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The Relationship between Overdrive Suppression and Overdrive Excitation in Ventricular Pacemakers in Dogs

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SUMMARY We studied the excitatory and inhibitory effects of overdrive on idiocentric pacemakers in anesthetized dogs with recently induced complete atrioventricular block. The following results were obtained: (1) a slow driving rate may induce a temporary rhythm which may be reinitiated with additional stimuli; (2) the induced rhythm may appear as coupled extrasystoles which, on interruption of the drive, are found to be self-sustaining; (3) during continued slow driving, extrasystoles may appear and disappear in a cyclical manner; (4) a short period of fast driving may be followed by a fast new rhythm, the rate and duration of which are a function of the rate and duration of drive; (5) fast driving may induce a new rhythm at a rate below predrive control; (6) after a long period fast driving, only suppression follows; and (7) intermittent periods of fast driving lead to a summation of inhibition with each successive period. These results suggest the following conclusions: (1) under certain conditions, electrical driving instead of inhibiting suppression may induce a rhythm ("overdrive excitation") at a rate similar to, faster than, or slower ("inhibited excitation") than control; (2) the duration of diastole and the number of driven beats are major factors in the induction of new rhythms; and (3) overdrive excitation is counteracted by overdrive inhibition, with development of the former requiring fewer beats than the latter.

IT HAS BEEN SHOWN repeatedly that stimulating the heart at a rate faster than that of its spontaneous pacemaker is followed by a temporary suppression of pacemaker activity. This phenomenon ("overdrive suppression") has been demonstrated both in vivo and in vitro. In Purkinje fibers superfused in vitro and exposed to norepinephrine, overdrive may not be followed by suppression, but, to the contrary, may be followed by initiation of spontaneous activity ("overdrive excitation"). It is not known whether the processes responsible for overdrive suppression and overdrive excitation can occur simultaneously or require different conditions that permit the occurrence of one but not the other phenomenon. It was decided, therefore, to study the effect of drive on ventricular pacemaker activity in dogs with complete atrioventricular block. Since it is well known that arrhythmias are more likely to appear shortly after cardiac surgery, the study was conducted within a few days after the induction of the atrioventricular block. It was found that under these conditions overdrive of the ventriciles may induce new rhythms. It also...

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was shown that the rhythms elicited are subject to overdrive suppression. It then was possible to select procedures in such a way that only overdrive suppression, overdrive excitation, or a graded mixture of the two occurred.

**Methods**

We studied 15 thiopental sodium-anesthetized mongrel dogs of either sex weighing 22-34 kg. Complete atrioventricular block was induced by placing a suture ligature around the His bundle during venous inflow occlusion. The dogs were allowed to recover for periods of 1-3 days. On the day of the experiment, the dogs were anesthetized with morphine sulfate (Lilly Laboratories), 5 mg/kg, im, and α-chloralose (Fisher Scientific Co.), 75 mg/kg, iv. Additional chloralose was given during the experiment to maintain adequate anesthesia. The dogs were ventilated with an Engström respirator (model 200, M1VAB Co.) and the chest was opened through a middernal incision. The aortic blood pressure was recorded by means of a polyethylene catheter connected to a Statham pressure transducer (model P23Db) and a lead II electrocardiogram (ECG) was recorded.

Bipolar electrograms were recorded by means of silver electrodes sutured to the right atrial epicardium and the ventricular epicardium (one electrode on the right and four on the left ventricle). The electrical stimuli used to drive the ventricles were delivered through silver electrodes sutured to the epicardium of either the right or the left ventricle.

