**Effect of Heart Rate on Electrically Induced Repetitive Ventricular Responses in the Digitalized Dog**

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**ABSTRACT**

After recovery from acetylstrophanthidin-induced ventricular tachycardia, a repetitive ventricular response (RVR) following a single diastolic stimulus could be elicited for 22 minutes. With atrial pacing at the maximum ventricular follow rate, RVR was obtainable for 70 minutes. A pause in pacing also evoked a ventricular ectopic beat; however, this persisted for only 27 minutes. The minimum heart rate required for RVR was always less than the minimum rate required for pause-induced ectopic beats. Extrasystoles following a pause during pacing, RVR in sinus rhythm, and RVR during rapid heart rates represent decreasing levels of ventricular automaticity corresponding to progressive dissipation of digitalis intoxication. The underlying mechanism for RVR probably is due to net loss of intracellular potassium, which can be induced both by digitalization and by rate acceleration.

**ADDITIONAL KEY WORDS**

acetylstrophanthidin digitalis toxicity atrial pacing ventricular premature beats ventricular tachycardia

The effect of a change in heart rate on the excitable properties of the digitalized heart has been inadequately studied. When the intact animal or man receives digitalis drugs, vagal stimulation unmasks ventricular ectopic mechanisms at a time when no overt toxic changes are evident (1-3). Vassalle et al. (4) demonstrated enhanced Purkinje fiber automaticity when the digitalized heart was slowed by transient suppression of sinus rhythm. One might anticipate that shortening cycle duration would diminish or abolish digitalis-induced ectopic activity (5). There is no evidence, however, as to the effect of increased heart rate in digitalis-induced alteration in cardiac automaticity.

In the past this problem could not be readily studied, since there existed no method for assessing the degree of digitalization as it related to glycoside-induced alterations in cardiac excitability. Demonstration of the phenomenon of repetitive ventricular response in the digitalized heart (6) has provided a method for such analysis. Following administration of 50 to 60% of the toxic dose of a cardiac glycoside, a single threshold stimulus delivered to the myocardium in early diastole results in a repetitive ventricular response (RVR) (7). As larger doses of digitalis are given, such extra responses can be elicited by stimuli delivered to nearly two-thirds of the diastolic interval. With increasing levels of digitalization, single threshold test stimuli evoke multiple responses as well as paroxysms of ventricular tachycardia. The morphology of the RVR frequently simulates the wave form of the ventricular tachycardia resulting from excessive glycoside. RVR can also be elicited after recovery from digitalis-induced arrhythmia.

The objective of the present experimental study was to determine the relationship...
between increased heart rate and elicitation of the RVR phenomenon in the digitalized animal.

**Methods**

Twenty-five mongrel dogs of both sexes, varying in weight from 15 to 30 kg, were studied. Animals were anesthetized with sodium pentobarbital (30 mg/kg iv) and ventilated with room air by means of a Harvard ventilatory pump through a cuffed endotracheal tube. A standard electrocardiographic lead II was monitored continuously on an oscilloscope and, when indicated, recorded on paper.

Testing for RVR.—Through a jugular vein, a Teflon-coated multistrand unipolar steel wire electrode was introduced into the right ventricle. It was regarded as properly positioned when a right ventricular endocavitary electrogram was recorded and a stimulus of less than 1 ms discharged in diastole evoked a propagated ventricular response. The indifferent electrode was attached to a needle positioned subcutaneously over the precordium. The test stimulus employed was a 2-msec constant-current pulse of adjustable amplitude that could be varied from 0.1 mA to 10 ma, with an accuracy of ±3%. The stimulus was synchronized to the R wave of the surface electrocardiogram and timed in the cardiac cycle through an adjustable delay permitting variations from 10 to 400 msec with an accuracy of ±3 msec. Since anodal and cathodal pulses were equally effective in evoking RVR, these were employed randomly. In each animal the threshold for a single propagated response was determined in mid-diastole. Throughout these experiments, a ventricular stimulus of twice threshold intensity was employed for eliciting RVR. Before infusion of acetylstrophanthidin, the entire cardiac cycle was systematically explored for RVR. This was accomplished by advancing the R-stimulus interval by 10-msec increments throughout diastole; successive tests were carried out after a lapse of 10 seconds. Once the cycle had been explored, testing for RVR was performed at the earliest part of the cardiac cycle where a stimulus of twice threshold intensity evoked a propagated ventricular depolarization as noted on the surface electrocardiogram. This portion of the cardiac cycle, generally coinciding with the downstroke of the T wave, has been found to yield the earliest and most reproducible RVR during digitalization (7).

