On the Mechanism of Idioventricular Pacemaker Suppression by Fast Drive

By Daniel J. Krellenstein, Michael B. Pliam, Chandler McC. Brooks, and Mario Vassalle

ABSTRACT

The role of vagal activity, potassium concentration, and temperature in overdrive suppression of ventricular pacemakers, was studied in anesthetized dogs with and without surgical atrioventricular block. The results were as follows. (1) Overdrive of an idioventricular pacemaker during vagal stimulation was followed by a second pause. (2) Hypothermia increased the duration of the vagal and overdrive pauses. (3) Coronary sinus plasma potassium concentration ([K_1]) decreased with the onset of vagal stimulation and increased with overdrive during vagal stimulation. (4) The increase in [K_1] during ventricular overdrive was greater in hypothermia than it was in normothermia when the same absolute rate of overdrive was used and was unchanged when the same relative rate of overdrive was used. (5) Hypothermia increased overdrive suppression more than can be accounted for by the decrease in spontaneous rate. (6) By predriiving the ventricles and then overdriving them, the increase in [K_1] was dissociated from the pause duration. It is concluded that during vagal stimulation ventricular arrest is due to the inhibition of idioventricular pacemakers by the sinus node by virtue of its faster rate and that changes in [K_1] are due to rate changes and not to acetylcholine release. Overdrive suppression can be dissociated from an increase in extracellular potassium concentration. Its prolongation in hypothermia provides evidence for a metabolism-dependent mechanism.

KEY WORDS coronary sinus plasma potassium concentration overdrive suppression vagal and surgical block low temperature ventricular arrest during vagal stimulation dogs

The stimulation of the vagus nerve usually leads not only to atrial arrest but also to ventricular arrest. The atrial arrest is due to an inhibitory effect of acetylcholine on atrial pacemakers (1), but the mechanism of the ventricular arrest is not known. Evidence has been collected which indicates that ventricular arrest during vagal inhibition is a particular case (2, 3) of the more general phenomenon called overdrive suppression: the vagus does not cause ventricular arrest directly but by inhibiting the sinus node reveals the inhibition that the node exerts on the ventricular pacemakers by virtue of its faster rate. This hypothesis agrees with the finding that acetylcholine fails to suppress spontaneously firing Purkinje fibers perfused in vitro (4). However, the problem of the vagal inhibition of ventricular pacemakers has recently been reopened by the observation of Bailey et al. (5) that the automaticity of specialized tissues below the atrioventricular (AV) node is depressed by acetylcholine. Thus, the first aim of the present investigation was to determine whether ventricular arrest during vagal stimulation results from acetylcholine release (as does atrial arrest) or a frequency-dependent inhibition by the sinus node.

The results obtained indicated that ventricular arrest was indeed caused by a frequency-dependent phenomenon. This finding elicited the question of the mechanism of overdrive suppression; an analysis of such a mechanism was the second aim of the paper. In the atria, overdrive sup-

From the Department of Physiology, State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203.

This work was supported by grants from the New York Heart Association.

This study was done in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Physiology, Downstate Medical Center, by Dr. D. J. Krellenstein under Training Grant 5-T01-GM-00968 from the National Institutes of Health. This work was also carried out while Dr. Vassalle was a recipient of a Sinsheimer Award. Dr. Vassalle is a Career Scientist of the Health Research Council of the City of New York.

A preliminary communication has appeared in abstract form (Am J Cardiol 23:122, 1969).

Received March 6, 1974. Accepted for publication July 31, 1974.
pression involves the release of acetylcholine (6–9) and possibly an accumulation of potassium (K) outside the cell membrane (7, 8). In the ventricles, overdrive suppression has been attributed to the activation of an electrogenic sodium (Na) pump (10). If such a pump is involved, then overdrive suppression should be enhanced at low temperature. In hypothermia, the passive influx of Na should be little altered, but its active extrusion should be reduced (11) during the overdrive. As a consequence of such a reduction, at the end of the overdrive the intracellular Na concentration would be higher than it is at normal temperatures and more Na would have to be extruded for a longer period of time.

