. His bundle pacing and His bundle premature beats were utilized in this experiment since atrial pacing failed to produce the sufficiently short cardiac cycles necessary for initiation of ventricular re-entry because of A-V nodal refractoriness. Panel B illustrates His bundle pacing at a cycle length of 245 msec. Note absence of fractionation of the IZ potential at this cycle length. Panel C shows that on further shortening of the pacing cycle length to 175 msec marked fractionation of the IZ potential periodically developed, resulting in multiple asynchronous spikes that extended for the entire diastolic interval (the periodic appearance of multiple asynchronous spikes is more clearly illustrated in panels D and E of figure 1). A re-entrant ventricular tachycardia broke through regular His bundle pacing starting with a ventricular fusion beat (marked F). The rate of the tachycardia was almost equal to or only slightly faster than that of His bundle pacing. Continuous electrical activity was present preceding the onset of the tachycardia as well as between consecutive beats of the arrhythmia. The electrogram recorded from the NZ closely adjacent to the IZ failed to show this continuous electrical activity.

**Abrupt Termination of Rapid Cardiac Pacing**

We have shown in part 1 of this study that in experiments showing 1:1 conduction in the IZ during spontaneous sinus rhythm, there was a critical range of rapid heart rates during which conduction in the IZ changed to a Wenckebach-like pattern. During the Wenckebach-like conduction pattern, part or all of the IZ potential showed periodic fractionation into multiple asynchronous spikes that could extend for part or all of the diastolic interval. In these experiments, abrupt termination of cardiac pacing at rates associated with periodic fractionation of the IZ potential could lead to the occurrence of one or more re-entrant ventricular beats. It was observed that re-entry would only occur if and when rapid cardiac pacing was abruptly terminated during those beats of a Wenckebach-like cycle associated with prolonged fractionation of the IZ potential that extended beyond the T wave of the surface electrocardiogram. This is illustrated in panels D and E of figure 1. Note that rapid His bundle pacing at a cycle length of 175 msec was associated with the periodic occurrence of multiple asynchronous spikes in the IZeg that extended for part or all of the diastolic interval. In

![Figure 2](http://circ.ahajournals.org/DownloadedFrom)
panel D, the penultimate His bundle paced beat was followed by multiple asynchronous spikes that extended up to the next beat. However, the last His bundle paced beat revealed relatively fewer deflections in the early part of diastole and was not followed by re-entry. By contrast, the penultimate His bundle paced beat in panel E showed few deflections early in diastole while the last paced beat was associated with prolonged fractionation of the IZ potential that did result in a re-entrant ventricular tachycardia. Panel E also illustrates the spontaneous termination of the tachycardia that was associated with a change in the QRS configuration of the last beat. The continuous electrical activity depicted by the IZeg during the re-entrant ventricular tachycardia abruptly terminated early in diastole following the last beat of the tachycardia.

Premature Beats with a Critical Coupling Interval

One or more re-entrant ventricular beats could be initiated by a single premature beat with a critically short coupling interval. The premature beat could be induced by atrial, His bundle, or ventricular stimulation. This is illustrated in figure 2 obtained from the same experiment shown in figure 1. The figure illustrates two induced His bundle premature beats during spontaneous sinus rhythm. The first premature beat with a coupling interval of 205 msec resulted in a limited degree of fractionation of the IZ potential (the latter is marked by an arrow during a sinus beat). The multiple asynchronous spikes did not extend beyond the T wave of the surface electrocardiogram and did not result in re-entry. The second premature beat, on the other hand, had a shorter coupling interval of 190 msec and was followed by more prolonged fractionation of the IZ potential that initiated a re-entrant ventricular tachycardia. The rate of this tachycardia, its QRS configuration in ECG leads, and the pattern of the IZeg were different from the re-entrant tachycardia shown in figure 1.

Of the three different procedures for initiation of re-entrant ventricular beats continuous rapid cardiac pacing was least successful in initiating re-entrant ventricular beats and tachycardia but could result in partial re-entry manifested as a change in the NZeg or ventricular fusion beats in surface leads. On the other hand, abrupt termination of rapid cardiac pacing and in particular single properly timed premature beats could successfully initiate re-entrant ventricular arrhythmias. Figure 3 illustrates the electrophysiologic mechanism underlying this observation. Panels A and B in figure 3 were obtained from two different experiments. Panel A shows two periods of rapid atrial pacing made respectively of three and four consecutive short cycles.

**Figure 3.** Panels A and B were obtained from two different experiments. Panel A illustrates the initiation of ventricular re-entry following abrupt termination of rapid atrial pacing. Re-entry only occurred when rapid cardiac pacing was terminated during those beats of a Wenckebach-like cycle associated with prolonged fractionation of the IZ potential (the second part of the record). Panel B shows that ventricular re-entry occurred following a single atrial premature beat with a coupling interval of 215 msec while it failed to occur following abrupt termination of rapid atrial pacing at the same cycle length of 215 msec. This is explained by the fact that the last paced beat was associated with block of the IZ potential. The arrows in panels A and B point to the unfractined IZ potential during a sinus beat.
of 215 msec. Abrupt termination of atrial pacing was followed by a re-entrant ventricular beat after the second and not the first period of pacing. Critical analysis of the IZeg shows that the first short cycle resulted in fractionation of the IZ potential (marked by an arrow) into a series of multiple asynchronous spikes that extended for the entire diastolic interval and up to the next paced beat. The second short cycle resulted in complete block of the IZ potential which was again normally inscribed following the third short cycle. Thus the three consecutive cycles of the first period of rapid atrial pacing presented in fact a 3:2 Wenckebach-like conduction pattern in the IZ. Pacing was abruptly terminated after the opening beat of the next potential Wenckebach period during which conduction in the IZ was relatively better, as reflected by the delayed but unfractiated IZ potential. This beat was not followed by re-entry.

The second pacing period consisted of four consecutive short cycles. The first three cycles represented a 3:2 Wenckebach-like conduction pattern in the IZ. This was followed by a second potential 3:2 Wenckebach-like conduction cycle. However, pacing was abruptly terminated following the second beat of the cycle which was "predictably" associated with marked fractionation of the IZ potential. This resulted in a re-entrant ventricular beat. The coupling interval of the re-entrant beat which reflected the re-entrant pathway conduction time was 225 msec. This was 10 msec longer than the pacing cycle length of 215 msec. Thus during regular pacing at a cycle length of 215 msec concealed or manifest re-entry failed to occur in spite of the periodic fractionation of the IZ potential that extended for the entire diastolic interval. This could be explained by the fact that, at this short cycle, the very terminal part of the re-entrant pathway was regularly being pre-excited by the activation wavefront advancing from the NZ.

