Chronotropic Effects of Ouabain and Heart Rate on Canine Atrium In Vivo

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ABSTRACT

Positive chronotropic effects from the combination of ouabain administration and rapid stimulation were sought in the atrium and ventricle of ten anesthetized vagotomized dogs with intact atrioventricular conduction during the infusion of ouabain (1 μg/kg min⁻¹) until the onset of ventricular tachycardia. Sinus rhythm was interrupted every minute by 15 seconds of atrial pacing at either 150 or 200 beats/min. Positive chronotropic effects were recognized immediately after pacing as (1) early ventricular escape beats during vagal stimulation, (2) early atrial escape beats during vagal stimulation, or (3) blunting of the normal postpacing atrial depression. Positive chronotropic effects were rate dependent in both chambers, but they were seen less often in the atrium than in the ventricle. Early ventricular escape beats occurred in all ten dogs at a pacing rate of 200 beats/min when 69 ± 12% of the dose of ouabain required to induce ventricular tachycardia had been administered. They occurred in six of ten dogs at 150 beats/min after infusion of 81 ± 6% of the dose of ouabain which induces tachycardia. Early atrial escape beats did not occur when the hearts were paced at 150 beats/min. However, they appeared in three of ten dogs paced at 200 beats/min after infusion of 93 ± 5% of the dose of ouabain which induces tachycardia. Blunting of the normal postpacing atrial depression occurred in six of ten dogs at both 150 and 200 beats/min at 100 ± 4% and 89 ± 5%, respectively, of the dose of ouabain required to induce ventricular tachycardia. Six additional dogs with heart block were paced at an atrial rate of 250 beats/min to facilitate positive chronotropic effects in the atrium with simultaneous ventricular pacing at 60 beats/min to delay the onset of positive chronotropic effects in the ventricle. This procedure allowed more consistent and relatively earlier detection of atrial positive chronotropic effects. In these experiments, early atrial escape beats occurred in five dogs after infusion of 80 ± 3% of the dose of ouabain required to induce ventricular tachycardia, and blunting of the normal postpacing atrial depression occurred in all six dogs after 78 ± 3% of the tachycardia-inducing dose of ouabain had been infused. It was concluded that toxic doses of ouabain induce positive chronotropic effects in the atrium of intact dogs. The effects occur later than do similar effects in the ventricle. Moreover, the positive chronotropic effects are heart rate dependent in both chambers and can be studied by atrial-ventricular differential rate experiments.

KEY WORDS

atrial automaticity
digitalis toxicity
ventricular automaticity
postspacing acceleration
vagal stimulation
transient depolarization
postspacing depression
atrial specialized fibers
atrial block
purkinje fibers
neous atrial automaticity in less than toxic doses. However, an increase in spontaneous rate at toxic doses sometimes occurs.

Work from this laboratory has demonstrated that early positive chronotropic effects in the ventricle are heart rate dependent during digitalization (5, 6). They occur only when rapid rates are present, and step increases in pacing rate cause step increases in postpacing ventricular rate. During studies on the relationships among heart rate, digitalis, and ventricular pacemaker activity, several observations have suggested that similar effects on atrial pacemakers might be induced by rapid drive. Although step increases in atrial rate cause progressive depression of the atrium during the early stages of digitalization, the opposite appears to occur during the later part of digitalization. Whereas vagal stimulation causes asystole during the early stages of digitalization, atrial escape beats often occur during vagal stimulation just prior to digitalis-induced ventricular tachycardia. These beats appear more frequently and exhibit a shorter coupling interval after relatively rapid atrial driving rates. Isolated examples of these effects have occurred in records from previous publications (5, 6), but they have not been studied in detail or discussed. Recently, evidence for a rate-dependent positive chronotropic effect in isolated atrial tissues has been reported (11). The present study was designed to determine systematically the relationships among heart rate, digitalis, and atrial pacemaker activity and to compare the findings with simultaneous observations on ventricular pacemakers in whole dogs.