An inhibitory role of K in overdrive suppression of ventricular pacemakers is still undetermined. Since there is a transient myocardial loss of K when the rate is suddenly increased (12–15), the role of a higher concentration of extracellular K ([K]l) in overdrive suppression was studied. We measured changes in coronary sinus plasma K concentration under several different conditions.

The results obtained provided evidence that ventricular standstill during vagal stimulation resulted from the fact that ventricular pacemakers were kept under suppression by the sinus node. The ventricular standstill was not caused by a release of acetylcholine in the ventricles or by an increase in [K]l. Also overdrive suppression could be dissociated from an increase in [K]l. The results at low temperature were consistent with the hypothesis that a metabolism-dependent decrease in the net inward current during diastolic depolarization caused the overdrive inhibition.

Methods

Male mongrel dogs weighing 11–25 kg were anesthetized with morphine sulfate (5 mg/kg, im) and alpha-chloralose (75 mg/kg, iv), and additional chloralose was administered at intervals as needed to maintain an even plane of anesthesia. The dogs were ventilated with a Jackson respirator (C. F. Palmer) attached to a tracheal cannula placed via a tracheostomy. Aortic blood pressure was measured via a polyethylene catheter connected to a Statham P23AA pressure transducer. The standard electrocardiogram (ECG) was recorded as lead II. Body temperature was monitored through an esophageal thermistor probe connected to a telemeterometer (Yellow Springs Instruments Co., model 43TW). Normal temperature was maintained using heating lamps as needed. The chest was opened through a midline incision, and a pericardial cradle was made. A bipolar silver electrode was sewn to the epicardial surface of the atrium to record the atriogram, and another bipolar electrode was attached to the right ventricle for electrical driving.

AV block was induced either by vagal stimulation or surgically. The dogs in which complete AV block was obtained by stimulating the vagus nerve will be referred to as “dogs with vagal block.” In these dogs, the vagi were isolated in the neck and crushed, and the peripheral end (usually of the left vagus) was used for stimulation. The dogs with complete AV block produced by suture-ligation of the His bundle during inflow occlusion will be referred to as “dogs with surgical block.” All of the dogs were given sodium heparin intravenously (2.5 mg/kg initially and 1.25 mg/kg each hour thereafter). A plastic T-tube was connected to three segments of plastic tubing (Pharmaseal Catheters). One tube had a fenestrated end which was placed 2–3 cm into the coronary sinus. The second tube was passed into the right atrium and allowed the coronary sinus blood to return to the circulation. The third tube was kept clamped except during the collection of coronary sinus samples, at which time the second tube was clamped (3). The pH and the oxygen saturation of arterial blood were measured at intervals, and any degree of acid-base imbalance was corrected by administering NaHCO3, adjusting the respirator, or both.

All recordings were made on a Sanborn four-channel recorder (model 964). The ECG and the atriogram were recorded using ECG preamplifiers (Sanborn, model 350–3200). Stimuli were provided by Grass S-4 stimulators. For vagal stimulation, the stimuli were 5 msec in duration, 3–8 v in strength, and 20 impulses/sec in frequency. The characteristics of the stimuli used for ventricular driving were 2 msec, 4–6 v, and 24–240 impulses/min. Plasma Na and K analyses were performed with a Beckman flame photometer (model 105) utilizing a lithium internal standard.

In dogs with vagal block, the left vagus nerve was stimulated for a period of 3 minutes. During the first minute, ventricular escape occurred; the idioventricular rhythm usually stabilized by the end of this period. During the second minute, the ventricles were driven at a selected rate for 1 minute. During the third minute, only the stimulation of the vagus nerve was continued. Arterial blood samples for determination of [K] were drawn from the femoral artery before and after each 3-minute stimulation. Coronary sinus blood samples were drawn immediately before, during, and after the procedure at intervals of 15 seconds. The dog was then cooled approximately 10°C, vagal stimulation and ventricular overdrive were repeated, and blood samples were again collected for analysis of [K]. Finally, the dogs were rewarmed to their original temperature, and the procedures were repeated once more.