Figure 3, panel B, was obtained from another experiment and contrasts the effect of a single short cycle of 215 msec and a series of consecutive and equally short cycles. The single atrial premature beat resulted in prolonged fractionation of the IZ potential (marked by an arrow during a sinus beat) and was followed by a re-entrant ventricular beat. The coupling interval of the re-entrant beat which reflected the re-entrant pathway conduction time was 285 msec. By contrast, the last beat of cardiac pacing showed block of the IZ potential and was not followed by re-entry. However, the first beat of cardiac pacing also resulted in marked fractionation of the IZ potential. The configuration of the fractionated IZ potential of this beat was almost identical to the first half of the fractionated IZ potential that followed the single atrial premature beat. This suggests that both beats pursued an almost identical pathway in the IZ. However, during rapid atrial pacing, the second paced beat interrupted the fractionated IZ potential of the first beat and re-entry did not occur. The IZeg of this beat showed block of the IZ potential. If the first paced beat had continued unimpeded in the IZ, the terminal part of the fractionated IZ potential would have been inscribed for the first 30 msec of the diastolic interval of the second paced beat. The failure of this to occur strongly suggests that the second paced beat did in fact conduct in the IZ and pre-excited the terminal part of the potentially re-entrant pathway rather than being blocked at the boundary between the NZ and the IZ.

In all experiments in which re-entrant ventricular beats were initiated by a single premature impulse there was a narrow critical range of coupling (10–60 msec) during which a premature beat could induce re-entry. Premature beats with longer or shorter coupling intervals failed to initiate the arrhythmia. The electrophysiologic mechanism that underlies this observation is illustrated in figure 4 which was obtained from a different experiment. Figure 4, panels A to D, illustrates the effect of single atrial premature beats with variable coupling intervals applied during regular sinus rhythm. Two different recordings were obtained from the IZ. The IZeg (Comp.) represents a composite electrode recording while the IZeg (Bip.) depicts the recording obtained from a close bipolar electrode. Panel A shows that an atrial premature beat with a relatively long coupling interval of 255 msec resulted in a limited fractionation and delay of the IZ potential (marked by arrows). Shortening of the coupling interval by 15 msec in panel B resulted in a relatively more prolonged fractionation of the IZ potential which did not, however, extend beyond the T wave of the surface ECG. Further shortening of the coupling interval by 15 msec in panel C was associated with more marked fractionation and delay of the IZ potential. The series of multiple asynchronous spikes extended late in the diastolic interval beyond the T wave of the surface ECG initiating a re-entrant ventricular beat. Panel D shows that an atrial premature beat with a shorter coupling interval of 210 msec failed to conduct in the IZ pathway as revealed by failure of inscription of the IZ potential. Panels A to D show that atrial premature beats had no effect on the initial part of the ventricular deflection in both the IZ electrograms which reflected activation of relatively normal myocardium. This experiment illustrates that only premature beats with a coupling interval longer than 210 msec and shorter than 240 msec (a range of 30 msec) could initiate re-entry. Premature beats with 240 msec or longer resulted in a limited degree of delay of conduction in the IZ. This did not allow sufficient time for the NZ to recover excitability and to become re-excited by the delayed electrical activity in the IZ. On the other hand, premature beats with a coupling interval of 210 msec or shorter that succeeded in capturing the NZ failed to conduct in the IZ pathway, which had a relatively longer refractory period. These beats also failed to induce re-entry.

Although the critical range of coupling intervals of a premature beat that would result in re-entry may differ slightly according to the basic cardiac cycle length, in a majority of the experiments it was found to be comparable to the range of cardiac cycles at which Wenckebach-like conduction and re-entry may occur. This is illustrated in figure 5 which was taken from the same experiment shown in figure 3, panel A. Figure 5, panels A to D, illustrate the effect of four atrial premature beats with variable coupling intervals applied during regular sinus rhythm on conduction in the IZ. Premature beats with relatively long coupling (panels A and B) showed a limited degree of fractionation and delay of the IZ potential (marked by an arrow during a sinus beat). Figure 4 showed a similar pattern. The premature beat with the shortest coupling (panel D) showed block of the IZ potential. These premature beats failed to induce re-entry. On the other hand, the premature beat with an intermediate coupling interval of 220 msec (panel C) was associated with sufficient
Figure 4. Recordings obtained from a different experiment illustrating the initiation of ventricular re-entry by a premature atrial beat with a critical coupling interval that was associated with prolonged fractionation and delay of the IZ potential (panel C) (marked by arrows). Premature beats with longer coupling intervals were associated with a lesser degree of fractionation and delay of the IZ potential and were not followed by re-entry (panels A and B). The premature beat with a shorter coupling interval resulted in block of the IZ potential and also failed to induce re-entry (panel D). The IZeg (Comp.) and the IZeg (Bip.) represent a composite and a bipolar electrode recordings from the infarction zone, respectively.

Figure 5. Recordings obtained from the same experiment shown in figure 3, panel A, illustrating the initiation of a re-entrant ventricular tachycardia by a premature atrial beat with a critical coupling interval that was associated with prolonged fractionation and delay of the IZ potential (panel C). Premature beats with both longer and shorter coupling intervals were associated respectively with a lesser degree of fractionation of the IZ potential (panels A and B) and complete block of the potential (panel D) and were not followed by re-entry. Note that the critical coupling interval of the premature beat that resulted in re-entry was comparable to the cardiac cycle associated with a Wenckebach-like conduction pattern of the IZ potential as shown in figure 3, panel A.
fractionation and delay of the IZ potential to result in a re-entrant ventricular tachycardia. This critical coupling interval was comparable to the critical cycle length associated with a Wenckebach-like conduction pattern in figure 3, panel A, of 215 msec.

Figure 6 obtained from the same experiment shown in figure 3A and figure 5 compares the effect of both atrial and ventricular premature beats with variable coupling in inducing ventricular re-entry. The IZeg in panels A to C were recorded with the filter frequencies set at 40–200 cycles/sec, the same as in figure 5, while the IZeg in panel D had a filter frequency of 12–200 cycles/sec, the same as in figure 3A. Figure 6, panel A, illustrates recordings obtained during relatively slow right ventricular pacing at a cycle length of 430 msec. The IZeg shows a relatively sharp multiphasic deflection with the IZ potential not clearly separated from the rest of the ventricular deflection compared to the IZeg during sinus rhythm shown in figure 5. Panel B shows that at a faster pacing cycle of 240 msec periodic fractionation of the IZ potential developed reflecting 3:2 Wenckebach-like conduction patterns in the IZ. This occasionally resulted in partial re-entry as revealed by change in configuration of the NZeg (marked by an arrow) and a slight narrowing of the QRS configuration of the paced ventricular beat reflecting a limited degree of ventricular fusion (marked F). In panel C, abrupt termination of ventricular pacing following the second beat of a 3:2 Wenckebach-like conduction pattern in the IZ was associated with prolonged fractionation of the IZ potential resulting in a single re-entrant ventricular beat (marked X). In panel D the ventricular pacing rate was adjusted to slightly higher than half the sinus rate so that a paced impulse followed each conducted sinus beat in a bigeminal pattern with gradual shortening of the coupling interval. The record shows that ventricular premature beats with shorter coupling resulted in more fractionation and delay of the IZ potential. The premature beat with a coupling interval of 215 msec gave rise to sufficient fractionation and delay of the IZ potential to result in a re-entrant ventricular beat (marked X). Figure 5 and figure 6, panel D, illustrate that both atrial and ventricular premature beats can induce a re-entrant ventricular arrhythmia at a similar critical range of R-R coupling intervals. Figure 6 also illustrates the occurrence of ventricular re-entry during continuous rapid ventricular pacing (panel B) and following abrupt termination of rapid ventricular pacing (panel C).

