Acceleration of Ventricular Pacemakers by Transient Increases in Heart Rate in Dogs during Ouabain Administration

By Stephen M. Wittenberg, M.D., Fritz Streuli, M.D., and Francis J. Klocke, M.D.

ABSTRACT
The present experiments describe effects of transient increases in heart rate on ventricular pacemakers during digitalization. Fifteen anesthetized, vagotomized dogs were studied during ouabain infusion or after recovery from ouabain-induced ventricular tachycardia. Vagal stimulation was used to assess baseline ventricular automaticity and 30-second periods of atrial pacing were utilized to evaluate the response of ventricular pacemakers following different increments in rate. After an average dose of 45 ± 3 (SE) μg/kg of ouabain, vagal stimulation unmasked an automatic ventricular focus in 14 animals and pacing was followed by ventricular acceleration in all 15 animals. The degree of ventricular acceleration varied directly with the pacing rate. The increment in ventricular rate above the level unmasked by vagal stimulation averaged 59 ± 4% of the increment in atrial rate. At the higher driving rates, a transient postpacing depression was present before the emergence of a rapid ventricular focus. These findings were unaffected by beta-receptor blockade with 4-(2-hydroxy-3-isopropylamino propoxy) acetanilide (AY21,011). The results indicate that transient increases in heart rate may accelerate rather than depress ventricular pacemakers during digitalization.

ADDITIONAL KEY WORDS
ventricular tachycardia conduction disturbance ventricular automaticity antiarrhythmic effect reentrant rhythm postpacing depression beta-receptor blockade Purkinje fibers atrial pacing ventricular pacing

In the absence of digitalis, transient increases in heart rate are followed by depression of all intrinsic pacemakers, with ventricular pacemakers affected to a greater degree than atrial (1). Although the effect of similar increases in rate during digitalization is unknown, increases in heart rate have been reported to facilitate digitalis-induced ventricular arrhythmias. Thus, if dogs are digitalized during pacing at two different heart rates, less glycoside is necessary to produce ventricular fibrillation (2) or ventricular tachycardia (3) at the higher rate.

In our own laboratory, we have observed ventricular tachycardia after transient rapid atrial pacing in digitalized dogs. In the following studies pacing was used for systematic study of the effects of rate on the behavior of ventricular pacemakers in the intact digitalized animal. The results indicate that transient increases in driving rate can reproducibly accelerate a latent ventricular focus to the point where it usurps the supraventricular pacemaker. The degree of ventricular acceleration increases with increasing pacing rate and persists in the presence of beta-receptor blockade.

Material and Methods
Fifteen mongrel dogs of both sexes weighing between 17 and 33 kg were anesthetized with 30...
mg/kg of sodium pentobarbital, intubated, and ventilated with room air using a constant-volume pump. Arterial blood gases were checked periodically and the ventilator adjusted accordingly. Inferior vena caval temperature was measured with a thermistor probe and maintained between 36° and 38°C with heating pads. Both vagus nerves were exposed in the neck and divided, and platinum electrodes were attached to the distal ends. Catheters were placed in a femoral artery for pressure recording and in a femoral vein for drug infusions. In five animals, to maintain mean arterial pressure constant, a large-bore catheter was placed in the other femoral artery and connected to a blood reservoir.

Nine closed-chest animals were studied. A tripolar electrode catheter was placed through the right external jugular vein into the ostium of the coronary sinus. This position was chosen because it did not change throughout an experiment and was reliable for pacing. The electrodes were located so that pacing through any two resulted in a supraventricular complex while the third could be used to record an atrio-ventricular electrocardiogram.

A right thoractomy was done on the remaining six animals. Bipolar stimulating electrodes were sutured to the right atrial appendage. The electrical activity of the atrium was recorded either from an intracavitary lead (two animals) or from additional surface bipolar leads (four animals). In four animals, the sinus node was also crushed in order to slow intrinsic rate. In two of these animals a junctional rhythm resulted.

