Effects of Altered Heart Rate on Chloroform-Epinephrine Cardiac Arrhythmia

By Robert L. Vick, Ph.D.

It was reported recently that cardiac arrhythmia induced in cyclopropane anesthetized dogs by infusion of epinephrine could be converted to normal sinus rhythm by vagal stimulation. The termination of multifocal ventricular tachycardia is interesting because it is not readily apparent how vagal influence, presumably limited to the A-V node or upper bundle of His, alters arrhythmia predominantly of ventricular origin. In exploratory studies designed to confirm the effects of vagal stimulation on ventricular arrhythmia in dogs anesthetized by chloroform, it was observed that when conversion to a supraventricular rhythm occurred it was invariably after slowing of the heart rate, i.e., rate as well as rhythm was changed in the conversion. This indication that decreased heart rate might be important in the conversion to sinus rhythm suggested that the frequency of ventricular excitation is a factor in the genesis of the arrhythmia. The data reported in this communication comprise a test and an apparent confirmation of that hypothesis.

Methods

A total of 16 mongrel dogs of either sex and weighing from 12 to 17 kg were used. The following procedures were done on 12 of them. After initial anesthesia with thiopental sodium (20 mg/kg, iv), a tracheal cannula was inserted and connected to a Harvard air pump to provide artificial respiration. A variable portion of the air intake of the pump was bubbled through chloroform permitting gradual substitution of chloroform anesthesia for that of the short-acting thiopental.

The sternum was split and the chest walls were retracted to expose the heart. Both vagus nerves were isolated in the neck and crushed. The peripheral nerve trunks were placed in sleeve electrodes and covered with liquid petrolatum. Small stainless steel clips, each forming a pair of stimulating electrodes, were placed on the right auricular appendage and on the right ventricle near the pulmonary conus. All stimuli were passed through stimulus isolation units. Records of each set of stimuli delivered were taken on separate recording channels by amplifying either the synchronizing signal from the stimulator or a portion of the input to the stimulus isolation unit.

Electrical concomitants of cardiac activity were measured by recording conventional lead II ECG and two special electrograms. One of the electrograms was used to evaluate atrial activity and the other was used to evaluate ventricular activity. The former was obtained using electrodes attached to the right atrial appendage and the chest wall over the third rib; the latter was obtained using electrodes on the ventricular surface in the septal area about half way between apex and base, and on the left hind leg. Aortic pressure was measured by a P23 AA Statham transducer connected to a tube passed through the left subclavian artery. The output of the transducer was amplified by a carrier preamplifier and recorded, along with the other traces, by a rectilinear pen-writing system.

The remaining four dogs were anesthetized by pentobarbital sodium (30 mg/kg), so that the duration of anesthesia would be increased and more extensive surgery could be performed. After the chest was opened at the fourth right interspace the azygous vein was ligated and both venae cavae were isolated. During complete venous occlusion the right atrium was opened, the contents aspirated, and a single stitch placed tightly about the area of the bundle of His, at the base of the medial cusp. The atrium was allowed to refill with blood, then the edges of the atrial incision were approximated in a noncrushing clamp and the venous occlusion was released. Inflow to the heart was stopped for not more than 90 seconds. Lead II of the ECG was observed, and if complete A-V block persisted the atrial
incision was closed with sutures. In all four ani-
mals A-V block was accomplished with a single
trial. The chest was closed and the pneumothorax
was reduced. The animal was then observed until
there were signs of decreasing depth of anes-
thesia (one to two hours), when chloroform
anesthesia was instituted and the procedures de-
scribed above were performed.

To produce arrhythmia, epinephrine was ad-
ministered by continuous intravenous infusion at
rates of 1 to 5 \( \mu \text{g/kg/min} \). The exact rate used
was determined by the sensitivity of each individ-
ual animal and by the type of arrhythmia de-
sired. A stable bigeminy could be maintained
up to 30 minutes by continuing the minimum
epinephrine infusion needed to produce arrhyth-
mia\(^3\). The proportion of ventricular ectopic beats
could be increased by increasing the rate of the
infusion.

The effects of peripheral vagal action were
determined by stimulating one or both vagi with
single biphasic shocks of 1 msec duration and
suprathreshold voltage. In each experiment the
stimulation was begun at 1/sec and not altered
while being applied. If conversion to regular
supraventricular rhythm did not occur in 60
seconds, stimulation was discontinued and fre-
quency was increased in a subsequent trial. A
conversion to regular supraventricular rhythm was
not attributed to vagal action unless the arrhyth-
mia resumed when vagal stimulation was stopped.
Arterial pressure usually remained constant or
increased if conversion to normal sinus rhythm
occurred before the atrial rate was slowed to
about 100/min. Bradycardia, atrial arrest, or
A-V block usually reduced arterial pressure and
hence limited the frequency of stimulation which
could be used. No lessening of arrhythmia which
coincided with decreased mean arterial pressure\(^4\) is included in the data.