**Initiation of Re-entry by Lengthening of the Basic Cardiac Cycle Length**

Figures 1–6 illustrate experiments in which an IZ pathway showed a 1:1 conduction pattern during the basic sinus rhythm. A shorter cardiac cycle length was always necessary to initiate re-entry. We have also analyzed other experiments in which re-entry was absent during the basic sinus rate (usually a sinus tachycardia of 120–175 beats/min in the anesthetized dog) and the arrhythmia could be induced only on critical slowing of the spontaneous heart rate to relatively bradycardic rates of 80–140 beats/min. On further slowing of the heart rate in those experiments the arrhythmia disappeared. The basic electrophysiologic mechanism for these observations is shown in figures 7 and 8 which were obtained from the same experiment. Figure 7, panel A, shows that
during spontaneous sinus rhythm at a rate of 171 beats/min (the first part of the record) there was no evidence of ventricular re-entry. However, on gradual slowing of the heart rate, a re-entrant ventricular rhythm occurred at a critical cardiac cycle of 450-460 msec (heart rate of 130-133 beats/min) (the last part of the record). The IZeg revealed a fractionated and delayed IZ potential in alternate beats during regular sinus rhythm (marked by arrows). During the relatively slow heart rate in the second part of the record, the IZ potential showed a 1:1 conduction pattern with a beat-to-beat increment of the fractionation and delay of the potential (marked by arrows). Following the last sinus beat, the fractionated IZ potential extended late in diastole and up to the re-entrant ventricular beat. The coupling interval of the re-entrant beat which reflects the re-entrant pathway conduction time was 365 msec, a value slightly longer than the basic sinus cycle length of 350 msec. This would explain why the delayed IZ potential following alternate sinus beats in a 2:1 conduction pattern failed to result in re-entry.

Figure 7, panel B, shows that when the basic heart rate was kept constant at a rate of 133-136 beats/min (cycle length of 445-450 sec) there was periodic occurrence of the re-entrant ventricular rhythm. The latter consistently started by a premature beat and continued for one or more beats before spontaneous termination and had a rate which was only slightly faster than the basic rate of 136 beats/min. The IZeg illustrates that the periodic appearance of the re-entrant ventricular rhythm was clearly related to a Wenckebach-like conduction pattern of the IZ potential (marked by arrows) which was not dissimilar to that shown in figure 7, panel A. The regular quadrigeminal rhythm shown in figure 7, panel B, was explained by a regular repetition of a 4:3 Wenckebach-like conduction pattern of the IZ potential at a constant cardiac cycle of 445-450 msec.

Figure 8 clearly shows that the re-entrant ventricular rhythm shown in figure 7 on critical slowing of the heart rate was in fact due to a tachycardia-dependent Wenckebach-like conduction pattern in an IZ pathway. Figure 8, panel A, illustrates the presence of an underlying slow automatic rhythm during vagal-induced sinus bradycardia and A-V block. Figure 8, panel B, shows that during a slow sinus rhythm of 91 beats/min, the IZ potential is regularly inscribed following every sinus beat in a 1:1 conduction pattern and has a relatively more synchronized configuration (marked by arrows). Figure 8, panel C, illustrates that on gradual acceleration of the heart rate, the re-entrant ventricular rhythm occurred following a critical cardiac cycle of 445 msec. The IZ potential showed a beat-to-beat increased fractionation and delay prior to the onset of the arrhythmia in a pattern which was remarkably similar to the one shown in figure 7, panel A, on gradual slowing of the heart rate. The IZeg also showed the presence of continuous electrical activity that bridged the diastolic interval between consecutive re-entrant beats.

The experiment shown in figures 7 and 8 also illustrates that re-entrant ventricular rhythms may be relatively slow
(90–140 beats/min), a rate which was usually slower than the spontaneous sinus rate in the anesthetized dog. These ventricular rhythms may only appear on vagally-induced slowing of the sinus rate and disappear on return to the spontaneous rate. They may also start by a very late coupled or even a fusion beat with the coupling interval being sometimes approximately equal to the ectopic cycle length. These characteristics may closely simulate those ascribed to automatic rhythms.

**Termination of Re-entrant Ventricular Tachycardias**

**Spontaneous Termination**

Three different patterns for spontaneous termination of re-entrant ventricular tachycardias were observed. These are 1) spontaneous termination with no detectable change in the ectopic cycle length; 2) slight or significant lengthening of the last one or few cycles of the tachycardia sometimes to almost double the preceding cycles (This observation will be illustrated in a subsequent figure); 3) spontaneous change in the re-entrant pathway for the last one or few cycles before termination (This manifested as a change in the QRS configuration in the surface ECG as well as in the configuration of the fractionated IZ potential in the IZ electrograms [fig. 1E]). In all instances of spontaneous termination of re-entrant ventricular tachycardia, the multiple asynchronous spikes that bridged the entire diastolic interval between consecutive re-entrant beats came to an abrupt termination early in the diastolic interval that followed the last beat of the tachycardia.

**Induced Termination**

Re-entrant ventricular tachycardias could be terminated by either a single properly timed premature beat applied to the atria, His bundle or the ventricles, or by a series of two or more premature beats in close succession. Usually tachycardias with relatively slower rates (cycle length of 225–300 msec) could be terminated by a single premature beat. On the other hand, tachycardias with relatively fast rates (cycle length of 170–220 msec) usually required a short run (three or more beats) of rapid cardiac pacing at a rate equal or only slightly faster than the spontaneous rate of the tachycardia.

