On the Cause of Ventricular Asystole during Vagal Stimulation

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ABSTRACT

In anesthetized dogs the vagus nerve was stimulated for 2 min; during the first minute the ventricles were driven at a rate higher than the control sinus rate; after discontinuation of the drive, the duration of asystole was prolonged. When the ventricles were driven at a rate lower than the sinus rate during vagal stimulation the subsequent asystole was shortened. Slowing sinus activity by graded vagal stimulation before maximal vagal stimulation led to a shorter asystole. Driving the ventricles at a rate higher than the sinus node rate before vagal stimulation resulted in longer asystole. In animals with chronic atrioventricular block, "overdriving" the ventricles resulted in subsequent temporary inhibition of ventricular pacemakers. In dogs with atrioventricular block, coronary sinus plasma potassium increased during the period of ventricular overdriving, and the magnitude of the rise was a function of the driving rate. These results support the concept that ventricular asystole results from the suppressive action of the fast rate imposed by the sinus node upon the slowly discharging ventricular pacemakers. Suppression of sinus node activity by the vagus reveals the rate-dependent inhibition of ventricular pacemakers. The mechanism of inhibition may be related to changes in ionic concentration gradients.

ADDITIONAL KEY WORDS

rate-dependent pacemaker inhibition
cardiac standstill
heart rate and potassium
ventricular pacemakers
sinus rate and ventricular pacemakers inhibition
potassium and inhibition of ventricular pacemakers
ventricular escape
anesthetized dogs

Reflex stimulation of the vagus nerve may lead to a period of cardiac arrest. The inhibition of the sinus node pacemaker activity by the vagus is readily understood, but the simultaneous inactivity of the ventricular pacemakers is not easily explained since vagal effects on the mammalian ventricular automaticity are subject to question (1). On the other hand, there seems to be little doubt that the inactivity of ventricular pacemakers is also the result of an inhibitory process, since the duration of the period of ventricular asystole is usually longer than the interval between 2 consecutive beats of the ventricular escape rhythm. As to the nature of this inhibitory process, it has been demonstrated that driving atrial pacemakers at a rate higher than their intrinsic rate results in temporary inhibition of atrial pacemaker activity (2, 3, 4). Results of recent experiments suggest that inhibition of ventricular pacemakers during vagal stimulation can be explained on the same basis; namely, the ventricular asystole may be due to the persistence of the inhibitory effect of the prior fast sinus rate upon the slowly discharging ventricular pacemakers (5). By this concept the role of the vagus in producing the ventricular asystole would appear to be confined to suppression of sinus node activity; as a consequence of the sinus
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arrest, the inhibition of ventricular pacemakers would be revealed.

The aim of the present experiments was to gain further information about the mechanism of ventricular asystole by studying the inhibition of ventricular pacemakers in the presence and in the absence of vagal stimulation. In the first series of experiments the ventricles were driven electrically at rates higher and lower than the control sinus nodal frequency during the first minute of a 2-min period of vagal stimulation. We reasoned that if inhibition of ventricular pacemakers was rate-dependent, a driving rate higher than that of the sinus node should prolong and a lower driving rate should shorten the ventricular asystole recorded during vagal stimulation.

In the second series of experiments, the inhibition of ventricular pacemakers was studied without employing stimulation of the vagus by driving the ventricles of animals in which permanent atrioventricular block was produced. Examples of the inhibitory action of fast drive upon ventricular pacemakers have been reported (6-8); however in these studies, indirect excitation of the vagus nerve was not ruled out. To ascertain whether the development of "postdrive" asystole was due to excitation of vagal endings by the electrical stimulus, the procedure was performed before and after administration of neostigmine. We assumed that an inhibitory effect of acetylcholine should be potentiated in the presence of neostigmine. There is also another way in which the vagus might be involved in producing "postdrive" inactivity: a driving rate faster than the idioventricular rate usually results in an increase in blood pressure and this, in turn, leads to a reflex excitation of the vagus. The possible inhibitory action of this vagal reflex was investigated by comparing the results obtained before and after transecting both vagi.

