Supraventricular Pacemaker Underdrive in the Absence of Sinus Nodal Influences in the Conscious Dog

JEROD M. LOEB, DAVID K. MURDOCK, WALTER C. RANDALL, AND DAVID E. EULER

SUMMARY The ability to reduce and maintain heart rate by electrical stimulation (underdrive) was tested in three groups of chronically instrumented dogs: sinoatrial node intact, ectopic atrial pacemaker produced by injection of rapidly hardening latex into the sinoatrial nodal artery, and idioventricular pacemaker produced by injection of formalin into the atrioventricular node. In the conscious unsedated state, underdrive of sinoatrial or idioventricular pacemakers resulted in competition between driven and intrinsic foci. However, the cycle length of ectopic atrial pacemakers could be increased by 148.4 ± 30.7 msec (P < 0.001) and maintained at that value. Cessation of underdrive resulted in a period of pacemaker suppression similar to that produced following overdrive. Single premature stimuli produced marked cycle length prolongations in dogs with ectopic atrial foci. Total autonomic blockade had no significant effect on the production of underdrive. Thus, the results of the present experiments provide evidence for maintained capture of cardiac pacemakers at rates significantly below intrinsic control and indicate that underdrive varies as a function of pacemaker site. Underdrive may explain the failure of junctional escape in the presence of slower atrial rhythms. Circ Res 44: 329-334, 1979

IT IS generally recognized that cardiac pacemakers will follow electrical drive at rates in excess of their inherent rate and that the cessation of pacing normally is followed by a period of quiescence called

overdrive suppression (Vassalle, 1977). It has been demonstrated that the susceptibility to overdrive suppression varies such that the sinus node is least susceptible, whereas increasing susceptibility is shown by ectopic atrial, atrioventricular (AV) junctional, and ventricular pacemakers, respectively (Lange, 1965). Overdrive suppression has also been used to explain the hierarchical dominance of cardiac pacemakers (Vassalle, 1970). However, it is clear that prolonged drive is not a prerequisite in order to provoke pacemaker suppression. Thus, transitory


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depression in cardiac pacemaker activity has been shown to follow the introduction of a single premature stimulus into the cardiac cycle of both in vitro (Bonke et al., 1968; Bonke et al., 1971; Klein et al., 1973) and in vivo preparations (Pick et al., 1951; Strauss et al., 1973). Jalife and Moe (1976) recently have shown for Purkinje fibers that electrotonic influences, acting early in the cycle, prolong the following cycle. Single premature atrial stimuli have been shown to prolong subsequent cycle lengths in patients exhibiting symptoms of sinus node dysfunction (Strauss et al., 1973). However, the maintained capture of any cardiac pacemaker at a rate less than its spontaneous control rate has not been shown and would seem to be electrophysiologically incompatible with current theories of pacemaker function. In fact, Lange (1965) reported that stimulation at or near the control cycle length resulted in the production of competition between driven and inherent beats and subsequent flutter or fibrillation. In the absence of sinus nodal influences, Rosenblueth (1955) was able to briefly capture subsidiary pacemakers at a rate below the inherent rate in the anesthetized animal. The present study therefore was undertaken to characterize the ability of cardiac pacemakers to be driven electrically at rates below their inherent rate in the conscious animal. Specifically, the following questions were posed: (1) Can subsidiary pacemakers be captured and maintained at rates below the spontaneous control rate? (2) What is the susceptibility of various pacemakers to this effect? (3) What is the response of subsidiary pacemakers to single premature stimuli?

**Methods**

**Preparation**

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg). The trachea was intubated and the animal ventilated with a Bird Mark 7 respirator. With sterile procedures a thoracotomy was performed at the 4th right intercostal space. The heart was exposed and a pericardial cradle constructed. In eight dogs (group I), the sinus node artery was identified and isolated for approximately 1.0 cm above the atrioventricular sulcus. The artery was tied proximally and catheterized distally using PE50 polyethylene tubing (Clay-Adams). Lead II of the electrocardiogram was monitored at all times. The distribution of the artery was verified both by inspection and by injection of 0.3 ml of indocyanine green (Cardio-Green, H. W. and D., Inc.). Injection bradycardia and the appearance of dye in the region of the sinus node were used to document the distribution of the vessel. A solution of red vinyl (Carolina Biological Supply) was then rapidly introduced into the vessel in a volume sufficient to clear the indocyanine green (usually 0.5 ml). This material rapidly (within 5 seconds) hardened within the distribution of the nodal artery, thus preventing both antegrade and retrograde perfusion of the region. The catheter then was removed from the vessel. A bipolar plaque electrode with stainless steel pins was sewn to the right atrial appendage and the wires exteriorized in the neck. The chest was closed in the usual fashion and the dog was allowed to recover. A group of five sham-operated control animals also were prepared in which the sinus node artery was left intact and a similar electrode sewn to the right atrial appendage (group II).