Figure 9 illustrates the effect of single premature beats of variable coupling applied during a re-entrant ventricular tachycardia. The cycle length of the tachycardia was remarkably constant at 225 msec. Panel A shows that an induced His bundle premature beat with a coupling interval of 210 msec succeeded in completely capturing the NZ but failed to change the regular sequence of the tachycardia since the following cardiac cycle was fully compensatory. This suggests that the premature beat did not engage any part of the regular re-entrant circuit. In panel B a more premature His bundle ectopic beat resulted in a change of the re-entrant pathway as revealed by change in configuration of the QRS complexes in the surface ECG as well as in the configuration of the IZeg. The cardiac cycle following the premature beat

**Figure 8.** Recordings obtained from the same experiment illustrated in figure 7 showing that the re-entrant ventricular rhythm was due to a tachycardia-dependent Wenckebach-like conduction pattern in an IZ pathway. The figure shows that a gradual increase of the heart rate from a cycle length of 660 msec to 445 msec was associated with a change of the IZ potential from a regular 1:1 pattern with a relatively synchronized configuration (panel B) to a beat-to-beat increased fractionation and delay of the potential prior to the onset of the re-entrant arrhythmia (panel C). Panel A reveals an underlying slow automatic rhythm during vagal-induced A-V block.
was less than compensatory. This suggests that the premature beat did in fact activate part of the original re-entrant circuit and forced the re-entrant wavefront to change its pathway. The new re-entrant ventricular tachycardia was, however, self limited and lasted for only three beats. It also showed lengthening of the last cycle prior to spontaneous termination.

Panel C shows that the tachycardia could be terminated by a slightly more premature His bundle beat. The IZeg of this beat showed failure of inscription of a part of the IZ potential (marked by an arrow during a sinus beat). There was also no evidence of the multiple asynchronous spikes that occupied the diastolic interval between consecutive re-entrant beats. It is suggested that the premature beat advancing from the NZ activated a relatively large part of the re-entrant pathway (evidence for this activation could not be detected by analysis of the IZeg) and collided in the IZ with the re-entrant wavefront. In contrast to the situation in panel B, the re-entrant wavefront failed to find an excitable alternate pathway and re-entry was abruptly terminated.

Figure 10 illustrates the termination of a re-entrant ventricular tachycardia by a series of premature beats in close succession. The first three beats in figure 10, panel A, are parts of a fast re-entrant ventricular tachycardia with a cycle length of 180 msec. Note evidence of continuous electrical activity between consecutive re-entrant beats in the form of multiple asynchronous spikes bridging the diastolic intervals in the IZeg. The next four beats represent a short run of His bundle pacing at a rate slightly faster than the spontaneous rate of the tachycardia. The paced beats completely captured the NZ as evidenced by the supraventricular QRS configuration in the surface ECG. The IZeg shows, however, that the paced beats conducted in the IZ with marked fractionation of the IZ potential, resulting in multiple asynchronous spikes that extended for the entire diastolic interval between consecutive paced beat as well as late in the diastolic interval that followed the last paced beat. This would explain the fact that re-entry still followed the abrupt termination of His bundle pacing though it was self limited. As an alternative explanation of the observation in panel A it could be assumed that the four paced beats completely captured the NZ but failed to engage the re-entrant pathway in the IZ. The continuous re-entrant circuit in the IZ remained undisturbed but was unable to re-excite the NZ because of prior activation by the paced impulse. On termination of pacing, the re-entrant activation front was able to excite the NZ, resulting in manifest re-entrant beats. Alteration of the conduction characteristics of some part of the re-entrant pathway presumably resulted in self termination of re-entry.

Figure 10, panel B, illustrates a successful trial to terminate the tachycardia by a short run of His bundle pacing. The recording in panel B was obtained 5 min after a bolus in-

![Figure 9](http://circ.ahajournals.org/) Recordings showing termination of re-entrant ventricular tachycardia by an induced His bundle premature beat (PI) with a critical coupling interval of 180 msec (panel C). Premature beats with longer coupling intervals either failed to interrupt the re-entrant pathway (panel A) or forced a change in the re-entrant pathway (panel B).
jection, of 2 mg/kg of lidocaine. Lidocaine resulted in gradual slowing of the rate of ventricular tachycardia (from a cycle length of 180 msec in panel A to 230 msec in panel B). There was also evidence of further fractionation and delay of the IZ potential as suggested by the decrease in amplitude and increase in number of the multiple asynchronous spikes that bridged the diastolic interval between consecutive re-entrant beats; there was only a slight change in the gain of the IZeg in panels A and B. Figure 10, panel B, shows that the first pacer spike failed to capture the ventricles while the second spike partially captured the NZ resulting in a ventricular fusion beat (marked F). This beat still revealed fractionation of the IZ potential. The third pacer spike, however, completely captured the NZ, resulting in a supraventricular QRS configuration in the surface ECG. This beat was not followed by a fractionated IZ potential. Instead, there was a single relatively sharp deflection inscribed midway in diastole. The next paced beat showed the same deflection with a larger amplitude and a shorter duration inscribed further on in diastole. In the last paced beat the deflection failed to be inscribed. Abrupt termination of pacing at this point was followed by resumption of sinus rhythm. The IZeg recording suggests that two of the last three paced beats may have activated the IZ in a relatively more synchronized fashion compared to activation during re-entry. The behavior of the single IZ deflection suggests a Wenckebach-like conduction pattern in part of the IZ. Termination of pacing immediately following the beat associated with conduction block in the Wenckebach-like cycle ended re-entry.

Re-entry versus Automaticity

In the experimental model used in this study enhanced automaticity that follows ligation of the anterior descending artery has completely subsided in almost all cases. In some dogs studied in the third or fourth postinfarction day evidence of automatic activity probably arising from the IZ could still be detected firing at much slower rates compared to 24–48 hours after the infarction. Some of these automatic rhythms had remarkably similar QRS configuration in surface ECG to re-entrant ventricular beats arising from the IZ. This is shown in figure 8 where the slow automatic rhythm unmasked by vagal-induced sinus arrest had a similar configuration to the re-entrant ventricular beats.

The IZeg can help to differentiate automatic from re-entrant beats having the same QRS configuration in surface ECG. In automatic beats, the IZeg never showed the multiple asynchronous spikes of the fractionated IZ potential that immediately preceded the ventricular deflection of a re-entrant beat reflecting electrical activity closer to the “exit” of the re-entrant wavefront (see fig. 8). However, multiple asynchronous spikes could immediately follow the ventricular deflection of an automatic beat in the same way it might follow the ventricular deflection of a conducted supraventricular beat or a paced ventricular beat having the same cycle length as the automatic beat. This would reflect conduction delay of the automatic beat in the IZ with fractionation of the IZ potential. This point is illustrated in figure 11 which was obtained from a different experiment.