In dogs with surgical block, the ventricles were overdriven for 1 minute at two and four times the intrinsic rate at normal temperatures. Pauses
were measured, and blood samples were collected for determination of [K]. The dogs were then cooled and the experimental procedures were repeated. At hypothermic levels, the heart was also predriven for 5 minutes at the control normothermic rate and then overdriven at twice this rate for 1 minute. Once the dogs had been rewarmed to their original temperature, the experimental procedures were repeated with overdrive at twice the intrinsic rate.

Each procedure was repeated more than once (usually three times), and the results were averaged.

Results

Dogs with Vagal Block

Overdrive Suppression of Idioventricular Pacemakers at Normal and Low Temperature.—If the ventricular arrest which occurs at the beginning of vagal stimulation is due to a frequency-dependent suppression by the sinus node, driving of the ventricles at the same rate as that of the sinus node during the ventricular escape rhythm should be followed by a pause similar to the initial pause. The results of one of these experiments are shown in Figure 1 (top). As indicated at the bottom of the figure, at the upright arrow vagal stimulation was initiated; it was promptly followed by a vagal pause of 12 seconds (first section). By the end of the first minute of vagal stimulation, the ventricles had reached a steady rhythm of 22 beats/min (second section, first two complexes). During the second minute of vagal stimulation, the ventricles were electrically driven at a rate comparable to that of the sinus rate (120 beats/min). The cessation of the drive (third section) was followed by a period of ventricular arrest, an overdrive pause 7 seconds in duration. The resumption of the idioventricular rhythm was characterized by a progressive acceleration to a steady rate as seen during vagal stimulation alone. The cessation of vagal stimulation (fourth section) was followed by a transient acceleration of the sinus node (postvagal tachycardia) (16).

Results obtained during hypothermia are also illustrated in Figure 1 (bottom). In hypothermia, the sinus rate had decreased to 100 beats/min and the vagal pause had increased to 20.3 seconds (first section). The idioventricular rate at the end of the first minute of vagal stimulation was 12 beats/min (second section). The pause following the cessation of the 1 minute of overdrive at 120 beats/min was increased to 16 seconds (third section). The onset of atrial fibrillation dur-
Effect of cooling and rewarming on vagal and overdrive pauses.

The average duration of the vagal pause in ten dogs at 38°C was 10.0 ± 2.2 seconds (Fig. 2). The average overdrive pause duration in the same ten dogs was 7.9 ± 2.5 seconds. In seven of the ten dogs, the overdrive pause was shorter than the vagal pause, but in the remaining three dogs it was longer. The difference between the vagal and the overdrive pause was not statistically significant (P > 0.1).

The duration of both the vagal and the overdrive pause was increased consistently and markedly by hypothermia, as shown in Figure 2. At 28°C the vagal pause increased to an average of 25.0 ± 3.8 seconds and the overdrive pause to an average of 19.9 ± 3.7 seconds. Both pauses were significantly longer in hypothermia (P < 0.01). Six of the ten dogs were rewarmed to 38°C and the experiments were repeated (Fig. 2); the average vagal pause was 9.5 ± 3.8 seconds and the average overdrive pause was 5.5 ± 0.9 seconds.

**Coronary Sinus Plasma Potassium Concentration and Overdrive at Normal and Low Temperature.**—The changes in the plasma K concentration of the blood in the coronary sinus ([K]cs) during vagal stimulation and overdrive at normal temperature are illustrated in Figure 3. There were two periods during which [K]cs fell below control levels, namely, during the first minute of vagal stimulation and during the recovery from overdrive. There were also two periods during which [K]cs increased above control levels, namely, during overdrive and after the end of vagal stimulation. The latter increase occurred in association with postvagal tachycardia.