**Results**

**BIGEMINY**

Bigeminy could be converted to regular su-
praventricular rhythm by vagal stimulation in
each of the 12 experiments. Typical results
are illustrated in figure 1. The control bigemi-
nal rhythm of 164/min is shown in the first
panel. During right vagal stimulation the rate
slowed and regular rhythm began at 104/min
(second panel). Since slowing of the cardiac
rate accompanied every such conversion,
the effect of restoring the faster heart rate
during the vagal action was studied by
driving the atrium at a rate about equal to
that at which bigeminy had occurred. Typi-
cally, characteristic bigeminy was restored
(third panel). When spontaneous beating re-
sumed (fourth panel), the rhythm was regular
and at about the same rate as that preceding
the period of driving. When vagal stimula-
tion was stopped the heart rate increased
spontaneously and bigeminy returned again
(last panel).

The effect of heart rate on the occurrence
of bigeminy was tested in still another way.
After it was determined in a given experiment
that stable bigeminy could be produced by
infusion of epinephrine, the rate of infusion

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

**FIGURE 1**

Effect on cardiac bigeminy of vagal stimulation and subsequent restoration of heart rate.
Expt. 7/3/63. Dog under chloroform anesthesia; 1 \( \mu \text{g/kg/min} \) epinephrine infused throughout.
was gradually decreased until regular rhythm returned. Then the atrium was driven at a rate approximating that at which bigeminy had occurred. Typical results are shown in figure 2. The rate of epinephrine infusion was insufficient to disrupt normal rhythm at the spontaneous heart rate (96/min), but bigeminy occurred within seconds when the heart rate was increased to 156/min (panel 1). Regular rhythm returned when the slower

spontaneous rate resumed (panel 2). This maneuver was performed successfully at least once in each of eight experiments for a total of 53 times in 57 attempts.

TACHYCARDIA

Arrhythmias involving more frequent ectopic beats were also converted to regular supraventricular rhythm by vagal stimulation in each of seven dogs. Typical results are shown in figure 3. In the first panel vagal stimulation began to reduce the atrial rate almost immediately, but there was a period during which the ventricular rate continued independently of the declining atrial rate and without slowing before abrupt conversion to sinus rhythm. In the second panel, after vagal stimulation was stopped, the heart rate accelerated and regular sinus rhythm persisted until a rate of 162/min was reached. Ventricular ectopic beats appeared at that point and increased in frequency until the control rate (about 180) and pattern of ventricular excitation returned (last panel).

Restoring the heart rate by driving the atrium reinduced arrhythmia in every one of 39 attempts in this series. In 13 attempts only bigeminy resulted, while in the remainder ventricular tachycardia was restored.
Increasing the rate of epinephrine infusion in each of the seven experiments eventually produced tachycardia which did not revert to normal rhythm during vagal stimulation, but which slowed in rate. Still more rapid infusion produced tachycardia which was unaffected by vagal stimulation. In each experiment the intractable arrhythmia always had a faster rate than that which could be slowed or converted to sinus rhythm.

Arrhythmia could be reinduced by driving the ventricles to restore the faster ventricular rate after conversion to normal rhythm by vagal stimulation. While this method was less dependable than driving the atrium, arrhythmia returned during the drive in four of five dogs for a total of 24 times in 43 attempts. In 20 of the successful attempts spontaneous ventricular activity persisted for several seconds to several minutes after the drive was stopped. Figure 4 shows such an experiment. During vagal stimulation which had resulted in regular supraventricular rhythm (panel 2) the ventricles were driven at 171/min. They soon developed an independent rhythm (panel 3) of 224/min. The spontaneity of this ventricular action is clearly shown when it persists after the ventricular drive is stopped (panel 4). The ventricular rate did not slow before the abrupt termination and conversion to supraventricular control. When vagal stimulation was stopped the spontaneous rate resumed and bigeminy returned (last panel).

During epinephrine infusion which did not disrupt normal rhythm at spontaneous rates, driving the ventricles induced arrhythmia in three of five dogs for a total of 8 times in 31 attempts. In several experiments short runs of accelerated ventricular activity occurred when the drive was stopped, possibly indicating that some spontaneous ventricular activity had been obscured by the drive.

**Hearts With A-V Dissociation**

Additional experiments were performed on four dogs with A-V conduction block in the bundle of His. Initial ventricular rates in these animals ranged from 38/min to 63/min, and were not changed by vagal stimulation intense enough to produce atrial arrest. Infusion of epinephrine up to 5 \( \mu \)g/kg/min resulted in heart rates of 58/min to 88/min with no arrhythmia. Increasing the ventricular rate by driving the ventricles over a range of rates from 129/min to 211/min produced arrhythmia in three of the four dogs even with epi-
nephrine infusion as low as 1 μg/kg/min. Typical results are shown in figure 5. The ventricles were driven at 176/min, beginning in the first panel. After about 10 seconds, spontaneous ventricular tachycardia ensued at a rate of 200/min. When the ventricular drive was stopped (3rd panel) the tachycardia continued without a change in rate for another 10 seconds, then abruptly disappeared with reversion to the control rate and rhythm. Arrhythmia was caused in this way in 36 of 80 attempts (36 of 48 in the three dogs in which any attempts were successful). As in the previous attempts to produce arrhythmia by driving the ventricles, changes in rate and rhythm were seen after stimulation was discontinued, even though none may have been apparent during stimulation. These effects included the appearance or continuation of tachycardia for a few seconds after driving was stopped or the persistence of an accelerated rate which declined subsequently to control levels either with regular ventricular rhythm or with patterns including more than one configuration displayed in the electrogram. Such effects were seen in 24 of 32 attempts in the dog which showed no arrhythmia during ventricular drive and in 7 of the 12 unsuccessful attempts in the other three dogs.