The mechanism by which a fast driving rate causes pacemaker inhibition has been attributed to a rise in potassium (4). For this reason, a third series of experiments was carried out in which potassium levels were determined for the coronary sinus blood of animals with acute atrioventricular block before, during and after ventricular drive.

The results obtained in these three series of experiments are reported.

Methods

Mongrel dogs weighing 19 to 27 kg were anesthetized with morphine sulfate (5 mg/kg subcutaneously) and chloralose (75 mg/kg intravenously). The animals were intubated and placed on a Jefferson respirator. In the first series of experiments, a right thoracotomy was performed and bipolar electrodes were sutured on the epicardial surface of the right atrium and right ventricle. The atrial electrode was employed to record atrial activity and the ventricular electrode for electrical driving. A catheter was introduced into the aorta and blood pressure was measured with a Statham transducer. Lead II of the electrocardiogram was recorded. The right vagus was isolated in the neck and crushed; the peripheral end was used for stimulation. The stimulus frequency was 20/sec and the duration 3 to 5 msec. An American Electronics Laboratories stimulator was employed to drive the ventricles; the square pulses were delivered through a stimulus isolation unit at the selected frequency.

In the second series of experiments, atrioventricular block was produced in anesthetized dogs by ligating the His bundle during inflow occlusion. Electrodes were sutured on the right atrium and right ventricle; the wires from these electrodes were brought out through the skin and the chest was closed. Four to twelve days postoperatively, the animals were anesthetized as described above and the ventricles were driven electrically through the implanted electrode. The frequency of stimulation varied from just above the idioventricular rate to 180/min. The ventricles were driven at a fixed rate (120/min) and the duration of the drive was varied from a few seconds to 10 min. These procedures were repeated after intravenous injection of 0.1 mg/kg of neostigmine methysulfate (Prostigmine Methysulfate Roche). In some animals the driving procedure was repeated after cutting both vagi in the neck.

In a third group of dogs, acute atrioventricular block was produced as described above and, in
addition, the coronary sinus was cannulated for the collection of blood samples. A plastic "T" tube was connected to three short pieces of plastic tubing; one tube was sutured into the coronary sinus of the heparinized dogs during inflow occlusion; a second tube was passed through the right atrial appendage and permitted the coronary sinus blood to return to the atrial cavity; the third tube from the "T" cannula was clamped except during the collection of coronary sinus blood samples, at which time the second tube was clamped. Samples of coronary sinus blood were collected for plasma potassium determination before, during and after vagal stimulation or ventricular drive. Heparinized canine blood, freshly drawn, was infused intravenously to replace the blood withdrawn for potassium determination. Potassium levels were determined with a flame photometer. Arterial blood was collected at intervals for the determination of pH, \( \text{Pco}_2 \), and \( \text{Po}_2 \), and any degree of acidosis was corrected by the administration of \( \text{NaHCO}_3 \). The temperature of the animals was measured by means of a thermocouple placed in the esophagus and was maintained at about 37°C with the use of heat lamps as needed.

**Results**

**VAGAL STIMULATION AND VENTRICULAR DRIVE**

Typical results obtained with simultaneous ventricular drive and vagal stimulation are illustrated in Figure 1. The lead II electrocardiogram is shown; the blood pressure and atriole tracings have been omitted. The first trace (control) shows the effect of vagal stimulation alone: the initiation of stimulation

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1**

*Effect of simultaneous vagal stimulation and ventricular drive on the duration of ventricular asystole. Control: vagal stimulation only; the duration of the asystole in this and the following traces is indicated by the interval between the two arrows. Driving rate: rate at which the ventricles were driven during the first minute of a 2-min vagal stimulation. The numbers indicate the driving rate per minute.*

![Figure 2](http://circres.ahajournals.org/)

**FIGURE 2**

*Effect of sinus bradycardia on the duration of ventricular asystole. The first trace is the control record. The sinus impulses occasionally were not transmitted to the ventricles: 77 is the average rate per minute of the sinus impulses transmitted to the ventricles before vagal stimulation. The duration of asystole is indicated by the two arrows. The second trace shows the sinus bradycardia (44/min) induced by graded vagal stimulation. At the first arrow maximal vagal stimulation was applied; at the second arrow ventricular escape occurred.*