Figure 11, panel A, shows a re-entrant ventricular tachycardia induced by abrupt termination of rapid atrial pacing. The IZeg reveals multiple asynchronous spikes in the last part of the diastolic interval and immediately preceding the ventricular deflection of the re-entrant beat (marked by arrows). This reflects electrical activity closer to the “exit” of the re-entrant pathway. The spontaneous termination of the re-entrant tachycardia was associated with abrupt lengthen-

**FIGURE 10.** Recordings showing termination of re-entrant ventricular tachycardia by a series of premature beats in close succession. Panel A shows that a series of induced His bundle premature beats (PI) failed to interrupt the re-entrant tachycardia, which, however, spontaneously terminated two beats later. The paced beats were associated with a fractionated IZ potential that continued after the last paced beat. On the other hand, panel B shows successful termination of the re-entrant tachycardia following a short period of His bundle pacing. The paced beats resulted in a Wenckebach-like conduction pattern in the IZ (marked by arrows). Termination of pacing following the beat associated with conduction block in the Wenckebach-like cycle resulted in termination of re-entry. Panel B was obtained a few minutes after a lidocaine bolus. F = fusion beat.
ing of the last tachycardic cycle to slightly less than double the preceding cycles. The last beat was also immediately preceded by the multiple asynchronous spikes characteristic of re-entry. The major ventricular deflection of the following two sinus beats was followed by a limited fractionation of the IZ potential reflecting conduction delay in the IZ during regular sinus rhythm. Vagal-induced sinus arrest in this experiment showed the presence of an automatic rhythm with a cycle length of 750 msec that had the same QRS configuration as the re-entrant ventricular tachycardia. Injection of 2 μg/kg adrenaline bolus resulted in a gradual increase of the rate of the automatic focus to a cycle length to 335-345 msec. The response to adrenaline supported the contention that the arrhythmia was automatic.

Figure 11, panel B, shows that the enhanced automatic rhythm started with two ventricular fusion beats (marked F). The IZeg reveals that the onset of the ventricular deflection of automatic beats was simultaneous with the onset of the QRS deflection in the surface ECG and was characteristically not preceded by the multiple asynchronous spikes that preceded the re-entrant beats in panel A. The major ventricular deflection of the automatic beat was, however, followed by a limited fractionation of the IZ potential similar but not identical to the conducted sinus beats with essentially the same cycle length. It should be stressed that the cycle length of the automatic rhythm in panel B was shorter than the last cycle of the re-entrant ventricular tachycardia in panel A. Our observations suggest that in this setting analysis of the IZeg can offer the best available means for differentiating automatic versus re-entrant rhythms that may have the same QRS configuration in surface ECG. In the absence of evidence of continuous electrical activity preceding the re-entrant beat, another indication of re-entry, is the illustration of electrical activity closer to the “exit” of the re-entrant pathway in the form of multiple asynchronous spikes that immediately precede the major ventricular deflection of the re-entrant beat. However, since the IZeg may in some cases fail to depict the “exit” of the re-entrant pathway, the absence of this finding does not prove or disprove an automatic etiology.

Re-entrant Beats with Short Coupling and the Relationship of the R-on-T Phenomenon to the Onset of Ventricular Fibrillation

In this study it was observed that the majority (85%) of spontaneous or induced re-entrant ventricular beats had relatively long coupling intervals (R-R/Q-T > 1). This finding was not unexpected in view of the mechanism of re-entry that entailed marked conduction delay in the IZ. Fewer re-entrant beats showed relatively short coupling and some of these were examples of the R-T phenomenon (R-R/Q-T < 1). In some experiments there was strong evidence to suggest that the early coupled re-entrant beat was in fact related to markedly delayed conduction in the IZ of the beat that immediately preceded the one to which the re-entrant

**Figure 11.** Recordings obtained from a different experiment illustrating the value of the IZeg in differentiating re-entrant and automatic ventricular rhythms having the same QRS configuration in ECG leads. Panel A shows a re-entrant ventricular tachycardia induced by abrupt termination of rapid atrial pacing. The re-entrant beats are characteristically preceded by a fractionated IZ potential reflecting electrical activity closer to the “exit” of the re-entrant pathway. Note marked lengthening of the last re-entrant cycle with the fractionated IZ potential still immediately preceding the last re-entrant beat. Panel B illustrates an accelerated idioventricular rhythm induced by adrenaline injection having the same QRS configuration as the re-entrant rhythm in panel A. The automatic beats fail to show a fractionated IZ potential immediately preceding the ventricular deflection. F = fusion beats.
beat was apparently coupled. This is illustrated in figures 12 and 13, which were obtained from the same experiment.

Figure 12, panel A, shows two sinus beats followed by a period of rapid atrial pacing (PI), the abrupt termination of which was followed by a late coupled re-entrant ventricular beat. The IZeg of the sinus beats showed limited fractionation of the IZ potential. During atrial pacing there was 2:1 inscription of the fractionated IZ potential. A superficial analysis of the record may suggest that the first paced beat blocked in the IZ, ushering in the 2:1 conduction ratio. However, on abrupt termination of atrial pacing, the fractionated IZ potential was inscribed very late in diastole and was followed by a late coupled re-entrant beat. The last fractionated IZ potential was obviously related to conduction in the IZ of the last paced beat, and was inscribed, as expected, from a regular 2:1 ratio, 400 msec from the preceding IZ potential (the pacing cycle was 200 msec). This strongly suggests a pattern of conduction in the IZ during atrial pacing as shown in the schematic diagram with the IZ potential related to delayed conduction not of the beat that immediately preceded the potential but of the one prior to it.

The first part of figure 12, panel B, shows the termination of a period of atrial pacing with the IZ potential inscribed very late in diastole. However, it did not result in re-entry because it was anticipated by conduction of the following sinus beat. This also explains failure of this sinus beat to conduct in the IZ as shown by absence of its IZ potential. The second part of figure 12, panel B, shows another period of atrial pacing. In contrast to panel A, the different IZ potentials were irregularly spaced in spite of the regular pacing cycles. Also some of the IZ potentials (marked by arrows) were actually superimposed on the major ventricular deflection instead of regularly following it. This means that the IZ potential cannot be due to conduction of the beat on which it is superimposed but rather to the beat preceding it. The bottom diagram suggests that conduction in the IZ was in the form of alternating 3:2 Wenckebach-like pattern and 2:1 block. As mentioned elsewhere, this conduction sequence was not uncommonly seen in this study. The last four paced beat showed regular 2:1 block as in panel A. In contrast to panel A, however, pacing was abruptly terminated following the beat that blocked in the IZ. Still, however, the fractionated IZ potential related to delayed conduction of the penultimate paced beat succeeded in re-exciting the NZ, giving rise to a re-entrant ventricular beat. This beat was obviously shortly coupled when related in the surface ECG to the last paced beat.