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**Results**

**INDUCTION OF NEW RHYTHMS BY DRIVE**

The induction of a new ventricular rhythm by a slow driving rate is illustrated in Figure 1. The first two QRS complexes show the control idioventricular rhythm at 50 beats/min. The first driven beat interrupted the preceding diastole and was followed by four spontaneous beats which were completely different from control in configuration and occurred at a slightly more rapid rate (average rate 52/min). The second stimulus fell in the refractory period and failed to activate the ventricles. The ventricular electrograms (not shown) made clear that the fifth ECG complex after the first driven beat is a fusion beat. The fusion beat is followed by three QRS complexes with the same configuration as control. The third stimulus elicited a driven beat which initiated again the same rhythm as the first (see configuration of last QRS). The same pacemaker shift was present regularly after each driven beat as long as stimulation was continued. Slow driving caused a shift in pacemaker activity in 36 runs in nine experiments. It was reasoned that if the driving rate were somewhat faster, it might be possible to sustain this new rhythm during the drive. This is shown in Figure 2. The ventricles were driven at 36/min (panel A) and each driven beat is labeled with a dot. It is apparent that at this driving rate the new rhythm was maintained during the drive. Similar results were obtained in nine runs in four experiments.

It is interesting that after the end of the period of driving (Fig. 2, panel A) the activity of the new pacemaker continued for several seconds but at a rate slower than that of the control (not shown). The slowing and the eventual cessation of the new pacemaker might have been due to the fact that, during the drive, the rate of discharge of the ventricles was double that of the control since in 1 minute there were 36 driven beats plus 36 beats from the new pacemaker site. This overdrive might have been responsible for the eventual suppression of both the new and control rhythms. We studied this point by using a faster rate of drive (180 beats/min) for a longer period of time (1 minute). As shown in Figure 2, panel B, this overdrive resulted not only in the usual suppression of the control pacemaker, but also in the induction of the new rhythm. However, the new rhythm also underwent inhibition, as shown by its delayed onset, low rate, and the typical, progressive acceleration during the recovery from drive. These findings indicate that a faster and longer drive induces overdrive excitation and, at the same time, overdrive inhibition of both the control and the new rhythm. This is an example of “inhibited excitation," a phenomenon characterized by the induction of a
rhythm but at a rate slower than the control rhythm. Similar results were obtained in 21 runs in six experiments.

As shown in Figures 1 and 2, the new pacemaker activity induced by overdrive resulted in QRS complexes with the same polarity as those of the driven beats. However, this was a matter of chance, as shown by the fact that there was no correlation between driving from the left and the right ventricle, on the one hand, and the onset and polarity of the elicited beats, on the other.

ELIMINATION OF INDUCED RHYTHMS BY ENHANCEMENT OF INHIBITION

The fact that driving may at the same time elicit and inhibit spontaneous rhythms suggested that an enhancement of inhibition may abolish excitation. This was tested as illustrated in Figure 3. In the top strip, the first 4 beats show the control idioventricular rhythm. The ventricles then were driven at 48/min and the first driven beat (labeled with a dot) elicited a new rhythm as shown by the changed QRS complexes. This new rhythm was faster than the imposed drive and tended to subside. When the electrical stimuli occurred after the refractory period, the ventricles were activated and the new rhythm was restored temporarily. After this run had been recorded, the ventricles were driven at a rate of 180/min for 3 minutes to induce a substantial degree of overdrive inhibition. The drive (beginning of the middle strip) was followed by a period of suppression. The first three QRS complexes after the drive show the same QRS configuration as the induced rhythm in the top strip but occur at a markedly lower frequency (inhibited excitation). The interesting point is that, in the bottom strip (recorded 13 seconds after the middle strip), resumption of the drive at 48/min failed to induce the new rhythm. After a few minutes (as the inhibition by the rapid drive wore off), the same slow drive once more elicited the same rhythm as that shown in the top strip.

SELF-INHIBITION OF INDUCED RHYTHMS

The presence of extrasystoles increases the total ventricular rate; therefore it should initiate a frequency-dependent inhibition (Fig. 4). In the top panel, the first 2 beats are the control idioventricular rhythm. At the upward shift of the lower trace, driving was initiated at 60/min. Each driven beat is labeled with a dot. After the fifth driven beat, an extrasystole followed each driven beat. It is apparent that the extrasystole occurred progressively earlier in the driven cycle until the coupling interval stabilized for a certain period of time. This is shown in the graph (bottom of Fig. 4). The interval between the driven beats and the extrasystole initially shortened, stabilized for a while, and eventually lengthened. In the bottom three traces of Figure 4 the extrasystole following the third driven beat originated so late in the cycle that it prevented activation of the ventricles by the ensuing electrical stimulus. This signaled the disappearance of the arrhythmia. That inhibition was indeed present is shown by the fact that cessation of driving was followed by a period of ventricular standstill. The standstill shows that both normal and abnormal rhythms were inhibited by the increase in rate caused by the extra beats.