Digitalization was carried out with acetylstrophanthidin† infused into a peripheral vein at a constant rate of 133 μg/min. The infusion was stopped when four successive ventricular ectopic beats, designated as ventricular tachycardia, occurred. The termination of ventricular tachycardia was defined by the recurrence of normal sinus rhythm sustained for at least 30 seconds.

Atrial Pacing.—A Teflon-coated multistrand steel wire electrode was introduced into the right atrium through a jugular vein. Its position in the atrium was determined by recording a right atrial endocardiovascular electrogram. The indifferent electrode was attached to a subcutaneous needle positioned over the precordium. Atrial pacing was performed with a recurrent pulse similar to that used for right ventricular stimulation. The rate could be varied from 60/min to 500/min. Stimulus intensity was maintained at the threshold required for a propagated atrial response. The atrial rate was progressively increased until atrioventricular conduction failure prevented further augmentation of ventricular rate. This defined the limit of atrioventricular conduction and was designated as the maximum follow rate of the ventricles to atrial stimulation.

The RVR phenomenon is characterized by a pause between the electrically evoked response and the ensuing repetitive response (Fig. 1). This pause resulted from blocking of the P wave by the refractory state induced through premature depolarization of the ventricle and perhaps the A-V conduction system by the electrical stimulus. In the presence of sinus rhythm, this pause is consistently longer than the underlying cycle interval. When a rapid rate is maintained by atrial pacing, the pause following the electrically induced ventricular response would be abolished by the atrial drive stimulus which would capture the ventricle and thereby prevent emergence of RVR. To permit development of RVR after delivery of the right ventricular test stimulus, the atrial pacemaker was shut off automatically for an interval just sufficient to block a single atrial drive stimulus. This was accomplished by electronically detecting the occurrence of the ventricular stimulus and short-circuiting the output of the atrial pacemaker for an adjustable period of time.

**EXPERIMENTAL STUDIES**

Rapid Heart Rate and RVR.—The aim of this study was to determine whether, in the digitalized animal, rapid heart rates promoted development of RVR. As a control, RVR was searched for in 25 animals prior to digitalization, both in sinus rhythm and while the right atrium was being paced at rates up to the maximum follow rate. This rate was consistently higher than 270/min.

After recovery from acetylstrophanthidin-in-
HEART RATE AND REPETITIVE VENTRICULAR RESPONSES

Record from dog digitalized with acetylstrophanthidin. An electrical stimulus of twice threshold intensity (0.8 ma) delivered at the junction of the T wave with the isoelectric baseline (R-stimulus interval 180 msec) produces a propagated ventricular response followed by a ventricular ectopic beat, designated as repetitive ventricular response (RVR). The interval between the stimulated beat and the repetitive response was 470 msec, exceeding the mean cycle length of the underlying sinus mechanism (410 msec). Note that the P wave was blocked by the initiating premature beat, permitting the longer interval for RVR to occur. The P wave was also blocked by the RVR complex. (In all illustrations, lead II is recorded.)

Dosed ventricular tachycardia, testing for RVR was begun in sinus rhythm and was continued until RVR disappeared (18 digitalizations in 14 dogs). As soon as RVR was no longer obtainable in sinus rhythm, atrial pacing was initiated at a rate 20 to 50 beats/minute faster than the underlying sinus mechanism. At this rate, testing was carried out until RVR was extinguished, then the rate was again increased, and testing was repeated. A progressive increase in heart rate was continued until the maximum follow rate was reached, manifested by the appearance of atrioventricular block.