The basic goal was to study the behavior of ventricular pacemakers during vagal stimulation and after rapid pacing. The distal vagus nerves were stimulated with impulses of 11 to 12 volts, 5-msec duration, and frequencies between 5 and 30 cps (AEL 104A Stimulator, 106 Constant Current Regulator, and 112 Stimulus Isolator). Pacing was accomplished with a 1 to 2 milliampere (ma) square-wave impulse of 2.5-msec duration (SD 5A Grass Stimulator). Studies were done before and after administration of ouabain, given as an initial intravenous dose of 30 μg/kg followed 15 to 30 minutes later by an infusion of 0.5 μg/kg/min. If an animal developed spontaneous ventricular tachycardia during ouabain infusion, the latter was discontinued and testing resumed after the animal had returned to an atrial rhythm.

In the initial phase of these experiments it became apparent that rapid pacing was consistently followed by ventricular acceleration when the animal was close to the point of spontaneous ventricular tachycardia. Furthermore, the degree of postpacing ventricular acceleration appeared to be related to prior driving rate. Thus, at a time when a postpacing arrhythmia initially appeared, the infusion of ouabain was stopped and the following protocol was adopted: (1) 4 to 10 seconds of vagal stimulation was used to assess baseline ventricular automaticity; (2) 30-second periods of atrial pacing were used to evaluate the response of the ventricular pacemaker after different driving rates. Testing was performed at random as well as stepwise. A recovery period of 30 seconds was allowed between pacing trials or between the end of a postpacing arrhythmia and the start of another trial. Recordings were made on a direct-writing oscillograph at a paper speed of 50 mm/sec and the postpacing ventricular rate was determined by averaging the intervals between the first 5 to 7 consecutive ventricular beats. In four animals, the same protocol was repeated with ventricular pacing, with bipolar electrodes sutured to the right ventricle. Finally, in five animals, the atrial pacing studies were repeated after intravenous administration of 3.2 mg/kg of 4-(2-hydroxy-3 isopropylamino propoxy) acetanilide (AY21,011), a beta-receptor blocking agent with virtually no "quinidine-like effect" (4). The presence of beta-receptor blockade was verified by the absence of tachycardia after 0.5 to 1 μg/kg of isoproterenol.

**Results**

**Vagal Stimulation**

Before ouabain administration, responses to vagal stimulation varied, including complete asystole, asystole with occasional atrial escape beats and atrial slowing. After an average dose of 45 ± 3 (se) μg/kg of ouabain, vagal stimulation was followed by the emergence of a slower ventricular focus in 14 animals (Fig. 1). In 9 of the 14, there was no significant delay between the initiation of vagal stimulation and the emergence of a ventricular focus, i.e., the cycle length between the last supraventricular beat and the first ventricular beat was within ±2 sd of the average cycle length during the ventricular escape rhythm.

**Atrial Pacing**

Before ouabain administration, 30-second periods of atrial pacing were followed by a transient depression of the atrial pacemaker. In some animals the initial depression was followed by late supraventricular acceleration;

^1AY21,011 was generously supplied by Ayerst Laboratories, Montreal, Canada.

*Circulation Research, Vol. XXVI, June 1970*
FIGURE 1

Effects of vagal stimulation after ouabain. Middle: (RA) is a right atrial surface electrogram. Each sharp spike represents atrial depolarization. Bottom: (L2) is a standard lead II electrocardiogram. The animal's sinus node was crushed, and before vagal stimulation, the spontaneous rhythm was junctional at a rate of 115. Atrial depolarization can be seen to follow a ventricular depolarization in both RA and L2. Vagal stimulation results in atrial asystole and a ventricular escape rhythm at a rate of 107. Time markings of one second are shown below the bottom panel. (Art. Pr. = arterial pressure; Vagal Stim. = vagal stimulation.)

FIGURE 2

Effects of vagal stimulation and a 30-second period of atrial pacing before ouabain. Spontaneous atrial rate is 136 (top). Vagal stimulation causes asystole with a late atrial escape beat. Atrial rate is 138 (bottom). Thirty seconds of atrial pacing at a rate of 207 is followed by depression of the first postpacing atrial beat. (RA = intra-atrial; Art. Pr. = arterial pressure.)