The arrhythmia seen in Figure 4 could be characterized as bigeminy. However, it is possible that the appearance of more than one extra beat after each driven beat might have been prevented by the fact that the driven beats occurred before the new pacemaker could discharge again. This is illustrated in Figure 5. The first panel shows the control idioventricular rhythm. In the second panel, the ventricles were driven at 55/min. After 4 driven beats, there was a run of three extrasystoles. The next driven beat was followed by two extrasystoles and each of the succeeding driven beats was followed by one extrasystole. The evidence that these extrasystoles can be self-sustaining is shown in the third panel. Here, a brief interruption of the drive (as shown by the upward shift of the bottom trace) revealed a regular succession of extrasystoles for as long as the drive was discontinued. Resumption of the drive led to the reestablishment of the 1:1 relationship between the extrasystoles and the driven beats. In records in the fourth panel, the extrasystoles disappeared; when the driving was again interrupted (in the absence of extrasystoles) suppression of normal and abnormal activity was revealed. It should be noted that the rate of discharge of the elicited rhythm during the interruption of the drive (third panel) was faster than the rate of discharge of the initial three extrasystoles (second panel), as one would expect from the events illustrated in Figure 4.

The temporary presence of extrasystoles during slow driving as shown in Figures 4 and 5, was observed in 38 runs in four experiments. The disappearance of the extrasystoles during driving should lead to the eventual disappearance of inhibition because there is a reduction in the rate of discharge. As inhibition is dissipated, the extrasystoles should return. This was tested in two experiments by driving continuously at a slow rate for a prolonged period of time; it was found that the arrhythmias would appear, last for a period of time, and then disappear. This cycle repeated itself for as long as driving was continued.

THE ONSET OF ARRHYTHMIAS AFTER FAST DRIVING

At a fast rate of drive, extrasystoles are unlikely to appear during driving but abnormal rhythms might appear after driving. In fact, a fast drive may induce arrhythmias when a slow drive fails to do so. This is illustrated in Figure 6. Here the ventricles were driven at two different rates, 50 and 120/min, for approximately the same number of beats (8 and 9, respectively). The slower drive (upper two traces)
failed to affect the spontaneous rhythm to any significant extent, but the faster drive (lower two traces) was followed by a new rhythm at a rate of 85 beats/min. The cessation of this rhythm, in turn, was followed by moderate inhibition of the control pacemaker. The induced rhythm was typical in that it slowed slightly and then ceased abruptly. That the rate of drive (and not the drive per se) is the important variable in inducing new rhythms is suggested also by Figure 7. The number of beats delivered during driving was again approximately the same. However, when the rate of drive was progressively decreased no arrhythmias followed (top trace), whereas when the rate of drive was progressively increased a new rhythm ensued (bottom trace). Fast (but not slow) driving was followed by a new rhythm in 21 runs in five experiments. An accelerating (but not a decelerating) drive was followed by a new rhythm in six runs in two experiments.