Methods

GENERAL PREPARATION

Sixteen mongrel dogs of both sexes weighing 14–20 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv), intubated, and ventilated with a mixture of room air and oxygen. The constant-volume ventilator and the oxygen supplement were adjusted periodically to keep arterial P0₂ above 60 mm Hg and pH between 7.35 and 7.45. All dogs underwent right thoracotomy for placement of bipolar stimulating and recording electrodes on the surface of the heart. Subsequently the lungs were carefully reinflated and the chest was closed with clips to facilitate maintenance of temperature and blood gases. Catheters were inserted into a femoral artery for pressure recording and a femoral vein for drug infusion. A standard lead II electrocardiogram (ECG) was recorded in addition to surface atrial electrograms. The vagus nerves were exposed in the neck and cut. The distal end of the right vagus nerve was stimulated with a bipolar platinum electrode using square-wave impulses (11 v, 2.5 msec, 5–30 Hz). Studies were done before and during infusion of ouabain (1 μg/kg min⁻¹). Experiments were usually continued until 10 or 15% more than the dose of ouabain necessary to induce ventricular tachycardia had been administered. Ventricular tachycardia was defined as spontaneous ventricular rhythm which was consistently more rapid than spontaneous atrial or artificially paced ventricular rhythm.

DOGS WITH INTACT ATRIOVENTRICULAR CONDUCTION

Studies in ten dogs with intact atrioventricular (AV) conduction were designed (1) to assess changes in spontaneous atrial rate, (2) to determine the effects of different atrial pacing rates on postpacing atrial depression and on the tendency of atrial pacemakers to escape during vagally induced atrial arrest, and (3) to evaluate the concomitant effects of these same pacing rates on the tendency of ventricular pacemakers to escape during vagally induced atrial arrest. The protocol for these experiments involved the following measurements repeated sequentially until after the onset of digitalis-induced ventricular tachycardia. The cycle length of the first postpacing atrial beat was determined after 15 seconds of atrial pacing at 150 beats/min and at 200 beats/min; then atrial and ventricular escape beats were sought during 5 seconds of vagal stimulation after 15 seconds of atrial pacing at 150 beats/min and at 200 beats/min. Spontaneous atrial rhythm was allowed for 45–60 seconds between each of the periods of pacing, and atrial rate was assessed at the end of the periods of spontaneous beating. The effects of atrial pacing at 150, 175, 200, and 230 beats/min were also assessed during the control period and late in the experiment when definite atrial changes were present. This assessment was done by determining the cycle length of the first postpacing atrial beat after 15 seconds of atrial pacing at each of these rates.

Five of the ten dogs received the β-receptor blocking agent propranolol intravenously in doses of 0.3 mg/kg initially followed by 0.15 mg/kg every 20–30 minutes. Propranolol in these doses was helpful in achieving consistent vagally induced atrial arrest and did not appear to influence the data.

DOGS WITH HEART BLOCK

Studies in an additional six dogs were designed so that the atra and the ventricles could be driven at different rates. Complete AV block was produced by placing a ligature in the area of the His bundle through an atriotomy during temporary venous inflow occlusion. Care was taken to avoid injuring the sinus node artery. The atrial protocol involved intermittent atrial pacing at 250 beats/min for 15 seconds to assess the cycle length of the first postpacing atrial beat and alternately to search for atrial escape beats during 4 seconds of vagal stimulation immediately following pacing. As before, 45–60 seconds of spontaneous atrial rhythm was allowed between the periods of pacing, and spontaneous atrial
rate was assessed at the end of each of the spontaneous periods. The ventricle was paced continuously at 60 beats/min. All of these dogs received propranolol as described above.

Results

SPONTANEOUS ATRIAL RATE (ALL DOGS)

There was a small increase in spontaneous atrial rate between the control period and the onset of ventricular tachycardia (136 ± 4 [SE] beats/min vs. 144 ± 4 beats/min), but the increase was not statistically significant (Table 1). Propranolol uniformly decreased spontaneous atrial rate in a given dog, but the variability in rate among dogs was so great that there was no significant difference between the 5 dogs that were not subjected to β-receptor blockade and the 11 dogs that were during the control period (134 ± 6 beats/min vs. 138 ± 5 beats/min) or at the time of ventricular tachycardia (137 ± 5 beats/min vs. 148 ± 6 beats/min).