Circulation Research, Vol. XXVI, June 1970
Effects of vagal stimulation and 30-second periods of atrial pacing after ouabain. See text for details.

there were no idioventricular beats. After 45 ± 3 µg/kg of ouabain, at a time when vagal stimulation revealed an automatic ventricular focus in 14 animals, atrial pacing was followed by ventricular acceleration in all 15 animals. As the pacing rate was increased, the degree of postpacing ventricular acceleration also increased. Figures 2 to 4 illustrate in detail a single experiment in a closed-chest animal. Before digitalization (Fig. 2) vagal stimulation caused asystole, and 30 seconds of atrial pacing at a rate of 207 was followed by a transient postpacing depression of the supraventricular pacemaker. After 47 µg/kg of ouabain (Figs. 3 and 4), the animal's spontaneous supraventricular rate was 133. Vagal stimulation revealed an automatic ventricular focus at a rate of 128. Atrial pacing at rates between 154 and 226 was followed by ventricular acceleration to rates between 135 and 176. The postpacing ventricular rate was always higher than the spontaneous supraventricular rate, which remained constant at 133. The ventricular rate was most rapid initially and slowed within a few seconds. Thus, at the lowest pacing rate, an atrial rhythm emerged after 11 ventricular beats.

Figure 5 summarizes an experiment in which the animal's sinus node was crushed to slow intrinsic rate. The spontaneous rate at the time of initial testing was 99. During vagal

stimulation, an automatic ventricular focus emerged at a rate of 90. Atrial pacing at rates between 111 and 150 increased the postpacing ventricular rate from 101 to 120. Between
Relation between atrial rate before vagal stimulation or during atrial pacing (abscissa) and subsequent ventricular rate (ordinate) for all animals. The first point on each line relates the spontaneous atrial rate to the ventricular rate during vagal stimulation. The subsequent points relate atrial pacing rates to postpacing ventricular rates. (Format as in Figs. 4 and 5.)

**TABLE 1**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Ouabain dose (µg/kg)</th>
<th>Before β-receptor blockade</th>
<th>After β-receptor blockade</th>
<th>Ventricular pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>0.62 ≤ .01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>0.89 &lt; .01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>0.53 &lt; .01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>0.56 &lt; .05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>0.53 &lt; .01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>0.83 &lt; .01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>0.41 &lt; .01</td>
<td>0.49 ≤ .01</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>0.52 ≤ .2</td>
<td>0.54 &lt; .1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>0.63 &lt; .05</td>
<td>0.76 ≤ .01</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td>0.78 &lt; .01</td>
<td>0.55 ≤ .01</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>0.56 &lt; .01</td>
<td>0.52 ≤ .01</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>55</td>
<td>0.50 &lt; .01</td>
<td></td>
<td>0.28 ≤ .01</td>
</tr>
<tr>
<td>13</td>
<td>37</td>
<td>0.53 &lt; .01</td>
<td></td>
<td>0.37 &lt; .01</td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>0.57 &lt; .01</td>
<td></td>
<td>0.62 &lt; .02</td>
</tr>
<tr>
<td>15</td>
<td>47</td>
<td>0.67 &lt; .01</td>
<td></td>
<td>0.63 &lt; .01</td>
</tr>
<tr>
<td>Average ± SE</td>
<td>45 ± 3</td>
<td>0.59 ± 0.04</td>
<td>0.57 ± 0.04</td>
<td>0.48 ± 0.08</td>
</tr>
</tbody>
</table>

Pacing trials, the spontaneous atrial rate rose from 99 to 120. Emergence of the ventricular focus was therefore due to a combination of transient postpacing atrial depression and ventricular acceleration. As the atrial pacing rate was increased from 160 to 222, the
Effect of transient rapid atrial pacing after ouabain. The spontaneous rhythm is atrial at a rate of 118. Thirty seconds of atrial pacing at a rate of 152 is followed by ventricular acceleration to a rate of 135. A-V dissociation is evident in both the atrial electrogram and L2 during the first 5 postpacing beats. The last two ventricular beats are consistent with retrograde atrial conduction. RA = right atrial surface electrogram; L2 = standard lead II electrocardiogram.

Postpacing ventricular rate rose from 127 to 156, while the spontaneous supraventricular rate remained between 114 and 120. In these latter runs, ventricular acceleration was a sufficient explanation for the observed postpacing rhythm.