The same surgical exposure was used for six additional dogs (group III) to produce complete heart block by a modification of the technique described by Scherlag et al. (1967). A 25-gauge needle was inserted 1.5 cm lateral to the coronary sinus through the free wall of the right atrium. The needle was directed inferiorly toward the region of the AV node. The needle position was adjusted until lidocaine injection produced a transitory period of 2° or 3° heart block. When the position was assured, 0.2 ml of 37% formalin was then introduced into the region. This resulted in the immediate production of complete heart block. A bipolar plaque electrode was sewn to the right ventricle, and the wires were exteriorized in the neck region. The chest was closed in the usual fashion and the animal allowed to recover.

**Stimulation**

Studies were begun 24 hours postoperatively when the dogs were conscious and alert. A continuous record of lead II of the electrocardiogram was obtained and displayed on a Grass model 7 polygraph. The paper speed was 25 mm/sec. Stimuli to the pacing electrode were provided via a digital stimulator (Pulsar 4i; Frederick Haer and Co.) using pulse durations of 5.0 msec and suprathreshold voltages. For each dog, responses to atrial or ventricular pacing for 30 seconds at 100% above spontaneous rate were determined. The corrected pacemaker recovery time was calculated as pacemaker recovery time minus the average control cycle length over the 1-minute period immediately preceding drive. In addition, the response of subsidiary pacemakers to single premature stimuli, imposed at various times in the cardiac cycle, was examined.

The susceptibility of dogs from each group to electrical drive at rates below spontaneous control was tested next. After a determination of the control cycle lengths, pacing was begun at a cycle length slightly greater than control cycle length. Underdrive cycle lengths were increased in 10-msec increments until the heart could no longer follow the pacing stimulus without competition from the intrinsic focus. Underdrive was defined as the ability to pace without competition from the inherent focus at a cycle length at least 50 msec greater than control, maintenance of pacing at this rate for at least 30 seconds and, on cessation of pacing, a return to control cycle length. Corrected underdrive times
were calculated as underdrive cycle length minus average spontaneous cycle length for the 1-minute period immediately preceding the underdrive.

Several of the dogs in group I were studied after atropine (0.1 mg/kg) and propranolol (0.5 mg/kg) were administered intravenously. Maximum cycle length prolongations were again determined and calculated as above.

The data were analyzed using Student's $t$-test for paired data, and values were considered statistically significant when the $P$ value was less than 0.05. In all cases, the mean ± standard error of the mean (SEM) is expressed.

**Results**

**Group I Dogs**

Previous studies of subsidiary pacemaker function have used techniques ranging from radon destruction of the sinus node (Borman and McMillan, 1927), infusion of eserine into the sinus nodal artery (Urchaler et al., 1973), and exclusion of the sinus node (Sealy et al., 1973) to a partial or complete excision of the node (Randall et al., 1978; Jones et al., 1978), to unmask subsidiary pacemakers. Since distribution of the sinus node artery is extensive (Hardie et al., 1976), it was reasoned that blockade of sinus node artery distribution might be expected to produce a more reasonable model for pathological unmasking of subsidiary atrial pacemakers. Using this technique, most, if not all, of the primary pacemaking cells would be rendered ischemic. In all group I dogs, the immediate response to vinyl injection through the sinus nodal artery was the prompt abolition of sinus activity and the production of a junctional pacemaker (Fig. 1). After induction of anesthesia with pentobarbital, the mean sinus rate was 133.9 ± 9.1 beats/min. After vinyl injection through the nodal artery, the rhythm became junctional and the rate decreased to 81.7 ± 6.2 beats/min ($P < 0.001$). The dogs in group I were studied at various times from 1 through 12 days postoperatively.