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Effect of ventricular "overdrive" for 60 sec on idioventricular pacemaker activity in the presence of chronic A-V block. Each trace begins with the control idioventricular rhythm; the initiation of the ventricular drive is recognized by the abrupt change of the QRS complex polarity from negative to positive. The numbers on the left side of the figure indicate the driving rate per minute. Most of the record of the 60-sec period of drive has been omitted (break in the traces). Discontinuation of the drive is indicated for all traces by the arrow at the bottom of the figure. Ventricular asystole is of progressively longer duration as the driving rate increased from 90 to 180/min.

(first arrow) led to the usual ventricular arrest, which was followed by ventricular escape (second arrow) although vagal stimulation continued. The second trace begins with the record of sinus rhythm; the stimulus artifact marks the simultaneous initiation of vagal stimulation and ventricular drive. Most of the record of the 1-min ventricular drive and simultaneous vagal stimulation has been omitted, as indicated by the break in the trace; the second portion of the trace begins with the last driven beats. At the first arrow the ventricular drive was discontinued while vagal stimulation was maintained for another minute. The second arrow marks the beginning of ventricular escape rhythm. In the second trace, the average rate of the sinus node impulses reaching the ventricles was 77/min and the driving rate was 90/min; the duration of the asystole was essentially the same as in the control tracing. In the third trace, the ventricular driving rate was lowered to 30/min and was followed by a ventricular asystole much shorter than those recorded in the control trace. In the fourth trace, the driving rate was increased above the sinus rate to 180/min and the ventricular pause was much prolonged (26.5 sec versus 16.5 sec in the control tracing). When the driving rate during vagal stimulation was lower than the sinus node rate, the average duration of ventricular asystole decreased consistently from a control value of 9.1 to 2.1 sec (three experiments); with a driving rate of 180/min,
the duration of ventricular asystole increased consistently from a control value of 7.6 to 17.4 sec (five experiments).

These findings suggested that slowing the sinus node rate before vagus-induced cardiac standstill should decrease the duration of asystole. Thus, the test period of maximal vagal stimulation was preceded by a period of stimulation at a frequency which reduced the sinus rate without producing atrioventricular (A-V) block. The results obtained with this procedure are illustrated in Figure 2. The first trace shows the ventricular asystole (between arrows) recorded during control vagal stimulation. In the second trace, the sinus rate was slowed by means of graded vagal stimulation to 44/min for 1 min. At the first arrow, maximal vagal stimulation was applied; the ventricular asystole was shortened from the control value of 15.7 to 3 sec. In four experiments, the average sinus rate of 91 beats/min was reduced to 49.5 beats/min during graded vagal stimulation; on maximal vagal stimulation the duration of the asystole was 3.2 sec as compared to the control value of 12.2 sec. In other tests the ventricles were driven at rates higher than that of the sinus node rate before vagal stimulation. At the end of 1 min, the drive was discontinued and vagal stimulation was initiated. In such tests the duration of the asystole lengthened to values similar to those obtained with simultaneous vagal stimulation and ventricular drive (four experiments). Thus, in Figure 1, driving at 180/min during vagal stimulation resulted in a period of asystole of 26.5 sec; in the same animal, driving at 180/min prior to vagal stimulation resulted in a period of asystole of 27 sec.

**Ventricular Drive in Dogs with Block of the A-V Node**

The ventricles of dogs with block of the A-V node were driven at a constant rate for 1 min and then the ventricular drive was...
Ventricular asystole and vagus

Ventricular driving rates and the average duration of subsequent asystoles. The open circles have been slightly displaced on the abscissa to avoid superimposition with the solid circles. The vertical bars indicate the standard error of the mean. See text for further explanation.