Figure 6 and Table 1 illustrate the similar response to pacing found in all 15 dogs. The relationship between atrial driving rate and the rate of the accelerated ventricular focus is significant at the level of $P < .01$ in 12 of the 15 animals. When regression lines are constructed for each experiment, the increment in ventricular rate averages $59 \pm 4\%$ (se) of the increment in atrial driving rate. Findings in the five animals whose blood pressure was maintained constant did not differ from those in the remaining animals.
The duration of ventricular tachycardia after pacing ranged from a few beats to more than 30 minutes. In over half of the trials, it lasted less than 30 seconds. Although the duration appeared to be related to the ventricular rate in some animals, the variability in others was too large to allow a general conclusion.

Evidence that the postpacing focus originated below the A-V node was obtained in all 15 animals. Using the atrial recordings and standard lead II, it was always possible to document A-V dissociation (Figs. 7, 8).

Ventricular Pacing

In the four animals also studied with ventricular pacing, a similar response was observed, i.e., the termination of pacing was followed by ventricular acceleration (Fig. 9). The degree of acceleration was again related to the pacing rate (Table 1).

Postpacing Depression

Figure 10 illustrates representative findings concerning the delay between the termination of pacing and the onset of spontaneous electrical activity. The data is taken from the experiment illustrated in Figure 5. Following vagal stimulation and at the lower pacing rates, there is no significant difference between the first cycle length after pacing (i.e., the interval between the last paced beat and the first postpacing beat) and the average cycle length during ventricular acceleration. However, when pacing at cycle lengths shorter than 540 msec, the first cycle becomes significantly longer than the average cycle during ventricular rhythm. Similar results were obtained in all 15 animals (Table 2). The absolute value of the first cycle length after pacing decreases with increasing pacing rates. However, this decrease is less than the decrease in average cycle length during ventricular acceleration. Defined in this way, a postpacing depression is evident despite the subsequent emergence of a rapid ventricular focus.
An illustration of transient postpacing depression before the emergence of an accelerated ventricular focus (same animal as shown in Fig. 5). Top: Ordinate on left depicts findings before AY21,011. Bottom: Ordinate on right findings after AY21,011. The upper line in each portion of the figure represents the relation between atrial cycle length before vagal stimulation or during atrial pacing (abscissa) and average cycle length of the subsequent ventricular pacemaker as measured from the first 5 to 7 consecutive ventricular beats (ordinate). The lower line in each portion of the figure represents the similar relation between atrial cycle length and the first ventricular cycle length (i.e., the interval between the last paced beat and the first postpacing beat). The vertical bars designate ±1 so. Open circles represent data for vagal stimulation and solid circles data for atrial pacing.

In addition, although a ventricular rhythm always ensued after pacing, the first beat after pacing was not always a ventricular beat. Postspacing ventricular acceleration was often preceded by one and occasionally two atrial beats (Fig. 11). When this occurred, it was not possible to measure the first ventricular cycle length after pacing, although the latter was obviously longer than the cycle length of the supraventricular beat which emerged. Ventricular rhythms were also occasionally interrupted by atrial beats.

**BETA-RECEPTOR BLOCKADE**

Four of the five dogs receiving AY21,011 developed ventricular tachycardia after slowing of the atrial rate. This response has been described in a previous report (4). After spontaneous return to sinus rhythm, testing with vagal stimulation and atrial pacing was carried out in the usual fashion. The findings are given in Tables 1 and 2, the lower half of Figure 10 and Figure 12. Ventricular escape rates following vagal stimulation averaged 97 ± 3% of the values in the same animals after ouabain but before beta-receptor blockade (P > .5). Increases in ventricular rates following pacing were similar to those observed before beta blockade, i.e., slopes of regression lines relating atrial rate to subsequent ventricular rate were similar before and after beta-receptor blockade (P > .5). Finally, the postpacing depression defined above persisted after beta-receptor blockade.

**Discussion**

Several workers have studied the effects of heart rate on the development of digitalis toxicity. In single muscle fibers, ouabain-induced deterioration to the point of inexcitability occurs earlier during rapid driving (5). In the intact dog, ouabain-induced ventricular fibrillation develops at a significantly lower dose if the animal is paced with paired stimuli (2). Similarly, during single pacing at two different rates, ventricular tachycardia develops more rapidly at the higher rate (3). These studies suggest that the total time necessary for development of digitalis toxicity is inversely proportional to the heart rate during drug administration. However, they do not describe the effect of transient increases in rate on the behavior of ventricular pacemakers during digitalization. In normal dogs, transient increases in rate are always followed by depression (1). In contrast, the present report demonstrates that increases in rate during digitalization may accelerate rather than depress ventricular pacemakers. Ventricular rate is enhanced in relation to the spontaneous automaticity of the ventricle (i.e., in relation to the rate of the ventricular pacemaker unmasked by vagal stimulation). The increase in ventricular rate averages 59% of a given increment in atrial driving rate. These results may explain the observations of previous investigators that runs of ventricular extrasystoles sometimes occur concomitantly with
TABLE 2
Relationship between First Cycle Length during Vagal Stimulation or after Pacing and Average Cycle Length of Subsequent Ventricular Pacemaker