The changes in [K]cs with vagal stimulation and overdrive in hypothermia are also illustrated in Figure 3. It is apparent that the changes in [K]cs with vagal stimulation and overdrive in hypothermia paralleled those at normal temperature but that K loss was more pronounced and K uptake less pronounced.

The results obtained in all dogs studied are reported in Table 1. At normal temperature, the average arterial [K] was 4.03 ± 0.24 mEq/liter and the average [K]cs was 4.02 ± 0.24 mEq/liter: the hearts did not lose or gain K in any consistent manner during the control period. It is apparent that during the first minute of vagal stimulation, [K]cs fell consistently (column labeled vagal pause). The average fall was 0.80 mEq/liter, a decline of 20%
with respect to control concentration ($P < 0.001$). During ventricular overdrive (column labeled overdrive), $[K]^c$, increased quickly by 0.89 mEq/liter over the average original control level (+22%, $P < 0.001$). However, since $[K]^c$, was always less than control just prior to the overdrive period, the actual increase was greater. Usually, $[K]^c$, was falling before the end of the overdrive period, although it always remained above the original control concentration. After cessation of the overdrive (column labeled overdrive pause), $[K]^c$, consistently fell by an average of 1.33 mEq/liter with respect to the maximum value during overdrive (−35%, $P < 0.001$). The coronary $[K]$ during postvagal tachycardia (column labeled PVT) increased in eight of the nine dogs ($P < 0.01$).

At low temperature, the average arterial $[K]$ was 3.77 ± 0.35 mEq/liter and the average control $[K]^c$, was 3.75 ± 0.30 mEq/liter. $[K]^c$, during the first minute of vagal stimulation fell by 0.43 mEq/liter (−11%, $P < 0.02$). With overdrive, average $[K]^c$, increased by 1.36 mEq/liter over the original control value (+36%, $P < 0.005$). During the third minute of vagal stimulation, $[K]^c$, fell by 1.81 mEq/liter (−35%, $P < 0.001$). Therefore, the fall in $[K]^c$, during the vagal pause was less ($P < 0.05$) and the increase during overdrive was more ($P < 0.05$) than at normothermia, although there was no difference during the postdrive period ($P > 0.3$).

In one experiment, the ventricles were overdriven at a rate equal to their hypothermic sinus rate as opposed to the usual overdrive at the normothermic sinus rate. The increase in $[K]^c$, during the overdrive period in this dog was of a magnitude similar to that seen in normothermia.

**DOGS WITH SURGICAL BLOCK**

Overdrive Suppression of Idioventricular Pacemakers at Normal and Low Tempera-
Figure 4

Overdrive suppression in a dog with surgical block at two (top) and four (bottom) times the idioventricular rate. Overdrive 100/min and 200/min = ventricular overdrive at 100 and 200 beats/min for 1 minute; other abbreviations are the same as in Figure 1.

ture.—In dogs with vagal block, the driving rate was the same both at normal and low temperature; therefore, the rate of overdrive was relatively greater in hypothermia, since the idioventricular rate fell at the lower temperature. This fact might have accounted for the larger K loss and the longer pause. For this and several other reasons, dogs with surgically induced block were studied, and the overdrive rate was the same multiple of whatever idioventricular rate was present at normal or low temperatures.

A typical experiment with overdrive at two rates in a dog with complete surgical block is illustrated in Figure 4. The QRS complexes were negative and far slower than the atrial complexes. The control idioventricular rate was 50 beats/min. During the period indicated by the arrows, the ventricles were driven at two and four times the idioventricular rate. Most of the record during the 1-minute drive period has been omitted (break in the traces). In the second section of each panel, a pause in the ventricular rhythm followed the cessation of the overdrive, but the atrial rate was not affected.

It is of interest that quite often the resumption of the idioventricular rhythm after the pause was characterized by a shift in the pacemaker site, as shown in Figure 4. The shift was transitory, and the last section of both panels shows the return of the ECG to the control pattern.