EXCITATION AND INHIBITION FOLLOWING DRIVES OF DIFFERENT DURATIONS

In animals with chronic atrioventricular block, the longer the period of driving, the more pronounced is the ensuing overdrive suppression. However, it is not known how the duration of the period of driving might affect overdrive excitation. The results obtained by driving at 180/min for varying periods of time are shown in Figure 8. Two beats were sufficient to elicit a new rhythm at a rate somewhat faster than control (first strip). As the duration of driving was increased to 4, 6, and 14 beats, the rate of the induced rhythm increased. The rhythms induced by 4 or more beats apparently originated from two different sites. This is suggested by the different configuration of the QRS complexes, the different configuration of the electrograms (not shown), and the abrupt slowing of the rate when the pacemaker site changed (see graph in Fig. 8). The graph also shows that the rate initially increased and then declined as a function of time. The cessation of the induced rhythm

FIGURE 4 The self-inhibition of extrasystoles during driving. The upper trace (LVd) is an electrogram from the anterior distal aspect of the left ventricle, the middle trace (L11) is lead II, and the lower trace indicates the drive. The extrasystoles are recognized by the fact that both the QRS and T waves are smaller than those of the electrically induced complexes. The cessation of driving is indicated by the return of the bottom trace to its original level. The graph includes data from a proportion of the tracing not shown. The ordinate shows the reciprocal of the cycle length between each driven beat and the following extrasystole; the abscissa shows the successive extrasystolic beats. In the graph, the dot labeled with an asterisk refers to the first extrasystole which differs from all the other extrasystoles because of the negativity of QRS complex.

FIGURE 5 Drive excitation and drive inhibition. The QRS complexes of the extrasystoles induced by driving are much larger than those of the electrically induced beats.

FIGURE 6 Induction of a new rhythm by fast drive. Each driven beat is labeled with a dot. The explanations of the lettering are the same as in the legend of Figure 1.
revealed an overdrive suppression that increased progressively as a function of the total number of beats. It thus appears that (1) the rate of the induced rhythm increases with the duration of the drive for the durations studied; (2) the induced rhythm tends to slow gradually; and (3) the subsequent inhibition is more pronounced when the induced rhythm is longer and faster. Short periods of fast driving were followed by an induced rhythm and subsequent suppression in 65 runs in four experiments. On other occasions, increasing the rate of drive resulted in a slowing of the induced rhythm below the control rate (inhibited excitation). Therefore, both excitation and inhibition can be induced at the same time with different patterns which depend on the patterns of drive.

If excitation can be induced with fewer beats than inhibition, it should be possible to obtain an initial excitation with a short period of driving and only inhibition with a long period of driving. In Figure 9, the duration of drive was varied from 5 to 30 seconds. It is apparent that driving for 5 seconds induced a fast rhythm (average rate = 100/min) which was followed by the usual suppression (see also graph in Fig. 9). As the duration of drive was increased progressively, the rate and the duration of the induced rhythm gradually decreased. After driving for 30 seconds there was only suppression. The key factor in the gradual transition from excitation to suppression is the duration of the period of fast driving. Induction of a new rhythm with a short period of driving and suppression with a long one was obtained in 35 runs in seven experiments.

This finding elicits the question whether overdrive would suppress an induced rhythm in the same fashion as it suppresses a normal idioventricular rhythm. In Figure 10, driving at 180/min for 4.5 seconds induced a fast rhythm (171/min). Overdriving the ventricles during the induced rhythm at 240/min for 23 seconds led to the abolition of this rhythm and to a pronounced inhibition. Thus, inhibition can be made to prevail over established excitation. Suppression of a fast rhythm by overdrive was obtained in 22 runs in six experiments. If overdrive excitation requires a short period of driving to become established, overdrive suppression requires more time to be dissipated. This difference suggested that it might be possible to obtain inhibition even with...
short periods of driving: the only requirement would be that the short periods be repeated at sufficiently short intervals. This was done by driving repeatedly at 180/sec for 5 seconds, every 10 seconds, as shown in Figure 11. In the top trace, driving elicited a fast rhythm which slowed gradually (curve 1 in the graph). In the second trace, the drive was still followed by a fast rhythm which, however, slowed abruptly within a few beats (curve 2). In the third trace, the drive was followed only by 4 induced beats at a rapidly decreasing rate (curve 3) and in the fourth trace by only 1 beat. Finally, in the fifth trace, the drive was followed only by a suppression of the control idioventricular pacemaker. The experiment demonstrates that the inhibition can summate, and this appears to be the mechanism by which excitation is eliminated and inhibition is obtained even with short periods of driving. Similar results were obtained in five runs in three experiments.