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of animals</th>
<th>FVCL-VS (msec)</th>
<th>AVCL-VS (msec)</th>
<th>FVCL-MPR (msec)</th>
<th>AVCL-MPR (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial pacing before</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beta-receptor blockade</td>
<td>8*</td>
<td>515 ± 33</td>
<td>507 ± 34</td>
<td>410 ± 47</td>
<td>348 ± 7†</td>
</tr>
<tr>
<td>Atrial pacing after</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beta-receptor blockade</td>
<td>4*</td>
<td>535 ± 40</td>
<td>538 ± 46</td>
<td>430 ± 11</td>
<td>381 ± 12‡</td>
</tr>
<tr>
<td>Ventricular pacing</td>
<td>4</td>
<td>506 ± 26</td>
<td>405 ± 35</td>
<td>420 ± 18</td>
<td>351 ± 11‡</td>
</tr>
</tbody>
</table>

*This table includes 8 of the 15 animals tested with atrial pacing before beta-receptor blockade and 4 of the 5 animals tested with atrial pacing after beta-receptor blockade. In the remaining animals, an atrial beat preceded the emergence of an accelerated ventricular pacemaker (e.g., Figure 11, lower two panels). Although the first ventricular cycle length after pacing could not be calculated in these instances, it was obviously greater than the cycle length of the atrial beat which emerged. FVCL-VS for these animals was 467 ± 16 and AVCL-VS 450 ± 19.

The cycle length between the last paced beat at maximal drive and the subsequent atrial beat was 381 ± 13. The average ventricular cycle length after pacing was 338 ± 7. Values are means ± se.

†Paired P < 0.01 in comparison with FVCL-MPR.
‡Paired P < 0.05 in comparison with FVCL-MPR.

FVCL-VS = cycle length between last atrial beat and first ventricular beat during vagal stimulation; AVCL-VS = average ventricular cycle length during vagal stimulation; FVCL-MPR = cycle length between last paced beat and first ventricular beat after pacing at maximal drive rate; AVCL-MPR = average ventricular cycle length after pacing at maximal drive rate.

FIGURE 11
Emergence of atrial beats before ventricular acceleration. The rates at the far left and in the middle refer to both atrium and ventricle. The arrows denote the termination of atrial pacing. The rates at the far right are ventricular, as calculated from L2. Top: Atrial pacing at 130 is followed by ventricular acceleration to 121. A ventricular focus emerges immediately after pacing. Middle and Bottom: Progressive ventricular acceleration occurs after more rapid atrial pacing. In each instance, however, the termination of atrial pacing is followed by an atrial beat before the emergence of a ventricular rhythm. A-V dissociation is evident in the initial portions of all three postpacing records. The last 2 to 5 beats in each record are consistent with retrograde atrial conduction. Definitions same as for previous figures.
increases in rate during ouabain treatment (6). Neither this study nor the others cited provides definitive information about the effect of increased rate on the time course of development of digitalis effects on ventricular tissues. All are consistent with either shortening of the entire time course of toxicity, or enhancement of toxicity at some later point in time.

Evaluation of the present findings in terms of postpacing depression of ventricular foci requires consideration from two points of view. Postpacing depression is absent if, as is customary, the cycle length between the last paced beat and the first ventricular beat is compared to the average cycle length before pacing. It is present if the first cycle length after pacing is compared to the average cycle length of the ventricular pacemaker which emerges. In the absence of depression, the first postpacing cycle length should be identical to the average postpacing cycle length. Although this tended to be the case after vagal stimulation and pacing at lower rates, it was not the case after pacing at higher rates. In this sense, a transient postpacing depression was present before the emergence of a rapid ventricular focus.