ATRIAL PACING (DOGS WITH INTACT AV CONDUCTION)

Fifteen seconds of atrial pacing was uniformly followed by depression of the first postpacing atrial beat prior to ouabain administration. The percent depression was calculated as the cycle length of the first postpacing beat minus the average prepacing cycle length divided by the average prepacing cycle length and multiplied by 100. Depression averaged 128 ± 5% after pacing at 150 beats/min and 124 ± 10% after pacing at 200 beats/min. A progressive decrease in postpacing atrial depression (previously termed blunting of postpacing depression in studies on the ventricle [6]) was seen in six of ten dogs during ouabain administration. Postpacing atrial acceleration (cycle length of the first postpacing beat shorter than the average prepacing cycle length) was also seen in four of these six dogs. Three of the six dogs that showed blunting of postpacing atrial depression received propranolol and three did not. Three of the dogs that exhibited postpacing atrial acceleration received propranolol and one did not. Figure 1 illustrates an atrial electrogram from an experiment in which blunting of postpacing atrial depression and postpacing atrial acceleration were present. The numbers in the left-hand columns at both pacing rates refer to the average prepacing cycle length (msec). The numbers in the right-hand columns give the cycle length of the first postpacing atrial beat (msec). In the control period, there was considerable depression of the first postpacing atrial beat which was more marked after pacing at 200 beats/min than it was after pacing at 150 beats/

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MEAN ± SE

151 ± 7*  138 ± 5*  136 ± 4†  144 ± 4†  131 ± 5  147 ± 4

AV conduction was intact in experiments 1-10 and was interrupted in experiments 11-16.

*Paired P < 0.01.
†Paired P was not significant.
ATRIAL EFFECTS OF HEART RATE AND OUABAIN

Effect of ouabain infusion on spontaneous atrial cycle length and on the cycle length of the first atrial beat after 15 seconds of atrial pacing at 150 and 200 beats/minute. On and off refer to the beginning and the end of atrial pacing. Times indicate minutes after initiation of ouabain infusion. The recordings are from experiment 5 (Table 1). See text for details.

min. This depression persisted until 61 minutes after initiation of ouabain infusion when the cycle length of the first postpacing atrial beat decreased abruptly to 502 msec after pacing at 200 beats/min. There was a progressive decrease in the cycle length of the first postpacing beat as seen in the 67-minute recording. A similar but quantitatively smaller change was seen after pacing at 150 beats/ min at 65 minutes. The dog developed ventricular tachycardia almost immediately after the 67-minute recording. It can be seen that loss of postpacing atrial depression occurred very late, i.e., very close to the onset of ventricular tachycardia at both pacing rates. However, it was detected first and was slightly more marked after pacing at 200 beats/min as opposed to pacing at 150 beats/ min at 65 minutes. The dog developed ventricular tachycardia almost immediately after the 67-minute recording. It can be seen that loss of postpacing atrial depression occurred at 89 ± 5% and at 100 ± 4% of the dose of ouabain necessary to induce ventricular tachycardia at the pacing rates of 200 and 150 beats/min, respectively. At the time of ventricular tachycardia, step increases in atrial rate caused progressive decreases in the cycle length of the first postpacing atrial beat in all six dogs. Figure 2 shows the effect of step increases in rate in the experiment illustrated in Figure 1. The left of Figure 2 shows atrial pacing at several rates prior to the start of ouabain infusion. Increases in pacing rate caused modest increases in postpacing atrial depression. The right of Figure 2 shows pacing at the same rates after the onset of ventricular tachycardia (67 minutes or more after initiation of ouabain infusion). Increases in pacing rate were accompanied by blunting and, at a rate of 175 beats/ min and above, by acceleration of the first postpacing atrial beat.

VAGAL STIMULATION (DOGS WITH INTACT AV CONDUCTION)

Five seconds of vagal stimulation was accompanied by atrial and ventricular asystole in all dogs during the control period. Figure 3 illustrates the usual sequence of vagally induced escape beats in the two chambers during digitalization. The top recording at each pacing rate is a lead II ECG and best shows ventricular escape, and the bottom recording is an atrial electrogram and best illustrates atrial escape. During the control period, vagal stimulation was followed by atrial and ventricular asystole at both pacing rates. The first digitalis effect was early ventricular escape; it was seen 30 minutes after initiation of ouabain infusion after rapid pacing at 200 beats/min. This effect was progressive with earlier and more frequent escape beats as ouabain infusion continued. The next change was early ventricular escape after pacing at 150 beats/min occurring at 39 minutes; it was also progressive. The coupling interval of the first escape beat seen after pacing at 150 beats/min at 39 minutes was longer than that of the beat seen earlier at 200 beats/min. Early atrial escape first occurred after pacing at 200 beats/min at 40 minutes. Its origin in the atrium was established by its precedence over the first ventricular escape beat. A similar beat with a slightly shorter coupling interval was seen at 45 minutes. Early atrial escape was not seen at all after pacing at 150 beats/min.