Discussion

These experiments indicate that vagal stimulation converts ventricular arrhythmia induced by epinephrine in dogs anesthetized with chloroform to regular supraventricular rhythm by slowing the heart rate, and that changes in heart rate strongly influence such arrhythmias. Slowing of the heart rate invariably accompanied conversion of arrhythmia to normal rhythm, and a return to a faster heart rate reestablished the arrhythmia. Increasing the heart rate during epinephrine infusion produced arrhythmia or increased the proportion of ventricular ectopic beats. Thus the vagal influence on ventricular activity is indirect and mediated through the frequency of excitation entering the ventricles. This interpretation differs from that offered by Dresel and Sutter in which the arrhythmia was considered to arise in areas directly under vagal influence. It is consistent with the observation of Moore et al. that the ectopic beats originate distal to the bundle of His. The means of influencing excitation of the ventricles from supraventricular sources is readily apparent in bigeminy where every second beat comes from the atrium and only one ventricular ectopic beat follows each atrial beat. It is more difficult to account for the influence of atrial rate on arrhythmia predominantly of ventricular origin.

While there is adequate evidence of independent ventricular activity, it may be that periodically, activity originating in the atrium is propagated into the ventricle. Thus the ventricular tachycardia which was affected by atrial slowing may have depended upon occasional atrial input, which, by maintaining a
minimum frequency of ventricular excitation, helped perpetuate independent ventricular activity. Vagal stimulation, by increasing the interval between atrial beats, could bring on the termination of the ventricular arrhythmia by decreasing the probability of a propagated impulse of atrial origin entering the ventricle at a critical time. When ventricular tachycardia was unaffected by atrial slowing, the idioventricular rate stayed above any critical minimum and hence did not depend on atrial input.

It is not known how an increased heart rate favors the emergence of idioventricular activity during hydrocarbon anesthesia, but there are indications that it may do so by increasing the possibility of re-entry excitation. Because of progressive increase in refractory period of specialized ventricular conducting tissue from the bundle of His to its peripheral fibers, premature beats are likely to encounter delay or even local conduction block in one or more branches of the Purkinje system. These conditions combined with the short refractory period of ventricular myocardium make re-entry excitation possible.7 The action of chloroform on Purkinje tissue has not been studied, but in the myocardium it is known to increase the refractory period and to decrease the uniformity of recovery after excitation.8 If the effects of chloroform on Purkinje tissue are even qualitatively similar to those on the myocardium, an increasing heart rate might eventually make every beat effectively premature because of the conditions encountered during propagation. Consistent with this hypothesis the polypeptide bradykinin, which inhibits bigeminy induced by infusion of epinephrine into chloroform anesthetized dogs,9 has been shown to equalize the refractory periods of myocardium and Purkinje tissue by selectively decreasing that of the latter.10

However, as pointed out earlier by Dresel et al.,8 the action of a hydrocarbon anesthetic alone is not sufficient to induce arrhythmia, even in the presence of increased arterial pressure or increased heart rate, but an adrenergic agent with cardiac stimulating action is also needed.

This essential role of epinephrine or a similar substance has not been satisfactorily explained. Norepinephrine decreased the prolonged refractory period of ventricular myocardium, but not the non-uniformity of recovery of excitability brought about by chloroform.8 In the absence of data on the action of the adrenergic agent on Purkinje tissue it is difficult even to speculate as to what this might mean in terms of re-entry excitation. As an alternative explanation it may be that, in addition to its other effects, increased frequency of ventricular excitation somehow also enhances the action of epinephrine to increase ventricular automaticity.11 There are indications that the influence of arterial pressure may be exerted in this way.15-18

**Summary**

In chloroform-anesthetized dogs receiving epinephrine, slowing of the heart rate invariably accompanies conversion of arrhythmia to normal supraventricular rhythm by vagal stimulation, and restoring the faster heart rate reestablishes arrhythmia. Increasing the heart rate during epinephrine infusion can induce arrhythmia or increase the proportion of ventricular ectopic beats. These observations are taken to indicate that the vagal influence on ventricular arrhythmia in these conditions is indirect and mediated through the frequency of excitation entering the ventricle.

It is suggested that during chloroform anesthesia an increased heart rate favors the emergence of ventricular arrhythmia when activity propagated after successively shorter intervals encounters delay or local conduction block in the Purkinje system, and re-entry excitation is made possible. It is proposed that in these conditions ventricular tachycardia is a self-sustaining arrhythmia that must maintain a critical frequency, either intrinsically or from
external (supraventricular) input. The arrhythmia is susceptible to termination by vagal stimulation when atrial slowing decreases the probability of an atrial impulse entering the ventricle at a critical time.

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References

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