Figure 13, panel A, illustrates the effect of a single atrial premature beat with a coupling interval of 200 msec (similar to the pacing cycle length in figure 12) on conduction in the

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**Figure 12.** Recordings obtained from a different experiment illustrating a mechanism for ventricular re-entrant beats with short coupling. Panels A and B show two re-entrant ventricular beats following abrupt termination of rapid atrial pacing. The re-entrant beat in panel A has a long coupling interval while the one in panel B has a short coupling. The diagrammatic analysis of conduction in the IZ at the bottom of the records suggest that the re-entrant beat with short coupling was in fact related to delayed conduction in the IZ of the beat prior to the one to which it was apparently coupled. V = ventricles; IZ = infarction zone.
IZ which lends direct support to the diagrammatic analysis of the arrhythmia in figure 12. The record illustrates that a premature beat (PI) with a coupling interval of 300 msec had the same conduction pattern in the IZ as the sinus beat. The premature beat with a coupling interval of 200 msec showed markedly delayed inscription of the IZ potential which failed to induce re-entry, because of the anticipated activation of the NZ by the following sinus beat. This was similar to the pattern shown in the first part of figure 12, panel B. This sinus beat also failed to conduct in the IZ.

Figure 13, panel B, illustrates the initiation of ventricular fibrillation by two closely coupled atrial premature beats. The first atrial premature beat showed slight aberration of the QRS configuration while the second beat revealed an intraventricular conduction defect of the right bundle block pattern associated with prolongation of the H-V interval. This beat was immediately followed by a spontaneous ventricular beat (marked X) which was inscribed on the ascending limb of the T wave of the second paced beat, representing a marked example of the so-called R-on-T phenomenon. This was followed by very rapid and disorganized ventricular activity leading to ventricular fibrillation. Critical analysis of the IZeg shows that the delayed fractionated IZ potential related to the first paced beat was inscribed after the major ventricular deflection of the second paced beat (marked by an arrow). This potential was the only source for re-entry that can explain the beat marked X, a situation not unlike the one shown in the last part of figure 12, panel B. However, in this instance the re-entrant ventricular beat which was very shortly coupled to the preceding beat apparently set forth the disorganized electrical activity in the ventricle leading to fibrillation.

In summary, this experiment illustrates that re-entrant ventricular beats with short coupling showing the R-on-T phenomenon may be due to delayed conduction in the IZ of the penultimate and not the last conducted beat and that this arrangement can sometimes set the stage for ventricular fibrillation.

Discussion

Initiation and Termination of Re-entry

In parts 1st and 2 of this study, we have described in detail the electrophysiologic mechanisms for the initiation and termination of re-entry. Re-entry can occur either during regular cardiac rhythm or following a premature beat that interrupts an otherwise regular cardiac rhythm. For re-entry to occur during regular cardiac rhythm, the heart rate should be within the relatively narrow critical range of rates during which conduction in a potentially re-entrant pathway shows a Wenckebach-like pattern. During a Wenckebach-like conduction cycle, a beat-to-beat increment in conduction delay will occur until the activation wavefront is sufficiently delayed for certain parts of the myocardium to recover excitability and become re-excited by the delayed electrical activity. If the heart rate is relatively slower, the pathway will show a 1:1 conduction pattern with significantly less conduction delay than is necessary for re-entry to occur. On the other hand, if the heart rate is relatively faster, a Wenckebach-like conduction sequence will change to a 2:1 conduction pattern.

Some potentially re-entrant pathways will show lesser conduction delay during the conducted beat of a 2:1 pattern compared to the conduction delay during a Wenckebach-like sequence which would also negate the chance for re-entry. However, other potentially re-entrant pathways may still show significant conduction delay during a 2:1 conduction pattern (see fig. 7A). This may or may not result in a re-entrant beat regularly following every sinus impulse in a bigeminal pattern, depending on the relationship between the re-entrant pathway conduction time (reflected by the coupling interval of the re-entrant beat) and the basic cardiac cy-

![Figure 13](https://circ.ahajournals.org/content/71/1/711024164v1/suppl/doi:10.1161/hc0116.1024164v1/1221217569155)
cyle length. A shorter basic cardiac cycle length would result in concealment of re-entry due to the anticipated pre-excitation of the terminal part of the re-entrant pathway (the first part of fig. 7A). On the other hand, if the heart rate is so adjusted as to result in regular repetition of a Wenckebach-like conduction sequence, this may give rise to regular extrasystolic grouping (e.g., trigeminal and quadrigeminal arrangements for a 3:2 and 4:3 Wenckebach-like cycles respectively) (fig. 7B). The pathophysiology of re-entrant bigeminal rhythms and extrasystolic grouping will be discussed in more detail in a separate report.

This study has shown that conduction characteristics of different, potentially re-entrant pathways may vary widely in their relationship to the heart rate. This means that some potentially re-entrant pathways may show the Wenckebach-like conduction pattern associated with re-entry only during a relatively slow, sometimes bradycardic heart rate. During “normal” heart rate those pathways may reveal a 2:1 or higher degree of conduction block and no re-entry. Other potentially re-entrant pathways will conduct in a Wenckebach-like pattern only during relatively fast heart rates while during “normal” rates they reveal a 1:1 conduction that will not result in re-entry. Still, in a third group of experiments, a Wenckebach-like conduction pattern in a potentially re-entrant pathway would take place during “normal” sinus rhythm. In these cases, spontaneous re-entrant arrhythmias would recur periodically in a regular or irregular fashion depending, among other things, on slight alterations in the sinus rate.

Re-entry can manifest as a “premature” ectopic beat or a fusion beat or can be concealed and only detected by changes in the electrograms recorded from parts of the myocardium closely bordering the re-entrant pathway without a change in the surface ECG. This is principally governed by a simple relationship between the re-entrant pathway conduction time and the basic cardiac cycle length. This explains why it is more common to see fusion beats or concealed re-entry in those cases where the heart rate critical for a Wenckebach-like conduction pattern in a potentially re-entrant pathway is relatively fast (see figure 2 in part 19). In these cases, the re-entrant pathway conduction time may be about equal to the basic cardiac cycle. If the potentially re-entrant pathway conduction time is longer than the basic cardiac cycle, the pathway may show regular repetition of a Wenckebach-like conduction sequence with the conduction delay periodically extending for the entire diastolic interval, but with no evidence of re-entry. In these cases, it is assumed that the conducted cardiac impulse may regularly pre-excite the terminal part of a potentially re-entrant pathway. Re-entry can only become manifest in these circumstances if the fast heart rate is abruptly terminated following the beat of a Wenckebach-like cycle associated with the greatest conduction delay.