Discussion

It is generally agreed that overdriving cardiac pacemakers results in their subsequent suppression (overdrive suppression). The present results show that under suitable conditions driving ventricular pacemakers induces new rhythms (overdrive excitation). To induce a new rhythm, the driving rate may be similar, slower, or faster than the control idioventricular rhythm. The induced rhythm may be made to appear during the period of driving or afterward, depending on the driving rate. Within certain limits, the faster the drive, the faster is the induced rhythm. The present results make clear that the increased rate of discharge (by electrical driving, by the induced rhythm, or by both) also induces overdrive suppression. Therefore, overdrive suppression and overdrive excitation can be present at the same time and interfere one with the other. The antagonism between suppression and excitation can assume one of the following forms: (1) delayed onset or elimination of pacemaker shifts; (2) self-suppression of the induced rhythms; (3) slower induced rhythms of short duration; (4) induced rhythms slower than control (inhibited excitation); (5) complete suppression of excitation; and (6) prevention of excitation.
Furthermore, since suppression is dissipated slowly, it is possible to induce a rhythm with a short period of driving and suppress it by repeated short periods of driving (summation of inhibition).

The factors responsible for overdrive excitation are not clear. It could be proposed that the onset of new rhythms in the present experiments was due to excitation of sympathetic fibers by the stimuli used for electrical driving. This appears unlikely for several reasons. A single stimulus was sufficient to elicit a new rhythm, as shown in Figure 1; yet, a single stimulus 1 msec in duration should have stimulated sympathetic fibers only once and the norepinephrine liberated should have been insufficient to induce a rhythm persisting for several beats. Direct support for this concept is provided by events associated with the second stimulus (Fig. 1). The second stimulus fell during the absolute refractory period of the ventricles and therefore failed to excite cardiac cells; still, it should have excited sympathetic nerve fibers, and norepinephrine should have been liberated again. The induced rhythm subsided in spite of the renewed liberation of norepinephrine, and this indicates that the activation of cardiac cells and not that of sympathetic nerve fibers is important for inducing or sustaining the new rhythm.

Another argument against the excitation of sympathetic fibers as the cause of arrhythmias is that QRS complexes of the same configuration (and therefore probably originating from the same site) can be elicited by driving either ventricle. Driving from a site in one ventricle should not activate the same sympathetic fibers as driving from another site in the other ventricle. Therefore, it appears unlikely that the activation of different sympathetic fibers by the driving stimuli may be responsible for the onset of pacemaker activity in the same location. Also, it is unlikely that the arrhythmias are caused by a reflex sympathetic discharge because the arrhythmias occurred regardless of whether the blood pressure increased or decreased during the period of driving.

Catecholamines still could play a role in the mechanism of overdrive excitation. It must be pointed out here that catecholamine levels were not measured in this study but it has been shown that catecholamines in the blood are increased by operative and postoperative stress. It is realized that the operation required to produce atrioventricular block is likely to have resulted in other disturbances such as electrolyte shifts across cell boundaries. These disturbances also could be important in the genesis of the arrhythmias. That catecholamines do play a role here is suggested by the following: In dogs studied a week or more after induction of complete atrioventricular block (and presumably at a time when catecholamines had returned to normal levels), ventricular driving results in suppression of normal pacemaker activity and not in excitation of abnormal pacemaker activity. During administration of norepinephrine or stimulation of cardiac nerves in dogs with complete atrioventricular block, ventricular driving may induce sustained arrhythmias with characteristics similar to those reported here (unpublished experiments). In fact, sudden ventricular tachycardias may occur with stimulation of a stellate ganglion or of the adrenal medulla even in the absence of ventricular driving.