The presence of a depression clarifies the observation that the first beat after pacing was not always a ventricular beat. If the enhanced ventricular pacemaker can be momentarily depressed, the origin of the first beat after pacing will depend on the relative temporal depression of the various potential pacemakers. It is therefore plausible to posit a sequence in which the first beat or two is atrial but the atrial beats are followed by the emergence of a rapid ventricular focus. Such a sequence was seen in approximately half of the present studies (Fig. 11).

The production of beta-receptor blockade by AY21,011 was followed by a transient period of ventricular tachycardia in four of five dogs. This was previously shown to be due to transient slowing of the sinus node with emergence of a ventricular pacemaker (4). Failure of beta-receptor blockade to avert subsequent rate-related acceleration of the ventricular focus is consistent with findings indicating that digitalis-induced ventricular arrhythmias can occur in the presence of beta-receptor blockade (7). However, interpretation with respect to antiarrhythmic action of a beta-receptor blocking agent also requires consideration of the agent's effect on the rate of arrhythmia. Even if a beta-receptor blocking agent does not terminate a digitalis-
induced ventricular arrhythmia, it may decrease its rate (8). The present study indicates that the decrease in rate may itself further decrease the rate of discharge of a ventricular pacemaker. The effects of specific beta-receptor blocking agents on rate are variable. For example, AY21 011 does not greatly alter rate, but (2-isopropylamino-1-hydroxy-ethyl) methane sulfonanilide (MJ 1999) has been reported to do so (8). Some agents may therefore have an "indirect" antiarrhythmic action mediated through slowing of the ventricular rate.

The basis for postpacing ventricular acceleration during digitalization is not clear. Since changes in rate were induced by external drive, the possible role of the driving stimulus must be considered. Electrical stimulation is known to release stored catecholamines from nervous elements within the myocardium (9), and catecholamines may facilitate digitalis-induced arrhythmias (10). The persistence of postpacing ventricular acceleration after beta-receptor blockade suggests that catecholamines were not involved. Alternatively, toxic doses of cardiac glycosides and increases in driving rate both cause important changes in ionic balance at the membrane level and their combined effects might act synergistically to enhance ventricular pacemakers. Finally, myocardial ouabain uptake may be increased at higher driving rates (2).

The electrophysiological events underlying rate-dependent acceleration of ventricular pacemakers are also not apparent. Ouabain has been shown to decrease the maximum diastolic potential and to increase the rate of spontaneous depolarization of Purkinje fibers in vitro (5) and, despite a decrease in excitability (11), to increase the automaticity of ventricular pacemakers in vivo (6). In the absence of digitalis, increases in driving rate tend to reverse the effects on maximum diastolic potential and slow diastolic depolarization (12). However, no systematic study of the effect of increased rate has been made during digitalization. In the presence of near-toxic amounts of glycoside, rapid drive might produce electrophysiological changes favoring increased automaticity or reentrant activity.

The results reported here may have relevance for the design of experimental studies on digitalis-induced arrhythmias. Most studies on antiarrhythmic drugs have not been controlled for rate. Controversies over the relative effectiveness of antiarrhythmic agents in the treatment of digitalis toxicity may be due to differences in heart rate. The present studies also suggest an alternative method to vagal stimulation for the detection of digitalis-induced effects on ventricular pacemakers before overt ventricular arrhythmias. An advantage of the method is that manipulation of rate at a given point during digitalization may be useful for quantitative evaluation of ventricular pacemaker behavior before and after a given intervention. Finally, although the investigations were performed on dogs, they may have relevance to patients. Pacing is being used as an antiarrhythmic maneuver (13), and caution may be appropriate in the setting of digitalis toxicity.

Acknowledgment

The authors are grateful to Drs. Andrew G. Wallace, Martin Dolgin, and Perry Hogan for their discussion of several aspects of this work.

References

6. VASSALLE, M., GREENSPAN, K., AND HOFFMAN, B. F.: Analysis of arrhythmias induced by...


Acceleration of Ventricular Pacemakers by Transient Increases in Heart Rate in Dogs during Ouabain Administration
STEPHEN M. WITTENBERG, FRITZ STREULI and FRANCIS J. KLOCKE

Circ Res. 1970;26:705-716
doi: 10.1161/01.RES.26.6.705
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1970 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/26/6/705

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/