In five additional dogs, a more systematic study was made of the minimum increase in heart rate required to recall the RVR phenomenon after its dissipation in sinus rhythm. Testing for RVR was initiated 2 to 5 minutes after termination of acetylstrophanthidin-induced ventricular tachycardia and repeated at intervals of 2 to 5 minutes. Once RVR could no longer be evoked in normal sinus rhythm, atrial pacing was begun. The heart rate was increased by increments of 10 beats/ min, and pacing was maintained for the brief time required for elicitation of RVR. Between tests for RVR, atrial pacing was discontinued. If RVR failed to develop, the atrial rate was increased by 10 beats/minute. This stepwise rate increase was continued until the maximum follow rate was reached. Within 30 minutes after extinction of RVR during maximum follow rate atrial pacing, digitalization was repeated. After recovery from the second episode of drug-induced ventricular tachycardia, the relation of heart rate to RVR was reexamined.

The minimum number of short cycles required to recall RVR in the digitalized animal was determined in five experiments. When RVR was no longer obtainable in normal sinus rhythm after recovery from acetylstrophanthidin-induced ventricular tachycardia, the atrial rate was increased to a level at which RVR could be reproducibly observed. This rate ranged from 250 to 280/min. After a variable number of short cycles, not exceeding 15, pacing was interrupted by RVR testing. This experimental procedure was limited to 5 minutes so that all tests in any one animal were accomplished at a constant level of digitalization.

The persistence of the effect of rate increase on elicitation of RVR was studied in eight animals from 30 to 100 minutes after recovery from ventricular tachycardia, when RVR could no longer be obtained in the absence of an increase in heart rate. The atria were then paced at a rate at which RVR could be consistently obtained. Pacing was maintained for 20 seconds, then stopped, and testing for RVR was carried out after one or more normally conducted sinus beats.

Ectopic Activity Evoked by a Pause in Atrial Pacing.—The RVR phenomenon is characterized by a pause between the electrically evoked depolarization and the RVR. Usually, stopping atrial pacing also results in a pause before the sinus node resumes as dominant pacemaker (8-10). To determine the role of a pause in the emergence of ventricular extrasystoles, the effectiveness of discontinuing pacing was studied in 20 dogs at pacing rates varying from 200/min to the maximum follow rate. The atria were paced for 30 seconds, and then the pacing was abruptly...
Tracings taken at 5-minute intervals, beginning 5 minutes after termination of acetylstrophanthidin-induced ventricular tachycardia. Variations in sinus rate from 100/min to 140/min required progressive shortening of the Q stimulus interval. Dissipation of the RVR phenomenon is characterized by a decrease in the number of repetitive responses and by the occurrence of fusion beats.

stopped. This procedure was carried out before digitalization as a control and at different time intervals after recovery from acetylstrophanthidin-induced ventricular tachycardia.

In five digitalized animals, the minimum heart rate required to elicit RVR after its disappearance during sinus rhythm was compared to the effect of a pause at the same heart rate. Pacing was maintained for 30 seconds at this minimum heart rate and then stopped; this resulted in a pause. The same procedure was repeated at increasing pacing rates corresponding to the increasing heart rate required for recalling RVR.

Results

Rate Acceleration and RVR.—In the non-digitalized animal, RVR did not occur, whether testing was carried out during sinus rhythm or during atrial pacing up to the maximum follow rate of the ventricles. Immediately after recovery from acetylstrophanthidin-induced ventricular tachycardia, however, RVR was produced consistently by diastolic stimuli. With recovery from digitalis intoxication, the repetitive response occurred after a progressively longer interval after the electrically evoked response. This permitted partial sinus capture of ventricular depolarization and gave rise to fusion complexes (Fig. 2). With further recovery from digitalis intoxication, the fusion beats simulated more closely the normally
HEART RATE AND REPETITIVE VENTRICULAR RESPONSES