The results of all ten experiments of this type
are summarized in Figure 4 and Table 2. Ventricular escape beats occurred in ten of ten dogs after pacing at 200 beats/min and began at an average of 69 ± 12% of the dose of ouabain which induces ventricular tachycardia. Ventricular escape beats were seen in six of ten dogs after pacing at 150 beats/min and began at an average of 81 ± 6% of the dose which induces ventricular tachycardia. Atrial escape beats during vagal stimulation were seen in only three of ten dogs after pacing at 200 beats/min and occurred at 93 ± 5% of the dose necessary to induce ventricular tachycardia in those three dogs. Atrial escape beats were not seen in any dog after pacing at 150 beats/min. It is evident that all of the atrial effects occurred approximately at the time of ventricular tachycardia.

RELATIONSHIPS BETWEEN HEART RATE AND ATRIAL AND VENTRICULAR CHRONOTROPIC EFFECTS (DOGS WITH INTACT AV CONDUCTION)

The dose of ouabain necessary to produce ventricular tachycardia varied considerably from dog to dog with a range of 34 to 67 μg/kg and a mean of 49 ± 3 μg/kg. Since previous studies have shown the rate dependence of early digitalis-induced increases in ventricular automaticity (5, 6), an attempt was made to relate spontaneous atrial rate throughout the present experiments with the dose of ouabain required to produce ventricular tachycardia. Spontaneous atrial rate was important in this protocol, since it dominated during most of each experimental period. In Figure 5 the ten dogs were separated arbitrarily into two groups of five on the basis of spontaneous rate. In one group (solid circles) the rate was generally high to begin with and did not decrease during the experiment. In the other group (open circles) the rate was either low to begin with or decreased considerably during the experiment. Although there was some overlap in rate between the groups during the control period, they completely separated after 35 minutes of ouabain infusion (five dogs above and five dogs below 120 beats/min) and remained essentially separate for the remainder of the experiment. The time (or dose) required for induction of ventricular tachycardia is represented by the last data point on the right for each dog. The high-rate group developed ventricular tachycardia at a mean dose of 40 ± 2 μg/kg, whereas the low-rate group required a dose of 58 ± 3 μg/kg (P < 0.01). It is evident that atrial effects were seen more often and earlier in relation to ventricular tachycardia when the tachycardia was delayed by spontaneous heart rate.
ATRIAL EFFECTS OF HEART RATE AND OUABAIN

Table 2
Cumulative Ouabain Dosage (μg/kg) at Onset of Positive Chronotropic Effects in Dogs with Intact AV Conduction

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<th>Expt.</th>
<th>Propranolol</th>
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<th>Atrial blunting</th>
<th>Atrial escape during vagal stimulation</th>
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Mean ± SE

|       | 39 ± 4      | 33 ± 2        | 56 ± 5        | 47 ± 3        | 51 ± 5        | 49 ± 3        |

VT = ventricular tachycardia.

ATRIAL-VENTRICULAR DIFFERENTIAL RATE EXPERIMENTS (DOGS WITH HEART BLOCK)

The experiments on dogs with intact AV conduction demonstrated that digitalis-induced atrial effects occurred earlier and more frequently after pacing at 200 beats/min than they did after pacing at 150 beats/min. In addition they illustrated that ventricular tachycardia occurred later at relatively low ventricular rates. The atrial-ventricular differential rate protocol was devised to facilitate atrial toxicity by pacing the atrium at 250 beats/min and to delay ventricular toxicity by pacing the ventricle at 60 beats/min. Figure 6 illustrates an atrial-ventricular differential rate experiment. The top trace in each section is a lead II ECG, and the bottom trace is an atrial electrogram. The left of
the figure illustrates the effects of 15 seconds of atrial pacing at 250 beats/min on the cycle length of the first postpacing atrial beat. The right is intended to show atrial escape beats during vagal stimulation. The separation of atria and ventricles is most easily seen in the lead II ECG recordings on the right of the figure just prior to vagal stimulation. Blunting of the postpacing atrial depression (in this case actual postpacing acceleration) occurred at 52 minutes, and early atrial escape beats during vagal stimulation were evident at 53 minutes. Both changes were progressive. Atrial arrhythmia could be studied for 13 minutes before the dog developed ventricular tachycardia at 65 minutes. The 58- and 59-minute records illustrate that drive-induced acceleration of atrial pacemakers was characterized by deceleration of the beats succeeding the first postpacing beat (as has been shown previously to occur in the ventricle).