Figure 2 shows an example of a dog studied 3 days postoperatively. The upper trace in panel A is lead II of the electrocardiogram, and the lower trace is an atrial electrogram recorded simultaneously with the electrocardiogram. Note that the cycle lengths of both the atrial and junctional pacemakers are variable, and, periodically, isorhythmic AV dissociation may be present. Panel B shows the control cycle length (545 msec) with the institution of underdrive at the downward arrow (857 msec). The seventh stimulus captured and maintained the heart at a cycle length of 857 msec (312 msec longer than the average control). The rate was maintained at this level for 60 seconds. Panel C shows the last four of the underdriven beats (arrows). Underdrive was terminated at the fourth downward arrow, and a period of pacemaker suppression is apparent, with return to approximately control rate (500 msec) within a short period. Although in this case the first return cycle showed the greatest suppression, in some instances secondary pauses were apparent. Seven of eight dogs in group I showed underdrive capture, and summary data for these animals are presented in Table 1. Underdrive significantly reduced the rate below the inherent control ($P < 0.001$). The corrected recovery times following 30 seconds of overdrive, recorded on the same day as underdrive, also are shown. Corrected recovery times were significantly greater than control cycle lengths ($P < 0.001$).

In two group I dogs, because the subsidiary atrial pacemaker was quite unstable and control rate varied, underdrive could not be tested under control conditions. Panel A of Figure 3 shows an example of this phenomenon. Failure of the subsidiary atrial pacemaker frequently resulted in escape beats of either junctional or idioventricular origin. The fact that these pauses were autonomically mediated is shown in panel B. This was recorded after the administration of both atropine and propranolol. The rate has stabilized at 64 beats/min and no pauses are demonstrable. The same abolition of arrhythmias was produced by atropine alone, and the administration of only propranolol prolonged
TABLE 1  Correlation between Pacemaker Location, Maximum Underdrive, and Maximum Overdrive

<table>
<thead>
<tr>
<th>Dog</th>
<th>Days post-op</th>
<th>Rhythm</th>
<th>Mean control cycle length (msec)</th>
<th>Maximum corrected underdrive (msec)</th>
<th>Maximum corrected overdrive recovery time (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>JR</td>
<td>811</td>
<td>71</td>
<td>2235</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>EA/JR</td>
<td>285</td>
<td>158</td>
<td>1770</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>EA/JR</td>
<td>682</td>
<td>151</td>
<td>4590</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>JR</td>
<td>682</td>
<td>68</td>
<td>2570</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>JR</td>
<td>671</td>
<td>129</td>
<td>1750</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>EA/JR</td>
<td>500</td>
<td>312</td>
<td>3860</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>EA/JR</td>
<td>600</td>
<td>150</td>
<td>3740</td>
</tr>
</tbody>
</table>

Mean 5.0 ± 1.4

JR = junctional rhythm, EA/JR = ectopic atrial/junctional rhythm.

* P < 0.001

Following the stimulus is a pause of 4600 msec. The cycle length then gradually returned toward the control level. Maximal prolongation in the first poststimulation cycle was not always the rule. In Figure 5, a junctional rhythm was present. Following the third complex (at the arrow), a single premature atrial stimulus was delivered 20 msec early (840 msec). This was followed by a gradual prolongation of cycle lengths, reaching a maximum with the fourth cycle (5360 msec). The cycle length then gradually decreased below control with eventual return to the control value within about 20 seconds. Spontaneous slowing of this nature never was observed unless induced by either an electrical premature stimulus or a spontaneous premature beat. In all dogs tested in which underdrive was produced, marked cycle length prolongations followed the interposition of single premature atrial stimuli. This prolongation decreased as the pacemaker became more stable.

Group II Dogs

Since little suppression is apparent after atrial overdrive with an intact sinus node (Lange, 1965),
underdrive was studied in five animals with intact sinoatrial (SA) nodes, using the same protocol as previously described. Each of the dogs was studied while resting quietly and unsedated. The mean control cycle length in this group was 622.2 ± 55.9 msec. The mean corrected recovery time was 226.6 ± 60.8 msec. In no case did underdrive stimulation capture and maintain the rate at a level below the inherent control. In addition, single premature stimulation did not prolong cycle length in the manner previously described in subsidiary atrial pacemakers.

**Group III Dogs**

Since idioventricular pacemakers do show a marked susceptibility to overdrive suppression (Vassalle, 1977), a group of six animals with idioventricular rhythms was prepared to determine whether their susceptibility to underdrive also would be marked. In this group, the mean control cycle length was 1471.3 ± 199.2 msec. The mean corrected recovery time was 6848.7 ± 1308.9 msec (P < 0.001). However, in no instance did underdrive pacing capture and maintain the rate at a level below control. Figure 6 shows a typical example of the results obtained in this group. The first trace in the upper panel (A) shows the control idioventricular rhythm at a rate of 32 beats/min. At the arrow, overdrive was initiated (120 beats/min) and maintained for 30 seconds. The central portion of the trace was omitted and the last three paced beats are shown. Note the prominent pacemaker suppression following the drive. During the suppression, the P-P interval gradually decreased. The lower panel (B) shows the response to underdrive. The control rate is 32 beats/min. Underdrive was initiated at the arrow at a rate of 25 beats/min. Note that both the inherent and driven beats appear to be competing. Underdrive, in all dogs with complete heart block, resulted in a similar pacemaker competition, and in no case was maintained underdrive capture produced.