abruptly discontinued. The driving rates selected were just above the idioventricular rate, 90, 120, 150, and 180/min. The results of ventricular driving on ventricular pacemaker activity are illustrated in Figure 3. On the left hand side of the figure the control tracing is shown; the beginning of ventricular drive is indicated by the change in polarity of the QRS complex. The numbers at the beginning of the traces indicate the driving rate per minute. Most of the record taken during the ventricular driving has been omitted (break in the traces) and the beginning of the second portion of the traces shows the last driven beats. At the time indicated by the arrow at the bottom of the figure, the ventricular driving was discontinued. There was no ventricular asystole following a driving rate of 48/min (first trace); with faster rates, the ventricular asystole increased progressively in duration as illustrated by the subsequent traces. The resumed idioventricular rhythm was characterized by a progressive acceleration to a steady value as typically seen in ventricular escape. The procedure illustrated in Figure 3 was repeated after the administration of neostigmine. As shown in Figure 4, the atrial rate was markedly reduced by the drug, but the duration of ventricular asystole was essentially the same as that before the administration of neostigmine. The results

FIGURE 5

Effect of ventricular driving at a constant rate for different periods of time on the duration of subsequent asystole. The ventricular driving rate was 120/min; the QRS of the driven beats is positive. The duration of the period of drive is indicated in seconds by the numbers at the beginning of each trace. Only the last driven beats are shown for driving periods of 10 sec or more.

FIGURE 6
Reflex sinus node slowing associated with overdrive in the presence of A-V block. In the upper section of the figure are shown traces recorded with the vagi intact and in the lower section traces recorded after sectioning the vagi. RA is the atriogram. BP = aortic blood pressure in millimeters of mercury; the zero reference line is the straight line recorded below the blood pressure trace. L2 is lead II of the electrocardiogram. The traces begin with the control records; the initiation of the ventricular drive is indicated by the abrupt change in the QRS complex. Most of the recording during 1 min driving was omitted (break in the traces). The traces restart with the last driven beats and discontinuation of drive is indicated by the arrow at the bottom of the figure. Note the sinus bradycardia on trace RA in the upper section of the figure during the driving period.

obtained in five experiments have been plotted in graphic form (Fig. 5). For the purpose of comparison, the control spontaneous ventricular rates have been included in the graph and are represented by the two isolated circles. The solid isolated circle (before administration of neostigmine) and the open isolated circle (after administration of neostigmine) indicate on the abscissa the idioventricular rate and on the ordinate the interval in seconds between 2 consecutive idioventricular beats. The circles connected by lines show the results obtained with the driving procedure. The solid circles connected by the continuous line indicate on the abscissa the ventricular driving rate and on the ordinate the duration of asystole before the administration of neostigmine. The open circles connected by the dashed line indicate driving rates and duration of the asystoles after the adminis-
Average coronary sinus potassium levels plotted as percent change of control values. Time is indicated on the abscissa and percent potassium change on the ordinate. In the upper section of the figure the ventricles of animals with A-V block were driven for 60 sec at a rate just above idioventricular rate (−) and at 90, 120, and 150/min. In the lower section of the figure, the ventricles were driven at a constant rate for 15, 30, and 60 sec. The three samples collected after the end of drive have been plotted at 5-sec intervals; it should be noted that this is an approximate time interval since this interval varied after each driving procedure.

tration of neostigmine. With a spontaneous idioventricular rate of 45.8 beats/min, the interval between 2 beats was 1.39 sec; after a period of driving at the rate of 49.8/min, the pause was 1.59 sec. Driving at a rate of 90/min led to longer asystole in all instances; when the rate was increased above 90/min there was a further prolongation of the average asystole, but in some instances the duration of asystole tended to plateau. The idioventricular rate after administration of neostigmine was 42.2/min; the atrial rate was 87/min as compared to 167/min before neostigmine. There was no substantial difference in the duration of the asystole before and after the administration of neostigmine. In these same animals, the ventricles were driven for progressively longer periods of time at a fixed rate and a typical result is shown in Figure 6. As the duration of the driving period was increased, the duration of the subsequent asystole also increased. After driving periods of 30 sec, 1 min, and 2 to 10 min, the average values and their standard error of the ventricular pause were 4.4 ± 0.5, 5.8 ± 0.8, and 7.2 ± 0.9 sec, respectively (five experiments). After the administration of neostigmine, the ventricular pause for the same periods of drive were 4.2 ± 0.6, 5.0 ± 0.8, and 5.9 ± 1.31.
Coronary Sinus Plasma Potassium in Milliequivalents per Liter Before, During and After Period at Different Rates

TABLE 1

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Average Values

- 2.86
- 2.90
- 2.94
- 2.86
- 2.78
- 2.80

C = control period. Drive = Ventr. R. = period of driving at a rate just above the idioventricular rate. Recovery = end of the driving periods. Drive 90/min, Drive 120/min, Drive 150/min = periods of ventricular drive at the rate of 90, 120, and 150/min, respectively.