In the dogs with intact AV conduction atrial pacing at 200 beats/min decreased the time of appearance of atrial effects over pacing at 150 beats/min. In the dogs with heart block the atrium was paced at 250 beats/min. The additional increase in atrial rate was not accompanied by an additional reduction in the time of appearance of atrial escape (56 ± 5 minutes for dogs with heart block paced at 250 beats/min vs. 51 ± 5 minutes for dogs with intact AV conduction paced at 200 beats/min). Nor did it hasten the onset of blunting of postpacing
ATRIAL EFFECTS OF HEART RATE AND OUABAIN

atrial depression (53 ± 3 minutes vs. 47 ± 3 minutes). In contrast, continuous ventricular pacing at a rate of 60 beats/min in the dogs with heart block delayed the onset of ventricular tachycardia significantly beyond that seen in the dogs with intact AV conduction and ventricular rates 2-2.5 times as great. The net effect was to allow relatively earlier and more consistent detection of atrial effects. Atrial escape was seen in five of six atrial-ventricular differential rate experiments at a mean of 80 ± 3% of the dose of ouabain required to induce ventricular tachycardia. Atrial blunting was seen in six of six of the experiments at a mean of 78 ± 3% of the dose which induced ventricular tachycardia (Table 3).

Discussion

The results of the present study are consistent with those of previous investigators (9) showing no significant change in spontaneous atrial rate in denervated animals digitalized to an end point of ventricular tachycardia. However, this study demonstrates that the combination of rapid pacing and digitalis is associated with significant positive chronotropic effects in the atrium during this time period. These effects include (1) progressive blunting of the normal postpacing atrial depression, leading eventually to postpacing atrial acceleration, and (2) the development of atrial escape beats during vagal stimulation. The magnitude of these effects at a given dose of glycoside varies with the heart rate and is greater at faster rates. The chronotropic response of the atrium to the combination of rapid rate and digitalis is qualitatively similar to that described previously for the ventricle of intact dogs (6) and for isolated canine Purkinje fibers perfused with ouabain (12).

Although the relationships among heart rate, digitalis, and postpacing chronotropic response appear to be qualitatively similar in ventricle and atrium, the present study demonstrates important quantitative differences. At a given heart rate and systemic administration rate of glycoside, ventricular escape beats during a few seconds of vagal stimulation are seen earlier and more frequently than are blunting of postpacing atrial depression and atrial escape beats. In fact, when heart rate is the same in both chambers, as in dogs with intact AV conduction, the atrial effects occur at a time very close to the onset of ventricular tachycardia. The late onset and the rate dependence of digitalis-induced positive atrial chronotropic effects may explain why they have not been observed more often in the past.

The reasons why atrial changes occur later and are less marked than those in the ventricle are not clear. Several possibilities must be considered. Studies utilizing tritiated ouabain and digoxin in the guinea pig and the rat have shown that the atrium accumulates glycoside at a slower rate than does the ventricle and that the final quantity bound per unit volume of tissue is also less (13, 14). A similar distribution has been found in human tissues using radioactive digitoxin (15). Even if the glycoside level at the membrane is the same, differential sensitivities of atrial and ventricular tissues may exist. It is also possible that morphological differences between the atrium and the ventricle play a role. The number of latent pacemaker cells undoubtedly is greater in the ventricle than it is in the atrium. Thus, other things being equal, there is a statistical likelihood that ventricular effects might precede those in the atrium. In addition, ventricular specialized tissues traverse relatively long distances free of any connections to muscle, whereas atrial specialized tissues probably make frequent connections to muscle throughout their course. It has been postulated that muscle contiguous to atrial

### Table 3

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<td>56 ± 3</td>
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*Circulation Research, Vol. XXXIV, February 1974*
specialized tissue exerts an electronic effect which tends to delay the onset of positive chronotropic responses in the atrium (11). Finally, parasympathetic nerve endings exerting an inhibiting effect on atrial but not on ventricular pacemaker tissues must also be considered.