Duration of Toxicity in 18 Animals Following Acetylstrophanthidin-Induced Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>VT (min)</th>
<th>RVR (min)</th>
<th>RVR during pacing (min)</th>
<th>Heart rate (beats/min)</th>
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</thead>
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<tr>
<td>1</td>
<td>30</td>
<td>70</td>
<td>120</td>
<td>103</td>
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<td>33</td>
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<tr>
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<td><strong>13</strong></td>
<td><strong>22</strong></td>
<td><strong>70</strong></td>
<td><strong>165</strong></td>
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Duration of toxic state was determined by duration of ventricular tachycardia (VT) and repetitive ventricular response (RVR) during sinus rhythm (SR) and during atrial pacing at the maximum follow rate (MFR) of the ventricle.

Conducted beat. Once RVR was no longer obtainable while the animal was in sinus rhythm, increasing the heart rate reproducibly recalled this phenomenon (Fig. 3). It should be noted that the more rapid the rate of pacing, the earlier the RVR occurred in relation to the electrical stimulus. The morphology of RVR during pacing was identical to that obtained previously in sinus rhythm and was not altered by shifting the position of the catheter in the ventricle.

In 18 animals, the mean duration of RVR after recovery from acetylstrophanthidin-induced ventricular tachycardia was 22 minutes, with a range from 1 to 77 minutes. With rate increase by means of atrial pacing, the period for occurrence of the RVR phenomenon was extended for an additional mean duration of 48 minutes. The total mean duration of RVR after recovery from ventricular tachycardia was 70 minutes, with a range of 27 to 140 minutes (Table 1). The mean heart rate at the time of disappearance of RVR without pacing was 165/min and with pacing it was 285/min, which represented the maximum follow rate. There was no statistically significant correlation between the total duration of RVR and the maximum follow rate at which RVR disappeared (r = 0.274).

In five animals, the minimum heart rate required for eliciting RVR during recovery from digitalization was determined (Fig. 4). With the lapse of time after recovery from drug-induced ventricular tachycardia, it was necessary to increase the heart rate progressively to demonstrate the RVR phenomenon. A similar sequence was observed during a second digitalization 30 minutes after RVR could no longer be produced at the maximum follow rate. Table 2 summarizes the data of nine digitalizations in these five dogs. It should be noted that the mean dose of acetylstrophanthidin for producing the endpoint of ventricular tachycardia was about 30% less in the second series of digitalizations. Despite the lower dose of drug, the duration...
TABLE 2

Dissipation of Acetylstrophanthidin Intoxication in Two Successive Digitalizations in Five Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>AS (ug)</th>
<th>VTR</th>
<th>RVR at SR</th>
<th>RVR at MFR</th>
<th>MFR* (beats/min)</th>
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</thead>
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<tr>
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<td>1230</td>
<td>4</td>
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<tr>
<td></td>
<td>900+</td>
<td></td>
<td></td>
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<td>20†</td>
</tr>
<tr>
<td>2</td>
<td>1430</td>
<td>10</td>
<td>2.5</td>
<td>42.5</td>
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<td>330</td>
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<td>1910</td>
<td>12</td>
<td>17.5</td>
<td>60</td>
<td>310</td>
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<td>1600</td>
<td>7</td>
<td>20</td>
<td>92.5</td>
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<td>1480</td>
<td>6</td>
<td>12.5</td>
<td>102.5</td>
<td>290</td>
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<tr>
<td>5</td>
<td>2330</td>
<td>23</td>
<td>5</td>
<td>35</td>
<td>330</td>
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<td></td>
<td>1980</td>
<td>12</td>
<td>12.5</td>
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<td></td>
<td>Mean</td>
<td>1836</td>
<td>11.6</td>
<td>9.5</td>
<td>43.6</td>
</tr>
</tbody>
</table>

AS = acetylstrophanthidin. For other abbreviations, see footnote to Table 1.

*At disappearance of RVR. †Dog died in ventricular fibrillation 15 minutes after termination of ventricular tachycardia.

of ventricular tachycardia was unaltered, and the time course of dissipation of RVR was delayed (Fig. 5).