As in the dogs with vagal block, hypothermia enhanced overdrive suppression of idioventricular pacemakers. Figure 5 shows the results obtained at normal temperature in seven dogs. At normal temperature, the average idioventricular rate was 48.8 ± 5.1 beats/min. After an overdrive period, the average pause was 2.7 ± 0.3 seconds at twice and 7.9 ± 1.8 seconds at four times the intrinsic rate. Hypothermia increased the overdrive suppression in six dogs. The average idioventricular rate in hypothermia was 24.1 ± 2.4 beats/min. After an overdrive period, the average pause was 5.04 ± 0.6 seconds at twice and 12.0 ± 2.0 seconds at four times the intrinsic rate. Comparing the pauses at the same ratios of overdrive reveals a significant increase during hypothermia ($P < 0.001$). Comparing the results obtained with the same absolute drive rates, the increase in the duration of suppression was naturally greater ($P < 0.001$).

Four dogs were rewarmed until their idioventricular rate was the same as it had been prior to hypothermia. The temperature at this time was within 1°C of the control value. At twice the intrinsic rate, the average pause was 2.8 ± 0.3 seconds (not significantly different from the precooling control, $P >$...
suggesting that the changes in ventricular rate and overdrive suppression were reversible.

Temperature and Spontaneous Rate.—The changes in sinus rate with temperature (Fig. 6) were measured in 18 dogs (8 intact and 10 with surgical AV block). At 36.5 ± 0.2°C, the average atrial rate was 147.8 ± 5.9 beats/min. At 28.9 ± 0.3°C, the average atrial rate was 86.9 ± 5.92 beats/min (−41.2%). The decrease was equal to 8 beats/min°C−¹ over the range studied (Qm = 1.85).

The changes in idioventricular rate with temperature were measured in 12 dogs (2 with vagal block and 10 with surgical block). At 37°C, the average idioventricular rate was 48.8 ± 4.8 beats/min. At 30.0°C, the idioventricular rate was 23.7 beats/min (−51.4%).

The decrease was equal to 3.5 beats/min°C−¹ (Qm = 2.53).

Coronary Sinus Plasma Potassium Concentration and Overdrive at Normal and Low Temperature.—The changes in [K]cs with overdrive are illustrated in Figure 7. The idioventricular rate was 36 beats/min. At an overdrive rate of 72 beats/min, [K]cs increased within 30 seconds of overdrive from 3.9 mEq/liter to 4.5 mEq/liter. After the overdrive, [K]cs fell below and then slowly returned to the control level. At four times the intrinsic rate (144 beats/min), the increase in [K]cs was far larger than that seen at 72 beats/min. After overdrive, [K]cs fell sharply to a rather low value.

In these nine dogs, the average arterial [K] was 3.64 ± 0.1 mEq/liter and the average [K]cs was 3.63 ± 0.1 mEq/liter. The average idioventricular rate was 50.2 ± 5.5 beats/min. [K]cs consistently increased during the period of overdrive. When the overdrive was twice the spontaneous idioventricular rate, the average maximum increase in [K]cs was 0.83 ± 0.1 mEq/liter (+22%, P < 0.001) and the
Effect of 1 minute of overdrive at twice (2x) and four (4x) times the idioventricular rate (IVR) on the coronary sinus plasma $K$ concentration ($[K]_{cs}$). The open circle with a dot inside near the ordinate indicates the arterial $[K]$. The average fall in $[K]_{cs}$ after the overdrive was $0.36 \pm 0.07$ mEq/liter ($-10\%, P < 0.01$). When the rate of overdrive was increased to four times the spontaneous rate, $[K]_{cs}$ changes were significantly greater: the increase during overdrive was $1.31 \pm 0.2$ mEq/liter ($+32\%, P < 0.01$) and the decrease after the overdrive was $1.6 \pm 0.1$ mEq/liter ($-29\%, P < 0.01$).