Inspection of Figures 3, 4, and 6 shows that during asystole the atrial rate was initially slow and accelerated progressively toward a steady value. This suggested that overdrive led to reflex vagal discharge which might have been in part responsible for the postdrive asystole. For this reason the ventricles were driven before and after sectioning the vagi. In Figure 7 the trace labeled RA shows the bipolar atrioagram. The blood pressure trace is marked BP and L2 indicates the lead II electrocardiogram. In the upper section of the figure, both systolic and diastolic pressures increased as soon as the ventricles were driven at 120/min; at the same time, the atrial rate slowed from 200 to an average of 128/min (see trace RA). Most of the record of 1-min drive has been omitted (break in traces) and the second portion of the traces shows that at the end of the driving period peak systolic pressure had returned within the control range, but the atrial rate was still slower than the control. As soon as the drive was discontinued, the blood pressure declined while the atrial rate accelerated toward its control value. The procedure was repeated after both vagi had been cut and the results are shown in the lower section of Figure 7. The increase in blood pressure caused by the ventricular drive was associated with a far less pronounced slowing of sinus node activity (from 175 to 159/min) but the duration of ventricular asystole was essentially unchanged.

After driving the ventricles for 1 min at 120/min, the average ventricular asystole was 6.5 sec before and 6.3 sec after sectioning both vagi (five experiments).

VAGAL STIMULATION IN DOGS WITH BLOCK OF THE A-V NODE AND DETERMINATION OF POTASSIUM LEVEL OF CORONARY SINUS BLOOD

In 5 animals with chronic A-V block, the control sinus rate was 151.4/min and the ventricular rate 44.8. Stimulation of the vagus for 1 min reduced the atrial rate to 23.6 beats/min and the ventricular rate to 40.2 beats/min. After cessation of the stimulation, the rates increased to 171.6 and 49 beats/min, respectively. The slight slowing of ventricular rhythm during vagal stimulation began only a few seconds after the beginning of stimulation and reached a maximum after 10 to 20 sec as contrasted with the immediate suppression of the activity of the S-A node. In these same animals after the administration of neostigmine, the sinus rate was 135.6 beats/min and the ventricular rate 43.6 beats/min. During vagal stimulation, the atrial rate decreased to 2.8 beats/min and the ventricular rate to 35.2 beats/min. Following stimulation, the sinus rate was 128.4 and the ventricular rate 39.6.

In 6 dogs with acute A-V block, the potassium concentration was determined in duplicate on arterial plasma; the average value was 3.34 ± 0.17 mEq/liter. The plasma potassium of coronary sinus blood measured in
VENTRICULAR ASYSTOLE AND VAGUS

The effect of different driving rates on the coronary sinus plasma potassium was investigated next. The values obtained are reported in Table 1 and the percent changes are illustrated in Figure 8, upper section. In this figure the abscissa shows the time in seconds, the ordinate shows the percent change in coronary sinus potassium level with respect to control values.