The recall of RVR by increasing the ventricular rate required a sequence of at least three short cycles (Fig. 6). As the number of conditioning short cycles was increased, RVR occurred earlier after the electrically evoked response. This decreased the occurrence of fusion complexes with the normally conducted sinus impulse.

A sequence of conditioning short cycles was required for the redevelopment of RVR after its extinction in sinus rhythm. It was, therefore, of some interest to determine whether the altered state of excitability, predisposed to by the rapid heart rate, was maintained after discontinuing pacing. The persistence of RVR was analyzed in 47 tests during eight digitalizations with acetylstrophanthidin. It was found that if the electrical stimulus to the right ventricle was delivered after the last paced beat, RVR consistently followed. When, however, the stimulus was applied following more than one normal sinus cycle after discontinuing pacing, RVR failed to develop in 35 of the 47 trials (Fig. 7). In each of the 12 instances in which RVR persisted after pacing was stopped, the prevailing sinus rate was more rapid than during the control period immediately preceding the pacing (Fig. 8).

Thus, when the sinus rate remains unaltered, there does not appear to be any facilitation of

![Figure 4](http://circres.ahajournals.org/)

Dissipation of RVR as a function of heart rate and time after recovery from acetylstrophanthidin-induced ventricular tachycardia in one dog. Circles indicate time span during which RVR could be reproduced at a given rate. Lines connecting x's define the time course of the maximum heart rate at which RVR was no longer obtainable. The curve terminates at an atrially paced rate of 300, which corresponds to the maximum follow rate.

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the RVR phenomenon upon cessation of atrial pacing.

Role of the Pause in Development of RVR.—In the nondigitized animal, ventricular ectopic beats did not occur during the pause between cessation of pacing and resumption of sinus rhythm. When pacing was stopped at rates approaching the maximum follow rate, a few ventricular ectopic beats were occasionally observed; however, this arrhythmia was not reproducible. Immediately after recovery from acetylstrophanthidin-induced ventricular tachycardia, stopping of atrial pacing consistently resulted in ventricular ectopic activity (Fig. 9). Initially, the ectopic activity consisted of short paroxysms of ventricular tachycardia; shortly thereafter, only a single ventricular ectopic beat or a fusion complex resulted from discontinuing pacing. In 16 digitalizations, the pause-induced ectopic activity was observed for an average of 27 minutes after recovery from ventricular tachycardia, and in only four instances did it last for more than 1 hour. In each of these animals, RVR persisted long beyond the disappearance of extrasystoles resulting from stopping the pacer.

In five animals, the effect of stopping the pacer after maintaining the heart at the minimum rate required to recall the RVR phenomenon after its disappearance in sinus rhythm was investigated. Under these circumstances, discontinuation of atrial pacing never resulted in ventricular ectopic mechanism (Fig. 10).

Discussion

The present investigation demonstrates that abbreviating cycle duration facilitates development of the RVR phenomenon. A series of
Rate
144/min Sinus R.

230 Atrial Pacing Normal Cycles

60 min after VT

Tracings taken 60 minutes after termination of acetylstrophanthin-induced ventricular tachycardia. RVR was no longer present in sinus rhythm (top strip). When rate increased by atrial pacing to 230/min, RVR occurred even after a single normal cycle; however, when a sequence of two cycles of sinus rhythm intervened, the RVR phenomenon was extinguished (bottom strip).

three short cycles is adequate to restore RVR after its subsidence in the undriven heart. In the digitalized animal, the occurrence of spontaneous or electrically evoked repetitive ventricular ectopic beats has been interpreted as an indication of drug toxicity (7). The present work permits classification of the recovery period from an overdose of cardiac glycoside into three temporal phases of toxicity. First is the phase of overt drug toxicity with manifestations ranging from sporadic ventricular premature beats to sustained bouts of ventricular tachycardia. In the second phase, ectopic activity is exposed either by the pause following transient acceleration or by the RVR phenomenon. In the third phase, the presence of RVR is demonstrated by shortening the duration of the cardiac cycle prior to RVR testing. There are thus one overt and two latent phases during recovery from digitalis intoxication.