The results of an experiment in which the overdrive was a constant multiple of idioventricular rate at normal and low temperature are illustrated in Figure 8. The idioventricular rate was 36 beats/min at 36°C. Overdrive at four times this rate caused $[K]_{cs}$ to increase to a maximum of 5.6 mEq/liter. At 30°C, the idioventricular rate had decreased to 18 beats/min. Overdrive at four times this lower rate caused $[K]_{cs}$ to increase from the same control level to a maximum of 5.4 mEq/liter. At normal temperature the number of beats imposed during overdrive (144 beats/min) was twice (72 beats/min) the number imposed at low temperature, yet K loss was approximately the same. $[K]_{cs}$ fell during the postdrive period but less at low than at normal temperature.

The average idioventricular rate in hypothermia was $25.1 \pm 2.7$ beats/min. The average control $[K]_{cs}$ was $3.47 \pm 0.5$ mEq/liter.

The maximum increase in $[K]_{cs}$ during overdrive at twice the intrinsic rate (eight dogs) was $0.92 \pm 0.1$ mEq/liter ($+26.5\%, P < 0.01$). During the postdrive period, the minimum concentration was $0.36 \pm 0.1$ mEq/liter less than control ($-10.4\%, P < 0.02$). When the overdrive rate was increased to four times the spontaneous idioventricular rate (six dogs), the maximum increase averaged $0.93 \pm 0.1$ mEq/liter ($+31.7\%, P < 0.01$). During the postdrive period the concentration fell by $0.75 \pm 0.29$ mEq/liter ($-25.6\%, P < 0.001$) with respect to control. Four dogs were rewarmed to normal temperature. The maximum increase in $[K]_{cs}$ was $0.68 \pm 0.1$ mEq/liter during overdrive at twice the spontaneous idioventricular rate ($+15.4\%$). During the postdrive period, the minimum concentration was $0.45 \pm 0.1$ mEq/liter less than control ($-10.3\%$).

Two-Step Overdrive.—A variable introduced by cooling the dogs was the slower idioventricular rate. To learn more about the effect of this variable on K loss, the following procedure was adopted in six dogs (Fig. 9). Cooled ventricles were overdriven for 1 minute at four times the intrinsic rate (solid curve); this procedure constituted the con-
trol experiment. The ventricles were then predriven (broken curve) at twice the intrinsic rate for 5 minutes (first step); this predrive caused an increase in coronary [K] (not shown) which subsided by the time the overdrive at four times the intrinsic rate for 1 minute was carried out (second step). The second step was identical to the control procedure in that the absolute driving rate was the same but differed from it in that the step increase in rate was less. The graph in Figure 9 makes it clear that the increase in [K] was much higher in the control experiment (+35%) than it was during the second step of the two-step overdrive (+13%).

Average results were obtained for six dogs. [K] during overdrive increased 24.8 ± 2.9% in the control experiment and 15.3 ± 1.6% in the second step of two-step overdrive ($P < 0.05$); yet the pause duration was 10.7 ± 1.8 seconds in the control experiment and 10.8 ± 2.4 seconds in two-step overdrive. The difference in pause duration was not statistically significant ($P > 0.9$).

**Discussion**

The present results suggest the following conclusions. (1) Ventricular arrest during vagal stimulation is but one instance of overdrive suppression by the activity of the sinus node. (2) Depression of active transport by hypothermia enhances overdrive suppression. (3) Changes in [K], can play a role in the suppression and the initiation of ventricular automaticity, but an increase in [K], is not essential for overdrive suppression.

The temporary standstill of the ventricles at the beginning of vagal stimulation indicates that the idioventricular pacemakers are under some form of inhibition. The inhibition could be caused by a negative chronotropic action of acetylcholine on ventricular automaticity (5) as in the case of the sinus node. Alternatively, the inhibition could result from the relatively fast discharge rate imposed by the sinus node on idioventricular pacemakers rather than from a direct vagal action. Vagal stimulation, by suppressing the activity of the sinus node, would merely reveal the inhibition which the sinus node was exerting on idioventricular pacemakers (2, 3).