The results show that driving for 60 sec at a rate just above the idioventricular rate did not alter coronary potassium level. Driving at 90, 120 and 150/min resulted in an increase in potassium concentration which occurred in each experiment and was roughly proportional to the rate of the drive. After discontinuing the faster drives, potassium concentration fell temporarily to a level below that of the control. In another series of experiments carried out on the same animals, the ventricles were driven at a rate approximately three times faster (150/min) than the intrinsic ventricular rate; the driving rate was maintained constant and the duration of the driving periods was changed (15, 30 and 60 sec). The changes in coronary sinus potassium obtained with this procedure are reported in Table 2 and the percent changes are shown in the lower section of Figure 8. The coronary sinus potassium level increased above that of the control in each experiment and decreased after discontinuation of the drive to or below the control value. The elevated potassium level was maintained during the period of driving. In 1 animal the ventricles were driven at the rate of 150/min for 10 min. The average control value was 3.05 mEq/liter; during the first minute of driving, the three blood samples taken gave potassium values of 3.51, 3.83, and 3.67; at the tenth minute of driving, two blood samples were taken and the potassium level had returned to control values, namely 3.00 and 3.02. After the cessation of the drive, the potassium level fell below control with values of 2.74, 2.78, and 2.74 mEq/liter.

**Discussion**

The results of the present experiments provide further support for the suggestion (5) that inhibition of ventricular pacemakers during vagal stimulation is a rate-dependent process and is not caused by the vagal stimulation per se. The data also indicate that the duration of the asystole of ventricular pacemakers is, within limits, a function of the rate at which the ventricles are driven and the duration of the drive period. Finally, the results
TABLE 2
Coronary Sinus Plasma Potassium in Milliequivalents per Liter Before, During and After a 150/min Drive for Different Time Periods

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C and Recovery = see footnote to Table 1. 15, 30, and 60 sec = driving periods of 15, 30, and 60 sec, respectively, at a fixed rate of 150/min. Part of the data shown in Table 1 for the rate of 150/min are shown again in Table 2 under the heading of 60 sec to allow comparison with the data obtained with the driving periods of 15 and 30 sec.
suggest that overdrive inhibition is associated with a change in potassium gradient across the cell membrane and that this change, in turn, is rate-dependent.

The evidence in favor of rate dependence of the inhibition of ventricular pacemakers during vagal stimulation is based on the following findings: (1) driving the ventricles at a rate higher than the control sinus node rate during the first minute of a 2-min vagal stimulation led to a prolongation of ventricular asystole; (2) repeating the above procedure, but driving at a rate below the sinus node rate, shortened the asystole; (3) induction of bradycardia prior to maximal vagal stimulation markedly shortened ventricular asystole, while an increase in heart rate before vagal stimulation increased the duration of the asystole; and (4) asystole was induced in animals with block of the A-V node by driving the ventricles at a rate higher than the idioventricular rate. Thus, it is possible to vary the duration of ventricular asystole in the presence of a constant vagal stimulation by altering the driving rate of the ventricles during or before vagal stimulation. Furthermore, asystole can be produced by overdriving the ventricles in dogs with A-V block in the absence of vagal stimulation and after sectioning the vagi.

It has been demonstrated that stimulation of the vagus in dogs with block of the A-V node does not produce ventricular asystole and this could be attributed to interruption of vagal fibers in the process of producing A-V block (9). Results obtained in the present experiments in animals without A-V block and, therefore, without damage to vagal fibers, show that vagal stimulation is not responsible for ventricular asystole. During A-V block the ventricular pacemakers are no longer subjected to the inhibitory influence of the faster sinus rate; under these circumstances suppression of the sinus rhythm by the vagus would not be expected to affect the idioventricular pacemaker automaticity. Although maximal vagal stimulation does not induce ventricular asystole in animals with block of the A-V node, it frequently causes a slight slowing of the idioventricular rhythm. The observation that the slowing of idioventricular rate reaches its maximum 10 to 20 sec after the initiation of vagal stimulation could indicate that acetylcholine diffuses to the ventricular pacemaker sites rather than being liberated in loco (10). The more pronounced effect of vagal stimulation on the automaticity of ventricular pacemakers after administration of neostigmine can be interpreted on the same basis.