These investigations help clarify some aspects of the RVR phenomenon. Enhanced automaticity caused by digitalis glycosides can be exposed by inducing a pause in heart rhythm. The effectiveness of a pause is related to the duration of the preceding three or more cycles. The shorter these conditioning cycles, the more likely is a given pause to precipitate digitalis-related ventricular ectopic beats. Thus the unmasking of latent digitalis toxicity depends upon a combination of two elements, namely, a sequence of several short cycles and pause.

It may be that RVR represents but a similar combination of short cycle and pause. As the animal recovers from digitalis toxicity, it is no longer possible to induce an extrasystole by a pause resulting from cessation of pacing; however, RVR still can be demonstrated, possibly because RVR is evoked from very early in the cycle and therefore represents an ultrashort cycle. Generally, RVR is produced most consistently from the downslope of the T wave, representing an R-stimulus interval ranging from about 100 to 150 msec, equivalent to heart rates of 400 to 600/min and much beyond the rate of A-V junctional conduction. With additional recovery from the effect of cardiac glycoside, RVR disappears, but it can be reproduced by increasing the heart rate. This would suggest that the effect of an ultrashort cycle is potentiated by several antecedent short cycles.

This hypothesis helps explain a number of hitherto puzzling observations. With progressive digitalization, RVR is first demonstrable from the downslope of the T wave, but its zone then extends to encompass most of diastole. As more digitalis is administered, the R-stimulus interval needed to initiate RVR thus becomes progressively longer. Inability to demonstrate RVR from the P wave or P-R interval is due to the fact that the initiating
Discontinuation of atrial pacing at 340/min resulted in a pause-induced extrasystole followed by sinus tachycardia at 250/min during which RVR was elicited. However, when rate slowed to control level of 180/min, only a single response followed test stimulus. This study was conducted 60 minutes after recovery from acetylstrophanthidin-induced ventricular tachycardia, when RVR could not be produced without atrial pacing.

It has been observed that when bradycardia is present, RVR can be produced inconsistently, if at all. RVR is readily and reproducibly demonstrated in the digitalized animal anesthetized with sodium pentobarbital, but not when morphine-chloralose is employed (Lown et al., unpublished observations). In the former, heart rates generally exceed 150/min, but in animals anesthetized with morphine-chloralose, heart rates are 100/min or less. This would suggest that the cycles preceding the ultrashort cycle initiating RVR need to be abbreviated as well if the electrical cycle is too long. Furthermore, stimulating this late in diastole does not result in a compensatory pause. With recovery from digitalization, the zone for eliciting RVR recedes to the T wave. When RVR can no longer be produced with threshold stimuli, suprathreshold discharges of high energy content may still demonstrate its presence. However, these discharges must be delivered in the relative and even the absolute refractory period. In effect, extreme abbreviations of the R-stimulus interval are necessary for demonstrating RVR at that stage of recovery from digitalis intoxication.

Since 1970, it has been demonstrated that when bradycardia is present, RVR can be produced inconsistently, if at all. RVR is readily and reproducibly demonstrated in the digitalized animal anesthetized with sodium pentobarbital, but not when morphine-chloralose is employed (Lown et al., unpublished observations). In the former, heart rates generally exceed 150/min, but in animals anesthetized with morphine-chloralose, heart rates are 100/min or less. This would suggest that the cycles preceding the ultrashort cycle initiating RVR need to be abbreviated as well if the electrical cycle is too long. Furthermore, stimulating this late in diastole does not result in a compensatory pause. With recovery from digitalization, the zone for eliciting RVR recedes to the T wave. When RVR can no longer be produced with threshold stimuli, suprathreshold discharges of high energy content may still demonstrate its presence. However, these discharges must be delivered in the relative and even the absolute refractory period. In effect, extreme abbreviations of the R-stimulus interval are necessary for demonstrating RVR at that stage of recovery from digitalis intoxication.
In sinus rhythm, RVR could be evoked 5 minutes after termination of acetylcholine-induced ventricular tachycardia (1), but disappeared after 13 minutes (2). Twenty minutes after recovery from ventricular tachycardia, the minimum rate of atrial pacing required for RVR was 210/min (3). After pacing at the same rate during 30 seconds, stopping the pacer produced no pause induced extrastoles (4). Note the identical shape of RVR in sinus rhythm and during atrial pacing.
the electrically induced ventricular stimulus would block the next atrial beat and thereby provide a pause for Purkinje discharge.