The present findings support the concept of overdrive inhibition but not that of an inhibitory role of vagally released acetylcholine on ventricular pacemakers. The induction of ventricular standstill by overdrive during constant vagal stimulation shows that the important factor in suppression is overdrive not vagal stimulation. Thus, it is only necessary to reimpose on the ventricles a rate similar to that of the sinus node to reproduce a similar temporary standstill in the presence of a constant vagal stimulation. Ventricular standstill at the beginning of vagal stimulation entirely due to an inhibitory action of acetylcholine would imply that, in spite of its faster rate, the sinus node does not exert any inhibition at all. This idea is clearly contradicted by the effects of driving the ventricles at a rate similar to the sinus node during vagal stimulation (Fig. 1) or in dogs with surgical complete AV block (Fig. 4). The similar duration of the vagal and overdrive pauses indicates that the acetylcholine has little, if any, effect. It could be objected that electrical pacing of the ventri-
cles stimulates vagal fibers and that this stimulation is responsible for the subsequent inhibition. This effect is rather unlikely since the vagal fibers were already maximally stimulated. In addition, it has been shown that administration of eserine does not affect overdrive suppression in ventricles paced at a fast rate (3) and that atropine does not shorten overdrive suppression in Purkinje fibers driven in vitro (9). The prolongation of both the vagal pause and the overdrive pause with hypothermia (Fig. 2) also suggests that the same process is involved in both pauses.

Overdrive suppression of the ventricular pacemakers by the activity of the sinus node has been shown to result from an electrogenic Na extrusion (10). If this pump is the major mechanism, there must be several other factors which can interfere with it. One of these factors is the sympathetic nervous system and the sympathetic amines (17–19). Another factor could be an increase in [K]s, which is known to inhibit the spontaneous discharge of Purkinje fibers (20). This report makes it clear that, although an increase in [Kl] can contribute to overdrive suppression, this suppression can be dissociated from changes in [K]s. In the second step of the two-step experiments, K was lost; however, the loss was less than it was during the control experiments (Fig. 9), since the absolute rate was the same but the relative increase was less. The fact that the pause was the same in spite of the difference in [K]s shows that the contribution of an electrogenic Na extrusion to overdrive suppression overrides the influence exerted by changes in K levels. This finding is in agreement with the fact that during a long period of overdrive [K]s returns to its control value but on cessation of the overdrive a pause still follows (3). Also, during ventricular standstill, [K]s falls and does not increase (Fig. 3).

Experiments have shown that in Purkinje fibers perfused in vitro an increase in [K], prolongs overdrive suppression (21). This finding is an expected one, since a higher [K], decreases the spontaneous rate of discharge of Purkinje fibers. Because there is a linear relationship between the spontaneous idioventricular rate and the pause which follows overdrive (unpublished experiments), slower pacemakers should remain suppressed for a longer time.

An apparent discrepancy in the relationship between K loss and vagal stimulation must be discussed. It is usually stated that vagal stimulation or acetylcholine increases K loss from the heart (22); yet, in our experiments [K]s fell during the initial part of vagal stimulation (Fig. 3). This net K uptake during vagal stimulation is abolished if the ventricles are electrically driven at the same rate as the sinus node during the first minute of vagal stimulation (2), indicating that the fall in [K]s at the beginning of vagal stimulation is caused by a change in rate rather than by vagal stimulation as such. Whatever the effects of vagal discharge on the K fluxes of the atria, they are overcome by the more powerful influence of the fall in ventricular rate. It should be pointed out in this regard that most of the blood in the coronary sinus drains from the ventricles.