**Discussion**

Current theories of pacemaker (both true and subsidiary) function are not compatible with the idea of a maintained electrical reduction in heart rate (Brooks and Lu, 1972). However, Rosenblueth (1955) did demonstrate a brief reduction in the rate of junctional pacemakers after crushing the sinus node in the anesthetized dog. No further characterization of this phenomenon was undertaken. The results of the present experiments provide evidence for the maintained capture of cardiac pacemakers at rates significantly below the inherent control rate and indicate that underdrive varies as a function of pacemaker location. Thus, subsidiary atrial pacemakers were shown to be susceptible to underdrive, whereas sinus nodal and idioventricular pacemakers could not be underdriven. True pacemaker suppression, not exit block, of the inherent focus is suggested by the experiments in which premature stimuli were used (see Fig. 4). The single premature impulse markedly prolonged the subsequent cycle length in a fashion not characteristic of exit block but, rather, resembled the prolongation of overdrive suppression. In addition, underdrive capture for 30 seconds was followed by a period of pacemaker suppression (Fig. 2).

Single premature atrial stimuli have been shown to produce brief periods of cardiac depression in the presence of the sinoatrial node (Pick et al., 1951). Jalife and Moe (1976) recently have shown that, in Purkinje fibers, electrotonic potentials arriving early in the cycle prolong the following cycle. This has been explained by a reactivation of the pacemaker current (iK1) such that the slope of diastolic depolarization is reduced. The present study shows that subsidiary atrial foci, in the conscious animal, regularly respond to premature atrial stimuli with a marked and prolonged pacemaker suppression (Figs. 4 and 5). It is clear also that the prolongation of cycle length is not necessarily maximal with the first return cycle following a premature beat. Instead, cycle length may gradually increase and only then return to the spontaneous level (Fig. 5). Similar cycle length prolongations have been noted in patients with suspected sinus node disease following rapid atrial pacing (Benditt et al., 1976).

The finding that underdrive rates were maintained for long periods and were still followed by
suppression after termination of the drive is quite interesting. It could indicate that a common mechanism exists for overdrive and underdrive. As the subsidiary atrial pacemaker stabilized with time postoperatively, the susceptibility to overdrive suppression was greatly diminished and the susceptibility to underdrive disappeared. Also, the marked suppression following the single premature beat was abolished. This increased pacemaker stability may reflect the gradual recovery of anatomically higher (within the distribution of the SA nodal artery) pacemakers which were only temporarily damaged during the operative procedure.

The fact that a single premature stimulus can markedly suppress certain pacemakers could explain underdrive. When a stimulus arrives at a premature point in the cycle, the subsequent cycles may be prolonged so that further paced impulses are eventually able to capture the suppressed focus and thus maintain the underdrive. However, it must be pointed out that the mere susceptibility to overdrive is not necessarily correlated with underdrive. Thus, idioventricular pacemakers, which were markedly susceptible to overdrive suppression, were not susceptible to underdrive. Neither were these pacemakers sensitive to marked suppression by single premature stimuli. Electrophysiological differences between cardiac pacemakers may be responsible for the varying susceptibilities shown for underdrive. With respect to overdrive suppression, different mechanisms have been proposed, depending on the tissue studied. Thus, overdrive suppression in the atrium has been reported to be attributable to a stimulation-induced release of acetylcholine as well as an extracellular accumulation of potassium (Lu et al., 1965). In the present experiments, the use of total autonomic blockade rules out the effects of a stimulation-induced release of acetylcholine as being responsible for underdrive. Thus, in the presence of both atropine and propanolol, no significant differences were noted in the ability to underdrive.

Several important clinical implications are suggested by the present experiments. The fact that a single premature beat can markedly suppress a focus evokes questions as to the interpretation of prolonged sinoatrial conduction times in patients with sinus node disease (Strauss et al., 1973). Such a finding may actually represent pacemaker suppression rather than prolonged conduction into and out of the SA node.

The question as to whether underdrive could play a physiological role in pacemaker activity can only be hypothesized. Mandel et al. (1975) have suggested that, in the sick sinus syndrome, the failure of junctional escape in the presence of a slow sinus rhythm indicates coexisting junctional disease. However, the present results suggest that underdrive also could explain the failure of junctional escape without the necessity for concurrent junctional disease.

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