A number of studies have attempted to define the electrophysiological mechanism responsible for blunting of postspacing depression and postspacing acceleration in ventricle and atrium (11, 12, 16-19). In the isolated Purkinje fiber perfused with ouabain, rapid drive leads to a decrease (shift toward zero) in maximum diastolic potential and a proportionate decrease in threshold potential. A marked increase in the slope of early diastolic depolarization also occurs and appears to be the most important change favoring the onset of spontaneous beating (12). In the isolated Purkinje-papillary muscle preparation, spontaneous beating does not always occur following rapid drive (17). Instead, the increase in phase 4 depolarization may lead to a local potential which has been termed a transient depolarization (TD) by Ferrier et al. (16, 19) and a low-amplitude potential (LAP) by Rosen et al. (18). Spontaneous firing, as opposed to a TD or LAP, has been shown to be more common when the extracellular potassium concentration is low (2.5 mmoles/liter instead of 4.0 mmoles/liter), when the tissue is stretched, or both (18). In similar studies the plateau fibers of the atrium (20) have also been found by Hashimoto and Moe (11) to develop TDs. When they are studied as free-running strands, they also develop spontaneous beating following rapid drive. Interestingly, when Purkinje fibers and atrial plateau fibers were studied in the same perfusion, the atrial tissue developed TDs later than did the ventricular tissue. This finding is consistent with those reported in this paper for whole dogs. It is not yet clear whether a TD or LAP is qualitatively similar to an increase in automaticity, i.e., whether the only difference is the failure to reach threshold potential or whether important ionic differences exist between these local potentials and classical automaticity.

The appearance of atrial escape during vagal stimulation in intact dogs is consistent with earlier work by Toda and West (21), demonstrating a similar phenomenon in the isolated sinoatrial node of the rabbit. These investigators found a decrease in the negative chronotropic response to vagal stimulation during perfusion with \(2 \times 10^{-6}\) g/ml of ouabain. They suggested that this decrease could result either directly from an increase in the automaticity of atrial pacemaker tissue or from interference with the neural control of the tissues. The experiments reported in the present paper favor the former explanation. Atrial escape beats during vagal stimulation occurred at about the same time as isolated rate effects, i.e., blunting of postspacing atrial depression and postspacing atrial acceleration. In addition, an increase in pacing rate at a given dose of ouabain caused an increase in frequency and a decrease in coupling interval of either atrial escape beats during vagal stimulation or early atrial postspacing beats. This response cannot be explained by interference with neural control. Externat drive is known to act in part through parasympathetic stimulation (22). Since our electrodes were sutured in the area of the sinus node—an area heavily innervated by the vagus—increases in rate should have antagonized rather than facilitated decreases in neural control. Two additional experiments not reported in Results supply some direct evidence that antagonism of neural control was not involved. Two dogs were studied after atropinization (0.04 mg/kg every 0.5 hours), and electrodes were sutured to the left atrial appendage to avoid areas heavily innervated by the vagus. Although vagal stimulation could not be employed, blunting of postspacing atrial depression and postspacing atrial acceleration occurred with the same temporal sequence as they did in other dogs. Thus, our data favor a direct positive chronotropic effect of rate and glycoside on atrial pacemaker tissues. During vagal stimulation early atrial escape beats would be expected to occur when the magnitude of this increase was enough to overcome the competitive negative chronotropic effect of parasympathetic stimulation.

Although atrial dysrhythmias are thought to constitute approximately a third of the rhythm abnormalities due to digitalis in patients (23), little is known about the mechanisms which cause them, partly because no reproducible model in the whole animal has been available for study. Two observations are presented which appear to be helpful in the development of such a model. (1) Digitalis-induced chronotropic changes occur later in the atrium than in the ventricle. (2) These changes are rate dependent in both chambers. Based on these observations several approaches to the study of digitalis-induced atrial chronotropic effects in the intact animal appear potentially fruitful. Ventricular toxicity may be retarded by maintaining slow ventricular rate, as described in the atrial-ventricular differential rate experiments. An alternative ap-
proach would be to avoid ventricular toxicity completely by using sinus node perfusion, as described by other investigators (24, 25). Early atrial chronotropic changes can be detected by observing the response of atrial pacemakers to a period of rapid pacing as was done in the atrial-ventricular differential rate experiments. An alternative approach might be to use single early atrial depolarizations following rapid pacing, as described by other investigators for the ventricle (4).

The observation that rapid rate is important in the development of a positive chronotropic response to digitalis in the atrium may also have clinical relevance. Atrial rates over 200 beats/min in patients are not uncommon and may contribute to the development of digitalis-induced atrial tachyarrhythmias.

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