If the mechanism of overdrive suppression is a metabolism-dependent extrusion of Na, a fall in temperature should result in a larger accumulation of Na by the end of the overdrive and therefore should prolong overdrive suppression. Since at low temperature [K]s is the same as it is at normal temperature, a new steady state must be reached, perhaps at the expense of a higher intracellular Na concentration [Na]. However, the ability of the pump to handle the sudden overload caused by overdrive is certainly impaired, since [K]s rises in hypothermia to the same level as control even when the extra number of beats is only half as great as that imposed under control conditions (Fig. 8). In agreement with this finding, [K]s increases above the normothermic control level when the extra number of beats imposed during overdrive is the same at normal and lower temperatures (Fig. 3, Table 1). Since passive K loss in hypothermia must be similar to that at normal temperature, the enhanced net K loss with overdrive should reflect an inability of active transport to match the increased demand. Such an inability has two consequences which may explain the longer pauses: (1) [Na] increases more during overdrive and (2) the Na debt is paid by the electrogenic pump over a longer period of time during the recovery. At normal as well as at low temperatures, at the beginning of the pause the rate of Na extrusion should be higher than that before the overdrive. During the pause, the rate of extrusion should
progressively decline toward its predrive value as the extra Na is pumped out of the cell and \([Na]\) declines toward its predrive value. At low temperature, however, there are two major differences. The concentration of intracellular Na at the beginning of the pause is higher and the absolute rate of extrusion is lower. If the rate is decreased, it will take longer to decrease \([Na]\) toward the predrive value. In other words, the decline in the rate of Na extrusion after the overdrive will take longer at low temperature due to the slower decline in \([Na]\). The electrogenic Na extrusion per unit time may be less than it is at normal temperature, but this difference matters little as long as the protracted Na extrusion maintains the potential negative to threshold. The important point is that at low temperature the rate of electrogenic Na extrusion is probably initially lower than it is at normal temperature and the extrusion and therefore the inhibition last longer. Even if the larger increase in \([Na]\) at the beginning of the pause were to counteract the effect of the low temperature on the pumping rate, the larger amount of Na to be extruded should prolong the pause.

It is possible that the coronary flow changes during hypothermia, but such a change certainly is not the cause of the larger \([K]\), during overdrive in the cooled dogs, since in hearts perfused in vitro with a constant coronary flow at normal and low temperature the changes in \([K]\), during overdrive are similar to those described in the present paper (unpublished results from this laboratory). At low temperature the idioventricular rate falls more than the sinus rate, and in the dogs with vagal block the pacing rate during vagal stimulation was the same at normal and low temperatures. However, the longer pauses during hypothermia do not merely result from the slower idioventricular rate, for in dogs with complete AV block the ratio of overdrive rate to spontaneous rate was kept constant. Yet, the suppression was longer at low temperature (Fig. 5).

The results of the two-step overdrive (Fig. 9) can be explained by a metabolic mechanism. Predriving the ventricles leads to the usual loss of K and to a stimulation of the ion-exchange pump. When the second step of overdrive is begun, the pump is already stimulated by the relatively fast rate imposed by the first step, and in addition the difference in the rate between the first and the second step is less than the one-step increase in the control experiment. As a result, the K loss is less than it is in the control experiment, but the final pump stimulation is the same. Therefore, if the pump is as active as it is during the control experiment and if electrogenic Na extrusion is responsible for the suppression, the pause will be as long as it is in the control experiment.

The implication of the present experiments is that a sudden sinoatrial arrest by the vagus will be followed by a longer ventricular standstill the faster the sinus rate prior to the vagal action. The same will occur when the ventricles are driven not by the sinus node but by an implanted pacemaker or when a sudden AV block spontaneously occurs. Furthermore, the hypothermic heart will undergo a more prolonged ventricular standstill under the same conditions due to the metabolism dependence of the current responsible for the inhibition.

References

On the Mechanism of Idioventricular Pacemaker Suppression by Fast Drive
DANIEL J. KRELLENSTEIN, MICHAEL B. PLIAM, CHANDLER McC. BROOKS and MARIO VASSALLE

Circ Res. 1974;35:923-934
doi: 10.1161/01.RES.35.6.923

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 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/35/6/923

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/