Ventricular overdrive in the presence of A-V block (6-8) has been carried out with the vagi intact and published figures [Fig. 5 (7) and Fig. 19 (8)] show that overdrive was followed not only by ventricular asystole, but also by a temporary sinus bradycardia; this is in agreement with our findings (Figs. 3, 4, 6). The results illustrated in Figure 7 (top) suggest that the slowing of the sinus rate is caused by a rise in blood pressure which accompanies ventricular overdrive and elicits reflex vagal discharge. This interpretation is corroborated by the substantial abolition of the sinus bradycardia after sectioning of the vagi (Fig. 7, bottom). The unaltered duration of ventricular asystole before and after the vagi were cut seems to exclude a reflex vagal discharge as the cause of the inhibition of the ventricular pacemakers. With the vagi cut, the slight residual sinus bradycardia during ventricular overdrive could be due to sympathetic withdrawal. That sympathetic withdrawal is not responsible for the ventricular asystole is indicated by the finding that ventricular asystole occurs in the presence of a constant blood pressure in dogs on total cardiopulmonary bypass; in addition, overdrive produces inhibition of spontaneously active Purkinje fibers perfused in vitro (5). The possibility that asystole was caused by a direct release of acetylcholine from vagal endings by the driving stimulus appears unlikely, for driving the ventricles at a rate just above the spontaneous ventricular rate did not result in any appreciable pause. Furthermore, the failure of ventricular asystole to increase in duration after the administration of neostigmine (Fig. 5) suggests that the
driving rate and not the release of acetylcholine by the stimulus is the factor involved in the suppression of ventricular pacemakers.

The present evidence thus indicates that ventricular pacemakers are suppressed by a faster driving rate; the question then arises as to the mechanism of such rate-dependent suppression. The proposal that inhibition of pacemakers by overdrive is due to an accumulation of potassium outside the cell membrane (4) is supported by the present findings that the potassium concentration of coronary sinus blood increased when the ventricles were driven at a rate faster than the spontaneous ventricular rate (Fig. 8). That an increase in heart rate causes potassium loss from myocardial cells has been shown previously (11-13); the present results indicate that there is a correlation between the ventricular driving rate, the coronary sinus potassium increase and the duration of the subsequent asystole (Fig. 3 and Fig. 8, top). An increased [K]o enhances potassium conductance of Purkinje fibers and leads to cessation of spontaneous activity (14, 15). Thus, the observed increase in potassium levels could account for the temporary inhibition of ventricular pacemakers. A requirement for this explanation is the assumption that the increase in coronary sinus potassium level represents an increase in [K] outside Purkinje fibers as well as ventricular fibers, a point on which evidence is not available. After a prolonged period of drive, the potassium loss subsides (16), which is in agreement with the result obtained when the potassium level was determined at the tenth minute of driving. If diffusion of K+ is restricted by a local barrier, it is possible that the potassium concentration in close proximity to the cell membrane is still elevated when coronary sinus potassium has returned to control value during prolonged driving. Also, a change in concentration gradients of Na+ as well as K+ across the cell membrane as a consequence of overdriving (17) might contribute to the ensuing asystole. A rise in [Na]i would be expected to reduce the inward current during diastolic depolarization. A change in ionic gradient might explain the results illustrated in Figure 8, bottom: the coronary sinus potassium levels at the end of the drive periods were not very different, and yet asystole was longer for longer periods of driving. At higher frequencies, the diastole is markedly shortened, as indicated by the electrocardiogram (e.g., Fig. 3). It is conceivable that active extrusion of Na+ could be curtailed under this circumstance and an intracellular accumulation of Na+ might result. However, no data are available on this point, and it remains to be established whether a significant change in sodium intracellular concentration may occur after a period of driving below 1 min duration.

In Figure 8, it is apparent that driving at faster rates (upper graph) or for longer periods of time (lower graph) was followed by a more pronounced fall in coronary sinus K levels. This was not unexpected since the more pronounced fall in potassium corresponded to the longer periods of asystole during which the electrochemical force driving K+ inward is larger; also the fall may have resulted from enhanced activity of the sodium-potassium pump following a period of sustained activity.

During vagal stimulation coronary sinus potassium falls; this has been attributed to the fall in heart rate which accompanies vagal stimulation since the decrease in coronary potassium was avoided by driving the ventricles during vagal stimulation (5). Support for this interpretation is provided by the present finding that vagal stimulation in dogs with block of the A-V node is not associated with a decrease in coronary sinus potassium in the presence of a maintained idioventricular rhythm.

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