These considerations do not, however, explain how a single early ventricular stimulus without conditioning by rapid pacing evokes additional responses at a time when a pause in the cardiac cycle is without such effect. It is not known whether a single short cycle increases phase 4 depolarization in the ensuing cycles of Purkinje fibers. Abrupt shortening of the diastolic interval results in prolongation of phase 2 of the canine action potential of myocardial fibers and is accompanied by a steeper phase 3 (12). There is, however, no consistent alteration in action potential duration. Present electrophysiologic theory does not satisfactorily account for the phenomenon of RVR.

The effect of rate acceleration in favoring RVR may relate to increase in quantity of glycoside bound to the myocardial cell. Over 50 years ago, Weizsäcker (13) found that in the frog heart, development of glycoside-induced cardiac standstill was related to the number of beats. Wilbrandt et al. (14) showed that in the electrically driven frog heart, K-strophanthoside-induced increase in isometric contractile force was proportional to the number of contractions. Levi (15) demonstrated that the heart made inactive during glycoside exposure did not develop a positive inotropic effect once removed from the digitalis medium. Sanyal and Saunders (16) observed that guinea pig ventricular strips treated with ouabain increased force as a function of the frequency of stimulation. Moran (17) showed in rabbit atria that the positive inotropic effect of ouabain was related to the total number of contractions.

A study of the uptake of tritiated digoxin by isolated guinea pig atria at different heart rates has been carried out by Kuschinsky et al. (18). They observed that left auricles took up glycoside more slowly when resting than when the beating was maintained at rates of 30 and 180/min; however, the maximum uptake of labeled digoxin at equilibrium was approximately similar. Frequency appears to influence the rate of uptake rather than the amount of glycoside accumulated. As there is no difference in the rate of glycoside exchange at different pacing frequencies, it seems unlikely that the present experimental findings relating RVR to the length of the preceding cardiac cycles are a function of altered glycoside binding to the myocardial cell. To demonstrate RVR, only three conditioning short cycles are required; this conditioning effect is dissipated after one cycle in normal sinus rhythm. It seems unlikely that binding of acetylstrophanthinid should change significantly within a single cycle.

A significant body of evidence indicates that beta-receptors contribute to the arrhythmias resulting from digitalis overdose (19-23). There is also evidence that electric discharge activates autonomic nerve endings in the heart and liberates norepinephrine (24). Recent observations, however, indicate that beta-receptor blockade does not modify detectably the RVR phenomenon (25, 26). When the heart is digitalized by drugs administered directly into the left anterior descending coronary artery alone, threshold stimuli delivered through a bipolar electrode placed on myocardium not perfused by this vessel and presumably not receiving digitalis still evoke RVR (Lown et al., unpublished observations).

It is possible that digitalization (27) and cycle length abbreviation (28) produce similar effects on the potassium balance of the myocardial cell, namely, a net loss of intracellular potassium. This results in a decreased transmembrane potassium gradient and a lower resting membrane potential which, in turn, increases Purkinje fiber automaticity (29). This may be the ionic mechanism for the repetitive ventricular responses which can be evoked in the digitalized heart and for the facilitation for RVR induced by a brief salvo of rapid beats.

References


1. HAGEMEIJER, LOWN


Effect of Heart Rate on Electrically Induced Repetitive Ventricular Responses in the Digitalized Dog
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