A potentially re-entrant pathway will show a Wenckebach-like conduction pattern and re-entry at a critical regular heart rate and 1:1 conduction with lesser delay at a slower rate. If, during the relatively slow regular rate, a premature beat is introduced within a critical range of coupling intervals it can result in sufficient conduction delay to provoke re-entry. A longer coupling interval fails to initiate re-entry, while a shorter coupling interval will induce conduction block in the potentially re-entrant pathway, again negating the chance for re-entry. The critical range of coupling intervals of a premature beat that would result in re-entry is usually comparable to the range of cardiac cycles of the regular heart rate at which a Wenckebach-like conduction pattern and re-entry may occur (figs. 3A and 5). However, as explained above, a premature beat with a critical coupling interval will result in re-entry while a regular cardiac rhythm at a comparable cycle length may fail if the re-entrant pathway conduction time is longer than the basic cardiac cycle length (see fig. 3).

Spontaneous termination of a re-entrant ventricular rhythm may be associated with a change in the QRS configuration and/or the configuration of the fractionated IZ potential of the last one or few beats. This would suggest conduction block somewhere along the original re-entrant pathway, with the re-entrant wavefront engaging an alternate pathway that is unable to sustain continuous re-entry. Lengthening of the last one or few cycles of a re-entrant rhythm suggests a conduction delay along the re-entrant pathway, or a conduction block with the re-entrant wavefront making a minor or major detour from the original pathway. In some re-entrant rhythms, the last one or few cycles were almost double the original cycle length (fig. 11A). This may suggest that the re-entrant impulse can regularly sweep around the re-entrant pathway but is only capable of re-exciting the NZ during alternate sweeps due to the presence of a 2:1 conduction block in a final common pathway close to the exit to the NZ. This pattern simulates a 2:1 exit block from an automatic focus. Abrupt termination of a re-entrant rhythm without a noticeable change in the ectopic cycle length or the configuration of the fractionated IZ potential would suggest that conduction along one part of the re-entrant pathway came to a sudden halt. Recent studies on conduction of the cardiac impulse have shown that intermittent failure of conduction is almost always preceded by some increment of conduction delay that may be in the magnitude of one or a few msec (the so-called Mobitz type II block)49. It is reasonable to assume that a second degree block with a few msec increment of conduction delay develops in part of the re-entrant pathway in those instances in which a re-entrant ventricular rhythm abruptly terminates.

Re-entrant ventricular rhythms may be successfully terminated by one or more properly timed premature beats. The success of a single premature beat decreases the faster the rate of the re-entrant rhythm which would mean that components of the re-entrant pathway recover excitability in a shorter time span between the head of one re-entrant sweep and the tail of the next sweep. This decreases the chance of a single premature beat engaging part of the re-entrant pathway that momentarily recovers excitability. This also explains why one or more of a series of premature beats in close succession has a better chance to pre-excite part of the re-entrant pathway, especially if the rate of the paced rhythm is faster than the ectopic rate. A faster paced rhythm will more likely succeed in capturing the NZ and invading the re-entrant pathway than a slower rhythm. If a single premature beat successfully engages part of the re-entrant pathway, it may result in abrupt termination of re-entry if an alternative pathway is not available or it may force a change in the re-entrant pathway to one which may not sustain re-entry.
Our observations on the initiation and termination of re-entrant arrhythmias both confirm and extend previous experience. Review of the literature reveals that for many years authors have utilized electrocardiographic, experimental, and microelectrode techniques to show that premature beats or rapid heart rates can initiate or terminate cardiac arrhythmias and some have strongly suggested re-entry as the underlying mechanism. As early as 1889, Loven showed that a single stimulus applied to the ventricles of a frog early in diastole, at a time he called the "critical period" of the heart, leads to a series of responses rather than one response. Mines, De Boer, and Wiggers and Wegria showed that an electrical stimulus applied at a certain critical instant immediately after the conclusion of the absolute refractory period during what Wiggers and Wegria called the "vulnerable phase" of the ventricles can result in repetitive response and/or fibrillation. For many years a certain cardiac arrhythmia, namely, the return extrasystole was considered the result of re-entry in the A-V node. In 1966, Mendez and Moe utilized microelectrode techniques to demonstrate A-V nodal re-entry. They showed that properly timed premature stimulation and/or rapid pacing can produce nonuniform conduction of the impulse in the A-V node resulting in slow conduction and unidirectional blocks which were recognized as essential prerequisites for re-entry. Similar observations were later demonstrated by Janse et al. and Wit et al. in canine Purkinje fibers depressed by high extracellular K+. Sasyniuk and Mendez also demonstrated re-entry during premature stimulation at the Purkinje fiber-muscle junctions.

With the direct application of the electrical stimulation procedures in the human heart, several authors have shown that supraventricular tachycardias in patients with or without the Wolff-Parkinson-White syndrome could be initiated or terminated by a properly-timed premature stimulation and that the arrhythmias could also be induced by a critical rate of rapid cardiac pacing. These authors showed that the short cardiac cycle must result in a sufficient degree of A-V nodal conduction delay before the onset of arrhythmia, presumably setting the stage for re-entry. Premature beats with a relatively narrow critical range of coupling intervals called the "echo zone" could induce the arrhythmia while earlier or later coupling failed. Utilizing similar techniques and criteria, several authors suggested that ventricular tachycardias of presumably re-entrant origin could be initiated and terminated by a properly timed premature beat or critical rapid cardiac pacing, although the exact site of ventricular re-entry was open to speculation. However, epicardial mapping in the studies by Fontaine et al. suggested re-entry in the ventricular muscle by demonstrating late epicardial activation sites. Most of the above studies made a good case for re-entry but fell short of unequivocally documenting re-entry because of the failure to depict the electrical activity of the whole re-entrant pathway in a consistent and reproducible fashion.

Two observations on the initiation of re-entry described in this study deserve special emphasis. One is the interesting electrophysiologic mechanism by which abrupt termination of rapid cardiac pacing may induce or "unmask" re-entry. Similar clinical observations are rare in the literature. Recently, Vassalle et al., in an experimental study, demonstrated that abrupt termination of a critical rate of fast driving may induce an ectopic rhythm which they ascribed to "overdrive excitation" of an automatic pacemaker. In view of the evidence presented in this study, a re-entrant mechanism cannot be excluded in these experiments. Also, our demonstration that ventricular re-entry frequently requires critical shortening of the cardiac cycle which could very well be provided by supraventricular rather than ventricular stimulation lends support to the rather fragmentary reports in the literature of ventricular arrhythmias induced by an atrial premature beat or tachyarrhythmia. Similar observations on the initiation and termination of re-entry described by Fontaine and Mendez show that ventricular tachycardias induced by an atrial premature beat could be initiated and terminated by ventricular stimulation which lends support to the rather fragmentary reports in the literature of ventricular arrhythmias induced by an atrial premature beat or tachyarrhythmia. These authors suggested that, at slow heart rate, conduction through a potentially re-entrant pathway