If steepening of diastolic depolarization is a possible mechanism it is certainly not the only one, since a few beats may initiate a tachycardia in vivo (Fig. 8) but not in vitro. Other mechanisms must be operative. Although these mechanisms are not understood at the present time, a few considerations are in order. When a single beat elicits a new rhythm, of necessity the preceding diastole is shorter than normal. The shortening of the preceding diastole is a major prerequisite for the development and continuance of these arrhythmias (Figs. 1 and 2). This also is stressed by the fact that arrhythmias followed an accelerating but not a decelerating drive (Fig. 7). The experiments suggest that whatever modification a short diastolic interval induces, this modifi-
ation summates over successive cycles. This is reinforced by the fact that a given number of beats induced an arrhythmia when delivered at a fast but not at a slow rate (Fig. 6). Summation of excitation was seen also when the ventricles were driven continuously at a relatively slow rate: extrasystoles appeared only after a certain number of driven beats (Figs. 4 and 5). Furthermore, increasing the number of beats at a constant rate was followed by a faster rhythm (Fig. 8).

These findings indicate that the following factors are important in relation to the mechanism of overdrive excitation: (1) the duration of diastole preceding the driven beats, (2) the number of beats at a given rate, and (3) the rate of drive for a given number of beats. However, the experimental conditions are markedly changed when a fast drive is continued for a sufficiently long time. The inhibition generated by prolonged overdrive decreases both duration and rate of the induced rhythm or prevents it altogether (Fig. 9). The inhibition persists longer than excitation (Fig. 3, third strip): no excitation was induced by a slow drive shortly after the end of the long drive. For the establishment of inhibition, the driving does not need to be continuous provided its interruption is not too long (Fig. 11). Each time the driving is renewed, there is still a residual inhibition upon which the freshly induced inhibition is superimposed (summation of inhibition). As a result, the degree of excitation is progressively reduced and that of inhibition progressively increased. The coexistence of inhibition and excitation also is shown by the fact that a long period of driving may induce rhythms at rates considerably below the control rate (Figs. 2 and 3). This indicates that the excitatory phenomenon persists under inhibitory conditions that lengthen the diastolic interval beyond that of the control rhythm (inhibited excitation). Thus, these experiments establish that overdrive not only suppresses normal pacemakers but also can induce and suppress abnormal pacemaker activity.

It is of interest that several years ago García Ramos and Rosenblueth found that, in an auricle functionally isolated from the rest of the atrium and exposed to norepinephrine, electrical driving was followed by repetitive activity characterized by the presence of a diastolic depolarization. Although the finding is of obvious interest in relation to the present experiments, it is still unclear what relationship there is between the two sets of results. Thus, in the experiment of García Ramos and Rosenblueth the auricles and not the ventricles were used; the auricles were quiescent in the absence of stimulation, the repetitive activity also was obtained after exposure to acetylcholine, and the minimum driving rate needed to obtain repetitive activity was higher than that used in our present experiments.

Reentry has been demonstrated to be responsible for a variety of arrhythmias in vitro and, therefore, it might be proposed that the arrhythmias observed here were due to reentry rather than to induction of new pacemaker activity. Although this is possible, the available evidence does not permit a conclusion one way or the other. However, it should be pointed out that the conducting system was damaged in our present experiments only to the extent that the His bundle had been ligated near the atrioventricular node. No other procedures were performed which would account for the presence of depressed conduction and slow action potentials in the ventricles. On the other hand, findings from in vitro experiments show that, in fibers with normal action potentials, overdrive excitation can be produced by steepening of diastolic depolarization and that overdrive suppression of normal pacemakers results from a depression of diastolic depolarization.

At the membrane level, excitation may involve a progressive enhancement of a pacemaker potential or a reentrant pathway; inhibition, instead, might be related to the activation of an electrogenic sodium pump. The sodium-potassium pump is believed to operate with a time lag with respect to the onset of drive. Therefore, after a short period of driving excitation prevails and a new rhythm ensues. After a long period, the inhibitory process is fully established and only suppression follows. At intermediate durations of drive, the processes of excitation and inhibition blend and the induced rhythm will be slower and shorter. If these processes of excitation and suppression apply to certain arrhythmias, it would not be difficult to understand why those arrhythmias appear in a cyclical manner.

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