Heart Rate and Frequency of Re-entry

The relationship between the frequency of ventricular arrhythmias and the underlying heart rate has been a subject of considerable interest and controversy over the years. That bradycardia may be associated with frequent ventricular ectopic rhythms has been clearly demonstrated in the setting of both experimental and clinical myocardial ischemia. This observation is of particular clinical significance since sinus bradycardia and/or atrioventricular block is more prevalent with certain types of myocardial infarction and may be associated with more frequent ventricular arrhythmias. A critical increase of the ventricular rate in these cases may successfully suppress the ectopic rhythm. An electrophysiologic explanation offered for the mechanism of bradycardia-related ventricular arrhythmia is that of Han who attributed it to increased dispersion of refractoriness of ischemic myocardium at slow rates which would favor re-entry through a mechanism of focal re-excitation. Han's data, however, showed that dispersion of refractoriness was in the order of 40 msec, a value far less than is necessary to evoke ventricular re-entry since the impulse destined to re-enter the ventricle must survive for considerably longer periods of time if it is to outlast the ventricular refractory period.

Several recent reports have demonstrated the arrhythmogenic potential of increased heart rate in the setting of acute myocardial ischemia, and still other studies have emphasized a more complex relationship between heart rate and the frequency of ventricular arrhythmia. These studies showed that ventricular arrhythmias possibly due to re-entry may occur frequently at a slow heart rate, become less frequent or disappear at a moderate rate, become more frequent again at a higher rate and become less frequent at a still higher rate. Probably the only discussion of electrophysiologic mechanisms involved in these observations was that of Wit et al. These authors suggested that, at slow heart rate, conduction through a potentially re-entrant pathway
may be slow enough to permit re-entry. An increase in the rate may improve conduction by a mechanism of post-excitatory hyperpolarization of depressed Purkinje fibers. Re-entry re-appears at higher rates because of the appearance of rate-dependent delay in the potentially re-entrant pathway. The disappearance of re-entry at still higher rates is due to complete block in the pathway.

Both electrophysiologic mechanisms suggested by Wit et al. to explain the relationship of heart rate and the frequency of re-entry are, however, open to question. The role of post-excitatory hyperpolarization of depressed fibers was purely speculative since it was not demonstrated in their preparation. In addition, the contention by Wit et al. that a tachycardia-dependent complete block in the pathway is always necessary for re-entry to disappear is not supported by the results of this study. Their contention was probably based on the belief that when conduction in a potentially re-entrant pathway changes from a Wenckebach-like pattern to a 2:1 pattern, every conducted beat during the 2:1 sequence will be associated with sufficient conduction delay to result in re-entry in a bigeminal rhythm. Although a tachycardia-dependent paroxysmal block in the re-entrant pathway has been demonstrated in this study in several experiments, the transition of a Wenckebach-like conduction delay in the pathway to a 2:1 conduction sequence resulted in relative improvement of conduction of alternate impulses, thus negating the chance for re-entry. Previous studies that showed re-entry at both slow and fast heart rates maintained the unwarranted assumption that re-entry occurred through the same pathway. This has never been proven by either in vivo or in vitro experiments. In some of the experiments in this study, re-entry could be seen at both the slow and fast heart rates. Different re-entrant pathways were probably involved as far as we can ascertain from the difference in the configuration of the fractionated 1Z potential. We have shown that conduction in ischemic myocardium is consistently tachycardia-dependent, meaning that it improves at relatively slower rates and worsens at relatively faster rates. We have also illustrated that conduction characteristics of different, potentially re-entrant pathways can vary widely in their relationship to heart rate. Some pathways only operate at slow heart rates, others at faster rates. The electrophysiologic mechanism consonant with our findings to explain the complex relationship of the basic heart rate and the frequency of re-entry is that different re-entrant pathways with varying conduction characteristics at different heart rates are involved.

In summary, this study provides enough insight into ventricular re-entry in the in vivo heart to help to remove it from the realm of a plausible hypothesis into the domain of an established pathophysiologic mechanism, the details of which we can now examine directly. In addition to unequivocally establishing re-entry as the mechanism for the ventricular arrhythmias shown in this study, we have clearly demonstrated that re-entry was based on characteristic rate-dependent conduction disorders in the ischemic myocardium.

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Augmentation of Serum CPK Activity by Digitalis in Patients with Acute Myocardial Infarction

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SUMMARY The effect of acetyl strophanthin on the rate of creatine phosphokinase (CPK) efflux was evaluated in 59 predominantly class I and II patients randomly allocated between treated and control. Therapy (0.5 mg) was begun 11-15 hours after the onset of symptoms and repeated four hours later (0.25 mg). Accumulated CPK activity (ACA) was determined from serial serum CPK changes sampled every two hours and compared to predicted CPK activity (PDA) determined from the first seven hours of CPK changes. In the control group, ACA was not significantly different from PCA. Digitalis consistently resulted in an augmentation of CPK efflux into serum which was temporally related to drug administration and resulted in a corresponding increase in ACA (P < 0.001). Thus acetyl strophanthin appears to increase apparent CPK activity in serum in class I and II patients.

THE THERAPEUTIC ROLE of digitalis during acute myocardial infarction remains controversial. Digitalis has been recommended since 1912 for the treatment of acute myocardial infarction because of the similarity of the hemodynamic state associated with myocardial infarction to that of heart failure. Since digitalis can increase the contractility of both normal and ischemic tissue, digitalis theoretically will increase myocardial function following myocardial infarction. However, there is much controversy about the role of digitalis in myocardial infarction. Although digitalis can improve myocardial performance, its effect on performance during an evolving infarction appears dependent on the time of administration, clinical class of the patient and degree of hemodynamic impairment. Moreover, experimental evidence in open-chest animals suggests that digitalis may be deleterious to ischemic regions in the nonfailing heart, resulting in increasing signs of electrical injury, and beneficial to ischemic regions of failing hearts resulting in decreasing epicardial ST-segment elevation. Changes in serial serum creatine phosphokinase (CPK) have been used to estimate "infarct size" in experimental animals and in man, the analysis of these changes by a one compartment model can be referred to as the accumulated CPK activity (ACA). Early changes in CPK activity have also been used to predict the time course of later CPK changes by computer curve fitting; these projected CPK activity values are not consistent with early experimental observations. This study was designed to determine the effect of acetyl strophanthin on the rate of CPK efflux in patients with acute myocardial infarction.
Re-entrant ventricular arrhythmias in the late myocardial infarction period. 2. Patterns of initiation and termination of re-entry.
N El-Sherif, R R Hope, B J Scherlag and R Lazzara

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